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Investigating a New Approach to Film Casting for Enhanced Drug Content Uniformity in Polymeric Films

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Films prepared by conventional casting onto trays such as teflon-coated perspex trays (TCPTs) suffer from poor drug content uniformity. The aim of this study was to prepare a silicone-molded tray (SMT) with individual wells for film casting and to evaluate it in terms of enhancing drug content uniformity. Films were prepared by solvent evaporation or emulsification and cast onto TCPT and SMT. Preparation of films by the SMT method was superior in terms of meeting drug content uniformity requirements. As compared with the TCPT method, the SMT casting method also reduced the variability in mucoadhesivity, drug release, and film thickness. Reproducibility of the SMT method was demonstrated in terms of drug content, mucoadhesion, and drug release.

Keywords films; buccal; drug uniformity; mucoadhesion; drug release

INTRODUCTION

Mucoadhesive controlled release drug-loaded films are being extensively studied for the buccal route (Ahmed, Barry, Williams, & Davis, 2004; Khoo, Frantzich, Rosinski, Sjostrom, & Hoogstrate, 2003; Lin, Lee, & Lin, 1995; Okamoto, Taguchi, Iida, & Danjo, 2001; Yoo, Dharmala, & Lee, 2006). Films are particularly advantageous for the buccal route because they offer 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 & Wong, 1999). Films are conventionally prepared by the solvent-casting method in which the drug and polymer(s) of similar solubilities are dissolved in a single vehicle and cast onto trays, which are then left to dry to facilitate solvent evaporation. This forms a sheet of film which is cut into desired sizes to provide a specified dose of drug (Amnuaikit, Ikeuchi, Ogawara, Higaki, & Kimura, 2005; Dhanikula & Panchagnula, 2004; Perugini, Genta, Conti, Modena, & Pavanetto, 2003; Remunan-Lopez, Portero, Vila-Jato, & Alonso, 1998). Simultaneous optimization of mucoadhesivity and drug release profiles of monolayered films may require the blending of drug and polymer(s) of opposing solubilities and therefore may not be simply dissolved in a single vehicle for film casting. Such films have been recently prepared by a novel emulsification/solvent evaporation method but were conventionally cast onto trays as mentioned above, which forms film sheets that can be cut into predetermined sizes to provide specified doses (Perugini et al., 2003). Preliminary investigations in our laboratories using both methods of film preparation and casting onto teflon-coated trays as above for cutting into specified sizes indicated nonuniform drug distribution across the individual film units. A prerequisite for therapeutic efficacy, safety, and regulatory approval of a medicine is drug content uniformity. 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, nonreproducible effects, and, importantly, toxic effects to the patient.

An extensive literature search with respect to drug content uniformity in polymeric films showed that although the literature is replete with formulation and several physicochemical characterization studies on films, surprisingly, the majority of papers did not report any assay values (Table 1). Of the very few that did, in three researchers had measured drug content by dissolving a known weight of the film for analysis (Ahmed et al., 2004; Amnuaikit, Ikeuchi, Ogawara, Higaki, & Kimura, 2005; Dhanikula & Panchagnula, 2004). This is not an accurate reflection of drug uniformity because 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

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TABLE 1
Summary of Film Characterization Studies and Reported Drug Content Uniformity/Assay Results from a Literature Search

Polymer(s)	Drug	Film Characterization 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, Holborow, Rathbone, Jones, & Tucker, 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, Fourier transform infrared spectroscopy (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, Peltonen, & Jarvinen, 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
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 & Panchagnula, 2004
PVA, PVP	S-nitrosogluta-thione (GSNO)	DSC, mechanical properties, SEM, dissolution, diffusion of GSNO	Not Reported	Seabra, Ganzarolli, & de Oliveira, 2004
Dextran-PCL co-polymer	Paclitaxel	Swelling, DSC, X-ray diffraction, in vitro release, morphology	Not Reported	Shi and Burt, 2004

(*Continued*)

TABLE 1
(*Continued*)

Polymer(s)	Drug	Film Characterization Studies	Assay Results	Reference
PLGA	Ethacrynic acid	In vitro release, SEM, water uptake, pH value, weight loss, in vivo eye test	Not Reported	Wang, Challa, Epstein, & Yuan, 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, Shin-ya, Hong, & Kajiuchi, 2005
Sodium alginate, gelatin	Ciprofloxacin HCl	FTIR, X-ray diffraction, in vitro release, morphology, mechanical properties, swelling	Not Reported	Dong, Wang, & Du, 2006
CHT, guar gum	Celecoxib	Swelling, mucoadhesion, in vitro and in vivo degradation, drug release	Not Reported	Haupt, Zioni, Gati, Kleinstern, & Rubinstein, 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

