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Process control of a dropwise additive manufacturing system for pharmaceuticals using polynomial chaos expansion based surrogate model

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ABSTRACT

The paper presents a dropwise additive manufacturing process for pharmaceutical products (DAMPP) as an alternative to conventional methods. This mini manufacturing process for the production of personalized pharmaceutical products utilizes drop-on-demand (DoD) printing technology for the deposition of active pharmaceutical ingredient (API) onto edible substrates. Here we present a process control framework for DAMPP, including on-line monitoring, automation and closed loop control, in order to produce individual dosage forms with the desired critical quality attributes, including formulation composition, drop size, deposit morphology and dissolution performance. In order to achieve desired product morphology, a surrogate model based on polynomial chaos expansion is developed to relate the critical process parameters to deposit morphology using dissolution data of the active pharmaceutical ingredient. The proposed process control strategy can effectively mitigate variations in the dissolution profiles due to variable dosage amounts and enable the application of the DoD system for the production of individualized dosage regimens.

1. Introduction

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 part of this renewed emphasis on improvement of manufacturing, the pharmaceutical industry has begun to shift toward continuous processing and to develop more efficient production systems with more intensive use of on-line measurement and sensing, real time quality control and process control tools (Gernaey et al., 2012; Troup and Georgakis, 2012). Improved production processes offer the potential for reduced production costs, faster product release, reduced variability, increased flexibility and efficiency, and improved product quality (Stephanopoulos and Reklaitis, 2011).

Under the US National Science Foundation supported Engineering Research Center for Structured Organic Particulate Systems (NSF ERC-SOPS), a dropwise additive manufacturing process for solid oral drug production has been developed. The process 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, using a semi-continuous operation suitable for low volume production of personalized dosage forms (Hirshfield et al., 2014). Using DoD, different formulations with a wide range of properties can be deposited, including solvent-based and melt-based systems.

The main advantages of using DoD technology for drug printing are the ability to produce small droplets of controlled sizes and to deposit these drops with high placement accuracy (de Gans et al., 2004). The advantages of liquid processing and reproducible production of small droplets create an opportunity in the production of low dose, high potency drugs. By changing the drop size and the composition of the formulation, the dosage amount and delivery characteristics can be adjusted according to the patient's needs thereby enabling the process to produce individualized dosage products.

As with any process for producing a drug product, the desired critical quality attributes (CQA), which are its essential physical, chemical and biological characteristics, must be within the appropriate limits defining the desired product quality (Food and Drug Administration CDER, 2008). In order to achieve the desired CQA's, i.e. dosage amount, product morphology and dissolution performance, the critical process parameters (CPP) should be controlled.

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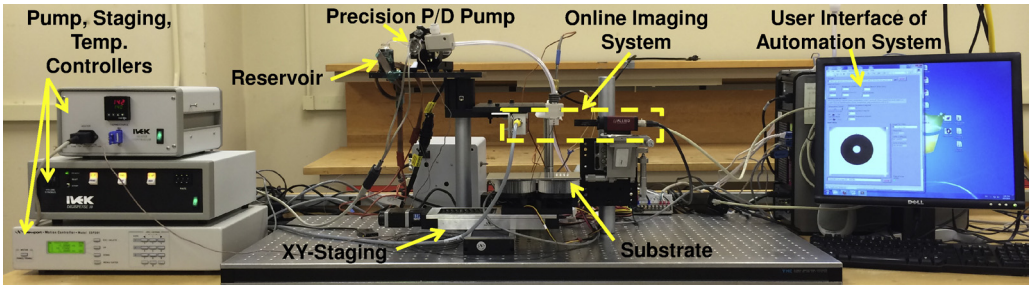

Fig. 1. Dropwise additive manufacturing system.

