

20 **Abstract:**

21 Ink-jet printing is a versatile, precise and relatively inexpensive method of depositing small
22 volumes of solutions with remarkable accuracy and repeatability. Although developed
23 primarily as a technology for image reproduction, its areas of application have expanded
24 significantly in recent years. It is particularly suited to the manufacture of low dose medicines
25 or to short production runs and so offers a potential manufacturing solution for the paradigm
26 of personalised medicines. This review discusses the technical and clinical aspects of ink-jet
27 printing that must be considered in order for the technology to become widely adopted in the
28 pharmaceutical arena and considers applications in the literature.

29

30 **Key words:**

31 Ink-jet printing; pharmaceutical; narrow therapeutic index; personalised medicine;
32 piezoelectric printer

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34

35 **1. Introduction**

36 How should medicines be delivered in the 21st century? Should the tradition of mass-
37 producing dosage forms aimed at the general population remain or is there the opportunity
38 to design bespoke medicines, with doses and/or drug combinations tailored to individual
39 patients? There is growing awareness of the limitations of mass-produced medicines and at
40 the same time new technologies are being developed that offer tantalising glimpses ahead
41 of a vision where medicines can be made more personal. One of those technologies is ink-
42 jet printing, which offers the potential to deposit very small doses of drugs onto unit dosage
43 forms. Moreover, printing medicines offers the potential to manufacture individual dosage
44 forms, which can vary in dose for each patient. The purpose of this review is to explore the
45 potential of printing medicines in developing the paradigm of personalised-dose medicines,
46 with specific focus on considering how each step in the printing process might be impacted
47 by pharmaceutical requirements.

48

49 **1.1 Drug delivery and need for personalised medicine**

50 Personalised medicine has become a frequently used term yet it does not have a clear
51 definition. It is often linked to genomics (Fierz, 2004; Lee, 2010), the effects of the genome
52 on response to medicines, and so to the potential of identifying patient groups with different
53 responses to drugs and tailoring treatments to them. This view of personalised medicine is
54 often criticised for being narrow and not providing a holistic view because it excludes
55 aspects such as delivery of the active pharmaceutical ingredient (API) (Møldrup, 2009; Fierz,
56 2004). Indeed, it has been speculated that the benefits from developments of diagnostic and
57 molecular biology might be lost unless more means of personalised medicine delivery are
58 developed (Florence and Lee, 2011). Such development will require new methods of
59 manufacture, capable of producing products in small numbers.

60

61 An alternative definition of personalised medicine is the dosing and delivery of medicines to
62 individuals in a safe and effective manner. The Medicines and Healthcare Regulatory
63 Authority (MHRA) recognises the importance of correct dose delivery by defining
64 personalised medicine as the individualisation of drug therapy in both choice and dose
65 (MHRA, 2006; Reidenberg et al. 2003). Crommelin et al. (2011) define personalised
66 medicines and note that such therapies are distinct from mass-oriented delivery systems.
67 Florence and Lee (2011) also argue that personalised medicine must mean more than
68 simply new drugs matched to the genetic profiles of patients; rather it should include an
69 enhanced method of delivery of these drugs to patients and patient groups. In essence,
70 therefore, personalised medicine covers all aspects of treatments meaning individualised
71 dosing delivery systems are important components.

72

73 According to Hippocrates, treatment of the individual aspects of the patient supersedes that
74 of the underlying pathophysiology in his advice to future generations 'to treat the person not
75 the disease'. Such treatment requires more than just efficacious medicines but an effective
76 and personalised delivery system consistent with humans being diverse and with a
77 continuum of dosing needs, rather than discrete entities which are catered for by the
78 currently available oral solid dosage forms which are present in distinct strengths, not
79 reflective of the population's true drug distribution diversity (Florence, 2010).

80

81 Oral solid doses are mass-manufactured in predefined strengths, which are chosen during
82 early clinical trials to exert a therapeutic effect in the greatest portion of the population
83 (Cohen, 2001; Pardeike, 2011; Herxheimer, 1991). An example is the production of
84 fluoxetine (Prozac®). The manufacturer chose a dose of 20 mg for mass production as it
85 exerted an effect in 64% of the target population; however 54% had shown a beneficial
86 effect at 5mg and the lower dose has been reported to result in fewer adverse effects and
87 dropout rates during the trials than did the higher dose (Cohen, 1999).

88

89 After medicines are introduced, they begin to be used for a wider population and greater
90 diversity of indications, and the inflexibility of fixed dose forms begins to appear. An example
91 is the antihypertensive atenolol, introduced in 1976 in only 100 mg tablets. Elderly patients
92 required lower doses so, in 1980, 50 mg tablets were introduced followed by the release of
93 25 mg tablets in 1989 (Herxheimer, 1991). At the individual patient level, Pies (1995) reports
94 the case of zolpidem, which was prescribed to an insomniac using the lowest available 5 mg
95 dose. The dose did not achieve a sufficient quality of sleep, so the available 10 mg tablet
96 was prescribed instead. Adverse effects ensued, diminishing the patient's acceptability of the
97 therapy with the drug. A 7.5 mg dose has been suggested to meet the patient's need, but a
98 tablet of such strength does not exist.

99

100 Patients' responses to doses vary widely and providing such a diverse population with
101 limited doses will inevitably result in groups experiencing the desired therapeutic outcome
102 and others receiving higher or lower doses than required, causing either adverse effects or
103 inadequate therapeutic levels (Cohen, 2002). The prevalence of adverse effects due to
104 untailored therapy has been estimated to be anywhere from 75-85% (Cohen, 1999). Discrete
105 strengths are inadequate in providing the precise dose needed for the majority of patients,
106 as the response can vary 10-30 fold or more amongst those administering the dose (Ma and
107 Lu, 2011; Cohen, 1999).

