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Formulation of monolayered films with drug and polymers of opposing solubilities

V.A. Perumal[a], D. Lutchman[b], I. Mackraj[c], T. Govender[a,*]

[a] School of Pharmacy and Pharmacology, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa
[b] Abbott South Africa, Abbott Place, 219 Golf Club Terrace, Constantia Kloof, Gauteng, South Africa
[c] School of Medical Sciences, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa

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ABSTRACT

The aim of this study was to prepare and characterise monolayered multipolymeric films (MMFs) comprising of a hydrophilic drug (Propranolol HCl) (PHCl) and polymers of opposing solubilities. Films were prepared by emulsification and casted by a new approach using a silicone-molded tray with individual wells. MMFs comprising of PHCl with Eudragit® 100 (EUD100) and Chitosan (CHT), i.e. films with drug and polymers of opposing solubilities were successfully prepared (PHCl:EUD100:CHT; 1:10:0.5) and demonstrated uniform and reproducible drug content (100.71 ± 2.66%), thickness (0.442 ± 0.030 mm), mucoadhesivity (401.40 ± 30.73 mN) and a controlled drug release profile. Drug release followed Higuchi's square-root model. Maximum swelling of the films occurred after 1 h and 28.26% of the films eroded during the 8-h test period. Mechanical testing revealed that the MMFs displayed a greater abrasion resistance, were more elastic and also required more energy to break, rendering them tougher and more suitable for buccal delivery than the monopolymeric PHCl:EUD100 film. The inclusion of CHT to the film led to a more porous surface morphology. The surface pH of the films remained constant at neutral pH. This study confirmed the potential of the above MMFs as a promising candidate for buccal delivery of PHCl.

1. Introduction

The selection of optimal polymers in a drug delivery system remains pivotal in the formulation of controlled release buccal delivery systems for enhancing mucoadhesivity and obtaining controlled drug release profiles. 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 polylactide-*co*-glycolide (PLGA) which is not a good mucoadhesive is however ideal for prolonging drug release (Senel et al., 2000; Perugini et al., 2003). Also, single polymers may not be able to provide desired drug release profiles or mucoadhesivity.

More recently, researchers have been focusing on the blending of polymers to provide improved mucoadhesion and drug release. 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 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 and casted onto trays as a sheet to be cut into specified sizes, have been widely reported (Woolfson et al., 1995; Senel et al., 2000; Padula et al., 2003; Yoo et al., 2006). However, the preparation of optimal films with a specified drug release profile or desired multifunctionalities such as mucoadhesivity and controlled drug release properties may require the film to comprise of drug and polymer/s of opposing solubilities. While multi-layered films (Perugini et al., 2003) and wafers (Bromberg et al., 2001) may be considered for these systems, 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, exemplify the need for monolayered multipolymeric systems (Perugini et al., 2003). The preparation technique of such a system comprising polymers and drug of opposing solubilities, presents a challenge since the drug and polymers cannot be dissolved in a single vehicle to form a solution to be casted as a monolayered film, and therefore requires further investigation. Although some preliminary data on the formation of monolayered films formulated from a combination of polymers and a hydrophobic drug have been reported (Perugini et al., 2003), there has been

* Corresponding author. Tel.: +27 31 260 7358; fax: +27 31 260 7792.
E-mail address: govenderth@ukzn.ac.za (T. Govender).

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no further development in this technology as well as a detailed *in vitro* characterisation of this system. This will be essential for optimising its design, preparation and suitability for patient use. There are also no studies using a hydrophilic drug. Further, there are no reported studies on even a homopolymeric monolayered film containing a drug of opposing solubility.

