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Comparing in vitro and in vivo studies of microcontainers and microspheres for enhanced oral drug delivery

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PURPOSE

- To compare microcontainers (**MC**) and microspheres (**MS**), loaded with paracetamol, with regard to in vitro release and oral absorption in rats. Both MC and MS were coated with low molecular weight 50-190 Da chitosan (**Chitosan**) or PEG 12kDA (**PEG**), both with a topcoat of Eudragit ® S100. Control MC and MS were only coated with Eudragit® S100 (**Eudragit**).
- *In vitro* drug release was determined in a two-step *in vitro* model with a 30 min step in a simulated fasted rat gastric medium (**RGM**) and a 30-90 min step in a simulated fasted rat intestinal medium (**RIM**) (1).
- The pharmacokinetic profile was determined in rats after oral gavage of MC or MS. *In vitro in vivo* correlation was investigated for both MC and MS.

METHODS

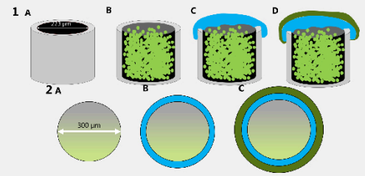

Fig. 1. A: MC made of the epoxy polymer SU-8 by two photolitography steps, baking and UV exposure. **B:** MC filled with paracetamol. **C:** Coated with chitosan or poly(ethylene) glycol (PEG). **C.** Top coating of Eudragit.

Fig 2.A: MS made of MCC and paracetamol by dry mixing, granulation, and spheronization. **B:** coated with chitosan or PEG. **C:** Top coating Eudragit

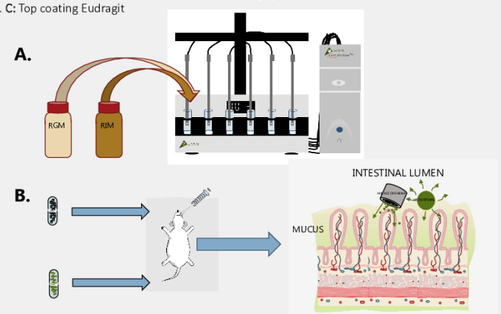

Fig. 3. A: An *in vitro* two-step release model in the **µDiss Profiler™**: The first step consisted of a chip of MC or a corresponding dose of MS in 30 min in RGM and the second step consisted of 30-90 min in RIM. **B:** *In vivo* pharmacokinetic studies in rats.

Table 1. Composition of the developed rat gastro-intestinal media and concentrated bile buffer, based on characterization of rat gastrointestinal fluids. A mix in a ratio of 2:1 of RGM and bile buffer results in RIM (1).

Properties	RGM	RIM	Bile buffer
pH	2.4*	7.5	7.5
Osmolality (mOsm/kg)	230	312	476
BS:PL ratio	1.6	6.5	7.3
Composition			
HCl (mM)	4	-	-
HEPES (mM)	-	100	300
Sodium taurocholate (mM)	1.3	24.1	69.7
Lyso-phosphatidylcholine (mM)	0.8	3.7	9.5
Sodium chloride (mM)	111.7	119.6	139.4
NaOH/HCl (pH adjustment)	*q.s.*	*q.s.*	*q.s.*

*mean value of the pH in the forestomach and the glandular stomach.

RESULTS

Microcontainers and microspheres

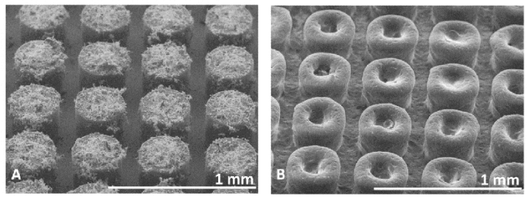

Fig 4. A: Paracetamol filled MC. B: Eudragit coated, paracetamol filled MC.

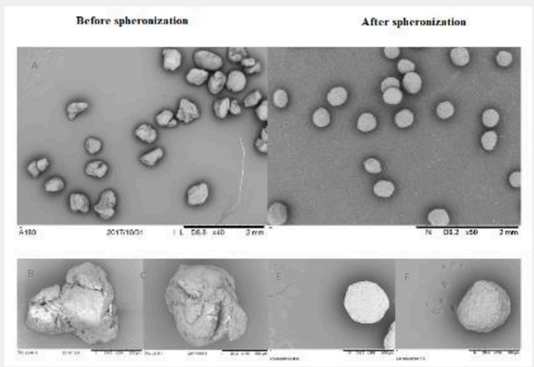

Fig. 5. MS production. MCC/paracetamol MS made by dry mixing and granulation. A,B,C: Before spheronizaton. D,E,F: After spheronization.

