1   Ink-jet printing versus solvent casting to prepare oral films: effect

2   on mechanical properties and physical stability

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19 **Abstract**

20

21 The aim of this work was to compare and contrast the mechanical properties and

22 physical stabilities of oral films prepared with either thermal ink-jet printing (TIJP) or

23 solvent casting (SC). Clonidine hydrochloride was selected as a model drug because

24 of its low therapeutic dose and films were prepared using cellulose polymers.

25 Mechanical testing showed that printed films had Young's moduli and tensile strength

26 values similar to the free film, while casted films were significantly more brittle. The

27 drug also appeared to crystallise out of casted films during stress testing whereas

28 printed films remained unchanged. The dissolution behaviour of printed and cast

29 films were similar, because of the rapid disintegration of the polymer. The conclusion

30 is that printing resulted in a better film than casting because the drug resided *on* the

31 film, rather than *in* the film where it could exert a plasticising effect.

32

33 **Key words**

34

35 Thermal inkjet printing, oral films, clonidine, dynamic mechanical analysis, critical

36 humidity.

37

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

66 structure of the API incorporated. A further concern is that if the drug is formulated at

67 a super-saturated concentration, relative to its solubility in the polymer, it is likely to

68 phase separate by crystallising during storage. Crystallisation could potentially

69 change the mechanical properties of the film, alter the dissolution rate, change the

70 mouth feel and/or taste of the product and possibly alter the *in-vivo* fate of the drug

71 (Cespi et al., 2011).

72

73 An alternative route of manufacture is to cast a free film and then deposit the API

74 onto it. One approach is to use flexography (a contact printing method that uses

75 rotating rollers to deposit the printing solution onto the substrate). Genina et al (2012)

76 used flexographic printing to formulate films for controlled release while Janßen et al

77 (2013) used flexography to dispense rasagiline mesylate solution and tadalafil

78 suspension onto hydroxypropylmethylcellulose films. Incorporation of

79 hydroxypropylcellulose seemed to reduce drug crystallisation after printing. However,

80 the main limitations of flexography are the risk of contamination, the relatively low

81 resolution and the need to prepare a print roller, which means it is most suited to

82 medium-scale production runs (Gonzalez-Macia et al., 2010).

83

84 The API may also be deposited with thermal inkjet printing (TIJP). TIJP has the

85 advantage of being able to deposit very small volumes (5-15 pL per droplet) with high

86 precision. We have demonstrated before the deposition of low doses of salbutamol

87 sulphate onto commercially available starch-based films with using conventional

88 desktop printers (Buanz et al., 2011). TIJP technology has also been used to

89 manufacture modified-release dosage forms by printing dots of solution onto a

90 substrate (Scoutaris et al 2011, 2012) and it has been shown possible to fabricate

91 three-dimensional particles by printing aqueous droplets into liquid nitrogen and

92 subsequently freeze-drying (Mueannoom et al, 2012; Sharma et al, 2013).

93

94   Since TIJP deposits API solution *onto* a substrate, rather than dispersing API *within* a

95   substrate, it seems reasonable to assume that printed films would maintain

96   mechanical properties similar to that of the free film, and hence offer potential

97   benefits compared with solvent casting for ensuring long-term stability. Testing this

98   hypothesis is the specific aim of this work. Clonidine (CLN) was selected as a model

99   drug. Clonidine is an antihypertensive drug that acts centrally by blocking α2-

100   adrenoreceptors. It also has sedative and analgesic effects (Ambrose et al., 2000).

101   The drug is available as tablets of 100 and 300 µg as the chloride salt (Paediatric

102   Formulary Committee, 2011) and the required dose to induce pre-operative sedation

103   is 1- 5 µg/kg (Bergendahl et al., 2006). Such low doses make CLN an ideal candidate

104   for formulation as oral films.

105

106   **2.   Materials and methods**

107   2.1   Materials

108   CLN, polyvinyl alcohol (PVA) 98% hydrolysed (Mw 13000-23000) and

109   carboxymethylcellulose sodium salt medium viscosity (SCMC) were purchased from

110   Sigma Aldrich (UK). Glycerol (analytical grade) was purchased from Fischer

111   Scientific (UK). Bidistilled water (99.5%) was purchased from VWR International Ltd

112   (UK), and methanol, absolute ethanol and acetonitrile (HPLC grade) were all

113   purchased from Fischer Scientific (UK). Sodium 1-hexanesulphate (99%) was

114   purchased from Acros organics (USA).

115

116   2.2   Film preparation

117   Films were prepared either by solvent casting or ink-jet printing. Concentrations were

118   based on the minimum and maximum doses for sedation for children aged 6 months,

119   5 and 14 years (Table 1).

120

121   2.2.1   Printed films

122   The free film was composed of PVA and SCMC at 1:1 ratio with 24%w/v glycerol

123   (Soutari et al, 2012). PVA (3.75g) was first dissolved in water (about 100mL) by

124   heating to 80°C with continuous stirring. SCMC (3.75g) was then added and the

125   solution was left to cool to room temperature with mixing, following which glycerol

126   was added (36g) and the final volume was adjusted to150mL with water. The solution

127   was poured into a non-stick baking tray (450cm^2) and dried in an oven at 30°C. The

128   resulting film sheets were used as substrates for printing.

129

130   An HP printer (HP Deskjet 460, Hewlett-Packard Inc.) was used to print drug solution

131   onto the film. Solutions of CLN (50mg/mL, prepared in 20% v/v methanol in water

132   with 10%v/v glycerol) were printed from an HP 338 black cartridge. The cartridge was

133   prepared by cutting off the top, removing the ink and rinsing with absolute ethanol. A

134   2cm x 2cm black template was created in Word 2007 (Microsoft Inc., USA) and used

135   to fire the cartridge. It was found that per print pass, 316.0 µg of CLN were deposited

136   per strip (4cm^2), equivalent to 79.0 µg/cm^2. This value was then used to prepare CLN

137   solutions suitable for printing films with doses equivalent to those given in Table 1.