EUD, Eudragit; EC, ethylcellulose; HPMC, hydroxypropylmethyl cellulose; CHT, chitosan; PHCl, propranolol hydrochloride; PCL polycaprolactone; PLGA, poly(D,L lactide-co-glycolide); PAA, poly(acrylic acid); PEO, poly(ethylene oxide); PVP, polyvinylpyrrolidone; PAOMA polyalkyleneoxide-maleic acid; PVA, poly(vinyl alcohol); PEG, poly(ethylene glycol); HPC, hydroxypropyl cellulose; SDS, sodium dodecyl sulphate.

films. In addition, Dhanikula and Panchagnula (2004) only stated that uniformity results in their study indicated that the variation in drug distribution was <15%, but they did not report any data, whereas Perugini et al. (2003) reported assay values as a statement of drug content being more than 70%. The lack of reported data on this crucial characterization 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 characterization. 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 some patent applications that attempted to directly address the problems encountered with nonuniformity in films were identified. Although the identification of these 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 characterization studies (Table 1) without focusing on overcoming this simple but mandatory prerequisite for development of any drug delivery system. In these patent applications, it was explained that films prepared via the conventional casting technique, as used in the literature, suffered from the aggregation or conglomeration of particles, which rendered them inherently nonuniform 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 content 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. The incorporation of 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 is described (US Patent No. 60/443,741, 2004). 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). Also, approaches described 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 that uses minimal additional excipients into the formulation, uses simple technology, and also provides uniform drug content throughout the film clearly needed to be identified. Instead of considering 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 because the drug would be entrapped in each film unit, irrespective of the migration of the active within that well during drying. Such an improvement will not only be useful in the field of buccal drug delivery for formulation optimization, but it will also impact on other fields because mucosal films are used for a variety of other routes of administration, that is, vaginal, rectal, and ocular.

Therefore, the aim of this study was to develop and evaluate a specially designed silicone-molded tray (SMT) with built-in predetermined wells for film casting as a method for achieving drug uniformity. Propranolol hydrochloride (PHCl) was used as the model drug. Initially, the SMT was evaluated with a simple homopolymeric film containing drug and polymer of similar solubilities. Thereafter, its applicability to monolayered multipolymeric films with drug and polymers of both similar and opposing solubilities was also assessed. In addition to drug content uniformity, thickness, and morphology, the films from the trays were also characterized in terms of mucoadhesivity and in vitro drug release properties. These two properties measure retention on the mucosae and drug release behavior, respectively, and are essential in the evaluation of drug delivery systems for the buccal route.

MATERIALS AND METHODS

Materials

Chitosan (CHT) (MW 110 000) (Primex Ingredients ASA, Avaldsnes, Norway), Hydroxypropylmethylcellulose (HPMC) (Fluka, Buchs, Switzerland), Propranolol HCl (PHCl) (Frankel Chemicals, Johannesburg, SA), Mucin (Sigma-Aldrich, Dorset UK), Lactic Acid (BDH Lab Supplies, Poole, UK), Perspex (Maizey Plastics, Durban, SA), and Teflon (Coated Fabrics, Johannesburg, SA) were purchased and used as received. Eudragit® RS100 (EUD100) (Rhom Pharma, Darmstadt, Germany) was donated by Degussa Africa (Pty) Ltd. Wacker Silicone M4514 (Elastosil®) (amt Composites, Durban, SA) was mixed with its supplied catalyst (T 26) prior to use. All other chemicals used were of analytical or reagent grade.

Methods

Preparation of Trays for Film Casting

Drug containing polymeric solutions/emulsions were cast onto conventional teflon-coated perspex trays (TCPTs) as well as onto two other trays, that is, TCPTs with a removable chamber system and SMTs with built-in wells. The description and preparation of these trays are presented hereunder. Digital photographs of the trays are presented below in Figure 1.

