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LOADING OF MICRO-CONTAINERS FOR ORAL DELIVERY WITH SUPERCRITICAL CO_2 AIDED IMPREGNATION

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PURPOSE

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 micrograms.

INTRODUCTION

During the last twenty years nanotechnology has substantially contributed with innovative systems in the micro and nano scale[1] for the oral delivery of poorly soluble drugs. An increasing interest has arisen in micro-reservoir devices which protect the drug against degradation in the GI tract, concomitantly with providing unidirectional drug release[2]. 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 1a. As described in previous work[3], 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. Supercritical CO_2 ($scCO_2$) is used as both dissolution agent and as a physical carrier for the drug in the PVP. 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.

MATERIALS AND METHODS

Cylindrical micro-containers are fabricated in a biocompatible epoxy resin, using photolithography on silicon slides. Micro-containers cavities are 200 µm in diameter and 250 µm in depth (volume of 8 nL). Polymer solution was prepared by dissolving poly(vinyl pyrrolidone) PVP K10 (10 kDa, Sigma Aldrich) in DI water (10% w/w) and dispensed inside the micro-containers using a inkjet printer (Nanoplotter NP 2.1 GeSiM). Supercritical impregnation was performed on chips 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 placed in the reactor in weighted amounts corresponding to saturation conditions in $scCO_2$ according to MacNaughton et al.[4]. After impregnation, chips were individually weighted and analyzed by scanning electron microscopy (Nova 600 NanoSEM, FEI). Dissolution of PVP and ketoprofen from micro-containers was determined in 10 ml DI water at 37°C using a µDISS profiler (Pion). After dissolution the emptying of micro-containers were checked with an optical microscope.

RESULTS AND DISCUSSION

A SEM picture of the impregnated container is shown in figure 2a. The dissolution profiles of impregnated PVP-filled containers are shown in figure 2b. The loaded drug amounts increases with CO_2 pressure and with time of impregnation. As a control experiment, micro-containers without PVP were sujected to ketoprofen impregnation (200 bar 40°C 4 h). As shown by the

dissolution profile in fig. 2b (empty containers), a negligible quantity of drug is deposited in absence of polymer. It is concluded that the contribution of PVP swelling is essential in the drug impregnation.

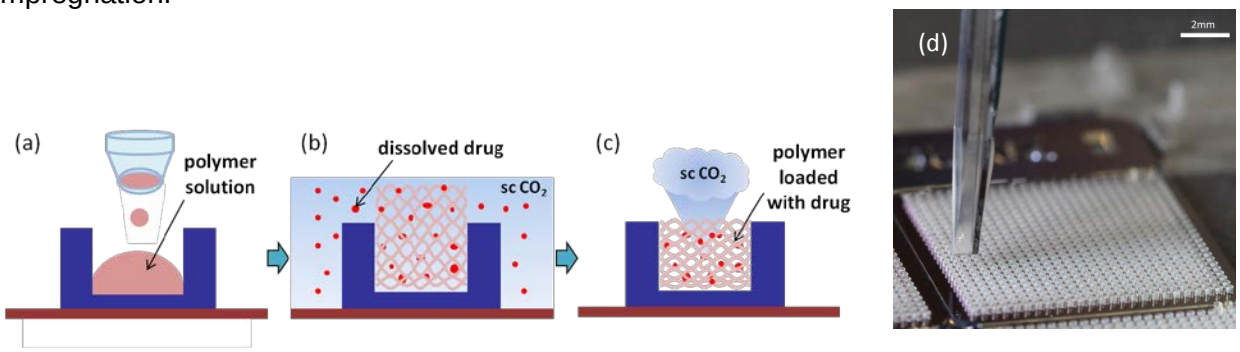

Fig. 1: Drug loading process: (a) Inkjet printing of PVP solution; (b) scCO₂ impregnation: pressurization and polymer swelling, (c) depressurization and de-swelling. (d) Silicon slide placed on the microspotter tray and dispensing pipette. Each slide contains 625 containers.

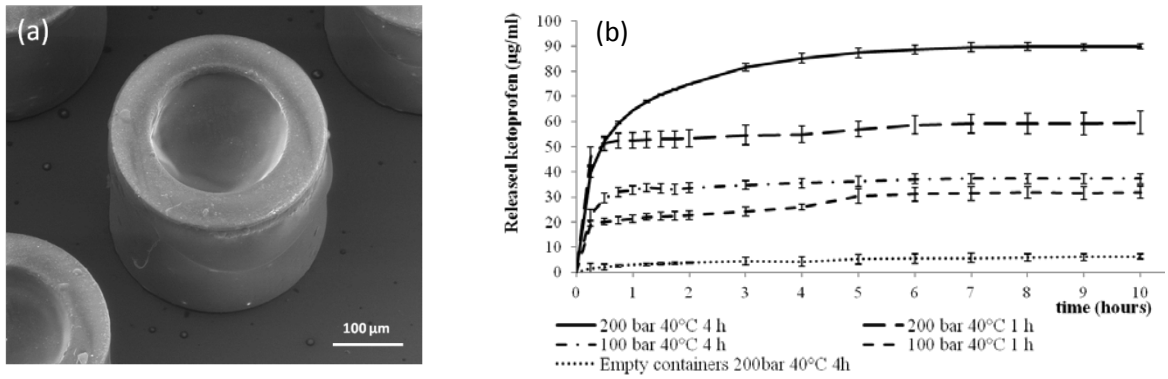

Fig 2: (a) SEM pictures of a microcontainer impregnated at CO_2 pressure of 100 bar. (b) Dissolution profiles of impregnated micro-containers at different conditions (N=3)

CONCLUSIONS

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 CO_2 impregnation. The quantity of loaded drug can be controlled by changing either the pressure of the CO_2 or the time of the impregnation. The loading can reach a drug/polymer weight ratio of 0.48.

FUTURE WORK

New methods for polymer deposition other than inkjet printing will be investigated, and new drugs will be impregnated in order to validate the feasibility of this loading technique.

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