Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement

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03.29.11
Presentation Outline

- Strategies for Oral Delivery and Bioavailability Enhancement of Poorly Soluble Drugs
  - Drug Substance Modification
  - Drug Formulation Technologies

- Softgel Technology for Lipid-Based Oral Drug Delivery Systems - Current Approaches

- Softgel Technology for Lipid-Based Oral Drug Delivery Systems - Future Approaches

- Summary

- Q&A
NCE Outlook– Poorly Water-Soluble Drugs

**New Chemical Entities**

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

- **BCS Class I** (~5%)
- **BCS Class II** (~70%)
- **BCS Class III** (~5%)
- **BCS Class IV** (~20%)

L. Benet, Predicting Drug Disposition by Application of BDDCS, AAPS, 2008
Strategies For Oral Delivery of Poorly Soluble Drugs

- **Depend on unique properties of every drug substance**
  - Physical – physical state (melting point); crystal form (polymorph); particle size distribution and surface area; physical stability (hygroscopicity)
  - Chemical – salt form; molecular weight; solubility (aqueous, pH solubility profile, intrinsic dissolution); chemical stability; compatibility with excipients
  - Biological – mechanism of absorption (passive diffusion or active transport); site of absorption; first-pass metabolism; efflux; enterohepatic circulation; drug dosing requirements
Strategies For Oral Delivery of Poorly Soluble Drugs

- **Drug Substance Modification**
  - Salts
  - Crystal Forms (polymorphs)
  - Amorphous Form
  - Hydrates or Solvates
  - Prodrugs
  - Cocrystals
Strategies For Oral Delivery of Poorly Soluble Drugs

- **Formulation Strategies**
  - Lipid-based drug delivery systems
  - Nanocrystals
  - Solid solutions/dispersions
  - Solid-lipid nanoparticles
  - Inclusion complexes (cyclodextrins), etc.

- **Dosage Form Options**
  - Softgel capsules (gelatin or plant-based)
  - Hardshell capsules (gelatin, HPMC, plant-based; liquid or powder filled)
  - Oral solutions or suspensions
  - Tablets
Softgel Technology for Lipid-Based Drug Delivery Systems – Current Approaches

Lipophilic excipients and resulting formulations are most often liquid or semi-solid in nature

Proven dosage form for lipid-based formulation

- Good developability (compatible with a wide range of excipients and formulations)
- Good manufacturability (number of NDA approved products and unit volumes)
- Uncompromised in-vivo performance (fast release of fill formulation)
## Lipid-Based Drug Delivery Systems

### Classification:

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type IIIA</th>
<th>Type IIIB</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides or mixed</td>
<td>100</td>
<td>40-80</td>
<td>40-80</td>
<td>&lt;20</td>
<td>N/A</td>
</tr>
<tr>
<td>glycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surfactants (HLB&lt;12)</td>
<td>N/A</td>
<td>20-60</td>
<td>N/A</td>
<td>N/A</td>
<td>0-20</td>
</tr>
<tr>
<td>Surfactants (HLB&gt;12)</td>
<td>N/A</td>
<td>N/A</td>
<td>20-40</td>
<td>20-50</td>
<td>30-80</td>
</tr>
<tr>
<td>Hydrophilic cosolvents</td>
<td>N/A</td>
<td>N/A</td>
<td>0-40</td>
<td>20-50</td>
<td>0-50</td>
</tr>
<tr>
<td><strong>In vivo behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance upon dispersion</td>
<td>Non-dispersing</td>
<td>Turbid</td>
<td>Clear or almost</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(droplet size 250-2,000)</td>
<td>clear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavior upon dispersion</td>
<td>Poor solvent capacity</td>
<td>Solvent capacity unaffected</td>
<td>Possible loss of solvent capacity</td>
<td>Likely loss of solvent capacity</td>
<td>Loss of solvent capacity</td>
</tr>
<tr>
<td>Digestibility</td>
<td>Crucial</td>
<td>Not crucial, likely</td>
<td>Less likely</td>
<td>Not likely</td>
<td>Not likely</td>
</tr>
</tbody>
</table>

*C.W. Pouton, 2006*
Lipid-Based Drug Delivery Systems Formulation

“Begin With The End In Mind”

- Achieving drug solubility in the formulation pre-administration
- Maintaining drug solubility in the formulation (or the formulation’s digestion products) post-administration

Liquid Technologies

- Lipid 82%
- Hydrophilic 18%
Lipid-Based Formulations for Solubility and Bioavailability Enhancement
Suspension Formulations
Example: Prometrium® Softgels 100, 200 mg (progesterone)

**API Physical-Chemical Properties**
- Molecular weight 314.47
- Practically insoluble in water
- Soluble in alcohol, acetone and dioxane; sparingly soluble in vegetable oils

**Finished Product**: 
- Micronized drug suspension in peanut oil, lecithin
- Tmax ~3 hours
- Absolute bioavailability unknown, estimated <10% (even after micronization, dispersion in LCT)
- Food effect (increased BA)
- Some patient-to-patient variability

