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Inkjet printing of paracetamol and indomethacin using electromagnetic technology: Rheological compatibility and polymorphic selectivity

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ABSTRACT

Drop-on-demand inkjet printing is a potential enabling technology both for continuous manufacturing of pharmaceuticals and for personalized medicine, but its use is often restricted to low-viscosity solutions and nano-suspensions. In the present study, a robust electromagnetic (valvejet) inkjet technology has been successfully applied to deposit prototype dosage forms from solutions with a wide range of viscosities, and from suspensions with particle sizes exceeding 2 µm. A detailed solid-state study of paracetamol, printed from a solution ink on hydroxypropyl methylcellulose (HPMC), revealed that the morphology of the substrate and its chemical interactions can have a considerable influence on polymorphic selectivity. Paracetamol ink crystallized exclusively into form II when printed on a smooth polyethylene terephthalate substrate, and exclusively into form I when in sufficient proximity to the rough surface of the HPMC substrate to be influenced by confinement in pores and chemical interactions. The relative standard deviation in the strength of the dosage forms was < 4% in all cases, for doses as low as 0.8 mg, demonstrating the accuracy and reproducibility associated with electromagnetic inkjet technology. Good adhesion of indomethacin on HPMC was achieved using a suspension ink with hydroxypropyl cellulose, but not on an alternative polyethylene terephthalate substrate, emphasising the need to tailor the binder to the substrate. Future work will focus on lower-dose drugs, for which dosing flexibility and fixed dose combinations are of particular interest.

1. Introduction

There are compelling arguments to replace conventional pharmaceutical manufacturing, based on large-scale batch production of tablets, with more flexible processing methods and dosage forms.

Flexibility, accuracy and precision in the dosage delivery are unmet needs of the conventional manufacturing methods. Flexibility in dosage delivery is required in order to mitigate type A adverse drug events, which account for more than 80% of the adverse drug reactions (Cohen, 1999; Cohen, 2001; Munir Pirmohamed et al., 1998), and to personalize medicines based on patient-specific needs, co-morbidities and polypharmacy (Breitkreutz and Boos, 2007; Florence, 2010). Narrow therapeutic index drugs, and low-dose drugs with dose strengths as low as 0.25 µg, require accuracy and precision in the dosage delivery as the slightest deviation of mass due to uneven excipient mixing or feeding during conventional tabletting can result in a significant deviation in the active pharmaceutical ingredient (API) content of the final dosage forms (Am Ende et al., 2008).

Inkjet printing is a promising solution for alternative manufacturing in pharmaceuticals and for personalised medicine. Drop-on-demand inkjet printing technologies allow small volumes of a liquid to be reproducibly dispensed drop-wise and accurately positioned on a substrate, without contact. The scalability of this approach has been proven in graphics printing, and it is increasingly being applied in industrial applications (Singh et al., 2010). As a digital printing method, it is also well suited to short-run production: the printed pattern, i.e. the distribution of liquid, can be changed instantly without modifying the production line. This is a potential enabling technology for distributed production and personalised medicine: enabling the dose, or combination of APIs, to be adjusted to suit an individual patient.

Inkjet printing has been investigated by various research groups as a method to produce personalised doses of drugs (Buanz et al., 2011; Sandler et al., 2011), to tailor controlled release dosage forms (Genina et al., 2012), to enhance the dissolution behaviour of poorly soluble

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drugs such as piroxicam (Raijada et al., 2013), ciprofloxacin (Cheow et al., 2015), indomethacin (Wickstrom et al., 2015) and felodipine (Scoutaris et al., 2011), and to study the solid state transformations associated with printing processes (Hirshfield et al., 2014; Meléndez et al., 2008). The majority of this research has focussed on using piezoelectric and thermal print heads, whose application is typically limited to solution and nano-suspension inks with a narrow range of rheological properties. The need to expand this processing window has been acknowledged by some authors, e.g. Planchette et al., who proposed using a combination of piezoelectric and solenoid valve inkjet technologies to accommodate suspensions and viscous solutions; although their initial experimental study still focussed on nano-suspensions and solutions with a viscosity in the < 10 mPa s range accessible for piezoelectric printing (Planchette et al., 2016).

More than 40% of new chemical entities developed in the pharmaceutical industry are poorly soluble. Formulation of a nano-suspension is a challenging process, with each of the production methods having advantages and disadvantages (Patravale and Kulkarni, 2004); and undesirable solid state transformations can sometimes result, due to high pressure or other process parameters associated with nano-suspension production (Liu et al., 2015; Sharma et al., 2011). Henceforth, it is essential to develop technologies capable of handling coarser suspensions, which can be developed by less complex production methods.

In this article, inkjet printing using electromagnetic (valvejet) technology has been investigated as a means of depositing solutions with a broader range of viscosity (3–15 mPa s) and suspensions with average particle sizes exceeding 2 μm. Paracetamol and indomethacin were selected to demonstrate the feasibility of formulating soluble and poorly soluble APIs in the form of solution and suspension inks respectively. Hydroxypropyl methylcellulose (HPMC) was chosen as the substrate, considering its excellent film forming properties and wide acceptance as a pharmaceutical excipient (Dixit and Puthli, 2009; Elele et al., 2012). Aqueous inks were avoided as they can cause re-dissolution of the substrate, resulting in deformation of the final product.

