Lipid-Based Excipients with Advanced Functionality

Sharareh Salar-Behzadi

Research Center Pharmaceutical Engineering, GmbH, Graz, Austria
Department of Pharmaceutical Technology and Biopharmacy, University of Graz, Austria
RCPE at a Glance

Key facts
- Located in Graz, Austria
- Non-university, independent research company in the field of pharmaceutical process and product development
- Founded on 1st of July 2008
- > 111 employees and researchers
- Turnover 2018/2019: € 11,8 M
- > 25 Scientific Partners, > 130 Industrial Partners

Our Mission:
- Develop Innovative science driven platform knowledge for process and product design & development
- Increase the sustainability profile by reducing costs and time in pharmaceutical development (e.g. enlarge the knowledge space)
- Create business advantages for our partners

- > € 4 Mio. Gerätewert Labor
- > € 15 Mio. Gerätewert Technikum / Pilot Plant
- Arbeit mit Wirkstoffen bis OENB Klasse 4
- Zertifiziert:
  - ISO 9001 (Qualität)
  - ISO 14001 (Umwelt)
  - ISO 90003 (Software Qualitätsmanagement)
Global DDF Summit, 9-11 March 2020, Berlin

Area I: Modeling and Prediction
- Pharmaceutical process modeling & simulation
- Granular flows
- Fluid mixing and multiphase flows
- Molecular simulations and structure optimization
- Material Science & Characterization

Area II: Advanced Products and Delivery
- Pharmaceutical proteins, Protein drugs
- Oral & Inhaled Dosage forms
- Nano technology
- Novel drug delivery systems
- Simplification on OOFs

Area III: Process and Manufacturing Science
- Continuous processing development and implementation
- Process Understanding & Control (including PAT)
- Process development & Scale up
- Design Space and CPPs qualification

Area IV: CC Flow – Continuous Flow Synthesis and Processing
- Novel flow chemistries
- Designer reagents for flow
- Reactor and process engineering
- PAT and process simulation, Process integration
- API synthesis in flow

Industrial partners:

Scientific partners:

Supporting partners:
Innovative Approach for Manufacturing of Stable Lipid-Based Formulations

- Next Generation Group of Lipid-Based Excipients
Lipid-based Excipient

- Low toxic with the better patient tolerance, bio-compatible and they are easily available
- Nano, micro, macro-scale drug development
  - Solid lipid nanoparticles (SLN), nano lipid carriers (NLC), SEDDS/SMEEDDs, coated multiparticulate systems, tablet matrix, etc.
- Extended release, solubility/permeability enhancer, encapsulation purposes
- Applications
  - Dermal
  - Pulmonary
  - Injectable dosage forms
  - Oral drug delivery

Savla et al. (2017), Review and analysis of FDA approved drugs using lipid-based formulation, DOI: 10.1080/03639045.2017.1342654
Pharmaceutical Excipient

- Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API)
- They are intentionally included in a drug delivery system.
- They are essential for product manufacturing and performance.
- Thus, the successful manufacture of a pharmaceutical product requires the use of well-defined excipients and manufacturing processes that consistently yield a quality product.

Pharmaceutical Excipient

- Pharmaceutical excipients market by the source is segmented as animal-based, plant-based, mineral-based and synthetic based excipients
- Plant-based excipients held the highest revenue in 2018 and it is a fastest growing segment from 2018 to 2025
- Because plant-based excipients (among them oleochemicals) are low toxic with the better patient tolerance, bio-compatible and they are easily available.

Ideal Excipient Properties

Solid State of Lipids

- Polymorphism, phase separation, Crystallite growth, etc.
  - Spontaneous
  - Process-induced
  - Drug-induced

https://www.pharmaexcipients.com/pharmaceutical-excipients-some-definition/
Solid State of Lipids

Molecules containing a fatty acid in their chemical structure, mixtures thereof and modified lipid structures.

Fatty acids

MAG, DAG and TAGs

Polyoxylglycerides
**Solid State of Lipids**

(Adapted from: Structure-Function Analysis of Edible Fats, ed.: A. G. Marangoni, AOCS Press, USA)

- **Polymorphism**
  - Nanocrystal size (0.4-500 nm)
  - Lamellae
  - Nuclei

- **Microstructure**
  - Crystal nanoplatelet
  - Crystal clusters

- **Microstructure**
  - Crystal networks

- **3D structure of crystals**

- **Macroscopic world >0.2 mm**
  - (rheology, mechanical strength, sensory impressions)

**Molecular structure**

TAG: Tripalmitin

*11th Global DDF Summit, 9-11 March 2020, Berlin*
Process and environmental parameters such as temperature and shear force,
Adding defined emulsifier to the system
Solid State of Lipids, X-Ray Powder Diffraction

α-form

SAXS

\[ \text{Intensity} \rightarrow \text{FWHM} \]

