New Perspectives on Lipid and Surfactant based DDS for Oral Delivery of Poorly Soluble Drugs

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Distribution of Marketed Drugs

High Solubility

Class 1
~35%
High solubility
Rapid dissolution
High permeability
Ext. Metabolism
Minimal transporter

Class 3
~25%
High solubility
Low permeability
Poor metabolism
Transporters & efflux

Low Solubility

Class 2
~30%
Low solubility
High permeability
Ext. Metabolism
Efflux in gut

Class 4
~10%
Low solubility
Low permeability
Poor metabolism
+ Transporters & efflux

Adapted from Les Benet
Distribution of New Molecular Entities

High Solubility  Low Solubility

High Permeability

Class 1
5%

Class 2
70%

Low Permeability

Class 3
5%

Class 4
20%

Adapted from Les Benet, EDAN 2007
Four Scenarios:
Four Different Patient Needs, Four Target Profiles

1. **Scenario 1**: I need it now!
   - Graph showing concentration over time with a peak at 0 hours.

2. **Scenario 2**: Now AND later
   - Graph showing concentration over time with a peak at 0 hours and another peak later on.

3. **Scenario 3**: Just in time delivery
   - Graph showing concentration over time with a peak just after the delivery time.

4. **Scenario 4**: Keeping your head above water.
   - Graph showing concentration over time with a flat line above the water level.
Strategies to improve solubility

Molecular level
- Salt formation
- Co-solvents
- Prodrugs
- Cyclodextrins

Colloidal level
- SEDDS
- SMEDDS
- SEDDS
- Micro-emulsions
- Lipid solutions
- Emulsions
- Metastable polymorphs
- Particle size reduction
- Amorphous systems

Particulate level
Poorly water-soluble drugs

HYDROPHOBIC

"brickdust"

LiPOPHILIC

"greaseballs"

Physico-chemical properties determine formulation approach
Poorly water-soluble drugs

HYDROPHOBIC

"brickdust"

\[ \equiv \]

LIPOPHILIC

"greaseballs"

Lipid-based drug delivery

Drug already in solution! no dissolution step
Lipid-based drug delivery systems

What are lipids?

- Chemically diverse structures
- Limited affinity to water

Retinol (Vitamin A)

Phospholipid structure

Cholesterol
Lipid-based Drug Delivery Systems

Why lipids?

- Essential part of our diet
- Body well equipped for lipid uptake & processing...

![Evolution of Lipid Consumption]

Positive Food Effect on many poorly soluble drugs

Bioavailability increased

- Propranolol
- Metoprolol
- Labetalol
- Propafenone
- Hydralazine
- Griseofulvin
- Nitrofurantoin
- Mebendazole
- Flubendazole
- Halofantrine
- Phenytoin
- Dicoumarol

- Melander et al. (1977a)
- Melander et al. (1977a)
- Daneshmend & Roberts (1982)
- Axelsson et al. (1987)
- Melander et al. (1977b)
- Palma et al. (1986)
- Rosenberg & Bates (1976)
- Munst et al. (1980)
- Michiels et al. (1982)
- Milton et al. (1989)
- Melander et al. (1979b)
- Melander & Wahlin (1978)
FIGURE 1

Approved Drugs: Use of Solubilization Technologies Since the 1980s

- Lipids
- Solid dispersions
- Nanocrystals
- Amorphous APIs

Number of Approved Products

Year


0 5 10 15 20 25 30 35
Lipid-based Drug Delivery Systems

Lipid based formulations deliver the drug in solution to the GI tract - thereby overcoming the solubility / solubilization problem – and increasing bioavailability.

Transfer between colloid phases
Critical; avoidance of precipitation

Examples:
- Oil solution
- Emulsions
- Microemulsions
- Liposomes
- Dry emulsions
- Solid lipid nanospheres (SLN)
- Self-emulsifying Drug Delivery Systems
- Self-(Nano) Emulsifying Drug Delivery Systems
Lipid-based Drug Delivery Systems

Lipid based formulations deliver the drug in solution to the GI tract - thereby overcoming the solubility / solubilization problem – and increasing bioavailability.

