



A Clinical Assessment of Delayed-Release Coated Capsule Compositions for Regional Gastrointestinal Delivery using Gamma Scintigraphy

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Introduction

- **Learning Objectives**

- Understand the utility of gamma scintigraphy in monitoring transit of an oral dosage from through the gastro intestinal (GI) tract.
- Understand the utility of gamma scintigraphy in assessing the anatomical location of disintegration and release of contents from capsules with different delayed release coating systems.
- Gain an appreciation of the impact of fed versus fasted dosing on the GI transit of coated capsule systems.

- **Study Purpose**

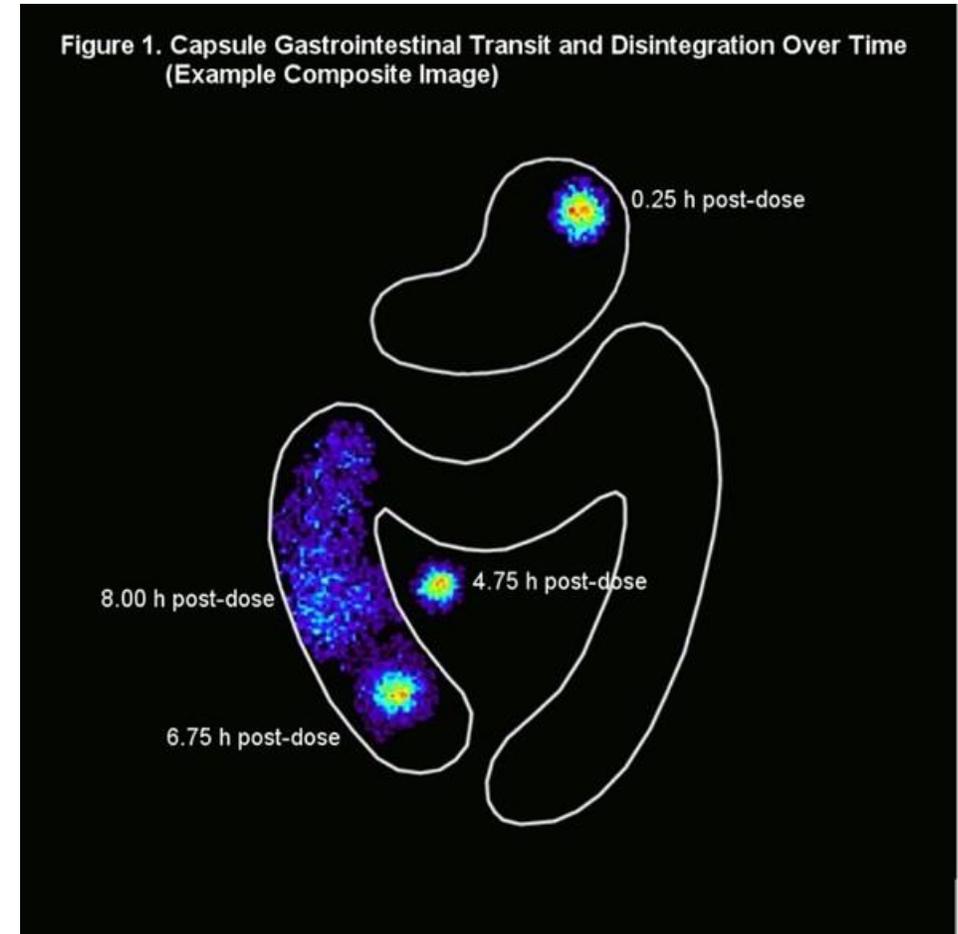
- Applied Molecular Transport Inc. are evaluating targeted drug delivery capsules for administration of locally acting drugs directly to the site of action in the GI tract.
- This study used gamma scintigraphy to evaluate GI transit and release from 3 capsule prototypes with different coating systems (1).
- In addition, data on pH, temperature and pressure during GI transit was obtained using SmartPill® and correlated with scintigraphy data (2).

