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 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 crystallise out of casted films during stress testing whereas printed films remained unchanged. The dissolution behaviour 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 plasticising effect.

Key words

Thermal inkjet printing, oral films, clonidine, dynamic mechanical analysis, critical humidity.
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 manufacture 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 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 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 plasticising effect on polymers, which means 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 crystallising during storage. Crystallisation 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 hydroxypropylmethylcellulose films. Incorporation of hydroxypropylcellulose seemed to reduce drug crystallisation after printing. However, the 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 inkjet printing (TIJP). TIJP has the advantage of being able to deposit very small volumes (5-15 pL per 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 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% hydrolysed (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). Sodium 1-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).
2.2.1 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 (3.75g) was first dissolved in water (about 100mL) by heating to 80°C with continuous stirring. SCMC (3.75g) was then added and the solution was left to cool to room temperature with mixing, following which glycerol was added (36g) and the final volume was adjusted to 150mL with water. The solution was poured into a non-stick baking tray (450cm²) 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 (50mg/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 2cm x 2cm 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 (4cm²), equivalent to 79.0 μg/cm². This value was then used to prepare CLN solutions suitable for printing films with doses equivalent to those given in Table 1.

2.2.2 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 one hour 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 cm²) and stored over silica gel in a desiccator until use.
2.3 Drug content analysis

Films were dissolved in a solution of 20% methanol in water (4 cm² in 20 mL). Solutions were filtered through a 0.45 µm filter (Millex syringe-driven filter unit, Millipor Ltd, Ireland). The filtrate was analysed 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 trifluoroacetic 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 (250mm x 4.6mm x 4µm; Phenomenex Synergy max, USA) kept at 40°C and the injected sample volume was 10µL. Peaks were evaluated at 220nm. 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 to 300 µg/mL, n=9) was 98.29 ± 1.82%. Limit of detection and limit of quantification were found to be 0.15µg/mL and 0.68µg/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 ($r^2 =0.9997$).

2.4 Characterisation of films

2.4.1 X-Ray Powder Diffraction (XRPD)

Powder diffraction data were collected with a PW3830 diffractometer (Philips, Netherlands) operated with Cu K-alpha radiation ($\lambda = 1.540598$ Å) at 45 kV and 30 mA. Scanning was performed from 5° to 30° 2θ at 0.02° step size and 2.85 seconds per step. Xpert data viewer software (PANalytical B.V, Netherland) was used to analyse the data.

2.4.2 Thermogravimetric analysis (TGA)

Measurements were performed with a Pyris-6 TGA (PerkinElmer, UK). Samples were heated at 10°C/min using nitrogen as purge gas (20mL/min). Data collection and
analysis were performed using Pyris software (version 3.18). Mass loss (%w/w) and/or onset temperature were calculated and reported as mean ± SD.

2.4.3 Fourier Transform Infrared (FTIR)

FTIR spectra were collected with a PerkinElmer Spectrum 100 FTIR spectrometer in the range of 4000 to 650 cm\(^{-1}\) at ambient conditions. Spectra were analysed with Spectrum Express software (application version 1.02.00.0014, 2008).

2.4.4 Tensile testing

An Instron Universal Testing Instrument (Model 5567, Instron Ltd, Norwood, USA) was used to measure the mechanical properties of films (2cm x 2cm) at a rate of 10mm/min and 100N static load (2kg). The cut-off point was when the film was completely separated into two pieces. The tensile strength and Young’s modulus were measured. Data were analysed using Bluehill software 2 (version 2.6).

2.4.5 Dynamic Mechanical Analysis (DMA)

A Q800 Dynamic Mechanical Analyser (TA instruments, Waters LLC) was used to measure the mechanical properties of the films. Advantage software for Q series version 2.8.0.394 was used to collect the data and TA Universal Analysis software (V4. 7A TA 2000) to analyse the data. Samples were held in a film tension clamp. Experimental parameters were amplitude, 15-20um; preforce load, 0.01N; force track, 125%; frequency, 10Hz. Experiments were performed at 3°C/min from room temperature to 200°C.