To date, films have been prepared by casting polymeric solutions onto trays such as Teflon-coated perspex trays as a sheet of film to be cut into specific sizes containing the required doses (Remunan-Lopez et al., 1998; Perugini et al., 2003; Dhanikula and Panchagnula, 2004; Amnuaikit et al., 2005). Poor drug content uniformity has been identified as a limitation with films conventionally casted as above. This method causes aggregation or conglomeration of particles, which can render 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. Hence, the existence of patents addressing this issue to enhance drug content uniformity was identified Yang et al. (2004). No study thus far in the literature has explored other options of casting to improve drug content uniformity. We developed a novel silicone molded tray with predetermined wells for film casting which has been shown to be superior to the conventional casting method in terms of enhancing drug content uniformity as well as minimizing mucoadhesivity and drug release variability (Perumal et al., in press). The above film casting method, as well as the preparation 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 previously in the literature. Furthermore, there is a lack of detailed physicochemical/mechanical characterisation studies for such monolayered multipolymeric films with drug and polymer of opposing solubilities.

The aim of this study was, therefore, to formulate and evaluate multipolymeric monolayered mucoadhesive films comprising both hydrophilic and hydrophobic polymers for the controlled buccal delivery of a hydrophilic drug. Propranolol HCl was chosen as a model hydrophilic drug due to its short half-life and extensive first pass metabolism making it a suitable candidate for buccal drug delivery (Gomeni et al., 1997). The monolayered films prepared by a new casting approach were characterised in terms of mucoadhesivity, drug release kinetics, hydration dynamics, mechanical properties, morphology and surface pH.

2. Materials and methods

2.1. Materials

Chitosan (CHT) (MW 110,000) [Primex Ingredients, ASA, Norway]; Propranolol HCl (PHCl) [Frankel Chemicals, SA] and Mucin [Sigma–Aldrich, UK] were purchased and used as received. Eudragit® RS100 (EUD100) [Evonik Rohm GMBH, Germany] was kindly sponsored by Degussa Africa (Pty) Ltd. All other chemicals used were of analytical or reagent grade.

2.2. Methods

2.2.1. Preparation of films

While film casting in the literature has been undertaken on conventional trays onto which the polymeric solutions are casted and then cut into predetermined sizes after drying, in this study a specially designed silicone molded tray (SMT) containing individual 1 cm × 3 cm wells were employed since it has been shown by us to enhance drug content uniformity (Perumal et al., in press).

Homopolymeric films comprising of EUD100 (hydrophobic polymer) and PHCl (hydrophilic drug) were prepared as follows in varying ratios: specified quantities of EUD100 and plasticiser (triethyl citrate) at 30% (w/w) of polymer weight were dissolved in acetone (15 mL); and combined by a modified emulsification method (Perugini et al., 2003) with a solution of PHCl in water (15 mL) to form an o/w emulsion. Briefly, both the organic and aqueous phases were individually brought to 20 °C and then combined with homogenization at 9500 rpm for 5 min (IKA Homogeniser, Germany) while maintaining the resulting emulsion on an ice bath. Thereafter 1 mL of each polymeric emulsion containing 15 mg of PHCl was pipetted into each well. The drug–polymeric emulsion in the SMT was allowed to dry in an oven (Series 2000, Scientific, SA) at 30 °C for approximately 24 h, 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.

Multipolymeric films comprising of PHCl and EUD100 in combination with CHT in varying ratios were prepared as described above. In this case PHCl and CHT were dissolved in the aqueous solution.

2.2.2. Characterisation of films

2.2.2.1. Assay of Propranolol HCl films. A 1 cm × 3 cm film as a unit from the SMT 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 with washings of water/ethanol solution as a solvent system. Following mechanical agitation and appropriate dilution, the samples were analysed by UV spectrophotometry at 290 nm (UV Spectrophotometer, 1650 PC, Shimadzu, Japan).

2.2.2.2. 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 ± S.D. of five replicate determinations.