Transfer between colloid phases
Critical; avoidance of precipitation

Examples:
- Oil solution
- Emulsions
- Microemulsions
- Liposomes
- Dry emulsions
- Solid lipid nanospheres (SLN)
- Self-emulsifying Drug Delivery Systems
- **Self-(Nano) Emulsifying Drug Delivery Systems**
  - Administration in capsules – as preconcentrate
  - Fast gastro-intestinal dispersion of drug in a nano-emulsion
  - Enhance bioavailability of poorly soluble drugs
SNEDDS - Homogenous Preconcentrate in Capsule
• Oil
• Surfactants
• Co-solvent

“SNEDDS are isotropic mixtures of oil and surfactants forming fine oil-in-water emulsions when introduced into water under gentle agitation”

Lipid phase
triacylglycerides, diacylglycerides

Hydrophobic surfactants (HLB <12)
Span, Maisine, Labrafil®

Hydrophilic surfactants (HLB >12)
Gelucire®, Cremophor®, Tween, Labrasol®

Drug compound

Hydrophilic co-solvents
ethanol, PEG, propylene glycol, transcutol®

Dispersion (not to scale!)
Cryo-TEM of SNEDDS (1:100)

DLS: 30 nm

Buffer, pH 6.5

5 mM BS / 1.25 mM PL, pH 6.5

SNEDDS A29E:
18% Sesame oil
10% Oleic acid
45% Cremophor RH40
10% Ethanol
## Lipid-based Formulation Classification System (LFCS)

<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>Typical composition</td>
<td>Oil solution</td>
<td>SEDDS</td>
<td>SEDDS, SNEDDS</td>
<td>SNEDDS</td>
<td>Micelles</td>
</tr>
<tr>
<td>TG, DG, MG</td>
<td>100</td>
<td>40-80</td>
<td>40-60</td>
<td>&lt;20</td>
<td>-</td>
</tr>
<tr>
<td>Surfactants (HLB&lt;12)</td>
<td>-</td>
<td>20-60</td>
<td>-</td>
<td>-</td>
<td>0-20</td>
</tr>
<tr>
<td>Surfactants (HLB&gt;12)</td>
<td>-</td>
<td>-</td>
<td>20-40</td>
<td>20-50</td>
<td>30-80</td>
</tr>
<tr>
<td>Hydrophilic cosolvents</td>
<td>-</td>
<td>-</td>
<td>0-40</td>
<td>50-100</td>
<td>0-50</td>
</tr>
<tr>
<td>Particle size (nm)</td>
<td>coarse</td>
<td>250-2000</td>
<td>100-250</td>
<td>50-100</td>
<td>30-80</td>
</tr>
</tbody>
</table>

Pouton 2006, EJPS
Lipid-based Drug Delivery Systems: Examples on the market

Oil solutions

\[
\text{Marinol}^\text{®} \quad \text{(dronabinol)}
\]

\[
\text{Rocaltrol}^\text{®} \quad \text{brand of calcitriol}
\]

\[
\text{Rocaltrol}^\text{®} \quad \text{brand of calcitriol}
\]
Cyclosporin A

Figure 2.1. Structure of cyclosporin A (1). Abu, l-2-amino-3-methylbutyric acid; Bmt, (4R)-4-{{E}-2-butenyl}-4-methyl-l-threonine (= (+S)-3R, 4R, 6[T]-2-amino-3-hydroxy-4-methylfoc-6-enoic acid); Sar, sarcosine.
Neoral - Cyclosporin A

Cyclic peptide
11 amino acids
Molecular weight: 1202
Lipophilic drug, very low water solubility
Fair oil solubility (4% in olive oil)

Old formulation (Sandimmune): emulsion concentrate
Bioavailability: 30%, variable (10 - 60 %)

Neural – reduced Food Effect!
Inactive Ingredients:
Corn oil
Labrafil M 2125 CS
(polyoxyethylated glycolysed glycerides)

Crude O/W emulsion
Food effect (37%)

SNEDDS, 30 nm
Absorption of cyclosporin from Sandimmune and Sandimmune Neural in healthy Mexican volunteers

**Figure 1.** Whole blood cyclosporine concentrations against time curve after administration of two oral formulations to 23 Mexican healthy volunteers. (○) corresponds to Sandimmune® and (●) corresponds to Neoral®. Data are expressed as mean ± SEM.
Saquinavir

Invirase

Fortovase
Development of SNEDDS

**Composition:**
Lipids (liquid)
Surfactant (hydrophilic)
Co-surfactant (hydrophobic)
Co-solvent

API in solution ($< s_{eq}$)

**Development parameters:**
- API solubility....
- Homogenous preconcentrate...
- Dispersion rate...
- Droplet size..
- Precipitation of drug upon dispersion..
- Digestion of SNEDDS...
- Precipitation of drug upon dispersion..
- Absorbability of drug from SNEDDS...

