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Preparation of Personalized-dose Salbutamol Sulphate Oral Films with Thermal Ink-Jet Printing

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ABSTRACT

Purpose To evaluate the use of thermal ink-jetting as a method for dosing drugs onto oral films.

Methods A Hewlett-Packard printer cartridge was modified so that aqueous drug solutions replaced the ink. The performance of the printer as a function of print solution viscosity and surface tension was determined; viscosities between 1.1 and 1.5 $mm^2\ s^{-1}$ were found to be optimal, while surface tension did not affect deposition. A calibration curve for salbutamol sulphate was prepared, which demonstrated drug deposition onto an acetate film varied linearly with concentration ($r^2 = 0.9992$). The printer was then used to deposit salbutamol sulphate onto an oral film made of potato starch.

Results It was found that when doses were deposited in a single pass under the print head, then the measured dose was in good agreement with the theoretical dose. With multiple passes the measured dose was always significantly less than the theoretical dose. It is proposed that the losses arise from erosion of the printed layer by shearing forces during paper handling. The losses were predictable, and the variance in dose deposited was always less than the BP limits for tablet and oral syrup salbutamol sulphate preparations.

Conclusions TIJ printing offers a rapid method for extemporaneous preparation of personalized-dose medicines.

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INTRODUCTION

Commercially available medicines are generally available in only a few discrete doses. In cases where delivery of a precise dose is paramount, such as for highly potent actives, drugs with a narrow therapeutic index, or paediatric formulations (where the dose is based on body mass), the individual dosage unit may need to be divided prior to administration. Several studies have reported an unfavourable effect on dose uniformity of breaking tablets into smaller units (1,2), and of course tablet division is not applicable to enteric-coated systems. A second approach is preparation of minitablets (3), but control of dose uniformity is still challenging during minitablet manufacture, and the exact dose cannot be varied in proportion to patient body mass.

Perhaps the best methodology would be to have a manufacturing process that allows precise control, and extemporaneous preparation, of dose on a patient-to-patient basis. One way of achieving this is to develop a universal carrier system, such as a polymeric oral film, and then deposit the drug onto it in a final dosing step—the pharmacist would be able to prepare a dose personalized to a specific patient. One option would be to use a micropipettor to dispense the dose, but there is the risk that significant volumes might be dispensed onto small areas, leading to dissolution or degradation of the film and/or variance in dose. Alternatively, desktop printing technology is cheap, yet affords extremely fine control of liquid droplets, and hence uniformity of drug dose. Two common technologies are employed: piezoelectric (PE) and thermal-

ink-jetting (TIJ). The use of PE to deposit drugs onto edible carriers has been recently discussed (4). This paper focuses on the use of TIJ.

Briefly, a TIJ system comprises a reservoir of liquid to be jet mounted above a print head. The print head, usually produced with photolithography, consists of a number of small chambers, filled with liquid from a reservoir, each in contact with a resistive element. Pulsing a current through the element results in a rapid rise in temperature, causing vaporisation of some of the liquid, nucleation and then expansion of a vapour bubble. As the bubble expands, some liquid is ejected from the chamber, forming a droplet. Eventually, the vapour bubble collapses, causing a vacuum that is filled with fresh liquid from the reservoir. The process repeats, controlled by the current pulses, producing droplets-on-demand (DOD). The resistive element can reach a temperature of up to 300°C, resulting in bubble expansion over 3–10 μs and a droplet ejected at up to 10 m s^{-1}, while droplet volumes of 2–180 pL can be achieved (5). Although this temperature seems excessive, it lasts for only a few ms, and less than 0.5% by volume of the sample is exposed (5); it has been reported that solutions of protein (human growth hormone and insulin) were not denatured by TIJ (6).

Such fine control of liquid deposition lends itself to pharmaceutical applications, and TIJ has been used to prepare drug-loaded biodegradable microspheres (7) and drug-loaded liposomes (8), as well as for patterning microelectrode arrays (9) coating and loading drug eluting stents (10), and is the topic of many US patents (for instance, 11–13). The design characteristics of desktop TIJ printers mean they are perfectly suited for deposition of liquids onto flat substrates, such as oral or buccal films. In the context of personalized-dose medicines, TIJ allows extemporaneous preparation of specific doses, either by varying the concentration of the solution to be jetted, changing the area of film given to the patient, or altering the number of print passes over the substrate.

