



Distribution and quantitative analyses of drugs loaded by supercritical CO₂ in microcontainers

Mazzoni, Chiara; Tentor, Fabio; Antalaki, Anastasia ; Jacobsen, Rasmus Due; Mortensen, Jacob ; Slipets, Roman; Ilchenko, Oleksii; Keller, Stephan Sylvest; Nielsen, Line Hagner; Boisen, Anja

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Mazzoni, C., Tentor, F., Antalaki, A., Jacobsen, R. D., Mortensen, J., Slipets, R., ... Boisen, A. (2018). Distribution and quantitative analyses of drugs loaded by supercritical CO₂ in microcontainers. Abstract from 44th International conference on Micro and Nano Engineering, Copenhagen, Denmark.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Distribution and quantitative analyses of drugs loaded by supercritical CO₂ in microcontainers

Chiara Mazzoni, Fabio Tentor, Anastasia Antalaki, Rasmus Due Jacobsen, Jacob Mortensen, Roman Slipets, Oleksii Ilchenko, Stephan Sylvest Keller, Line Hagner Nielsen, Anja Boisen

The Danish National Research Foundation and Villum Foundation's Center for Intelligent Drug Delivery and Sensing Using Microcontainers and Nanomechanics (IDUN) - Department of Micro- and Nanotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark
e-mail: chimaz@nanotech.dtu.dk

Keywords: Oral drug delivery, micro devices, supercritical CO₂ impregnation

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 CO₂ (scCO₂) impregnation. The different diameters of the microcontainers (MCs) provided different surface areas of polymer exposed to the scCO₂ 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 scCO₂ 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 scCO₂ impregnation (Fig. 1b). Ketoprofen was loaded using 100 bar, 40°C for one hour as scCO₂ 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 μ DISS 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:

- [1] K. Thanki, R.P. Gangwal, A.T. Sangamwar, S. Jain, J. Control. Release. 170 (2013) 15–40.
- [2] L.H. Nielsen, S.S. Keller, K.C. Gordon, A. Boisen, T. Rades, A. Müllertz, Eur. J. Pharm. Biopharm. 81 (2012) 418–425.
- [3] H. Grohgan, P.A. Priemel, K. Löbmann, L.H. Nielsen, R. Laitinen, A. Mullertz, G. Van den Mooter, T. Rades, Expert Opin. Drug Deliv. 11 (2014) 977–989.
- [4] C. Mazzoni, F. Tentor, S.A. Strindberg, L.H. Nielsen, S.S. Keller, T.S. Alstrøm, C. Gundlach, A. Müllertz, P. Marizza, A. Boisen, J. Control. Release. 268 (2017) 343–351.

	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

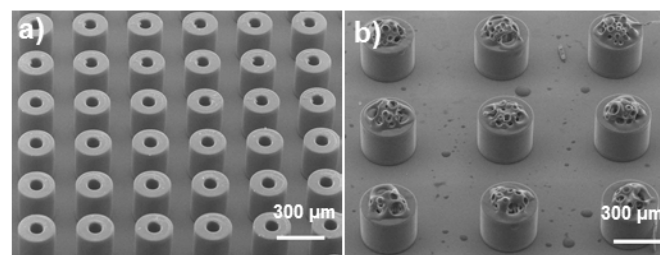


Figure 1. SEM images of a) small empty MCs and b) ketoprofen-loaded medium MCs.

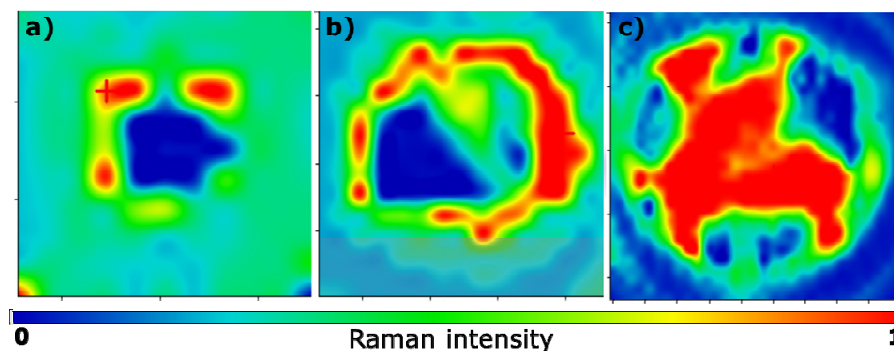


Figure 2. Raman map on peak 1003 cm⁻¹ representing the distribution of ketoprofen in the uppermost layers inside the of a) small, b) medium and c) large MCs.