Influence of proximity on the permeability enhancing effect of microcontainers for oral insulin delivery

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Introduction

Microcontainers have the potential of increasing oral insulin bioavailability by confining the effective intestinal absorptive area and improving co-localisation with excipients by unidirectional release (Fig. 1). The principle has previously increased oral bioavailability of small molecules\textsuperscript{1,2}.

Aims

- Gain \textit{in vitro} proof-of-concept by studying the transport of insulin upon release in combination with sodium caprate (C\textsubscript{10}) from microcontainers.
- Evaluate the influence of proximity by controlling the distance between microcontainers and the barrier.

Methods

Microcontainers were fabricated by photolithography in SU-8 on silicon wafers and cut into chips (12x12 mm), each holding 625 microcontainers. A powder mixture of human insulin and C\textsubscript{10} (1:1 w/w) was then loaded by centrifugation (Fig. 2).

Transport study conditions are given in Table 1. Loaded chips were placed with the openings of the microcontainers facing the barrier, either directly on top, or with elevation (0.2, 0.5 or 2.0 mm) obtained by polytetrafluoroethylene (PTFE) carvings (Fig. 3). Integrity assessments were done after 2 h transport or upon subsequent 24 h incubation in cell growth medium at 37 °C and 5% CO\textsubscript{2}.

Results – Transport studies

Fig 4. Representative SEM images of microcontainers, A: empty, B: insulin + C\textsubscript{10} (1:1 w/w).

Fig 5. A: TEER values of the monolayers, relative to initial values, after 2 h (left of dotted line) and after subsequent 24 h incubation (right of dotted line), B: Transport profiles obtained with different distances between microcontainers and the monolayer. Equivalent amounts of insulin (0.1 mM) and C\textsubscript{10} (3 mM) were used for the solution. Mean ± SD (n = 3).

Results – Microscopy

Fig 6. Representative confocal laser-scanning micrographs of Caco-2 monolayers with Hoechst 33342 nuclei staining. A: After 2 h, d = 0.0 mm, B: After 2 h, d = 0.2 mm, C: After 2 h, d = 0.5 mm, D: After 24 h incubation, d = 0.0 mm. Scale bars represent 100 μm (n = 2).

Conclusion

Confining the effective absorptive area and improving co-localisation of insulin and C\textsubscript{10} significantly improved insulin permeability across Caco-2 monolayers, either by non-destructive paracellular permeation enhancement or local reversible deterioration of the barrier.

References


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