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Supercritical impregnation of polymer matrices spatially confined in microcontainers for oral drug delivery: Effect of temperature, pressure and time

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ABSTRACT

The present study is aimed to enhance the oral bioavailability of ketoprofen by inserting it into the matrix of poly(vinylpyrrolidone) (PVP) K10 spatially confined into microcontainers, by means of supercritical CO_2-aided impregnation. Microcontainers are cylindrical reservoirs, with typical sizes in the micrometer range, with a cavity open on one side, where the drug formulation is loaded. Differently to traditional tablets, microcontainers have a higher surface area per unit volume, and release the drug only in one direction. This design is meant to enhance the absorption of problematic drugs, like those with poor solubility in water. In a previous study we introduced a novel technique for drug loading of microcontainers, based on inkjet printing and supercritical impregnation (SCI). We showed that SCI produces accurate and reproducible drug loading for large arrays of microcontainers. In the attempt of enhancing the throughput of the loading methods, we propose the replacement of polymer inkjet printing with an easier manual compression of the PVP powder into the microcontainers. As the second step, the polymer powder filled-microcontainers were submitted to SCI. The separate role of different impregnation parameters (temperature, pressure, time, drug concentration in the supercritical phase) was elucidated with respect to the loading capacity. The microcontainer filling was observed by means of optical macroimaging, X-ray microtomography and scanning electron microscopy. The physical state of the drug was investigated by means of Raman spectroscopy and compared with selected representative PVP-ketoprofen physical mixtures. Finally, the drug loading was estimated by means of *in vitro* dissolution tests.

The characterization study shows that the present loading method is a valuable alternative to the one previously described. The drug loading can be controlled with high accuracy and reproducibility and the impregnated drug is in amorphous state. These results demonstrate that SCI can be used as a high throughput loading technique for microfabricated devices for oral drug delivery.

1. Introduction

Among the different drug delivery routes oral administration is still the most preferred one for its simplicity, minimal invasiveness, and high patient compliance. Nevertheless, the human digestive system presents a sequence of physiological barriers which drastically reduce the bioavailability of many active pharmaceutical ingredients (API): enzymatic degradation, hydrolysis in the gastric acidic environment, thick mucus layer covering the intestinal mucosa, selective transport action of peptide receptors in the epithelial cells [1]. In particular, oral delivery of APIs that exhibit either low solubility in water or low permeability through biological membranes or both is challenging. The solid state properties of drugs have a strong influence on their solubility. Whilst amorphous drug candidates exhibit an enhanced solubility and dissolution rate compared to their crystalline counterparts, amorphous forms often suffer from rather short thermodynamic stability and they spontaneously tend to crystallize [2]. As a result, stabilization of amorphous forms is necessary in order to preserve the above-mentioned advantages [3]. Physical stabilization of the

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amorphous form can be achieved by the addition of a polymeric carrier wherein the drug is confined in supramolecular domains or even molecularly dispersed [4]. Together with the solid state properties, the solubility and dissolution rate can be improved by reducing the particle size of the formulation [5]. Among the several formulation approaches [6] supercritical fluid based technology is a promising technique to produce micro- and nanoparticulate systems with high drug dispersion and enhanced stability and dissolution properties [7].

Besides the properties of the drug formulation, an important role in the therapeutic performance is often played by the design of the administration form. Conventional oral dosage forms like tablets provide an omni-directional drug release through their limited interfacial area when exposed to the physiological fluids. Furthermore, drug release from tablets is often slow compared to the peristaltic flow in the small intestine, where the most permeable tissue for drug absorption is located. As a result, a large amount of API is not delivered, and patients need to ingest multiple drug doses to receive the desired therapeutic benefit. This increases the occurrence of potentially harmful side effects in patients [8].