2.4.6 Polarised light microscopy (PLM)

A Nikon microphot-FXA light microscope was used to collect optical images with an Infinity 2 digital camera and capture application software (version 3.7.5).
Films were placed in a glass pan for Dynamic Vapour Sorption (DVS-1) (Surface Measurement Systems, London, UK) at 30°C and kept at 0% RH for 90 minutes. Relative humidity was then scanned from 0 to 95% with intervals of 5% RH over 10 minutes. The change of sample weight due to water uptake or loss was recorded gravimetrically with the ultra-microbalance. The relative humidity (RH) around the sample was controlled by mixing saturated and dry carrier gases (Nitrogen) with electronic mass flow controllers.

2.4.8 Thickness and disintegration

Thickness of films (2cm x 2cm) was measured using a digital micrometer at five points of each sample, at the four corners and the centre in triplicate, and reported as mean ± SD.

The disintegration test described by Zhao et al (2009) for capsule and tablet coatings was modified to suit oral films. A device was constructed to hold the film between two clamps and a weight of 725mg was placed on top of the film. The disintegration medium used was 15 mL (37 ± 1 °C) of a simulated saliva solution (Peh and Wong, 1999) containing Na$_2$HPO$_4$ (2.38 g), KH$_2$PO$_4$ (0.19 g) and NaCl (8 g) in distilled water (1 L). The pH of the solution was adjusted to 6.75 with phosphoric acid. The time taken for the film to break was measured by filming with a black and white CCD camera (model ART-CAM-130MI-VM). Images were analysed with FTA 32 software (Version 2.0, First Ten Angstroms Inc, USA). The disintegration time was calculated as the time between adding the disintegration medium and visual observation of the film breaking (n = 3).
2.4.9 *In vitro* drug release

Dissolution tests were conducted in a water-jacketed glass vessel (outer and inner diameters of 8 and 6 cm, respectively and 150mL capacity). Films were placed on a plastic sieve of 3cm in diameter and 40 mL of simulated saliva solution was used as a dissolution medium. A PTFE magnetic stirrer was used for agitation (size of 10cm x 6cm) and the temperature was maintained at 37 ± 1 °C with the help of a refrigerating/heating circulator with programmable digital temperature controller (Polyscience, Division of Preston Industries, Inc., USA). Samples of 1mL were collected at time intervals of 0.5, 1, 2, 4, 8, 12, 16 and 30 min and replaced with a fresh medium kept at ~ 37 °C. Samples were then filtered through 0.45 µm filters and analysed with HPLC in accordance with the method above.

2.5 Statistical analysis

Results were analysed and compared with Student t-test (α=0.05) using Origin® 8.6 software (OriginLab Corporation, USA).

3. Results and discussion

3.1 Drug content and dose uniformity

The amount of CLN deposited by printing showed a linear correlation with the drug feed solution concentration as shown in Figure 1 ($r^2 = 0.9997$). This is consistent with the salbutamol sulphate (SS) data reported in an earlier study (Buanz et al, 2011).

Films prepared by blending CLN with the polymer and casting had a lower drug content than films prepared by printing (Table 2). The variation of dose was higher with solvent casting method (CV= 10.8 ± 6.0%) compared with printing (CV= 2.5 ± 2.2%). The higher dose variability in casted films may be a result of inhomogeneity in blending or variability in film thickness, but the results immediately indicate the
potential utility of ink-jet printing for preparing low dose and narrow therapeutic index medicines.

3.2 Characterisation of films

In general, pharmaceutical polymer films should have good flexibility, elasticity and softness but possess enough strength to withstand mechanical stresses during manufacturing and dispensing (Preis et al., 2013; Prodduturi et al., 2004). Hydrophilic polymers are commonly used in pharmaceutical oral dosage forms (Prodduturi et al., 2004), which generally means that exposure to humidity during storage and use can affect their properties (Gontard and Ring, 1996). Here, mechanical testing and polarised-light microscopy were used to characterise the films after manufacture and following exposure to elevated humidity.