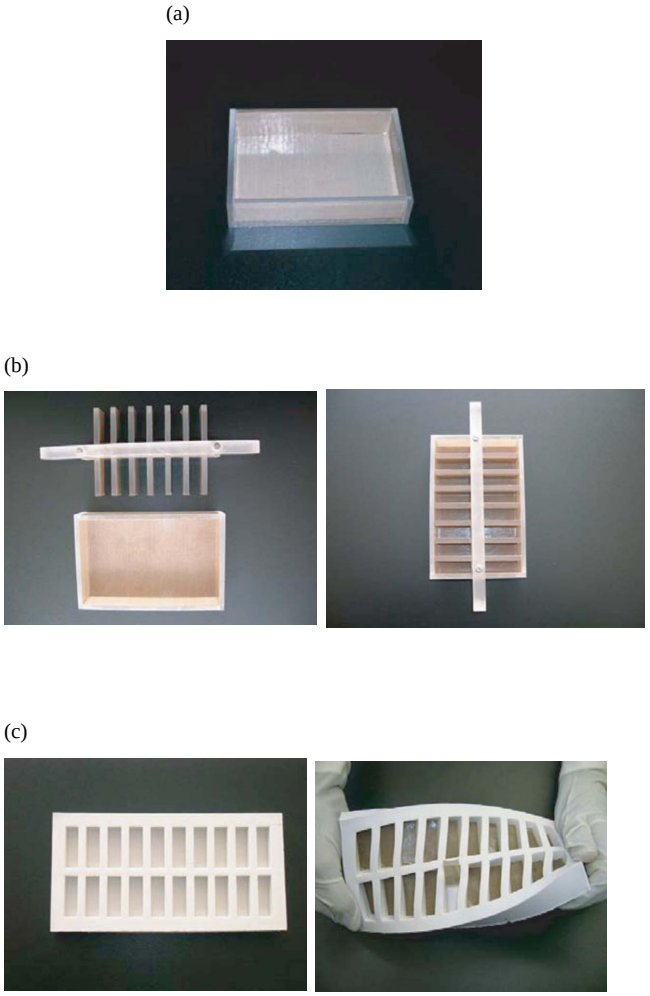


FIGURE 1. Digital photographs of trays used for casting of drug-polymeric films. (A) Conventional teflon-coated perspex tray (TCPT); (B) TCPT with a removable chamber system, (i) separate components and (ii) chambers inserted into TCPT; (C) silicone-molded tray (SMT) (i) without inserts and (ii) with teflon-coated perspex inserts.

Teflon-Coated Perspex Trays. TCPTs were prepared by gluing together pieces of 4-mm clear perspex (Maizey Plastics) to form a tray of dimensions 11 × 7 × 3 cm with an area of 77 cm^2. Thereafter, the trays were coated with a self-adhesive fabric teflon (Cofab, Johannesburg, SA) and were ready for immediate use. The TCPT yielded a sheet of film that was then cut into individual 1 × 3 cm^2 film units for analyses. The tray is shown in Figure 1A.

TCPT with a Removable Chamber System. The TCPT was prepared as described in the Section "Teflon-Coated Perspex Trays," and the removable chamber system was prepared by gluing together pieces of perspex to form a grid that formed 16 individual compartments of 1 × 3 cm^2 each when inserted into the TCPT. These compartments were coated with teflon fabric (Cofab). Films that were of 1 × 3 cm^2 size were retrieved from each compartment. The tray is shown in Figure 1B.

Silicone-Molded Trays. SMTs were prepared by combining Wacker silicone (150 mL) with its catalyst (T 26) (7.5 mL) (AMT Composites) in a glass beaker, by stirring with a glass rod for approximately 8 min to form a silicone mixture with a pot life of 20 min, and then pouring it into a greased wooden mold and allowing it to cure at room temperature (20°C) for 5 h. The cured silicone was then demolded to yield a flexible silicone tray with 20 individual 1 × 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 pieces (Maizey Plastics) into 1 × 3 cm^2 rectangles and coating them with the self-adhesive fabric teflon (Cofab). These inserts were then firmly placed into each well of the SMT prior to film casting. The SMT yielded individual film units of 1×3 cm^2 from each well. The tray is shown in Figure 1C.

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 × 3 cm^2 film unit theoretically contained a 15 mg/3 cm^2 dose. The total volume of PHCl containing polymeric solution/emulsion was cast onto the TCPT, whereas 1 mL of the solution was cast into each well of the SMT. All trays containing the cast polymeric solutions/emulsions were allowed to dry in an oven (Series 2000, Scientific, South Africa) 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. The preparation of the polymeric solutions/emulsions for casting onto the different trays is described below.

Homopolymeric Films. Homopolymeric films containing CHT and PHCl were prepared at a 1:1 ratio. The required amount of CHT and plasticizer, that is, glycerol (30% wt/wt of polymer weight), was dissolved in a 1% lactic acid solution (30 mL) under magnetic stirring. PHCl was then dissolved in the above CHT solution. The resulting drug containing polymeric solution was allowed to stand until air bubbles were removed before casting onto a TCPT or SMT. The quantities used ensured that each 1 × 3 cm^2 film unit would theoretically comprise 15 mg PHCl.