(1) Wilding IR, Coupe AJ, Davis SS. The role of gamma-scintigraphy In oral drug delivery. *Adv Drug Del Rev* 2001; 46: 103–124.

(2) Maqbool S, Parkman HP, Friedenber FK. Wireless Capsule Motility: Comparison of the SmartPill® GI monitoring system with scintigraphy for measuring whole gut transit. *Dig Dis Sci* 2009; 54:2167-2174.

Methods

- 12 healthy subjects (8 males and 4 females), all non smokers aged 32 to 65 years old with BMI of 20.5 to 30.1 kg/m² and no significant history of gastrointestinal disease or surgery, received 3 delayed release Eudragit® coated size 0 capsules containing Indium-111 radiolabel in the fasted state plus a selected capsule in the fed state.
- Scintigraphic analysis determined time and anatomical location of initial and complete radiolabel release from the test capsule alongside gastric emptying and colon arrival times for the capsule prior to complete disintegration (Figure 1).



Methods

- The capsules administered were radiolabelled via a “drill-fill-seal” approach (Figure 2), determined to have a negligible effect on coating integrity and dissolution.
- Coatings contained a controlled-release layer with a variable ratio and weight gain of Eudragit[®] FS30 and Eudragit[®] L30D55 polymers, which target dissolution above pH 7 and pH 5.5 respectively.
- Capsule Coating 1 was 75 mg of 50:50 FS30D:L30D55, Coating 2 was 75 mg of 70:30 FS30D:L30D55 whilst Coating 3 was 45 mg of 80:20 FS30D:L30D55.
 - In addition, capsule banding was used with Capsule Coatings 2 and 3
- During each fasted period, 4 of the 12 subjects were co-administered a SmartPill[®] to obtain a pH, temperature and pressure vs time profile during GI transit (Figure 3).
 - This resulted in a single profile for each of the 12 volunteers after the 3 fasted study periods.
 - The SmartPill[®] profiles allowed gastric residence time, small intestine transit time, colonic arrival time, colonic transit time and whole gut transit time to be generated for each subject from the time of administration until defecation.

Figure 2. Drilled capsule (L) and capsule sealed with surgical bone cement (R) post filling with Indium-111 radiolabel