138

139   2.2.2   Casted films

140   Appropriate volumes of CLN solutions (3.3, 1.18, 0.66, 0.5, 0.24 and 0.1 mg/mL to

141   prepare 250, 90, 50, 38, 18 and 7.6 µg/strip, respectively) were added to a

142   PVA:SCMC solution (prepared as above) to obtain the required dose. Solutions were

143   left to stir for one hour and then were cast in a non-stick baking tray and dried at

144   30°C. The resulting films were cut to the required size (4 cm^2) and stored over silica

145   gel in a desiccator until use.

146

147   2.3   Drug content analysis

148   Films were dissolved in a solution of 20% methanol in water (4 cm² in 20 mL).

149   Solutions were filtered through a 0.45 μm filter (Millex syringe-driven filter unit,

150   Millipor Ltd, Ireland). The filtrate was analysed with high performance liquid

151   chromatography (HPLC) equipped with a UV-diode-array detector (Agilent

152   Technologies 1200 series, Germany). The mobile phase was a mixture of 0.1% v/v

153   triflouroacetic acid in water and acetonitrile (80:20% v/v) delivered at a rate of 1.0

154   mL/min. The stationary phase was a Phenomenex Synergy max C-12 column

155   (250mm x 4.6mm x 4μm; Phenomenex Synergy max, USA) kept at 40°C and the

156   injected sample volume was 10μL. Peaks were evaluated at 220nm. The percentage

157   recovery calculated for solutions made with blank film sheets dissolved in the

158   solutions spiked with known amount of CLN (in the range of 100 to 300 μg/mL, n=9)

159   was 98.29 ± 1.82%. Limit of detection and limit of quantification were found to be

160   0.15μg/mL and 0.68μg/mL, respectively. Method calibration was performed with a

161   series of standard CLN solutions in 20% methanol in water. A linear response was

162   seen between 0.25 and 100 μg/mL (r^2 =0.9997).

163

164   2.4   Characterisation of films

165   2.4.1   X-Ray Powder Diffraction (XRPD)

166   Powder diffraction data were collected with a PW3830 diffractometer (Philips,

167   Netherlands) operated with Cu K-alpha radiation (λ = 1.540598 Å) at 45 kV and 30

168   mA. Scanning was performed from 5° to 30° 2θ at 0.02° step size and 2.85 seconds

169   per step. Xpert data viewer software (PANalytical B.V, Netherland) was used to

170   analyse the data.

171

172   2.4.2   Thermogravimetric analysis (TGA)

173   Measurements were performed with a Pyris-6 TGA (PerkinElmer, UK). Samples were

174   heated at 10°C/min using nitrogen as purge gas (20mL/min). Data collection and

175   analysis were performed using Pyris software (version 3.18). Mass loss (%w/w)

176   and/or onset temperature were calculated and reported as mean ± SD.

177

178   2.4.3   Fourier Transform Infrared (FTIR)

179   FTIR spectra were collected with a PerkinElmer Spectrum 100 FTIR spectrometer in

180   the range of 4000 to 650 cm^{-1} at ambient conditions. Spectra were analysed with

181   Spectrum Express software (application version 1.02.00.0014, 2008).

182

183   2.4.4   Tensile testing

184   An Instron Universal Testing Instrument (Model 5567, Instron Ltd, Norwood, USA)

185   was used to measure the mechanical properties of films (2cm x 2cm) at a rate of

186   10mm/min and 100N static load (2kg). The cut-off point was when the film was

187   completely separated into two pieces. The tensile strength and Young's modulus

188   were measured. Data were analysed using Bluehill software 2 (version 2.6).

189

190   2.4.5   Dynamic Mechanical Analysis (DMA)

191   A Q800 Dynamic Mechanical Analyser (TA instruments, Waters LLC) was used to

192   measure the mechanical properties of the films. Advantage software for Q series

193   version 2.8.0.394 was used to collect the data and TA Universal Analysis software

194   (V4. 7A TA 2000) to analyse the data. Samples were held in a film tension clamp.

195   Experimental parameters were amplitude, 15-20um; preforce load, 0.01N; force

196   track, 125%; frequency, 10Hz. Experiments were performed at 3°C/min from room

197   temperature to 200°C.

198

199   2.4.6   Polarised light microscopy (PLM)

200   A Nikon microphot-FXA light microscope was used to collect optical images with an

201   Infinity 2 digital camera and capture application software (version 3.7.5).

202

203   2.4.7   Dynamic Vapour Sorption (DVS)

204   Films were placed in a glass pan for Dynamic Vapour Sorption (DVS-1) (Surface

205   Measurement Systems, London, UK) at 30°C and kept at 0% RH for 90 minutes.

206   Relative humidity was then scanned from 0 to 95% with intervals of 5% RH over 10

207   minutes. The change of sample weight due to water uptake or loss was recorded

208   gravimetrically with the ultra-microbalance. The relative humidity (RH) around the

209   sample was controlled by mixing saturated and dry carrier gases (Nitrogen) with

210   electronic mass flow controllers.

211

212   2.4.8   Thickness and disintegration

213   Thickness of films (2cm x 2cm) was measured using a digital micrometer at five

214   points of each sample, at the four corners and the centre in triplicate, and reported as

215   mean ± SD.

