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A novel unit-dose approach for the pharmaceutical compounding of an orodispersible film

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ABSTRACT

Orodispersible films (ODF) have clinical potential as extemporaneous pharmacy preparations for individualized pharmacotherapy. However, the conventional method of ODF preparation using a film applicator may limit its application, due to content uniformity challenges arising from viscosity changes of the casting solution and varied operator manipulation. This study proposes the unit-dose (UD) plate as an alternative to the film applicator for compounding individual ODFs. Using a design-of-experiments approach, we developed an extemporaneous ODF formulation for an antiemetic drug, ondansetron hydrochloride dihydrate (OND), at a clinically relevant dose. ODFs cast with the UD plate showed excellent content uniformity independent of the viscosity of the casting solution and drug concentration. Formulations were evaluated for performance with respect to patient acceptability and product quality. The effects of critical process parameters on critical quality attributes of the ODF were studied. HPMC concentration and volume of casting solution were the main factors affecting disintegration time and mechanical properties of the film, while drug concentration had no significant effect. However, further studies incorporating different drugs in larger concentration ranges are needed to investigate the impact of drug concentration and to establish a design space. Nevertheless, our results indicate the potential of using the UD plate to prepare ODFs with customized drug doses from a generic casting solution. Results from this study provide a framework for an extemporaneous ODF platform.

1. Introduction

The pharmaceutical and clinical research industry is moving towards a new paradigm of personalized medicine. Individualized pharmacotherapy in terms of customized drug dosing, drug combinations and specially tailored dosage forms are increasingly sought-after, heralding a potential shift from industry-manufactured medicines to personalized, point-of-care pharmacotherapy. This opens up a window of opportunity for small-scale, extemporaneous preparations in the pharmacy setting. Orodispersible films (ODF) can be an extemporaneous pharmacy preparation (Visser et al., 2016). More recently, a quality control method has been developed for extemporaneous ODFs using miniaturized near-infrared spectroscopy (Foo et al., 2018). ODFs are well-suited to address the needs of special populations such as pediatric, geriatric and patients suffering from dysphagia, nausea/vomiting or on restricted fluid intake. These patient groups often require specially compounded pharmacy preparations as they are unable to swallow traditional solid dosage forms. Compared to conventional extemporaneous oral suspensions which must be poured out and measured to obtain a single dose, ODFs offer the advantage of administration convenience and dose accuracy since each film will contain precise drug content.

Various methods have been explored for the production of ODFs, namely solvent casting (Cilurzo et al., 2010; Preis et al., 2012), hot-melt extrusion (Low et al., 2013; Repka et al., 2008), electrostatic spinning (Illangakoon et al., 2014; Nagy et al., 2010), inkjet or flexographic printing (Genina et al., 2013; Janßen et al., 2013) and electrostatic spraying (Davidson, 2014). Inkjet printing holds promise for small-scale

Abbreviations: ODF, orodispersible film; OND, ondansetron hydrochloride dihydrate; UD, unit-dose; HPMC, Hydroxypropyl methylcellulose; ANOVA, analysis of variance; BCS, Biopharmaceutics Classification System; HPLC, high performance liquid chromatography; PLM, polarizing light microscope; XRD, X-ray diffraction; GRAS, Generally Recognized as Safe; LOD, loss on drying; US FDA, United States Food and Drug Administration; HCl, hydrochloric acid; PBS, phosphate buffer solution; pK_a, logarithmic acid dissociation constant

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application but is at the preliminary developmental stage, encountering challenges such as drug loading limitations and crystallization of the active pharmaceutical ingredient (API) on the substrate surface (Sandler et al., 2011; Scoutaris et al., 2011). Solvent-casting has been established as a platform technology for industrially manufactured ODFs. It is a simple process with low set-up costs, hence well-suited for extemporaneous compounding on a small-scale. Indeed, the feasibility of solvent-casted ODFs as an extemporaneous pharmacy preparation has recently been demonstrated (Visser et al., 2015b). The use of a film applicator to prepare a master film is ubiquitous in all ODF solvent-casting studies, but it can lead to lack of API content uniformity. Incorporation of different drugs, drug doses and utilization of different shear rates during casting have been found to alter formulation rheology, wet film thickness and consequent dose variability (Visser et al., 2015b). This poses a significant problem for extemporaneous preparations since ODFs containing different drugs or even the same drug in different doses must be re-formulated independently, thus invalidating the application of a generic, one-size-fits-all casting solution. Furthermore, individual ODFs must be cut to size from a master film. This requires cumbersome manipulation by an operator who may introduce inaccuracies or errors during cutting.