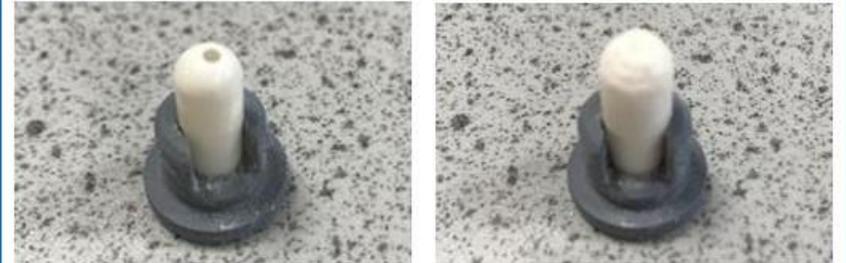
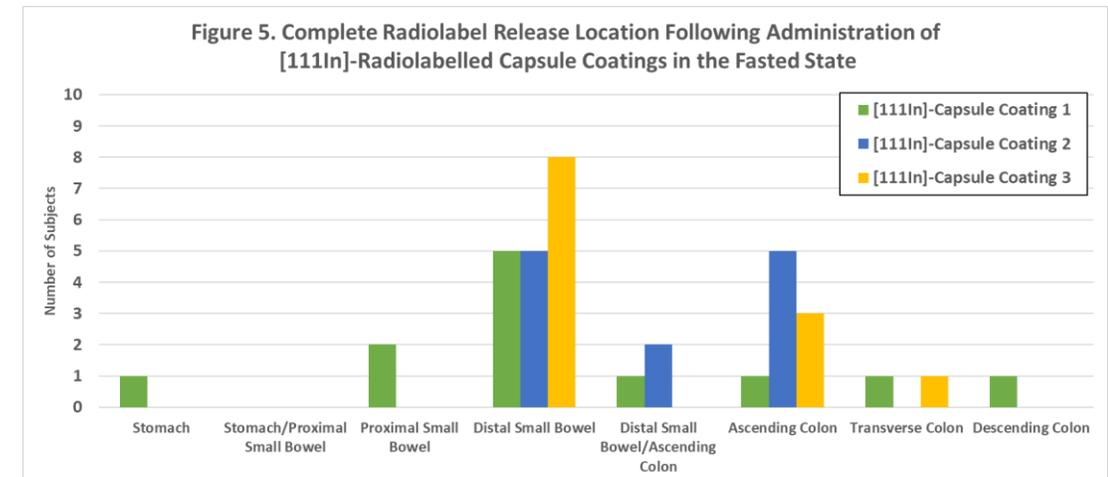
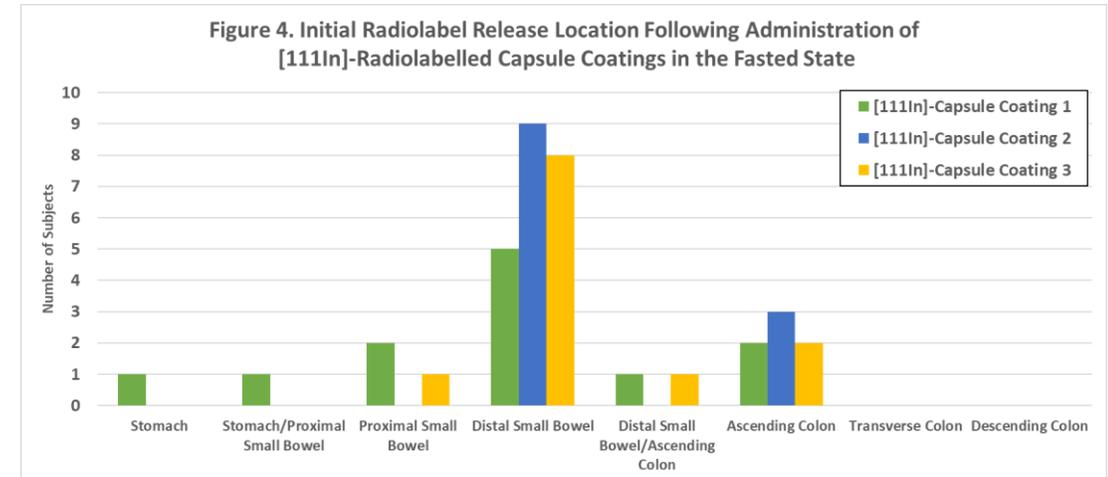


Figure 3. SmartPill[®]



