MULTIPOLYMERIC MONOLAYERED MUCOADHESIVE FILMS FOR DRUG THERAPY

by

Velisha Ann Perumal

(BSc (UDW) Hons (UKZN), SA)

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Supervisor: Associate Professor Thirumala Govender

Co-supervisor: Mr Dhamend Lutchman

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"Consult not your fears but your hopes and dreams,
Think not about your frustrations but about your unfulfilled potential,
Concern yourself not with what you tried and failed in,
But with what it is still possible for you to do."

- Pope John XXXIII -

In loving memory of my grandmother

Theresa Rebecca Peters

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RESEARCH OUTPUT

The following posters were presented from data generated in this study:

International:

- Perumal, VA, Lutchman, D and Govender, T, Development of a Silicone Molded Compartmentalised Tray: An Approach to Enhance Drug Uniformity in the Preparation of Polymeric Films, **AAPS Annual Meeting and Exposition**, San Antonio, Texas, USA, 29 October-02 November 2006.

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- Perumal, VA, Lutchman, D and Govender, T, Development of a Silicone Molded Compartmentalised Tray: An Approach to Enhance Drug Uniformity in the Preparation of Polymeric Films, **4th International Conference on Pharmaceutical and Pharmacological Sciences**, Vanderbiljpark, Gauteng, SA, 20-23 September 2006.

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ABSTRACT

The use of the oral cavity membranes as sites of drug administration has been a topic of increasing interest for the past decade. The buccal route, in particular, offers several advantages over the per oral route and may prove to be a viable alternative to other routes for drug delivery, as it bypasses hepatic first pass metabolism, thereby improving the systemic bioavailability of the administered drug. A controlled drug release formulation may further enhance the therapeutic efficacy of a buccal drug delivery system. Propranolol HCl (PHCl), a non-selective β-blocker, primarily advocated in the treatment of hypertension, has a short half-life (3 - 6 hours) and is also subjected to extensive hepatic first-pass metabolism following oral administration, resulting in a low oral bioavailability, therefore rendering it an ideal candidate for buccal drug delivery. For optimal controlled release and mucoadhesivity of a buccal delivery system containing PHCl, the blending of polymers and drug of opposing solubilities may be required for the formation of monolayered films. The aim of this study was therefore to formulate and characterise multipolymeric monolayered mucoadhesive films containing drug and polymer/s of opposing solubilities for the buccal delivery of PHCl.

First, preparation parameters for the formation of monolayered multipolymeric films (MMFs) and homopolymeric PHCl films comprising drug and polymer/s of opposing solubilities, i.e. Chitosan (CHT) and Poly(D,L-lactide-co-glycolide) (PLGA) by an emulsification/casting/solvent evaporation method were investigated. MMFs could be prepared at all homogenisation speeds (6000, 9000, 12000, 15000 rpm) and times (1, 5, 15, 25 minutes). The films showed micromatrices embedded in the film matrix due to the inclusion of the PLGA polymer. Increased homogenisation speed and time resulted in a reduction in the size of the micromatrices. Phase separation occurred at temperatures below 20 °C. Emulsifiers employed in the study (Poly(vinylalcohol) (PVA) and Tween 80®) adversely affected the morphology and appearance of the film and were therefore not considered feasible for inclusion in the formulation. The preparation parameters identified for emulsification without phase separation and the subsequent generation of monolayered films, without phase separation during solvent evaporation and drying, were emulsification at 20 °C and homogenisation at 9500 rpm for 15 minutes.

It was discovered through preliminary investigations and a comprehensive literature search that the conventional film casting method of film preparation suffered from poor drug content uniformity. To address this problem of non-uniformity, a specially designed silicone-molded tray (SMT) for film casting was prepared and evaluated in terms of enhancing drug content uniformity. These

investigations confirmed that the SMT with teflon-coated perspex inserts provided a reproducible method for the preparation of both homopolymeric and multipolymeric (including drug and polymers of similar and opposing solubilities) films that met drug content uniformity requirements (assay values were within 92-107.5%) and also reduced the variability in mucoadhesivity ($p=0.2922$), drug release (f_2 values = 92.76, 90.99 and 86.06) and film thickness for all three trays.

The final phase of this study involved the identification of a suitable polymeric blend for the preparation of MMFs comprising hydrophilic and hydrophobic polymers for the controlled buccal delivery of PHCl and subsequent characterisation of these films in terms of their physicochemical/mechanical properties. Initial investigations of different polymers for the formation of homopolymeric films showed that the combination of drug and polymer/s of opposing ionic states was not possible due to complexation. PHCl film formation as homopolymeric films was achievable with hydrophilic polymers, Hydroxypropylmethylcellulose (HPMC) and CHT, and hydrophobic polymers, Ethylcellulose (EC) and Eudragit® RS100 (EUD100). It was also found that combining PHCl, a hydrophilic drug, with a hydrophilic polymer (CHT or HPMC) failed to retard drug release (> 80% at 1 hour), whilst the release of PHCl from a homopolymeric film comprising a hydrophobic polymer (EC or EUD100) was retarded. A PHCl:EUD100 (1:10) film provided controlled release but was too retarded (< 67% at 8 hours) for the purposes of this study. Hence, the polymeric content of the formulation was altered by the addition of a hydrophilic polymer CHT, to obtain the desired controlled release profile. A PHCl:EUD100:CHT (1:10:0.5) polymeric blend (MMF) was found to be suitable for the controlled release of PHCl and was reproducible in terms of drug content uniformity ($p=0.1964$), drug release (f_2 values = 83.18; 82.03 and 71.19) and mucoadhesivity ($p=0.9971$). Drug release followed Higuchi's square-root model ($r^2=0.9426$). Scanning electron microscopy revealed that the addition of CHT to the PHCl:EUD100 (1:10) film formulation rendered it more textured, which contributed to the faster drug release observed with the PHCl:EUD100:CHT (1:10:0.5) MMF. Swelling and erosion studies indicated that maximal swelling of the films occurred after 1 hour and 28.26% of the film eroded during the 8 hour test period. The system also demonstrated acceptable mucoadhesivity and mechanical properties. The surface pH of the films also remained constant at neutral pH throughout the study.

The data obtained in this study confirmed the potential of this multipolymeric monolayered film system as a promising candidate for the controlled buccal delivery of PHCl.

Key words: Films; Buccal; Multipolymeric; Mucoadhesive; Controlled drug release; Propranolol HCl

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
AUC	Area under the curve
CHT	Chitosan
Chx	Chlorhexidine
CMC	Carboxymethylcellulose
CV	Coefficient of variation
EC	Ethylcellulose
EUD	Eudragit
GL	Glycyrrhizic acid
HLB	Hydrophile-lipophile balance
HPC	Hydroxypropylcellulose
HPMC	Hydroxypropylmethylcellulose
LDC	Lidocaine hydrochloride
MC	Methylcellulose
MDF	Maximum detachment force
MMF	Multipolymeric monolayered film
Na Alginate	Sodium Alginate
PAA	Poly(acrylic acid)
PAOMA	Polyalkyleneoxide-maleic acid
PBS	Phosphate buffered saline
PC	Polycarbophil
PCL	Polycaprolactone
PEG	Polyethylene Glycol
PEO	Poly(ethylene oxide)
PLGA	Poly(DL-lactide-co-glycolide)
PVA	Poly(vinyl alcohol)
PVP	Polyvinlypyrrolidone
rpm	Revolutions per minute
SCMC	Sodium carboxymethylcellulose
SD	Standard deviation
SEM	Scanning electron microscopy
SMT	Silicone molded tray
TCPT	Teflon coated perspex tray
TPA	Textural profile analysis
UV	Ultraviolet

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MOTIVATION FOR AND AIM OF STUDY

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1.1 MOTIVATION FOR STUDY

Among the various routes of drug delivery, the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages that prohibit the administration of certain classes of drugs, e.g. peptides and proteins, and also compromises the bioavailability of other classes of drugs such as antihypertensives. Consequently, other absorptive mucosa such as the nasal; vaginal; rectal; ocular and oral linings, are considered as potential sites of drug administration (Shojaei *et al.*, 2001). The use of the oral cavity membranes as sites of drug administration has been the topic of increasing interest for the past decade. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are associated with peroral administration (Remunan-Lopez *et al.*, 1998; Kurosaki and Kimura, 2000; Varshosaz and Dehghan, 2002; Hao and Heng, 2003, Langoth *et al.*, 2003, Akbari *et al.*, 2004). In addition to systemic therapy, the oramucosal route can also be used for the delivery of drugs for localised therapy in the mouth for oral infections, e.g. periodontitis (Deasy *et al.*, 1989; Schwach-Abdellaoui *et al.*, 2001; Perugini *et al.*, 2003; Jones *et al.*, 2004; Perioli *et al.*, 2004). Drugs administered via the oral mucosal route can therefore offer superior therapeutic outcomes for drugs that benefit from the circumvention of hepatic first-pass metabolism and also those for localised therapy.

One such route is the buccal route, which has been investigated for both local and systemic delivery of therapeutic agents (Ishida *et al.*, 1981; Rathbone, 1991; Cassidy *et al.*, 1993; Guo, 1994; McQuinn *et al.*, 1995; Han *et al.*, 1999). Drugs administered via the buccal route: (1) achieve higher plasma concentrations by avoidance of both the

intra-alimentary canal and hepatic first-pass metabolism (Hussain *et al.*, 1987), (2) have improved systemic bioavailability (Bond, 1988; Huupponen *et al.*, 1995), and (3) have improved absorption, as this is not affected by variations in the gastric emptying rate or the presence of food (Kaus *et al.*, 1999; Senel and Hincal, 2001). The buccal route also offers a series of other advantages such as good accessibility, robustness of the epithelium, facile removal of the dosage form in the case of need, relatively low enzymatic activity, possibility of elimination of the administered dosage form from the buccal area by natural clearance mechanisms and satisfactory patient acceptance and compliance (McElnay, 1990; Rathbone *et al.*, 1994; Chidambaram and Srivatsava, 1995; Burgalassi *et al.*, 1996; Khanna *et al.*, 1998; Shojaei, 1998; Lee *et al.*, 2000; Varshosaz and Dehgha, 2002; Langoth *et al.*, 2003; Geresh *et al.*, 2004). Classes of drugs that may benefit from buccal delivery include hypoglycaemics (Ilango *et al.*, 1997), antiretrovirals (Xiang *et al.*, 2002), antibiotics (Jones *et al.*, 2000) and antihypertensives (Guyot and Fawaz, 2000).

Since the buccal route may prove to be a viable alternative to other routes for drug delivery, attempts have been made to formulate various buccal delivery systems, which included tablets (Ali *et al.*, 1998; Perioli *et al.*, 2004; Munasur *et al.*, 2006), films (Kohda *et al.*, 1997; Remunan- Lopez *et al.*, 1998), disks (Parodi *et al.*, 1996; Ali *et al.*, 2002), strips (Ilango *et al.*, 1997), patches (Wong *et al.*, 1999; Nafee *et al.*, 2003) and gels (Shin *et al.*, 2000).

An important aspect for buccal drug delivery systems is that of controlled drug release, as controlled drug delivery systems provide a continuous delivery of drugs at predictable and reproducible kinetics for a pre-determined period. The potential advantages of this concept are: minimisation of drug related side effects (due to controlled therapeutic blood levels instead of oscillating blood levels)

and improved patient compliance (due to reduced frequency of dosing) (Jantzen and Robinson, 1996). Therefore, administration of drugs via the buccal route together with controlled drug release will optimise drug therapy. Controlled drug delivery is acquired by combining a polymer, natural or synthetic, with an active ingredient in such a way that the active ingredient is released from the material in a predesigned manner. Hence controlled release is ultimately achieved by the judicious selection of polymers.

Another important property essential for drug delivery systems for administration via the oral mucosal route is retention on the mucosae, i.e. mucoadhesivity, brought about by the use of polymers such as chitosan (Senel *et al.*, 2000; Perugini *et al.*, 2003), hydroxypropylmethylcellulose (HPMC) (Ali *et al.*, 2002), sodium carboxymethylcellulose (SCMC) (Wong *et al.*, 1999) and poly (acrylic acid) (PAA) (Shojaei *et al.*, 2000). Mucoadhesive polymers interact with and adhere to mucin molecules in the mucus lining and are thus retained on the surface epithelium for extended periods of time (Ahuja *et al.*, 1997). Mucoadhesive polymers have attracted considerable attention for controlled drug delivery, as prolonged residence time of the delivery system at the site of action leads to increased contact to the absorbing mucosa, thereby resulting in a steep concentration gradient which favours drug absorption as well as localisation in specific regions to improve and enhance the bioavailability of the drug (LueBen *et al.*, 1994). Therefore maximising mucoadhesivity, especially for controlled drug delivery, remains an important goal in oral mucosal delivery.

The selection of optimal polymers in a drug delivery system remains the pivotal goal in the formulation of controlled release buccal delivery systems for enhancing mucoadhesivity and obtaining controlled drug release profiles. The literature has revealed that, thus far,

mucoadhesive systems have been formulated using mainly homopolymeric systems (Woolfson *et al.*, 1998; Guyot and Fawaz, 2000; Eouani *et al.*, 2001). With homopolymeric systems one may find that a polymer such as chitosan, which has been shown to display excellent mucoadhesivity, is nevertheless unable to prolong drug release, while a polymer such as poly lactide-co-glycolide (PLGA) is not a good mucoadhesive but ideal for prolonging drug release (Senel *et al.*, 2000; Perugini *et al.*, 2003). Thus, for suitable therapeutic outcomes, these two properties need to be optimised in a delivery system to achieve prolonged retention time as well as specified release kinetics such as zero-order.

More recently, researchers have been focusing on the blending of polymers to provide improved mucoadhesion and drug release. For example, patches and films formulated with chitosan blends with hydrophilic polymers were superior as compared to chitosan alone in terms of dissolution, improved comfort and reduced irritation, ease of processing and improved film flexibility (Khoo *et al.*, 2003). Hence chitosan, in combination with hydrophilic polymers, could be a promising candidate for formulation of oral mucosal delivery systems. Therefore a need for identifying and optimising ideal polymeric blends for novel systems using simple technologies exists. This is essential for the development of a mucoadhesive drug delivery system with superior therapeutic outcomes.

While tablets and disks may allow for the blending of polymers, the addition of other excipients required for compressibility leads to increased thickness and size, which in turn results in both patient discomfort and non-compliance. In addition, expensive tabletting technology results in an increased cost to the manufacturer and ultimately to the patient. A reduction of these factors is therefore a goal in the development of multipolymeric systems (Kurosaki and

Kimura, 2000). Films with polymeric blends as a drug delivery system would be ideal for delivery of drugs in the oral cavity due to its flexibility and comfort and may be preferred over adhesive tablets. Films can also circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva (Peh and Wong, 1999). The use of homogenous films where the drug and polymer are dissolved in the same vehicle has been reported in the literature (Woolfson *et al.*, 1995; Padula *et al.*, 2003). However, the need for optimal polymeric blends may require the blending of drugs and multi-polymers each with varying degrees of hydrophilicity and lipophilicity. Such blends will render the above procedure unsuitable. While multi-layered films (Perugini *et al.*, 2003) and wafers (Bromberg *et al.*, 2001) may be considered for these polymers, again the increased costs due to multi-step processes and also the reported benefits of monolayered films over multi-layered films in terms of drug release, mucoadhesivity and size, compel the need for multipolymeric monolayered systems (Perugini *et al.*, 2003). The preparation technique of such a system comprising polymers and drug of opposing solubilities presents a challenge and requires further investigation. Currently there are no such products commercially available in South Africa or internationally.

Although some preliminary data on the formation of monolayered matricial films formulated from a combination of polymers have been reported (Perugini *et al.*, 2003), to date there has been no further characterisation of this system, which will be essential for optimising its design and preparation. Further, there are no reported studies on even a homopolymeric monolayered film containing a drug of opposing solubility. Both the process and formulation variables need to be identified for the preparation of multipolymeric monolayered films with drug and polymers with opposing solubilities that offer desired drug release kinetics and optimal mucoadhesivity.

The drug selected for incorporation into the film formulation in this study was Propranolol Hydrochloride (PHCl), a nonselective β-adrenoreceptor blocker, widely used in the treatment of various cardiovascular disorders such as angina pectoralis, cardiac arrhythmias, myocardial infarction and hypertension (Riddell *et al.*, 1987; Reynolds, 1989; Corbo *et al.*, 1990). Since PHCl has a short half-life (3 – 6 hours) and is also subjected to extensive hepatic first-pass metabolism following oral administration, resulting in a low oral bioavailability (Reynolds, 1989; Corbo *et al.*, 1990; Guyot and Fawaz, 2000), it presents itself as an ideal candidate for incorporation as a model drug. Furthermore, although several controlled release propranolol dosage forms have been developed over the years, very few or no studies to date have investigated multipolymeric monolayered mucoadhesive propranolol-loaded films for buccal delivery. This is evident from a summary (Table 1.1) of propranolol dosage forms.

The potential benefits of formulating a drug delivery system like the one proposed in this study, may include the following:

- Delivery of drugs via the oral mucosal route and modified drug release are currently a major focus of international pharmaceutical science research for enhancing drug therapy. This study will lead to the development of cost-effective dosage forms which will contribute to an improvement in disease management. This in turn will lead to an improvement in the quality of life and ultimately to a reduction in health care costs in South Africa and internationally due to a reduction in work absenteeism.

Table 1.1 Summary of propranolol dosage forms investigated for buccal controlled drug delivery

DOSAGE FORM	POLYMERS	CHARACTERISATION STUDIES	REFERENCE
Tablets	HPMC, PAA	*In vitro* and *in vivo* drug release, interpolymer complexation, *in vitro* bioadhesion	Taylan, *et al.*, 1996
Bilayered Tablets/ Bilayered Laminated Films	Chitosan glutamate, EC	Morphology studies using SEM, *in vitro* drug release studies, water uptake and device erosion, bioadhesion of tablets	Remunan-Lopez *et al.*, 1998
Tablets	HPMC, polycarbophil	Turbidity measurements, bioadhesive strength, dissolution studies, kinetic modeling	Akbari *et al.*, 2004
Tablets/Adhesive cups	HPMC, Carbopol	Evaluation of physical properties: weight and thickness uniformity, hardness and friability tests, swelling studies , *in vitro* mucoadhesive studies, *in vitro* drug release studies, stability studies, *in vivo* human acceptability studies	Desai and Kumar, 2004
Discs	Chitosan salt	*In vitro* drug release, swelling and erosion, *in vitro* mucoadhesion studies	Cafaggi *et al.*, 2005
Tablets	PAA, PVP, CMC	Mucoadhesivity, assay and *in vitro* drug release studies, kinetic analysis of drug release profiles and model fitting, swelling and erosion studies, textural profile analysis, surface pH evaluation	Munasur *et al.*, 2006

- The reduced thickness and size of these polymeric-blended systems will afford improved patient comfort/acceptance and hence patient compliance. Easy insertion onto the buccal site for systemic or local delivery will also be facilitated.

- This concept may also have cost benefits, as the use of simpler technology compared to tabletting will be cheaper. Moreover, the reduction in the multi-step manufacturing procedure for multi-layer films also has the potential to lower the cost of the dosage form to both the manufacturer and patients.

- This concept also facilitates the loading of drugs, which may be insoluble in one of the desired polymers, into monolayered films.

- The development of this technology and polymeric system will also lend itself to the development of mucoadhesive systems for other routes (vaginal, rectal, ocular) and also for a range of other disease conditions significantly affecting South Africa and other countries globally, e.g. diabetes, tuberculosis and HIV/AIDS.

- Since there are no such products commercially available in South Africa or internationally, it will foster international competitiveness in the lucrative global market for pharmaceutical products.

Therefore the formulation of propranolol-loaded multipolymeric monolayered mucoadhesive films offers a novel and promising concept for enhancing drug therapy.

1.2 AIM AND OBJECTIVES OF THE STUDY

The main aim of this study was therefore to formulate and evaluate multipolymeric monolayered films (MMFs) containing a model drug (PHCl).

In order to achieve the above aim, the specific objectives of the study were to:

- Identify a suitable technique for the preparation of monolayered films containing drugs and polymers of opposing solubilities.

- Identify suitable polymer combinations for the preparation of drug loaded MMFs with enhanced mucoadhesivity and controlled drug release.

- Characterise the prepared films in terms of drug content uniformity, weight, thickness, drug release kinetics, mucoadhesivity, mechanical strength, morphology, swelling and erosion.

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CHAPTER TWO

THEORETICAL CONCEPTS OF CONTROLLED RELEASE MUCOADHESIVE DRUG DELIVERY VIA THE ORAL MUCOSA

Table of Contents

2.1 INTRODUCTION

This chapter provides a theoretical overview of concepts relating to this study. Since the desired route of drug delivery for the purpose of this study is the buccal route, special emphasis on the buccal mucosa is presented. Concepts and principles of mucoadhesion and controlled release are also described, as these are fundamental aspects required for the formulation of a mucoadhesive controlled release buccal drug delivery system. Finally, delivery systems for buccal delivery as reported in the literature are reviewed, with a special emphasis on films.

2.2 THE ORAL CAVITY

2.2.1 Introduction

Among the various routes of drug delivery, transmucosal routes, which utilize the mucosal linings of the nasal; rectal; vaginal; ocular; and oral cavities, offer distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of first-pass effects and avoidance of presystemic elimination within the gastrointestinal tract (Shojaei *et al.*, 2001). Figure 2.1 below illustrates the difference between oral and buccal drug administration and hence shows the bypass of presystemic elimination achieved via buccal drug administration.

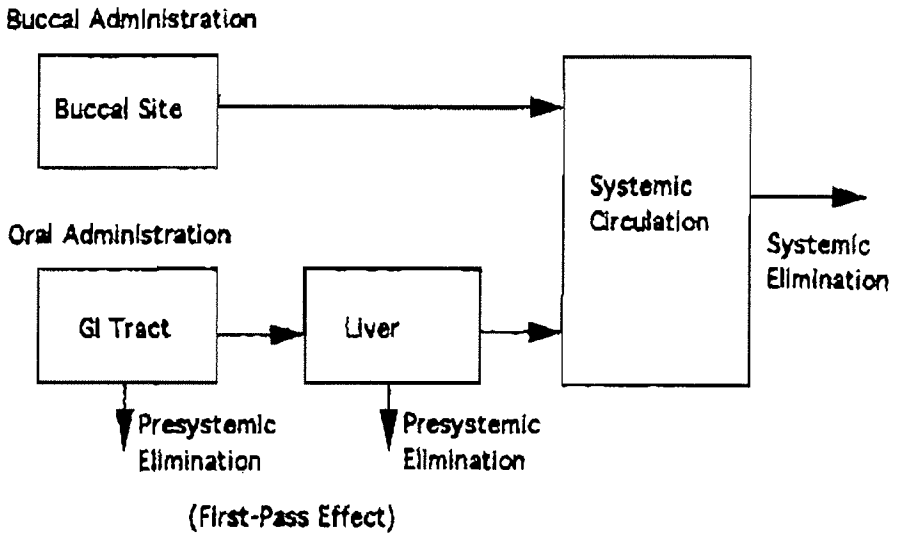

Figure 2.1. Buccal route of administration avoiding presystemic elimination of drug (Iga and Ogawa, 1997)

The potential irritation of and the irreversible damage to the ciliary action of the nasal cavity from nasal dosage forms, as well as the large intra- and intersubject variability in mucous secretion that affects drug absorption from this site, make the nasal cavity less attractive for drug delivery. Also, poor patient acceptance and compliance associated with ocular, rectal and vaginal drug delivery reserves these routes for effective local applications rather than for systemic drug administration (de Vries *et al.*, 1991; Shojaei *et al.*, 2001).

Considering the drawbacks of the abovementioned mucosal routes, the oral mucosal route, by virtue of its relatively large surface area and easy accessibility, poses as an excellent route for drug delivery (Wertz and Squire, 1991). Other advantages of this route include: increased patient compliance; reduced side effects associated with other routes; improved drug bioavailability, and optimised local therapy for treatment of oral infections (de Vries *et al.*, 1991). The oral mucosa is robust and shows short recovery times after stress or damage (de Vries *et al.*, 1991; Squire, 1991) and the virtual lack of Langerhans cells

(Bodde *et al.*, 1990) makes the oral mucosa tolerant to potential allergens, thus making it a feasible site for drug delivery.

2.2.2 Overview of the Oral Mucosa

Absorption of drug via the oral mucosal membranes was noted as early as 1847 (Sobrero, 1847), whilst the first reported systemic studies of oral cavity absorption were noted in 1935 and 1944 (Walton and Lacey, 1935; Walton, 1944). Research in oral mucosal drug delivery has since been a topic of tremendous interest (Katz and Barr, 1955; Gibaldi and Kanig, 1965; Squier and Johnson, 1975; Ishida *et al.*, 1981; Rathbone, 1991; Parodi *et al.*, 1996; Ali *et al.*, 2002; Nafee *et al.*, 2003; Perioli *et al.*, 2004; and Munasur *et al.*, 2006).

2.2.2.1 Classification of the Oral Mucosal Cavity

Within the oral mucosal cavity, delivery of drugs is classified into the following three categories:

2.2.2.1.1 Sublingual Delivery

The sublingual route of delivery involves administration of drug via the membrane of the tongue's ventral surface and floor of the mouth into the systemic circulation. The sublingual route is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs. This route has been extensively used for delivery of drugs which require a rapid onset of action, e.g. nitroglycerine (Ahuja *et al.*, 1997). Hence, many sublingual drug delivery systems have been designed to give rapid drug release, leading to high local drug concentrations in the sublingual region. As a result of salivary flow, these concentrations are sustained for a relatively short period of time, probably in the order of only minutes (Harris and Robinson, 1992).

The sublingual area does not appear to have an expanse of smooth and relatively immobile mucosa that would be suitable for the attachment of a retentive delivery system. For this reason, the main application of the sublingual route is likely to remain for delivery of small permeants for which short delivery times and infrequent delivery intervals are appropriate, or for which a rapid onset of action is desirable (Harris and Robinson, 1992).

2.2.2.1.2 Buccal Delivery

Buccal delivery is the administration of drug via the buccal mucosa, i.e. the inner lining of the cheeks and the upper and lower lips (Rossi *et al.*, 2005). Buccal mucosa is nonkeratinised and is reported to have an approximate thickness of 500 – 600 μm, a surface area of 50.2 cm^2 and a turnover time of 5 – 6 days. This route is also well vascularised with venous blood draining the buccal mucosa and reaching the heart directly via the internal jugular vein (Shojaei *et al.*, 2001, Hao and Heng, 2003).

The buccal site differs from the sublingual in a number of important respects. First, the buccal mucosa is less permeable than that of the sublingual and does not give the rapid onset of absorption seen with sublingual delivery. Second, the buccal mucosa appears to be better suited to the use of retentive systems, such as a mucoadhesive tablet or patch system, in that it has an expanse of smooth and relatively immobile surface for placement of such a system (Harris and Robinson, 1992; Shojaei *et al.*, 2001).

The buccal route appears to offer a series of other advantages, such as good accessibility, robustness of the epithelium, facile removal of the dosage form in case of need and satisfactory patient acceptance and compliance (Burgalassi *et al.*, 1996; Senel and Hincal, 2001). Also,

because the buccal cavity does not contain the aggressive peptidase enzymes encountered in the stomach and small intestine, it may be a suitable site for the delivery of certain therapeutic agents such as peptides, proteins (Woodley, 2001) and beta-blocking agents, e.g. propranolol (Taylan *et al.*, 1996; Akbari *et al.*, 2004).

The buccal route is therefore promising for systemic delivery of drugs that are subjected to extensive first-pass metabolism, and for orally inefficient drugs. It further offers a feasible alternative for non-invasive delivery of potent peptide and protein drug molecules (Shojaei *et al.*, 1998).

2.2.2.1.3 Local Delivery

Local delivery is drug delivery into the oral cavity for the treatment of over 400 different types of oral cavity disorders. This therapy provides the opportunity to deliver drugs directly to the disease site and with minimal risk of systemic side effects (Wertz and Squire, 1991). Studies for localized therapy include conditions such as: toothache (Ishida *et al.*, 1982); bacterial and fungal infections (Samaranayake and Ferguson, 1994); apothous and dental stomatitis (Nagai, 1985) and periodontal disease (Elkayam *et al.*, 1988; Collins *et al.*, 1989, Khanna *et al.*, 1996, Perugini *et al.*, 2003 and Perioli *et al.*, 2004).

2.2.3 Advantages of Drug Delivery via the Oral Mucosa

Drug delivery via the oral mucosa is advantageous as: it bypasses both intra-alimentary canal and hepatic first-pass metabolism (Remunan-Lopez *et al.*, 1998; Kurosaki and Kimura, 2000; Akbari *et al.*, 2004); is not influenced by varying gastric emptying rates or the presence of food (Kaus *et al.*, 1999); has a more rapid onset of absorption than the peroral pathway (Anders and Merkle, 1989); has

excellent accessibility (Burgalassi *et al.*, 1996; Senel and Hincal, 2001) which facilitates easy removal of dosage forms in emergencies; is generally more permeable than skin (Ahuja *et al.*, 1997); is less prone to damage or irritation than nasal mucosa (Anders and Merkle, 1989; de Vries *et al.*, 1991); is not sex-specific (de Vries *et al.*, 1991); and has better patient acceptance and compliance than vaginal or rectal dosage forms (Anders and Merkle, 1989; Burgalassi *et al.*, 1996). It permits the utilization of (a) unidirectional delivery devices, whereby only oral mucosa absorption occurs (de Vries *et al.*, 1991) and (b) buccal delivery devices which prevent diffusion-limiting mucous build-up (de Vries *et al.*, 1991).

2.2.4 Limitations of Drug Delivery via the Oral Mucosa

While there are several advantages, the oral mucosal route does possess certain disadvantages such as: the limited surface area of the oral cavity (≈ 100cm^2), which limits the dosage form size and amount of drug that can be loaded onto it (Hao and Heng, 2003); decreased buccal delivery time (≈ 4 – 6 hrs) as eating and/or drinking may require delivery device removal (Alur *et al.*, 2001); varying drug absorption by continually changing permeability characteristics due to rapid turnover of buccal mucosal epithelium (3 – 8 days) (Veuillez *et al.*, 2001); drug loss due to involuntary swallowing of saliva; varying drug levels in locally administered buccal systems due to non-uniform drug distribution within saliva; poor patient compliance or acceptance due to unpleasant tasting or rough textured dosage forms; hindered drug transport through the epithelia due to drug-mucin interactions; (Khanvilkar *et al.*, 2001) and limited drug use as drugs which change the physiological condition of the oral cavity may not be suitable for oral transmucosal delivery (Hao and Heng, 2003).

Nonetheless, the distinct advantages and recent progress made in delivering a variety of compounds render the disadvantages of this route much less significant. Hence there is significant research internationally in controlled release buccal drug delivery systems (Salamat-Miller *et al.*, 2005).

2.3 FUNDAMENTAL ASPECTS OF MUCOADHESION

A key element for drug delivery via the oral cavity is adhesion of the dosage form to the oral mucosa, achieved through the concept of mucoadhesion. This section highlights important concepts and mechanisms through which mucoadhesion is achieved.

2.3.1 Concepts of Mucoadhesion

Since the concept of mucoadhesives was introduced into the field of drug delivery, numerous definitions for adhesion have been proposed. The most popular definition is: a bioadhesive is a synthetic or biological material, which is capable of adhering to a biological substrate or tissue (Helliwell, 1993). When the biological substrate is mucous, the term "mucoadhesion" is employed (Park, 1989).

