Fabrication of printed drug-delivery systems

Natalja Genina(1), Ruzica Kolakovic(1), Mirja Palo (1), Daniela Fors(2), Helka Juvonen(2), Petri Ihalainen(2), Jouko Peltonen(2), Niklas Sandler(1)

(1)Pharmaceutical Sciences Laboratory, Department of Biosciences, Abo Akademi University, Turku, Finland, (2) Center of Excellence for Functional Materials, Laboratory of Physical Chemistry, Abo Akademi University, Turku, Finland

Abstract

Printing technologies specifically digital inkjet printing, offer possibilities in the production of individualized medicines. The main advantage of inkjet printing includes the ability to dispense uniform droplets in the picoliter range with high degree of accuracy to allow dose personalization. The pharmaceutical ink formulation has to be designed with respect to its viscosity and surface tension to guarantee continuous printing and high reproducibility of the forming droplets to allow dose uniformity. The aim of this paper is demonstrate the combined use of inkjet and flexographic printing to fabricate pharmaceutical solid dosage forms with controlled release properties of drug substances. Also the characterization of substrates and final drug-delivery systems is studied with various techniques and discussed.

Introduction

Printing technologies such as inkjet and flexographic printing, offer possibilities in the production of more individualized medicine. The main advantage of inkjet printing includes the ability to dispense uniform droplets in the picoliter range with high degree of accuracy to allow dose personalization [1]. The pharmaceutical ink formulation has to be designed with respect to its viscosity and surface tension to guarantee continuous printing and high reproducibility of the forming droplets to allow dose uniformity. During the last decade, this technology has opened new perspectives when designing individual dosage forms. Inkjet printing to directly deposit drug solutions or suspensions containing active pharmaceutical ingredients (API) and excipients onto carrier materials such as porous substrates and biodegradable films, offers innovative ways for fabrication of oral solid dosage forms with controlled physical properties of the API. Recently, drug release profiles have been altered by inkjet printing of API(s) and polymer(s) mixtures at different molar ratios. The aim of this work was to demonstrate the combined use of inkjet and flexographic printing to fabricate pharmaceutical solid dosage forms with controlled release properties of drug substances as described in [2]. A different range of analytical techniques were used and evaluated to characterize the substrates and final dosage forms.

Materials and methods

Model drugs and substrates

In the study we used riboflavin sodium phosphate (RSP) and propranolol hydrochloride (PH) as theophylline (TH) model drugs. Three different types substrates were used as porous model carriers for drug delivery. Active pharmaceutical ingredient (API) containing solutions were printed onto 1 cm × 1 cm substrate areas using an inkjet printer. The printed APIs were coated with water insoluble ethylcellulose (EC) films of different thickness using flexographic printing. Two ink formulations formulated to print the drug substances on the substrates. The propranolol containing ink was prepared by dissolving 50 mg/ml propranolol powder in PG:water mixture (30:70, vol%). The RSP containing ink was made by mixing 31.5 mg/ml of RSP powder with glycerol:ethanol:water (10:10:80, vol%). The ink solutions were filtered with 0.45 lm and 0.2 lm polypropylene membrane filters (WhatmanTM, GE Healthcare, Piscataway, NJ, USA) before printing. The polymeric coating solution for flexography was prepared by dissolving 5% (wt%) EC in ethanol under continuous stirring [2].

Printing

Theophylline printing experiments were performed with an unmodified Canon thermal inkjet printer (Pixma MP495, Canon Inc., Japan). Inkjet printing for PH and RSP was performed with a Dimatix DMP-2800 inkjet printer (Fujifilm Dimatix Inc., Santa Clara, California). A MEMS-based cartridge-styled printhead with 16 nozzles linearly spaced at 254 lm that produce a typical drop size of 10 pl was used. Each cartridge could hold 1.5 ml of ink. Printing was performed in ambient conditions at 45.5±5% relative humidity (RH) and 21 ± 1 °C with a single nozzle (20 micron orifice diameter) at firing voltages of 30 V and 35 V for PH and RSP, respectively. The cartridge temperature was 30 °C, and the drops were deposited at a drop spacing of 10 micrometers. The drugs were printed in squares (n = 10–20 for each paper substrate and ink formulation) of 1 cm x 1 cm, making according to the Dimatix software the total number of drops in one square equal to 1,002,001, which theoretically correspond to approximately 10.02 microliters per cm squared, when assuming a drop volume of 10 pl.

Dissolution and content uniformity

The dissolution rate of API from the paper substrates was studied by using USP paddle method. 500 ml of purified water was used as a dissolution medium. The paper samples were put in spiral capsule sinkers to prevent floating. For content uniformity measurements the printed drug areas on the substrates were immersed into 50 ml of 0.1 N HCl. The volumetric flasks were shaken vigorously and were let to stay for 1 h. Consequently, the absorbance of the obtained solutions was measured at 220 nm for

propranolol and 267 nm for riboflavin with a UV–VIS spectrophotometer (PerkinElmer, Lambda 25, USA).

