# Lipid-Based Excipients with Advanced Functionality

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Bundesministerium Digitalisierung und Wirtschaftsstandort
Bundesministerium Verkehr, Innovation und Technologie
Das Land Steiermark
COMET Competence Centers for Excellent Technologies
FFG
SFG

K1 Competence Center - Initiated by the Federal Ministry for Transport, Innovation & Technology (BMVIT) and the Federal Ministry of Digital and Economic Affairs (BMDW). Funded by FFG, Land Steiermark and Steirische Wirtschaftsförderung (SFG).

TU Graz Graz University of Technology
UNI GRAZ
JOANNEUM RESEARCH

# RCPE at a Glance

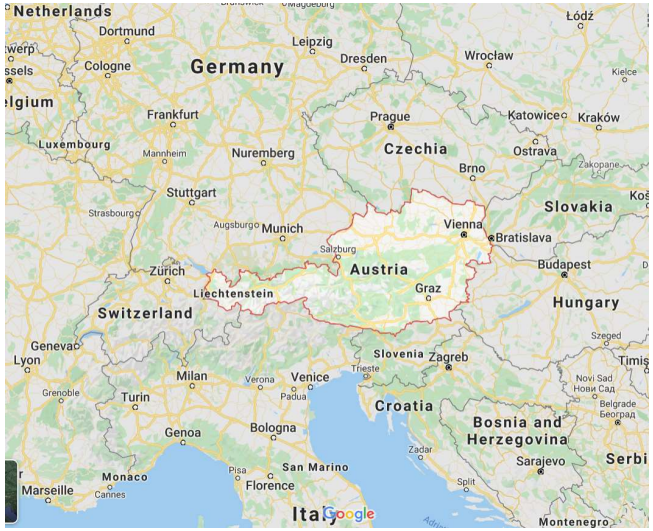
## Key facts

- 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

- > **€ 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)

## 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




## 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 form
Nano technology
Novel drug delivery systems
Simplification on ODFs

## 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
Reaction and process engineering
PAT and process simulation, Process integration
API synthesis in flow

QbD/PAT

Innovation for our partners

### Industrial partners:


### Scientific partners:


### Supporting partners:

# Innovative Approach for Manufacturing of Stable Lipid-Based Formulations

- Next Generation Group of Lipid-Based Excipients

research center pharmaceutical engineering

IOI OLEOCHEMICAL

# 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/SMEDDs, coated multiparticulate systems, tablet matrix, etc.
- Extended release, solubility/permeability enhancer, encapsulation purpose
- 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.**

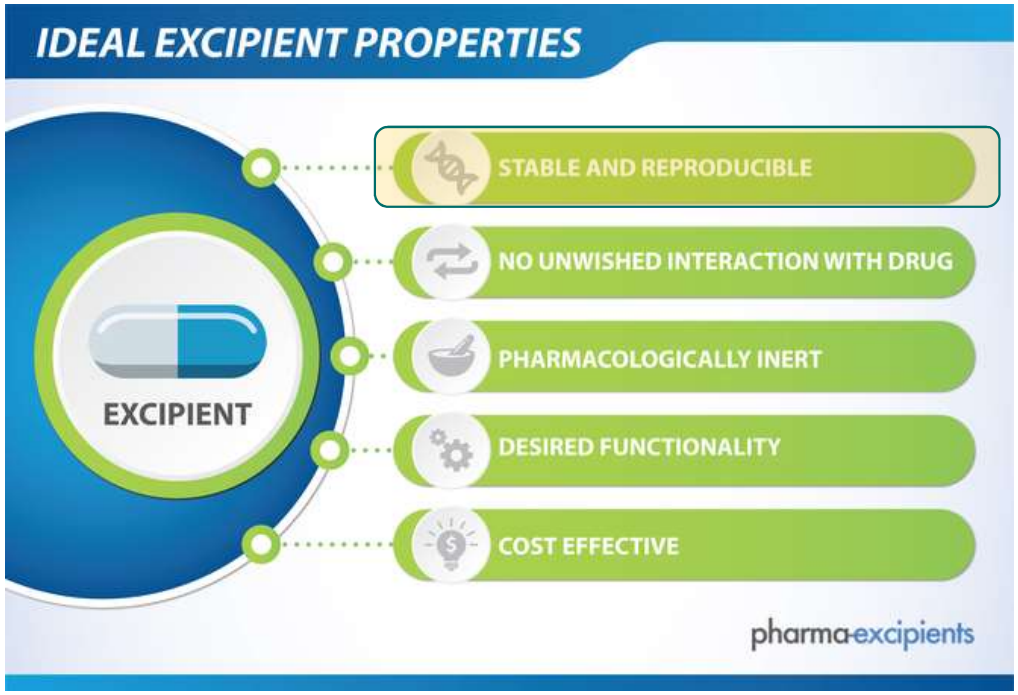
https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf

# 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.

NEW YORK, Aug. 26, 2019 /PRNewswire/ -- Read the full report: https://www.reportlinker.com/p04155351/?utm_source=PRN

# Ideal Excipient Properties



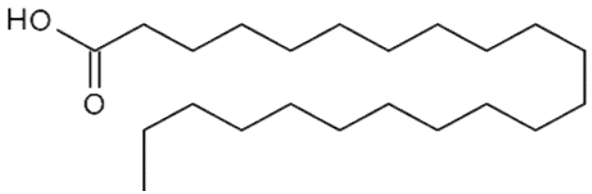

https://www.pharmaexcipients.com/pharmaceutical-excipients-some-definition/

Solid State of Lipids

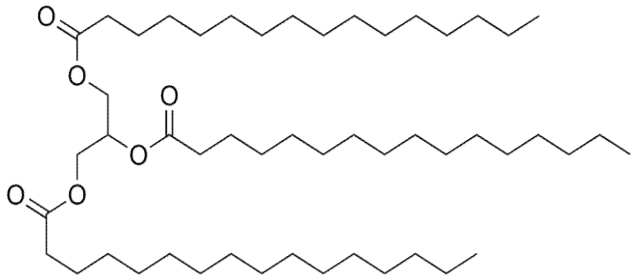
- Polymorphism, phase separation, Crystallite growth, etc.
  - Spontaneous
  - Process-induced
  - Drug-induced

# Solid State of Lipids

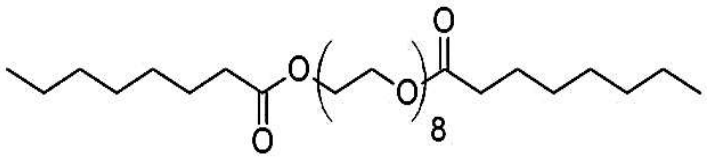
Molecules containing a fatty acid in their chemical structure, mixtures thereof and modified lipid structures.