Mucoadhesive materials are hydrophilic macromolecules containing numerous hydrogen bond-forming groups. These materials can therefore be used for specific targeting of a drug to a particular region of the body for prolonged periods of time (Kamath and Park, 1994).

2.3.1.1 The Mucous Layer: Composition and Structure

The tissue layer primarily responsible for formation of the adhesive interface is mucous. The membranes of the oral cavity are covered with mucous and continuously supplied with fresh serous and mucous saliva (de Vries *et al.*, 1991). Mucous is a translucent and viscous

secretion from the goblet cells lining the epithelia, or from special exocrine glands with mucous cells acini, which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies between 50 - 450 μm (Kamath and Park, 1994). Mucous plays a vital role in protecting the mucosa against many aggressions: mechanical; chemical; bacterial or viral. An understanding of mucoadhesion is facilitated by significant knowledge of the mucous.

Apart from water, which represents more than 95% of the mucous, its other components are glycoproteins (0.5 - 5%), lipids in low proportions, mineral salts (1%), and free proteins (0.5 - 1%). However, the exact mucous composition varies depending on its source (Ahuja *et al.*, 1997). Glycoproteins are the main component responsible for the adhesive and cohesive properties of mucous. These are high molecular weight protein cores possessing attached oligosaccharide units (Figure 2.2. (a)). These units contain an average of 8 - 10 monosaccharide residues of five different types: L-fucose; D-galactose; *N*-acetyl-D-glucosamine; *N*-acetyl-D-galactosamine and sialic acid. The glycoprotein previously thought to be a tetramer (Figure 2.2. (b)) is now believed to be a terminally linked chain with numerous cross-linkings (Longer and Robinson, 1986).

Based on the structure of mucin, the mucous layer has four characteristics related to mucoadhesion:

- It is a network of linear, flexible and random coiled mucin molecules
- It is negatively charged due to sialic acid and sulphate residues
- It is a cross-linked network due to disulphide bonds and entanglement between mucin molecules
- It is highly hydrated.

At a pH > 2.8, the network is negatively charged, and it is this charge density that contributes to mucoadhesion (Duchene *et al.*, 1988).

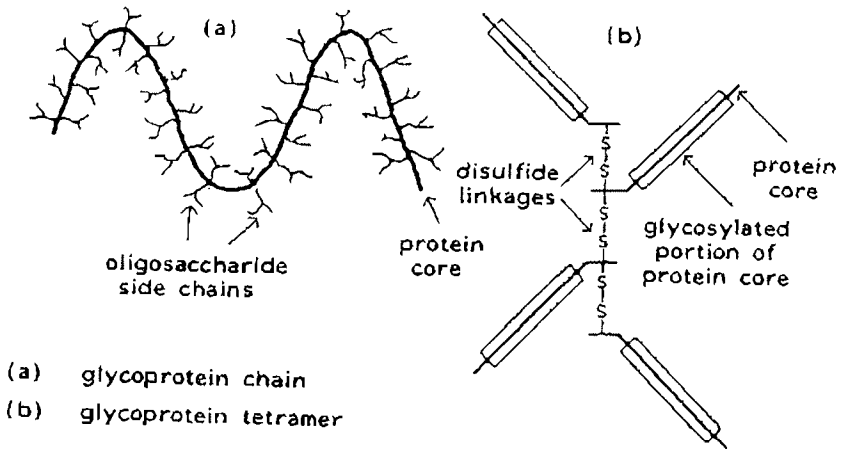

Figure 2.2. Schematic representation of mucous (a) glycoprotein chain (b) glycoprotein tetramer (Duchene *et al.*, 1988)

2.3.1.2 Mucoadhesion Mechanism

For mucoadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a mucoadhesive and a membrane, either from a good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive.

In the second stage, after contact has been established, penetration of the mucoadhesive into the crevice of the tissue surface, or interpenetration of the chains of the mucoadhesive with those of the mucous, takes place. Low chemical bonds can then settle (Duchene, *et al.*, 1988). An examination of the hydration rates of polymeric formulations with different mucoadhesive characteristics might be helpful to explore the mechanism underlying mucoadhesion (Eouani *et al.*, 2001).

2.3.1.3 *Theories of Mucoadhesion*

Several theories to explain the mechanisms of mucoadhesion have been proposed and extensively reviewed (Longer and Robinson, 1986; Duchene *et al.*, 1988; Gandhi and Robinson, 1988; Mikos and Peppas, 1990; Jimenez-Castellanos *et al.*, 1993; Ahuja *et al.*, 1997 and Lee *et al.*, 2000). In a particular system, one or more theories can equally well explain or contribute to the formation of mucoadhesive bonds. The proposed theories appearing in the literature are summarised and presented in Table 2.1.

2.3.2 Overview of Mucoadhesive Polymers

Mucoadhesive polymers have been used extensively in drug delivery systems to improve dosage form retention on the mucosae (Shojaei *et al.*, 2001), thereby providing an intimate contact between the dosage form and the absorbing tissue, which may result in high drug concentration in a local area (essential for localised therapy) and hence high drug flux through the absorbing tissue (important for systemic therapy) (Ahuja *et al.*, 1997). Formulations composed of mucoadhesive polymers find application at various sites, viz. eye; nose; gastrointestinal tract; rectum; vaginal cavity; and buccal cavity (Park and Robinson, 1984).

Polymers that adhere to the mucin-epithelial surface can be conveniently divided into three categories: (a) Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness; (b) Polymers that adhere through non-specific, non-covalent interactions, which are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant); and (c) Polymers that bind to specific receptor sites on the cell surface.

Table 2.1 Summary of theories of mucoadhesion

THEORY	DESCRIPTION OF THEORY	REFERENCE
Electronic Theory	The adhesive polymer and mucous have different electronic characteristics. When these two layers come into contact, a double layer of electrical charge forms at the interface, resulting in adhesion brought about by the attractive force from electron transfer across the electrical double layer.	Deryaguin *et al.*, 1997
Adsorption Theory	Adhesion of the polymer to the mucous is as a result of secondary surface forces such as van der Waal's forces, hydrogen bonds, or hydrophobic interactions. For a bioadhesive polymer with a carboxyl group, hydrogen bonding is considered to be the dominant force at the interface, whilst hydrophobic interactions provide an explanation for the fact that a bioadhesive may bind to a hydrophobic substrate more tightly than to a hydrophilic surface.	Wake, 1982
Wetting Theory	Primarily applicable to liquid bioadhesive systems and emphasises the intimate contact between the adhesive polymer and mucous. Thus a wetted surface is controlled by structural similarity, degree of cross-linking of the adhesive polymer, or use of a surfactant.	Helfand and Tagami, 1972
Diffusion Theory	Explains that the substrate and the adhesive polymer interpenetrate one another to a sufficient depth to create a semi-permanent adhesive bond. The penetration rate depends on the diffusion coefficients of both interpenetrating polymers, and the diffusion coefficient is known to depend on molecular weight and cross-linking density.	Wake, 1978
Mechanical Theory	Assumes that adhesion is a result of an interlocking of a liquid adhesive (upon setting) into regularities on a rough surface. Rough surfaces also provide an increased surface area available for interaction together with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.	Peppas and Sahlin, 1996
Fracture Theory	Differs from the others in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. This assumes that the failure of the adhesive bond occurs at the interface. However, failure usually occurs at the weakest component, which is typically a cohesive failure within one of the adhering surfaces.	Ahuja *et al.*, 1997

All three polymer types can be used in drug delivery (Ahuja *et al.*, 1997).

An ideal polymer for a mucoadhesive drug delivery system should possess the following characteristics. The polymer and its degradation products should be non-toxic and non-absorbable from the gastrointestinal tract. The polymer should be a non-irritant to the mucous membrane; preferably form a strong non-covalent bond with mucin-epithelial cell surfaces; adhere quickly to moist tissue and possess some site specificity; allow easy incorporation of the drug and offer no hindrance to its release; not decompose on storage or during the shelf life of the dosage form; not be expensive, so that the prepared dosage form remains competitive (Jimenez-Castellanos *et al.*, 1993).

Diverse classes of polymers have been investigated for their potential use as mucoadhesives and for many years, polymers which can adhere to either hard or soft tissue have been used in surgery and dentistry. These include: "superglue" polymers and monomeric alpha-cyanoacrylate esters which have been most frequently investigated and used; synthetic polymers such as polyurethanes, epoxy resins, polystyrene, acrylates and natural product cements (Park and Robinson, 1984).

In 1984, Park and Robinson used a fluorescent technique to investigate the mucoadhesive properties of several polymers. They concluded that cationic and anionic polymers bind more effectively than neutral polymers; polyanions are better than polycations in terms of binding/potential toxicity; water-soluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers; anionic polymers with sulphate groups bind more effectively than those with carboxylic groups; the

degree of binding is proportional to the charge density on the polymer; highly binding polymers include carboxymethyl cellulose, gelatin, hyaluronic acid, carbopol, and polycarbophil.

An interesting study by Smart (Smart *et al.*, 1984) has lead to the classification and ranking of mucoadhesive polymers and mucoadhesive force respectively, in relation to Pectin. This list, adapted from Junginger (1990), is presented in Table 2.2.

Table 2.2 Classification of mucoadhesive polymers (Junginger, 1990)

Test Polymer	Adhesive Force (Mean±SD)	Qualitative Bio(muco)adhesive Property
Sodium carboxymethyl cellulose	192.4 ± 12.0	Excellent
Poly(acrylic acid)	185.0 ± 10.3	
Tragacanth	154.4 ± 7.5	
Poly(methyl vinylether co-maleic anhydride)	147.7 ± 9.7	
	128.6 ± 4.0	
Poly(ethylene oxide)	128.0 ± 2.4	
Methylcellulose		
Sodium alginate	126.2 ± 12.0	Satisfactory
Hydroxypropylmethylcellulose	125.2 ± 16.7	
Karaya gum	125.2 ± 4.8	
Methylethylcellulose	117.4 ± 4.2	Fair
Soluble starch	117.2 ± 3.1	
Gelatin	115.8 ± 5.6	
Pectin	100.0 ± 2.4	Poor
Poly(vinyl pyrrolidone)	97.6 ± 3.9	
Poly(ethylene glycol)	96.0 ± 7.6	
Poly(vinyl alcohol)	94.8 ± 4.4	
Poly(hydroxyethylmethacrylate)	88.4 ± 2.3	
Hydroxypropylcellulose	87.1 ± 13.3	

Current mucoadhesive polymers are classified as "first generation" and "second generation" polymers (Lee *et al.*, 2000). The first generation or "off-the-shelf" polymers lack specificity and targeting capability. They adhere to mucous non-specifically, and have short retention times due to the rapid turnover of the mucous. Typical examples of such polymers are carbomers, chitosan, sodium alginate and the cellulose derivatives (Smart, 2005). The new generation of

mucoadhesives (except thiolated polymers) can adhere directly to the cell surface, instead of to the mucous. They interact with the cell surface by means of specific receptors or covalent bonding rather than non-specific mechanisms, characteristic of the previous polymers. Examples of such recently discovered mucoadhesive polymers include the incorporation of L-cysteine into thiolated polymers and the target-specific, lectin-mediated adhesive polymers (Salamat-Miller *et al.*, 2005).

In a study conducted by Bernkop-Schnurch *et al.* (2000), a positive correlation between the adhesive properties and increasing amounts of the polymer in dry compacts of polycarbophil covalently bound to L-cysteine was reported. The total work of adhesion of the 16:1 and 2:1 polycarbophil cysteine conjugates was 191 ± 47 µJ and 280 ± 67 µJ respectively, which was 2 – 3 times greater than the unmodified polymer (104 ± 21 µJ), thereby illustrating the improved mucoadhesive properties of thiolated polymers.

In an investigation by Clark and co-workers (2000), it was observed that lectin binding on human buccal cells occurred within 20 seconds and appeared not to be detached by saliva flushing, thus indicating the effectiveness of lectin-mediated polymers.

These classes of polymers prove promising for the delivery of a variety of drug molecules, particularly macromolecules. This generates new possibilities for more site-specific drug receptor interactions and improved targeted drug delivery.

2.3.3 Factors Affecting Mucoadhesive Properties

The adhesiveness of a mucoadhesive polymer is determined by its intrinsic polymeric properties and the environment in which it is

placed. It is also influenced by many factors (Duchene *et al.*, 1988; Jimenez-Castellanos *et al.*, 1993) as summarized below:

2.3.3.1 Polymer Related Factors

2.3.3.1.1 Molecular Weight

The optimum molecular weight for maximum mucoadhesion is dependent upon the type of mucoadhesive polymer. Their nature dictates the degree of swelling in water, which in turn determines interpenetration of polymer molecules within the mucous. Mucoadhesive forces increase with the molecular weight of the polymer up to 100 000, beyond which any further increase has no effect (Gurny *et al.*, 1984). The fact that mucoadhesiveness improves with molecular weight implies that interpenetration is more critical for lower molecular weight polymers to be a good mucoadhesive, while entanglement is important for higher molecular weight polymers. To allow chain interpenetration, the polymer molecule must have an adequate length. Size and configuration are also important factors (Ahuja *et al.*, 1997).

2.3.3.1.2 Concentration of Active Polymer

Bremecker (1983) argues that there is an optimum concentration of polymer corresponding to the best mucoadhesion. However, in highly concentrated systems, there is a significant decrease in adhesive strength because the coiled molecules become solvent poor, while the chains available for interpenetration are not numerous. This result seems to be of interest only for liquid mucoadhesive dosage forms since Duchene *et al.* (1988) showed in their study that, for solid dosage forms, the higher the polymer concentration is, the stronger the mucoadhesion becomes.

2.3.3.1.3 Flexibility of Polymer Chains

Chain flexibility is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked, the mobility of the individual polymer chains decreases and thus the effective length of the chain that can penetrate into the mucous layer decreases, which in turn reduces mucoadhesive strength (Lee *et al.*, 2000).

2.3.3.1.4 Spatial Conformation

Apart from molecular weight or chain length, spatial conformation of a molecule is also important. It has been shown that despite the large difference in the molecular weights of dextrans and polyethylene glycol (PEG) (19,500,000 and 200,000 respectively), they have similar adhesive strengths. This occurs because the helical conformation of dextran may shield many adhesively active groups primarily responsible for adhesion, unlike the PEG polymers, which have a linear conformation (Ahuja *et al.*, 1997).

2.3.3.2 *Environment-related Factors*

2.3.3.2.1 pH

pH was found to have a significant effect on mucoadhesion, as it influences the charge on the surface of both the polymer and the mucous. Mucous will have a different charge density depending on pH because of differences in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptide backbone (Lee *et al.*, 2000).

2.3.3.2.2 Applied Strength

To place a solid mucoadhesive system, it is necessary to apply a defined strength. Irrespective of the polymer, the strength of adhesion increases with applied strength or with the duration of its application up to an optimum (Duchene *et al.*, 1988). However, Smart (1991) showed that a small adhesive force was required to hold a dosage form in place. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin (Ahuja *et al.*, 1997).

2.3.3.2.3 Initial Contact Time

The initial contact time between mucoadhesives and the mucous layer determines the extent of swelling and the interpenetration of polymer chains. Together with the initial pressure, the initial contact time can dramatically affect the performance of a system. The mucoadhesive strength increases as the initial contact time increases. However, longer initial contact time should be based on tissue viability (Ahuja *et al.*, 1997).

2.3.3.2.4 Selection of the Model Substrate Surface

Since physical and biological changes may occur in the mucous gels or tissues under certain experimental conditions, the handling and treatment of biological substrates become important factors during testing of mucoadhesives. Biological substrate viability should be confirmed by examining certain properties such as permeability, electrophysiology, or histology. Such studies may be necessary before and after performing *in vitro* tests using tissues (Kamath and Park, 1994).

2.3.3.2.5 Swelling

The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. Swelling depends on polymer concentration, ionic strength as well as on the presence of water. During the dynamic process of mucoadhesion, maximum mucoadhesion *in vitro* occurs with optimum water content. When swelling is too great due to overhydration, a slippery mucilage forms and a decrease in mucoadhesion occurs. Such a phenomenon must not occur too early, in order to lead to a sufficient action of the mucoadhesive system. Its appearance allows easy detachment of the mucoadhesive system after the discharge of the active ingredient (Ahuja *et al.*, 1997; Lee *et al.*, 2000).

2.3.3.3 *Physiological Variables*

2.3.3.3.1 Mucin Turnover

The natural turnover of mucin molecules from the mucous layer is important for the following two reasons (Kamath and Park, 1994). Firstly, the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucous layer. Irrespective of the mucoadhesive strength, mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesives; however, there is no available information on this aspect. Secondly, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they interact with the mucous layer. In addition, mucin turnover may also depend on other factors such as the presence of food (Ahuja *et al.*, 1997).

2.3.3.3.2 Disease States

The physicochemical properties of mucous are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract, and inflammatory conditions of the eye. The exact structural changes taking place in mucous under these conditions are not clearly understood. Therefore, if mucoadhesives are to be used in disease states, the mucoadhesive property needs to be evaluated under the same conditions (Kamath and Park, 1994).

2.4 CONTROLLED DRUG DELIVERY

2.4.1 Concept of Controlled Release

The advantages of a mucoadhesive buccal drug delivery system can be further enhanced by ensuring that the drug is released in a controlled manner from the system. Controlled release drug administration does not only imply a prolonged duration of drug delivery, as in sustained release and prolonged release, but also implies predictability and reproducibility of drug release kinetics (Chien, 1982). Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period; it may be cyclic over a long period; or it may be triggered by the environment or other external events. The purpose of controlling the drug delivery is to achieve an improved therapeutic effect while eliminating the potential for both under- and overdosing (Brannon-Peppas, 1997). Administration of drugs in conventional dosage forms often results in peak-valley fluctuations of drug concentrations in systemic circulation, i.e. the blood levels may rise above the therapeutic range, causing an

unwanted reaction, then fall within the therapeutic range for an hour or two before dropping below this range rendering the drug pharmacologically inactive (Chien, 1982). This cycle is repeated upon administration of subsequent doses and results in drug delivery that produces desired effects for approximately 40 – 60% of the time (Sanders, 1985). Conventional dosage forms provide only a single transient burst of drug and a pharmacological effect is evident only whilst the drug concentration is within the therapeutic range which may pose problems for drugs with a narrow therapeutic window (Jantzen and Robinson, 1996). Therefore to maintain the therapeutic blood level within an effective range, conventional dosage forms require frequent dosing at specific time intervals. A well-designed, controlled release drug delivery system can significantly reduce the frequency of dosing and also maintain a steady drug concentration in the blood within a narrow therapeutic window (Chien, 1982) as depicted in Figure 2.3.

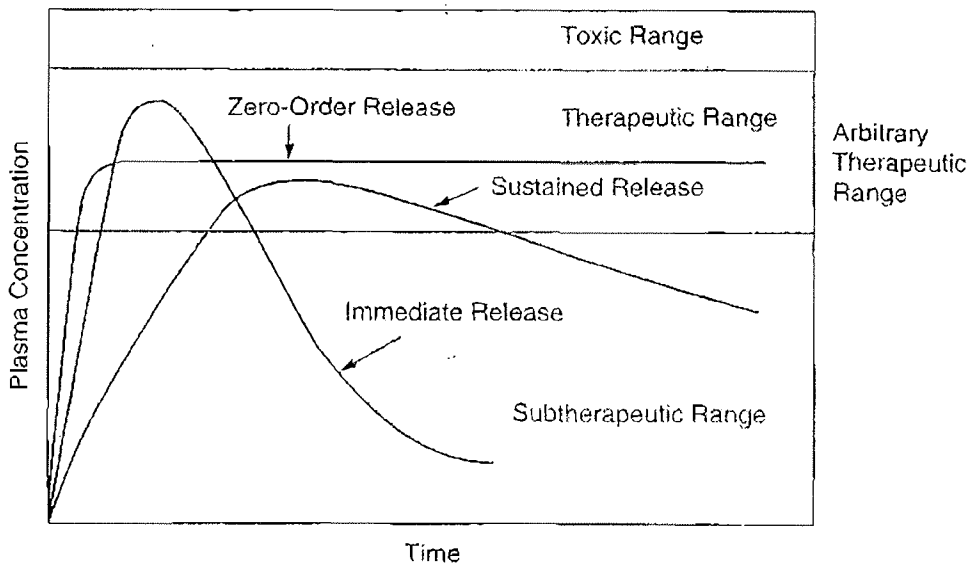

Figure 2.3 Drug Levels vs Time Profile Depicting Differences between Zero Order Controlled Release, First Order Controlled Release and Release from a Conventional Dosage Form (Jantzen and Robinson, 1996).

Ideally, a desirable drug delivery system should be one that can deliver the drug at a constant rate directly to the site(s) of pharmacologic action, with the body as a whole acting as a perfect sink for the rapid elimination of the drug (Levy, 1973).

2.4.2 Benefits of Controlled Drug Delivery

The success of drug therapy is critically dependent upon the ability of the patient to comply with the regimen, and most often failure to respond to treatment is as a result of patient non-compliance. This may be resolved by administration of a controlled release drug delivery system, as its prolonged release characteristics minimise the need for frequent dosing which in turn assures better compliance with the dosage regimen (Chien, 1982), ultimately reducing patient care time (Ranade, 1991; Majeti *et al.*, 2001).

The ability of controlled release drug delivery systems to maintain constant blood drug concentrations within a narrow therapeutic window avoids undesirable therapeutic plasma levels (Livingstone and Livingstone, 1988), thereby minimizing the incidence and severity of adverse side effects (Levy, 1973). This aids in improving patient compliance.

Controlled drug delivery systems may prove more cost effective for the patient, as a single dose of the modified release product might cost less than an equivalent conventional drug dose that requires frequent administration (Shargel and Yu, 1985).

Controlled release systems may also enhance the bioavailability of shorter half-life drugs through predictable and reproducible release rates for an extended duration (Kellaway, 1988).

The controlled release system can also be designed to release drugs in the vicinity of the target tissues that require treatment, thereby minimizing drug exposure to non-target tissue. This localisation of drug administration significantly reduces the dose and adverse side effects of the drug are eliminated (Chien, 1982).

2.4.3 Types of Controlled Release Drug Delivery Systems

In recent years, there have been numerous developments in polymeric carriers and controlled release systems. From the literature it is evident that two types of oral modified release dosage forms exist (Ritschel, 1989a), i.e. single unit (capsules and tablets) and multiple unit (microcapsules and granules) dosage forms. The latter are often referred to as the bead or pellet type preparation (Shargel and Yu, 1985). Examples of controlled release systems mentioned in the literature are described below:

- Monolithic devices whereby the drug is in a polymer matrix (Douglas *et al.*, 1987; Davis & Illum, 1988; Perugini *et al.*, 2003)
- Reservoir devices whereby the drug is contained by the polymer (Lehman *et al.*, 1979; Oppenheim, 1981)
- Polymeric colloidal particles such as microparticles, microspheres or nanoparticles in the form of matrix or reservoir devices (Oppenheim, 1981; Douglas *et al.*, 1987; Govender *et al.*, 2005)
- Drug contained by a polymer containing a hydrophilic and/or leachable additive, e.g. surfactant, to give a porous device, or a device in which the drug may be osmotically controlled (both reservoir and matrix devices) (Muhammed *et al.*, 1991)
- Enteric coatings that ionise and dissolve at a suitable pH (Muhammed *et al.*, 1991)

- Polymers with attached pendant drug molecules (Chafi *et al.*, 1992)
- Devices where the release rate is controlled dynamically, such as the osmotic pump

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled release systems can respond to changes in the biological environment and deliver or cease to deliver drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered (Brannon-Peppas, 1997).

2.5 BUCCAL DRUG DELIVERY

The limitations of current drug therapies have driven the impetus to explore the development of novel drug delivery systems, such as mucoadhesive controlled release buccal drug delivery systems. Such systems should serve to circumvent problems and optimise treatment for numerous medical conditions.

2.5.1 Candidate Drugs and Disease States

A number of relevant buccal mucoadhesive dosage forms have been developed for a variety of drugs. Drugs with short half-lives; requiring a sustained effect; and exhibiting poor permeability, sensitivity to enzymatic degradation, and poor solubility may be successfully delivered via a mucoadhesive oral delivery system (Ahuja *et al.*, 1997). Drugs which undergo gastrointestinal degradation and peptides may

benefit from buccal delivery. Several peptides, including a thyrotropin-releasing hormone, insulin, octreotide, leuprolide, and oxytocin, have been delivered via the buccal route, albeit with relatively low bioavailability (0.5 - 1%) (Veuillez *et al.*, 2001) owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa. Other drugs that undergo extreme first pass metabolism can also benefit from buccal delivery. These include: β-blockers, e.g. propranolol HCl for hypertension; hypoglycaemics e.g. glibenclamide for diabetes mellitus and antiretrovirals e.g. 2', 3'-dideoxycytidine for HIV/AIDS therapy.

2.5.2 Design of Buccal Dosage Forms

Buccal mucoadhesive dosage forms can be categorised into three types based on their geometry, as depicted in Figure 2.4. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In Type II devices, an impermeable backing layer is superimposed on top of the drug-loaded mucoadhesive layer, creating a double-layered device, thus preventing drug loss from the top of the dosage form into the oral cavity. Type III is a unidirectional release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every surface of the dosage form, except the one in contact with the buccal mucosa (Hao and Heng, 2003; Salamat-Miller *et al.*, 2005).

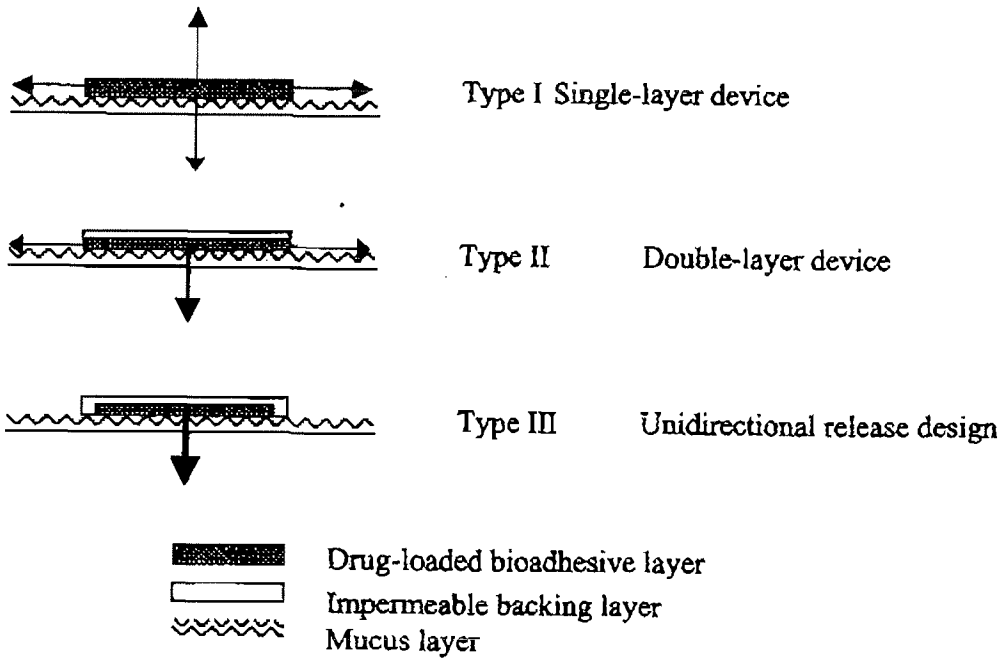

Figure 2.4. Schematic representation of buccal dosage form design (Hao and Heng, 2003)

Buccal dosage forms can also be classified as either a 'reservoir'- or 'matrix'-type. In the reservoir-type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate. In the matrix-type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network (Salamat-Miller *et al.*, 2005).

2.5.3 Characteristics of a Buccal Delivery System

In general, dosage forms designed for buccal drug delivery should be small and flexible enough to be acceptable for patients, and should not cause irritation (Shojaei, 1998). Other desired characteristics of a buccal mucoadhesive dosage form include: high drug loading capacity; controlled drug release; good mucoadhesive properties; smooth surface; tastelessness; and convenient application. Erodible formulations can be beneficial because they do not require system

retrieval at the end of desired dosing intervals (Salamat-Miller *et al.*, 2005).

2.5.4 Types of Buccal Delivery Systems

Due to the advantages associated with delivering drugs via the buccal route, as illustrated in the above mentioned examples, buccal delivery of the desired drug has been the subject of interest since the early 1980's. In light of this, various delivery systems have been investigated for administration via this route. These include: tablets, gels, ointments, patches, and films, which are described in greater detail below.

2.5.4.1 Buccal Tablets

To date tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat and oval with a diameter of approximately 5 – 8 mm (Rathbone *et al.*, 1994). Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in the position until release is complete. The major drawback of these tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use (Salamat-Miller *et al.*, 2005). An example of a buccal tablet is that formulated by Remunan-Lopez *et al.* (1998). Bilayered tablets were prepared by compressing the propranolol/chitosan mixture onto a previously obtained backing ethylcellulose tablet using a compressing machine. Propranolol release from these tablets was rapid, with almost 100% release within 4 hours. This is in contrast to a study conducted by Munasur *et al.* (2006) in which PAA/CMC/PVP tablets exhibited a desired controlled release profile, i.e. 10.27% and 84.37% propranolol was released at 1 hour and 8 hours respectively.

2.5.4.2 Buccal Gels and Ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches and films. Poor retention of the gels at the site of application has been overcome by using mucoadhesive formulations (Senel *et al.*, 2000; Ikinci *et al.*, 2002; Tsutsumi *et al.*, 2002). Hydrogels are also a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion (Martin *et al.*, 2003). The application of mucoadhesive gels provides an extended retention time in the oral cavity, adequate drug penetration, as well as high efficacy and patient acceptability.

A major application of adhesive gels is the local delivery of medicinal agents for the treatment of periodontitis (Salamat-Miller *et al.*, 2005). Mucoadhesive ointments have not been as extensively described in the literature as other dosage forms, especially when compared to tablets and patches (Ishida *et al.*, 1983a). Ointments are composed mainly as a hydrogel suspension in a hydrophobic base and primarily adhere to the mucous layer where they swell to form gel after contact with aqueous media (Anlar *et al.*, 2003). However, it is possible for them to overhydrate to form a slippery mucilage which may limit their use (Smart *et al.*, 1984; Smart, 1991). Ishida *et al.* (1983b) formulated a highly viscous gel containing carbopol and hydroxypropylcellulose for ointment dosage forms that were maintained on the tissue for up to 8 hours. Senel *et al.* (2000) prepared a chitosan hydrogel for the treatment of candidiasis. The viscosity of a 2% chitosan gel was higher than that of a 1% gel, which made it more applicable for topical application due to ease of spreading. In collaboration with

antimicrobial studies, it was concluded that a 2% chitosan gel containing 0.1% chlorhexidine could be used for this purpose.

2.5.4.3 Buccal Patches

Mucoadhesive patches may range from simple erodible and nonerodible adhesive disks to laminated systems (Ishida *et al.*, 1981). Patches are laminates consisting of an impermeable backing layer, a drug reservoir layer from which the drug is released in a controlled manner, and a mucoadhesive surface for mucosal attachment. The most successful approach for buccal mucosal delivery of peptides has been a mucoadhesive formulation that offers increased contact with the mucosa (Veuillez *et al.*, 2001). Generally, patches are designed with dimensions ranging from 1 – 3 cm^2 so as to be convenient and comfortable to the patient. Patches must also be flexible and may be ellipsoid in shape to fit onto the centre of the buccal mucosa (Merkle *et al.*, 1990). Patches can be designed to provide either unidirectional or bidirectional release of the drug (Ahuja *et al.*, 1997). Anders and Merkel (1989) developed patches consisting of two-ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The patch adhered to the mucosa for 30 minutes in the case of HEC and up to 15 minutes was achieved for HPC containing patches. Nafee *et al.* (2003) also prepared patches containing HPC. The patches contained 10 mg micoazole nitrate. *In vitro* residence time on mucosa observed for patches composed of HEC and PVP was 6-10 hours, which was much longer than that obtained in the study by Anders and Merkel (1989) mentioned above.