216

217   The disintegration test described by Zhao et al (2009) for capsule and tablet coatings

218   was modified to suit oral films. A device was constructed to hold the film between two

219   clamps and a weight of 725mg was placed on top of the film. The disintegration

220   medium used was 15 mL (37 ± 1 °C) of a simulated saliva solution (Peh and Wong,

221   1999) containing Na_2HPO_4 (2.38 g), KH_2PO_4 (0.19 g) and NaCl (8 g) in distilled water

222   (1 L). The pH of the solution was adjusted to 6.75 with phosphoric acid. The time

223   taken for the film to break was measured by filming with a black and white CCD

224   camera (model ART-CAM-130MI-VM). Images were analysed with FTA 32 software

225   (Version 2.0, First Ten Angstroms Inc, USA). The disintegration time was calculated

226   as the time between adding the disintegration medium and visual observation of the

227   film breaking (n = 3).

228

229   2.4.9   *In vitro* drug release

230   Dissolution tests were conducted in a water-jacketed glass vessel (outer and inner

231   diameters of 8 and 6 cm, respectively and 150mL capacity). Films were placed on a

232   plastic sieve of 3cm in diameter and 40 mL of simulated saliva solution was used as

233   a dissolution medium. A PTFE magnetic stirrer was used for agitation (size of 10cm x

234   6cm) and the temperature was maintained at 37 ± 1 °C with the help of a

235   refrigerating/heating circulator with programmable digital temperature controller

236   (Polyscience, Division of Preston Industries, Inc., USA). Samples of 1mL were

237   collected at time intervals of 0.5, 1, 2, 4, 8, 12, 16 and 30 min and replaced with a

238   fresh medium kept at ~ 37 °C. Samples were then filtered through 0.45 μm filters and

239   analysed with HPLC in accordance with the method above.

240

241   2.5   Statistical analysis

242   Results were analysed and compared with Student t-test (α=0.05) using Origin® 8.6

243   software (OriginLab Corporation, USA).

244

245   **3.   Results and discussion**

246

247   3.1   Drug content and dose uniformity

248   The amount of CLN deposited by printing showed a linear correlation with the drug

249   feed solution concentration as shown in Figure 1 (r^2 = 0.9997). This is consistent with

250   the salbutamol sulphate (SS) data reported in an earlier study (Buanz et al, 2011).

251   Films prepared by blending CLN with the polymer and casting had a lower drug

252   content than films prepared by printing (Table 2). The variation of dose was higher

253   with solvent casting method (CV= 10.8 ± 6.0%) compared with printing (CV= 2.5 ±

254   2.2%). The higher dose variability in casted films may be a result of inhomogeneity in

255   blending or variability in film thickness, but the results immediately indicate the

256   potential utility of ink-jet printing for preparing low dose and narrow therapeutic index

257   medicines.

258

259   3.2   Characterisation of films

260   In general, pharmaceutical polymer films should have good flexibility, elasticity and

261   softness but possess enough strength to withstand mechanical stresses during

262   manufacturing and dispensing (Preis et al., 2013; Prodduturi et al., 2004). Hydrophilic

263   polymers are commonly used in pharmaceutical oral dosage forms (Prodduturi et al.,

264   2004), which generally means that exposure to humidity during storage and use can

265   affect their properties (Gontard and Ring, 1996). Here, mechanical testing and

266   polarised-light microscopy were used to characterise the films after manufacture and

267   following exposure to elevated humidity.

268

269   3.2.1   Tensile test

270   Tensile stress at the break point and Young's modulus were calculated for drug-

271   loaded films (Table 3). Films prepared by SC had higher tensile stress values, which

272   indicates that the films were harder than those made by TIJP (Garsuch and

273   Breitkreutz, 2010). Skulason et al (2009) reported that Carpabol films prepared by

274   SC have high tensile strength and low elasticity. In general, higher Young's modulus

275   values for films made by SC also reflect their increased brittleness (Biliaderis et al.,

276   1999).

277

278   Residual water in films can affect their mechanical properties and lead to increased

279   elasticity by its plasticizing effect (Karisson and Singh, 1998) and thus any variation

280   in water content between films prepared by TIJP and SC could be the reason for the

281   difference in their mechanical properties. However, as shown by values of water

282   content given in Table 3, the difference was not significant ($p > 0.05$). This suggests

283   that location of drug within the films is in fact the critical factor.

284

285   3.2.2   Glass transition measurement

286   XRPD patterns shown in Figure 2 confirm the amorphous nature of the free and

287   drug-loaded films. The glass transition temperature (Tg) of a polymer is one of the

288   important parameters that reflects its mechanical properties with temperature and is

289   associated with a small change in the heat capacity of the system due to the strong

290   glass forming properties of polymers (Fadda et al., 2010). There is no single

291   temperature at which Tg occurs; rather, the value depends on the technique and

292   experimental parameters used to measure it.

293

294   DMA was used to measure the glass transition temperatures of the films. Tg is

295   usually defined as a peak in the tan delta signal (the ratio of the storage to loss

296   moduli) or the inflection point of the decrease in storage modulus (Gontard and Ring,

297   1996). Here, it was not possible to use either point. The storage modulus data are

298   shown in Figure 3. It is apparent that there is an increase in storage modulus after

299   100 $^{\circ}$C. This is because the films lost water during heating and so became very

300   brittle. Similarly, there was no peak in the tan delta signal (data not shown) because

301   the polymers thermally degraded. This highlights one significant problem when using

302   thermal methods at slow heating rates. The increase in temperature acts to dry the

303   sample and since water is often a plasticiser the mechanical properties of the film

304   change during measurement. Hence, it was not possible to determine the Tg values

305   of the films.

306

307   FTIR data, however, did show evidence of CLN-polymer interactions at room

308   temperature (Table 4). Shifts are noticeable in the bands at 3274.8 (broad), 2941.6

309   and 1380.5 (from the free film) in the drug-loaded films, which can be assigned to

310   hydroxyl (OH) stretch, and carbon-hydrogen (C-H) stretch and C-H bend,

311   respectively (Coates, 2000), suggesting that the drug interacts with PVA but not with

312   SCMC, possibly through hydrogen bond with the PVA OH group. Larger shifts from

313   the free film values are seen in the case of SC samples, indicating the drug is more

314   dispersed in the polymer matrix than in the printed films. It is noticeable that the main

315   bands characteristic for CLN, such as the secondary amine N-H stretch, bend and

316   aliphatic secondary amine C-N stretch (at 3330, 1649 and 1338) are not seen, which

317   could be because they are masked by peaks from the polymers or because the drug

318   concentration is very low.