*Fatty acids*




*MAG, DAG and TAGs*




*Polyoxylglycerides*

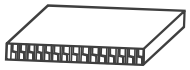
# Solid State of Lipids

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

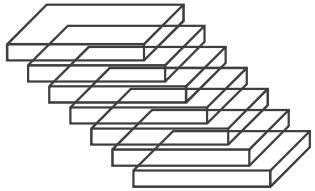
Microstructure (0.5-200 µm)

Polymorphism Nanocrystal size (0.4-500 nm)

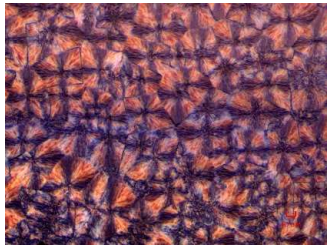
Crystal nanoplatelet



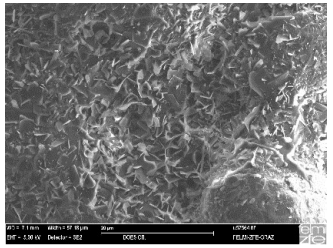
Crystal clusters



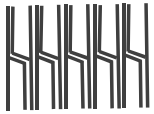
Crystal networks



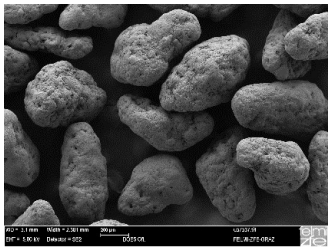
3D structure of crystals



Lamellae

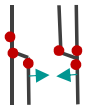


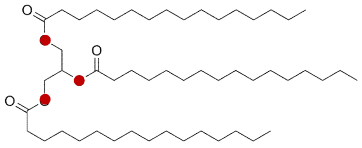
Macroscopic world >0.2 mm (rheology, mechanical strength, sensory impressions)

Molecular structure

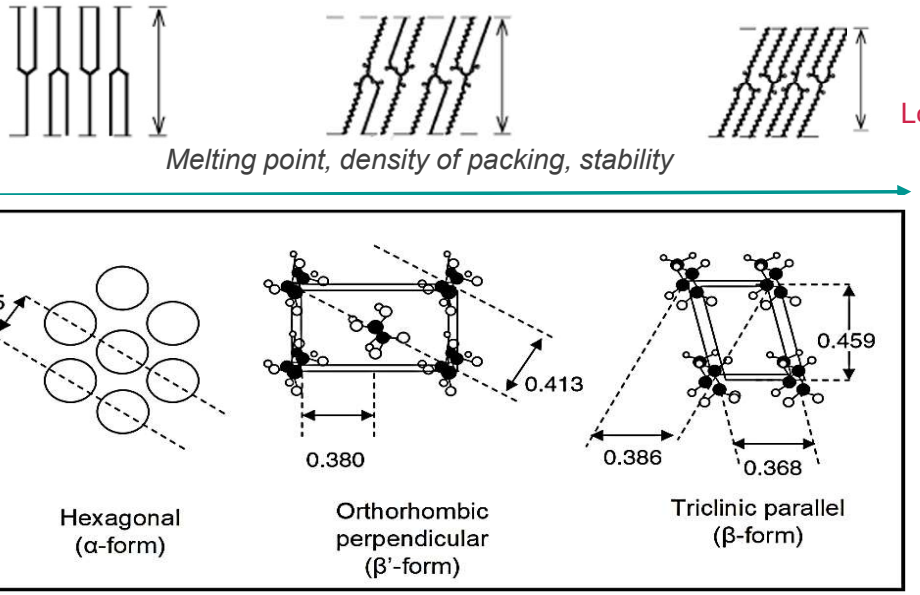
Nuclei

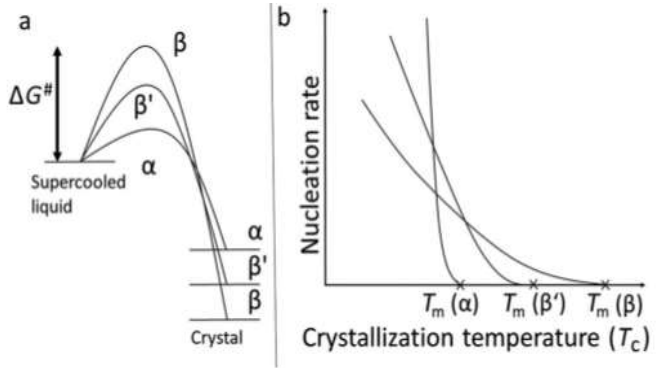




*TAG: Tripalmitin*

# Solid State of Lipids



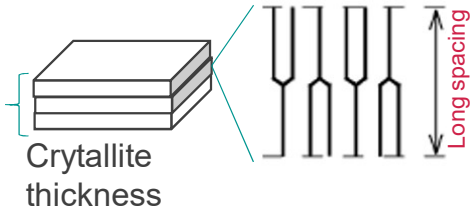

Process and environmental parameters such as

temperature and shear force,

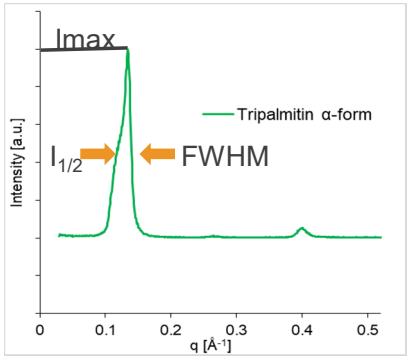
Adding defined emulsifier to the system

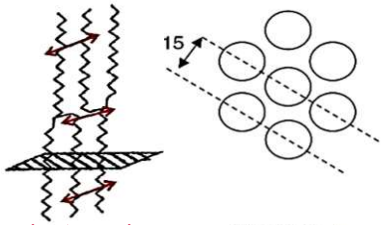
# Solid State of Lipids, X-Ray Powder Diffraction

