Enabling Lipid Formulations That Harness Supersaturation and Drug Absorption in the GI Tract

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Enabling Lipid Formulations That Harness Supersaturation and Drug Absorption in the GI Tract

- Generation of supersaturation during digestion and dispersion
- Lessons learned from digestion testing
- Polymeric precipitation inhibitors
- Future perspectives
Lipid Based Drug Delivery Systems – basic concepts

Aim is to avoid drug precipitation ($D_{\text{ppt}}$) during dispersion and/or digestion.

Dissolution rate from crystalline solid drug is likely to be limiting for poorly water-soluble drugs.

Generation of supersaturation during digestion and dispersion in the gastrointestinal tract

- Although the digestion of formulations and interaction with bile can provide a matrix for solubilization of drug, in practice many formulations can lead to drug precipitation.
- Precipitation can take place during dispersion or digestion
- Supersaturation will drive more rapid absorption as well. If this happens before precipitation then it may be a benefit.
LBDDS May Also Promote Supersaturation

Drug solubility in GIT fluids plus (digested) lipids, surfactants in LBDDS

Drug solubility in GIT fluids

Supersaturated LBDDS

Supersaturation Effect

Dispersed and digested LBDDS

Solubilisation Effect

Conventional IR solid dose form
Lessons learned from digestion testing

• The Lipid Formulation Classification System (LFCS) Consortium was formed in 2010 (www.lfcsconsortium.org)
• During 2011-2014 the Consortium funded studies on dispersion and digestion testing and performed some IVIVC studies in dogs which have advanced our understanding
  - but there is a lot more research to be done
Introducing the LFCS Consortium

A non-profit organization that sponsors and conducts research on lipid-based drug delivery systems (LBDDS) for the oral administration of poorly soluble drugs (www.lfcsconsortium.org) The Consortium is in its third year of operation.

Industrial Full Members
- Capsugel
- Sanofi Aventis

Associate Members
- Actelion
- BMS
- Gattefossé
- Merck-Serono
- NicOx
- Roche

Academic Members
- Monash University
- University of Copenhagen
- University of Marseille
What do lipid formulations consist of?

**LIPIDS/OILS**
- Soybean oil, corn oil, Miglyol®, Maisine™ 35-1, Capmul®

Include for:
- Dissolving highly lipophilic drugs.
- Maintaining solubilization post-dispersion.
- Harnessing natural digestion, absorption/lymphatic pathways.

**NON IONIC SURFACTANT(S)**
- Tween® 85 (low HLB), Tween® 80, Cremophor® EL (higher HLB)

Include for:
- Emulsification of the oil component
- Minimizing loss of solubilization on dispersion/digestion

**COSOLVENTS**
- Ethanol, PEG 400, propylene glycol etc.

Include for:
- Higher drug loading capacity
- Better dispersibility

Drug is usually dissolved, and therefore, ‘molecularly dispersed’ in the formulation.

Commercial examples: Neoral®, Agenerase®, Fortovase® etc.

Further reading:
Pouton and Porter 2008 Advanced Drug Delivery Reviews 60, 625-637
### Current Lipid Formulation Classification System

#### Formulations classified according to composition

<table>
<thead>
<tr>
<th>Composition</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>Typical composition (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides or mixture of glycerides</td>
<td>100</td>
<td>40-80</td>
<td>40-80</td>
<td>&lt;20</td>
<td>-</td>
</tr>
<tr>
<td>Water insoluble surfactant</td>
<td>-</td>
<td>20-60</td>
<td>-</td>
<td>-</td>
<td>0-20</td>
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<tr>
<td>Water soluble surfactant</td>
<td>-</td>
<td>-</td>
<td>20-60</td>
<td>20-50</td>
<td>30-80</td>
</tr>
<tr>
<td>Cosolvent</td>
<td>-</td>
<td>-</td>
<td>0-40</td>
<td>20-50</td>
<td>0-50</td>
</tr>
</tbody>
</table>

The 8 lipid formulations investigated by the LFCS

Lipids:
- Long-chain: Corn oil and Maisine™ 35-1 (in a 1:1 ratio)
- Medium-chain: Captex® 300 and Capmul® MCM EP (in a 1:1 ratio)

Lipophilic surfactant: Tween® 85

Hydrophilic surfactant: Cremophor® EL

Cosolvent: Transcutol HP

Variation in:
- Composition
- Drug Loading Capacity
- Dispersibility
- Digestibility
Metrohm® titration apparatus for *in vitro* digestion testing

- pH-stat titrator to maintain constant pH during digestion.
- Rate and total titrant added informs of LBF digestibility.
Drug load (saturation) very important for MC

Type II-MC

Drug loading (% sat sol in formulation)

Increasing drug load from 20-90% of saturated solubility in formulation, significantly decreases % solubilised post digestion

Williams et al Mol Pharmaceutics (2012)
Drug load (saturation) very important for MC

Degree of precipitation most significant in least lipophilic formulations (ie more cosolvent, more hydrophilic surfactants)

Williams et al Mol Pharmaceutics (2012)
Drug load (saturation) less critical in LC formulations

Long chain lipid containing formulations resist ppt more favourably and are less sensitive to drug load.

