DEVELOPMENT OF THE

MORPHINE HYDROGEL SUPPOSITORY

Thesis for the Degree of Doctor of Medicine

Submitted to the University of Leicester

By

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Submitted June 1996
INTRODUCTION

The development of the morphine hydrogel suppository has taken nearly fifteen years from the initial concept to the present state when commercial exploitation and widespread clinical usage appears a reality. The concept of a sustained release analgesic preparation with close to zero-order delivery kinetics occurred during a chance meeting with Professor Neil Graham of the Department of Applied Chemistry, University of Strathclyde in 1981. He had been developing a family of hydrophilic polymer gels based on poly(ethylene oxide) for use as drug delivery systems. Work had commenced on a vaginal pessary for the administration of Prostaglandin E2 and preliminary results were promising. I suggested that the hydrogel could be used for the rectal delivery of drugs such as morphine and would have the advantage over the oral route that the vehicle could be removed in the event of an adverse reaction.

Professor Graham took up the idea and proceeded to make some prototypes to my specification assisted by Dr Marion McNeil, a pharmacist working in his department. A number of different shapes were evaluated before the hollow cylinder was devised and tested in patients. Over the succeeding years, the device, christened the Morphine Hydrogel Suppository or MHS has undergone further development and clinical trial in collaboration with Professor Graham and with Controlled Therapeutics (formerly Advanced Therapeutics Systems). Latterly, Controlled Therapeutics transferred the rights to Core Technology who are continuing the development.

This thesis details the work carried out, particularly the evaluations in patients and volunteers and the results obtained. Considerable work remains to be done before a marketable product can be produced, but the MHS appears to offer the possibility of a once-daily preparation which will hopefully be of benefit to patients in both chronic and acute pain.

The work described in this thesis has been conducted over a long period, during which the knowledge on rectal drug delivery has increased greatly. Thus ideas and concepts which seem self-evident today were still in the future when much of the work was conducted. As a consequence, many of the steps in the development seem naïve in retrospect. The work should be judged in that light.
ACKNOWLEDGEMENTS

These studies would not have been possible without the enthusiastic support of Professor Neil Graham and his staff, particularly Dr Marion McNeil. Controlled Therapeutics supported the work both financially and practically in the earlier stages of development. In particular, Dr Harrison Langrall, Ms Trish Faire and Dr Art Michaelis from Malvern, Philadelphia and Dr Steve Robertson and Ms Karen Quinn from East Kilbride have been unstinting in their help. Latterly, the MHS project was passed to Core Technologies and the collaboration and support of Dr Jim Pickard, Ms Fiona McLaren and Mrs Cheynee Whipps is gratefully acknowledged.

Over the years, a number of research nurses have worked long and hard at the various studies including Pat Parry, Lorraine Hopkins, Maureen Brody, Inge Windram and Jenny Allott. Kohath Achola, Liz Valender and Jim Strupish as Chief Technicians of the Department of Anaesthesia have contributed advice and the analysis of a considerable number of blood and urine samples. Latterly, Simon Joel of St Bartholomew’s Hospital has performed the assays of morphine and metabolites and has been generous in his helpful and instructive comments, I have been ably assisted in the various studies by junior members of the Anaesthetic Department both NHS and academic. These include Drs Andrew Vickers, Louise Cole, Mary Mushambi and Susan Bailey. Dr Sam Ahmedzai of the LOROS Hospice and Dr John Taylor of St Gile’s Hospice have helped with the discussions on chronic pain management.

Professor G Smith has helped in many ways with support and encouragement for the projects as well as advice not the least of which has been the prompting, both gentle and otherwise, to ensure completion of this thesis. My academic colleagues, Alan Aitkenhead, David Fell, David Lambert and David Rowbotham have all helped with advice and encouragement.

To all these friends and colleagues I give my thanks for their contributions which have made the project possible and enjoyable.

I also thank my wife, Margaret, and children, Caroline, Ian and Eleanor and my parents for their patience and forbearance while the work was completed. Without their love and encouragement the writing would never have been started.
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RECTAL ABSORPTION OF DRUGS

1.1 HISTORY

The rectal route for the administration of drugs has been used by mankind since at least the time of the Pharaohs. The Egyptians and Greeks were known to administer powdered drugs by dipping a plant rhizome in molten fat and then into the drug before insertion into the rectum. Hippocrates records the use of "Magerarta", suppositories based on silver and acorns (de Rosemont, 1931). They were generally used for their local effects for treating constipation, haemorrhoids and anal irritation (Aiache et al, 1984). It has been suggested that the term suppository is derived from the Latin "supponere", to substitute, as they were invented as a substitute for rectal lavage (Lemery, 1763). Little information is available on the use of rectal medications in the Dark and Middle Ages although Rufus of Ephesus, Galen (131-200) and Avicenna (980-1037) described suppositories based on honey, herbs and fruit. These prescriptions remained largely unchanged until the 16th century (Aiache, 1984). The North American Indians were known to use rectal tobacco smoke as a means of resuscitating the near drowned. The efficacy of the method is not recorded.

De Meuve (1605) distinguished between solid suppositories with an active coating and those based upon cooked honey and, by the end of that century, Moyse Charas (1682) and Constant de Rebecque (1683) were describing a variety of formulations although still largely for the treatment of local conditions.

In the 18th century, the French pharmacist Bauné (1762) ushered in the modern era by the use of cocoa butter as a vehicle for suppositories. The concept of administering drugs to treat conditions other than those of the lower bowel was gradually introduced (Pharmacopée Francaise, 1818). By the middle of the 19th century, opium suppositories in a base of cocoa butter were well established in medical use (Guibourg and Henri, 1841). Subsequently, other fatty vehicles were developed and other methods such as micro-enemas and capsules were introduced. The last twenty years has seen renewed interest in the rectal route of administration and several groups have concentrated on a more scientific understanding of the influence of the vehicle and the role of adjuvants in facilitating absorption. Other groups have concentrated on the rectal route for sustained release medication. The Morphine Hydrogel Suppository (MHS) is one of these formulations and is the subject of this thesis.
1.2 ANATOMY

The rectum is the terminal portion of the gastrointestinal system, extending from the recto-sigmoid junction to the sphincters of the anal canal and is about 12.5cm long in the normal adult. The surface area of the rectal mucosa is about 200-400 cm$^2$ in the adult which is about 0.01% of that of the small intestine which is about 200 m$^2$. Its capacity for absorption of fluid, electrolytes and drugs is thus limited in comparison with the small intestine or colon.

The anal canal is about 4cm in length and is comprised of the internal and external sphincters. Functional integrity of this region is important to rectal administration of drugs. If the sphincter is not functional then the entire suppository may be expelled. If it is leaky then micro-enemas will not be retained or rectal fluid will escape with consequent loss of drug. Secondly, if the suppository is placed within the anal canal then drug release and absorption will be unpredictable and the patient will experience pain. The relevance of this is shown by a volunteer given an MHS described in Section 7.3-4. The design of applicators to aid the insertion would be also influenced by these observations.

1.2.1 Mucosa

The rectal mucosa is comprised of three layers, the epithelium, the lamina propria and the muscularis mucosae. The surface of the mucosa is described as flat in contrast to the surface of the colon and small intestine. Convolutions are present but the surface area relative to volume is less even than the colon. The predominant surface cell is a tall, ciliated columnar type with a striated apical border. These cells continue into the frequent intestinal crypts which are the predominant source of mucus production. Mucus is produced by the relatively sparse goblet cells opening directly on the surface and by those in the numerous intestinal glands or crypts. The normal mean turnover time of the rectal epithelium has been shown to be about 3.7 days and to be prolonged in conditions such as ulcerative colitis (Shorter et al., 1966).
1.2.2 Blood supply

**Arterial supply**

The arterial supply to the rectum is predominantly from the superior rectal artery which is a continuation of the inferior mesenteric artery. Some contributions are made by the middle and inferior rectal arteries and the median sacral.

Rectal, colonic, gastric and small bowel mucosal blood flow has been measured by laser doppler flowmetry (Ahn et al., 1986a). Mean relative flows (expressed in volts) were stomach, 7.9 (Ahn et al., 1988), jejunum, 7.6, ileum 6.1 (Ahn et al., 1986b), colon, 5.4 (Ahn et al., 1986a) and rectum, 0.75 (Srivastava et al., 1990). Rectal mucosal flow has been shown to be increased by proctitis and ulcerative colitis but decreased by cigarette smoking to a degree proportional to the plasma nicotine concentration (Srivastava et al., 1990). The drug administered might itself affect absorption if it had an effect on blood flow. Morphine induces vasodilatation both directly and through histamine release. The effect, if any, of these factors on rectal drug absorption remains unknown.

**Venous drainage**

In common with the rest of the gastrointestinal system, the rectum has a submucosal venous plexus which drains through the bowel wall (Figure 1.1) continuous with that of the colon. The blood from the upper part of the rectum drains into the superior rectal vein and thus into the portal circulation to the liver. The middle and lower parts of the rectum drain through the middle and inferior rectal veins respectively. The middle rectal vein is often insignificant. The middle rectal vein passes above the Levator ani muscle and drains into the systemic circulation via the internal iliac veins. The inferior rectal vein drains the area of the rectum adjacent to the anal verge, the anal and peri-anal skin and the external anal sphincter. It drains into the systemic circulation via the internal iliac veins.

The rectal submucosal venous plexus is one of the areas of anastomosis between the portal and systemic circulations. It is impossible to predict in an individual to which circulation a particular area of rectal wall will drain. It will depend not only on the anatomical arrangements of the venous system at that point but also on the venous pressures in the two circulations. As a general rule, the further is the area from the anus, the more likely is the venous drainage to be portal rather than systemic. Anatomists give
Figure 1.1. Venous drainage of the rectum
the site of the anastomosis as the anal canal, largely on the basis of the venous changes that occur during portal hypertension (McMinn, 1990). This is contradicted by the pharmacological studies that show variations in bioavailability from the lower to upper rectum. The disparity may be due to the nature of the veins in the anal canal making them more liable to distension and thus visible to the surgical eye. Physiological evidence suggests that the area of anastomosis is higher and more variable in extent.

The direction of venous drainage is important for those drugs which are susceptible to first pass hepatic metabolism of which morphine is a good example. This will be discussed more fully in sections 1.4.1 and 2.1.3.

1.2.3 Anal sphincter

Continence and the complete emptying of the rectum on defaecation depends upon the integrity of the external anal sphincter. This comprises three loops of muscle (Shafik, 1975) which encircle the rectum (Figure 1.2). The lower loop is at the anal margin and provides the final closure of the anus and ensures that it remains watertight. The intermediate and upper loops pull in opposing directions to ensure both final emptying of the rectum by vermicular contractions and continence. The result is a pressure gradient in the rectum which is greatest at the anal verge. The mean anal canal pressure is about 75mmHg which decreases to about 15mmHg during sleep. Muscle activity in the rectum is characterised by cyclical pressure changes, rectal motor complexes, which last about 15 minutes and occur about 1-1½ hours and are associated with increases in anal canal pressure (Ferrara et al., 1993).

Morphine increases the activity and peak intraluminal pressures in the sigmoid colon (Painter and Truelove, 1964). It can be presumed that it has the same effect on the rectum. Supportive evidence comes from studies of the effect of morphine on the electrical activity in the rectum (Bouvier et al., 1987). The mechanism of action seems to be in some doubt. The effects are attenuated by mu receptor antagonists, such as naloxone, but appear to be, at least in part, mediated by cholinergic mechanisms. Morphine has been shown to have an anticholinergic effect on colonic muscle (Burleigh and Trout, 1986), the ileum (Galligan, 1993), the airway (Johansson et al., 1989, Belvisi et al., 1992), gastrointestinal cholinergic enzymes (Oriaku and Soliman, 1989), the brain (Lydic et al., 1993), the bladder (Igawa et al., 1993) and sexual function (Zarrindast et al., 1994). It appears that opioid agonists may act at prejunctional receptors to inhibit the release of acetyl choline and reduce cholinergic activity. Morphine may also bind to
Figure 1.2. Muscles of the external anal sphincter. The three bands pull in opposing directions to ensure continence and empty the anal canal. They are shown "pulling" a suppository into the rectum by vermicular contractions. (Abd-el-Maeboud et al 1991)
muscarinic receptors, reducing the effect of acetyl choline and other cholinergic agonists. The former mechanism may be susceptible to antagonism by opioid antagonists but not the latter. Naloxone has been shown to antagonise some, but not all of the effects noted above and given alone increases central cholinergic activity, possibly by an effect on endogenous endorphins (Walker et al., 1991). It would be reasonable to conclude that morphine would not only have an effect on the rectal smooth muscle but might also have an effect on rectal mucus production as this is under some cholinergic control. Morphine would thus reduce rectal mucus production and reduce the barrier to diffusion and absorption. This, however, is supposition as the rectum has been little studied, researchers concentrating predominantly on the stomach, small intestine and colon.

The consequences of changes in intraluminal pressure for rectal medication are discussed in section 1.4.4. and on mucus production in section 1.3.2.

1.3 PHYSIOLOGY

The function of the rectum is the final conduit and store of faeces. It has a secondary function of fluid and electrolyte absorption, although this is of little relevance to man. It is normally empty and the walls are opposed to each other separated by a few millilitres of rectal fluid.

1.3.1 Rectal fluid

The rectum normally contains only 3-4ml of fluid comprising water and mucins. The electrolyte composition of the fluid differs considerably from that of plasma and the pH is slightly alkaline (7.9) (Bitterman et al., 1967). The rectal epithelium has the capacity to absorb and secrete ions and water, although not to the same extent as the colon. Sodium and chloride are actively absorbed and potassium and bicarbonate secreted. The latter is the likely cause of the alkaline pH. Studies using rectal perfusion show that the absorption is principally transcellular rather than paracellular (Böttger et al., 1984) confirming the observation that the intercellular junctions between the epithelial cells are tight. This enables the rectum to maintain considerable ionic and electrical gradients across the epithelium. The capacity to secrete bicarbonate is considerable and this is presumably a response to the production of organic acids by bacteria. Acids such as salicylic have been used to augment absorption of drugs through the rectum. The mechanism is thought to be an opening of the tight intercellular junctions rather than a change in pH (Edmonds, 1984, Hawker and Turnberg, 1983).
The rectal mucosa has been shown to be capable of secretion of sodium and water in response to a variety of stimuli, both physiological and chemical. It is not known whether secretion is a usual occurrence or whether it only occurs under abnormal circumstances. The consensus would seem to be that there is a small constant secretion which is normally masked by the much greater absorption. This is relevant to the administration of MHS which requires a certain volume of water for rehydration. Clearly, if the rectal water volume was insufficient and water secretion did not occur, rehydration and drug release would be impaired. This is discussed further in Sections 9 and 10.

1.3.2 Mucus

Mucus is present as a water insoluble gel adherent to the mucosal surface and as a viscous solution in the lumen. It is a complex mixture of glycoproteins, water, various serum and intracellular macromolecules, electrolytes, micro-organisms and sloughed cells (Neutra and Forstner 1987). The major components are glycoproteins collectively known as mucins and produced by the goblet cells. The structure, molecular size and composition of mucus varies from one region of the gastrointestinal tract to another (Allen et al., 1984). The molecular building blocks of mucin are glycopeptides of molecular weights ranging from 250,000 to 2x10^6 Daltons and oligosaccharide side chains. The components combine in different proportions and structures to give gels of different viscous properties (Carlstedt and Sheehan, 1984). The glycoprotein content varies between 20-55 mg.ml^-1 (Allen et al., 1984). In general, colonic mucins are larger or more aggregated and contain more protein than those of the proximal gut. They also contain more sialic acid residues and thus have a lower pKa. Thus at near neutral pH, they have an ability to bind positively charged compounds.

The function of mucus is to lubricate and protect the mucosa. Removal of the mucus layer leads to oedema of the epithelium suggesting that it controls the hydration of the epithelium by restricting access of water. The permeability to water is inversely proportional to the concentration of mucins (Forstner, 1978). The hydrophilic and viscoelastic properties of mucin (Bloomfield, 1983) ensures that it adheres well to particulate matter in the bowel. This is relevant to controlled release preparations as they will become covered with a layer of mucus which may act as a diffusion barrier and compete for available water with those preparations such as hydrogels which require water. Mucus also has a role in protecting the mucosa from potentially pathogenic micro-organisms. This layer will also act as an unstirred fluid layer through which drugs must diffuse before they can be absorbed by the mucosa. The thickness of the layer varies greatly from 10-1000μm (Allen et al., 1984) the mean thickness being about 150μm.
Differences in mucus composition have been noted in patients with colonic and rectal carcinoma (Habib et al., 1985).

Control of mucus secretion is predominantly under the control of the parasympathetic nervous system via muscarinic cholinergic receptors (MacAdam, 1993), although synthesis is thought to be influenced by sympathetic activity (Forstner, 1978). In rats, the effects of cholinergic stimulation are most prominent in the upper gastrointestinal tract (Rubinstein and Tirosh, 1994). Local irritation, both mechanical and chemical seems to be a major stimulus to mucus release from goblet cells (MacAdam, 1993).

1.3.3 Detection of rectal material

The rectum is generally empty of faeces until just before defaecation when a mass movement in the colon forces faeces past the functional sphincter at the recto-sigmoid junction. Unlike the colon, the rectum does not show frequent resting waves of contraction. A volume of at least 50ml is required to initiate defaecation and relax the internal anal sphincter (Schuster et al., 1963) and the sensation of rectal fullness is not perceptible until a volume of at least 25ml is introduced rapidly (Duthie and Bennett, 1963) although smaller volumes may be expelled by voluntary effort. This is important for the design of sustained release preparations whose final volume must be less than the detectable volume to ensure patient acceptability.

1.4 DRUG ABSORPTION

Passage of a drug from a rectal preparation into the circulation and thus to its site of action requires a number of steps (de Boer et al., 1982, van Hoogdalem et al., 1991). Firstly, it must be released from the vehicle into the rectal fluid. This will depend upon the nature of the vehicle and the drug as well as the conditions within the rectum which include temperature, pH, electrolyte composition and quantity of fluid. Secondly, it must diffuse from the site of release to the epithelium. This will depend upon the physical distances and the presence of any barriers such as mucus and faeces as well as the characteristics of the drug, in particular its solubility in water and pKa. Finally the drug must pass through the epithelium and into the blood stream.

Diffusion through the epithelium depends upon the solubility of the drug and its ionisation. Transport mechanisms may be important for some drugs, while with others increasing water uptake appears to facilitate absorption.
It is probably more true of the rectal route of drug administration than of any other route that minor differences in formulation can have large effects on drug absorption. For example, doubling the volume of a suppository to increase the dose can have unexpected effects on absorption simply because of the physical characteristics of the larger mass of vehicle.

Interpretation of the many studies is also complicated by the differing aims of the investigators. Some were aiming for rapid absorption in order to attain peak plasma concentrations comparable to those attained with parenteral or oral administration. Others were seeking completeness of absorption while a prolonged effect is the goal of many. One of the advantages of the rectal route is that, in many cases, each of these goals may be achieved by the appropriate use of vehicles and adjuvants.

The study of rectal preparations is also complicated by the lack of a reliable in vitro test system (de Blay and Polderman, 1980). Preparations may be suspended in a suitable medium at body temperature and drug release into the medium determined. However, it is difficult to mimic the conditions in the rectum with intermittent contraction waves and variable distribution of mucus. Opinions vary as to whether an in vitro test system should be stirred or not. Stirring the system eliminates any boundary effect between the preparation and the medium but these effects may be important in vivo. If the system is left unstirred then the investigator is faced with the dilemma as to where in the system he should sample to determine drug release. As a consequence, animal models are often used. However, such studies should be treated with caution as they may not be directly applicable to human experience. The rectums of rats, rabbits and dogs differ from those of humans not only in size but also in morphology, blood supply and mucosal function. In addition, as mentioned previously, scaling up from animal to human dosages may markedly alter the characteristics of the delivery system.

Techniques have been developed for perfusion of the rectal lumen in humans (Böttger et al., 1984) which should facilitate studies of drug absorption. However, they will not assist in the evaluation of drug vehicles where empirical investigation will continue to be essential.
1.4.1 Rectal Wall

**Diffusion**

The rectal epithelium with its associated mucus coating appears to behave generally as a simple lipidic barrier and the absorption of drugs can be predicted on the basis of pH partitioning between the lumen and the tissue (Schanker, 1962, Muranishi, 1984). Passage of the drug may be transcellular or paracellular through the intercellular junctions. These junctions are tight in comparison with the small intestine and thus most absorption is likely to be transcellular. A further aspect of water absorption is given by the work of Hayashi and colleagues (1985). They studied the water influx and sieving coefficients of the rat nasal, jejunal and rectal mucosae. They concluded that although the pore size of the water channels in the jejunum and rectum were similar, the rectum had fewer channels and its maximum water influx was half that of the jejunum. Recent work has suggested that the pH partitioning theory is generally true but does not entirely fit experimental evidence (Jackson, 1987). The pH partitioning theory implies that a drug is only absorbed in the un-ionised form across the lipid cell membrane of the epithelium and that this constitutes the rate limiting step. There is evidence that ionised drugs may be absorbed through the paracellular route. This would be particularly important for those drugs which are highly ionised at physiological pH. This is supported by the observation that adjuvants, whose role in facilitating absorption is likely to be in part due to enhancement of the paracellular route by opening the tight intercellular junctions, are particularly useful with this group of drugs (Section 1.4.4).

Several studies with adjuvants have shown a parallel increase in water and sodium absorption with the increase in drug absorption (for example Shiga et al., 1985, 1986). It has been suggested that this implies some linkage between the two. This may be true but it is more likely that the effect is secondary to luminal changes such as an increase in drug concentration or an opening of trans- or para-cellular channels.

Diffusion through the epithelium is only part of the distance which a drug must traverse before it is taken up into the blood stream. Disorders of the mucosa which cause thickening or oedema would be likely to impair absorption by increasing diffusion distances. Inflammation might also affect pH partitioning by reducing the tissue pH. However, this might be countered by the increased blood flow that accompanies inflammation, steepening the diffusion gradient. These changes are purely theoretical as there are no studies which have addressed this problem. Clinically, most authorities would counsel caution in administering any drug, except those with purely local effects in
the presence of rectal pathology. The possibility of causing discomfort or damage would probably outweigh any advantage. A recent study of ketoprofen following anal surgery has shown the wisdom of this advice (Kanamoto et al., 1988). Absorption from both fatty suppositories and gelatin capsules was significantly less than in normal subjects. The deficit was variously attributed to local oedema, reduction of rectal fluid volume and decreased mucosal blood flow.

It is generally assumed that the blood flow through the bowel wall does not limit the absorption of drugs (Winne, 1979). This appears to hold true in practice although there have been no studies on humans in conditions where rectal blood flow might be expected to be impaired. It has been suggested that the blood supply to the rectum might be greater in women and is the explanation for the faster absorption of drugs in women compared with men (Moolenaar and Schoonen, 1980). However, no evidence has been advanced in support of this hypothesis although a study of the absorption of aspirin in volunteers and patients with fever showed better absorption in the latter group (Dalvi et al., 1985). It would appear that the blood flow to the rectum may be a limiting factor when immediate release preparations are used but is less likely to be so for delayed release preparations.

Any interface between a liquid medium and a membrane is characterised by an unstirred liquid layer. The presence of the unstirred layer must be taken into account in any consideration of diffusion through the membrane. For aqueous liquids the contribution to the diffusion barrier is probably small but a mucus layer appears to be more significant. Smithson and colleagues (1981) investigated the ability of carbohydrates to gain access to the epithelium in perfused rat jejunum. They calculated that the effective thickness of the unstirred barrier layer was about 0.7mm. This corresponds well to estimates of the thickness of the mucus layer. It appears that the mucus layer is a barrier to the diffusion of small carbohydrate molecules, proteins (Edwards, 1978), water (Forstner J, 1978) and hydrogen ion (Williams and Turnberg, 1980). It is thus reasonable to assume that it also acts as barrier to diffusion of drugs. Surfactants may facilitate absorption by allowing drug particles to penetrate the mucus layer from the vehicle thus increasing the drug concentration in the aqueous phase. Alternatively, they may alter the gel state of the mucus increasing the diffusion rate of both drug molecules and drug particles.

Early studies suggested that the intestinal mucus merely acted as an unstirred water layer but more recent studies suggested that it was more of a barrier than water alone (Hughes, 1988). Artursson's group (Wikman et al., 1993, Karlsson et al., 1993) have
studied the transfer of drugs through monolayers of cultured human intestinal goblet cells, with and without the presence of a mucus layer. The mucus layer contributed 78% of the total barrier to absorption of testosterone. Bhat and colleagues (1995) used a modified *in vitro* diffusion apparatus that placed a layer of mucus constrained by ultrafiltration membranes between a donor and receiver cell. They studied a number of anti-tubercular drugs and showed that a reconstituted mucin solution was a greater barrier to diffusion than an equivalent thickness of bovine serum albumin solution. They concluded that the barrier to diffusion through mucus was related to factors other than protein binding of the drug. Hughes (1988), using a similar apparatus, showed that the barrier to diffusion to caffeine was greater with small intestinal mucus rather than gastric mucus, presumably due to the former's great content of sialic acid and thus greater binding. He also showed that changes in mucin content produced minimal changes in the barrier to diffusion suggesting that the structure of the gel was more important that the protein concentration. Similar results were shown by Winne and Verheyen (1990) who studied a range of compounds and showed that the H⁺ ion was most hindered. Further studies by Desai and Vadgama (1991a,b) showed the importance of molecular size and charge, the slowest diffusion being seen with large molecules and those possessing a positive charge.

It has been shown that drugs may affect their own absorption by an effect on the mucus layer. Cimetidine increases mucus synthesis and thus the thickness of the mucus layer slowing its absorption (Kakei et al., 1986). Morphine has been shown to reduce salivation in a dose dependent manner (Westerling et al., 1993, 1995) and it has been suggested that the same effect may be seen throughout the gut (Hedner and Cassuto, 1987). If this were true in the rectum, then morphine might increase its own absorption by decreasing the thickness of the mucus barrier. Aspirin decreases the glycoprotein content of gastric mucus but the effect on drug absorption is unknown. It is suggested that the ability of aspirin and NSAIDs to induce gastric ulceration is due to an effect on the integrity of the mucus layer allowing the gastric acid to reach the underlying mucosa. This may also be the means by which these compounds facilitate the absorption of compounds from the rectum (Section 1.4.4. Adjuvants).

There appear to be two means by which mucus hinders the diffusion of drugs (MacAdam, 1993). Firstly by binding drugs to the glycoproteins. Rectal mucus has a high proportion of sialic acid residues and thus will bind charged molecules, including morphine. This will have a reservoir effect and also reduce diffusion gradients. The second means is probably most important, the hindering of diffusion by increasing the diffusion distance and decreasing the apparent pore size. The mucus subunits are chained
and crosslinked to produce a gel which holds water within the molecular structure. The water is thus not available for diffusion, hindering the passage of solutes. The concept that the drug molecules must take a tortuous path through the gel to avoid relatively "hydrophobic" domains is reminiscent of diffusion through hydrogels which is discussed in Section 3.2.4. Whatever the mechanism, it is clear that the mucus layer plays a major role in drug absorption and must be considered in any study of rectal drug absorption.

The intestinal mucosa has been known for a number of years to possess many of the enzymes necessary for biotransformation of drugs (Rance and Shillingford, 1978) and that it may contribute to the first-pass metabolism and thus reduced oral bioavailability. The enzymes include those necessary for hydroxylation, dealkylation, glucuronidation, sulphation and acetylation. The contribution can be significant in the case of some drugs. For example, in rats, the conjugation rate for glucuronidation of morphine in the intestine is one third that of liver while for p-nitrophenol the intestinal rate is ten times that of the liver (del Villar et al., 1974). The capacity for glucuronidation varies through the intestine, being greatest in the small bowel (Koster et al., 1985). An interesting study by Hartiala and colleagues (1964) suggested that the activity of glucuronyl transferase in rats altered with the seasons and was greater in the winter than the spring. There is no evidence that this occurs in man although it would be interesting to examine changes in morphine requirements in patients with chronic pain over the year although any effect might be obscured by seasonal changes in mood.

It can be assumed that these enzyme systems will have a $T_{\text{max}}$ in common with many other systems. This maximum rate may not be exceeded in the small bowel where the surface area is large and the drug concentration may be relatively low. In contrast, in the rectal wall, the small surface area and relatively high drug concentration should ensure that the $T_{\text{max}}$ is exceeded. In that case, the overall contribution of bowel wall metabolism will be reduced. This may be one mechanism in any reduction of first-pass metabolism by rectal administration. These assumptions are pure hypothesis as there is no experimental evidence that bowel wall metabolism is at all important in rectal drug administration.

The bacterial flora of the bowel may also be capable of metabolising drugs. Their contribution is unknown and for the rectum is probably small at least for those preparations when drug release from the vehicle and absorption is accomplished over a short time span. The contribution when sustained release vehicles are used remains a matter for conjecture.
Rectal absorption of drugs. Page 1.13

**Mucosal transport**

It is generally held that the absorption of opioids is by passive diffusion. However, carrier mediated mechanisms have been proposed to explain the accumulation of opioid bases in the kidney (Hug, 1967) and the choroid plexus (Takemori and Stenwick, 1960, Hug, 1967) and two studies have suggested that additional mechanisms may be important at least in some areas of the bowel. Jackson (1981) observed the movement of seven opioid analgesics and antagonists across the gastric, small intestine and colonic wall of the rat *in vitro*. He showed that uptake was best in the small intestine and negligible in the stomach. No evidence was found for an active carrier mechanism at any site but uptake still occurred in the presence of adverse pH and electrical gradients. He proposed a mechanism based upon the different permeability of the epithelial cells and basement membrane to ions and an asymmetry of the acid base metabolism of the epithelium. The pH in the lateral intercellular space differs from the mucosal and serosal fluids. These factors act as the driving force for net movement of weak electrolytes from mucosa to serosa.

Jackson (1981) was unable to demonstrate any metabolism of the opioids during their absorption in contrast to the *in vivo* studies of Rance and Shillingford (1976).

Tan and colleagues (1989) repeated Jackson’s studies using both *in vivo* and *in vitro* preparations in the rat and measuring morphine and its metabolites by HPLC. They confirmed that morphine was well absorbed in the order jejunum > duodenum > ileum > middle intestine > rectum with negligible absorption from the stomach. In the jejunal and duodenal sites, metabolic inhibitors reduced absorption and brush border membrane vesicles showed concentration dependant uptake of morphine. They concluded that carrier mediated mechanisms existed for morphine at these two sites but not in the lower intestine and rectum where absorption was passive. They also found that the major metabolite was morphine-3-glucuronide and that the proportion of morphine metabolised varied between 10 and 30%. They attributed some of the variation to seasonal differences in glucuronyl transferase activity in the rat small intestine (Hartiala et al., 1964).

Kondo and colleagues (1996) examined the glucuronidation of morphine during its absorption through an isolated rabbit rectal mucosal model. Approximately 10% of the absorbed morphine was metabolised to M3G while no M6G could be detected. Morphine concentrations were of the order of 1m.molar and the degree of glucuronidation did not
change with morphine concentration suggesting that enzyme saturation had not occurred. The process was inhibited by α-cyclodextrin which was thought to impair the lipid membrane which is thought to be the site of enzymic activity.

The contribution of active transport to overall absorption of drugs and opioids, in particular in man, remains undetermined. However, it would appear most unlikely that it plays any significant role in absorption through the rectal mucosa.

**First pass metabolism**

Drugs with a high hepatic clearance show a reduced bioavailability when given orally because of first-pass metabolism as the drug passes through the liver from the portal vein. It has been suggested that rectal administration may at least partially avoid the first-pass metabolism as some of the venous drainage is into the systemic circulation (See Section 1.2.2). In common with many areas of research on rectal absorption of drugs, this hypothesis has been difficult to prove until recently and has depended to a large extent on the drug vehicle. In theory, systemic absorption should be best close to the anal sphincter. Unfortunately, liquid vehicles and those which melt at body temperature very rapidly spread throughout the rectum and even reach the colon (Moolenaar and Schoonen, 1980, Quevauviller and Jund, 1951). The extent of spread has been challenged by Jay and colleagues (1985) who showed much less movement of a Witepsol suppository using external scintigraphy and concluded that avoidance of first pass metabolism was feasible.

Studies in man have shown that there is at least partial avoidance of first pass metabolism with lignocaine (de Boer et al., 1979), propanolol and salicylamide sodium (de Boer and Breimer, 1980), pethidine (Glynn and Mather, 1982) and morphine (Westerling et al., 1982, Cole et al., 1990). Studies in rats have gone further and shown that the degree of avoidance of first pass metabolism is greatest when the drug is absorbed close to the anal sphincter (de Leede et al., 1983, 1984).

