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

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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

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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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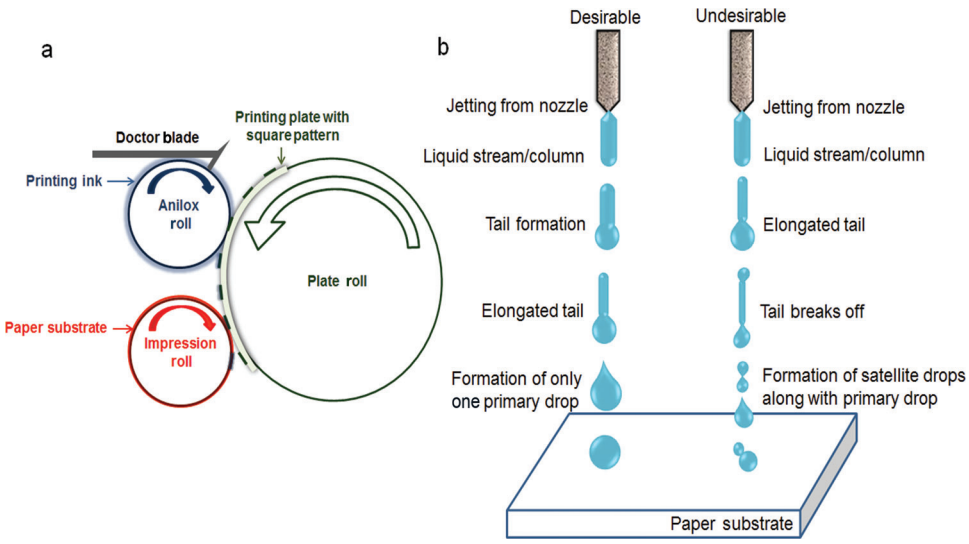

Figure 1. Schematic diagram explaining the principle of (a) flexography (b) drop formation in piezoelectric inkjet printing.

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.

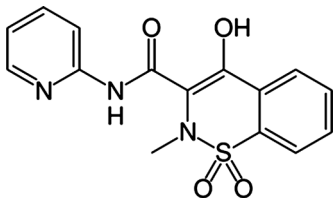

Figure 2. Chemical structure of piroxicam.

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.

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