*Data collected from Drugs@FDA, NDA 019781, patient package insert*
Lipid-Based Solution Formulations
Example: Avodart® Softgels 0.5 mg (dutasteride)

API Physical-Chemical Properties
- Molecular weight 528.5
- Hydrophobic (log P = 5.09)
- Solubility in water 0.038 ng/mL
- Soluble in ethanol (44 mg/mL), methanol (64 mg/mL), PEG 400 (3 mg/mL)

Finished Product*:
- Drug solution in mixture of mono-, diglycerides of caprylic and capric acid
- Tmax = 1-4 hours
- Absolute bioavailability ~60%
- Slight food effect
- Some patient-to-patient variability
- Better bioavailability than PEG 400 formulation

*Data collected from Drugs@FDA, NDA 021319, patient package insert
Self-Emulsifying Drug Delivery Systems

Formulation of Self-Emulsifying Drug Delivery Systems

- Lipid-Based “Preconcentrate” of Solubilized Drug
- Typical Composition
  - Lipid excipients
  - Surfactants (hydrophilic, high HLB)
  - Co-surfactants (lipophilic, low HLB)
  - Co-solvents (ethanol)

Desired Characteristics Upon Dilution With the G.I. Fluids

- Spontaneous Formation of Micro/Nanoemulsion
- Drug Stays in Solution and Does Not Precipitate
Softgels for Self-Emulsifying Lipid-Based Formulations Undergoing Lipolysis

Lipid formulation containing dissolved drug

Lipid formulation spontaneously emulsifies in gastric juice

Nano/Microemulsion (<100nm) disperses in stomach

Rapid process

Softgel Rupture: 5 to 10 minutes
Softgels for Self-Emulsifying Lipid-Based Formulations Undergoing Lipolysis

- Multilamellar vesicles
- Unilamellar vesicles
- Mixed micelles
- Lipase
- Bile salts
- Colipase

Lipolysing nano/microemulsion and vesicle droplets
Self-Emulsifying Drug Delivery Systems
Example: Cyclosporin A (the Neoral® Story)

API Physical-Chemical Properties
- High molecular weight (1202.63)
- Hydrophobic
- Poorly soluble in G.I. fluids

API Pharmacokinetic Properties
- Poor and variable absorption

Initially Introduced as a Lipid-based Formulation in a Softgel - Sandimmune®

Reformulated as a Microemulsion Preconcentrate in a Softgel - Neoral®
- Rapid gastric dispersion due to self-emulsifying properties
- Maintain drug in solution using a solvent system which prevents precipitation
- High drug concentration at the site of absorption
Pharmacokinetic Profiles for Sandimmune® and Neoral®

12 Fasting Human Volunteers; 150mg Dose
Effect of Food Intake on the Absorption of Sandimmune® and Neoral®

Neoral® is less affected by food intake
Lipid-based Formulations for Permeability and Bioavailability Enhancement

**Permeability Enhancement**

- Passive transport through enterocytes
- Passive transport around enterocytes (tight junctions)
- Enterocyte-based active transport and metabolic processes (P-gp, CYP3A4, lipoproteins)

**Bioavailability Enhancement – Alternate Absorption Routes**

- Lymphatic transport
Saquinavir (a P-gp substrate) oral bioavailability was significantly increased when co-administered with Cremophor EL


Average plasma concentration-time curves of a single dose of saquinavir 600 mg with co-administration of Cremophor EL® (○ 0 mg; ▲ 100 mg; ■ 1000 mg; ● 5000 mg)
Softgel Technology as a Delivery Tool for Lipid-Based Delivery Systems

GELATIN + Plasticizer + water

Lipophilic, Hydrophilic, or Mixed Vehicle

Solution, Suspension or highly viscous formula of Drug

Colors, Opacifiers, Flavors
Softgel Technology as a Delivery Tool

**Good NCE Candidates:**
- BCS class II and IV drugs
- Highly potent, low dose
- Oxygen sensitive
- Light sensitive
- Liquid or low melting point

**Other Advantages:**
- Proven technology
- Robust dosage form (no brittleness or leaking)
- Appropriate for low to high viscosity formulations (up to ~15,000 cps)
- Fill formulation temperature up to ~40°C
- Minimal to no scale-up issues
Modified Release Softgels Using Vegicaps® Capsule Technology

- Semi-solid/solid lipid fill matrix for modified drug release of poorly soluble and water-soluble drugs

- Compounds that exhibit a short half-life/frequent dosing or high peak blood levels/unacceptable side effects
Softgel Technology for Lipid-based Drug Delivery Systems – Future Approaches

Modified Release Softgels Using Vegicaps® Capsule Technology

Typical Composition of Gel/Shell

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP starch/carrageenan blend</td>
</tr>
<tr>
<td>Plasticizer</td>
</tr>
<tr>
<td>Water *</td>
</tr>
</tbody>
</table>

* Includes buffer salt
Vegicaps® Capsule Technology

Vegicaps® capsule shell polymer system undergoes thermal transitions at higher temperatures than traditional, gelatin-shell systems. This allows encapsulation of lipid fills at high temperatures that are semi-solid or solid-like at room temperature.