## α-form

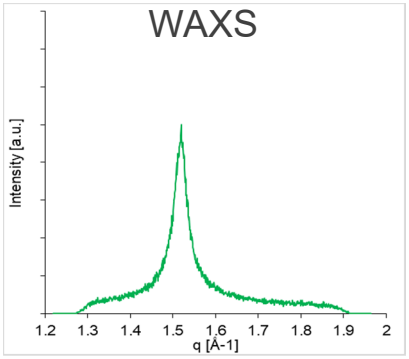



SAXS

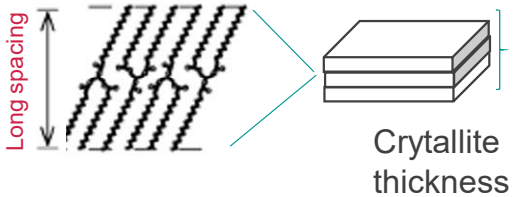


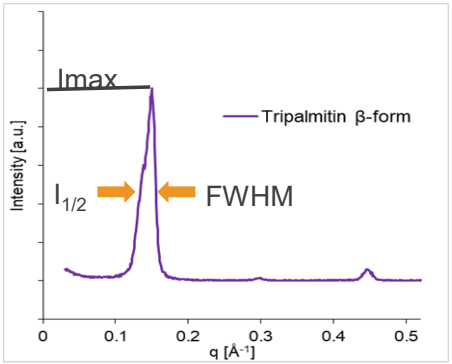

WAXS

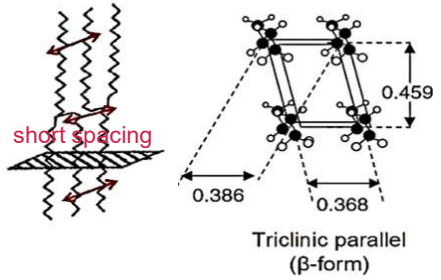



## β-form

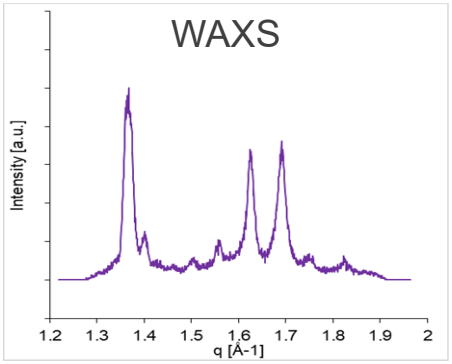



SAXS



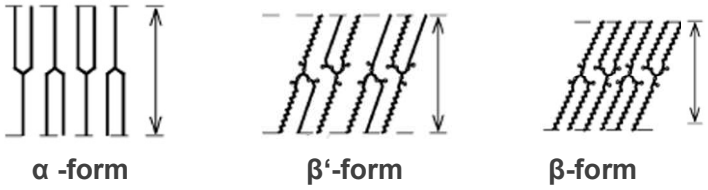

WAXS

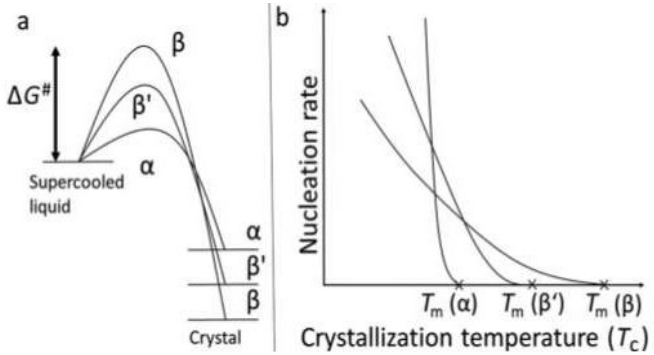


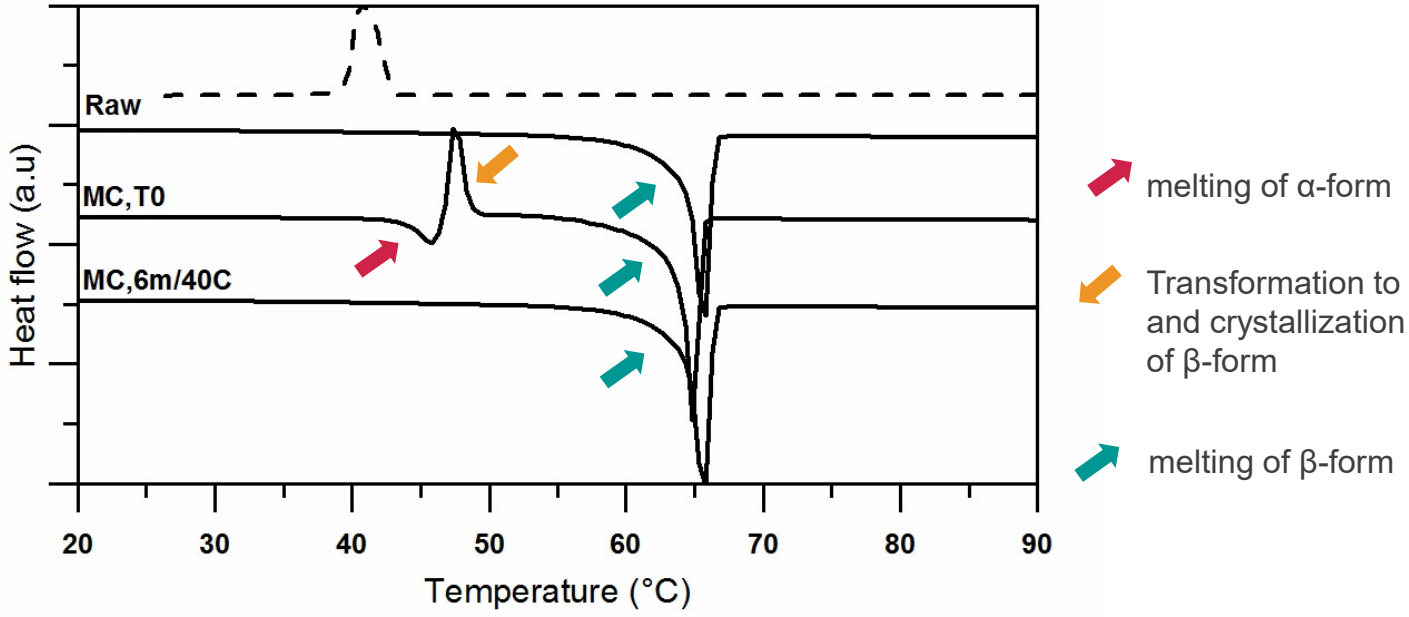

Small Angle X-Ray Scattering
(SAXS)
(0.06°<2θ<8°)
(10-1500Å)

Wide Angle X-Ray Scattering
(WAXS)
(16-25°)
(3.3-4.9Å)