Note: Type IIIA-LC formulations are incompletely digested in the fixed volume available (low density oil phase is shown in yellow)

Williams et al Mol Pharmaceutics (2012)
Drug load (saturation) less critical in LC formulations

Why do LC formulations resist ppt more effectively?

- Generate intestinal colloids with intrinsically higher drug solubility?
- Stabilise supersaturated drug concentrations?

*Williams et al Mol Pharmaceutics (2012)*

www.lfcsonsortium.org
Towards a classification based on performance

<table>
<thead>
<tr>
<th>Performance test</th>
<th>A-type</th>
<th>B-type</th>
<th>C-type</th>
<th>D-type</th>
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<tbody>
<tr>
<td>Dispersion</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Digestion (fasted)</td>
<td>✔️</td>
<td>✔️</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Digestion (stressed)</td>
<td>✔️</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grading (✔️/✗) based on level of drug precipitation

Decreasing performance

- A traditional “Type IIA-MC” formulation might be classified B-type at high drug loading but demonstrate A-type performance at low drug loading.

- Sub-classification of the A-type might be required e.g. LBFs showing A-type properties across a wide-range of drug loadings might be called a “A*-type”
Quantifying supersaturation in lipid based formulations

The greater the maximum supersaturation ratio, the greater the driving force to precipitation \( \Rightarrow \) dependent on drug loading (ie saturation level)

Does maximum (initial) supersaturation ‘pressure’ dictate precipitation profiles?
In vitro digestion testing

In vitro digestion data at a fixed 125 mg fenofibrate dose
Does $SR_{\text{MAX}}$ predict the likelihood of drug precipitation?
Saturation study: the trends based on supersaturation

<table>
<thead>
<tr>
<th></th>
<th>High BS</th>
<th>Fasted</th>
<th>Highly diluted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>II-MC</td>
<td>30</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>IIIA-MC</td>
<td>30</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40%</td>
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<td>IIIB-MC</td>
<td>30</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>IV</td>
<td>30</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40%</td>
<td>60%</td>
</tr>
</tbody>
</table>

% non-precipitated dose
- **Red**: < 40%
- **Orange**: 40-70%
- **Green**: >70%
Saturation study: the trends based on supersaturation

<table>
<thead>
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<th>Highly diluted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min 40% 60% 80%</td>
<td>20% 40% 60% 80%</td>
<td>40% 60% 80%</td>
</tr>
<tr>
<td>II-MC</td>
<td>30 3.1 4.7 6.2</td>
<td>1.5 3.1 4.6 6.2</td>
<td>7.6 11.5 15.3</td>
</tr>
<tr>
<td></td>
<td>60 3.1 4.7 6.2</td>
<td>1.5 3.1 4.6 6.2</td>
<td>7.6 11.5 15.3</td>
</tr>
<tr>
<td>IIIA-MC</td>
<td>30 2.7 4.0 5.3</td>
<td>1.4 2.8 4.3 5.7</td>
<td>5.0 7.6 10.1</td>
</tr>
<tr>
<td></td>
<td>60 2.7 4.0 5.3</td>
<td>1.4 2.8 4.3 5.7</td>
<td>5.0 7.6 10.1</td>
</tr>
<tr>
<td>IIIB-MC</td>
<td>30 4.5 6.8 9.1</td>
<td>2.0 3.9 5.9 7.8</td>
<td>3.6 6.0 8.0</td>
</tr>
<tr>
<td></td>
<td>60 4.5 6.8 9.1</td>
<td>2.0 3.9 5.9 7.8</td>
<td>3.6 6.0 8.0</td>
</tr>
<tr>
<td>IV</td>
<td>30 7.5 11.2 15.0</td>
<td>2.9 5.7 8.6 11.5</td>
<td>5.7 8.5 11.4</td>
</tr>
<tr>
<td></td>
<td>60 7.5 11.2 15.0</td>
<td>2.9 5.7 8.6 11.5</td>
<td>5.7 8.5 11.4</td>
</tr>
</tbody>
</table>

% non-precipitated dose

- Low SR$_{\text{MAX}}$ = Green (good solubilisation)
- High SR$_{\text{MAX}}$ = Red (precipitation)
SR^M ‘predicts’ drug fate during in vitro digestion of LBFs:

- **Tolfenamic acid**
  - Threshold SR^M ~3.0

- **Danazol**
  - Threshold SR^M ~2.5

- **Fenofibrate**
  - Threshold SR^M ~3.0

- ‘SR^M threshold identified in each case.
- Above this supersaturation threshold, formulation performance is variable/poorer due to precipitation.

