Oral Delivery Update
New Technologies / Old Approaches

• Introduction
  • Market Preference and Precedence
  • Peptide Properties and Challenges
• Old Approaches - Development Examples
• Peptides for Localized Oral Delivery
• Marriage of New Peptide and Old Approaches
• New Technologies and Opportunities
Market Preference for Delivery Technology Approaches

Simple >> Complex
Once per day > BID >>> TID

Market Preference

Patients ~ Doctors

Injection

Oral

Nasal
Buccal
Sublingual
Transdermal
Limited Non-Invasive Precedents
No Significant Oral Peptide...Yet
Peptides and Delivery Needs

- Typically water soluble > 1 mg/ml
- Stability in solution is often limited (2-8C storage)
- Half-life typically 1 to 2 hrs (unmodified a.a.)
- Immunogenicity a concern for larger peptides
- First drug product is usually solution for injection
- Life cycle interest in non-injection / sustained release injection
Common Challenges for Oral Delivery of Peptides

- Variability in exposure (Cmax, AUC, Tmax)
- Food effect on permeation enhancing technologies
- Low bioavailability impact on cost and mfg scale
- Stability of peptide in standard oral formulations
- Maturity of the technology (commercial or clinical?)
- Scale up experience, manufacturing systems
- Regulatory experience (some new excipients)
Peptide and Oral Delivery Technology Evolution

| Semaglutide - Long-acting Peptide and Permeation Enhancer & Linaclotide - Stable Peptide for Local Oral Delivery | Microneedles and Long-Acting Peptides Others???
|---|---|
| Salmon Calcitonin and Octreotide in Permeation Enhancing Systems | Microneedle Advances Applied to Oral Delivery (Rani, MIT)

New Delivery Approaches

Improvements in Peptide Structure
Peptide and Oral Delivery Technology Evolution

**Semaglutide** - Long-acting Peptide and Permeation Enhancer & **Linaclotide** - Stable Peptide for Local Oral Delivery

**Salmon Calcitonin and Octreotide in Permeation Enhancing Systems**

**Microneedles and Long-Acting Peptides Others??**

**Microneedle Advances Applied to Oral Delivery (Rani, MIT)**

**New Delivery Approaches**
Peptides in Permeation Enhancing Technology for Systemic Delivery

- Many technologies evaluated in last 20 to 40 years
  Most focused on permeation enhancing excipients
  - Mechanistic focus on transiently opening tight junction
  - sCT focus from Unigene, now Enteris and Tarsa Therapeutics
  - Octreotide focus from Chiasma

- Some exceptions
  - Emisphere technology – SNAC excipients
    - Mechanism somewhat unclear – not tight junction opening
    - Potentially exposing hydrophobic surfaces to enhance absorption
  - Generex – liposomal buccal spray formulation

- Summary – despite significant effort
  - Bioavailability still substantially less than 5% versus SC injection
sCT Oral Formulation
Tarsa Ther. (Enteris / Unigene)

- Bioavailability ~ 1% vs SC
- Phase 3 study: 200 microgram
- Food effect – reduction in exposure

MW 3431.85 g/mole

Ref: Osteoporos Int, volume 25, issue 11, pages 2649-2656
Octreotide Oral Formulation
Chiasma Phase 3 program

- **Bioavailability ~ 0.5% vs SC**
- **Phase 3 study: 40 mg QD and BID (80 mg)**
- **Food effect – 90% reduction in exposure**

Single Dose Human PK
3, 10, 20 mg

Single Dose Human PK
20 mg Oral Compared with 0.1 mg SC

Ref: J Clin Endocrinol Metab, July 2012, 97(7):2362–2369
Linaclotide Example
Peptides for Local Oral GI Delivery

- Take advantage of peptide properties – no oral absorption
- Ironwood focused on GI disease (as well as others)
  - Inflammatory bowel disease, chronic constipation, etc...
  - Platform focus on guanylate cyclase-C agonists
- Linaclotide shows no oral bioavailability
  - Immediate release capsule formulation, standard excipients
  - 290 micrograms sprayed onto microcrystalline cellulose pellets
  - Technology focused on stability of peptide and process technology
  - Amorphous peptide dissolves quickly in gut
  - RT stability for 2 years

C59H79N15O21S6
MW 1526.8 g/mole
12.3 Pharmacokinetics

Absorption
LINZESS is minimally absorbed with low systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma are below the limit of quantitation after oral doses of 145 mcg or 290 mcg were administered. Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (Cmax), and half-life (t1/2) cannot be calculated.

