Specialized Analytical and Formulation Tools for the Successful & Timely Development of Lipid-based Drug Delivery Systems
Presentation Outline

- The Need to Integrate Formulation & Analytical Activities
- The Important Role Lipid-based Drug Delivery Systems (LBDDS) Play in the Bioavailability Enhancement of Challenging Drugs
- The Basic Elements of a Successful LBDDS Development Program
- Preformulation Studies and Analytical Tools for the Rationale Selection of Lipid Excipients
- Examples: Impact of Selecting the Right Lipid Excipients for Desired Formulation Performance
- Formulation Development Studies and Analytical Tools for LBDDS
- Examples: Effective Development of LBDDS Formulations for Enhanced Bioavailability
The Need to Integrate Formulation and Analytical Activities

• The patient is waiting – more, faster, better
• Demand for medicines increasing – 2010 sales of 600B Euro
Time to Market is Critical...

- Top 200 drug products generated $133.2B in sales in 2008, or an average annual sales of ~$666M per product

- Within 6 months of patent expiry, a brand may lose more than 80% of market share

- Because patent life starts at filing, any reduction in the time-to-market will increase revenues over the lifetime of the drug product
  - 6 months improvement in getting a drug to market could equate to $200M in additional revenues over the product’s life

- Expediting the early stages of drug development to verify a drug candidate’s drugability as well as establishing POC for drug delivery technology

The Important Role Lipid-based Drug Delivery Systems (LBDDS) Play in the Bioavailability Enhancement of Challenging Drugs
Outlook For The Future

New Chemical Entities

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

- BCS Class I: ~5%
- BCS Class II: ~70%
- BCS Class III: ~5%
- BCS Class IV: ~20%

L. Benet, EDAN, Leuven, BE, March 18-20, 2007
Why The Interest in Lipid-Based Formulations?

- NCE’s with low solubility and/or poor permeability often result in the following:
  - Sub-therapeutic levels due to limited absorption
  - Greater subject-to-subject variability in absorption
  - Significant food effects potentially resulting in altered bioavailability
  - More difficult, costly and lengthy development programs

- Lipid-based formulations represent a viable option for the oral delivery of poorly water soluble, poorly permeable drugs
How Do LBDDS Enhance Bioavailability?

- Increase solubilization
- Reduce the impact of various biological factors
- Affect membrane permeability
- Influence absorption pathway
- Interact with intestinal based efflux and/or metabolism

Fig from Porter CJH et al., Nature Reviews | Drug Discovery, 2007, 6:231-248
Two Important Factors For Developing LBDDS Are...

Dispersion

Digestion

Fig from Porter CJH et al., Nature Reviews | Drug Discovery, 2007, 6:231-248
The Basic Elements of a Successful LBDDS Development Program
Basic Elements of a LBDDS Development Program

**Preformulation Studies**
- Solubility screening
- Compatibility studies
- Digestion studies: rate and extent; API solubility in pre-digested excipients
- Permeation studies
- Analytical methods development to support preformulation studies

**Formulation Development Studies**
- Formulation dispersion: phase diagrams for determining phase behavior as a function of formula composition; dispersion (droplet size) characterization and stability
- Formulation digestion: rate and extent; API solubility in pre-digested formulations
- Analytical methods development to support formulation development studies
Preformulation Studies and Analytical Tools for the Rationale Selection of Lipid Excipients
Solubility Screening: Typical Program

**Identify Lipid Excipients That Solubilize The Desired Dose in the Minimum Volume of Excipients for Encapsulation**

- Determine single excipient solubility (but most likely multiple excipients will provide the greatest solubility)
- Based on the drug compound’s structure, screen a range of excipients
  - Various of chemical classes
  - Various lipophilicity/hydrophilicity profiles
- Determination of the dissolved fraction of API at up to 3 time points
  - Visual or quantitative measurement of solubility (UHPLC)
- Analysis of the solid-state (XRPD or DSC with Raman spectroscopy)
Solubility Screening: Solubility Prediction Software

**Benefits**
- Predict solubility of BCS Class II compounds in pharmaceutical excipients with no API needed
- To speed-up solubility screening during pre-formulation activities