An alternative explanation for avoidance of first pass metabolism by rectal administration is uptake into the lymphatic system. Caldwell and colleagues (1982) have shown that effective uptake of water soluble, highly polar drugs depends upon an intact lymphatic vasculature. Uptake into the lymphatics seems to be particularly important when adjuvants such as 5-methoxysalicylate are used (Caldwell et al., 1984). The mechanism is unclear but may represent a greater flow in the lymphatics consequent on greater water
and sodium uptake. Alternatively, the adjuvant may reversibly damage epithelial and endothelial permeability increasing lymph flow and increasing drug uptake.

However, for drugs which have pharmacologically active metabolites such as morphine, there may be little advantage in avoiding first pass metabolism. This is considered further in Sections 2.1.4-5.

1.4.2 Rectal fluid

The rectal fluid comprises about 3-4ml of slightly alkaline mucus. The quantity is small in relation to that in the small intestine and may be a limiting factor if the vehicle requires water for dissolution or rehydration. The buffer capacity is small and seems to be determined by the ability of the mucosa to secrete bicarbonate. Bechgaard (1973a,b) found that a buffer capacity of only 0.01 was sufficient to maintain a pH of 5.9 in the rectal fluid during perfusion of the rectum in humans. It has been assumed that the pH of the liquid is the same as that at the surface of the mucosa. However, this study together with those of de Blaey and Polderman (1980) and Desai (1975) suggest that the two may differ. Thus changes in free rectal fluid pH may be less significant than would be expected from a hypothetical standpoint and this seems to be born out by experimental studies (de Blaey and Polderman, 1980).

For those drugs which are presented as particles in fatty bases the surface tension may be important in allowing the particles to pass into the liquid phase by altering the contact angle between the particle and the liquid/vehicle interface. Of equal or greater importance are the changes in pressure within the rectum which accompany movement. This has been emphasised by groups from Holland (de Boer et al., 1979, Moolenaar and Schoonen, 1980) although the experimental evidence in favour of these assertions is scant (Bennett et al., 1978).

1.4.3 Drug substance

To be successfully absorbed, drugs must not be either completely insoluble or highly soluble in water. In the former case, insufficient drug will be passed from the vehicle to the rectal fluid and little will be absorbed, despite the high lipophilicity (Kilian, 1973) while in the latter case, the lack of lipophilicity will hinder absorption through the epithelial cell membrane (Morimoto et al., 1987). A further consideration is the solubility of the drug in the vehicle. In summary, water soluble compounds are poorly released
from hydrophilic bases and lipid soluble compounds are poorly released from fatty bases (de Blaey and Polderman, 1980). Voigt and Falk (1968) investigated the relationship between release rate from fatty vehicles and water solubility in 35 compounds and found a direct relationship. For example, theophylline is very poorly absorbed from lipophilic bases such as Witepsol but very well from hydrophilic bases such as Novosup (a mixture of polyethylene glycol esters with free fatty acids) (Minkov et al., 1984).

Some drugs are available as poorly soluble bases and as soluble salts, e.g., salicylic acid, sulphonamides, phenobarbital (Minkov et al., 1985) and theophylline (Minkov et al., 1984). In most cases, the soluble form is better absorbed because of better release from the vehicle even if the pKa of the more soluble compound is less favourable (Nelson, 1958). A good example is that of indomethacin where the calcium and magnesium salts were better absorbed than the parent compound (Ogiso et al., 1984). As noted above, highly ionised drugs such as quaternary ammonium compounds are also poorly absorbed. The bronchodilator, thiazinamium methylsulphate was given in both a fatty (Witepsol) and hydrophilic (polyethylene glycol) vehicle (Jonkman et al., 1979). Bioavailability was only 6% with the former vehicle and negligible with the latter reflecting the high water solubility of the compound.

The size of drug particles in the vehicle is also important. Large particles (>150μm) are generally not advised as release may be slow and unpredictable. However, the results are conflicting on the use of smaller particles. Some studies have shown an improved absorption with smaller particles while others have shown decreased absorption (Schoonen et al., 1979, de Blaey and Polderman, 1980). It appears that for less water soluble compounds, reducing particle size enhances absorption while for very water soluble compounds, the converse is true. The reasons for this disparity are unclear but may relate to the ability of the particles to breach the interface between the vehicle and the rectal fluid. The effect may be small as Minkov and colleagues (1986) were unable to demonstrate any effect of particle size.

1.4.4 Vehicles

The purpose of the vehicle is to store the contained drug without degradation and to present the drug in a form where it can be released for absorption at the rate determined by the producer. It must also be in a form where insertion through the anal sphincter is possible.
Fusible suppositories

Molded suppositories which melt at body temperature are still the most widely used as well as the oldest vehicles for rectal drug delivery. Fatty (lipophilic) bases use either a natural compound such as cocoa butter, modified if necessary with bee's wax or oils, or synthetic materials of which Witepsol is the most common. Hydrophilic bases are usually polymers such as the macrogols. Compounds with reverse thermal gelation which are liquids at room temperature but which gel at body temperature have been tried experimentally but have not been commercially used. Miyazaki and colleagues (1987) investigated the use of the hydrophilic Pluronic gels on the absorption of indomethacin in rabbits. A sustained release effect was shown in excess of 10 hours. These compounds also form micelles which may facilitate the absorption of poorly soluble compounds through the epithelial cell membrane.

The most important feature of a fusible vehicle is the rate at which it melts and the ease with which it flows to coat the rectal wall (Schoonen et al., 1979). These rheological properties are amongst the most difficult to standardise and constitute the major reason for differences between different formulations and even different batches of suppositories. Attempts to alter the viscosity often also change the melting characteristics and thus interpretation of studies is difficult although Baichwal and Lohit (1970) showed an inverse relationship between release rate and viscosity. Other constituents of the suppository may influence release. For example, Moolenaar and colleagues (Moolenaar et al., 1988) showed that the concentration of lactose as an inert excipient in a morphine suppository with a Witepsol base had a marked effect in vitro on the release profile, a faster release being achieved with a greater content of lactose. They suggested that the addition of lactose increased the sedimentation flow of the morphine particles by the enhanced transport of the lactose across the lipid/water interface. However, the in vivo absorption did not vary with lactose content which they suggest was due to the movement and mixing of the molten lipid base by rectal and colonic contractions.

Such changes in intraluminal pressure and peristaltic activity, described in Section 1.2.3, are another possible factor with fusible vehicles, increasing the spread of the vehicle and increasing mixing. This problem has not been investigated. Morphine increases motor activity (Painter and Truelove, 1964) and might thus improve its own absorption.

A disadvantage of fatty bases is that of softening and degradation if stored at high environmental temperatures. This problem was investigated by Saito and colleagues
(1994) who measured the Solid fat index (SFI) as a measure of the melting state of the fatty Witepsol base. Storage of morphine suppositories at 30°C for two weeks significantly reduced the release rate in vitro. The SFI was found to be related to drug release for a number of agents.

The water soluble polyethylene glycols are more stable and, in the case of metronidazole, give a better absorption profile (Vromans et al., 1984). A further disadvantage of fatty bases is that they may have an interaction with the drug. Valproic acid softens conventional suppository bases making insertion impossible. This has been overcome by the use of hollow Witepsol suppositories containing the drug in an oily liquid (Watanabe et al., 1986).

The surface effects at the vehicle/rectal fluid interface are also regarded as important (de Blaey and Polderman, 1980, Schoonen et al., 1980). However, attempts to manipulate this factor with surface active agents have not always met with success. An alternative approach is the use of mucosa adhesive vehicles (Smart et al., 1984). These are hydrophilic gels which adhere to the mucus overlying the epithelium. They have been used to a small extent with buccal preparations but have not been used for rectal administration as yet.

The shape of the standard fusible suppository is that of a "torpedo" with an apex close to the widest diameter tapering to a blunt base and was first proposed by Henry Wellcome in 1893 (Wellcome, 1893) (Figure 1.3). This form is widely used but there has been little research as to whether this is the optimal shape for insertion, retention or drug delivery.

Insertion and retention

The conventional method of insertion of the traditional suppository is with the apex foremost (Wellcome, 1893, Senior, 1969) and this method is recommended in most textbooks of nursing and pharmacy. However, Abd-el-Maeboud and colleagues have questioned this advice based upon a consideration of the structure of the anal sphincter (Abd-el-Maeboud et al., 1991). They noted that insertion was easier and retention better if the base of the suppository was inserted foremost. The anal sphincter muscles appeared to draw the suppository into the rectum by "reverse vermicular contractions" thus obviating the need to insert a digit into the rectum to place the suppository correctly (Figure 1.2).
Figure 1.3. The conventional "torpedo" shaped suppository (Wellcome 1893)
Hollow vehicles

Gelatine capsules and other hollow vehicles have been used as a convenient means to encapsulate active agents for insertion into the rectum. Matsumoto and colleagues (1993) described hollow suppositories containing either morphine hydrochloride as a powder or as an aqueous solution and compared them with a conventional formulation in Witepsol in rabbits. Absorption was better from the powder containing suppositories as shown by a greater AUC\(_{0-6h}\) for morphine with less formation of morphine 3 glucuronide (M3G). This was presumably due to a greater concentration of morphine low in the rectum, there being less spread of morphine powder than with the aqueous or fatty formulation.

Micro enemas

For many drugs, this method of administration gives the fastest uptake and greatest blood levels (Moolenaar and Schoonen, 1980). However, probably for reasons of practicality they have not been widely adopted. Concern is generally expressed at the possibility of leakage of the drug and vehicle from the anus, particularly if an oily vehicle is used. They have been most used when a local effect has been required, for example a steroid or when a very rapid response is required in children, for example rectal thiopentone for induction of anaesthesia or diazepam for the treatment of convulsions.

A pH optimised microenema has been shown to give the fastest uptake of morphine (Moolenaar et al., 1985). This paper is discussed further in Section 2.1.3.

Adjuvants

It would be advantageous to be able to give a number of drugs rectally which are poorly absorbed. These include antibiotics and some peptides such as insulin. A number of substances have been investigated as adjuvants and have had some success although the mucosa does not always recover completely (Nakanishi et al., 1983b). However, at present the safety of these compounds on the rectal mucosa in humans is still in question and they are not generally used.

A list of some of the agents used as adjuvants is given in Table 1.1. The main group are those which present a high sodium load to the rectal wall. Several studies have shown that their use is associated with an increased uptake of sodium and water together with
Table 1.1: Rectal absorption of drugs. Table 1.1

Absorption Promoting Adjuvants

**Increased Sodium load** -
- Sodium salicylate
- Sodium 5 methoxysalicylate
- Sodium deoxycholate
- Sodium lauryl sulphate
- Sodium EDTA

**Non-steroidal anti-inflammatory drugs (NSAID)**

**Surfactants** -
- Tween
- Polysorbates
- Polyethylene glycol (PEG)
- Polycrylic acid
- Alginic acid
the drug. This is thought to be due to increased permeability of the cell membrane to water as a consequence of the increased sodium uptake (Nakanishi et al., 1982). The same mechanism seems to be responsible for the adjuvant effect of the NSAIDs (Nakanishi et al., 1984). The efficacy of some of these adjuvants is reduced by ouabain which inhibits the sodium pump and agents which interfere with glucose uptake and metabolism (Caldwell et al., 1984).

The mode of action of the other adjuvants is unknown. The surfactants may work by improving the exchange of drug from the vehicle into the rectal fluid or in the creation of micelles which are taken up by the cell membrane (Muranishi, 1984, Caldwell et al., 1984, Djimbo and Moes, 1986) as well as an effect on the rectal mucosa (Nakanishi et al., 1983a). An alternative explanation for many of these compounds, including those that present a sodium load, is that they affect the mucus layer overlying the mucosa, thinning it or altering its viscosity and permeability thus facilitating diffusion of drug from the vehicle to the mucosa (Morimoto et al., 1987).

Uekama and colleagues (1995, Kondo et al., 1996) reported a series of studies on the absorption of morphine in rabbits from Witepsol based suppositories with a hollow core containing powdered morphine mixed with different absorption modifying agents. The cyclodextrins did not influence the release of morphine *in vitro*, but *α*-cyclodextrin increased the bioavailability both *in vivo* and in an isolated rabbit colon model. This effect may have been due to partitioning of the drug between the oleaginous vehicle and the cyclodextrin but an effect on the mucus barrier cannot be excluded. The authors attributed the improved absorption to disruption of the lipid layers of the epithelial cells, reducing the diffusion barrier to morphine. The addition of xanthan gum delayed *in vitro* release of morphine, gave a prolonged effect *in vivo* and improved the bioavailability, probably by retaining the morphine in the rectum and restructuring movement into the colon. Histological studies showed some effect on the rectal mucosa when cyclodextrins were used and they concluded that this might limit the usefulness in human applications. This preparation shows some promise but further studies are necessary in humans to determine its true potential.

Another Japanese group (Matsumoto et al., 1995) used hollow suppositories to deliver morphine mixed with viscous solutions of sodium hyaluronate and found that increasing concentrations produced a sustained release effect and increased bioavailability. The mechanisms for these effects is unclear although, as they were conducted in rabbits, the improved bioavailability may have simply been due to restriction of the morphine to the
rectum with reduced spread to the colon. The sodium hyaluronate may have acted like mucus in creating a diffusion barrier to the passage of morphine to the mucosa.

**Sustained release**

For many drugs, a sustained plasma concentration is more important than the attainment of an early peak. The rectal route is suitable for sustained release vehicles and a number have been evaluated. The major difficulty is to ensure that the release from the vehicle is the rate limiting step in the absorption. They are summarised in Table 1.2.

Microencapsulation of the drug which is released as the outer coating is dissolved has been used in animals (Kuroda et al., 1983) and in humans (Beckett et al., 1978) and is also widely used for oral sustained release preparations. Beckett and colleagues (1978) obtained prolonged release of lignocaine from a wax/cellulose matrix. A number of groups have used oral sustained release preparations of morphine given rectally (see Section 2.1.3). Kanamoto and colleagues (1992) have taken this principle a stage further by using a hollow suppository containing both morphine powder and an MST sustained release tablet (Napp Laboratories). They compared this preparation in rabbits with MST in an oleaginous base given rectally and standard oral MST. They found a greater bioavailability for rectal MST than oral MST and showed that the time to peak concentration could be varied by changing the quantity of powdered morphine in the encapsulated preparation without changing the sustained release nature of the preparation.

An alternative approach, which has also been used orally, is the osmotic powered mini-pump (Breimer et al., 1983). These comprise a rigid shell with a semi-permeable membrane containing an osmotically active material. The drug is contained within a flexible reservoir within the shell. Diffusion of water into the osmotically active material increases the pressure in the shell and forces the drug out through a fine tube (Urquhart, 1982). Alternatively, the drug and osmotically active substance are mixed and both are forced out through the fine tube or orifice. These systems have been used to deliver antipyrine (de Leede and de Boer, 1981) and ranitidine (de Bree and de Boer, 1987) amongst others (Breimer et al., 1983).

A prolonged effect of nifedipine was obtained in one study by the rectal administration of the normal oral capsules which had been perforated with a needle (Ishikawa et al., 1986).
Table 1.2

Sustained release rectal vehicles

Microencapsulation
Osmotic pumps
Polymers
  - membrane limited reservoirs
  - biodegradable/bioerodable
  - diffusion limited
    - preswollen
    - dehydrated

Modified oral preparations
Modified vehicles
  Lipophilic bases with lipophilic drugs
  Hydrophilic bases with hydrophilic drugs
  Diffusion limiters (gels)
The difference between the rectal and oral response was not striking but was claimed to be sufficient for clinical purposes.

The majority of sustained release rectal vehicles have utilised polymers (Langer, 1980). In general, the drug is retained within the matrix of the polymer and then released when the polymer is placed in the rectum. The polymers fall into two groups (Langer and Peppas, 1981). The first group are soluble or degradable and the drug is released as the surface of the suppository is eroded (Heller, 1986, Fischel-Ghodsian and Newton, 1993). The second group rely on diffusion from the polymer matrix. This group may be subdivided into those where the polymer is fully hydrated on insertion into the rectum and those where the polymer must absorb water before release can occur. In the former case the drug release profile is dependent upon the diffusion of the drug through the polymer matrix and into the rectal fluid. In the latter case, the absorption of water is an additional factor in the release profile. The drug may also be placed in a cavity within a hollow cylinder of polymer in these groups as well as incorporated in the polymer matrix (Ranade, 1990a,b).

A variety of different chemical structures have been used in polymer based systems for example, polyvinyl alcohol (Morimoto et al., 1989), polymeric starch (Harris et al., 1982), polyethylene oxide (PEO) (the MHS see Section 3), hydroxyethyl methacrylate (de Lede et al., 1986), hyaluronic acid (Mataumo et al., 1995) and pluronic gels (Miyazaki et al., 1987). The latter group are interesting as they show reverse thermal gelation, that is they are liquid at room temperature but become solid at body temperature.

Morgan and colleagues (1992) have demonstrated the importance of the interaction between the drug and its delivery system. They investigated the properties of suppositories made with the water soluble hydrochloride salt of morphine and the lipophilic alkaloid using both water soluble PEO vehicles and water insoluble hard fat vehicles (Massuppol and Novata BBC). There was no difference between the in vitro release profiles for morphine hydrochloride and morphine alkaloid in the PEO vehicle and morphine HCl in the hard fat vehicle. However, the morphine alkaloid in the Novata BBC vehicle showed a prolonged release profile with 100% release requiring about 10 hours, not dissimilar to that of some of the morphine hydrogel suppositories which are the subject of this thesis (see Section 3). In vivo studies confirmed the prolonged absorption which was thought to be due to the partitioning of the alkaloid between the lipophilic base and the aqueous rectal fluid.
A similar approach was taken by Moolenar and colleagues (1995) who mixed morphine with lipophilic Aerosil R972 to prevent sedimentation and hydroxypropylmethylcellulose in a Witepsol base and tested the resulting suppositories and MST tablets in volunteers. The release profiles of the two preparations were very similar with over 90% of the administered drug absorbed over 6-8 hours.

Several of these formulations show promise as sustained release preparations of medium (6-8 hour) duration but only the hydrogel based preparations offer the possibility of a once daily preparation. The most promising, the morphine hydrogel suppository is described in Sections 3-10.

1.5 ADVANTAGES

The advantages and disadvantages of rectal drug administration are summarised in Table 1.3. (Hanning, 1985). The principle advantage of the rectal route is that it can be used to administer a drug when the oral route is not available either because of nausea and vomiting, difficulty in swallowing or poor gastrointestinal motility including impairment of gastric emptying (Aronson, 1991, Hermann, 1995). This may be particularly relevant with opioids which themselves delay gastric emptying and thus delay absorption. It avoids the necessity for the drug to be given parenterally, a considerable advantage for many patients who fear and dislike injections.

This latter advantage is particularly relevant to children who may also dislike oral medication if it is presented in tablet form or has an unpleasant taste. Rectal administration is a simpler skill for the unqualified carer to acquire than that of parenteral injection. This is relevant for children and for the elderly and debilitated who are at home rather than in hospital.

The ingestion of food may affect the absorption of oral medication, particularly if the meal has a high fat content which will impair gastric emptying. This phenomenon has been demonstrated for morphine (Gourlay et al., 1989) although a subsequent multiple dose study did not show any difference between the fed and fasted states (Bass et al., 1992).

The rectal route may reduce the proportion of a drug which is metabolised or degraded by the gut contents or mucosa. In addition the drainage of some of the venous blood to
Table 1.3.

Advantages and disadvantages of rectal administration.
(From Hanning 1985)

**Advantages**
- Independent of gastric emptying
- Unaffected by nausea and vomiting
- Some bypass of first pass metabolism
- Administration easily stopped
- Suitable for sustained release preparations

**Disadvantages**
- Patient and physician acceptability
- Variable inter-individual absorption
- Slow onset
the systemic circulation suggests that first pass hepatic metabolism may be reduced particularly for those drugs with high hepatic clearance such as morphine.

The rectal route is also suitable for sustained release vehicles and has the advantage that administration may be discontinued by removing the vehicle. This may be an important safety feature if the vehicle contains a large quantity of the drug and there is a potential for 'dose-dumping'.

Morphine in the vehicles used for rectal administration might be thought to be less liable to abuse or diversion to illicit purposes than oral preparations, particularly liquid forms. This would be especially so for sustained release preparations based upon hydrogels. Addicts have shown considerable ingenuity in extracting morphine from different preparations but, as in the case described by Bitar and Gomez (1993) where a stroke followed the intravenous injection of a melted suppository, may have tragic consequences.

1.6 DISADVANTAGES

Patient acceptability is usually given as the principal disadvantage of rectal administration. It has been pointed out that this perception may be more in the minds of the medical profession than the public (Anonymous, 1983). A study of pentazocine suppositories and pethidine injections in 500 patients commented that "the administration of suppositories was acceptable to the patients.." (Copsidas and Ward-McQuaid, 1979). Similar findings were reported by the author in a study of meptazinol suppositories (Moore et al., 1988). It should be noted that rectal medication is much more commonly used on the Continent, particularly in France, than in Great Britain although there are no known differences between the two races in terms of anatomy. A more practical objection is that self medication may be difficult for patients with arthritis and that the presence of local anal disease such as haemorrhoids or a fissure will render insertion difficult or painful.

The changing or vacillating public perception of rectal medication was illustrated by a recent medico-legal case. Rectal administration of diclofenac to provide postoperative analgesia has become a popular practice for many minor operations. Commonly the suppository is inserted while the patient is still anaesthetised. However, the inadvertent insertion into a patient's vagina raised the question of informed consent and led to the anaesthetist being admonished by the General Medical Council (Mitchell, 1995). Vyvyan
and Hanafiah (1995) subsequently questioned 100 patients regarding their attitudes to rectal medication and their preferences as compared to oral medication. Over half expressed reservations about rectal administration. However, the wording of the questionnaire was open to criticism for introducing bias and a more neutrally worded format might have given a different result. Subsequent correspondence in the journal suggested that this criticism was justified (Anaesthesia 1996;51:401-2). A contrary view on the acceptability of rectal medication was given by Mallinder et al. (1995) who found that they were well accepted but still less acceptable than intramuscular injections. Skinner and Christie (1996) administered a similar questionnaire to a slightly older group of patients with similar results. A major criticism of all these surveys are that they are conducted on younger healthy patients whose experience of any form of medication is often more theoretical than practical. A common theme of all these papers is a desire for more information by the patients and the value of such a stratagem is shown by a recent survey of patients attitudes to pain and pain relief after surgery (Brydon et al., 1996).

There are no formal studies of the acceptability of rectal medication in chronic pain patients although there are a number of favourable reports in studies of rectal morphine in this group (for example Pannuti et al, 1982). They are considered further in section 2.2.2.

In common with oral medication there is a wide variation between individuals in the degree of absorption with rectal administration although the variation within the same individual with time is generally small. The small surface area of the rectum may hinder or limit absorption as will the release of the drug from the vehicle. The rectal mucosa may not be accessible to the drug if the rectum is already occupied by faeces and constipation may be a limiting factor in determining the advisability of rectal medication. Similarly, drug administration will be interrupted by defaecation.

1.7. CONCLUSIONS

Many drugs are absorbed readily through the rectal mucosa and it is a suitable route for sustained release vehicles. It has not been much used in recent years, more through squeamishness than any pharmacological deficiency.
RECTAL ABSORPTION OF MORPHINE

2.1 MORPHINE

Morphine is an opioid analgesic and is a constituent of opium which is derived from the opium poppy, *Papaver somniferum*. It is regarded as a strong analgesic and is classed as a narcotic analgesic subject to legislative control because of its addictive properties.

Morphine was previously regarded as being solely of vegetable origin and not naturally occurring in animals. However, the enzymes for its synthesis exist in the mammal and traces of morphine and other opioids have been detected in the CNS (Kosterlitz, 1987, Weitz et al., 1988) and in the skin of toad, rat and rabbit (Spector et al., 1985). These findings are discussed further in section 2.1.5.

2.1.1 Physical characteristics

The chemical composition of morphine is $C_{17}H_{19}NO_2.H_2O$ and its structural formula is shown in Figure 2.1. Morphine is available as four salts, acetate, hydrochloride, sulphate and tartrate which are water soluble and as the alkaloid which has a water solubility 1/200 of the salts (Morgan et al., 1992). The hydrochloride and the sulphate are the most widely used in pharmaceutical practice. Morphine sulphate is a white, fine, odourless crystal or powder, which discolours upon exposure to light even when in an ampoule. Its melting point is 250°C. One gram is soluble in 15.5ml water and 565ml alcohol at 25°C and it is insoluble in chloroform and ether (Gilman et al., 1985).

2.1.2 History

Charles Louis Derosne (1780-1846) separated a crystalline substance from a syrupy aqueous extract of opium about 1800 but did not characterise it further. Armand Seguin (1768-1835) isolated the active principle of opium which he described in a paper to the Institute of France on Christmas Eve 1804 but he failed to recognise the basic character of the substance and the results were not published until 1814 (Seguin, 1814). The honour of the isolation of morphine from opium thus goes to Frederick William Sertürner (1783-1841), a pharmacist from Einbeck in Hanover. He achieved the isolation in about 1804 and subsequently demonstrated its chemical nature and action (Sertürner,
Morphine
\[ R_1 = H; \ R_2 = H \]
Morphine-6-glucuronide
\[ R_1 = H; \ R_2 = \text{C}_6\text{H}_9\text{O}_6 \]
Codeine
\[ R_1 = \text{CH}_3; \ R_2 = H \]
Diamorphine
\[ R_1 = \text{CH}_3\text{CO}; \ R_2 = \text{CH}_3\text{CO} \]
Monoacetyl-morphine (MAM)
\[ R_1 = H; \ R_2 = \text{CH}_3\text{CO} \]

Figure 2.1. The structural formula of morphine
Prior to this time, opium and its various extracts were used for their analgesic, soporific, euphoric and stimulant properties. The first use of opium is hidden in the mists of time although there are records of its use from as early as 3000 BC by the Sumerians, and subsequently by the Cretans, Egyptians, Ancient Greeks and Romans (Benedetti and Premuda, 1990, Bisset, 1994). They took it orally, rubbed it onto the skin and administered rectally as a powder applied to fat covered rhizomes and roots or impregnated onto wool. Galen, the leading physician of the second century AD wrote extensively on the uses and preparations of opium. He states:

"Opium is the strongest of drugs which numb the senses and induce a deadening sleep; its effects are produced when it is soaked in boiling water, taken up onto a flock of wool and used as a suppository."

The Romans were enthusiastic users and it was known to the Jews of biblical times (Merrilees, 1988/9). It is postulated that the drugged wine offered to Jesus before His crucifixion contained opium and other herbs (Matthew 27:34, Mark 15:23). It was commonly given to those sentenced to death but Jesus refused it. The Romans introduced the use of opium during their conquests and it can be assumed that they brought it to Great Britain. It is possible that the effects of infusions of poppy heads were known prior to this time as part of general herbal knowledge. Opium production is difficult in this country as the conditions for cultivation are unsatisfactory. Attempts were made in the 19th century but commercial production was never achieved (Berridge and Edwards, 1987). Opium was generally obtained from Turkey although attempts were made to import from India in the 18th and 19th centuries but the quality was never sufficiently high to encourage trade despite the prerogatives of Empire.

Little is known of the use of opium in the Dark Ages but its use was well established in several centres. The Medical School at Salerno, influenced by the Arabs who invaded much of southern Europe bringing their use of opium with them, reported the use of "surgical sleeping draughts" in the 10th century. The use of opium diminished during the
Middle Ages under the influence of religious beliefs that held that suffering was beneficial and attempts to relieve it a sin, punishable by death. Its use increased with the Renaissance and by the 18th century had become generally popular for a wide range of ailments. It was supplied in a wide range of products including pills, lozenges, powders, infusions, plasters, liniments, enemata and fatty suppositories. The various extracts such as laudanum were widely taken by the population during the 19th century and one estimate suggested that at its peak about 10lbs (4.5kg) of opium was consumed annually per 1000 of the population (Berridge and Edwards, 1987). One liniment for piles described in Buchan's *Domestic Medicine* of 1803 comprised two ounces of emollient ointment, half an ounce of laudanum mixed with the yolk of an egg applied to the affected parts. The strength of the laudanum varied but the preparation given could have contained up to 1gm of morphine. More than enough to alleviate even the discomfort of piles! Addiction and death were rife and led to the various Acts of Parliament which curtailed and controlled the manufacture, prescribing and possession of opioids.

The widespread use of morphine by injection as well as by the traditional routes from about 1830 onwards appeared to give a boost to the use of opioids with many prominent persons consuming considerable quantities. Dr Simpson's Morphia Suppositories were produced by Duncan and Flockhart of Edinburgh in about 1857 and were composed of morphia and sugar of milk (lactose) dipped into white wax and lard plaster melted together and were described in the *Medical Times and Gazette* of that year (Anonymous, 1857). The dose of morphine per suppository was half a grain (about 30mg) and they were commended as being more efficient than the usual soap and opium in common pill previously administered per rectum. One district surgeon in South Africa lacking the normal excipients used mutton fat with the result that his dog swallowed a batch of suppositories containing 12 grains of morphine (about 720mg) (Rees, 1883). The dog recovered after a dose of apomorphine and was fortified with brandy and cold tea.

Morphine suppositories have been part of the British Pharmacopoeia since its inception and are available in several strengths formulated in fatty bases such as cocoa butter and Witepsol (Anonymous, 1979).

### 2.1.3 Absorption

The absorption of morphine from the rectum appears to be entirely passive. There is no evidence of active transport in the rectum although there is in the upper intestine. For a fuller consideration see Section 1.4.1.
Bioavailability

The number of studies which have examined the bioavailability of morphine administered rectally is small. Their interpretation is complicated by the different vehicles used, the methodology and the assays employed. Comparison with other routes, in particular the oral route, is also difficult for similar reasons. However, a number of conclusions seem to evident. Firstly, the bioavailability of morphine given rectally is greater than the oral route particularly when single doses are given. The evidence is less clear when prolonged treatment is given but there is a suggestion that the dosage requirements for rectal administration are less than those for oral therapy.

Human Studies

The first study of rectal bioavailability was performed by Westerling and colleagues in 1982 (Westerling et al., 1982). They gave morphine 0.3mg.kg\(^{-1}\) by intramuscular injection and by rectal solution to six healthy women on two occasions. Plasma morphine was measured by gas chromatography. The mean (range) bioavailability was 31% (12-61%). The same group (Westerling and Andersson, 1984) repeated the study in seven women using a starch hydrogel in an attempt to improve absorption by improved mucosal contact. Mean (range) bioavailability on this occasion was 48% (31-72%). The hydrogel also prolonged the duration of action to about 8h.

Pannuti and colleagues (1982) gave morphine to patients in chronic neoplastic pain by the oral, rectal, sublingual and intramuscular routes in a single dose of 10mg before starting a longer term evaluation over several weeks of the former three routes. The rectal morphine was given as a 2ml mini-enema and the oral and sublingual dose as a 1mg.ml\(^{-1}\) and 20mg.ml\(^{-1}\) aqueous liquid respectively. They suggested that pain relief was more rapidly achieved by the rectal route and was more effective. The average daily dose was about 42mg orally and 31mg rectally. Plasma morphine concentrations were similar by the oral and rectal route for the single dose study. Little reliance can be placed on these values as the assay technique was an RIA method. No details of cross-reactivity with morphine glucuronides are given but the plasma morphine concentrations quoted are at least three times greater than might be expected. Plasma morphine concentrations of 15-ng.l\(^{-1}\) were reported as being present 24h after the single dose. This implies considerable cross-reactivity with the glucuronides of morphine (See Section 2.1.4.).
Ellison and Lewis (1984) compared the plasma concentrations of morphine and M3G measured by HPLC in patients given a single dose of oral morphine solution and a fat based suppository on separate occasions. No pharmacokinetic parameters were calculated but the plasma concentrations of morphine were consistently greater for the rectal route and the concentrations of M3G consistently less during the early part of the study. The latter observation suggests that some bypassing of first pass metabolism occurred although this could have been in the gut rather than in the liver. An approximate estimate of the relative bioavailability between the two routes suggests that it was approximately 50% greater by the rectal route. The approximate equivalence of oral and rectal administration was challenged by Lipman and Anderson (1984) more on theoretical and clinical than pharmacokinetic grounds. However, their view was refuted by Wehling (1984).

Morphine was administered from a fatty based suppository in the study by Jonsson and colleagues (1988). They showed a mean bioavailability of 53.3% compared with intravenous administration in eight patients using an RIA assay for morphine.

Moolenaar and colleagues (1988) compared the absorption of morphine in volunteers from a Witepsol based suppository and oral solution. They found that the bioavailability was greater rectally than orally.

