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Microcontainers improve oral bioavailability of furosemide

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INTRODUCTION & AIM

Microcontainers have been proposed as a novel approach to improve the oral bioavailability of drugs. Microcontainers are small polymeric cylinders on a flat base (Fig. 1). The microcontainers allow for protecting the drug in the harsh environment of the stomach and also provide the possibility of unidirectional release of the drug directly to the small intestinal epithelium (Fig. 2).

AIM: To investigate the in situ interaction between the microcontainers and the small intestinal membrane and to evaluate the in vitro performance of the microcontainers filled with amorphous sodium salt of furosemide (ASSF) after oral dosing to rats (Fig. 3).

METHODOLOGY

Fabrication of microcontainers

SU-8 (epoxy-based photosensitive) microcontainers were fabricated through two steps of photolithography to define the base and the walls (Fig. 4). This resulted in microcontainers with inner diameter of 223 µm (Fig. 1). Silicon wafers supporting the microcontainers were cut into squares of 12.8 x 12.8 mm² resulting in 25 x 25 microcontainers with a pitch of 450 µm (Fig. 5).

Preparation of the amorphous sodium salt of furosemide

Furosemide + NaCl + ethanol + water

Spray drying

Amorphous sodium salt of furosemide (ASSF)

Filling of microcontainers with ASSF

Powder drug distribution

a) In situ intestinal perfusion studies

In situ intestinal perfusion studies were performed in fasted rats with a weight of approximately 200 g (Fig. 9).

RESULTS

Preparation of the ASSF

ASSF was successfully prepared by spray drying. The drug form showed promising in vitro properties in terms of high solubility and increased dissolution rate at pH 8.6.

Filling of microcontainers with drug powder

Loading of drug powder into the microcontainers was shown to be a very useful method for quickly filling the microcontainers while avoiding deposition of drug powder in between the microcontainers (Fig. 7). Moreover, the method can be utilised for all type of drugs.

Coating of drug-filled microcontainers

The drug-filled microcontainers were spray coated with a lid of either the pH-sensitive polymer, Eudragit® L100 or the mucoadhesive polymer, chitosan.

In situ intestinal perfusion studies

In situ intestinal perfusion studies were performed in fasted rats with a weight of approximately 200 g (Fig. 8).

Oral bioavailability studies in rats

The coated, ASSF-filled microcontainers were dosed with 10 mL of phosphate buffer at pH 8.5 directly to the small intestine. As controls, a solution of furosemide in phosphate buffer, as well as empty microcontainers, were dosed. Blood samples (200 µL) were drawn every 5 min for 30 min. After the 30 min, the small intestine was harvested from the rat and imaged under a UV microscope.

Coating of drug-filled microcontainers

Fig. 8 shows a drug-filled SU-8 microcontainer coated with either Eudragit® L100 or chitosan. The thickness of the polymer layer was in both cases measured to be approximately 10 µm.

In situ intestinal perfusion studies

After the oral dosing of the rats with either ASSF-filled microcontainers or ASSF-filled capsules, the plasma concentrations were measured in the small intestine, but the microcontainers exhibited a prolonged release of ASSF (Fig. 10) resulting in a bioavailability of 250% compared to the drug-capsules (Table 1).

CONCLUSION

- SU-8 microcontainers with inner diameter of 223 µm were fabricated
- Microcontainers were filled with powder drug using a fast and widely-applicable method.
- The microcontainers interacted with the intestinal mucus layer
- In rats ASSF in microcontainers exhibited an oral bioavailability of 250% compared to capsules filled with ASSF
- Microcontainers are proposed as a promising oral drug delivery system

REFERENCES

[Boisen et al. J Pharm. Pharmacol., 61, 1116-23 (2009)]
[Villum Fonden, University of Copenhagen, Copenhagen, Denmark

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Table 1: Microcontainers' pharmaceutical parameters of ASSF following oral administration in rats

| Coating of microcontainers | Eudragit coated microcontainers | Eudragit coated capsules | Micro containing
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<tr>
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<tr>
<td>Eudragit coated microcontainers</td>
<td>254.1 ± 2.7</td>
<td>68.0 ± 3.7</td>
<td>100.0 ± 2.5</td>
</tr>
<tr>
<td>Eudragit coated capsules</td>
<td>191.0 ± 4.0</td>
<td>173.0 ± 5.5</td>
<td>185.0 ± 3.5</td>
</tr>
<tr>
<td>Micro containing</td>
<td>189.0 ± 3.5</td>
<td>180.0 ± 4.0</td>
<td>180.0 ± 3.5</td>
</tr>
</tbody>
</table>

Relative bioavailability (%) | 250.0 ± 2.5 | 250.0 ± 2.5 | 100.0 ± 2.5 |