A secondary objective of the study was to investigate and characterise the polymorphic transitions that could be encountered while using solution inks due to rapid solvent evaporation or interactions with the substrate. Paracetamol, with its extensively reported polymorphic forms and reasonable solubility in pharmaceutically accepted organic solvents such as isopropyl alcohol, was chosen as the model drug to investigate post-printing solid state transformations.

The APIs were printed on HPMC films; and the structure, crystallography, concentration and mechanical robustness of the resulting coatings were characterised. In addition, the effect of the physical and chemical nature of the substrate on the polymorphic selectivity of the paracetamol was studied by comparing samples printed on HPMC and polyethylene terephthalate (PET) substrates.

It was not intended to produce pharmacologically relevant doses in this initial study: a further study will apply the methods prototyped here to lower-dose APIs, for which dosing flexibility and fixed dose combinations (FDCs) are of more interest.

2. Materials and methods

Paracetamol (PML), indomethacin (IND), docusate sodium salt (DS), were purchased from Sigma Aldrich (Arklow, Ireland), isopropanol (IPA) and ethanol were purchased from Fisher Scientific UK (Leics, UK). Metolose 6OSH-50, i.e. hydroxypropyl methylcellulose (HPMC) with a nominal viscosity of 50 mPa s (2% solution) was supplied by Shin-Etsu (Livingstone, UK), and hydroxypropyl cellulose (HPC) with an average molecular weight ~100,000 was purchased from Alfa Aesar (Lancashire, UK).

2.1. Preparation of substrate and inks

2.1.1. Substrates

HPMC films were produced by a solvent-casting technique using an 8 wt% aqueous solution of HPMC. A weighed amount of HPMC was dispersed in water at 85 °C and allowed to cool to room temperature, producing a clear solution. The solution was sonicated and allowed to stand overnight to remove any air bubbles. This solution was then poured into the reservoir of the micrometric film applicator (Elcometer 3570, Manchester, UK) placed on a polyethylene terephthalate (PET) film resting on a flat surface. The gap between the PET film and the bevelled blade of the applicator was adjusted to 800 μm using the micrometer screw. The applicator was manually dragged over the PET film to achieve a uniform wet film, which was then transferred to the oven to be dried at 40 °C for 3 h. After drying, the HPMC film was released from the PET substrate with the help of a scalpel. The thickness of each film after drying was measured using a flat anvil dial thickness gauge (Model 7327, Mitutoyo) to be in the range of 45–60 μm.

In addition, some samples were printed directly on PET film to distinguish the effects of surface roughness and of HPMC-specific substrate interactions.

2.1.2. Inks

Fluids for inkjet printing (inks) were prepared as solutions or micro suspensions in alcohols, to minimise solubility of the HPMC substrate, with additions of polymer and surfactants as required to adjust the surface tension and keep the viscosity in the range 3–15 mPa s.

Solution based inks, 5 wt% PML and 2 wt% HPC, were prepared using IPA and ethanol as the solvents respectively.

The IND suspension was prepared using DS as a surfactant and HPC as a viscosity modifier. DS (0.5 wt%) was dissolved in ethanol, and HPC (1.5 wt%) was then added slowly under stirring, which continued for 2 h to thoroughly dissolve the HPC. IND, as received, was dry milled using a mixer mill (Retsch MM 400, Haan, Germany) in a 25 mL grinding jar with a single ball at 20 Hz for 15 min. Milled IND was then slowly dispersed in the above solution, yielding a stable suspension after a further two hours of stirring. Suspensions with DS concentrations 0.1, 0.25, 0.5 and 0.75 wt% were evaluated for their stability based on sedimentation volume observed over a period of 24 h. Suspensions with a sedimentation volume of 1 (i.e. no visible evidence of sedimentation) for at least 6 h were considered to be sufficiently stable, taking into account the time required for printing, which is less than one hour. Suspensions with DS concentrations 0.5 and 0.75 wt% were both found to be stable, but the lower surfactant concentration (0.5 wt%) was used for the final ink formulation so as to minimise the use of excipients. The suspension was passed through an in-line particulate filter with a pore size of 15 μm before printing to avoid clogging of the nozzle. The suspension before and after filtration was analysed using HPLC, to identify any change in the drug content caused by filtration, and to calculate the actual concentration of the drug used for printing.

Development of a stable suspension that does not phase-separate while printing, and a fine suspension that does not clog the nozzle, are the important formulation aspects for inkjet printing of suspension inks. Phase separation of the suspension while printing will result in inconsistency in the amount of drug printed with time, and could result in blockages. The particle size of the suspended particles limits the choice of printing device: some authors propose a maximum particle size 1/50 of the orifice diameter (Hutchings and Martin, 2012), but there are additional constraints provided by fluidic paths and filters, so this is best determined empirically.

2.2. Inkjet printing

Drop-on-demand inkjet printing was performed using single-nozzle jetting devices based on miniature solenoid valves, sometimes referred