Clinical support for greater bioavailability rectally compared with the oral route comes from a clinical study where patients receiving sustained release morphine tablets (MST) orally were given the same tablets rectally (Maloney et al., 1989). In 11 of the thirty patients the dose was decreased with maintenance of pain control implying better absorption of morphine. Contradictory results were obtained by Kaiko and colleagues (1992) who compared controlled-release tablets (MST) given both orally and rectally with immediate release suppositories in volunteers. The AUC ratio for MST rectally was 90% of the oral route and the peak concentration was considerably delayed. The study also showed some mucosal erythema and oedema for both rectal formulations. They concluded that MST was not suitable for rectal use. However, this group are employees of Purdue Frederick, the company that makes MST and they have gone on to produce a sustained release rectal formulation (Babul et al., 1992, 1993). They measured the oral and rectal absorption of morphine sulphate in a crossover study in human volunteers using the new formulation. The ratio of the AUC of morphine to morphine-6-glucuronide (M6G) and M3G were greater after oral than rectal administration suggesting avoidance of first pass hepatic metabolism. They also suggested that availability of morphine was
better from rectal than oral administration. This preparation was evaluated also by Bruera and colleagues (1995) in a double blind crossover study of 30 patients with subcutaneous morphine. A parenteral/rectal potency ratio of 1:2.5 was assumed. The controlled release suppository was administered 12 hourly and the subcutaneous morphine 4 hourly. Pain scores were slightly better in the suppository group.

The potential for bypassing hepatic metabolism was emphasised by a comparison of the absorption of morphine from a suppository administered rectally and into a colostomy in the same patients at different times (Hojsted et al., 1990). Eight patients were studied and the mean (range) bioavailability of the colostomy compared with the rectum was 43% (0.1-127%).

In an attempt to shed further light on the efficacy of morphine given by different routes, Breda and colleagues (1991) administered 10mg of morphine orally, rectally, sublingually and by injection to six patients. Samples were analysed for morphine, M6G and M3G by HPLC. No difference was found between any of the routes as measured by AUC and morphine to M6G ratio. However, examination of the time/concentration curves shows significant concentrations of morphine to be present up to 20 hours after administration which suggests that the assay was unreliable.

Wilkinson and colleagues (1992) conducted a randomised crossover study of sustained release morphine tablets given by the oral and rectal routes in chronic pain patients who were already stabilised on oral morphine therapy. Morphine and metabolites were measured by HPLC. There were no differences in the AUC for morphine given by either route although the peak concentration was less and delayed for rectal administration. The AUCs for M3G and M6G for rectal administration were about half those for oral administration which lends support to the bypassing of first pass metabolism by the rectal route. There were no differences between the two routes with respect to pain relief and side effects. The authors concluded that MST can be successfully given by the rectal route.

Morgan and colleagues (1992) as part of an evaluation of a sustained release preparation of morphine alkaloid in a fatty base, studied the absorption of oral morphine solution and morphine hydrochloride in a PEO vehicle. Morphine concentrations were measured with RIA. There was no significant difference in \( C_{\text{MAX}} \), \( t_{\text{MAX}} \) or AUC for either immediate release formulation.
An interesting approach to the administration of morphine by the rectal route was taken by Koopman-Kimenai and colleagues (1994). They administered nicomorphine which acts as a prodrug for morphine. The nicotinyl esters improve the lipid solubility of morphine and should enhance absorption. Subsequent hydrolysis rapidly releases the parent compound. Eight patients were studied. No nicomorphine was detected in plasma but morphine rapidly appeared and had a high bioavailability compared with previous studies.

De Conno and colleagues (1995) compared oral morphine solution with a microenema in a double blind placebo controlled study in 34 opioid naive patients with cancer pain. Pain relief was much faster with rectal administration (10 minutes compared with 60 minutes) and lasted longer (180 versus 120 minutes). They concluded that rectal morphine was an acceptable alternative to oral medication and was suitable when rescue medication was required.

**Animal studies**

There have been relatively few studies of rectal bioavailability of morphine in animals presumably because they are more convenient to perform on man and morphine is known to be well absorbed. They all confirm the human observation that rectal bioavailability is better than oral and that there is some bypassing of first pass hepatic metabolism.

Katagiri and colleagues (1988) found the oral and rectal bioavailabilities to be 10% and 90% respectively in rats. They also found a slightly greater bioavailability if spread of the morphine solution was restricted to the lower rectum close to the anus.

Tan and colleagues examined the rectal absorption of morphine from three fatty based suppositories in the rat (Tan et al., 1990a) and the dog (Tan et al., 1990b). In the former study they found that rectal bioavailability was greater than oral and that the plasma concentration of M3G was less. These findings were confirmed in the latter study and in addition they demonstrated that rectal lavage could further enhance availability presumably by reducing the effectiveness of the mucus diffusion barrier (Section 1.3.2) by thinning or diluting the mucus.

The addition of alginic acid to the suppository base prolonged the absorption in a study in rabbits (Kawashima et al., 1990). They showed a rectal bioavailability of 30-98% in
comparison with a mean value of 13.5% for oral administration. The enhanced analgesic activity consequent on the increased bioavailability was confirmed in a study in rats (Kita et al., 1990). The rectal potency was approximately twice that of an oral solution.

Kanamoto and colleagues (1991, 1992) investigated several different formulations of morphine suppository based upon various preparations of Witepsol and also a Witepsol base containing a controlled release morphine tablet (MS Contin, Napp Laboratories). All preparations gave better bioavailability than the same dose given orally.

Conclusions

The evidence of the human and animal studies is that the rectal route of administration for morphine is associated with some bypassing of first pass hepatic metabolism. The degree to which this is achieved depends upon the species, the position of the preparation within the rectum, the degree of spread of the drug, the rate of release of the drug and interindividual variation. The bypassing results in a change in the ratio of morphine to its glucuronide metabolites. While this is of pharmacological interest, the relevance to clinical treatment remains to be determined. A decrease in first pass metabolism might be thought to be advantageous. However, since M6G production will be decreased and it is now thought that this compound is important in the analgesic efficacy of morphine (see Section 2.1.5), the effect on analgesic potency might be less pronounced. Such evidence as there is to date suggests that there is little overall difference between the two routes with respect to comparability of dose and thus the differences in metabolism between the routes are not likely to be of clinical relevance.

2.1.4 Metabolism and Excretion

Metabolism

Following absorption, either from the gastrointestinal tract or site of injection, morphine is widely distributed throughout the body but is mainly concentrated in the liver, kidneys and spleen (Brunk and Delle, 1974). Small amounts enter the brain and muscles. The role of the lung has generated some interest and it was briefly suggested that the organ might participate in metabolism (Persson et al., 1986, Bodenham et al., 1989). However, this suggestion has been refuted (Ratcliffe, 1989). The lung acts as a reservoir of the drug, although not to a great extent. Less than 5% of an injected dose was taken up into the lungs during the first pass after central venous injection and subsequently returned to the
circulation as the plasma concentration decreased (Roerig et al., 1987). Lung has been shown to have a binding affinity two orders of magnitude less than brain but a receptor density 100 times as great (Cabot et al., 1994).

Morphine is strongly bound to plasma proteins, of which albumin is the most important (Leow et al., 1993). The binding was independent of plasma morphine concentration over the therapeutic range but was dependent upon protein concentration, bound fractions of morphine increasing with increasing concentrations of albumin and α1-acid glycoprotein. Under conditions of normal pH and temperature, 35.3% of morphine was protein bound. An increase in plasma pH secondary to hyperventilation increases the free morphine and thus brain concentration (Nishitateno et al., 1979).

The liver appears to be the major site of metabolism of morphine and glucuronidation is the major pathway mainly to the 3- and 6- glucuronides (M3G and M6G). On oral administration, the gut mucosa metabolises a significant fraction of the absorbed morphine by membrane bound diphosphate glucuronyltransferases located in the epithelial cells at the tip of the villi, mostly to M3G at a rate approximately half that of the liver (Rane et al., 1984, Pacifici et al., 1986). The liver then metabolises a considerable proportion of the remaining drug on the first pass through the organ from the portal circulation with subsequent excretion in the bile (Hanks et al., 1988). This is seen as a lower ratio of the plasma concentrations of glucuronides to morphine in subjects given morphine parenterally rather than orally (Peterson et al., 1990) and in subjects with hepatic impairment due to cirrhosis (Hasselstrom et al., 1990). Some enterohepatic recirculation of morphine appears to occur as shown by secondary peaks of unconjugated morphine plasma concentrations in patients given oral morphine either as an elixir or as sustained release preparation (Poullain et al., 1988, Westerling et al., 1995)). The enterohepatic recirculation is probably in part a result of the deconjugation of the metabolites by gut bacteria and reabsorption of the morphine (Goldman, 1980) as well as reabsorption of the metabolites themselves.

The influence of hepatic blood flow on glucuronidation is seen in studies of the influence of food on morphine absorption (Gourlay et al., 1989). Chronic pain patients, not normally receiving morphine, were given 50mg orally either in the fasted state or after a high fat breakfast. Plasma morphine concentrations, measured by HPLC showed increased and prolonged absorption in the fed state. The conclusion is that the increased hepatic blood flow in the fed state decreased the proportion of morphine glucuronidated during first-pass through the liver.
The unique circumstances of the anhepatic phase of liver transplantation were used to evaluate the possibility of extrahepatic morphine metabolism in man (Bodenham et al., 1989). Detectable concentrations of M6G, M3G and normorphine were detected after the injection of morphine at the start of the anhepatic phase confirming that extrahepatic glucuronidation was present, most likely in the kidney or bowel. These data must be interpreted with care as it is unlikely that gut and renal blood flow were normal during this phase of the operation and quantification of the degree of extrahepatic metabolism is difficult. Anaesthesia itself may alter the pharmacokinetics of injected morphine and metabolites (Sear et al., 1989). Studies in the dog have shown that glucuronidation in the absence of a liver was reduced to 56% of control but with no delay in the appearance of the glucuronides in plasma (Jacqz et al., 1986). They also showed that if the liver was intact but the bile duct and ureters ligated to prevent excretion, elimination of morphine itself was increased suggesting that in the normal animal excreted glucuronides were hydrolysed to the parent compound and reabsorbed. This suggests a mechanism for enterohepatic recirculation. Sawe and colleagues (1985) measured in vivo morphine and metabolite kinetics and in vitro hepatic UDP glucuronyl transferase activity in the same patients. They found that the oral bioavailability of morphine varied from 30-69% and was correlated with the plasma clearance of morphine and the in vitro enzyme activity. This provides further evidence of the pre-eminence of hepatic glucuronidation in morphine metabolism although renal metabolism may be significant (McQuay et al., 1983).

There is considerable interest in the possibility of central nervous system metabolism of morphine. While contributing little to the elimination of the drug, the production of active metabolites is of great relevance to the analgesic properties. Wahlstrom and colleagues (1988) studied glucuronide formation in post mortem brain tissue from 19 chronic pain patients exposed to opiates during their final days of life. Glucuronidation was found in only six of the specimens and in only two was M6G detected. In a clinical study however, no CSF M6G was detected when morphine was given intrathecally (Hanna et al., 1990). The situation remains unclear but it would appear that if glucuronidation occurs it is not of any great magnitude.

The capacity for glucuronidation is dependent on age. During an infusion of morphine, M6G was only detectable in 5/9 neonates but in all children tested (Choonara et al., 1989). The authors concluded that the production of both M6G and M3G were reduced in the neonate and that both glucuronidation pathways developed in parallel. There is no evidence that the capacity for glucuronidation is decreased in the elderly. Plasma
concentrations of both M6G and M3G are generally increased, probably as a result of reduced clearance (Sear et al., 1989, McQuay et al., 1990).

The major difference between elderly and young subjects in the handling of morphine is in the initial volume of distribution. Owen and colleagues (1983) showed that the higher initial plasma concentrations of morphine in the elderly after intravenous administration were due to reductions in the volume of both the central and peripheral kinetic compartments. The \( \beta \) elimination phase was more rapid in the elderly but plasma clearance was reduced so that peripheral compartment concentrations remained greater in the elderly for at least 90 min after dosing.

Increasing dose requirements in patients with chronic pain may be due to three factors, increased metabolism, increasing tolerance or increased pain. The former factor was studied in four patients who required increasing doses over a 5-8 month period (Sawe et al., 1983). The doses were increased 16-23 fold without any change in the relationship between the dose and the plasma concentrations of morphine, M6G and M3G or between morphine and the metabolites. The authors concluded that these metabolic pathways were not dose limited or subject to auto-induction.

The glucuronides are the major metabolites but there are a number of others that have been detected including normorphine, 6-acetyl morphine (Weitz et al., 1988), morphinone and morphinone-gluthathione adduct (Kumagi et al., 1990) and morphine-3 and -6-sulphate (Choonara et al., 1990). This latter pathway appears to be relatively important in the neonate where glucuronidation is less active.

Codeine is converted to morphine by \( \text{O}-\text{demethylation} \) in both adults (Quiding et al., 1986) and children (Quiding et al., 1992) whence it is glucuronidated for excretion.

**Excretion**

The glucuronides are highly polar, water soluble compounds and are excreted through the kidney and bile. The major determinant of their elimination is renal function and there are a number of studies and case reports showing prolonged elimination half-lives and prolonged clinical effects (Osborne et al., 1986, Sear et al., 1989c, Peterson et al., 1990, McQuay et al., 1990). In contrast the elimination half-life of morphine itself is virtually unchanged in renal failure (Aitkenhead et al., 1984).
Morphine is also eliminated through breast milk but the quantities are judged to be too small to affect the infant (Feilberg et al., 1989). A peak concentration of 500 ng ml⁻¹ was found which suggests that the total dose per feed will be less than 100 μg.

Gut bacteria also metabolise some morphine, usually by dehydrogenation. Two enzymes have been identified with Pseudomonas sp., beta-hydroxysteroid dehydrogenase and an NADP dependent morphine dehydrogenase (Bruce et al., 1990).

**Analysis of morphine and metabolites**

It is not the purpose of this section to provide a detailed critique of each method but to illustrate some of the problems inherent in the analyses which have relevance to the clinical studies. In particular, those which will help to explain some of the differences between studies.

Analyses have three elements, sample collection, sample separation and sample detection. Morphine is highly plasma bound and thus the type of collecting tube used to collect and store the samples may be relevant. Hoskin and colleagues (1989) showed that plasma concentrations of M3G were significantly less than those in serum from the same sample. The use of citrate as an anticoagulant in glass tubes was associated with lower concentrations of morphine and M3G and M6G. They recommended the use of plasma samples collected in heparinised plastic tubes for future studies.

The sample separation and preparation ready for analysis is the area of measurement which gives the most problems, particularly when chromatographic techniques are to be used. The techniques generally involve deproteination and then extraction using a separate column (Aitkenhead et al., 1984, Svensson, 1986, Joel et al., 1988, Venn and Michalkiewicz, 1990). Recovery of 95-100% of the morphine is considered adequate. Konishi and Hashimoto (1990) have described an on-line system for sample separation and preparation.

Two techniques have been used for sample analysis, chromatography and radio immunoassay (RIA). The latter technique relies on the specificity of the antibody for the compound to be tested (Spector, 1971, Hand et al., 1987). It is convenient to use and sample preparation is less complex. A major problem has been cross-reactivity between morphine and its metabolites, particularly M3G (Aherne and Littleton, 1985). This
compound is present in quantities considerably greater than morphine. Peak concentrations are up to four times greater but during the elimination phase of morphine the concentration in individual samples may be 100 times greater. Thus a cross reactivity of 1% which might seem to be acceptable may result in considerable overestimation of morphine concentrations. In one early study where RIA and high pressure liquid chromatography (HPLC) were compared, the slope of the correlation was 0.6 (Savarese et al., 1986). More recent studies have improved the assay (Jonsson et al., 1988, Kalso et al., 1990) but the variable effect of cross-reactivity remains a concern with RIA assays.

Chromatographic assays remain the assays of choice. Gas chromatography has been used in the past with mass spectrometry for sample detection (Edlund, 1981, Westerling et al., 1982) but has now been replaced by HPLC. A variety of detectors have been advocated for different compounds including electro-chemical, fluorescence and ultra-violet. Methods have been described by Atikenhead et al., 1984, Svensson, 1986, Joel et al., 1988, Venn and Michalkiewicz, 1990, Konishi and Hashimoto, 1990, Mason et al., 1991, Wright et al., 1994, amongst others and are reviewed by Tagliaro and colleagues (1989).

2.1.5 Mode of action

Morphine acts predominantly at the mu opioid receptors in the central nervous system to produce its analgesia and other effects. It does not appear to have any direct effect on peripheral nerves or tissue (Moore et al., 1991). Following receptor activation, it inhibits the cell by opening potassium channels via cyclic AMP and/or G proteins as intermediaries. The neurone is hyperpolarised and its firing rate is reduced or calcium ion influx is reduced and transmitter release inhibited in the case of a nerve terminal. If the inhibited neurone is itself inhibitory then there will be increased activity in those cells which it normally inhibits. Thus morphine may both decrease and increase nervous activity. In the spinal cord the major site of action is around the C-fibre terminal zones in lamina one and the substantia gelatinosa. The mu receptor is predominant and comprises about 70% of the total receptor population (Besse et al., 1990).

A variety of naturally occurring peptides are present both in the central nervous system and throughout the body (Kosterlitz, 1985). They seem to have a variety of roles in the modulation of sensory, particularly pain transmission as well as hormonal release, gut motility and circadian functions (Knapp et al., 1990). There is now evidence that morphine may also be a naturally occurring transmitter in the brain (Kosterlitz, 1987, Weitz et al., 1988, Kosterlitz and Paterson, 1990, Benyhe, 1994). Considerable work is
required on this aspect of pain transmission but it raises the possibility of influencing either secretion or elimination of the naturally occurring compound.

The location of opioid receptors in the supraspinal nervous system is well documented but the mechanism by which analgesia is produced is still unclear (Dickenson, 1991). Receptors are found at several sites in the medial brain stem around the nucleus raphe magnus and adjacent to the periaqueductal and periventricular grey areas. A large proportion are mu receptors and microinjection studies have shown that these areas are involved in the analgesia produced by systemic morphine administration (Yaksh et al., 1988). Delta and possibly kappa receptors are also involved in the production of analgesia.

Two theories have been advanced for the mechanism of action of opioids at supraspinal levels. The first is based on the concept of Diffuse Noxious Inhibitory Controls (le Bars and Villaneuva, 1988). The contrast between a discrete pool of activated nociceptive neurones and a surrounding pool of ongoing innocuous activity is perceived by higher centres as pain. Supraspinal morphine reduces the contrast rather than the activation of nociceptive neurones and thus blurs the perception of pain. The second theory is that cells in the brain stem are inhibited by incoming noxious stimuli thus permitting the perception of pain. Morphine both activates these cells while also inhibiting another group of cells which are activated by noxious stimuli (Fields et al., 1988).

Opioids are not effective for all forms of pain and in clinical practice it is observed that the efficacy of opioids varies with many factors. Opioid receptors display, at least in animal studies, a considerable degree of functional plasticity. The activity and sensitivity of receptors varies with the gonadal hormones, ageing, food deprivation and with circadian rhythms (Giardino et al., 1990). The contribution of these animal observations to human experience is unknown.

**Role of Morphine-6- and Morphine-3-Glucuronide**

Two conundrums have puzzled researchers over a number of years. Firstly, the inability to determine a consistent relationship between plasma morphine concentrations and analgesic efficacy (Vater et al., 1984) and physiological effects (Rigg, 1978) and secondly, the discrepancy between the oral bioavailability of morphine on single dose administration and its efficacy on chronic oral dosing (Sawe et al., 1983b, Hanks et al.,
1987). These problems were answered in part by the observation that a metabolite of morphine, morphine-6-glucuronide was a potent analgesic.

Its analgesic properties were described in animals by Shimomura and colleagues (1971) and Abbott and Palmer (1988) and its potential contribution to the analgesic properties of morphine in humans proposed by a number of workers (Hand et al., 1987a, McQuay et al., 1987, Hanks et al., 1987). Its cumulation in patients with renal failure and the clinical evidence of morphine's prolonged action in these patients provided further evidence (Osborne et al., 1986). Purified M6G did not become available until 1988 and Osborne and his colleagues subsequently demonstrated that it was an analgesic in man (Osborne et al., 1988). Img of the drug produced good pain relief lasting about 4-6 hours and no morphine or M3G was detectable in the plasma at any time. It appears that M6G is about ten times more potent than the parent compound and is present in quantities from two to eight times that of morphine. This suggests that M6G may be the main source analgesia from morphine administration. Morphine itself may be to a large extent a prodrug. However, there are no studies showing a correlation between either plasma or CSF concentrations of morphine and M6G and analgesia (van Dongen et al., 1994). 20% of an administered dose of morphine can not be accounted by addition of the amounts of drug and known metabolites excreted by all routes (Hasselstrom and Sawe, 1993) suggesting that there may be other metabolites, currently unidentified that might be pharmacologically active.

These preliminary studies have been followed by others in humans and animals confirming the role and potency of M6G. Intrathecal M6G given in the lumbar region to patients with chronic cancer pain was shown to be approximately twice as potent as morphine as measured by a sparing effect on self administered pethidine (Hanna et al., 1990). Animal studies have shown it to have greater selectivity for mu and kappa receptors and considerably increased antinociceptive potency (45-60 fold) than morphine (Frances et al., 1990). Paul and colleagues (1989) showed that M6G was only twice as potent as morphine when given subcutaneously but was 90 times as potent given into the cerebral ventricles and 650 times as potent when given into the spinal CSF. The implication is that M6G does not penetrate the blood brain barrier as well as morphine although the latter compound itself is relatively poorly transferred (Oldendorf et al., 1972). This would be expected from its known chemical characteristics of being highly polar and water soluble. However, it has been suggested that M6G and to a lesser extent M3G are more lipophilic than predicted (Carrupt et al., 1991). It is suggested that the molecules are in conformational equilibrium between extended and folded forms. In the latter form, the polar groups are "hidden" giving the molecule greater ability to pass
through lipophilic barriers. However, M6G has been shown to have a smaller volume of distribution and clearance than morphine (Hanna et al., 1991). In contrast, D'Honneur and colleagues (1994) measured morphine, M6G and M3G concentrations in plasma and CSF of normal patients and those with renal failure after a single dose of morphine 30mg. Peak concentrations of M6G and M3G in the CSF were found 12 hours after administration in normal patients but were delayed to 24 hours in patients with renal failure with CSF M6G concentrations 15 times greater at 24 hours in the renal failure patients. They concluded that the metabolites readily crossed the blood brain barrier despite their apparent lack of lipophilicity.

M6G has also been shown to be more potent (5-10 fold) than morphine when injected into the cisterna magna in studies of ventilatory responses in the intact awake dog (Pelligrino et al., 1989). Interestingly, M3G was shown to cause slight respiratory stimulation at high concentrations. The abuse potential of M6G was shown in animal studies to be as great as morphine when given systemically but about 150 times as potent when given into the cerebral ventricles (Abbott and Franklin, 1991).

M3G was generally held to be an inactive metabolite of morphine but a recent study in rats has suggested that it is an antagonist at the mu receptor (Smith et al., 1990). Analgesia induced by morphine or M6G was antagonised irrespective of the route or timing of administration suggesting a competitive blockade. This evidence is in concert with that on respiratory effects cited above (Pelligrino et al., 1989). Accumulation of M3G has been suggested as the explanation for "Paradoxical pain" (Bowsher, 1993) where pain is refractory to morphine and may worsen as the dose is increased. Cramond has treated such patients by substituting direct intra-ventricular injection of small doses of morphine for the large oral or parenteral doses (Cramond and Smith, 1993). The pain relief is excellent thus lending support to the suggestion that the pain is only refractory to morphine by reason of an antagonist.

6-Acetylmorphine has recently been isolated from several tissues in different mammals suggesting that it may be a naturally occurring morphinan (Weitz et al., 1988). It is known to be a metabolite of heroin and to be pharmacologically active. It is interesting to hypothesise that there may be other active metabolites of morphine that contribute to its analgesia.

The relevance to a consideration of rectal morphine administration is that if there is significant bypassing of first pass hepatic metabolism then the production of M6G may be
altered. A reduction in the ratio of M6G/morphine might reduce the analgesic potency of the preparation. For the patient this is only of relevance when a change is being made from one preparation or route of administration to another when equivalency of dosage must be maintained to avoid either overdosage or pain breakthrough. It is also possible that a route of administration that resulted in the production of high concentrations of M3G might be less effective in terms of analgesia.

It would appear that the analgesic potency of morphine is more complex than was originally thought. Further studies of morphine metabolites and routes of administration may be clinically useful in improving the quality of analgesia.

2.2 RECTAL MORPHINE: CLINICAL STUDIES

Rectal morphine has been used clinically for many years but there have been relatively few studies either of the treatment of acute or chronic pain. Several authors have commented that the rectal route has been underused particularly for the management of chronic pain (Brook-Williams and Hoover, 1982, Anonymous, 1983, Lipman and Anderson, 1984).

2.2.1 Acute pain

Premedication with opioids is a common anaesthetic practice to provide sedation and to contribute towards intra- and postoperative analgesia. The rectal route is popular for children who particularly dislike injections and may decline oral medication. Lindahl and colleagues (1981) administered a combination of morphine, diazepam and hyoscine in an oily propylene glycol base to 20 children. Plasma morphine concentrations of about 10ng.ml⁻¹ were attained which were considerably less than expected which was attributed to the use of a lipophilic vehicle. The authors did not comment on the analgesia obtained.

The same group reported the effect of the same rectal premedication on cardiac arrhythmias and the sympathetic and endocrine responses during the induction of anaesthesia (Sigurdsson et al., 1983). Compared with a group who received sublingual diazepam, the study group had fewer arrhythmias and a reduced sympathetic and endocrine response. The results were attributed to the improved sedation rather than any specific effect of the study drugs. However, a later study from the same author
(Sigurdsson, 1985) showed that although the induction of anaesthesia with enflurane was smoother in the group given rectal morphine there was a greater incidence of apnoea and a greater end-tidal carbon dioxide concentration and he did not recommend it when spontaneous breathing was to be maintained.

Diazepam was compared with a combination of diazepam, morphine and scopolamine given rectally as premedication to 208 children undergoing minor surgery (Haagensen, 1985). No difference was found between the treatments and no adverse effects were noted.

Guldbrand and Mellstrom (1995) compared a combination of morphine and scopolamine given either rectally in a hydrogel or by intramuscular injection to children undergoing minor ENT surgery. The rectal hydrogel was better tolerated by the children who experienced less nausea but slightly more pain.

Westerling and her colleagues from Lund in Sweden have undertaken a series of studies on the rectal absorption of morphine. The first study was of rectal morphine 0.3mg.kg⁻¹ in aqueous solution given as a premedicant to 21 healthy women (Westerling et al., 1982). The mean plasma concentration was about 9ng.ml⁻¹. They concluded that further investigation was required with other dosage forms. No comment was made on the analgesia obtained. Subsequently a starch hydrogel was developed as a vehicle (Harris et al., 1982) and evaluated in women as a premedicant (Westerling et al., 1984) in a dose of 0.55mg.kg⁻¹. Mean plasma concentrations of about 20ng.ml⁻¹ were recorded and the duration of action was prolonged compared with simple aqueous administration. No side effects other than sedation were reported but there was no comment on the analgesia obtained. The starch formulation was later assessed in children as a premedicant for eye surgery (Westerling, 1985). Six children were given the same mixture used by Lindahl et al. (vide supra), and 11 given the starch hydrogel preparation in a dose of 0.5mg.kg⁻¹. The plasma concentrations of morphine in the second group were twice that of the first but were not prolonged. One child in each group required additional analgesia and two children in the first group and three in the second vomited. It was concluded that the starch preparation was effective and well tolerated. This formulation is not however commercially available at the time of writing and no further studies have been published.

A case report from New Zealand (Gourlay and Boas, 1992) illustrated a number of points for the safe use of potent analgesics. A 9kg, 7½ month old child underwent a nephrectomy. Postoperative analgesia was originally prescribed as morphine 1.5mg IM
as required. This was changed to a 4mg suppository, 4hrly pm after humanitarian concern was expressed at the injections. The suppositories were given 4hrly without any assessment of pain. 22½ hours after operation, cardiac arrest occurred and resuscitation was unsuccessful. The plasma morphine concentration taken shortly after the arrest was about 8 times that usually associated with postoperative analgesia in similar patients. The assumed ratio of parenteral to rectal dosage of 1:2.7 was probably too high in this infant and the combination of impaired elimination and metabolism and the regular rather than prn dosing resulted in marked cumulation of morphine and metabolites, respiratory depression and death.

A conventional fatty based formulation was used by Jonsson and colleagues (1988) in the postoperative period in a bioavailability study compared with intravenous administration. No comment was made on the analgesia obtained.

The initial evaluations of the morphine hydrogel suppository (Hanning et al., 1983, 1984, 1986, 1988) were conducted in patients undergoing surgery and volunteers. The device was effective as the sole analgesic for the first 12-24 hours when given as a premedicant. The incidence of nausea seemed to be less than with conventional therapy. These studies are discussed further in Sections 4-8.

The major limiting factor in the treatment of acute pain by the rectal route is the delayed onset of analgesia compared with parenteral administration. However, this is less of an issue for operative pain which can be anticipated (Hanning, 1985).

2.2.2 Chronic pain

Rectal medication is a more appropriate route of administration for chronic pain than acute pain. Rectal morphine formulations have been in the Formularies for many years but their use is commonly overlooked. Several authoritative reviews of opioid therapy for chronic pain make no mention of the route although other, more exotic routes such as spinal administration are often included (Walsh and Cheater, 1983, Brescia, 1987, Gordon, 1988, McQuay, 1991). This is surprising as one study showed that 30-40% of cancer patients suffer from upper gastrointestinal symptoms that limit oral and sublingual drug administration (Hanks, 1983).
Twycross (1978) advocated the use of morphine suppositories and stated that they were equipotent with oral morphine. Brook-Williams and Hoover (1982) used soluble morphine tablets in gelatine capsules in ten patients with severe pain for periods of up to four weeks. They reported successful control of the pain and asked for other experiences to be reported. Salkind and Angelucci (1984) subsequently confirmed the value of rectal administration, particularly for those patients with dysphagia or nausea.

Pannutti and colleagues (1982, 1984) reported successful control of chronic pain of advanced cancer in a number of patients using rectal, oral and sublingual administration. Rectal morphine was administered as mini-enemata every four hours. Pain was controlled more rapidly and with a lesser dose than by the oral or sublingual routes. Patient and physician satisfaction was greatest for the rectal route. Twice as many patients in the oral group discontinued treatment as in the rectal group. They emphasised that the rectal route was as effective as oral administration and should be considered at an early stage in management.

Lipman and Anderson (1984) welcomed the introduction of a commercial suppository comprising a soluble capsule containing morphine in a vegetable oil base. They commented that "the rectal route was useful but often overlooked for many patients who cannot take drugs orally". They stated that they found that the dose requirement by rectal administration was 2-2.5 times greater than orally. They did not state the formulation used in these observations and the only paper cited in support (Lipman, 1975) makes no reference to rectal medication. The response from the manufacturer (Wehling, 1984) claimed comparability of dosage which is in accord with other studies.

The perverse and often blinkered nature of physicians is illustrated by two articles in the Journal of Pain and Symptom Management. In the first in 1986, Rogers described the available rectal opioids in the USA and the use of rectal morphine in a patient who was unable to swallow. Two issues later, a supplement on the management of cancer pain made no reference to rectal administration (Brescia, 1987). The journal has subsequently carried a review of rectal opioids (Cole and Hanning, 1990).

The more widespread use of suppositories on the Continent is illustrated by the report of Lakdja and colleagues from Bordeaux (1986). They reported 25 patients with cancer pain who required oral morphine every four hours including the middle of the night. A suppository comprising the normal nocturnal dose of morphine in a base of a fat and silica gel was administered at night with complete success.
The experience of the Royal Marsden Hospital in the management of chronic pain was reported in 1988 (Hoskin and Hanks, 1988). 131 patients were treated with oral morphine and 5 with rectal opioids (4 morphine, 1 oxycodone). 85 patients received parenteral diamorphine at some time due to an inability to take oral morphine. The figures show the considerable proportion of patients for whom an alternative to oral therapy would be useful and also the poor use of rectal therapy. Clearly, there are two explanations for this state of affairs. Firstly, that those caring for the patients do not consider rectal therapy and secondly, the formulations that are available compare poorly with oral and parenteral preparations in terms of convenience and efficacy. The attempts by two groups to make their own morphine suppositories using gelatine capsules containing either morphine tablets (Brumley, 1988) or sustained release tablets (Maloney et al., 1989) suggests that this latter point has some validity.

More recently a number of groups have investigated the value of administering sustained release oral tablets by the rectal route (Kaiko et al., 1989, Maloney et al., 1989, Wilkinson et al., 1992). The formulation of these tablets (MST) is a waxy matrix designed to produce delayed and sustained release over a 6-8 hr period. Although they are not designed for rectal administration, the clinical response has generally been favourable. They may prompt the development of formulations specifically for rectal administration as the acceptance of that route increases.

2.3. CONCLUSIONS

Morphine is well absorbed rectally, with a bioavailability that is probably better than that of the oral route. There is some by-passing of first pass hepatic metabolism but the benefits in terms of altered patterns of metabolites remains to be determined. Nevertheless, the rectal route remains a very useful alternative to oral administration for patients in acute and, particularly, chronic pain.
THE MORPHINE HYDROGEL SUPPOSITORY

3.1 INTRODUCTION

The morphine hydrogel suppository (MHS) was developed in response to the conclusions of the preceding chapters. Morphine is the most widely used and acceptable analgesic drug and is the standard against which others are measured. It is well absorbed from the rectum but in the presently available formulations is not well accepted or widely used. The rectum is a good route for the administration of sustained release vehicles. A considerable proportion of patients in pain are unable to take an oral preparation. The possibility offered by the hydrogels to develop a sustained release suppository seemed to be both feasible and potentially a useful addition to the analgesic armamentarium.