Most commercial TIJ systems are designed to print aqueous inks, which means they are ideally suited to jetting aqueous drug solutions. However, the volume deposited, and hence dose obtained, will be dependent upon a number of factors, some involving the solution to be jetted (concentration, viscosity, surface tension) and some inherent to the printer (orifice size, current pulse, software settings etc.). The specific aim of this work was thus to define the design space in which a typical desktop TIJ printer (in this instance manufactured by Hewlett-Packard) can reproducibly dose an aqueous drug solution onto a pharmaceutical substrate. Once characterized, the system was used to dispense a drug onto an oral film with drug doses suitable for paediatric patients. Salbutamol sulphate (SS) was chosen as a model drug, since it is indicated for treatment of asthma in children under 2 at an oral dose of 100 μg per kg of body weight (14). An oral film made of potato starch was used as the substrate onto which the drug was deposited.

MATERIALS AND METHODS

Materials

Micronised salbutamol sulphate (SS, Micron Technologies, England), glycerine (Analytical grade, Fisher Scientific) and Sodium 1-hexanesulphonate (99%, Acros organics, USA) were used as received. Solvents used were absolute ethanol (Fisher Scientific) and methanol (HPLC grade).

Preparation of Salbutamol Sulphate Solutions

Two series of SS solutions were prepared in distilled water. The first series had a constant concentration of SS (0.5% w/v) with increasing concentrations of glycerine (1, 2, 3, 5, 10, 20, 40, 50 and 60%v/v). Glycerine was selected, as it acts both to increase viscosity and as a humectant, slowing crystallisation of the solute and evaporation of the solvent and helping to ensure that the cartridge orifice does not become blocked (5). An alternative material would be propylene glycol (15). The second series of solutions had a constant concentration of glycerine (10% v/v), since this was found to be optimal for jetting, with increasing concentrations of SS (0.5, 1, 1.5, 2, 2.5 and 3% w/v). In all cases, the appropriate weight or volume of each component was weighed into a volumetric flask (50 mL) before the solution was made up to the mark with distilled water. Solutions were sonicated for 10–15 min to ensure complete dissolution.

Measurement of Viscosity

Viscosity was determined using an Ostwald U-tube viscometer (size B, Technico, UK). The time required for the solution to pass between two marks as it flowed under gravity through the vertical capillary of the viscometer was determined, and viscosities were calculated with reference to data for distilled water. All measurements were performed with the viscometer mounted in a thermostatted water bath (25±0.5°C) (Grant Instruments Ltd., Cambridge, UK). Three replicates were performed for each solution and the results are presented as mean ± standard deviation.

Measurement of Surface Tension

Measurements were made with a Kibron Delta 8 multi-channel microtensiometer (Kibron Inc, Finland) using 50 μl of the sample solution to fill each well of the DynePlate (n=8). The measurement is based on withdrawing a probe

from the solution and recording the maximum force exerted on the surface tension (Du Nouy ring/maximum pull force method). Data were captured with Delta-8 Instrument Setup software, and calibration was performed with distilled water as a reference (surface tension = 72.8 mN m^{-1} at 20°C) in accordance with the manufacturer's instructions. Data are presented as mean ± standard deviation.

Modification of the Ink-Jet Printer Cartridge

All experiments were performed with an unmodified Deskjet D1660 thermal ink-jet printer (Hewlett-Packard Inc). Ink cartridges (black and tricolour, model numbers CC640E and CC643E, respectively) were modified by cutting off the top, removing the foam pad and rinsing out the ink with distilled water, followed by absolute ethanol. The cartridges were loaded with the appropriate solution to be jetted and replaced in the carrier in the printer. Templates (consisting of geometric shapes of a specific colour) to be printed were prepared in Word 2007 (Microsoft Inc.). The print settings were individual cartridge, normal print quality, highest resolution. Where the template was black, the printer software was set to use the black cartridge only. The RGB settings for the blue and red templates were 0, 112, 192, and 255, 0, 0, respectively. After each use, the cartridge was rinsed with distilled water, then absolute ethanol.