2.2.2.3. In vitro drug release. A modified shaking water bath dissolution method was employed to determine drug release profiles of the films. The shaking water bath apparatus (100 strokes/min) 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, were secured in the holders of the holder plate. Phosphate buffered saline (PBS) (100 mL) equilibrated to 37 ± 0.5 °C was used as the dissolution medium. A minimum of three replicate determinations was performed for all dissolution tests. At specified time intervals, 2 mL aliquots of sample was removed from each vessel using a syringe and filtered through a Millipore® Filter (0.45 μm). An equal volume (2 mL) of fresh PBS was replaced into each dissolution vessel, to ensure a constant volume of dissolution medium throughout the duration of the test. All dissolution samples were analysed using a UV spectrophotometer (Shimadzu, Japan) at a wavelength of 289 nm.

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:

$$Q = k_H t^{1/2} \quad (1)$$

where Q is the amount of drug released after time t and k_H the release rate constant.

2.2.2.5. Mucoadhesivity of films. The mucoadhesivity of the films was measured with the aid of a software-controlled penetrometer, TA-XT2*i* texture analyser (StableMicroSystems, UK) equipped

with a 5 kg load cell, a force measurement accuracy of 0.0025% and a resolution distance of 0.0025 mm. A removable stainless steel probe with dimensions 1 cm × 3 cm was used for all measurements. A sample of the prepared polymeric film (1 cm × 3 cm) was attached to the base of the probe with cyanoacrylate 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 2 min pre-hydration phase. Upon completion of the pre-hydration period, the film was brought into contact with mucin (30%, w/w at 37 °C) for 30 s. 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 10 replicate determinations was performed.

2.2.2.6. Swelling and erosion studies. Swelling and erosion of the films were determined under conditions identical to those described above for the dissolution tests. 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):

$$\text{Degree of swelling} = \frac{\text{wet weight} - \text{original dry weight}}{\text{original dry weight}} \quad (2)$$

$$\text{Erosion (\% mass loss)} = \frac{\text{original weight} - \text{remaining dry weight}}{\text{original weight}} \times 100 \quad (3)$$

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.

2.2.2.7. Film morphology. Film morphology was 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 min 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). The images were captured on an Ilford PANF 50 black and white 35 mm film.

2.2.2.8. Textural profile analysis (mechanical testing). Mechanical properties of the films were evaluated using a texture analyser, TA-XT2*i* (StableMicroSystems, UK) equipped with a 5 kg load cell. Each film strip (1 cm × 3 cm), free from physical imperfections, was held between two tensile grips positioned at a distance of 3 cm. 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 10 determinations was performed. Mechanical properties of the films were evaluated using the following equations (Heng et al., 2003):

$$\text{Tensile strength (N/m}^2\text{)} = \frac{\text{force at break}}{\text{initial cross-sectional area of the sample}} \quad (4)$$

$$\text{Elongation at break (\%)} = \frac{\text{increase in length}}{\text{original length}} \times 100 \quad (5)$$

2.2.2.9. Surface pH evaluation. Weighed films (3 cm^2) 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, and 8 h were recorded with the aid of a pH meter (Hanna Instruments pH 211, Portugal). These measurements were conducted by bringing a glass microelectrode near the surface of the films and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate.

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).

3. Results and discussion

3.1. Identifying a suitable polymeric blend for monolayered films with drug and polymers of opposing solubilities

Several hydrophobic and hydrophilic polymers were initially investigated in our laboratories to identify their film forming and drug release modification properties with PHCl. These preliminary investigations identified EUD100 as a potential hydrophobic polymer and CHT as a potential hydrophilic polymer for the formation of MMFs with PHCl and polymers of opposing solubilities. Since EUD100 showed potential for film formation and drug release retardation, homopolymeric films comprising of PHCl and EUD100 only were initially prepared and the effect of drug:polymer ratio on drug release was investigated. As the ratio of PHCl:EUD100 increased from 1:1 to 1:10, the drug release decreased with distinct differences in drug release profiles observed (Fig. 1). The 1:10 ratio in particular, exhibited a significantly retarded drug release profile. This could be attributed 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). It was therefore concluded that a hydrophobic polymer such as EUD100 in an appropriate ratio was required for the controlled release of a hydrophilic

