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ABSTRACT SUMMARY

In this work we present an effective loading technique of micro-containers for oral drug delivery of a poorly water soluble drug in a solid dispersion with polymer. By combining inkjet printing and supercritical CO_2 impregnation we load ketoprofen in a solid dispersion with poly(vinylpyrrolidone) (PVP) into cylindrical micro-containers providing unidirectional release. Both the printing and the impregnation step can be tuned in order to control drug loading with accuracy in the range of micro-grams.

INTRODUCTION

During the last two decades a big effort has been made in the pharmaceutical industry to improve the bioavailability of poorly water soluble drugs for oral administration. In more recent years, nanotechnology has substantially contributed with innovative drug delivery systems in the micro and nano scale[1]. In particular there has been an increasing interest in reservoir-based micro-devices for oral delivery of active pharmaceutical ingredients, like poorly water soluble compounds and fragile biomolecules with short plasma half-lives[2]. Micro-containers are designed to provide protection against drug degradation in the GI tract, concomitantly with providing unidirectional drug release[3]. However, there is little work in this field which focuses on optimizing the drug loading step and on the improvement of the drug dissolution rate in physiological fluids. Here, we propose a loading technique for micro-containers applied to a poorly soluble drug, combining inkjet printing and supercritical fluid impregnation. A schematic representation of the fabrication process is shown in figure 1.

As described in previous work[4], inkjet printing is a suitable technique to dispense PVP solutions into large arrays of micro-containers with a quasi-no-waste performance, a high precision, and in a fast and reproducible way. Unfortunately, the direct spotting of drug-polymer solutions does not exhibit the same accuracy, primarily due to too high viscosity and precipitation. Therefore, supercritical CO_2 processing has been considered as an alternative solution for the drug loading. $ScCO_2$ is used as both dissolution agent and as a physical carrier for the drug in the PVP[5,6]. The use of $scCO_2$ has several advantages: (i) low processing temperatures, (ii) easy removal from polymeric materials when the process is completed, (iii) substitution of potentially toxic organic solvents and (iv) safe, non-flammable and ecologically-friendly chemical.

The aim of this study is to elucidate the suitability of $scCO_2$ as loading vehicle of ketoprofen into PVP-filled micro-containers.

EXPERIMENTAL METHODS

Cylindrical micro-containers are fabricated in SU-8, an epoxy resin with biocompatible properties[7], using photolithography[8] on silicon slides. Micro-containers cavities are 200 µm in diameter and 250 µm in depth corresponding to a volume of around 8 nL. A silicon slide is divided into 10 squared chips, each having 625 micro-containers arranged in a 25×25 matrix. The slide fits the microspotter tray slots as shown in figure 2a. Polymer solution has been prepared by dissolving poly(vinyl pyrrolidone) PVP K10 (10 kDa, Sigma Aldrich) in deionized water with a concentration of 10%(w/w) and dispensed inside the micro-containers using a micro spotter (Nanoplotter NP 2.1 GeSiM, Germany). After polymer deposition the slide is easily cleaved into chips. The chips with polymer-filled containers were weighted individually and stored in a glass dessicant for 48 h. Supercritical impregnation was performed in a 100 ml stirred reactor (Thar SFC) at 40°C and CO_2 pressures of 100 and 200 bar. Experiments were ran for 1 and 4 h. Ketoprofen was weighted and placed in the reactor in amounts corresponding to saturation conditions in $scCO_2$ according to MacNaughton et al.[9]. After impregnation, chips were individually weighted, analyzed by scanning electron microscopy (Nova 600 NanoSEM, FEI) and stored for 24h in a glass dessicant for residual CO_2 release. Dissolution of PVP and ketoprofen from loaded micro-containers was determined in 10 ml deionized water at 37˚C using a µDISS profiler (Pion). For the detection of ketoprofen release, the UV probe wavelength was set at 259 nm. After dissolution, the micro-containers were checked with an optical microscope to ensure complete emptying.

RESULTS AND DISCUSSION

A SEM picture of the microspotted PVP in the containers is shown in figure 2b. The weight of polymer deposited by inkjet printing into 625 containers corresponded to 1.6±0.04 mg. As shown in figure 3a the $scCO_2$ treatment causes a swelling of the polymer, which is more pronounced at high pressure (figure 3b).

The dissolution profiles of impregnated PVP-filled containers are shown in figure 4.

