A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs

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Received 18 April 2013; revised 20 June 2013; accepted 2 July 2013

Published online 31 July 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23678

ABSTRACT: The purpose of this study was to formulate printable dosage forms for a poorly soluble drug (piroxicam; PRX) and to gain understanding of critical parameters to be considered during development of such dosage forms. Liquid formulations of PRX were printed on edible paper using piezoelectric inkjet printing (PIJ) and impression printing (flexography). The printed dosage forms were characterized using scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM–EDX) and the amount of drug was determined using high-performance liquid chromatography. Solutions of PRX in polyethylene glycol 400 (PEG-400):ethanol (40:60) and in PEG-400 were found to be optimal formulations for PIJ and flexography, respectively. SEM–EDX analysis revealed no visible solid particles on the printed dosage forms indicating the drug most likely remained in solution after printing. More accurate drug deposition was obtained by PIJ as compared with flexography. More than 90% drug release was achieved within 5 min regardless of printing method used. The solubility of drug in solvents/cosolvents, rheological properties of formulations, properties of substrate, feasibility and accuracy of the printing methods, and detection limit of analytical techniques for characterization of printed dosage forms are some of the concerns that need to be addressed for development of printable dosage forms of poorly soluble drugs. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3694–3704, 2013

Keywords: personalized medicine; preformulation; inkjet printing; flexography; SEM–EDX; physical characterization; poorly water-soluble drugs; oral drug delivery; formulation; microscopy

INTRODUCTION

The need for developing personalized medicine is a subject of current discussion, as each human being is unique, for example, in terms of metabolizing capacity, genetic profile, and age. Furthermore, individualized therapy by coadministration of multiple medicines might be a viable option. Therefore, it may be important to personalize drug doses to ensure safe and effective treatment.[1] Moreover, dose-escalation studies during early clinical trials also require dosage forms that could be delivered and made in a flexible way.[2] In such a scenario, printable dosage forms can provide an efficient solution for the delivery of personalized medicines by allowing dosage flexbility and the possibility to accurately manufacture microdoses of potent drugs.[3,4]

There have been recent development and advancements toward manufacturing of pharmaceuticals by various printing techniques such as inkjet and flexographic printing techniques, offering the possibility for dosing of personalized medicines.[3–10] A novel approach for personalized delivery of salbutamol sulfate by thermal-inkjet printing of the low-dose drug onto commercially available oral starch films has been proposed by Buanz et al.[4] Moreover, a new approach for tailoring controlled-release oral dosage forms by depositing accurate amount of drug using inkjet printing and applying variable polymer coatings by flexographic printing to achieve desired drug release has been suggested by Genina et al.[7] A drop printing technique was used by Hsu et al.[9] to fabricate naproxen–polyvinylpyrrolidone (PVP) solid dispersions with chitosan and hydroxypropyl methylcellulose films. Moreover, the application of flexography for preparation of immediate-release orodispersible films has been demonstrated by Janßen et al.[10]

Figure 1 depicts the schematic diagram explaining the basic principle for flexography and for drop formation in piezoelectric inkjet printing (PIJ). As shown in Figure 1a, flexographic printing unit mainly consists of the following components: (1) a printing plate (with desired printing pattern in form of embossed pattern on a rubber/polymeric film) attached to a plate roll that rotates anticlockwise against the clockwise rotation of (2) an anilox roll that carries the uniform layer of printing ink, scratched by (3) a doctor blade that removes the excess ink. The ink is then transferred to the embossed pattern (square pattern in this case) on the printing plate, which then carries the ink to the paper substrate attached to (4) an impression roll that rotates in clockwise direction, leading to the impression of the printing ink on the paper substrate.[11] The same cycle can be repeated several times on the same area of the paper to generate several printed layers on top of each other.[7,10]

In case of PIJ, drop formation is quite crucial (Fig. 1b). For an optimal ink, there is a formation of liquid stream or column after jetting from the nozzle, followed by formation of an elongated tail, which then ends up in a single primary drop as it

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This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com.

Journal of Pharmaceutical Sciences, Vol. 102, 3694–3704 (2013)

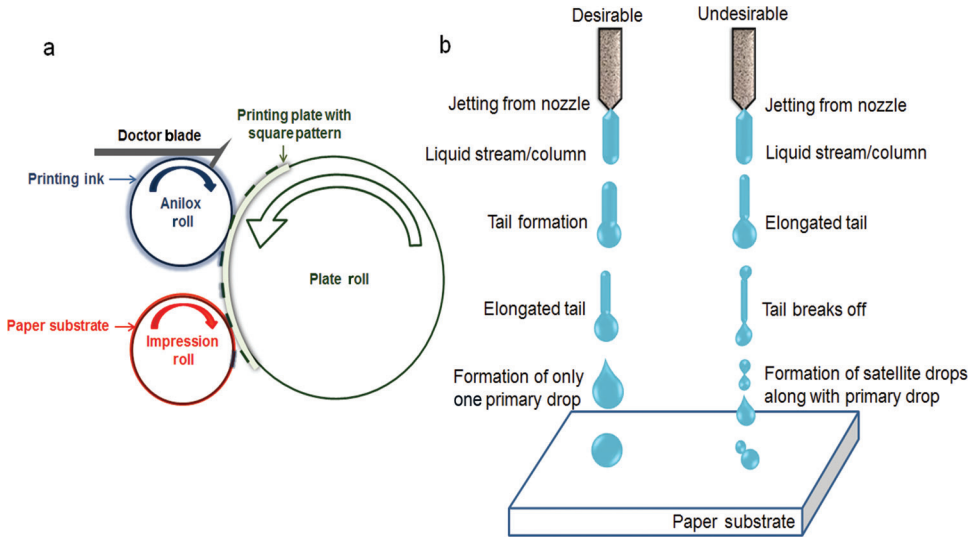

Figure 1. Schematic diagram explaining the principle of (a) flexography (b) drop formation in piezoelectric inkjet printing.

approaches the substrate, resulting in a good quality print. On the other hand, if the ink is not optimal in terms of viscosity and surface tension, there is a possibility that the tail breaks off on its way toward the substrate resulting in formation of satellite drops along with the primary drop, resulting in a bad quality print.[12–14]

In the present study, piroxicam (PRX) was selected as a model compound (Fig. 2) to manufacture printable dosage forms. PRX is known to have a slow dissolution rate and poor aqueous solubility.[8] The drug was printed on edible paper substrates using two printing methods: (1) inkjet printing and (2) flexography. The printed dosage forms were evaluated for drug content, distribution of PRX on the substrate, and dissolution behavior and, the results from both printing techniques were compared. Moreover, in this paper, we propose a roadmap as a preliminary guide for formulation and manufacturing of printable medicines.