Multipolymeric Films. Multipolymeric films, in which drug and polymers were all of similar solubilities (i.e., PHCl+CHT+HPMC) and also those in which 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. Plasticizer was added at 30% wt/wt of polymer weight.

Monolayered multipolymeric films, in which PHCl and the polymers (CHT and HPMC) were all hydrophilic, were prepared as follows: CHT and glycerol as plasticizer (30%, wt/wt) were dissolved in a 1% 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 cast onto the respective trays and dried as described above.

Monolayered multipolymeric films with the hydrophilic drug PHCl and a hydrophilic (CHT) as well as a hydrophobic polymer (EUD100) were prepared as per a method modified from Perugini et al. (2003): CHT and glycerol (30%, wt/wt) were dissolved in a 1% lactic acid solution (15 mL), and thereafter PHCl was added and allowed to dissolve. EUD100 and triethyl citrate (30%, wt/wt, used as a plasticizer) were separately dissolved in acetone (15 mL). Both polymeric solutions were brought to the same temperature (20°C) and then combined by emulsification (IKA Homogenizer, 9,500 rpm for 5 min). During homogenization, the polymeric solution was maintained in an ice bath. The resulting drug-containing emulsion was cast onto the respective trays and dried as described above.

Evaluation of Films

Assay of PHCl Polymeric Films. A 1×3 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 (water or water/ethanol), 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 h before being brought up to volume with additional solvent. This stock solution (0.15 mg/mL) was also agitated for 5 min and then filtered (Millipore® Filter, 0.45 μm). A subsequent 1 in 10 dilution was performed before UV analysis of the solution at 290 nm (UV-Spectrophotometer, 1650 PC, Shimadzu, Tokyo, Japan). 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. Precision and accuracy tests were undertaken and confirmed the validity of the assay method used.

In Vitro Drug Release Profiles. A modified shaking water bath dissolution method was employed to determine drug release profiles of the films. The shaking water bath apparatus (100 strokes per minute) 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. Phosphate-buffered saline (PBS) (100 mL) equilibrated to 37 ± 0.5°C was used as the dissolution medium. A minimum of three replicate determinations were performed for all dissolution tests. At specified time intervals (0.25; 0.5; 0.75; 1; 2; 3; 4; 5; 6; 7; and 8 h), 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 was replaced into each dissolution vessel, to ensure a constant volume of dissolution medium throughout the duration of the test. All dissolution samples were analyzed using a UV spectrophotometer (Shimadzu) at a wavelength of 289 nm.

Mucoadhesivity of Films. The mucoadhesivity of the films was measured with the aid of a software-controlled penetrometer, TA-XT2*i* texture analyzer (Stable Micro Systems, Surrey, UK) equipped with a 5-kg load cell, a force measurement accuracy of 0.0025%, and a resolution distance of 0.0025 mm. The pretest, 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 1×3 cm^2 was used for all measurements. A sample of the prepared polymeric film (1×3 cm^2) was attached to the base of the probe with cyanoacrylate (superglue) and prehydrated 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 to undergo hydration for the remaining period of the 2 min prehydration phase. In the interim, 1 mL of mucin (30%, wt/wt 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 min), the film was brought into contact with the mucin 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, Piccerelle, Prinderre, Bouret, & Jaochim, 2001). A typical force/distance curve generated for each mucoadhesivity measurement from which the MDF and/or work performed was determined is illustrated in Figure 2. A minimum of 10 replicate determinations was performed.

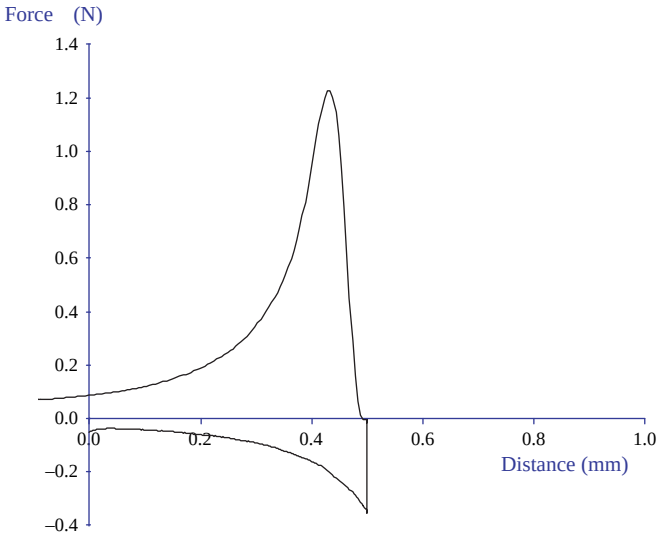


FIGURE 2. A typical detachment profile (force–distance curve) for the mucoadhesivity testing of a polymeric film.