**Types**
- Computing process based on quantum chemistry theory
  - Input: API or excipient (molecule chemical structure)
  - Database
  - Output: predicted solubility values
- Computing process based on thermodynamic theory
  - Input: API ($\Delta H_m$, $T_m$, solubility values); excipient (VLE or LLE data)
  - Database
  - Output: predicted solubility values
## Solubility Screening: High-Content versus High-Throughput Approaches

<table>
<thead>
<tr>
<th>Application</th>
<th>High-Content Screening Platform</th>
<th>High-Throughput Screening Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Product/material understanding</td>
<td>• Relative assessments</td>
</tr>
<tr>
<td></td>
<td>• Performance assessment</td>
<td>• Rank-ordering</td>
</tr>
<tr>
<td></td>
<td>• Modeling</td>
<td>• Structure-activity relationships</td>
</tr>
<tr>
<td>Attributes</td>
<td>• Refined phase-separation techniques</td>
<td>• Generic phase-separation techniques</td>
</tr>
<tr>
<td></td>
<td>• Material-specific analyses (e.g., quantitation)</td>
<td>• Generic analyses (e.g., semi-quantitative)</td>
</tr>
<tr>
<td></td>
<td>• Precise data</td>
<td>• Closely estimated data</td>
</tr>
<tr>
<td></td>
<td>• Generally slower</td>
<td>• Faster</td>
</tr>
<tr>
<td></td>
<td>• Semi-automated</td>
<td>• Highly automated</td>
</tr>
</tbody>
</table>
Solubility Screening: Example of High-Content Approach

• Tier I Solubility Screening
  – Select 25 vehicles (chemical classes and HLB)
  – Dispense API and vehicle in 1:100 ratio to achieve ~10 mg per gram of vehicle
  – Incubate/mix at 25°C (liquid vehicles) and 50°C (semi-solid vehicles) for 48 hours
  – Examine samples visually and by polarized light microscopy for the presence and absence of API crystals

• Tier II Solubility Screening
  – Select vehicles from Tier I screening that showed absence of API crystals
  – Prepare suspensions of API in the vehicles and incubate/mix at 25°C (liquid vehicles) and 50°C (semi-solid vehicles) for 48 hours
  – Isolate the suspensions/solutions using a Millipore™ Ultrafree-MC Centrifugal Filter Unit (Pore size: 22um)
  – Analyze the solution by UHPLC for API solubility and the residual solid by XRPD
API-Excipient Compatibility Studies: Basic Design

- Weigh binary mixtures of API and each excipient (as well as neat API and excipients) into capped and uncapped glass vials in duplicate.
- Prepare a stock solution/suspension of each binary mixture at desired API concentration (1:1 or excipient ratio to API in formulation) and aliquot into separate vials for each time point.
- Store vials at 40°C, 40°C/75%RH and 60°C for a period of up to 4 weeks.
- Monitor for signs of physical instability and analyze samples for assay/related substances by UHPLC/MS to characterize/elucidate degradation products/pathways.

### 4-Week Excipient Compatibility Study

<table>
<thead>
<tr>
<th>Storage Condition</th>
<th>Interval (Weeks)</th>
<th>Initial</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40°C</td>
<td></td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>40°C/75%RH</td>
<td></td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>60°C</td>
<td></td>
<td>-</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
</tr>
</tbody>
</table>

X = appearance and assay/related substances
( ) = optional testing
Digestion Studies: *In-Vitro* Measurement Using pH Stat Methods

- Pancreatic lipase catalyses the lipolysis (also termed hydrolysis or de-esterification) of oils, a process that results in the production of fatty acids.

- The rate of fatty acid generation is followed via continuous titration by NaOH with a pH-stat (pH-meter / autoburette / autotitration unit).

$$(1 \text{mole}) \text{TG} \rightarrow (2 \text{moles}) \text{FA} + (1 \text{mole}) \text{MG}$$
Digestion Studies: *In-Vitro* Solubilization in Pre-digested Lipid Excipients

**Objective:** To Identify Digestible Lipid Excipients That Will Potentially Keep The Drug in Solution *In-Vivo*

- Measure solubility of drug in pre-digested lipid excipients
- Select excipients with greatest “reservoir effect”

![Graph showing solubility of progesterone in pre-digested triglycerides](image)