EXPERIMENTAL

Materials

Piroxicam (USP32) was purchased from Chr. Olesen Pharmaceuticals A/S (Gentofte, Denmark) and was found to be anhydrate form-I (CSD Refcode: BIYSEH) by X-ray powder diffraction. Polyethylene glycol 400 (PEG) (Sigma–Aldrich, Steinheim, Germany), ethanol (≥96.1%; Etax A, Altia OYj, Finland), acetone, 2-propanol, water (Milli-Q; Millipore, Billerica, Massachusetts), glycerol (≥85%; J.T. Baker, Deventer, Holland) and propylene glycol (PG) (≥99.5%; Sigma–Aldrich, Germany) were used to optimize formulations for printing. Edible icing sheets, used as printing substrates, were purchased from Sutton Valence, Kent, UK. The edible icing sheets (hereafter referred to as edible paper) were composed of corn starch, corn syrup (maltose and oligosacharides), corn syrup solids (dextrose), cellulose, glycerine, sugar, vegetable oil, gum arabic (polysaccharides), polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate), vanilla (vanillin, piperonal), titanium dioxide, and citric acid. Potassium dihydrogen phosphate (Sigma–Aldrich) and phosphoric acid were of analytical grade and used for phosphate buffer preparation in high-performance liquid chromatography (HPLC) analysis. Acetonitrile (HiPerSolv CHROMANORM, VWR International, Leuven, Belgium) and MiliQ water (Millipore) were used for mobile phase and sample preparation in HPLC analysis.

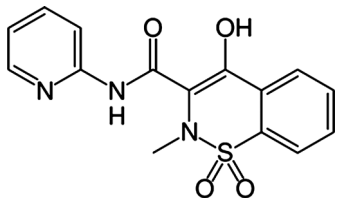

Figure 2. Chemical structure of piroxicam.

Solubility Studies in Various Solvents and Cosolvents

An excess amount of PRX anhydrate form-I was suspended in 1 mL of different solvents namely, water, ethanol, 2-propanol, acetone, glycerol, PG, and PEG. The suspensions were kept on a thermo shaker (Biosan; PST-100 HL) at 25°C and 700 rpm for 24 h. The suspensions were then centrifuged at 7000 rpm for 10 min and the supernatant was analyzed using a UV/Vis spectrophotometer (PerkinElmer; Lambda 25) to detect dissolved amount of PRX. The residual form of the drug was detected using optical microscopy (EVOS XL; AMG), and ATR-FTIR spectroscopy (SpectrumTwo, UATR Two, PerkinElmer, Llantrisant, UK).

Preparation of Printable Formulations

Different ratios of PEG:ethanol formulations (30:70, 40:60, 50:50) were used for inkjet printing, whereas 100% PEG-400 solution was printed using flexography. The PRX solutions used for inkjet printing were filtered with 0.45 μm and then with 0.2 μm polypropylene membrane filters (Whatman, GE Healthcare, Piscataway, New Jersey) before printing, whereas an unfiltered solution of PEG-400 was used for flexography. The prepared solution and suspension (PEG–ethanol) formulations were also deposited on the edible paper by manually pipetting 10 μL of each formulation.

Viscosity and Surface Tension Measurement

Viscosity measurements of the printable formulations were conducted with a Physica MCR 300 rheometer (Anton Paar, Ostfildern, Germany) at 22°C for the flexographic ink formulation and at 30°C for the inkjet ink formulations. Surface tension values of the ink formulations were measured using the pendant drop method at 22°C (CAM 200; KSV Instruments Ltd., Helsinki, Finland). The viscosity and surface tension measurements were performed with ink solutions without PRX and in triplicates.

Piezoelectric Inkjet Printing

Piezoelectric inkjet printing was performed with a Dimatix DMP-2800 printer (Fujifilm Dimatix Inc., Santa Clara, California), using a replaceable cartridge (DMC-11610) with 16 nozzles, each producing a typical drop volume of 10 pL. Printing was performed under ambient conditions [45 ± 5% relative humidity (RH) and 21 ± 1°C] with single nozzle at the firing voltage of 30 V and cartridge temperature of 30°C. The drops were deposited at a drop spacing of 10 μm as 1 cm × 1 cm squares on the edible paper substrate. This was equal to a total of 1,002,001 drops per square (1 cm^2) according to Dimatix software. The total delivery volume in one square was approximately 10.02 μL/cm^2 (equivalent to 50.1 μg drug/cm^2).

Flexography (Contact/Impression Printing Method)

Flexographic printing was carried out using a laboratory scale printability tester (IGT Global Standard Tester 2; IGT Testing Systems, The Netherlands) at 22°C/50% RH. The amount of PRX solution was controlled with an anilox roll having a cell angle of 45°, a cell volume of 20 mL/m^2 and a line count of 40 lines/cm. The drug was transferred to the printing substrate using a patterned photopolymer plate (Ohkaflex, Espoon Painolaatta, Finland) consisting of 2 × 8 array of 0.5 cm^2 squares. The pressure between the anilox roll and the printing plate was 100 N, whereas the pressure between the printing plate and the substrate was 50 N. The printing speed was 0.5 m/s. Two different amounts of layers (10 layers and 20 layers) were printed on the same square and the photopolymer plate was cleaned in between printing of each layer.

Determination of % Assay Values by HPLC

The printed area of the edible paper was cut and dispersed in 1:1 ACN(Acetonitrile)–water mixture. The dispersions were sonicated and then filtered through 0.22 μm nylon filter paper (Q-max® RR Syringe filters). The filtrates were analyzed using HPLC (Merck LC System; Hitachi Ltd., Tokyo, Japan). Chromatographic separations were achieved on a C-18 column (100 × 2.1 mm^2 internal diameter, particle size 5 μm; Supelco Discovery). Mobile phase system was a mixture of 95% of 10 mM potassium dihydrogen phosphate buffer (pH 3, adjusted with phosphoric acid) and 5% of ACN as the mobile phase A and 100% ACN as the mobile phase B. An injection volume of 50 μL was used and the flow rate was 1 mL/min. Peaks were evaluated at 360 nm, and the method was linear between 1 and 100 μg/mL.

Scanning Electron Microscopy–Energy-Dispersive X-Ray Spectroscopy (SEM–EDX)

A field emission Zeiss XB-1540 Scanning Electron Microscope (Carl Zeiss GmbH, Oberkochen, Germany) was used for morphological characterization of printed dosage forms. A thin carbon coating was evaporated onto the sample surfaces for enhanced conductivity. SEM images were acquired at 3 kV for high resolution structural information.

