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Polymeric microcontainers improve oral bioavailability of a poorly soluble drug

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ABSTRACT SUMMARY

Here we present *in situ* and *in vivo* studies in rats showing the promise of polymeric microcontainers as an oral drug delivery system for the poorly water-soluble drug, furosemide. The microcontainers showed interaction with the intestinal mucus and an increased oral bioavailability of furosemide was found when dosed in microcontainers compared to the powder form.

INTRODUCTION

Oral delivery of drugs is the preferred administration route. For some drugs, it can be necessary to employ drug delivery systems e.g. to reduce variability in oral bioavailability and/or to protect the drug from the harsh environment of the stomach [1]. Microcontainers are a promising advanced drug delivery system. The size and shape of the microcontainers can easily be controlled and therefore, polydispersity is avoided as seen for e.g. micro- and nanoparticles. Microcontainers are polymeric, cylindrical devices in the micrometer size range (Fig 1A), and a major advantage is that these microcontainers allow for unidirectional release, as only one side is open. Moreover, the drug can be protected inside the cavity of the microcontainer until release is desirable e.g. in the small intestine [2].

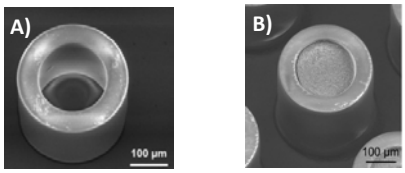

Fig 1: A) Image of a polymeric microcontainer and B) filled with the amorphous sodium salt of furosemide

The aim of the current study was to investigate interactions between the microcontainers and the small intestine *in situ* and furthermore, to evaluate the *in vivo* performance of the microcontainers filled with amorphous sodium salt of furosemide (ASSF) after oral dosing to rats (Figure 2).

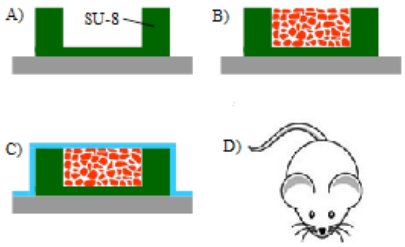

Fig 2: Illustration of the experimental set-up with drug-filled microcontainers (B), coated with a pH-sensitive or mucoadhesive membrane (C), and then tested using an intestinal perfusion set-up and in a pharmacokinetic study (D).

EXPERIMENTAL METHODS

SU-8 microcontainers were produced using two steps of photolithography and the fabrication resulted in microcontainers with a size of 223 µm (Fig 1A). Following the fabrication, the microcontainers were filled with the ASSF powder (Fig 1B) [3]. Subsequently, the drug-filled microcontainers were spray coated with a polymeric lid of either the pH-sensitive polymer, Eudragit® L100 or the mucoadhesive polymer, chitosan.

In situ intestinal perfusion studies were performed in rats [4]. The coated and drug-filled microcontainers were dosed together with 10 mL of phosphate buffer, pH 6.5 to the small intestine. Furthermore, a solution of furosemide in phosphate buffer as well as empty microcontainers, were dosed as controls. 200 µL

of sample was withdrawn every 5 min for 30 min. At the end of the study, the small intestine was harvested from the rat and imaged under a UV and fluorescence microscope.

For the *in vivo* studies, the rats were dosed orally with gelatin capsules (size 9) loaded with drug-filled microcontainers coated with Eudragit® L100. As control, capsules were filled with the powder of ASSF followed by coating of the capsules with Eudragit® L100. Ten samples of 200 µL blood were withdrawn from the tail vein during 24 h.

RESULTS AND DISCUSSION

The microscope images of the small intestine after the perfusion studies showed that the microcontainers interacted with the mucus in the small intestine, and the microcontainers were engulfed by the intestinal mucus (Fig 3). By these qualitative results, it was observed that also without coating, the microcontainers interacted with the intestinal mucus (Fig 3C).

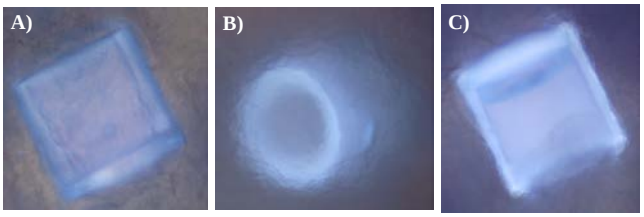

Fig 3: Microcontainers in intestinal mucus following *in situ* intestinal perfusion studies. Microcontainers were filled with ASSF and coated with a lid of A) Eudragit® L100 and B) chitosan. C) empty microcontainers without drug and coating.

The oral bioavailability study showed that the relative oral bioavailability of ASSF in microcontainers was found to be 220±43% when comparing to drug-filled capsules coated with Eudragit. This was reflected by a larger area under the curve (AUC) for the ASSF in microcontainers (Fig 4).

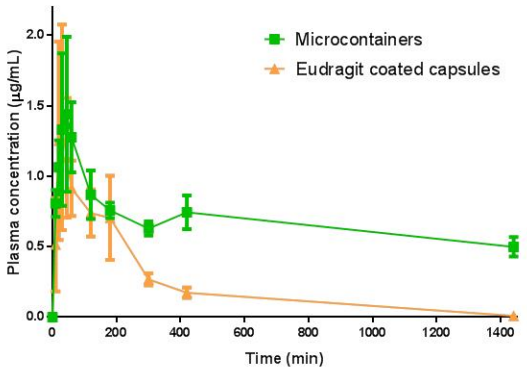

Fig 4: Plasma concentrations of microcontainers filled with ASSF coated with Eudragit® L100 and filled into capsules and ASSF dosed in capsules with Eudragit coating after orally dosing to rats

CONCLUSION

Microcontainers were shown to interact with the intestinal mucus after the *in situ* studies. Furthermore, furosemide confined in microcontainers showed a prolonged absorption resulting in an oral bioavailability of 220% compared to furosemide in a coated capsule. The use of microcontainers therefore shows considerable potential as a new oral drug delivery approach.

REFERENCES

1. Eaimtrakarn S et al. Int J Pharm. (2001) 224: 61-67
2. Nielsen LH et al. Eur J Pharm and Biopharm. (2012) 81: 418-25
3. Nielsen LH et al. Eur J Pharm and Biopharm. (2013) 85: 942-951
4. Doluisio JT et al. J Pharm Sci. (1969) 58: 1200-1202

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