108

109 Personalisation for paediatric and geriatric patients is in dire demand. Dosing requirements
110 change due to the fast changes in physiological and metabolic functions in the former and GI
111 pathologies, body fat and renal clearance changes in the latter (Florence, 2010). In the case
112 of the elderly, personalisation is further complicated with polypharmacy and co-morbidities;
113 patients aged 65 years or more take on average 13 medicines and as many as 28 (Florence
114 and Lee, 2011). This further emphasises the need for strict dose control, to reduce the
115 potential for interactions and ensure effective treatment.

116

117 **1.2 Current approaches to dose personalisation**

118 The ideal personalised dosing method should be simple, accurate, cheap and best suited for
119 the greatest number of patients (Wening and Breitzkreutz, 2011). Solid dosage forms, like
120 tablets, are amenable to personalised dosing by means of splitting; however, this can result
121 in variation in the drug content each part contains (Hill et al., 2009). Pharmacists and
122 pharmacy students were also unable to split tablets in a way that resulted in an acceptable
123 dose variation of the split tablets (Rosenberg et al., 2002; van Riet-Nales et al., 2014).
124 Different methods to split tablets will result in excessive variation whether split by hand,
125 knife, scissors or tablet splitters (Verrue et al., 2011; Shah et al., 2010; van Riet-Nales et al.,
126 2014).

127

128 Liquid dosage forms are considered to be suitable for personalised dose production by
129 volume-dose calculation, assuming a homogenous drug product (Brown et al., 2004).
130 Volume is measured by dosing aids usually accompanying the medicine. These aids come
131 at an affordable cost but have been associated with a number of potential sources of
132 inaccuracies, such as counting errors for drops, shape effects of the spoon on dosing
133 accuracy and confusing graduations on syringes and measuring cups (Grießmann et al.,
134 2007; Walsh et al., 2011; Yin et al., 2010). Furthermore, those methods also require the
135 patient's and/or carer's dexterity and cognition to dose precisely and accurately (Peek et al.,
136 2002).

137

138 Against this background, ink-jet printing offers significant potential, because it can be used to
139 deposit a large range of doses onto generic substrates (such as tablets or oral wafers) with
140 fine control of dose. It is also capable of producing single dosage forms and so its
141 development could herald a new future for manufacturing personalised doses. There are an
142 increasing number of reports in the literature of ink-jet printing being used to manufacture
143 medicines (Kolakovic et al, 2013), but for its use to become widespread consideration must
144 be given to the specific requirements of manufacturing pharmaceutical products.

145

146 **2. Ink-jet printing**

147 Lord Rayleigh first discussed the basics of an ink-jet system in the nineteenth century,
148 describing the breaking of a liquid stream (jet) into droplets (Basaran and Suryo, 2007). The
149 concept has been developed into technology that can dispense continuous streams of
150 droplets, known as continuous ink-jetting (CIJ) (Priest et al., 1997). An alternative method is
151 drop-on-demand (DOD) ejection of droplets (Wang and Bokor, 2007), which produces
152 precise droplets at high speeds when needed (Elele et al., 2012). Due to its relative
153 simplicity, lower cost and high precision, DOD printing is favoured over continuous inkjet
154 printing in desktop printer markets, and it is the technology that is most often used in printing
155 applications (Le, 1999; Pond, 1996; Jang et al., 2009). The two main technologies of DOD
156 printers are piezoelectric and thermal (or bubblejet) printing (Day and Shufflebottom, 2001).

157
158 Thermal inkjet printing (TIJ) uses brief heat pulses generated by a resistive element to jet
159 fluid (Goodall et al., 2002). Each print head contains a micro-resistor which heats up rapidly
160 on receipt of electric pulses, forming a superheated vapor bubble, as shown in Figure (1).
161 The vapor bubble expands, forcing out the fluid from the nozzle and producing a droplet.
162 The vapor bubble then collapses, creating a partial vacuum that pulls fluid from the ink
163 reservoir to refill the thermal inkjet chamber (Meléndez et al., 2008). The temperature at the
164 surface of the resistor can reach up to 300 °C, but such high temperatures exist for only a
165 few ms and only ca. 0.5% by volume of the sample is exposed, so the technology does not
166 usually degrade thermally labile components.

167
168 In piezoelectric printing, each nozzle is surrounded by a piezoelectric element usually made
169 from lead zirconate titanate (PZT). When a voltage is applied to the element, it deforms,
170 creating pressure waves leading to the ejection of the fluid (Sumerel et al., 2006). Once the
171 element returns to its normal shape, the nozzle refills with ink, ready to be reactivated
172 (Figure 2) (Scoutaris et al., 2011).

173
174 Irrespective of the technology, ink-jet printers jet, on demand, a precisely controllable volume
175 of solution to definable coordinates on a substrate (Arney, 2010). Where the 'ink' is a
176 solution of an API, varying the volume of solution jetted and/or changing the concentration of
177 the feed solution determines the amount of drug deposited (Bohórquez, 1994). Printing is
178 especially valuable in minimising wastage of expensive drugs (Tarcha et al., 2007). Because
179 of this versatility ink-jet printing has been used in a wide range of applications, including
180 deposition of large human cells (Wilson and Boland, 2003), cartilage fabrication (Cui et al.,
181 2014), DNA array fabrication (Okamoto et al., 2000), polymer deposition (de Gans et al.,

182 2004) and in drug discovery (Zhu et al., 2012). Ink-jet printing has also been used as a
183 method to load a microneedle array with miconazole (Boehm et al, 2014).

184

185 **3. Pharmaceutical applications of ink-jet printing**

186 Ink-jet printing of medicines is growing in popularity, as the increasing number of
187 publications over the past two decades shows (Figure 3). One reason for the growing
188 popularity of the technique is its versatility in depositing liquids for different applications, the
189 relative ease with which it can be controlled by computer and the repeatability with which it
190 dispenses volumes of liquid.

