Dropwise Additive Manufacturing of Pharmaceutical Products for Solvent-Based Dosage Forms

LAURA HIRSHFIELD,[1] ARUN GIRIDHAR,[1] LYNNE S. TAYLOR,[2] MICHAEL T. HARRIS,[1] GINTARAS V. REKLAITIS[1]

[1]Department of Chemical Engineering, Purdue University, West Lafayette 47907-2100, Indiana
[2]Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette 47907-2100, Indiana

Received 28 August 2013; revised 25 October 2013; accepted 6 November 2013

Published online 5 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23803

ABSTRACT: In recent years, the US Food and Drug Administration has encouraged pharmaceutical companies to develop more innovative and efficient manufacturing methods with improved online monitoring and control. Mini-manufacturing of medicine is one such method enabling the creation of individualized product forms for each patient. This work presents dropwise additive manufacturing of pharmaceutical products (DAMPP), an automated, controlled mini-manufacturing method that deposits active pharmaceutical ingredients (APIs) directly onto edible substrates using drop-on-demand (DoD) inkjet printing technology. The use of DoD technology allows for precise control over the material properties, drug solid state form, drop size, and drop dynamics and can be beneficial in the creation of high-potency drug forms, combination drugs with multiple APIs or individualized medicine products tailored to a specific patient. In this work, DAMPP was used to create dosage forms from solvent-based formulations consisting of API, polymer, and solvent carrier. The forms were then analyzed to determine the reproducibility of creating an on-target dosage form, the morphology of the API of the final form and the dissolution behavior of the drug over time. DAMPP is found to be a viable alternative to traditional mass-manufacturing methods for solvent-based oral dosage forms. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:496–506, 2014

Keywords: amorphous; crystal structure; dissolution; drug delivery; polymers; process development; processing; process analytical technology; X-ray diffractometry

INTRODUCTION

In recent years, the US Food and Drug Administration (FDA) has encouraged pharmaceutical companies to place renewed emphasis on process development and manufacturing to improve product quality among other factors and supply chain reliability. The Process Analytical Technology and Quality by Design initiatives in particular have stimulated innovations, which are advancing the transition from the traditional large batch manufacturing mode to more efficient pharmaceutical manufacturing processes that integrate online monitoring, advanced process control, and model-driven optimization strategies.[1] Continuous manufacturing of both drug substance and drug product are now subjects of intensive investigation as are innovative small-scale manufacturing platforms that can offer reduced development times, simplified scale-up, reduction in waste, improvements in product quality, and flexibility in accommodating multiple products and multiple dosage amounts.

This paper presents dropwise additive manufacturing of pharmaceutical products (DAMPP), an innovative pharmaceutical manufacturing platform that differs substantially from traditional drug product manufacturing processes and minimizes the handling of powders and granules. Drop-on-demand (DoD), a technology commonly used in inkjet printers that is now receiving significant attention in 3D printing applications, is utilized in DAMPP to print a formulation containing an active pharmaceutical ingredient (API) onto a substrate to create a base product that can be further postprocessed as needed into various final product forms. With careful selection of process parameters and printing materials, DAMPP allows for precise and accurate control of the dosage amount, composition, phase, morphology, and release profile of the drug, all while monitoring and controlling critical process parameters and critical product quality attributes.

Drop-on-demand is a production method based on dropwise deposition of a fluid formulation onto a substrate material on an as-needed basis. DoD is best known for its use in inkjet printing technology.[2] However, in more recent years, DoD has grown from this original use to exploitation in a variety of manufacturing applications because of its simplicity, flexibility, precision, high speed, and ability to employ a wide variety of printing materials, including nanoparticles,[3] sol-gel materials,[4] structural polymers,[5] ceramics, molten metals,[6] suspensions, and polymer melts. DoD printing techniques have now been used to manufacture cell cultures and patterning,[7,8] electronics,[8,9] solar cells,[10] 3D structures,[11] and tissue and organ printing.[12]

Drop-on-demand technology has also been used in some pharmaceutical applications, including creation of three-dimensional dosage forms,[13] coating of drug stents,[14] and printing of API dissolved in a liquid.[15,16]. DoD technology can also be used for large-scale production of tablets, as demonstrated by GlaxoSmithKline's Liquid Dispensing Technology[17] but can also form the core of a mini-manufacturing platform such as DAMPP that can be used to create individual dosages tailored for individual patients. It thus offers a path to individualized medicine for drugs in which the therapeutic effect varies highly for each patient. Individualized medicine is an emerging focus in pharmaceuticals in which a dosage regimen is determined for a patient based on that patient's specific therapeutic response to the API. Currently, the determination of the most

Correspondence to: Laura Hirshfield (Telephone: +2488084087; Fax: +765-4940805; E-mail: lhirshfi@gmail.com)

Journal of Pharmaceutical Sciences, Vol. 103, 496–506 (2014)

appropriate regimen is carried out by physicians via trial and error beginning with the nominal dosage. With the use of pharmacokinetic and pharmacodynamic models, given parameter distributions determined from population clinical data coupled with a limited number of plasma samples from a given patient, optimization-based methods have been reported for predicting a regimen that has the highest probability of meeting the therapeutic needs of that patient.[18] DAMPP could produce that predicted dosage at the compounding pharmacy or clinic. Thus, tablets would not need to be mass produced in multiple variations of dosage loading. Creating dosage forms via DAMPP in the compounding pharmacy also mitigates potential issues with stability of drugs as it reduces the time between manufacturing and patient consumption.

