Oral Lipid-based Formulations

Addressing an Urgent Industrial Need

David J. Hauss, Ph.D.
Hauss Associates
Princeton, New Jersey USA
www.HaussAssociates.com

Tel. (609) 924-4213  Email: David.Hauss@verizon.net
Topics to be Covered

- Lipophilicity and pharmacologic efficacy
- Lipid digestion and hydrophobic drug absorption
- Food effect mitigation
- Formulation development and evaluation
- Current challenges and future prospects
<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
</table>
| - High solubility  
- High permeability | - Low solubility  
- High permeability |

<table>
<thead>
<tr>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
</table>
| - High solubility  
- Low permeability | - Low solubility  
- Low permeability |
Are biopharmaceutical properties limiting drug development?

Top 200 Marketed Drugs (USA) by BCS Category

- BCS I: 31%
- BCS II: 23%
- BCS III: 30%
- BCS IV: 6%
- Unc: 10%

NCE Prevalence by BCS Category

- BCS I: 5%
- BCS II: 70%
- BCS III: 20%
- BCS IV: 5%
The Problem

- Approximately 70% of all NCE are poorly water-soluble
  - Are we under-exploiting our richest source of potential drug products?
- Conventional formulations yield unacceptably low and variable bioavailability
  - Significant, positive food effect
But can’t we find more soluble compounds if we look harder?

- Work with the medicinal chemist to synthesize more water-soluble pharmacophores
  ✓ This assumes creation of a more soluble molecule is feasible!

- Is hydrophobicity really an undesirable property?
  ✓ May be correlated with high pharmacologic activity
‘Drug Development should not be Chemistry Driven….’

- Current drug development paradigms favor highly water soluble NCE’s
  - Driven by over-reliance on conventional formulation technology?

- What is being lost by failing to more fully exploit these compounds?
  - ‘Drug space’ is small relative to the total universe of chemical possibilities
The Universe of Chemical Possibilities vs. Drug Space or, what CombiChem taught us………

- Assuming just 150 hydrogen substitutions, there are a staggering $10^{29}$ possibilities!

- There are an estimated $10^{11}$ stars in the Milky Way and perhaps the same number of galaxies within the known universe.
# Pharma’s Favorite Drug Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Number of drugs (n = 483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPCRs</td>
<td>217</td>
</tr>
<tr>
<td>Enzymes</td>
<td>135</td>
</tr>
<tr>
<td>Hormones and factors</td>
<td>53</td>
</tr>
<tr>
<td>Unknown</td>
<td>34</td>
</tr>
<tr>
<td>Ion channels</td>
<td>24</td>
</tr>
<tr>
<td>Nuclear receptors</td>
<td>10</td>
</tr>
<tr>
<td>DNA</td>
<td>10</td>
</tr>
<tr>
<td>Product</td>
<td>BCS</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>Zyprexa®</td>
<td>2</td>
</tr>
<tr>
<td>Claritin®</td>
<td>2</td>
</tr>
<tr>
<td>Risperdal™</td>
<td>2</td>
</tr>
<tr>
<td>Imigran™</td>
<td>3</td>
</tr>
<tr>
<td>Cozaar®</td>
<td>1</td>
</tr>
<tr>
<td>Seretide®</td>
<td>2</td>
</tr>
<tr>
<td>Singulair®</td>
<td>1</td>
</tr>
<tr>
<td>Gastridin™</td>
<td>1</td>
</tr>
<tr>
<td>Zantac/Tagamet™</td>
<td>1</td>
</tr>
<tr>
<td>Zirtec™</td>
<td>1</td>
</tr>
<tr>
<td>BuSpar®</td>
<td>2</td>
</tr>
<tr>
<td>Gaster®</td>
<td>1</td>
</tr>
</tbody>
</table>
Non-aminergic GPCR’s.... an untapped treasure trove of new drugs?

- Important target which is under-represented by marketed drugs
  - *Ex.* CCR1-11, opioid (δ, κ, μ), endothelin, melanocortin

- Peptidic GPCR ligand properties are at odds with oral delivery
  - High MW, *high lipophilicity*, hydrogen bonding potential.
Classification of target families on the basis of optimized ligand physicochemical properties

J. Med. Chem. 2006, 49, 2969-2978
Why consider lipid-based formulations?
Biopharmaceutical Advantages

- Lipid-based formulations solubilize the drug in the excipient matrix
  - Substantial increase in drug absorption relative to conventional formulation
  - Eliminates variability associated with reliance on GIT for solubilization
    - Reduction / elimination of food effect
  - Reduction in cost and complexity of drug development

- Conventional formulations rely on GIT to solubilize drug
  - Deals with stable, crystalline form of drug
    - Reduce particle size
    - Salt formation
    - Other: Prodrug synthesis, complexing agent, physical form modification
Product Development Advantages

- **Does not require:**
  - Modification to NCE molecular structure
  - Complex or unfamiliar production procedures
    - Liquid-filled HGC readily prepared

- **Minimize environmental impact**
  - Solvent-free formulation process
  - Less un-absorbed drug ends up in the environment

- **Pharmaceutical grade excipients and manufacturing equipment readily available**
Lipid Digestion and Drug Absorption
Gastrointestinal Lipid Digestion

- Precedes lipid absorption
  - Hydrolyzes triglyceride to monoglyceride and free fatty acid
  - Facilitates emulsification of lipid by bile
- Critical process for the efficient absorption of hydrophobic drugs
Lipase
Bile Salt
Fatty Acid
Triglyceride
Monoglyceride
Viscous Isotropic Phase
Micellar Phase
Oil Phase

Adapted from: Eldem P and Speiser E Pharmazie 44:444-447 (1989)
Micellar Phase

Viscous Isotropic Phase
(Dietary lipid OR lipid formulation)

Oil Phase

Water Channel

Lipase

Adapted from: Eldem P and Speiser E Pharmazie 44:444-447 (1989)
Drug in Lipid

Drug in Mixed Micelle

Unstirred Water Layer
Food Effect Mitigation
The cancer drug lapatinib is, like many pills, supposed to be taken on an empty stomach. But University of Chicago oncologists say that patients who take it after eating might actually require less of the expensive drug: But taking it after a full meal would boost the amount of the drug circulating in the body by 167 percent, and taking it after a high-fat meal would boost it by 325 percent, the researchers found. That might allow patients to use 40 percent less to achieve the same effect as taking it on an empty stomach. At a cost of $2,900 a month, the change could save each patient, or insurers, $1,740 or more a month, the researchers said.

Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL.
Exposure Multiples (Fed vs. Fasted)

- Low Fat 100 mg: 0.9X
- Low Fat 1500 mg: 0.8X
- Low Fat 1500 mg High Fat: 1.7X
- Low Fat 1500 mg (Low Fat): 2.7X
- Low Fat 1500 mg (High Fat): 5.7X
- Low Fat 1500 mg: 24X

Exposure Multiples (Fed vs. Fasted)

- Cmax
- AUC (0-24h)
- Rel %F (SMEDDS vs Sporanox)

- Sporanox®
- SMEDDS
Microemulsions

- Creates a drug-solubilizing, micellar structure
- 1 mL of dispersed lipid creates the following amounts of interfacial surface area:
  - Droplet size = 0.25 µm
    - Total ISA = 8,450 sq. ft.
  - Droplet size = 0.1 µm
    - Total ISA = 21,450 sq. ft.

- Football field = 58,000 sq. ft.
- May provide greater API solubility than that achievable in individual bulk excipients
Formulation Development and Evaluation
Basic Excipient Classes

- **Natural product oils**
  - Mixtures of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation
  - Fractionated glycerides

- **Semi-synthetics**
  - Produces excipients with specific physicochemical properties
  - Hydrogenated glycerides
  - Macrogol glycerides

- **Synthetics**
  - Polyethylene glycols
  - Poloxamers

- **Surfactants**
  - Promote self-emulsification
Preformulation Considerations

1. Identify excipient (or excipient combination) capable of solubilizing entire dose in the fill volume of a single oral capsule

2. Formulation physical properties
   1. Self-emulsification
   2. Liquid vs. semi-solid
      1. Need for sealing

3. Compatibility with drug substance
   1. Identify and control excipient critical impurities
   2. Monitor stability of drug and excipient
   3. Drug:excipient ratio may influence stability

4. Compatibility with capsule shell
   1. Exchange of capsule and formulation components
   2. Hygroscopicity
   3. Oxygen permeability
Physical Stability

- **Microemulsions**
  - Phase changes due to migration of components between capsule shell and formulation matrix
    - Drug precipitation
  - Interaction of formulation with capsule shell
    - Moisture exchange
    - Glycerol

- **Semisolids**
  - Complex and dynamic phase and polymorphic changes possible
    - May result in drug crystallization
    - Decreased mobility may enhance drug chemical stability
So.....why aren’t drugs being formulated with lipids??
# Marketed Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Water Solubility</th>
<th>Marketed Formulation</th>
<th>Lipid Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>Practically insoluble</td>
<td>SGC, 100 mg (micronized)</td>
<td>Peanut oil</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Very slightly soluble</td>
<td>HGC, 250 mg</td>
<td>Corn oil</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Practically insoluble</td>
<td>SGC, 0.25, 0.5 mcg</td>
<td>MCT</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>Practically insoluble</td>
<td>SGC, 2.5 mcg</td>
<td>MCT</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Insoluble</td>
<td>SGC, 0.5 mg</td>
<td>MCM</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Practically insoluble</td>
<td>HGC, 200 mg</td>
<td>Gelucire 44/14</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Very slightly soluble</td>
<td>SGC, 25, 100 mg</td>
<td>Labrafil M-2125CS</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Practically insoluble</td>
<td>SGC, 150 mg</td>
<td>TPGS</td>
</tr>
<tr>
<td>Ibudilast</td>
<td>Slightly soluble</td>
<td>HGC, 10 mg</td>
<td>Cremophor RH 60</td>
</tr>
</tbody>
</table>
Obstacles to Greater Implementation

- Unaddressed Technical Challenges
- Loss of Technical Expertise
- Lack of Fundamental Knowledge
- Organizational Dynamics
Unaddressed Technical Challenges

- Current oral drug development paradigms do not consider solution dosage forms
  - Limited API availability during early development
  - Physical and chemical stability considerations
- Pharmacologic activity of lipid excipients
  - Confounded interpretation of DSE results
  - Interference with drug efficacy models
  - Potential difficulty in scaling nonclinical results to man
Loss of Technical Expertise

“Despite the growing need for innovative products and advanced pharmaceutical science and technology, industrial pharmacy education has experienced a decline in number, size, and curricular emphasis in recent years.” - The National Institute of Pharmaceutical Technology and Education (2008)
Organizational Dynamics

- Better communication required between ALL stages of pharmaceutical development, toxicology, marketing, senior management/decision makers.
- Must build consensus on dosage form quickly and early on in the development process:
  - HGC or SGC
  - Liquid, solid, semi-solid matrix, SMEDDS, etc.
The Bottom Line…..

- Molecules with drug-like properties are a precious commodity.
- The greatest opportunity for new drug discovery is likely to be found with poorly water soluble NCE’s.
- Implementation of strategies to develop, and technologies to deliver, poorly water soluble drugs has not kept pace with the rate of discovery of these compounds.