**Critical Quality Attributes (CQA)**
Development of SNEDDS

System A

Cremophor RH40

Sesame oil

Oleic acid

System A with 10% ethanol

Cremophor RH40

Sesame oil

Oleic acid

- Inhomogeneous mixture
- Homogeneous mixture
- Homogeneous mixture that forms a nano-emulsion in water (1+100)

A. Larsen et al, in prep.
Effect of fenofibrate on micro-emulsification space

Response surface methodology (MODDE):
4 formulation variables:
• Oil (rapeseed oil, 10-35%)
• Surfactant (Cremophor RH 40, 20-35%)
• Co-surfactant (Maisine 35-1, 30-60%)
• Co-solvent (ethanol, 0-15%)

No fenofibrate

With fenofibrate
Lipolysis of surfactants

Impact on digestion of drug delivery systems

5 mM BS : 1.25 mM PL, 1 g surfactant / 100 ml medium

(Larsen et al, 2005)
Simulating the Gastro-Intestinal Tract

- Mouth
- Saliva
- Amylase
- Stomach
- HCl
- Pepsin
- Gastric lipase
- Duodenum
- Pancreas
- Enzymes
- Jejunum
- Bile
- Ileum
- Colon
- Microbiota

Hydrodynamics
- Liquid volumes
- Transit times
Drug fate during *in vitro* lipolysis of SNEDDS

**SNEDDS**
- Vehicle phase
- Dissolved drug

**Biorelevant medium (Fasted state)**

**Emulsification Lipolysis**

**Pancreatic extract**

**Continued Lipolysis**
- Solubilized drug
- Micelle
- Vesicles (uni-/multilamellar)
- Microemulsion droplet
- Pancreatic lipase
- Pancreatic co-lipase
- Precipitated free drug
- Co-Precipitates of free drug and lipids
Dynamic *in vitro* lipolysis

Controlling the rate of lipolysis

Enzyme inhibition

(Ultra)centrifugation

HPLC

HPLC XRPD

Dissolution
Lipid DDS – going solid…..

Solid Lipid Nanoparticles
Solid Lipid Extrusion
Nanostructured lipid particles

Dry emulsions

Microporous adsorbents
Microporous silica
Mesoporous silicon dioxide
Magnesium aluminometasilicate (Neusilin)
Aerosil
silica-lipid hybrid microparticles

## Lipid-based drug delivery systems

| Protection   | • By dosing in lipids  
|             | • By encapsulation in nano-emulsions |
| Solubilization | • Drug dosed in solution  
|              | • Digestion of excipients  
|              | • Solubilization in mixed micelles |
| Permeability | • Medium chain fatty acids – can open tight junctions |
| Efflux transporters | • Some surfactants are inhibitors of efflux pumps |
| Cyp enzymes | • Some surfactants inhibit Cyp3A4 |
| Lymphatic transport | • Long chain fatty acids can induce lymphatic transport  
|              | • \( \log P > 5; S_{TG} > 50 \text{ mg/g} \) |
Lipid-based drug delivery systems

Uptake of Drug from Lipid Based Formulations

From Porter, Trevaskis and Charman, 2007, Nature Reviews vol. 6, 231-248
Absorption to the systemic circulation

- Major pathway
  - GI-tract
  - Portal blood
  - Lymph
- Minor pathway
  - Hepatic metabolism
  - Systemic circulation
The lymphatic system

Anatomy:
- Lymph vessels are distributed along the blood vessels. Not circulating.

Function:
- Maintain the body’s water balance.
  - Drain extracellular fluid from tissue to the blood
- Important role in the immune system (lymphocytes).
- Transport of absorbed lipids from the intestine to the blood.