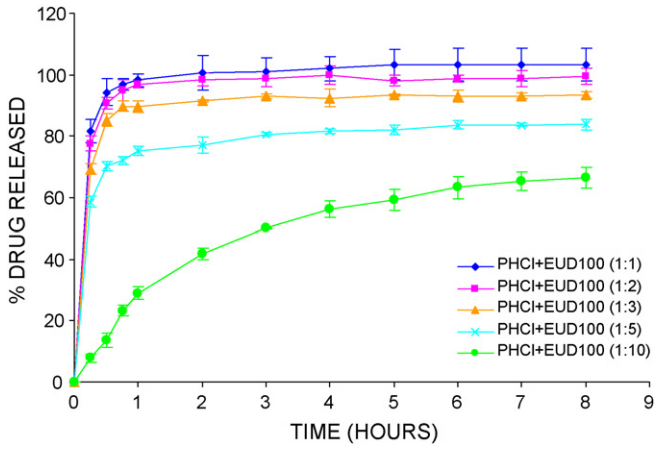


Fig. 1. Drug release profiles for hydrophobic homopolymeric EUD100 films containing PHCl.

Table 1
Drug content uniformity and film thickness data for MMFs with varying polymer ratios

Ratio	Assay (%)		Thickness (mm)	
	Mean ± S.D.	CV (%)	Mean ± S.D.	CV (%)
PHCl:EUD100:CHT				
1:10:0	96.96 ± 2.92	3.01	0.376 ± 0.017	4.52
1:10:0.1	96.30 ± 6.13	6.37	0.403 ± 0.021	5.21
1:10:0.25	100.53 ± 5.50	5.47	0.401 ± 0.016	3.99
1:10:0.5	100.71 ± 2.66	2.64	0.442 ± 0.030	6.78

drug such as PHCl. Also, this study confirmed that monolayered homopolymeric films with drug and polymer of opposing solubilities, i.e. PHCl and EUD100 can be successfully prepared by this emulsification method.

From the dissolution profile obtained for the PHCl:EUD100 (1:10) film formulation (Fig. 1), 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 h. A formulation with an appropriate controlled release profile with at least 80% drug release over an 8-h period was desired for the purpose of this study. Decreasing the EUD100 content to increase the amount of drug released at 8 h was not considered feasible, since this would have increased the drug release significantly in the initial periods (Fig. 1), which would not be considered appropriate for a controlled drug release profile. Hence, modifications to the polymeric content of the formulation were performed to obtain the desired controlled release profile.

To increase the release of PHCl from this formulation, the selected hydrophilic polymer, i.e. CHT was incorporated into the PHCl:EUD100 (1:10) formulation in varying ratios and the resulting films were characterised in terms of drug content and thickness uniformity (Table 1). All films prepared with PHCl in combination with polymers of opposing solubilities, i.e. CHT and EUD100 were monolayered indicating no phase separation during the emulsification and drying phases of film preparation. As shown in Table 1, CHT in combination with EUD100 were capable of forming uniform MMFs, as assay values for all formulations indicate uniform drug content with low CV values for each tray and were also within the required compendial specifications, i.e. within 92–107.5% (BP, 2003). In addition, thickness values for all combinations with CHT had low CVs, indicating uniform distribution of the film components. Therefore, the incorporation of CHT into the PHCl:EUD100 (1:10) formulation led to the successful production of MMFs comprising of drug and polymer/s of opposing solubilities. Since poor drug content uniformity is a limitation with films conventionally casted onto trays as a sheet to be cut into specified sizes, these results are positive since the SMT method of film casting provided multipolymeric films with opposing drug–polymer solubilities with uniform drug content. In our previous paper (Perumal et al., in press); the preparation of monopolymeric films via the SMT method was significantly superior to the conventional casting technique in terms of drug content, mucoadhesivity and drug release. From the release profiles for the MMF formulations containing EUD100 + CHT (Fig. 2), it can be seen that at low concentrations of CHT, i.e. ratios of 0.25 and 0.1, a decrease in PHCl release,

