Breakthroughs in Targeted Delivery

NOVEL BIMODAL COLONIC DRUG AND BIOLOGIC DELIVERY SYSTEM: EVALUATION BY GAMMA SCINTIGRAPHY

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Agenda

- The problem in delivery to the colon
- Approaches
- A better approach
- GEMICEL™
- Data

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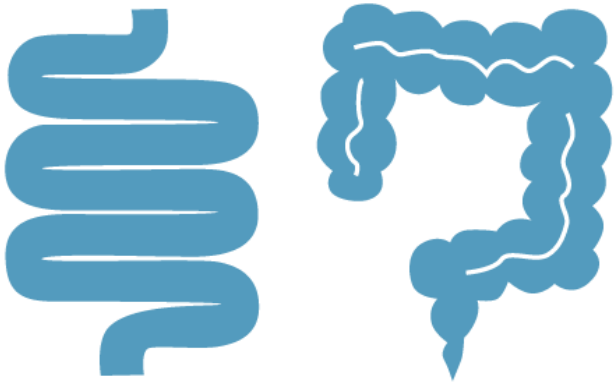
Misconception: GI Delivery Easy

- Delivery to small intestine is easy(‘er)
- Delivery to the colon is quite challenging

6 meters
Small intestine: complex physiology and pH



1.5M
Large intestine: Complex flora

- Despite challenges, the colon is an attractive site for oral drug delivery
  - Unique microbial flora implicated in health and disease
  - Peyer’s patches relevant to mucosal immunity
  - Improved drug utilization

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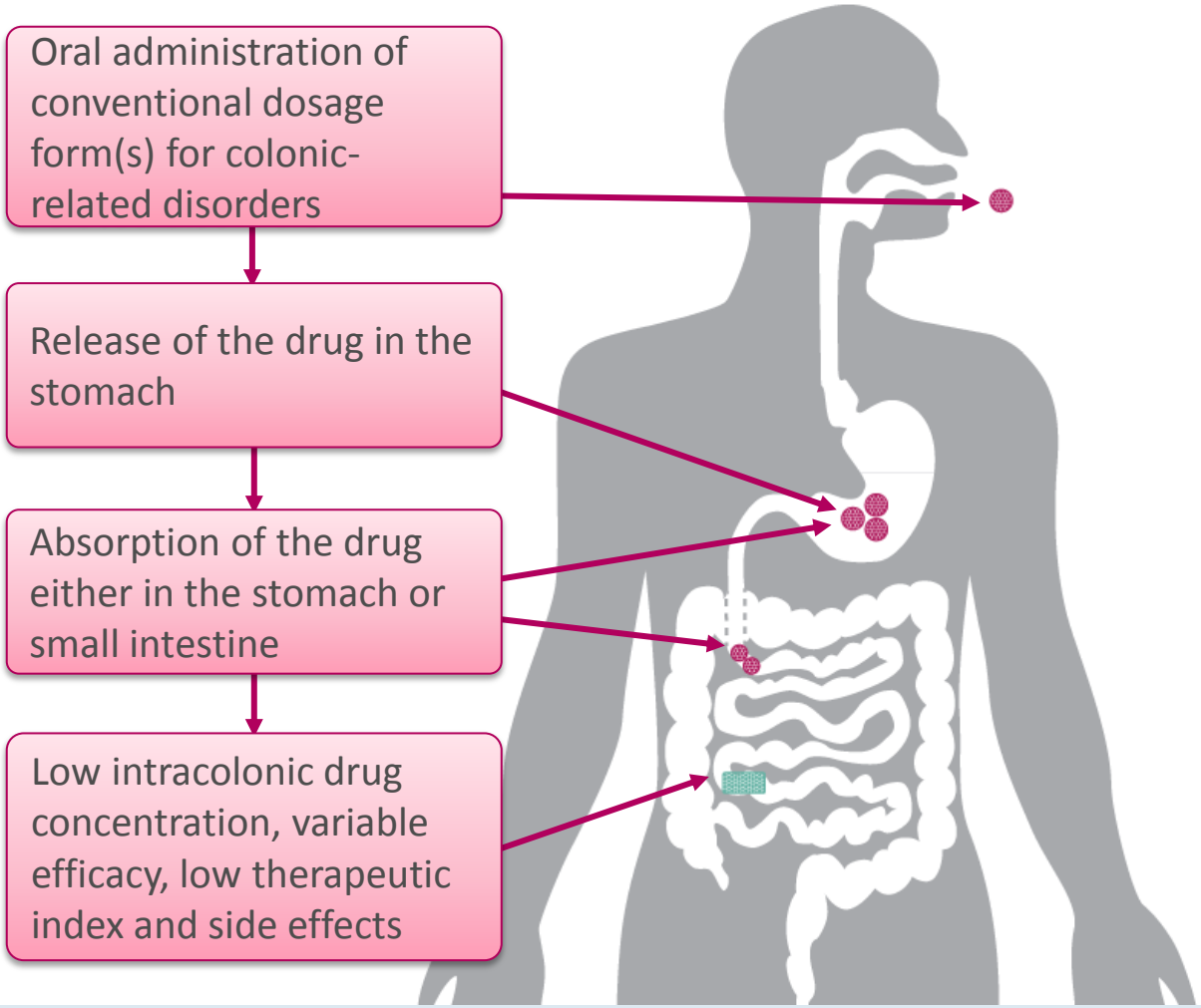
Conventional Dosage Forms



