Dropwise Additive Manufacturing of Pharmaceutical Products for Amorphous and Self Emulsifying Drug Delivery Systems

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Abstract

The improvements in healthcare systems and the advent of the precision medicine initiative have created the need to develop more innovative manufacturing methods for the delivery and production of individualized dosing and personalized treatments. In accordance with the changes observed in healthcare systems towards more innovative therapies, this paper presents dropwise additive manufacturing of pharmaceutical products (DAMPP) for small scale, distributed manufacturing of individualized dosing as an alternative to conventional manufacturing methods. A dropwise additive manufacturing process for amorphous and self-emulsifying drug delivery systems is reported, which utilizes drop-on-demand printing technology for automated and controlled deposition of melt-based formulations onto inert tablets.

The advantages of drop on demand technology include reproducible production of droplets with adjustable sizing and high placement accuracy, which enable production of individualized dosing even for low dose and high potency drugs. Flexible use of different formulations, such as lipid-

based formulations, allows enhancement of the solubility of poorly water soluble and highly lipophilic drugs with DAMPP. Here, DAMPP is used to produce solid oral dosage forms from melts of an active pharmaceutical ingredient and a surfactant. The dosage forms are analyzed to show the amorphous nature, self-emulsifying drug delivery system characteristics and dissolution behavior of these formulations.

Keywords: drug printing, self-emulsifying drug delivery system, amorphous, solid dispersion, processing, solid dosage form, oral drug delivery, quality by design (QbD), surfactants

1. Introduction

The average life expectancy has increased dramatically during the 20th century. The ceaseless improvement in human health care systems consisting of the development of new treatments and the increasing accessibility to medicine has a significant effect on this achievement. Nevertheless, medicine still targets therapy to the broadest patient population that might possibly benefit from it, and relies on statistical analysis of this population's response for predicting therapeutic outcome in individual patients (Mancinelli et al., 2000). Therapists make decisions both about the choice of drug and appropriate dosage based on information derived from population averages. Worldwide use of these drugs has revealed substantial inter-individual differences in therapeutic response (Blau et al., 2013; Mancinelli et al., 2000). With the recent developments in pharmacology and genomics, the traditional "one drug fits all" approach is evolving into an individualized approach to therapy (Laínez et al., 2011; Redekop and Mladi, 2013; Sadée, 1998). The trend is towards a future health care system, in which personalized or precision medicine becomes the common model (Collins and Varmus, 2015). Personalized

therapy is defined as therapy with the right drug at the right dose for the right patient, which implies the delivery of personalized medicine and individualized dosing (Food and Drug Administration, 2013; Redekop and Mladsi, 2013; Sadée, 1998).

As health care systems keep improving, the development of innovative drug delivery and production methods become crucial. The current level of innovation in dosage form design and drug product manufacturing cannot meet the needs of personalized therapies (Rantanen and Khinast, 2015). While innovation is the key to success within the pharmaceutical industry, it has been largely sought through new drug discovery and development, while the development of new manufacturing methods has received inadequate attention (Içten et al., 2016a). Traditionally the pharmaceutical industry has manufactured its products in large scale batch processes with limited use of on-line process monitoring and active process control technologies. In recent years, the US Food and Drug Administration (FDA) introduced the Quality by Design (QbD) approach and Process Analytical Technology (PAT) guidance to encourage innovation and efficiency in pharmaceutical development, manufacturing and quality assurance (Food and Drug Administration CDER, 2004). As a result of emerging technologies and encouragement from the regulatory authorities, the pharmaceutical industry has begun to develop more efficient production systems with more intensive use of on-line measurement and sensing, real time quality control and process control tools, which offer the potential for reduced variability, increased flexibility and efficiency, and improved product quality (Acevedo et al., 2016; Cervera-Padrell et al., 2012; Simon et al., 2015; Stephanopoulos and Reklaitis, 2011).