Printing of Salbutamol Sulphate Solutions

For the purpose of assay development, individual squares (10×10 cm) of SS solution (up to 3% w/v) were printed onto clear acetate films (A4 Ryman inkjet printer transparencies, Ryman Ltd., UK). Each printed film layer was rinsed off the acetate substrate with distilled water to known volume, and the absorbance was measured at 276 nm using UV-spectroscopy (Cary 3E UC-Visible spectrophotometer, data capture with Cary Win UV (version 3.00) 2002 Varian Australia Pty Ltd.). Each solution was printed in triplicate, and the UV absorbance of each solution was measured nine times. Measurements are reported as mean ± standard deviation. Printing different colour templates assessed the performance of each ink cartridge.

For the purpose of dispensing SS onto oral films, aqueous SS solution (3%w/v) containing glycerine (10% v/v) was printed onto a commercial potato starch film (Easybake edible paper, NJ Products Ltd., UK). Images were printed as black squares with areas of 4, 6 and 64 cm^2 (physical dimensions 2×2 cm, 1.5×4 cm and 8×8 cm, respectively).

HPLC Assay for Salbutamol Concentration

Printed starch paper sheets were dissolved in distilled water (4 cm^2 film in 50 mL and larger films in 100 mL), sonicated until full disintegration of the starch paper had occurred, and filtered (0.45 μm, Millex syringe-driven filter unit, Millipore Ltd., Ireland). Filtrates were analysed with High Pressure Liquid Chromatography (HPLC) fitted with a UV-detector (Hewlett-Packard, Germany) using a mixture of 5 mM sodium-1-hexanesulphonate in water and methanol (75:25% v/v), containing glacial acetic acid (1% v/v), as the mobile phase delivered at a rate of 1.0 mL min^{-1}. The stationary phase was a Discovery® C-8 column (150 mm×4.6 mm× 5 μm; Supelco analytical, USA) kept at 40°C, and the injected sample volume was 20 μL. Peaks were evaluated at 276 nm, and the method was linear ($r^2 = 0.9993$) between SS concentrations of 0.5 and 80 μg/ml.

Dissolution Testing

There is no pharmacopeial dissolution test for oral films. Garsuch and Breitkreutz (15) used two simple methods when comparing oral films; one was to place a drop of dissolution medium in the centre of the film and record the time taken for a hole to form, and the other was to place the film on top of 2 mL of distilled water in a petri dish and measure the time taken for complete dissolution to occur. The starch paper used in this work requires some mechanical action to dissolve completely (which would be provided by the tongue when given to a patient) and so neither of these methods was particularly suitable. Hence, the second method was modified, so that the time taken for complete gelation, rather than dissolution, to occur was recorded.

RESULTS AND DISCUSSION

The effects of viscosity and surface tension on print volume were assessed by varying the quantity of glycerine in the feed solution (up to 60%), each solution having the same quantity of salbutamol sulphate (0.5% w/v). Viscosity and surface tension data are given in Table I. Drug deposition data as a function of solution viscosity (Fig. 1) and surface tension (Fig. 2) are given for the black and colour cartridges.

Viscosity appears to have a significant effect on drug deposition; when the viscosity is greater than 2 $mm^2\ s^{-1}$, deposition is minimised, because the solution is too viscous for the cartridge to jet. Similarly, poor deposition is seen with viscosities below 1 $mm^2\ s^{-1}$, presumably because the liquid flows through the cartridge orifice under gravity, which acts to block the ink-jetting action. At both extremes the standard deviations are large. Between these extremes there is a range of viscosities where drug deposition is maximised and standard deviations are minimised, from 1.1 to 1.5 $mm^2\ s^{-1}$, corresponding to glycerine concen-

Table I Kinematic Viscosity and Surface Tension Values for the Glycerine Solutions Used in the Work

Glycerine concentration %v/v	Kinematic viscosity/mm^2 s^{-1}		Surface tension/mN m^{-1}	
	Mean	SD	Mean	SD
1% v/v	0.95	0.002	N/D	N/D
2% v/v	0.95	0.005	64.8	3.19
3% v/v	0.97	0.003	69.8	1.41
5% v/v	1.03	0.002	70.9	0.77
10% v/v	1.11	0.014	46.4	2.93
20% v/v	1.52	0.015	56.6	3.93
30% v/v	2.03	0.007	52.3	3.32
40% v/v	3.49	0.008	64.4	1.24
50% v/v	4.42	0.010	62.0	2.16
60% v/v	8.90	0.027	66.1	1.61

trations of 10–20%v/v. This indicates the region in which the print head has good control of the solution and defines a viscosity range in which to formulate solutions for ink-jetting with this printer.