2.5.4.4. Buccal Films

The use of polymeric films for buccal delivery has not yet been widely investigated, although they have been extensively employed in

pharmaceutical tablet-coating formulations to protect tablet cores from environmental extremes, improve appearance, mask undesirable taste, and control the drug release (Deshpande *et al.*, 1997). Films are the most recently developed dosage form for buccal administration, as illustrated in Table 2.3 which provides a summary of buccal films investigated. As seen from the table, little work that is targeted specifically to buccal films containing propranolol HCl has been done. Only one investigation into the design and evaluation of bilaminated chitosan films containing an ethyl cellulose backing layer which was done by Remunan-Lopez *et al.* (1998) has been reported. Therefore, a study on multipolymeric monolayered buccal films containing propranolol HCl is warranted.

Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva (Anders and Merkle, 1989). Moreover, in the case of local delivery for oral diseases, the films also aid to protect the wound surface, thus helping to reduce pain and treat the disease more effectively (Peh and Wong, 1999). An ideal film should be flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It must also possess good mucoadhesive strength in order to be retained in the mouth for the desired duration of action. In order to prevent discomfort, swelling of the film, if it occurs, should not be too extensive (Peh and Wong, 1999; Salamat-Miller *et al.*, 2005). For these reasons, it has become critical and essential to evaluate the mechanical, mucoadhesive, and swelling properties of buccal films.

Table 2.3. Summary of investigated buccal films

ACTIVE INGREDIENT	POLYMERS USED	REFERENCE
Tetracaine, Thiamphenicol, Triacetin	HPC	Yotsuyanagi *et al.*, 1985
Tetracycline	Atelocollagen	Minabe *et al.*, 1989
Insulin	Gelatin, CP 934P	Ritschel *et al.*, 1989b
Isosorbide dinitrate	HPC, HPMC	Danjo *et al.*, 1994
Nifedipine	Sodium Alginate, MC, PVP, PEG	Save *et al.*, 1994
Chlohexidine diacetate	EC	Jones and Medlicott, 1995
Glibenclamide	Chitosan , PVP	Ilango *et al.*, 1997
Lidocaine HCl	EC, HPC	Kohda *et al.*, 1997
Tetracycline, Ofloxacin, Miconozole, Guaiazulene, Triacetin	HPC	Oguchi *et al.*, 1998
Acyclovir	Copolymer of acrylic acid and PEG	Shojaei *et al.*, 1998
Nifedipine, Propranolol HCl	Chitosan, EC	Remunan-Lopez *et al.*, 1998
Dipotassium glycyrrhizate	PC, HPC, EC	Rhee *et al.*, 1999
Chlorhexidine digluconate	Chitosan	Senel *et al.*, 2000
Lidocaine	HPC	Okamoto *et al.*, 2001
Salmon calcitonin	PC, Eudragit® S-100	Cui and Mumper, 2002b
CMV-β-gal plasmid DNA or β-gal protein	PC, Eudragit® S-100	Cui and Mumper, 2002a
Chlorhexidine	Chitosan	Ikinci *et al.*, 2002
Testosterone	PC, Eudragit® S-100	Jay *et al.*, 2002
Lidocaine	HPC	Okamoto *et al.*, 2002
Thiocolchicoside	Gelatin, CMC	Artusi *et al.*, 2003
Acyclovir	Chitosan HCl, PAA sodium salt	Rossi *et al.*, 2003
Myoglobin	5-Methyl-pyrrolidinone chitosan	Colonna *et al.*, 2006

2.6 FILMS

Since this study focused on the investigation films, the following section will focus on the following aspects:

- Preparation methods for films
- Characterisation studies on films
- Therapeutic applications of films

2.6.1 Methods of Film Preparation

There are two methods widely used for the preparation of polymeric films: one is a solvent evaporation method, and the other is a solvent-free, hot-melt method (Crank and Park, 1968).

2.6.1.1 Film Casting

The primary method currently employed for the manufacture of mucoadhesive films is a solvent casting technique using organic or aqueous solvent systems (Crowley *et al.*, 2004, Repka *et al.*, 2004). The drug and polymer(s) are first dissolved in a casting solvent or solvent mixture. The solution is then cast into films, dried, and finally laminated with a backing layer or a release liner. The backing layer helps retard the diffusion of saliva into the drug layer, thereby enhancing adhesion time and reducing drug loss into the oral cavity (Salamat-Miller *et al.*, 2005).

The choice of proper solvents for polymer dissolving is an important issue in this method. A solvent with a large molar volume is preferred due to easy evaporation during the film formation process. However, the toxicity of the organic solvent residues and the influence of environmental protection are major problems incurred in this method (Lin and Lee, 2003). Although this method is cost effective and does

not require the use of sophisticated apparatus, it has certain limitations. These limitations are due to the use of relatively long drying times during which the formation of agglomerates randomly distributes the film components and any active present as well. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of drug for the recommended treatment, which is ultimately harmful to the patient (US Patent No. 60/443,741, 2004). Perugini *et al.* (2003) used a solvent-casting method to prepare both monolayered and multilayered ipriflavone-loaded films for insertion into the periodontal pocket for the treatment of periodontitis. They concluded that monolayered films were more suitable for utilisation in the periodontal cavity, as they were thinner than the multilayered films produced.

2.6.1.1.1 Emulsification of Immiscible Liquids for Film Casting

The above method of polymer-drug solution preparation for casting onto trays clearly cannot be used where the drug and polymer/s are of opposing solubilities and therefore dissolved in immiscible liquids. In this study, an emulsification of the immiscible organic and aqueous phases (Chapter Three) was employed to obtain a uniform dispersion of both phases to enable film casting as a single layer.

Since films and not emulsions were of focus as a drug delivery system in this study, a comprehensive review of emulsions as drug delivery systems is not presented. Such reviews should rather be found in Reiger (1986) and Billany (2002). Also, several original research articles on emulsions as a drug delivery system are available in the literature (Riess and Weers, 1996; Nasirideen *et al.*, 1998; Bjerregaard *et al.*, 1999; Norden *et al.*, 2001; Ueda *et al.*, 2003; Wang *et al.*, 2006). This section presents a brief summary of essential theoretical concepts for emulsification only, as described in Reiger (1986) and Billay (2002).

2.6.1.1.1.1 Definition and Types of Emulsions

Emulsions are normally formed by "mixing" two immiscible liquids. An emulsion is therefore defined as two immiscible liquids, one of which is finely subdivided and uniformly distributed as droplets throughout the other. The emulsion may be stabilised by the incorporation of an emulsifying agent/emulgent. The dispersed liquid or internal phase usually consists of globules with diameters down to 0.1 μm, which are distributed within the external or continuous phases. There are various types of emulsions which consist of mixtures of an aqueous phase with various oils and/or waxes. An oil-in-water emulsion is one where the oil droplets are dispersed throughout the aqueous phase, while a water-in-oil (w/o) emulsion is one where the water is dispersed throughout the oil. Multiple emulsions, where a small water droplet can be enclosed in a larger oil droplet which is itself dispersed in water, may also be obtained. This results in a "water-in-oil-in-water" (w/o/w) emulsion. The alternative o/w/o emulsion is also possible (Billany, 2002).

2.6.1.1.1.2 Formulation Components for Emulsions

In addition to the oil and water phases, an emulsifying agent is one of the most important components in an emulsion. The emulsifying agent/s is necessary to ensure emulsification during manufacture and also to ensure emulsion stability during the shelf life of the product. They function by having the ability to form an adsorbed film around the dispersed droplets between the two phases, thereby maintaining emulsion stability. Emulsifiers can be divided into three main classifications, i.e. synthetic or semi-synthetic surface-active agents, naturally occurring materials and their derivatives, and finely divided solids. The type and quantity of emulsifier are important for producing the most physically stable emulsion for a particular oil/water combination; hence a useful method, i.e. the hydrophile-lipophile (HLB) balance method, has been devised. This method is described in Billany (2002). Buffers can also be added to maintain chemical

stability, control tonicity or ensure physiological compatibility. Density modifiers such as sucrose can be added to further enhance stability by preventing sedimentation or creaming. Humectants may also be added to reduce evaporation of water from the packaged product when the closure is removed or from the surface of the skin after application. Other formulation additives include antioxidants, flavours, colours, perfumes and sweetening agents (Reiger, 1986; Billany, 2002).

2.6.1.1.1.3 Preparation of Emulsions

Emulsions rarely form spontaneously. Rather, emulsion preparation by the commonly employed dispersion method requires a sequence of processes for breaking up the internal phase into droplets and for stabilizing them in the external phase (Reiger, 1986). The choice of suitable equipment for emulsification of the two immiscible liquids depends mainly on the intensity of shearing required to produce a suitable globule size and viscosity to achieve physical stability. Often simple blending of the oil and water phases with a suitable emulgent system may be sufficient to produce satisfactory emulsions. The initial blending may be achieved on a small scale by the use of a mortar and pestle or by using a mixer fitted with an impeller-type of agitator. Additional, processing using a homogeniser can also be undertaken in order to reduce globule size still further and enhance stability. A more intense rate of shearing can also be achieved using a turbine mixer such as the Silverson mixer-homogeniser. Colloid mills are also suitable for preparing emulsions on a continuous basis (Billany, 2002).

During manufacture, the disperse phase is usually added to the continuous phase during initial mixing. The other ingredients are dissolved, prior to mixing, in the phase in which they are soluble. Oil-in-water emulsions can, however, sometimes be made by the phase inversion technique. In this method the aqueous phase is added slowly to the oil phase during mixing. Initially, a w/o emulsion is formed, but as

further aqueous phase is added, the emulsion inverts to form the intended product. If any of the oily excipients are of solid or semisolid consistency, they must be melted before mixing. The aqueous phase must be heated to the same temperature to avoid premature solidification of the oil phase by the colder water before emulsification has taken place. Because of the increased kinetic motion of the emulgent molecules at the oil/water interface, however, it is necessary to continue stirring the emulsion during cooling to avoid demulsification. Volatile ingredients such as flavours and perfumes are usually added after the emulsion has cooled (Billany, 2002).

2.6.1.1.1.4 Physical Stability of Emulsions

A stable emulsion is one where the dispersed globules retain their initial character and remain uniformly distributed throughout the continuous phase. Several types of deviations from this ideal behaviour can occur. These deviations, together with approaches to avoid them, are summarized below from Billany (2002).

2.6.1.1.1.4.1 Creaming

Creaming involves the separation of an emulsion into two regions: one of which is richer in the disperse phase than the other. This is not considered serious since a uniform dispersion can be reobtained simply by shaking the emulsion. It is, however, undesirable because it increases the chances of droplets coalescing due to their close proximity to one another. The rate of creaming can be reduced by producing an emulsion of small droplet size, increasing the viscosity of the continuous phase, reducing the density difference between the two phases, and controlling the disperse phase concentration.

2.6.1.1.1.4.2 Flocculation

Flocculation occurs when there is aggregation of the dispersed globules into loose clusters within the emulsion preparation. While the

individual droplets retain their identities, each cluster behaves physically as a single unit. As flocculation must precede coalescence, any factor that prevents or reduces flocculation would therefore maintain emulsion stability. Redispersion of the emulsion can be easily achieved by shaking. Primary minimum flocculation, however, is more serious and redispersion is not so easy.

2.6.1.1.1.4.3 Coalescence

The coalescence of oil globules in an o/w emulsion can be resisted by the presence of a mechanically strong adsorbed layer of emulsifier around each globule. This is accomplished either by the presence of a condensed mixed monolayer of lipophilic and hydrophilic emulgents, or by a multimolecular film of a hydrophilic material.

2.6.1.2 Hot-melt Extrusion

Hot-melt extrusion (HME) is one of the most widely applied processing techniques in the plastic industry. For pharmaceutical systems, several research groups have recently demonstrated that the HME technique is a viable method to prepare numerous drug delivery systems (Repka *et al.*, 2004). It has recently been used to produce thin, flexible films for topical drug delivery using Eudragit® E100. In this study, HME films were compared to cast films, and differences were observed in the drug dissolution rate and mechanical properties. It was also reported that lidocaine HCl was able to plasticise the HME film and it was concluded that the differences in dissolution rate and mechanical properties were due to dissolution of the drug in polymer when prepared by HME (Aitken-Nichol *et al.*, 1996). In a study by Crowley *et al.* (2004), the optimal HME process parameters for the preparation of polyethylene oxide films were as follows: the extruder was equipped with a nitalloy 135M screw; a 6 inch flex film die; a screw speed of 40 rpm; three heating zones and die temperature set to 60, 75, 90 and 100°C;

residence time of materials in the extruder was approximately 2-3 minutes. Polymers with low melting points can be candidates for this method (Lin and Yu, 2001). Although hot-melt extrusion may overcome the drawbacks of the simple solvent-casting technique, this method requires the use of expensive and sophisticated equipment, such as an extruder, to fabricate films.

2.6.2 Characterisation of Films

Since an ideal buccal film should be flexible and elastic for improved patient comfort and acceptance; soft yet strong enough to withstand stress due to mouth movements; possess good mucoadhesive strength to remain attached to the mucosa for prolonged periods; and release drug in a controlled manner in controlled release systems, evaluation of the films by means of *in vitro* and *in vivo* characterisation studies during formulation has become imperative for the production of a superior quality film. The most common characterisation studies include mechanical; mucoadhesive; swelling and erosion; drug release testing and surface morphology analysis using scanning electron microscopy. These will be briefly described in the following section. Other characterisation studies include: weight; thickness and surface pH measurements; thermal characterisation and permeation studies.

2.6.2.1 Mechanical Testing

Mechanical properties of a film can be evaluated using a texture analyser, e.g. TA-XT2*i*, or similar equipment. The stress-strain curve obtained from TPA allows the calculation of mechanical properties of the product. These include, among others, tensile strength; elasticity; and compressibility (Jones *et al.*, 1996). Tensile testing gives an indication of the strength of the film reflected by the following

parameters: tensile strength (TS); elastic modulus (EM); elongation at break (E/B); and strain (S) (Peh and Wong, 1999). For example, a soft and weak polymer is characterised by a low TS, EM and E/B (Aulton *et al.*, 1981).

2.6.2.2 Mucoadhesive Testing

Tensile testing using a TA-XT2*i* texture analyser is also a useful technique for characterising the mucoadhesive properties of pharmaceutical dosage forms, including films. For mucoadhesive measurements, a sample of the prepared polymeric film is attached to the base of a probe which is fixed to the mobile arm of the TA-XT2*i*. A piece of mucosa or mucin is mounted on a platform of the TA-XT2*i* and hydrated for a predetermined time. Upon contact between the film and mucous layer, a constant force is applied for a predetermined time. The mucoadhesive performance of the sample is determined by measuring the resistance to the withdrawal of the probe (Maximum Detachment Force; MDF in Newtons) which reflects the mucoadhesion characterisation of the film with mucous, and the area under the force-distance curve (AUC in *mJ*) represents the work or energy required for the detachment of the two systems (mucosa/polymeric film) (Eouani *et al.*, 2001). Peh and Wong *et al.* (1999) used this method to compare the mucoadhesive strength of drug-free films of SCMC and HPMC, both containing varying amounts of CP. They reported that SCMC films were slightly more mucoadhesive than HPMC films of similar compositions.

2.6.2.3 Swelling and Erosion

The swelling of polymeric films is evaluated by measurement of weight (Peh and Wong, 1999; Eouani *et al.*, 2001). Each film is weighed before and after wetting with an appropriate medium such as artificial saliva,

and the degree of swelling is calculated (Peh and Wong, 1999). They also highlighted that swelling properties are important when film integrity is evaluated (Perioli *et al.*, 2004). It impacts on mucoadhesion, as studies have shown that shortly after the beginning of swelling, adhesion does occur (Chen and Cyr, 1970). A marked increase in surface area during swelling can promote drug release. However, the increase in diffusional pathlength of the drug may paradoxically delay the release. In addition, the thick gel layer formed on the swollen polymeric surface is capable of preventing matrix disintergration and controlling additional water penetration (Rodriguez *et al.*, 2000). Surface erosion also controls drug release when the weight loss of the matrix is equal to drug release rate (Gopferich, 1996).

2.6.2.4 Drug Release Studies

No standard *in vitro* method has yet been developed for dissolution studies of buccal dosage forms, including films. Different investigators have used apparatus of varying designs depending on the shape and application of the dosage form developed (Ahuja *et al.*, 1997). The most common methods employed for film dissolution studies are the USP paddle method (Remunan-Lopez *et al.*, 1998; Wong *et al.*, 1999; Perugini *et al.*, 2003), and the use of Franz Diffusion cells (Senel *et al.*, 2000; Rossi *et al.*, 2003).

2.6.2.5 Morphology Studies

Morphology of dosage forms can be evaluated using scanning electron microscopy (SEM). This technique makes possible the analysis of surface and cross-sectional morphological characteristics of the sample such as thickness (Perugini *et al.*, 2003); surface comparisons between different samples (Seabra *et al.*, 2004); and changes before and after dissolution and mucoadhesion (Govender *et al.*, 2005).

2.6.3 Therapeutic Applications of Films

The advantages and vast applications of mucoadhesive dosage forms with particular reference to films necessitates formulation studies in this area. Hence, research in this field has become very active. This section therefore aims to describe a few therapeutic examples of films investigated for both local and systemic therapy since the 1980's.

Yotsuyanagi *et al.* (1985) designed a mucoadhesive, moderately water-soluble polymeric buccal film containing analgesics and antibiotics for the treatment of lesions and to relieve the associated pain. The film consisted of HPC-M and contained tetracaine, thiamphenicol, and triacetin.

In 1994, Danjo *et al.* prepared a mucoadhesive buccal film dosage form for isosorbide dinitride, using HPC and HPMC phthalate. The film exhibited a sustained release of drug for up to 6 hours, and the addition of glycyrrhizic acid increased the dissolution of the drug.

Chitosan, a hydrophilic biopolymer obtained by alkaline deacetylation of chitin, has been claimed to act both as a mucoadhesive and permeabilizer, making it a candidate system for oral mucosal drug delivery (Needleman *et al.*, 1998). Moreover, chitosan itself possesses antimicrobial activity (Staroniewicz *et al.*, 1994). Based on this, Ikinci *et al.* (2002) studied the effect of chitosan films, alone and with chlorhexidine (Chx), on a periodontal pathogen *Porphyromonas gingivalis*. Their investigations showed that the combination of chitosan with Chx exhibited a higher activity when compared to that of Chx alone, which would provide Chx application at lower concentrations, thus avoiding its unwanted side effects.

An oral adhesive film dosage form containing a local anaesthetic is a useful system that can deliver an anaesthetic without pain and first-pass effect for dental analgesia. Film dosage forms containing lidocaine, dibucaine and buprenorphine have been reported. A study by Kohda *et al.* (1997) to attempt the clinical use of a solid dispersion film involved the formation of a film-type preparation with a solid dispersion system as a drug-reservoir of lidocaine hydrochloride (LDC) for application to the buccal mucosa. The release rate of LDC from the solid dispersion film was well controlled at EC/HPC composition ratios of 5/5, and the film for clinical use, which had 30% LDC, adhered almost completely to the buccal mucosa for 60-120 minutes. Another study investigating lidocaine penetration and release rate from films was conducted by Okamoto *et al.* (2001). The addition of glycyrrhizic acid (GL) to the HPC films increased the LDC release rate almost GL-content-dependently, while an optimum GL content was observed for the LDC penetration.

Films appear to be a suitable dosage form to deliver drugs into the periodontal pocket because the anatomic construction of the pocket allows for relatively easy insertion of such a delivery device (Steinberg and Friedman, 1999). Moreover, the use of biodegradable polymers can increase patient compliance, as the inserted film does not need to be removed. Steinberg *et al.* (1990) formulated a degradable controlled release film composed of a cross-linked protein containing chlorhexidine as the therapeutic agent. They concluded that their work presented a new dental drug delivery system that could be used as an adjunct in the treatment of periodontal diseases. Perugini *et al.* (2003) prepared a chitosan/PLGA film containing ipriflavone for periodontal pocket delivery for the treatment of periodontitis.

Onychomycosis, a fungal infection of the fingernails or toenails, has recently received much attention due to the high incidence of nail

infections and problems associated with its therapy (Myoung and Choi, 2003) owing to the poor penetration of drugs into the nail plate. It was suggested that a sustained release hydrophilic polymer film drug delivery system may be applicable for the human nail plate that has been etched. Therefore, Repka *et al.* (2004) developed a HPC and/or PEO HME film containing ketoconozole.

Films also appear to have potential for local sustained delivery of cancer chemotherapeutic agents. Following the surgical removal of a tumour, these implantable systems may be placed in the resection cavity to elicit a local response at the biophase; further, they may be secured by suturing at the site to prevent any displacement problems, as suggested by Dhanikula and Panchagnula (2004) in their investigation into the development of paclitaxel-loaded chitosan films.

Lu *et al.* (1999) investigated the *in vitro* degradation of thin PLGA films for applications in retinal pigment epithelium (RPE) transplantation and guided tissue regeneration. Thin PLGA films may be useful as temporary carriers for subretinal implantation of organised sheets of RPE. PLGA films can serve as barriers to seal off a maxillofacial defect to prevent other tissues from interfering with the regeneration of periodontal ligament and alveolar bone (Linde *et al.*, 1993). This has a further beneficial effect due to the osteoconductivity of PLGA (Ishaug *et al.*, 1997).

Recently, Yoo *et al.* (2006) developed a mucoadhesive polymeric film as a controlled drug delivery system against sexually transmitted diseases in females. The vaginal films, composed of various compositions of carbopol, HPMC and PEG and containing sodium dodecyl sulphate, were formulated by a casting method. It was demonstrated that the films had proper physico-dynamic properties

and compliable physical appearance for a controlled drug delivery system in females.

The above examples emphasise the diverse therapeutic applications of films. Hence technological studies on the formulation and evaluation of films have the potential to impact on several routes of drug delivery and disease states.

2.7. CONCLUSION

The preceding discussions have highlighted the theoretical concepts pertaining to the formulation and evaluation of mucoadhesive controlled release buccal delivery systems, particularly films, for enhancing drug therapy. While this is an area that is being studied internationally, it is clear that the full potential of novel drug delivery systems for this route has not yet been fully realised and such systems need to be investigated further.

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CHAPTER THREE

IDENTIFICATION OF OPTIMAL PARAMETERS FOR THE PREPARATION OF MONOLAYERED FILMS WITH DRUG AND POLYMER/S OF OPPOSING SOLUBILITIES

Table of Contents

3.1 INTRODUCTION AND AIM

As described in Chapter Two, there are two methods commonly employed for the preparation of films, viz. solvent casting and hot-melt extrusion methods. In this study, the solvent casting method was employed, as it is a simple technique and does not require the use of sophisticated, expensive apparatus as required by the hot-melt extrusion method. Preparation of the films by the conventional solvent casting method involves dissolving the drug and polymer in a single liquid vehicle and then pouring/spreading the resulting solution onto teflon-coated trays which are then left to dry to facilitate solvent evaporation. This forms a sheet of film which is then cut into desired sizes to provide a specified dose of drug.

The preparation of films containing drug and a single polymer (homopolymeric films) or a combination of polymers (multipolymeric films) of similar solubilities by the solvent casting method, where the drug and polymer/s are all dissolved in a single vehicle, have been widely reported (Woolfson *et al.*, 1995; Senel *et al.*, 2000; Ikinci *et al.*, 2002; Padula *et al.*, 2003, Ahmed *et al.*, 2004; Yoo *et al.*, 2006). However, the preparation of optimal films with desired multifunctionalities such as mucoadhesivity and controlled drug release properties may require the film to comprise of drug and polymer/s of opposing solubilities. In this instance, simply dissolving the drug and polymer/s in a single vehicle and casting onto trays is not possible. To overcome this, Remunan Lopez *et al.* (1998) prepared multipolymeric drug containing films of opposing solubilities as a multilayered system. The advantages of monolayered films over multilayered films were described in Chapter One (1.1) and were therefore specifically considered in this study. The challenge in the preparation of monolayered multipolymeric films with drug and polymers of opposing solubilities was that to enable casting as a single

layer, a method had to be identified whereby the drug and polymers could be homogeneously dispersed despite having opposing solubilities.

Perugini *et al.* (2003) recently reported an emulsification process (oil in water) for the preparation of such films containing a lipophilic drug, ipriflavone. Briefly, an organic phase containing ipriflavone and a hydrophobic polymer were added to the aqueous phase containing a hydrophilic polymer under homogenisation and then cast onto trays. In our study, a hydrophilic drug, Propranolol HCl, was employed and would clearly require different parameters/variables for film formation. The preparation method and characterisation of a monolayered film containing a hydrophilic drug and polymer/s, both as homopolymeric and multipolymeric systems of opposing solubilities, have not been reported to date in the literature.

The aim of this phase of the study, as outlined in this chapter, was therefore to identify suitable parameters for the preparation of monolayered multipolymeric films containing a hydrophilic drug, Propranolol HCl, and polymers of opposing solubilities by an emulsification/casting/solvent evaporation method. The suitability of the parameters identified, for their application to a monolayered homopolymeric film, was also confirmed.

3.2 MATERIALS AND METHODS

3.2.1 Materials

Chitosan (CHT) (MW 110 000) [Primex Ingredients, ASA, Norway]; Eudragit® RS100 (15 mPa.s) (EUD100) [Rhom Pharma, Germany]; Poly(vinylalcohol) (PVA) [Sigma, Germany]; Tween 80® [Merck Chemicals, Germany]; Poly(D,L-lactide-co-glycolide) (50/50 0.39dL/g)

(PLGA) [Absorbable Polymers, USA]; Propranolol HCl (PHCl) [Frankel Chemicals, SA] and Lactic Acid [BDH Lab Supplies, UK] were purchased and used as received. All other chemicals used were of analytical or reagent grade. Distilled water was used in all studies.

3.2.2 Methods

3.2.2.1 Preparation of Monolayered Multipolymeric Films (MMFs) with Drug and Polymers of Opposing Solubilities.

The method described by Perugini *et al.* (2003), i.e. emulsification, was considered as a basis for film preparation in this study. Films of fixed area (11 x 7 cm^2) containing both hydrophilic and hydrophobic polymers were prepared by an emulsification/casting/solvent evaporation technique. An o/w emulsion was formed by adding 1 g PLGA dissolved in 5 mL CH_2Cl_2 to 14.925 g of a 2% w/w CHT in lactic acid solution (1% v/v) containing glycerol (75 mg) and PHCl (385 mg). Glycerol was added as a plasticiser to impart film flexibility and elasticity (Perugini *et al.*, 2003). Both the organic and aqueous phases were individually brought to the same temperature before being combined and homogenised at predetermined speeds and times (IKA Homogensier, Germany) whilst maintaining the resulting emulsion on an ice bath. The emulsion was then cast onto a teflon-coated perspex tray and allowed to dry overnight in an oven at 37 °C (Series 2000, Scientific, SA) for 24 hours (drying times were predetermined by drying to constant weight). The films were then cut into specified sizes as individual doses.

3.2.2.2 Preparation of Monolayered Homopolymeric Films with Drug and Polymer of Opposing Solubilities

As described above, the identified optimal variables for MMFs were used to prepare monolayered homopolymeric films with drug and a polymer of opposing solubilities. Two hydrophobic polymers, i.e. PLGA and EUD100 were investigated. PHCl (385 mg) was dissolved in water (20 mL) and added either to (a) PLGA (1 g) dissolved in CH_2Cl_2 (20 mL) or (b) EUD100 (1 g) dissolved in acetone (20 mL) via the emulsification method described above. The resulting emulsions were then cast and allowed to dry.

3.2.2.3 Effect of Preparation Parameters on Film Formation

The following parameters for emulsification of the organic and aqueous phase prior to film casting were considered.

3.2.2.3.1 Effect of Homogenisation Speed and Time

Films were prepared as described in 3.2.2.1 above, with varying homogenisation speeds (6000, 9000, 12000, 15000 rpm for 5 minutes) and times (1, 5, 15, 25 minutes at 9500 rpm) to determine the optimal homogenisation speed and time parameters for emulsification.

3.2.2.3.2 Effect of Temperature

Films were prepared as described in 3.2.2.1 above with varying temperatures of the aqueous and organic phases prior to homogenisation (15, 17, 19, and 20 °C) to determine the optimal temperature for emulsification. A homogenisation speed of 9500 rpm for 15 minutes was employed.

3.2.2.3.3 Effect of Emulsifiers

Films were prepared as described in 3.2.2.1 above with varying concentrations of one of two emulsifiers, i.e. PVA (0.5, 1, 2% w/w) or Tween 80® (1, 5, 10% w/w). The emulsifier was added to the aqueous phase before homogenisation at 9500 rpm for 15 minutes.

3.2.2.4 Evaluation of Films

Preparation parameters for emulsification of the organic and aqueous phases that did not cause phase separation and its casting into films which were monolayered indicating no phase separation during solvent evaporation and drying, were required. Films were evaluated in terms of thickness, appearance and micromatricial morphology and flexibility. The methodologies for these evaluations are described below.

3.2.2.4.1 Thickness Measurements

The thickness of each film was measured at five different locations (centre and four corners) using an electronic digital micrometer (Mitutoyo Co., Japan). Data are represented as a mean±SD of five replicate determinations.

3.2.2.4.2 Appearance and Morphology

Film surface was evaluated optically by a digital camera (Nikon Coolpix 5900, Japan). Film morphology was also characterised by scanning electron microscopy. Samples were mounted on round brass stubs (12 mm diameter) using double-backed adhesive tape and then sputter-coated for 8 minutes at 1.1 LV under argon atmosphere with gold (Polaron SC 500 Sputter Coater, UK) before examination under

the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). Different magnifications were used to examine the areas of the samples. The images were captured on an Ilford PANF 50 black and white 35 mm film.

3.3 RESULTS AND DISCUSSION

3.3.1 Effect of Homogenisation Speed and Time

While simple blending of the oil and water phases with a suitable emulgent system may be sufficient to produce satisfactory emulsions, globule size reduction by homogenisation can further enhance emulsion stability. They work on the principle of forced discharge of the emulsion under pressure through fine interstices formed by closely packed metal surfaces in order to provide an intense shearing action (Billany, 2002). Determination of homogenisation speed and times for emulsification was therefore important.

Tables 3.1 and 3.2 indicate the thickness and also show the digital and scanning electron micrographs of films prepared. At all homogenisation speeds and times investigated, an emulsion without phase separation was formed. Films that were formed were all also monolayered, indicating no phase separation during the solvent evaporation and drying stages. All films containing PLGA showed the appearance of micromatrices dispersed throughout the film surface. The formation of micromatrices within a film matrix is not common and may be attributed to the inclusion of PLGA, specifically since the preparation of particulates, e.g. nanoparticles and microparticles, with PLGA under similar solvent evaporation methods have been reported (Scholes *et al.*, 1993; Govender *et al.*, 1999; Huo *et al.*, 2005; Virto *et al.*, 2007). Therefore, the inclusion of PLGA may have led to formation of these micromatrices as a result of homogenisation. A

similar observation with PLGA and CHT films was reported by Perugini *et al.* (2003). Since monolayered films were obtained at all homogenisation speeds and times, uniformly dispersed micromatrices embedded on the film surface were further used as a measure of film suitability.