3.2 HYDROGELS

Hydrogels are polymers which will absorb and swell with water without dissolution and were first used for drug delivery in the late 1950's (Wichterle and Lim, 1960, Kim, 1983). They include those based on naturally occurring compounds such as cross-linked proteins, starches or cellulose derivatives and synthetic compounds based on hydroxy alkyl methacrylates, N-vinyl-pyrrolidone, acrylamide, acrylic and methacrylic acids, cross-linked poly(glutamic acid) and poly(ethylene oxide) (PEO). The latter compounds comprise a multiplicity of connecting units with the structure \(-\text{CH}_2\text{CH}_2\text{O}\) and are the basis of the MHS. The ethylene oxide monomer can be polymerised with a variety of catalysts to linear compounds with molecular weights up to 10,000 (Graham, 1987). The crystalline structure of linear PEO has been shown to be a \(7_2\) helix (Koenig and Angood 1970) that is, it is a coil comprising \(3\frac{1}{2}\) ethylene oxide groups per turn and a repeat unit of seven groups. A characteristic of these compounds is their crystallinity with melting points well above body temperature (typically 65-68°C) for those used in the manufacture of the MHS.

PEO of varying molecular weights are extensively used in processed foods, as suppository and ointment bases and as fibre forming aids in the textile industry. They are combined with hydrocarbons to form surface active agents for use in polishes, lubricants, mould-release agents and in water treatment (Bailey and Koleske, 1976).
The linear PEO molecules can be crosslinked to produce water insoluble hydrogels which swell by absorbing water. Five techniques are described for inducing the crosslinking (Graham, 1986). High doses of gamma irradiation from a $^{60}$Co source have been used and is probably related to the creation of hydroxyl and other radicals. It is expensive and little used. High molecular weight PEOs can be entangled in a cross-linked network of acrylic or vinyl monomers. The resultant product is physically weak and contains quantities of PEO which can be extracted on swelling. Covalent crosslinking of PEG with aromatic or aliphatic disocyanates and a triol or polyol is the most common reaction and is discussed further in section 3.2.1. One interesting use for variations of this reaction is the production of expanding foams used for a wide variety of medical and non-medical uses (Graham, 1987). Other reactions allow the resultant polymer to be biodegradable (Graham, 1978) (Section 1.4.4). Block copolymers can be created by the blending of PEO with other polymers such as polystyrene. They have also been used for drug release, generally in a membrane form (Graham, 1987). Association complexes between PEO of MW>2000 and polymethacrylic acid produces a hydrogel similar in properties to those formed by covalent crosslinking. There are no medical uses for these compounds.

Cross-linked PEO hydrogels have been used for other medical purposes than the administration of morphine (Gander et al., 1985) including the administration of chloroquine by rectal administration (Okor and Nwanko, 1988). Professor Graham's group has produced a vaginal pessary for the release of prostaglandin E$_2$ for cervical ripening which has achieved commercial production (See Embrey et al., 1980, 1986, Graham et al., 1980, 1985, McNeill and Graham, 1984, McLaren et al., 1987).

The properties of the hydrogel matrix may be altered by the addition of porogens which induce microporosity, facilitating the diffusion and release of larger molecules such as Vitamin B12. The porogens, such as naphthyl acetic acid, are incorporated into the structure during synthesis but are eluted during swelling of the hydrogel in water leaving a microporous structure which showed a significantly greater equilibrium water uptake (Badiger et al., 1993).

3.2.1 Chemistry

Poly(ethylene glycols) (PEG) are PEO with terminal hydroxyl groups and have the general formula:
Figure 3.1. Crosslinking of PEG with Dicyclohexyl methane 4,4'-diisocyanate and 1,2,6-hexane triol to form the PEO hydrogel used in the morphine hydrogel suppository
HO-(CH₂CH₂O)n-H

PEG with molecular weights of 1500-8500 were used in the development of the MHS. Two compounds are used to cross-link the PEG to form the hydrogel base, dicyclohexyl methane 4,4'-diisocyanate (Desmodur W) and 1,2,6-hexane triol (HT).

Dicyclohexyl methane 4,4'-diisocyanate has two functions in the reaction with PEG. The first is to extend the length of the PEG chains by joining them together in a urethane link. This reaction predominates when it is mixed in isomolar proportions with the PEG. When present in excess, as in the manufacture of the MHS, it co-reacts with HT to form a crosslinked network (Nwachuku, 1977) (Figure 3.1).

1,2,6-hexane triol is widely used as a cross-linking agent in the production of ointment and suppository bases. It acts as a plasticising agent to soften the PEGs. The molar proportion of HT to PEG determines the degree of crosslinking and thus its physical structure, including the crystallinity, swelling rate and characteristics for diffusion of substances through the polymer matrix.

**Synthesis**

Hydrogels for the MHS were made from PEG of molecular weights between 4000 and 8000 (K&K Greef Ltd, Croydon) (McNeill and Graham, 1987). Molten PEG was mixed in a fixed stoichiometric ratio with 1,2,6 hexane triol (Aldrich Ltd, Poole) and dicyclohexylmethane 4,4' diisocyanate (Bayer Ltd, Newbury) with anhydrous ferric chloride (FSA Ltd, Loughborough) as a catalyst (Graham and McNeil, 1984, McNeil and Graham, 1984) at a controlled temperature above the melting point of the final hydrogel. The suppository shape was formed by moulding in a cylindrical former. The cooled hydrogel was separated from the mould and purified by swelling and drying in a solvent to remove any unlinked reactants. The precise details of the reaction are a commercial secret.

The cross-linking compound has been changed latterly to the aliphatic isocyanate, Hylene W or biscyclohexylmethane-4,4'-diisocyanate and all toxicological studies were performed using this compound.
3.2.2 Structure

The hydrogel retains about 45% of the original crystallinity of the parent PEG after polymerisation. The formation of the crystals is important in the diffusion characteristics and drug release profile of the hydrogel (See Section 3.2.4) (Graham and McNeill, 1988). The dry hydrogel has the structure shown in Figure 3.2a where the ordered crystalline PEG molecules are arranged in an open matrix. The crystalline areas are linked with hydrophobic domains formed by the cross-linkers, HT and Desmodur. The crystalline nature is shown by the microscopic image taken with polarised light shown in Figure 3.3. Drug crystals are trapped within the amorphous matrix and are released on hydration.

The addition of water leads to swelling of the hydrogel with gradual dissolution of the crystalline areas. The final open structure is illustrated in Figure 3.2b where the hydrophobic crosslinker domains are now separated by an amorphous water filled network of PEG molecules. The final water content depends upon the degree of crosslinking and the molecular weight of the PEO used. The hydrogel used in the preliminary studies had an equilibrium water content at 37°C of 210 parts per hundred of the original dry weight (McNeill and Graham, 1987). 68% of the fully swollen hydrogel is water. The swelling in water is quite different from other solvents in that the degree of equilibrium swelling decreases linearly with temperature, whereas with other solvents the relationship shows discontinuities. (Graham et al., 1982).

The dry structure is a rigid solid and can be shaped by drilling or filing. The fully swollen hydrogel is rubbery but has little strength. Small nicks in the surface rapidly extend into tears and the material fractures readily if distorted.

3.2.3 Drug impregnation

Drugs may be introduced into the gel matrix either by incorporation during polymerisation, when the hydrogel is molten or swelling the dry polymer in a solution of the drug. The former methods have the disadvantage that the drug may not be heat stable and potentially toxic residual components of the polymerisation reaction may be leached from the preparation together with the drug on hydration (Graham and Wood, 1984).

Swelling the hydrogel in a solution of the drug was the method chosen for the MHS and is described in more detail in Section 3.3.2. It should be noted that this method also
Figure 3.2a. Structure of dry hydrogel showing the crystalline PEG \( \sim \) and amorphous PEG \( \sim \) linked by Desmodur \( \bullet \) joining the hydrophobic crosslinker domains. Drugs may be held in the amorphous areas between the crystalline domains. (Graham and McNeill 1988)

Figure 3.2b. Hydration breaks down the crystalline areas as the PEG becomes amorphous releasing drugs held between the crystalline areas and permitting diffusion.
Figure 3.3. Changes in crystallinity with hydration in a flat slip of hydrogel. Left: fully dehydrated and opaque showing presence of crystalline areas throughout the hydrogel. Centre: Partially hydrated showing rim of translucent gel without crystalline areas. Right: Fully hydrated and translucent showing absence of crystalline areas. (Photograph by courtesy of Prof N Graham.)
allows the possibility of varying the concentration of drug through the thickness of the hydrogel with consequent effects on the release profile (See Section 3.2.4).

An additional benefit of the multiple swelling and drying process is that it gives a more uniform gel matrix. Regions of disorder exist in the polymer made in the initial bulk polymerisation reaction (Graham and McNeill, 1984). These regions exhibit overswelling on the first swelling which then decreases as the disordered domains order themselves in the matrix aided by the plasticization of the long chain molecules in water. Thereafter swelling is reproducible and predictable and the hydrogels show a greater degree of crystallinity.

3.2.4 Diffusion characteristics

The factors affecting the diffusion of drugs from the polymer matrix are summarised in Table 3.1.

The drug release profile from fully swollen hydrogel is essentially exponential with the rate of release declining rapidly with time, that is, it is Fickian in nature (Peppas, 1985, McNeill and Graham, 1993a,b). The controlling factors are the rate at which the drug diffuses through the swollen polymer (diffusion coefficient) which is dependent on the water content and the degree of cross-linking (Davis, 1974, Wood et al., 1982), the length of the diffusion pathway and the concentration gradient between the polymer and the surrounding fluid. Figure 3.4 illustrates the relationship between the degree of crosslinking and the diffusion of a water soluble drug. The crosslinked areas form hydrophobic domains which impede the passage of the drug. The greater the degree of crosslinking, the slower the diffusion and thus release of drug from the hydrogel.

In the dry hydrogel the situation is much more complex and the release profile may be constant, increase or decrease with time until the fully swollen state pertains when the release rate decays rapidly as shown above (Chandrasekaran and Paul, 1982, Lee, 1985)). The situation is clarified by reference to Figure 3.5 which depicts a slab of hydrogel exposed to water on one surface. Swelling commences at the outer surface and after a short time the outer layer will be fully swollen (C), beneath which will be a layer which is partially swollen (B) and then a dry layer (A) which acts as a "reservoir" of drug. Diffusion through the outer layer will be dependent on the diffusion coefficient of the swollen gel and the thickness of the layer and will follow Fickian principles for diffusion. In the partially swollen layer, the diffusion coefficient will vary with the degree
Table 3.1. Factors affecting release of drugs from hydrogels.

HYDROGEL RELATED
Crystallinity of hydrogel
- MW and crystallinity of PEG
- Degree of crosslinking
Shape and thickness of hydrogel vehicle
Degree and Rate of swelling of hydrogel

DRUG RELATED
Drug affinity for hydrogel
Rate of diffusion through hydrogel
Solubility of the drug in water (body fluid)
Concentration of drug in the gel matrix
Distribution of drug in the gel matrix
Concentration in the surrounding fluid
Figure 3.4. Diagram to show the diffusion path of a drug molecule through a hydrogel. The circles represent hydrophobic crosslinker domains. The greater the degree of crosslinking, the longer the diffusion pathway.
Figure 3.5. Stages governing the diffusion of drug in a swelling slab of hydrogel. A: Dry hydrogel containing drug. B: Partially swollen hydrogel. C: Fully swollen hydrogel. See text for details (Section 3.2.4)
of swelling, the difference in coefficient changing by up to a 1000 fold from the dry to fully swollen state. The increasing diffusion distance is thus offset by the decreasing diffusion coefficient. As the crystalline domains hydrate, drug from adjacent amorphous areas diffuses in rather than diffusing outwards to layer C until full swelling has occurred. As a result of these properties, drug diffusion does not follow Fickian kinetics and if properly designed and loaded will be constant until full swelling has occurred when the rate will decline exponentially. An example of this property is seen in Figure 3.6 which shows the release of caffeine from hydrogel slabs of different compositions and thicknesses. Note that the rate of drug release (change in total released/time) is constant in all cases and then declines exponentially once full hydration has occurred.

The rate of swelling is determined by the availability of water from the surrounding fluid, the diffusion coefficient of water through the matrix and the diffusion distance. A further complication is the capacity of the crystalline areas to take up water at the expense of the amorphous areas of gel matrix. This phenomenon may be seen as a "dip" in the swelling profile. Drug will also diffuse from adjacent amorphous areas into the previously crystalline areas thus acting as an "internal reservoir" and slowing the diffusion of drug to the surface. The capacity of the hydrogel to display a constant release profile seems to be dependent to a large extent on the presence of crystalline areas. This is a unique property of the PEO type of hydrogel (Peppas and Korsemeyer, 1987).

The drug itself will be in a crystalline form in the matrix and the ease with which it dissolves in water and its solubility may also affect the release profile as will the affinity of the drug for the polymer. This is discussed further below.

The release profile shown in Figure 3.6 may be altered if the concentration within the dry gel is varied. If the inner layer of gel is given a greater drug concentration than the outer layer then this will tend to offset the decreased release rate consequent on attaining the fully swollen state. Similarly, if the surface layer is given a high concentration then the initial release rate will be greater than the later rate.

**Drug properties and release rate**

Five categories of compound can be considered for release from hydrogel.

1. Drugs of moderate molecular weight (about 250-2000) which are water soluble and have no significant interaction with the polymer. These agents are the most common
examples of the use of hydrogels and include morphine. In these cases the release profile is determined by the composition and geometry of the hydrogel rather than the agent and the attainment of a constant release profile can be relatively easily obtained.

2. Drugs of moderate molecular weight which interact with the polymer. A characteristic of this class is that they exhibit two or more constant plateaux of drug release. An example is promazine which displayed three constant release plateaux (Sloan, 1982). It was postulated that the first plateau represented the release of free drug while the later, less distinct plateaux represented two states of association between the drug and the ether groups of the PEO. Each ether group can associate with two drug molecules thus giving two binding states and two release states.

3. Hydrophobic drugs of moderate molecular weight and very low water solubility. P-aminoazobenzine, a yellow dyestuff, is such a compound whose solubility in water is only 70µg.mL⁻¹. Constant release of this compound into an aqueous medium was achieved from a small regular cylinder of hydrogel (Graham and McNeill, 1984). The hydrogel effectively acted as a diffusion controller at the boundary layer with the aqueous phase.

4. High molecular weight compounds which can diffuse through water, for example proteins. The rate of diffusion through hydrogel would be very slow and the matrix would have to be fully hydrated before much of the agent would be released. Release would then decrease with time as described above. The advantage of such a preparation would be that release would be prolonged over several days or even weeks by correct choice of the matrix structure.

5. Highly water soluble compounds which increase the rate of swelling of the hydrogel. This class of compounds has not been studied extensively as there are none of practical use. Lithium chloride is one example.

**Influence of the surrounding medium**

All of the above examples assume that water is freely available in the surrounding medium and this is generally the case with *in vitro* experiments. Swelling of hydrogel pessaries and suppositories in the vagina (McNeill and Graham, 1984, Embrey et al., 1986) and in the rectum (Cole et al., 1990) respectively is slower than in vitro. Two possible but not exclusive explanations can be proffered. Firstly that the body cavity contains insufficient water and the secretory capacity is inadequate to replace the uptake
from the hydrogel. Secondly, the mucus layer which will coat the device acts either as a diffusion barrier to water or, more likely, competes osmotically for the available water with the hydrogel. This subject is considered further in Section 9.

The pH of the swelling fluid has little effect on either the equilibrium (Nwachuku, 1977) or the rate of swelling (Graham and McNeill, 1984). The greatest difference in equilibrium swelling was less than 15% over a range of pH from 1.5-11. The difference in the rate of swelling in gastric fluid at pH values of 1.4 and 7.4 was less than 5%. The differences which would be experienced over the physiological range to be found in the rectum would be negligible.

Measurement of Release Rate

The in vivo and in vitro release rates may be very different for the reasons outlined above. However, the in vitro release rate may be regarded as a guide to that which may be obtained in vivo, and particularly as the maximum that might be expected. There are a number of difficulties inherent in the determination of the in vitro release rate. Essentially, the device is placed in a known volume of solvent, usually water, and samples taken at intervals, the drug concentration determined and the quantity released calculated. The volume of solvent is important since an increasing concentration with time will tend to decrease the concentration gradient between the solvent and the device. This can be countered by replacing the solvent at each measurement point but this may cause loss of drug if the device is wiped between insertions and will disrupt the boundary layer. A further consideration is whether the solvent should be stirred. The standard USP dissolution tests for oral preparations require stirring. The advantage is that a more reproducible result is obtained but the disadvantage is that stirring will tend to remove the boundary layer which has an important contribution to the release profile and the value obtained will bear less resemblance to that obtained in vivo. However, if the solvent is unstirred then vibration or movement of the test device can influence the results. In an unstirred test the site from which samples are taken is important unless fresh solvent is used at each time point. A further complication is that the released drug may be spontaneously hydrolysed particularly if the preparation is maintained at body temperature. This is the case for morphine particularly in the presence of light.

The method adopted for the preliminary studies was as follows: The MHS were suspended in 10ml of water at 37°C in the dark. The solvent was unstirred and was
replaced at each time point. The MHS was wiped once with a tissue before being replaced in the solvent. The assay for morphine was as described in Section 4.2.1.

3.2.5 Biocompatibility

The PEO hydrogels have been extensively tested for biocompatibility before clinical use and found to be safe. The PEG compounds are approved by both the British and US Pharmacopeia for use as excipients in the manufacture of ointments and suppository bases.

Tissue compatibility of the hydrogels was tested by the Bioengineering Department of the University of Strathclyde in mouse fibroblast cultures both directly after manufacture and after aqueous extraction and found to be non-toxic (Gilchrist et al., 1981).

Standard intramuscular implantation testing was conducted by the Huntingdon Research Centre (Kynoch et al., 1983). Eight strips of hydrogel and four control strips of plastic were implanted into the muscle of two rabbits. No difference was noted between the hydrogel and control sites after 72 hours confirming a lack of in vivo toxicity. The same organisation conducted a 28 day dietary toxicity test in male and female rats (Elliott et al., 1984). There were no signs of toxicity other than mild evidence of dehydration in those animals fed the highest dose of hydrogel (100 mg kg⁻¹ day⁻¹).

Studies in humans, both volunteers and patients have not shown any evidence of local irritation to the rectum which could be attributed to the hydrogel (see Sections 4-8).

3.3 MORPHINE HYDROGEL SUPPOSITORY

3.3.1 Rationale

As noted in the introduction, the concept of the MHS was the result of a meeting between the author and Professor Neil Graham. At that time the Department of Applied Chemistry at the University of Strathclyde had considerable information on the use of the hydrogels to obtain constant or zero-order release of drugs. Pharmacokinetic theory shows that if a drug is given at a constant rate of infusion then the attainment of a steady state concentration will require about four times the elimination half-life ($t_{1/2}$) of the drug (Hull 1985). The $t_{1/2}$ for morphine is about 2-3 hours (Lasagna and Beecher, 1954, Berkowitz et al., 1975, Berkowitz, 1976, Dahlstrom et al., 1982, Aitkenhead et al.,
1984) and thus for morphine an effective analgesic plasma concentration would not be attained for up to 10-12 hours. The usual response to such a problem is to give a loading dose of the drug to speed the attainment of the required plasma concentration.

The second problem in the initial stages of the project was that there was little published data on the rectal bioavailability of morphine. It could be estimated that the average hourly requirements for morphine given parenterally were about 1-3mg.h\(^{-1}\) (mean 2.6) (Dahlstrom et al., 1982), corresponding to a plasma morphine concentration of about 20ng.ml\(^{-1}\) and that a 5mg bolus as a loading dose would be appropriate for the average adult. It was assumed that the rectal bioavailability would be about 50% and thus the values for rectal administration would be doubled. The formulation requested of Prof. Graham was thus a "bolus" release of 10mg and a constant release of 4mg.h\(^{-1}\) for the remainder of a 12h period. It must be emphasised that these values were empirical, based on the available knowledge and erring on the side of safety. Subsequent work by Graves and colleagues (Graves et al., 1985) has suggested that Dahlstrom's estimates were too low and that an hourly dose and a plasma concentration twice that originally given were more appropriate. However, they used an RIA assay and they may have overestimated the morphine requirements.

3.3.2 Development

Dr Marion McNeill undertook the production of the first prototype using the draft formulation given above. Initial studies examined the diffusion of morphine from fully hydrated gel. A slab of hydrogel 2.8mm thick was swollen to equilibrium in an aqueous solution of morphine at 37°C, rinsed and then transferred to water at 37°C and the release of morphine determined. As expected the release profile was proportional to \(t^{0.5}\) and 50% of the morphine was released in 0.75 hours (Figure 3.7). Release from the dried slab was flattened and the t\(_{50}\) of morphine prolonged to 1.75 hours. From these experiments, diffusion coefficients were calculated for fully and partially swollen hydrogel to aid in the final formulation.

A slab of hydrogel is suitable for vaginal administration but not for rectal insertion. A solid rod of hydrogel would be expected to have a rapidly decreasing release profile compared with the slab as the surface area of the unswollen gel would diminish with respect to the exterior surface as swelling progressed and this is shown in Figure 3.8. In contrast, a hollow cylinder approximates to a rolled up slab, the thinner being the walls, the more closely it approximates. In practise, the internal diameter should not be less
Figure 3.7. Release of morphine from a fully hydrated slab of hydrogel ● and a dry slab of hydrogel ○ in water at 37°C (from McNeil and Graham, 1987)
Figure 3.8. Release of morphine from a solid cylinder of PEO hydrogel 9.5mm in diameter and 40mm long.
than half the outer diameter. A cylinder of hydrogel was swollen to equilibrium with morphine to ensure even drug distribution and dried. The ends were closed so that swelling and morphine release would only occur from the outer surface. The release profile is shown in Figure 3.9 and demonstrates that it is similar to the slab but with the $t_{1/2}$ extended to seven hours.

As noted above, the surface layer is still swelling when all the crystallites have dissolved in the centre of a slab and morphine is still being released from the surface layer. Therefore there exists a concentration gradient from the inner to the outer surface of the slab. It was realised that this process would hold in reverse as dry hydrogel was swollen in a solution of morphine and it should be possible to create areas of the gel matrix with a higher concentration of morphine than others. A high concentration on the inner surface of the cylinder would compensate for the increasing diffusion distance and a high concentration on the outer surface could provide the desired "bolus" release. The concentrations on the inner and outer surfaces could be varied by swelling them in solutions of differing strengths and thus considerable control over the release profile could be attained. The distribution of morphine across the annulus of the cylinder is shown diagrammatically in Figure 3.10.

Evaluation of several different devices showed that the desired release profile could be attained. Figure 3.11 shows the release profile of three of those tested. Two had the same dimensions of outer diameter 9.5mm and inner diameter of 5mm. One was swollen in morphine solution 20mg.ml$^{-1}$ (content 34.8mg) and the other in 40mg.ml$^{-1}$ (content 67.2mg) as described below. The third had a smaller internal diameter of 3mm and was swollen in morphine 40mg.ml$^{-1}$ (content 64mg). All showed the desired profile of a "bolus" release plus a constant release for several hours. The sample with morphine content of 67.2mg came closest to the required profile and was developed as MHS prototype I.

### 3.3.3 Prototype I

The chemicals described in Section 3.2.1 were mixed and poured into heated moulds made of polypropylene 9.5mm in diameter and 50mm deep. The hollow centres were formed by positioning stainless steel pins 5mm in diameter mounted on a plate centrally in the cavities. The prepolymer was cured at 95°C for four hours. It gradually became increasingly viscous, gelled and solidified over a 30-40 minute period.
Figure 3.9. Release of morphine from a hollow cylinder of hydrogel with a uniform dispersion of morphine across the annulus.
Figure 3.10. Diagrammatic representation of the concentration of morphine across the annulus of a prototype MHS.
Figure 3.11. Release profile of three hollow cylinders of hydrogel with a concentration gradient across the annulus of internal diameter and morphine content:

- 5mm, 67.2mg
- 5mm, 34.8mg
- 3mm, 64mg

(from McNeill and Graham, 1987)
The cured suppositories were freed from the mould and residual chemicals eluted by swelling in distilled water for 24h and drying at room temperature in a vacuum.

The blank suppositories were placed upright in small test tubes slightly larger than their swollen dimensions and a solution of morphine 40mg.ml⁻¹ was introduced around and within the blank. Swelling was allowed to proceed for about 1.5 hours with "topping up" of the solution as necessary. The MHS(I) was then removed from the solution, the cavity emptied of fluid and the suppository dried, firstly in a laminar flow cupboard and subsequently under vacuum. The suppositories were then trimmed to 40mm overall length and cavity length 32mm. The open ends were rounded for ease of insertion and the end of the cavity plugged with a 3mm length of hydrogel rod 5mm in diameter.

Release profile

The release profile in vitro is shown in Figure 3.12. It approximates very closely to the proposed profile and releases 11.4 mg of morphine in the first hour and 4.1 mg.hr⁻¹ for the next 11 hours. The total morphine content was 59mg.

Withdrawal mechanism

It was regarded as essential to incorporate a withdrawal mechanism in the event of an adverse reaction. As noted above, the fully swollen hydrogel is rubbery and fractures easily. It was found that the force required to pull the suppository through the anus was such that a thread passed through a hole in the hydrogel was inadequate as it cut through the hydrogel. The base of the dry hydrogel was thus drilled for a thread and reinforced with a collar of silicone rubber (Figure 3.13). This formulation was tested in clinical trials described in Section 4.

3.3.4 Prototype II

There were three principle criticisms of the initial prototype. Firstly, the plasma morphine concentrations attained were only about half of those thought to be necessary for analgesia in the postoperative period (Dahlstrom et al., 1982). Secondly, the single dosage form did not allow any flexibility in dosage. Thirdly, the silicone rubber reinforcement ring was felt to be rather harsh, did not always stay in place and prevented full swelling of the suppository at its base (Figure 4.1).
Figure 3.12. Release of morphine from a prototype MHS(I) suppository of total content 59mg.
Figure 3.13. Prototype MHS(I) showing silicone collar, withdrawal thread and plug to occlude the central cavity. Right: dehydrated. Left: fully swollen.
The response to these criticisms was to produce two half suppositories of different release profiles which could be joined by a length of hydrogel rod (Figure 3.14). The advantages were as follows. Firstly a choice of three "strengths" was available. Secondly, the device was "streamlined" facilitating insertion and withdrawal.

**Release profile**

The revised specifications for the release profiles was that one device should be 50% greater than MHS(I) and the other should be 100% greater. Thus one device should have a bolus of 15mg and a steady release of 6mg.h\(^{-1}\) and the other 20mg and 8mg.h\(^{-1}\) respectively for a period of 12 hours. These specifications could be met either by increasing the size and surface area of the device or by increasing the concentration of morphine within the matrix. The former course was felt to be unacceptable as the size of MHS(I) was already felt to be a maximum. Increasing the concentration of morphine required the use of a greater concentration in the solutions in which the hydrogel was swollen. This would not have been a limiting factor for the outer surface but was for the inner as the maximum solubility of morphine in water is approximately 40 mg.ml\(^{-1}\). The solubility increases with temperature but may accelerate the breakdown of morphine which occurs in aqueous solution. In addition, the swelling of hydrogel is adversely affected by increased temperature, the PEO used decreasing at approximately 3ppm/°C.

New moulds were made having a tapered cylindrical shape with a rounded end. PEO was cast in the moulds and, after curing, a 5mm cavity was drilled into the centre of the block. Short lengths of 5mm diameter hydrogel rod were used to join the two halves as shown in Figure 3.14. It was also intended that each half-suppository could be used separately and the flat end could be made acceptable for insertion with a gelatin cap (Figure 3.15). The rounded ends of the half-suppositories were drilled with a 1mm hole through which was passed a braided nylon thread secured by a "button" of silicone rubber within the cavity of the device.

The half suppositories were impregnated with morphine by swelling from both the outer surface and the cavity at 37°C, which was felt to be an acceptable compromise. The outer surface was swollen in a solution of 30mg.ml\(^{-1}\) for 30 minutes and the inner surface in a solution of 60mg.ml\(^{-1}\) for 2 hours for the lesser dose and swollen for 1 hour and 3 hours respectively for the greater dose. The release profiles obtained for joined pairs of the two devices, MHS(IIa) and MHS(IIb) are shown in Figure 3.16. Three combinations were thus possible:
Figure 3.14. Prototype II MHS comprising two half suppositories joined by a length of hydrogel rod. Note the withdrawal thread anchored by a silicone rubber "button". Right: dehydrated. Left: fully swollen.
Figure 3.15. "Half suppository" of Prototype II MHS showing gelatin cap to facilitate insertion. Left: fully swollen. Right: dehydrated.
Figure 3.16. Release of morphine into distilled water at 37°C from a pair of MHS(IIa) ○ and a pair of MHS(IIb) •.
Two MHS(IIa).

Bolus 12 mg Release rate 5mg.h⁻¹ Total Dose 76mg

One MHS (IIa) and one MHS(IIb)

Bolus 16 mg Release rate 6.5mg.h⁻¹ Total Dose 103mg

Two MHS(IIb).

Bolus 20 mg Release rate 7.7mg.h⁻¹ Total Dose 130mg

These combinations were felt to be a sufficiently good approximation to the revised specifications and they were evaluated in a further series of patients described in Section 5.

Withdrawal mechanism

The revised withdrawal system of a braided nylon thread passed through a hole in the end of the half suppository and secured with a silicone rubber "button" was expected to be less successful than the previous silicone rubber collar. In vitro experiments confirmed the expectation that the thread would cut through the fully hydrated hydrogel. However, it was felt that overdosage was mostly likely to occur soon after insertion and thus withdrawal would be possible as the hydrogel would still be largely in the dry state. In addition, the initial studies had given confidence that "dose-dumping" was highly unlikely and thus urgent removal was not envisaged.

3.3.5 Prototype III

The results of the patient study described in Section 5 gave further support to the hypothesis that the MHS was able to attain and maintain steady plasma concentrations of morphine and to provide either complete analgesia for surgical patients or a useful contribution towards analgesia. The morphine release profile was not ideal in that a period of three to four hours was required to achieve "plateau" plasma concentrations. However, this was not felt to be a problem as the onset appeared to be predictable which would permit its use as a premedicant and for the management of chronic pain.
discussed in Sections 1 and 2, the rectal route is rarely suitable for the management of acute pain and thus a delay in onset was not seen as a major disadvantage. As it proved impossible to withdraw the MHS after 12 hours to assay for residual morphine content and no plasma samples were taken after that time, the complete profile of morphine release and plasma morphine concentrations was unknown.

A consideration of the theoretical changes of plasma morphine concentration suggested that if a second MHS with an initial bolus release was administered while a first device was still releasing morphine then there was a probability of a sudden increase in plasma morphine concentration and thus overdosage. The degree of increase in plasma morphine concentrations would depend upon whether the release rate of the first device was still in the zero-order phase or whether it was declining as the device became spent. It was proposed that a device which released morphine with zero-order kinetics only would be needed for second and subsequent administrations and that the changes in plasma morphine concentration at the time of changeover should be investigated.

The lack of correlation between plasma morphine concentrations and dose of morphine, whether corrected for weight or not, suggested that for adult subjects it was probably unnecessary to provide a wide range of doses. Two would probably suffice and would have the considerable advantage of simplifying production.

The withdrawal mechanism was less than ideal but for reasons outlined in Section 5.4. it was not thought necessary to make major changes at this time as it would have required a considerable investment in moulding techniques. As there was still doubt as to the efficacy of the device, this investment was not felt to be warranted.

**Release profile**

Further MHS were produced in the same manner and with the same release profile as described in Section 3.3.4. These were designated MHS(B) as they had both a bolus and a zero order release. The method of production of the half suppositories was as described in Section 3.3.4.

A sustained release alone device, designated MHS(S), was made by swelling from the inside of the cylinder with a high concentration of morphine (60mg/ml) and from the outside with a lower concentration (10mg/ml). A low and a high dose formulation were produced by swelling for two and three hours respectively.
The half suppositories were joined to make two strengths of MHS(B) and MHS(S) with the characteristics given below.

**MHS(B) low dose**

- **Bolus** 15mg  Release rate 6.5mg hr\(^{-1}\)  Total dose 103mg

**MHS(S) low dose**

- No bolus  Release rate 5mg hr\(^{-1}\)  Total dose 73mg

**MHS(B) high dose**

- **Bolus** 20mg  Release rate 7.7mg hr\(^{-1}\)  Total Dose 130mg

**MHS(S) high dose**

- No bolus  Release rate 7.1mg hr\(^{-1}\)  Total Dose 110mg

The release profiles are given in Figure 3.17.