To meet the needs for producing more innovative personalized therapies, we propose dropwise additive manufacturing of pharmaceutical products (DAMPP) as a novel technology for small scale, distributed manufacturing of individualized drug dosing. A dropwise additive manufacturing process for solid oral drug production has been developed, which utilizes the drop on demand (DoD) printing technology for predictable and highly controllable deposition of active pharmaceutical ingredients (API) onto an edible substrate, such as a polymeric film or placebo tablet (Hirshfield et al., 2014; Içten et al., 2015a). This manufacturing method has tremendous potential for individualized dosing because through a combination of drop size and number of drops, the dosage can be precisely and reliably controlled to match the prescribed amount for a patient. In addition, the ‘batch size’ can be as small as the number of tablets or drops required for one patient and the transitions from one dose to another made with minimal or no waste in a very short time. The dropwise additive manufacturing system offers great promise as a tool for advancing personalized therapies by allowing the precise production of convenient solid oral dosages tailored to the patient on site at hospitals, clinics and even pharmacies.

The DAMPP process allows flexible change of formulations, which can be developed to enhance the bioavailability of poorly water soluble drugs. Although oral drug delivery is the major route for the administration of many drugs, increasing the oral bioavailability of most compounds is still a challenge. It has been suggested that more than 40% of new chemical entities (NCE) have low aqueous solubility, which leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality (Haus, 2007; Morgen et al., 2012). In recent years, several delivery methods are being investigated to eliminate these disadvantages. These methods include use of solution or emulsion based formulations, nanocrystals, solid dispersions,

amorphous formulations and lipid based formulations among others (Blagden et al., 2007; Hauss, 2007; Morgen et al., 2012; Mosquera-Giraldo et al., 2014; Neslihan Gursoy and Benita, 2004). We have demonstrated that via the DAMPP process, solubility and dissolution rate of poorly water soluble drugs can be enhanced by using solvent-based amorphous or crystalline formulations (Hirshfield et al., 2014) and melt-based crystalline formulations (İçten et al., 2015a).

In this study, we investigate alternative dosage forms to improve the release properties of poorly water soluble drugs that can be used in the DAMPP system. The solubility of active ingredients can be increased by formulating the drug in the amorphous form. In recent years, there has been a growing interest in amorphous solid dispersions and their incorporation into solid dosage forms (Morgen et al., 2012; Yu, 2001). The drawback of amorphous drug formulations is their propensity for higher chemical and physical instability. In comparison to amorphous forms, crystalline forms have lower energy states and are thermodynamically favored. Although stability is a critical issue in amorphous drug formulation, in some cases it can be overcome with the use of polymer additives that inhibit crystallization (Liu et al., 2015; Mosquera-Giraldo et al., 2014) or with a process control strategy that slows down or prevents crystallization of the compound. Performing stability analysis is common practice to assure that the final drug product contains the desired API form over the shelf-life of the product. On-demand production systems, such as DAMPP, have a great advantage for the manufacture of amorphous drug products, because the dosage forms is produced following the prescription of the medicine by the physician and consumed within the prescription time. Thus, using the DAMPP process, the long-term shelf-life constraints on the final dosage would be reduced.

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116 Another way to increase the solubility of poorly water soluble and highly lipophilic drugs is
117 using lipid-based formulations in the DAMPP system. Since DAMPP is a temperature controlled
118 process which can readily process melt-based formulations; melts of lipids or surfactants can be
119 used in the manufacture of dosage forms. Lipid-based formulations involve incorporating the
120 drug into inert lipid vehicles such as oils, surfactants, emulsions and self-emulsifying drug
121 delivery systems (SEDDS) (Neslihan Gursoy and Benita, 2004; Soliman and Khan, 2005).
122 SEDDS are defined as isotropic mixtures of oils, solid or liquid surfactants, or alternatively, one
123 or more hydrophilic solvents and co-solvents/surfactants (Neslihan Gursoy and Benita, 2004).
124 The most frequently used excipients for lipid based formulations are reported as dietary oils and
125 various pharmaceutically-acceptable surfactants (Hauss, 2007). Self-emulsifying drug delivery
126 systems form oil in water (o/w) emulsions upon dilution and mild agitation in aqueous
127 environment. After the drug products enter the GI tract, emulsion is achieved which makes
128 SEDDS easy to manufacture and stabilize compared to emulsions. Consequently, for lipophilic
129 drug compounds displaying dissolution rate-limited absorption, SEDDS systems can improve the
130 rate and extent of absorption and result in more reproducible bioavailability profiles (Neslihan
131 Gursoy and Benita, 2004).