Surface tension does not appear to affect deposition. Calvert (16) states that the minimum surface tension needed to jet satisfactorily is 35 mN m^{-1}, while aqueous ink has a surface tension of 55 mN m^{-1}. The solutions used in this work had surface tensions from 46 to 71 mN m^{-1}, well within the jettable range.

Notable also from the data in Fig. 1 is the variation in drug deposition from the black and colour cartridges, the colour cartridges jetting less volume of solution. This is because the colour cartridges produce smaller droplets (1.3 and 4.7 pL) for blue and red, respectively than the black cartridge

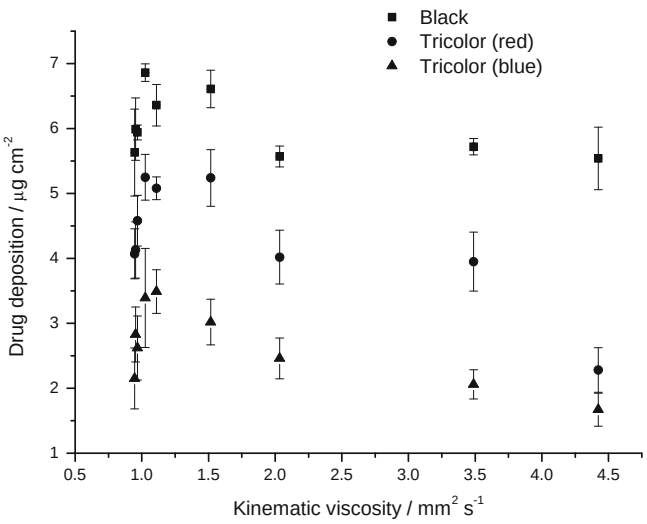

Fig. 1 Drug deposition per single pass onto an acetate film as a function of solution viscosity for the black and colour printer cartridges (drug concentration; 0.5%w/v).

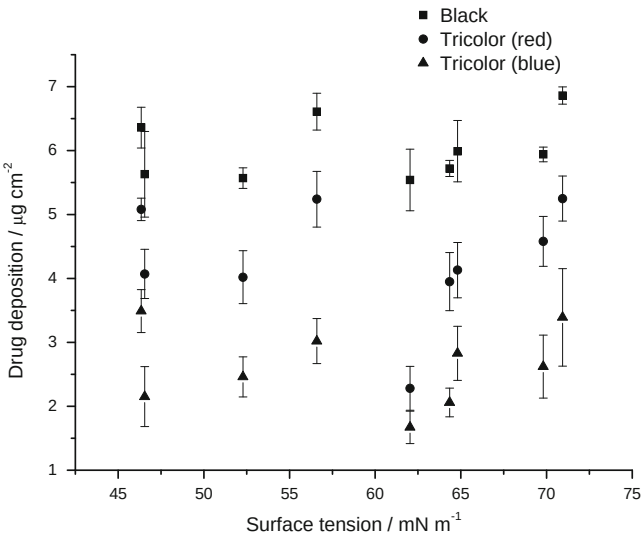

Fig. 2 Drug deposition per single pass onto an acetate film as a function of solution surface tension for the black and colour printer cartridges (drug concentration; 0.5%w/v).

(13.8 pL) (17). SEM images of the cartridge orifices (Fig. 3) suggest the possibility that the technique may be used to jet aqueous suspensions, so long as the diameters of the dispersed particles were well below that of the particular orifice (ideally they would be nanoparticulate) and a method of overcoming particle settling during printing could be found.

All further experiments were conducted using the black cartridge only, since this ensured the highest throughput of solution, but we note that it would be possible to print multi-drug formulations or include other excipients by using the colour cartridge.