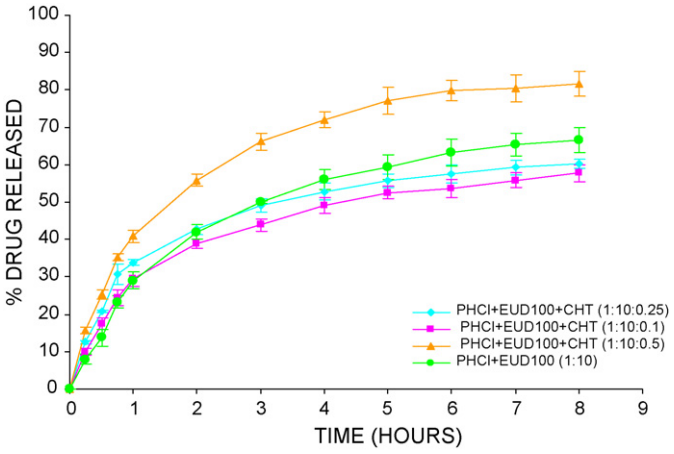


Fig. 2. Drug release profiles of EUD100 + CHT multipolymeric films prepared at various ratios.

below that observed with the PHCl:EUD100 (1:10) formulation, occurred. However, at a higher concentration of CHT inclusion, i.e. a 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 its disintegrant properties at certain concentrations (Nigalaye et al., 1990; Munasur et al., 2006). This phenomenon may have occurred in this study, altering the surface morphology of the film upon dissolution and thus leading to an increase in drug release. This is confirmed later in Section 3.3.3 by SEMs showing the morphology of PHCl:EUD100 and PHCl:EUD100:CHT films. The PHCl:EUD100:CHT (1:10:0.5) formulation was considered suitable for 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 while still maintaining a controlled release profile throughout the study.

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 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 (Table 2). 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 since 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 resulting 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 for-

Table 2
Mucoadhesivity and mechanical test data of homopolymeric and multipolymeric films

Film	*MDF (mN)	*Work (mJ)	*Tensile strength (N/m²)	*Elongation (%)	*Elastic modulus (N/m²)	*Toughness (MPa%)
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	95.07 ± 2.86	29.29 ± 1.93	0.415 ± 0.13	751.45 ± 87.41
PHCl: EUD100:CHT (1:10:0.5)	401.40 ± 30.73	84.36 ± 4.08	332.09 ± 5.65	17.37 ± 3.57	1.55 ± 0.19	1656.80 ± 188.61

*Results are represented as mean ± S.D.

Table 3
Film characterisation data for reproducibility studies on MMF preparation (PHCl:EUD100:CHT; 1:10:0.5)

Characterisation study	Batch A		Batch B		Batch C	
	Mean ± S.D.	CV (%)	Mean ± S.D.	R.S.D. (%)	Mean ± S.D.	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

mulation (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. 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 a MMF containing drug and polymer/s of opposing solubilities prepared by the emulsification/solvent evaporation/SMT casting method.

3.2. Reproducibility study

This study was undertaken to confirm the reproducibility of the emulsification and SMT method of film casting for the preparation of the suitable MMF formulation identified with drug and polymers of opposing solubilities, i.e. PHCl:EUD100:CHT (1:10:0.5). Three batches (A, B and C) of this formulation were prepared and compared in terms of assay values, mucoadhesivity, thickness and drug release of films (Table 3). 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 ($p = 0.1964$ and $p = 0.9971$, respectively). Consistent thicknesses of individual film units 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 Fig. 3, appeared to be almost super-imposable. To confirm the similarity of these dissolution profiles, the similarity factor (f_2) was used and was 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. 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 PHCl:EUD100:CHT (1:10:0.5) MMFs with drug and polymers of opposing solubilities by the emulsification/SMT casting method was indeed reproducible.