Hyperspectral imaging NIR imaging

NIR hyperspectral images were acquired for the TH samples using the hyperspectral chemical imaging workstation SisuCHEMA (SPECIM, Spectral Imaging Ltd, Oulu, Finland), which utilizes a SPECIM MCT based Spectral Camera. The spectral range used was 970 – 2500 nm, with 10 nm spectral resolution, producing hyperspectral images with 320 spatial pixels and 256 wavelength channels. The length of the scan can be set in a flexible manner according to the sample in question. The spectral camera builds the image by scanning one line at a time while the sample is moving on a sample tray (Figure 2). Evince (Umbio AB, Sweden) software was used for multivariate visualizations.

Results and discussion

Content uniformity

An example of RSP containing solutions that were printed onto 1 cm × 1 cm substrate areas using an inkjet printer are shown in Fig. 1.The results revealed that the amount of propranolol was 0.503 ± 0.003 mg (10.06 ± 0.06 microliter), which is similar to the expected value of 0.501 mg (10.02 microliters) for 50 mg/ml API solution. The amount of RSP printed per square was 0.340 ± 0.002 mg (the concentration of the printing solution for RSP was 31.5 mg/ml), which means that 10.80 ± 0.06 microliter was printed per 1 cm2.

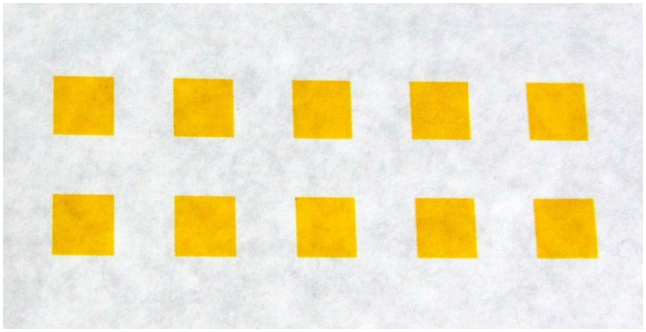

Figure 1. *Inkjet-printed riboflavin sodium phosphate on the porous substrate.*

Dissolution rate

Immediate release behavior was shown by the printed drug substances without any polymer coating (**Fig. 2**). The EC layers printed using flexographic printing resulted in a sustained drug release with increasing amount of layers as anticipated. The release profile was different for the different substrates used. The results indicate that the drug release is therefore influenced by the properties of the substrates in combination with the polymer layering. In conclusion, the use of combined printing technologies to deposit drug substances onto porous cellulose substrates is a promising approach in the production of solid medicines with distinct characteristics and tailored release behavior.

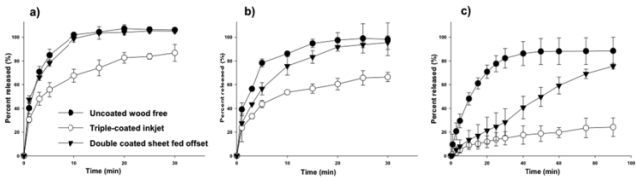

Figure 2. Riboflavin sodium phosphate printed on the different paper substrates: (a) without any coating; (b) after 5 layers of ethyl cellulose (EC) coating; (c) after 30 layers of EC coating. Data are presented as mean ± standard deviation (n = 3).

Content uniformity

The results show that the hyperspectral NIR technology used was easily applicable for quality control of the printed drug substances studies. By the use of PCA it was easy to extract the relevant spectral information with regard to the API and to visualize the printed substances on the substrates used (Figures 3a-c). Figure 3 illustrates the visaulisation for the TH samples. A sample of multiple printed areas of API with varying concentration can be scanned within a few seconds and then grouped using PCA scatter 2D density plot.

In the recent years Near Infrared (NIR) hyperspectral imaging has become available, also raising the potential for NIR chemical imaging to be used to assess the spatial distribution of pharmaceutical compositions in delivery systems [3]. Usually in NIR hyperspectral imaging tens of thousands of spectra are collected in a one measurement. Each spectrum relates to a specific area or a pixel on the sample surface, which creates spatially resolved information on the nature and quantity of chemical components. The vast quantity of data contained within a single hyperspectral image (3D hypercube) makes the use of chemometric data compression techniques necessary to allow image interpretation. Therefore, multivariate modelling techniques such as Principal Component Analysis (PCA) are often applied to reveal trends that would be otherwise undetectable [4,5].