Appearance and Morphology. Film surface was evaluated optically by a digital camera (Nikon Coolpix 5900, Tokyo, Japan). Film morphology was also characterized 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, Watford, UK) before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Avaldsnes, Japan). The images were captured on an Ilford PANF 50 black and white 35-mm film.

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

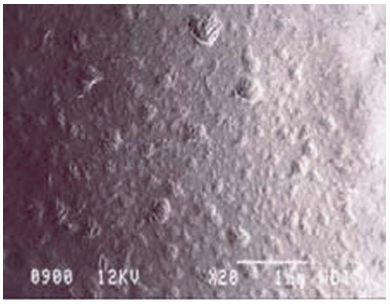
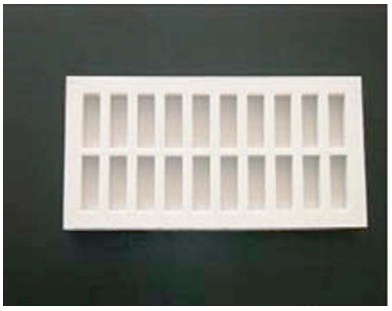
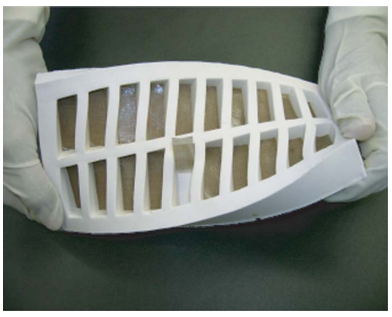
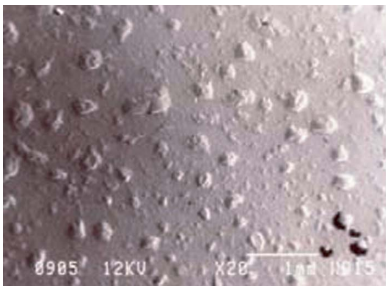
Statistical Analysis. All statistical analyses of data were undertaken using GraphPad Instat, version 3.05 (GraphPad Software Inc., San Diego, CA, USA), whereas all mathematical calculations were undertaken with Microsoft Excel® (Version 2002, USA). The assay data were specifically analyzed using a Kruskal–Wallis test with Dunn's Post Hoc tests, whereas the mucoadhesivity data were analyzed using one-way ANOVA with Bonferroni Post Hoc tests. Data were considered statistically significant if $p < 0.05$.

RESULTS AND DISCUSSION

Development of Trays for Enhancing Drug Uniformity in Films

Table 2 depicts the pictures of trays used in the study for film casting and a summary of the assay and morphology of films generated. Homopolymeric CHT films were initially

TABLE 2
Description of Tray Development and Film Characteristics

Tray Type	Picutre 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%	

TCPT, teflon-coated perspex tray; SMT, silicone-molded tray.

prepared by employing the conventional casting technique whereby the polymeric solution is cast onto TCPTs to form a sheet of film that is cut into individual film units of desired sizes. This yielded films with uniform surface morphology but poor drug content uniformity values, i.e., 110.00 ± 66.63%, indicating a large coefficient of variation (CV) of 60.57%. The poor drug uniformity with these TCPTs was attributed to the reasons given in several patent applications, that is, 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 × 3 cm^2) was developed. This was an attempt to contain the drug-containing polymeric solution dispensed into each chamber within that chamber. Although this method improved the drug uniformity as compared with the TCPT, that is, 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 because it was detachable and the solution could seep from one chamber to the next. The difficulty also experienced with this type of tray was the inability to remove the dried films without damage due to rigidity of the tray This, coupled with the poor assay values, led to the realization 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 satisfy 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 minimizes the risk of chemical reaction with drug (Maillard-Salin, Becourt, & Couarraze, 2000). Silicones also resist acids, bases, solvents, chemicals, oils, and water. Furthermore, it has been previously used in the literature as a component of novel drug delivery systems (Maillard-Salin et al., 2000; Schierholz, Jansen, Jaenicke, & Pulverer, 1994).