**Withdrawal mechanism**

The withdrawal mechanism was modified slightly in an attempt to improve the safety of the device. The half suppositories were linked with a short length of hydrogel tube and a withdrawal thread was passed through one end of a half suppository, along the length of the device through the tube and out through the other half suppository where it was anchored by a silicone rubber cap over the "nose" of the device. This method was recognised as being less than ideal but the expense of retooling precluded any change.

The MHS(B) and MHS(S) were evaluated in the study described in Section 6.
Figure 3.17. Release of morphine (mg.h\(^{-1}\)) from MHS(B) low dose \(\bigcirc\) and MHS(S) low dose \(\bullet\) and MHS(B) high dose \(\triangledown\) and MHS (S) high dose \(\blacksquare\).
3.3.6 Prototype IV

The earlier patient studies had suggested that the MHS had potential but that evaluation required the more controlled circumstances of a volunteer study rather than the uncertainties of clinical practise. Experience with the earlier prototypes suggested that a simple cylinder with a plug to close the central cavity would be the best shape for the first volunteer study. The device had been proven in the three prototype studies and while the hollow device was potentially difficult to manufacture, mostly with the impregnation with morphine, the in vivo evaluation of different shapes was not felt to be relevant at that time.

Release profile

The hydrogel was prepared by polymerising polyethylene glycol 4000 (K&K Greef Ltd, Croydon), 1,2,6 hexane triol (Aldrich Ltd, Poole) and dicyclohexylmethane 4,4’ disiocyanate (Bayer Ltd, Newbury) with anhydrous ferric chloride (FSA Ltd, Loughborough) as a catalyst (Graham and McNeil, 1984, McNeil and Graham, 1984). Molten polyethylene glycol was combined with the other constituents in a fixed stoichometric ratio and the suppository shape formed by moulding in a cylindrical former. The polymer was then purified before impregnation with morphine sulphate BP (McFarlane Smith Ltd, Edinburgh) by swelling in a solvent with a concentration of 60mg/ml until a charge of 100mg was obtained. The MHS(IV) was then dried to remove solvent to give a finished suppository weighing approximately 1.8g.

A plug of hydrogel with the same swelling characteristics as the MHS(IV) was used to cap the centre cavity of the suppository to prevent in vivo release of morphine from the inner surface.

The in vitro release rate of morphine was determined by swelling in 900ml water at 37°C buffered to pH 7.9 with a phosphate buffer in a Caleva 8-ST USP dissolution apparatus stirred at 50 rpm. The central cavity of the MHS(IV) was plugged with a silicone elastomer to ensure that release only occurred from the outer surface, mimicking the in vivo release. The dissolution media was pumped continuously with a peristaltic pump through the measuring chamber of a UV spectrophotometer (Philips Analytical PU8620) set at 210nm. Morphine concentration was calculated and stored by an on-line computer. The MHS(IV) used were found to contain a total of 103.2mg of morphine sulphate. The in vitro release profile is shown in Figure 3.18 and was approximately 20mg h⁻¹ for the
first hour and 10mg.h\(^{-1}\) for the next eight hours. The mean release achieved \textit{in vivo} in Volunteer Study I described in Section 7 is shown for comparison.

\textit{Withdrawal mechanism}

A small hole was drilled in the base of the MHS and a length of polyester thread secured by means of a button of reinforced Silastic sheeting (Dow-Corning, Reading) within the cavity (Figure 3.19). The thread was intended as a means of removing the MHS at the end of the experimental period or in the event of an adverse effect.

Prototype IV was evaluated in Volunteer study I described in Section 7.

3.3.7 Prototype V

The results of the volunteer study on Prototype IV were encouraging and suggested that the MHS was capable of delivering morphine over a 24-hour period. However, the commercial constraints of manufacturing and impregnating a cylindrical structure were formidable and it was felt that further thought should be given to the shape before development could proceed. A further source of delay was the transfer of the intellectual rights from Controlled Therapeutics to Core Technologies but this proved to be a good opportunity to review all the available information and plan future development.

Zero-order release of drug is most easily achieved from the surface of a block of hydrogel as described in section 3.2.4. A ribbed structure as shown in Figure 3.20 may be regarded as a folded flat surface in the same way as a cylinder may be regarded as a rolled surface. The \textit{in vitro} release profile was found to be similar to the cylinder and was much easier to mould. The centre may be drilled for a withdrawal thread if necessary. Four and five ribbed cross-section suppositories were tested and were very similar in their release profiles (Figures 3.21). Four ribbed structures, being easier to mould, were used for subsequent studies.

\textit{Release profile}

The MHS (V) comprised a four ribbed block of polymer weighing 1.6g, 4cm in length and 9mm maximum diameter with 2mm central bore and containing a mean dose of morphine 93mg. The \textit{in vitro} release profile was measured by the USP paddle method.
Figure 3.18 Release of morphine sulphate with time from prototype MHS(IV). n=3. ▼ in vivo release in volunteers.
Figure 3.19. Prototype MHS(IV) showing withdrawal mechanism of polyester thread secured by a silicone rubber "button" within the cavity.
Figure 3.20. Four ribbed prototype MHS(V). Left: Fully swollen. Right: Dehydrated.
Figure 3.21. Release of morphine (% of total content) with time from 4 ribbed (○) and 5 ribbed (●) prototype MHS V suppositories (USP stirred method).
Figure 3.22. Release of morphine with time from prototype MHS(V) in volunteer study 2 (with overnet) in vitro ○ and in vivo ●
(Section 3.2.4) and is shown in Figure 3.22 together with the in vivo release estimated from the residual morphine content of the MHS after retrieval.

Withdrawal mechanism

The difficulties in removal using a withdrawal thread during the previous study were noted. It was felt that, as this was to be a volunteer study, a withdrawal mechanism was necessary. The MHS were therefore enclosed in an inert mesh bag with a drawstring which would pass through the anus (Figure 3.23).

Prototype V was evaluated in the study described in Section 8.

3.3.8 Prototype V (Study 2)

The first volunteer study with Prototype V showed that it was capable of delivering morphine for 24 hours. However the presence of the mesh overnet withdrawal mechanism proved to be a considerable barrier to the swelling and release of morphine, such that the plasma concentrations achieved were only about half of that expected. It was clear that the withdrawal mechanism was a major barrier to successful development. It had been argued previously that a withdrawal mechanism was unnecessary. Dose dumping was impossible and a specific antagonist of morphine (naloxone) was widely available. In addition, toxicity would normally be expected to be evident within the first few hours after dosing when the hydrogel would not have fully hydrated and would have sufficient structural rigidity to be removable by manual extraction through the anus. Even when fully hydrated and easily fractured, the hydrogel would be removable either by manual extraction or through a proctoscope. The hydrogel would not be expected to leave the rectum for the colon, particularly when fully hydrated. These options still give a considerable safety margin over orally administered preparations where no retrieval is possible.

It was therefore concluded that the trial should be repeated, in volunteers, using the same protocol but without an overnet. The trial would also provide some indication as to the ease with which the fully hydrated hydrogel could be expelled by voluntary effort.

The importance of the rectal mucus in influencing the hydration and release of morphine from the hydrogel was highlighted also by the work described in Section 8.6-9 This was
Figure 3.23. Withdrawal mechanisms for prototype MHS. From left: thread passed through central core secured with silicone button, vaginal pessary with "fluffy" withdrawal thread, compressed fibre bag with drawstring, solid hydrogel drilled through base, knitted polyester overnet bag containing four-ribbed MHS(V).
investigated further with an in vitro study of the swelling rate of hydrogel in different solutions, described in Section 9.

**Release profile**

The dimensions and morphine content were identical to the MHS described above except that the central bore was only 1.5mm in diameter. The release profile was similar to that described in section 3.3.7 and is shown in Figure 3.24. The evaluation in volunteers is described in Section 8.

**3.4 CONCLUSIONS**

The development of the MHS outlined above and the associated studies described in Sections 4-9 have demonstrated that the original premise was correct that the hydrogel is able to deliver morphine through the rectal mucosa in a controlled fashion for periods of up to 24 hours. Considerable further work is necessary before the system could be used widely and could be granted a product licence by the Medicines Control Agency. The outstanding problems and the studies proposed to elucidate the answers are described in Section 10.
Figure 3.24 Release of morphine from Prototype MHS (V) in volunteer study 3 in vitro (○) and in vivo (●).
4.1 INTRODUCTION

The MHS(I) with the characteristics outlined in the previous chapter (Section 3.3.3) was tested in patients undergoing surgery normally requiring an opioid analgesic. Plasma morphine concentrations were measured by high pressure liquid chromatography (HPLC) using the method described by Aitkenhead et al., (1984).

The results of this study were presented to the Winter 1982 meeting of the Anaesthetic Research Society and the abstract published in Hanning et al., 1983 and a full report given in Hanning et al., 1988.

4.2 PATIENTS AND METHODS

Approval for the study was sought from the Leicestershire Ethics Committee and was granted on the 5th February 1982. Healthy adult patients of American Society of Anesthesiologists (ASA) classification I or II were invited to give their informed consent to the study. They were scheduled to undergo surgery for which an opioid would normally be given for intraoperative analgesia.

Patients were excluded if they were unwilling to participate or had significant cardiovascular, respiratory, renal or hepatic disease. They were also excluded if they had any allergy to morphine or were taking any drugs containing or metabolised to morphine. Patients were also excluded if they had diarrhoea, constipation or other disorder of the anal canal or rectum except in the case of two patients who were to undergo excision of the rectum for carcinoma where histological examination of the rectal wall in contact with the MHS(I) was proposed.

Patients were prepared for surgery in the usual manner, including bowel preparation if necessary and an MHS(I) administered by the ward staff as a premedicant prior to the proposed surgery. The MHS(I) was inserted with the patient in the left lateral position and the nurse instructed to ensure that the MHS(I) was placed just within the rectum beyond the anal canal. The nurse was permitted to apply a small quantity of a water-soluble lubricant gel (K-Y Jelly) to facilitate introduction of the MHS(I) into the rectum.
Anaesthesia was induced and maintained in a standard fashion except that no further morphine was administered in those subjects where the MHS(I) was given as a premedicant and further intraoperative analgesia if required, was provided with fentanyl, phenoperidine or pethidine. Postoperatively, analgesia was provided by pethidine 100mg IM on demand and was administered by the ward staff at their discretion. The MHS(I) was removed 12h after insertion whereby the patient's management reverted to the usual pattern.

Venous blood was sampled prior to insertion of the MHS(I) and then 30, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 720 minutes thereafter and in some cases after removal of the MHS(I). The blood was centrifuged and the supernatant plasma transferred to polypropylene tubes and stored at -70°C until analysis.

Patients were questioned with regard to any discomfort or rectal irritation on insertion or during application of the MHS(I).

4.2.1 Plasma morphine assay

Plasma samples and control samples "spiked" with morphine were analysed in duplicate (Aitkenhead et al., 1984). A control sample was analysed at the commencement and conclusion of every set of samples and after every fifth test sample. The morphine was extracted from a 1ml aliquot of plasma by mixing with 1g of NaCl, approximately 1ml borate buffer (pH 9.2) to a pH of 8.2, 100μl of an aqueous solution of nalorphine 250ng.ml⁻¹ as an internal standard and 9ml chloroform and shaking mechanically for 15min. The mixture was centrifuged for 5min at 3000rpm, the aqueous layer discarded and the organic layer transferred to a conical centrifuge tube before evaporating to dryness under nitrogen at 60°C in Buchler evaporator. The residue was dissolved in 180μl of 50% methanol and injected into the column. Recovery of morphine from aqueous standards was 100.9±0.5% (mean± SEM).

The column consisted of reverse-phase μ-Bondapak C₁₈, 25cm in length and 4.4mm internal diameter. The mobile phase was 0.08M potassium dihydrogen phosphate with 200ml HPLC grade methanol and 3ml 0.1M sodium 1-heptane sulphonic acid per litre and was recirculated. The mobile phase flow rate was 1.5ml.min⁻¹ and the eluents were detected with an electro-chemical detector set at 0.64v. Peaks due to morphine were determined by reference to the internal standard and the concentration of morphine in the sample determined by comparing its area to that of the control morphine peak. Analyses
were repeated if the paired values differed by more than 10%. The coefficient of
variation for the analysis was less than 5%. The lower limit of sensitivity of the method
was approximately 1ng.ml⁻¹

The morphine content of retrieved MHS(I) was determined by placing them in 1 litre of
water at room temperature on the laboratory bench for 72 hours. An aliquot was
withdrawn and analysed for morphine content using the method given above.

4.3 RESULTS

4.3.1 Clinical details

Five patients (two female) with mean age 46.8 years (range 22-65) and mean weight
79kg (range 67-89) were given the MHS(I) and plasma samples collected. Patient 1 was
given an MHS(I) on two occasions four days apart. The details of operation, timing of
MHS(I) administration, analgesic requirements and demographic information are given in
Table 4.1.

Insertion of the MHS(I) was uneventful in all patients, although the nursing staff
commented that the silicone collar made insertion difficult. The MHS(I) was removed
intact in all patients except Patient 5 where no trace of the MHS(I) could be found. They
were found to be almost completely hydrated apart from the base of the device
underlying the silicone collar. The plug was present in all cases and had generally moved
a short distance down the interior of the device (Figure 4.1).

All subjects were sedated but rousable. None complained of nausea and no anti-emetic
drugs were required. Two patients, however, were worthy of individual comment.

Patient 1

This patient was a 65 year old male with carcinoma of the rectum. He was scheduled to
undergo abdomino-perineal excision of the tumour on the 15th June 1982. Bowel
preparation was performed with oral mannitol and phosphate enemata over the preceding
48 hours. An MHS(I) was administered at 0815 on that morning and blood samples
taken for six hours until 1415. Anaesthesia was induced thereafter and was accompanied
by severe hypotension and bronchospasm. The operation was abandoned and he was
transferred to the Intensive Therapy Unit where he made a rapid recovery. No further
Table 4.1. Demographic data of subjects receiving the first prototype MHS.


<table>
<thead>
<tr>
<th>Patient</th>
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<td>63</td>
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<td>75</td>
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<td>89</td>
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<td>Operation</td>
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<td>LIH</td>
<td>Nephrectomy</td>
<td>Breast lump</td>
<td>V &amp; P</td>
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<td>MHS given preop (hrs)</td>
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<td>-12</td>
<td>-8</td>
<td>-13</td>
<td>-6</td>
</tr>
<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
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<td>No</td>
<td>Ph 2mg</td>
<td>F 25μg</td>
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<tr>
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<td>N/A</td>
<td>Dis 2</td>
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Figure 4.1. A prototype MHS used in the first patient study after removal. Note that the silicone withdrawal collar has remained in place. The hydrogel plug which closed the cavity of the device is *in situ* but has migrated into the cavity.
bowel preparation was deemed necessary as the patient had only taken liquids. A second MHS(I) was administered on the 19th July at 2120 and blood samples taken intermittently for 12 hours until induction of anaesthesia when the MHS(I) was removed. Morphine was used as the analgesic both intraoperatively and postoperatively. The planned operation was then performed.

**Patient 2**

This patient was a 56 year old male presenting for repair of a left inguinal hernia. He also had severe asthma and chronic bronchitis and was scheduled to undergo repair of the hernia under epidural anaesthesia. An MHS(I) was given at 0800 on the 22nd July 1982 and blood samples taken intermittently thereafter. Surgery was commenced at 1600 on the same day. Analgesia was reported as excellent and a second MHS(I) was administered at 2030 hours but no further blood samples were taken. The only additional analgesia required was two Distalgesic tablets at 2140 on the day of operation.

4.3.2 Plasma morphine concentrations

The plasma morphine concentrations are given in Table 4.2 and shown in Figure 4.2. Morphine was detectable in all patients and with the exception of the first exposure of Patient 1, the plasma concentrations were reasonably stable throughout the period of administration. Plasma morphine concentrations were measured after removal of the MHS(I) in Patients 3 and 4. In both, the concentrations tended to be maintained up to two hours after morphine administration ceased. In the light of the results obtained in later volunteer studies the accuracy and specificity of the assay must be questioned.

No residual morphine was found in any of the retrieved MHS(I).

4.3.3 Rectal mucosal histology

Two male patients aged 65 (Patient 1) and 70 (Patient 6) with known carcinoma of the rectum scheduled to undergo surgical excision of the rectum were given an MHS(I) 12 hours prior to the expected surgery. The MHS(I) was removed after induction of anaesthesia and prior to the start of surgery. Blood samples were only taken from Patient 1. Both patients had had standard bowel preparation including phosphate enemata and oral mannitol and had undergone sigmoidoscopic examination and rectal examination...
Table 4.2. Plasma morphine concentrations (ng.mL$^{-1}$) in five patients given the first prototype MHS.

<table>
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<td>9.4</td>
<td>3.8</td>
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<td>6.4</td>
<td>3.1</td>
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<tr>
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<td>4.7</td>
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<td></td>
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<td>16.7</td>
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<tr>
<td>360</td>
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<td>5.8</td>
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<td>600</td>
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<td>6.1</td>
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</table>
Figure 4.2 Plasma morphine concentrations in five patients following the first prototype MHS. ○ and ● Patient 1, ▼ Patient 2, ▼ Patient 3, □ Patient 4, ■ Patient 5.
prior to surgery. Patient 2 had also had injection of BCG into the rectal mucosa two weeks prior to the surgery in an attempt to enhance the immune response to the tumour.

Sections of anal and rectal mucosa were taken, prepared in formalin, embedded in wax, sectioned, stained and examined by light microscopy. The reports were as follows:

**Patient 1. (Aged 65) Reported by Dr A. Fletcher, 23rd July 1982.**

A piece of anal mucosa measuring 6x3.5x1 cm was examined and appeared macroscopically normal. Microscopic examination showed a normal glandular architecture with no loss of goblet cells and there was no evidence of inflammation in the lamina propria.

**Conclusion:** Normal rectal mucosa.

**Patient 6 (aged 70) Reported by Dr K. O'Reilly, 14th June 1983.**

The specimen consists of rectum and anus. An annular flat ulcerated area is present 5cm from the anal margin which is a moderately differentiated adenocarcinoma. Chronic inflammatory cells and mycobacteria were found in the submucosa distal to the tumour. A block taken from the anal margin shows neutrophil polymorphs infiltrating the epithelium of the transitional zone and superficial ulceration of the most distal part of the rectal mucosa, with a mild acute inflammatory cell infiltrate and focal areas where crypts are partially destroyed and infiltrated by neutrophil polymorphs to form crypt abscesses. These changes may be related to administration of suppositories.

**Conclusion:** Moderately differentiated rectal adenocarcinoma extending through bowel wall into fat, with lymph node metastases. Focal
granulomatous reaction to BCG injection. Superficial ulceration and acute inflammation at anal margin, possibly related to suppositories.

Comment

The first case showed no reaction of the rectal mucosa underlying the MHS(I) after 12 hours of exposure. However the second case showed inflammatory changes which may have been related to administration of suppositories. This patient had had a number of rectal examinations, enemata and the administration of BCG per rectum which necessitated the passage of a proctoscope on at least one occasion. The histological changes suggested an inflammatory process of more than 12 hours duration as shown by the presence of crypt abscesses. It was concluded that the changes were not solely the result of MHS(I) administration although a contribution could not be excluded.

4.4 DISCUSSION

This initial study is open to considerable criticism on many grounds. The study population is heterogenous, comprising patients of both sexes and a wide range of age and general health. One of the patients had undergone bowel preparation with phosphate enemata while the others had not. The possible confounding factor of anaesthesia was present during the sampling period in four of the subjects, although generally only for the last few hours.

The assay technique was newly developed and while the extraction from aqueous samples was satisfactory, difficulties were experienced with plasma samples. No assay was available at that time for the measurement of M6G or other metabolites of morphine and it was impossible to determine whether there was any cross-reactivity between the compounds. A rapid decline in plasma morphine concentrations was seen in the volunteer studies described in Chapters 7 and 8 after the withdrawal of the MHS(I). The assay used on those occasions was specific for morphine and its principle metabolites and had been extensively validated. It must be concluded that the assay used in the present study was not specific for morphine and that there was cross-reactivity with either morphine metabolites or some other unknown compound.

The failure to find any residual morphine in the retrieved MHS(I) was also surprising in view of the incomplete hydration but no obvious reason could be found despite a review
of the methodology. A possible explanation is that the contained morphine was eluted into a large quantity of water which was left on the laboratory bench in bright sunshine. It is possible that the dilute solution of morphine was hydrolysed and was thus not detectable with the assay.

Nevertheless, the studies confirmed the original supposition that the MHS(I) was capable of releasing morphine over sustained periods of time and that it was absorbed by the rectal mucosa in sufficient amounts to have an analgesic and sedative effect and to be detectable by the assay used. The concentrations were about two-thirds of those commonly measured in patients following surgery in the laboratory at Leicester Royal Infirmary, where the assays were undertaken.

Morphine was detected in the plasma of all patients at the first sample point, 30 minutes after administration of the MHS(I). The values were not greatly different from those seen at later time points. This suggests that the "bolus" release mechanism of the MHS(I) was effective and that it was possible to rapidly achieve effective plasma concentrations. Those measured towards the end of the study period were also comparable to those at the beginning and end of the study period suggesting that the predicted zero-order release was being achieved and was able to sustain the plasma concentrations. An alternative explanation is that the true concentration of morphine was declining but cross-reactivity in the assay and a rising concentration of metabolites gave the appearance of a sustained plasma concentration.

As noted above, the greatest plasma concentrations and the most variability were seen in Patient 1 after the first administration. This subject was also the only one to have had bowel preparation with both oral mannitol and phosphate enemata. Several compounds have been shown to enhance rectal absorption of drugs (Nakanishi et al., 1983b) and these are discussed in Section 1.4.4 and listed in Table 1.2. The effects of mannitol are principally on the large intestine by the osmotic retention of water. The phosphate enema contains a high concentration of sodium, the absorption of which seems to be a major mechanism for facilitating drug absorption in the rectum. A typical Fletcher's phosphate enema (Pharmax) has a sodium content of 1088 mmol.L⁻¹, about six times that of plasma and an osmolality of 3196 mosmol.kg⁻¹. The effect of the enema on the mucosal cells as barriers to the absorption of drugs is unknown but it would be reasonable to suppose that paracellular absorption would be enhanced. Both mannitol and the phosphate enema also may reduce and disrupt the mucus layer, thus reducing the diffusion distance and
increasing the effective absorptive area by allowing a better and closer contact between the MHS(I) and the rectal mucosa.

The high osmolality of the two preparations would also tend to draw water into the bowel and dilute the mucus. There would thus be more water available for rehydration of the MHS(I) and less osmotic composition with the mucins (Section 3.2.4). Morphine release and absorption would thus be quicker although it might be offset by an increase in the thickness of the mucus layer.

The withdrawal mechanism was robust and was successful in all but one subject where no trace of the MHS(I) could be found. Either it had migrated further up the rectum beyond the reach of the nurses' finger or it had been passed without patient or nursing staff being aware. The former explanation is most likely. However the nursing staff were of the opinion that the silicone collar was likely to be traumatic and complicated the insertion. There were no subsequent complaints from the patient of anal irritation or injury or difficulty with defaecation.

4.5 CONCLUSIONS

The conclusion of these initial studies was that the MHS(I) had potential for the administration of morphine by the rectal route. Modifications would be necessary and these would comprise an increase in the total dose and the release rate, a means of varying the administered dose to allow for differences in patient size and analgesic requirements and an improved and stream-lined shape.

These modifications were incorporated into the second prototype MHS(I) (II) described in Section 3.3.4 and described in Chapter 5.
5.1 INTRODUCTION

The MHS(II) a and b described in Section 3.3.4 were evaluated as a premedicant in a further series of patients undergoing surgery. Plasma morphine concentrations and additional analgesic requirements were determined. The results of the study were presented to the Anaesthetic Research Society and published in abstract (Hanning et al, 1984) and as part of Hanning et al, 1988.

5.2 PATIENTS AND METHODS

Approval for the study was granted by the Ethics Committee of the Leicestershire District Health Authority. Twelve otherwise healthy patients of ASA grade I and II gave their informed consent to the study. All were to undergo surgery for which opioid analgesics would normally be required but which did not normally require any specific bowel preparation and were not on the rectum or anal canal. Patients were also excluded if they were receiving any morphine or codeine containing medication or were sensitive to opioids. They were also excluded if they had any disorder of the gastrointestinal tract which might interfere with rectal drug absorption (diarrhoea, constipation, haemorrhoids).

The patients underwent the usual ward preparation appropriate for their procedure. A pair of MHS(II) joined by a hydrogel rod was administered by the ward staff two hours prior to the anticipated operation time. The insertion technique was identical to that described in Section 4.2. The intention was that patients weighing less than 59kg would be given a pair of MHS(IIa) (Total dose 76mg, Bolus 12mg, Release rate 5mg.h⁻¹), those weighing 60-69kg would be given one MHS(IIa) and one MHS(IIb) (Total dose 103mg, Bolus 16mg, Release rate 6.5mg.h⁻¹) and those weighing more than 70kg would be given a pair of MHS(IIb) (Total dose 130mg, Bolus 20mg, Release rate 7.7mg.h⁻¹). This course was followed at the commencement of the study but due to shortage of MHS(IIb) suppositories, the latter four subjects, all of whom weighed more than 70kg, were given one MHS(IIa) and one MHS(IIb) (Total dose 103mg, Bolus 16mg, Release rate 6.5mg.h⁻¹).
Anaesthesia was induced and maintained at the discretion of the anaesthetist with the exception that no morphine was given. Additional analgesia intra-operatively was achieved with fentanyl, pethidine or phenoperidine and postoperatively with pethidine 100mg IM on demand. Anti-emetic drugs were not given unless required by the complaint of nausea or vomiting.

Venous blood samples were taken prior to insertion of the MHS and then 30, 60, 90, 120, 240, 360, 480 and 720 minutes thereafter. Samples were processed and the plasma morphine concentration measured in the same manner as described in Section 4.2.1.

An attempt was made to retrieve the MHS at the end of the study period and the residual morphine assayed as described in Section 4.2.1.

5.3. RESULTS

5.3.1. Clinical details

Twelve patients were given the MHS(II) of which six were female. Mean age (range) was 43.1 (18-68) and mean weight 76kg (47-105). One patient received a pair of MHS(IIa), six received an MHS(IIa) with an MHS(IIb) and five received a pair of MHS(IIb). The mean dose of morphine given was 112mg, 1.49mg.kg⁻¹ (1.21-1.73). Details of each patient are given in Table 5.1.

Nine patients required no additional analgesia throughout the operative period or in the postoperative period until after the attempt at MHS withdrawal. Three patients, all of whom were undergoing upper abdominal surgery (gastrectomy, vagotomy and pyloroplasty and cholecystectomy), required intra- and postoperative supplementary analgesia. No patient required an anti-emetic although one (Patient 6) was given droperidol 5mg IV as part of one anaesthetist's usual practice. One patient (No 10) who had had a cholecystectomy, complained of nausea but no treatment was required.

No problems were experienced in inserting the MHS. However, when attempts were made to remove the fully hydrated suppositories, in all cases the braided nylon thread cut through the hydrogel and removal was impossible. As all the patients were well, no further attempt at removal was made and all suppositories were subsequently passed at
<table>
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<tr>
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<th>Male</th>
<th>Female</th>
<th>Average Age</th>
<th>Average Dose</th>
<th>Average Weight</th>
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<td>82</td>
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<td>11</td>
<td>85</td>
<td>35</td>
<td>45</td>
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<td>1</td>
<td>37</td>
<td>70</td>
<td>35</td>
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<td>84</td>
<td>65</td>
<td>49</td>
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<td>1</td>
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<td>63</td>
<td>33</td>
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<tr>
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<td>1</td>
<td>39</td>
<td>84</td>
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<td>1</td>
<td>65</td>
<td>75</td>
<td>46</td>
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</tbody>
</table>

Table 5.1: Demonstrates demographic data, morphologic dosage, and dosage requirements and operation of patients given a prototype (MSPH): For...
defaecation without problems. In view of the delay in retrieving the suppositories no attempt was made to assay the residual morphine content.

5.3.2 Plasma morphine concentrations

In three subjects (Nos 7, 11, 12) no detectable peak corresponding to morphine could be detected on the chromatogram and there are therefore no results available for analysis. The plasma morphine concentrations with time for the remaining nine subjects are shown in Table 5.2 and Figures 5.1 and 5.2.

No morphine was detected in the plasma of three of the nine patients (2, 3, 10) 30 minutes after administration, in two at 60 minutes (3, 10), one at 90 minutes (10) and morphine was detectable in all patients by 120 minutes. There was an apparent peak corresponding to morphine in two patients (3, 6) in the samples taken prior to administration.

The general pattern of plasma morphine was a slower rise than with the MHS(I) to a plateau at about four hours after administration. The mean plasma morphine concentration at this point was about 17 ng.ml⁻¹, although there was a three fold difference between the least and greatest values achieved (10-30ng.ml⁻¹). There were no apparent differences between the patient with the least concentration and the patient with the greatest concentrations. The morphine dose (mg.kg⁻¹) was greater in the former patient than the latter (1.73 vs 1.56mg.kg⁻¹).

There was no relationship between the dose of morphine, expressed as mg.kg⁻¹, and the plasma concentration measured six hours after administration which was taken as representing the "plateau" concentration (Figure 5.3). There was a tendency for there to be an inverse relationship between dose and plateau concentration but this was not statistically significant.

5.4. DISCUSSION

The results confirmed the findings of the initial pilot study that the MHS were capable of attaining and maintaining plasma morphine concentrations which were either analgesic or near-analgesic. A variety of surgical procedures were undertaken but all are acknowledged as inducing pain which would be expected to be classed as moderate to severe and to require opioid analgesics during the procedure and in the early
Table 5.2: Plasma morphine concentrations in nine subjects and mean and SEM values after the administration of a prototype NISP4

<table>
<thead>
<tr>
<th>Time</th>
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<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
<th>P10</th>
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<td>90</td>
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</table>

Note: The table shows the plasma morphine concentrations in nine subjects following the administration of a prototype NISP4, with data expressed at specific time points and mean±SEM values.
Figure 5.1. Plasma morphine concentrations in 9 patients given a prototype MHS(II) suppository.
Figure 5.2. Plasma morphine concentrations in 9 patients given a prototype MHS(II) suppository. Mean (SEM)
Figure 5.3. Relationship between plasma morphine concentration 6h after an MHS(II) and morphine dose
postoperative period. Nine of the 12 patients required no other analgesics during the study period.

In three of the patients, morphine was not detectable for up to 60 minutes after administration and in two for up to 90 minutes. The "plateau" morphine concentrations in these patients were also amongst the smallest. All three of these patients were undergoing major upper abdominal surgery and all required supplementary analgesia both intra- and postoperatively. The reason for the lesser morphine concentrations is unknown but several possibilities exist.

The most likely is the introduction of the MHS into a rectum already full of faeces. This would result in a delayed absorption as morphine diffused through the faeces to the rectal wall. The longer diffusion distance would also result in a lesser but more prolonged absorption. As the plasma morphine concentrations were not followed beyond 12 hours and the MHS could not be removed, the total morphine absorbed could not be determined and this must remain a matter for conjecture.

An alternative explanation would be that absorption was at a normal rate in these subjects but that a greater proportion of the absorbed morphine was subject to first-pass hepatic metabolism. These patients may also have had a greater capacity for metabolising morphine. At the time that this study was conducted, no assay for M-6-G was available and its contribution to the analgesic properties of morphine not realised. If these suppositions were correct then it might be expected that the quality of the analgesia in these patients would be as good or better than the others. These patients were the only ones to require additional analgesia, suggesting that these suppositions are incorrect. However, the patients were also undergoing procedures which are generally regarded as very painful and the question remains open.

It is of interest that all three patients were undergoing major abdominal surgery and some factor related to the surgery might have affected absorption. It is possible that these patients were under greater psychological stress than the other patients because of the nature of the surgery to be performed. The stress could have induced a reduced mucosal blood flow and thus impaired absorption. This is known to occur in the gastric mucosa, but not whether the rectal mucosa is similarly affected. Gastrointestinal motility would also have been affected but this factor does not normally affect rectal absorption unless it also causes constipation. The nursing staff did not report any evidence of constipation.
when the MHS were inserted but they did not perform a full digital examination of the rectum.

It is very unlikely that the differences in plasma concentration were due to differences in morphine dose. Figure 5.3 shows that there was no relationship between the weight adjusted morphine dose and the plasma morphine concentration six hours after administration which was taken as representing the "plateau" concentration. This also suggests that it is unnecessary to produce a variety of different dosages.

Only one of the patients, who had undergone a cholecystectomy, complained of nausea and none vomited. In an unselected group such as that studied, the incidence of nausea and vomiting can not be reliably estimated. However, as these patients would otherwise have been given injectable opioids a significant proportion would have been expected to have become nauseated or vomited. The MHS thus appears to be associated with a reduced incidence of these complications. The probable explanation is that the analgesic plasma concentration is achieved without the peak plasma concentrations associated with parenteral administration.