The SEM was equipped with an energy dispersive X-ray spectroscopy system (Oxford Instruments, Oxfordshire, UK), which was used for elemental identification and mapping. SEM–EDX is a widely used method for elemental analysis in various other fields.[15,16] In pharmaceutical field, it has been used for monitoring inorganic elements during coating of tablets[17] and for foreign matter identification of solid dosage forms.[18] By scanning the electron beam across the sample surface and detecting the emitted X-rays from each pixel, the elemental distribution can be point located and related to the SEM image. Beam energy of 20 kV was used to yield sufficient X-ray signal for mapping, and the resulting mapping images were processed as TruMaps.

Drug Release and Stability Studies

Drug release studies were performed using simulated gastric fluid media (without pepsin) [as suggested in United States Pharmacopeia (USP) for dissolution of PRX capsules]. The buffer media was prepared by dissolving 2 g sodium chloride and 14 mL of 5 N HCl in 1000 mL water (pH 1.2). The printed formulations were dispersed in 10 mL of the media at 37°C and filtrate (0.22 μm filer) was analyzed at predetermined time intervals (5, 10, 30, 60 min).

For preliminary evaluation of stability, the printed dosage forms were kept under ambient conditions (20°C–25°C/30%–40%RH) and analyzed for physical and chemical stability using SEM-EDX and HPLC, respectively.

RESULTS

Solubility in Different Solvents and Cosolvents

Solubility of PRX in different solvents was determined to select the solvent with high PRX solubility and practical feasibility for printing. Table 1 shows the solubility values of PRX in various solvents and the residual solid form, determined by ATR-IR spectroscopy and light microscopy (Supplementary Section A). Solubility was found to be the highest in acetone. However, acetone was not suitable for printing either by inkjet printing or by flexography due to a rather low boiling point (56.2°C).[19] Considering the solubility values, water, ethanol, PG, and PEG-400 were selected to determine various cosolvent systems for subsequent printing. Although solubility was relatively low in water, it was included as component in the cosolvent systems due to the specific interest to obtain monohydrate form of PRX after recrystallization. Thus, cosolvent systems were chosen to obtain both AH and MH forms, so that it is possible to investigate the difference in behavior of printed AH and MH forms. However, as shown in Table 2, solubility was quite low (<2 mg/mL) in all cosolvent systems containing water. Therefore, PEG–ethanol and PEG were selected for PIJ and flexographic printing methods, respectively.

Formulation Optimization for Printing

The key feature for successful printing with piezoelectric inkjet techniques is formation of stable and repeatable droplets having uniform velocities and volumes during jetting from the

 DOI 10.1002/jps.23678

Table 1. Solubility of PRX in Different Solvents

Solvent	Dynamic Viscosity (mPa s)[19]	Surface Tension (mN/m)[19]	Solubility (mg/mL)	Residual Solid Form
Water	1.002	72	0.01	MH
Ethanol	1.074	22.1	1.5	AH-I + AH-II
2-Propanol	2.4	21.2[a]	0.7	AH-I
Acetone	0.3[a]	22.9[a]	25	AH-I+II
Glycerol	1490[20]	63.4	0.15	AH-I
PG	58.1	40.1	1.7	AH-I
PEG	105–140	44	14	AH-I

[a]Values from Dortmund data bank (www.ddbst.com) (Note: AH—anhydrate; MH—monohydrate).

Table 2. Solubility of PRX in Different Cosolvent Systems

Cosolvent	Ratio	Solubility (mg/mL) at 25°C	Residual Solid Form
EtOH–water	50–50	0.2	MH
PG–water	30–70	0.12	AH-I + MH
PG–EtOH	30–70	1.9	AH-I
PG–EtOH–water	30–35–35	0.9	AH-I + MH
PEG–water	30–70	0.2	AH-I + MH
PEG–EtOH	30–70	4.3	AH-I
PEG–EtOH–water	30–35–35	1.6	AH-I + MH
PEG–EtOH	40–60	6.3	AH-I
PEG–EtOH	50–50	8.7	AH-I

Table 3. Measured Dynamic Viscosity and Surface Tension Values of Printable Formulations

Formulation	Dynamic Viscosity (mPa s)	Surface Tension (mN/m)	Printing Method
PEG:Ethanol (30:70)	3.5 ± 0.1	24.9 ± 0.2	Piezoelectric inkjet
PEG:Ethanol (40:60)	4.9 ± 0.1	27.6 ± 0.4	
PEG:Ethanol (50:50)	7.1 ± 0.1	29.4 ± 0.4	
PEG (100%)	94 ± 0.2	42.2 ± 0.3	Flexography

nozzle. Therefore, viscosity and surface tension of the ink formulation are the most crucial physical properties. The desirable viscosity and surface tension of piezoelectric inkjet inks are in the range of 1–30 mPa s and 25–50 mN/m, respectively.[21–23] Additionally, the concentration of drug in the solution used as ink formulation should be below saturation solubility of the API to avoid crystallization on the nozzle tip.[7] Considering these, the PRX solutions were prepared in 30:70, 40:60, and 50:50 (v/v) ratios of PEG:ethanol with the concentrations of 4, 5, and 6 mg/mL, respectively. As shown in Table 3, viscosity and surface tension of all the three formulations were within the range of printability. During jetting, all formulations showed similar drop formation with drops forming liquid columns, which transform into elongated tails and then to actual droplets (Fig. 1b). However, in case of PEG–ethanol (30:70) formulation, the tail breaks off resulting in the formation of satellite drops, which were observed during jetting (Fig. 1b). Satellite drops are highly undesirable during jetting because the formation of satellite drops negatively influences the shape of the dots on a substrate, affecting the quality of the print.[12] Satellite formation was not detectable with the other two formulations. However, clogging of the nozzles for PEG:ethanol formulation (50:50) was observed if printing was continued overnight. Thus, the PEG:ethanol formulation (40:60) was found to be the optimal formulation for printing of PRX as it showed the best performance regarding reliability in jetting stable drops for long periods. The PRX dosage forms prepared by PIJ printing on edible paper are shown in Figure 3.