Taking these factors into consideration, an SMT with 20 individual separate wells was developed. Instead of being cast as a single film to be cut up into different sizes, a specified volume of drug–polymeric solution/emulsion was cast into each well of the SMT and dried to form individual film units. Films prepared using this tray exhibited assay values of 104.06 ± 3.31%, that is, a CV of 3.18% (Table 2). Hence as compared with the TCPT method, the SMT method significantly reduced the CV for assay values from 60.57 to only 3.18%, thus confirming its suitability to enhance drug content uniformity. 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 (Table 2). This could possibly be due to the physical nature of silicone when it is heated and dried, that is, adhesion of the films directly onto the silicone surface may have resulted in the film porosity observed. Because the TCPT produced films with nonporous, uniform morphology, teflon-coated perspex inserts were designed for insertion into each well to overcome the poor surface morphology. This modification, that is, using the SMT with inserts, resulted in films that satisfied the desired requirements, that is, good surface morphology and once again acceptable assay values of 104.84 ± 1.30% were achieved, as required by compendial specifications for PHCl dosage forms (92–107.5%) (British Pharmacopoeia, 2003).

The above studies showed that the SMT proved successful in enhancing drug content uniformity. In addition to drug content uniformity, mucoadhesivity and thickness of films from the SMT and TCPT were also compared. A comparison of the assay, mucoadhesivity, and thickness of films cast onto the TCPT and the newly developed SMT with the perspex inserts showed significant improvements in uniformity of the films in terms of the above properties with the SMT (Table 3). As a result of aggregation, 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 nonuniform mucoadhesive performance of films from the TCPT.

Reproducibility Study

As 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 the Section "Homopolymeric Films," using three different SMTs with teflon-coated perspex inserts. These batches were subjected to characterization 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.

TABLE 3
Summary of Results for Characterization Studies on Films Prepared with the TCPT and SMT Methods of Film Casting

Characterization 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

TCPT, teflon-coated perspex tray; SMT, silicone-molded tray.

TABLE 4
Summary of Results for Characterization Studies to Evaluate Reproducibility of the SMT for Film Casting

Characterization 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

SMT, silicone-molded tray; MDF, maximum detachment force.

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% (British Pharmacopoeia, 2003). The mean assay values between the three trays were statistically analyzed using a Kruskal–Wallis test with Dunn's Post Hoc tests. Data were considered statistically significant if $p < .05$. Statistical analyses indicated no significant differences between the three trays for assays because $p = .3407$. The intra-batch variability for the mucoadhesivity of films from the SMTs was less than 30% and was consistent with those reported in the literature for other preparations (Eouani et al., 2001; Shojaei, Paulson, & Honary, 2000). The differences between the mean MDF values for mucoadhesion of the three trays were statistically analyzed using one-way ANOVA with Bonferroni Post Hoc tests. Statistical analyses indicated no significant differences between the three trays for mucoadhesivity because $p = .2922$. 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 3. The profiles for films from all three trays appeared to be almost superimposable. To confirm the similarity of these dissolution profiles, the similarity factor was used. The *similarity factor* denoted as f_2 (Moore & 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:

$$f_2 = 50 \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left|R_j - T_j\right|^2\right]^{-0.5}\right\}\times 100 \qquad (1)$$

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 three trays.

Analyses of the data for drug content, mucoadhesivity, and thickness, coupled with the above f_2 values showing similarity in drug release profiles, confirmed the intra- and inter-batch reproducibility of the SMT method for film casting and preparation.

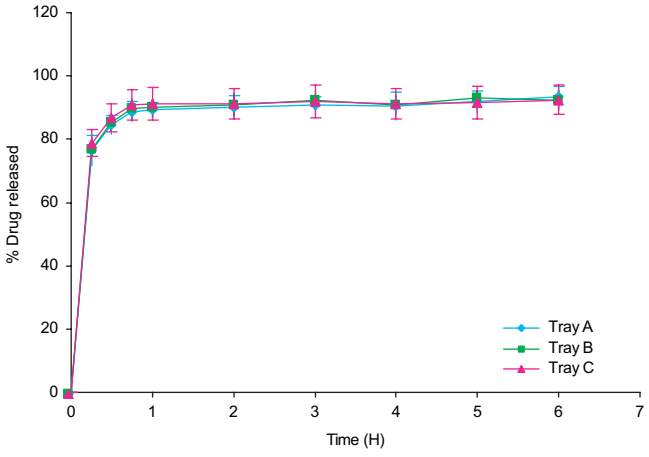


FIGURE 3. Drug release profiles of films prepared from the silicone-molded tray (SMT) for reproducibility studies.