β-form

SAXS

\[ \text{Intensity} \rightarrow \text{FWHM} \]

WAXS

\[ \text{Short spacing} \]

Hexagonal (α-form)

small spacing

Small Angle X-Ray Scattering (SAXS)

(0.06°<2θ<8°)

(10-1500Å)

Wide Angle X-Ray Scattering (WAXS)

(16-25°)

(3.3-4.9Å)

11th Global DDF Summit, 9-11 March 2020, Berlin
Solid State of Lipids, DSC

α-form
β'-form
β-form

melting of α-form
Transformation to and crystallization of β-form
melting of β-form
Correlation between solid state of lipids and stable performance of lipid-coated formulations

Manufacturing process: hot melt coating
API: N-acetylcystein (N-ac) crystals
Lipids as coating material:
glyceryl monostearate,
behenoyl polyoxyl-8 glyceride

**Behenoyl polyoxyl-8 glyceride:**
PEG-8 mono and di-esters of behenic acid (>50%), mono, di and triglycerides and free PEG

**Glyceryl monostearate:**
monoglycerides (40-55%), diglycerides (30-45%) and triglycerides (5-15%)
Correlation between solid state of lipids and performance of lipid-coated formulations

**API:** N-ac crystals

**Coating material:** glycercyl monostearate

Salar-Behzadi et al. (2019), https://doi.org/10.1016/j-ijpharm.2019.05.036
Correlation between solid state of lipids and performance of lipid-coated formulations

**API:** N-ac crystals

**Coating material:** behenoyl polyoxyl-8 glyceride

Salar-Behzadi et al. (2019), https://doi.org/10.1016/j-ijpharm.2019.05.036
Next-Generation Lipid-Based Excipients: Polyglycerol esters of fatty acids (WITEPSOL® PMF)
Polyglycerol Esters of Fatty Acids (WITEPSOL® PMF)

- Molecules, composing of polyglycerols (PGm) esterified with saturated fatty acids (Cn).
- Nomenclature of the used PGFAs: "PGm-Cn full/partial":
  - “m” = number of glycerol moieties polymerized
  - “n” = number of carbons of the fatty acid chain
  - “full/partial” → if the polyglycerol is fully or partially esterified
Polyglycerol Esters of Fatty Acids (PGFAs)

- Number of PG moieties
- Full or partial esterification
- Length of fatty acid
- Different HLB
- Different wettability and water uptake
- Different melting points
- Different melt viscosities
Solid State of PGFAs

Triacylglycerols (TAG)

Intermolecular interactions among fatty acid chains: driving the transformation towards the most thermodynamically stable geometry

Polyglycerol fatty acid esters (PGFAs)

Larger space among chains, caused by the ether bond connecting PG moieties, might impair the intermolecular interactions among fatty acid chains: avoiding tilting and polymorphic transformation

Stable solid state
### Solid State of PGFAs

<table>
<thead>
<tr>
<th>PGm</th>
<th>Cn</th>
<th>Esterification</th>
<th>Witepsol® PMF</th>
<th>HLB</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG2</td>
<td>C18</td>
<td>Full</td>
<td>282</td>
<td>2.6</td>
<td>59.4</td>
</tr>
<tr>
<td>PG2</td>
<td>C22</td>
<td>Full</td>
<td>222</td>
<td>1.8</td>
<td>72.5</td>
</tr>
<tr>
<td>PG3</td>
<td>C16/C18 Partial</td>
<td>1683</td>
<td>5.1</td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>PG4</td>
<td>C16 Partial</td>
<td>164</td>
<td>6.0</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C16/C18 Full</td>
<td>2684</td>
<td>3.3</td>
<td>52.8</td>
<td></td>
</tr>
<tr>
<td>PG6</td>
<td>C16/C18 Full</td>
<td>2686</td>
<td>3.1</td>
<td>53.6</td>
<td></td>
</tr>
</tbody>
</table>

https://doi.org/10.1016/j.ejpb.2020.01.012

- a) Melt casting (MC) T0
- b) MC, 6 months RT
- c) MC, 6 months, 40°C
- d) solvent casting (SC)
Application of PGFAs in pharmaceutical product development

- Immediate release multiparticulate systems via hot melt coating
- Extended release matrix tablets
- Solid lipid nanosuspensions
- Spray drying for development of DPI
Immediate release multiparticulate systems via hot melt coating

API: N-ac crystals

Coating material:
PG3-C16/C18 partial (Witepsol® PMF 1683)
PG4-C18 partial (Witepsol® PMF 184)
PG6-C18 partial (Witepsol® PMF 186)