Closely related to lipid digestion and absorption
Lacteals in villi drain the endothelial cells

Pore radius 100-150 Å
Lipid Absorption and Transport

(Porter et al., 2007)
The Intestinal Lymphatics:

**Chylomicrons**

- Lipoprotein particle
- Formed in the endothelial cells from absorbed and endogenous lipids
- TG core coated with cholesterol, phospholipids and apolipoproteins
- 75-1200 nm
- 1-2% of mesenteric lymph
- Degraded by lipoprotein lipase to chylomicron remnants that are cleared in the liver.
Lymphatic Transport of halofantrine
Canine model

Lymphatic transport

Only relevant for lipophilic compounds:

LogP > 5
Solubility in TG > 50 mg/g

That are dosed with LIPIDS

Development of Lipid-Based DDS
Dynamic Lipolysis Model

Principle: pH-stat, pH 6.5, 37°C
Titration of generated fatty acids

<table>
<thead>
<tr>
<th>Component</th>
<th>Initial concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>5 mM</td>
</tr>
<tr>
<td>Lecithin</td>
<td>1.25 mM</td>
</tr>
<tr>
<td>Trizma maleate</td>
<td>2 mM</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>150 mM</td>
</tr>
<tr>
<td>SNEDDS</td>
<td>1.5 g</td>
</tr>
<tr>
<td>Drug</td>
<td>X mg</td>
</tr>
<tr>
<td>Pancreatic lipase</td>
<td>800 UPS /ml</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.045 mmol/min</td>
</tr>
</tbody>
</table>
in vitro lipolysis

Titration of generated fatty acids with NaOH
Drug fate during \textit{in vitro} lipolysis of SNEDDS

- **SMEDDS**
  - Vehicle phase
  - Dissolved drug

- **Lipolysis medium** (Fasted state)
  - Micelle

- **Pancreatic extract**

- **Emulsification Lipolysis**

- **Continued Lipolysis**

- **Solubilized drug**
- **Micelle**
- **Vesicles (uni-/multilamellar)**
- **Microemulsion droplet**
- **Pancreatic lipase**
- **Pancreatic co-lipase**
- **Precipitated free drug**
- **Co-Precipitates of free drug and lipids**
Cryo-TEM of Lipolysis media

$t = 5$ min

**Fasted state**
5 mM BS / 1.25 mM PL

**Fed state**
20 mM BS / 5 mM PL
Human intestinal fluids

Fed state: 60 min after intake of an emulsion
Dynamic *in vitro* lipolysis

Controlling the rate of lipolysis

Enzyme inhibition

(Ultra)centrifugation

HPLC

Controlling the rate of lipolysis
Example:
Bioavailability study in mini-pigs

Purpose:

- Influence of emulsion particle size of SEDDS (nm $\geq \mu$m)
- Compare SEDDS with simple oil solution and powder
- Impact of concurrent food administration

Nielsen et al EJBP, 2008
Mini-pig study

Sixway cross over – Latin square design
Fasted vs Fed state (high-fat meal)

Model drug: **Probucol**
\[ \text{logP} > 10 \]
MW = 516
\[ S_w : 2-5 \text{ ng/ml} \]

**Control:**
Powder (18.3±0.6µm)
1:1 w/w dispersion with lactose

**Lipid based formulations:**
- Oil solution
- SNEDDS
- SMEDDS
- Cremophor RH40 micellar system

**I.V.:**
o/w emulsion for infusion

Nielsen et al EJBP, 2008
Case study: Does size matter? Mini-pig study – Probucol (LogP = 10)

### Composition and particle size

<table>
<thead>
<tr>
<th></th>
<th>Cremophor solution</th>
<th>SMEDDS</th>
<th>SEDDS</th>
<th>Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Micelles</td>
<td>30:60:10</td>
<td>26.67:53.33:20</td>
<td>00:90:10</td>
</tr>
<tr>
<td>Cr RH40</td>
<td>109.3</td>
<td>36.4</td>
<td>36.4</td>
<td>0</td>
</tr>
<tr>
<td>M:O</td>
<td>0</td>
<td>72.8</td>
<td>72.8</td>
<td>109.3</td>
</tr>
<tr>
<td>EtOH</td>
<td>12.1</td>
<td>12.1</td>
<td>27.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Probufol</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

| Admin per kg         | Saline             | 14.5 ±0.3 nm | 45.0 ±3.4 nm | 4.58 ±0.84 µm | NA            |
|                      | FaSSIF             | 12.5 ±0.9 nm | 42.6 ±1.5 nm | 2.56 ±1.49 µm | -             |
|                      | FeSSIF             | 13.5 ±0.5 nm | 44.1 ±1.0 nm | 3.06 ±0.58 µm | -             |

| Droplet size         |                   |              |              |               |
|                      | Saline             | 14.5 ±0.3 nm | 45.0 ±3.4 nm | 4.58 ±0.84 µm | NA            |
|                      | FaSSIF             | 12.5 ±0.9 nm | 42.6 ±1.5 nm | 2.56 ±1.49 µm | -             |
|                      | FeSSIF             | 13.5 ±0.5 nm | 44.1 ±1.0 nm | 3.06 ±0.58 µm | -             |
|                      | Dispersion time    | <10 min      | <3.5 min     | <1.5 min      | NA            |