# Solid State of Lipids, DSC



# Correlation between solid state of lipids and stable performance of lipid-coated formulations

**Manufacturing process:** hot melt coating

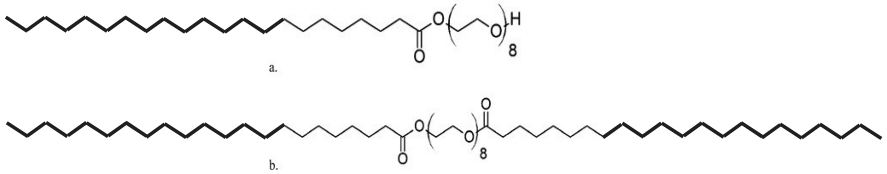
**API:** N-acetycystein (N-ac) crystals

**Lipids as coating material:**

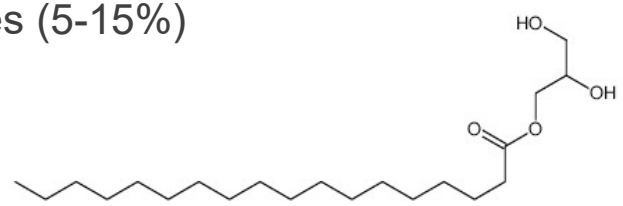
glyceryl monostearate,

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



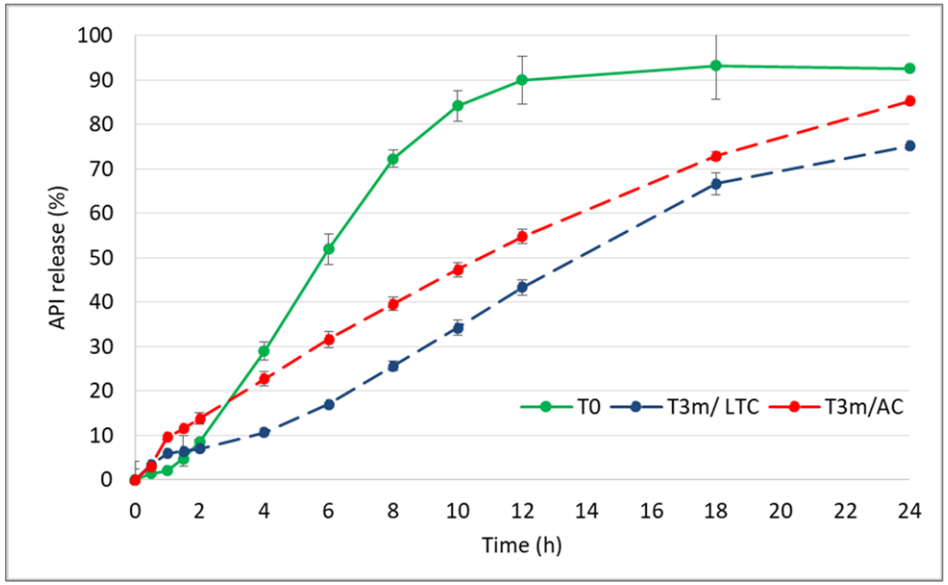

**Glyceryl monostearate:**
monoglycerides (40-55%), diglycerides (30-45%) and triglycerides (5-15%)



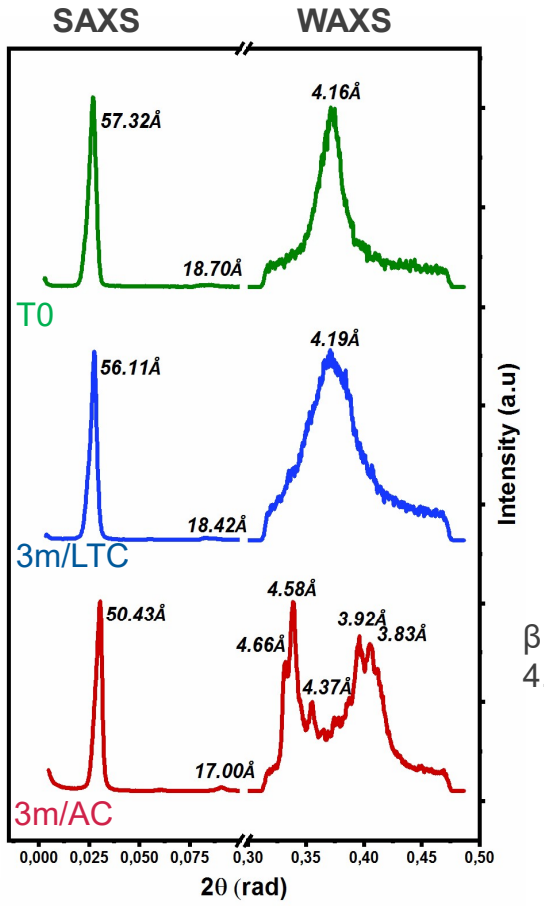
# Correlation between solid state of lipids and performance of lipid-coated formulations

**API:** N-ac crystals

**Coating material:** glyceryl monostearate




Salar-Behzadi et al. (2019), https://doi.org./10.1016/j-ijpharm.2019.05.036



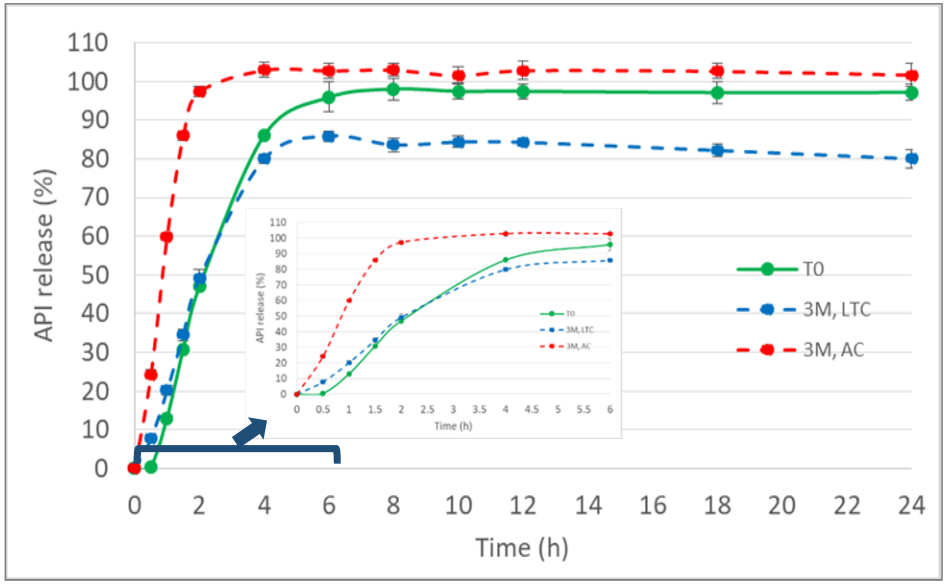

α: 4.15Å

β:
4.59, 3.86, 3.68Å

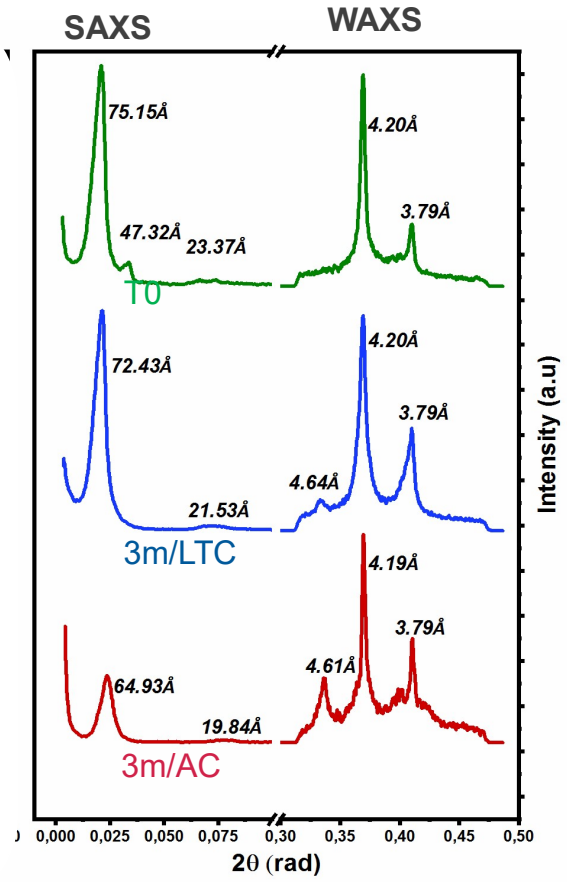
# Correlation between solid state of lipids and performance of lipid-coated formulations