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133 In the next sections, first a process description is presented for lipids processing, focusing on the
134 scientific and engineering principles of the process development. Then dropwise additive
135 manufacturing of amorphous and self-emulsifying melt-based solid oral dosage forms is
136 demonstrated for improved oral delivery of lipophilic drugs. Finally, the produced dosage forms

are analyzed to demonstrate reproducibility of dosages and their solid state, emulsion and dissolution characteristics.

2. Dropwise Additive Manufacturing Process for Lipid-based Formulations

The proto-type DAMPP process is shown in Figure 1. The DAMPP process enables predictable and controllable deposition of API containing formulations onto edible substrates using the drop on demand printing technology. The system consists of a material reservoir, precision positive displacement pump, xy-staging, online imaging and sensing, air based heating system and other temperature controlled heating elements, temperature, pump and stage controllers. During process operation, the API-containing formulation is placed in the material reservoir. The precision positive displacement pump is used to generate drops of controlled sizes, which are ejected through the nozzle. Drop sizes can cover a range between 5 to 25 μl depending on the nozzle sizes, printing settings of the pump and material rheological properties. Changing the nozzle and printing setting allows adjustment of the drop size and therefore the dosage amount for individual patients. The effect of formulation material properties on drop rheology is of course important but is discussed in our previous publications in detail (Hirshfield et al., 2014; Içten et al., 2015a). Following drop ejection from the nozzle, the imaging system automatically acquires an image of the falling drop, which is used to calculate the volume of each drop in real time (Hirshfield et al., 2015). The imaging system consists of a camera, backlight, motion sensors to detect the falling drop; and it is shown within the dotted box in Figure 1. The drop containing the formulation deposits on to an edible substrate of choice. The deposition of red colored melt-based drops on placebo tablets is shown in Figure 1. The synchronized execution of pump, xy-staging and other process units allows execution of the desired deposition pattern such

as a grid or boustrophedon pattern. The DAMPP process has been used to process both solvent- and melt-based formulations. In order to process melt-based formulations, the temperature of the formulation to be printed is controlled in each step. The temperature of the reservoir, pump, tubing-nozzle line are controlled using heating tape, pump heater and air-based heating system and associated temperature controllers. Controlling process temperature is crucial to maintain constant fluid rheology during printing. The temperature of the deposits on the substrate is controlled using Peltier devices and the associated temperature controller. Controlling product temperature is shown to affect the drug morphology and can be used to achieve a desired product dissolution property (Içten et al., 2015b).

Automation of online monitoring and control systems for DAMPP is implemented in LabVIEW (National Instruments, n.d.). The details of the automation program are detailed in our previous publication (Hirshfield et al., 2015). The program enables executing process units in a synchronized fashion while monitoring critical quality attributes, such as dosage amount and drug morphology, online, and controlling critical process parameters, such as drop size, product and process temperatures (Içten et al., 2016a). The automation program is integrated with a Knowledge Management System, which allows the user to save the data provenance related with each drop dose produced via DAMPP (Içten et al., 2016b). This documentation is especially important for highly regulated pharmaceutical products.

In recent years, pharmaceutical printing applications have been receiving increased attention. Although the majority of the formulations are based on solvent or suspension based formulations (Alomari et al., 2015; Kolakovic et al., 2013), the advance of additive and 3D manufacturing

enable processing of hot-melt based formulations (Norman et al., 2016). While developing a temperature controlled system to process melt-based formulations, the focus has to be not only on successful processing of melts of polymer-API or lipid-API mixtures but also on avoiding degradation of the active ingredients. In the following section, the effect of temperature and formulation are investigated for lipid based self-emulsifying formulations printed via DAMPP.