319

320   3.2.3   Critical humidity measurement

321   The critical humidity (cRH) is the humidity at a particular temperature that will cause

322   a phase transition (such as glass transition). Its determination is important along with

323   the threshold temperature in order to define the storage conditions required to

324   prevent phase changes during processing and storage (Burnett et al., 2004).

325

326   DVS is commonly used to determine cRH. cRH is usually taken to be the RH where a

327   reduction in mass is seen, corresponding to expulsion of absorbed water as the

328   sample crystallises. For CLN films the sample weight continued to increase with a

329   increasing of RH (Figure 4), and so it was not possible to determine a cRH value.

330   Presumably, this is because the majority of the sample is polymer. The method of

331   preparation (TIJP or SC) did not seem to have an effect on water sorption at lower

332   humidity as the changes of weight with time (and humidity) of both samples appear to

333   be superimposed. However, at higher humidity a higher weight increase is observed

334   for printed films. Possible reasons for this difference are discussed below.

335

336   3.2.4   Physical stability

337   Stability here refers to physical form rather than chemical degradation. Upon

338   exposure to increased temperature and/or humidity the films may absorb water and

339   be plasticised thus increasing the rate of molecular mobility of dispersed drug

340   molecules and potentially causing phase separation by crystallisation.

341

342   Films containing the highest doses of CLN (90 and 250 µg/strip) were subjected to

343   high temperature and humidity (60°C and 75 %RH) in the DMA for about 13 hours.

344   The DMA signal (storage modulus) did not change after initial equilibration to the test

345   parameters. This indicates that there was no significant change in the mechanical

346   properties of the films over the test period. However, PLM images (Figure 5) showed

347   clear signs of crystallisation in the 250 µg/strip prepared by SC. No such

348   crystallisation was observed for the lower dose film prepared by SC or films prepared

349   by TIJP.

350

351   In addition, the films used during the DVS and DMA experiments were also checked

352   with PLM (Figure 6). These films were exposed to relative humidity from 0 to 90% RH

353   at 30°C. No signs of crystallisation can be seen in films tested with DMA but clear

354   crystallisation is evident in the 250 µg/strip films prepared by SC tested with DVS and

355   the beginning of crystal growth is seen in the 90 µg/strip films. Drug in films prepared

356   by TIJP showed no evidence of crystallisation.

357

358   3.2.1   Disintegration and drug release

359   Typical disintegration times for ODFs range from 5 to 30 s (Banhart, 2008). There

360   have been several attempts to mimic *in vivo* conditions, particularly the low volume of

361   saliva, such as the slide frame method and the Petri dish method (Garsuch and

362   Breitkreutz, 2010; Hoffmann et al., 2011). Measurement of the contact angle with

363   time as a drop of water is placed on a film has also been used to assess

364   disintegration (Garsuch and Breitkreutz, 2009). The lack of official tests makes the

365   comparison between various published results a challenging task.

366

367　　Here, the images for film disintegration were captured with the help of a CCD

368　　camera, allowing precise time measurement. For the dissolution test a volume of 40

369　　mL was the lowest that allowed the film (placed on the plastic mesh) to float freely

370　　while the medium was mixed. The results of both tests are described below.

371

372　　The results from the disintegration test show that the time taken for the samples to

373　　disintegrate is in the range of 20 to 60 s (the time recommended by the FDA is 30 s,

374　　Centre for Drug Evaluation and Research, 2008). This means that some samples

375　　exceeded the recommended limit. The main factor for that would be the thickness as

376　　it is a key factor in determining the disintegration time (Garsuch and Breitkreutz,

377　　2010).

378

379　　Figure 7 shows the release profiles of films containing 250 µg/strip of CLN prepared

380　　by either TIJP or casting (SC) in simulated saliva fluid. It is noticeable that both

381　　samples achieved more than 50 ($t_{50\%}$) and 80% ($t_{80\%}$) of drug release within 8 and 30

382　　min, respectively. To compare the release profiles of films prepared by TIJP with

383　　films prepared by SC, difference (f_1) and similarity (f_2) factors were calculated from

384　　equations 1 and 2 (n = 3). f_2 can have a value of 0 to 100 where 100 means the

385　　profile of the tested product is the same as that of the reference and 0 means they

386　　are completely different (Costa and Sousa Lobo, 2001). The FDA adopted both

387　　factors as a way to assess the similarity of *in vitro* dissolution profiles where a value

388　　of 0 to 15 for (f_1) and 50 to 100 for (f_2) indicate the two profiles to be similar (Center

389　　for Drug Evaluation and Research, 1997). f_1 and f_2 for films containing 250 µg/strip

390　　prepared by TIJP were calculated to be 1.25 and 64.7, respectively, which means

391　　that the release profile of TIJP films is similar to that of films prepared by SC.

392

393　　$$f_1 = \{[\sum_{t=1}^{n}(R_t - T_t)] \, / \, [\sum_{t=1}^{n} R_t]\} \times 100 \qquad \textbf{Equation 3.1}$$

394 $$f_2 = 50\,log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\right\} \times 100 \qquad \textbf{Equation 3.2}$$

395

396 Where *n* is the number of data points and *R* and *T* are the cumulative release

397 percentages for the reference (SC) and the test (TIJP) films at time *t*.