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Diverse Approaches in Lower GI Delivery

Approach	Example	Limitations
Bio-adhesives	Under development	Mostly limited to small molecules. Sustained and slow release
Multi-matrix (MMX)	Cosmo	
Osmotic controlled	ORDS-CT	
Timed-release	Multivitamins	
Pro-drugs	Sulfasalazine	Inefficient, mostly limited to small molecules. Can only deliver sustained or slow release
Carriers degraded by colonic bacteria	CODESTM	Limited to small molecules. Requires normal gut flora
pH-sensitive coatings	Probiotics	Historically have used inappropriate pH targeting

Novel approaches required for oral delivery of Biological drugs targeting the lower GI tract

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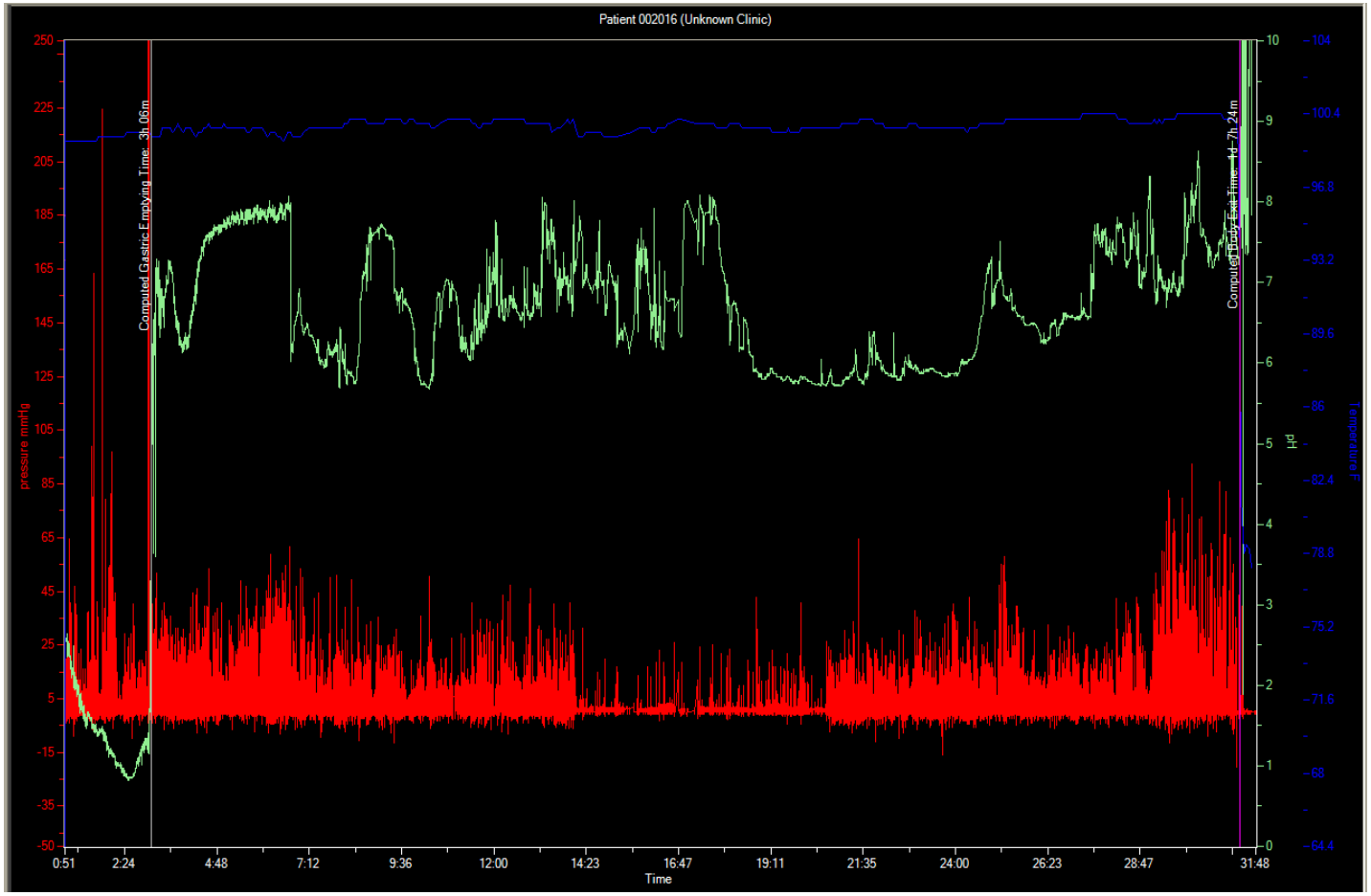
Typical Human GI tract pH profile



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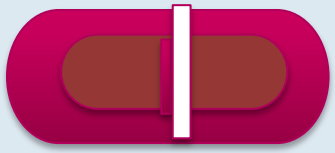
Better solution: GEMICEL™ Delivery System



- GEMICEL™ is an enabling delivery platform technology
  - Proprietary construction with potential to allow for pH sensitive targeted oral delivery of live biotherapeutics, vaccines, complex macromolecules as well as small molecules while protecting from acid/enzymatic degradation.

