Formulation Strategies for Solid Oral Drug Products to Prevent or Treat Diseases of the Gut Microbiome

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“Pioneering elegant solutions that leverage the microbiome to improve global health”
Targeted, oral delivery of medicines to the gut microbiome

Excipient and enteric protection selection

Example 1: SYN-004 (ribaxamase), biological β-lactamase, for prevention of *C. difficile* infection (CDI)

Example 2: SYN-010, small molecule lovastatin lactone, targeting *M. smithii*, for Irritable Bowel Syndrome with Constipation (IBS-c)
Clinicaltrials.gov search term “gut microbiome”:
349 clinical trials in US
1,317 clinical trials Worldwide
Oral Delivery of Biological Products to be Absorbed

Holy Grail: to deliver biological medicines systemically via oral route: No needles, no inhalers, etc.

**Classic example: Insulin**
First tried in humans in 1922, with poor results
Drug developers still trying, making limited progress

**Barriers to absorption:**
Physical:
- mucous layer
- intestinal epithelium
- tight junctions

Biochemical:
- low pH
- digestive enzymes (proteases)

Formulation:
- chemical modification (eg. PEG)
- co-administration with protease inhibitors, permeation enhancers
- microspheres, liposomes, nanoparticles
Oral Delivery of Biological Products to the Gut

Marketed oral enzymes and their excipients:

**Beano®** (α-galactosidase): mannitol, povidone, corn starch, water, sodium stearyl fumarate, polyvinyl acetate, less than 1% of: maltodextrin, silicon dioxide, calcium gluconate, triacetin, natural & artificial flavor, red no. 40 lake, acetic acid, sodium lauryl sulfate.

**Lactaid®** (lactase): Microcrystalline Cellulose, Croscarmellose Sodium, Crospovidone, Magnesium Stearate, Colloidal Silicon Dioxide.

**Creon®** (pancreatic replacement enzymes: lipase, protease, amylase): cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, triethyl citrate.

Each of these are aids to digestion, but do not target the gut microbiome.
Considerations for Targeted Delivery of Biological Drugs

**Drug Product Release:**
- pH at target region
- Time (GI transit)
- Osmotic pressure
- Enzymatic (chitinase)
- Combination of these

- Excipients can deliver via these mechanisms
- Compatibility with active ingredient

- Coated capsules, coated tablets, coated spheres, coated microspheres
  - Depends on indication, patient population, mfg. process

**Drug Substance:**
- Stability of chemical or biological: engineered for stability
- Solubility in intestinal environment
- Activity in intestinal environment: pH ~4.8 to 8.2
- Variability of target molecule/organism presence
Pharmaceutical Excipients: Properties and Testing

Technological Factors
- Particle size
- Surface area
- Crystal structure
- Flowability
- Compressibility
- Porosity
- Moisture content

Analytical Factors
- Chemical analysis
- Impurities analysis
- Structural analysis
- SEM imaging
- Thermo analysis
- NMR, FTIR

Stability Factors
- pH stability
- Moisture activity
- Solid state stability
- Degradation forces
- Microbial limits

Compatibility testing
Formula optimization
Robust formulations

Active Ingredient
**Enteric Coating Polymers to Target Desired Release Profile**

**Enteric protection:**

Eudragit, based on methacrylic acid polymers
- Stomach
- Duodenum
- Jejunum
- Ileum, colon

HPMC phthalate
Ethycelulose
Polyvinyl acetate phthalate

From: Evonik Industries
SYN-004 (ribaxamase)
**Clostridium difficile**

*C. difficile* infection (CDI), *C. difficile*-associated disease (CDAD)

- Gram positive, spore forming bacteria
- Leading cause of antibiotic associated diarrhea
- Elaborates three primary toxins: Toxin A, Toxin B, and binary toxin
- Antibiotic resistance is a growing concern:
  - *Diarrhea*  *Pseudomembranous Colitis*
  - *Toxic Megacolon*  *Death*
Disruption of the Gut Microbiome Can Lead to \textit{C. difficile} Infection