3.2.1 Tensile test

Tensile stress at the break point and Young’s modulus were calculated for drug-loaded films (Table 3). Films prepared by SC had higher tensile stress values, which indicates that the films were harder than those made by TIJP (Garsuch and Breitkreutz, 2010). Skulason et al (2009) reported that Carpabol films prepared by SC have high tensile strength and low elasticity. In general, higher Young’s modulus values for films made by SC also reflect their increased brittleness (Biliaderis et al., 1999).

Residual water in films can affect their mechanical properties and lead to increased elasticity by its plasticizing effect (Karisson and Singh, 1998) and thus any variation in water content between films prepared by TIJP and SC could be the reason for the difference in their mechanical properties. However, as shown by values of water content given in Table 3, the difference was not significant (p > 0.05). This suggests that location of drug within the films is in fact the critical factor.
3.2.2 Glass transition measurement

XRPD patterns shown in Figure 2 confirm the amorphous nature of the free and drug-loaded films. The glass transition temperature (Tg) of a polymer is one of the important parameters that reflects its mechanical properties with temperature and is associated with a small change in the heat capacity of the system due to the strong glass forming properties of polymers (Fadda et al., 2010). There is no single temperature at which Tg occurs; rather, the value depends on the technique and experimental parameters used to measure it.

DMA was used to measure the glass transition temperatures of the films. Tg is usually defined as a peak in the tan delta signal (the ratio of the storage to loss moduli) or the inflection point of the decrease in storage modulus (Gontard and Ring, 1996). Here, it was not possible to use either point. The storage modulus data are shown in Figure 3. It is apparent that there is an increase in storage modulus after 100 °C. This is because the films lost water during heating and so became very brittle. Similarly, there was no peak in the tan delta signal (data not shown) because the polymers thermally degraded. This highlights one significant problem when using thermal methods at slow heating rates. The increase in temperature acts to dry the sample and since water is often a plasticiser the mechanical properties of the film change during measurement. Hence, it was not possible to determine the Tg values of the films.

FTIR data, however, did show evidence of CLN-polymer interactions at room temperature (Table 4). Shifts are noticeable in the bands at 3274.8 (broad), 2941.6 and 1380.5 (from the free film) in the drug-loaded films, which can be assigned to hydroxyl (OH) stretch, and carbon-hydrogen (C-H) stretch and C-H bend, respectively (Coates, 2000), suggesting that the drug interacts with PVA but not with...
SCMC, possibly through hydrogen bond with the PVA OH group. Larger shifts from the free film values are seen in the case of SC samples, indicating the drug is more dispersed in the polymer matrix than in the printed films. It is noticeable that the main bands characteristic for CLN, such as the secondary amine N-H stretch, bend and aliphatic secondary amine C-N stretch (at 3330, 1649 and 1338) are not seen, which could be because they are masked by peaks from the polymers or because the drug concentration is very low.

3.2.3 Critical humidity measurement

The critical humidity (cRH) is the humidity at a particular temperature that will cause a phase transition (such as glass transition). Its determination is important along with the threshold temperature in order to define the storage conditions required to prevent phase changes during processing and storage (Burnett et al., 2004).

DVS is commonly used to determine cRH. cRH is usually taken to be the RH where a reduction in mass is seen, corresponding to expulsion of absorbed water as the sample crystallises. For CLN films the sample weight continued to increase with a increasing of RH (Figure 4), and so it was not possible to determine a cRH value. Presumably, this is because the majority of the sample is polymer. The method of preparation (TIJP or SC) did not seem to have an effect on water sorption at lower humidity as the changes of weight with time (and humidity) of both samples appear to be superimposed. However, at higher humidity a higher weight increase is observed for printed films. Possible reasons for this difference are discussed below.

3.2.4 Physical stability

Stability here refers to physical form rather than chemical degradation. Upon exposure to increased temperature and/or humidity the films may absorb water and
be plasticised thus increasing the rate of molecular mobility of dispersed drug
molecules and potentially causing phase separation by crystallisation.