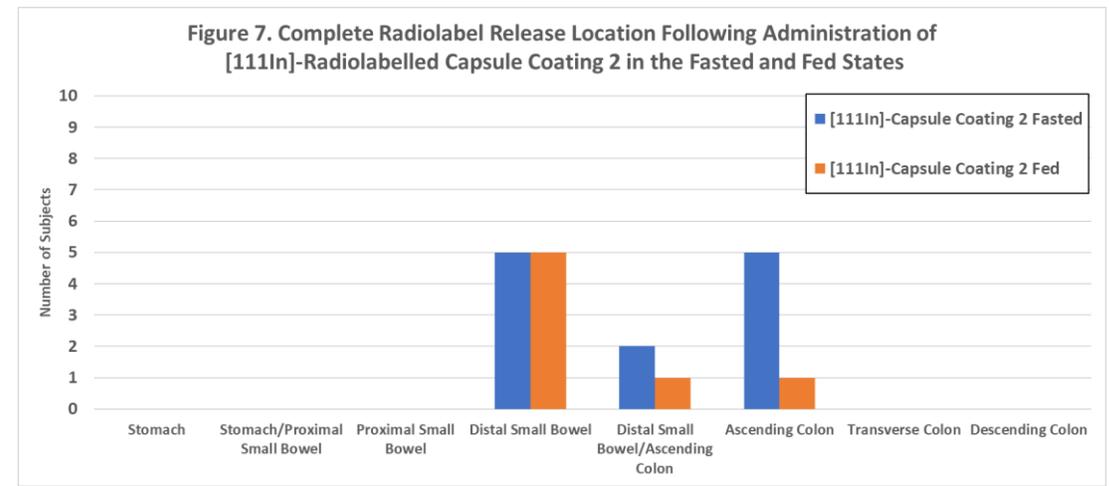
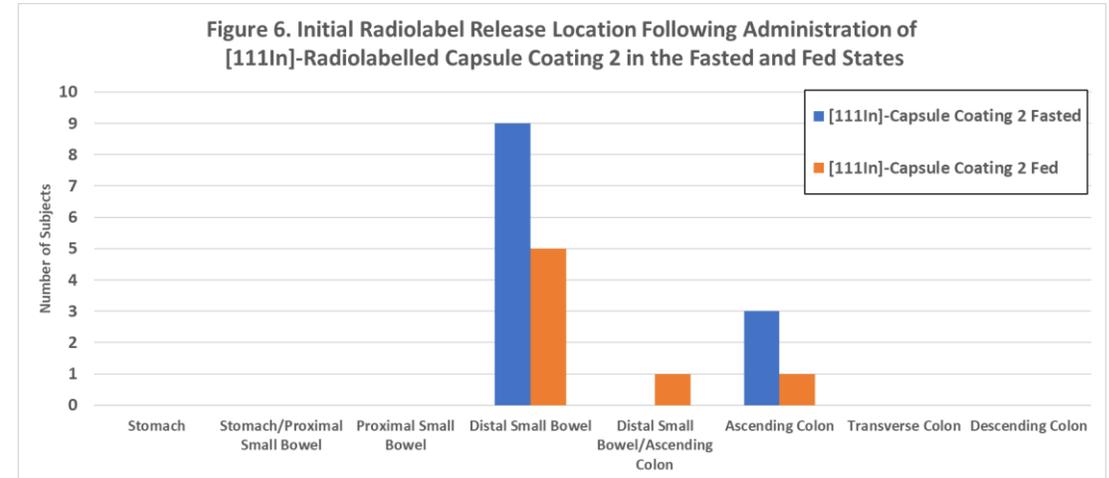
Scintigraphy Results – Fasted State

- Different in vivo disintegration rates resulted from varying Eudragit® combinations and capsule coating thickness.**
 - Capsule Coating 1 gave the earliest mean times for initial and complete disintegration (2.7 hours and 3.8 hours, respectively) with anatomical location of disintegration ranging from stomach to ascending colon for initial release, and from stomach to descending colon for complete release.
 - Capsule Coating 2 gave the latest mean times for initial and complete disintegration (4.9 hours and 6.2 hours, respectively) with anatomical locations of initial and complete disintegration being distal small bowel and ascending colon respectively.
 - Capsule Coating 3 exhibited slightly earlier mean times for initial and complete disintegration (4.1 hours and 5.3 hours, respectively) compared with Coating 2, with anatomical locations of release mainly in the distal small bowel and ascending colon.
- Capsule Coating 2 exhibited the most consistent disintegration locations (Figures 4 and 5) in the fasted state and was selected for administration in the fed state.**



Capsule Coating 2 – Fed vs Fasted State

- Mean times for initial and complete disintegration for Capsule Coating 2 in the fed state were delayed by approximately 10.0 hours and 9.0 hours respectively, compared to the fasted state.
- Capsule disintegration was beyond 24 hours for 4 subjects in the fed state. Locations of disintegration, where measurable, remained consistent between fed and fasted states (Figures 4 and 5).





SmartPill® Results

- In comparing the overlapping SmartPill® data sets with corresponding scintigraphy data (n = 4 subjects for each capsule coating formulation), the gastric emptying times indicate that the test product capsules and the SmartPill® did not transit at a similar rate in all cases.
- However, pH, temperature and pressure values measured in similar anatomical locations were consistent between subjects (Table 1).