An increase in the homogenisation speed led to a decrease in the size of the embedded micromatrices. For example, at homogenisation speeds of 6000 and 15000 rpm, micromatrices were 1.8 ± 0.2 and 0.8 ± 0.4 mm respectively, as is evident on the photographs and micrographs in Table 3.1. This decrease in globule/particulate size with increased homogenisation speeds has been documented in the literature (Scholes *et al.*, 1993; Das, 2006). However with increases in the homogenisation speed to 12000 and 15000 rpm, the emulsion and film appeared "foamy" which was considered undesirable.

Homogenisation speeds also influenced film thickness as films formed at lower speeds were relatively thicker (603 ± 152 and 593 ± 171 µm at 6000 and 9500 rpm respectively) than those formed at higher speeds (572 ± 174 and 457 ± 97 µm at 12000 and 15000 rpm respectively). Homogenisation at 9500 rpm instead of 6000 rpm was selected since micromatrices appeared more uniformly dispersed throughout the 77 cm^2 film.

An increase in the homogenisation time also led to a decrease in the size of the micromatrices. For example, an increase in the homogenisation time from 5 to 25 minutes led to a decrease in the size of the micromatrices from 1.9 ± 0.2 to 0.8 ± 0.6 mm. However, at a prolonged homogenisation time, i.e. 25 minutes or more, the emulsion became very viscous and casting onto trays was difficult. Since it is possible to increase the viscosity of an emulsion by a reduction in mean globule diameter by homogenisation (Billany, 2002); prolonged

homogenisation may have enhanced globule size reduction to a point that resulted in the significant increase in viscosity. A homogenisation time of 15 minutes was selected as micromatrices were smaller and more uniformly dispersed throughout the film.

The results above indicate that a homogenisation speed of 9500 rpm for 15 minutes was appropriate for emulsification and film formation of monolayered films containing drug and polymer/s of opposing solubilities.

Table 3.1 Effect of homogenisation speeds on film formation

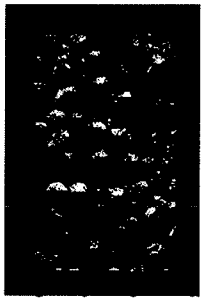
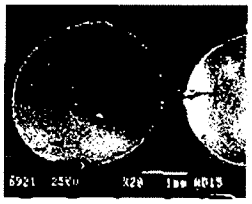
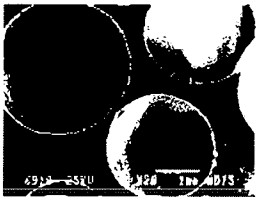
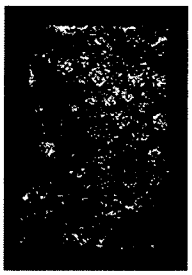
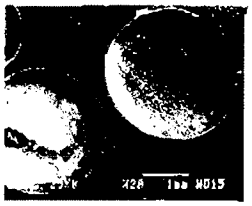
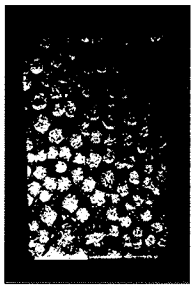
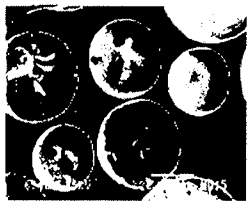
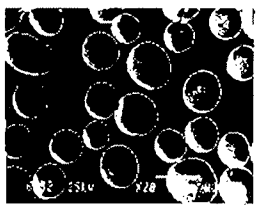
Homogenisation Speed (rpm) for 5 minutes	Film Thickness (μm)	Digital Photograph	Scanning Electron Micrograph
6000	603 ± 152		
9500	593 ± 171		
12000	572 ± 174		
15000	457 ± 97		

Table 3.2 Effect of homogenisation times on film formation

Homogenisation Time (minutes) at 9500 (rpm)	Film Thickness (μm)	Digital Photograph	Scanning Electron Micrograph
1	601 ± 117		
5	593 ± 171		
15	446 ± 137		
25	226 ± 43		

3.3.2 Effect of Temperature

When PLGA was dissolved in methylene chloride (23 °C), the temperature of the resulting solution decreased to 20 °C, indicating an endothermic reaction. PHCl and Chitosan dissolved in the aqueous phase resulted in a temperature of 22 °C. Since both phases were at different temperatures, it was necessary to bring them to the same temperature prior to addition of the organic phase to the aqueous phase for emulsification. Therefore, several temperatures, i.e. 15, 17, 19, 20 °C were investigated. Temperatures above 20 °C were not investigated as this would have required undesirable heating of the organic phase and also ultimately increased manufacturing costs. Temperatures of the phases were reduced by placing them in an ice bath. At temperatures of 15, 17 and 19 °C, phase separation occurred whilst at 20 °C emulsification was achieved (Table 3.3). A possible reason for this is that at temperatures below 20 °C, the system may not have sufficient energy to facilitate emulsion formation whilst at 20 °C it may have been adequate.

Table 3.3 Effect of temperature on emulsion formation

TEMPERATURE (°C)	DESCRIPTION OF EMULSION
15	Phase separation
17	Phase separation
19	Phase separation
20	Emulsion formation

3.3.3 Effect of Emulsifiers

Emulsifiers can be added to emulsions to enhance their stability (Billany, 2002). In this study, two common emulsifiers, i.e. PVA and Tween 80®, were investigated to examine their influence on film

integrity and appearance. As observed from Table 3.4, the addition of emulsifiers at varying concentrations did not improve film formation. The physical properties (appearance and mechanical strength) of the films were compromised. Therefore, the use of emulsifiers in subsequent formulations was considered unnecessary since emulsification and film formation could be achieved by homogenisation only, and the resulting effect on film morphology rendered it unfeasible under the conditions of this study. Perugini *et al.* (2003) also did not require emulsifiers for film formation. Homogenisation may have therefore been adequate to sufficiently reduce the diameter of the globule size to achieve stability without the need of an emulsifier.

Table 3.4 Effect of emulsifiers on film formation

EMULSIFIER TYPE AND CONCENTRATION	DESCRIPTION OF FILM
PVA 0.5% w/w	Flexible and porous
PVA 1% w/w	Flexible and porous with a foamy surface
PVA 2% w/w	Flexible and porous with a very foamy surface
TWEEN 80® 1% w/w	Flexible and mechanically weak
TWEEN 80® 5% w/w	Very flexible, sticky and mechanically weak
TWEEN 80® 10% w/w	Extremely flexible, oily and extremely mechanically weak

3.3.4 Summary of Parameters for the Preparation of Monolayered Multipolymeric Films with Drug and Polymers of Opposing Solubilities

The above studies (3.3.1, 3.3.2 and 3.3.3) indicated that monolayered multipolymeric films could be prepared by emulsification at 20 °C and homogenisation at 9500 rpm for 15 minutes, followed by drying at 30

°C for 24 hours. A schematic presentation of this process is indicated hereunder.

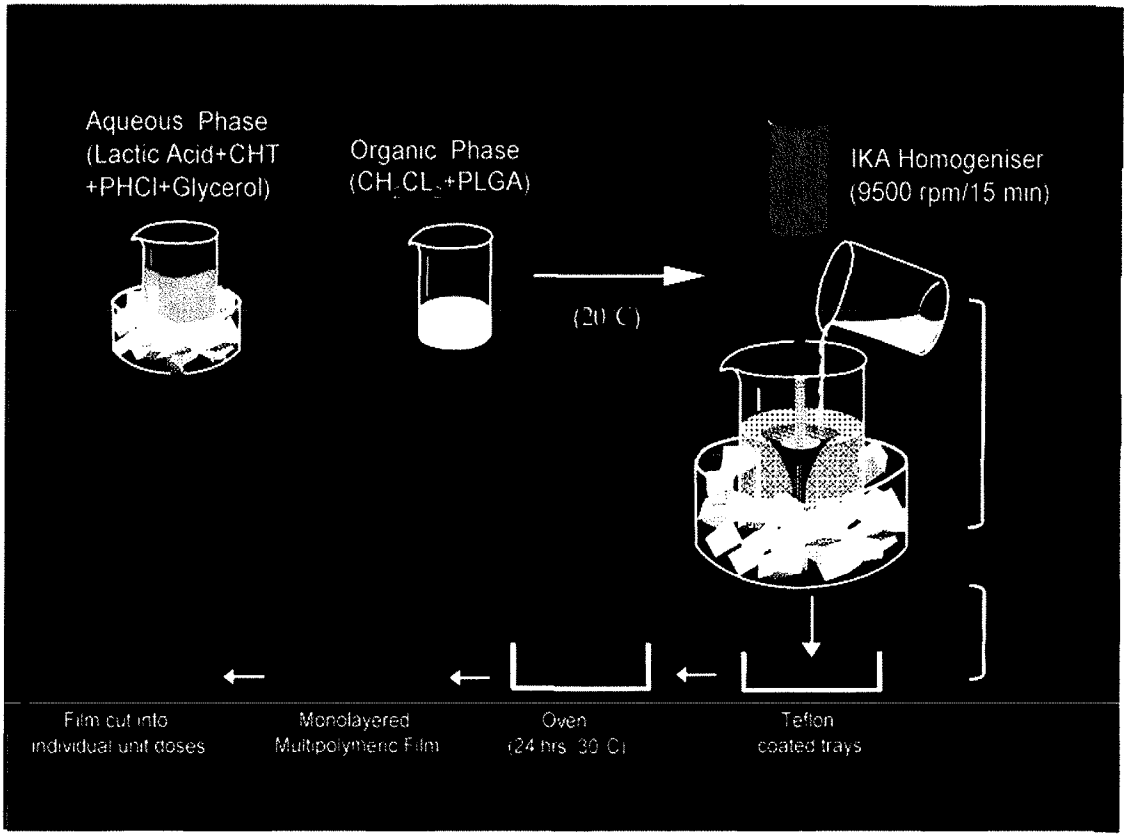


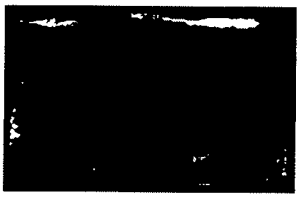
Figure 3.1 Schematic presentation of the preparation process for MMFs

3.3.5 Confirmation of Parameters for the Preparation of Monolayered Homopolymeric Films with Drug and Polymer of Opposing Solubilities

The above studies have shown that a monolayered multipolymeric film with a hydrophilic drug and polymers of opposing solubilities can be prepared by an emulsification/casting/solvent evaporation technique with parameters of homogenisation at 9500 rpm for 15 minutes and emulsification at 20 °C. The above process parameters were used to confirm whether a monolayered homopolymeric film could also be prepared by the method and process parameters since this has also not been reported in the literature to date and may be required for

certain drug delivery systems. An organic phase consisting of a hydrophobic polymer, EUD100 was added to the aqueous phase consisting of PHCl under similar conditions as above. Upon addition of the two phases, an emulsion with no phase separation formed. Further, the film generated was monolayered, indicating no phase separation during solvent evaporation and drying. A homogenous, smooth film without micromatrices was obtained as expected, since it did not include PLGA (Table 3.5). However, a successful preparation of PLGA films with PHCl could not be achieved. Upon addition of the PLGA organic phase to the aqueous phase, it immediately complexed to form a precipitate. This could be due to complex formation between the cationic drug and anionic polymer at the concentrations used in this study and therefore films could not be formed. EUD100 is a cationic polymer and perhaps therefore did not complex with the cationic drug to form a precipitate. With multipolymeric films prepared earlier, i.e. PLGA and CHT in combination with PHCl, this precipitation was not observed. This could have been due to the anionic PLGA reacting selectively with the several positively charged sites on the chitosan polymer instead of with PHCl. These observations emphasised the importance of identifying appropriate polymers and critical concentrations for homogenous film formation.

Table 3.5 Results of combining a hydrophilic drug and hydrophobic polymer for the formation of homopolymeric monolayered films

Polymer Type	Emulsion Formation	Picture of Film
EUD100 (cationic)	No phase separation	
PLGA (anionic)	No emulsion	No film

3.4 CONCLUSIONS

In this chapter, preparation parameters for the formation of monolayered multipolymeric and homopolymeric PHCI films with drug and polymer/s of opposing solubilities were investigated. Monolayered multipolymeric films could be prepared at all homogenisation speeds and times. The films that were generated showed micromatrices embedded in the film matrix and were attributed to the PLGA polymer. The size of the micromatrices was reduced with an increase in homogenisation speed and time. Phase separation occurred at temperatures below 20 °C. Emulsifiers used in the study adversely affected film morphology and appearance and were not considered feasible for inclusion into the formulation. The preparation parameters identified for emulsification without phase separation and the subsequent generation of monolayered films, without phase separation during solvent evaporation and drying, were emulsification at 20 °C and homogenisation at 9500 rpm for 15 minutes. The above preparation parameters could also be used to generate monolayered

homopolymeric PHCl films with EUD100, a hydrophobic polymer. It was not possible to prepare PLGA films since it formed a precipitate immediately upon addition to the PHCl solution.

The above parameters, i.e. emulsification at 20 °C with homogenisation at 9500 rpm for 15 minutes, and subsequent drying in an oven at 30 °C for 24 hours, were used throughout this study, unless otherwise stated.

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CHAPTER FOUR

ENHANCING DRUG CONTENT UNIFORMITY IN POLYMERIC FILMS

Table of Contents

4.1 INTRODUCTION AND AIM

Optimal parameters for the emulsification/casting/solvent evaporation technique identified in Chapter Three showed potential for the preparation of films containing drug and polymers of opposing solubilities (MMFs). The emulsified phases were cast onto teflon-coated perspex trays to form a sheet of film (77 cm^2) for cutting into predetermined sizes containing specified doses. This is the standard method of film casting as described in the literature (Kohda *et al.*, 1997; Remunan-Lopez *et al.*, 1998; Okamoto *et al.*, 2001; Perugini *et al.*, 2003; Yoo *et al.*, 2006). A pre-requisite for therapeutic efficacy, safety and regulatory approval of a medicine is drug content uniformity. Therefore initial characterisation studies on MMFs encompassed assays of the films. However, the preliminary data indicated non-uniform drug distribution across the individual film units.

Failure to achieve a high degree of accuracy with respect to the amount of drug in individual unit doses of the film can result in therapeutic failure, non-reproducible effects and, importantly, toxic effects on the patient. Hence, drug content uniformity is mandatory for regulatory approval of new medicines by regulatory authorities, i.e. the Medicines Control Council (MCC) (SA), Food and Drug Administration (FDA) (USA) and the European Medicines Agency (EMEA) (UK). Current requirements by various world regulatory authorities specify small variations only from the stated active amount in a dosage form. Generally, a ±5% deviation from the stated active amount is allowed. For registration and commercialisation of products by regulatory bodies and, more importantly, for reproducible therapeutic effects in patients, it is essential that drug uniformity across the individual film units be achieved.

In an attempt to address the problem of drug content non-uniformity, several initial approaches were investigated. Firstly, it was initially thought that the drug content non-uniformity in the films was due to interactions between the drug and polymers of opposing solubilities and the fact that it was a multipolymeric and not homopolymeric film as widely prepared in the literature. Therefore, it was decided to investigate drug uniformity by initially simplifying the system and focusing on conventional single polymeric films with drug and a polymer of similar solubilities, i.e. PHCl and CHT only. This homopolymeric system, together with the decision to change to another water soluble polymer i.e. HPMC, also led to poor drug content uniformity data. Since it was established that it was neither the polymer type, solubilities nor whether it was a homo or multipolymeric system that led to the poor drug content uniformity, other approaches included varying the drying techniques employed for solvent evaporation and film formation. Drying the casted films in a cupboard at room temperature (20 °C); under extraction in a fume cupboard at room temperature (20 °C); in a warm room at 30 °C; and in a convection oven at 30 °C, was also unsuccessful in improving the poor assay results.

Having failed in the above mentioned attempts to achieve drug uniformity, it was decided to conduct an extensive literature search with respect to drug content uniformity in polymeric films to acquire sufficient knowledge to address the shortcoming of non-uniformity in films prepared by the casting technique in this study. Table 4.1 provides a summary of this literature search. While the literature is replete with formulation and several characterisation studies on films, surprisingly, the majority of papers did not report any assay values. Of the very few that did, three had measured drug content by dissolving a known weight of the film for analysis (Ahmed *et al.*, 2004; Dhanikula and Panchagnula, 2004; Amnuaikit *et al.*, 2005).

Table 4.1 Summary of film characterisation studies and reported drug content uniformity/assay results in literature search

Polymer/s	Drug	Film Characterisation Studies	Assay Results	Reference
EUD E100	Piroxicam	Transparency and SEM, peel adhesion test, drug-polymer interaction study, *in vitro* membrane permeation study	Not Reported	Lin *et al.*, 1995
EC, HPC	Lidocaine HCl	*In vitro* dissolution, DSC, IR, measurement of pore size distribution, adhesion of films	Not Reported	Kohda *et al.*, 1997
EC, CHT glutamate	PHCl, Nifedipine	*In vitro* drug release, morphology (SEM),	Not Reported	Remunan-Lopez *et al.*, 1998
PCL	Chlorhexidine	*In vivo* test	Not Reported	Medlicott *et al.*, 1999
HPC	Lidocaine	*In vitro* permeation, dissolution studies, determination of penetration rate and release rate	Not Reported	Okamoto *et al.*, 2001
Polycarbophil, EUD S100,	Plasmid DNA, β-Galactosidase	Release studies, rabbit immunization studies	Not Reported	Cui and Mumper, 2002
CHT, PVA, PEO, PVP	Model drug	Swelling and erosion studies, *in vitro* drug release, *in vivo* animal studies, thermal transitions, FTIR, tensile testing	Not Reported	Khoo *et al.*, 2003
PLGA, CHT glutamate	Ipriflavone	Morphology, water absorption capability, degradation, *in vitro* dissolution, drug content uniformity, *in vitro* drug release	Reported	Perugini *et al.*, 2003
PAA, CHT HCl	Acyclovir	Hydration, rheology, mucoadhesion, drug release, permeation	Not Reported	Rossi *et al.*, 2003
Potato starch, potato starch acetate	Timolol, Sotalol-HCl	*In vitro* release, weight loss and water content	Not Reported	Tuovinen *et al.*, 2003
EUD NE30D, PVP	Penciclovir	Drug content, microscopy, DSC, X-ray diffraction, Higuchi release kinetics	Reported	Ahmed *et al.*, 2004
CHT	Nystatin	Water uptake, *in vitro* release, gel stability, *in vivo* studies on hamsters	Not Reported	Aksungur *et al.*, 2004
Gelatin, carrageenan	Timolol	Water uptake, drug release, washability test, mucoadhesion	Not Reported	Bonferoni *et al.*, 2004

Polymer	Drug	Film Characterisation Studies	Assay Results	Reference
CHT	Paclitaxel	Stability of Paclitaxel, content uniformity, release studies, film thickness, tensile strength, DSC, FTIR, SEM, X-ray diffraction, *in vivo* implantation, histology	Reported	Dhanikula and Panchagnula, 2004
PVA, PVP	S-nitrosogluta-thione (GSNO)	DSC, mechanical properties, SEM, dissolution, diffusion of GSNO	Not Reported	Seabra *et al.*, 2004
Dextran-PCL co-polymer	Paclitaxel	Swelling, DSC, X-ray diffraction, *in vitro* release, morphology	Not Reported	Shi and Burt, 2004
PLGA	Ethacrynic acid	*In vitro* release, SEM, water uptake, pH value, weight loss, *in vivo* eye test	Not Reported	Wang *et al.*, 2004
EC, PVP	PHCl	Thickness, drug content, moisture uptake, *in vitro* drug release, *in vitro* skin permeation	Reported	Amnuaikit *et al.*, 2005
CHT, PAOMA co-polymer	Model drug	*In vitro* drug release, kinetic analysis, SEM,	Not Reported	Yoshizawa *et al.*, 2005
Sodium alginate, gelatin	Ciprofloxacin HCl	FTIR, X-ray diffraction, *in vitro* release, morphology, mechanical properties, swelling	Not Reported	Dong *et al.*, 2006
CHT, guar gum	Celecoxib	Swelling, mucoadhesion, *in vitro* and *in vivo* degradation, drug release	Not Reported	Haupt *et al.*, 2006
PLGA, PVA-g-PLGA	Paclitaxel	DSC, wide angle X-ray diffraction, size exclusion chromatography, SEM, *in vitro* release, *in vitro* degradation	Not Reported	Westedt *et al.*, 2006
Carbopol, PEG, HPMC	SDS	Film thickness, drug content, tensile strength, measurement of contact angle, swelling, erosion, SDS release	Reported	Yoo *et al.*, 2006

Key: **EUD** = Eudragit
CHT = Chitosan
PEO = Poly(ethylene oxide)
PVA = Poly(vinyl alcohol)
EC = Ethylcellulose
PCL = Polycaprolactone
PVP = polyvinlypyrrolidone
HPC = Hydroxypropylcellulose
HPMC = Hydroxypropylmethylcellulose
PLGA = Poly(D,L lactide-co-glycolide)
PAOMA = Polyalkyleneoxide-maleic acid

This is not an accurate reflection of drug uniformity since sheets of film are cut into unit doses. An assay of film area rather than weight would be more appropriate for assessing drug content uniformity in such films. In addition, Dhanikula and Panchagnula (2004) merely stated that uniformity results in their study indicated that the variation in drug distribution was <15%, but they did not report any data, while the drug content statement by Perugini *et al.* (2003) about it being more than 70% was unclear. The lack of reported data on this crucial characterisation property of any novel drug delivery system led to the assumption that researchers in this field may also have been experiencing difficulty with this aspect of film characterisation. Yet no paper to date, to the best of our knowledge, in the published pharmaceutical literature has highlighted this difficulty.

It was only a search of patent applications that confirmed the assumption that difficulties with achieving uniform drug distribution in films did indeed exist as numerous patent applications that attempted to directly address the problems encountered with non-uniformity in films were identified. While the identification of several patents confirmed the existence of this problem, it was intriguing that the published pharmaceutical literature omitted the reporting of assay values yet revealed the undertaking of other complex characterisation studies (Table 4.1) without focusing on overcoming this simple but mandatory prerequisite for development of any drug delivery system. In the patent applications it was explained that films prepared via the conventional casting technique suffered from the aggregation or conglomeration of particles, which rendered them inherently non-uniform in terms of all film components, including polymers and drug. It was found that the formation of agglomerates randomly distributed the film components as well as any active present, thus leading to the poor drug uniformity (US Patent No. 60/443,741, 2004).

The formation of agglomerates was attributed to the relatively long drying times, which facilitated intermolecular attractive forces, convection forces and air flow which aided in the formation of such conglomerates (US Patent No. 60/443,741, 2004). Some approaches that attempted to prevent agglomeration are described briefly. Schmidt (US Patent No. 4,849,246 in US Patent No. 60/443,741, 2004) abandoned the concept that a monolayered film may provide accurate dosing and instead attempted to solve the problem of aggregation by forming a multilayered film. Horstmann *et al.* and Zerbe *et al.* ((US Patent No. 5,629,003 and US Patent No. 5,948,430 in US Patent No. 60/443,741, 2004) incorporated additional excipients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods had the disadvantage of requiring additional components, which translated to additional cost and manufacturing steps. Furthermore, these methods employed the use of time-consuming drying methods such as high-temperature air-bath using a drying oven, drying tunnel, vacuum dryer, or other such drying equipment, all of which aided in promoting the aggregation of film components and active. In addition, such processes subjected the active to prolonged exposure to moisture and elevated temperatures, which might render it ineffective or even harmful (US Patent No. 60/443,741, 2004).

Patent applications, such as those of Yang *et al.* ([US Patent No. 60/443,741] and Zerbe *et al.* [US Patent No. 5,948,430] in US Patent No. 60/443,741, 2004) for enhancing drug uniformity, required sophisticated drying equipment and additional pharmaceutical excipients, which lead to unfeasible increased manufacturing costs and multi-step processing. Thus, a method which uses minimal additional excipients into the formulation, simple technology and which also provides uniform drug content throughout the film clearly

needed to be identified. Instead of adding additional excipients or introducing new expensive and complicated drying technologies, a specially designed tray with built-in predetermined wells for forming polymeric films with uniform drug content was proposed and evaluated in this study. It was expected that this simple approach, which would involve casting specified volumes of polymer-drug mixtures into wells, would lead to improved drug uniformity since the drug would be entrapped in each film unit, irrespective of the migration of the active within that well during drying.

Therefore, the aim of the investigation reported in this chapter was to develop and evaluate a specially designed tray for film casting as a method for achieving drug uniformity. Initially, the tray was evaluated with a simple homopolymeric film containing drug and polymer of similar solubilities, i.e. CHT and PHCl. Thereafter, its applicability to multipolymeric films with drug and polymers of similar and opposing solubilities was assessed. In addition to drug content uniformity, the films from the trays were also characterised in terms of mucoadhesivity, *in vitro* drug release properties and film thickness.

4.2 MATERIALS AND METHODS

4.2.1 Materials

Propranolol HCl [Frankel Chemicals, SA]; Chitosan (MW 110 000) [Primex Ingredients, ASA, Norway]; Eudragit® RS100 (15 mPa.s)[Rhom Pharma, Germany]; Hydroxypropylmethylcellulose (4000 mPa.s) [Fluka, UK]; Mucin [Sigma-Aldrich, UK]; Lactic Acid [BDH Lab Supplies, UK]; Perspex [Maizey Plastics, SA], and Teflon [Coated Fabrics, SA] were purchased and used as received. Wacker Silicone M4514 (Elastosil®) [amt Composites, SA] was mixed with its supplied catalyst (T 26) prior

to use. All other chemicals used were of analytical or reagent grade. Distilled water was used in all studies.

4.2.2 Methods

4.2.2.1 Preparation of Trays for Film Casting

Drug containing polymeric solutions/emulsions was casted onto the conventional teflon-coated trays as well as onto two other trays, i.e. teflon-coated perspex trays with a removable chamber system and silicone-molded trays with built-in wells. The description and preparation of these trays are described hereunder.

4.2.2.1.1 Teflon-coated Perspex Trays (TCPT)

TCPTs were prepared by gluing together pieces of 4 mm clear perspex (Maizey Plastics, SA) to form a tray of dimensions 11 x 7 x 3 cm with an area of 77 cm^2. Thereafter the trays were coated with a self-adhesive fabric teflon (COFAB, SA) and were ready for immediate use. The tray is shown in Figure 4.1.

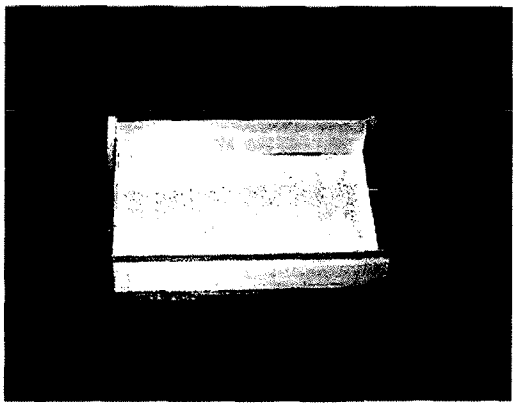
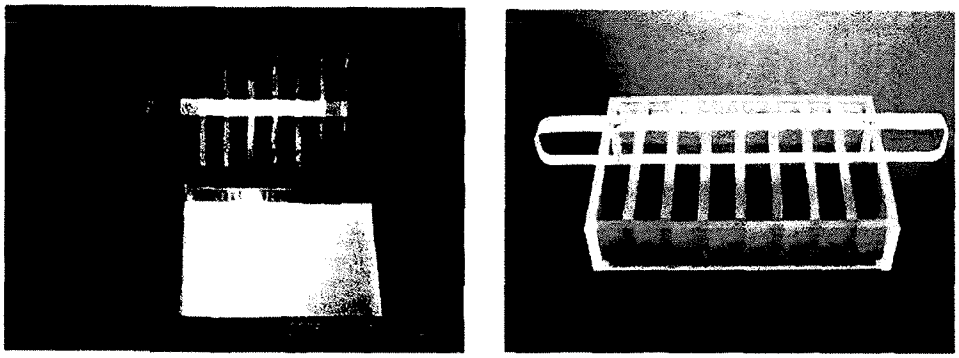


Figure 4.1 Picture of a teflon-coated perspex tray

4.2.2.1.2 TCPT with a Removable Chamber System

The TCPT was prepared as described in 4.2.2.1.1 and the removable chamber system was prepared by gluing together pieces of perspex to form a grid with 16 compartments for insertion into the TCPT. These compartments were coated with teflon fabric (COFAB, SA). The tray is shown in Figure 4.2.



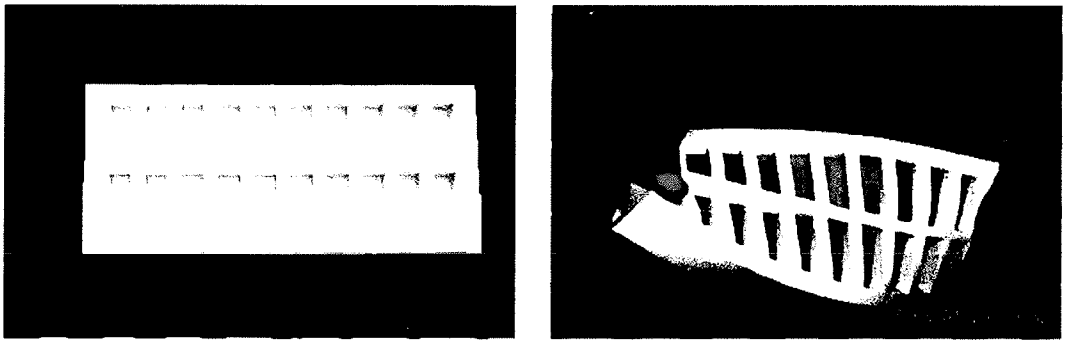
(a) (b)

Figure 4.2 Pictures of a TCPT with a removable chamber system (a) separate components and (b) chambers inserted into TCPT.

4.2.2.1.3 Silicone-molded Trays (SMT)

SMTs were prepared by combining wacker silicone (150 mL) with its catalyst (T 26) (7.5 mL) (amt Composites, SA) in a glass beaker, stirring with a glass rod for approximately 8 minutes to form a silicone mixture with a pot life of 20 minutes and then pouring it into a greased wooden mold and allowing it to cure at room temperature (20 °C) for 5 hours. The cured silicone was then demolded to yield a flexible silicone tray with 20 individual 1 x 3 cm^2 wells. This tray was also investigated with the addition of teflon-coated perspex inserts into each tray. The inserts were prepared by cutting 4 mm clear perspex (Maizey Plastics, SA) into 1 x 3 cm^2 rectangles and coating them with

the self-adhesive fabric teflon (COFAB, SA). These inserts were then firmly placed into each well of the SMT prior to film casting. The tray is shown in Figure 4.3.