2.1 Formulation Selection and Temperature Control

Using the DAMPP process, a variety of melt-based drug formulations can be printed. The melt formulations consist of a low melting point carrier and an API, which are mixed and heated above the melting temperature of the mixture in order to produce hot melts. Different carrier systems including low molecular weight polymers: PEG and pluronic, surfactants: gelucire and lipids: compritol, precirol have been studied. Depending on the desired final solid state form of the API, different carriers can be used in the formulation of solid dispersions. The key characteristics affecting the solid state form are the nucleation and crystallization growth rates of the API during melt cooling (Baird et al., 2010). In addition to the crystallization cooling rates, selection of the carrier is an important factor in drug morphology, since specific polymers or surfactants may for instance inhibit or promote crystallization of the drug (Mosquera-Giraldo et al., 2014; Trasi and Taylor, 2012). Lipids or other carriers can also have an effect on the bioavailability of the drug by enhancing the dissolution or by sustaining the release of the drug (Morgen et al., 2012; Shah et al., 2013). Lipids, surfactants or polymers not only help to control drug solid state properties, but also establish formulation composition and material rheological properties. Depending on the ratio of drug and carrier present in the formulation, the dosage

amount can be adjusted. The material processing characteristics of the formulation depend on the surface tension and viscosity values of different molten carriers used.

For the DAMPP process, carriers with low melting temperature ($\leq 100\text{ }^{\circ}\text{C}$) and with low melt viscosity are preferred. The former is bounded by the operating temperature of the proto-type DAMPP system and the latter is a requirement for the printability of the melts. For instance, in the DAMPP process, lipids with a melting temperature within the operating range are preferred. The main limitation on the operating temperature is the stability of the drug used in the formulation. The formulations are produced by dissolving the API in the molten carrier at relatively high temperatures ($\leq 100\text{ }^{\circ}\text{C}$). Therefore stability of the drug products produced via DAMPP should be established and shelf-life determined. Shelf-life is determined by testing samples for product attributes susceptible to change during storage and shipping, and likely to influence quality, safety and efficacy of the drug (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003). These include chemical attributes, e.g., pH, degradation; physical attributes, e.g., appearance, particle size; in vitro drug release, e.g., dissolution; and biological attributes, e.g., potency. Conventional drug products are tested for long term or under accelerated storage conditions. Using the DAMPP system at distributed sites is envisioned to shorten the assured shelf-life of drug products. However a protocol for establishing stability of the drug products should nonetheless be developed. Currently, for the dosage forms produced via DAMPP, the chemical stability of the API is verified using HPLC measurements and in vitro drug release is analyzed through dissolution testing.

2.2 Substrate Selection

Using this process, the formulations can be printed on a variety of substrates including polymeric films and placebo tablets or into capsules. Printing melt-based formulations on edible polymeric films and on placebo inert tablets are shown in Figure 2. In Figure 2b, red food color is added to the formulations to help the reader to differentiate between the white placebo tablet and red drop deposition. Surface properties of the substrate onto which the drops are deposited have an effect both on drop deposition characteristics and on the solid state of the drug. The use of polymeric films or inert tablets of different porosities can have an effect on the crystallization and dissolution profiles of the formulations (Içten et al., 2015a). It has been shown that by printing on films containing HPMC or chitosan the microstructure, crystallinity and even the dissolution of drug deposits can be controlled (Hsu et al., 2013). The surface chemistry of chitosan films, such as its capability of forming H-bonds with the drug, also effects the crystallization of drugs (Hsu et al., 2015). The surface properties of the substrate, such as roughness, also can have an effect on product morphology (Kolakovic et al., 2013; Sandler et al., 2011). Thus the substrate should be selected by considering the desired end product properties.

3. Investigation of Amorphous and Self-Emulsifying Drug Delivery Systems for DAMPP

The two aims of this study are to create an amorphous drug product and also to investigate self-emulsifying drug delivery systems. For this purpose, celecoxib is chosen as the model API since it exhibits lipophilic properties and low solubility in aqueous environment. Several lipids and surfactants are investigated for the use with the DAMPP process. While selecting the lipid and surfactants used in the formulations, material properties that affect the printability of the formulations, such as the melting temperature and viscosity, are taken into account.

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252 The excipients that are investigated for the use in the DAMPP process are shown in Table 1. All
253 materials were provided by Gattefosse (Paramus, New Jersey). The main reason for selecting
254 these excipients was their relatively low melting points. The current DAMPP prototype system is
255 best suited for formulations with melting temperatures around 70 °C, which can be readily
256 increased by suitable design of the temperature control system. However, when increasing
257 operating temperatures, it is important to assure acceptable stability of the API.