The aim in this paper is to demonstrate the use of hyperspectral imaging in the qualitative analysis of printed pharmaceutical delivery systems.. To demonstrate the concept standard copy paper was used as a substrate for printed drug formulation of TH. The spectral range used was 970 – 2500 nm, with 10 nm spectral resolution, producing hyperspectral images with 320 spatial pixels and 256 wavelength channels. The spectral camera builds the image by scanning one line at a time while the sample is moving on a sample tray. Principal Component Analysis was used to study the hyperspectral images of the printed drug substances on the paper substrates. The results show that the applied NIR technology was easily applicable for quality control of the printed drug substances studies (Fig 3a-c). By the use of PCA it was easy to extract the relevant spectral information with regard to the APIs and to visualise the printed substances on the substrates used. A sample of multiple printed areas of APIs can be scanned within a few seconds. The NIRs imaging through the use of hyperspectral imaging proved to be a fast and very powerful tool for use in the characterization and quality control of printable pharmaceuticals. More studies are needed to exploit the full potential of the technology in this novel way to manufacture drug delivery systems by printing. A sample of multiple printed areas of

API with varying concentration can be scanned within a few seconds and then grouped using PCA scatter 2D density plot. A contour plot (PCA model) of the original image with selected pixels of interest is shown in middle image of figure 3 and the PCA scatter 2D density plot that with detected classes of similar pixels shown in the bottom figure 3.

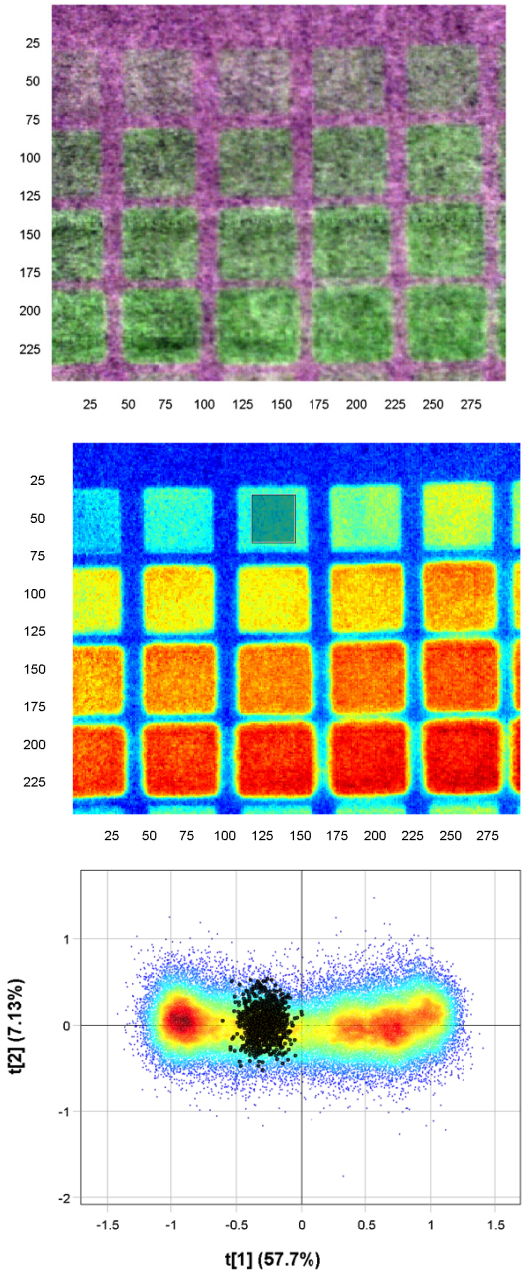

Figure 3. Theophylline printed on the copy paper: (top) RGB image of the original sample (concentration of the drug is increasing in each printed area from left to right); (middle) a contour plot (PCA model) of the original image in order to select pixels of high interest; (bottom) the PCA scatter 2D density plot that is very useful for detecting classes of similar pixels.

Conclusion

In conclusion, the use of printing technologies to deposit drug substances onto porous cellulose substrates is a promising approach in the production of solid medicines with distinct characteristics, tailored release behavior and dose precision. Also the approach allows personalization of the doses accurately. Suitable quality control methods have to be further studied to allow height quality therapeutically safe and efficient products.

References

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Author Biography

Niklas Sandler received his MSc in pharmaceutical sciences from the University of Helsinki, Finland (1998) and his PhD in pharmaceutical technology from University of Helsinki (2003). Between 2003-2006 he worked at the Univ. Helsinki and Univ. Otago, New Zeeland and in the pharmacetuial industry (AstraZeneca, UK) between 2006-2008. Currently he is professor in pharmaceutical technology at Abo Akademi Universtiy, Turku Finland working with research on solid drug dosage forms and printing technologies for drug-delivery application.