Table 1. Gastric Emptying and Capsule Disintegration Times and related Location pH Values for Capsule Coatings 1, 2 and 3 in the Fasted State: Scintigraphic Data Comparison with SmartPill® Data.

Capsule Coating Formulation	Subject ID	Gastric Emptying Time (h post-dose)		Stomach pH ^c	Initial Capsule Disintegration ^a		Initial Disintegration Location pH ^c	Complete Capsule Disintegration ^a		Complete Disintegration Location pH ^c
		TP ^a	SmartPill ^b		Time (h post-dose)	Location		Time (h post-dose)	Location	
1	001	0.38	2.72	0.9 (0.6 – 6.3)	2.63	PSB	6.9 (1.1 – 7.8)	4.13	DSB	6.9 (1.1 – 7.8)
	002	0.37	0.47	1.4 (0.9 – 7.0)	1.63	DSB	7.3 (1.0 – 7.8)	2.88	DSB	7.3 (1.0 – 7.8)
	003	1.89	2.88	1.0 (0.5 – 5.2)	2.14	DSB	7.2 (1.2 – 8.0)	2.39	DSB	7.2 (1.2 – 8.0)
	004	2.13	0.77	1.9 (0.9 – 6.1)	2.38	PSB	6.9 (1.2 – 7.6)	2.88	PSB	6.9 (1.2 – 7.6)
2	005	2.39	1.03	0.5 (0.1 – 6.6)	6.14	DSB	7.0 (3.1 – 7.6)	6.89	DSB	7.0 (3.1 – 7.6)
	006	0.63	0.30	1.5 (1.1 – 4.0)	5.88	DSB	6.5 (1.2 – 7.3)	9.53	DSB/AC	6.5 (1.2 – 7.3) / 6.5 (5.0 – 8.2)
	007	0.62	0.42	1.0 (0.5 – 4.8)	4.38	DSB	6.8 (0.6 – 7.5)	5.13	DSB	6.8 (0.6 – 7.5)
	008	0.88	0.50	1.1 (0.5 – 5.8)	4.38	DSB	6.2 (0.9 – 7.7)	5.13	DSB	6.2 (0.9 – 7.7)
3	009	1.40	2.60	0.4 (0.3 – 5.8)	3.65	DSB	7.3 (0.3 – 8.1)	4.14	AC	6.5 (6.0 – 7.5)
	010	1.63	0.47	1.3 (0.6 – 6.3)	3.88	DSB	7.1 (1.9 – 7.5)	4.13	DSB	7.1 (1.9 – 7.5)
	011	1.63	0.23	3.2 (2.3 – 6.9)	2.63	PSB	7.3 (2.7 – 7.6)	2.88	DSB	7.3 (2.7 – 7.6)
	012	0.38	0.13	2.8 (1.8 – 6.8)	2.38	DSB	7.2 (2.2 – 7.5)	2.88	DSB	7.2 (2.2 – 7.5)

AC: ascending colon; DSB: distal small bowel; PSB: proximal small bowel; TP: test product

