International Journal of Pharmaceutics 525 (2017) 5–11

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing

Qijun Li[a], Haoyang Wen[a], Danyang Jia[c], Xiaoying Guan[a], Hao Pan[d], Yue Yang[a], Shihui Yu[a], Zhihong Zhu[a], Rongwu Xiang[b,*], Weisan Pan[a,*]

[a] Department of Pharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China
[b] School of Medical Instrument, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China
[c] Department of Pharmaceutical Information, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China
[d] College of Pharmacy, Liaoning University, 66 Chongshan Middle Road, Shenyang 110036, China

ARTICLE INFO

Article history:
Received 20 August 2016
Received in revised form 6 March 2017
Accepted 26 March 2017
Available online 2 April 2017

Keywords:
Three dimensional printing
Controlled-release
Hot melt extrusion
PVA
Multiple drug concentration distributions
Double-chamber design

ABSTRACT

The purpose of this study was to explore the feasibility of combining fused deposition modeling (FDM) 3D printing technology with hot melt extrusion (HME) to fabricate a novel controlled-release drug delivery device. Glipizide used in the treatment of diabetes was selected as model drug, and was successfully loaded into commercial polyvinyl alcohol (PVA) filaments by HME method. The drug-loaded filaments were printed through a dual-nozzle 3D printer, and finally formed a double-chamber device composed by a tablet embedded within a larger tablet (DuoTablet), each chamber contains different contents of glipizide. The drug-loaded 3D printed device was evaluated for drug release under in vitro dissolution condition, and we found the release profile fit Korsmeyer–Peppas release kinetics. With the double-chamber design, it is feasible to design either controlled drug release or delayed drug release behavior by reasonably arranging the concentration distribution of the drug in the device. The characteristics of the external layer performed main influence on the release profile of the internal compartment such as lag-time or rate of release. The results of this study suggest the potential of 3D printing to fabricate controlled-release drug delivery system containing multiple drug concentration distributions via hot melt extrusion method and specialized design configurations.

1. Introduction

Three-dimensional printing (3DP) technology has attracted worldwide attention in recent years as a novel technology for rapid prototyping, which constructs solid objects by layer-by-layer deposition. Nowadays 3DP is promoting enormous innovations in many diverse fields, including the equipment manufacturing, architecture, archaeology, biomedical research and pharmacy (Katakam et al., 2015; Khaled et al., 2015; Melocchi et al., 2015; Norman et al., 2016; Prasad and Smyth, 2016; Rattanakit et al., 2012; Yu et al., 2008). It seems to be an epoch of the next industrial revolution changing our lifestyle. Along with the technology updates and promotion, it is convenient to acquire design templates online and print objects.

Personalized medicine provides a number of advantages to patients, which is widely believed as a key factor for future improvement in disease treatment. The concept of personalized medicine means a customization of healthcare to an individual patient. However, the industrial production of tablets/capsules can only provide limited dose range due to the complex manufacture process and equipment restriction. In order to overcome the challenges, novel productive technologies such as 3DP technology which possess significant potential of high shaping accuracy (Alomari et al., 2015; Buanz et al., 2011; Skowyra et al., 2015), improvement on the inherent properties and diverse fabrication process, should be applied and adapted in the pharmaceutical industry (Martini and Crowley, 2011).

Fused deposition modeling (FDM) 3D printing is one of the 3DP technique, which constructs solid objects by process of fusing and deposition. Fused-deposition modeling (FDM) was studied and explored to accord with the requirement of diverse unit dose fabrication (Melocchi et al., 2016). In FDM 3DP polymer filament is heated and extruded through a heated nozzle, and thereafter solidifies on a build plate. Then the build plate descends and the next

* Corresponding authors.
E-mail addresses: xrwlove@163.com (R. Xiang), pppwwwsss@163.com (W. Pan).

http://dx.doi.org/10.1016/j.ijpharm.2017.03.066
0378-5173/

layer is deposited on the previous layer (Gibson et al., 2015). The object can be manufactured in several such processes in a few minutes. In order to print drug-loaded dosage forms, the drug can be loaded on the polymer filament as a solid dispersion via hot melt extrusion (HME) (Goyanes et al., 2015a,b; Patil et al., 2016; Shah and Repka, 2013).

Glipizide is a second-generation sulfonylurea that stimulates pancreatic β cells to secrete insulin, which is a common prescription drug to treat non-insulin dependent diabetes mellitus. As glipizide is relative thermostabilization with a high melting point of 208–209 °C, it is feasible to load glipizide into polyvinyl alcohol filaments via HME method.

Thus, the purposes of the present study are to produce glipizide-loaded filaments with different drug concentrations suitable for printing into pharmaceutical dosage forms and to create a double-chamber glipizide dosage form with two kinds of drug concentration distributions. The compatibility of the HME process to manufacture glipizide-loaded filaments was evaluated, and also the influence of the internal structure (3D design) on the drug in vitro dissolution.

2. Materials and methods

2.1. Materials

Commercial water soluble filament made of Polyvinyl alcohol (PVA), a synthetic polymer with a molecular formula of $((C_2H_4O)_n)$, was purchased from YiSheng Inc., China (1.75 mm diameter, print temperature 190–210 °C).