The MHS(II) proved to be easier to insert than the MHS(I) and no complaints were received from either nursing staff or patients. All patients reported that the devices were not uncomfortable while in situ but several reported that they were aware of their presence. It is not known whether this was a genuine sensation or a reaction to the insertion of a suppository and a knowledge of its presence. Removal of the fully hydrated suppository proved to be impossible, with the thread cutting through the swollen hydrogel with less force than was required to extract the device through the anal sphincter. All the devices were subsequently expelled at the next defaecation without difficulty. One problem that was not envisaged was the separation of the two halves of the MHS when partially swollen. This was probably due to the wall of the MHS swelling at a faster rate than the linking rod. The rod, therefore, did not reach to the ends of the cavities and the swelling tended to squeeze the two halves apart and allowed them to separate.

Despite the apparent safety of the device, concern over delayed absorption and difficulty in removing the MHS raised the possibility of overdosage if they were given at regular intervals. Continuing release from the original device combined with the bolus release of the second could result in a sufficient increase in plasma morphine concentration to cause
an overdosage. Continuing administration of morphine with the MHS would require both an improved withdrawal mechanism and a device without the bolus release.

5.5. CONCLUSIONS

The MHS(II) were capable of attaining and maintaining plasma morphine concentrations which are analgesic or near-analgesic. Considerable variation exists between individuals with regard to plasma concentration but not to a greater extent than may be seen after oral administration. Further development was indicated and, in particular, the development of a sustained release only device, without an initial bolus dose, and investigation of the changes in plasma morphine concentration following the insertion of a second dose. These matters were addressed in the third prototype study described in Section 3.3.5 and Chapter 6.
6.1 INTRODUCTION

The bolus + sustained release MHS(B) and the sustained release alone (MHS(S)) described in Section 3.3.5. were compared in a group of healthy women undergoing hysterectomy. The principal aim of the study was to determine the changes in plasma morphine concentration over the period when the MHS(B) was replaced by the MHS(S) and to determine the ability of the devices to maintain the plasma morphine concentration up to 24 hours. Secondary aims were to compare the analgesic efficacy and side effects of MHS supplemented by additional opiates with those of morphine IM on demand.

The study was open because placebo suppositories were not available and because the necessity to compare two techniques precluded such a trial design.

A preliminary report of this study was presented to the VIIth European Congress of Anaesthesiology, 7-13th September 1986 and the abstract published in the meeting report (Hanning et al, 1986) and a fuller account published in Hanning et al, 1988.

6.2 METHODS

6.2.1. Patients

Following approval by the Ethics Committee of the Leicestershire District Health Authority, the informed consent of healthy women (ASA grades I and II) scheduled to undergo abdominal hysterectomy was obtained. They were excluded if they had any evidence of renal or hepatic disease or any other disorder likely to influence the course of the study. They were also excluded if they were receiving any opioid analgesics prior to surgery.

All patients were starved from the night prior to surgery and all were given a simple phosphate enema the day before surgery.

Patients were randomly allocated to one of two groups:
**MHS group**

These women were given an MHS(B) two hours prior to surgery and an MHS(S) 12 hours thereafter. The technique of insertion was as described in Section 4.2. Those patients weighing less than 70 kg were given the lesser dose (Low dose: 103 and 73mg respectively) and those weighing 70kg or greater were given the greater dose (High dose: 130 and 110mg respectively). An attempt was made to retrieve the MHS at the 12 hour time point before the insertion of the MHS(S) and at 24 hours. Further postoperative analgesia was provided with pethidine 100mg IM on demand at the discretion of the ward nursing staff. Nausea or vomiting was treated with metoclopramide 10mg IM or prochlorperazine 12.5mg IM at the discretion of the nursing staff who were instructed only to give an anti-emetic in the event of patient complaint rather than as a routine with each dose of analgesic.

The choice of anaesthetic technique was at the discretion of the anaesthetist except that intraoperative analgesia was supplemented with fentanyl or pethidine and no morphine was administered.

The number and magnitude of doses of supplementary analgesia and anti-emetic medication and their timing was recorded for the intraoperative and postoperative period.

**IM Morphine group**

These patients were given morphine 10mg IM with metoclopramide 10mg one hour prior to the expected operation time. Postoperatively, analgesia was provided with morphine 10mg IM on demand at the discretion of the ward nursing staff. Nausea or vomiting was treated with metoclopramide 10mg IM or prochlorperazine 12.5mg IM at the discretion of the nursing staff who were instructed only to give an anti-emetic in the event of patient complaint rather than as a routine with each dose of analgesic.

The choice of anaesthetic technique was left to the discretion of the anaesthetist, including the choice of any additional intraoperative analgesia.

The number and magnitude of doses of supplementary analgesia and anti-emetic medication and their timing was recorded for the intraoperative and postoperative period.
6.2.2. Plasma morphine concentrations

Venous blood was sampled from the patients receiving MHS at 4, 12, 13, 14 and 24 hours after dosing and at equivalent times in the patients receiving IM morphine. No attempt was made to synchronise the administration of IM analgesia and blood sampling. The samples were separated, stored and analysed as described in Section 4.2.1.

Retrieved MHS were stored at -20°C and an attempt made to measure the residual morphine as described previously.

6.2.3. Symptom scoring

10 cm Linear analogue scales (LAS) were used to assess the symptoms of pain, nausea, sedation and dizziness. Four parallel 10 cm horizontal lines, representing each of the symptoms as listed, spaced down a single sheet of paper were presented to the patients 4, 8, 12 and 24 hours after the administration of the MHS and the equivalent time in the IM morphine group. The left hand end of each line represented the absence of the symptom and the right hand end represented the worst possible manifestation of the symptom. A fresh sheet was used for each time point and the patient was invited to make a short vertical mark on the line to indicate the severity of the symptom at that time point. In addition patients were asked at the 24 hour time point, after they had completed the four symptom sheet to complete two further LAS which represented their assessment of the average and maximum pain experienced over the whole of the study period.

Patients who were asleep at the times of LAS measurements were not woken but pain was scored as zero and sedation as 10. No values were recorded for nausea and dizziness and those time points were omitted from the analysis.

The Rank Sum test was used to compare the symptom scores between groups and a p of <0.05 was taken as statistically significant.

Patients were also asked at the 24 hour time point to rate the quality of pain relief, discomfort of the technique and their preference in comparison to the other technique with a five point scale (Table 6.1). Opportunity was also given for any spontaneous comments to be recorded.
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<td>Strongly Disagree</td>
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<td>Agree</td>
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</tr>
</tbody>
</table>

The method of delivery was preventative to support/expectation. Cause any discomfort. The expectation of the patient was not met during the operation. Pain relief after the operation.

Prototype Study II Table 6.1
6.3. RESULTS

18 women entered the study, eight received MHS and ten received morphine IM. Three were withdrawn, one in the MHS group and two in the IM morphine group. The withdrawal in the MHS group (No: 13) was a 54 years old woman who underwent an uneventful total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO). A low dose MHS(B) was administered 1.75 hours prior to surgery. Pethidine 100mg and prochlorperazine 12.5 mg was administered 5.25 hours thereafter. 8.25 hours after MHS administration she became pale and hypotensive. The MHS was removed and she was returned to the operating theatre where intra-abdominal haemorrhage was controlled. She made an uneventful recovery. The first withdrawal in the IM morphine group (No: 11) underwent uneventful TAH and LSO. She received two doses of morphine 10mg, one preoperatively and one 4 hours later. Nine hours after the initial dose of morphine she developed a rash over the face, neck and torso which was thought to be related to morphine and the analgesic was changed to pethidine. A single dose of chlorpheniramine 10mg was given and the rash resolved. The second withdrawal (No: 15) did not undergo a TAH.

In addition to the MHS(B) mentioned above removed after 8.25 hours, three of the MHS(B) were removed intact at 12 hours (No: 3,5,14) and four MHS(S) at 24 hours. In the other cases, a straight pull could not be achieved on the device and the thread cut through the swollen gel. The devices were subsequently passed at defaecation without problems. No injury was caused to any patient during attempted or successful withdrawal. Once again the attempt to measure the residual morphine in the MHS was unsuccessful.

The demographic details and analgesic and anti-emetic requirements for the seven patients in the MHS group and the eight patients in the IM morphine group are given in Tables 6.2 and 6.3. There were no significant differences between the groups with respect to age, height and weight. The MHS group received an average of 350mg of pethidine (range 100-500) in 3.6 doses (1-5) in the postoperative period. The IM group received an average of 41mg of morphine (range 10-60) in 4.3 doses (range 3-6). There were no significant differences in this respect. The MHS group received a mean of 11mg of metoclopramide (range 0-20) and 16mg prochlorperazine (range 0-75) in a mean of 2.1 doses (range 0-7). The IM morphine group received a mean of 20mg of metoclopramide (range 0-60) and 41mg prochlorperazine (range 0-75) in a mean of 5.3 doses (range 4-7). The difference in the number of doses of anti-emetic was statistically significant (p<0.05).
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*Note: M9S = Menstrual age, H9S = Hemoglobin level, N9S = Number of doses, P9S = Prenatal age.*
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Note: These data are preliminary and subject to further refinement and analysis.
6.3.1 Plasma morphine concentrations

The plasma morphine concentrations in the individual patients are shown in Table 6.4 and displayed graphically in Figures 6.1, 6.2 and the mean values in Figure 6.3. Some values were not available due to difficulty with the analysis in three of the seven subjects given MHS and one of the subjects given IM morphine. The mean plasma morphine concentrations were approximately twice as great in the group given IM morphine (9ng.ml⁻¹ c.f. 16ng.ml⁻¹). The plasma morphine concentrations in the MHS group tended to remain steady throughout the study period whereas those in the IM morphine group tended to decrease with time. One subject in the MHS group showed an increased plasma morphine concentration at 24 hours compared with earlier values (No 5). This subject had no measurable plasma morphine 4 hours after insertion of the MHS suggesting a delayed absorption. The MHS in this patient were both withdrawn intact, suggesting that full hydration had not taken place. There was much greater variability in the plasma morphine concentrations in the IM morphine group.

An attempt was made to analyse the retrieved MHS for morphine content as described previously but again, no values could be obtained.

6.3.2 Symptom scores

The LAS symptom scores for individual subjects are given in Tables 6.5-6.8 and shown graphically in Figures 6.4 and 6.5. Pain scores were less in the MHS group at all time points but were not statistically significant. The average and maximum pain scores were also less in the MHS group and in the case of the latter value was statistically significant (p<0.05). Nausea scores also tended to be less in the MHS group although there were no statistically significant differences. There were no differences between the groups with respect to sedation and dizziness.

Patients who received MHS were generally satisfied with the quality and comfort of the analgesic technique and preferred it to injections (Table 6.9). One patient in the MHS group (No 3) complained of discomfort shortly after insertion of the MHS. This was found to be due to the device being positioned in the anal canal rather than the rectum. It was inserted further and the patient did not complain of any further discomfort. In contrast, those given IM morphine were less satisfied. One preferred injections to suppositories and another expressed the contrary view. The majority had no opinion.
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Figure 6.1. Plasma morphine concentrations (ng.ml\(^{-1}\)) in seven patients given an MHS(B) followed by an MHS(S).
Open symbols: High dose, Closed symbols: Low dose.
Figure 6.2. Plasma morphine concentrations in eight patients given morphine IM on demand following hysterectomy
Figure 6.3. Mean (SEM) plasma morphine concentration in patients given an MHS(B) followed by an MHS(S) (n=7) ○ and in patients given IM morphine on demand (n=8) ○
Table 6.5. Linear analogue pain scores in women given prototype MHS(B) followed by MHS(S) and in those given IM morphine. Times are from insertion of MHS and equivalent times for the IM morphine patients. S: Asleep, NS: not significant.

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Table 6.6. Linear analogue nausea scores in women given prototype MHS(B) followed by MHS(S) and in those given IM morphine. Times are from insertion of MHS and equivalent times for the IM morphine patients. S: Asleep, NS: not significant.

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Figure 6.4. Linear analogue scores for pain (above) and nausea (below) in women given MHS (left bars) and IM morphine (right bars). *: p<0.05 between groups.
Table 6.7. Linear analogue sedation scores in women given prototype MHS(B) followed by MHS(S) and in those given IM morphine. Times are from insertion of MHS and equivalent times for the IM morphine patients. 10: Asleep, NS: not significant.

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Table 6.8. Linear analogue dizziness scores in women given prototype MHS(B) followed by MHS(S) and in those given IM morphine. Times are from insertion of MHS and equivalent times for the IM morphine patients. S: Asleep, NS: not significant.

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Figure 6.5. Linear analogue scores for dizziness (above) and sedation (below) in women given MHS (left bars) and IM morphine (right bars).
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24 hours after administration of the MSH (t).

Table 6.9, Answer to Patient Questionnaire administered to women given either placebo MSH (t) followed by MSH (t) or the hormone.
6.4. DISCUSSION

The study again confirmed that MHS were able to attain and maintain steady plasma morphine concentrations. It also suggested that there was little likelihood of overdosage if an MHS(B) was followed by an MHS(S). The analgesia provided by the MHS was as good or better than that provided by IM morphine and required fewer injections. Only one patient in the MHS group complained of severe pain (LAS >8.0) at one time point while three patients in the IM group had similar complaints at a total of four time points. This suggests that the variability in analgesia with the MHS is less than with IM morphine.

The plasma concentrations of morphine achieved were less than those found in the previous study (Section 5) although the doses administered were comparable and the \textit{in vitro} release profiles were similar. There are several possible explanations for this observation. Firstly, the stress of impending abdominal surgery reduced mucosal perfusion in the rectum and delayed absorption. This would be supported by the observation that the patients in the previous study with delayed absorption were all undergoing abdominal procedures (Section 5.4). However, anaesthesia would be expected to return rectal mucosal blood flow and thus absorption to normal. This would have tended to give an increasing plasma concentration. This pattern was not observed although the lack of measurements before the four hour time point makes it difficult for this point to be clearly answered. Secondly, the hydrogel may have failed to hydrate \textit{in vivo} at the same rate as in previous studies and \textit{as in vitro}. Manufacture of the hydrogel is complex and minor changes in procedure can alter its properties markedly. This latter explanation is thought to be the most likely. Unfortunately, assay of the withdrawn MHS for residual morphine content was not possible and the theory cannot be confirmed.

The study also confirmed the suggestion in the previous study that use of the MHS was associated with less nausea. The MHS group had lesser nausea scores although the difference was not statistically significant. They also required fewer doses of anti-emetic ($p<0.05$). However, this conclusion must be treated with some suspicion. Despite the instructions to the ward nursing staff to only give anti-emetics when indicated, an examination of the timing of the injections suggests that they followed their usual practice of giving an anti-emetic with an analgesic. This seemed to be particularly true for the IM group. However, despite the increased administration of anti-emetic drugs, the IM morphine group had greater rather than lesser LAS for nausea suggesting that the hypothesis was correct that the MHS was less likely to cause nausea. Two possible explanations can be advanced. Firstly, that the avoidance of sudden variations in plasma
morphine concentration is effective in reducing nausea and secondly, that pethidine is less likely to cause the symptom. There is no clear evidence in favour of the latter point and most authorities, if they comment at all, suggest that the emetic potential of pethidine is similar to that of morphine in equi-analgesic doses.

Removal of the fully hydrated MHS was again very difficult. The swollen hydrogel again fractured readily and was easily cut by the thread. Traction along the length of the device proved to be difficult to achieve and it commonly buckled before fracturing. However, the ability to withdraw the partially hydrated device and the safety factor that that bestows was illustrated by one case who became hypotensive as a result of blood loss where the MHS was removed as part of resuscitation.

The results of the study were not as clear cut as had been hoped. It was clear that further development would be needed on release rates and on the likely maximum duration of release. Information published shortly after completion of the study, on the analgesic potency of morphine-6-glucuronide (Osborne et al., 1988) suggested that further information on the rectal bioavailability of morphine by the rectal route and the production of morphine-6-glucuronide would be of value.

Although the implications of the MHS for the management of chronic pain were recognised, no attempt had been made to study such patients as it was felt to be unethical to do so when the supply was uncertain. It would have been wrong to offer a patient such treatment and then not to have been able to maintain it had it been successful. However, a single patient was treated, without the author's consent, and the results are described below.

6.5 CHRONIC PAIN: CASE REPORT

The patient was a 53 year old male admitted to Leicester General Hospital on the 20th December 1986. He complained of abdominal pain, weight loss and fatigue. Examination revealed a large abdominal mass which on investigation proved to be an inoperable renal tumour with probable bone and lung metastases. He complained of increasing pain which was initially treated with mild analgesics (Distalgesic) but which required the addition of sublingual buprenorphine on the 22nd December. This proved ineffective and he was commenced on morphine elixir and slow release morphine tablets (MST, Napp Laboratories) on the 23rd December. Pain control was initially satisfactory but was associated with increasing sedation and nausea so that by the 17th January the patient
was refusing the proffered morphine elixir and food. A small stock of prototype morphine hydrogel suppositories were held by the Pharmacy which were surplus to the preliminary studies reported by Hanning et al. (1988). It was decided that, in view of the patient's desperate condition and prognosis, a trial of MHS was justified. He was given a total of seven suppositories over a four day period from the 18th to 22nd January 1987. His general condition improved such that he slept better, became much less nauseated and drowsy and began to take some food. Oral morphine elixir was recommenced and he was restabilised on oral medication. Pain control remained adequate and he was transferred for radiotherapy. He died on the 12th February 1987. Post mortem examination was not performed.

6.5.1. Comment

This patient was the first with chronic pain to be treated with Morphine Hydrogel Suppositories. The very small stock of suppositories available to us prevented treatment for more than a few days. However, they were effective in re-establishing pain control in a patient suffering from intractable nausea and vomiting induced by oral morphine. The clinical response was most gratifying and was an indication of what might be possible when supplies were adequate.

6.6. CONCLUSIONS

The study further confirmed the ability of the MHS to deliver morphine by rectal administration and that successive doses were feasible and safe. The complexity of the present system was impractical from a manufacturing standpoint and simpler structures would be required. The difficulty in withdrawal of fully swollen MHS due to the fragility of the hydrogel was a drawback and further development was warranted.

Nevertheless, the prototype studies were felt to be a sufficient indication of the potential clinical applications and commercial value for further studies to be undertaken. At this point in the development, Advanced Therapeutics Systems (latterly Controlled Therapeutics) and Polysystems became involved in the project. It was felt that further studies should be in volunteers to reduce the inter-subject variability and these are described in Sections 3.3.6-8.
7.1 INTRODUCTION

Previous studies in patients had suggested that the MHS were capable of maintaining steady plasma concentrations of morphine. The first volunteer study was undertaken to investigate the absorption of morphine from MHS(IV) and the production of metabolites in the more controlled situation of healthy male volunteers.

7.2 METHODS

7.2.1. Volunteers

Six male volunteers aged between 20 and 35 years gave informed written consent to the study which was approved by the local Ethics committee. All gave a full medical history and underwent a physical examination prior to the study. Blood was taken for an automated full blood count and biochemical screen (SMA12). Urine was taken for standard urinalysis (Bililabatric) and screening for drugs of abuse. Subjects were excluded if they displayed any evidence of renal, hepatic or psychiatric disease or had a history of abuse of drugs or alcohol. They were also excluded if they were not within 10% of ideal body weight (Metropolitan Life Insurance Tables). Subjects were observed by the author and a trained research nurse throughout the study period which was conducted in the Day Ward of Leicester Royal Infirmary.

7.2.2. Study conduct

A venous cannula was inserted in the non-dominant arm and a 10ml blood sample taken. Baseline measurements of pulse and respiratory rates, arterial blood pressure (sphygmomanometer) and oral temperature were taken together with five point verbal rating (VRS) and 10cm linear analogue scores (LAS) of sedation, nausea and dizziness.

Subjects were questioned to ensure that their rectum had been emptied by recent defaecation. A 100mg MHS(IV) was then inserted by the research nurse with the subject in the right lateral position. A small quantity of water-soluble gel (K-Y jelly) was used to lubricate the MHS(IV). Care was taken to ensure that the MHS(IV) was placed just inside
the rectum. The MHS(IV) was removed 12 h after insertion, examined, weighed and stored at -70°C for measurement of residual morphine.

Blood samples were taken 2, 3, 5, 6, 8, 10, 12, 15, 18 and 24 hours after insertion of the MHS(IV) for measurement of plasma morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). Observations were repeated at 2, 4, 6, 8, 10 and 12 h after insertion. Measurements of vital signs were made at 14, 16, 18, 20 and 24 hours and the VRS and LAS measured if the subject was awake. Consecutive 12 h urine collections were taken during the study period for measurement of morphine and metabolites.

Subjects were discharged from the study facility when they were alert and symptom-free.

7.2.3. Plasma morphine assays

Venous blood was collected into heparinised polypropylene tubes, centrifuged immediately and the plasma stored at -70°C until analysis. The concentrations of morphine, M6G and M3G in plasma and urine were measured by high pressure liquid chromatography (HPLC) using electrochemical and fluorosence detection (Joel et al., 1988). The lower limits of detection were 1ng.ml^-1, 1ng.ml^-1 and 5ng.ml^-1 and the interday coefficients of variation were 5.2%, 6.2% and 4.5% for the assay of morphine, M6G and M3G respectively. Coefficients of variation were calculated from the assays of standard solutions of 10, 20 and 30ng.ml^-1 for morphine and M6G and 100, 200 and 300ng.ml^-1 for M3G.

The residual morphine content of the MHS(IV) was assayed by swelling in a 2:1 solution of acetonitrile and ethanol, grinding in a blender to ensure full extraction and subsequent measurement by HPLC.

The areas under the concentration curves from time zero to 24 h (AUC_{0-24}) for morphine and metabolites were calculated using the trapezoidal method.

7.3 RESULTS

One of the volunteers had a plasma gamma glutaryl transferase activity of 91iu.ml^-1 (normal for males <50iu.ml^-1) which was thought to be related to earlier alcohol ingestion. All other liver function tests were normal but he was excluded.
One other subject had a serum inorganic phosphate concentration of 0.68 mmol.l\(^{-1}\) (normal range 0.8-1.4 mmol.l\(^{-1}\)). This was not regarded as clinically significant and he was included in the study.

The demographic data and the dose of morphine administered to the five subjects (A-E) are shown in Table 7.1. All completed the study period and were fit for discharge after 24 h.

7.3.1. Plasma morphine concentrations

The plasma concentration-time profiles for morphine and its metabolites in each of the volunteers are shown in Figures 7.1-3 and Tables 7.2-4. The plasma concentrations of both morphine and its metabolites increased rapidly after insertion and had peaked by 4-5 hours. There was three-fold difference between the lowest and greatest concentrations. A steady concentration was maintained until withdrawal at 12 hours when the concentrations decreased rapidly in all subjects except one (C) where they were maintained up to the end of sampling although at a lesser concentration to the previous period. A "biphasic" pattern was seen in three of the subjects with a reduced concentration during the middle of the dosing period, increasing again just prior to removal. The differences were not great and might have been due to random variation.

The urinary excretion of morphine, M\text{6G} and M\text{3G} and the AUC\(_{0,24}\) for each subject is given in Table 7.5.

7.3.2. Symptom scores

Sedation was noted by all subjects, mainly during the early part of the study. The mean LAS was 2.3 cm (range 0-3.8) and was never sufficiently severe to prevent normal activities (watching television, reading, eating). Three subjects complained of nausea at one time point and one vomited after eating (attributed to an excess of pizza by the subject). Two complained of dizziness. At no time were the symptoms disabling and no treatment was required.

Symptom scores are shown in Tables 7.6-8.
Table 7.1 Demographic data and morphine dose of five volunteers given an MHS(IV) prototype morphine suppository containing a mean of 103.2mg of morphine.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Morphine residual (mg)</th>
<th>Morphine dose (%)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>28.4</td>
<td>74</td>
<td>1.75</td>
<td>44.3</td>
<td>58.9 (57)</td>
</tr>
<tr>
<td>B</td>
<td>23.1</td>
<td>76</td>
<td>1.81</td>
<td>49.6</td>
<td>53.6 (52)</td>
</tr>
<tr>
<td>C</td>
<td>20.3</td>
<td>60</td>
<td>1.64</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>32.4</td>
<td>84</td>
<td>1.83</td>
<td>59.2</td>
<td>44.0 (43)</td>
</tr>
<tr>
<td>E</td>
<td>22.5</td>
<td>73</td>
<td>1.78</td>
<td>40.4</td>
<td>62.8 (61)</td>
</tr>
</tbody>
</table>
Table 7.2. Plasma morphine concentrations (ng.ml$^{-1}$) with time in five volunteers (A-E) given an MHS(IV) prototype.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
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<td>6.80</td>
<td>10.50</td>
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</tr>
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<td>18.00</td>
<td>7.90</td>
<td>14.60</td>
</tr>
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<td>11.40</td>
<td>15.10</td>
<td>5.00</td>
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</tr>
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<td>16.50</td>
<td>7.30</td>
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</tr>
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<td>12.00</td>
<td>13.40</td>
<td>10.40</td>
<td>20.60</td>
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</tr>
<tr>
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<td>2.10</td>
<td>2.40</td>
<td>9.90</td>
<td>0.00</td>
<td>1.80</td>
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<td>2.30</td>
<td>8.20</td>
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</tbody>
</table>
Figure 7.1 Plasma morphine concentrations with time in five volunteers given an MHS(IV) prototype.
Subject A ○, B ●, C ▽, D ▼, E □
Table 7.3. Plasma morphine 6 glucuronide concentrations (ng.ml\(^{-1}\)) with time in five volunteers (A-E) given an MHS(IV) prototype.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
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<td>34.00</td>
<td>32.40</td>
<td>34.90</td>
<td>10.20</td>
<td>40.40</td>
</tr>
<tr>
<td>3.00</td>
<td>47.70</td>
<td>41.50</td>
<td>40.10</td>
<td>17.10</td>
<td>39.90</td>
</tr>
<tr>
<td>5.00</td>
<td>60.20</td>
<td>42.10</td>
<td>44.10</td>
<td>20.70</td>
<td>36.70</td>
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<td>60.20</td>
<td>21.60</td>
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</tr>
<tr>
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<td>55.50</td>
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</tr>
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<td>30.60</td>
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</tr>
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<td>25.30</td>
<td>3.20</td>
<td>4.80</td>
</tr>
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</table>
Figure 7.2. Plasma morphine 6 glucuronide concentration with time in five volunteers given an MHS(IV) prototype.

Subject A O , B ● , C ▼ , D ▼ , E □
Volunteer Study 1. Table 7.4

Table 7.4. Plasma morphine 3 glucuronide concentrations (ng.ml\(^{-1}\)) with time in five volunteers (A-E) given an MHS(IV) prototype.

<table>
<thead>
<tr>
<th>Time (Hours)</th>
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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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Figure 7.3 Plasma morphine 3 glucuronide concentration with time in five volunteers given an MHS(IV) prototype.

Subject A ○, B ●, C ▽, D ▼, E □
Table 7.5. AUC(0-24) and urinary excretion of morphine, morphine 6 glucuronide (M6G) and morphine 3 glucuronide (M3G) in the first 12 hours (0-12) and the second 12 hours (12-24) in five volunteers given an MHS(IV) prototype.

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC(ng.ml⁻¹.h⁻¹)</th>
<th>Urinary excretion (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M6G</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>M6G</td>
</tr>
<tr>
<td>A</td>
<td>337</td>
<td>964</td>
</tr>
<tr>
<td>B</td>
<td>271</td>
<td>711</td>
</tr>
<tr>
<td>C</td>
<td>347</td>
<td>998</td>
</tr>
<tr>
<td>D</td>
<td>114</td>
<td>381</td>
</tr>
<tr>
<td>E</td>
<td>190</td>
<td>767</td>
</tr>
</tbody>
</table>

Volunteer Study 1. Table 7.5
Table 7.6 Verbal rating scores (VRS) (1=none, 2=mild, 3=moderate, 4=severe, 5=intolerable) and Linear analogue scores (LAS) (10cm scale) for sedation in five volunteers (A-E) given an MHS(IV) prototype. S= subject asleep.

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
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<td>LAS</td>
<td>VRS</td>
<td>LAS</td>
<td>VRS</td>
</tr>
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<td>0</td>
<td>1</td>
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<td>1</td>
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<td>18</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<td>1</td>
<td>0</td>
<td>1</td>
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</table>
Table 7.7 Verbal rating scores (VRS) (1=none, 2=mild, 3=moderate, 4=severe, 5=intolerable) and Linear analogue scores (LAS) (10cm scale) for nausea in five volunteers (A-E) given an MHS(IV) prototype. S= asleep

<table>
<thead>
<tr>
<th>Subject</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<tbody>
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<td>LAS</td>
<td>VRS</td>
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</tr>
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<tr>
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<td>S</td>
<td>S</td>
<td>S</td>
</tr>
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<td>24</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 7.8 Verbal rating scores (VRS) (1=none, 2=mild, 3=moderate, 4=severe, 5=intolerable) and Linear analogue scores (LAS) (10cm scale) for dizziness in five volunteers (A-E) given an MHS(IV) prototype. S= asleep

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Subject</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
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<tr>
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<td>LAS</td>
<td>VRS</td>
<td>LAS</td>
<td>VRS</td>
<td>LAS</td>
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<td>4</td>
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<td>1.3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1.0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0.5</td>
<td>1</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
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<td>0.5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>0.3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
7.3.3. MHS(IV) insertion and withdrawal

Insertion of MHS(IV) was satisfactory in four volunteers (ABCE) and could not be detected by them when in situ. One subject (D) complained of discomfort which persisted throughout the study period. Examination of the MHS(IV) on removal showed that the base was poorly hydrated. The residual morphine content was greater and the average plasma morphine and metabolite concentrations less than those in other subjects. This was the only MHS(IV) removed intact. All of the others fragmented with the thread separating from the hydrated gel. However, and in all subjects but one (C) they were completely retrieved by a combination of manual removal and voluntary straining at stool. In this subject less than 50% of the MHS(IV) was retrieved and he had morphine and metabolite concentrations consistently greater than the other subjects during the second 12 h period. Although well at 24 h and considered fit for discharge at approximately 10am, he subsequently reported that he slept for most of the rest of the day.

7.4 DISCUSSION

The study confirmed that MHS(IV) were capable of attaining and maintaining plasma morphine concentrations for up to 12h and with a suggestion that it was capable of delivery for up to 24h. Support for this assertion comes from the residual morphine content of the MHS(IV) which showed that only 43-55% of the contained morphine was released in the 12h administration period. This contrasts with the in vitro release profile which showed c80% release in the same time period. Further support for the potential 24h release profile comes from volunteer C in whom only about 20-30% of the MHS(IV) could be retrieved at the 12h point. He continued to show mild sedation for up to 36h and his plasma morphine concentration was 8.2ng.ml⁻¹ at 24h in contrast to the other subjects which ranged from <1.0-2.3ng.ml⁻¹.

The mean plasma morphine concentration in this study was about 15ng.ml⁻¹ during the "steady state" period from 4-12h after administration. Savarese and colleagues (Savarese et al., 1986) gave morphine 30mg twice daily orally as a sustained release preparation (MS-Contin, Purdue-Frederick) to volunteers for three days. Plasma morphine concentrations were measured by an RIA method but were corrected to be comparable with an HPLC method using a factor given by the authors. Trough and peak plasma morphine concentrations were 3.5 and 12ng.ml⁻¹ respectively. Similar results were obtained by Shepard and colleagues (Shepard et al., 1988) with two different sustained release tablets which gave a mean plasma morphine concentration of 13ng.ml⁻¹, although this study used an RIA and the accuracy of the assay must be in doubt. Osborne (personal communication)
gave a 10mg sustained release preparation (MST, Napp Laboratories) in a single dose to volunteers and obtained mean plasma morphine concentrations of 2.5ng.ml$^{-1}$. A clinical study of patients treated chronically with oral morphine in a mean dose of 184mg daily (range 60-600mg) showed mean plasma morphine concentrations measured by HPLC of 35ng.ml$^{-1}$ (Sloan et al., 1987). A small study of six patients given oral sustained release morphine sulphate tablets (MST) 30mg 12 hrly showed a peak and trough plasma morphine concentration of 30 and 13ng.ml$^{-1}$ respectively (Anzalone et al., 1989). The latter group concluded that a plasma morphine concentration of 13ng.ml$^{-1}$ was appropriate for analgesia in their patients. Extrapolating from these studies suggests that the MHS(IV) used in the present study is equivalent to about 100-120mg of oral morphine. It is at least equipotent at these doses.

Increased potency implies that there has been some bypassing of first-pass metabolism. The ratio of the AUC$_{0-24}$ for morphine to that of M6G in the present study was a mean of about 3.0 (Table 7.9). In contrast, that of Osborne (Osborne et al., 1987) for oral administration was 8.6. This might suggest a considerable bypassing of first-pass metabolism. However, this is not entirely supported from a consideration of the ratios of peak concentrations. The ratio between the C$_{max}$ for morphine and M6G in the present study was about 3.5 which is not dissimilar to a value of 4.0 reported by Osborne and a value of 3.9 reported by McQuay in a study of patients receiving chronic oral treatment (McQuay, personal communication). The overall conclusion is that there is some bypassing of first-pass metabolism which is in accord with Jonsson and colleagues (Jonsson et al., 1988). The effect of any differences between oral and rectal administration on analgesic efficacy remains to be determined.