^a generated from scintigraphic data

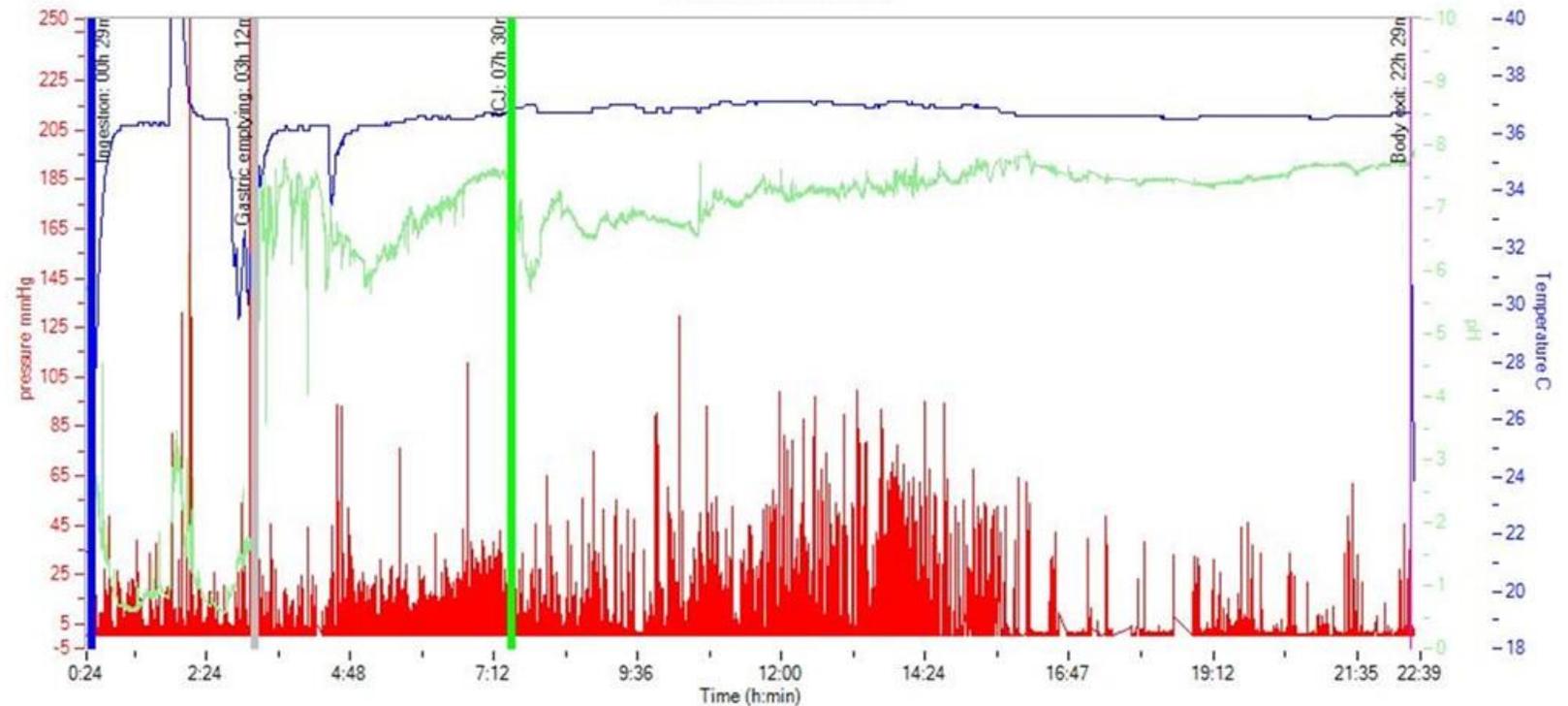
^b physician confirmed; generated from SmartPill data

^c pH median (pH low – pH high); taken from SmartPill data generated in either the stomach, small bowel or colon physician-defined SmartPill locations which most closely represent the scintigraphic capsule locations defined.

SmartPill® Data Example and Study Safety Results

- SmartPill® GI transit times, pH, temperatures and pressures were found to be as expected for healthy volunteers in the fasted state (Figure 8).
- There were no serious or severe adverse events reported during the study. Only 3 mild adverse events were reported, none of which were related to the coated capsule or SmartPill®.

Figure 8. Example SmartPill® Combined pH, Temperature and Pressure vs Time Chart (Including Physician Defined Markers for Ingestion, Gastric Emptying, Colon Arrival [ICJ] and Body Exit) for Subject 001.





Conclusions

- **This study successfully compared in vivo performance of three different capsule coatings using gamma scintigraphy.**
- **There were no safety issues during the conduct of the study**
- **Results identified a coating formulation for future development with acceptable variability and the potential to deliver to a specific region of the GI tract.**

Thank You