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, because polymer blending is common for optimizing both mucoadhesivity and drug release profiles. Although polymer blending with drug and polymers of similar solubilities have been widely reported in the literature for the preparation of monolayered multipolymeric films (Ahmed et al., 2004; Khoo et al., 2003; Rossi, Sandri, Ferrari, Bonferoni, & Caramella, 2003; Yoo, Dharmala, & Lee, 2006), the blending of polymers and drug of opposing solubilities using an emulsification method has only been recently described by Perugini et al. (2003). Their study used a conventional film casting technique

and a hydrophobic drug. The preparation of monolayered multipolymeric films with a hydrophilic drug and polymers of opposing solubilities as well as it being cast into individual wells such as the SMT method has not been reported before. Therefore, multipolymeric films with PHCl+CHT+HPMC (drug and polymers with similar solubilities) and films with PHCl+CHT+EUD 100 (drug and polymers with opposing solubilities) were prepared by using the conventional TCPT and the SMT with inserts for film casting. The findings for both these methods were compared. Table 5 indicates the assay values, whereas Table 6 presents a composite summary of the drug release profiles of the films prepared in both types of trays. As is evident from Table 5 all films prepared with the SMT were within compendial specifications (92–107.5%) (British Pharmacopoeia, 2003) and all CVs for assays were low, that is, 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, that is, as high as 60%, indicating the unsuitability of these trays for all types of film preparation.

As can be seen from the drug release profiles (Table 6), the percentage drug released from all films prepared in the TCPT have relatively large *SD*s at each time point, whereas those prepared in the SMT with inserts have relatively small *SD*s. These results can be attributed to the migration of drug that occurs during the formation of aggregates during the drying process, leading to nonuniform drug content resulting in nonreproducible drug release profiles in the case of the TCPT. The small *SD*s 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 that prevents drug migration during drying and that maintains uniformity of content (US Patent No. 60/443,741, 2004). Furthermore, changes to the polymer ratio of PHCl:CHT:EUD100 from 1:0.5:05 to 1:0.5:10 to modify the drug release profile to achieve a more controlled release of PHCl confirmed the suitability of the SMT for again enhancing the drug content uniformity and minimizing variability in the drug release profile (Tables 5 and 6).

It is therefore evident from Tables 5 and 6 that the SMT with inserts can be successfully used to prepare both homo- and multipolymeric films with drug and polymers of both similar and opposing solubilities.