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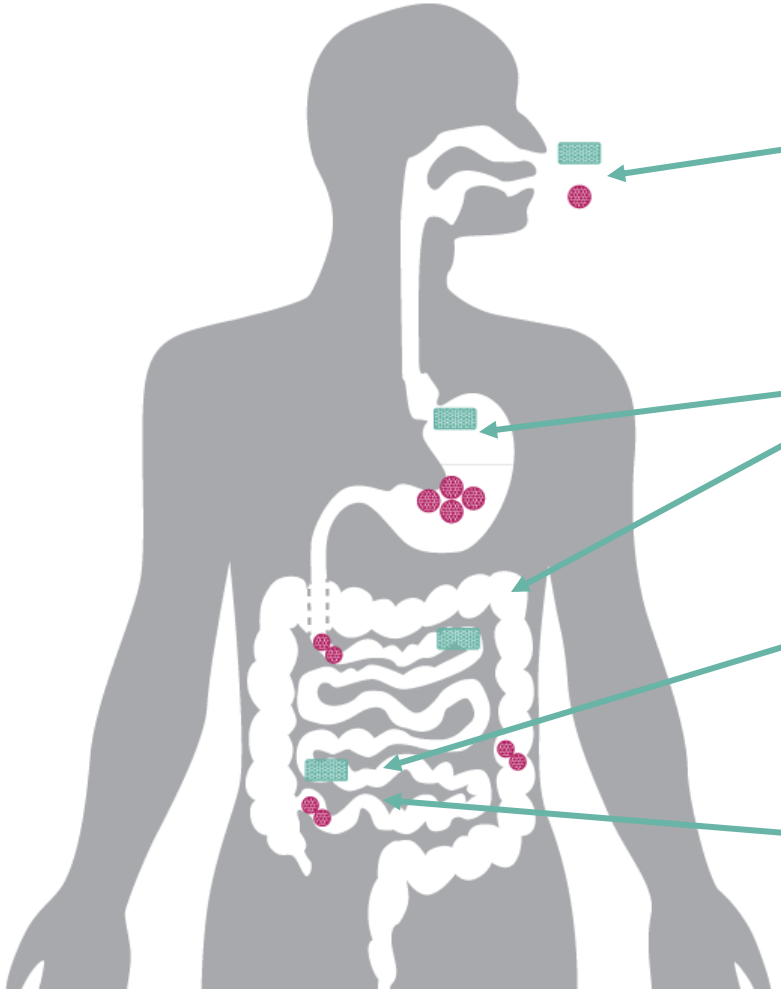
Distal Ileum/Colon Targeted Delivery Plan



Oral administration of colon targeted drug delivery system(s)

Remains intact in the stomach and upper small intestine

Release of the drug in the distal ileum/colon

Potential for High intraileal/colonic drug concentration, dose reduction, improved efficacy and high therapeutic index

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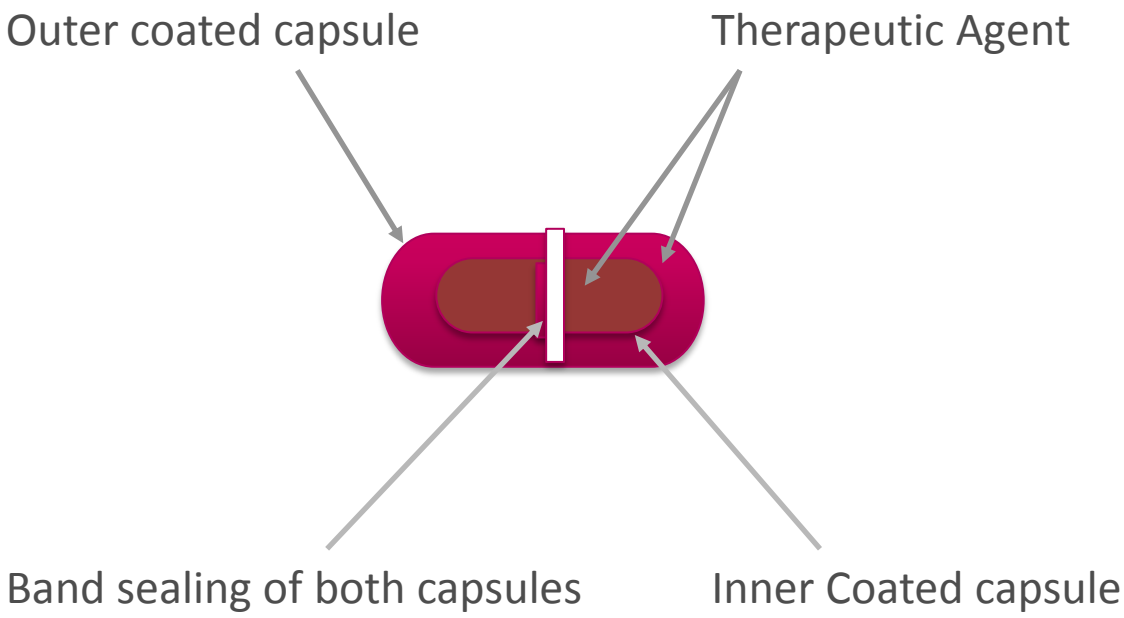
GEMICEL™ Bimodal Dosage form



