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

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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.

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, 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

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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 et al., 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 5 mg 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 to 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 homogeneous 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 ink-jet 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 ink-jet 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 vapour bubble, as shown in Fig. 1. The vapour bubble expands, forcing out the fluid from the nozzle and producing a droplet. The vapour bubble then collapses,

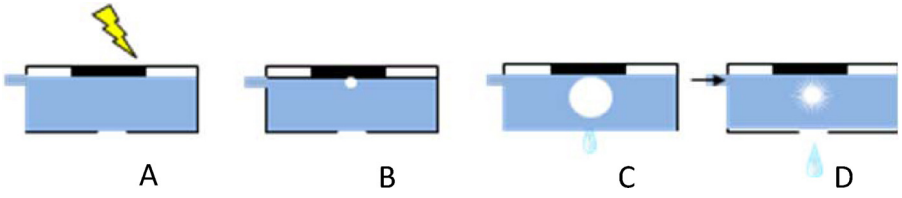

Fig. 1. Thermal ink-jet drop generating chamber showing (A) rising of the resistor temperature upon receipt of an electrical pulse (B) nucleation due to formation of superheated vapour bubble (C) growth of the bubble and deposition of a droplet and (D) collapse of the bubble and refilling.

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