191

192 The most immediate potential of ink-jetting for personalised medicines is as a technology for
193 extemporaneous manufacturing of unit doses. Clinical teams can choose the exact dose
194 needed by the patient and then print it in the pharmacy ready for dispensing. Once entered
195 into the printer software, the dose can be deposited onto a substrate suitable for human
196 administration (such as an oral wafer or tablet core). However, manufacture of medicines is
197 an intricate and regulated process involving a number of key elements, including ensuring
198 stability, dose and sterility and must be performed under conditions of good manufacturing
199 practice (GMP). The key steps in the printing process must be considered and understood
200 within this manufacturing framework.

201

202 **3.1 Before Printing**

203 The first requirement is to formulate the API into a solution with suitable properties to be
204 jetted by the print head. Clearly, the physicochemical properties of the solution will be
205 dependent upon the printer system used and whether it is of the thermal or piezoelectric
206 type. Issues arising from suboptimal formulation include puddling (ink rushing with
207 momentum overflowing drop generators and nozzles), ink spooling (coalescing of drops upon
208 printing) and feathering (excessive spreading) (Stringer and Derby, 2010; Bohórquez, 1994).
209 Solvent selection is also critical and is usually dependent on drug solubility. A wide range of
210 solvents has been printed, Table 1. One point to note is that in general aqueous solutions
211 are more easily jetted with a thermal printer while PZT systems are more suited to organic
212 solvents. Rajjada et al., (2013) make the sensible suggestion that the concentration of the
213 drug should be kept below its solubility to reduce the risk of clogging of the nozzles.

214

215 The viscosity and surface tension of any solvent mixture are very important. The surface
216 tension should be high enough to enable the formation of spherical droplets and to resist
217 leakage from the print head when the printer is not in operation. The viscosity should be low
218 enough that the fluid can be jetted but sufficiently high that it is not ejected too early, which

219 can lead to the formation of a tail, producing satellite droplets (Pardeike et al., 2011;
220 Hirshfield et al., 2014). Satellite drops (also known as secondary drops) not only affect
221 formation of the primary droplet, but may also impact the location of drug deposition on the
222 substrate. It is important that drops land in their designated coordinate on the substrate,
223 because otherwise dose uniformity cannot be assured. Ideally a satellite drop would
224 recombine with the primary drop or fall not far away on the substrate (Shimoda, 1996;
225 Hirshfield et al., 2014). Viscosity and surface tension also affect the refilling phase of the
226 drop generator as the solution passes through spouts into the nozzle firing chambers
227 (Bohórquez, 1994).

228

229 Clearly, the ranges of suitable values for surface tension and viscosity will depend on the
230 printer being used. Table 1 shows a list of drugs and formulations that have been printed,
231 and their viscosities and surface tensions. Figures 4 and 5 show the viscosity and surface
232 tension values for solutions against the technology used to print them; no obvious patterns
233 are seen for the different printers involved, which means solutions must be optimised in each
234 case. Of course, this assumes the parameters of the printer are fixed. Some printer systems
235 allow user-control of the parameters (such as the droplet generating wave-form or the
236 pressure above the print solution) and so can be tuned to print a particular solution (Pond,
237 1996). For example, a piezoelectric print head is operated by a driving waveform, which can
238 be manipulated to control the volume of droplet dispensed for solutions of different
239 viscosities and surface tensions (Doraiswamy et al., 2009).

240

241 Excipients may be added to the solvent to obtain a solution with suitable viscosity and
242 surface tension. Glycols such as propylene glycol (PG), polyethylene glycol (PEG) and
243 glycerol are the most commonly used viscosity modifiers (Genina et al., 2012; Genina et al.,
244 2013a; Sandler et al., 2011). The compatibility between the chosen glycol and the jetting
245 liquid should be inspected. Genina et al. (2012) found that riboflavin, which is highly soluble
246 in water, precipitated in the presence of polyethylene glycol; glycerol was thus used instead.
247 An additional benefit of using glycols is their role in reducing the evaporation of the solvent,
248 as they act as humectants (Raijada et al., 2014). Rapid evaporation of the solvent can lead
249 to the clogging of the nozzle due to the precipitation of the components of the formulation at
250 the nozzle's tip. Polyethylene glycol, however, has been reported to have central nervous
251 system-related adverse side effects in children in large doses (Walsh et al., 2011).

252

253 Ethanol has been used at high concentrations in a number of studies (for instance, 60% v/v,
254 Raijada et al., 2013; 80% v/w Meléndez et al., 2007; and 95% v/v, Scoutaris et al., 2011).
255 FDA guidelines stipulate that medicines should not produce a blood concentration of more

256 than 25mg/100ml of ethanol, and over-the-counter preparations of ethanol cannot contain
257 more than 5% v/v ethanol. Ethanol is a central nervous system depressant (Zuccotti and
258 Fabiano, 2011) and so it is desirable to avoid its use in formulations.

259

260 From a pharmaceutical perspective, the shelf-life of the jetting liquid should extend beyond
261 the time required for production of many doses but the issue of stability is often not the focus
262 of the literature. A notable exception is the study by Pardeike et al. (2011) who evaluated the
263 stability of a nanosuspension for the deposition of the poorly-water soluble drug folic acid.

264

265 **3.1.1 Dose flexibility**

266 The ability to dispense a wide range of doses covering different patient populations is one
267 requirement of a successful flexible dosing system (Wening and Breitzkreutz, 2011). A dosing
268 model defines the relationship between an independent variable and the final formulation
269 and may be limited by the capacity of the printer. An example of a model with fixed
270 limitations is provided by Genina et al. (2013b), in which the spaces between deposited
271 droplets are varied to control the total dose. The limited selection of settings controlling the
272 drop spacing ultimately fixed the range of doses that could be printed. Conversely, Buanz et
273 al. (2011) found a linear relationship between the concentration of the jetting solution and
274 the resulting dose. Despite the narrow range of the dose achieved, in theory the system
275 could be set up to print any desired dose, by careful selection of the jetting solution
276 concentration.

277

278 Another parameter that has been used to control the dose deposited is to change the area
279 printed (Genina et al., 2013b; Buanz et al., 2011). When deposited onto an orodispersible
280 film, the medicine needs to achieve a therapeutic dose in an area with administrable
281 dimensions (Dixit and Puthli, 2009). The administrable area of orodispersible films ranges
282 from 1 – 20 cm², with children aged 6 months and above being able to take films of 6 cm²
283 (Bala et al., 2013; Orlu-gul et al., 2014).