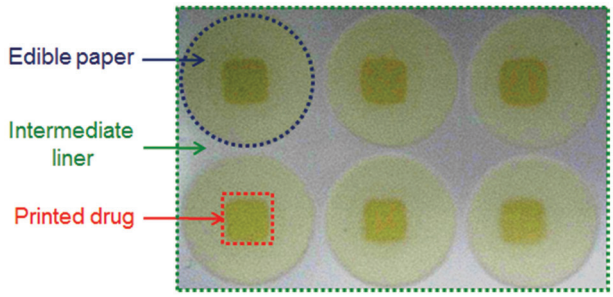

Figure 3. Printed dosage forms of piroxicam (PRX) prepared by piezoelectric inkjet printing. (Note: Printable ink is 40:60 PEG–ethanol solution containing 5 mg/mL PRX).

The PEG:ethanol (40:60) solution and suspension were also deposited by manual pipetting onto the edible papers. The concentration of PRX in suspension was kept at 12 mg/mL so that at least 5 mg/mL of the drug is in the solid state (considering the solubility of 6–7 mg/mL), that is, the same amount of the drug in solid state corresponding to the concentration of PRX in the solution formulation for PIJ printing. The reason for printing suspension formulation was to use it as a positive control in observing possible crystallization of PRX after printing of the solution formulations.

Flexographic printing inks have a much wider window regarding required ink properties as compared with the inkjet

printing inks. The desired properties for the inks with respect to surface tension and dynamic viscosity are typically <40 mN/m and 50–500 mPa s.[24] The use of viscous solution is preferred for flexographic printer used in the current study, so that the formulation can retain on the doctor blade (Fig. 1a) without leaking from the sides during printing. Considering both, solubility and viscosity, the API solution in pure PEG solvent was found to be the optimal formulation for flexography. The same solution was also deposited on edible paper by manual pipetting of 10 μL PRX solution in PEG (14 mg/mL).

Evaluation of Printable Dosage Forms

Determination of Printed Amount of Drug

Table 4 summarizes formulations for different printing methods, the size of the area of the printed dosage forms, the obtained amount of drug in each printed area and the related %RSD values. The theoretical drug amount was 50.1 μg/cm^2 for PIJ, with an experimentally obtained amount of 52 μg/mL. The theoretical amount of the printed drug per unit area for flexography needs to be estimated on a different basis. This is because of the fact that the amount of the printed drug depends on the characteristics of the formulation, the substrate and the printing parameters used. In addition, some unknown factors also affect the printed amount in flexography. In the current study, actual printed amounts of the drug with flexography were found to be 7.6 μg per 0.5 cm^2 (10 layers) and 13.2 μg per 0.5 cm^2 (20 layers). Moreover, %RSD values were found to be higher for flexography as compared with inkjet printing and manual pipetting. It is also worth noticing that the amount/layer for the sample with 20 printed layers is slightly less than the amount/layer for 10 printed layers. This gives an indication of a "smearing effect" while printing multiple layers on top of one over another on the same area. Moreover, the number of subsequently printed layers without losing the drug from the previous layer depends on the absorbing capacity and porosity of the printing substrate as well as on the evaporation rate of the ink solvent. Thus, in case of flexography, it is critical to validate the printed amount of the drug if changes have been made either in formulation or substrate or number of layers or printing parameters. Overall, PIJ was found to be more accurate and precise printing method as compared with flexography and manual pipetting.

Table 4. Determination of Drug Amount in Printed Dosage Forms (by HPLC)

Formulation	Printing Method	Concentration of PRX in mg/mL (solubility)	Area of the Paper Containing Drug in cm^2	Amount on Each Square in μg	%RSD in drug Amounts
40:60 PEG–ethanol solution	Piezoelectric inkjet	5 (6.3)	1	52 (50.1[a])	1.4
	Manual pipetting	5 (6.3)	2	46.7 (50[a])	3.1
PEG solution	Flexography (10 layers)	14 (14)	0.5	7.6	14.3
	Flexography (20 layers)	14 (14)	0.5	13.2	14.8
	Manual pipetting	14 (14)	2.5	135.8 (140[a])	2.6
40:60 PEG–ethanol suspension	Manual pipetting	12 (6.3)	2	119.6 (120[a])	4.8

[a]Theoretical/calculated amount; theoretical amount was unknown for flexography samples.

Characterization of Printed Dosage Forms

Routine solid-state analytical techniques (XRPD, Raman/NIR/ATR-IR spectroscopy) were not able to detect the drug in the printed dosage forms. This may be attributed to the fact that (1) the drug content in the printable formulations was very low, and, (2) there was background interference from ingredients of edible paper and ink formulation components.

The morphology of the printed dosage forms was observed by SEM. As shown in Figures 4b–4e, no visible solid drug particles were detected in any of the printed dosage forms containing solution formulation. Needle-shaped crystals were observed in the dosage forms prepared from suspension formulation (Fig. 4f).

Scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM–EDX) was used to understand the distribution of PRX in the printed dosage forms. The idea was to detect the drug through thorough elemental analysis (specifically detecting sulfur) of the SEM images of the printed dosage forms.

