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Three dimensional structural insight of laser drilled orifices in osmotic pump tablets

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ABSTRACT

The orifice drilled in the membrane as a channel for drug delivery is the key functional part of the osmotic pumps for a controlled drug release system. Reported conventional microscopic evaluations of these orifices have been limited to measurement of two-dimensional cross-section diameters. This study was aimed at establishing a novel method to measure quantitatively the three-dimensional architectures of orifices based on synchrotron radiation X-ray microcomputed tomography (SR-μCT). Quantitative analysis of architectures extracted from captopril osmotic pumps drilled by a range of operating parameters indicated that laser power correlated with the cross section area, volume, surface area and depth of the orifices, while scanning speed of laser beam showed inverse relationships with the above structure characters. The synchrotron radiation based Fourier transform infrared microspectroscopy mapping showed that there was no apparent chemical change in the surrounding area of the orifice compared with the normal membrane region. Thus SR-μCT was successfully applied to marketed felodipine osmotic pumps for architectural evaluation of the orifices. In conclusion, the first three-dimensional structural insight of orifices in osmotic pump tablets by SR-μCT and structural reconstruction for the architectures has provided deeper insight into improving the design of advanced osmotic pumps for controlled drug release.

1. Introduction

The field of drug delivery has gained increasing attention for decades in the pharmaceutical sector and drug delivery systems (DDSs) remain extremely important for pharmacological and therapeutic efficacy optimization of many drugs (Rosen and Abribat, 2005). Osmotic pump drug delivery systems (OP-DDSs) are widely regarded as one of the most reliable techniques for controlled delivery of therapeutic drugs, such as anti-hypertension, antidiabetic, and anti-angina compounds, as well as hormones and other agents (Herrlich et al., 2012; Malaterre et al., 2009). Compared with other approaches used in controlled release formulations, drug release from OP-DDSs is independent of the external pH and hydrodynamics, which attributes minimal patient-to-patient variability and allows accurate prediction of in vivo performance from in vitro dissolution in many cases (Kaushal and Garg, 2003). With such highly predictable drug release rates, OP-DDSs generate various attractive biomedical advantages, e.g., reduced dosage and constant release rate leading to less side effects (Sareen et al., 2012). In terms of the clinical benefits and good in vivo-in vitro correlations (IVIVC), OP-DDSs provide a promising technology for extending product life-cycles and optimization of therapeutic effects (Malaterre et al., 2009). In addition, OP-DDSs can be designed to deliver either highly soluble drugs or sparingly soluble drugs (Malaterre et al., 2009) in zero-order release profiles or other release behaviors, e.g., sigmoidal shape release (Narisawa et al., 1997) and pulsatile release (Kaushal and Garg, 2003).

The OP-DDSs generally consist of a core tablet containing drug(s) mixed with osmotic agents and other excipients, and a semipermeable membrane with an orifice(s) for release of dissolved drug substance (Verma et al., 2000). Release of the drug(s) from the OP-DDS is driven by the osmotic pressure gradient across the membrane from the inner-side to the outer-side as well as the solubility of the drug, the penetrability of the coating membrane to external aqueous liquids, and the size and the number of the delivery orifices (Tuntikulwattana et al., 2010). A typical OP-DDS has at least one delivery orifice, for which the structure is critical for uniform drug release (Verma et al., 2002). The

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size and number of the delivery orifices must be optimized in order to achieve the desired drug release rate. A tablet with an undersized delivery orifice may lead to the burst of the membrane and dysfunction of the OP-DDSs caused by internal high hydrostatic pressure. On the other hand, the delivery orifices with too large a size could result in solute diffusion dominated drug release through the orifices (Verma et al., 2000). However, the effects of the shape, depth and other structural parameters of delivery orifices on OP-DDSs have not been reported.

Methods used to create delivery orifices in the coating membranes of OP-DDSs include: mechanical drilling, passageways formed in situ, and laser drilling (Verma et al., 2002). Mechanical drilling generally involves the use of a micro drill to create orifices on the surface of the tablets after coating (Ozdemir and Sahin, 1997; Prabakaran et al., 2003; Thombre et al., 2004) or modifying the upper punch of the tableting machine with a needle to produce an indentation at the center of the surface of the tablet cores (Liu and Che, 2006; Liu et al., 2007; Liu and Xu, 2008). The orifices formed in situ are formed by adding a pore-forming agent to the semipermeable membrane composition (Kanagale et al., 2007; Patel et al., 2013; Tuntikulwattana et al., 2010) or by preparing the asymmetric membrane systems by controlled phase separation (Patel et al., 2012; Yang et al., 2014b). However, the OP-DDSs prepared by inclusion of a pore forming agent and asymmetric membrane methods are usually limited by the solubility of active ingredients. Laser drilling is the most widely used industrialized technique to create delivery orifices in the membrane of the OP-DDSs with high efficiency, accuracy and reliability.