The ability to remove the MHS in the event of overdosage or adverse reaction is one of the principal potential advantages of the technique. The present study confirmed that removal by means of a string is impossible with a fully hydrated suppository due to the tendency of the crystalline gel to fracture. Clearly, improvements to the withdrawal mechanism are necessary if such a mechanism were deemed necessary.

A further concern was the possibility that a reservoir of morphine might develop in the rectum, stored in mucus or faecal material. This does not seem to be the case as plasma morphine concentrations declined rapidly in the four subjects in which complete removal was achieved. The circumstances of the study were not appropriate for the calculation of elimination constants but the rate of decline was similar to that seen in single dose parenteral studies where the elimination half-life was calculated at about 2-3 hours.
Table 7.9. AUC(0-24h) for morphine, morphine 6 glucuronide and morphine 3 glucuronide (same data as in Table 7.5) and ratios of the metabolites to morphine in five volunteers given an MHS(IV) prototype.

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC(ng.ml(^{-1}.h(^{-1}))</th>
<th>AUC ratio</th>
<th>AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M6G</td>
<td>M3G</td>
</tr>
<tr>
<td>A</td>
<td>337</td>
<td>964</td>
<td>6418</td>
</tr>
<tr>
<td>B</td>
<td>271</td>
<td>711</td>
<td>4186</td>
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<tr>
<td>C</td>
<td>347</td>
<td>998</td>
<td>7609</td>
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<td>D</td>
<td>114</td>
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<td>2532</td>
</tr>
<tr>
<td>E</td>
<td>190</td>
<td>767</td>
<td>6458</td>
</tr>
<tr>
<td>Mean</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The present study also emphasised the importance of placing the MHS in the rectum. Subject D complained of discomfort throughout the study and on removal of the MHS(IV) it was found to be unevenly hydrated. His plasma morphine and metabolite concentrations were less than those of the other subjects and the residual morphine in the withdrawn MHS(IV) proportionately greater. Education of inserters of the device, greater use of lubricant or the use of an introducer will be necessary for future development. The latter proposal will be particularly necessary if self insertion is to be considered.

7.5 CONCLUSION

Prototype IV seemed to be capable of attaining and maintaining plasma morphine concentrations close to those necessary for analgesia in some patients with chronic pain. Bioavailability seemed to be better than with oral medication and it seemed probable that it could be a once-a-day preparation. Further investigation and development was appropriate.
8.1. STUDY II: INTRODUCTION

The previous volunteer study had confirmed the ability of the MHS to maintain plasma concentrations of morphine for 12 hours and the experience in one subject suggested that it could be maintained for 24 hours. It was clear that in vivo rehydration of the MHS was about half as fast as in vitro and that as a consequence only half the predicted dose of morphine was released and absorbed. It was thus evident that two further areas of study were necessary, one to investigate possible reasons for the slow in vivo rehydration and the other to investigate the feasibility of using the MHS as a 24 hour preparation. The former is described in Section 9 and the latter in this chapter.

8.2. METHODS

8.2.1. Subjects

Six healthy male volunteers gave their informed consent to the study which was conducted at the Leicester Clinical Research Centre. The volunteers were paid an inconvenience allowance. The Centre's independent Ethics Committee gave its consent to the study. Subjects were to be aged between 18 and 50 years and were to be normal on physical, biochemical and haematological investigation. Subjects would be excluded if they had any allergy or sensitivity to morphine or related compounds. They would be excluded also if they had any history suggestive of addiction or abuse of any drug or if a urine drug screen (Toxilab) showed the presence of any compounds of abuse. Subjects who had participated in other analgesic trials within the preceding 3 months or any trial where narcotic analgesics were administered within the previous 12 months were excluded also.
8.2.2. Study Conduct

Subjects were admitted to the study facility the night prior to administration of the Prototype MHS(V) described in Section 3.3.7. The physical and laboratory investigations outlined above were performed as was the screening for drugs of abuse.

On the following morning subjects were asked to empty the bladder and an aliquot was kept for analysis for morphine content. An indwelling venous cannula was inserted and a 10 ml sample of blood collected into heparinised polypropylene tubes for analysis for morphine content. Samples were centrifuged at 1200 g for 10 minutes at room temperature and the plasma separated and stored at -20°C until analysis.

The prototype MHS(V), within an ovenet, was inserted into the rectum by a trained nurse with the subject in the lateral position. A small quantity of aqueous gel (KY Jelly) was permitted to facilitate insertion into the rectum. Subjects were then permitted to move around the facility as they felt able. Blood pressure, heart rate and respiratory rate were monitored and recorded at regular intervals throughout the study period. The adequacy of respiration was monitored using a pulse oximeter while the subjects were asleep. A normal diet was permitted except that breakfast was omitted on the morning of dosing. In accordance with the standard procedures of LCRC, no xanthine containing drinks were permitted.

Samples of venous blood (10ml) were taken through the cannula at 2,3,5,6,8,10,12,15,18 and 24 hours after dosing and at 30 and 36 hours post dosing after the MHS(V) had been withdrawn. Three consecutive 12 hour urine collections were made and a 10ml aliquot frozen for future analysis.

The MHS(V) was withdrawn using the ovenet and withdrawal thread after 24 hours and note made of the ease of withdrawal, the presence of any irritation or injury to the rectum and anus and whether the MHS(V) could be withdrawn intact.

At the end of the study, volunteers were asked to complete a brief questionnaire seeking their views on the ease of insertion of the MHS(V), whether they were aware of its presence both initially and before withdrawal, the length of the retrieval cord and the ease of removal of the MHS(V).
The nursing staff responsible for insertion of the MHS(V) were asked to complete a similar questionnaire.

All subjects returned to the centre ten days after completion of the study for a routine examination and check of laboratory values.

8.2.3. Plasma morphine assays

Venous blood was collected into heparinised polypropylene tubes, centrifuged immediately and the plasma stored at -70°C until analysis. The concentrations of morphine, M6G and M3G in plasma and urine were measured by high pressure liquid chromatography (HPLC) using electrochemical and fluorescence detection (Joel et al., 1988). The lower limits of detection were 1ng.ml⁻¹, 1ng.ml⁻¹ and 5ng.ml⁻¹ and the interday coefficients of variation were 5.2%, 6.2% and 4.5% for the assay of morphine, M6G and M3G respectively. Coefficients of variation were calculated from the assays of standard solutions of 10, 20 and 30ng.ml⁻¹ for morphine and M6G and 100, 200 and 300ng.ml⁻¹ for M3G.

The residual morphine content of the MHS(V) was assayed by swelling in a 2:1 solution of acetonitrile and ethanol, grinding in a blender to ensure full extraction and subsequent measurement by HPLC.

The areas under the concentration curves from time zero to 24 h (AUC₀₋₂₄) for morphine and metabolites were calculated using the trapezoidal method.

8.3. RESULTS

Six subjects, all male, were recruited and completed the study which was uneventful.

The MHS(V) were found to have delivered a mean of 52mg of morphine (56% of content) (range 44-59). Of the mean of 41mg remaining in the MHS(V) and overnet, 35mg was in the MHS(V) (range 27-42) and 6mg in the overnet (range 3-9). Mean swelling was only 168% of dry weight (range 156-175)(weight 4.1-4.4g) (Table 8.1)
Volunteer studies II&III. Table 8.1

Table 8.1. Morphine dose, weight, area under the curve to 36h (AUC\textsubscript{0-36}), AUC\textsubscript{0-36} corrected to a weight of 70kg, C\textsubscript{max} and T\textsubscript{max} in six volunteers given an MHS(V) prototype suppository with an overnet.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dose (mg)</th>
<th>Weight (kg)</th>
<th>AUC\textsubscript{0-36} (ng.ml.h\textsuperscript{-1})</th>
<th>AUC\textsubscript{0-36 (wt)} (ng.ml.h\textsuperscript{-1})</th>
<th>C\textsubscript{max} (ng.ml\textsuperscript{-1})</th>
<th>T\textsubscript{max} (h)</th>
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<td>1</td>
<td>52</td>
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<td>213</td>
<td>240</td>
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<td>6</td>
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<td>57</td>
<td>68.4</td>
<td>208</td>
<td>186</td>
<td>13.4</td>
<td>8</td>
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<td>3</td>
<td>51</td>
<td>70.8</td>
<td>147</td>
<td>142</td>
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<td>10</td>
</tr>
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<td>4</td>
<td>44</td>
<td>68</td>
<td>77</td>
<td>91</td>
<td>7.1</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>64</td>
<td>208</td>
<td>193</td>
<td>19.3</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>63.6</td>
<td>193</td>
<td>221</td>
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<td>5</td>
</tr>
<tr>
<td>Mean</td>
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<td>66.2</td>
<td>175</td>
<td>179</td>
<td>12.7</td>
<td>7.3</td>
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<tr>
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<td>3.4</td>
<td>53</td>
<td>54.5</td>
<td>4.6</td>
<td>2.3</td>
</tr>
</tbody>
</table>
8.3.1. Plasma morphine and metabolite concentrations

The plasma morphine and metabolite concentrations increased rapidly and peaked at around 6-8 hours after dosing (Figures 8.1-3). The mean plasma morphine concentration at this point was only 10ng.ml\(^{-1}\). It subsequently declined to a concentration of 4-5ng.ml\(^{-1}\) until removal of the MHS(V) when the concentration declined rapidly.

The plasma concentration-time curves for the metabolites, M6G and M3G were similar to that of morphine with mean ratios of morphine to M6G of about 1:4-5 and of morphine to M3G of 1:20. The pharmacokinetic variables for morphine and metabolites are shown in Table 8.2 and the residual morphine content of the retrieved MHS, overnet and plastic retrieval bag are shown in Table 8.3.

8.3.2. Adverse events

Nine adverse events were recorded in five subjects (range 1-3). No specific treatment was required and all were classed as mild. They included one episode of repeated hypoxaemia (SpO\(_2\) <90%) lowest value 86%, during sleep which resolved with arousing the subject. Dizziness was noted in three subjects on four occasions and responded to rest in recumbency in all cases. Constipation, headache and bradycardia (<40bpm) were noted in one, one and two subjects respectively.

The pattern and incidence of adverse events is less than that seen in the previous study and reflects the lesser plasma concentrations of morphine.

8.3.3. MHS(V) insertion and withdrawal

One subject found the MHS(V) easy to insert while the remainder graded it as giving some difficulty. Three were very definitely aware of the MHS(V) immediately after insertion, while two rated it as significant and one slightly. By the end of the study period, only one subject was very definitely aware of the MHS(V), one could not detect its presence and the remainder were slightly aware of its presence. Two graded the removal as easy while the remainder experienced some difficulty.
Figure 8.1 Plasma concentration of morphine with time in six volunteers given an MHS(V) prototype with an overnet.
Figure 8.2. Plasma concentrations of M-6-G with time in six volunteers given an MHS(V) Prototype with an overnet.
Figure 8.3. Plasma concentrations of M–3–G with time in six volunteers given an MHS(V) Prototype with an overnet.
Table 8.2. AUC_{0-36}, C_{max} and T_{max} for M6G and M3G in six volunteers given an MHS(V) prototype suppository with an ovemet.

<table>
<thead>
<tr>
<th>Subject</th>
<th>M-6-G</th>
<th></th>
<th>M-3-G</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AUC_{0-36}</td>
<td>C_{max}</td>
<td>T_{max}</td>
<td>AUC_{0-36}</td>
</tr>
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<td>(ng.ml.h^{-1})</td>
<td>(ng.ml^{-1})</td>
<td>(h)</td>
<td>(ng.ml.h^{-1})</td>
</tr>
<tr>
<td>2</td>
<td>836</td>
<td>43</td>
<td>5</td>
<td>3578</td>
</tr>
<tr>
<td>3</td>
<td>646</td>
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<td>3372</td>
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</tr>
<tr>
<td>6</td>
<td>831</td>
<td>52</td>
<td>5</td>
<td>4101</td>
</tr>
<tr>
<td>Mean</td>
<td>758</td>
<td>47</td>
<td>5.8</td>
<td>3907</td>
</tr>
<tr>
<td>SD</td>
<td>114</td>
<td>6.2</td>
<td>1.2</td>
<td>743</td>
</tr>
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</table>
Table 8.3. Residual morphine content (mg) in the MHS, overnet and containing plastic bag and dose delivered in six subjects given an MHS V prototype suppository with an overnet.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Residual morphine content (mg)</th>
<th>MHS</th>
<th>Overnet</th>
<th>Bag</th>
<th>Total</th>
<th>Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.11</td>
<td>3.65</td>
<td>0.01</td>
<td>40.77</td>
<td>52.23</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>27.18</td>
<td>8.89</td>
<td>0.02</td>
<td>36.09</td>
<td>56.91</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33.62</td>
<td>7.95</td>
<td>0.03</td>
<td>41.6</td>
<td>51.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42.39</td>
<td>6.55</td>
<td>0.01</td>
<td>48.95</td>
<td>44.05</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30.86</td>
<td>3.00</td>
<td>0.02</td>
<td>33.88</td>
<td>59.12</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>38.5</td>
<td>6.33</td>
<td>0.04</td>
<td>44.87</td>
<td>48.13</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>34.94</td>
<td>6.06</td>
<td>0.02</td>
<td>41.02</td>
<td>51.98</td>
</tr>
</tbody>
</table>
The nursing staff responsible for the study did not report any difficulty in insertion of the device but reported some difficulty in withdrawal and noted some blood staining in three cases. There were no reports of injury to the anal canal and no longer term sequelae.

8.4. DISCUSSION

The study confirmed that the MHS(V) is capable of releasing morphine for 24 hours. The plasma concentrations obtained were about half of those seen in the previous volunteer study with a device with a different shape but similar in vitro release profile. The major difference between the two devices was the provision of the overnet in the present study. It is likely that the presence of the device stimulated the production of mucus which formed a layer around the bag and between the MHS(V) and the overnet. This would have taken some hours to develop fully and may explain the early peak and subsequent decline in plasma morphine concentrations. The shape of the MHS(V) would have contributed also in that mucus would have accumulated in the grooves between the ribs. The mucus layer would have constituted a diffusion barrier to morphine by lengthening the diffusion pathway and by increasing the thickness of the unstirred barrier layer immediately adjacent to the surface of the hydrogel. Diffusion from the hydrogel in the grooves would have been much slower than from the ribs due to the thicker layer of overlying mucus.

The observation that the morphine release was in proportion to the swelling suggests that the trapped mucus may have also been a barrier to diffusion of water into the hydrogel.

The pattern of metabolite concentrations once again provides evidence of some by passing of first pass metabolism in that the ratios of morphine to metabolites is less than with oral administration.

8.5. CONCLUSIONS

The study confirmed the ability of the MHS(V) to deliver morphine for prolonged periods and emphasised the importance of the rate of hydration of the hydrogel in regulating drug release. The overnet was clearly not suitable as a retrieval technique and alternative methods would be required if a withdrawal mechanism was felt to be necessary for the marketed preparation. The inherent safety of the MHS(V) was further demonstrated and supported the view that a withdrawal mechanism might not be
necessary, particularly as effective safe antidotes for morphine are readily available and manual extraction of the device would always be possible.

8.6. STUDY III: INTRODUCTION

The influence of the overinet on morphine release and the added confidence in the inherent safety of the system led to the third volunteer study which followed an almost identical protocol to that described in sections 8.1-5, with the exception that the MHS(V) was inserted without a withdrawal mechanism.

8.7 METHODS

8.7.1. Subjects

Twelve healthy male subjects gave their informed consent to the study after approval by an independent Research Ethics Committee. The study was carried out at the Leicester Clinical Research Centre. The admission and exclusion criteria were identical to those given in Section 8.2.1.

8.7.2. Study Conduct

Subjects were admitted to the study facility the night prior to administration of the Prototype MHS(V) described in Section 3.3.7. The physical and laboratory investigations outlined in Section 8.2.1 were performed as was the screening for drugs of abuse.

On the following morning subjects were asked to empty the bladder and an aliquot was kept for analysis for morphine content. An indwelling venous cannula was inserted and a 10 ml sample of blood collected into heparinised polypropylene tubes for analysis for morphine content. Samples were centrifuged at 1200 g for 10 minutes at room temperature and the plasma separated and stored at -20 C until analysis.

The prototype MHS(V), without an overinet, was inserted into the rectum by a trained nurse with the subject in the lateral position. A small quantity of aqueous gel (KY Jelly)
was permitted to facilitate insertion into the rectum. Subjects were then permitted to move around the facility as they felt able. Blood pressure, heart rate and respiratory rate were monitored and recorded at regular intervals throughout the study period. The adequacy of respiration was monitored using a pulse oximeter while the subjects were asleep. A normal diet was permitted except that breakfast was omitted on the morning of dosing. In accordance with the standard procedures of LCRC, no xanthine containing drinks were permitted.

Samples of venous blood (10ml) were taken through the cannula at 2,3,5,6,8,10,12,15,18 and 24 hours after dosing, at removal or passage of the MHS(V) and at 6 and 12 hours post dosing thereafter. Three consecutive 12 hour urine collections were made and a 10ml aliquot frozen for future analysis.

Subjects were asked to pass the MHS(V) 24 hours after insertion by voluntary effort. If unsuccessful then they were asked to continue voluntary expulsion for a further six hours when a glycerine suppository was inserted.

At the end of the study, volunteers were asked to complete a brief questionnaire seeking their views on the ease of insertion of the MHS(V), whether they were aware of its presence both initially and before expulsion, and the ease of expulsion of the MHS(V).

The nursing staff responsible for insertion of the MHS(V) were asked to complete a similar questionnaire.

8.7.3. Plasma morphine assays

Sample handling, analysis and data analysis was as described in Section 8.2.3

8.8. RESULTS

Twelve subjects, all male, were recruited and completed the study which was uneventful.

Mean retention time for the MHS(V) was 28 hours (range 24.17-35.75). Nine of the subjects were able to expel the MHS(V) voluntarily by straining at stool. Three required assistance, two by administration of a glycerine suppository and the third by manual evacuation using a gloved finger (his own).
The MHS(V) were found to have delivered a mean of 72.5mg of morphine (78% of content) (range 60-87mg) (Table 8.4). Mean swelling was 164% of dry weight (range 132-184)(weight 3.696-4.537g). Three of the retrieved MHS(V) were noted to be curved suggesting uneven rehydration and they tended to have swollen less than those that were straight. One was split into two pieces but was complete, while two were noted to have small pieces missing.

8.8.1. Plasma morphine and metabolite concentrations

The plasma morphine and metabolite concentrations increased rapidly after insertion and decreased rapidly after expulsion or removal (Figures 8.4-6). Mean plasma concentrations together with those for Volunteer study II (Section 8.3.1) are shown in Figures 8.7-9. In several subjects, a "biphasic" pattern of plasma concentration was seen with an increase in morphine concentrations just before expulsion or removal (Figure 8.4 and 7). Mean peak plasma morphine concentration was 17.1ng.ml⁻¹ (range 9.5-35.2) and occurred a mean of 9.3 hours after dosage (range 2-25). The pharmacokinetic data for morphine are given in Table 8.4.

The plasma concentration-time curves for M6G and M3G were similar to those of morphine (Figures 8.7-8). The AUC, Cmax and Tmax values are given in Table 8.5. The mean ratio of morphine to M6G and M3G were 1:3.5 and 1:13 respectively.

8.8.2. Adverse events

The adverse event profile was similar to that seen in Volunteer study II. 10 events were reported by 9 subjects. Four felt nauseated or vomited, two felt dizzy, one complained of constipation, one of backache, one of stomach ache and one of a blocked nose. The first four symptoms were attributed to the study drug and the remainder to incidental causes.

8.8.3. MHS(V) insertion and withdrawal

Insertion was rated as easy by seven subjects and causing some difficulty in five. Five subjects were aware of the MHS(V) immediately after insertion, two slightly, one significantly and two very definitely. Five subjects were aware of the MHS(V) just before expulsion, three slightly, one significantly and one very definitely.
Table 8.4. Dose of morphine administered, body weight, duration of administration, AUC to end of sampling (AUC_{0-tm}), AUC corrected to weight of 70kg, $C_{\text{max}}$ and $T_{\text{max}}$ in twelve volunteers given an MHS(V) prototype suppository without an overrun.

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<th>Subject</th>
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<th>Weight (kg)</th>
<th>Time (h)</th>
<th>AUC_{0-tm} (ng.mL.h^{-1})</th>
<th>AUC_{0-tm} (wt) (ng.mL.h^{-1})</th>
<th>$C_{\text{max}}$ (ng.mL^{-1})</th>
<th>$T_{\text{max}}$ (h)</th>
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<tr>
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Figure 8.4. Plasma Morphine concentrations with time in 12 subjects given an MHS(V) prototype suppository without an overnet. ↓ indicates time of withdrawal.
Figure 8.5. Plasma M6G concentrations with time in 12 subjects given an MHS(V) prototype suppository without an overnet. Indicates time of withdrawal.
Figure 8.6. Plasma M3G concentrations with time in 12 subjects given an MHS(V) prototype suppository without an overnet. \( \downarrow \) indicates time of withdrawal.
Figure 8.7. Mean (SD) plasma morphine concentrations with time in 12 volunteers given an MHS(V) prototype suppository without an overnet (○) and six volunteers given the same MHS with an overnet (●).
Figure 8.8. Mean (SD) plasma M6G concentrations with time in 12 volunteers given an MHS(V) prototype suppository without an overnet (○) and six volunteers given the same MHS with an overnet (●).
Figure 8.9. Mean (SD) plasma M3G concentrations with time in 12 volunteers given an MHS(V) prototype suppository without an overnet (○) and six volunteers given the same MHS with an overnet (●).
Volunteer studies II&III. Table 8.5

Table 8.5. AUC₀-tₚ, Cₘₐₓ and Tₘₐₓ for M6G and M3G in 12 volunteers given an MHS(V) prototype suppository without an ovemet.

<table>
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<th>M-3-G</th>
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<tr>
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<td>Tₘₐₓ</td>
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</tr>
<tr>
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<td>(h)</td>
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The nurses rated insertion as easy in 10 subjects and presenting slight difficulty in two.

As noted above, nine subjects were able to voluntarily expel the MHS(V) within a mean time of 4 hours from first request to expel (range 10min to 5h45min). Three subjects required assistance, two with a glycerine suppository and one removed the MHS(V) himself using a gloved finger. Four subjects rated the removal as easy, six as giving some difficulty and two as very difficult. No long term sequelae were reported at the routine follow-up visit.

8.9. DISCUSSION

The study described in Sections 8.6-8 confirmed that the MHS(V) without an ovacet were capable of attaining and maintaining plasma morphine concentrations suitable for analgesia for periods of at least 24hours. The plasma morphine concentrations were greater than those in Volunteer study II but were in keeping with the increased dose released (Mean AUC corrected for wt and dose 3.51 v 3.64 ng.m\(^{-1}.h\)l.70kg\(^{-1}.mg\)l). Plasma morphine concentrations were well maintained even in those subjects where expulsion was delayed for nearly 12 hours.

The biphasic pattern in plasma morphine concentrations was most marked in five subjects and has several possible explanations. Firstly, there might have been a reduction in absorption during the time 12-18 hours after dosing. This would have coincided with sleep in the subjects and it is possible that gut blood flow was reduced in parallel with a reduction in gut motility. Secondly, enterohepatic recirculation of morphine may have occurred. This explanation is the most likely and the mechanism is discussed in Section 2.1.4.

The ratio of morphine to its metabolites was lower than is seen with oral administration (Section 2.1.3) confirming considerable by-passing of first-pass hepatic metabolism. There were marked differences between subjects in the degree of hepatic metabolism. Subject 1 absorbed morphine well, 85% of the administered dose in 25.5 hours of exposure. Plasma morphine concentrations were high and metabolite ratios low (morphine:M6G, 1:2) suggesting less influence of hepatic metabolism while subject 11 had similar absorption (89% of dose in 32.8 hours) but lower plasma morphine concentrations and higher M:M6G ratio of 1:8 suggesting greater hepatic metabolism.
The mean ratios of M:M6G and M3G increased during the study period from 1:3 to 1:4 and 1:10 to 1:15 respectively. This suggests that either morphine absorption was taking place higher in the rectum thus exposing more of the drug to first pass hepatic metabolism or liver enzyme induction had taken place. Whatever the reason, the observation of increased conversion of morphine to its metabolites helps to explain the apparent decrease in plasma morphine concentrations during the study period.

The ability of 9 of the 12 volunteers to voluntarily expel the fully hydrated MHS(V) was encouraging despite the fact that most were either unaware or only slightly aware of its presence in the rectum. This suggests that repeated use in chronic pain patients might be easier than had been envisaged if no withdrawal mechanism was provided.

8.10. OVERALL DISCUSSION AND CONCLUSIONS

Comparison of the results of Volunteer studies II and III shows that the presence of the overnet was a major barrier to the rectal absorption of morphine from the MHS(V), the AUC being decreased by 56%. The overnet would have trapped a layer of mucus within its fibres and this would have hindered release of morphine by two mechanisms. Firstly, the mucus could have competed with the hydrogel for the available water and slowed rehydration. Secondly, it could have acted as a diffusion barrier, reducing the movement of morphine from the hydrogel to the mucosa and water to the hydrogel. The degree of swelling of the hydrogel was very similar in the two studies, suggesting that there was no effect of the overnet on swelling and that any effect of an increased mucus layer on water diffusion was minimal. The second explanation is therefore the more likely that the thickness of the mucus layer was the limiting factor in drug release and absorption. The importance of the mucus layer for absorption of drugs is discussed in Section 1.4.1.

The overall pattern of plasma morphine concentration with time suggested that the release from the MHS(V) was following first order rather than zero order kinetics, that is the release decreased with time rather than staying steady. As discussed in Section 3.2.4 and 3.3.7, the ideal release profile is most easily achieved from the surface of a block of hydrogel. This was initially obtained from a hollow cylinder which approximated to a "rolled up" thin block of hydrogel. Initial studies, Sections 4-7, suggested that a close to zero order release could be obtained. Production difficulties dictated that an alternative shape should be evaluated and the four and five ribbed structures were developed which approximate to a "corrugated and rolled up" thin block of hydrogel. In vitro studies using standard USP dissolution apparatus (Section 3.3.7) showed that this shape could...
achieve close to zero order release. However, the in vivo studies suggested that this pattern was not achieved. The likely explanation for this is that the "grooves" between the ribs became filled with mucus forming a diffusion barrier. The amount of mucus held in the grooves and thus the thickness of the layer would increase with swelling as the overall dimensions of the device increased. As the mucus layer increased in thickness, so the diffusion distance would increase and release would be impaired.

Several conclusions may be drawn from these studies. Firstly, that the MHS is a potential vehicle for the delivery of morphine by the rectal route as a once daily preparation for patients with chronic pain. Secondly, that the lack of a withdrawal mechanism is not a bar to successful use of the device as voluntary expulsion is successful in the majority of cases. The increased experience with the devices also strengthened the belief that the system was inherently safe as "dose-dumping" was impossible. Further studies in volunteers and patients are therefore merited and a planned programme is discussed in Section 10.

Thirdly, the vital role of the rectal mucus layer in controlling the absorption of drugs from devices such as the MHS is emphasised. Initial theories held that its main role was in competing with the hydrogel for available water. However, the studies described in this Section suggest that the major role may be as a diffusion barrier. It is possible that the two theories may overlap in that absorption of water from mucus adjacent to the surface of the hydrogel would make it more viscid and therefore potentially a greater barrier to drug diffusion. This is investigated further in Section 9 and discussed in Section 10.
The volunteer and patient studies described in the preceding chapters and the theoretical consideration outlined in Section Three show that the in vivo hydration and morphine release of the hydrogel suppositories is only about 50% of that achieved in vitro. There are three possible explanations for this observation. There may be insufficient water in the rectum to satisfy the requirements of the hydrogel. There may be oncotic competition for the available water between the rectal mucus and the hydrogel. The mucus may be a barrier to the diffusion of water from the mucosa to the hydrogel (Forstner, 1978). These possibilities are not mutually exclusive. There is no information on the normal balance of fluid secretion of fluid in the rectum but the volume of rectal fluid should be adequate to rehydrate the hydrogel. However, the quoted volume is based upon a single paper (Bitterman et al. 1967) and the method of collection, by aspiration, may have induced mucus secretion by physical irritation and thus over estimated the normal, resting volume. The hydrogel is only adjacent to a small part of the rectal wall (c.10%) and the water away from this area might not be freely available. In addition, not all the water may be available to the hydrogel as mucin holds water in the molecular structure. See Section 1.3.2.

Information on the factors influencing in vivo rehydration are important for clinical safety. For example, if an enema had been given shortly before administration of an MHS, as suggested by the first patient in Section 4, or the volume of mucus or its concentration was altered by disease such as colitis or a mucus secreting tumour, then swelling and morphine release might be increased resulting in relative overdosage.

This laboratory investigation was designed to determine the rate of hydration of hydrogel in mucus and to compare it with that in electrolyte solutions.

There are considerable problems in obtaining quantities of mucus for such a study. The composition and properties of mucus varies along the digestive tract and with time depending upon the activity of that part of the digestive tract and the presence of any irritation. Earlier studies made use of mucus obtained by scraping the lining of the intestines of animals, especially the pig, after slaughter. Separation of the mucus from
food residues is difficult and bacterial degradation of the mucus when kept at 37°C is very likely. One possibility is the use of saliva but it tends to be less viscous and more watery than intestinal mucus and bacterial contamination remains a problem.

It was therefore decided to use commercially available freeze dried mucin, this preparation is derived from animal sources but is processed in large batches and there is thus some standardisation. The preparation which renders it sterile probably denatures some of the mucin and reduces some of the cross linking. The concentration of mucin can be varied and thus the effects of "thick" and "thin" mucus can be simulated. The disadvantage of it not being a "natural" product were felt to be not such as to outweigh the difficulties of obtaining mucin direct from an animal or human source.

9.2 METHODS

Thirty six hydrogel suppositories (without morphine) of the shape and composition described in Section 3.3.7 except that the centre had not been drilled (Batch 0200:00896, manufactured 7/3/96, Core Technologies) and used in the volunteer studies described in Section 8, were divided into six groups of three. Groups of three were immersed in the test solutions for four time periods, 1, 2, 4 and 8 hours and in three different solutions, distilled water, mucin 2% and mucin 5%.

The mucus was reconstituted from a single batch of freeze-dried mucin prepared from pig stomach (Mucin type II, partially purified from Porcine stomach, Sigma Chemicals) and contained approximately 1% bound sialic acids. 200ml quantities were reconstituted by adding 4 and 10g of mucin powder respectively to 200ml of warm water to produce 2 and 5% solutions. The mucin powder was well mixed prior to being added to the water to eliminate any hard lumps. The solutions were stirred until as much as possible of the mucin had dissolved and then allowed to stand for 30 minutes and stirred again prior to use.

The dry hydrogels were individually weighed on electronic scales with an accuracy of ±10mg and placed in screw capped 20ml containers with sufficient of the test solution to ensure that they would be fully covered throughout the study period. At the end of the test period, the hydrogels were removed from the solution, rinsed quickly under a stream of water to remove all mucin, dried using absorbent paper and reweighed.
The results were tabulated and the mean percentage change in weight calculated for each time point and test solution.

9.3. RESULTS

There were no differences in rate of swelling between the three solutions (Tables 9.1-3, Figure 9.1).

The two mucin solutions were clearly of different consistency although they both coated the containers and the hydrogels but neither had the "slimy" feel of normal mucus or formed "strings" when poured.

9.4. DISCUSSION

The study showed that in the presence of excess mucin solution there was no competition between the mucin and the hydrogel for the available water. In the rectum, the water present should be sufficient for full hydration of the hydrogel, there being approximately 3.5ml of rectal fluid assuming that all the water is available to the hydrogel. In addition there is no reason to suppose that additional water could not diffuse freely from the rectal mucosa into the mucus layer. However, the rectal and colonic mucosa is adapted for the absorption of water as part of the physiological mechanisms for water conservation (see Section 1.3) and it is possible that diffusion of water into the mucus layer may not be unrestricted.

The reconstituted mucin solution clearly differs considerably from natural mucus and it is possible that the results obtained bear little or no relationship to those that might be obtained with natural mucus. However, the difficulties in obtaining a sufficient quantity of mucus of a composition which approximates to that of normal human rectal mucus are formidable and repetition of the experiment must await the development of alternative methods. These are developed in more detail in Section 10.

The most likely explanation for the slow in vivo swelling is that the hydrogel initially takes water from the surrounding mucus. Not all the water in the mucus is available and although initial swelling may be rapid, further water must be drawn from the mucosa and diffuse through the mucus layer which may constitute as significant a barrier to diffusion of water as it does to drugs. Morphine appears to have an anticholinergic effect on the
Table 9.1. Swelling of four-ribbed hydrogel with time in water at 37°C.