DOI 10.1002/jps.23678

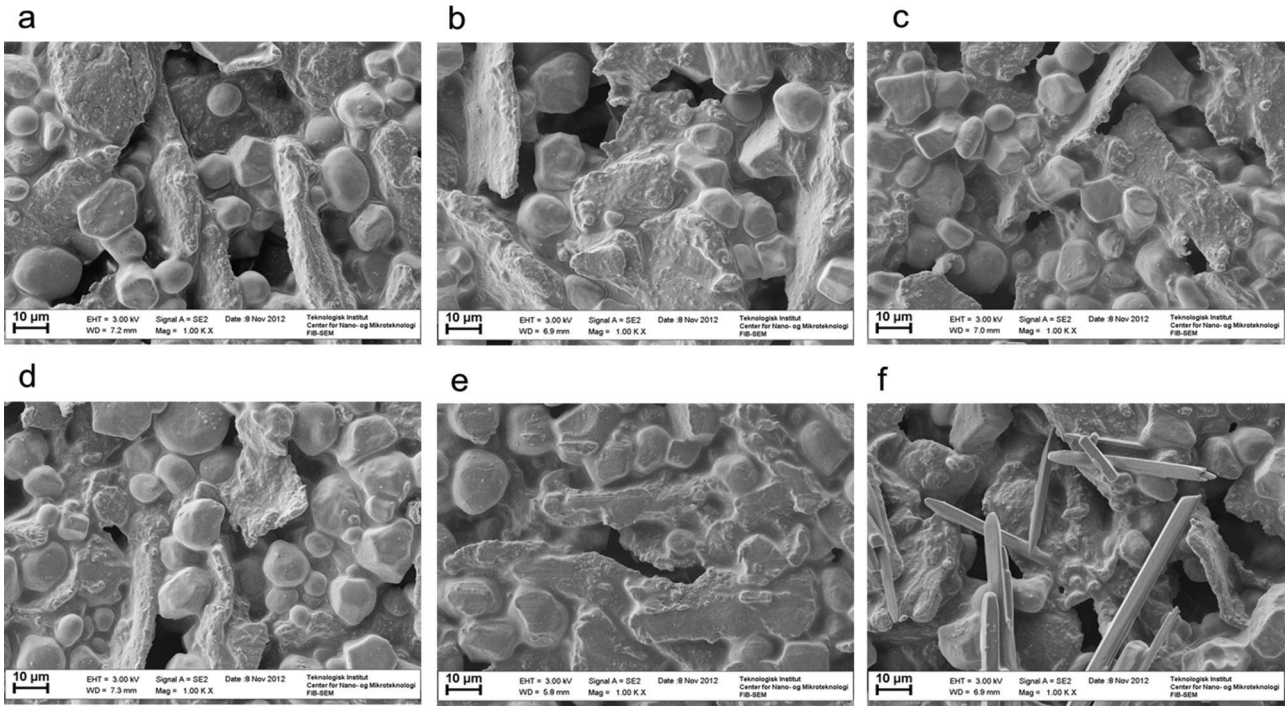

Figure 4. SEM images of (a) blank edible paper; printed dosage forms prepared by (b) inkjet printing, and, (c) manual pipetting of PEG–ethanol solution, (d) flexography, (e) manual pipetting of PEG-400 solution, (f) manual pipetting of PEG–ethanol suspension.

This was possible because none of the ingredients of edible paper consisted of sulfur as part of their chemical structure [cf. material section and also confirmed by EDX (Supplementary Section B)]. So, the hypothesis was to detect the areas on the printed dosage forms consisting of sulfur that would indirectly reflect the areas consisting of PRX. This will give information about the distribution of PRX throughout the edible paper in the printed dosage forms.

In case of PEG–ethanol suspension deposited on the edible paper, sulfur was detected in the EDX spectra (Fig. 5a). The detected sulfur was observed in the form of "needle-pattern" (Fig. 5e), corresponding to the same "needle-pattern" as in the electron image (Fig. 5a). The "needle-pattern" was quite distinctly visible in the sulfur mapping image (Fig. 5e). Although in the carbon and oxygen mapping images (Figs. 5c and 5d), the "needle-pattern" was merged with background because of the presence of these elements in both PRX and in the components of the edible paper. In the printed dosage forms, some kind of "pattern" of particles could be assumed in the sulfur mapping image, corresponding to possible crystallization of the drug in the printed dosage forms prepared from solution-type ink formulations. However, as shown in Figure 6b, sulfur was detected at very low level and was found to be evenly distributed throughout the edible paper (Fig. 6e). This indicates that there were no solid particles in the detectable range of SEM–EDX. Perhaps, the signal from the mapped area was too low as sulfur was evenly distributed throughout the edible paper. This gives an indirect indication for the drug being in solution state/molecularly dispersed state during or after printing on to the edible paper. If there would have been formation of crystalline or amorphous particles, the sulfur would have been detected in form of some "pattern" resembling the drug particle morphologies that would be distinguishable from the background.

Drug Release and Stability Studies

Piroxicam is known to have a slow dissolution rate.[8] There have been several attempts for improving solubility and dissolution rates of PRX through preparation of its amorphous form by solid dispersion[25] or by milling[26] approaches. In the present study, printed dosage forms generated by both printing methods (PIJ and flexography) showed more than 90% drug release in SGF media (USP) within 5 min. The faster drug release may be attributed to the fact that the drug was in solution state and therefore, immediate release from the edible paper substrate can be achieved upon contact with the dissolution media. The printed dosage forms were found to be chemically and physically stable for 1 month under ambient conditions (20°C–25°C/30%–40% RH).

DISCUSSION

Formulation of printable API-containing ink is a challenging task. There is no universal composition of the ink to be selected that would be suitable for each drug to be printed either with inkjet (piezoelectric or thermal) or flexographic printing techniques. Here, we aim to give a suggestion for a preliminary preformulation approach for development of printable dosage forms for inkjet and flexographic printing. The proposed methodology has been delineated in Figure 7. The properties of the API, especially its solubility in different solvents, viscosity, surface tension, and evaporation rate of the solvent are the key factors to consider. If the drug is water soluble (hydrophilic), it is advisable to go for the safest water-based formulation, where water will be the main component. In case of poorly water-soluble or practically water-insoluble compounds (either hydrophilic or hydrophobic), it would be recommended to choose a pharmaceutically approved solvent with the highest