- IV Antibiotics
- Probiotics & Prebiotics
- Dysbiosis
- FMT & Bacterial Replacement Therapy
- Antibiotics & Vaccines
- mAbs & Vaccines
- ribaxamase
Ribaxamase (SYN-004)

Orally administered, $\beta$-lactamase enzyme (29 kDa) that is designed to degrade penicillins and cephalosporins

- Formulated for oral delivery with release at pH ≥ 5.5 (proximal small intestine)
- Expected to be administered during, and after administration of certain intravenous (IV) $\beta$-lactam-containing antibiotics, like ceftriaxone
- Intended to degrade the residual antibiotics that are excreted into the small intestine via the bile duct
- Designed to prevent disruption of the healthy gut microbiome and thus protect from opportunistic GI pathogens like *C. difficile*

[Diagram of penicillin degradation by ribaxamase]
Desired Formulation Profile:

- Solid oral dosage form
- High dose of SYN-004
- Protection of active enzyme in gastric environment
- Multi-particulate
- Release in duodenum and proximal small intestine
- Simple, safe, well-known, readily available excipients
- Favorable stability for 2+ year shelf-life
- SYN-004 DS is purified from *E.coli*, supplied as liquid in phosphate buffer

Capsule containing:

- Multi-particulate pellets
- Enteric coated
- SYN-004 layered
- 75mg per capsule
SYN-004 (ribaxamase) Formulation Development (2)

SYN-004/Binder excipient screening/compatibility study using droplet film casting

**Binder excipients:**
Polyvinyl pyrrolidone (PVP) K-12
PVP K-25
PVP K-12 + glycerol
PVP K-12 + lactose
PVP K-12 + mannitol
PVP K-12 + sucrose
PVP K-12 + corn starch
PVP K-12 + PlasAcryl
Eudragit L30 D55 + glycerol
Eudragit NM 30D
HPC
HPMC

**Additional excipients:**
PEG 400
Triethyl citrate
Glycerol
1,2-propanediol
Glycerol monostearate
Polysorbate 80

**Enteric coat:**
Eudragit L30 D55

Binder excipients were mixed with several ratios of SYN-004 enzyme solution
In total, 123 free film castings were prepared and tested
Binder Excipient Screening; Compatibility with SYN-004

Casting of Free Films

**Polyvinyl pyrrolidone : SYN-004**

The binding excipient PVP K-12 was mixed with SYN-004 at ratios of:

1:1 (sample 22)
1:0.75 (23)
1:0.5 (24)
1:0.25 (25)
1:0.125 (26)

The films were dried to completion, stressed mechanically, and then photographed.

**Smoothness can predict success in fluid bed coating process**
The binding excipient HPC was mixed with SYN-004 at ratios of:

1:0.45 (sample 109)
1:0.40 (110)
1:0.35 (111)
1:0.30 (112)
1:0.25 (113)

The droplet films were dried to completion, stressed mechanically, and then photographed.

Smoothness can predict success in fluid bed coating process.
**Drug Layering on Sucrose Cores by Fluidized Bed Spray Application**

**SYN-004** with binder **PVP K-12**
Coated onto sucrose cores in a fluidized bed
Examined by SEM

Result:
Deep surface cracks, poor matrix uniformity
**Drug Layering on Sucrose Cores by Fluidized Bed Spray Application**

**SYN-004 with binder HPC**
Coated onto sucrose cores in a fluidized bed
Examined by SEM

Result:
Smooth surfaces, uniform density
Enteric Coating of Drug Layered Cores by Fluidized Bed Spray Application

**SYN-004** with binder **HPC**
Sprayed onto sucrose cores;
Cores sprayed with **Eudragit L30 D55**
Examined by SEM

Result:
Smooth surfaces, uniform density

Drug layer 200-250 µm thick
Enteric coating 40-50 µm thick
SYN-004 (ribaxamase) Oral Formulation