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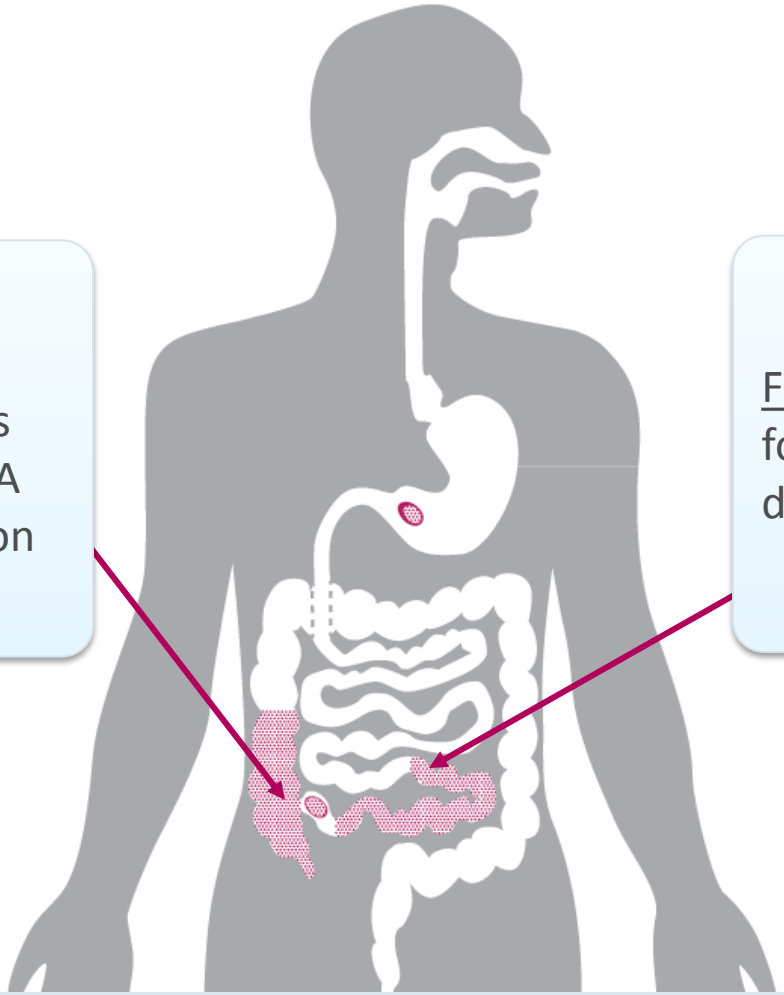
GEMICEL™ Formulation Strategy (Capsule-in-Capsule)