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<tr>
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In vitro swelling. Table 9.2

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Table 9.2. Swelling of four-ribbed hydrogel with time in mucin 2% at 37°C.
In vitro swelling. Table 9.3

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<th>Final weight (g)</th>
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Table 9.3. Swelling of four-ribbed hydrogel with time in mucin 5% at 37°C.
Figure 9.1. Swelling (% of dry weight) of four-ribbed hydrogel in water ○, mucin 2% ● and mucin 5% ▽ with time at 37°C.
bowel (see Section 1.3) and the reduction in mucus production would tend to reduce the available water and ensure that the mucus was viscid and thus more of a barrier. However, in vivo swelling is less than in vitro even when blank hydrogels are used (McNeil, personal communication, 1994) and so the pharmacological effect of morphine may be relatively minor in affecting rehydration of the hydrogel.

9.5 CONCLUSION

The present study has served to confirm that, using reconstituted mucin, there is no competition between the mucin and hydrogel for the available water when mucin is present in excess. However, the results may bear little relationship to the conditions in vivo and further experiments are necessary.
The preceding sections have outlined the steps in the development of the MHS from a working hypothesis to a product with potential for use as a once daily analgesic for patients in chronic pain. The development is by no means complete but the present position marks the end of the prototype stage and the beginning of the studies necessary for registration of the formulation with the regulatory authorities and subsequent marketing. The work presented has raised questions regarding the physiology of rectal drug absorption, the evaluation of sustained release preparations, the future development of the MHS and its place in the armamentarium of drugs for the management of chronic pain. The purpose of this section is to discuss these issues and to outline further studies.

10.1. MHS IN THE TREATMENT OF CHRONIC PAIN

Morphine has been the preferred analgesic for the management of chronic pain for thousands of years, generally administered in an immediate release form as a solution or as a simple pill. As noted in Section 1 and 2, rectal formulations have been used also, particularly when the oral route was not available. The introduction of the hypodermic needle and syringe offered an alternative to rectal medication and a faster onset of action. Other sedative and centrally active drugs were often added to preparations of morphine and a wide variety of different formulations were available during the 19th and early part of the 20th century, e.g. Dover's powders and latterly the "Brompton cocktail".

A major drawback of morphine is that it has a relatively short elimination half-life of 2-4 hours and doses must be given as frequently as 3-4 hourly in some cases although 6 hourly is often regarded as the median frequency. Frequent administration is disliked by patients for several reasons. Firstly, the inconvenience of having to keep the formulation readily to hand which is restricting and embarrassing. Secondly, the variations in plasma concentration may increase the incidence of undesirable, dose related side effects such as sedation, nausea and vomiting. Thirdly, those patients who require more frequent dosing often find that their sleep is disrupted by pain and a dose in the middle of the night is required. An alternative is to give a double dose at sleep onset but this increases the risk of excessive sedation and increased side effects. A preparation which permits once or twice daily dosage is therefore of great value in these patients.
A large proportion of patients with chronic pain are unable to take oral medication at some point in their illness. The reasons for this inability include involvement of the disease process in the upper gastrointestinal tract, e.g. carcinoma of the oesophagus and infections of the upper gastrointestinal tract, e.g. candidiasis with oesophagitis. A further group of patients simply become too weak and debilitated to swallow in the terminal phase of the disease process. Others dislike taking tablets and prefer an alternative route of administration. The side effects of morphine, particularly nausea and vomiting are a problem with a further large group of patients. Episodes of nausea and vomiting may occur in some patients where a "vicious circle" may be set up. Some factor, such as an increase in morphine dose or disease progression causes nausea and vomiting, this decreases morphine absorption and exacerbates the pain. The reaction to this is often to increase the dose of oral morphine and administer an anti-emetic. In many cases this leads to further vomiting and so on. The usual response to this sequence of events is to transfer the patient to parenteral morphine and anti-emetic drugs when the symptoms will usually subside permitting a gradual return to oral medication. There is an impression that the oral administration of morphine is associated with a greater incidence of the side effect of nausea and vomiting than other routes of administration. This may be due to a direct effect of morphine on the stomach and upper intestine as well as an effect on the chemoreceptor trigger zone in the medulla. An alternative explanation is a difference in the pattern of metabolites between oral and other routes of administration, there being a greater conversion of morphine to M6G and M3G with the former route due to first pass hepatic metabolism (Osborne et al., 1989, Janicki et al., 1991). A further explanation for the difference in the pattern of metabolites would be differences in the metabolic enzymes of gut wall and liver. If the gut wall produced proportionately more M3G than the liver then this would contribute to the observed differences.

Differences in the pattern of metabolites have been implicated in the development of tolerance (Bowsher, 1993). A few patients with severe pain on large doses of morphine appear to develop "morphine resistant pain" where increasing the dose of morphine may paradoxically increase the pain. Studies by Cramond have suggested that high concentrations of M3G within the brain may have an antagonistic effect (Cramond and Smith, 1993). Increasing the dose of oral morphine, increases M3G production and further antagonises the morphine and M6G. Her response to these observations has been to treat such patients with very small doses of intrathecal morphine with good effect suggesting that the problem is not due to down regulation of receptors but due to antagonism by M3G.
Oral administration

There can be no doubt that the great majority of patients prefer to take oral medication in preference to parenteral or rectal medication and until 1981, this was satisfied with immediate release preparations of morphine either as tablets or as liquid formulations. The latter were often formulated with other compounds such as cocaine and phenothiazines to improve mood and reduce emetic side effects. In 1981, MST tablets were introduced by Napp Pharmaceuticals (Twycross, 1981). This formulation was based upon a waxy matrix which delayed the release of morphine and twice daily medication was advocated by the manufacturer. However, examination of the typical plasma concentration-time curve suggests that 8 hourly administration would be more appropriate and many authorities suggest changing from bd to tid dosing as requirements increase. A large number of studies have been conducted subsequently which show that the MST and related formulations from other manufacturers produce significant benefits to patients over immediate release morphine (see Hanks, 1990 and Thirlwell et al, 1990 for a review). These formulations now form the mainstay of the opioid management of chronic pain although they are not interchangeable (Bloomfield et al, 1993).

Further developments in oral medication include the introduction of much greater doses of morphine and a 200mg MST tablet has been recently introduced. Sustained release gel formulations are under development and will form a useful alternative for patients who can still swallow but have difficulty in taking tablets.

Nevertheless, there remains a considerable body of patients who can not or will not take oral medication both for short periods, possibly related to nausea and vomiting, and for prolonged periods, for example with head and neck or oesophageal cancer. These patients would require an alternative route of administration. A survey by Hoskin and Hanks (1988) of patients in an hospital based continuing care unit showed that while 82% of patients were successfully managed with oral morphine, 54% had to be given parenteral diamorphine at some point due to inability to take oral morphine. Only 3% received a rectal preparation. A more recent study (Brooks et al., 1995) of the practice in palliative care centres in Trent showed that 10.6% of those patients requiring strong opioids were using a non-oral route of administration, predominantly subcutaneous injection. Only one of 424 patients was receiving rectal morphine from immediate release suppositories. These studies emphasise the need for an alternative to oral medication in a large proportion of chronic pain patients but the present poor usage of the rectal route and is exemplified by the case report in Section 6.5.
A major concern in some countries has been the possibility of diversion of legally prescribed opioids to illicit purposes. This has often severely restricted the range of strong opioids available for prescription. Immediate release forms of drugs are most likely to be misappropriated and these include concentrated solutions in syringes or other reservoirs for parenteral use. Sustained release preparations are less easily diverted, particularly if the drug can not be readily extracted for immediate use.

Conclusions

Oral preparations of morphine will be suitable for most patients for most of the time. However, there is a significant group of patients who will need an alternative route of administration at some time. The next section reviews the available alternatives.

10.1.1. Alternative routes of administration

As noted above, there are a considerable number of patients for whom an alternative to oral medication is desirable. Parenteral, intrathecal, extradural, transdermal, inhaled, buccal and rectal have all been used and are appropriate for some patients.

Parenteral

Intramuscular, subcutaneous and intravenous administration by frequent intermittent administration or continuously by syringe pump are commonly used for inpatients. The frequent administration may be given by the staff or by the patient using a patient controlled analgesia system (PCAS). The two methods may be combined by using a continuous "background" infusion which the patient supplements by self-administered "demands" as necessary. Such systems are effective for initial titration of analgesic requirements or in an emergency when analgesic requirements are varying but the size and cost make them unsuitable for ambulatory or home use. Devices have been described which do not require electrical power but these are relatively unsophisticated and only permit either a continuous infusion or patient initiated demands.

Failure of the controller may result in sudden rapid administration of the contents of the reservoir with fatal consequences. Siphoning of the contents of the syringe into the patient from syringe drivers and PCAS pumps has been reported also.
The great advantage of parenteral administration is the ability to rapidly attain and maintain effective plasma concentrations of analgesic drugs and to vary the dosage to individual patient requirement. They would thus seem to be most useful for initiating pain control and when sudden changes in analgesic requirements might be expected, for example during or after a therapeutic intervention. The expense and complexity would seem to make them less suitable for routine use and the presence of a large reservoir of opioid raises concerns over dose-dumping or of diversion of the drug for illicit purposes.

Transdermal administration

The transdermal administration of opioids is not new. Discorides, a Greek physician, recommended patients over 2000 years ago to "take the seed of the poppy, finely ground, mix with water, make into a poultice and bind on the brow and temples". Other formulations advocated the addition of ant's eggs to the mixture, the formic acid presumably acting both as a counter-irritant and increasing skin blood flow and absorption. However, the relative insolubility and lack of potency or morphine make it an unsuitable drug for transdermal administration and the technique had to await more modern drugs before it could be successfully re-introduced.

Drugs of the piperidine series, including fentanyl, are suitable for transdermal administration being potent and having high lipid solubility. A delivery system was introduced in 1986 which comprised a drug reservoir with a rate-limiting membrane to control release which is applied to the skin (Caplan et al., 1986, Plezia et al., 1986). The system was able to maintain analgesic concentrations of fentanyl for periods of up to 72 hours. The onset time was delayed by up to eight hours and plasma concentrations decayed slowly after removal suggesting a substantial reservoir of the drug in the epidermis and dermis. The system has been shown to be effective in patients with cancer pain and has achieved popularity in some centres. However, it does not seem to have displaced morphine from its pre-eminent position as the analgesic of choice for chronic pain management. This may be due to the cost of the preparation as well as the difficulty in adjusting dosage and the delay in achieving effective plasma concentrations. It might be supposed that patients would be attracted to a device which appeared to be as convenient as a sticking plaster but this does not seem to be the case and it is possible that the therapeutic effect of the drug is not as good as that of morphine.

More recently, a technique has been described for applying drugs to a denuded area of dermis created by applying sufficient suction to create a blister and then deroofing the
blisters (Westerling et al., 1994). Absorption appears to be sufficient to achieve adequate concentrations of morphine in volunteers but the prospect of requiring a new raw area on the forearm every 3-4 days is unlikely to be attractive to patients.

**Buccal**

The buccal route for the administration of drugs has many similarities to the rectal route. The surface area for absorption is similar, about 200cm² and there is the potential for avoidance of first pass hepatic metabolism by absorption into the systemic circulation. Except for the most lipophilic of drugs, absorption is slow and is probably mostly through the stomach and small intestine via swallowed saliva. Buprenorphine, a partial agonist opioid has been used for several years but has never achieved a significant place in pain therapy due to its side effects (Hanning, 1985).

Morphine has been administered by the buccal route, but the absorption is poor and the bitter taste of the morphine has prevented further use. Muco-adhesive preparations are under investigation but their usage will be limited by the taste of the contained drug.

**Inhalation of drug**

The smoking of opium and absorption of morphine by inhalation has been practiced for many centuries and achieves a rapid increase in plasma concentration with ready titration of dosage. First pass hepatic metabolism would also be avoided. However, the problems of passive smoking are such that it is difficult to envisage that the method would become popular in Western medical practice.

Nebulised morphine and other analgesics have been used occasionally but have not been subject to rigorous study (Masters et al., 1985)

**10.1.2. Summary**

The evidence reviewed above suggests that there is a need for an alternative route to oral for the delivery of morphine from a sustained release vehicle. The rectal route is the only viable alternative as other routes are precluded either because absorption is ineffective or the means is cumbersome and expensive. The conclusion must be that the Morphine
Hydrogel Suppository has potential to provide an alternative to sustained release oral morphine when that route is unavailable or inappropriate.

10.2. FURTHER DEVELOPMENT OF THE MHS

10.2.1. Formulation

The studies set out in Sections 4-8 and the development described in Section 3 have demonstrated that the original hypothesis was correct, namely that the MHS was capable of delivering morphine over a prolonged period in a predictable manner. However, there are a number of areas which are less than satisfactory and require further development.

Release profile

The original intention was to produce a formulation with zero-order drug delivery kinetics. This was achieved with the original structure described in Sections 4-7 which was a hollow cylinder. This shape was selected as it approximated to the single surface of a slab described in Section 3.2.4. which has ideal release characteristics. Practical, manufacturing considerations dictated that the shape was changed to a ribbed structure described in Section 3.2.7. This had a good in vitro release profile but seemed to have first-order release when tested in vivo with decreasing release with time. The most likely reason for this difference was the collection of mucus in the grooves between the ribs thus effectively reducing the surface area available for diffusion. This was exacerbated by the addition of an overnet as a retrieval mechanism. The important role of mucus as a barrier to diffusion was not appreciated at the outset of the study but it is clear that any method which will reduce the thickness of the mucus layer will be important.

It is thus likely that future development of the MHS will see a return to the original hollow cylinder design but some compromise may be possible on the dimensions of the central cavity. One of the present difficulties is that the standard USP dissolution apparatus is of little value in assessing the likely in vivo performance of a preparation. The USP method is designed to eliminate any unstirred boundary layer between the preparation and the solvent whereas, in vivo, the boundary layer of fluid and mucus is a significant contribution to the rehydration of the hydrogel and the release of morphine.

The major difficulty in designing an in vitro test is the changing size of the hydrogel as it swells and the need to maintain a relatively constant layer of mucus over the surface of
the hydrogel. Simply dipping the dry hydrogel in mucus before rehydration would not be suitable as the thickness of the mucus layer would decrease as the hydrogel increased in diameter and length. One possible method would be to enclose the dry hydrogel in a tube of ultrafiltration membrane whose dimensions were those of the fully hydrated hydrogel and an overlying layer of mucus of an appropriate thickness (0.2-0.5mm). The redundant membrane would be approximated down one side and end of the hydrogel as shown in Figure 10.1. The hydrogel inside the membrane would then be swollen in the USP apparatus, stirred to prevent boundary effects and the release rate measured. Swelling could be estimated by intermittently removing the tube and hydrogel for weighing.

An advantage of such a system would be that relatively small quantities of mucus would be required (1-2ml). This would enable natural mucus to be used rather than reconstituted mucin. As noted in Section 9, this latter material, while convenient, reproducible and sterile, does not have the same gel consistency as natural mucus, possibly due to fragmentation of the long chain mucins during the production and reconstitution process. Natural mucus could be obtained from animal or human sources by gentle scraping of the bowel wall after washing to remove faecal residues.

One problem with such a test system would be to ensure that the thickness of the mucus layer remained relatively constant as the hydrogel increased in volume. A further difficulty would be that the release rate into the water phase would depend not only upon the diffusion through the mucus but also on the rate of rehydration of the hydrogel. The effects of mucus on inhibiting the transfer of water are unknown but if an effect were present, the contribution to changes of release rate could not be easily determined. One approach might be to only study the release from fully swollen hydrogel. A cylindrical block of hydrogel would be fully swollen in a solution of morphine. It would then be enclosed in a cylinder of ultrafiltration membrane of diameter 0.5-1mm greater than the hydrogel with the residual space being filled with an even layer of mucus. The release of morphine would show an exponential decline (Section 3.2.4) but comparison between different types of mucus and shapes of hydrogel would be easier as the results ought to be more reproducible.

The test system described above would also serve to investigate the effect of the mucus barrier on the transfer of water to the hydrogel for swelling. The aqueous phase would be replaced by a solution of albumin with an oncotic pressure identical to that of cellular contents. The ultrafiltration membrane would thus represent the epithelial cell membrane and the effects of different types of mucus could be studied.
Figure 10.1. Representation of Hydrogel before swelling within a "bag" of ultrafiltration membrane with a covering layer of mucus
The present dosage form of approximately 100mg daily will be suitable for a large proportion of patients with chronic pain but will not suit all. There will be a need to develop greater and lesser dosages. The former will be useful for the 25-30% of patients who require a daily dosage in excess of 150mg (Brooks et al., 1995). However, the solubility of morphine in water and thus the dose which can be incorporated into the hydrogel may be limiting factors on the dose and size of device. Early work by Professor Graham included a hollow hydrogel device with crystalline morphine in the cavity. In these circumstances, the swollen hydrogel acted as a rate limiting membrane in the diffusion from the cavity. This device produce steady release for periods of up to 50 hours (Graham NB, personal communication). The danger with such a device is that of dose dumping if the hydrogel cylinder is ruptured. However, it may be possible to enclose the crystalline morphine in such a way as to prevent such an occurrence.

An alternative would be the direct incorporation of morphine into the hydrogel during manufacture. This would eliminate the time consuming steps of swelling and drying to load the device with morphine and would also permit higher doses to be incorporated into smaller devices. Some preliminary work on thermoplastic hydrogels based upon poly(ethylene oxide)-c-(propylene oxide) has been undertaken by Professor Graham's group (Moran, 1986). These block co-polymers are soluble in ethanol but not in water which enables them to be plasticized sufficiently to permit injection moulding after mixing with powdered morphine. Additional plasticizers such as propylene glycol and benzyl alcohol could also be used to vary the physical properties. To date, no further development work has been undertaken on these formulations.

Lesser dosage forms might be useful for the treatment of children who often have difficulty swallowing tablets and dislike injections. For adults and larger children, the "standard" MHS could simply be cut down, preserving the release profile. For smaller children a smaller diameter device would be necessary.

Withdrawal mechanism

The ability to remove the MHS and thus rapidly stop the administration of morphine was seen to be an important safety feature. However, as has been shown by the preceding studies, this is difficult to achieve in practice. The unswollen gel is sufficiently firm to be able to drill and to resist the cutting force of a withdrawal thread. In contrast the swollen gel is soft and friable, fracturing readily. Two questions are apparent, is a withdrawal device necessary and, if so, what form should it take?
A withdrawal mechanism is likely to be required for safety purposes if there is a possibility that an excessive amount of morphine is administered, either from the device itself or by another route. The latter event should not be a common occurrence and would be regarded as a misadventure. The experience to date with the MHS and a theoretical consideration of its function suggests very strongly that dose-dumping, the sudden absorption of a large proportion of the contained dose is impossible. This is in contrast to oral sustained release preparations, especially in opioid naive subjects, where the effect of morphine on gastric emptying may result in dissolution of the preparation within the stomach but little absorption due to the unfavourable pH. Subsequent opening of the pylorus can result in rapid absorption of morphine. The rectum has no similar reservoir potential and the rapid decline in plasma morphine concentration after removal of the MHS suggests that little morphine is held in the rectal wall and contents.

A withdrawal device would be necessary also if the MHS could not be removed or passed before insertion of a further dose for continuing treatment. The answer to this question depends very much on how the MHS will be used in clinical practice. Patients on chronic morphine therapy are commonly constipated but most palliative care centres take care to ensure that sufficient bulk or other laxatives are administered to ensure a regular bowel action. If this achieved and the patient has a bowel movement once each day, then a new MHS would be inserted by a carer immediately after defaecation. However, if the bowels are opened less often, then either the MHS will have to be removed when spent after about 24 hours and replaced or a new MHS inserted alongside the previous device. Absorption is likely to be satisfactory unless the rectum fills with faeces. The ability of most of the volunteers to expel the swollen MHS by voluntary effort as described in Section 8 gives some hope that patients may also be able to expel the device readily and facilitate continuing treatment. Long term studies in patients with chronic pain will be necessary to answer this point.

The choice of removal mechanism remains unclear. Methods involving a thread passed through the hydrogel, even when supported by silicone "buttons", are clearly unsatisfactory as the swollen gel is unable to take even minor stress without fracturing. One option which has been considered is incorporating a mesh or network of threads within the gel, thus spreading the load during withdrawal and reducing the likelihood of gel fracture. However, the mesh would have to be able to expand with the gel as it rehydrates. Failure to perfectly follow the movement of gel would create minor fractures between the gel and thread. A further option was to strengthen the gel by the addition of fibres but similar drawbacks could be foreseen and the drug release properties would
have been impaired. The ovemet was satisfactory as a withdrawal device, but as seen in section 8 markedly reduced drug absorption, probably by trapping a layer of mucus and increasing the barrier to diffusion. The problem was exacerbated by the shape of the hydrogel which held mucus in the grooves between the ribs. A return to a cylindrical shape would reduce this problem and considerable development is possible to the ovemet by reducing the thickness of thread used in the material and creating a more open structure. This would reduce the abrasiveness of the material, reducing mucus secretion and reduce the amount of mucus trapped around the device.

Thus the need for a withdrawal mechanism remains unanswered at this time but, as there are possibilities for refining the present mechanism, development will continue.

**Insertion devices**

Many patients for whom MHS will be suitable will be unable to insert the device themselves due to age, physical disability or dislike of the procedure. A carer, who might be a family member will therefore have to administer the medication. It is likely that many carers will find the use of an introducer more acceptable than a digit, even if gloved, to insert the MHS. A further benefit will be that the device will be accurately placed in the rectum and not either left in the anal canal when discomfort would ensue or placed so high in the rectum that portal rather than systemic absorption would occur.

Similar devices have been designed for the administration of vaginal pessaries and the insertion of rectal gels and foams. The simplest form would be of a cylindrical tube of internal diameter just greater than the outer diameter of the dry MHS. The rounded end would protrude from the end of the tube which would have a large flange about 3cm from its end. An internal plunger would enable the MHS to be pushed from the tube. The carer would be instructed to place the MHS into the introducer and, after lubrication, pass the device through the anus until the flange was at the anal margin. The plunger would then be depressed and the introducer withdrawn, leaving the MHS correctly placed in the lower rectum.

**10.3. FUTURE RESEARCH PROGRAMME**

Much remains to be done before the MHS can be offered as a commercial preparation, not least ensuring that the appropriate shape of device, release profile and withdrawal mechanism is chosen. In some respects, the studies for approval by the regulatory
authorities are more straightforward than those for a new drug. In this case, the analgesic properties of morphine are not in doubt and the studies need only to show the comparability between the MHS and existing formulations in terms of bioavailability and duration of action. These will be explored in a series of studies in volunteers set out below. Supportive evidence for registration will comprise more open studies in patients with chronic pain which are also outlined below. At the time of writing these studies are either in progress or being planned.

The work described in the preceding Sections has also raised a number of questions regarding rectal drug administration and, in particular, the role of mucus as a barrier to absorption. Present methods of assessing release from suppositories are also clearly unsuitable for sustained release preparations and alternative methods will be necessary. Possible areas of future study are described below.

10.3.1. Volunteer studies

A major ethical issue in volunteer studies of opioid drugs is a concern over possible induction of addiction in susceptible individuals. This concern may be more apparent than real as there are no published cases of addiction after clinical trials and the author, who chairs the Ethics Committee of a preclinical research centre, has not heard of any anecdotal cases despite diligent enquiry. A further concern is the level of side-effects in volunteers exposed to the high doses of morphine necessary for clinical treatment of chronic pain. The median dose of oral morphine required by such patients is about 90mg per day (Brooks et al., 1995). The degree of side effects induced in volunteers by single doses of this magnitude appear to be tolerable. However, a considerable proportion of patients require doses in excess of 200mg daily and preparations containing this and greater doses could not be tested in volunteers as the side effects would be intolerable. Similar concern exists for giving repeated doses of morphine to volunteers over several days.

One response to such concerns has been to administer an opioid antagonist simultaneously. Kaiko and colleagues (1995) described a study of 200mg MST tablets in volunteers who had been pretreated with naltrexone. The latter compound is a long acting opioid antagonist usually used in the management of opioid addicts who have been successfully weaned from their drug of abuse and do not wish to return to their habit if tempted. Naltrexone is almost without effect when taken alone but it markedly reduces the effects of simultaneously administered opioids and thus reduces the likelihood of
returning to addiction. The side effects reported by the volunteers in Kaiko's study were less than those reported by the volunteers in the studies described in Sections 7 and 8. The study showed that the $C_{\text{max}}$ of morphine from orally administered MST was earlier in the presence of naltrexone but the elimination half life was unchanged. This suggest that naltrexone antagonised the delay in gastric emptying induced by morphine but had no effect on its metabolism.

Two studies have been planned with the MHS. The first is a three way crossover study in volunteers between MST 60mg and the MHS 100mg with and without co-administration of naltrexone. At the time of writing, the preliminary results of the study show that naltrexone was successful at reducing the symptoms but that the absorption of morphine as measured by AUC was less in the presence of naltrexone. The AUC for M6G and M3G were reduced in parallel suggesting that the effect was not due to altered metabolism. Explanations which are currently under investigation are an effect of naltrexone on the protein binding of morphine and its metabolites and reduction of morphine absorption by an effect on mucus production. As noted earlier in this thesis, over the course of the studies, the importance of mucus as a barrier to rectal absorption from the MHS had become apparent. It is hypothesised that morphine has an effect on reducing rectal mucus production via cholinergic receptors. The reduced mucus layer facilitates absorption. Naltrexone antagonises this effect and reduces absorption.

The second volunteer study will determine the pharmacokinetics of steady state administration of morphine administered from MHS and from MST. In a crossover design, volunteers will take either MST 60mg bd or MHS 100mg once daily for four days and then change to the other treatment for a further four days. Naltrexone will be given throughout. Blood samples will be taken on days one, two and three of each treatment limb to ensure that a steady state is attained and multiple samples will be taken on day four for pharmacokinetic analysis.

10.3.2. Clinical studies

Studies of the value of the MHS in patients with chronic pain will be the ultimate test of the worth of the development programme. To date the development has utilised volunteers and small numbers of patients in acute pain and thus the practical difficulties, side-effects and indications for chronic pain patients are unknown.
The planned patient study will be predominantly in patients where there is a good clinical indication for non-oral therapy who are unable to take or tolerate oral preparations. Discussions with Professor S Ahmedzai, Professor of Palliative Care, University of Sheffield and formerly, Director of the Leicestershire Hospice have resulted in the following outline proposals for a suitable study.

Patients who are presently stable on oral morphine therapy with a total daily dose of 90-120mg who are either willing to participate in the study or become unable or unwilling to take oral medication will give their informed consent. Baseline measurements of the intensity of symptoms and a quality of life inventory will be performed before the patients are commenced on regular daily MHS. Immediate release oral or subcutaneous morphine will be given as rescue medication to achieve pain control. A standard antiemetic will be given as necessary. A successful outcome will have been achieved when the patient is established on MHS either alone or with a stable dose of supplementary morphine. At this point, the quality of life inventory and symptom scores will be repeated together with patient and carer views on the treatment. The outcome measures for the study will be the proportion of patients with a successful outcome, the time taken to achieve success and the average daily dose of morphine required. Secondary measures will be changes in quality of life and symptom scores. Patients who wish to continue on MHS after completion of the study period will be allowed so to do, with regular reports on progress being made.

All retrieved MHS will be analysed for residual morphine content to enable dose administered to be calculated and blood samples will be collected when opportunity presents for measurement of plasma concentrations of morphine and its metabolites. These values will not be primary measures of outcome but will provide additional information, particularly for the question of route of administration and side effects.

Route of administration of morphine and side-effects

There is no doubt that the route of administration of morphine determines the pattern of metabolites. Oral administration is associated with greater production of M6G and M3G than parenteral administration, presumably due to first-pass hepatic metabolism (Peterson et al., 1990, Osborne et al., 1990, Janicki et al., 1991, Babul and Darke, 1993). The discovery of the analgesic properties of M6G, with a potency of about ten times that of morphine helped to explain the discrepancy between the pharmacokinetic studies which
showed an oral bioavailability of 10% and the dose equivalency studies which suggested a ratio of 3:1 oral:parenteral.

The avoidance of first-pass metabolism therefore became potentially a disadvantage rather than an advantage which would have conferred little theoretical benefit on rectal administration. However, the side-effects of oral morphine therapy and the development of morphine resistant pain have been attributed to the metabolites of morphine, particularly M3G, discussed above (Section 10.1).

There is therefore a possibility that rectal administration of morphine might be associated with a reduction in side-effects and a reduced likelihood of the development of tolerance and morphine resistant pain. The early patient studies described in Section 6 suggested that nausea and vomiting was less with the MHS than with parenteral morphine, possibly due to the reduced variability in plasma morphine concentrations. A direct effect of morphine on the stomach might contribute to nausea and vomiting also which would be avoided by rectal medication.

These suppositions will require large scale studies which will probably follow rather than proceed marketing of the MHS as they will require patients to be given the devices for many months and compared with patients receiving conventional oral therapy.

10.3.3. Basic science

The preliminary studies have demonstrated the paucity of knowledge on the mechanisms of rectal absorption. Section 1.4 outlined the process as it is understood currently. Of the barriers to absorption and to the availability of water for rehydration of the hydrogel, the role of the mucosa and its blood flow and the mucus barrier are the least understood but probably the most important. The latter problem will not be easily resolved, not least because the available methods for measuring rectal mucosal blood flow are unreliable and technically difficult (Srivastava, 1990, Rhodes J, 1996 Personal communication). Resolution will require either the development of new methods of assessing mucosal blood flow or the use of experimental animals. As noted previously, the anatomical structure and function of the rectum in most laboratory animals differs considerably from man.
The former area of investigation, the contribution of the mucus layer is more amenable to investigation and some future areas of interest are outlined below.

**Role of mucus in rectal absorption**

The hypothesis which has emerged from the studies outlined previously and other reported work, is that the thickness of the mucus layer plays a major role in slowing absorption from the rectum. The effect on diffusion will depend upon the type of mucus and the drug, particularly its pK and the lipophilicity, as well as the thickness of the mucus layer. Investigation of the differing effects can be readily studied in the laboratory using modified diffusion apparatus such as that described by Bhat and colleagues (1995). Briefly, a layer of mucus is held between two ultrafiltration membranes which separate two chambers, one of which contains a solution of the drug and the other a receiving solution which is sampled regularly to measure diffusion of the drug through the mucus. It is planned to use such an apparatus to investigate the effects of different types and thickness of mucus on the diffusion of morphine.

Studies of the effects of the mucus barrier on absorption should also be possible in human subjects by the co-administration of two or more drugs. For example, the effect of the absorption of two drugs of similar lipophilicity but differing pK from the same vehicle and vice versa would be of interest. Alternatively, the thickness and nature of the mucus layer could be altered. Co-administration of an anti-cholinergic drug such as atropine or hyosine would be expected to decrease mucus production, decrease the thickness of the mucus layer and increase absorption. Conversely, co-administration of a muscarinic agonist such as carbachol would be expected to increase mucus production and decrease absorption. Finally, the nature of the mucus could be altered by co-administration of mucolytic agents such as N-acetylcysteine. However, these studies would not provide definite confirmation of the effects of morphine on rectal mucus secretion and animal studies might be necessary.

**Effects of morphine on mucus secretion**

The anti-cholinergic properties of morphine have not been much studied, particularly with regard to mucus production. The studies by Westerling (1993, 1995) have provided an explanation for the symptom of dry mouth which has been reported as a minor side-effect of morphine for many years. She showed that stimulated salivation was reduced by morphine and the reduction was linearly related to plasma morphine concentration. To
date no studies have determined whether this effect is reversible by opioid antagonists suggesting an effect via opioid receptors or not reversible suggesting an effect on muscarinic receptors. This and other studies on the cholinergic effects of morphine outlined in Section 1.2.3 suggest that at least some of the effects are mediated through opioid receptors and are antagonised by naloxone while others are unaffected by opioid antagonists.

This raises a number of interesting questions on the interaction between morphine and cholinergic receptors and links between opioid and cholinergic receptors. Preliminary studies in the Department of Anaesthesia, University of Leicester in cultured cells expressing muscarinic m3 receptors, shows that morphine has an affinity for these receptors by displacement of $^3$H-N-methylscopolamine with a $K_i$ of 280μM and an EC50 of 872μM (Lambert D, personal communication, 1996). This concentration is several orders of magnitude greater than plasma concentrations generally obtained but are close to the concentrations that might be found in the mucosa of the rectum during administration of an MHS. Demonstration of affinity does not show that a drug has any action at that receptor but the results indicate that further work is justified.

10.4. CONCLUSIONS

The MHS appears to be able to deliver morphine through the rectal mucosa over a prolonged period and in a consistent manner. It has promise as an analgesic preparation for patients in chronic pain with the possibility of once daily medication. Considerable further investigation is necessary before marketing is possible but sufficient potential has been demonstrated to justify the effort.

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