Nielsen et al EJPS 2008
Plasma profiles

Fasted state

-fed state
Development of SNEDDS

Traditionally:
- API in solution at 70-80% of SNEDDS solubility
- NO precipitation during in vitro lipolysis

BUT:
- Solubility of API in SNEDDS is often LOW!
- API precipitation common during in vitro lipolysis

SO:
- What about supersaturation... suspensions etc...?

And – does precipitation during in vitro lipolysis matter
SNEDDS Loading Schemes

- Super-SNEDDS solution (200%) 0.2 g lipid
- Super-SNEDDS suspension (200%) 0.2 g lipid
- Chasing principle 0.4 g lipid
- SNEDDS 80% 0.4 g lipid
- Stability
  - In vitro lipolysis
  - In vivo
  - PK studies
- Aqueous suspension

In vivo performance

SNEDDS 80%

0.4 g lipid

Super-SNEDDS solution (200%)

0.2 g lipid

Chasing principle

0.4 g lipid

SNEDDS 80%

0.4 g lipid
super-SNEDDS preparation

prepare SNEDDS by mixing lipid, surfactant, cosolvent

add drug above $s_{eq}(150\%)$

suspension

heating cycle 3 h at 60°C

cooling cycle overnight at 37°C

supersaturated solution

super-SNEDDS

in vitro characterisation physical stability
Halofantrine Super-SNEDDS

Antimalarial drug: $pK_a \approx 9$, $\log P \approx 8.5$, BCS II
- MC-SNEDDS: 28.2 mg HAL (75%); 1x, 2x
- MC-super-SNEDDS: 56.4 mg HAL (150%); 1x

Polarised light microscopy:
- no drug crystals in (MC) S-SNEDDS detected

Stability > 8 months ($25^\circ C$) in glass vials

Chemical stability:
97% of declared HAL content found after 5 months storage at $25^\circ C$ of MC-super-SNEDDS
Solubilization during *in vitro* Lipolysis: halofantrine

Thomas et al. JCR 2012
Precipitation during *in vitro* Lipolysis: halofantrine

Halofantrine precipitate amorphous during *in vitro* lipolysis
In vivo performance – SNEDDS with halofantrine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MC-SNEDDS 1 Caps (28.2 mg HAL)</th>
<th>MC-SNEDDS 2 Caps (56.4 mg HAL)</th>
<th>MC-super-SNEDDS 1 Caps (56.4 mg HAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>$388 \pm 64.5^a$</td>
<td>$621 \pm 256^{ab}$</td>
<td>$1167 \pm 245^b$</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>$2.7 \pm 0.3$</td>
<td>$3.0 \pm 0.4$</td>
<td>$2.5 \pm 0.2$</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-28)}$ (ng·h/ml)</td>
<td>$4458 \pm 639^a$</td>
<td>$6826 \pm 2234^{ab}$</td>
<td>$11263 \pm 1719^b$</td>
</tr>
<tr>
<td>Absolute bioavailability (%)</td>
<td>$41.0 \pm 5.0$</td>
<td>$31.5 \pm 10.4$</td>
<td>$53.2 \pm 8.6$</td>
</tr>
</tbody>
</table>

Thomas et al. JCR 2012
What about rats?

Smaller dose – smaller gastro-intestinal volumes
Higher gastric pH
Continuous bile secretion

But – preferred preclinical species

Will super-SNEDDS work?