(a) (b)

Figure 4.3 Pictures of the SMT (a) without inserts and (b) with teflon-coated perspex inserts

4.2.2.2 Preparation of Polymer-Drug Solutions/Emulsions for Film Casting

All PHCl-containing polymeric solutions/emulsions were prepared at a concentration of 15 mg/mL to ensure that each 1 x 3 cm^2 film unit theoretically contained a 15 mg/3 cm^2 dose. The total volume of PHCl containing polymeric solution/emulsion was casted onto the TCPT whilst 1 mL of the solution was casted into each well of the SMT. All trays containing the casted polymeric solutions/emulsions were allowed to dry in an oven (Series 2000, Scientific, SA) at 30 °C for approximately 24 hours, until the solvent had evaporated (until constant weight). Films were stored in foil bags in a tightly sealed amber bottle at room temperature (20 °C) until further use. The preparation of the polymeric solutions/emulsions for casting onto the different trays is discussed below.

4.2.2.2.1 Homopolymeric Films

Homopolymeric films containing CHT and PHCl were prepared at a 1:1 ratio, i.e. 0.385 g each of drug and polymer for films casted onto the TCPT and 0.450 g each of drug and polymer for films casted onto the SMT. The required amount of CHT and glycerol (30% w/w), used as a plasticiser, was dissolved in a 1% v/v lactic acid solution (30 mL) under magnetic stirring. PHCl was then dissolved in the above chitosan solution. The resulting drug containing polymeric solution was allowed to stand until air bubbles were removed before casting onto a TCPT or SMT. These quantities ensured that each 1 x 3 cm^2 film unit would theoretically comprise 15 mg PHCl.

4.2.2.2.2 Multipolymeric Films

Multipolymeric films, where drug and polymers were all of similar solubilities (i.e. PHCl+CHT+HPMC) and also those where drug and polymers were of opposing solubilities (i.e. PHCl+CHT+EUD100) were prepared for evaluation. The films were prepared in a 1:0.5:0.5 drug : polymer : polymer ratio. For the TCPT these amounts were PHCl (0.385 g) : CHT (0.1925 g) : HPMC / EUD100 (0.1925 g), and for the SMT, PHCl (0.450 g) : CHT (0.225 g) : HPMC / EUD100 (0.225 g). Plasticiser was added at 30% w/w.

Hydrophilic combination films were prepared as follows: CHT and glycerol (30% w/w) was dissolved in a 1% v/v lactic acid solution (15 mL). and thereafter PHCl was added and allowed to dissolve. HPMC was dissolved separately in water (15 mL) and then added to the PHCl-CHT preparation and allowed to mix under magnetic stirring. When this drug-containing multipolymeric solution was homogenously combined, it was casted onto the respective trays and dried as described above.

Hydrophobic combination films were prepared as follows: CHT and glycerol (30% w/w) were dissolved in a 1% v/v lactic acid solution (15 mL) and thereafter PHCl was added and allowed to dissolve. EUD100 and triethyl citrate (30% w/w, used as a plasticiser), were separately dissolved in acetone (15 mL) and then combined by emulsification with the PHCl-CHT preparation as described in Chapter Three 3.2.2.2.1, with the exception of the homogenisation time being modified to 5 instead of 15 minutes in this case, as acetone is a volatile solvent and prolonged homogenisation time resulted in its rapid evaporation. The resulting drug-containing emulsion was casted onto the respective trays and dried as described above.

4.2.2.3 Drug Quantification in Films

4.2.2.3.1 Wavelength Scan of Propranolol HCl to Determine the Maximum Absorbance (λ_{max})

Wavelength scans of PHCl in two solvent systems, i.e. H_2O/Ethanol (1 in 20) and PBS pH 6.8, were determined as assays were undertaken with the H_2O/Ethanol solvent system and the *in vitro* dissolution studies with the PBS pH 6.8 medium. The preparation of PBS pH 6.8 is shown in Appendix 1.

The ultraviolet (UV) absorption spectrum of PHCl (30 µg/mL) in H_2O/Ethanol was obtained using a UV-Spectrophotometer, 1650 PC (Shimadzu, Japan) and 1 cm quartz cells. The solution was scanned to determine the wavelength of maximum absorbance (wavelength range of 200 – 400 nm) and was found to be 290 nm (Appendix 2).

The above was repeated using PBS pH 6.8 as a solvent. The wavelength of maximum absorbance was determined and found to be 289 nm (Appendix 2).

The λ_{max} of PHCl correlated with that found in the literature (Moffat *et al.*, 2004) (Appendix 3). All subsequent UV analyses were performed using the same instrument and cells. It should be noted that at the outset, it was established that all solvents, polymers and other excipients employed in this study did not interfere with drug analysis at the reported wavelengths.

4.2.2.3.2 Preparation of the Calibration Curve

Calibration curves of PHCl were prepared in two solvent systems, i.e. H_2O/Ethanol (1 in 20) and PBS pH 6.8.

A stock solution was prepared by dissolving 100 mg of PHCl in 100 mL H_2O/Ethanol solvent to generate a concentration of 1 mg/mL. Subsequently, a series of dilutions was performed to provide standard solutions with concentrations of 10; 20; 30; 40 and 50 µg/mL of PHCl in 100 mL volumes. Thereafter, using the H_2O/Ethanol solvent as a reference solution, the UV absorbance of each standard solution was determined at 290 nm. Linear regression analysis was performed using the statistical function of the software found in Microsoft Excel® (Version 2002, USA).

The above was repeated for PBS pH 6.8 and the UV absorbance of each standard solution was determined at 289 nm.

The calibration curves were used for all assays and *in vitro* dissolution studies. Before each analysis for the various investigations for the duration of the study, standard solutions of 10 and 50 µg/mL were prepared in triplicate and the concentration determined from the calibration curve. The relative standard deviations for the concentration were all less than 0.3%, confirming the reproducibility of the system for data quantification.

4.2.2.3.3 Assay of Propranolol HCl Films

A 1 x 3 cm^2 film, either as a unit from the SMT or cut into this specified size with a scalpel from the film sheet of a TCPT, was cut into pieces with a surgical blade in a mortar. Thereafter, the contents of the mortar were transferred into a 100 mL volumetric flask. The mortar was washed several times with the selected solvent system which was also transferred into the flask after each washing. The mixture was then mechanically agitated in a shaking water bath maintained at 40 °C for 24 hours before being brought up to volume with additional H_2O/Ethanol solution. This stock solution (0.15 mg/mL) was also agitated for five minutes and then filtered (Millipore® Filter, 0.45 µm). A subsequent 1 in 10 dilution was performed before UV analysis of the solution. Assays for each tray were undertaken in triplicate.

4.2.2.3.4 Precision and Accuracy Measurements

In order to ascertain the validity and reliability of the assay method for drug quantification, accuracy and precision measurements were undertaken. These measurements were performed to ensure consistency and reproducibility of the results obtained as well as to determine the accuracy of the UV data obtained.

Precision was determined by undertaking five replicate determinations of three known standard solutions, i.e. 10, 30 and 50 µg/mL prepared from a stock solution containing 1 mg/mL PHCl in both H_2O/Ethanol and PBS pH 6.8. The measured concentration for each replicate was used to determine the precision of the method. Accuracy was determined by undertaking absorbance and concentration measurements of five replicate standard solutions of 10, 30 and 50 µg/mL each. All standard solutions prepared for these determinations

were separate from those employed for the construction of the calibration curves.

4.2.2.4 In Vitro Drug Release Method

4.2.2.4.1 Selection of a Suitable In Vitro Dissolution Method

Currently, there are no official methods for the *in vitro* dissolution testing for buccal mucoadhesive controlled release dosage forms. Therefore, researchers are using several different methods as described in the literature. These include: rotating basket in a beaker (Ishida *et al.*, 1981); USP rotating paddle method (Remunan Lopez *et al.*, 1998; Perugini *et al.*, 2003); shaking water bath (Govender *et al.*, 2005) and Franz diffusion cells (Rossi *et al.*, 2003). For the purpose of this study, a modified shaking water bath dissolution method was employed. The shaking water bath apparatus consisted of a water bath, thermostatically controlled at 37 ± 0.5 °C and a mechanical shaker platform onto which a bottle holder plate was positioned. Glass bottles (125 mL), the caps of which were modified to hold a stainless steel basket into which each film was placed so as to contain all fragments of the dosage form as it disintegrated during the dissolution process, were secured in the holders of the holder plate. The baskets used were dissolution baskets with a height of 35 mm, a diameter of 20 mm and a mesh size of 0.4 mm. The dissolution medium used was PBS pH 6.8, prepared as described in Appendix 1. PBS (100 mL) was added to each bottle and the cap screwed on to prevent evaporation of the dissolution medium whilst it equilibrated to 37 ± 0.5 °C.

In the interim, each film was placed into a separate basket and the basket holder tightly screwed on to prevent dislodging during the shaking process. When the dissolution medium reached the required temperature of 37 ± 0.5 °C, the film-containing baskets were attached

and secured to the cap of each bottle before being introduced into the dissolution vessel. A minimum of three replicate determinations was performed for all dissolution tests.

At the beginning of the dissolution test (0 hours), the film-containing baskets attached to the cap were lowered into the dissolution vessels and tightly screwed onto the bottle. The shaking apparatus was switched on and maintained at 100 strokes per minute. At specified time intervals (0.25; 0.5; 0.75; 1; 2; 3; 4; 5; 6; 7 and 8 hours), 2 mL aliquots of sample were removed from each vessel using a syringe and filtered through a Millipore® Filter (0.45 µm). An equal volume (2 mL) of fresh PBS, also maintained at 37 ± 0.5 °C, was replaced into each dissolution vessel, to ensure a constant volume of dissolution medium throughout the duration of the test. Sample withdrawal and PBS pH 6.8 replacement was completed in approximately one minute.

4.2.2.4.2 Analysis of Dissolution Samples

All dissolution samples were analysed using a UV spectrophotometer (Shimadzu, Japan) at a wavelength of 289 nm. Prior to analysis, a 1 in 10 dilution of the sample was performed to ensure the sample concentration would fall within range of the calibration curve. The calibration curve was prepared as explained in section 3.2.2.3 with the exception of the solvent (PBS pH 6.8) for the dissolution test. Percentage drug released was calculated taking into account correction for dilution as a result of sample removal and replacement. The computation of the percentage drug released was facilitated with the aid of a spreadsheet generated using the computer software programme, Microsoft Excel® (Version 2002, USA).

4.2.2.5 Determination of the Mucoadhesivity of Films

The mucoadhesivity of the films was measured with the aid of a software-controlled penetrometer, TA-XT2*i* texture analyser (Stable Micro Systems, UK) equipped with a 5 kg load cell, a force measurement accuracy of 0.0025% and a resolution distance of 0.0025 mm. The pre-test, test and post-test speeds were set at 1.0, 0.5 and 1.0 mm/s respectively, with an acquisition rate of 200 points per second. A removable stainless steel probe with dimensions 1 x 3 cm^2 was used for all measurements.

A sample of the prepared polymeric film (1 x 3 cm^2) was attached to the base of the probe with cyanoacrylate (superglue) and pre-hydrated with PBS pH 6.8 (20 µL) before being fixed to the mobile arm of the TA-XT2*i* where the film was allowed to continue hydrating for the remaining period of the two minute pre-hydration phase. In the interim, 1 mL of mucin (30% w/w at 37 °C) was spread onto a glass slide that was firmly attached to the base plate of the TA-XT2*i*. Upon completion of the prehydration period (2 minutes), the film was brought into contact with the mucin for 30 seconds. The mucoadhesive performance of the samples was determined by measuring the Maximum Detachment Force (MDF) (mN) and/or work (mJ). The MDF represents the force required to detach the film from the mucin. The area under the Force/Distance curve was also determined to represent the work or energy required for detachment of the two systems (mucin/polymeric film) (Eouani *et al.*, 2001). A minimum of ten replicate determinations was performed. The equations used to calculate Force and Work are shown below (Martin, 1993) and a typical Force/Distance curve generated for each mucoadhesivity measurement from which the MDF and/or Work performed was determined, is illustrated in Figure 4.4.

Equation 4.1:

Force (N) = Mass (kg) x Acceleration (m^2/s)

Equation 4.2:

Work (J) = Force (N) x Distance (m)

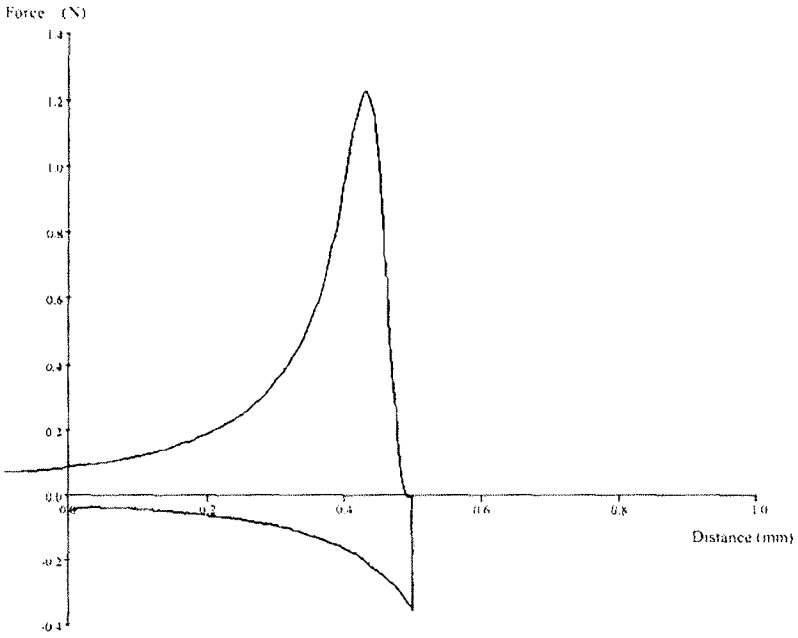


Figure 4.4 A typical detachment profile (Force-Distance curve)

4.2.2.6 Thickness Measurements

The thickness of each film was measured as described in Chapter Three (3.2.2.4.1).

4.2.2.7 Appearance and Morphology

The appearance and morphology of each film were evaluated as described in Chapter Three (3.2.2.4.2).

4.2.2.8 Statistical Analysis

All statistical analyses of data were undertaken using GraphPad Instat, version 3.05 (GraphPad Software Inc., San Diego, California, USA) while all mathematical calculations were undertaken with Microsoft Excel® (Version 2002, USA).

4.3 RESULTS AND DISCUSSION

4.3.1 Calibration Curves for Drug Quantification

The calibration curves obtained for drug quantification of PHCl (λ_{max} = 290 nm) in H_2O/Ethanol for assays and (λ_{max} = 289 nm) in PBS pH 6.8 for drug release are illustrated in Figures 4.1 and 4.2 below. The linear correlation coefficient obtained for both these curves was 0.999. These calibration curves were used for all subsequent drug quantification studies.

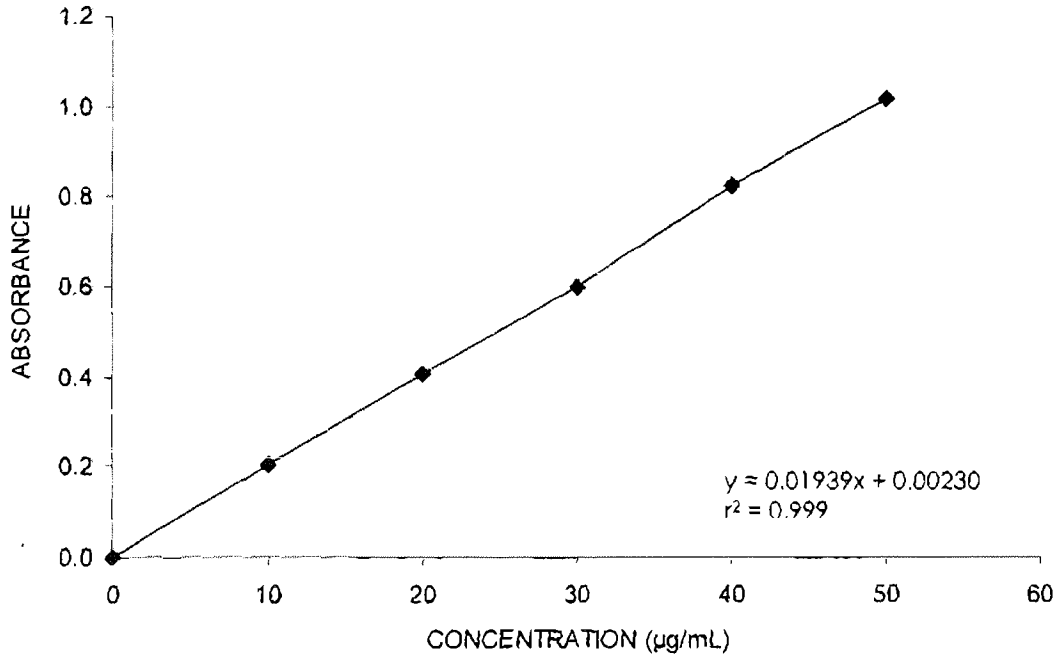


Figure 4.5 Calibration curve of PHCl in H_2O/Ethanol (n = 3; SDs < 0.01)

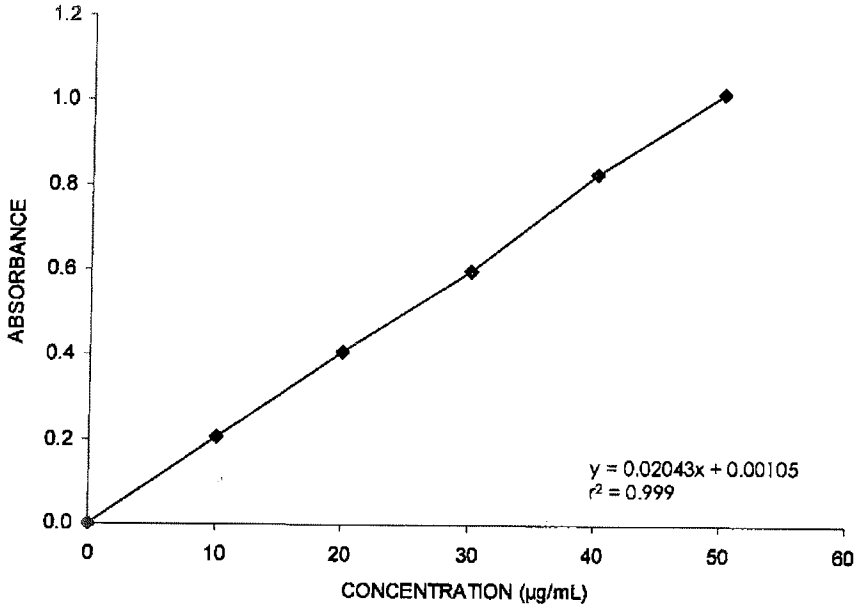


Figure 4.6 Calibration curve of PHCl in PBS pH 6.8 (n = 3; SDs < 0.01)

The accuracy of the UV analytical method in H_2O/Ethanol and PBS pH 6.8 was determined by calculating the percentage recovery of PHCl from five replicate standard solutions of 10, 30 and 50 µg/mL PHCl. The data obtained are represented in Tables 4.2 - 4.5.

Table 4.2 Accuracy determinations for PHCl assay method in H_2O/Ethanol solvent system

SAMPLE CONCENTRATION (µg/mL)	SAMPLE STANDARDS	CONCENTRATION ADDED (µg/mL)	CONCENTRATION FOUND (µg/mL)	% RECOVERY
10	1	10	9.91	99.10
	2	10	9.93	99.30
	3	10	9.98	99.80
	4	10	9.91	99.10
	5	10	9.92	99.20
	Mean		9.93	99.30
	SD		0.03	0.29
	CV(%)		0.29	0.29
30	1	30	29.97	99.90
	2	30	29.96	99.87
	3	30	30.00	100.00
	4	30	29.99	99.97
	5	30	29.96	99.87
	Mean		29.97	99.92
	SD		0.02	0.06
	CV(%)		0.61	0.06
50	1	50	49.98	99.96
	2	50	49.95	99.90
	3	50	49.99	99.98
	4	50	49.98	99.96
	5	50	49.99	99.98
	Mean		49.98	99.96
	SD		0.02	0.03
	CV(%)		0.033	0.033

Table 4.3 Precision determinations for PHCl assay method in H_2O/Ethanol solvent system

CONCENTRATION (µg/mL)	UV ABSORBANCE OF SAMPLE REPLICATES							
	1	2	3	4	5	MEAN	SD	CV (%)
10	0.205	0.199	0.20	0.201	0.201	0.0201	2.3×10^{-3}	1.13
30	0.607	0.605	0.603	0.605	0.606	0.605	1.4×10^{-3}	0.245
50	1.019	0.016	1.019	1.02	1.018	1.018	1.5×10^{-3}	0.15

Table 4.4 Accuracy determinations for PHCl assay method in PBS pH 6.8

SAMPLE CONCENTRATION (µg/mL)	SAMPLE STANDARDS	CONCENTRATION ADDED (µg/mL)	CONCENTRATION FOUND (µg/mL)	% RECOVERY
10	1	10	9.98	99.80
	2	10	9.96	99.60
	3	10	9.99	99.90
	4	10	9.96	99.60
	5	10	9.98	99.80
	Mean		9.974	99.74
	SD		0.01	0.13
	CV(%)		0.13	0.13
30	1	30	29.99	99.97
	2	30	29.98	99.93
	3	30	29.99	99.97
	4	30	29.98	99.93
	5	30	29.98	99.93
	Mean		29.98	99.95
	SD		0.01	0.02
	CV(%)		0.02	0.02
50	1	50	49.97	99.94
	2	50	49.98	99.96
	3	50	49.95	99.90
	4	50	49.98	99.96
	5	50	49.97	99.94
	Mean		49.97	99.94
	SD		0.01	0.02
	CV(%)		0.02	0.02

Table 4.5 Precision determinations for PHCl assay method in PBS pH 6.8

CONCENTRATION (µg/mL)	UV ABSORBANCE OF SAMPLE REPLICATES							
	1	2	3	4	5	MEAN	SD	CV (%)
10	0.195	0.197	0.199	0.198	0.199	0.198	1.6×10^{-3}	0.85
30	0.593	0.591	0.593	0.591	0.592	0.592	1.0×10^{-3}	0.17
50	0.972	0.969	0.973	0.972	0.973	0.972	1.6×10^{-3}	0.17

The CVs of 10, 30 and 50 µg/mL samples for both accuracy and precision measurements for both the H_2O/Ethanol and PBS pH 6.8 solvent systems were very low, i.e. less than 1.5%, illustrating that this method of detection for determination of PHCl release in both H_2O/Ethanol and PBS pH 6.8 is accurate and precise.

4.3.2 Development of Trays for Enhancing Drug Uniformity in Films

Table 4.6 depicts the pictures of trays used in the study for film casting and a summary of the assay and morphology of films generated. Films were initially prepared by employing the conventional casting technique whereby the polymeric solution is casted onto TCPTs. This yielded films with uniform surface morphology but poor drug content uniformity values, i.e. 110.00 ± 66.63%, indicating a large CV of 60.57%. The poor drug uniformity with these TCPT trays was attributed to the reasons given in several patent applications, i.e. to the formation of conglomerates and migration of drug throughout the tray during the drying process. To prevent this from occurring, a TCPT with a removable unit that encompassed chambers (each chamber = 1 x 3 cm^2), was developed. This was an attempt to contain the drug-containing polymeric solution dispensed into each chamber within that chamber. Whilst this method improved the drug uniformity as compared to the TCPT, i.e. the CV decreased from 60.57% to 24.34%, the values were still unacceptable for regulatory approval. This poor drug uniformity may have been due to seepage of the polymeric mixture to adjacent chambers since it was detachable and the solution could seep from one chamber to the next. The difficulty also experienced with this type of rigid tray was the inability to remove the dried films without damage. This, coupled with the poor assay values, lead to the realisation that a flexible tray for easy film removal was required and that the tray should also possess individual predetermined wells completely separate from one another, to facilitate entrapment of the polymeric solution.

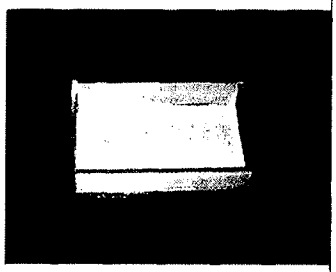
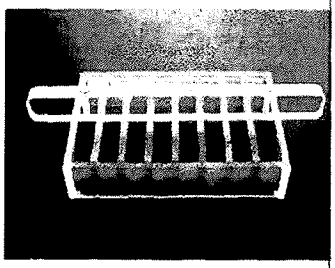
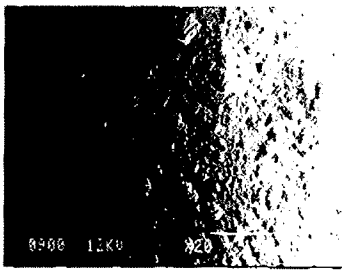
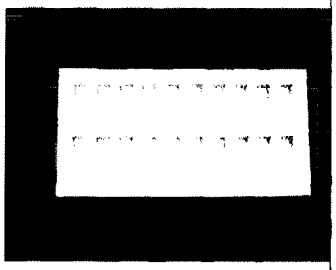
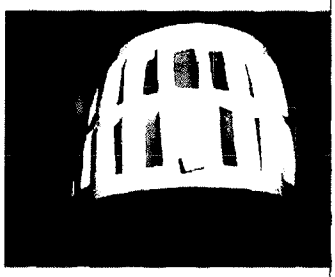
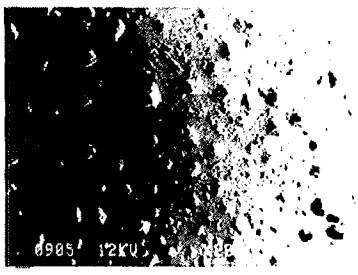
One of the suitable materials that satisfied the abovementioned factors is silicone, as it can be easily molded to yield a flexible product. In addition, silicone products have a relative inert state that minimises the risk of chemical reaction with drug (Maillard-Salin *et al.*, 2000).

Silicones also resist acids, bases, solvents, chemicals, oils and water. Furthermore, it is extensively used in medical applications (Advantages/characteristics of silicone rubber). It has also been used as a drug delivery system (Maillard-Salin *et al.*, 2000). Silicone rubbers have not caused health reactions in clinical testing or field application (Advantages/characteristics of silicone rubber).

Taking these factors into consideration, a SMT with 20 individual separate wells was developed, which met the desired requirements. Films prepared using this tray exhibited assay values of 104.06 ± 3.31%, i.e. a CV of 3.18%. Also, flexibility of the molded tray enabled the easy removal of films for evaluation. However, the films from this tray displayed poor surface morphology as they appeared porous. This could possibly be due to the physical nature of silicone when it is heated and dried, i.e. adhesion of the films directly onto the silicone surface may have resulted in the film porosity. Since the TCPT trays produced films with non-porous, uniform morphology, teflon-coated perspex inserts were designed for insertion into each well to overcome the poor surface morphology.

Films prepared using the SMT with inserts satisfied all requirements, i.e. good surface morphology and excellent assay values of 104.84 ±1.30% were achieved, as required by compendial specifications for PHCl dosage forms currently (92 - 107.5%) (BP, 2003).

Table 4.6 Description of tray development and film characteristics

TRAY TYPE	PICTURE OF TRAY	ASSAY (%) MEAN±SD	ELECTRON MICROGRAPH OF FILM
TCPT		110.00 ± 66.63 CV = 60.57%	
TCPT WITH REMOVABLE CHAMBERS		116.33 ± 28.31 CV = 24.34%	
SMT		104.06 ± 3.31 CV = 3.18%	
SMT WITH TEFLON-COATED PERSPEX INSERTS		104.84 ±1.30 CV = 1.24%	

4.3.3 Reproducibility Study

A comparison of the assay, mucoadhesivity and thickness of films casted onto TCPT and the newly developed SMT with the perspex inserts, showed significant improvements in uniformity of the films in terms of the above properties (Table 4.7). Since the SMT with inserts showed excellent assay values and acceptable film surface morphology, this tray was selected for reproducibility studies to validate this method of film preparation. Three batches of the homopolymeric films, i.e. PHCl and CHT, were prepared as described in 4.2.2.2.1, using three different SMTs with teflon-coated perspex inserts. These batches were subjected to characterisation studies in terms of assays, drug release, mucoadhesion and thickness measurements. The assay, mucoadhesion and thickness data obtained for the three formulations for the reproducibility study are shown in Table 4.8.

Table 4.7 Summary of results for characterisation studies for films prepared with the TCPT and SMT

Characterisation Study	TCPT		SMT	
	MEAN±SD	CV (%)	MEAN±SD	CV (%)
Assay (%)	110.00±66.63	60.57	106.87±0.59	0.55
Mucoadhesivity (mN)	154±82	53.68	134±28	20.88
Thickness (mm)	0.21±0.10	47.62	0.13±0.02	15.38

Table 4.8 Summary of results for characterisation studies for reproducibility studies (SMT with inserts)

Characterisation Study	Tray A		Tray B		Tray C	
	MEAN±SD	CV (%)	MEAN±SD	CV (%)	MEAN±SD	CV (%)
Assay (%)	106.87±0.59	0.55	104.84±1.30	1.24	104.06±3.31	3.19
Mucoadhesivity MDF (mN)	134±28	20.88	168±45	26.97	143±26	18.40
Thickness (mm)	0.13±0.02	15.38	0.13±0.02	15.38	0.10±0.01	10.00

The CV for assay values for each tray was low, indicating minimal intra-tray variability. Also these values were all within the compendial specifications of 92-107.5% (BP, 2003). The mean assay values between the three trays were statistically analysed using a Kruskal-Wallis test with Dunn's Post Hoc tests. Data were considered statistically significant if $p<0.05$. Statistical analyses indicated no significant differences between the three trays for assays since $p=0.3407$. As a result of aggregation, however, the absence of thickness uniformity, as observed in the TCPT films, detrimentally affected uniformity of component distribution throughout the film. This directly impacted on the mucoadhesive property of the individual film doses, as the mucoadhesive polymer was randomly distributed, resulting in non-uniform mucoadhesive performance. The intra-batch variability for the mucoadhesivity of films from the SMT trays was less than 30% and was consistent with those reported in the literature for other preparations (Shojaei *et al.*, 2000; Eouani *et al.*, 2001). The differences between the mean MDF values for mucoadhesion of the three trays were statistically analysed using one-way ANOVA with Bonferroni Post Hoc tests. Statistical analyses indicated no significant differences between the three trays for mucoadhesivity since $p=0.2922$. Minimal intra-tray variability for thickness was noted as CVs were very low, i.e. less than 16% for all three trays.

The *in vitro* drug release profiles of films from the three trays were also compared, as shown in Figure 4.7.