284

285 **3.1.2 Substrates**

286 Substrates are an administrable carrier on which the drug solution is printed. For oral
287 administration it is important that the substrate can be ingested. While the ability to jet many
288 drugs has been demonstrated, some studies do not deposit the active onto substrates fit for
289 human consumption. Table 2 lists the substrates used in the literature. The use of a range of
290 different substrates, including edible substrates such as icing sheets, polymeric and starch
291 films and non-edible substrates, such as paper and acetate, has been reported.

292 Initial studies usually focus on the practical and technical aspects of printing particular
293 solutions with less attention given to the substrate. However, as printed dosage forms
294 progress in development, consideration of edible substrates is vitally important. It is also
295 becoming evident that the nature of the substrate can determine the polymorphic form of any
296 crystals produced as the solvent evaporates. For instance, Hsu et al (2013) noted that the
297 substrate affected the crystallisation of naproxen when printed onto various solid amorphous
298 dispersions while Buanz et al (2013) used ink-jet printing as a screening method for isolating
299 pharmaceutical co-crystals.

300

301 As the field grows and ink jetting is established as a method of dispensing medicines,
302 expanding on patient-acceptable edible substrates will be the next step in the development
303 of individualised doses. The acceptability of the dosage form is a key element in compliance
304 to the therapy and can influence the safety and efficacy of the therapy (EMA, 2011). A future
305 opportunity is the capacity for the substrate choice to influence the release profile of the
306 administered medicine, assuming an ingestible dosage form is produced. The impact of
307 employing substrates of different flavours could also be of potential for orodispersible
308 substrates.

309

310 **3.2. During printing**

311 **3.2.1 Dose and placement accuracy**

312 One of the advantages of inkjet printing is the precise deposition of liquids, both in terms of
313 volume and placement (Akagi et al., 2014). Placement accuracy refers to the printer's ability
314 to place drops on the desired coordinates of a substrate with accuracy; this factor is relevant
315 both in terms of controlling dose but also in terms of appearance. Printers deliver droplets
316 consistently within small tolerances. For instance, HP's Optical Media Advance Sensor
317 (OMAS) achieves placement accuracy of ± 0.1 mm (Casaldàliga et al., 2011). Dosing
318 accuracy in the drug delivery context refers to the deviation of the predicted dose from the
319 observed one. Ink-jet printers would be expected to deposit solutions with very high
320 accuracy and, indeed, many studies do report low standard deviations, often less than 5%
321 (Hirshfield et al., 2014; Buanz et al., 2011; Rajjada et al., 2013; Sandler et al., 2011).

322

323 However, deviations in printed dose have been reported in the literature. For instance,
324 Buanz et al. (2011) attempted to increase the amount deposited onto a substrate by placing
325 it back into a printer multiple times. A clear deviation from the predicted dose was seen and
326 it was argued that this was due to the contact of the substrate with the rollers of the printer.
327 Genina et al. (2013a) observed high standard deviations in deposited drugs that were
328 unacceptable (maximum deviations of 11.8%, 24.3% and 34.9% for copy paper, acetates

329 and orodispersible films respectively). It was also argued this was due to smearing from
330 printer head from printing multiple passes. Similarly, Genina et al. (2013b) used a PZT
331 printer to deposit solutions of loperamide and caffeine on edible substrates. The maximum
332 loperamide variation was 11.5% exceeding the pharmacopoeial limits of 5% (BP, 2014a).
333 The variation for caffeine was much lower at 3.6%. When theophylline was printed onto a
334 range of substrates the relative standard deviations were (RSD) $\pm 5.1\%$, ± 6.3 and ± 6.25 for
335 copy paper, coated paper and PET films substrates respectively. All were outside the BP
336 content variation limits of $\pm 5\%$ for theophylline tablets (BP, 2014b; Sandler et al., 2011). A
337 wide variation in the dose dispensed could potentially compromise the therapeutic outcome.
338 It is especially important when printing actives with a narrow therapeutic index, a subgroup
339 for which ink-jet printing is ideally suited.

340
341 Many of the publications printed on copy paper. Genina et al. (2013a) found that printing on
342 copy paper produced low standard deviations, potentially due to the absorptive nature of the
343 substrate; with copy paper designed for printing, the ink can penetrate into the paper
344 avoiding smearing. This perhaps highlights an area for future consideration; to develop
345 substrates that readily absorb printed solutions. It is important to note here that many of
346 these studies used off-the-shelf printers that are not designed for printing pharmaceutical
347 solutions, but the principle remains that an ink-jet printer jetting a solution with optimal
348 physicochemical properties should better the BP limits in the majority of cases.

349

3501. **3.2.2 Dose printing time**

351 This is defined as the time required to produce the final dosage form and it is a relevant
352 criterion because extemporaneous dispensing can be inconvenient for patients if waiting for
353 a lengthy amount of time is involved. Since printing technology has evolved to produce prints
354 at high speed, most reports cite short times for dose production. Meléndez et al. (2007)
355 calculated that to deposit 8mg of API onto 5.08cm x 1.27cm (2"x0.5") substrate took a total
356 of 2 minutes, while Genina et al., (2013a) took only a few seconds to print a row of five
357 16mm x 26mm rectangles. Tarcha et al., (2007) jetted fenofibrate onto a stent; they
358 determined that the whole process, on average, took between 6.5 and 7 minutes using a
359 PZT printer, although the actual dispensing of the drug itself took less than 2 minutes.
360 Rajjada et al., (2013) conversely, reported printing samples overnight.

