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Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets

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ABSTRACT

The main objective of this work was to explore the potential of coupling fused deposition modeling in three-dimensional (3D) printing with hot-melt extrusion (HME) technology to facilitate additive manufacturing, in order to fabricate tablets with enhanced extended release properties. Acetaminophen was used as the model drug and different grades and ratios of polymers were used to formulate tablets. Three-point bending and hardness tests were performed to determine the mechanical properties of the filaments and tablets. 3D-printed tablets, directly compressed mill-extruded tablets, and tablets prepared from a physical mixture were evaluated for drug release rates using a USP-II dissolution apparatus. The surface and cross-sectional morphology of the 3D-printed tablets were assessed by scanning electron microscopy. Differential scanning calorimetry and thermogravimetric analysis were used to characterize the crystal states and thermal properties of materials, respectively. The 3D-printed tablets had smooth surfaces and tight structures; therefore, they showed better extended drug release rates than the directly compressed tablets did. Further, this study clearly demonstrated the feasibility of coupling HME with 3D printing technology, which allows for the formulation of drug delivery systems using different grades and ratios of pharmaceutical polymers. In addition, formulations can be made based on the personal needs of patients.

1. Introduction

Solid dispersions represent a promising formulation approach undertaken by many pharmaceutical scientists to improve the bioavailability of active pharmaceutical ingredients (API) with poor aqueous solubility (Baghel et al., 2016; Popescu et al., 2015; Vasconcelos et al., 2007). Hot-melt extrusion (HME) is one of the preferred methods in pharmaceutical solid dispersion development. This is because the technology can generate extrudates/granules with favorable properties. In addition, it is free from the use of organic solvents and suitable for continuous processing (Sareen et al., 2010; Sarode et al., 2013; Thiry et al., 2015).

HME was first used in the plastics and rubber industry. However, since the 1970s, the use of HME has been promoted in pharmaceutical research (Feng et al., 2015; Repka et al., 2013). The pharmaceutical use of HME is currently under investigation as a method for increasing the release rate of poorly water-soluble APIs. The bioavailabilities of such APIs are enhanced by melt-mixing them with hydrophilic, water-soluble polymers (Patil et al., 2016; Stanković et al., 2015). Apart from increasing the bioavailability of an API, HME can be used to develop modified-release drug systems with delayed drug delivery characteristics and the ability to mask the bitter taste of an API (Gross et al., 2014; Tiwari et al., 2016). Moreover, HME can be easily coupled with other technologies, such as high-pressure homogenization, to prepare solid lipid nanoparticles (Patil et al., 2016) and nanocrystals (Ye et al., 2016). It can also be used with high-pressurized carbon dioxide to enhance milling efficiency and to prepare a floating drug delivery system by creating porous extrudates (Ashour et al., 2015; Vo et al., 2016). In recent years, researchers have started exploring the conjugation of HME with three-dimensional (3D) printing to prepare pharmaceutical dosage forms (Goyanes et al., 2015a,b; Melocchi et al., 2016).

Abbreviation: HME, hot-melt extrusion; API, active pharmaceutical ingredients; 3DP, 3D-printed; EC, ethyl cellulose; HPMC, hydroxypropyl methylcellulose; FDM, fused deposition modeling; APAP, acetaminophen; BCS, Biopharmaceutics Classification System; HPLC, high-performance liquid chromatography; PLA, polylactic acid; SEM, scanning electronic microscopy; AM, additive manufacturing; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis.

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3D printing is a layer-by-layer production of 3D objects with the help of digital designs (Gross et al., 2014). It is also known as additive manufacturing (AM) (ISO/ASTM 52900, 2015). AM equipment and materials were developed in the early 1980s, mainly for chemistry, optics, and robotics research (Norman et al., 2016). The first powder-based free-form fabrication using 3D printing methods became available in 1993 at the Massachusetts Institute of Technology (MIT) (Sachs et al., 1993), in which a standard inkjet head was used to print binders onto loose powders in a powder bed.

Compared with the traditional process of manufacturing dosage forms, 3D printing can create complex products, personalized products, and products made for immediate consumption (Jonathan and Karim, 2016).

Based on the advantages offered by 3D printing technology, interest in this technique within the pharmaceutical industry has grown over the last few years. This is reflected in the increasing number of scientific reports and patents describing the pharmaceutical applications of 3D printing. Recently, the U.S. Food and Drug Administration (FDA) approved the first 3D-printed (3DP) orally disintegrating tablet SPRITAM® (levetiracetam), which was manufactured based on the ZipDose® Technology (Aprecia Pharmaceuticals, Langhorne, PA, USA).