398 The release kinetics of CLN from the films were examined with four mathematical

399 release models; zero-order, first-order, Higuchi and Hixson-Crowell models

400 (Equations 3 to 6) (Costa and Sousa Lobo, 2001). Where Q_t and Q_0 are the amount

401 released after time *t* and initial amount of the drug, respectively while *k* is the release

402 constant.

403

404 $$Q_t = Q_0 + Kt \qquad \textbf{Equation 3}$$

405 $$\ln Q_t = \ln Q_0 + Kt \qquad \textbf{Equation 4}$$

406 $$Q_t = K\sqrt{t} \qquad \textbf{Equation 5}$$

407 $$Q_t^{1/3} = Q_0^{1/3} + Kt \qquad \textbf{Equation 6}$$

408

409 The correlation coefficients (r^2) for films prepared by TIJP or SC are given in (Table

410 5). The highest r^2 value was for Hixson-Crowell model. This suggests that drug

411 release from both samples followed this model, which indicates drug release by

412 erosion (Costa et al., 2003). This could be a result of incorporating SCMC in the

413 formulation (Dabbagh et al., 1999; Hussain et al., 1994). This could be related to the

414 presence of ionisable carboxylic acid group in SCMC, which increases the dissolution

415 of the polymer (Hussain et al., 1994). Dabbagh et al (1999) noticed a decrease in

416 matric erosion when propranolol hydrochloride was added, which they suggested to

417 be a result of an interaction between the drug and the polymer. In this work the FTIR

418 data presented earlier suggest that clonidine hydrochloride interacts with PVA and

419 not SCMC in the tested films. This supports the suggestion that the carboxylic acid

420 groups of SCMC are available for ionisation and thus allows the polymer erosion.

421   Hussain et al (1994) also reported that when comparing the erosion rate of SCMC

422   matrices containing either a drug that interacts with the polymer or not, a faster rate

423   is observed when no interaction is present.

424

425   **4.   Conclusion**

426   The results indicate that films prepared by printing are significantly different in terms

427   of mechanical properties and stability compared with films prepared by casting. In

428   particular, the properties of the printed films are much more similar to those of the

429   free film. It seems likely that the process of solvent casting results in a molecular

430   dispersion of CLN throughout the polymer, analogous to a solid-amorphous

431   dispersion. FTIR data confirm chemical interaction between the drug and the

432   polymer. The drug appears to exert an anti-plasticising effect, increasing the

433   brittleness of the film. When stored at elevated temperature and humidity the drug is

434   seen to phase separate, resulting in crystal formation.

435

436   The exact nature of the printed film is harder to elucidate from the data. It is clear that

437   immediately after printing the drug will be present in solution as droplets on the

438   surface of the polymer film. Previous experience with printing drug solutions (Buanz

439   et al, 2013) has shown us that the small droplets evaporate very quickly, resulting in

440   formation of small (<5 μm) crystals. Thus, a reasonable hypothesis would be that in

441   the printed films the drug exists either on the surface or in the top layer of the film as

442   small crystallites. The drug is thus not acting as an anti-plasticiser and so the

443   mechanical properties of the printed film remain similar to those of the free film. The

444   printed film appears amorphous by XRPD because the drug content is low and small

445   crystals do not diffract sufficiently to appear in the pattern. Upon storage at elevated

446   temperature and humidity the printed film remains stable because it has already

447   phase separated. Again, it is likely that the small size of any crystallites mean they

448   were not visible with PLM.

449

450   Janßen et al (2013) did not observe any effect on the mechanical properties of films

451   upon printing drug solutions using flexographic printing. They argue that in

452   manufacturing oral films by this method the properties of the plain films can be

453   assessed and it would not be necessary to evaluate the medicated films, which they

454   envisage to add flexibility to the manufacturing process. Our work indicates a similar

455   conclusion can be drawn in regard to ink-jet printing.

456

457

458 **5. References**

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567

568

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

569

570 **Table 1. Clonidine hydrochloride doses and the required solution**

571 **concentrations used for depositing the drug by TIJP.**

572

Target conc. (µg/strip)	Calculated Concentration (µg/strip)					
	SC (weight-based)		SC (area-based)		TIJP (area-based)	
	Mean ± SD	% Difference	Mean ± SD	% Difference	Mean ± SD	% Difference
7.6	9.9 ± 1.3	30.1 ± 17.4	10.6 ± 0.5	39.1 ± 6.5	12.2 ± 0.4	60 ± 5.0
18	26.0 ± 2.6	44.3 ± 14.3	18.6 ± 1.0	3.5 ± 5.8	19.1 ± 1.1	5.9 ± 5.9
38	31.1 ± 15.0	-18.3 ± 39.5	30.3 ± 6.5	-20.3 ± 17	36.5 ± 1.7	-4 ± 4.4
50	51.8 ± 2.3	3.6 ± 4.5	42.7 ± 4.3	-14.7 ± 8.5	45.9 ± 0.1	-8.1 ± 0.3
90	116.7 ± 43.5	29.4 ± 48.3	73.5 ± 8.4	-18.3 ± 9.3	80.4 ± 0.4	-10.7 ± 0.4
250	226.7 ± 5.8	-9.3 ± 2.3	203.9 ± 23.9	-18.4 ± 9.6	252.8 ± 2.5	1.1 ± 1

573

574 **Table 2. A comparison between drug content in films prepared by SC and TIJP**

575 **methods.**

576

577

Sample	Free film	250 µg/strip	
		SC	TIJP
Tensile stress (MPa)	19.3 ± 2.9	41.9 ± 1.9	25.2 ± 1.1
Young's modulus (MPa)	547.8 ± 54.2	1423.8 ± 259.1	658.2 ± 127.6
Water content (%w/w)	8.9 ± 0.1	5.8 ± 0.3	6.6 ± 1.1
Thickness (mm)	0.1 ± 0.02	0.1 ± 0.01	0.1 ± 0.01
Disintegration time (seconds)	NA	23.3 ± 5.6	30.5 ± 4.6