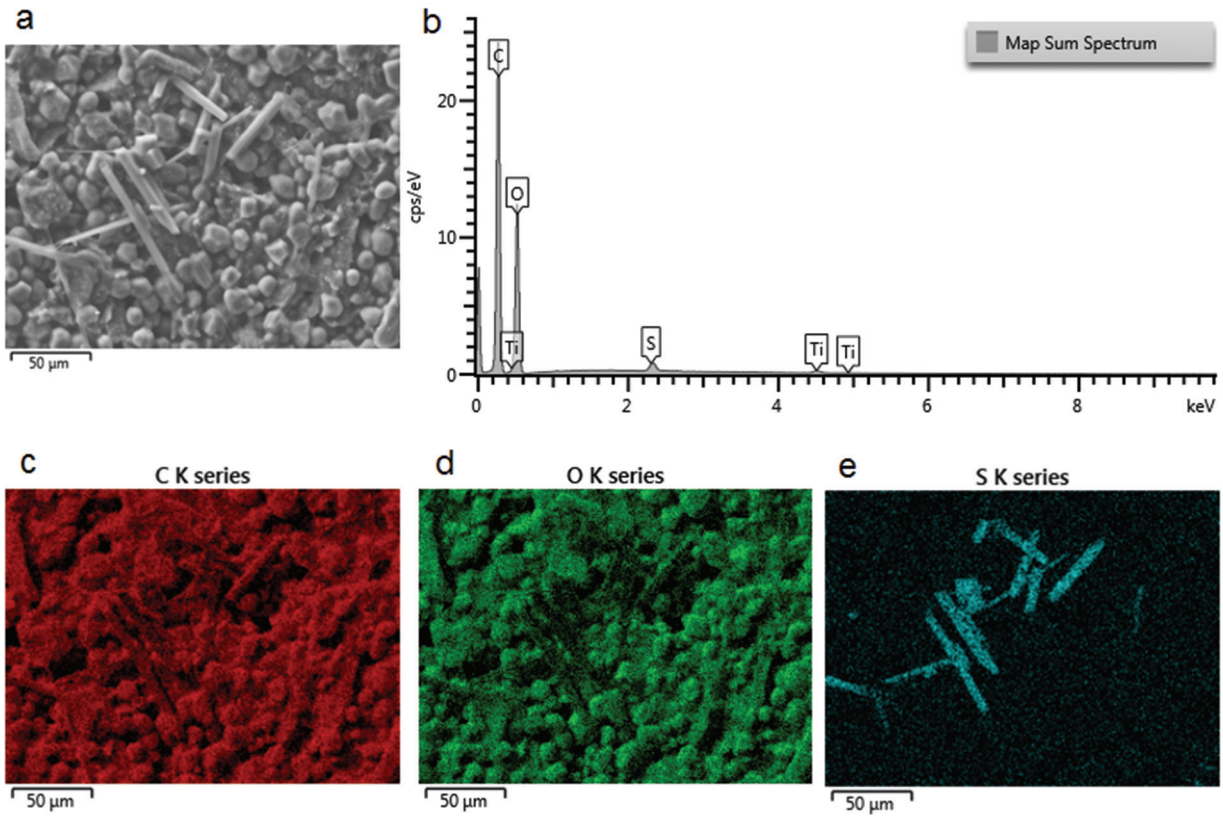

Figure 5. SEM–EDX images of printed dosage forms prepared by manual pipetting of PEG–EtOH suspension: (a) SEM image (20 kV), (b) EDX elemental spectrum, (c) carbon mapping, (d) oxygen mapping, (e) sulfur mapping.

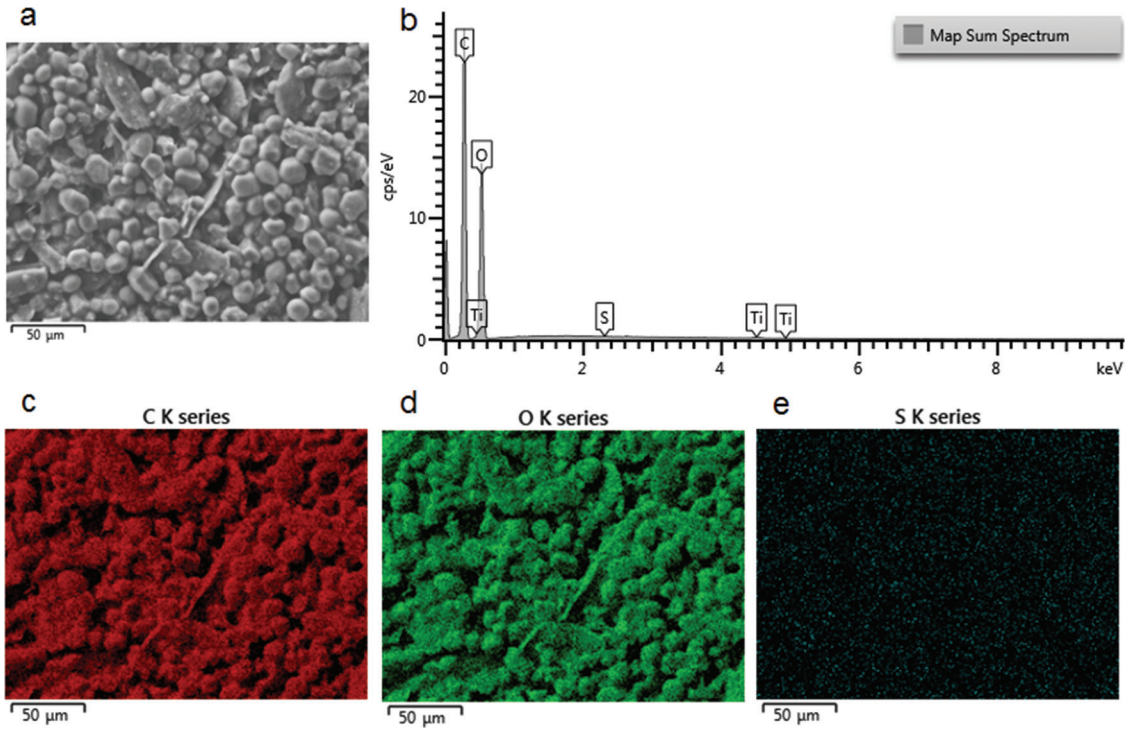

Figure 6. SEM–EDX analysis for printed dosage forms prepared by inkjet printing: (a) SEM image (20 kV), (b) EDX elemental spectrum, (c) carbon mapping, (d) oxygen mapping, (e) sulfur mapping.

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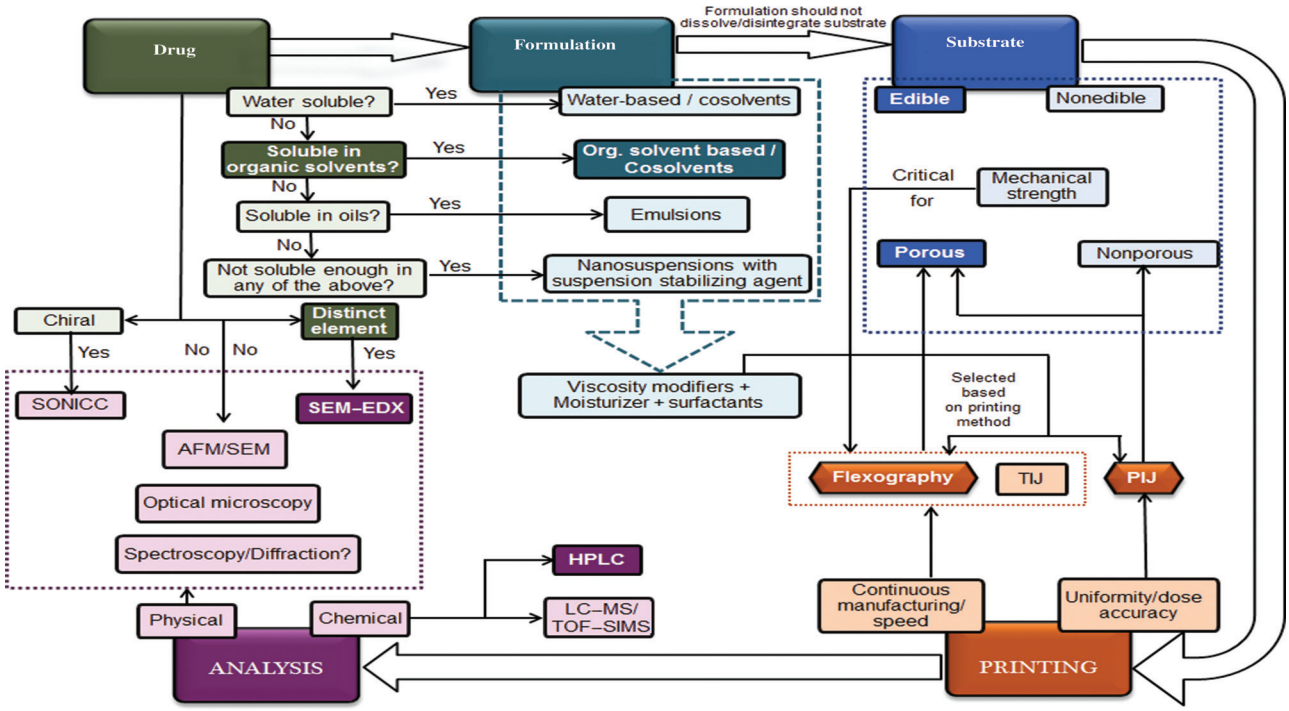