*Williams et al Mol Pharmaceutics (2012) in press*
Profiling danazol precipitation during in vitro digestion

Initiation of digestion

On digestion, solubilising capacity lost to varying degrees

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Cuine et al, Pharm Res 24, 748-757, 2007
Comparison of in vitro digestion vs in vivo exposure

In vitro dispersion and digestion

In vivo exposure after oral administration to beagle dogs

Lack of in vitro precipitation correlated well with enhanced in vivo exposure

Use of digestion tests increasingly popular...but some variation in methods across laboratories

Cuine et al, Pharm Res 24, 748-757, 2007
**In vivo results summary**

<table>
<thead>
<tr>
<th>Type</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$AUC_{0-\infty}$ (µg.h/ml)</th>
<th>$T_{\text{max}}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IIIA-LC</td>
<td>7.4 ± 1.6</td>
<td>34.0 ± 4.4</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Type IIIA-MC</td>
<td>4.8 ± 1.0</td>
<td>29.1 ± 2.9</td>
<td>1.4 ± 0.5</td>
</tr>
<tr>
<td>Type IV</td>
<td>6.8 ± 3.4</td>
<td>26.1 ± 6.6</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Type IIIB-MC</td>
<td>5.9 ± 1.3</td>
<td>25.3 ± 3.2</td>
<td>1.4 ± 0.3</td>
</tr>
</tbody>
</table>

Decreasing AUC

*no significant differences were observed across the four LFCS formulation types*
**In vitro-in vivo correlations**

**In vitro summary:**

- **In vitro** performance data at a fixed 125 mg fenofibrate dose

- Differences in *in vivo* exposure were comparatively small compared to differences *in vitro*

**Calculate AUC and plot vs. in vivo AUC**

\[ R^2 = 0.9182 \]
Polymeric precipitation inhibitors

- HPMC and HPMC-AS are polymeric excipients that have been used to produce amorphous spray-dried dispersion formulations of drugs.
- These polymers inhibit the precipitation of some drugs after dissolution of the formulations.
- In recent years similar approaches to precipitation inhibition have been explored with lipid systems – but this research is in its infancy.
Effect of HPMC on precipitation of danazol during digestion

- HPMC effectively reduced ppt from MC SEDDS in conc dependent manner
- Conc required ~ 10 fold higher than in screening assay
It is at the \( S_{RM} \) threshold when:

Polymer precipitation inhibitors have the greatest effect:

- HPMC inhibits precipitation at the threshold, but exhibits a lower utility at high supersaturations (i.e., >5).

- \( S_{RM} \) is shown during dispersion (triangles) or digestion (circles) from formulations containing danazol at either 40% (orange) or 80% (black) solubility in formulation. Purple formulations are identical but also contain 5% HPMC.

Future perspectives

• For weak electrolyte drugs the production of novel salts in the form ionic liquids is an interesting new option.

• We need to develop a better understanding of the consequences of supersaturation in the gastrointestinal tract. This will require laboratory models that incorporate absorption.

• In the long-term IVIVC studies with a range of drugs will be required to build a database to help formulators predict in vivo performance.
Example Ionic liquid forms of CIN

CIN octadecylsulphate
$T_m$ 78-81ºC

CIN triflimide
$T_m$ 38-43ºC

CIN decylsulphate
Viscous liquid at RT

CIN oleate
$T_m$ 93-98ºC

CIN free base $T_m$ 118-120ºC

Solubility of CIN ionic liquids in two lipid formulations

- Solubility of CIN.IL forms substantially higher (up to 10-fold), some (decyl sulphate and triflimide) essentially miscible

*In vivo* performance of CIN.DS containing lipid formulations

- CIN.DS IL allowed >3.5 increase in CIN dose
- Despite increased CIN/formulation ratio, absorption maintained

In situ rat loop model combined with in vitro digestion testing → better IVIVC
The LFCS Consortium

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- Capsugel
- Sanofi Aventis

**Associate Members**
- Actelion
- BMS
- Gattefossé
- Merck-Serono
- NicOx
- Roche

**Academic Members**
- Monash University
- University of Copenhagen
- University of Marseille
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