A range of aqueous SS concentrations (up to 3%w/v) was prepared with glycerine (10%v/v). This gave a series of drug solutions with a kinematic viscosity of 1.1 mm^2 s^{-1}, optimal for print-head control. Solutions were printed onto acetate sheets and the quantity of drug deposited determined; the data are shown in Fig. 4. An excellent linear correlation (r^2 = 0.9992) between drug concentration in the feed solution and drug deposition is seen, with drug concentrations on the film ranging from 5 to 40 µg cm^{-2} per print pass. Importantly, the standard deviations of the deposited drug concentrations are very low, critical when preparing low-dose formulations.

Having determined the optimum solution viscosity for printing and demonstrated that the deposited dose was proportional to feed concentration, the use of the printer to deposit salbutamol sulphate onto an oral film was assessed. Salbutamol sulphate is indicated for treatment of asthma in children under 2 at an oral dose of 100 µg per kg of body weight (14). Although the BP monograph does not include an oral film preparation, it does specify dose tolerances of 92.5–107.5% for tablets and 90–105% for oral syrups. The substrate film selected was a commercially available edible

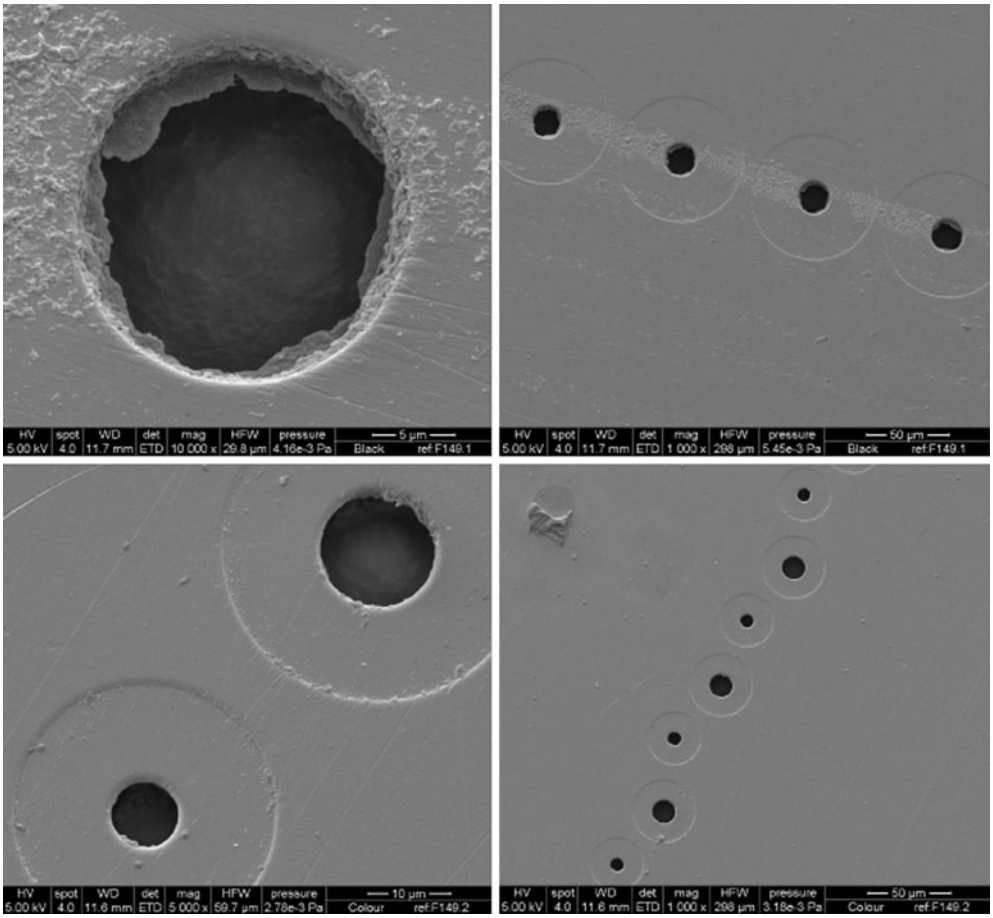

Fig. 3 SEM images of the cartridge orifices at 10,000x (*left*) and 1000x (right) magnifications for the black cartridge (*top*) and colour cartridge (*bottom*).

starch paper, chosen for its homogeneity, flat surface, pleasant taste and rapid oral disintegration. Various size squares of drug solution (3% w/v) were printed, and doses were deposited in either single or multiple passes under the printer head. Concentrations of deposited drug were determined with HPLC; these were compared with the theoretical dose (i.e. calculated from the calibration line in Fig. 4). Results are given in Table II.