3.3. Characterisation of the MMFs prepared with the SMT method

The PHCl:EUD100:CHT (1:10:0.5) film formulation was then subjected to a detailed characterisation in terms of release kinetics, swelling/erosion, surface morphology, mechanical testing and surface pH.

3.3.1. Release kinetics

Although there are many models available for the interpretation of controlled release behaviour of delivery systems, few kinetic analysis studies on films exist and these have mainly used the Higuchi's square-root model (Ahmed et al., 2004; Amnuaikit et al., 2005). 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 (min) (Fig. 4). 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. $t^{1/2}$ plot, and was found to be 574.99 μg cm^{-2} min$^{-1/2}$.

3.3.2. Swelling and erosion studies

To obtain further evidence regarding the behaviour of the films upon dissolution testing, swelling and erosion studies were conducted (Fig. 5). EUD100 is an insoluble, low permeable, cationic

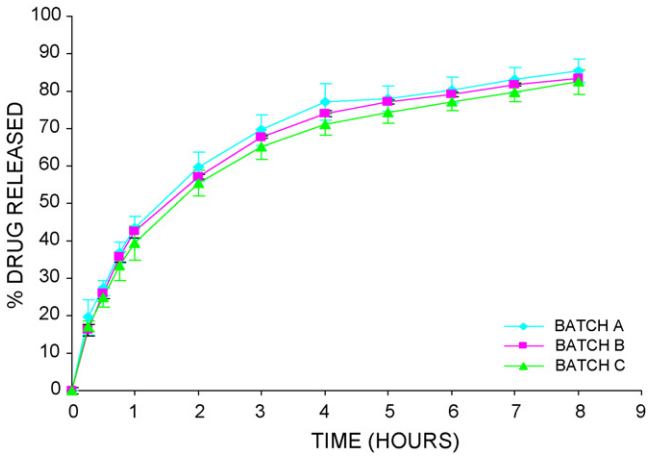


Fig. 3. Reproducibility of *in vitro* drug release profiles from PHCl:EUD100:CHT (1:10:0.5) MMFs.

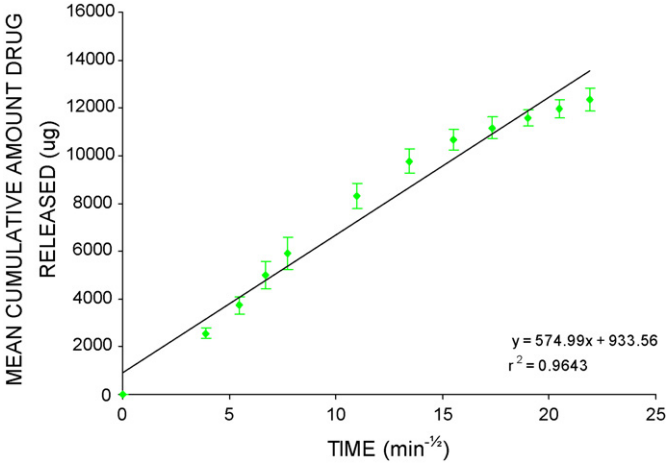


Fig. 4. Higuchi square-root of time plot for PHCl release from PHCl:EUD100:CHT (1:10:0.5) MMFs.

