MICROCONTAINERS FOR INTESTINAL DRUG DELIVERY

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INTRODUCTION

Among all the drug administration routes, the oral one is the most preferred by the patients being less invasive, faster and easier.

Oral drug delivery systems designed to target the intestine are produced by powder technology and capsule formulations. Those systems including micro- and nano-particulate systems (i.e. vesicles, polymer nanoparticles, dendrimers etc.) suffer the non-unidirectional release of the drug to the epithelium of the intestine, which entails an inevitable loss in the lumen and, therefore, the reduction of the drug delivered to the intestinal epithelium. A new promising approach focuses on reservoir based microdevices serving as carriers for poorly soluble drugs, hereby called microcontainers (1).

Microcontainers have a cylindrical geometry and provide a unidirectional release due to their design meanwhile protecting the drug formulation from the low gastric pH and the enzymatic degradation. Here, we present the preparation of microcontainers with enteric coating (2) efficiently loaded with drug and able to target the intestine as a multi-particulate system.

MATERIALS AND METHODS

25 x 25 array of microcontainers were fabricated (Figure 1a) on a Silicon chip as previously described (1) implementing a sacrificial layer in polyacrylic acid (PAA) (Mw = 100 kDa, Sigma-Aldrich) (3). This allows the release of the microcontainers from the Silicon support upon PAA solubilisation in deionized water (Figure 1d).

Microcontainers on the PAA layer were filled with polyvinylpyrrolidone K10 powder (Mw = 10 kDa, Sigma-Aldrich) removing the excess with compressed air.

Polymer filled microcontainers (Figure 1b) were then impregnated with ketoprofen (Sigma-Aldrich) by means of supercritical impregnation technology (100 Bar, 40 °C for 1 hour), as previously shown (4).

Drug loaded microcontainers were coated through a nickel shadow mask (5) using a solution of Eudragit L100® 2% w/V (Evonik Mw = 125 kDa) with Dibutylsebacate 5% w/w (Sigma-Aldrich) as plasticizer in 2-propanol. The Eudragit film was deposited on top of the microcontainers (Figure 1c) *via* spray coating (Sonotek, U.S.).

Microcontainers were released from the supporting layer by dissolution of the underlying PAA layer in DI water at pH = 3.25 (Figure 1d). Containers were then poured in dialysis tubes and inserted in Biorelevant gastric medium (pH = 1.65) – FaSSGF for 2 hours at 37 °C. The same tubes were subsequently placed in Biorelevant intestinal medium (pH = 6.5) – FaSSIF for 6 hours at 37 °C.

Samples were prelevated during ketoprofen release (Figure 1e) and analysed by means of UV-Spec at λ = 259 nm (NanoDrop, Thermo Scientific).

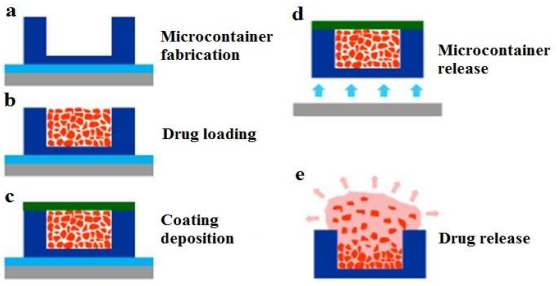

Fig. 1: Scheme of the process.

RESULTS AND DISCUSSION

Microcontainers with PAA layer were successfully loaded by supercritical impregnating PVP K10 with ketoprofen using pressured CO_2 as a solvent (Figure 2a). Drug loaded microcontainers were coated with Eudragit L100® to avoid the drug being released in the gastric medium (Figure 2b) since the polymer is not dissolved in the gastric fluid (pH = 1.65, fasted state) while it is quickly solubilized upon reaching the intestinal, less acidic, environment.

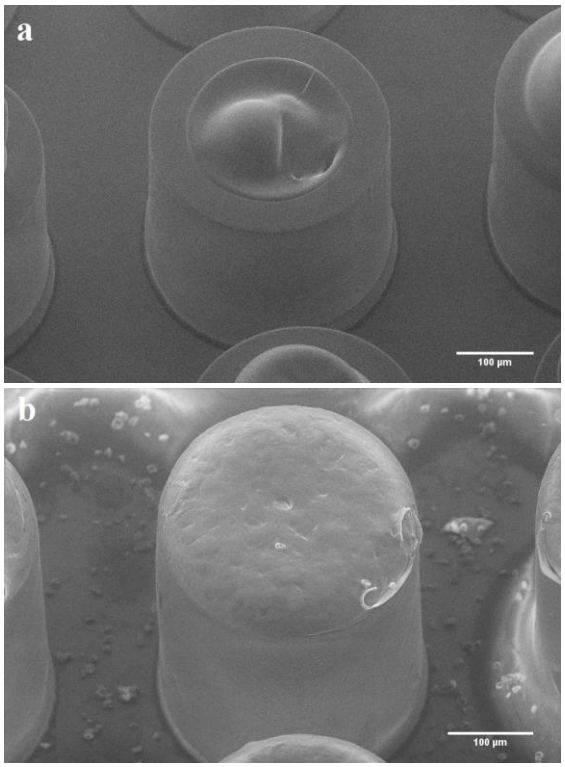

Fig. 2: SEM picture of drug loaded microcontainer: (a) before and (b) after the Eudragit L100® coating.

Due to the underlying PAA layer we successfully detached the microcontainers from the silicon support through immersion in deionized water (pH = 3.25) for about 2 minutes. The PAA layer is dissolved releasing the containers.

Ketoprofen is released differently between coated and uncoated microcontainers as shown in Figure 3.

After 2 hours at pH 1.65 approximately 70% of ketoprofen is released from the uncoated microcontainers while less than 20% is released from the coated microcontainers.

At pH 6.5 coated and uncoated microcontainers released the drug with very similar profiles. Coated microcontainers showed a burst release as soon as the pH was changed, proving the fast dissolution of both the Eudragit L100® and the impregnated PVP containing the drug.

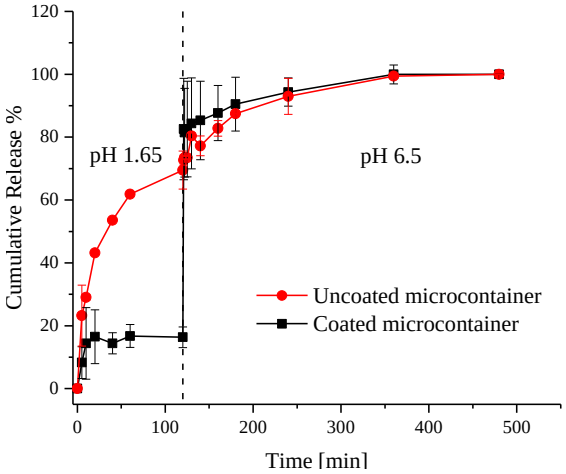

Fig. 3: Ketoprofen dissolution profiles represented as cumulative release (%); the evident difference between the black and the red profiles defines the efficacy of the enteric coating preventing the drug to be released in the acidic pH (before 120 min).

CONCLUSIONS

Microcontainers fabricated on a sacrificial PAA layer were successfully used as drug carriers for the targeted release of ketoprofen in the intestine.

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