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Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability

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ABSTRACT

The aim of this work was to compare and contrast the mechanical properties and physical stabilities of oral films prepared with either thermal ink-jet printing (TIJP) or solvent casting (SC). Clonidine hydrochloride was selected as a model drug because of its low therapeutic dose and films were prepared using cellulose polymers. Mechanical testing showed that the printed films had Young's moduli and tensile strength values similar to the free film, while casted films were significantly more brittle. The drug also appeared to crystallize out of casted films during stress testing whereas printed films remained unchanged. The dissolution behavior of printed and cast films were similar, because of the rapid disintegration of the polymer. The conclusion is that printing resulted in a better film than casting because the drug resided on the film, rather than in the film where it could exert a plasticizing effect.

1. Introduction

Oro-dispersible films (ODFs) have gained a lot of attention in recent years as a novel technology to overcome some of the common issues associated with conventional oral dosage forms, such as difficulty of swallowing (tablets and capsules) and stability (solutions and suspensions) (Banbury and MacGregor, 2011; Jeong et al., 2010; Saigal et al., 2008). ODFs are the size of a postage stamp and typically made from good film-forming polymers that dissolve or disintegrate rapidly upon contact with saliva (Banbury and MacGregor, 2011). They are flexible, which makes transportation and consumer handling much easier (Borsadia et al., 2003), and their manufacturing can be cost effective (Reiner et al., 2010).

ODFs are not, however, without drawbacks. One is their limited drug loading capacity, which makes them most suitable for highly potent, low-dose active pharmaceutical ingredients (APIs). Other limitations include the need for solvents and heat in the manufacturing process and the issue of taste masking. The main formulation challenge is to produce films with a rapid disintegration/dissolution time without compromising the mechanical properties (Hoffmann et al., 2011).

Well-established technologies such as solvent casting (SC) and hot-melt extrusion (HME) are used commercially to manufacture ODFs. In either case a polymer network is produced that is cut into strips of the required size. Both methods require the drug and the polymer to be mixed prior to forming the film. HME processing may not be suitable for APIs that are thermally labile or are degraded following shear stress (Janßen et al., 2013). One issue is that the ODFs manufactured via these methods are essentially solid amorphous dispersions, with the API molecularly dispersed in the polymer matrix. It is well known that small molecular weight organic compounds typically exert a plasticizing effect on polymers, which means that the mechanical properties of the film may change depending on the amount and/or chemical structure of the API incorporated. A further concern is that if the drug is formulated at a super-saturated concentration, relative to its solubility in the polymer, it is likely to phase separate by crystallizing during storage. Crystallization could potentially change the mechanical properties of the film, alter the dissolution rate, change the mouth feel and/or taste of the product and possibly alter the *in vivo* fate of the drug (Cespi et al., 2011).

An alternative route of manufacture is to cast a free film and then deposit the API onto it. One approach is to use flexography (a contact printing method that uses rotating rollers to deposit the printing solution onto the substrate). Genina et al. (2012) used flexographic printing to formulate films for controlled release while Janßen et al. (2013) used flexography to dispense rasagiline mesylate solution and tadalafil suspension onto hydroxypropyl methylcellulose films. Incorporation of hydroxypropyl cellulose seemed to reduce drug crystallization after printing. However, the

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main limitations of flexography are the risk of contamination, the relatively low resolution and the need to prepare a print roller, which means it is most suited to medium-scale production runs (Gonzalez-Macia et al., 2010).

The API may also be deposited with thermal ink-jet printing (TIJP). TIJP has the advantage of being able to deposit very small volumes (5–15 pL/droplet) with high precision. We have demonstrated before the deposition of low doses of salbutamol sulphate onto commercially available starch-based films with using conventional desktop printers (Buanz et al., 2011). TIJP technology has also been used to manufacture modified-release dosage forms by printing dots of solution onto a substrate (Scoutaris et al., 2011, 2012) and it has been shown possible to fabricate three-dimensional particles by printing aqueous droplets into liquid nitrogen and subsequently freeze-drying (Mueannoom et al., 2012; Sharma et al., 2013).

Since TIJP deposits API solution onto a substrate, rather than dispersing API within a substrate, it seems reasonable to assume that the printed films would maintain mechanical properties similar to that of the free film, and hence offer potential benefits compared with solvent casting for ensuring long-term stability. Testing this hypothesis is the specific aim of this work. Clonidine (CLN) was selected as a model drug. Clonidine is an antihypertensive drug that acts centrally by blocking α2-adrenoreceptors. It also has sedative and analgesic effects (Ambrose et al., 2000). The drug is available as tablets of 100 and 300 μg as the chloride salt (Paediatric Formulary Committee, 2011) and the required dose to induce pre-operative sedation is 1–5 μg/kg (Bergendahl et al., 2006). Such low doses make CLN an ideal candidate for formulation as oral films.