Second Inner Coated for bolus release of drug A or B in right colon



First Outer Coated for bolus release of drug A in Ileum

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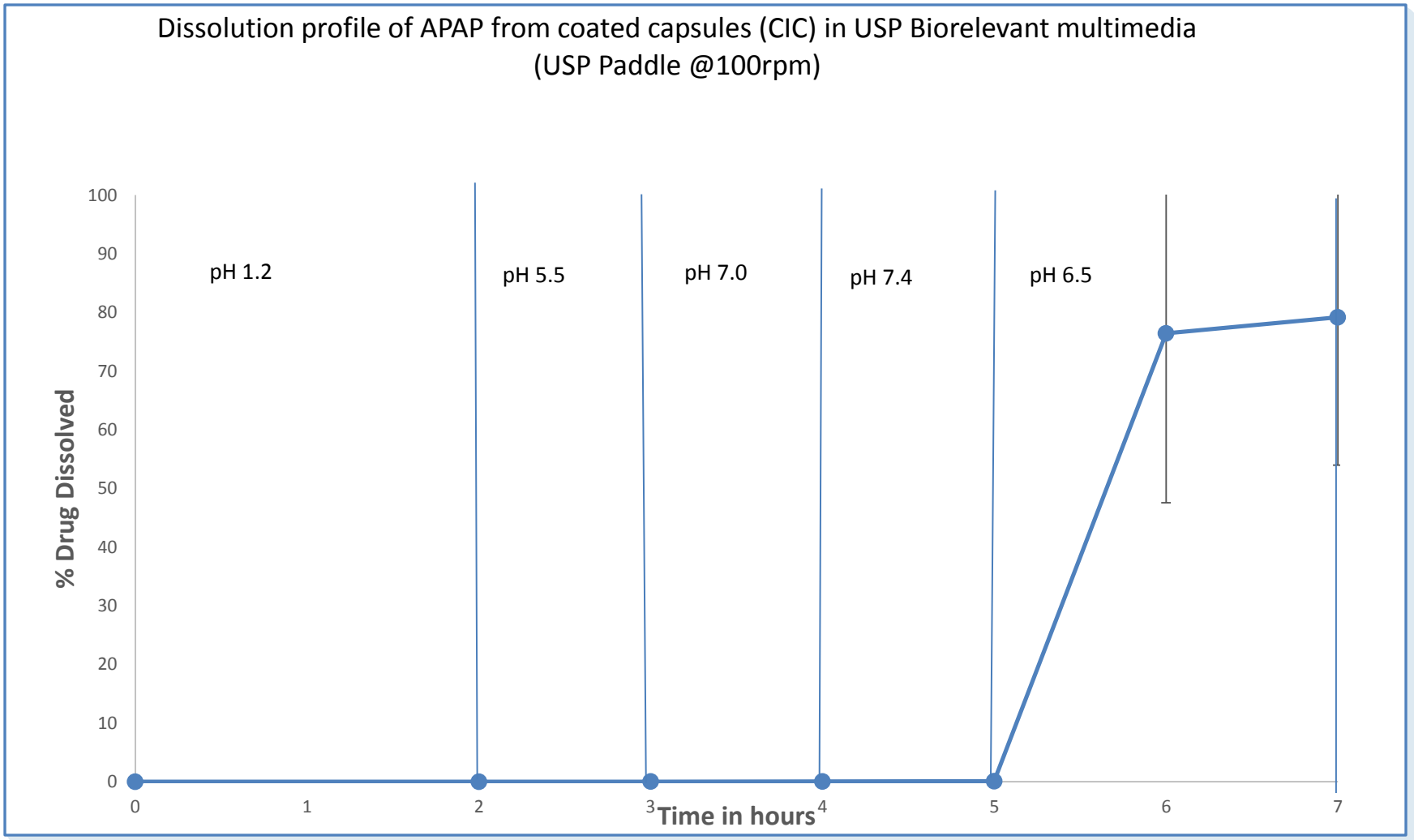
Evaluation of GEMICEL™ Delivery – In Vitro



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Evaluation of GEMICEL™ Delivery – Bacterial Viability

- Goal - Preservation of obligate anaerobes during product storage and testing
- Used *Oxalobacter formigenes* (commonly found in the human gut)
- Manufactured and stored coated capsules (CIC) at **37°C for 7 hours** to mimic pH dissolution testing
- Suspended the powders from capsules in buffer
- Compared bacterial CFUs of the 6 stressed coated with 6 uncoated capsules
- Result: no drop in CFUs after coating and storage

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Evaluation of GEMICEL™ Delivery – Human Scintigraphy

- Human clinical study: Single center, open label, in healthy male subjects (n=9).

