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Loading of poorly soluble drugs by supercritical CO₂ impregnation into microcontainers for oral drug delivery

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INTRODUCTION

Among the various administration routes, oral drug delivery is the most preferred, as it is non-invasive, simple and with high patient compliance¹. However, the administration of drugs with low aqueous solubility (biopharmaceutics classification system (BCS) class II and IV drugs) has proven to be challenging². One way to improve the solubility and dissolution rate of the poorly soluble drugs is to prepare the amorphous form of the drug; however, it is often necessary to stabilize this form. Microcontainers (MCs) can be used for this purpose³. MCs are cylindrical microdevices with only the top side open, fabricated with the epoxy polymer SU-8². MCs can be loaded with drugs using supercritical CO₂ (scCO₂) impregnation into a polymer matrix previously loaded into them⁴. The aim of this study was to investigate the amount, distribution and solid state form of indomethacin and naproxen (BCS class II drugs) loaded in three different sizes of MCs (Table 1 and Figure 1). The different diameters of the MCs provide to different surface areas of polymer exposed to the scCO₂ during the drug loading process.

MATERIALS AND METHODS

SU-8 MCs with different diameters were fabricated on silicon chips (Figure 1a-c) using two-steps of photolithography (Table 1). MCs were filled manually with polyvinylpyrrolidone (PVP) K10 powder. The number of MCs per chip was chosen to keep the total surface area of

PVP exposed to scCO₂ constant for the three different sizes. Therefore, the total volume (amount) of PVP per chip was constant. Polymer-filled MCs were then impregnated with ketoprofen or naproxen by means of scCO₂ impregnation. Ketoprofen was loaded into the MCs using 100 bar, 40°C for one hour as scCO₂ impregnation parameters. In order to have the same solubility of the two compounds in the scCO₂, the pressure for loading naproxen was set at 120 bar and at a temperature of 45°C for one hour. The loading of ketoprofen and naproxen was analyzed by *in vitro* release of impregnated MCs in PBS solution at 37 °C using a μ DISS profiler utilizing a UV wavelength of 258 and 230 nm for ketoprofen and naproxen, respectively. For evaluation of the solid state form and the distribution of the drug in the MCs for the different sizes, Raman Spectroscopy maps were acquired using a DXR Raman microscope.

RESULTS

The amount of the drug loaded among the different sizes of MCs (example in Figure 1d) and between the two drugs was not statistically different (Table 1). MCs having larger or smaller surface areas only showed differences for naproxen loaded in the smallest MCs size. The release from drug-loaded MCs showed similar kinetics for the different sizes and for the two drugs reaching 90 % release within the first 10 min (Figure 2). Raman spectroscopy was useful to evaluate if the exposed surface area influenced the distribution of the drugs in the MCs.

	Ø int. [µm]	h int. [µm]	Number of MC per chip	Total amount of ketoprofen loaded [µg] (n=4, STD)	Total amount of naproxen loaded [µg] (n=2, STD)
Small	110	225	1024	267.2 ± 112.2	76.2 ± 8.2
Medium	220	225	256	198.8 ± 41.6	167.7 ± 45.4
Large	440	225	64	180.6 ± 53.0	130.3 ± 14.4

Table 1 : Dimensions, number of microcontainers per chip (array) for the different sizes of microcontainers and total amounts of drug loaded