2. Materials and methods

2.1. Materials

CLN, polyvinyl alcohol (PVA) 98% hydrolyzed (Mw 13000-23000) and carboxymethylcellulose sodium salt medium viscosity (SCMC) were purchased from Sigma–Aldrich (UK). Glycerol (analytical grade) was purchased from Fischer Scientific (UK). Bidistilled water (99.5%) was purchased from VWR International Ltd. (UK), and methanol, absolute ethanol and acetonitrile (HPLC grade) were all purchased from Fischer Scientific (UK). Sodium1-hexanesulphate (99%) was purchased from Acros organics (USA).

2.2. Film preparation

Films were prepared either by solvent casting or ink-jet printing. Concentrations were based on the minimum and maximum doses for sedation for children aged 6 months, 5 and 14 years (Table 1).

2.3. Printed films

The free film was composed of PVA and SCMC at 1:1 ratio with 24% w/v glycerol (Soutari et al., 2012). PVA (3.75 g) was first dissolved in water (about 100 mL) by heating to 80 °C with continuous stirring. SCMC (3.75 g) was then added and the solution was left to cool to room temperature with mixing, following which glycerol was added (36 g) and the final volume was adjusted to 150 mL with water. The solution was poured into a non-stick baking tray (450 cm^2) and dried in an oven at 30 °C. The resulting film sheets were used as substrates for printing.

An HP printer (HP Deskjet 460, Hewlett-Packard Inc.) was used to print drug solution onto the film. Solutions of CLN (50 mg/mL, prepared in 20% v/v methanol in water with 10% v/v glycerol) were printed from an HP 338 black cartridge. The cartridge was prepared by cutting off the top, removing the ink and rinsing with absolute ethanol. A 2 cm × 2 cm black template was created in Word 2007 (Microsoft Inc., USA) and used to fire the cartridge. It was found that per print pass, 316.0 μg of CLN were deposited per strip (4 cm^2), equivalent to 79.0 μg/cm^2. This value was then used to prepare CLN solutions suitable for printing films with doses equivalent to those given in Table 1.

2.4. Casted films

Appropriate volumes of CLN solutions (3.3, 1.18, 0.66, 0.5, 0.24 and 0.1 mg/mL to prepare 250, 90, 50, 38, 18 and 7.6 μg/strip, respectively) were added to a PVA:SCMC solution (prepared as above) to obtain the required dose. Solutions were left to stir for 1 h and then were cast in a non-stick baking tray and dried at 30 °C. The resulting films were cut to the required size (4 cm^2) and stored over silica gel in a desiccator until use.

2.5. Drug content analysis

Films were dissolved in a solution of 20% methanol in water (4 cm^2 in 20 mL). Solutions were filtered through a 0.45 μm filter (Millex syringe-driven filter unit, Millipor Ltd., Ireland). The filtrate was analyzed with high performance liquid chromatography (HPLC) equipped with a UV-diode-array detector (Agilent Technologies 1200 series, Germany). The mobile phase was a mixture of 0.1% v/v triflouroacetic acid in water and acetonitrile (80:20% v/v) delivered at a rate of 1.0 mL/min. The stationary phase was a Phenomenex Synergy Max C-12 column (250 mm × 4.6 mm × 4 μm; Phenomenex Synergy Max, USA) kept at 40 °C and the injected sample volume was 10 μL. Peaks were evaluated at 220 nm. The percentage recovery calculated for solutions made with blank film sheets dissolved in the solutions spiked with known amount of CLN (in the range of 100–300 μg/mL, $n = 9$) was 98.29 ± 1.82%. Limit of detection and limit of quantification were found to be 0.15 μg/mL and 0.68 μg/mL, respectively. Method calibration was performed with a series of standard CLN solutions in 20% methanol in water. A linear response was seen between 0.25 and 100 μg/mL ($r^2 = 0.9997$).

Table 1
Clonidine hydrochloride doses and the required solution concentrations used for depositing the drug by TIJP.

Age/body weight	Target dose (μg/strip)	Required feed solution conc. (mg/mL)
6 months/7.6 kg	7.6	1.20
	38	2.85
5 year-old/18 kg	18	6.01
	90	7.91
14-year old/50 kg	50	14.23
	250	39.54

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