The traditional process of manufacturing pharmaceuticals involves a complex downstream procedure, which includes milling extrudates, sieving, compressing, and coating. However, 3D printing technology can streamline these processes. Compared to the traditional process of manufacturing pharmaceutical products, combining HME and 3D printing into a continuous process can offer advantages. These include increased solubility and bioavailability of drugs, as well as production of more complex-structured dosage forms and personalized drug products. In addition, combining the two technologies can simplify the downstream process and make it more effective and economical (Fig. 1). In particular, the FDA encourages drug manufacturers to produce oral solid dosage forms that meet the increasing demands of oral drug delivery, in terms of API bioavailability and drug release characteristics, in a continuous and controlled process (O'Connor et al., 2016).

Based on the advantages of coupling the two technologies, the elementary steps involved in producing dosage forms by continuous HME-3D printing are as follows: 1) dosage form design and conversion to a printer-readable format; 2) preparation of raw materials (such as powders, particulates, granules, or pastes); 3) preparation of hot-melt extruded filaments; 4) cooling of the filaments; 5) 3D printing; and 6) removal of printed material and downstream processes such as cooling, drying, and packing. However, for continuous pharmaceutical HME and 3D printing, extruding the 3D-printable filaments is a very important elementary step, along with dissolving the poorly water-soluble API in molten polymeric excipients and mixing them to improve the bioavailability of the API.

Previous studies have used powder/binder-based biodegradable polymers, such as polyethylene oxide/polycyclooctene (Wu et al., 1996), ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC) E50, polyvinylpyrrolidone K30 (Yu et al., 2007), and Eudragit® L100 (Rathbone, 2008), to print pharmaceutical dosage forms. Recently, biodegradable polymer filaments, prepared from HPMC K100M CR (Khaled et al., 2015) and polyvinyl alcohol (Goyanes et al., 2015a,b), were manufactured by 3D printing.

The present study investigated the use of different types of pharmaceutical polymers to prepare fused filaments suitable for 3D printing of a desired pharmaceutical formulation. The main objectives of this study were as follows: 1) to couple fused deposition modeling (FDM)-based 3D printing with HME technology to print controlled-release tablets, 2) to screen different grades of pharmaceutical polymers suitable for 3D printing based on the HME-fused filaments' physical and chemical properties, and 3) to study the drug release profiles of 3DP tablets in comparison to those of directly-compressed milled extrudate and physical-mixture tablets.

2. Materials and methods

2.1. Materials

Acetaminophen (APAP) (Spectrum Chemical, New Brunswick, NJ, USA) was used as the model API. APAP is a crystalline Class I

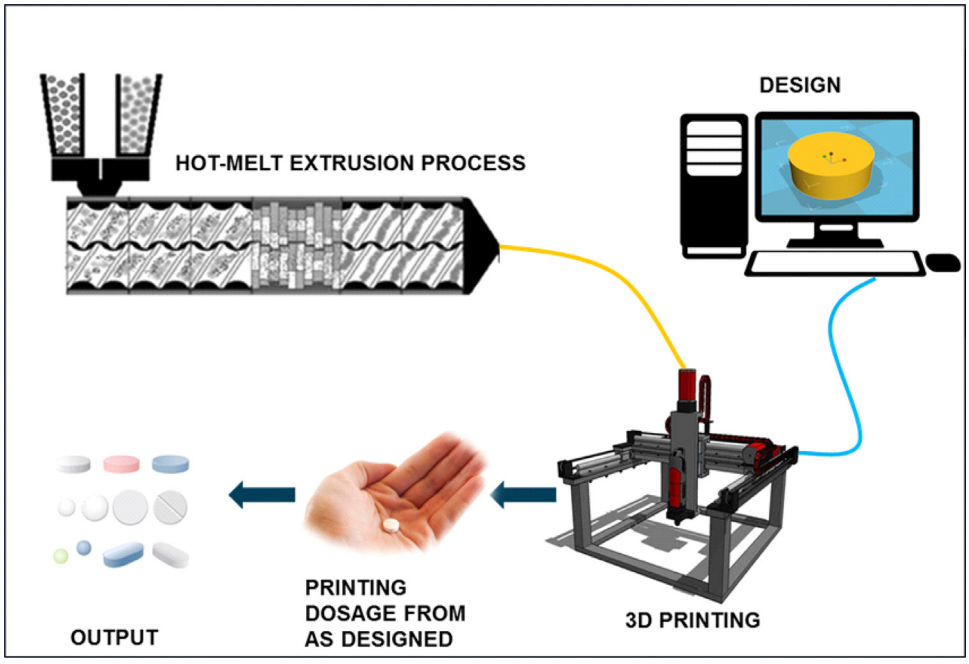

Fig. 1. Schematic of the combination of HME and 3D process.