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
Misconception: GI Delivery Easy

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

<table>
<thead>
<tr>
<th>6 meters</th>
<th>1.5M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine: complex physiology and pH</td>
<td>Large intestine: Complex flora</td>
</tr>
</tbody>
</table>

- 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
Conventional Dosage Forms

Oral administration of conventional dosage form(s) for colonic-related disorders

Release of the drug in the stomach

Absorption of the drug either in the stomach or small intestine

Low intracolonic drug concentration, variable efficacy, low therapeutic index and side effects
# Diverse Approaches in Lower GI Delivery

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

*Novel approaches required for oral delivery of Biological drugs targeting the lower GI tract*
Typical Human GI tract pH profile
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.
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
GEMICEL™ Bimodal Dosage form

- Outer coated capsule
- Therapeutic Agent
- Band sealing of both capsules
- Inner Coated capsule
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
Evaluation of GEMICEL™ Delivery – In Vitro

Dissolution profile of APAP from coated capsules (CIC) in USP Biorelevant multimedia (USP Paddle @100rpm)

% Drug Dissolved

Time in hours

pH 1.2
pH 5.5
pH 7.0
pH 7.4
pH 6.5
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
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
### GEMICEL™: Three formulations evaluated

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Outer Capsule (Lutetium and Excipients)</th>
<th>Inner Capsule (Samarium and Excipients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target delivery A</strong></td>
<td>Distal ileum</td>
<td>Proximal Colon (Cecum)</td>
</tr>
<tr>
<td>Coating thickness A</td>
<td>Thick. Dual polymer system</td>
<td>Thin Single polymer system</td>
</tr>
<tr>
<td><strong>Target delivery B</strong></td>
<td>Distal ileum</td>
<td>Colon (cecum to hepatic flexure)</td>
</tr>
<tr>
<td>Coating thickness B</td>
<td>Thick Dual polymer system (Same as A)</td>
<td>Thick Single polymer system (Same as A)</td>
</tr>
<tr>
<td><strong>Target delivery C</strong></td>
<td>Proximal ileum</td>
<td>Colon (cecum to hepatic flexure)</td>
</tr>
<tr>
<td>Coating thickness C</td>
<td>Thicker Dual polymer system (different from A and B)</td>
<td>Thick Single polymer system (Same as A)</td>
</tr>
</tbody>
</table>
Human Scintigraphy (representative) data

- GEMICEL™ (Sm-153)
# Gastric Emptying Times - GEMICEL™ Formulations A, B and C

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Formulation A</th>
<th>Formulation B</th>
<th>Formulation C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IntelliCap GE (hrs)</td>
<td>GEMICEL GE (hrs)</td>
<td>IntelliCap GE (hrs)</td>
</tr>
<tr>
<td>001</td>
<td>2.78</td>
<td>0.72</td>
<td>0.98</td>
</tr>
<tr>
<td>002</td>
<td>0.23</td>
<td>0.93</td>
<td>0.23</td>
</tr>
<tr>
<td>003</td>
<td>0.42</td>
<td>1.01</td>
<td>0.52</td>
</tr>
<tr>
<td>004</td>
<td>0.45</td>
<td>1.70</td>
<td>0.22</td>
</tr>
<tr>
<td>005</td>
<td>0.47</td>
<td>0.21</td>
<td>0.97</td>
</tr>
<tr>
<td>006</td>
<td>0.68</td>
<td>0.49</td>
<td>0.50</td>
</tr>
<tr>
<td>007</td>
<td>0.05</td>
<td>0.17</td>
<td>0.97</td>
</tr>
<tr>
<td>008</td>
<td>0.97</td>
<td>0.95</td>
<td>0.22</td>
</tr>
<tr>
<td>009</td>
<td>3.82</td>
<td>0.37</td>
<td>0.30</td>
</tr>
<tr>
<td>Avg</td>
<td>1.10</td>
<td>0.73</td>
<td>0.55</td>
</tr>
<tr>
<td>SD</td>
<td>1.30</td>
<td>0.48</td>
<td>0.34</td>
</tr>
</tbody>
</table>
## GEMICEL™ Formulations A, B & C – Summary of Release Location

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<th>Characteristics</th>
<th>Outer Capsule</th>
<th>Inner Capsule</th>
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<tbody>
<tr>
<td><strong>Target delivery A</strong></td>
<td>Distal ileum</td>
<td>Colon (Cecum to Hepatic Flexure)</td>
</tr>
</tbody>
</table>
| 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) |
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
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