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Printing pharmaceuticals by inkjet technology: Proof of concept for stand-alone and continuous in-line printing on orodispersible films

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ABSTRACT

Orodispersible films (ODFs) are promising dosage forms for special patient populations like paediatrics or elderly persons. By printing active pharmaceutical ingredients (APIs) onto orodispersible films, the flexibility of drug dosing is increased and therefore provides potential for personalized medicines. Until now, only small-scale experiments have been conducted, where continuous jetting was performed,but no continuous ODF production was realized. This study deals with the technology transfer from a small-scale inkjet printing system to a pilotscale process by incorporating the same print head assembly into a continuous ODF production process. ODFs made from hydroxypropylcellulose were non-continuously printed multiple times with test ink containing a blue colorant as model drug and were compared to continuously printed ODFs. To identify optimal manufacturing conditions, parameter settings like firing frequencies, resolution, voltage, etc. were varied and these effects were analysed by UV–Vis spectroscopy, image analysis and light microscopy. During continuous production, a linear correlation between firing frequency (100 to 600 Hz) and deposited colourant content could be observed (R = 0.999) as well as for the applied voltage (90–110 V) and the ink content (R = 0.998). A minor impact of the distance between the print head and the substrate was observed. By increasing the natural resolution (50 dpi) of the print head, the deposited ink amount could be doubled. A transfer from the non-continuous production (1 layer of 1 cm × 2 cm with a resolution of 750 dpi × 750 dpi) to the continuous production (corresponding to 380 Hz firing frequency on 6 cm^2 ODF) was successfully performed. Furthermore, image analysis was proven as useful tool for process analytical technology (PAT) of the continuously printed ODFs. The continuous ODF production with direct printing enabled various printing concepts, which may serve for individualized dosing in personalized medicine treatment in the near future.

1. Introduction

Orodispersible films (ODF) are thin strips of one or more layers of water-soluble polymers, which rapidly disintegrate when placed onto the tongue [1]. Due to the ingredients of this dosage form and also the mode of application, ODFs have been discussed in literature before as potential dosage forms for the elderly or paediatric population [1–3]. Furthermore, this dosage form provides potential applications in the field of individualized dosing, which gained popularity most recently [4]. The most common manufacturing technique is the solvent casting method [5], where the active pharmaceutical ingredient (API) is dissolved or dispersed in a polymer solution, which is cast onto an intermediate liner. After drying the wet film, a flexible and thin orodispersible film is obtained as the final product. Whereas the formulation development and academic often work non-continuously using film-casting benches [6] in a small-scale production, industry produces the ODFs in a continuous set-up, where the dried films are coiled up onto jumbo rolls directly after production [7].

To increase the dosing flexibility for individualized medicines [8–10] and to minimize the API waste, printing on orodispersible films has been discussed before. Janssen et al. printed ODFs with a flexographic printer, which is a contact printing technology [11]. A non-contact method is the inkjet printing technology, which recently gained popularity not only in pharmaceutical applications. It has been reported that this technology is also feasible to print metal-inks and produce solar cells, sensors or memory devices [12,13]. In the pharmaceutical area, inkjet printing has not only been discovered to print onto edible substrates [10] but was also utilized for printing microneedle systems [14], biomolecules and cell-based systems [15,16] or inhalable particles [17]. One of the main advantages of printing an API onto an edible substrate is the easy processing of poorly soluble drugs [18,19]. Due to the aqueous water solubility of the film former, poorly soluble APIs are

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only feasible to be incorporated into ODFs in form of a suspension, which might be quite challenging concerning the homogeneity of the casting solution. Inkjet printing is a possibility to overcome this issue. Buanz et al. compared ODFs prepared by the solvent casting method with printed ODFs and described better film characteristics for the printed films [20].

To our best knowledge, ODF inkjet printing was only performed non-continuously by printing small amounts of substrates like paper or ODFs until now. This study provides for the first time data of an in-line inkjet printing of continuously produced ODFs. For that purpose, a continuous film coating machine was modified by expanding the conveying unit until the dried ODFs reach a top-mounted print head assembly. This implies several differences between the continuous printing process and the non-continuous production. Whereas the non-continuous production enables multiple-layer printings on a defined area [21,22], during the continuous manufacturing only one printing step is feasible, because the print head is fixed to the coating machine and the printing velocity is determined by the speed of the intermediate liner of the film coater. Therefore, the effects of several parameter settings (e.g. firing frequencies, applied voltage and pulse shape, printing velocity and resolution) on the printed film should be investigated during continuous manufacturing and optimal production settings should be identified and evaluated. Furthermore, the continuously produced films should be compared to printed films by an industrial inkjet printer using the same print head. This enables the utilization of the non-continuous production as small-scale setup for formulation development in first experimental trials and later the transfer to the large-scale production process. Due to limited quality control methods for the continuous production of printed films, image analysis was employed as a new potential tool for in-line quality control as a process analytical technology (PAT).

