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Assessing Gastric Emptying of Gastro-Resistant Capsules in Pigs: Impact of Capsule Size

S. V. Hoffmann [a], B. T. Griffin [a], V. Jannin [b], J. P. O'Shea [a]

[a] School of Pharmacy, University College Cork, Cork, Ireland

[b] Capsugel France SAS, Colmar, France

CONTACT INFORMATION: sophia.Hoffmann@umail.ucc.ie

aaps PharmSci 360

PURPOSE

- Reliable pre-clinical large animal models are vital during drug development
- Pigs are a promising model for oral drug delivery due to anatomical and physiological similarities to humans [1].
- Large monolithic capsules show prolonged gastric retention, raising concerns about translatability [2].
- This limitation can potentially be addressed by administering prokinetic agents [3].
- This study investigates gastric emptying of gastro-resistant Capsugel® Enprotect ® capsules (sizes 0–2) and evaluates metoclopramide as a prokinetic intervention in the landrace pig model through pharmacokinetic analysis of rapidly absorbed marker compounds.

OBJECTIVE(S)

- Assess gastric emptying of enteric capsules of varying sizes in pigs
- Evaluate metoclopramide's effect on capsule transit
- Validate capsule endoscopy for *in vivo* imaging of gastric emptying
- Generate insights into the pig as a preclinical model

METHOD(S)

Design: Non-randomized, four-way crossover in fasted Landrace pigs

Treatments:

- Sizes 0, 1, and 2 capsules (paracetamol payload)
- Size 1 + metoclopramide (0.5 mg/kg i.m.)
- Capsule endoscope in 5 pigs
- Concurrent caffeine immediate-release (IR) tablets for dual PK markers

Sampling: 0-24 h plasma collection, LLE-HPLC quantification

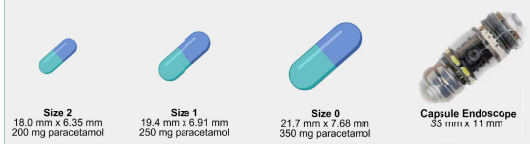

Figure 1. Schematic representation of Capsugel® Enprotect® capsule sizes (0, 1, 2) tested *in vivo*, each filled with paracetamol (200–350 mg) as a pharmacokinetic marker. ALICAM® capsule endoscopes were co-administered in selected study legs to visually assess gastric transit.

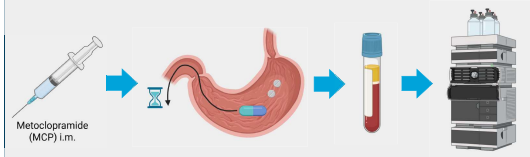

Figure 2. Overview of the study design in landrace pigs: one leg included intramuscular metoclopramide (0.5 mg/kg) 30 min prior to oral dosing. All pigs received one of three capsule sizes (0, 1, or 2) containing paracetamol, alongside caffeine IR tablets (100 mg). Blood samples were collected over 24 h and analysed via liquid-liquid extraction followed by HPLC.

RESULT(S)

Influence of Capsule Size

- All capsule sizes emptied from the stomach (MAT: 3.9–8.1 h)
- No significant differences between sizes, but trend toward slower emptying with larger capsules

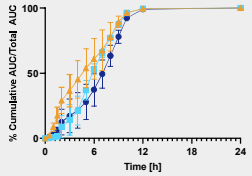

Figure 3. Cumulative AUC/AUC_{total} (%) over 24 hours following oral administration of Capsugel® Enprotect® paracetamol capsules of size 2 (▲), size 1 (■), and size 0 (●); Mean ± SEM, N = 5

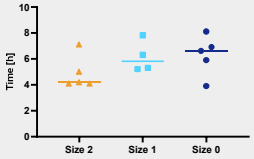

Figure 4. Mean absorption time (MAT, hours) following oral administration of Capsugel® Enprotect® paracetamol capsules of size 2 (▲), size 1 (■), and size 0 (●); Median and individual values, N = 5

Comparison to Immediate Release

- No significant differences between IR tablets and gastro-protective capsules
- Gastric residence longer than in humans for both IR tablets and gastro-protective capsules

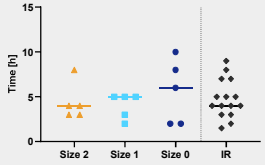

Figure 5. Time to maximum plasma concentration (t_{max}, hours) following oral administration of Capsugel® Enprotect® paracetamol capsules of size 2 (▲), size 1 (■), and size 0 (●) and IR (♦) caffeine tablets; Median and individual values; gastro-resistant capsules: N = 5; IR tablets: N = 15

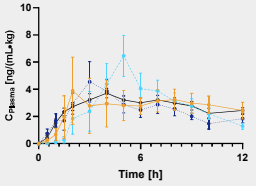

Figure 6. Plasma concentration-time profiles of paracetamol and caffeine in individual pigs following oral administration of Capsugel® Enprotect® paracetamol capsules of size 2 (●, N = 5), size 1 (●, N = 5), and size 0 (●, N = 5), along with IR caffeine tablets (●, N = 15); Mean ± SEM

Influence of Metoclopramide

No statistically significant acceleration of gastric emptying after MCP injection

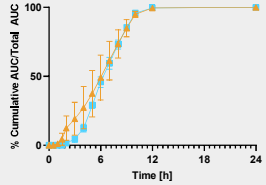

Figure 6. Cumulative AUC/AUC_{total} (%) over 24 hours following oral administration of Capsugel® Enprotect® paracetamol capsules (size 1, 250 mg): A with (●) and B without (■) prior intramuscular injection of 0.5 mg/kg MCP; Mean ± SEM, N = 4

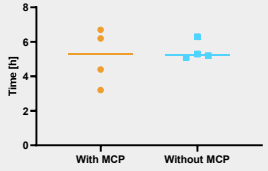

Figure 7. Mean absorption time (MAT, hours) following oral administration of Capsugel® Enprotect® paracetamol capsules (size 1, 250 mg), with (●) and without (■) prior intramuscular injection of 0.5 mg/kg MCP (Median and individual values, N = 4); differences were non-significant ($p > 0.05$)

Capsule Endoscopy

- Gastric retention of capsule endoscopes for prolonged time
- Visualisation of the gastric emptying process was unsuccessful due to problems with resolution and capsules moving out of the camera's focus

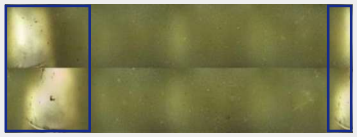

Figure 8. Image of Capsugel® Enprotect® capsule size 1 captured by ALICAM® capsule endoscope 3 hours after oral dosing following overnight fasting after liquid feed

CONCLUSION(S)

1. **All gastro-resistant capsules showed mean absorption times of 3.9-8.1 hours, supporting their use in pig studies.**
2. **Gastric emptying in pigs was found to be longer than in humans, necessitating careful consideration in human scaling predictions**
3. **Metoclopramide did not significantly influence gastric emptying, suggesting that it does not offer substantial benefits.**
4. **Visualisation of the gastric emptying process was not feasible using a capsule endoscope.**

These findings contribute to a more comprehensive understanding of the performance of non-disintegrating oral dosage forms in pigs and can guide on scaling factors in pig-human translation.

REFERENCES

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3. C. Suenderhauf et al., *Pharm Res*, vol. 31, no. 10, 2696–2707, 2014

ACKNOWLEDGEMENTS

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UCC University College Cork, Ireland Coláiste na hOllscoile Corcaigh

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