- Test articles and administration (Oral route)
  - A solution containing surrogate radiolabeled Tc-99m marker
  - IntelliCap® pH capsule
  - A GEMICEL™ capsule containing radiolabeled ^{177}Lu and ^{153}Sm
  - Food

- Gamma scintigraphy evaluation of GEMICEL™ release

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GEMICEL™: Three formulations evaluated

Characteristics	Outer Capsule (Lutetium and Excipients)	Inner Capsule (Samarium and Excipients)
Target delivery A	**Distal ileum**	**Proximal Colon (Cecum)**
Coating thickness A	Thick. Dual polymer system	Thin Single polymer system
Target delivery B	**Distal ileum**	**Colon (cecum to hepatic flexure)**
Coating thickness B	Thick Dual polymer system (Same as A)	Thick Single polymer system (Same as A)
Target delivery C	**Proximal ileum**	**Colon (cecum to hepatic flexure)**
Coating thickness C	Thicker Dual polymer system (different from A and B)	Thick Single polymer system (Same as A)

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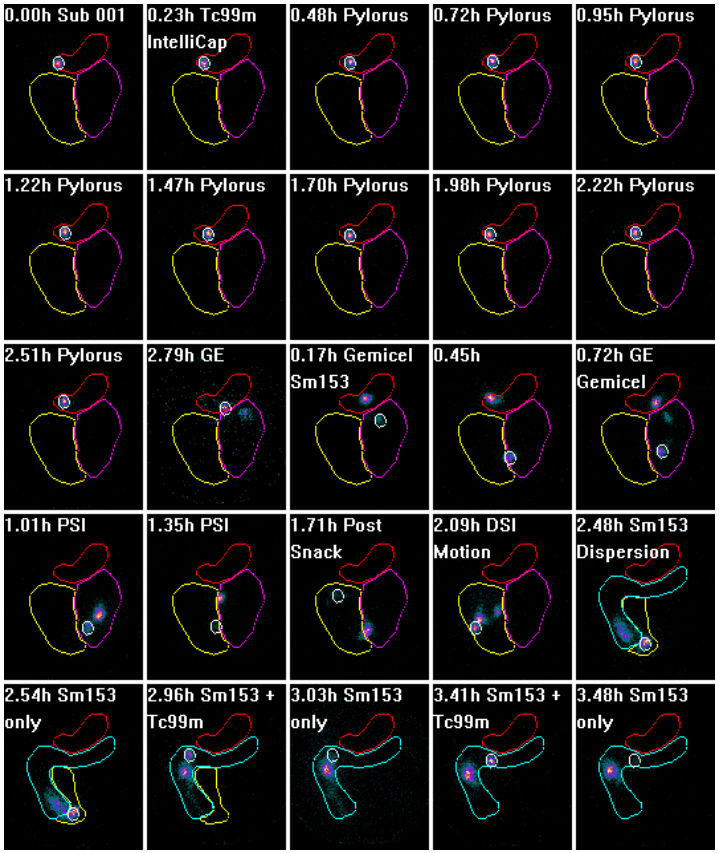
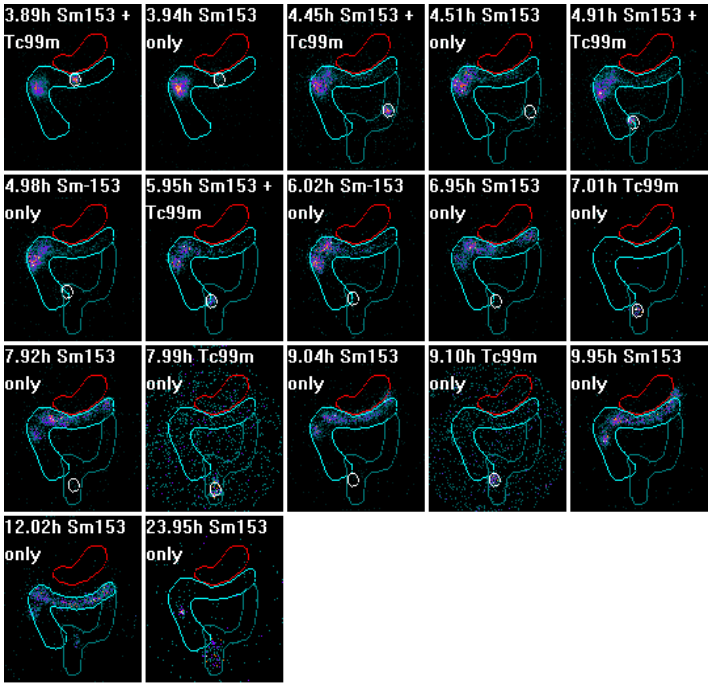
Human Scintigraphy (representative) data