In this study, we propose the unit-dose (UD) plate for compounding individual ODFs to circumvent the effect of viscosity and operator-to-operator variability. Our proposed method was based on the following criteria of an ideal pharmacy compounding process:

- Simple and does not require specialized training
- Basic set-up using inexpensive apparatus
- Easy-to-prepare formulation
- Minimal operator manipulation

The aim of this study was to develop an extemporaneous ODF preparation using the UD plate, which meets requirements for product quality and performance. Ondansetron hydrochloride dihydrate (OND) which is a Biopharmaceutics Classification System (BCS) I/ III drug (Takagi et al., 2006) was selected as the model compound. Its high solubility negates potential bioavailability issues common in extemporaneous preparations thus making it an appropriate drug for pharmaceutical compounding. Ondansetron is an antiemetic agent with a pediatric dosage of 0.1–0.25 mg/kg (4–8 mg for adults) every six hours. In local practice settings, OND is frequently compounded as an extemporaneous oral suspension from oral tablets (Williams et al., 1994) and parenteral solutions (Graham et al., 1993). The ODF presents a good avenue for formulation of OND pharmacy preparations, as the target patient population suffering from nausea/vomiting are frequently unable to swallow large amounts of oral liquids or solid dosage forms. Furthermore, the high potency (low-dose) and clinical requirement for rapid action of OND render it a suitable candidate as an ODF.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC, Methocel E5 Premium LV) was obtained from Colorcon (Singapore). Glycerol 99% was obtained from Sigma-Aldrich (Singapore) and OND was purchased from Chempure Private Limited (India). All other chemicals used were of analytical grade.

2.2. Design of experiments

A 2^3 full factorial design was employed to study the effects of various critical process parameters on critical quality attributes of the ODF (Table 1). The three independent process parameters studied were drug concentration (8, 16 mg/mL), HPMC concentration (5, 10% w/w) and volume of the casting solution, henceforth referred to as 'volume' (0.4, 0.8 mL). The concentration of the plasticizer, glycerol was fixed at 12% w/w of HPMC, as was optimized by Visser and co-workers (Visser et al., 2015a). ODF disintegration time and mechanical properties were identified as critical quality attributes of a good quality ODF. Experimental runs were randomized to reduce systematic errors and results were analyzed using the Design-Expert® Software, version 10 (StatEase®). The analysis of variance (ANOVA) test was performed and statistical significance was taken as $p < 0.05$.

Table 1
2^3 full factorial design of experiments. Parameters (High, low): Drug concentration (8, 16 mg/mL); HPMC concentration (5, 10% w/w); Volume (0.4, 0.8 mL).

Formulation	Drug concentration (OND free base) (mg/mL)	HPMC concentration (% w/w)	Volume of casting solution (mL)
F1	8	5	0.4
F2	16	5	0.4
F3	8	10	0.4
F4	16	10	0.4
F5	8	5	0.8
F6	16	5	0.8
F7	8	10	0.8
F8	16	10	0.8

2.3. Preparation of the casting solution

A casting solution of HPMC and glycerol was prepared by first dispersing HPMC in water at 90 °C under magnetic stirring. The dispersion was then cooled to form a clear solution at room temperature. Glycerol was added and the solution made up to the required weight with water. Subsequently, an appropriate amount of OND was dissolved in the casting solution under continuous stirring and made up to the volume required for the final drug concentration.

2.4. Preparation of ODFs using the UD plate

Each film unit was cast onto individual wells of the UD plate which are confined by circular bank structures (Fig. 1) using a direct-displacement, electronic repetitive pipette (HandyStep® electronic, Brand® GMBH & Co. KG, Wertheim, Germany). Films were dried at 40 °C overnight in a convection oven (Binder Inc., New York, USA). A moderate drying temperature was selected to give smooth films without bubble formation. At higher drying temperatures of 55–60 °C, the formation of bubbles which affected film appearance and mechanical properties, was observed during the drying process. This was postulated to be caused by nucleate boiling – a phenomena observed when temperature exceeds the vapor saturation temperature corresponding to the local liquid pressure (Tong and Ouano, 1985).

All ODFs were stored at room temperature above silica gel in a glass desiccator with a relative humidity of approximately 20% for at least 24 h. Characterization tests, except for evaluation of the coffee-ring effect and *in vitro* dissolution studies, were performed within a week of preparation.

2.5. Evaluation of casting solution

Each formulation was assessed based on the ease of preparation of the casting solution, such as degree of foaming, need for de-aeration and rate of API dissolution. Performance during the casting process was also evaluated in terms of solution spreadability and propensity for spillover.

2.6. ODF weight

Fifteen randomly chosen ODFs were weighed individually on an analytical balance with an accuracy of 0.1 mg. Mean and standard deviation were calculated.