Excipient	 %
Soybean oil	 27.5
Maisine 35-1	 27.5
Kolliphor RH40	 35
Ethanol	 10

Michaelsen MH et al, AAPS J, 2015
Formulations approaches

- **Super-SNEDDS solution (200%)**
  - 0.2 g lipid
- **Super-SNEDDS suspension (200%)**
  - 0.2 g lipid
- **Chasing principle**
  - 0.4 g lipid
- **SNEDDS 80%**
  - 0.4 g lipid
- **Aqueous suspension**
- **Stability**
  - *In vitro* lipolysis
  - *In vivo* PK studies

*University of Copenhagen*
*Department of Pharmacy*
Additional Question:

Can SNEDDS be transferred into a Controlled release drug Delivery system?

Tool: Orlistat (tetrahydrolipstatin)
Lipase inhibitor – lipid soluble

Michaelsen MH et al, AAPS J, 2015
Rat study – conclusions

• SuperSNEDDS work in rats
• Orlistat control release of Hf

Lipolysis needed for drug absorption?

Michaelsen MH et al, AAPS J, 2015
SNEDDS Loading Schemes

- **Super-SNEDDS solution (200%)**
  - 0.2 g lipid

- **Super-SNEDDS suspension (200%)**
  - 0.2 g lipid

- **Chasing principle**
  - 0.4 g lipid

- **SNEDDS 80%**
  - 0.4 g lipid

Stability
- *In vitro* lipolysis
- *In vivo* PK studies

- **Aqueous suspension**
**Case study:**
Can co-admin of SNEDDS and an aqueous suspension increase exposure in rats?

**5 Treatments:**
- SNEDDS 80%
- Super-SNEDDS solution 200%
- Super-SNEDDS suspension 100% + 100%
- Aqueous suspension
- Chasing principle: Aq suspension + placebo SNEDDS

*In vivo* study: Fasted rats
Oral Gavage of dispersions

**Model drugs:**
R3040 (Neutral, Log P: 10.4, $S_{\text{SNEDDS}}$: 205 mg/kg)
Cinnarizine (weak base, Log P: 5.8, $S_{\text{SNEDDS}}$: 25 mg/kg)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean oil</td>
<td>27.5</td>
</tr>
<tr>
<td>Maisine 35-1</td>
<td>27.5</td>
</tr>
<tr>
<td>Kolliphor RH40</td>
<td>35</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10</td>
</tr>
</tbody>
</table>

Siqueira et al (in prep)
Case study:
Can co-admin of SNEDDS and an aqueous suspension increase exposure in rats?

**R3040** (LogP: 10.4, $S_{SNEDDS}$: 205 mg/g)
Dose: 20 mg/kg

**Cinnarizine** (LogP: 5.8, $S_{SNEDDS}$: 25 mg/g)
Dose: 25 mg/kg

- R3040: SNEDDS 80% = super-SNEDDS solution > The other formulations
- Cinnarizine: SNEDDS 80% = Chasing Principle > The other formulations
**Case study:**
Can co-admin of SNEDDS and an aqueous suspension increase exposure in rats?

**R3040** (LogP: 10.4, $S_{SNEDDS}$: 205 mg/g)
Dose: 20 mg/kg

**Cinnarizine** (LogP: 5.8, $S_{SNEDDS}$: 25 mg/g)
Dose: 25 mg/kg

SNEDDS 80% = super-SNEDDS solution > The other formulations

SNEDDS 80% = Chasing Principle > The other formulations

More lipid (SNEDDS) dosed for the SNEDDS 80% and the Chasing Principle

**THUS:**

R3040 need to be dosed in solution for optimal absorption

Cinnarizine can dissolve in vivo – therefore co-dosing of SNEDDS (Chasing Principle) provide optimal absorption

**BUT –** what about IVIVC...?

*Siqueira et al (in prep)*
# One-step intestinal *in vitro* lipolysis model (R3040)

## Composition of lipolysis media

<table>
<thead>
<tr>
<th>Component</th>
<th>Initial composition (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>2.95</td>
</tr>
<tr>
<td>NaCl</td>
<td>50</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>0.26</td>
</tr>
<tr>
<td>Maleic acid</td>
<td>2</td>
</tr>
<tr>
<td>Tris</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>600 USP units/mL</td>
</tr>
</tbody>
</table>

---

Dias 70
**IVIVR...**

**R3040** (Log P: 10.4, $S_{\text{SNEDDS}}$: 205 mg/g)
Dose: 20 mg/kg

**In vitro – intestinal lipolysis:**
R3040 in aqueous phase

No rank order correlation with solubilization
How to improve the *in vitro* lipolysis model?