Solid Dosage Format
**In Vitro** Dissolution Profile of SYN-004 (ribaxamase)

- Early development Lot of SYN-004 enteric coated sucrose pellets
- USP Dissolution apparatus, type-2 (paddle)
Enteric-coated ribaxamase pellets remain intact at low pH, and the released enzyme retains biological activity for at least 6 hours in human intestinal chyme.
SYN-004 (ribaxamase) Publications/Presentations


SYN-010
SYN-010: Proprietary Modified-Release Lovastatin Lactone

Designed to reduce methane production by *M. smithii* in the intestine

*Bacteroides thetaiotaomicron* is one of many bacteria that ferment carbohydrates in the gut which releases $H_2$ and $CO_2$.

*Methanobrevibacter smithii* archea consumes hydrogen gas from *Bacteroides* and produces methane, which is lost from gut as “gas”.

Source: [commons.wikimedia.org/wiki/File:Intestine_and_stomach_-_transparent_-_cut.png](http://commons.wikimedia.org/wiki/File:Intestine_and_stomach_-_transparent_-_cut.png)
SYN-010 Formulation Design

Desired Formulation Profile:

- Solid oral dosage form
- Variable dose strength for Clin. Dev.
- Protection in gastric environment
- Dual pulse release: in duodenum and ileocecal junction
- Protect lovastatin lactone from conversion to the β-hydroxyacid (cholesterol lowering metabolite)
- Minimize or prevent systemic absorption
- Simple, safe, well-known, readily available excipients
- Favorable stability for 2+ year shelf-life

Lovastatin lactone API is supplied as dry powder
## Excipient Compatibility Testing

### Excipient Compatibility, Binary Mixing Study

Excipients were mixed with lovastatin lactone, subjected to stress conditions for 1 week, tested for degradation of lovastatin lactone

% β-hydroxyacid, by HPLC

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Excipient:</th>
<th>Day 0</th>
<th>5°C (7 days)</th>
<th>25°C/60% RH (7 days)</th>
<th>40°C/75% RH (7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB-18</td>
<td>N/A</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>SB-19</td>
<td>Pearlitol® 200SD</td>
<td>0.03</td>
<td>0.04</td>
<td>0.04</td>
<td>0.03</td>
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<tr>
<td>SB-20</td>
<td>Kollidon® VA64 Fine</td>
<td>0.04</td>
<td>0.05</td>
<td>0.04</td>
<td>0.05</td>
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<tr>
<td>SB-21</td>
<td>Kollidon® CL-F</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.06</td>
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<tr>
<td>SB-22</td>
<td>BHT</td>
<td>0.05</td>
<td>0.06</td>
<td>0.10</td>
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<tr>
<td>SB-23</td>
<td>Propyl Gallate</td>
<td>0.06</td>
<td>0.07</td>
<td>0.07</td>
<td>0.03</td>
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<tr>
<td>SB-24</td>
<td>Citric Acid Anhydrous</td>
<td>0.38</td>
<td>0.63</td>
<td>0.69</td>
<td>0.05</td>
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<tr>
<td>SB-25</td>
<td>AEROSIL® 200 Pharma</td>
<td>0.07</td>
<td>0.09</td>
<td>0.09</td>
<td>0.23</td>
</tr>
<tr>
<td>SB-26</td>
<td>EDTA</td>
<td>0.07</td>
<td>0.09</td>
<td>0.10</td>
<td>0.10</td>
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<tr>
<td>SB-27</td>
<td>PlasACRYL™ HTP20</td>
<td>0.08</td>
<td>0.12</td>
<td>0.12</td>
<td>0.22</td>
</tr>
<tr>
<td>SB-28</td>
<td>EUDRAGIT® L 30 D-55</td>
<td>0.11</td>
<td>0.19</td>
<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
<td>SB-29</td>
<td>EUDRAGIT® FS 30 D</td>
<td>0.11</td>
<td>0.18</td>
<td>0.19</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Excipients were blended with lovastatin lactone, compressed to 5mm round convex tablets, then tested.
SYN-010 Tablet Coating Trials