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259 In addition to material rheological properties, chemical properties of the excipients also play an
260 important role in the final drug product since their nature and amount determine the overall
261 quality of the emulsions obtained. Non-ionic surfactants with relatively high hydrophilic-
262 lipophilic balance (HLB) are recommended to be used with or without lipid excipients to
263 promote self-emulsification or micro emulsification. HLB reflects the proportion of water
264 soluble to lipid soluble moieties in each material. Due to their relatively low toxicity, the
265 acceptable quantities are limited primarily by their physical stability in the final dosage form
266 (Haus, 2007).

267

268 For a self-emulsifying formulation, lipid and surfactant amounts are suggested to range between
269 20 to 97% and more than 10% by weight, respectively (Burnside et al., 2004). Three lipid-based
270 formulations are investigated and printed using the DAMPP process.

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272 a. **The first formulation** consists of 60% compritol, 30% labrasol and 10% celecoxib. In
273 the DAMPP process, the temperatures of the reservoir, tubing and pump temperature

274 controllers are set at 90 °C, 95 °C and 70 °C, respectively. Although the operating
275 temperature is increased to the highest operating limit, some solidification is observed
276 within the tubing. Due to its high melting temperature, compritol is found not suitable for
277 use in the current prototype DAMPP system. However it is a promising lipid to be used
278 in future formulation development studies for self-emulsifying drug delivery systems
279 (Rahman et al., 2013).

280 b. **The second formulation** consists of 60% precirol, 30% labrasol and 10% celecoxib. This
281 formulation was printed successfully with the DAMPP process and the reproducibility of
282 the drops was within the desired 5 % range. The temperatures of the reservoir, tubing and
283 pump temperature controllers were set at 90 °C, 95 °C and 70 °C, respectively. However,
284 the formulation is very hydrophobic, an indicator of the poor solubility of the formulation
285 in aqueous media. When tested for the dissolution behavior, the dosage forms consisting
286 of this formulation neither dissolved nor formed an emulsion in water within the first 30
287 minutes. Potentially, this formulation could be used for a sustained release formulation.
288 For such applications, chloroform and methylene chloride could be used to clean the
289 DAMPP system.

290 c. **The third formulation** consists of 90% gelucire 44/14 and 10% celecoxib. After
291 unsuccessful formulations of SEDDS with the above formulations, lipids were eliminated
292 and replaced with a solid surfactant. Since gelucire has a melting temperature of 44 °C,
293 the DAMPP process can be run at lower temperatures than the maximum allowable
294 temperatures. The temperatures of the reservoir, tubing and pump temperature controllers
295 were set at 70 °C, 90 °C and 60 °C, respectively. This formulation is used to produce
296 dosage forms, which contain the amorphous form of celecoxib and yield self-

emulsification. The detailed analysis of dosage forms is presented in the following section.

4. Materials and Methods

4.1 Materials and Formulation

In this study, celecoxib (CEL) is chosen as the model API to form melt formulations with the surfactant, gelucire 44/14 (Lauroyl macrogol-32 glycerides EP). Celecoxib is purchased from ChemShuttle (Union City, California). Gelucire 44/14 is provided by Gattefosse (Paramus, New Jersey). Celecoxib and gelucire 44/14 are mixed in (10:90) weight ratio. The mixture is comelted at 70 °C until completely melted. The melt formulation is printed both onto inert tablets and onto polymeric films prepared with hydroxypropyl methylcellulose (HPMC) (E50). The inert tablets are provided by GlaxoSmithKline (Collegeville, Pennsylvania). HPMC (E50) is purchased from Sigma Aldrich Corporation (St. Louis, Missouri).

4.1.1 Film Preparation

In order to make a 5% (w/v) polymer solution, 1 g HPMC powder (E50) is dissolved in 20 ml water at 90 °C. The 5% (w/v) HPMC solution is stirred at room temperature overnight to ensure that the polymeric chains were homogeneously dispersed in the solution and cast onto a Petri glass. After drying is completed, the film is peeled off.