**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

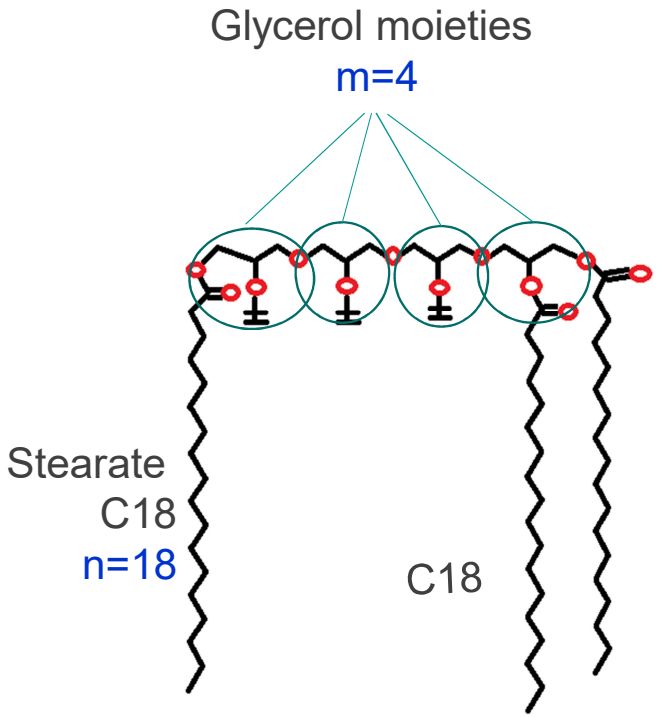


# Next-Generation Lipid-Based Excipients:

# Polyglycerol esters of fatty acids (WITEPSOL® PMF)

# Polyglycerol Esters of Fatty Acids (WITEPSOL® PMF)

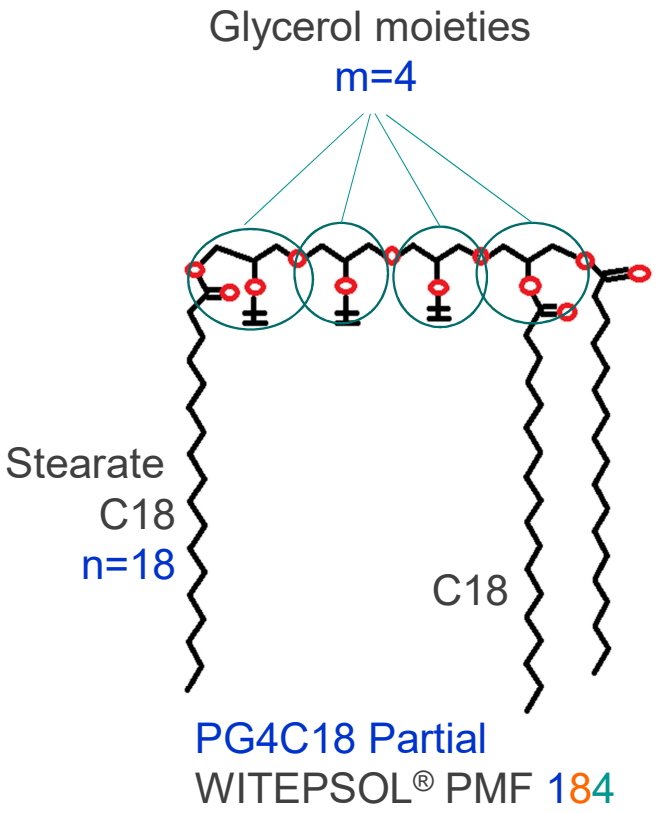
- Molecules, composing of polyglycerols (PGm) esterified with saturated fatty acids (Cn).
- Nomenclature of the used PGFAs: "PGm-Cn full/partial“:
  “m” = number of glycerol moieties polymerized
  “n” = number of carbons of the fatty acid chain
  “full/partial” → if the polyglycerol is fully or partially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

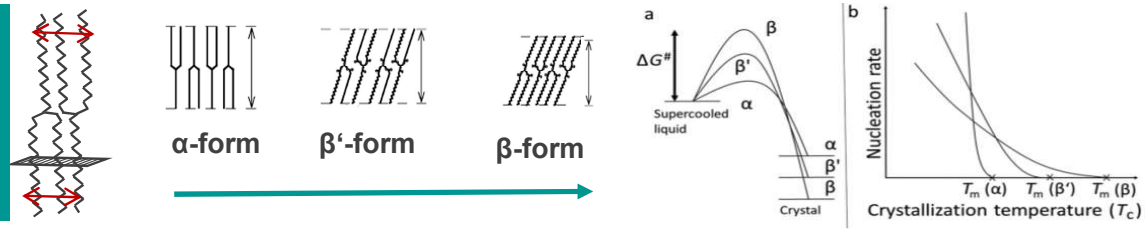



PG4C18 Partial
WITEPSOL® PMF 184

# Solid State of PGFAs

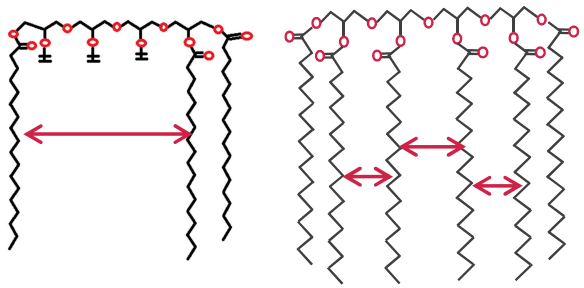
## Triacylglycerols (TAG)