**Solubility of Progesterone in Pre-Digested Triglycerides**
Preformulation Studies: Analysis Using UHPLC/MS

Benefits

• UHPLC enables faster and improved chromatography for generation of key solubility or compatibility data
  – Conventional (HPLC/UV) techniques must be modified (mobile phase, gradient, columns) to obtain an analyte-specific response
  – UHPLC systems equipped with multiple mobile phases and columns for screening of mobile phase composition and column properties

• UHPLC/MS allows identification of potential API degradation pathways to establish optimal formulation strategies
  – Technique is specific to API (as opposed to pharma ingredients) provided that ionization conditions are not affected by other ingredients

Improved Chromatography: Analysis Using UHPLC versus HPLC

Elucidation of Degradation Pathways: Analysis Using UHPLC-MS

### Improved Timelines: Analysis Using UHPLC-MS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Standard Approach (HPLC/UV)</th>
<th>Catalent Approach (UHPLC/MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method Evaluation</td>
<td>2 weeks</td>
<td>1 week</td>
</tr>
<tr>
<td>Solubility Screening</td>
<td>2 weeks</td>
<td>1 week</td>
</tr>
<tr>
<td>Compatibility Study Launch</td>
<td>4 days</td>
<td>1.5 days</td>
</tr>
<tr>
<td>Compatibility Study Time Point</td>
<td>4 days</td>
<td>1.5 days</td>
</tr>
<tr>
<td>(Analysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method Validation</td>
<td>6 weeks</td>
<td>3 weeks</td>
</tr>
</tbody>
</table>

*Typical timeframes for various components of analytical science.*

Examples: Impact of Selecting the Right Lipid Excipients for Desired Formulation Performance
Formulation Digestion Studies: Effects of Different Hydrophilic Surfactants on Lipolysis of a MCT

Triplicate determinations (Coefficient of Variation < 10%)
Formulation Digestion Studies: Effects of Different Lipophilic Surfactants on MCT Lipolysis in the Presence of Cremophor RH40

![Graph showing the effects of different surfactants on MCT lipolysis.](image-url)
Digestion Studies: *In-Vitro* Solubilization in Predigested Lipid Excipients

**Objective:** To study the impact of non-ionic surfactants digestion on solubilization

![Graph showing concentration of fatty acids titrated (mM) over time (minutes) for different surfactants: Labrasol, Gelucire 44/14, Tween 80, Cremophor EL, and Pluronic L64/Brij 97.](image)

Surfactants comprising glycerides or fatty acid esters (Labrasol, Gelucire 44/14, Cremophor EL, and Tween 80) were susceptible to digestion.

Both ether-based surfactants (Pluronic L64 and Brij 97) were not digestible.

Impact of Non-ionic Surfactants Digestion on Solubilization

**SEDDS**
70% Surfactant
20% LC lipid
10% EtOH

Drug solubilization on dispersion (t=0) good for all systems

For Tween 80, Cremophor EL, Gelucire and Labrasol formulations digestion reduced solubilization capacity

A MCT is not a MCT is not a MCT

Composition of Fatty Acids

<table>
<thead>
<tr>
<th></th>
<th>MCT (A) Specifications</th>
<th>MCT (B) Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caproic Acid (C6)</td>
<td>NMT 2.0%</td>
<td>NMT 3.0%</td>
</tr>
<tr>
<td>Caprylic Acid (C8)</td>
<td>50-80%</td>
<td>50-65%</td>
</tr>
<tr>
<td>Capric Acid (C10)</td>
<td>20-50%</td>
<td>35-50%</td>
</tr>
<tr>
<td>Lauric Acid (C12)</td>
<td>NMT 3.0%</td>
<td>NMT 3.0%</td>
</tr>
<tr>
<td>Myristic Acid (C14)</td>
<td>NMT 1.0%</td>
<td>NMT 1.0%</td>
</tr>
</tbody>
</table>

LBDDS formulated with MCT (B) was not bioequivalent to LBDDS formulated with MCT (A)!
Formulation Development Studies and Analytical Tools for LBDDS
Typical Formulation Development Plan for LBDDS

Preformulation Studies

• Characterization of the poorly water soluble API and choice of excipients based on solubility screening and compatibility studies

Formulation Development Studies

• Pseudo ternary diagrams on placebo
• Lipolysis profiles on placebo
• Select candidate prototype formulations based on placebo phase diagrams and lipolysis properties
• Dispersion and digestion studies on selected active prototype formulations
  – PSD (DLS or Light Diffusion) stability
  – Rate and extent of digestion, API solubility in pre-digested formulation
The Usefulness of Ternary Phase Diagrams in the Development of LBDDS...

