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Next Generation Lipid-Based Excipients: Solid State - Stability Relationship

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Background and Objectivie

Lipid-based excipients (LBE) are known as naturally occurring materials, being easily available, biocompatible, and attractive for manufacturing of a broad range of dosage forms. The main challenge is their solid state transformation, thus instability of their final product.

The purpose of this work was:

1. to design an advanced group of LBEs; polyglycerol esters of fatty acids (PGFAs) (Witepsol PMF®) (Figure 1), with stable solid state to overcome the stability issues of conventional LBEs,

2. structure-function analysis of selected molecules for their application as hot melt coating (HMC) excipients, matrix agent for direct compaction (DC) of extended release tablets and matrix agent for manfacturing of solid lipid nanosuspensions (SLN).

Lipid-Based Excipients

PGFAs are oligomeric hydroxyethers of glycerol, fully or partially esterified with fatty acids (Figure 1). Tuning the number of glycerol moieties, fatty acids chain length and free hydroxyl groups per molecule results in different HLB values, melting points, melt viscosities (1).

Application of PGFAs in Pharmaceutical Production; Case Studies

The DSC, SAXS and WAXS data revealed the crystallization of all selected lipids into a stable monophasic system in α-form without transformation and crystal growth during storage at 40 °C (1).

Dosage form	PGm	Cn	Esteri-fication	Witepsol® PMF	HLB	Melting Point (°C)
SLN	PG2	C18	Full	282	2.6	59.4
Matrix tablets (DC)	PG3	C22	Partial	123	3.7	74.4
	PG2	C22	Full	222	1.8	72.5
Hot melt coated particles	PG3	C16/C18	Partial	1683	5.1	54.2
	PG6	C18	Partial	186	6.2	59.26
	PG4	C18	Partial	184	5.6	60.33

PG4C18 Partial
WITEPSOL® PMF 184

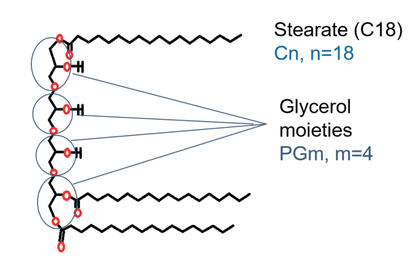
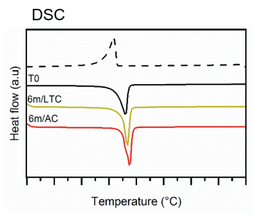
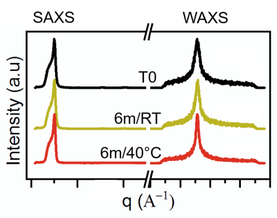


Figure 1- Chemical structure of selected PGFAs for using as LBE to manufacture matrix tablets, hot melt coated particles and SLNs, depiction of the chemical structure of PG4-C18 partial

Hot Melt Coating (2)

Stable solid state
Stable α-form





Hot melt coating properties

	Viscosity at 100°C (mPa.s)	Tc peak (°C)	FWHM of solidif. enthalpy	ΔT (Tm-Tc) (°C)	Δμ (j/g)	Water uptake ($\%_{w/w}$)
PG3-C16/C18 partial	27.1	45.4±1.01	7.04±0.28	13.4±1.9	22.3±3.4	10.4±0.8
PG4-C18 partial	34.2	54.3±0.2	6.4±0.3	10.1±0.6	14.1±0.9	15.9±1.8
PG6-C18 partial	44.1	52.2±1.4	7.2±0.4	10.0±1.6	12.4±1.4	24.2±0.1

Product performance

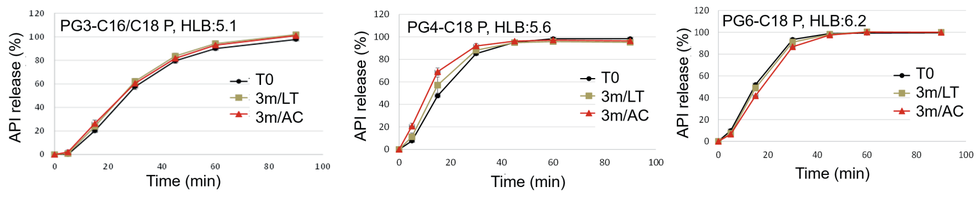
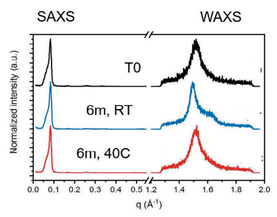