Taking the data for 2×2 cm squares first, it is apparent that for deposition in a single print pass the measured amount of drug on the film is in excellent agreement with the theoretical amount calculated from the calibration line (1.1% lower than expected, with a%CV of dose between squares of 2.9%). However, when drug solution is printed in multiple passes, the measured dose deposited is significantly less than expected (average reduction 11.4%). Since the deposited dose was never greater than expected, one concern was that the shearing action of the rollers, used to move the paper through the printer during printing of the films, was eroding the printed drug squares already on the surface. To eliminate this as a factor, drug solution was deposited in 1.5×4 cm rectangles on sections of paper that were not touched by the rollers. However, the data in Table II show again that while with a single pass, the deposited dose was close to the theoretical value (within 4.4%) with multiple passes the dose was significantly lower (10.7%). One design issue with Hewlett-Packard printers is

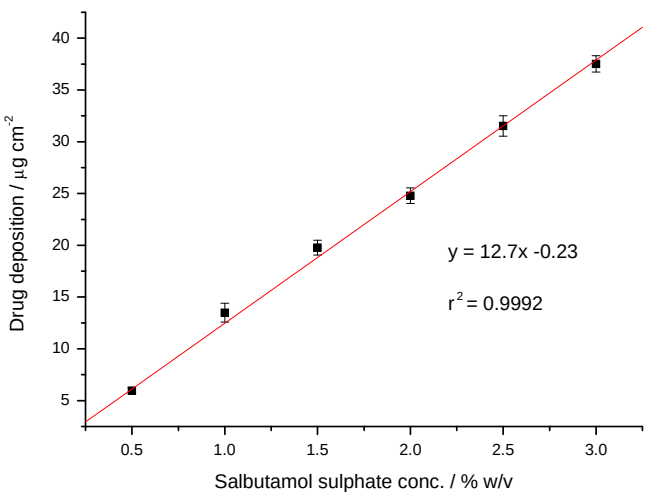

Fig. 4 Drug deposition per pass onto an acetate film as a function of salbutamol sulphate concentration from a black ink cartridge (glycerine concentration; 10% v/v).

Table II Deposition Data as a Function of Printed Area and Number of Passes Under the Print Head

Printed area/cm^2	Number of printed layers	n	Amount deposited (theoretical)/μg	Amount deposited (measured)/μg	% Difference from theoretical	% CV of measured dose
2×2	1	5	150.07	148.38±4.3	−1.1	2.9
2×2	3	6	450.21	398.92±11.7	−11.4	2.9
2×2	6	6	900.41	798.17±21.2	−11.4	2.7
1.5×4	1	3	225.10	235.0±5.0	4.4	2.1
1.5×4	2	2	450.20	402.1±6.6	−10.7	1.6
8×8[a]	1	1	600.27	577.10±27.2	−3.9	4.7
8×8[b]	1	3	600.27	546.79±17.1	−8.9	3.1
2×2[c]	1	3	150.07	132.80±4.2	−11.5	8.7

[a] 8×8 square cut into quarters by eye—data presented for 4×4 quarters

[b] 8×8 square overprinted with a cutting grid using a coloured food dye—data presented for data presented for 4×4 quarters

[c] 2×2 cm square printed during first pass under print head—the film was then loaded and passed through the printer but without printing any further drug

that the side of the paper to be printed is loaded face down in the paper tray and the paper sheet itself is turned through 180° prior to passing under the print head. Printing 2×2 cm squares of drug in a single pass under the print head and then passing the printed film through the printer a second time, but without printing any additional drug, also reduced the amount of drug deposited, Table II. It must therefore be assumed that there is a shearing force acting on the paper from the paper tray during uptake. Switching to a printer design that loads paper face-up may alleviate this issue.