578

579 **Table 3. Mechanical properties, water content, thickness and disintegration**

580 **times for films prepared by SC or TIJP methods.**

581

582

583

Sample	TIJP 250 µg/strip	SC 250 µg/strip	Free film	PVA powder	SCMC powder	CLN powder
Wavelength (cm^{-1})	3276.4	3270.8	3274.8	3278.7	3266.8	3330.8
	2938.0	2922.4	2941.6	2942.6	NA	3082.5
	2915.8	2913.6	2917.9	2907.7	2902.7	3041.7
	1594.8	1594.5	1593.6	1417.2	1589.4	2987.1
	1415.2	1414.8	1415.3	1420.0	1413.7	2950.0
	1378.7	1375.9	1380.5	1377.8	NA	2800.0
	1321.6	1321.5	1322.0	1323.7	1324.1	2741.2
	1092.3	1091.0	1092.3	1141.8	NA	1649.3
	1037.7	1036.1	1038.5	1088.3	1037.3	1606.4
	919.7	919.3	919.7	917.0	NA	1581.1
	848.2	847.3	847.1	833.4	NA	1445.5
	NA	NA	NA	NA	NA	1435.3
	NA	NA	NA	NA	NA	1494.0
	NA	NA	NA	NA	NA	1337.6

584

585 **Table 4. Main FTIR transmittance peaks of drug-free films and films containing**

586 **250 µg/strip prepared by SC or TIJP.**

587

Sample	SC			TIJP		
	r^2	b	a	r^2	b	a
Zero-order	0.891	2.2	26.7	0.881	2.2	26.7
1st order	0.747	0.05	3.3	0.685	0.05	3.3
Higuchi	0.988	14.4	9.6	0.983	14.0	10.0
Hixson-Crowell	0.997	29.7	6.8	0.996	29.0	6.2

588

589 **Table 5. Regression values for the dissolution profiles for 250 µg/strip CLN**

590 **films (r^2 is the correlation coefficient, a is the intercept and b is the slope).**

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The plot shows:
- Y-axis: Drug deposition/μg per strip (0 to 350)
- X-axis: Clonidine hydrochloride concentration in feed solution/mg.mL^{-1} (0 to 50)
- $r^2 = 0.9997$
- $y = 6.3351x - 0.411$

595
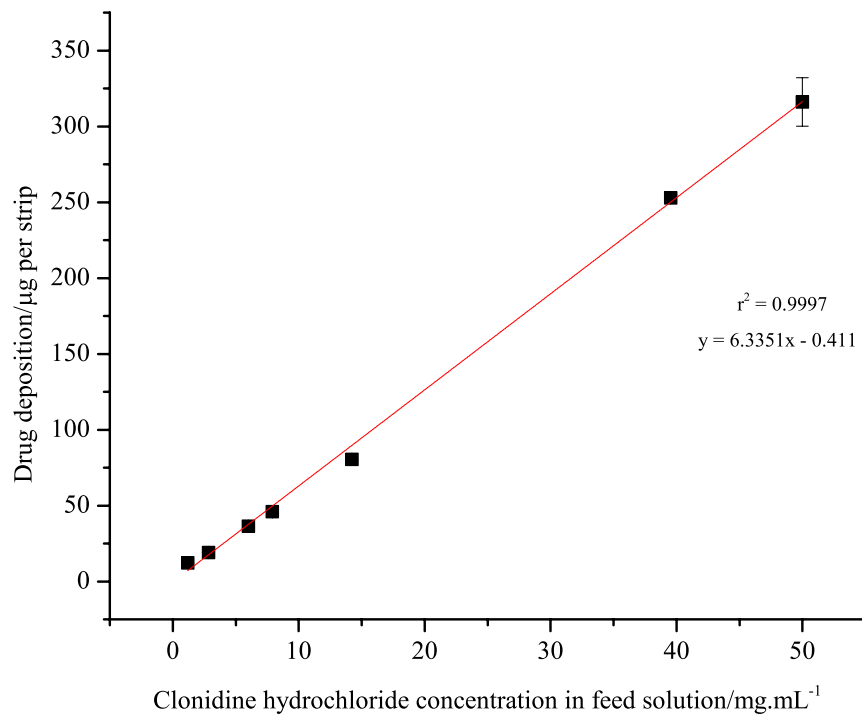
Figure 1. Amount of clonidine hydrochloride deposited as a function of feed solution concentration (some error bars are too small to appear on the graph)

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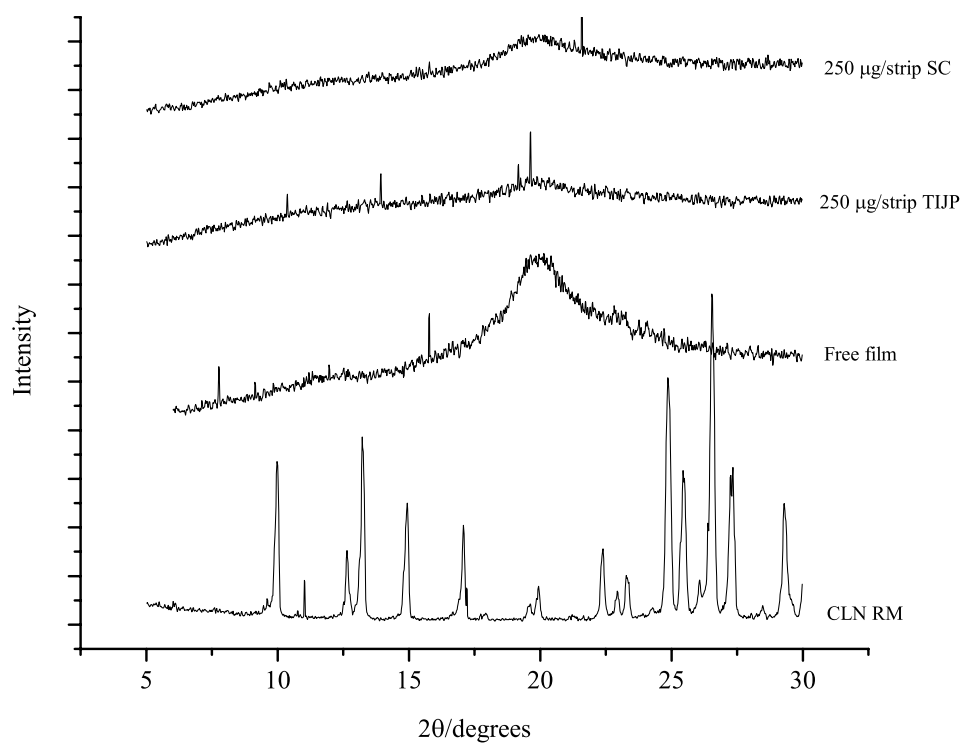
Figure 2. XRPD patterns of medicated films prepared by SC or TIJP in comparison to CLN raw material and the free film.