Films containing the highest doses of CLN (90 and 250 µg/strip) were subjected to
high temperature and humidity (60°C and 75 %RH) in the DMA for about 13 hours.
The DMA signal (storage modulus) did not change after initial equilibration to the test
parameters. This indicates that there was no significant change in the mechanical
properties of the films over the test period. However, PLM images (Figure 5) showed
clear signs of crystallisation in the 250 µg/strip prepared by SC. No such
crystallisation was observed for the lower dose film prepared by SC or films prepared
by TIJP.

In addition, the films used during the DVS and DMA experiments were also checked
with PLM (Figure 6). These films were exposed to relative humidity from 0 to 90% RH
at 30°C. No signs of crystallisation can be seen in films tested with DMA but clear
crystallisation is evident in the 250 µg/strip films prepared by SC tested with DVS and
the beginning of crystal growth is seen in the 90 µg/strip films. Drug in films prepared
by TIJP showed no evidence of crystallisation.

3.2.1 Disintegration and drug release

Typical disintegration times for ODFs range from 5 to 30 s (Banhart, 2008). There
have been several attempts to mimic in vivo conditions, particularly the low volume of
saliva, such as the slide frame method and the Petri dish method (Garsuch and
Breitkreutz, 2010; Hoffmann et al., 2011). Measurement of the contact angle with
time as a drop of water is placed on a film has also been used to assess
disintegration (Garsuch and Breitkreutz, 2009). The lack of official tests makes the
comparison between various published results a challenging task.
Here, the images for film disintegration were captured with the help of a CCD camera, allowing precise time measurement. For the dissolution test a volume of 40 mL was the lowest that allowed the film (placed on the plastic mesh) to float freely while the medium was mixed. The results of both tests are described below.

The results from the disintegration test show that the time taken for the samples to disintegrate is in the range of 20 to 60 s (the time recommended by the FDA is 30 s, Centre for Drug Evaluation and Research, 2008). This means that some samples exceeded the recommended limit. The main factor for that would be the thickness as it is a key factor in determining the disintegration time (Garsuch and Breitkreutz, 2010).

Figure 7 shows the release profiles of films containing 250 µg/strip of CLN prepared by either TIJP or casting (SC) in simulated saliva fluid. It is noticeable that both samples achieved more than 50 ($t_{50\%}$) and 80% ($t_{80\%}$) of drug release within 8 and 30 min, respectively. To compare the release profiles of films prepared by TIJP with films prepared by SC, difference ($f_1$) and similarity ($f_2$) factors were calculated from equations 1 and 2 ($n = 3$). $f_2$ can have a value of 0 to 100 where 100 means the profile of the tested product is the same as that of the reference and 0 means they are completely different (Costa and Sousa Lobo, 2001). The FDA adopted both factors as a way to assess the similarity of in vitro dissolution profiles where a value of 0 to 15 for ($f_1$) and 50 to 100 for ($f_2$) indicate the two profiles to be similar (Center for Drug Evaluation and Research, 1997). $f_1$ and $f_2$ for films containing 250 µg/strip prepared by TIJP were calculated to be 1.25 and 64.7, respectively, which means that the release profile of TIJP films is similar to that of films prepared by SC.

\[
f_1 = \left( \frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t} \right) \times 100
\]  
Equation 3.1
The correlation coefficients ($r^2$) for films prepared by TIJP or SC are given in (Table 5). The highest $r^2$ value was for Hixson-Crowell model. This suggests that drug release from both samples followed this model, which indicates drug release by erosion (Costa et al., 2003). This could be a result of incorporating SCMC in the formulation (Dabbagh et al., 1999; Hussain et al., 1994). This could be related to the presence of ionisable carboxylic acid group in SCMC, which increases the dissolution of the polymer (Hussain et al., 1994). Dabbagh et al (1999) noticed a decrease in matric erosion when propranolol hydrochloride was added, which they suggested to be a result of an interaction between the drug and the polymer. In this work the FTIR data presented earlier suggest that clonidine hydrochloride interacts with PVA and not SCMC in the tested films. This supports the suggestion that the carboxylic acid groups of SCMC are available for ionisation and thus allows the polymer erosion.
Hussain et al (1994) also reported that when comparing the erosion rate of SCMC matrices containing either a drug that interacts with the polymer or not, a faster rate is observed when no interaction is present.

