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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.

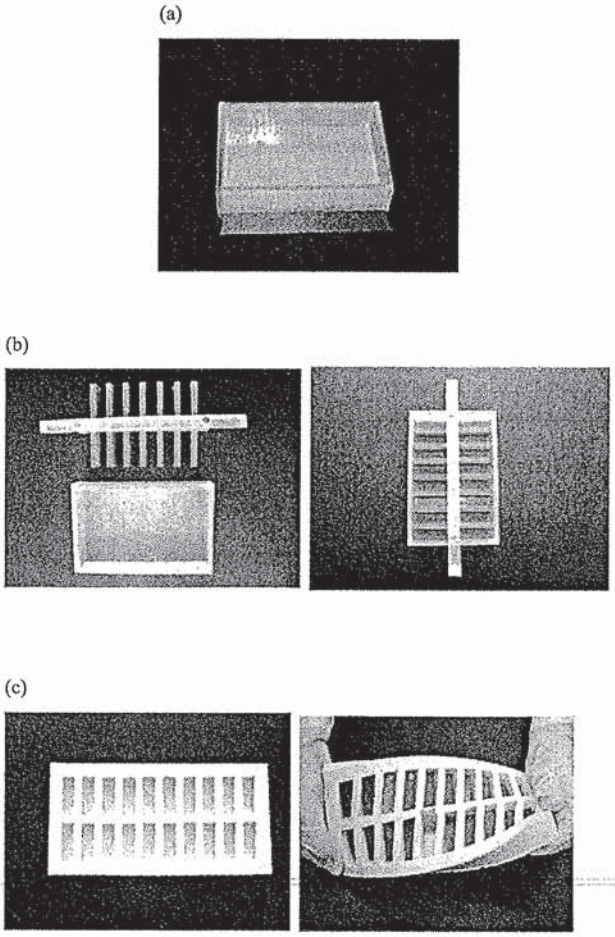


FIGURE 1. Digital photographs of trays used for casting of drug-polymeric films. (A) Conventional teflon-coated perspex tray (TCPT); (B) TCPT with a removable chamber system, (i) separate components and (ii) chambers inserted into TCPT; (C) silicone-molded tray (SMT) (i) without inserts and (ii) with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

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