4.2 Methodology

After deposition of the drops onto the film, the resulting dosage forms were analyzed for solid-state characteristics, self-emulsifying behavior of the formulation and dissolution behavior of the API. The dosage forms were created and analyzed immediately and thus varying ambient conditions, such as relative humidity, were not impactful on the results.

4.2.1 Reproducibility of Dosage Amounts

In this study, dosage forms are produced with target dosage of 1.5 mg of API. Each dosage form consists of a single drop containing the target dosing. The drop size can be altered by changing the pump and printing operating parameters such as nozzle diameter, displacement, volume strokes and rate. In addition, by changing the number of drops in a single dose, one can increase the dosage amount. The reproducibility is analyzed both gravimetrically and through image analysis. To analyze reproducibility gravimetrically, substrates are weighed on an Omega AL-201s balance. Next, a specific number of drops are deposited on the substrate to reach the target dosage amount. The dosage forms are then subjected to room temperature until the deposits solidify. After solidification of the drops, the substrates are weighed again to determine the total mass of the deposits on the film. The amount of drug is determined by multiplying this mass of solids by the composition of drug in the solution (10 %). These results are then used to analyze how consistently and accurately the dosage forms are created.

4.2.2 Raman Microscopy

A Thermo Scientific DRX Raman Microscope equipped with a 532 nm laser is used to analyze the solid state form of the drug present in the melt formulations. First, the spectra of pure crystalline celecoxib and gelucire 44/14 solid dispersion are obtained. Pure celecoxib and pure gelucire 44/14 are analyzed to obtain the spectra of pure compounds. The spectra of the melt formulation consisting of 10% celecoxib and 90% gelucire 44/14 are obtained by analyzing the drops of the melt formulation deposited using the dropwise additive manufacturing process.

4.2.3 X-ray Diffraction

X-ray analysis was performed to ascertain the form of the drug in the formulation. The samples were analyzed using a Rigaku Smartlab diffractometer (The Woodlands, Texas) with $\text{CuK}\alpha$ radiation source and a D/tex ultra-detector. The voltage and current were 40kV and 44mA respectively and the range of data collection was from 5 to 40° 2 θ at scan speed of 10°/min and a step size of 0.04°.

4.2.4 Nanoparticle Tracking Analysis (NTA)

NTA was utilized to characterize the solution formed after dissolving the SEDDS formulation containing 1mg of celecoxib in 160 mL of distilled water. The emulsion that was formed after dissolution of the dosage form was analyzed using the Nanosight LM10 (Malvern instruments, Massachusetts) instrument. The light source of the instrument was a green laser of 532 nm wavelength. The light scattered by the particles was visualized using a 20X magnification

objective which was attached to a CMOS camera. Particle size distribution analysis was performed by acquiring a 30 sec video and processing it using the Nanosight NTA 3.0 software.

4.2.5 Dissolution Testing and High Performance Liquid Chromatography Experiments

Dissolution testing of crystalline CEL and the SEDDS formulation was performed in 900 mL of pH 6.8 10mM phosphate buffer in a USP-I paddle dissolution apparatus. Experiments were performed at 100 rpm at 37°C. Aliquots were taken from the dissolution vessels and filtered through a 1µm glass filter. The volume of the sampled aliquots was replenished using fresh dissolution medium. The filtered samples were then analyzed using an Agilent 1100 series HPLC (Santa Clara, California) fitted with a UV detector. Samples were run through a Kinetex 2.6 µ C₁₈ column (150 x 3.0 mm) at a flow rate of 0.5 mL and a column temperature of 50°C. The mobile phase consisted of 30% pH 3.5 water adjusted using phosphoric acid and 70% methanol. The injection volume was 20µL and the absorbance was monitored at the wavelength of 250 nm. Each experiment was performed in triplicate.

5. Results and Discussion

The production of SEDDS is demonstrated with the DAMPP system. The melt-based SEDDS formulation consists of 10% celecoxib and 90% gelucire 44/14 by weight. Celecoxib is a lipophilic and poorly water soluble drug. Gelucire 44/14 is a non-ionic surfactant with a relatively high hydrophilic–lipophilic balance (HLB) of 14. The formulation is comelted at 70 °C and the temperature of the process is controlled at 70 °C during printing. The residence time of the formulation in the entire process is less than 5 min.