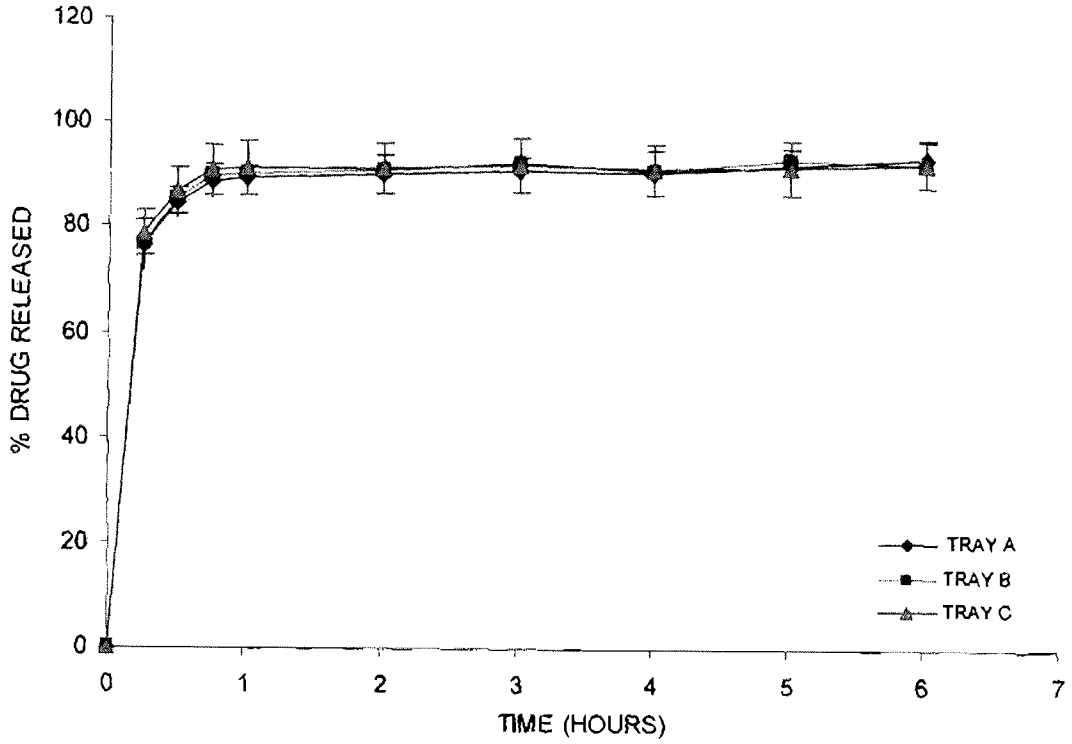


Figure 4.7 Reproducibility of *in vitro* drug release profiles

The profiles for films from all three trays appeared to be almost super-imposable. To confirm the similarity of these dissolution profiles, the similarity factor was used. The *similarity factor* denoted as f_2 (Moore and Flanner, 1996), directly compares the similarity between percentage drug dissolved per unit time for a test and reference product. The *similarity factor* (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference product R_j over all time points:

Equation 4.3:

$$f_2 = 50\log([1 + (1/n)\sum_{j=1}^{n}|Rj - Tj|^2]^{-0.5} \times 100$$

In general, f_2 values higher than 50(50-100) show similarity of the dissolution profiles. The calculated f_2 obtained for this study for Tray A

versus Tray B, Tray B versus Tray C and Tray A versus Tray C was 92.76, 90.99 and 86.06 respectively. These results confirmed that the drug release profiles were similar for films from all 3 trays.

Analyses of the data for drug content, mucoadhesivity and thickness, coupled with the above f_2 values showing similarity, confirmed intra- and inter-batch reproducibility of this method, and hence the use of the SMT with teflon-coated perspex inserts for the preparation of films with uniform drug content is validated.

4.3.4 Applicability of the SMT with Teflon Coated Perspex Inserts to Multipolymeric Films with Drug and Polymers of Similar and Opposing Solubilities

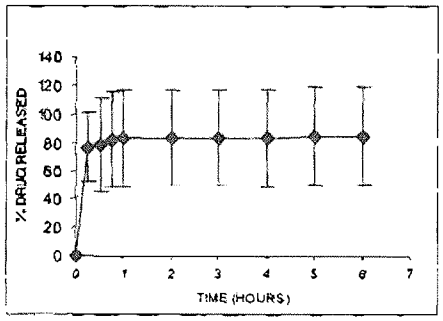
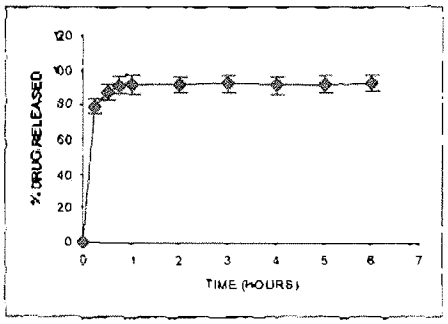
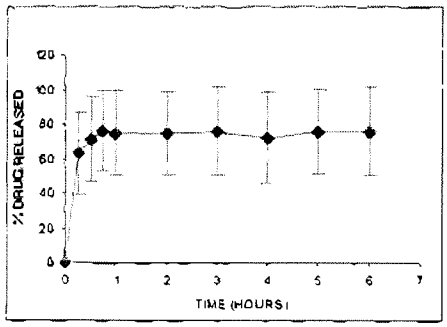
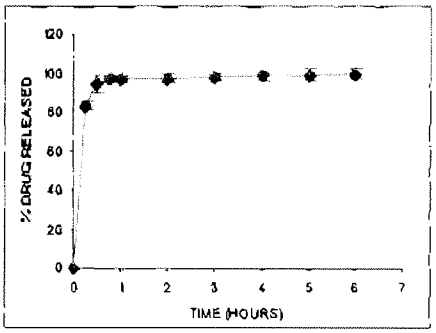
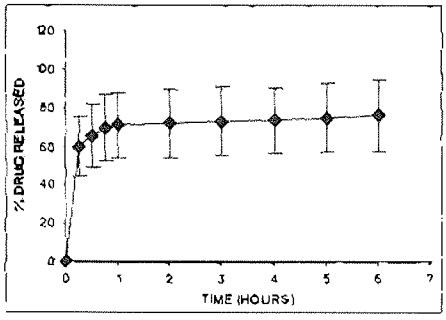
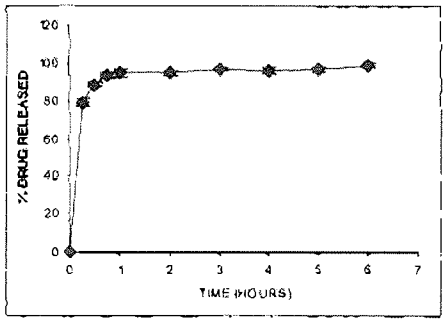
While the SMT with the inserts was demonstrated to provide drug content uniformity with monolayered homopolymeric films of drug and a single polymer with similar solubilities, it was essential to assess its applicability to the use of monolayered multipolymeric films with polymer/s and drug of similar and opposing solubilities, since this was the focus of this study. Therefore, multipolymeric films with PHCl + CHT + HPMC (polymers with similar solubilities) and films with PHCl + CHT + EUD 100 (polymers with opposing solubilities) were prepared by using the conventional TCPT and the SMT with inserts. The findings for both these methods were compared. Table 4.9 indicates the assay values, whilst Table 4.8 presents a composite summary of the drug release profiles of the films prepared in both types of trays.

Table 4.9 Assay values of homopolymeric and multipolymeric films prepared in the TCPT and SMT with inserts

FILM TYPE	TCPT ASSAY (%)		SMT ASSAY (%)	
	MEAN±SD	CV (%)	MEAN±SD	CV (%)
Homopolymeric Film PHCl+CHT	110.00±66.63	60.57	104.84±1.30	1.24
Multipolymeric Film Similar Solubilities PHCl+CHT+HPMC	114.04±22.78	19.97	97.62±3.05	3.13
Multipolymeric Film Opposing Solubilities PHCl+CHT+EUD100	113.76±13.21	11.61	104.08±1.33	1.28

As is evident from Table 4.9, all films prepared with the SMT were within compendial specifications (92 - 107.5%) (BP, 2003) and all CVs for assays were low, i.e. less than 4%, thus indicating the suitability of the SMT for the preparation of both homopolymeric and multipolymeric films with drug and polymer/s of similar and/or opposing solubilities. None of the films prepared with the TCPT were within compendial specifications. They exhibited very high CVs for assays, i.e. as high as 60%, indicating the unsuitability of these trays for all types of film preparation.

Table 4.10 Summary of PHCl release profiles from films prepared in the TCPT and SMT with inserts

FILM TYPE	TCPT	SMT WITH INSERTS
Monolayered Homopolymeric Film Drug + CHT (1:1)		
Monolayered Multipolymeric Film - Similar Solubilities Drug + CHT + HPMC (1:0.5:0.5)		
Monolayered Multipolymeric Film – Opposing Solubilities Drug + CHT + EUD100 (1:0.5:0.5)		

As can be seen from these profiles, the release curves of all films prepared in the TCPT have relatively large SDs, whilst those prepared in the SMT with inserts have relatively small SDs. These results can be attributed to the migration of drug that occurs during the formation of

aggregates during the drying process, leading to non-uniform drug content resulting in non-reproducible drug release profiles in the case of the TCPT. The small SDs and reproducible release profiles of all films prepared in the SMT with inserts are due to the containment of the drug within a predetermined well which prevents drug migration during drying and which maintains uniformity of content (US Patent No. 60/443,741, 2004). It is evident from Table 4.8 that the SMT with inserts can be successfully used to prepare both homo- and multipolymeric films with drug and polymers of similar and opposing solubilities.

4.4 CONCLUSIONS

Preliminary investigations in our laboratories, as well as a comprehensive search of the literature and patents filed, indicated that the conventional film casting method onto teflon-coated trays produced a sheet of film that suffered from poor drug content uniformity. The aim of this study was therefore to prepare a specially designed tray for film casting and to evaluate it in terms of enhancing drug content uniformity.

From these investigations, it was concluded that a specially designed silicone-molded tray with teflon-coated perspex inserts provided a reproducible method for the preparation of both homopolymeric and multipolymeric (including drug and polymers of similar and opposing solubilities) films that would meet drug content uniformity requirements and would also reduce the variability in mucoadhesivity, drug release and film thickness. The reproducibility of this SMT with inserts method was also demonstrated in terms of drug content, mucoadhesion and drug release. This method of film casting has not, to the best of our knowledge, been reported previously in the literature and therefore

makes a significant contribution to the formulation and evaluation of mucoadhesive films for mucosal delivery.

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CHAPTER FIVE

FORMULATION AND PRELIMINARY CHARCTERISATION OF MMFs FOR BUCCAL DELIVERY OF PHCl

Table of Contents

5.1 INTRODUCTION AND AIM

The design of the novel silicone molded tray with teflon-coated perspex inserts, as discussed in Chapter Four, provided a reproducible method for the preparation of films with uniform drug content. Since these trays were also shown to be applicable for the preparation of both homopolymeric and multipolymeric films comprising drug and polymer/s of either similar or opposing solubilities, it was employed for the preparation of films in the next stage of investigation as discussed in this chapter.

Although numerous other dosage forms of PHCl for buccal delivery have been investigated and reported in the literature (Table 1.1), Table 2.3 in Chapter Two, which provides a summary of buccal films, investigated, clearly shows that very few studies on monolayered PHCl buccal films particularly those consisting of drug and polymer/s of opposing solubilities, have been done. No such formulation studies have been described in the literature. Further, a lack of physicochemical/mechanical characterisation studies for such monolayered multipolymeric films with drug and polymer of opposing solubilities exists.

The aim of the investigation, as discussed in this chapter was therefore to formulate and evaluate multipolymeric monolayered mucoadhesive films comprising both hydrophilic and hydrophobic polymers for the controlled buccal delivery of PHCl.

5.2 MATERIALS AND METHODS

5.2.1 Materials

Propranolol HCl (PHCl) [Frankel Chemicals, SA]; Chitosan (CHT) (MW 110 000) [Primex Ingredients, ASA, Norway]; Eudragit® RS100 (15 mPa.s) (EUD100) [Rhom Pharma, Germany]; Eudragit® NE30D (50 mPa.s) (EUD NE30D) [Rhom Pharma, Germany]; Hydroxypropylmethylcellulose (4000 mPa.s) (HPMC) [Fluka, UK]; Carboxymethylcellulose (500-2500 mPa.s) (CMC) [Sigma-Aldrich, UK]; Polyethylene Glycol 4000 (PEG) [BDH Chemicals Ltd., UK]; Poly(vinyl pyrrolidone) (MW 40 000) (PVP) [Sigma-Aldrich, UK]; Poly(acrylic acid) 2100 (PAA) [Sigma-Aldrich, UK]; Poly(vinyl alcohol) (PVA) [Sigma-Aldrich, Germany]; Sodium Alginate (Na Alginate)[BDH Laboratories, UK]; Ethylcellulose (14cP) (EC) [BDH Chemicals Ltd., UK]; Poly(D,L-lactide-co-glycolide) (50/50 0.39dL/g) (PLGA) [Absorbable Polymers, USA] and Mucin [Sigma-Aldrich, UK] were purchased and used as received. All other chemicals used were of analytical or reagent grade. Distilled water was used in all studies.

5.2.2 Methods

5.2.2.1 *Preparation of Films*

5.2.2.1.1 Homopolymeric Films

Homopolymeric films containing either a hydrophilic or hydrophobic polymer and PHCl were prepared in various ratios. These ratios and amounts of drug and polymer are represented in Table 5.1. A plasticiser was added to all formulations at 30% w/w of the dry weight of the polymer.

Homopolymeric films, comprised of hydrophilic polymer, were prepared as follows: the required amount of polymer, i.e. CHT; CMC; HPMC; PEG; PVP; PAA; PVA; Na Alginate; EUD NE30D and plasticiser (glycerol) was dissolved in water (30 mL) or 1% v/v lactic acid solution in the case of CHT, under magnetic stirring. PHCl was then dissolved in the above polymeric solution. The resulting drug containing polymeric solution was allowed to stand until air bubbles were removed before casting onto the SMT and drying as previously described in 3.2.2.1.

Homopolymeric films, comprised of a hydrophobic polymer, were prepared as follows: EUD100 and plasticiser (triethyl citrate) dissolved in acetone (15 mL); EC and plasticiser (dibutylphthalate) dissolved in ethanol (15 mL) or PLGA dissolved in CH_2Cl_2 (15 mL) were combined by emulsification with a solution of PHCl in water (15 mL) as described in Chapter Three (3.2.2.1), with a homogenisation time of 5 minutes as these organic solvents are volatile and rapidly evaporated as a result of prolonged homogenisation time. The resulting drug-containing emulsion was casted onto the SMT and dried as previously explained in 3.2.2.1.

Table 5.1 Ratios and amounts of drug and polymer used for the preparation of homopolymeric films

Ratio (PHCl:Polymer)	PHCl (g)	Polymer (g)
1:1[a]	0.45	0.45
1:1.5[b]	0.45	0.68
1:2[c]	0.45	0.90
1:3[d]	0.45	1.20
1:5[d]	0.45	2.25
1:10[d]	0.45	4.50

[a] CHT; CMC; HPMC; PEG; PVP; PAA; PVA; Na Alginate; EUD NE30D; EUD100; PLGA
[b] CHT; HPMC
[c] CHT; HPMC; EC; EUD100
[d] EUD100

5.2.2.1.2 Multipolymeric Films

Based on the results obtained with homopolymeric films, various combinations of multipolymeric films were investigated. Multipolymeric films, where drug and polymers were all of similar and/or opposing solubilities, were prepared in the ratios represented in Table 5.2. Hydrophilic and hydrophobic combination films were prepared according to the method described in Chapter Four (4.2.2.2.2).

Table 5.2 Ratio and amounts of CHT and HPMC added to 1:10 PHCl:EUD100 formulation

Ratio	PHCl (g)	EUD100 (g)	CHT (g)	HPMC (g)
PHCl:EUD100:CHT				
1:10:0.1	0.45	4.5	0.045	-
1:10:0.25	0.45	4.5	0.1125	-
1:10:0.5	0.45	4.5	0.2250	-
PHCl:EUD100:HPMC				
1:10:0.1	0.45	4.5	-	0.045
1:10:0.25	0.45	4.5	-	0.1125
1:10:0.5	0.45	4.5	-	0.2250

5.2.2.2 Characterisation of Films

5.2.2.2.1 Assay of Propranolol HCl Films

All films were assayed for drug content uniformity as described in Chapter Four (4.2.2.3.3).

5.2.2.2.2 Thickness Measurements

The thickness of each film was measured as detailed in Chapter Three (3.2.2.4.1).

5.2.2.2.3 In Vitro Drug Release

Drug release studies on all film formulations were performed according to the method explained in Chapter Four (4.2.2.4).

5.2.2.2.4 Kinetic Analysis of Drug Release Profiles

Kinetic modeling of the dissolution data was performed using Higuchi's model, where the cumulative amount of released drug per unit area is proportional to the square root of time.

Equation 5.1:

$Q = k_H t^{1/2}$ where: Q = amount of drug released after time t,

k_H = release rate constant

The above model has been used in previous studies to describe drug release kinetics for films (Ahmed *et al.*, 2004; Amnuaikit *et al.*, 2005).

5.2.2.2.5 Swelling and Erosion Studies

Swelling and erosion of the films were determined under conditions identical to those described for the dissolution testing in Chapter Four (4.2.2.4). The degree of swelling (water uptake) and device erosion (mass loss) were determined gravimetrically according to the following equations (Peh and Wong, 1999; Wang *et al.*, 2004):

Equation 5.2:

$$\text{Degree of Swelling} = \frac{\text{wet weight} - \text{original dry weight}}{\text{original dry weight}}$$

Equation 5.3:

$$\text{Erosion (\% mass loss)} = \frac{\text{original weight} - \text{remaining dry weight}}{\text{original weight}} \times 100$$

At predetermined times; the hydrated films were carefully removed from the dissolution bottles and lightly blotted with filter paper to remove excess surface solution. After determining the wet weight, the films were dried at 30 °C until constant weight (Series 2000, Scientific, SA), before reweighing to determine the remaining dry weight. Experiments were performed in triplicate.

5.2.2.2.6 Appearance and Morphology

The appearance and morphology of each film were evaluated as described in Chapter Three (3.2.2.4.2).

5.2.2.2.7 Determination of the Mucoadhesivity of Films

The mucoadhesivity of the films was measured according to the method outlined in Chapter Four (4.2.2.5).

5.2.2.2.8 Textural Profile Analysis (Mechanical Testing)

Mechanical properties of the films were evaluated using a textural analyser, TA-XT2*i*, (StableMicroSystems, UK) equipped with a 5 kg load cell. Each film strip (1 x 3 cm^2), free from physical imperfections, was held between two tensile grips positioned at a distance of 3 cm. A cardboard was attached on the surface of the grips via double-sided tape to prevent the film from being damaged by the grooves of the grips. During measurement, the films were pulled by the top grip at a rate of 1.0 mm/s to a distance of 150 mm before returning to the

starting point. The force and elongation were measured when the films broke. A minimum of ten determinations was performed. Mechanical properties of the films were evaluated using the following equations:

Equation 5.4:

$$\text{Tensile Strength}\,(N/m^2) = \frac{\text{force at break}}{\text{initial cross-sectional area of the sample}}$$

Equation 5.5:

$$\text{Elongation at break}\,(\%) = \frac{\text{increase in length}}{\text{original length}} \times 100$$

5.2.2.2.9 Surface pH Evaluation

Weighed pieces of 3 cm^2 film were placed in glass tubes and allowed to swell in contact with PBS pH 6.8 (12 mL). Thereafter, surface pH measurements at predetermined intervals of 0.25; 0.5; 0.75; 1; 2; 3; 4; 5; 6; 7; 8 hours were recorded with the aid of a pH meter (Hanna Instruments pH 211, Portugal). These measurements were conducted by bringing a glass micro-electrode near the surface of the films and allowing it to equilibrate for 1 minute prior to recording the readings. Experiments were performed in triplicate.

5.2.2.2.10 Statistical Analysis

Statistical analyses of all data were undertaken using GraphPad Instat, Version 3.05 (GraphPad Software Inc., San Diego, California, USA) while all mathematical calculations were undertaken with Microsoft Excel® (Version 2002, USA).

5.3 RESULTS AND DISCUSSION

5.3.1 Selection of Polymers for Incorporation into MMFs

In order to select combinations of polymers for the preparation of MMFs, several polymers with various different characteristics were initially investigated for their film forming properties as homopolymeric systems. Their ability to form films and subsequent film characteristics are described in Table 5.3.

Table 5.3 Characteristics of several polymers investigated for incorporation into film formulations

	POLYMER (0.45 g)	IONIC STATE	FILM FORMING CAPABILITY	FILM CHARACTERISTICS
Hydrophilic polymers	CHT	Cationic	√	Smooth, translucent, easily removed from tray
	CMC	Anionic	X	Complexation → No film
	HPMC	Non-ionic	√	Smooth, transparent, easily removed from tray
	PEG	Non-ionic	√	Waxy, brittle, difficult to remove from tray
	PVP	Non-ionic	√	Too little polymer to form film
	PAA	Anionic	X	Complexation → No film
	PVA	Non-ionic	√	Brittle, difficult to remove from tray
	Sodium Alginate	Anionic	X	Complexation → No film
	EUD NE30D	Non-ionic	√	Brittle, difficult to remove from tray
Hydrophobic polymers	PLGA	Anionic	X	Complexation → No film
	EC	Non-ionic	√	Smooth, transparent, easily removed from tray
	EUD100	Cationic	√	Smooth, transparent

Key: √ = Formation of film

X = No formation of film

The results in Table 5.1 show that combining anionic polymers, such as CMC; PAA; Sodium Alginate and PLGA, with cationic PHCl, in 1:1 ratio used in this study for film formation, was not successful, as complexation occurred possibly due to interactions between the charged terminals on the drug and polymer. Thus, only cationic and non-ionic polymers could be successfully combined with PHCl to form homopolymeric films. From the hydrophilic polymers investigated, only films prepared with CHT and HPMC displayed film characteristics that were acceptable, i.e. not brittle and easily removable from the tray. With hydrophobic polymers, films were successfully prepared with EC and EUD100. PLGA, an anionic polymer, led to complexation again, possibly due to the interaction with the cationic drug. Interestingly, films with PLGA could be prepared with CHT (Chapter 3 and Perugini *et al.*, 2003). This therefore implies that, while some polymers may not be suitable for film formation as homopolymeric systems, they can nevertheless be incorporated into multipolymeric systems under the appropriate preparation methods. Since comparisons with homopolymeric films were required for the purposes of this part of the study, PLGA was not selected. Based on the above results, hydrophilic polymers, CHT and HPMC, and hydrophobic polymers, EC and EUD100, were selected for incorporation into subsequent formulations.

The hydrophilic polymers, i.e. CHT and HPMC, and hydrophobic polymers, i.e. EC and EUD100 identified above, were formulated in various ratios represented in Table 5.1. Preparation of polymeric solutions in ratios greater than 1:2 for CHT, HPMC and EC were not possible as these solutions were greater than 2% w/w and were very viscous, which prevented homogenous distribution of the drug within the solution as well as easy casting. The drug release profile for each of these homopolymeric films is depicted in Figures 5.1 and 5.2.

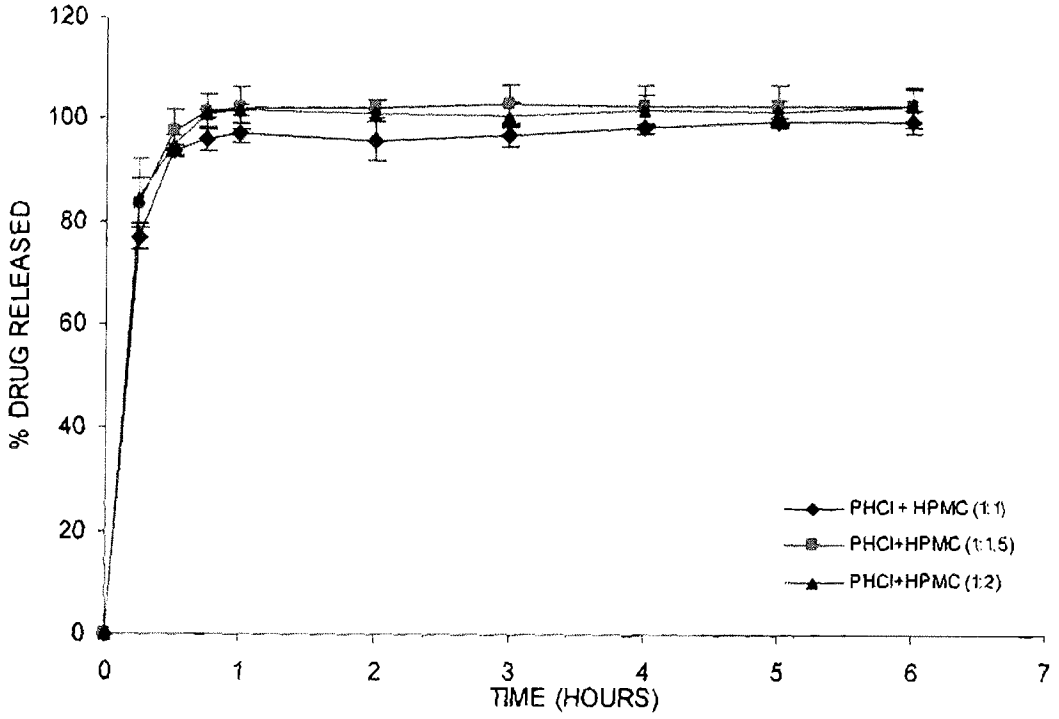


Figure 5.1A Drug release profiles for homopolymeric HPMC films containing PHCl

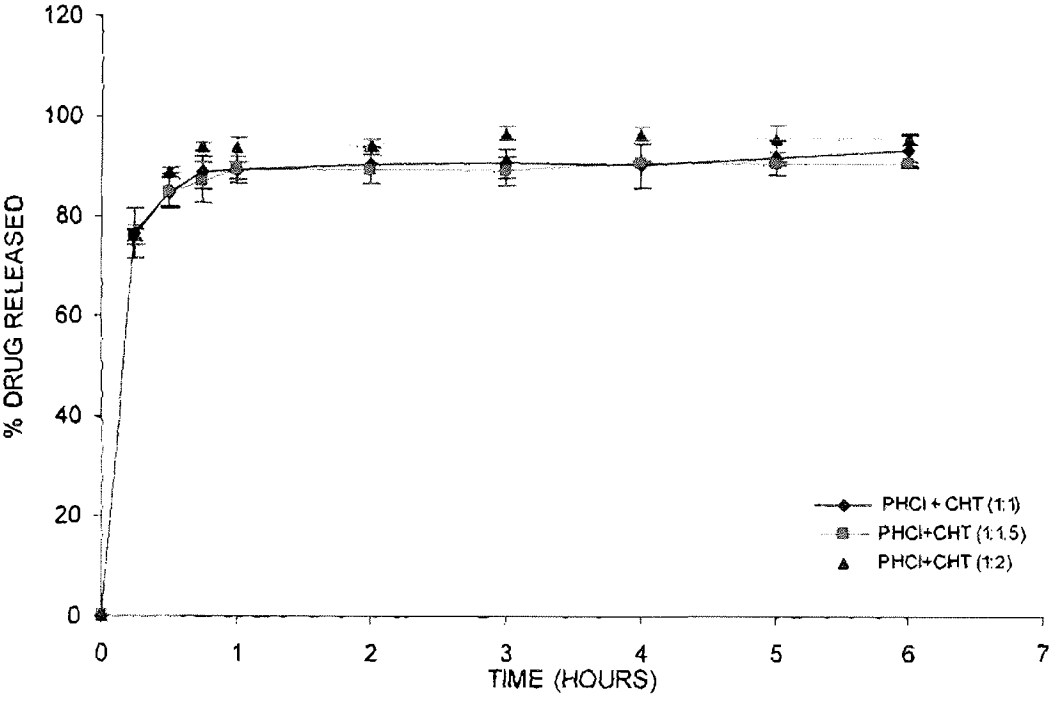


Figure 5.1B Drug release profiles for homopolymeric CHT films containing PHCl

From the *in vitro* drug release profiles represented in Figures 5.1A and B (homopolymeric films with hydrophilic polymers), it is evident that the incorporation of a hydrophilic drug such as PHCl with hydrophilic polymers such as CHT and HPMC did not lead to retarded drug release from the films, as more than 80% of the drug was released within the first hour for all formulations. In addition, an increased ratio of the hydrophilic polymer resulted in an increased release of the drug. This is in agreement with studies performed by Guyot and Fawaz (2000) who attempted to formulate HPMC PHCl-loaded transdermal patches. Their study showed that more than 70% of PHCl was released within the first hour from HPMC films, a hydrophilic polymer. A possible explanation could be that this was attributed to the hydrophilic character of the HPMC matrix which accelerates matrix hydration and swelling, leading to the burst effect (Guyot and Fawaz, 2000). Despite being able to form films, these hydrophilic polymers were therefore unable to provide a controlled release of PHCl.

Figures 5.2A and B (homopolymeric films with hydrophobic polymers) show that EC retarded PHCl release but plateaued after releasing approximately 60% of the drug. This, coupled with its increased viscosity in ratios greater than 1:2, rendered EC unsuitable and it was therefore omitted from further investigations. EUD100 however, showed potential for film formation since increasing the polymer ratios did not lead to viscosity problems. In addition, these increased ratios showed decreasing drug release properties for PHCl, i.e. as the ratio of PHCl:EUD100 increased from 1:1 to 1:10, the drug release decreased with distinct differences in drug release profiles being observed. The 1:10 ratio in particular, exhibited a significantly retarded drug release profile. This is in agreement with Wong *et al.* (1999) who also reported that drug release could be sustained and was governed by the Eudragit® content in the dosage form.