<table>
<thead>
<tr>
<th>Formula type</th>
<th>Base vehicle</th>
<th>Formulation characteristics at RT</th>
<th>Drug loading</th>
<th>Physical state of the formulation at 20°C</th>
<th>Physical state of the formulation at 40°C</th>
<th>Physical state of the formulation at 60°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sucrose acetate</td>
<td>Lipophilic, extremely viscous fluid</td>
<td>40-50%</td>
<td>Extremely viscous fluid</td>
<td>Extremely viscous fluid</td>
<td>Low viscosity fluid</td>
</tr>
<tr>
<td></td>
<td>isobutyrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PEG 6000</td>
<td>Hydrophilic, solid</td>
<td>35-43%</td>
<td>Solid</td>
<td>Solid</td>
<td>Viscous fluid</td>
</tr>
</tbody>
</table>
Vegicaps® Capsule Technology: Modified Drug Release Example

Fill Formulation:

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
</tr>
<tr>
<td>Mineral Oil</td>
</tr>
<tr>
<td>Paraffin Wax</td>
</tr>
<tr>
<td>Lipophilic Emulsifier</td>
</tr>
<tr>
<td>Hydrophilic Emulsifier</td>
</tr>
</tbody>
</table>
Vegicaps® Capsule Technology: Modified Drug Release Example

Comparison of Modified Release & Immediate Release Capsules: Single Dose in 8 Subjects

Modified Release Formulation Eliminates Drug Serum Spikes
Film Coated Softgels for the Targeted Delivery of Poorly Soluble, Poorly Permeable Drugs

- Post-gastric (targeted) drug delivery
- Protection of acid-labile drugs from gastric fluids
- Reduced local gastric side effects
- Potential for enhanced drug absorption
  - Rapid release of fill contents at targeted site of delivery following dissolution of film coat
  - High local concentrations of API and permeation enhancers
Softgel Film-coating Technology: Targeted Drug Release Example

**Fill Formulation**

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
</tr>
<tr>
<td><strong>Mono/Diglycerides of Capryl/Capric Acid</strong></td>
</tr>
<tr>
<td><strong>Caprylocapryl Macrogol Glycerides</strong></td>
</tr>
<tr>
<td><strong>Polysorbate 80</strong></td>
</tr>
</tbody>
</table>
Softgel Film-coating Technology: Targeted Drug Release Example

**Film Coat Formulation**

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L30D 55 Dispersion</td>
</tr>
<tr>
<td>PEG 400</td>
</tr>
<tr>
<td>Talc</td>
</tr>
<tr>
<td>Simethicone Emulsion</td>
</tr>
<tr>
<td>Purified Water</td>
</tr>
</tbody>
</table>

12% Weight Gain
## Softgel Film-coating Technology: Targeted Drug Release Example

### In-vitro Disintegration (min)

<table>
<thead>
<tr>
<th>USP &lt;701&gt;</th>
<th>T=0</th>
<th>T=3 mon</th>
<th>T=6 mon</th>
<th>T=9 mon</th>
<th>T=12 mon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGF, n=6</strong></td>
<td>No evidence of disintegration</td>
<td>No evidence of disintegration</td>
<td>No evidence of disintegration</td>
<td>No evidence of disintegration</td>
<td>No evidence of disintegration</td>
</tr>
</tbody>
</table>

**SGF**

**SIF**
In Summary...

• The bioavailability of poorly soluble drugs can often be enhanced from lipid-based formulations filled into softgels
• Self-emulsifying lipid-based formulations can enhance bioavailability and minimize absorption variability with little or no “food effect”
• Lipid-based solution or suspension formulations which are digested in-vivo by lipolysis can provide significantly improved bioavailability
• Bioavailability enhancement can be achieved by enzyme and/or efflux inhibition, modification of absorption route (lymphatic transport)
• Future approaches include modified delivery for improved safety and/or efficacy.
2010 AAPS Posters

- Manufacture of Phosal® MCT Softgels and Phosal® 50 PG Softgels and Stability Evaluation at Accelerated Conditions
- Effect of Kollicoat Protect Top-coat on Long-Term Physical Stability of Enteric Coated Softgels
- Gelatin-free Softgels: Compatibility Studies of SEDDS and SMEDDS Capsule Fill Formulations

*Cremophor is a registered trademark of BASF AG; Prometrium is a registered trademark of Solvay Pharmaceuticals, Inc.; Avodart is a registered trademark of Glaxosmithkline LLC; Neoral and Sandimmune are registered trademarks of Novartis AG; Vegicaps is a registered trademark of Catalent Pharma Solutions; Eudragit is a registered trademark of Evonik Roehm GmbH.*
Softgel Technology for Lipid-based Drug Delivery Systems

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Somerset, NJ
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