5.1 Reproducibility of Dosage Forms

Using the DAMPP system, dosage forms are produced using the nozzle with internal diameter of 1.150 mm, pump displacement of 2.5, pump volume stroke of 1 and pump rate of 500. The reproducibility of the dosage forms produced is analyzed as described in section 4.2.1. The dosage forms consisting of 10% celecoxib and 90% gelucire 44/14 have an average dosage amount of 1.58mg; and the relative standard deviation (RSD) is 2.64%. These RSD values are well within the 5% RSD limit required by the FDA. Typical images of the dosages used in the dissolution testing is shown in Figure 3. The images are recorded via the online imaging system, after the drops are ejected through the nozzle.

5.2 Solid-State Analysis

Celecoxib is a rapid crystallizer and its crystallization is shown to be inhibited by the presence of polymers such as HPMC in the solid state (Mosquera-Giraldo et al., 2014; Xie and Taylor, 2015). The form of celecoxib in the dosage forms is analyzed with a Raman microscope to investigate the effect of gelucire on crystallization of celecoxib within the deposits. Raman spectra of melt-based drug deposits of 90% gelucire and 10% celecoxib, pure gelucire and pure crystalline celecoxib are presented in Figure 4. The grey bands clearly show the differences in the peaks of crystalline drug and drug peaks found in the dosage forms. These differences in the peak position, intensity and width are compared with reference spectra of amorphous and crystalline celecoxib from the literature (Andrews et al., 2010; Xie and Taylor, 2015) and it is concluded that the celecoxib found in the dosage forms is in the amorphous form.

In Figure 4, the crystalline spectrum has a double peak at 1614 cm^{-1} with a slight shoulder at 1599 cm^{-1} , whereas the spectrum of the dosage form has a double peak with distinct maxima at 1616 cm^{-1} and 1597 cm^{-1} . Likewise, the spectrum of the dosage form contains a double peak with distinct maxima at 1185 and 1200 cm^{-1} whereas the spectrum of crystalline celecoxib contains a double peak with a maximum at 1192 cm^{-1} and a shoulder at 1201 cm^{-1} . These differences in the spectra are consistent with the reported amorphous and crystalline celecoxib spectra (Xie and Taylor, 2015).

The crystallinity of the dosage forms is further analyzed with X-ray diffraction. The XRD spectra of melt-based drug deposits of SEDDS formulation with 90% gelucire and 10% celecoxib, pure gelucire and pure crystalline celecoxib are presented in Figure 5. Crystalline peaks of celecoxib were not observed in the dosage forms produced with the SEDDS formulation. Along with the Raman analysis, the presence of amorphous celecoxib in the dosage forms is thus demonstrated.

5.3 Analysis of the Self-Emulsifying Drug Delivery System

The formulation displays spontaneous self-emulsifying characteristics upon dilution in aqueous media. In order to further analyze the resulting emulsion, a technique called nanoparticle tracking analysis (NTA) is used. NTA utilizes the properties of both light scattering and Brownian motion in order to obtain the particle size distribution of nanoparticles in solution.(Filipe et al., 2010) The size distribution profile of emulsion droplets obtained from the SEDDS containing of 10% celecoxib and 90% gelucire is presented in Figure 6. NTA also enables visualization and recording of particles. Figure 6 also displays a particle image that is

obtained during NTA analysis. White dots correspond to the particles that are observed in contrast to the black background. Using the software, the mean particle size is found as 160.76 nm. Thus, the celecoxib-gelucire (10:90) formulation results in the formation of a submicron spontaneous emulsion.

5.4 Dissolution Testing

Dissolution testing was performed on the dosage forms manufactured using the self-emulsifying formulation. In Figure 7, the dissolution profiles of the dosage forms are compared with that of crystalline celecoxib. The crystalline solubility limit of celecoxib has been reported to be in the range of 1.1 to 1.5 µg/ml (Chen et al., 2015; Xie and Taylor, 2016). The solubility limits are shown as the dotted black lines, which correspond to a release of 63-85% of the SEDDS dosage forms. The solubility between two limits is shown with the grey band in the figure. For the SEDDS formulation, a dissolution of 70% of the dose is reached in 10 min. The dissolution reaches a plateau at around 75% dissolution which indicates that the crystalline solubility limit is reached and increasing the testing time does not affect the release profile. On the other hand, the crystalline celecoxib reaches only 22% release in 2 hours under the same conditions. Thus, the SEDDS formulation promotes rapid dissolution of celecoxib up to the concentration equivalent to the crystalline solubility.