Each result is given by the average of three dissolution tests on a single chip. It can be seen that the loaded drug

amounts increase when the pressure of the supercritical fluid is higher and when duration of the impregnation is longer. As a control experiment, micro-containers without PVP were submitted to ketoprofen impregnation (200 bar 40°C 4 h). The results show that a negligible quantity of drug is deposited in absence of polymer. In table 1 the amounts of ketoprofen loaded at different conditions are shown. It is concluded that the contribution of PVP swelling is essential in the impregnation with drug.

CONCLUSION

We demonstrate that inkjet printing and sc impregnation are compatible technologies for drug loading into micro-containers. Ketoprofen was successfully loaded into the polymer filled micro-containers by means of supercritical fluid impregnation. The quantity of loaded drug can be controlled by changing either the pressure of the fluid or the time of the impregnation. The loading can reach a drug/polymer weight ratio of 0.48.

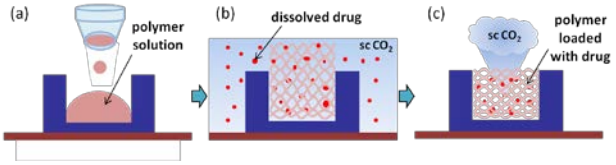

Figure 1 Drug loading process: (a) Inkjet printing of PVP solution; (b) $scCO_2$ impregnation: pressurization and polymer swelling, (c) depressurization and de-swelling.

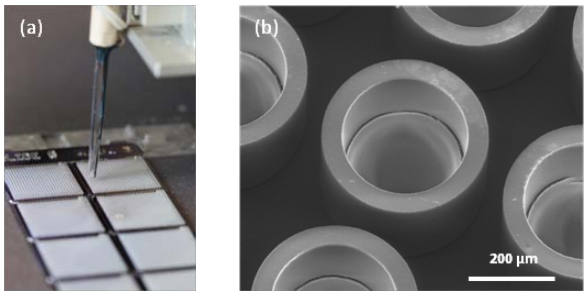

Figure 2 (a) Silicon slide placed on the microspotter tray and dispensing pipette. (b) SEM picture of micro-containers filled with PVP 10wt% in deionized water after solvent evaporation

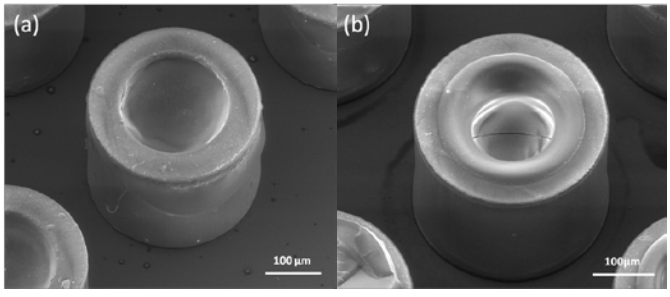

Figure 3 SEM pictures of microcontainer impregnated at a CO_2 pressure of 100 bar (a) and 200 bar (b).

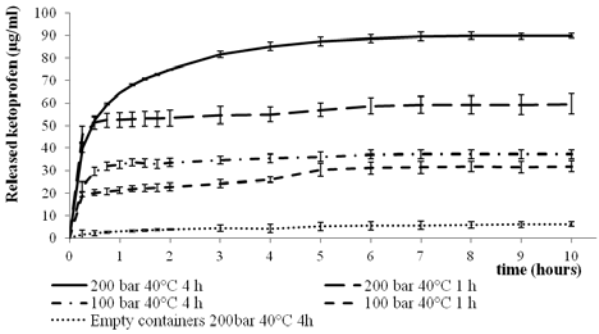

Figure 4 Dissolution profiles of PVP-filled containers at different conditions

Impregnation conditions	Loaded drug per chip (mg)	Ratio of loaded ketoprofen (mg)/ PVP (mg)	Drug weight fraction keto mg / (PVP+keto) mg
100 bar 40°C 1 h	0.33	0.17	0.10
100 bar 40°C 4 h	0.41	0.28	0.16
200 bar 40°C 1 h	0.61	0.37	0.18
200 bar 40°C 4 h	0.82	0.48	0.22
Empty containers (200 bar 40°C 4 h)	0.07	-	-

Table 1 Drug loading at different impregnation conditions.

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