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

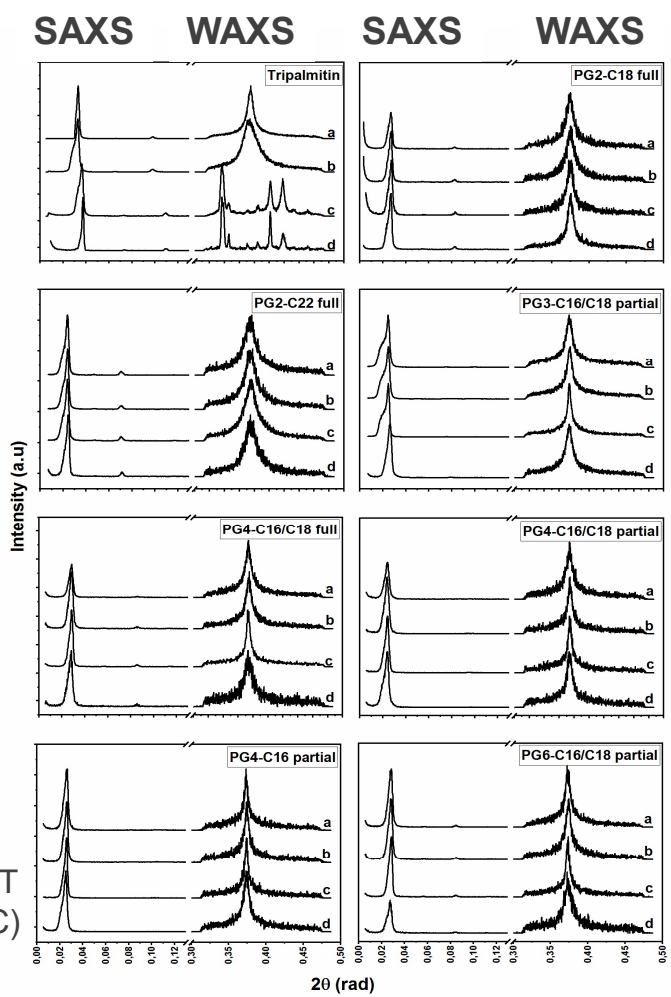


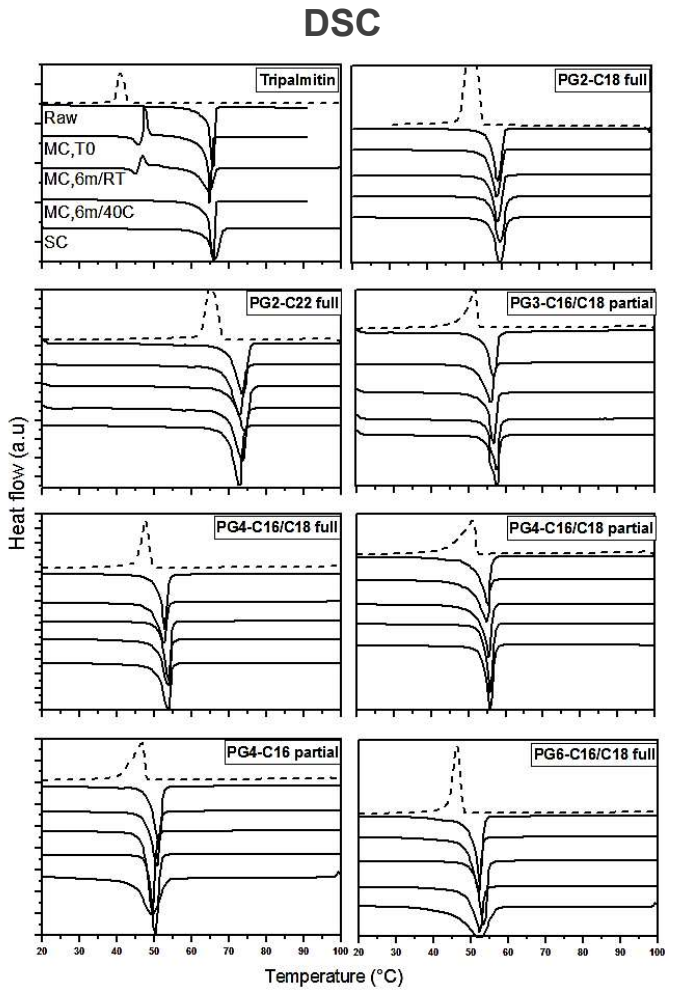
Stable solid state

# Solid State of PGFAs

| PGm | Cn | Esteri-fication | Witepsol® PMF | HLB | Melting Point (°C) |
|---|---|---|---|---|---|
| PG2 | C18 | Full | 282 | 2.6 | 59.4 |
| PG2 | C22 | Full | 222 | 1.8 | 72.5 |
| PG3 | C16/C18 | Partial | 1683 | 5.1 | 56.5 |
| PG4 | C16 | Partial | 164 | 6.0 | 50.8 |
| | C16/C18 | Full | 2684 | 3.3 | 52.8 |
| | C16/C18 | Partial | 1684 | 5.9 | 54.6 |
| PG6 | C16/C18 | Full | 2686 | 3.1 | 53.6 |

Corzo, C., et al. 2020. EJPB, 148:134-147
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

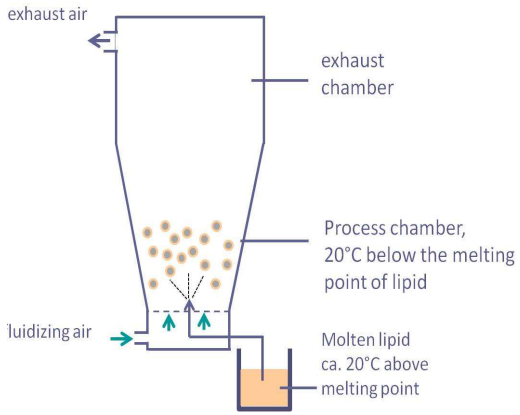
**API:** N-ac crystals

**Coating material:**

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

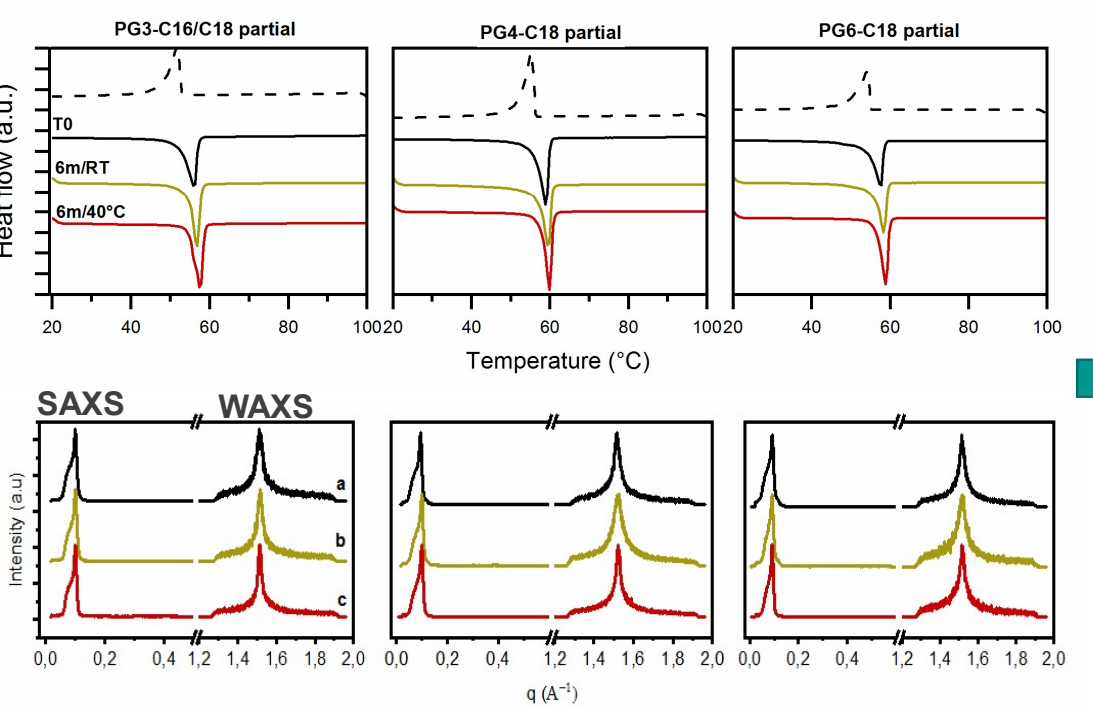
**Ventilus® V-2.5** fluid bed device (Romaco Innojet, Germany), equipped with HMCoater

Hot melt coating process

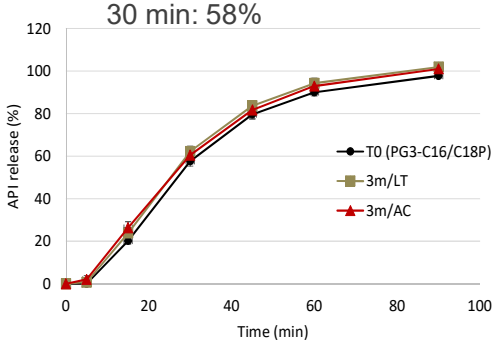



| PGFA | Viscosity of melt at 100°C (mPa.s) | Melting onset (°C) | Crystallization point (°C) | HLB | Water uptake (%) |
|---|---|---|---|---|---|
| PG3-C16/C18 Partial | 27.1 | 54.2±0.6 | 45.4±1.01 | 5.1 | 10.5±0.76 |
| PG4-C18 Partial | 34.2 | 60.3±0.1 | 54.3±0.25 | 5.6 | 15.92±1.83 |
| PG6-C18 Partial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

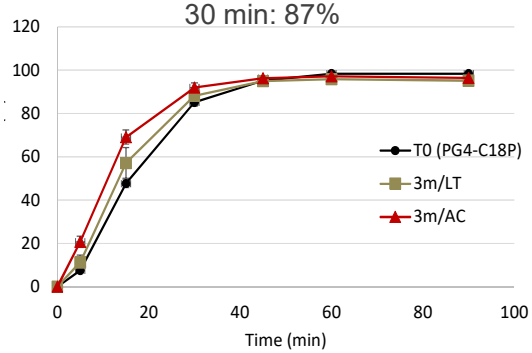
# Immediate release multiparticulate systems via hot melt coating