Glipizide powder of micronized grade was purchased from Xinxin Pharmaceutical Manufactory (Tianjin, China).

2.2. Methods

2.2.1. Preparation of PVA filament loaded with drug

The PVA filament was carefully sheared into small pieces (~2 mm) manually, milled in a EUPA TSK-927S grinder (Xiamen Cankun Inc., China) and sieved through a 1000 μm mesh. The milled PVA fine granules were blended with different amounts of glipizide with mortar and pestle individually, until no agglomerated particles of drug or polymer were observed. The mixtures were then extruded respectively using a LSJ20 single-screw extruder (Shanghai Kechuang Ltd., China) to manufacture filaments with different drug concentrations (temperature 180 °C, nozzle diameter 1.75 mm, screw speed 15 rpm). The filaments extruded were kept away from light and stored in a vacuum desiccator before printing. The drug-loading of the filaments was determined by HPLC analysis before printing process.

2.2.2. 3D printing of glipizide dosage forms

Drug delivery device was fabricated with the previously produced drug-loaded filaments using a commercial fused-deposition modeling 3D printer, Clouovo Delta-MK2 (Clouovo Technologies Inc., Shenyang, China) (Supplementary Fig. 1). The templates used to print the devices were designed with an opensource software and exported as a stereolithography file (.stl) into the 3D printer software (Replicator G v4.0, opensource software). The selected size for the device was $X = 10.5$ mm (diameter), $Y = 10.5$ mm (diameter) and $Z = 3.95$ mm (height), as the size of an average tablet (Fig. 1). Then the .stl file need to be transformed to G code in order to initiate printing, the following factors should be settled before the transformation. The infill percentage was set as 100% in order to produce solid dosage forms of high density and other printer settings were as follows: standard resolution (360 dpi) with the raft option deactivated and an extrusion temperature of 195 °C, speed while extruding (15 mm/s), speed while traveling (15 mm/s), number of shells (1), nozzle diameter (0.20 mm), layer height (0.20 mm), filament diameter (1.75 mm) (Goyanes et al., 2016).

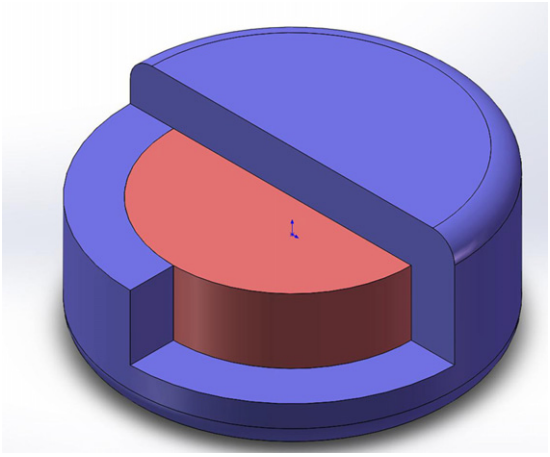

Fig. 1. 3D representation of the printed solid dosage form: sectioned DuoTablet (tablet in tablet).

2.3. Differential scanning calorimetry (DSC)

DSC analysis was performed by a DSC-60 differential scanning calorimeter (Shimadzu, Japan). Samples were heated from 30 °C to 260 °C with a heating rate of 10 °C/min. Nitrogen was used as a purge gas with a flow rate of 40 ml/min for all the experiments. The DSC was calibrated for temperature and cell constant according to the manufacturer instructions. Al_2O_3 was used as the reference (Tiwari et al., 2014).

2.4. Thermogravimetric analysis (TGA)

TGA analysis was performed by a TGA-50 thermal gravimetric analyzer (Shimadzu, Japan). Samples were heated from room temperature to 260 °C with a heating rate of 10 °C/min in open aluminum pans. Nitrogen was used as a purge gas at a rate of 40 ml/min. Percentages of weight loss (%w/w) were calculated for each sample (Goyanes et al., 2015b).

2.5. Characterization of the tablets and drug-loaded filaments

2.5.1. Determination of tablet strength

The crushing strength of ten drug-loaded DuoTablets was measured using a smart tablet hardness tester YD-20 (Shengda Sanhe optical instrument co., Ltd., Tianjin, China), whereby an increasing force is applied perpendicular to the tablet axis to opposite sides of a tablet until the tablet fractures.

2.5.2. Determination of tablet friability

Approximately 4.5 g of drug-loaded DuoTablets were weighed and placed into the drum of a Friability Tester CS-2 (Jingtuo instrument Science and Technology Ltd., Tianjin, China). The drum was then rotated at 25 rpm for 4 min and the samples were re-weighed. The friability value of the samples revealed in terms of weight loss, expressed as a percentage of the original sample weight.

2.5.3. Determination of filament tensile strength

The tensile strength of six high concentration drug-loaded filaments, six low concentration drug-loaded filaments and six blank filaments was measured using a WDS electronic control tensile strength tester (Ji'nan Kairui Machinery Equipment Co., Ltd., Ji'nan,