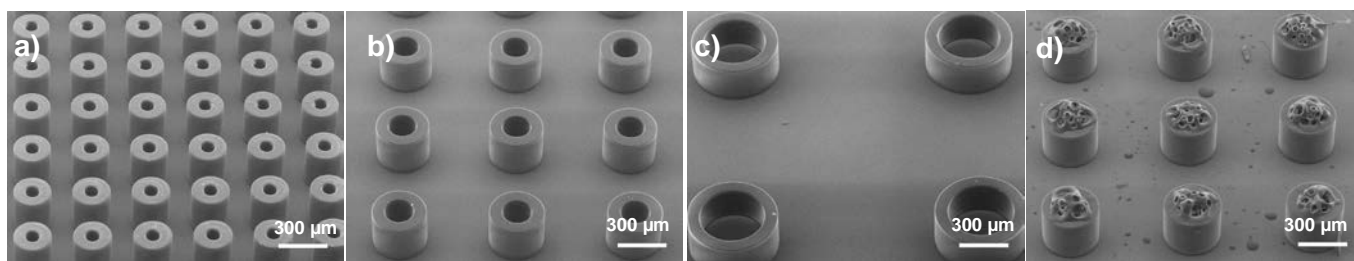


Figure 1: SEM images of a) small, b) medium, c) large sizes of MCs and d) example of drug-loaded MCs

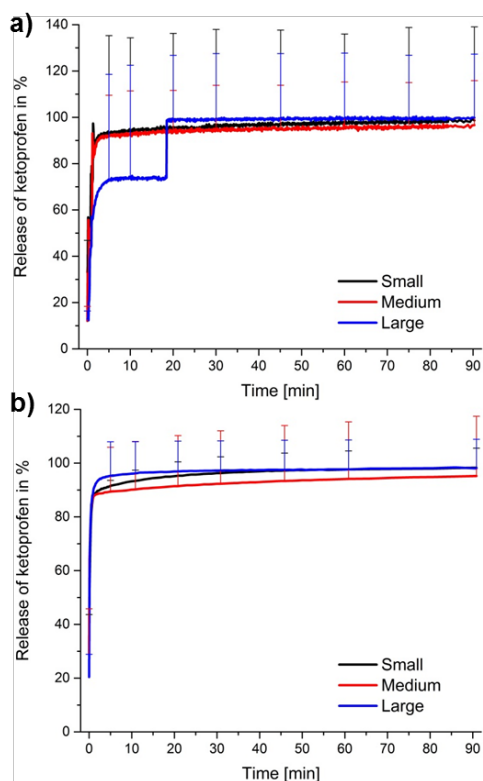


Figure 2: Release of drug from small, medium and large MCs in PBS pH 7.3 for a) ketoprofen and b) naproxen.

By the use of Raman maps, it is possible to show the location of drug in the MCs. An example with naproxen can be seen in Figure 3, where naproxen distribution (on the top (a) and inside (b) of the MC) can be evaluated. Selecting a wavenumber characteristic for PVP or drugs (as it is shown in Figure 3c for naproxen spectrum) it is possible to see their distribution on top and inside the different sizes of MCs. Ketoprofen loaded in MCs seen to be in the amorphous state and naproxen in a metastable form.

CONCLUSION

MCs having different surface areas exposed to the $scCO_2$ are not affecting the amount of loaded ketoprofen or naproxen. The only exception is the small MCs that show a lower amount of loaded drug. The release kinetics of the drugs in the different MCs sizes are all similar. Both drugs reach 90 % of release in few minutes. Having a

larger or smaller area of polymer exposed to the $scCO_2$ is not affecting the amount, the distribution or the solid state of the two class II drugs investigated.

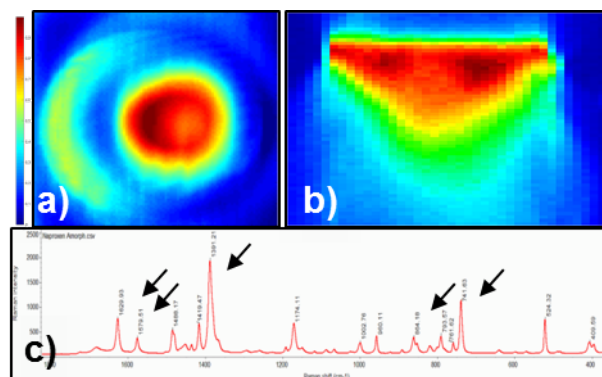


Figure 3: Example of a Raman map in the a) x-y and b) y-z planes of a MC. The darker red color indicates higher peak intensity of the characteristic peak of naproxen highlighted on the spectra (c).

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