Personalised dosing: printing a dose of one's own medicine

Mustafa Alomari, Fatima H. Mohamed, Abdul W. Basit and Simon Gaisford*

UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK

*Corresponding author

email: s.gaisford@ucl.ac.uk

Tel: +44(0) 207 753 5863

Fax: +44(0) 207 753 5942

Abstract:

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

Key words:

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

1. Introduction

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

1.1 Drug delivery and need for personalised medicine

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

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

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

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

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

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

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

1.2 Current approaches to dose personalisation

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

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

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

2. Ink-jet printing

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

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

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

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

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

3. Pharmaceutical applications of ink-jet printing

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

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

3.1 Before Printing

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

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

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

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

3.1.1 Dose flexibility

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

Another parameter that has been used to control the dose deposited is to change the area printed (Genina et al., 2013b; Buanz et al., 2011). When deposited onto an orodispersible film, the medicine needs to achieve a therapeutic dose in an area with administrable dimensions (Dixit and Puthli, 2009). The administrable area of orodispersible films ranges from 1 – 20 cm^2, with children aged 6 months and above being able to take films of 6 cm^2 (Bala et al.,2013; Orlu-gul et al., 2014).

3.1.2 Substrates

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

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

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

3.2. During printing

3.2.1 Dose and placement accuracy

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

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

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

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

3.2.2 Dose printing time

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

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

$$Throughput \propto Number\ of\ nozzles \cdot firing\ frequency$$

Equation 1

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) to10 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).

3.2.3 Maximum achievable dose

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

3.3 After Printing

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

3.3.1 Dose confirmation

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

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

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

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

3.3.2 Drying

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

3.3.3 Printed dose stability

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

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

3.4 Administration

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

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

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

4. General printing concerns

4.1 Sterility

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

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

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

4.2 Cost considerations

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

4.3 Scale up

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

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

4.4 Success factors for delivery systems

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

- Cover the complete patient population
- Not require parenteral administration because of patient acceptability and setting-applicability
- Promote strong patient adherence
- Be cost effective
- Be simple to use
- Be robust

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

5 Conclusions

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

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

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

Ink-jet printing will not replace traditional methods of manufacturing medicines, at least in the short term, and it is unlikely to be used for large-scale mass production. The small volumes the printer can dispense combined with the low concentrations needed to prevent clogging means the technology is more suited to printing drugs with low therapeutic doses. Knowledge of whether ink-jet technology could be expanded to print high dose drugs is unknown. In the meantime, for low dose drugs with narrow therapeutic windows, ink-jetting printing can produce precise, accurate and reproducible doses and offers the potential of fabricating doses specific to the patient.

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

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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	-	-
Mueannoom 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	-	-

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

Reference	Substrate(s)
Hirshfield et al., (2014)	Hydroxypropyl methyl cellulose (HPMC) films
Raijada 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

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 ($\mu L/cm^2$/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 cm^2 is assumed for comparison of results

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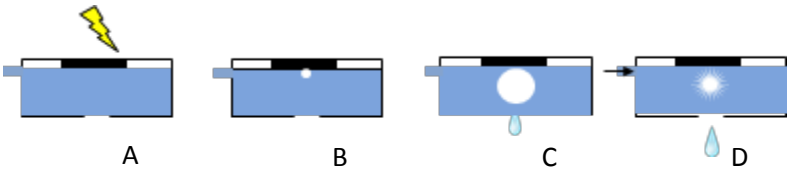

Figure 1. Thermal Inkjet drop generating chamber showing (A) rising of the resistor temperature upon receipt of an electrical pulse (B) nucleation due to formation of superheated vapour bubble (C) growth of the bubble and deposition of a droplet and (D) collapse of the bubble and refilling

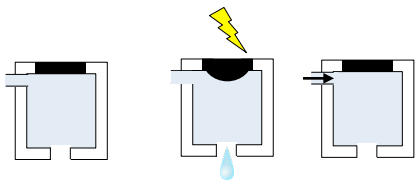

Figure 2. Piezoelectric drop generating chamber showing (A) the unactivated state (B) the movement of the piezo-element upon receipt of an electrical pulse resulting in the formation of a droplet and (C) refilling of the chamber