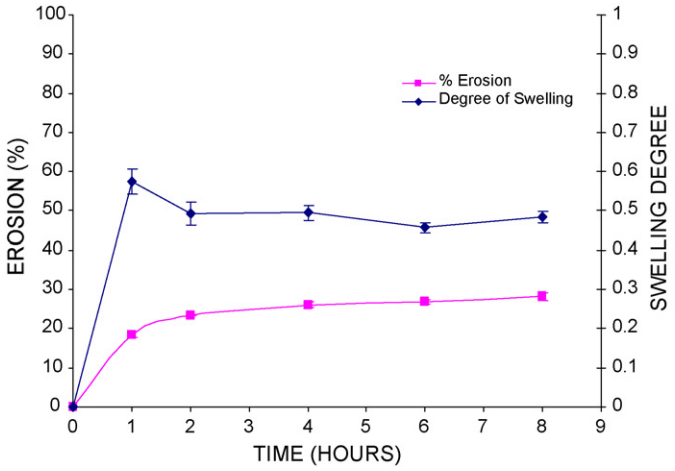


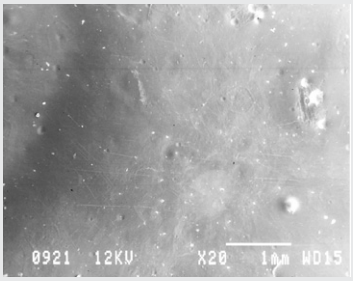
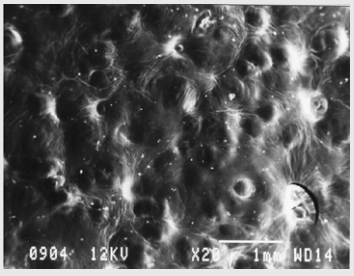
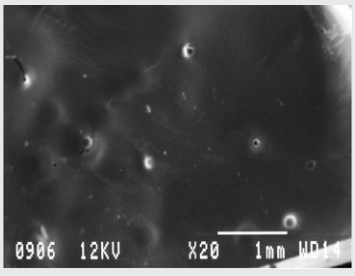
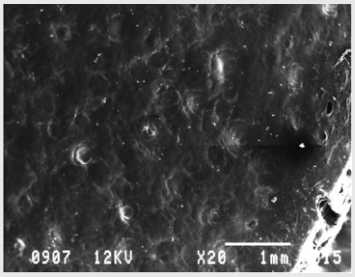
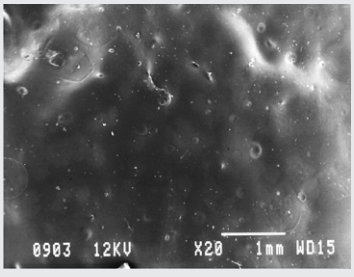
Fig. 5. Correlation of swelling and erosion profiles of PHCl:EUD100:CHT (1:10:0.5) MMFs.

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 h 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. In addition, it was observed that a maximum of 28.26% of the films eroded over the 8-h 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-h period. The swelling degree of these films may be considered not sufficient to cause discomfort (Peh and Wong, 1999). Also, the erosion data confirmed that the film could maintain its integrity for a prolonged period of time.

3.3.3. *Evaluation of surface morphology*

SEM was performed on the films to assess changes in their surface morphology prior to and after dissolution testing (Table 4). A smooth and compact surface was noted at time = 0 h for the 1:10 film, while 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. At 8 h 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. From these micrographs it can be concluded that the addition of CHT to the 1:10 PHCl:EUD100 film significantly affected the surface morphology of

Table 4
Effect of dissolution studies on the morphology of homopolymeric and multipolymeric films