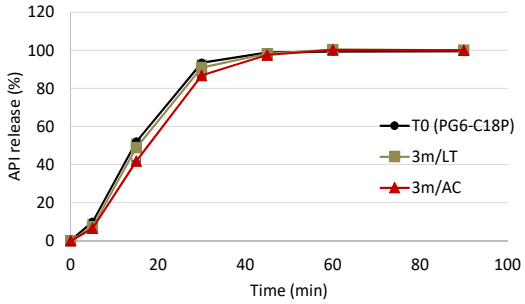

**P63-C16/C18 P, HLB 5.1**
5 min: 0.5%
30 min: 58%




**PG4C18 P, HLB 5.6**
5 min: 7.5%
30 min: 87%




**PG6-C18P, HLB 6.2**
5 min: 9.95%
30 min: 93%




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%$_{w/w}$)**:**

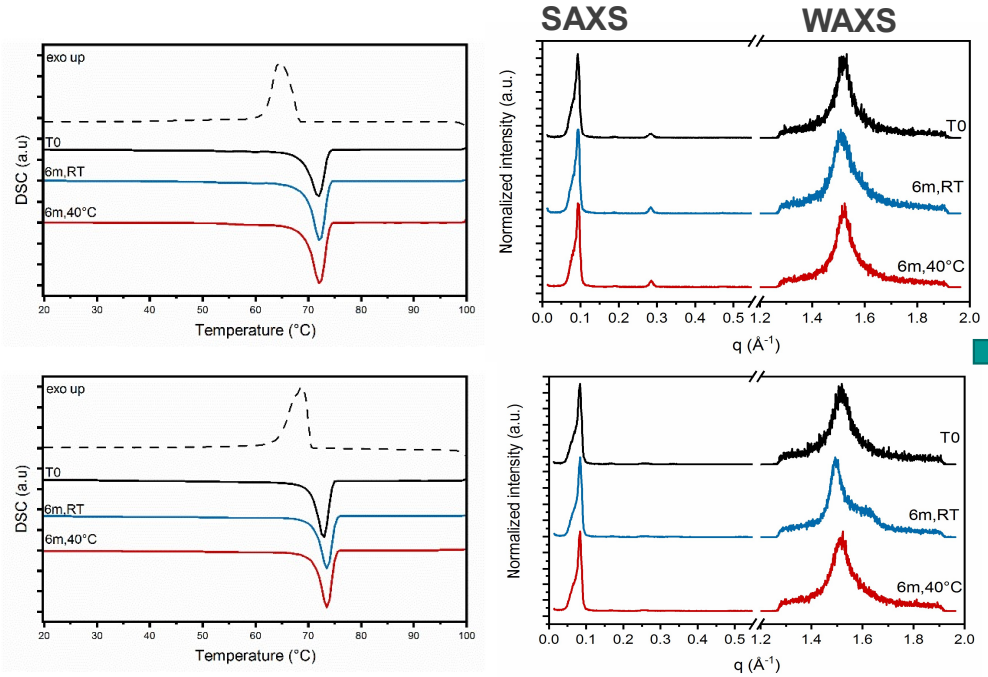
PG2-C22 Full (Witepsol® PMF 222)

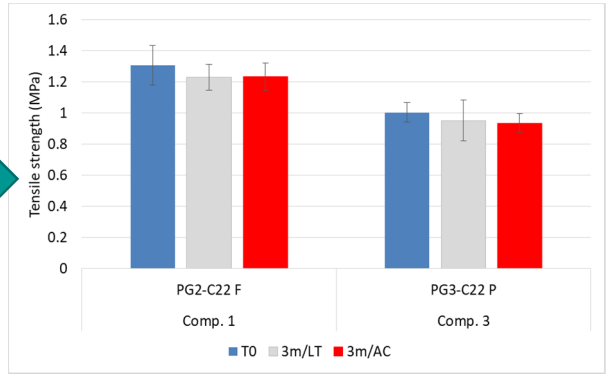
PG3-C22 Partial (Witepsol® PMF 123)

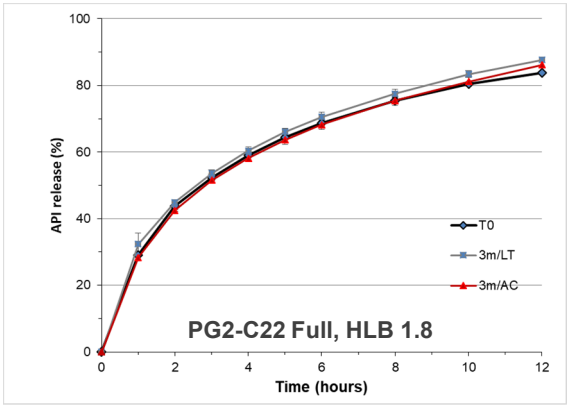
| PGFA | HLB | Melting onset (°C) |
|---|---|---|
| PG2-C22 Full | 1.8 | 72.5±0.1 |
| PG3-C22 Partial | 4.5 | 73.5±0.56 |

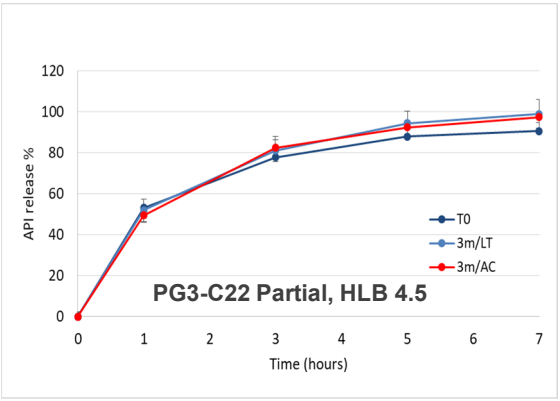
**Stylcam 200R** (Medelpharm, France)
Rotary press simulator

# Extended Release Matrix Tablets




Salar-Behzadi et al., EJPS, under review

# PGFAs for Manufacturing of Solid Lipid Nanoparticles

**API:** Dexamethasone (0.02%$_{w/w}$)

**Emulsifier:** Poloxamer 188 (HLB 29) 2.5%$_{w/w}$

**Lipid:**

PG2-C18 Full (Witepsol® PMF 282)