2. Materials

Film solutions were produced using 15% (m/m) hydroxypropylcellulose (HPC, Klucel, JXF Ashland, USA) and a mixture of ethanol/distilled water (50:50 m/m). Ethanol of analytical grade was purchased from VWR, Germany, and the distilled water was freshly produced shortly before use. Spectra XL 30 ink was utilized (Dimatix, USA) as ink solution consisting of polypropylene glycol, propylene carbonate and blue millijet dye 28 colorant.

3. Methods

3.1. Orodispersible film preparation

3.1.1. Non-continuous production

ODFs were produced in the non-continuous production mode using the film applicator Coatmaster 510 (Erichsen, Germany) at a casting velocity of 360 mm/min at 30 °C temperature setting for the vacuum plate. The casting was performed with a wet film thickness (WFT) of 400 µm on a silicon coated polyamide–polyethylene foil (Sidamil 50/50, Amcor, Melbourne, Australia). After the printing process, specimens of a sample size of 6 cm^2 (2 cm x 3 cm) were cut from the dried film material.

3.1.2. Continuous production

Continuous film manufacturing was conducted using the coating machine TGM-K-1.4 (Optimags, Dr. Zimmermann, Germany). Films were cast (12 cm coating width) onto an intermediate liner PPQ 76677 (100 µm silicone coated, Huhtamaki, Finland). A pump conveyed the polymer solution through a coating knife, where the WFT was adjusted to 400 µm (Fig. 1).

The coating velocity was set to 125 mm/min and the wet films were dried at 60 °C (first heating element) and 80 °C (second heating element) ca. 6.5 min. After passing the 80 cm long drying channel, the dry film was redirected to a print head assembly to enable direct printing by inkjet. The print head assembly allows a precise rotation of the print head (rotation angle can be adjusted from 0 to 180 °) to increase the natural resolution of the print head. The film was coiled up onto a jumbo roll directly after production. After printing onto the films, they were cut into a sample size of 6 cm^2 (2 cm × 3 cm).

3.2. Ink-jet printing

3.2.1. Non-continuous printing

Non-continuous printing was performed using a PIXDRO LP 50 printer (Meyer Burger, The Netherlands) equipped with a Spectra S Class SE print head (Fujifilm, USA). This print head features 128 linearly arranged nozzles with an average diameter of 30 µm. Following printing parameters were set: on both piezo elements voltages of 90 V were applied, a pulse shape was defined as 1 µs – 12 µs – 1 µs, the print head temperature was 30 °C. The printing was conducted with a step size and a quality factor of 1. On each film, a rectangle (1 cm × 2 cm) was printed, setting the resolution to 750 dpi x 750 dpi. One to seven layers were printed onto the film. After printing the film, each layer was dried for at least half an hour to ensure complete drying of the ink.

3.2.2. Continuous printing

Continuous printing was performed using a modified PIXDRO JS 20 jetting station (Meyer Burger, The Netherlands) equipped with the same Spectra S Class SE print head (Fujifilm, USA) as mentioned above. Following basic parameters were set: 90 V on both piezo elements, a printing frequency of 200 Hz, a pulse shape of 1 µs – 4 µs – 1 µs, the print head temperature was 30 °C. The velocity of the film moving below the print head was set to 125 mm/min. The distance between the print head nozzles and the substrate was set to 3 mm. To investigate the influence of the parameter setting on the printed substrates, the following parameters were varied: firing frequency, height of the print head, velocity of the substrate, adjusted voltage to the piezo elements and the pulse shape. Furthermore, the angle of the print head was varied.

3.3. Ink properties

3.3.1. Viscosity analysis

The dynamic viscosity of the blue test ink was determined using the rotational viscosimeter Kinexus (Malvern, UK) utilizing a cone-plate setting (1°). Measurements were performed at 25 °C at a shear rate of 1000 s^{-1}. The shear rate was chosen due to literature reports of high shear rates occurring within the print heads. Each sample was measured in triplicate. The mean and standard deviation were calculated.

3.3.2. Surface tension

The surface tension was measured using a K100 tensiometer (Krüss, Germany) utilizing a Wilhelmy plate at ambient conditions. The surface tension was measured at 10 points. Each sample was measured three times. The mean and standard deviation were calculated.

3.4. Morphological properties

The morphological properties were investigated via light microscopy (Leica Microsystems, Germany) and scanning electron microscopy (G2 Pro, Phenom, The Netherlands). Furthermore, a sample of 1 cm^2 (1 cm × 1 cm) was scanned using an Epson Perfection V800 Photo scanner (Epson, Japan) and visually inspected.

3.5. Content uniformity

3.5.1. UV–Vis

Due to the complex ink composition and the information lack of absolute quantities of the single ingredients by the ink manufacturer,