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

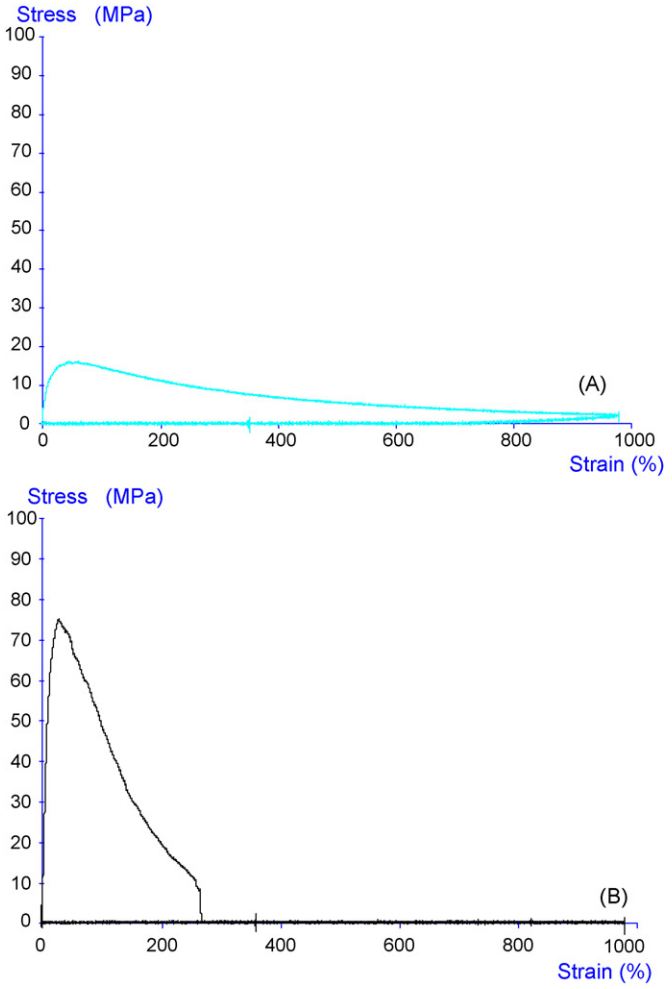


Fig. 6. (A) A typical stress–strain profile for the PHCl:EUD100 (1:10) homopolymeric film. (B) A typical stress–strain profile for the PHCl:EUD100:CHT (1:10:0.5) MMF.

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.

3.3.4. 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. 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 stress–strain profiles obtained for each film. There is a paucity of such studies on mucoadhesive controlled release films in the literature. No previous study on MMFs with polymers of opposing solubilities has been reported.

Studies were undertaken to obtain the stress–strain profiles for each film. Typical profiles are shown in Fig. 6A and B. These graphs were used to calculate the tensile strength (Eq. (4)), percent elongation (Eq. (5)), elastic modulus (slope of stress–strain curve) and toughness of the films (AUC), the values of which are shown in Table 2. As can be seen 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 $332.09 \pm 5.65\,N/m^2$, 0.415 ± 0.130 to $1.55 \pm 0.19\,N/m^2$ 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 $17.37 \pm 3.57\,N/m^2$. This may be explained by referring to the stress–strain profiles of the films depicted in Fig. 6A and B which show the distinct differences in the behaviour of the films during the elongation test period. 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 Fig. 6A, the PHCl:EUD100 (1:10) film reaches a peak but does not plateau to baseline as it does with the MMF (Fig. 6B). 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, while 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 the light of these findings (i.e. ease of handling, maintenance of integrity during dissolution and the aforementioned mechanical properties), it was suggested that the MMFs are preferred as a drug vehicle for buccal delivery over the PHCl:EUD100 (1:10) film.

3.3.5. 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 during the drug release period under investigation. The surface pH of the films remained fairly constant at a pH of approximately 6.7–6.8 over the 8-h test period, confirming that the surface pH of the films was within the neutral conditions of the saliva, pH 5.8–7.1 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.

4. Conclusions

The aim of this study was to prepare monolayered multipolymeric films comprising of a hydrophilic drug, Propanolol HCl, and polymers of opposing solubilities and to subsequently undertake a physicochemical/mechanical characterisation of a formulation

with a suitable polymeric blend. Monolayered multipolymeric films comprising of PHCl:EUD100:CHT at a ratio of 1:10:0.5, with drug and polymers of opposing solubilities, were successfully prepared by an emulsification/solvent evaporation method with casting by a new approach onto a silicone-molded tray with individual wells. The drug release, mucoadhesion and physicochemical/mechanical data obtained in this study, confirm the potential of this monolayered multipolymeric film as a promising candidate for controlled buccal drug delivery.

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