4. Conclusion

The results indicate that films prepared by printing are significantly different in terms of mechanical properties and stability compared with films prepared by casting. In particular, the properties of the printed films are much more similar to those of the free film. It seems likely that the process of solvent casting results in a molecular dispersion of CLN throughout the polymer, analogous to a solid-amorphous dispersion. FTIR data confirm chemical interaction between the drug and the polymer. The drug appears to exert an anti-plasticising effect, increasing the brittleness of the film. When stored at elevated temperature and humidity the drug is seen to phase separate, resulting in crystal formation.

The exact nature of the printed film is harder to elucidate from the data. It is clear that immediately after printing the drug will be present in solution as droplets on the surface of the polymer film. Previous experience with printing drug solutions (Buñan et al, 2013) has shown us that the small droplets evaporate very quickly, resulting in formation of small (<5 µm) crystals. Thus, a reasonable hypothesis would be that in the printed films the drug exists either on the surface or in the top layer of the film as small crystallites. The drug is thus not acting as an anti-plasticiser and so the mechanical properties of the printed film remain similar to those of the free film. The printed film appears amorphous by XRPD because the drug content is low and small crystals do not diffract sufficiently to appear in the pattern. Upon storage at elevated temperature and humidity the printed film remains stable because it has already phase separated. Again, it is likely that the small size of any crystallites mean they were not visible with PLM.
Janßen et al (2013) did not observe any effect on the mechanical properties of films upon printing drug solutions using flexographic printing. They argue that in manufacturing oral films by this method the properties of the plain films can be assessed and it would not be necessary to evaluate the medicated films, which they envisage to add flexibility to the manufacturing process. Our work indicates a similar conclusion can be drawn in regard to ink-jet printing.
5. References


mechanical properties, release characteristics, and stability. J. Pharm. Sci. 93, 3047-3056.


<table>
<thead>
<tr>
<th>Age/Body weight</th>
<th>Target dose (µg/strip)</th>
<th>Required feed solution conc. (mg/mL)</th>
</tr>
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<tr>
<td>6 months/7.6Kg</td>
<td>7.6</td>
<td>1.20</td>
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<tr>
<td></td>
<td>38</td>
<td>2.85</td>
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<tr>
<td>5 year-old/18Kg</td>
<td>18</td>
<td>6.01</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>7.91</td>
</tr>
<tr>
<td>14-year old/50Kg</td>
<td>50</td>
<td>14.23</td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>39.54</td>
</tr>
</tbody>
</table>

Table 1. Clonidine hydrochloride doses and the required solution concentrations used for depositing the drug by TIJP.
Table 2. A comparison between drug content in films prepared by SC and TIJP methods.