Although celecoxib in the SEDDS is in amorphous form, during dissolution testing it does not exceed the crystalline solubility. This is due to rapid crystallization of celecoxib when dissolved in the buffer solution. When the deposits are dissolved in buffer solution, the celecoxib within

the deposits recrystallizes after 5 min. Optical microscopy images of celecoxib crystals in buffer solution following dissolution of the SEDDS formulation are shown in Figure 8a.

Polymers are known to inhibit nucleation and crystal growth of drugs in solution (Chavan et al., 2016; Mah et al., 2016). One such polymer is HPMC which is known to inhibit the solution crystallization of celecoxib (Xie and Taylor, 2015). However dissolving the deposits in buffer solution containing pre-dissolved 100 µg/ml HPMC does not prevent crystallization of celecoxib in solution. Celecoxib crystals in this solution are shown in Figure 8b. Although gelucire 44/14 inhibits crystallization of celecoxib in solid state, it promotes solution crystallization of celecoxib even in the presence of a good solution inhibitor such as HPMC.

6. Conclusions

A dropwise additive manufacturing system of pharmaceutical products (DAMPP) has been developed and shown to be suitable for the production of melt-based dosage forms. This temperature controlled process enables the production of melt-based pharmaceuticals reproducibly and consistently. In this paper, we further investigated the use of DAMPP process for the production of alternative drug formulations, i.e. self-emulsifying drug delivery systems and amorphous dosage forms. For this purpose, various lipid based excipients are investigated for the use in the DAMPP process. A melt-based formulation consisting of celecoxib and gelucire (10:90) is developed which forms a submicron spontaneous emulsion system upon contact with water. It was shown that in this formulation the celecoxib is present in amorphous form, which results in enhancement of the dissolution rate of celecoxib relative to crystalline drug.

These results suggest that the DAMPP process is a promising tool as an on-demand production method for amorphous and self-emulsifying dosage forms. The on-demand production of amorphous dosage form not only addresses the solubility issues of poorly soluble active ingredient but it also reduces concerns with the shelf-life duration within which the active should remain in stable in the amorphous form. Of course, the additional advantage of the DAMPP process for any of the formulations is that it can be used to tailor the dosage regimen for individual patients and to produce low dose high potency drugs consistently.

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624

625 **List of Figures**

626 Figure 1 DAMPP Process (1:material reservoir, 2: precision pump, 3: nozzle, 4: camera, 5:
627 substrate, 6: xy-staging, 7-8: temperature controllers, dotted box: imaging system)

628

629 Figure 2 Melt-based formulations during deposition on a. polymeric films b. placebo tablets

630

631 Figure 3 Online monitored drop images

632

633 Figure 4 Raman spectra of SEDDS formulation (90% gel 10% cel), pure gelucire 44/14 and pure
634 crystalline celecoxib

635

636 Figure 5 XRD spectra of crystalline celecoxib, pure gelucire 44/14 and SEDDS formulation with
637 10% celecoxib and 90% gelucire 44/14

638

639 Figure 6 Size distribution profiles and particle images for SEDDSs

640

641 Figure 7 Dissolution of celecoxib found in SEDDS formulation and crystalline celecoxib

642

643 Figure 8 Optical microscopy images of dosage forms dissolved in a. 5ml buffer solution b. 5ml
644 buffer solution with pre-dissolved 100µg/ml HPMC

Table 1 Lipid-based excipients used in DAMPP system and their properties

Excipient	Type	Physical Form	Average Melting Temperature	Solubility / HLB
Compritol 888ATO	Lipid	Powder	70 °C	Insoluble in water
Precirol ATO 5	Lipid	Powder	56 °C	Insoluble in water / 2
Gelucire 44/14	Surfactant	Semi solid block	44 °C	14
Labrasol	Surfactant	Liquid	undetermined	12

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8a

Figure 8b