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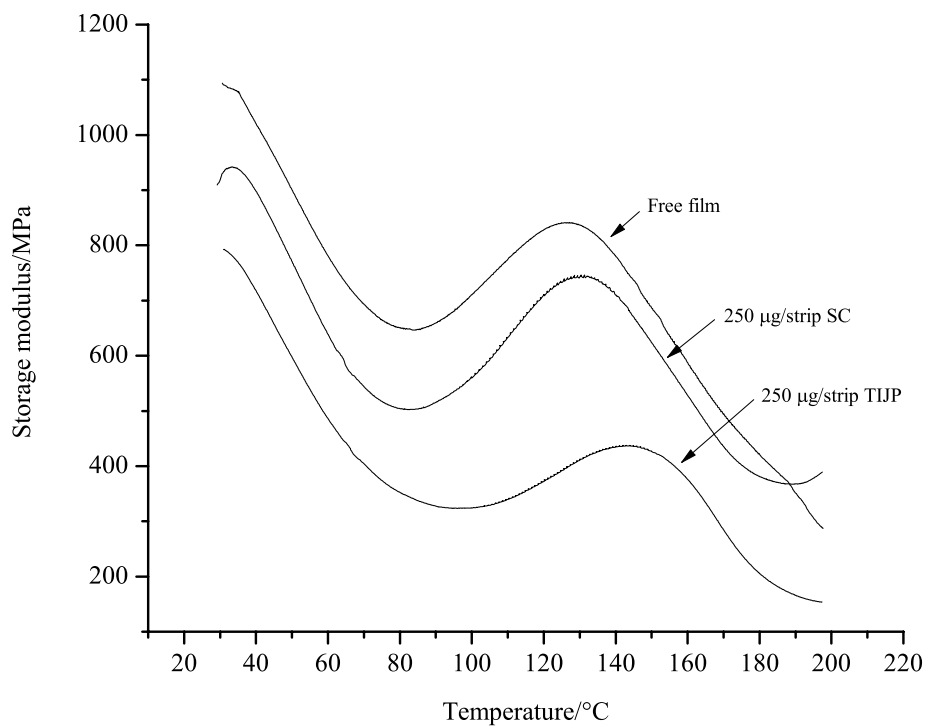
Figure 3. Storage modulus as a function of temperature for drug-free films and films containing 250μg/strip prepared by SC or TIJP methods.
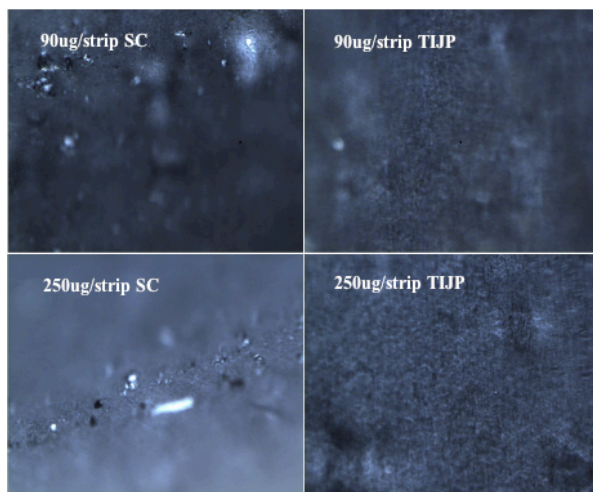
608
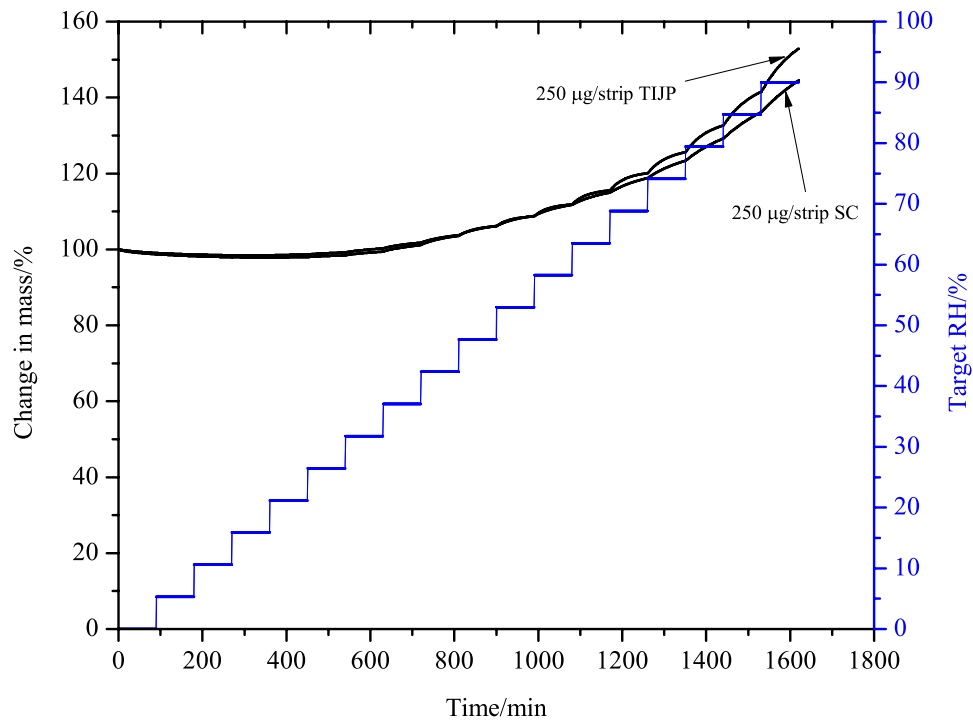
Figure 4. DVS results of relative humidity (RH) scan for films containing 250