In vitro two-step release model

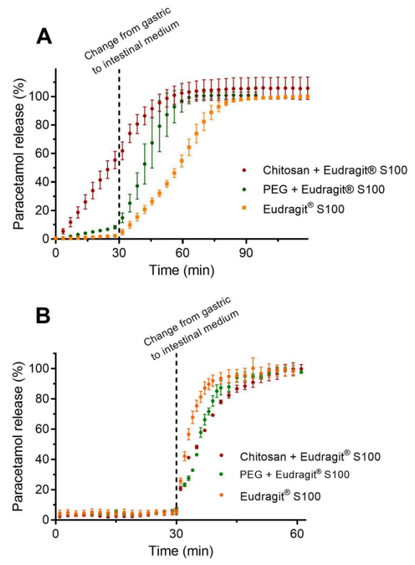

Fig. 6. *In vitro* two step release of paracetamol from A: MC, B: MS. At 30 min the medium is changed from RGM to RIM.

In vivo pharmacokinetic study

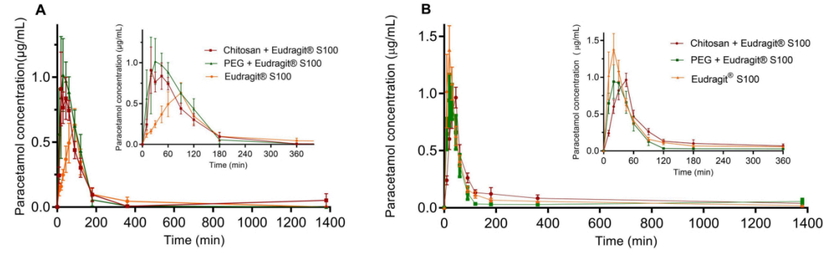

Fig. 7. *In vivo* pharmacokinetic study showing plasma concentration of paracetamol plotted against time. A: MC. B: MS

Table 1. Pharmacokinetic profiles of all formulations. MC: Microcontainers, MS: Microspheres. The same letters denote significant difference when compared by Student's t-test, p<0.05.

	Chitosan		PEG		Eudragit	
	MC	MS	MC	MS	MC	MS
T_{max} (min)	40±7[a]	42±6[b]	37±7[c]	22±5[d]	68±11[a,c,d,e]	20±7[b,e]
C_{max} (µg/mL)	1.2±0.2	1±0.2	1.3±0.4	1.1±0.4	0.7±0.1	1.4±0.6
$AUC_{(0\text{-}23\ h)}$ (µg·min/mL)	125±41	129±89	111±20	100±40	96±26	118±34

CONCLUSIONS

- ***In vitro* two-step release studies** revealed that the time for reaching 100% release of paracetamol from had a rank order as follows, for coated MC: **Chitosan < PEG < Eudragit** and for MS: **Eudragit< PEG < Chitosan.**
- ***In vivo* pharmacokinetic studies** revealed that MC had a T_{max} rank order as follows: **Chitosan=PEG< Eudragit** and for microspheres **Eudragit = PEG < Chitosan. No significant difference** in C_{max} or AUC were observed between MC and MS.
  - For T_{max}, there was no difference for Chitosan, whereas MC for both PEG and Eudragit had a longer T_{max} than MS: this was only significant for Eudragit.
- **Comparatively,** MC had a **slower release *in vitro* and *in vivo***, than the MS. The *in vitro* release (until 100% release) was significantly longer for MC coated with PEG and control formulation coated with Eudragit®. T_{max} for *in vivo* study showed significantly later T_{max} for MC coated with PEG and control formulation coated with Eudragit.
- **For both MC and MS the *in vitro* release model were predictive for the *in vivo* studies**. The *in vitro* release correlated well with T_{max}, both within the MC formulations and within the MS formulations. Further, the *in vitro* release model predicted a slower release of paracetamol from MC, than from MS, both for PEG coated formulations and Eudragit formulation. This was reflected in that T_{max} for paracetamol for PEG coated MC and Eudragit coated MC was significantly later than for **PEG coated MS and Eudragit coated MS.**

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1. Christfort et al., Developing a predictive in vitro dissolution model based on gastrointestinal fluid characterisation in rats Eu. J. Pharm. Biopharm. (2019). 142. 307-314.