Enteric coating of microcontainers for oral delivery of poorly water soluble drugs

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ABSTRACT SUMMARY

We present the integration of enteric coatings in microcontainers for oral delivery of poorly water soluble drugs. Eudragit L100 was spray coated on micro-reservoirs filled with solid dispersion of furosemide and the release in simulated gastric and intestinal fasted media was characterized.

INTRODUCTION

In oral drug delivery, one of the key challenges is to increase the bioavailability of poorly water soluble drugs. One solution is the modification of the actual drug formulations in classical drug delivery systems, such as capsules or tablets. In recent years, microfabricated drug delivery devices were proposed as alternative methods for oral drug delivery1,2. Desai et al. introduced microcontainers as a potential approach to address the issue of limited solubility of the drug in the intestinal media3. These microfabricated containers provide a cavity for filling with drug formulation. In this way degradation of the drug in the GI tract is prevented. In comparison to traditional spherical micro- and nanoparticles, one side of the microcontainers is open and can be functionalized with a mucoadhesive polymer. The combination of the two features allows a unidirectional delivery of the active substance directly to the intestinal mucosa. In vitro experiments showed promising results both in terms of mucoadhesion and unidirectional drug release4. A challenge that has not been addressed so far is the deposition of a lid on the open side of the container. Nevertheless, sealing of the cavity is required to prevent degradation and premature release of the drug in the gastric media. Here, we investigate the integration of enteric coatings in micro scale drug delivery devices. Eudragit L100 is spray coated on microcontainers filled with solid dispersion of furosemide and the drug release in simulated gastric and intestinal fasted media is characterized.

EXPERIMENTAL METHODS

Figure 1 shows a schematic of the experimental method. Cylindrical microcontainers were fabricated in SU-8, an epoxy resin with biocompatible properties5, using photolithography on silicon substrates6. 289 microcontainers are arranged in a 17x17 array on a silicon chip with dimension of 12.5 x 12.5 mm². Each micro-container has a diameter of 240 µm and a depth of 270 µm corresponding to a volume of 12.2 nL. Solid dispersion of furosemide was prepared by spray-drying in a Büchi Mini spray dryer. The solid content is 80:20 w/w% furosemide:hydroxypropyl methylcellulose (HPMC). Characterization of the formulation with X-ray powder diffraction (XRPD) and Raman spectroscopy showed that the drug is in the amorphous state (data not shown). The microcontainers were filled with furosemide and the silicon chips were weighed individually before and after filling. Furosemide solid dispersion between the containers was removed using pressurized air. A solution of 1 wt% Eudragit L100 (Evonik Industries, Germany) in Isopropyl alcohol was prepared. A spray coating system (ExactaCoat, Sono-Tek, USA) equipped with an ultrasonic nozzle actuated at 120 kHz was used for deposition of Eudragit on the filled microcontainers. The final film thickness was 7 µm. The containers were analyzed by scanning electron microscopy with a Nova 600 NanoSEM (FEI, The Netherlands) after each step of the sample preparation. Release of furosemide from loaded microcontainers was determined in 10 ml of simulated gastric fasted media (pH 2) and simulated intestinal fasted media (pH 6.5) at 37°C using a µDISS Profiler (pION, USA). For the detection of furosemide release, the UV probe wavelength was set to a range of 310-350 nm. After the release experiments, the microcontainers were imaged by SEM.

RESULTS AND DISCUSSION

Figure 2(a) shows a SEM micrograph of a container filled with furosemide. The weight of solid dispersion loaded in one chip with 289 microcontainers was 1.5-2.3 mg. This corresponds to 1.2-1.8 mg of furosemide per chip or 4.2-6.4 µg per microcontainer. Figure 2(b) presents a microcontainer after coating with Eudragit L100. Both, top surface and sidewalls of the structure are coated with polymer. The coating has a rough surface but no defects are identified.
Figure 2. Micrographs of a microcontainer filled with Furosemide solid dispersion (a) before and (b) after coating with 7 µm Eudragit L100.

Figure 3 and Figure 4 summarize the results of the release experiments for containers without and with coating of Eudragit L100 respectively. The duration of the experiments in gastric media was 2h. Longer immersion in this media is irrelevant as the transition time through the stomach typically is shorter. Each result is given by the average of six dissolution tests on single silicon chips. Without coating a fast release of furosemide was observed independent of the dissolution media (Figure 3). After 2h, 28% of the drug was released in gastric media (pH 2) compared to 62% in intestinal media (pH 6.5). This difference is explained with very low solubility of the drug formulation in acidic conditions. After 10h in intestinal media, 86% of the furosemide was dissolved. For containers coated with Eudragit L100 (Figure 4), less than 8% of the drug was released after 2h in gastric media. In intestinal media, drug release was comparable to the one from uncoated containers and 91% of the active substance was released after 10h. Figure 5 shows initially coated microcontainers after the release experiments presented in Figure 4. The polymer coating is still present on the container after immersion in gastric media (Figure 5(a)) although defects appear probably due to swelling of the solid dispersion in the cavity. Compared to that, the Eudragit is dissolved for the microcontainer immersed in intestinal media (Figure 5(b)) and only some residues of the solid dispersion are left at the bottom of the cavity.

CONCLUSION

In conclusion, we demonstrate the integration of enteric coatings in a new type of devices for oral drug delivery. Release experiments showed that release of furosemide in simulated gastric media is minimized and that drug release from the microcontainers is triggered in simulated intestinal media. In near future, removal of containers from the silicon handling substrate is planned, which will allow in vivo experiments.

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