**Consider the physiology of the rat**
- Volume to dose ratio
- Stomach:
  - Residence time
  - Gastric lipolysis (lingual)
  - Gastric pH 4 in rats
- Gastric emptying rate
- Intestine:
  - bile salt & phospholipid levels

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**Composition of NEW media**

<table>
<thead>
<tr>
<th>Compound</th>
<th>FaSSGF</th>
<th>FaSSIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>0.08</td>
<td>50</td>
</tr>
<tr>
<td>NaCl</td>
<td>34.2</td>
<td>70</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>0.02</td>
<td>3.7</td>
</tr>
<tr>
<td>Maleic acid</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tris</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>600 USPunits/mL</td>
<td></td>
</tr>
</tbody>
</table>

**pH**
- 4
- 6.5

*Concentrations before addition of gastric content*
Two-step “rat” in vitro lipolysis model

Added volumes of dispersed formulations

<table>
<thead>
<tr>
<th></th>
<th>R3040 (mL)</th>
<th>Cinnarizine (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNEDDS 80%</td>
<td>6.25</td>
<td>10.63</td>
</tr>
<tr>
<td>Chasing placebo SNEDDS</td>
<td>6.25</td>
<td>10.63</td>
</tr>
<tr>
<td>Chasing aq suspension</td>
<td>6.50</td>
<td>8.60</td>
</tr>
<tr>
<td>Super-SNEDDS</td>
<td>2.5</td>
<td>4.34</td>
</tr>
<tr>
<td>Aq suspension</td>
<td>6.50</td>
<td>8.60</td>
</tr>
</tbody>
</table>

Initial volume of gastric media: 10 mL

Initial volume of intestinal media: 32 mL

Volume of pancreatin (179 USP/mL): 3 mL

Replacement of the collected volume with intestinal media

Siqueira et al (in prep)
Two-step “rat” in vitro lipolysis model

**R3040** (Log P: 10.4, $S_{\text{SNEDDS}}$: 205 mg/g)
Dose: 20 mg/kg

**In vitro – intestinal step:**
R3040 in aqueous phase

The new model result in **Rank order correlation** with solubilization

Siqueira et al (in prep)
## Supersaturation and lipid drug delivery

<table>
<thead>
<tr>
<th></th>
<th>Halofantrin</th>
<th>Simvastatin</th>
<th>Cinnarizine</th>
<th>Danazol</th>
<th>Fenofibrate</th>
<th>R3040</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supersaturation in oil (preconcentrate)</strong></td>
<td>Yes (10 month)</td>
<td>Yes (10 month)</td>
<td>Short-term</td>
<td>Yes (days)</td>
<td>Short-term</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Supersaturation during lipolysis</strong></td>
<td>No</td>
<td>Yes (possibly)</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Precipitate during lipolysis</strong></td>
<td>amorphous</td>
<td>amorphous</td>
<td>amorphous</td>
<td>crystalline</td>
<td>crystalline</td>
<td>amorphous</td>
</tr>
<tr>
<td><strong>Super-SNEDDS Increase BA compared to SNEDDS</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
<td>Yes</td>
<td>=</td>
</tr>
</tbody>
</table>

### Considerations:
- Propensity to supersaturate in lipids
- Propensity to supersaturate during in vitro digestion
- Crystalline / amorphous precipitation during lipolysis
- API physchem properties
- etc
SUPERSATURATION
Drug absorption from SNEDDS

- Solubilized drug
- Amorphous drug
- Supersaturated drug
- Crystalline drug

- Dispersion and digestion
- Precipitation

- Mucus layer
- Intestinal epithelium

- Absorption of dissolved drug
- FAST dissolution and absorption
- Absorption of dissolved drug
- SLOW dissolution and absorption
Conclusion

Often drug are dosed in solution in lipid-based Drug Delivery Systems (LbDDS)

Supersaturated LbDDS – and suspensions - actually often also work!
This simplifies the use of lipids

Physiologically relevant models – e.g. including digestion – is often needed when developing LbDDS

Drug precipitation during “traditional” digestion is not necessarily a problem – also consider the solid state from of the precipitate!
Predictive *in vitro* models for enabling DDS

We have gone part of the way – still a long way to go – until we can Predict Bioavailability
The Rational Oral Drug Delivery Research Group

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UBC
Kishor Wasan
Thank you for your attention

Questions?

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