Figure 7. Suggested preliminary approach for preformulation of printable dosage forms, depicting critical factors to be considered at each stept. (Note: SONICC—second order nonlinear optical imaging of chiral crystals, SEM—scanning electron microscopy, EDX—energy dispersive X-ray spectroscopy, AFM—atomic force microscopy, TIJ—thermal inkjet, PIJ—piezoelectric inkjet). (Highlighted part under each section represents the methods selected in the current study.)

solubility of API in it. However, the solvent should be pharmaceutically approved one. Ethanol, isopropanol, or PG can be selected as first choices. It may be possible to prepare printable emulsions if there is a solubility advantage in oils. However, the use of emulsions for printing is neither reported in literature nor attempted by us and should be investigated in future studies. As already widely known, the liquid ink has to possess properties such as optimal viscosity and surface tension to guarantee controlled and continuous printing. The critical parameters are different for inkjet and flexographic printing techniques (Table 5). From Table 1, it is obvious that pure solvents of the first choice do not possess properties suitable for inkjet printing. Therefore, cosolvent systems such as PEG–water or PG–water or glycerol–water mixtures are needed to reach the optimal ink properties for inkjet printing. The ratio of solvents in the cosolvent system has to be determined to get the desired printing characteristics, whereas the used drug should still be in the dissolved state. Solid viscosity modifiers such as cellulose derivatives, PVA, PEG, PVP can be added to the solvent to reach an optimal viscosity level.[9,27,28] Surface active agents (surfactants) can also be added to the aqueous API solution to decrease its surface tension, to get an ink in the optimal range for printability. However, use of moisturizing agents such as PEG, PG, or glycerol may help in preventing clogging of the micrometer-sized nozzle due to evaporation of water in aqueous formulations to guarantee continuous inkjet printing.[29] These solvents could also act as viscosity modifiers and this property may also help in preventing evaporation of solvent in case of alcohol based formulations. However, in flexographic printing, inclusion of moisturizing agents is not critical as the cells with wide apertures are used. Heating of the ink formulation can be performed during an inkjet printing procedure to increase the solubility of the compound (or melt it) (or reduce viscosity of the formulation) presuming the printing device contains a heating element.[30] In the case of the flexographic printing technique, pure PEG-400 and PG solvents can be used without addition of any cosolvents if the drug is soluble in them. Another option is to use viscosity-modifying agents such as cellulose derivatives, to increase the viscosity of aqueous or alcoholic API solutions. Surfactants can be added in the case of very high surface tension of the obtained solution. For both printing techniques, solubilizing agents can be added to the ink formulation to enhance the solubility of poorly soluble compounds.[31] Controlled-release properties of the inkjet-printed formulations (API) can be obtained by inclusion of the release-modifying agents such as PVP or PLGA to the ink.[6,13,27]

If the solubility of the drug in any suitable solvent is an issue, formulation of the suspension should be considered. Nanosuspensions may be printed with an inkjet printer; however, a strict control over the particle size is essential to avoid agglomeration and precipitation of the API nanoparticles.[5] Therefore, a careful selection of suspension stabilizing agents is of great importance. The size of the suspended particles is less critical during flexographic printing. The summary for the composition of the printable formulation is presented in Table 5.

A suitable substrate for printing, which acts as the drug carrier is another aspect to be considered. Selection of the substrate depends, firstly, on the printing method in use. For example, mechanical strength and flexibility of the substrate is not crucial for noncontact printing methods. On the other hand, in case of thermal inkjet and flexographic printing techniques, the substrate should possess adequate mechanical strength

Table 5. Composition of Printable Formulations

Printing Technique	Parameters Viscosity (mPa s)/ Surface Tension (mN/m)	Main Solvent	Viscosity Modifying Agent		Surfactants/Stabilizer/ Solubilizing Agent	Moisturizing Agent
			Liquid	Solid		
Inkjet printing	1–30/25–50[13,32]	Water [3,4,7,29,33] ethanol[6,9,29] dimethylacetamide[13] isopropanol	PEG[28] PG[3,7] glycerol [4,7,29]	PVP[6,9,27] PLGA[13,27] cellulose derivatives[28] PVA[28] PEG[28,33]	Tween 20[5,33] PVP[9]	PG[3,7] glycerol[4,7] dimethylacetamide[13] PEG 8000[33]
Flexography	50–500/<40[24]	Water, ethanol[7,10] PEG 400, PG	PEG, PG, glycerol	Cellulose derivatives[7,10] PVP, starch	–	Not necessary

and should be flexible, as fragile substrates will be broken during their bending while feeding. Good absorptivity (wettability, porosity) of the substrate is a key factor, when several layers are printed to gain a therapeutic dose of API in a single unit. Inadequate penetration of the ink inside the substrate matrix in addition to insufficient attachment of the API material to the substrate will result in loss of the API during printing, transport, and storage and, subsequently, cause failure in dose uniformity. Secondly, the route of administration either transdermal, peroral, buccal, or sublingual will guide to the properties of the substrate to be chosen. Edible/digestible films of different composition[34] would be suitable substrates for peroral intake, whereas edibility of the substrate is obviously not of importance in the case of transdermal route of administration. Finally, the solubility and/or interaction of the substrate with the printing ink must be considered. The printable fluid should not cause dissolution or disintegration of the substrate. Therefore, Janßen et al.[10] used an ethanolic solution of rasagiline mesylate during printing onto a water-soluble orodispersible film (not soluble in ethanol) to avoid dissolution/disintegration of the substrate during flexographic printing, although solubility of the API in water is several times higher than in ethanol.[10]