**Enteric coat:**

- Hydroxypropyl methylcellulose
- Eudragit L30 D55
- Eudragit FS30D
- Glycerol monostearate
- Triethyl citrate
- Polysorbate 80
- FD&C Blue #1, Aluminum lake (DR tablets only)

Core tablets were pan-coated, then tested

**Coated tablet testing:**

- Weight gain on coating
- Weight gain in acid uptake, blistering
- Dissolution
- Degradation to β-hydroxyacid metabolite

<table>
<thead>
<tr>
<th>Batch #</th>
<th>Coat Loading (% w/w)</th>
<th>Weight of 6 Tablets Pre Acid Media (mg)</th>
<th>Weight of 6 Tablets Post Acid Media (mg)</th>
<th>Weight Gain (%)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANH-055</td>
<td>6.28</td>
<td>329.5</td>
<td>350.9</td>
<td>6.5</td>
<td>Blistering of coat visible</td>
</tr>
<tr>
<td>ANH-051</td>
<td>8.60</td>
<td>333.7</td>
<td>350.9</td>
<td>5.2</td>
<td>Fully intact tablets</td>
</tr>
<tr>
<td>ANH-052</td>
<td>10.38</td>
<td>337.0</td>
<td>353.8</td>
<td>5.0</td>
<td>Fully intact tablets</td>
</tr>
<tr>
<td>ANH-053</td>
<td>14.61</td>
<td>355.4</td>
<td>367.3</td>
<td>3.3</td>
<td>Fully intact tablets</td>
</tr>
</tbody>
</table>
SYN-010 Tablet Formulation

Solid Dosage Form

**SYN-010** lovastatin lactone compressed with dry excipients; Uncoated cores sprayed with **Eudragit L30 D55** or **Eudragit FS30D**; Examined by SEM

Result:
Tight, uniform matrix density
Smooth coated surface
In Vitro Dissolution Profile of SYN-010

- Early development Lot of SYN-010 enteric coated tablets, encapsulated
- USP Dissolution apparatus, type-2 (paddle)

1 x DR (pH 5.5-coated) tablet plus 5 x ICR (pH 7.0-coated) tablets combined in 1 x HPMC capsule (size 1) with a wire sinker
SYN-010 Oral Dosage Format

Desired Formulation Profile:

- Solid oral dosage form
- Variable dose strength for Clin. Dev.
- Protection in gastric environment
- Dual pulse release: in duodenum and ileocecal junction
- Protect lovastatin lactone from conversion of the to β-hydroxyacid (cholesterol lowering metabolite)
- Minimize or prevent systemic absorption
- Simple, safe, well-known, readily available excipients
- Favorable stability for 2+ year shelf-life

Capsule containing:

- 7mg tablet coated for release in duodenum (L30 D55)
- 7mg tablet coated for release in ileocecal junction (FS30D)
- Targeted API delivery can be dosed up or down in 7mg units
SYN-010 Publications/Presentations


• V. Wacher, et al. Pharmacokinetics of SYN-010 modified-release lovastatin lactone in healthy volunteers: methane-reducing drug levels are delivered to the colon at doses that alleviated symptoms of irritable bowel syndrome with constipation (IBS-C) in Phase 2a clinical trials. JDDW (2017).

• V. Wacher, et al. SYN-010, a Proprietary Modified-Release Formulation of Lovastatin Lactone, Lowered Breath Methane and Improved Stool Frequency in Patients with IBS-C. APDW (2016).

Conclusions

- Oral drug products for localized gut microbiome activity are an increasing new class of drug products
- Need for targeted intestinal delivery is important
- Whether a biological or small molecule, formulation is critical:
  - Protection from stomach
  - Desired release profile
  - Stability in intestinal environment
  - Limited absorption or non-absorbed
  - Co-localization to the drug’s target molecule or organism
- Considerations include excipient selection, compatibility screening studies, optimization studies, analytical methodology
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Questions?