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Printing medicines as orodispersible dosage forms: Effect of substrate on the printed micro-structure

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ABSTRACT

We present our recent advancements in developing a viable manufacturing process for printed medicine. Our approach involves using a non-contact printing system that incorporates both piezoelectric- and solenoid valve-based inkjet printing technologies, to deliver both active and inactive pharmaceutical materials onto medical-graded orodispersible films. By using two complimentary inkjet technologies, we were able to dispense an extensive range of fluids, from aqueous drug solutions to viscous polymer coating materials. Essentially, we demonstrate printing of a wide range of formulations for patient-ready, orodispersible drug dosage forms, without the risk of drug degradation by ink heating and of substrate damages (by contact printing). In addition, our printing process has been optimized to ensure that the drug doses can be loaded onto the orally dissolvable films without introducing defects, such as holes or tears, while retaining a smooth surface texture that promotes patient adherence and allows for uniform post-coatings. Results show that our platform technology can address key issues in manufacturing orodispersible drug dosage forms and bring us closer to delivering personalized and precision medicine to targeted patient populations.

1. Introduction

Printing of medicines is a promising but not yet fully developed process (Genina et al., 2013a; Hoffmann et al., 2013; Scoutaris et al., 2011; Wening and Breitkreutz, 2011; Schroedl et al., 2011), which has multiple advantages compared to other established manufacturing processes.

Firstly, printing active pharmaceutical ingredients (APIs) is potentially an enabling technique to produce personalized medicine. According to the FDA this is a "megatrend" of the pharmaceutical industry and health-care systems around the globe (U.S. Food and Drug Administration, 2013; Voura et al., 2013). The advantage of personalized medicine is the ability to tailor the dosage form to each individual patient, in contrast to the current state where a patient population is addressed with a single, uniform dosage form (U.S. Food and Drug Administration, 2013). Personalized medicine can be printed to adapt to the patients' specific characteristics such as age, weight, genetic makeup and lifestyle. Additionally, digital printing allows fine-tuning of the API doses in order to meet individual patient's needs. This is crucial, for example, within pediatric populations, or for drugs that require careful dose adjustment, such as opiates or hormones. Moreover, it is also possible to combine different APIs to form a combination product with the aim of reducing side effects, while suppressing the risks of wrongly administrated drug treatment. Furthermore, by using a printing process to manufacture drugs it is possible to include a personalized identification on the dosage form itself, without additional process equipment or manufacturing steps.

Secondly, printing medicine is uniquely suited for producing intraoral dosage forms, which can be classified regarding their dissolution and disintegration kinetics in rapidly-dissolving, slow-

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dissolving and non-dissolving delivery systems. Specifically, orodispersible films have gained increased popularity in this field (Hoffmann et al., 2013). These dosage forms can significantly improve treatment compliance, especially for patients who have problems swallowing pills or tablets. This is an important healthcare issue as, in addition to specific patients groups, such as pediatric and geriatric populations, about a third of the "normal" population suffers from dysphagia (Roden Dylan and Altman Kenneth, 2013; Stegemann et al., 2012). Currently, most of the available orodispersible drug films are produced by film casting (Genina et al., 2013a). Despite the apparent simplicity, it is potentially challenging to guarantee thickness and content uniformity when casting films over several meters (Janßen et al., 2013). Furthermore, cutting cast films with knifes or punches can create additional dosage error and unacceptable material waste (Janßen et al., 2013). In this context, manufacturing orodispersible films by printing APIs onto placebo substrates can overcome these limitations, increasing the production yield and quality.

Finally, printing medicine can be considered as a continuous manufacturing process. Combined with suitable on- and in-line monitoring tools and appropriate feedback loops, continuous processing can drastically improve the production efficiency by allowing real-time release testing (RTRt). Printing medicine under the framework of quality by design (QbD) can also significantly improve the product quality and streamline the drug supply chain (U.S. Food and Drug Administration, 2009; U.S. Food and Drug Administration, 2004).

Despite the potential advantages, there are still technical limitations for printing medicine that have not yet been overcome: most critically, inkjet printing of APIs has been restricted to low-viscosity fluids (Buanz et al., 2011; Preis et al., 2015). This limitation stems from the fact that primarily piezoelectric and thermal inkjet technologies have been used in the existing studies (Buanz et al., 2011; Alomari et al., 2015). Inkjet printing of viscous liquids has been achieved by using heated piezoelectric-based inkjet systems (Genina et al., 2013a; Buanz et al., 2011). The disadvantage of this approach is that many APIs are temperature-sensitive and can therefore degrade. Alternatively, contact printing techniques, such as flexography – common in industrial roll-to-roll printing – have been used (Janßen et al., 2013; Palo et al., 2015). However, substrate contact can lead to cross contamination and substrate damages. Furthermore, such printing technique can lead to excessive ink waste and their implementation on an industrial scale is associated with high capital costs.