361

362 The throughput (total volume deposited per unit time) and therefore the printing time
363 depends on the printer system used, the dose and the jetting patterns (Beeson, 1999);

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365 *Throughput \propto Number of nozzles \cdot firing frequency*

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The drop generation speed (measured in Hertz) has been increasing as technology has developed to minimise the jetting time. For example, for TIJ it has grown from 6.25kHz (Shimoda, 1996) to 10 kHz (O'Horo et al. 1996) and then 36 kHz (Bruch, 2002). Modern printers can function at even higher frequencies and purpose-built high throughput PZT printers are able to generate droplets at 100 times greater than the conventional printers, (Ehtezazi et al., 2014). The number of nozzles has also increased, with TIJ printers often reporting higher nozzle counts and packing density per the same unit area than PZT printers (Wang and Bokor, 2007).

377 **3.2.3 Maximum achievable dose**

378 Once printing is initiated, it is important to achieve a dose that can produce the therapeutic
379 level required to achieve the clinical outcome. Printers are designed to dispense low
380 volumes of intensely coloured inks (Gregory, 1996). This may have contributed to some of
381 the trials not achieving therapeutic levels, Table 3. Many studies did, however, achieve
382 doses within the therapeutic range, albeit slightly limited. For example, Naproxen was
383 dispensed by Hirshfield et al. (2014), but the dose achieved would only be suitable for a child
384 weighing 2kg. Buanz et al. (2011) were able to dispense a dose suitable for a child up to
385 50kg. Scoutaris et al. (2011) dispensed a felodipine dose within a suitable therapeutic range,
386 although the dose dispensed was indicated for the elderly and was only an initial dose.
387 Finally, Genina et al. (2013a,b) were able to dispense therapeutic doses of rasagiline and
388 loperamide.

389

390 **3.3 After Printing**

391 A number of factors must be considered once the printing process has been completed.
392 These include consideration, as noted above, of the interaction between the solvent and the
393 substrate (blotting), the physical form of the active (an amorphous dispersion or crystalline
394 particles), confirmation of dose and stability of the product. Such analyses may be performed
395 with differential scanning calorimetry, scanning electron microscopy and X-ray powder
396 diffraction.

397

398 **3.3.1 Dose confirmation**

399 Ink-jet systems can fail because of nozzle blockage, heater failure or bubble-collapse
400 damage (Burke et al., 1996; Kobayashi et al., 1998). TIJ is vulnerable to formation of
401 deposits on the heating element, which reduces the drop generating performance, a process
402 commonly known as kogation (koga being Japanese for scorching) (Shirota et al., 1996).

403 Kogation can be reduced using high purity jetting solution components (Reick, 2001),
404 deionised water as a solvent (Oka and Kimura, 1996) and a recovery pulse when needed
405 (Kobayashi et al., 1998). If a significant proportion of the nozzles fail, it will reduce the total
406 dose printed. Inline monitoring of nozzle performance is thus critical for printers used for
407 pharmaceutical applications.

408
409 Current commercial printers house a number of sensors, for example optical and
410 electrostatic detectors fitted in the print-heads, that are able to monitor the nozzles and
411 detect any that are non-functioning or malfunctioning. Algorithms are used to instruct other
412 nozzles to fire temporarily in lieu of the nozzle in question until the print session is finished,
413 when the print-head is recovered by the printer (Bruch, 2002). Such systems can check a
414 nozzle in less than 2 ms, (2000 nozzles can take about 5 seconds to check). Those sensors
415 and the accompanying algorithms may help reduce the deviation of doses as a result of
416 blocked nozzles.

417
418 There is, however, an ethical obligation on the part of the pharmacist to inspect and clinically
419 check the dose prior to dispensing the dose to the patient (Royal Pharmaceutical Society,
420 2011). Such checks should be non-destructive, fast and cheap. Takala et al. (2012) and
421 Genina et al. (2012) both dispensed a riboflavin ink formulation, which is an orange coloured
422 solution. The colour was used to visualise the deposited solution and might be used to
423 quantify the dose deposited. An alternative suggestion is the use of gravimetry, as
424 microbalances with high sensitivity can measure the weight of the substances deposited on
425 the substrate (Elele et al. 2012).

426

427 **3.3.2 Drying**

428 Drying helps in reducing the solvent content and enhances the uniformity of printed doses
429 (Carreira et al., 1996; Costello et al. 2010). In traditional printing on paper, absorptive drying
430 is the main mechanism at ambient conditions as the liquid penetrates the fibre network of the
431 papers (Carreira et al., 1996). Evaporative drying could also be employed to further shorten
432 the drying time using hot air convection, keeping temperatures below 50°C for sensitive
433 materials (Voura et al., 2011). It would also be possible to heat the substrate itself. It is
434 important to investigate the effect of drying on the physical state of the active, if any, and its
435 effect on the therapeutic outcome of the drug.

436

437 **3.3.3 Printed dose stability**

438 If the printed dosage form is required for administration at a later time, it is vital to ensure the
439 stability of the formulation on the substrate in question. Rajjada et al. (2013) explored the

440 stability of printed piroxicam on paper and found that it was stable for one month under
441 conditions of 20-25°C and 30-40% RH. Scoutaris et al. (2011) and Buanz et al. (2011) both
442 stated that if the medicines are to be consumed immediately after fabrication, the impact of
443 stability is minimal. Thermochromic (colour changing) containers could be used to indicate
444 when the printed doses are stored in temperatures in which shelf life is short (Elele, 1998).

445

446 **3.4 Administration**

447 An edible substrate, if it dissolved rapidly upon coming in contact with the salivary secretions
448 of the oral cavity, would release its contents and the drug present in the cavity facilitated by
449 the movement of the tongue. The dissolved film and its contents would then be swallowed.
450 Such films are found to be acceptable dosage form for paediatrics, patients with dysphagia
451 and those with fear of choking (Buck, 2013).