There are several aspects to consider for choosing among printing techniques. Dose uniformity and accuracy of the API in a single unit will be the highest with advanced (a software-guided) piezoelectric inkjet printers, where droplet size and droplet formation are easily controllable and that also allows the calculation of the drug amount to be deposited during printing. However, PIJ is a rather slow method. On the other hand, flexography lacks dosing precision. This method can be good for continuous manufacturing and when accurate dosing is not critical. For instance, flexography is suitable for printing drugs that do not have a narrow therapeutic window. In addition, it could be well applicable for deposition of different layers of API-free polymer inks for modified release purposes.[7] It is worth mentioning that, in case of flexography, the method needs to be validated for each new formulation to know the amount of drug to be printed in a single unit. This is because of the fact that the quantity of the drug printed per unit area depends on the properties of the ink used such as properties of formulation (viscosity, surface tension, evaporation rate, etc.), substrate (porosity, mechanical strength, etc.), and printing process parameters (speed, force). Also, it has been reported that an anilox roll with 11.71 mL/m^2 delivers more drug than an anilox roll with 80 mL/m^2.[10] However, once the method is validated, the printing process itself is fast and robust. Validation is needed also for the off-the-shelf consumer inkjet printers because it is impossible to control the droplet formation with relatively simple devices.[4] Both inkjet and flexographic printing techniques allow a limited amount of the ink to be transferred on the carrier surface. In addition, the properties of the substrate such as holding ability, wettability, and penetration depth toward the printing liquid dictate the amount of the ink that is possible to deposit. By using advanced inkjet printers, the dose (printed amount of the ink) is possible to vary by changing the amount of droplets jetted per square unit and/or by changing the area printed to produce a single dosage form. In case of flexographic printers and the off-the-shelf consumer inkjet printers, the dose is adjustable either by varying the area of the printing pattern (the same as for advanced inkjet printers) and/or by printing subsequent layers on top of already printed ones. The latter operation requires more time to allow drying of the previous printed layer

before applying a new one to avoid/minimize smearing effect. Changing the quality settings for printing (high, normal, low) in the off-the-shelf consumer inkjet printers, the amount of drug can be adjusted as well. However, preliminary experiments are needed to identify the quantity of the ink printed with each quality setting. Varying the concentration of the API in the ink can be another solution to adjust the dose for all printing techniques. However, as discussed previously, the ink transfer is relatively low; therefore, the most concentrated printable solution is preferably used to gain a therapeutic dose, to accelerate the dosing process, and to minimize the consumption of the substrate.[29] High volume production of solid dosage forms is not possible with current inkjet printing techniques. However, this limitation can be overcome if the nozzles with bigger aperture size are used to deliver bigger drops. Furthermore, the issue of clogging due to viscous solutions can be minimized by using bigger nozzles, and suspensions may also be used with bigger nozzles. Another strategy might be to use supersaturated solutions at high nozzle temperature such that the drug will crash out immediately after printing. This method may facilitate generation of metastable solid forms, which may be entrapped in the complex structures of substrates. Instead, flexographic printing technique has been found to be industrially applicable for mass production.[10] Automatic micropipetting is also an alternative method to printing.[29]

Characterization/quality control of the printed pharmaceuticals is another challenging task to consider. The choice of the analytical instruments for quantitative (semi-quantitative) and qualitative analysis depends on the physicochemical properties of the studied API, detection limit of the instrument (the amount of the printed drug is quite low) and specificity and selectivity of the instrument toward detection of the API by discriminating the API from the background interference. If the drug molecule contains an atom(s) that is discrete from atoms of ingredients of the printed ink and the substrate, it is sensible to go for SEM–EDX analysis and detect this distinct atom within a printed dosage form. If the studied drug molecule is chiral, second-order nonlinear optical imaging of chiral crystals will be a useful technique.[9] In case, the drug recrystallizes with distinguished crystal habit, microscopic techniques such as optical microscopy, SEM, and AFM[3,29] may be used. The same techniques, in addition to XRPD, could be used to confirm the presence of polymorphic transformations or the absence of the recrystallization event (e.g., amorphization) of the API after printing.[6,9,10,29] However, XRPD should always be used with the other complimentary techniques as the detection limit of XRPD is relatively poor and the background interference might be high; both the restrictions could lead to false conclusions. Raman, ATR-IR, and NIR, UV/VIS imaging techniques could be applicable as online quality-control methods if the spectrum of the studied API (and different polymorphs) is different from the background spectra.[6,29,30] As with any dosage forms, precise quantitative analysis (dose uniformity) can be conducted by using HPLC[4,10] and LC/MS.[3] Moreover, both techniques can also give indications for chemical stability issues of the printed dosage forms.[33] ToF-SIMS technique can also be used to identify chemical species of the printed API on the substrate surface.[3] Scoutaris et al.[6] used the localized thermal analysis (nanothermal analysis and scanning thermal microscopy) to study the formation and homogeneity of a nanoscale solid dispersion of the inkjet-printed formulations. The dissolution experiments at appropriate testing conditions could be conducted to evaluate the release properties of the API formulations printed using different techniques.[4,6,9,13]

CONCLUSIONS

Printed dosage forms may be considered as potential future drug delivery systems due to the flexibility in manufacturing of personalized medicines. Printing can also serve as a viable method to produce delivery systems for potent poorly soluble drugs to achieve faster drug release as shown in the current study. However, there are various issues yet to be resolved viz. (1) mechanical durability during packaging and storage; (2) understanding interactions between drug and various substrates; (3) understanding the influence of the ink formulations and printing parameters on print quality; (4) detection limit of the analytical techniques for the characterization of printed dosage forms. The development of printable dosage forms is still at an initial stage and research efforts are needed to further enhance the maturity of the approach and to fully explore the potential of the technology.

ACKNOWLEDGMENTS

Center of Excellence for Functional Materials at Abo Akademi University is acknowledged for providing the facilities for inkjet and flexographic printing. Funding from The Academy of Finland through the National Center of Excellence program is acknowledged. The Finnish Funding Agency for Technology and Innovation (Tekes) is also acknowledged for the financial support. Authors are also thankful for the funding from the Danish Council of Technology and Innovation for the Innovation Consortium NanoMorph (952320/2009), as well as Centre for Nano- and Microtechnology at Danish Technological Institute for providing facility to perform SEM–EDX measurement. Authors would also like to acknowledge funding from Danish Council for Independent Research (12–126515) and the Lundbeck Foundation (R108-A10760).

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