For this mini-manufacturing system, the CPP's, whose variability has an impact on the CQA's, are the drop size, product and process temperatures. Implementation of a supervisory control system on the process, including on-line monitoring, automation and closed-loop control, is essential for producing individual dosage forms with the desired critical quality attributes. This paper presents such a system, which assures precise control of formulation composition, drop size, deposit morphology and drug dissolution. In order to achieve proper product morphology, a data driven approach based on polynomial chaos expansion (PCE) is used to relate the critical process parameters to deposit morphology using dissolution data of the active pharmaceutical ingredient. The dissolution testing is a standardized off-line laboratory procedure widely used as indicator of bioavailability. The PCE-based surrogate model is then used in an optimal control framework to determine the required temperature profile to achieve a desired bioavailability. In pharmaceutical manufacture, the preferred product quality targets are those closer to reflecting the performance of the product in the patient, such as dissolution, than are traditional quality metrics, such as composition. As noted in recent FDA publications (Lee et al., 2015), the ultimate goal is real time release of product, that is, by passing of the traditional laboratory-based quality control step, such as dissolution testing, through use of measurement and advanced control methods during manufacture so as to allow product to be ready for release to the market immediately upon manufacture. The process control strategy reported in this paper is novel not only in providing effective control of the drop on demand manufacturing process but also is one of the first efforts in the literature demonstrating elements of model-based real time release (MBRTR) and the concept of quality-by-control (QbC), whereby product performance and consistent quality are achieved by the design of suitable control strategies.

2. Process control strategy

The dropwise additive manufacturing system consists of a precision positive displacement pump, xy-staging, a hot air based heating system, on-line imaging and sensing, and temperature, pump and stage controllers, as shown in Fig. 1. The interested reader is invited to refer to Hirshfield et al. (2014) and Içten et al. (2015) for more detailed description of the dropwise additive manufacturing system for solvent-based and melt-based pharmaceutical products, respectively. The above mentioned publications discuss the rationale for developing the drop-on-demand process for pharmaceutical applications and implementation of the DoD system for different pharmaceutical formulations. The Liquid Dispensing Technology (LDT) patented by GSK (Clarke et al., 2012) is used to produce pharmaceutical products by solvent deposition and operates in open loop where the drop sizes are monitored and off-spec tablets are simply rejected. The LDT has no supervisory control implemented for morphology; and quality control on dissolution is handled in a classical sampled fashion.

This paper presents a supervisory control strategy to achieve the critical quality attributes of solid oral dosages produced with the DoD system. The supervisory control strategy for the dropwise additive manufacturing process is shown in Fig. 2. The supervisory control strategy consists of two main parts: an automated low-level control system and a surrogate model based supervisory control layer, which are described in Sections 2.1 and 2.2, respectively. The low level control system provides effective control of the drop on demand manufacturing process, whereas the surrogate model based supervisory control layer demonstrates the indirect control of drug dissolution online and enables model-based real time release of solid oral dosages.

2.1. Low-level control system

Automation of the on-line monitoring and control systems is implemented using the LabVIEW (National Instruments) environment. The automation logic controls the pump, camera and xy-staging, simultaneously. An image of each drop is taken after it is ejected from the nozzle. The dosage amount of each drop is monitored using the corresponding drop volume calculated using real-time image analysis with arbitrary rotational symmetric shape model (Hugli and Gonzalez, 2000). By changing the pump and nozzle parameters, different drop sizes can be produced, which allows adjustment of the dosage amount for patients with different therapeutic requirements. The xy-staging and synchronization logic allows precise drop positioning on the substrate while printing and enables layering of different drugs, thus offering the flexibility of producing combination dosages. For more details on the real time process management strategy, including automation, online monitoring and exceptional events management, the interested reader is referred to Hirshfield et al. (2015), where the drop deposition, image processing and synchronized xy-staging operation is described.

Using this process, different drug formulations including polymer-API systems, i.e. melts, and solvent-polymer-API systems can be produced. The printability and reproducibility of melt formulations depend on the process temperature, which is maintained above the melting temperature and within the desired operating limits in order to produce hot-melts of API and a carrier such as a polymer or surfactant. Therefore temperature control is implemented on reservoir, pump, tubing and nozzle using heating tape, built-in pump heater and air heating system, respectively.

The product morphology depends on the formulation composition, on the selection of the substrate and on the CPP's, i.e. product temperature and drop size. The selection of the polymer used in the formulation can change the morphology by promoting or inhibiting crystallization of the drug (Trasi and Taylor, 2012). The surface properties of the substrate onto which the drops are deposited can also have an effect on product morphology (Hsu et al., 2013). In bulk crystallization processes, crystallization temperature is used to control the crystal properties including size distribution, shape and