Distribution
Given that linaclotide plasma concentrations following therapeutic oral doses are not measurable, linaclotide is expected to be minimally distributed to tissues.
Peptides with Long Half-Life in Permeation Enhancer Technology

- Peptides for chronic disease move to longer half-life
  - GLP-1 is a good example (all human half-lives by SC injection)
  - GLP-1 native half-life ~1-2 minutes
  - Exenatide half-life 1 to 2 hours (BID administration) 10 to 20 ug dose
  - Liraglutide half-life 13 hours (QD administration) 1 to 2 mg dose
  - Semaglutide half-life 165 hours (weekly administration) 0.25 to 1 mg
- Oral delivery of long-acting peptide relies on low dose
  - Novo has done a good job at optimizing albumin binding to lower dose
Native GLP-1: $t_{1/2}$ 2 min (IV)

Exenatide (Byetta): $t_{1/2}$ 1-2 hrs (SC)

Liraglutide (Victoza): $t_{1/2}$ 13 hrs (SC)

Semaglutide: $t_{1/2}$ 165 hrs (SC)

Vilsbøll T et al. JCEM 2003;88:220-224


Semaglutide for Oral Delivery
Novo optimized GLP-1

- Bioavailability ~ 0.25% vs SC
- Phase 2 study: 2.5 to 40 microgram orally
  - 40 mg Oral compares to 0.25 to 0.5 mg SC
- Standard permeation enhancing technologies
- Likely to experience food effect – may not be as important
- Novo relying on ability to manufacture recombinant GLP-1 cost effectively
- Structure is similar to Liraglutide
  - Acylated GLP-1 for albumin binding
  - Albumin binding optimized by changing alkyl structure and linker to albumin binder
Peptide and Oral Delivery Technology Innovation

- **Semaglutide**: Long-acting Peptide and Permeation Enhancer
- **Linaclotide**: Stable Peptide for Local Oral Delivery
- **Salmon Calcitonin and Octreotide**: in Permeation Enhancing Systems

**Microneedles and Long-Acting Peptides**

- Others???
- **Microneedle Advances Applied to Oral Delivery** (Rani, MIT)

**New Delivery Approaches**

**Improvements in Peptide Structure**
Oral Delivery Innovations

• **Greatest leap forward is from engineers**

• **Microneedle as an approach for oral delivery**
  - Capsule formulation / device containing pH activated microneedles
  - Rani Therapeutics (dissolving microneedles)
  - Bob Langer and MIT group

• **Addresses two of the three major issues of oral delivery**
  - Biologic protected from gastric fluid until released (stability)
  - Microneedles poke hole in lumen of gut and directly deliver drug (BA)

• **Risks**
  - Technology risk – very early exploratory studies, limited PK data
  - No safety data – safety of regularly penetrating lumen of gut
  - Drug loading, device complexity, manufacturing complexity
Rani Therapeutics
Dissolving Microneedle Approach

- Microneedle is crystalline solid
  - Peptide stability is good
- Enteric coated capsule is used
  - pH trigger as expected
- Microneedle and capsule release mechanism are new technique
- Bioavailability >50% vs SC
- Large biologics possible
- Long half-life opportunity

Rani Therapeutics comes from Mir Imran’s Incube Labs

www.ranitherapeutics.com
MIT Group
Metal Microneedles

- Microneedle is solid or hollow
- Group has an agreement with Novo to develop

MIT Group:
Bob Langer, Daniel Blankschtein, Daniel Anderson, Avraham Schroeder, Carlo Traverso, Baris Polat, Carl Schoellhammer

Ref: Traverso et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:362–367, 2015
Oral Peptide Delivery Summary

• Bioavailability still quite limited (e.g. 2% sCT)
  • Notwithstanding the potential success of the microneedle approach

• Permeation enhancers are still primary approach
  • Leads to sharp and narrow PK profiles
  • Unless molecules are engineered to long half-life (Novo)

• Promise of microneedle approach is significant
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