452

453 Should the taste of the drug (or a film component) be unacceptable the orodispersible route
454 of administration may be inconvenient for the patient. In such a case, flavoured substrates
455 can be used to facilitate the administration. Another possible administration method would
456 be to roll the substrate on which the drug was deposited, and insert it into a hard-shell
457 capsule that could be swallowed in a traditional fashion. Using this approach would spare
458 the patient the taste of the film but allow personalisation of the dose. However, it would
459 mean narrowing the population of patients able to administer the dose. According to the
460 European medicines agency (EMA) capsules are only preferentially acceptable in children
461 aged 6 years and above (EMA, 2006). Orodispersible dosage forms, on the other hand, are
462 acceptable for infants and toddlers (1 month to 2 years, EMA, 2006), with immediately
463 dissolving films being suitable for full-term newborn infants (0-28 days, Krause and
464 Breitzkreutz, 2008).

465

466 If rolled into a capsule, dissolution of the carrier film will take place downstream of the
467 gastrointestinal tract, at which point the formulation of the film may influence the release
468 profile of the ink-jetted medicine if designed for release-controlling purposes. The substrate
469 choice can allow an array of tastes for a given dose if a flavoured thin film is used. Other
470 substrate matrix types such as hydrophobic matrices can diversify the potential
471 pharmacokinetic spectrum of the delivery method.

472

473 **4. General printing concerns**

474 **4.1 Sterility**

475 Sterilisation is needed to prevent contaminations of the doses, and the product should be
476 manufactured under conditions of GMP. There has been only little mention in the literature of

477 the effect of sterilising the printer cartridge and printer nozzle in regards to dispensing
478 medicines. Using gas plasma treatment, Tirella et al. (2011) sterilised ink cartridges for cell
479 printing whereas Lee et al. (2012) cleaned the substrate prior to printing. Roth et al (2004)
480 described a method of sterilising the printer by the use of ethylene oxide for the purpose of
481 deposition of cell patterning. Buanz et al. (2011), Mueannoom et al. (2012) and Sharma et
482 al. (2013) cleaned ink cartridges with distilled water followed by absolute ethanol. Pardeike
483 et al. (2011) simply cleaned the nozzle with water, which can be deemed not enough and
484 that more sterilisation techniques would need to be implemented.

485

486 Thermal ink-jet printers might prove easier to sterilise, because the cartridge and nozzle are
487 in one unit and so can be more easily removed or replaced. With common desktop
488 piezoelectric inkjet printers, the nozzle is part of the printer and the ink cartridge simply acts
489 as a reservoir, therefore, sterilising the nozzles may require sterilisation of the whole printer
490 (Arney, 2006). The sterility of the solution is a concern over the duration of cartridge use.
491 Ehtezazi et al., (2014) have developed an inkjet device capable of dispensing high
492 throughput droplets of liquids using glass which is suggested to cause minimal
493 contamination of the liquid being dispensed due to the latter being an inert material.

494

495 **4.2 Cost considerations**

496 From the point of view of adoption, Wening and Breitzkreutz (2011) devised a classification
497 system for personalised dosing of medicines, which classifies the groups of technologies into
498 four classes depending on two important properties; cost and dosing flexibility. To minimise
499 the cost of producing an ink-jet drug manufacturing system, commercially-available thermal
500 ink-jet print-heads, amenable to cheap mass-production could be utilised (Arney, 2006).
501 Such systems have proven to be robust since they contain no moving mechanical parts.
502 While TIJ technology dominates the market (75% market share), the majority of
503 pharmaceutical studies used piezoelectric technology. In general, TIJ printers are cheaper
504 and suitable for aqueous solutions while PZT printers are more expensive but can be used
505 to jet organic solvents.

506

507 **4.3 Scale up**

508 Commercial mass production is always a consideration of any potential new technology,
509 although in this case printing probably offers most potential for extemporaneous
510 manufacture of relatively small numbers of unit dosage forms. In this context, scale up is not
511 an issue. However, should the need arise for ink-jet technology be adopted on a larger
512 commercial basis, scale up is relatively straightforward, requiring only an increase in the

513 number of nozzles (Hirshfield, 2014). This can be achieved with either a larger print head or
514 by operating multiple printers side-by-side.

515

516 **4.4 Success factors for delivery systems**

517 Florence and Lee (2011) argue that numerous factors contribute to the success of a therapy,
518 many of which are not linked to awareness of the genetic profile of the patient. Wening and
519 Breitzkreutz (2011) argue that for a dosing system to be successful, it must:

520

- 521 - Cover the complete patient population
- 522 - Not require parenteral administration because of patient acceptability and setting-
523 applicability
- 524 - Promote strong patient adherence
- 525 - Be cost effective
- 526 - Be simple to use
- 527 - Be robust

528

529 Ink-jet printing might be a good platform for manufacturing medicines, because of the
530 flexibility with which it can deliver medicated solutions for different populations and its ability
531 to print on oral films (which have a marketable advantage because they do not require water
532 for administration) (Siddiqui et al. 2011). The technology can be exploited further to control
533 drug release rates from ingested dosages, for instance by printing a layer of dissolution-rate
534 controlling polymers or by combination with other technologies that can control the drug
535 release (Genina et al., 2012).

536

537 **5 Conclusions**

538 Ink-jet printing is capable of printing solutions and/or nanosuspensions onto a wide range of
539 solid substrates, making it a suitable technology for the manufacture of a wide range for oral
540 dosage forms. When considering the use of ink-jet printing for pharmaceutical manufacture,
541 preformulation studies will be required to ensure solutions have suitable properties for
542 jetting; control of viscosity and surface tension are paramount, plus it is important to ensure
543 that the API doesn't precipitate from solution in the printer. Once a solution is optimised for
544 printing consideration must be given to the physical form of the drug in the dosage form.
545 When the basic formulation has been developed, there is the potential to use the technology
546 to fabricate personalised doses and/or drug combinations.

547

548 Desktop ink-jet printers are not optimised to print drug solutions but are an effective tool for
549 preformulation and evaluative studies. Use of such systems often requires additives to adjust

550 the physicochemical properties of the solution to match the requirements of the printer. For
551 production of medicines for human use the printer technology can be optimised for a
552 particular solution. Widespread adoption of ink-jet printing for pharmaceutical manufacture
553 will require consideration of GMP.