In the last 10 years advances in field of micro- and nanofabrication have allowed the development of alternative drug delivery systems [9]. In particular there has been an increasing interest in microfabricated devices based on the concept of microcontainers [10]. A microcontainer is a reservoir with the typical dimensions falling in the micrometer range, composed of a non-permeable and inert shell and a cavity for the drug formulation open on one side from which the drug is released unidirectionally. The size of these microcontainers are chosen to allow an enhanced intimate contact with the irregular surface of the mucosa with respect to other macroscopic drug delivery systems and to avoid typical issues of smaller micro- and nano-sized systems like clustering, physical stability and unspecific endocytosis. Several groups developed microcontainers in different shapes, materials and designs, where fabrication is typically performed on flat silicon substrates. By virtue of its asymmetric shape and by applying appropriate bioadhesive coatings on microcontainers Ainslie et al. [11] showed an increased intestinal retention time for these microdevices and an enhanced bioavailability for a model poorly water soluble drug. One of the largest challenges in the fabrication of microcontainers concerns the drug loading step. In a previous work [12], we showed the fabrication of cylindrical microcontainers, fabricated with the epoxy resin SU-8. The microwells were filled with poly(vinylpyrrolidone) (PVP) by inkjet printing. This method showed high accuracy and a minimal waste of materials. In a more recent work [13] we proposed the combination of inkjet printing and supercritical technology to impregnate the polymer-filled microcontainers with ketoprofen, a poorly water soluble drug. We demonstrated that the supercritical impregnation technique allows a highly accurate and reproducible drug loading of large arrays of microcontainers. In an attempt to enhance the throughput of this loading method, we propose a simplified variant of our previous work. Here the polymer printing was replaced by an easier filling method, consisting of a manual compression of the polymer powder into the microcontainer. Later, the powder filled-containers were submitted to supercritical impregnation (SCI) as previously described [13]. This process modification enabled a significant reduction in the sample preparation time and made it possible to investigate the effect of temperature, pressure and impregnation times on different aspects concerning the drug loading in more detail.

The loading procedure was characterized with different techniques. X-ray microtomography was used to measure the level of filling and the morphology of the polymer powder in the microreservoir cavities before and after the SCI. In addition, microcontainers were visualized by scanning electron microscopy (SEM)

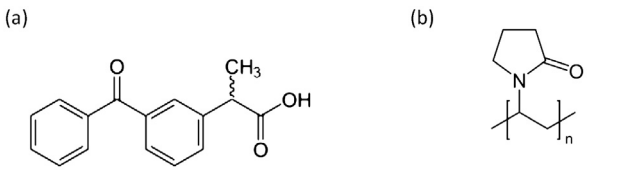

Fig. 1. Chemical structure of (a) ketoprofen, (b) monomer of poly(vinyl pyrrolidone) (PVP).

to observe the effect of the impregnation parameters on the polymer morphology. Raman spectroscopy was used to investigate the drug solid state in the impregnated matrices and drug-polymer interactions. Finally, *in vitro* dissolution tests were carried out and the total drug loading was estimated. The results showed that the replacement of inkjet printing with the powder filling method enhances the throughput of the microcontainer loading technique without compromising the accuracy or the reproducibility of the whole loading process.

2. Materials and methods

2.1. Fabrication of SU-8 microcontainers

2.1.1. Materials and fabrication of microcontainers

Silicon wafers (4-in. b100N n-type) were supplied by Okmetic (Vantaa, Finland). SU-8 2075 and SU-8 developer were purchased from Microresist Technology GmbH (Berlin, Germany).

Cylindrical microcontainers were fabricated with a similar procedure as previously described [12]. The microwells were fabricated with the epoxy-based photoresist SU-8 on silicon wafers. A microcontainer has a cavity of approximately 300 μm in diameter and 250 μm in depth and an approximated volume of 18 nL. After the fabrication the wafer was cut into square chips containing 625 microcontainers (DISCO DAD 321, Automatic Dicing Saw).

2.2. Drug loading of microcontainers

2.2.1. Materials

Ketoprofen (98%, racemate) and poly(vinylpyrrolidone) (PVP K10, Mw 10,000) were supplied by Sigma Aldrich. In Fig. 1 the molecular structures of the compounds are shown. Carbon dioxide was supplied by SIAD (99% purity). Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. In several pharmacopeias ketoprofen is considered as practically insoluble in water [14,15]. The solubility of the crystalline form of ketoprofen in pure water at room temperature (22–24 °C) was reported to be 0.010 mg/mL [15]. Thus, ketoprofen is classified as a class II active principle in the biopharmaceutical classification system (BCS): It exhibits low aqueous solubility and a high intestinal permeability.

2.2.2. Filling with poly(vinylpyrrolidone) PVP powder

Microcontainers were filled with PVP powder with the following procedure: The powder was deposited and compacted with a spatula onto the microwells and the residual amount, placed in between containers, was blown away by means of pressurized air. The chip was weighed before and after filling and the average PVP weight per chip was 1.93 ± 0.08 mg (calculated from 35 samples). The level of microcontainer filling was measured by X-ray microtomography at different positions on the chip.

2.2.3. Supercritical impregnation of polymer filled-microcontainers

After the powder deposition the drug was loaded into the polymer-filled microdevices by means of supercritical carbon