- GEMICEL™(Sm-153)





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Gastric Emptying Times - GEMICEL™ Formulations A, B and C

Subject #	Formulation A		Formulation B		Formulation C	
	IntelliCap GE (hrs)	GEMICEL GE (hrs)	IntelliCap GE (hrs)	GEMICEL GE (hrs)	IntelliCap GE (hrs)	GEMICEL GE (hrs)
001	2.78	0.72	0.98	0.63	3.45	1.55
002	0.23	0.93	0.23	3.30	0.47	0.47
003	0.42	1.01	0.52	0.62	0.52	0.92
004	0.45	1.70	0.22	0.40	1.97	0.34
005	0.47	0.21	0.97	0.30	0.25	0.39
006	0.68	0.49	0.50	0.66	0.48	0.38
007	0.05	0.17	0.97	0.17	0.50	0.64
008	0.97	0.95	0.22	0.23	0.25	0.44
009	3.82	0.37	0.30	>2.32	0.25	0.66
Avg	1.10	0.73	0.55	0.43	0.90	0.64
SD	1.30	0.48	0.34	0.21	1.09	0.39

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GEMICEL™ Formulations A, B & C – Summary of Release Location

Characteristics	Outer Capsule	Inner Capsule
Target delivery A	**Distal ileum**	**Colon (Cecum to Hepatic Flexure)**
Actual release location in subjects	• 9/9 preserved in stomach, duodenum & jejunum • 5/9 in distal ileum • 3/9 in proximal ileum; • 1/9 release in colon (cecum)	• 4/9 in colon (cecum to hepatic flexure) • 5/9 in distal ileum
Target delivery B	**Distal ileum**	**Colon (Cecum to Hepatic Flexure)**
Actual release location in subjects	• 7/9 preserved in stomach, duodenum & jejunum • 6/9 in distal ileum • 1/9 in proximal ileum	• 6/9 in colon (cecum to hepatic flexure) • 1/9 in distal ileum
Target delivery C	**Proximal ileum**	**Colon (Cecum to Hepatic Flexure)**
Actual release location in subjects	• 9/9 preserved in stomach, and duodenum; • 3/9 in proximal ileum; • 3/9 in jejunum • 3/9 in distal ileum	• 9/9 in colon (cecum to hepatic flexure)

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GEMICEL™ technology - Overall conclusions

- The formulation has been validated for distal delivery
- Potential applications:
  - Enables oral delivery of live therapeutics, vaccines, complex macro molecules as well as small molecules
  - Delivers high bolus doses in a reproducible manner
  - Formulation process is both scalable and relatively low cost

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Microbiome Anticipated Clinical Candidate For rCDI

- Efficacy: AB-M101 oral capsules will incorporate select strains of vegetative bacteria with a goal of achieving similar efficacy and safety as FMT in the treatment of rCDI
- Therapy including both spore and non-spore forming bacteria, delivered specifically to the lower GI tract
- Anticipate that AB-M101 will be scalable, cost efficient, reliable and consistent
- Patients may prefer oral dosing

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