<table>
<thead>
<tr>
<th>Target conc. (µg/strip)</th>
<th>Calculated Concentration (µg/strip)</th>
<th>SC (weight-based)</th>
<th>SC (area-based)</th>
<th>TIJP (area-based)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD % Difference</td>
<td>Mean ± SD % Difference</td>
<td>Mean ± SD % Difference</td>
<td>% Difference</td>
</tr>
<tr>
<td>7.6</td>
<td>9.9 ± 1.3 30.1 ± 17.4</td>
<td>10.6 ± 0.5 39.1 ± 6.5</td>
<td>12.2 ± 0.4 60 ± 5.0</td>
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<tr>
<td>18</td>
<td>26.0 ± 2.6 44.3 ± 14.3</td>
<td>18.6 ± 1.0 3.5 ± 5.8</td>
<td>19.1 ± 1.1 5.9 ± 5.9</td>
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<tr>
<td>38</td>
<td>31.1 ± 15.0 -18.3 ± 39.5</td>
<td>30.3 ± 6.5 -20.3 ± 17</td>
<td>36.5 ± 1.7 -4 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>51.8 ± 2.3 3.6 ± 4.5</td>
<td>42.7 ± 4.3 -14.7 ± 8.5</td>
<td>45.9 ± 0.1 -8.1 ± 0.3</td>
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<tr>
<td>90</td>
<td>116.7 ± 43.5 29.4 ± 48.3</td>
<td>73.5 ± 8.4 -18.3 ± 9.3</td>
<td>80.4 ± 0.4 -10.7 ± 0.4</td>
<td></td>
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<tr>
<td>250</td>
<td>226.7 ± 5.8 -9.3 ± 2.3</td>
<td>203.9 ± 23.9 -18.4 ± 9.6</td>
<td>252.8 ± 2.5 1.1 ± 1</td>
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<tr>
<td>Sample</td>
<td>Free film</td>
<td>250 µg/strip</td>
<td></td>
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<td>-------------------------</td>
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<tr>
<td></td>
<td>SC</td>
<td>TIJP</td>
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<tr>
<td>Tensile stress (MPa)</td>
<td>19.3 ± 2.9</td>
<td>41.9 ± 1.9</td>
<td>25.2 ± 1.1</td>
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<td>Young's modulus (MPa)</td>
<td>547.8 ± 54.2</td>
<td>1423.8 ± 259.1</td>
<td>658.2 ± 127.6</td>
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<td>Water content (%w/w)</td>
<td>8.9 ± 0.1</td>
<td>5.8 ± 0.3</td>
<td>6.6 ± 1.1</td>
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<td>Thickness (mm)</td>
<td>0.1 ± 0.02</td>
<td>0.1 ± 0.01</td>
<td>0.1 ± 0.01</td>
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<tr>
<td>Disintegration time (seconds)</td>
<td>NA</td>
<td>23.3 ± 5.6</td>
<td>30.5 ± 4.6</td>
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</table>

Table 3. Mechanical properties, water content, thickness and disintegration times for films prepared by SC or TIJP methods.
<table>
<thead>
<tr>
<th>Sample</th>
<th>TIJP 250 µg/strip</th>
<th>SC 250 µg/strip</th>
<th>Free film</th>
<th>PVA powder</th>
<th>SCMC powder</th>
<th>CLN powder</th>
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</thead>
<tbody>
<tr>
<td>Wavelength (cm⁻¹)</td>
<td></td>
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<td>3270.8</td>
<td>3274.8</td>
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<td>3266.8</td>
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<td>2941.6</td>
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</tbody>
</table>

Table 4. Main FTIR transmittance peaks of drug-free films and films containing 250 µg/strip prepared by SC or TIJP.
<table>
<thead>
<tr>
<th>Sample</th>
<th>SC</th>
<th>TIJP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>b</td>
</tr>
<tr>
<td>Zero-order</td>
<td>0.891</td>
<td>2.2</td>
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<tr>
<td>1st order</td>
<td>0.747</td>
<td>0.05</td>
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<tr>
<td>Higuchi</td>
<td>0.988</td>
<td>14.4</td>
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<td>Hixson-Crowell</td>
<td>0.997</td>
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</table>

Table 5. Regression values for the dissolution profiles for 250 µg/strip CLN films ($r^2$ is the correlation coefficient, a is the intercept and b is the slope).
Figure 1. Amount of clonidine hydrochloride deposited as a function of feed solution concentration (some error bars are too small to appear on the graph)

$r^2 = 0.9997$

$y = 6.3351x - 0.411$
Figure 2. XRPD patterns of medicated films prepared by SC or TIJP in comparison to CLN raw material and the free film.
Figure 3. Storage modulus as a function of temperature for drug-free films and films containing 250µg/strip prepared by SC or TIJP methods.
Figure 4. DVS results of relative humidity (RH) scan for films containing 250 µg/strip prepared by SC or TIJP methods.
Figure 5. PLM images of films after being tested with isothermal constant humidity experiments (60°C and 75% RH) in the DMA.
Figure 6. PLM images of films subjected to RH scan at 30°C in (left) DVS and (right) DMA.
Figure 7. Dissolution profiles for films containing 250 µg/strip CLN prepared by SC or TIJP methods (n = 3).