CONCLUSIONS

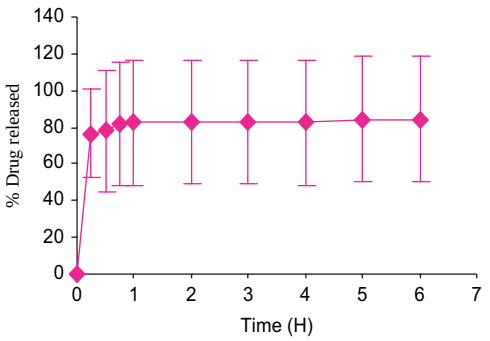
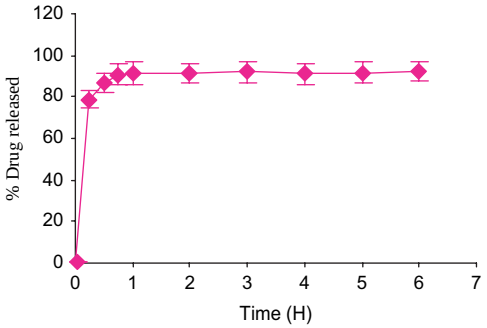
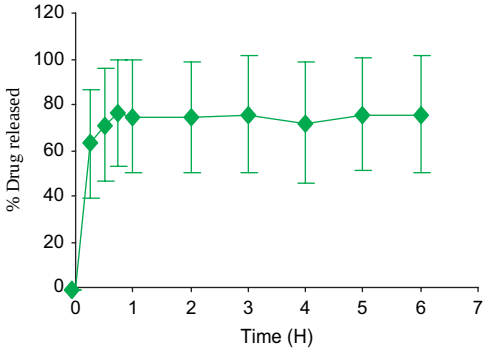
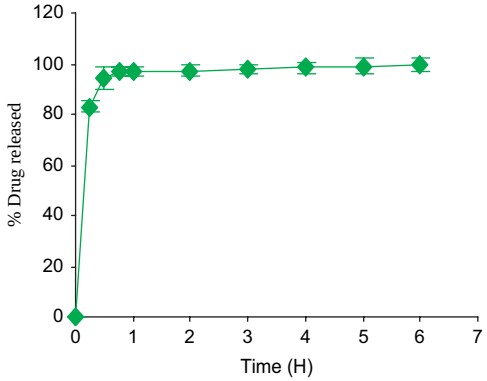
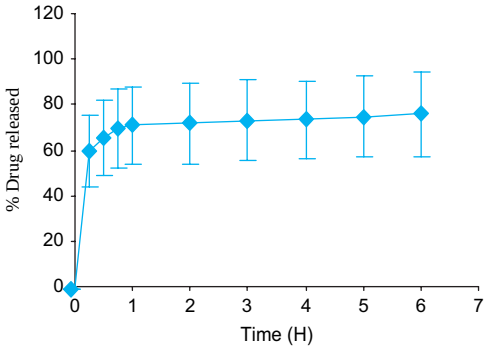
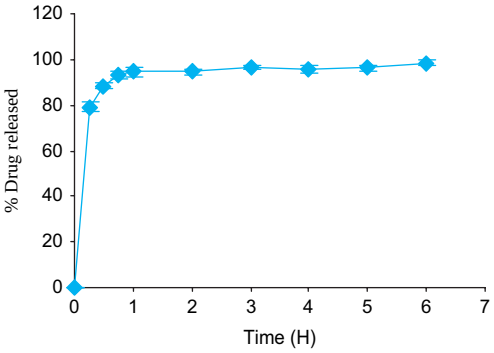
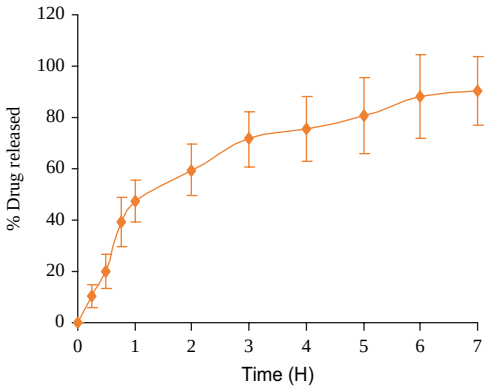
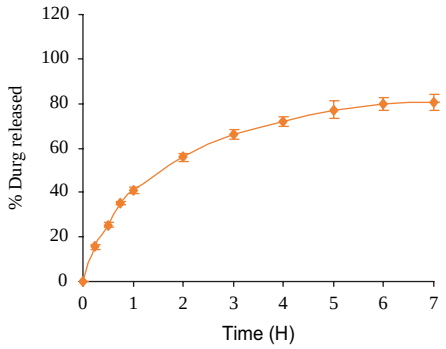
Preparation of homopolymeric and multipolymeric films (including drug and polymers of similar and opposing solubilities) via casting using a specially designed SMT was superior to the conventional TCPT method, in terms of meeting drug content uniformity requirements. This method of film casting as compared with the TCPT method also reduced the variability in mucoadhesivity, drug release, and film thickness. Reproducibility of this SMT method was also demonstrated in terms of drug content, mucoadhesion, and drug release. The use of a SMT with individual wells for film casting makes an important contribution to film formulation optimization for mucosal drug delivery.

TABLE 5
Assay Values of Homopolymeric and Multipolymeric Films Prepared in the TCPT and SMT with Inserts

	TCPT Assay (%)		SMT Assay (%)	
Film Type	Mean ± *SD*	CV (%)	Mean ± *SD*	CV (%)
Homopolymeric film: PHCl+CHT(1:1)	110.00 ± 66.63	60.57	104.84 ± 1.30	1.24
Multipolymeric film: similar solubilities PHCl+CHT+HPMC (1:0.5:0.5)	114.04 ± 22.78	19.97	97.62 ± 3.05	3.13
Multipolymeric film: opposing solubilities PHCl+CHT+EUD100 (1:0.5:0.5)	113.76 ± 13.21	11.61	104.08 ± 1.33	1.28
Multipolymeric film: opposing solubilities PHCl+CHT+EUD100 (1:0.5:10)	116.05 ± 14.42	12.43	100.71 ± 2.66	2.64

TCPT, teflon-coated perspex tray; SMT, silicone-molded tray; EUD, Eudragit; HPMC, hydroxypropylmethyl cellulose; CHT, chitosan; PHCl, propranolol hydrochloride.

TABLE 6
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)		
Monolayered multipolymeric film: opposing solubilities Drug+CHT+EUD100 (1:0.5:10)		

TCPT, teflon-coated perspex tray; SMT, silicone-molded tray; EUD, Eudragit; HPMC, hydroxypropylmethyl cellulose; CHT, chitosan.

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