The architecture of micro-structures formed after laser drilling contains not only the delivery orifices in the membranes, but also melting and solidification in the tablet cores adjacent to the drilled orifices. The effects of laser drilling parameters on the quality of delivery orifices and some structural parameters of the orifices have been reported in other fields, such as alumina ceramics and metals, using optical microscopic (Tu et al., 2014), and scanning electron microscopic methods (Bharatish et al., 2013). However, for OP-DDSs, the evaluations of delivery orifices have been mainly limited to cross section two-dimensional (2D) observations to determine the cross section diameter of the delivery orifice by microscopes using a pre-calibrated ocular micrometer (Gupta et al., 2009). An alternative approach was to measure the delivery orifice microscopically using empty shells obtained after complete dissolution of the contents of OP-DDS (Prabakaran et al., 2003), which is likely to introduce some errors or structural movement. In contrast, non-invasive imaging techniques are efficient tools which can reveal directly the internal structure and dynamic characteristics of OP-DDSs at different stages of the drug release process. Synchrotron radiation X-ray microcomputed tomography (SR-μCT) imaging is an attractive nondestructive technique for the visualization of the internal structures of pharmaceutical solid dosage forms (Yang et al., 2014a; Yin et al., 2013a). In our previous study, the internal microstructure of felodipine sustained release tablets (Linuo®) and the mechanism of the controlled drug release kinetics based on fractal structures have been investigated based on information revealed by SR-μCT (Li et al., 2012; Yin et al., 2013b).

As a critical structural feature of OP-DDSs, the structures of delivery orifices of OP-DDSs have been almost ignored in OP-DDSs development with an absence of published literature on this topic. The architectural detail extracted via SR-μCT can provide the real structures of laser drilled orifices with 3D visualization and enable quantitative assessment of the effects of laser drilling. Such structural details will provide deeper understanding of guiding the design of OP-DDSs to optimize their performance in controlled drug delivery to patients.

2. Materials and methods

2.1. Materials

Captopril was gifted by Changzhou Pharmaceutical Factory. Copovidone (Plasdone® S630) was provided by International Special Products (ISP, USA). Lactose (Ludipress® LCE) was provided by BASF (Germany). Sodium chloride was provided by Ciji Medicine Pharmacy (China). Magnesium stearate was provided by Anhui Sunhere Pharmaceutical Excipients Co., Ltd., China. Cellulose acetate (398-10NF) was provided by Easter Chemical Company (USA). Polyethylene glycol (4000 g/mol) was purchased from Sichuan Hanhua Pharmaceutical Excipients Co., Ltd. (China). The tablet cores for captopril osmotic pump tablets were composed of 42% captopril, 26% copovidone, 26% lactose, 5% sodium chloride and 1% magnesium stearate. Felodipine OP-DDS (Linuo®, batch No. 150,102) were provided by Anhui Lifeon Pharmaceutical Co., Ltd. (China).

2.2. Preparation of osmotic pump tablets

Captopril and excipients were passed through a 100 mesh sieve (mesh size of 150 μm), weighed accurately, and mixed in geometric proportions to form a uniform blend of powders prior to direct compression. The mixed powders were compressed on a rotary tablet press (ZP-5, Shanghai Tianjiu Machinery Factory) using 6.0-mm-diameter shallow concave punches. An acetone solution containing cellulose acetate and polyethylene glycol (3:1), at 2% w/w concentration was used in the coating process to form a semipermeable membrane on the surface of core tablet. The coating was carried out by spraying the coating solution in a high efficiency coating machine (BGB-5F, Zhejiang Xiaolun Pharmaceutical Machinery Co., Ltd., China) equipped with a hot air blower. The stainless steel and peristaltic pump were both set a rotating speed of 12 rpm. The temperatures of air intake and outlet were 40 °C and 30 °C, respectively. The rotate speed of air intake and outlet were set at 500 rpm and 1450 rpm, respectively, with coating continuing until a 4% weight increase in tablet weight was reached. The coated tablets were then dried to remove any residual solvent at 40 °C for 16 h. An orifice was then drilled through the coating membrane with laser drilling machine (CRS-C20D, Ceres Wuhan Photoelectric Technology Co., Ltd., China).

2.3. Investigation on laser drilling parameters

Since laser drilling involves selecting a set of operating conditions, including laser power, pulse width, pulse frequency, focus plane position, and number of pulses (Bharatish et al., 2013), laser drilling parameters that markedly affected the quality of orifices were investigated using the above mentioned laser drilling machine and the software Mark Studio (0x0001.1946) setting, developed by Shenzhen Earain (China). Power for laser drilling (2, 6, 10, 14 and 20 W) and movement speeds of laser spot (namely, scanning speeds of laser beam, 200, 400, 600, 800, 1000 and 2000 mm/s) that can be set in the software by user were investigated. The CRS-C20D laser drilling machine was assembled with the ultra-pulsed laser (max power of 20 W, Access, USA), optical offset mirror (Ceres, China), optical focusing mirror (Wavelength, USA), and control card (Ceres, China). The frequency of laser was 5 KHz. For the drilling, the coated tablets (diameter of 6 mm and thickness of 2 mm) were positioned in wells of a board and then placed in the operational stage 12.5 cm away from the laser light source.

2.4. Sample preparation for SR-μCT

The slight shake of samples can result in the poor image quality during the data acquisition process, so it is necessary to apply an appropriate method to fix the samples. In the present study, two osmotic pump tablets were positioned separately orifice to orifice in a plastic pipe with diameter of 6 mm. The pipe was then firmly attached to the sample stage in the beam line. For the marked felodipine OP-DDSs with diameters of 7 mm, the tablets were cut along with the edges carefully to avoid disturbance to the orifices and reduce the diameters to about 6 mm and then fixed in the plastic pipes.