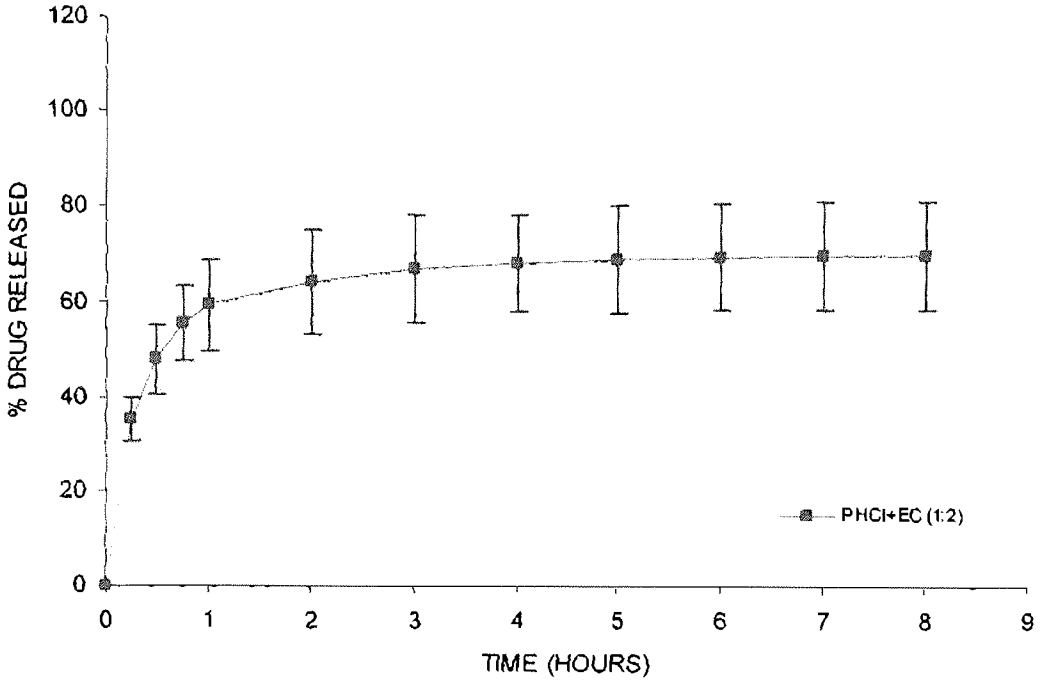


Figure 5.2A Drug release profiles for homopolymeric EC film containing PHCl

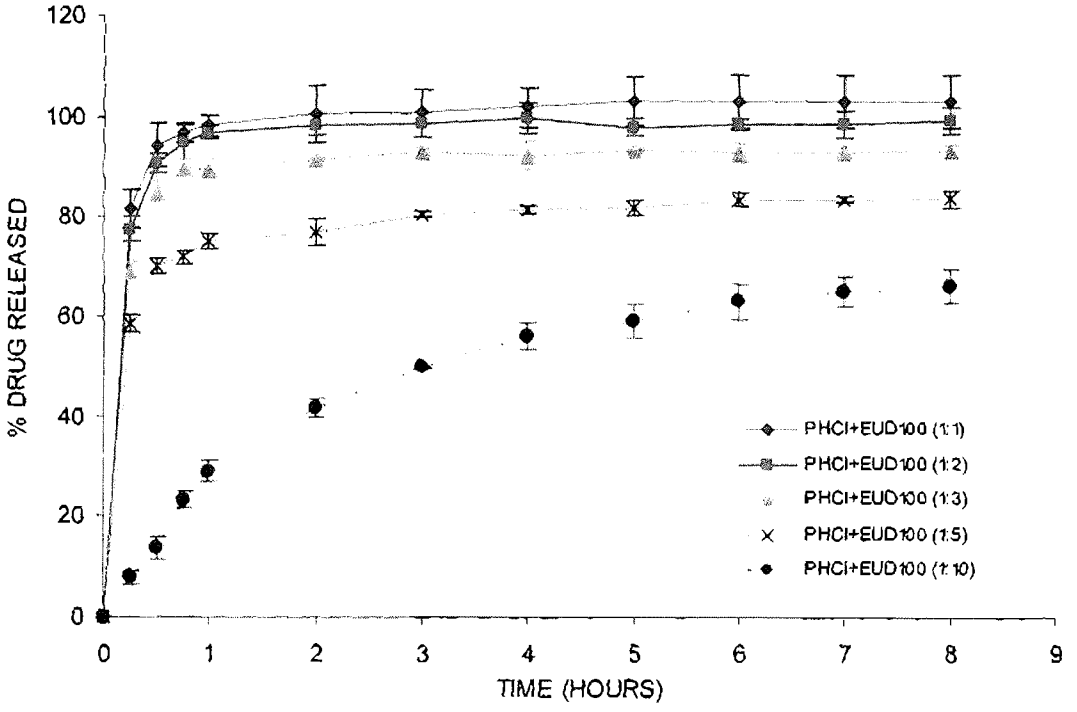


Figure 5.2B Drug release profiles for homopolymeric EUD100 films containing PHCl

A possible explanation could be that it was due to the high hydrophobic properties of the EUD100 when ratios were increased, which prevented free and deep water penetration into the film, thus only the PHCl that was near the external surface of the film was initially released into the dissolution medium (30% within the first hour). Further drug release occurred as the water reached the interior of the film. In addition, Bodmeier and Paeratakul (1994) have shown that films cast from organic solutions have a tighter, more compact structure than those prepared from aqueous dispersion and this is due to the tighter bound plasticiser in their polymeric chains. This phenomenon could therefore lower water permeability of the polymeric films, leading to low hydration and hence slower drug release as shown by EUD100 in the 1:10 ratio. It was therefore concluded that a hydrophobic polymer such as EUD100 in an appropriate ratio was required for the controlled release of a hydrophilic drug such as PHCl.

5.3.2 Optimising the Film for Controlled Release and Mucoadhesivity

From the dissolution profile obtained for the PHCl:EUD100 (1:10) film formulation (Figure 5.28), it was evident that while drug release was controlled, only approximately 66.53±3.31% PHCl was released from the film at the end of 8 hours. A formulation with an appropriate controlled release profile with at least 80% drug release over an 8 hour period was desired for the purpose of this study. Hence, modifications to the polymeric content of the formulation were attempted to obtain the desired controlled release profile.

To increase the release of PHCl from this formulation, the selected hydrophilic polymers capable of forming homopolymeric films, as shown in Table 5.3, were incorporated into the PHCl:EUD100 (1:10) formulation. CHT and HPMC were therefore separately added to the PHCl:EUD100 (1:10) formulation. Various ratios of these formulations

were prepared as shown in Table 5.2 and the resulting films were characterised in terms of drug content and thickness uniformity (Table 5.4).

Table 5.4 Summary of results for characterisation studies for different ratios of MMFs

Ratio	Assay (%)		Thickness (mm)	
	MEAN±SD	CV (%)	MEAN±SD	CV (%)
PHCl:EUD100:CHT				
1:10:0.1	96.30±6.13	6.37	0.403±0.021	5.12
1:10:0.25	100.53±5.50	5.47	0.401±0.016	3.88
1:10:0.5	100.71±2.66	2.64	0.442±0.030	6.78
PHCl:EUD100:HPMC				
1:10:0.1	96.40±1.12	1.26	0.514±0.035	6.79
1:10:0.25	93.72±4.55	4.85	0.443±0.036	8.16
1:10:0.5	96.06±3.44	3.58	0.477±0.029	6.03

As shown in Table 5.4, which provides a summary of the assay and thickness values of these films, CHT and HPMC in combination with EUD100 are capable of forming uniform MMFs, as assay values for all formulations indicate uniform drug content and are also within the required compendial specifications, i.e. within 92-107.5% (BP, 2003). In addition, thickness values for all combinations with either CHT or HPMC have low CVs, i.e. less than 8.5%, indicating uniform distribution of the film components. Therefore, the incorporation of CHT/HPMC into the PHCl:EUD100 (1:10) formulation lead to the successful production of MMFs comprising of drug and polymer/s of opposing solubilities. This can be concluded as no phase separation occurred during the emulsification or drying phases of film preparation, and the resulting MMFs displayed excellent content uniformity. The drug release profiles for each of these MMFs are shown in Figures 5.3A and B.

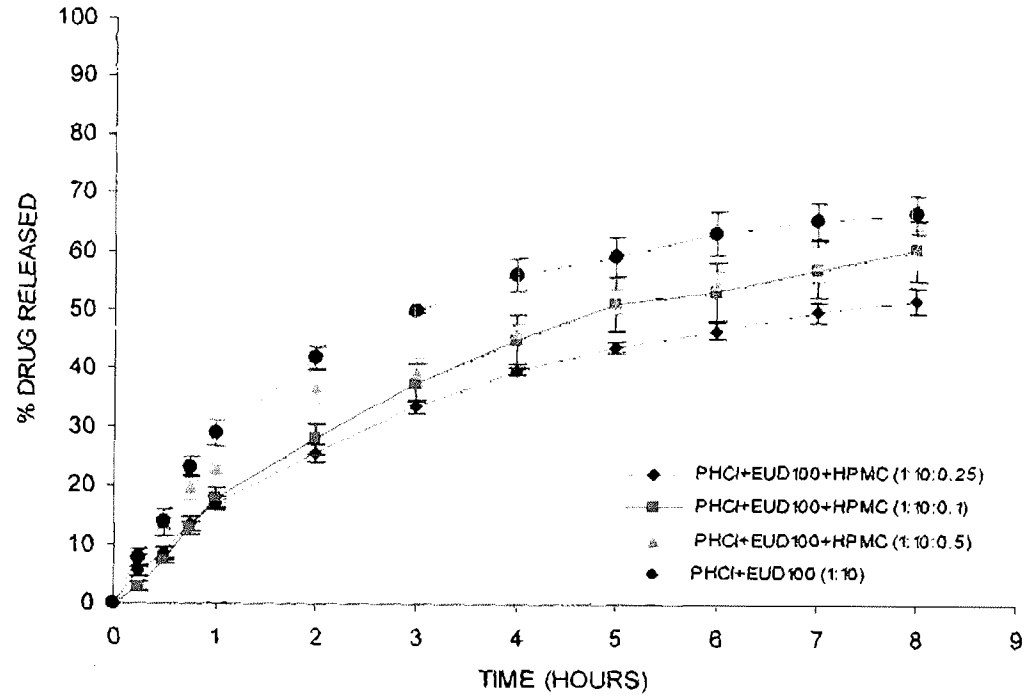


Figure 5.3A Drug release profiles of EUD100+HPMC films prepared at various ratios

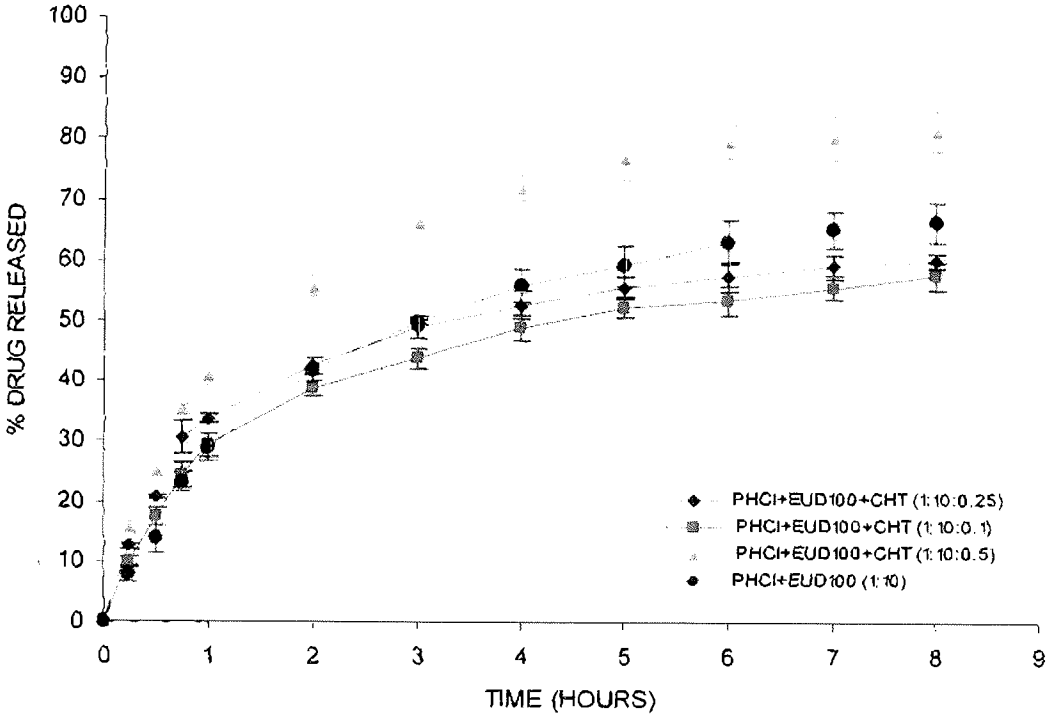


Figure 5.3B Drug release profiles of EUD100+CHT films prepared at various ratios

From Figure 5.3A, which depicts the release profiles of EUD100+HPMC MMFs, it can be seen that the addition of HPMC to the PHCl:EUD100 (1:10) formulation at all ratios i.e. 0.25; 0.1; 0.5, did not increase PHCl release above that achieved with the PHCl:EUD100 (1:10) formulation. Drug release was in fact further retarded. While unable to retard drug release on its own (Figure 5.1A), in combination with EUD100, HPMC could retard drug release. This may be attributed to the polymers in combination which may have formed a tighter polymeric network, thereby retarding drug release. The addition of HPMC was found unsuitable for enhancing PHCl release and was therefore not selected.

From the release profiles for the MMF formulations containing EUD100+CHT, depicted in Figure 5.3B, it can be seen that at low concentrations of CHT, i.e. ratios of 0.25 and 0.1, a decrease in PHCl release, below that observed with the PHCl:EUD100 (1:10) formulation, occurred whilst at a higher concentration, i.e. ratio of 0.5, an increase in PHCl release was observed. CHT is known to have varying effects on drug release based on its concentration. While it is able to retard drug release at certain concentrations, it can also enhance drug release which has been attributed to it acting as a disintegrant at certain concentrations (Nigalaye *et al.*, 1990; Munasur, 2004). A similar result may have occurred in this study, thereby altering the surface morphology of the film upon dissolution, thus leading to an increase in drug release. The PHCl:EUD100:CHT (1:10:0.5) formulation met the requirement of increasing PHCl release to a value greater than 80% at the 8th hour of dissolution as 81.53±3.34% PHCl was released from this film at this time.

This formulation was subsequently tested for its mucoadhesive properties, as a prerequisite for buccal controlled drug delivery systems is adhesion on the oral mucosa (Eouani *et al.*, 2001). A

measurement of the mucoadhesivity of the MMF formulated in this study was therefore of great importance as it is intended to remain in contact with the buccal mucosa for a prolonged period (up to 8 hours) to facilitate the controlled release of PHCl. Mucoadhesivity of the PHCl:EUD100:CHT (1:10:0.5) MMF was compared to that of homopolymeric films consisting of each of the polymers used in the formulation. The mucoadhesion data obtained are presented in Table 5.5.

Table 5.5 Data obtained for mucoadhesion measurements

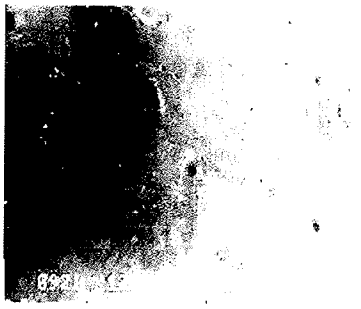
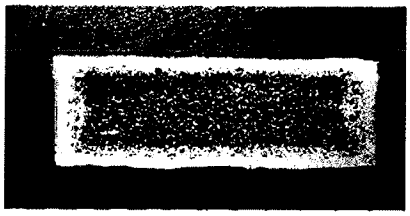
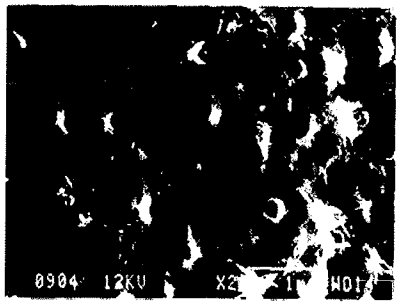
FILM	MDF (mN) MEAN±SD	Work (mJ) MEAN±SD
PHCl:CHT (1:0.5)	133.60±27.89	48.82±14.47
PHCl:EUD100 (1:10)	443.40±30.96	98.40±13.19
PHCl: EUD100:CHT (1:10:0.5)	401.40±30.73	84.36±4.08

CHT has been reported to be a good mucoadhesive (Senel *et al.*, 2000). However, when compared to EUD100, it exhibits almost one third of the mucoadhesive strength of EUD100, i.e. 133.60±27.89 as compared to 443.40±30.96 mN respectively. The increased adhesion of EUD100 may be due to its additives as it has been reported that the addition of plasticiser to EUD100 films may reduce the aggregate force caused by the intermolecular attraction of the polymer, and result in an increase in the adhesive strength of the film (Huntsberger, 1967; Salomon, 1970).

The addition of CHT to the EUD100 (1:10) films to form the MMF formulation (1:10:0.5), did not adversely affect its mucoadhesivity as only a slight decrease was observed, i.e. mucoadhesivity decreased from 443.40±30.96 to 401.40±30.73 mN when CHT was added. This decrease may not be considered pharmaceutically different in terms of retention time on the mucosa. Polymeric blending in delivery

systems may lead to a synergistic or antagonistic effect on drug release and mucoadhesivity of the system. In this case the polymeric blend identified did not have an antagonistic effect. Since the addition of CHT, at a ratio of 0.5, to the PHCl:EUD100 (1:10) formulation is capable of altering the drug release profile without significantly affecting the mucoadhesion of the film, it was considered suitable for further characterisation as MMFs containing drug and polymer/s of opposing solubilities prepared by the emulsification/casting/solvent evaporation method. Table 5.6 shows the digital photographs and electron micrographs for these formulations.

Table 5.6 Photographic illustration of the homopolymeric PHCl:EUD100 (1:10) film and PHCl:EUD100:CHT (1:10:0.5) MMF

FILM	DIGITAL PHOTOGRAPH	ELECTRON MICROGRAPH
Homopolymeric PHCl:EUD100 (1:10)		
MMF PHCl:EUD100:CHT (1:10:0.5)		

The above table illustrates the differences in appearance of the PHCl:EUD100 (1:10) and PHCl:EUD100:CHT (1:10:0.5) films. As can be seen, the EUD100 only film appears relatively smooth whilst the

combination film appears more textured. The change in surface morphology may be due to the addition of CHT.

5.3.3 Reproducibility Study

This study was undertaken to confirm the reproducibility of the suitable MMF formulation identified, i.e. PHCl:EUD100:CHT (1:10:0.5). Three batches of this formulation were prepared and compared in terms of assay values, mucoadhesivity, thickness and drug release of films. The data obtained are shown in Table 5.7.

Table 5.7 Summary of results for characterisation studies for reproducibility studies for the suitable MMF formulation

Characterisation Study	Batch A		Batch B		Batch C	
	MEAN±SD	CV (%)	MEAN±SD	RSD (%)	MEAN±SD	CV (%)
Assay (%)	106.17±2.68	2.52	100.78±4.33	4.30	99.02±4.94	4.99
Mucoadhesivity MDF (mN)	401.40±30.73	7.66	402.80±26.10	6.48	402.20±30.96	7.70
Thickness (mm)	0.44±0.03	6.82	0.45±0.03	6.67	0.44±0.03	6.82

The CV for assay values for each batch was low, indicating minimal intra-batch variability and they were all within the compendial specifications of 92 - 107.5 % (BP, 2003). Statistical analyses using a Kruskal-Wallis test with Dunn's Post Hoc tests for assays and one-way ANOVA with Bonferroni Post Hoc tests for mucoadhesion, indicated no significant differences between the three batches, since p=0.1964 and 0.9971, respectively. Consistent thicknesses of individual film dosages showed that the distribution of the components within the film were also consistent and uniform. This is evident from the low CVs which indicated minimal variation in all three batches.

The drug release profiles for films from all three batches of the suitable formulation, shown in Figure 5.4, appeared to be almost super-

imposable. To confirm the similarity of these dissolution profiles, the similarity factor (f_2) was used, as described in 4.3.4, and found to be 83.18 for A vs B, 82.03 for B vs C and 71.19 for A vs C. Since all three f_2 values were higher than 50(50-100), these results confirmed that the drug release profiles were similar for films from all three batches.

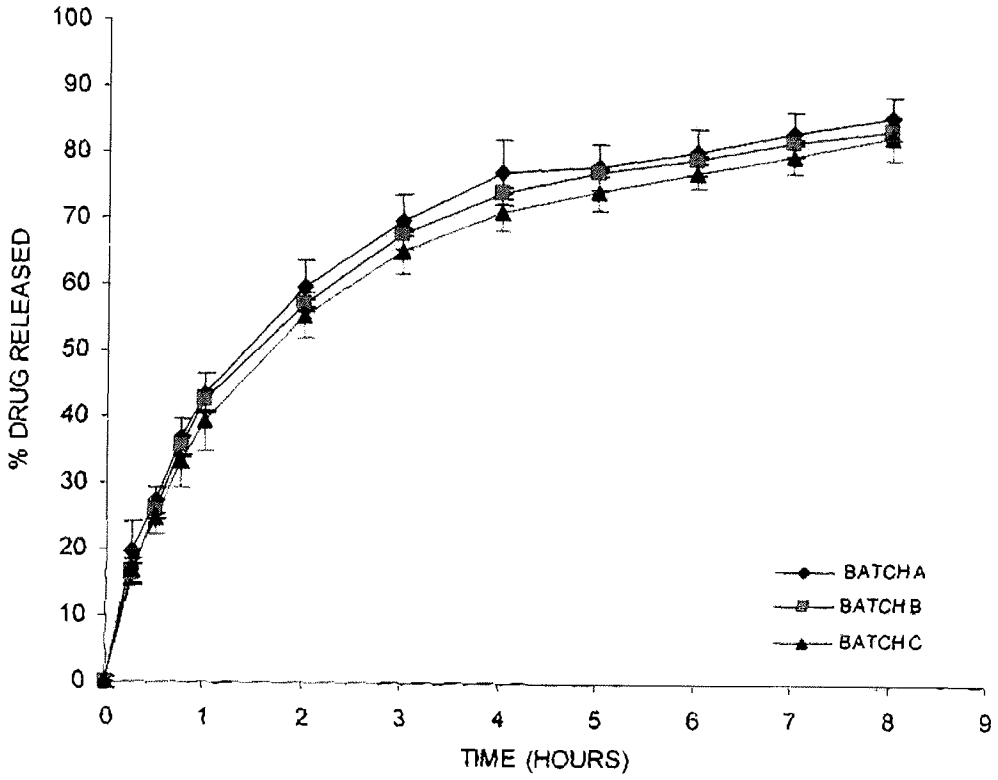


Figure 5.4 Reproducibility of *in vitro* drug release profiles

Analyses of the data for all three batches of the formulation in terms of assay values, mucoadhesivity, thickness and drug release showed that preparation of MMFs with a drug and polymer ratio of 1:10:0.5 PHCl:EUD100:CHT was indeed reproducible.

5.3.4 Characterisation of the Identified Suitable Formulation

The formulation was then subjected to a detailed characterisation in terms of release kinetics, swelling/erosion, surface morphology, mechanical testing and surface pH.

5.3.4.1 Release Kinetics

Dissolution data derived for the MMFs were subjected to model analysis to determine the mechanism of drug release. Although there are many models available for the interpretation of controlled release behaviour of delivery systems (*Wu et al.*, 2005), such as the power law expression (Peppas, 1985); Hopfenberg model (Hopfenberg, 1967) and Ritger-Peppas' empirical equation (Ritger and Peppas, 1987), there are few studies based on films and these mainly used the Higuchi's square-root model (Ahmed *et al.*, 2004; Amnuaikit *et al.*, 2005). Higuchi stated that release from a planar system having dispersed or dissolved drug in a homogenous film should follow a relationship where drug release (Q) is linear with the square root of time ($t^{1/2}$). Several assumptions apply for this relationship, e.g. that the drug is homogeneously distributed throughout the vehicle; that only the drug diffuses out and that sink conditions are maintained. Provided that these conditions are met, the plot of Q vs $t^{1/2}$ should be linear for at least 30% of loaded drug released, as verified by Bodomeier and Paeratakul (1989). The dissolution data obtained for the PHCl:EUD100:CHT (1:10:0.5) MMFs were subjected to modeling using the Higuchi square-root model. The cumulative percent drug released was plotted against the square-root of time (minutes) (Figure 5.5).

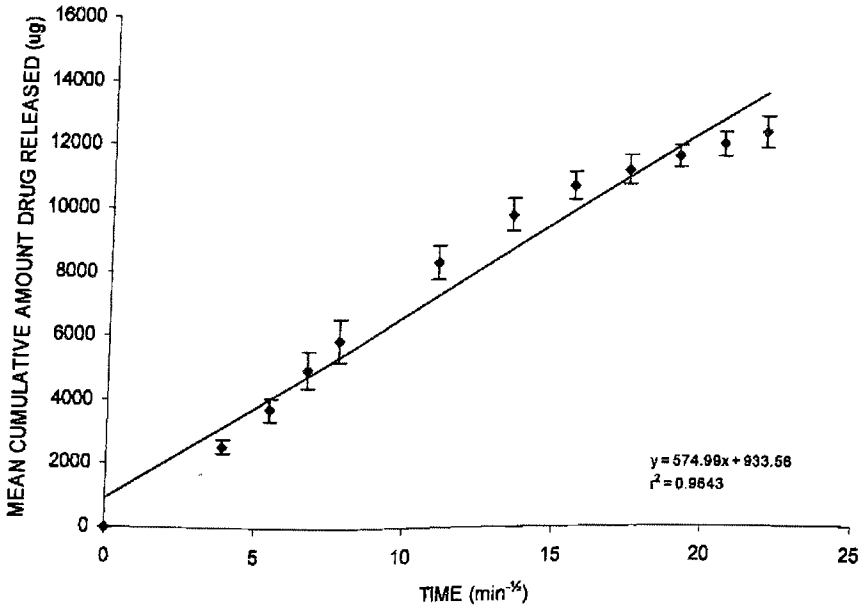


Figure 5.5 Higuchi square-root of time plot for PHCl release from PHCl:EUD100:CHT (1:10:0.5) MMFs

From the graph in Figure 5.5, it can be observed that a correlation coefficient of 0.9643 was achieved, indicating that PHCl release seemed to be described by this model. This confirms that drug release occurred via diffusion through the film matrix. The release rate constant, k_H, was calculated from the slope of the Q vs $t^{½}$ plot, and was found to be 574.99 μg cm^{-2} $min^{-½}$. Guyot and Fawaz (2000) and Amnuaikit *et al.* (2005) also reported that the Higuchi square-root model was the most suitable for modeling the release of PHCl from polymeric films.

5.3.4.2 Swelling and Erosion Studies

To obtain further evidence regarding the behaviour of the films upon dissolution testing, swelling and erosion studies were conducted. These profiles are depicted in Figure 5.6.

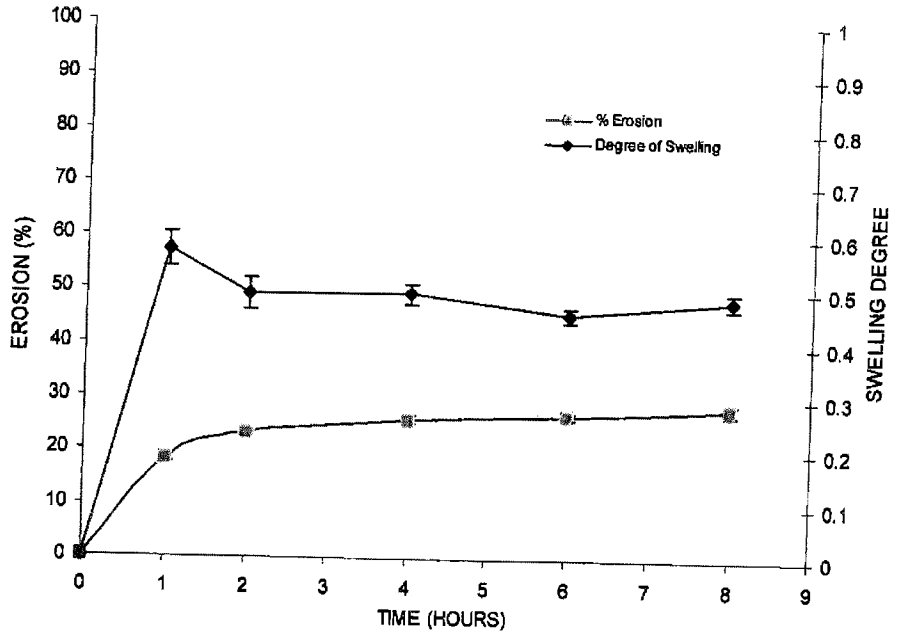


Figure 5.6 Correlation of Swelling and Erosion profiles of MMFs containing PHCl

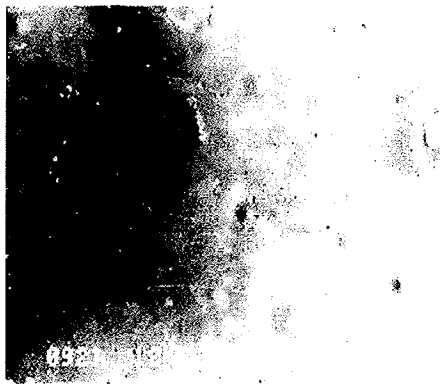
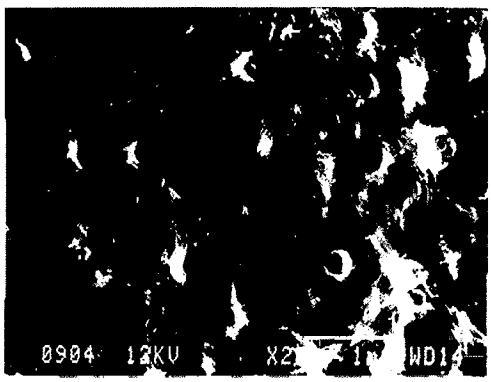
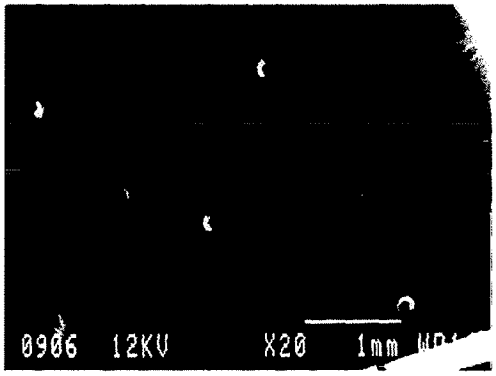
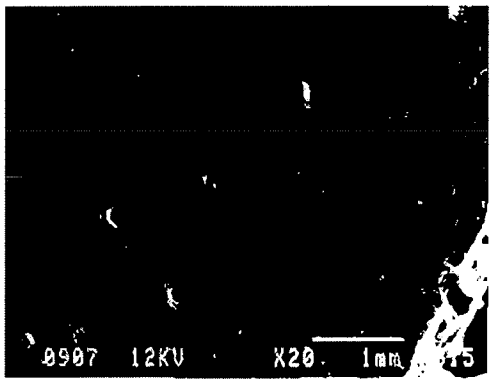
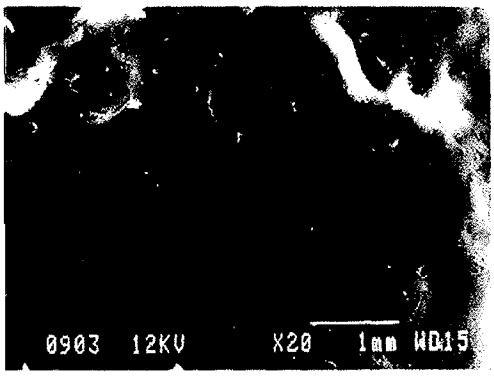
EUD100 is an insoluble, low permeable, catioinic copolymer of acrylate and methacrylates with quaternary ammonium groups which are in the chloride salt form. The dissociation of these quaternary ammonium groups in aqueous media is responsible for the hydration and swelling of the polymer films. The exchange of the chloride ion with the buffer anions of the dissolution medium could govern the degree of hydration and swelling (Akhgari, *et al.*, 2006). Akhgari *et al.* (2006) found that 100% EUD100 films had a swelling index of 0.10 - 0.30. This finding is in contrast to the results obtained in this study, as the

maximum degree of swelling achieved after 1 hour was 0.57. Thereafter, minimal changes in the swelling degree took place. These results may be attributed to the polymeric blending with CHT, as high molecular weight CHT (similar to that used in this study) has been reported to have a swelling index of 11.63 (Nunthanid *et al.*, 2001). These films were reported to have swelled greatly at the initial period and then decreased in volume with increased time, similar to the profile obtained in this study. This may be attributed to cross-linking between cationic amino groups of CHT and phosphate anions in the buffer. This is explained as follows: firstly, the films absorbed water and began to swell, and an amino group of CHT was simultaneously protonated. The phosphate anions in the medium penetrated the swollen film to cross-link at quaternary ammonium groups of CHT molecules. The cross-linking process increased as time progressed, resulting in the denser films with reduced volumes. In addition, it was observed that a maximum of 28.26% of the films eroded over the 8-hour period. This is similar to erosion data obtained by Perioli *et al.* (2004), who reported that Eudragit® RSPO/HPMC patches showed a 20-30% mass loss after a 5-hour period.

5.3.4.3 Evaluation of Surface Morphology

SEM was performed on the films to assess changes in their surface morphology prior to and after dissolution testing. Table 5.8 shows the scanning electron micrographs of the 1:10 and 1:10:0.5 films before dissolution as well as with increasing duration of dissolution time. A smooth and compact surface was noted at time = 0 hours for the 1:10 film, whilst a rough, less compact surface was observed for the 1:10:0.5 film. As dissolution time progressed to the first hour, both films appeared porous, the 1:10:0.5 film appeared more porous than the 1:10 film.