HLB = 2.6

Melting point = 59.4°C

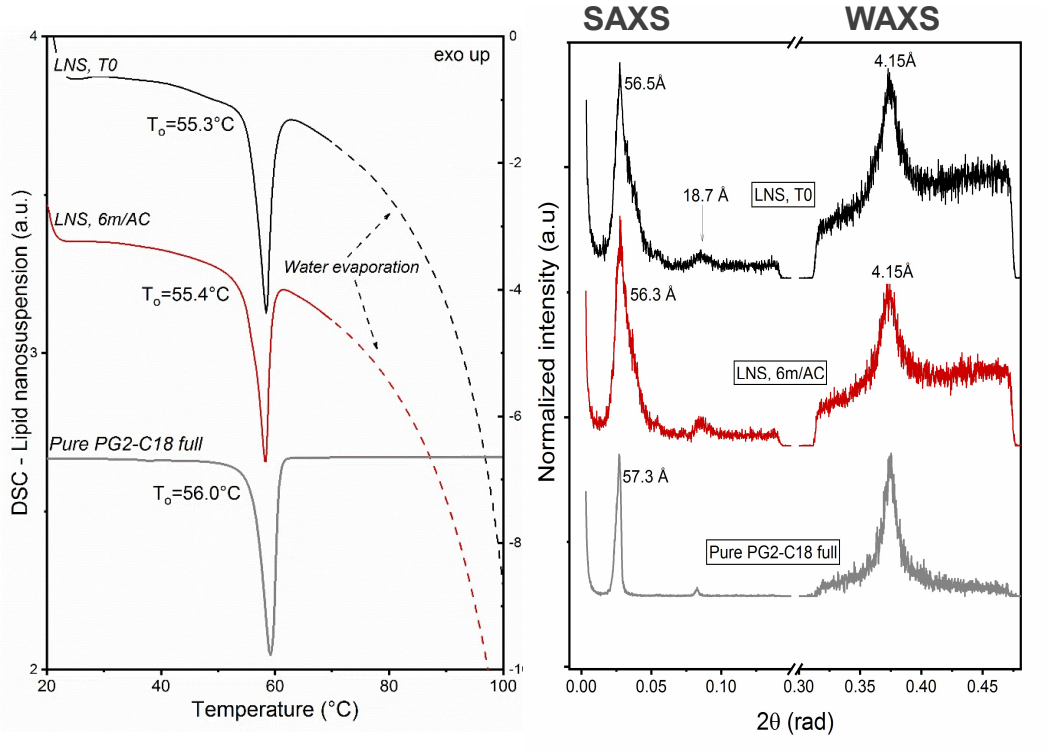
**Final dosage form:**

Lipid nanosuspension

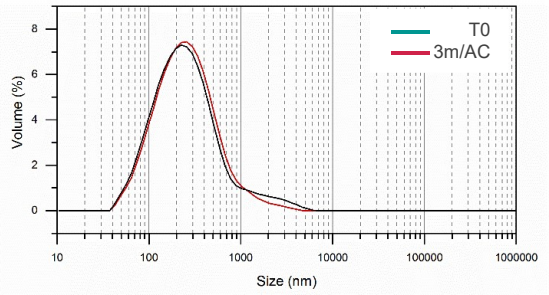
**Manufacturing Process:**

Melt-emulsification followed by hot high pressure homogenization (Panda K2, NS1001L GEA NiroSoavi, Germany).

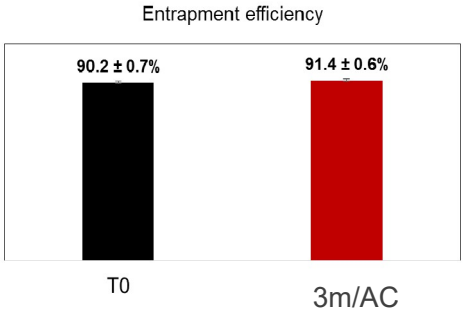
# PGFAs for Manufacturing of Solid Lipid Nanoparticles



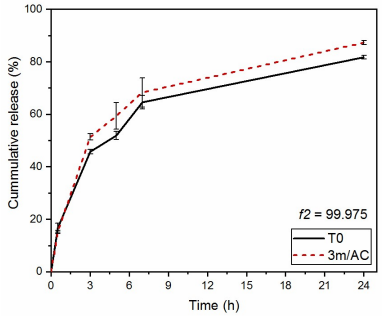

Stable solid state of PG2-C18 full within the lipid nanosuspension




No particle agglomeration




No API expulsion




Stable release profile

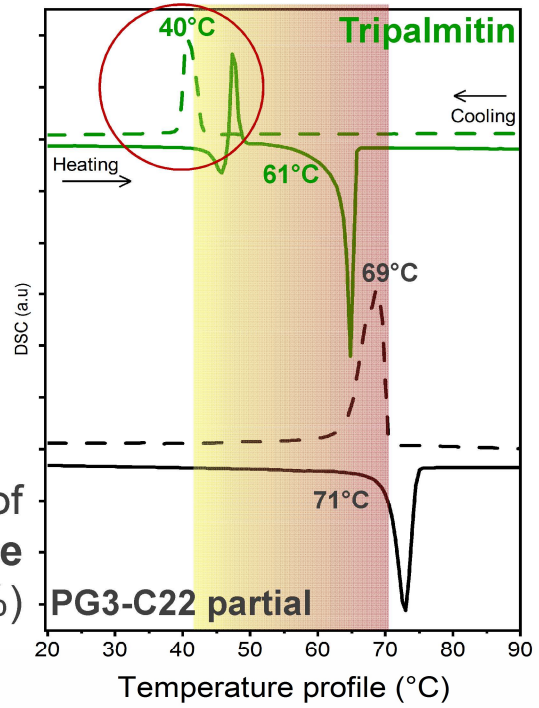
Stable performance of Solid Lipid Nanoparticles

Corzo, C., et al. EJPB, under revision

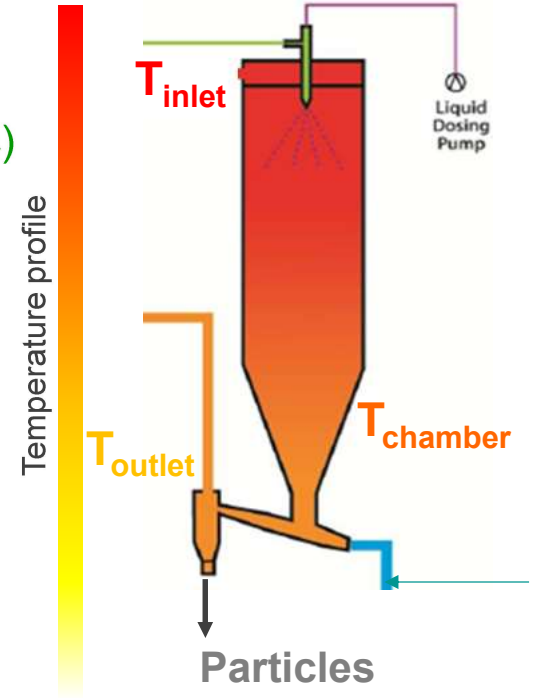
# PGFAs for Manufacturing of Dry Powder for Inhalation

Application of PGFAs-behenates to Spray drying (SD)

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




metastable polymorph (low Tc) -> **not processable**




High $T_o$ + 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

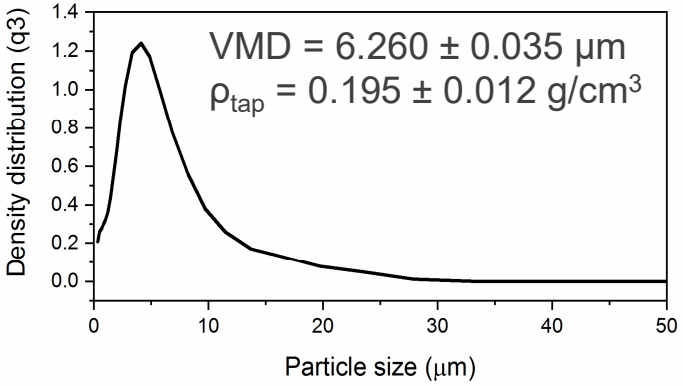
**Final dosage form:**

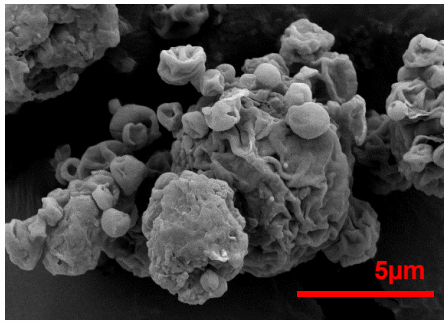
Lipid nanosuspension

**Manufacturing process:**

Co-spray drying of PGFA+API in tetrahydrofuran solution

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




| Inhalability via Next Generation Impactor | |
|---|---|
| MMAD (µm) | 4.121 ± 0.235 |
| Emitted dose (%) | 97.2 ± 2.7 |
| Fine particle fraction (%) | 28.6 ± 2.2 |

MMAD: median mass aerodynamic diameter
VMD: volume mean diameter
$\rho_{tap}$: Tapped density

# 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