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## Distribution and quantitative analyses of drugs loaded by supercritical CO<sub>2</sub> in microcontainers

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### Purpose

The aim of this study was to investigate the quantity, distribution and solid state form of the poorly water soluble drugs, ketoprofen and naproxen loaded into three different sizes of polymer-filled polymeric cylindrical microdevices (microcontainers) using supercritical CO<sub>2</sub> (scCO<sub>2</sub>) impregnation. The different diameters of the microcontainers (MCs) provided different surface areas of polymer exposed to the scCO<sub>2</sub> during the drug loading process.

### Introduction

Among the various administration routes, oral drug delivery is the most preferred, as it is non-invasive, simple and has high patient compliance [1]. However, the administration of drugs with low aqueous solubility has proven to be challenging [2]. 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 purpose [3]. MCs are cylindrical microdevices with only the top side open, fabricated in SU-8 [2]. MCs can be loaded with drugs using scCO<sub>2</sub> impregnation into a polymer matrix previously loaded into them [4].

### Methods

MCs of different diameters were fabricated in SU-8 (Fig. 1a) using two steps of photolithography resulting in cylinders (Table 1). The MCs were filled manually with polyvinylpyrrolidone (PVP) K10 powder and subsequently impregnated with ketoprofen or naproxen by means of scCO<sub>2</sub> impregnation (Fig. 1b). Ketoprofen was loaded using 100 bar, 40°C for one hour as scCO<sub>2</sub> impregnation parameters, whereas for naproxen, the parameters were set at 120 bar and 45°C for one hour. The *in vitro* release of ketoprofen and naproxen from the impregnated MCs was analyzed in 10 mM PBS solution at 37°C using a μDISS profiler. For evaluation of the solid state form of the drugs in MCs of different sizes, Raman spectroscopy and X-Ray Powder Diffraction were used. Raman maps were acquired using a DXR Raman microscope to analyze the distribution of the drug in the MCs.

### Results

For both drugs, the quantity of the drug loaded into the different sizes of MCs was not found to be statistically different (Table 1). The release of naproxen or ketoprofen from the MCs showed similar kinetics for the different sizes and for both drugs, reaching 90 % release within the first 10 min. By the use of Raman microscopy, it was evaluated if the exposed surface area influenced the distribution of the drugs in the MCs. An example with ketoprofen can be seen in Fig. 2, where the distribution of the drug in the uppermost layers inside the MCs was evaluated. Ketoprofen loaded into the MCs was found to be in its amorphous form, whereas naproxen was in a metastable form. We are currently working on a 3D chemical map of the MCs to understand how the drugs are distributed inside MCs of different sizes.

### References:

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	Ø int. [μm]	h int. [μm]	Number of MC per chip	Total amount of ketoprofen loaded [μg] (n=3, STD)	Total amount of naproxen loaded [μg] (n=3, STD)
Small	110	225	1024	300.4 ± 110.7	146.0 ± 7.8
Medium	220	225	256	195.4 ± 50.21	141.9 ± 12.3
Large	440	225	64	187.0 ± 63.0	152.0 ± 17.5

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

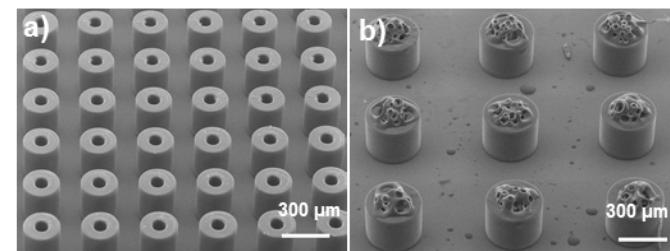


Figure 1. SEM images of a) small empty MCs and b) ketoprofen-loaded medium MCs.

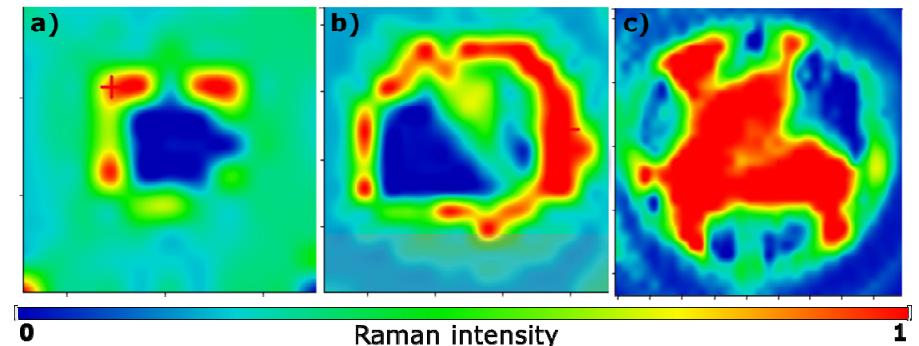


Figure 2. Raman map on peak 1003 cm<sup>-1</sup> representing the distribution of ketoprofen in the uppermost layers inside of a) small, b) medium and c) large MCs.