554

555 Ink-jet printing will not replace traditional methods of manufacturing medicines, at least in the
556 short term, and it is unlikely to be used for large-scale mass production. The small volumes
557 the printer can dispense combined with the low concentrations needed to prevent clogging
558 means the technology is more suited to printing drugs with low therapeutic doses.

559 Knowledge of whether ink-jet technology could be expanded to print high dose drugs is
560 unknown. In the meantime, for low dose drugs with narrow therapeutic windows, ink-jetting
561 printing can produce precise, accurate and reproducible doses and offers the potential of
562 fabricating doses specific to the patient.

563

564 Regulation procedures need to be examined and implemented if the future of inkjet printing
565 as a drug delivery method is to progress; this includes methods to confirm dose and sterility
566 procedures and consideration of factors affecting point-of-dispensing manufacture. If these
567 issues can be overcome, ink-jet technology may herald a new paradigm of personalised
568 medicines.

569

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Reference	Technology	Type of liquid	Ink formulation	API	Viscosity (mPa·s)	Surface tension (mN/m)
Hirshfield et al. (2014)	PZT	Solution	Ethanol	30:70 Naproxen/PVP	-	-
Raijada et al. (2013)	PZT	Solution	PEG:ethanol (40:60)	Piroxicam	4.9 ± 0.1	27.6 ± 0.4
Sandler et al. (2011)	PZT	Solution	PG–purified water (30:70 v/v)	Paracetamol, caffeine, and theophylline	3.1	52.0 ± 0.4
Scoutaris et al. (2011)	PZT	Solution	Ethanol:DMSO (95/5)	Felodipine and PVP	-	-
Lee et al. (2012)	PZT	Solution	10%(w/v) PLGA solution	Paclitaxel	5.99	35.4
Genina et al. (2013a)	TIJ	Solution	30:70 (vol%) PG:water	Rasagiline mesylate	≤5	
Genina et al. (2013b)	PZT	Solution	40:60 PG:ethanol	Loperamide	3.6 ± 0.2	25.7 ± 0.7
		Solution	30:70 of PG:water	Caffeine	2.6 ± 0.1	50.7 ± 1.0
Buanz et al., 2011	TIJ	Solution	10% Glycerol in water	Salbutamol sulphate	1.1 ± 0.014	46.4 ± 2.93
Pardeike et al. (2011)	PZT	Nano-suspension	Aqueous 3% (w/w) Tween 20	Folic acid	-	-
Genina et al. (2012)	PZT	Solution	PG:water (30:70, vol%)	Propranolol	2.7 ± 0.1	50.1 ± 1.0
		Solution	Glycerol:Ethanol: Water (10:10:80, vol%).	Riboflavin sodium phosphate	1.6 ± 0.1	49.4 ± 0.9
Meléndez et al. (2007)	TIJ	Solution	Ethanol, water, glycerol (80:17:3) vol%	Prednisolone	-	-
Takala et al. (2012)	TIJ	Solution	Glycerol in water	Riboflavin sodium	-	-

				phosphate		
Tarcha et al. (2007)	PZT	Solution	Isobutanol	Fenofibrate, ABT-578	-	-
Mueannoo m et al. (2012)	TIJ	Solution	Water	Salbutamol sulphate	-	-
Goodall et al. (2002)	TIJ	Solution	2% PEG 8000: 0.1% Tween 20 in water	hGH and Insulin	-	-
Sharma et al., 2013	TIJ	Solution	Water	Terbutaline sulphate	-	-

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811 **Table 1. Types of printers, medicated formulations and properties of the liquid printed**

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Reference	Substrate(s)
Hirshfield et al., (2014)	Hydroxypropyl methyl cellulose (HPMC) films
Rajjada et al., (2013)	Edible icing sheets
Sandler et al., (2011)	Uncoated paper, coated paper, and polyethylene terephthalate (PET) film
Scoutaris et al., (2011)	Glass cover slip coated in flutec fluid to increase hydrophobicity
Genina et al., (2013a)	Orodispersible films, copy paper, water impermeable transparency films
Genina et al., (2013b)	Icing sheet, PET film, HPC film
Buanz et al., (2011)	Clear acetate film, Starch film
Genina et al., (2012)	Uncoated wood-free paper, triple-coated inkjet paper, double-coated sheet
Meléndez et al., (2007)	PTFE films over a clear transparency film
Takala et al., (2012)	Copy paper and photocopy paper

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816 **Table 2. Substrates used for medicine printing as reported in the literature**

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Reference	Drug	Liquid Conc. (mg/ml)	Print Area (cm ²)	Number of passes	Total Volume (µL/cm ² /pass)	Total Dose (mg)	Minimum therapeutic dose (age group)
Buanz et al., (2011)	Salbutamol	30	4	6	0.06	0.04	15 µg/kg (2-18 years)
Genina et al., (2012)	Propranolol	50	1	1*	10.06	0.503	2 mg/kg (2-12 years)
	Riboflavin	31.5	1	1*	10.79	0.34	50 mg (1 month-18 years)
Hirshfield et al., (2014)	Naproxen	70	7	1*	22.86	11.2	5 mg/kg (1 month – 18 years)
Raijada et al., (2013)	Piroxicam	5	1	1*	10.02	0.0501	5 mg (6-18 years, under 15kg)
Sandler et al., (2011)	Theophylline	5.8	1	1*	13.45	0.078	9 mg/kg (2-12 years)
	Caffeine	19.3	1	1*	13.99	0.27	2.5mg/kg (Neonates)
	Paracetamol	9.9	1	1*	27.27	0.27	60 mg/kg (1-3 months)
Lee et al., (2012)	Paclitaxel	10	0.367405	1*	0.09	0.00034	-
Genina et al., (2013a)	Rasagiline mesylate	100	6	9	0.39	2.11	1 mg
Genina et al., (2013b)	Loperamide	50	4	1*	12.16	2.431	1 mg (4-8 years)
	Caffeine	20	4	1*	15.90	1.272	2.5mg/kg (Neonates)
Meléndez et al., (2007)	Prednisolone	50	6.4516	60	0.41	8	1-2 mg/kg (1 month-18 years)