Figure 2- Solid state and hot melt coating properties of selected PGFAs, release profile of N-acetycysteine from coating after manufacturing and after 3 months storage. AC= accelerated condition, LT = long term, RT = room temperature, Tc = crystallization temperature, Tm = melting temperature, Δμ = driving force for nucleation

Direct compaction (3)

Stable solid state
Stable α-form



Physical properties of LBEs and formulations

	Flow properties			Deformation behavior	
	Bulk density (g/ml) (±sd)	AIF (°) (±sd)	AWF (°) (±sd)	P_y (MPa) (±sd)	R^2 (±sd)
DCPA +1% MgSt	0.73 (±0.01)	19.87 (±0.5)	6.37 (±0.22)	577.5 (±24.4)	1
Control blend	0.77 (±0.01)	19.84 (±1.9)	7.86 (±0.7)	449.3 (±32.8)	1
Composition 1 PG2-C22 full	0.70 (±0.01)	16.99 (±1.68)	8.22 (±1.68)	307.4 (±11.68)	1
Composition 2 PG3C22 Partial	0.73 (±0.005)	17.79 (±0.83)	7.84 (±0.05)	359.47 (±29.6)	0.99

Product performance

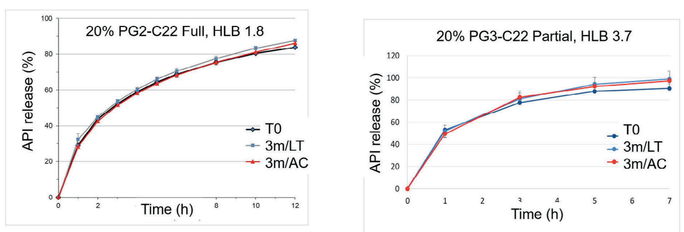
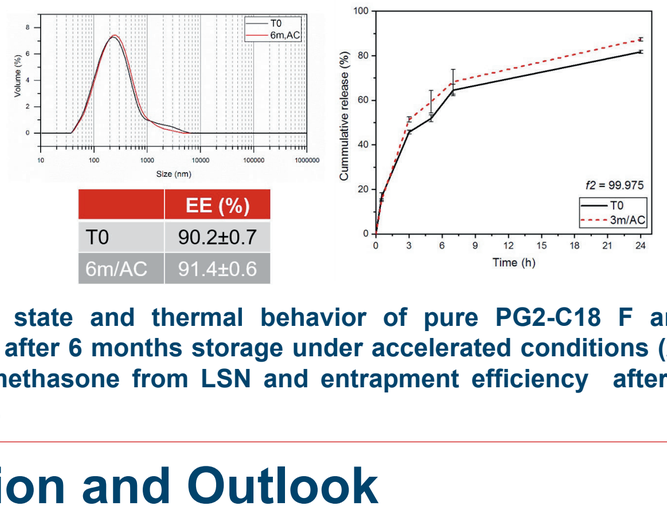


Figure 3- Solid state and tableting properties of selected PGFAs, release profile of metformin HCl from matrix tablets after manufacturing and after 3 months storage. AIF = angle of internal friction, AWF = angle of wall friction, Py = yield pressure

Solid lipid nanosuspension (4)

Stable solid state

Product performance



	EE (%)
T0	90.2±0.7
6m/AC	91.4±0.6

Figure 4- Solid state and thermal behavior of pure PG2-C18 F and the SLNs after preparation and after 6 months storage under accelerated conditions (25°C). PSD, release profile of dexamethasone from LSN and entrapment efficiency after preparation and 6 months storage.

Conclusion and Outlook

The monophasic crystallization of PGFAs into **stable α-form and no crystallite growth** lead to **stable performance** of developed product. The release profile can be tailored based on the HLB of selected PGFAs. Data on further applications for **spray-dried powder for inhalation and extrusion** are available.

References

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