- To identify formulations suitable for SEDDS or SMEDDS (physical state under infinite dilution)
- To optimize proportions of different components
- To rapidly screen a wide range of excipients
What is a Pseudo Ternary Diagram?

**Graphic overview of the physical state of an emulsion as function of the ratio of oil, surfactant/cosurfactant and water**

- Increasing amount of Surfactant / Cosurfactant
- Increasing amount of Oil
- Increasing amount of Water
How to Read a Pseudo Ternary Diagram?

From each of the initial compositions (start points), water is added drop by drop and different physical states are reported with the dilution.

Transition from a state to another state corresponds to a unique composition of Oil, C/CoS and Water.
What are the Different Physical States?

Upon dilution in aqueous, initial formulation can undergo five (5) different physical states:

- **Transparent**: finest W/O dispersion (thermodynamically stable)
- **Translucent**: very fine W/O dispersion (thermodynamically stable)
- **Bluish**: fine W/O dispersion (thermodynamically stable)
- **Cloudy**: opaque (slightly grey) O/W dispersion (thermodynamically unstable)
- **Milky**: opaque (white) O/W dispersion (thermodynamically unstable)
What is the Result?

Graphic overview of the different physical states occurring upon dilution

Red: Transparent
Orange: Translucent
Blue: Bluish
Grey: Cloudy
Black: Milky
Formulation Dispersion Studies: Phase Diagrams
Formulation Digestion & Digestion Studies: Phase Diagrams/Lipolysis

Key:
- Oil Ratio: 0.0
- Oil Ratio: 0.1
- Oil Ratio: 0.2
- Oil Ratio: 0.3
- Oil Ratio: 0.4
- Oil Ratio: 0.5
- Oil Ratio: 0.6
- Oil Ratio: 0.7
- Oil Ratio: 0.8
- Oil Ratio: 0.9
- Oil Ratio: 1.0

nFe/g (log)

Time (min)
Droplet Size Characterization Methods for LBDDS

- Optical microscopy with image analysis
- Electron microscopy
- **Laser light scattering**
- **Photon correlation spectroscopy**
- Coulter/electric sensing
- In-process systems, e.g. Lasentec
Formulation Dispersion Studies: Droplet Size Stability

**Droplet Size Assessment using Photon Correlation Spectroscopy @ 37°C in S.I.F.**

- **PSD (Initial)**: Mean Particle Diameter ~ 50nm
- **PSD (after 19 hours)**: Mean Particle Diameter ~ 60nm
Examples: Effective Development of LBDDS Formulations for Enhanced Bioavailability
The Neoral® Story: Cyclosporin A

**API Physical-Chemical Properties**
- High molecular weight
- 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®*
Pharmacokinetic Profiles for Sandimmune® and Neoral® Microemulsion Preconcentrate

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

**AUC (µL-1 h)**

- **Fed**
- **Fasted**

**Neoral® is less affected by food intake**
Cinnarizine

**Physiochemical Properties**
- High molecular weight (368.5)
- Hydrophobic drug
- Poor solubility in aqueous GI fluids (< 1 µg/ml in water)

**Pharmacokinetic Properties**
- Poorly absorbed
- Dose 30 mg
- Dissolution rate limited (BCS Class II)
Solubility of Cinnarizine in Pre-Digested Lipolytic Products

**Solubility (µg/ml)**

- **pH 7.5 Buffer**
- **Bile Salt Micelles**
- **MCLP**
- **LCLP**

The solubility of Cinnarizine is highest in LCLP compared to other conditions.
Comparative Rates of Lipolysis for Two Lipid-Based Solution Formulations Containing Cinnarazine
Plasma Concentration Versus Time Curves for 3 Formulations of Cinnarizine in the Dog (n=6)