Table 5.8 The effect of dissolution on film morphology

TIME	PHCl:EUD100 (1:10)	PHCl:EUD100:CHT (1:10:0.5)
Before Dissolution		
At 1st Hour of Dissolution		
At 8th Hour of Dissolution		

At 8 hours the surface morphology of both films showed significant changes in texture, to the extent that the 1:10:0.5 film developed clearly visible pores. These findings are in agreement with

morphological studies conducted by Lin *et al.* (2000) who showed similar textures and porous surfaces of Eudragit® E films before and after 24 hours of dissolution. From these micrographs it can be concluded that the addition of CHT to the 1:10 PHCl:EUD100 film drastically affected the surface morphology of the film, as the 1:10:0.5 film appeared significantly more textured before and more porous after dissolution. In addition, water uptake of films during dissolution considerably altered the surface morphology of both films. This may have contributed to the faster drug release observed with the inclusion of CHT in the 1:10:0.5 MMF formulation.

5.3.4.4 Mechanical Properties

The mechanical strength of films reflects their ability to withstand mechanical damage during production, handling and application (Yoo *et al.*, 2006), and it also determines their ability to remain intact during dissolution. In addition, an ideal buccal film should be flexible, elastic, soft, yet adequately strong to withstand breakage caused by mouth activities (Peh and Wong, 1999). Therefore, the mechanical properties of the PHCl:EUD100 (1:10) film and PHCl:EUD100:CHT (1:10:0.5) MMF were assessed. A textural analyser (TA-XT2*i*) was employed for these tests, as described in 5.2.2.2.8. Four mechanical properties, namely tensile strength, percent elongation, elastic modulus and toughness, which represent film abrasion resistance, ductility, stiffness/elasticity and energy respectively, were computed from the obtained stress-strain profiles (Aulton, 1982). Such studies on films are very few in the literature. No previous study on MMFs with polymers of opposing solubilities has been reported previously.

In order to facilitate an understanding of the data computed for the mechanical properties of the films, a brief description of each

property is provided. Thereafter, the results are presented and discussed.

The tensile strength of a material is the stress needed to break the sample. Stress is equivalent to the maximum force required to break the film divided by the cross-sectional area of the film (Equation 5.4) (Heng *et al.*, 2003). Tensile strength is an important property for polymers that are going to be stretched.

Elongation is a type of deformation. Deformation is simply a change in shape that any material undergoes under stress. When referring to tensile stress, the sample deforms by stretching or elongating. The percentage elongation of the film is calculated by dividing the increased length of the polymeric film by its original length and multiplying by 100 (Equation 5.5) (Heng *et al.*, 2003). Percentage elongation is an indication of the extent to which a material can be stretched before it breaks.

Elastic modulus is a key indicator of the stiffness or rigidity of polymer films. Young's modulus is the ratio of stress to strain. It is also referred to as the modulus of elasticity or the tensile modulus. It is the slope of the stress-strain profile (Heng *et al.*, 2003). Often these observed curves are not straight-line plots, which indicates that the modulus is changing with the amount of strain. In these cases, the initial slope is used as the modulus.

The toughness of a material is represented by the area under a stress-strain curve (AUC). Toughness is a measure of the energy required to break a sample (Dhanikula and Panchagnula, 2004).

Studies were undertaken to obtain the stress-strain profiles for each film. Typical profiles are shown in Figures 5.7A and B. These graphs

were used to calculate the tensile strength (Equation 5.4), percent elongation (Equation 5.5), elastic modulus (slope of stress-strain curve) and toughness of the films (AUC), the values of which are shown in Table 5.9.

Table 5.9 Summary of mechanical test results for PHCl:EUD100 (1:10) homopolymeric films and PHCl:EUD100:CHT (1:10:0.5) MMFs*

FILM	Tensile Strength (N/m^2)	Elongation (%)	Elastic Modulus (N/m^2)	Toughness (MPa.%)
PHCl:EUD100 (1:10) Homopolymeric Film	95.07±2.86	29.29±1.93	0.415±0.130	751.45±87.41
PHCl: EUD100:CHT (1:10:0.5) MMF	332.09±5.65	17.37±3.57	1.55±0.19	1656.80±188.61

* Results are represented as mean±SD

As can be seen in Table 5.9, the addition of CHT to the PHCl:EUD100 (1:10) film formulation greatly affected the mechanical properties of the film. The PHCl:EUD100:CHT (1:10:0.5) MMF displayed an increase in tensile strength, elastic modulus and toughness as compared to the PHCl:EUD100 (1:10) film as values increased from 95.07±2.86 to 332.09±5.65 N/m^2, 0.415±0.130 to 1.55±0.19 N/m^2 and 751.45±87.41 to 1656.80±188.61 MPa.% respectively. This indicated that the MMFs displayed a greater abrasion resistance, were more elastic and also required more energy to break. It could be concluded that these properties rendered it a tougher film than the PHCl:EUD100 (1:10) film.

However, the percentage elongation of the MMF showed a slight decrease from 29.29±1.93 to 17.37±3.57 N/m^2. This may be explained by referring to the stress-strain profiles of the films depicted in Figures

5.7A and B which show the distinct differences in the behaviour of the films during the elongation test period.

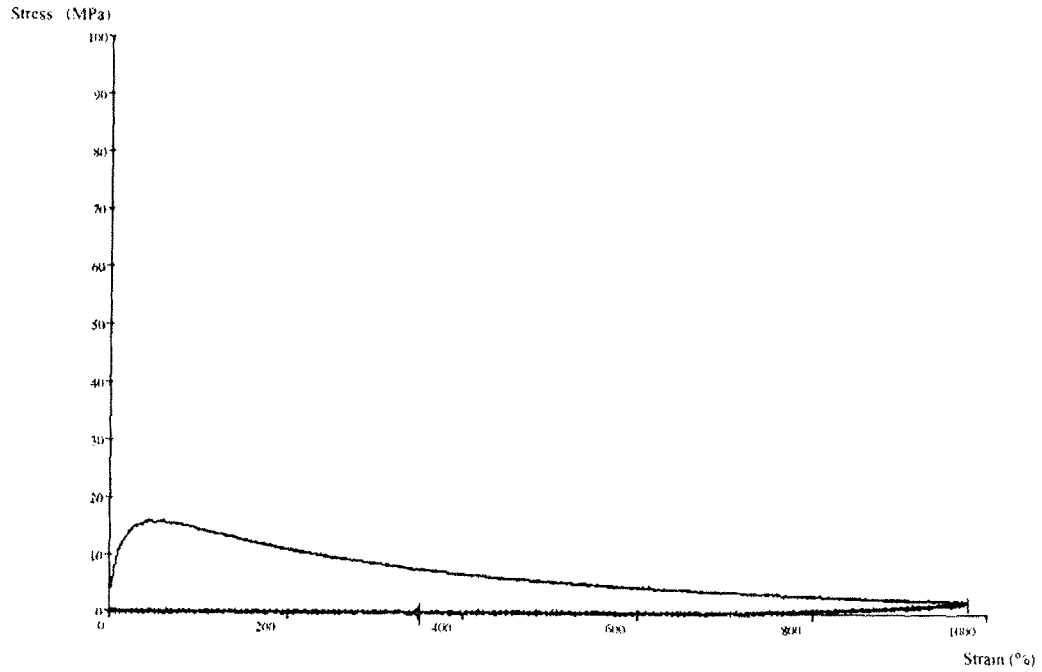


Figure 5.7A A typical stress-strain profile for the PHCl:EUD100 (1:10) homopolymeric film

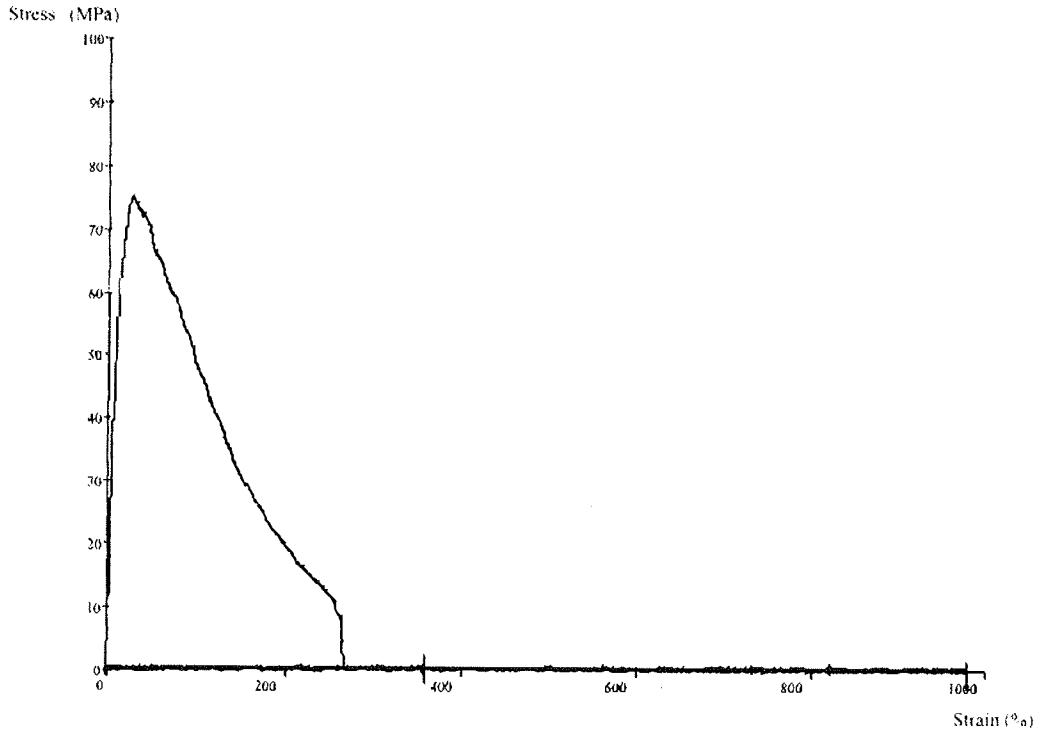


Figure 5.7B A typical stress-strain profile for the PHCl:EUD100:CHT (1:10:0.5) MMF

Elongation measurements are usually documented at the point of break, which is represented by the peak on the stress-strain curve. This occurred with the PHCl:EUD100:CHT (1:10:0.5) MMF but not with the PHCl:EUD100 (1:10) film. As is shown in Figure 5.7A, the PHCl:EUD100 (1:10) film reaches a peak but does not plateau to baseline as it does with the MMF (Figure 5.7B). Instead, the curve gradually decreases until the end of the test period, indicating that the film did not fracture. In this case the graph shows no break point at the peak of the curve, but rather a yield point (which was used to compute the percent elongation for this film), after which the film displayed a progressive failure (indicated by the gradual declining slope). During this period the film became very stringy and lost its integrity. It is also important to note that although the PHCl:EUD100 (1:10) film did not break, a much smaller force was required to reach the yield point. This indicates that film integrity was compromised at a lower force, whilst the MMF required a greater force to break. In addition, although the PHCl:EUD100 (1:10) film had a greater percent elongation than the MMF, it was not as strong, elastic or tough as the MMF. Furthermore, the PHCl:EUD100 (1:10) film was extremely pliable to the point that it rendered handling during testing very difficult. In light of these findings, (i.e. ease of handling, maintenance of integrity during dissolution and the abovementioned mechanical properties), it was suggested that the MMFs are preferred as a drug vehicle for buccal delivery over the PHCl:EUD100 (1:10) film.

5.3.4.5 Surface pH Evaluation

Surface pH evaluation of oral mucosal dosage forms is an important characterisation study, as *in vivo* studies by Bottenberg *et al.* (1991) demonstrated that an acidic or alkaline pH may cause irritation to the oral mucosa. It was therefore necessary to determine if any extreme surface pH changes occurred with the MMFs developed during the drug release period under investigation. These measurements are illustrated in Figure 5.8.

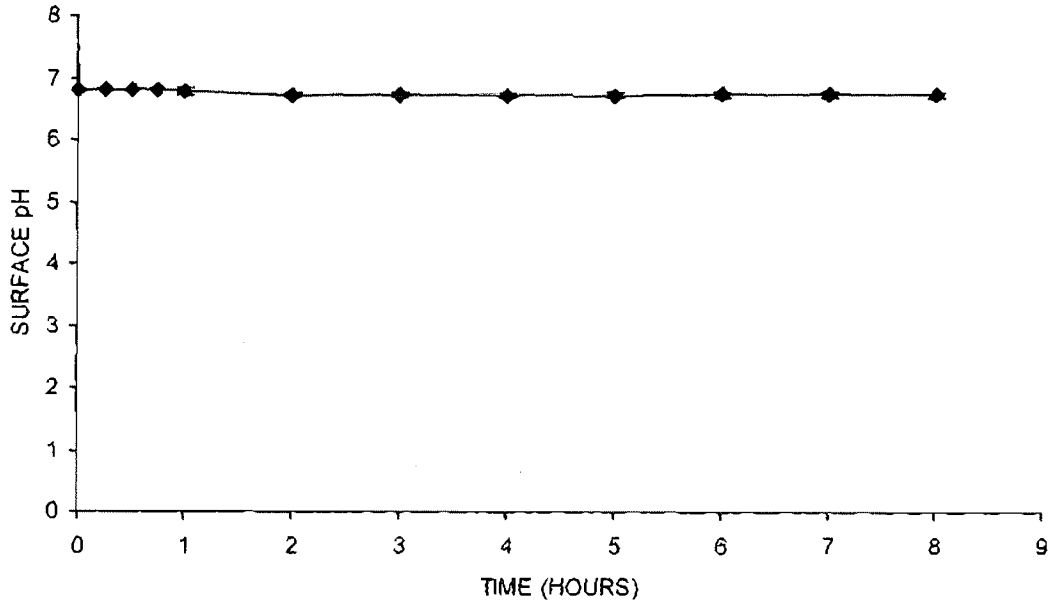


Figure 5.8 Surface pH changes of the optimised MMF

The surface pH of the films remained fairly constant at a pH of approximately 6.7 - 6.8 over the 8-hour test period, as can be seen in Figure 5.8. Therefore, this study confirmed that the surface pH of the films was within the neutral conditions of the saliva, pH 5.8 - 7.1 (de Vries *et al.*, 1991) and that no extremes in pH occurred throughout the test period. These results suggested that the polymeric blend identified was suitable for oral application owing to the acceptable pH measurements.

5.4 CONCLUSIONS

The aim of this phase of the study, as described in this chapter, was to identify a suitable polymeric blend for the preparation of multipolymeric monolayered mucoadhesive films comprising of hydrophilic and hydrophobic polymers for the controlled buccal delivery of PHCl and to subsequently undertake a preliminary physicochemical/mechanical characterisation of the identified formulation.

From initial investigations of different polymers for the formation of homopolymeric films, it became clear that film formation with the combination of drug and polymer/s of opposing ionic state was not possible due to complexation. This phenomenon played an important role in the selection of polymers for incorporation into the film formulation. PHCl film formation as homopolymeric films was achievable with hydrophilic polymers, HPMC and CHT, and hydrophobic polymers, EC and EUD100.

In addition, it was found that combining PHCl, a hydrophilic drug, with a hydrophilic polymer (CHT/HPMC) could not retard drug release as the cumulative amount of drug released at the end of 8 hours was too high. The release of PHCl from a homopolymeric film comprising a hydrophobic polymer (EC/EUD100) could be retarded. Furthermore, it was concluded that PHCl release from EUD100 films was governed by the content of EUD100 in the formulation, i.e. an increase in EUD100 content in the film lead to a decrease in PHCl release. However, the cumulative amount of drug released at the end of 8 hours with the PHCl:EUD100 (1:10) formulation was too low for the purposes of this study. Modifications to the polymeric content by the addition of CHT in a 0.5 ratio to yield a PHCl:EUD100:CHT (1:10:0.5) polymeric blend (MMF) altered the drug release profile of the film and controlled

release of PHCl was achieved. In addition, the system demonstrated acceptable mucoadhesivity as only a slight decrease was observed, i.e. mucoadhesivity decreased from 443.40±30.96 to 401.40±30.73 mN when CHT was added. This decrease may not be considered pharmaceutically different in terms of retention time on the mucosa. Mechanical testing revealed that MMFs displayed greater tensile strength, elastic modulus and toughness as compared to the PHCl:EUD100 (1:10) film, as values increased from 95.07±2.86 to 332.09±5.65 N/m^2, 0.415±0.130 to 1.55±0.19 N/m^2 and 751.45±87.41 to 1656.80±188.61 MPa.% respectively. However, the PHCl:EUD100 (1:10) film had a greater percent elongation than the MMF. This indicated that film integrity was compromised at a lower force, whilst the MMF required a greater force to break. These results indicated that the MMFs displayed a greater abrasion resistance, were more elastic and also required more energy to break, rendering the MMFs tougher and more suitable as a drug vehicle for buccal delivery than the PHCl:EUD100 (1:10) film. This formulation was found to be suitable for the controlled release of PHCl and was reproducible in terms of drug content uniformity, drug release and mucoadhesivity. Drug release followed Higuchi's square-root model with a correlation coefficient of 0.9426. SEM revealed that the addition of CHT to the PHCl:EUD100 (1:10) film formulation altered the surface morphology rendering it more porous, which ultimately contributed to the faster drug release observed with the PHCl:EUD100:CHT (1:10:0.5) MMF. Swelling and erosion studies indicated that maximal swelling of the films occurred after 1 hour and 28.26% of the films eroded during the 8-hour test period. The surface pH of the films also remained constant at neutral pH throughout the study.

The drug release, mucoadhesion and physicochemical/mechanical data obtained in this study, confirm the potential of this MMF system as a promising candidate for the controlled buccal delivery of PHCl.

The results reported in this chapter must contribute significantly to the pharmaceutical field, as such a detailed characterisation of MMFs, comprising of drug and polymer/s of opposing solubilities prepared by the emulsification/casting/solvent evaporation method, in terms of drug content and thickness uniformity; *in vitro* drug release; kinetic modelling of dissolution data; swelling and erosion; surface morphology; mucoadhesivity; mechanical testing and surface pH evaluation, has not been reported to date in the literature. Such characterisation is of significance for future formulation optimisation of monolayered multipolymeric films with drug and polymer/s of opposing solubilities.

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CHAPTER SIX

GENERAL CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

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6.1 GENERAL CONCLUSIONS

The buccal administration of drugs via a mucoadhesive controlled release delivery system offers several advantages. These include bypassing enzymatic degradation and hepatic first-pass metabolism, thereby improving the systemic bioavailability of the drug; minimal influence by potential variations in the gastric emptying rate or the presence of food; and improved patient acceptance and compliance. For optimal controlled release and mucoadhesivity, the blending of polymers and drug of opposing solubilities may be required for monolayered films. The aim of this study was therefore to formulate and characterise multipolymeric monolayered mucoadhesive films containing drug and polymer/s of opposing solubilities for the buccal delivery of PHCl. Thus, the objectives of the study were to identify a suitable technique for the preparation of monolayered films containing drugs and polymers of opposing solubilities; to identify suitable polymer combinations for the preparation of drug-loaded MMFs with enhanced mucoadhesivity and controlled drug release, and to characterise these MMFs in terms of drug content uniformity, thickness, mucoadhesivity, drug release kinetics, surface morphology, swelling and erosion, mechanical strength and surface pH evaluations.

In the first phase of this study, preparation parameters for the formation of monolayered multipolymeric and homopolymeric PHCl films comprising of drug and polymer/s of opposing solubilities by an emulsification/casting/solvent evaporation method were investigated. Monolayered multipolymeric films could be prepared at all homogenisation speeds and times. The films that were generated showed micromatrices embedded in the film matrix due to the inclusion of the PLGA polymer. Increased homogenisation speed and time resulted in a reduction in the size of the micromatrices. Phase

separation occurred at temperatures below 20 °C. Emulsifiers employed in the study adversely affected the morphology and appearance of the film and were therefore not considered feasible for inclusion into the formulation. The preparation parameters identified for emulsification without phase separation and the subsequent generation of monolayered films, without phase separation during solvent evaporation and drying, were emulsification at 20 °C and homogenisation at 9500 rpm for 15 minutes.

During the next phase of this study, it was discovered through preliminary investigations and a comprehensive search of the literature and patents filed, that the conventional film casting method of film preparation suffered from poor drug content uniformity. It was found that whilst the literature was replete with formulation and numerous characterisation studies on films, the majority of papers did not report any assay values. This lack of reported assay data led to the assumption that researchers may have been experiencing difficulty with this aspect of film characterisation; yet no paper to date, to the best of our knowledge, in the published pharmaceutical literature, has highlighted this difficulty. To address this problem of non-uniformity, a specially designed silicone-molded tray for film casting was prepared and evaluated in terms of enhancing drug content uniformity. These investigations confirmed that the specially designed silicone-molded tray with teflon-coated perspex inserts provided a reproducible method for the preparation of both homopolymeric and multipolymeric (including drug and polymers of similar and opposing solubilities) films that did not only meet drug content uniformity requirements, but also reduced the variability in mucoadhesivity, drug release and film thickness. This method of film casting has not, to the best of our knowledge, been reported previously in the literature and therefore makes a significant contribution to the formulation and evaluation of mucoadhesive films for mucosal delivery.

The final phase of this study involved the identification of a suitable polymeric blend for the preparation of multipolymeric monolayered mucoadhesive films comprising of hydrophilic and hydrophobic polymers for the controlled buccal delivery of PHCl and subsequent characterisation of these films in terms of their physicochemical/mechanical properties. Initial investigations of different polymers for the formation of homopolymeric films, demonstrated that film formation with the combination of drug and polymer/s of opposing ionic state was not possible due to complexation. This phenomenon affected the selection of polymers for incorporation into the film formulation. PHCl film formation as homopolymeric films was achievable with hydrophilic polymers, HPMC and CHT, and hydrophobic polymers, EC and EUD100. It was also found that a combination of PHCl, a hydrophilic drug, and a hydrophilic polymer (CHT or HPMC) was not able to retard drug release, whilst the release of PHCl from a homopolymeric film comprising a hydrophobic polymer (EC or EUD100) was retarded. In addition, it was concluded that PHCl release from EUD100 films was governed by the content of EUD100 in the formulation.

Although controlled release of PHCl was achieved with the PHCl:EUD100 (1:10) formulation, the cumulative amount of drug released at the end of 8 hours was too low for the purposes of this study. The polymeric content of the formulation was therefore modified by the addition of CHT in a 0.5 ratio to yield a PHCl:EUD100:CHT (1:10:0.5) polymeric blend (MMF) which suitably altered drug release from the film to that of the desired controlled release profile. This formulation was found to be suitable for the controlled release of PHCl and was reproducible in terms of drug content uniformity, drug release and mucoadhesivity.

Drug release followed Higuchi's square-root model with a correlation coefficient of 0.9426. SEM revealed that the addition of CHT to the PHCl:EUD100 (1:10) film formulation altered the surface morphology, rendering it more porous, which ultimately contributed to the faster drug release observed with the PHCl:EUD100:CHT (1:10:0.5) MMF. Swelling and erosion studies indicated that maximal swelling of the films occurred after 1 hour and 28.26% of the film eroded during the 8-hour test period. In addition, the system demonstrated acceptable mucoadhesivity as only a slight decrease was observed, i.e. mucoadhesivity decreased from 443.40±30.96 to 401.40±30.73 mN when CHT was added. This decrease may not be considered pharmaceutically different in terms of retention time on the mucosa. Mechanical testing revealed that MMFs displayed greater tensile strength, elastic modulus and toughness as compared to the PHCl:EUD100 (1:10) film, as values increased from 95.07±2.86 to 332.09±5.65 N/m^2, 0.415±0.130 to 1.55±0.19 N/m^2 and 751.45±87.41 to 1656.80±188.61 MPa.% respectively. However, the PHCl:EUD100 (1:10) film had a greater percent elongation than the MMF. This indicated that film integrity was compromised at a lower force, whilst the MMF required a greater force to break. These results indicated that the MMFs displayed a greater abrasion resistance, were more elastic and also required more energy to break, rendering the MMFs tougher and more suitable as a drug vehicle for buccal delivery than the PHCl:EUD100 (1:10) film. The surface pH of the MMFs also remained constant at neutral pH throughout the study.

This study contributes significantly to the pharmaceutical field, as such a novel, specialised method of film preparation that includes drug and polymer/s of opposing solubilities for enhancing drug uniformity, has not been reported previously. Furthermore, a detailed characterisation of MMFs with drug and polymers of opposing solubilities by this method of film preparation, in terms of drug content

and thickness uniformity; *in vitro* drug release; kinetic modelling of dissolution data; swelling and erosion; surface morphology; mucoadhesivity; mechanical testing and surface pH evaluation, has not been reported to date in the literature and is of significance for MMF formulation optimisation. The data obtained in this study confirm the potential of this multipolymeric monolayered film system as a promising candidate for the controlled buccal delivery of PHCl.

6.2 RECOMMENDATIONS FOR FUTURE STUDIES

This section highlights some further potential studies that can be undertaken to fully optimise and characterise the MMF drug delivery system.

- The use of a design of experiments approach to optimise the formulation variables in terms of polymer combinations for the preparation of the MMFs as well as the simultaneous optimisation of both mucoadhesion and controlled release can be undertaken by experimental designs such as the Box-Behnken. Formulation optimisation may be employed to develop an understanding of the inter-relationship among and between formulation and process variables for the preparation of drug-loaded MMFs. Furthermore, this approach represents an advance over the traditional trial-and-error method of formulation design and enables the optimisation of formulation and process variables to be conducted in a structured and cost-effective manner by means of experimental designs to design novel drug delivery systems.

- Short- and long-term chemical and physical stability studies to assess the stability of the PHCl-loaded MMFs generated should be undertaken to confirm the quality of the product as well as

to assess alterations in drug stability, drug release and mucoadhesion of the system.

- Although the use of organic solvents, such as methylene chloride (CH_2CL_2), for formulating drug delivery systems is documented in the literature, the toxicity of the organic solvent residues and the influence of environmental protection are major problems. Therefore, in future, the use of other solvents should be considered.

- *In vivo* studies using animals and human subjects should be performed to further test the formulation in terms of retention time of the dosage form on the mucosa. Bioavailability studies should be done to compare the buccal preparation with other per oral preparations.

- Permeation studies are of great importance as the epithelium that lines the oral mucosa acts as a barrier to the permeation of drugs. These studies should be undertaken as they are essential in providing an understanding of the mechanisms, pathways and efficiency of drug permeation through the mucosa. This is vital for successful drug delivery via the buccal route.

- Histological studies are also of great importance as prolonged exposure of drugs and polymers to the buccal mucosa may lead to histological changes in the epithelium. This can alter the mucosal permeability to the drug as well as the morphology of the mucosa, thereby impacting on the therapeutic efficacy and safety of the preparation. Such studies should be conducted to ensure therapeutic efficacy and patient suitability of the MMF generated.

- A scale-up method could be designed in order to assess the feasibility of the emulsification/casting into SMT/solvent evaporation method for application in the pharmaceutical industry.

APPENDIX 1

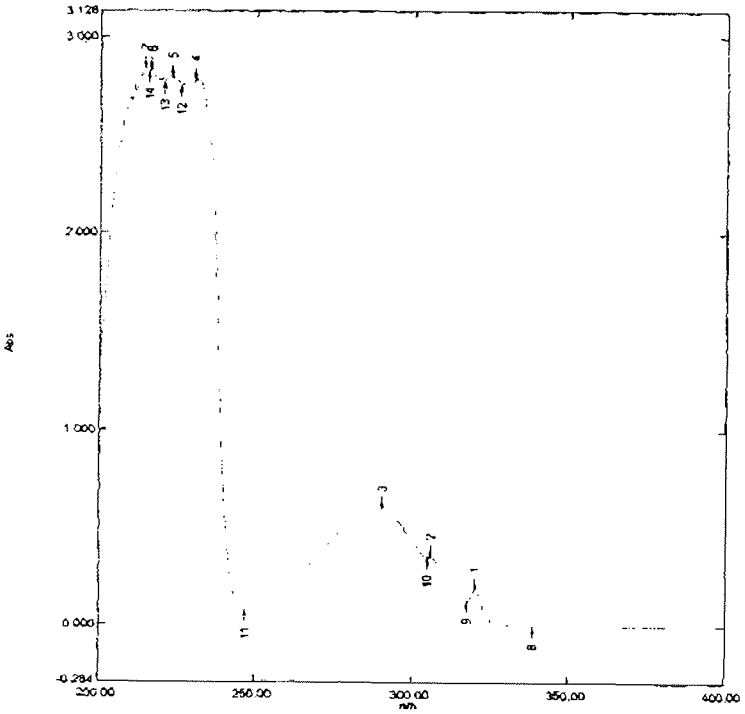
PREPARATION OF PHOSPHATE BUFFERED SALINE pH 6.8

British Pharmacopoeia, Volume II, 2003, Appendix IID

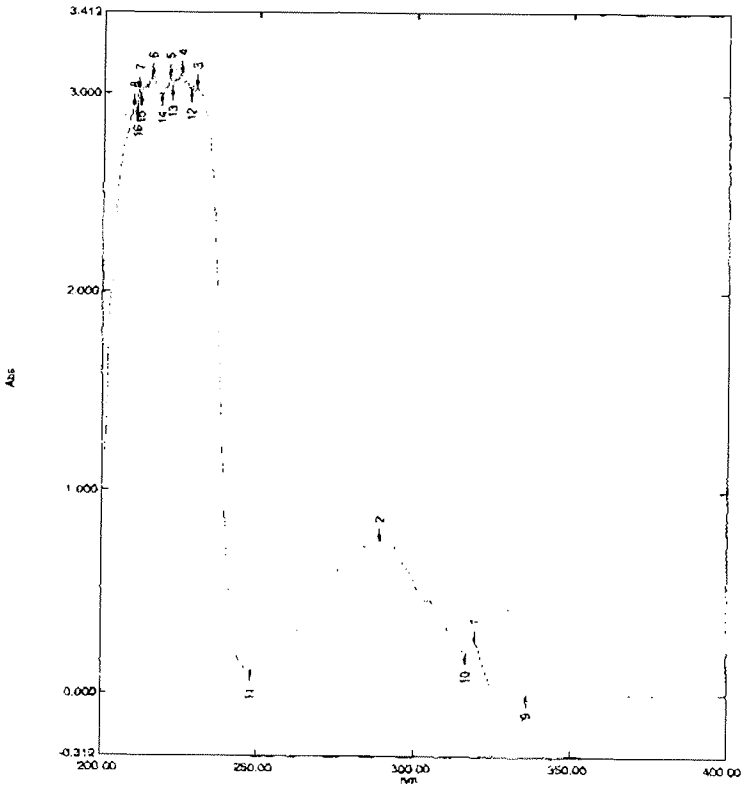
Dissolve 1.0 g of potassium dihydrogen orthophosphate, 2.0 g of dipotassium hydrogen orthophosphate and 8.5 g of sodium chloride in 900 mL of water, adjust the pH if necessary and sufficient water to produce 1000 mL.

APPENDIX 2

WAVELENGTH SCAN OF PROPRANOLOL HCl IN H_2O/ETHANOL



WAVELENGTH SCAN OF PROPRANOLOL HCl IN PBS pH 6.8



APPENDIX 3

WAVELENGTH SCAN OF PROPRANOLOL HCl

Moffat, AC, Osselton, MD, Widdop, B and Galichet, LY, ***Clarke's analysis of drugs and poisons in pharmaceuticals, body fluids, and post mortem material***, (Eds.), 3rd Edition. Pharmaceutical Press, London, 2004, pp1495-1497.