Drop-on-demand has a high-throughput capability, as it can print multiple drops per second and can be easily scaled up with the addition of multiple nozzles or multiple reservoirs. This means there is also an ease of change-over between different printing formulations. Because of this characteristic, DAMPP lends itself to the production of combination drugs: multilayered dosage forms that contain multiple APIs. Creation of dosage forms could be carried out by either depositing drops of the different API formulations sequentially onto one substrate or printing each formulation onto a specific polymeric film and then combining these films into a multilayered structure.[19]

Dropwise additive manufacturing of pharmaceutical products is also unique in that it allows for precise control over final product properties, including drug solid-state form, by manipulating the printing formulation. By selecting whether the API is being deposited in a solvent-based or polymer-melt-based formulation and choosing which polymer is being used in the formulation, the user has specific control over the final product's solid-state form. There has been much interest in formulating amorphous dosage forms, because of their higher dissolution rates and higher bioavailability; however, amorphous forms can be unstable both during processing and storage. The use of DAMPP allows not only for the creation of dosage forms of controlled crystallinity, but also completely amorphous forms that can be produced using optimized processing conditions and rational polymer selection.

There also are several technological benefits to using DoD technology for manufacturing purposes. As DoD is precise and releases material as needed, using it to print dosage forms means that only the necessary amount of the material is dispensed and thus there is very low waste compared with conventional manufacturing processes and lower costs associated with excipients.[11] Therefore, DAMPP is especially applicable for the production of highly potent drugs that in tablet form are composed of almost entirely excipient, thus making it difficult to control the composition of the active with narrow variation. The process is also beneficial for these products in minimizing API handling and reducing worker exposure. DoD systems are generally composed of simple, inexpensive unit operations and are straightforward in use, and thus, because of their simplicity, have lower operational costs. Moreover, as the critical steps involve fluid processing, the implementation of automation and low-level control for DoD systems is easier than for conventional systems involving powder handling.[11,20]

In this work, we present a proof-of-concept of the DAMPP method for solvent-based printing formulations. We first detail the manufacturing process and discuss the various technical considerations that were addressed when creating and assembling each step of the process, such as formulation control, drop formation and deposition, drug phase behavior control, and substrate selection and handling. We then demonstrate that the use of DAMPP is a flexible and viable production method for solvent-based pharmaceutical dosage forms, offering good reproducibility in dosage amount, composition, and morphology.

DROPWISE ADDITIVE MANUFACTURING PROCESS

There are a number of technical issues that must be addressed when assembling a robust DoD manufacturing process, especially for pharmaceutical products. This section presents a "process narrative" of the DAMPP system, describing each step in detail along with what process parameters and product specifications must be taken into consideration for the production of solvent-based dosage forms. It then discusses the specific DAMPP manufacturing process used in our prototype for the production of dosage forms created with solvent-based material formulations.

Process Narrative

There are a number of technical considerations that must be addressed in implementing a DoD pharmaceutical manufacturing process. Every step of the process must be carefully engineered and controlled, beginning with the preparation of the printing material to postprocessing of the dosage form, to ensure quality of the resulting drug product. These steps are outlined in Figure 1.

This section details each of these steps of the manufacturing process for solvent-based dosage forms, along with the scientific and engineering principles that are relevant.

Preparation of Formulation to Be Printed

Using DAMPP, the API can be dissolved in a solvent-based or a polymer-melt-based formulation. The solvent-based formulation includes a solvent, the API, and possibly a polymer. A polymer-melt-based formulation is solely a polymer and an API, mixed and liquefied at the mixture's melting point. The specifics of the use of DAMPP in depositing polymer-melt-based formulations will be presented in a subsequent publication.

The properties of the API being deposited and the final form desired dictate which type of formulation should be used. The key characteristics that must be considered are the nucleation and crystal growth rates of the API during solvent evaporation or melt cooling.[21] In general, APIs can be grouped into three main classes based on their crystallization behavior: class I molecules crystallize quickly because of high nucleation and growth rates; class II molecules can either be crystalline or amorphous depending on the kinetics of the process relative to crystallization kinetics; and class III molecules are more easily rendered amorphous.[22] Selection of the type of formulation (solvent-based or melt-based), the type and amount of other formulation additives, and the conditions of the process must made based on the class of the API and the desired phase outcome.

By considering the crystallization behavior of the API and the formulation selected, we can have specific control over the final dosage form solid-state properties. The inclusion of polymer in the printing both improves printability of the fluid, facilitates adhesion of the material to the substrate, and allows