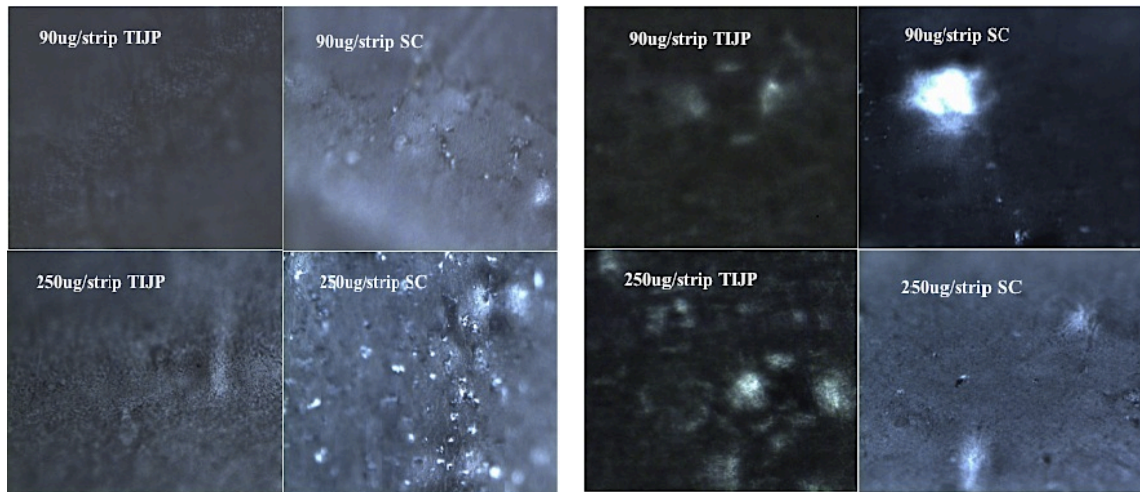**μg/strip prepared by SC or TIJP methods.**

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Figure 5. PLM images of films after being tested with isothermal constant humidity experiments (60°C and 75% RH) in the DMA.
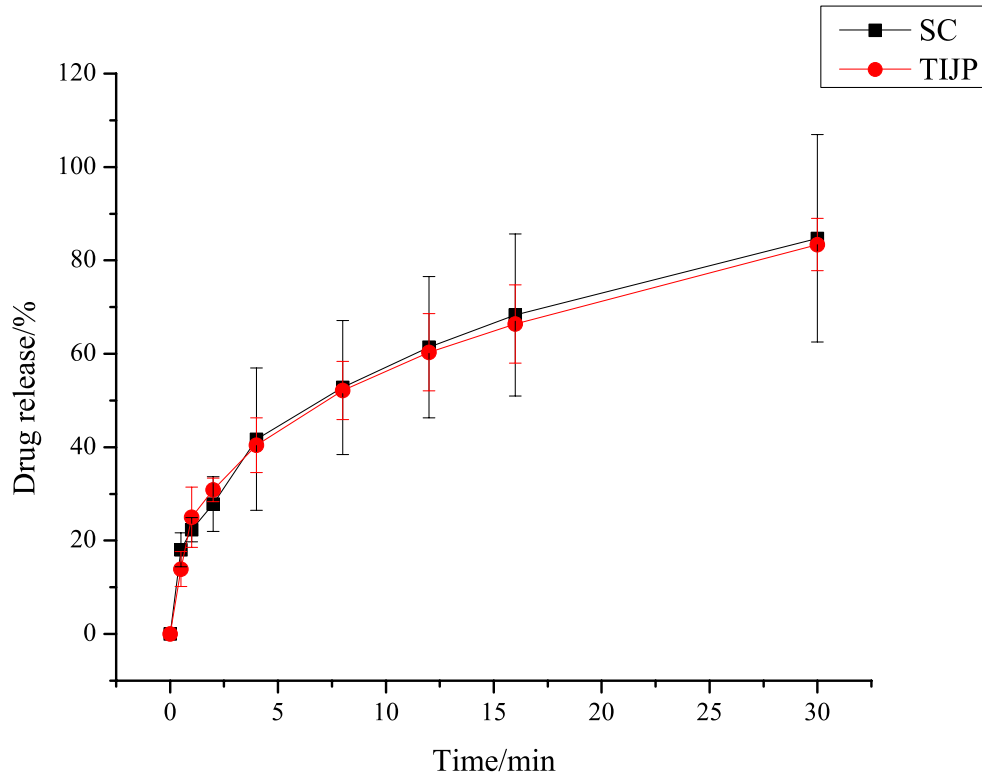
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Figure 6. PLM images of films subjected to RH scan at 30°C in (left) DVS and (right) DMA.

625

Figure 7. Dissolution profiles for films containing 250 µg/strip CLN prepared by

SC or TIJP methods (n = 3).

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