The majority of the published studies on printed medicine were conducted using non-edible substrates such as polytetrafluorethylene (PTFE) sheets (Genina et al., 2013b), glass plates and various paper substrates (Genina et al., 2013a; Genina et al., 2012). While a few studies have used edible icing sheets (Genina et al., 2013b; Pardeike et al., 2011) and placebo orodispersible films (Janßen et al., 2013; Buanz et al., 2011), the selections were far from extensive. Therefore, in the current study, we developed a unique printing platform using both piezoelectric and solenoid valve inkjet technologies to process a wide range of ink formulations, including suspensions and highly viscous fluids. To demonstrate the capability of our printing platform, we have tested three typical formulations: (i) an aqueous API solution, (ii) placebo nano-suspensions as drug delivery system for poorly soluble API (Pardeike et al., 2011) and (iii) polymeric coating solutions. Specifically, the aqueous solution contains sodium picosulfate, a laxative typically used in combination with opiate drugs to address their side effects. The nano-suspension comprises PEGylated poly (lactic-*co*-glycolic) acid (PLGA) nanoparticles suspended in water. The polymeric coating solutions, typically used to protect API against crystallization or for taste-masking purpose, consist of polyethylene glycol (PEG) 3000 and PEG 6000 in water.

Several pharmaceutical-grade placebo orodispersible films were used with these formulations to simulate the production of patient-ready dosage forms. The printed drug films were assessed qualitatively, to verify whether our approach is ready for manufacturing of personalized orodispersible drugs.

2. Materials and methods

2.1. Ink formulations

2.1.1. Sodium picosulfate ink

An aqueous solution of sodium picosulfate (Chemos GmbH, Regenstauf, Germany) with concentration of 200 mg/ml was prepared by dissolving the API in purified water (MilliQ, Millipore) and subsequently filtering the solution with 0.45 μm Nylon syringe filters (Roth GmbH, Karlsruhe, Germany).

2.1.2. Polymeric nano-suspension ink

The polymeric (PEGylated PLGA) nanoparticles were obtained by the emulsion solvent evaporation technique. 100 mg poly (lactic-*co*-glycolic) acid (Resomer RG 503H, Evonik Industries AG, Darmstadt, Germany) were dissolved in 5 ml ethyl acetate (Carl Roth GmbH & Co., KG, Karlsruhe, Germany) and the organic phase was continuously added to 5 ml of an aqueous solution of 25 mg/ml polyvinyl alcohol (Sigma–Aldrich, Munich, Germany) and 3 mg/ml polyethylene glycol 2000 (Sigma–Aldrich, Munich, Germany). Next, the primary emulsion was stirred using a Hermle Z300 centrifuge (Hermle Labortechnik GmbH, Wehingen, Germany) for 45 min at 1000 rpm and subsequently homogenized using a dispersing homogenizer (Ultra Turrax, model 985370, Biospec Products Inc.) at 17,000 rpm for 10 min. The mixture was diluted with water to yield a 50 ml solution and ethyl acetate was evaporated over 12 h ($n = 6$).

2.1.3. Polymeric coating inks

Two coating inks were prepared. The first was made of an aqueous solution of 15 wt% PEG 3000 (Clariant, Sulzbach, Germany). After dissolving the polymer by vigorous mixing, the ink was left to settle for 10 min and subsequently filtered with 0.45 μm Nylon syringe filters (Roth GmbH, Karlsruhe, Germany). The same procedure was used to obtain a 7.5 wt% PEG 6000 (Clariant, Sulzbach, Germany) aqueous solution with 20 wt% ethanol and 10 wt% glycerol.

2.2. Ink characterization

2.2.1. Viscosity

The viscosity of each formulation was measured using a cone plate rheometer (MCR 300, Anton Paar GmbH, Graz, Austria). After the sample temperature equilibrated at 20 °C, a fixed shear rate of 100 s^{-1} was applied for 2 min, during which 20 data points were recorded. The formulation viscosity was calculated as the average of these 20 values. Non-Newtonian and viscoelastic properties were therefore not considered here. All measurements were made in triplicate.

2.2.2. Density

The density of each formulation was measured with a digital oscillating U-tube density meter (Abbemat® RXA 170, Anton Paar GmbH, Graz, Austria) providing a typical accuracy of ±0.001%. All measurements were performed at 20 °C and in triplicate.