It is important to note, however, that although there is some loss of dose if the film must make several passes under the print head, the loss is predictable, and the variation in dose on the final film remained constant (%CV 2.9), well within the tolerances specified in the BP for tablets and oral syrups.

Since unit dose division is often used to prepare personalised doses, larger squares (8×8 cm) were printed onto the starch film. The squares were cut into quarters before drug concentrations were determined (Table II). When squares were divided by eye, a greater variance in dose was observed (%CV 4.7%). Repeating the experiment but overprinting grid-lines on top of the printed square with a green food dye from the colour cartridge significantly reduced the variance (%CV 3.1%), although in both cases the variation in dose is always well within the BP limits stated earlier.

One important consideration when preparing dosage forms is the physical form (amorphous or crystalline) of the drug, since this will materially affect dissolution rate. Here, drug solution is jetted onto the surface of a carrier; the solvent subsequently evaporates leaving the drug in a solid-state. Knowledge of the solid-state formed is important for determining product performance and long-term stability. It was not possible to use XRPD or DSC to determine the physical nature of the drug, since it was present at levels below the detection limits of either technique. Imaging the printed films with light microscopy and SEM did not show the presence of any SS crystals (data not shown). Since the jetted solution also contained glycerine, which can act to prevent crystal growth (5), it seems likely that the drug exists, at least initially, in an amorphous form (although the presence of nm scale crystals cannot be ruled out). Over time the drug may crystallise, but the purpose of using TIJ in this context is to prepare films for immediate use, and hence long-term stability is not a major issue.

Another consideration is the size of the final dosage form, especially when considering paediatric patients. Here, the TIJ system achieved deposition in a single pass of ca. 38 μg cm^{-2}. To achieve a final dose of 500–1000 μg would thus involve a reasonably large area of film (13–26 cm^2), but of course the same dose could be achieved by printing multiple times on a smaller area.

Finally, a recent study by Garsuch and Breitkreutz (15) showed that incorporation of certain drugs into fast-dissolving oral films resulted in an increase in dissolution time (a result of a slight increase in film thickness as well as an interaction between the drug and the polymer). Dissolution times (i.e. the time required for gelation to occur) for the plain and drug-printed starch films used here are given in Table III. There is no significant difference in gelation time between drug-loaded and plain

Table III Dissolution (gelation) Time for Plain and Drug-Loaded Starch Films

Film	Dissolution time/s
Plain starch	10.4±1.0
SS (single pass)	9.6±0.5

films ($p = 0.195$, $\alpha = 0.05$). This implies that preparation of a dose by deposition on a surface does not affect the mechanical properties of the carrier film in the way that blending of drug and polymer prior to film casting does. Clearly, if the drug changed physical form upon storage, then this may be manifest in a change in either the mechanical properties of the film or the mouth-feel of the product, but again the effects of long-term stability are not the main focus of this work.

CONCLUSION

TIJ technology is ideally suited to deposition of aqueous drug solutions onto thin polymer films. The printer employed in this work operated most effectively when the viscosity of the feed solution was between 1.1 and 1.5 $mm^2\ s^{-1}$, corresponding to glycerine concentrations of 10–20%v/v. The surface tension values of all solutions were in the acceptable range for jetting, so no effect of surface tension was seen. Hence, formulation of a drug solution to be printed simply requires control of viscosity, assuming the drug does not degrade significantly in aqueous solution, nor precipitate. Addition of glycerine helps achieve both aims. Drug deposition onto an acetate film was seen to vary linearly with feed concentration, which means that TIJ is ideally suited to preparation of low-dose medicines.

Salbutamol sulphate was successfully deposited onto an edible potato starch film. When deposition was achieved with a single pass under the print head, the measured dose was within ± 5% of the theoretical dose. When deposition was achieved with multiple passes under the print head, the measured dose was always lower, and outside the ± 5% limit, of the theoretical dose. It is posited that this is a result of shearing forces eroding the existing dose during paper handling. However, the losses are predictable, and the variation in dose, irrespective of the size of the printed area or number of passes under the print head, was always less than 5%.

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