<table>
<thead>
<tr>
<th>PGFA</th>
<th>Viscosity of melt at 100°C (mPa.s)</th>
<th>Melting onset (°C)</th>
<th>Crystallization point (°C)</th>
<th>HLB</th>
<th>Water uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG3-C16/C18 Partial</td>
<td>27.1</td>
<td>54.2±0.6</td>
<td>45.4±1.01</td>
<td>5.1</td>
<td>10.5±0.76</td>
</tr>
<tr>
<td>PG4-C18 Partial</td>
<td>34.2</td>
<td>60.3±0.1</td>
<td>54.3±0.25</td>
<td>5.6</td>
<td>15.92±1.83</td>
</tr>
<tr>
<td>PG6-C18 Partial</td>
<td>44.1</td>
<td>59.3±0.1</td>
<td>52.33±1.36</td>
<td>6.2</td>
<td>24.17±0.1</td>
</tr>
</tbody>
</table>

Ventilus® V-2.5 fluid bed device (Romaco Innojet, Germany), equipped with HMCoater

Hot melt coating process
Immediate release multiparticulate systems via hot melt coating

Specification:
- ≤10% within the first 5 min → Taste masking
- ≥85% within the first 30 min → immediate rel.

Salar-Behzadi et al., 2020. EJPB, 148:107-117
https://doi.org/10.1016/j.ejpb.2020.01.009
Extended Release Matrix Tablets

**API:** Metformin HCl ($15\%_{w/w}$) (freely water-soluble)

**Filler:** Dicalcium phosphate anhydrate ($64.5\%_{w/w}$)

**Lubricant:** Aerosil ($0.5\%_{w/w}$)

**Matrix agent ($20\%_{w/w}$):**
- PG2-C22 Full (Witepsol® PMF 222)
- PG3-C22 Partial (Witepsol® PMF 123)

<table>
<thead>
<tr>
<th>PGFA</th>
<th>HLB</th>
<th>Melting onset (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG2-C22 Full</td>
<td>1.8</td>
<td>72.5±0.1</td>
</tr>
<tr>
<td>PG3-C22 Partial</td>
<td>4.5</td>
<td>73.5±0.56</td>
</tr>
</tbody>
</table>

Stylcam 200R (Medelpharm, France)
Rotary press simulator
Extended Release Matrix Tablets

Salar-Behzadi et al., EJPS, under review
PGFAs for Manufacturing of Solid Lipid Nanoparticles

**API:** Dexamethasone (0.02%\textsubscript{w/w})

**Emulsifier:** Poloxamer 188 (HLB 29) 2.5%\textsubscript{w/w}

**Lipid:**
PG2-C18 Full (Witepsol\textsuperscript{®} PMF 282)
HLB = 2.6
Melting point = 59.4°C

**Final dosage form:**
Lipid nanosuspension

**Manufacturing Process:**
Melt-emulsification followed by hot high pressure homogenization (Panda K2, NS1001L GEA NiroSoavi, Germany).
Stable solid state of PG2-C18 full within the lipid nanosuspension

Stable performance of Solid Lipid Nanoparticles

Corzo, C., et al. EJPB, under revision
PGFAs for Manufacturing of Dry Powder for Inhalation

Application of PGFAs-behenates to Spray drying (SD)

- Processability of conventional lipids through spray drying is strongly limited.

High $T_0$ + no polymorphism: no risk of low crystallization forms -> processable (yield up to 70%)

Lipid crystallization in SD: solvent evaporation + melt solidification
**PGFAs for Manufacturing of Dry Powder Inhalation**

**API:** Ibuprofen free acid (10% w/w)

**Emulsifier:** Poloxamer 188 (HLB 29) 2.5% w/w

**Lipid:**
PG3-C22 Partial (Witepsol® PMF 123)

**HLB = 3.7**

**Solvent:** Tetrahydrofuran

**Final dosage form:**
Lipid nanosuspension

**Manufacturing process:**
Co-spray drying of PGFA+API in tetrahydrofuran solution

Inhalable particles (MMAD:1–5µm) with large size (VMD>3µm) and low density ($\rho_{\text{tap}}<0.4$) for systemic delivery of analgesics

<table>
<thead>
<tr>
<th>Inhalability via Next Generation Impactor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MMAD (µm)</td>
<td>4.121 ± 0.235</td>
</tr>
<tr>
<td>Emitted dose (%)</td>
<td>97.2 ± 2.7</td>
</tr>
<tr>
<td>Fine particle fraction (%)</td>
<td>28.6 ± 2.2</td>
</tr>
</tbody>
</table>

**VMD = 6.260 ± 0.035 µm**

$\rho_{\text{tap}} = 0.195 ± 0.012 \text{ g/cm}^3$
Conclusions

PGFAs are the next generation of lipid-based excipient

Diversity of compounds in terms of HLB, melting point, and wettability combined with stable solid state

Diversity of pharmaceutical dosage forms with advanced stable performance
Acknowledgements