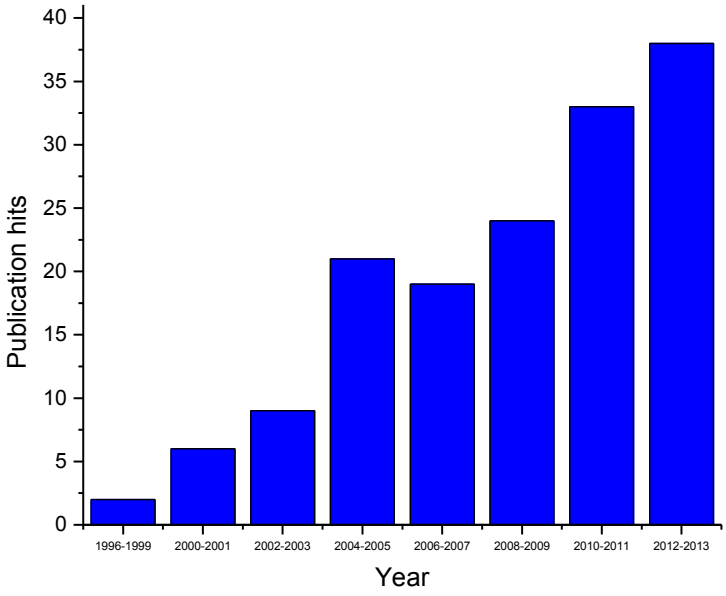

Figure 3. The number of publications on pharmaceutical ink-jet printing recorded on Web of Science since 1996.

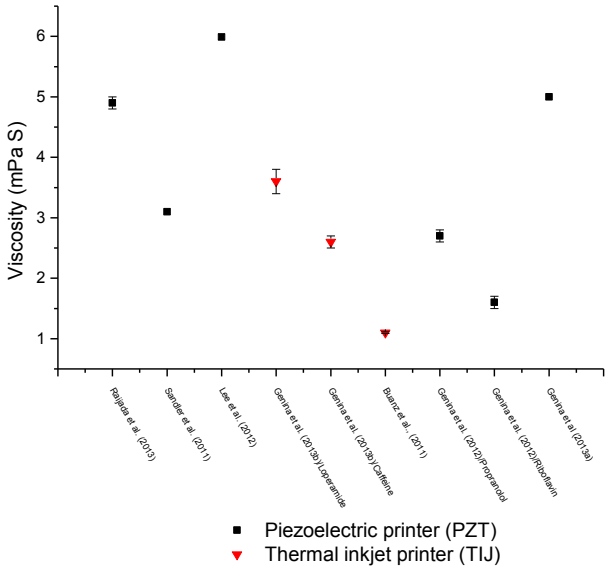

Figure 4. Viscosities of printed solutions from reported literature

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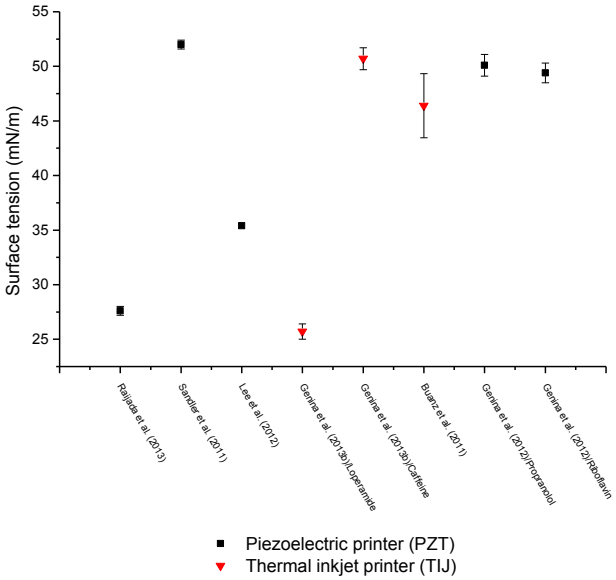

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860 **Figure 5. Surface tensions of printed solutions from reported literature**