Formulations:
- Softgel: LCT Lipolysing AUC(0-24hr) 665 ng.h/ml
- Softgel: Non-Lipolysing AUC(0-24hr) 451 ng.h/ml
- Tablet: AUC(0-24hr) 406 ng.h/ml
Progesterone

**Physiochemical Properties**
- High molecular weight (314.5)
- Hydrophobic drug
- Poor solubility in aqueous GI fluids (< 0.1 mg/ml in water)

**Pharmacokinetic Properties**
- Poorly absorbed
- Rapidly metabolised by the liver
- Slow dissolution and absorption from oral suspension provides steady flow of drug to liver where it is extensively metabolised
Solubility of Progesterone in Pre-Digested Triglycerides and Lipolyzed Formulation

Formulation composed of 1g triglyceride / lipophilic surfactant / hydrophilic surfactant / co-solvent
Progesterone Relative Bioavailability from a Lipolyzing Solution and a Suspension Formulation

Serum Concentration versus Time Curves following Single Dose Administration of 200mg Progesterone in 12 Healthy Post-Menopausal Volunteers

![Graph showing serum progesterone levels over time for Lipolyzing Solution Formulation and Commercial Suspension Formulation.](image-url)
Development Approach for Timely, Effective LBDDS Formulations for POC Studies in Humans
NCE Compound Y

Physiochemical Properties
- High molecular weight (~400)
- Hydrophobic drug
- cLog P > 8
- Drug is sensitive to oxidation

Pharmacokinetic Properties
- Drug with a very low Papp
- Drug belongs to BCS Class IV
- Active transport identified
Competing Formulation

- Liquid Filled Hard Shell Formulation, Semi-Solid SEDDS
  
  - Long chain fatty acid
  - Glycerol monoester of long chain fatty acid
  - Monoester of sorbitan and long chain fatty acid

  *Classified as Alternative Formulation Strategy (Pouton, 2008), "Pre-Digested" approach*

- Maximum strength was around 100 mg (micronized drug)
- Short shelf life assigned due to degradation
- Limited absorption
- Anticipate difficulties in scale-up & in dissolution method development
Solubility of NCE Compound Y in Pre-Digested Lipolytic Products

Is the digestion process likely to increase solubility?

- Reservoir effect in LCLP’s and MCLP’s

Solutions in LCT’s and MCT’s have proven acceptable stability
Animal Studies

PK study in rats

- Dispersion in MCT’s (#1)
- Dispersion in LCT’s (#2)
- LFHC pre-emulsified

<table>
<thead>
<tr>
<th>Formula</th>
<th>T max</th>
<th>Cmax (µM)</th>
<th>AUC 0-24h (µg.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFHC emulsified</td>
<td>8 h</td>
<td>1.53</td>
<td>8.6</td>
</tr>
<tr>
<td>Dispersion in MCTs</td>
<td>6 h</td>
<td>1.12</td>
<td>5</td>
</tr>
<tr>
<td>Dispersion in LCTs</td>
<td>4 h</td>
<td>2.05</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Potential for a LCT-based formulation
Selected Formulation

- Development of a drug substance suspension in LCT’s based on drug solubility in LCLP’s
- 45% drug loading
- Utilized milled drug substance
- Selected formulation is stable for 36 months
- Encapsulation into a softgel with FIH studies within 4 months
Pharmacokinetic Study in Humans

Comparative pharmacokinetic study for a LFHC versus a Softgel on 24 subjects in the fed state – 2.3 fold bioavailability improvement

Mean curves

Concentrations expressed as ng/mL

Time

Catalent Pharma Solutions data

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Summary

- There is a growing interest in LBDDS and their ability to enhance the bioavailability of poorly water soluble drug compounds

- Specialized analytical & formulation tools/methods are needed for the effective development and assessment of LBDDS

- This begins with the application of these tools/methods during preformulation studies for the rationale selection of lipid excipients that have the right performance characteristics to maintain the drug in a solubilized state \textit{in-vivo}

- It continues with the application of in-vitro tools/methods that are predictive of in-vivo performance for the evaluation and screening of LBDDS formulations

- Finally, the appropriate application/integration of analytical & formulation tools/methods and activities, along with the assumption of manageable risks, can lead to the rapid, effective development of LBDDS for human studies
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