Tarcha et al., (2007)	Fenofibrate	40	3.2	1*	115.06	14.728	67 mg
Scoutaris et al., (2011)	Felodipine	Variable (at 1:1 ratio 1000)	NA	1*	2.5**	2.5	2.5mg

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821 **Table 3. Doses and volumes of the drugs printed in the literature**

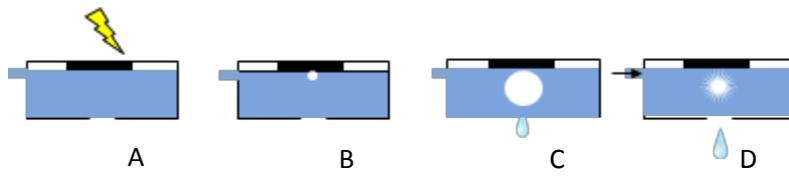
822 * PZT printers are assumed to use one pass only for printing

823 ** A print area of 1 cm² is assumed for comparison of results

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Figure 1. Thermal Inkjet drop generating chamber showing (A) rising of the resistor temperature upon receipt of an electrical pulse (B) nucleation due to formation of superheated vapour bubble (C) growth of the bubble and deposition of a droplet and (D) collapse of the bubble and refilling

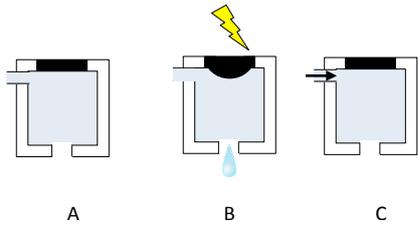
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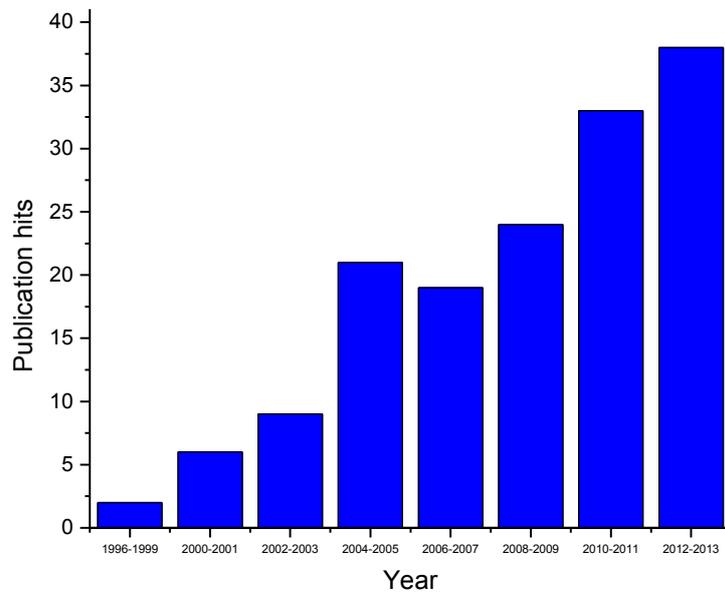
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839 **Figure 2. Piezoelectric drop generating chamber showing (A) the unactivated state (B)**
840 **the movement of the piezo-element upon receipt of an electrical pulse resulting in the**
841 **formation of a droplet and (C) refilling of the chamber**

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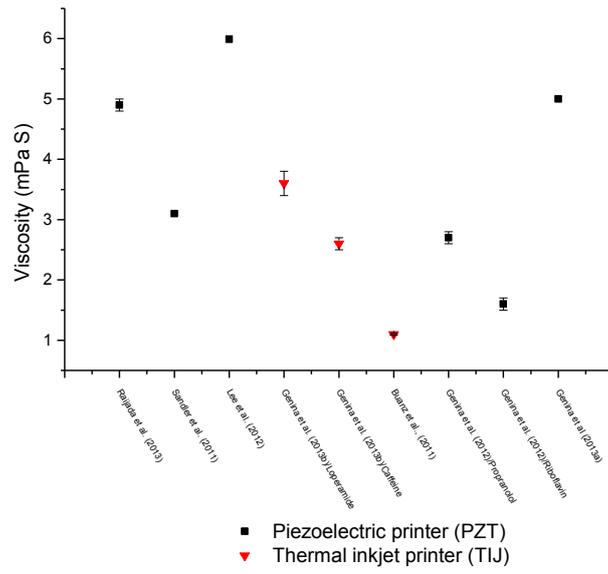


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Figure 3. The number of publications on pharmaceutical ink-jet printing recorded on Web of Science since 1996.

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855 **Figure 4. Viscosities of printed solutions from reported literature**

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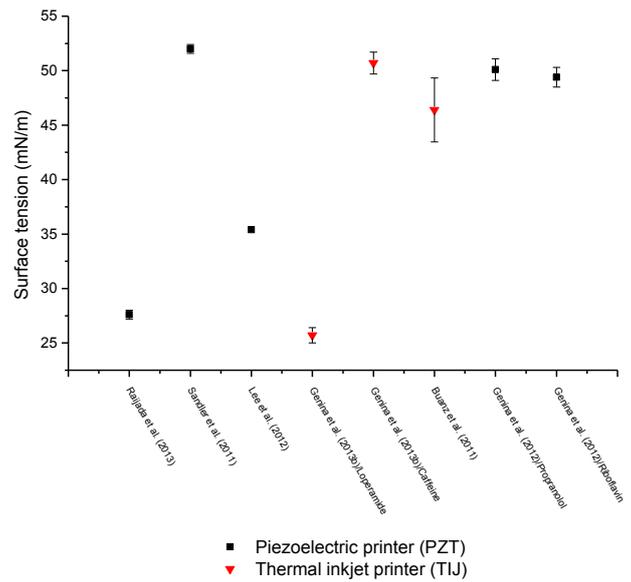


Figure 5. Surface tensions of printed solutions from reported literature