GRACE

Talent | Technology | Trust™

Mesoporous Silica DDS

An Option For Liquisolid Drug Delivery Systems

Fred Monsuur

New Business Development and
TCS Manager, Excipients

10th Global
DDF Summit
Drug Delivery & Formulation

A Range of Solutions for Pharma Customers

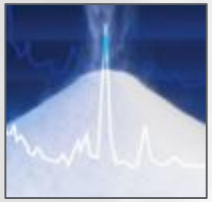
Grace is committed to consistently delivering high-quality products to our customers and well-equipped to meet the stringent regulatory demands in the pharmaceutical industry. We believe in seeking collaborative synergistic partnerships.

Fine Chemicals

- Custom Manufacturing
- Kilos to Tons cGMP Production
- Strong Collaborative Relationships

Formulation Excipients

- SYLOID® FP Silica – Trusted in Formulations for 50+ years
- SYLOID® XDP Silica Carrier for LBD - Liquisolid
- SILSOL® Innovative Carrier and Drug Delivery Technologies
- Industry Leading Quality Standards (IPEC-GMP / Excipact)

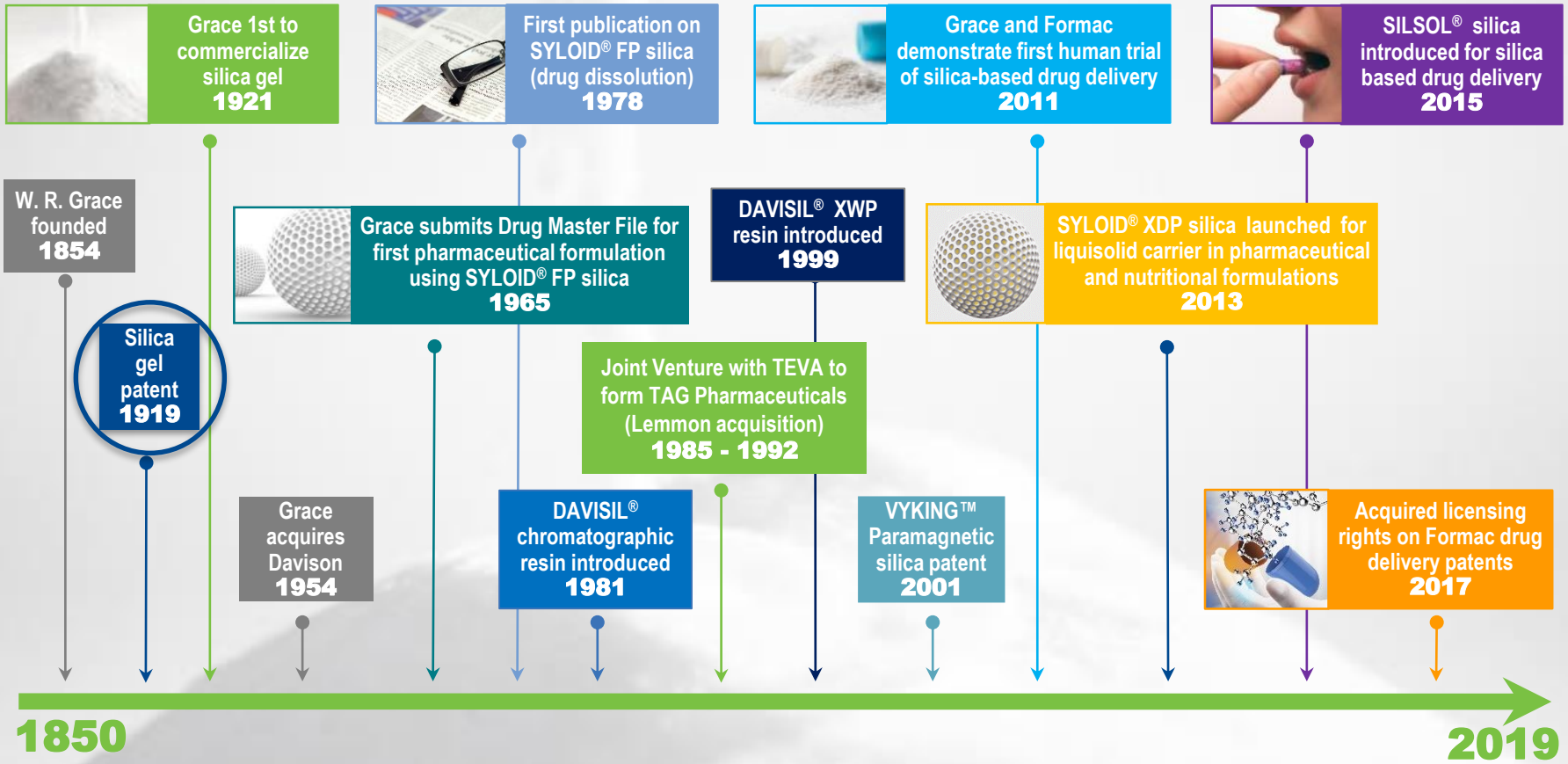


Chromatography Resins

- VYDAC® Protein and Peptide Purification Resins
- DAVISIL® Chromatography Resin for Small and Large Molecules
- Experienced Technical Support

Grace's History of Silica Innovation

170 Years of Innovation and Silica Expertise



Grace was the first to commercialize silica in 1921 and still innovating 100 years later, as the first to commercialize silica for drug delivery

Innovating in the Pharma Industry for 50+ Years

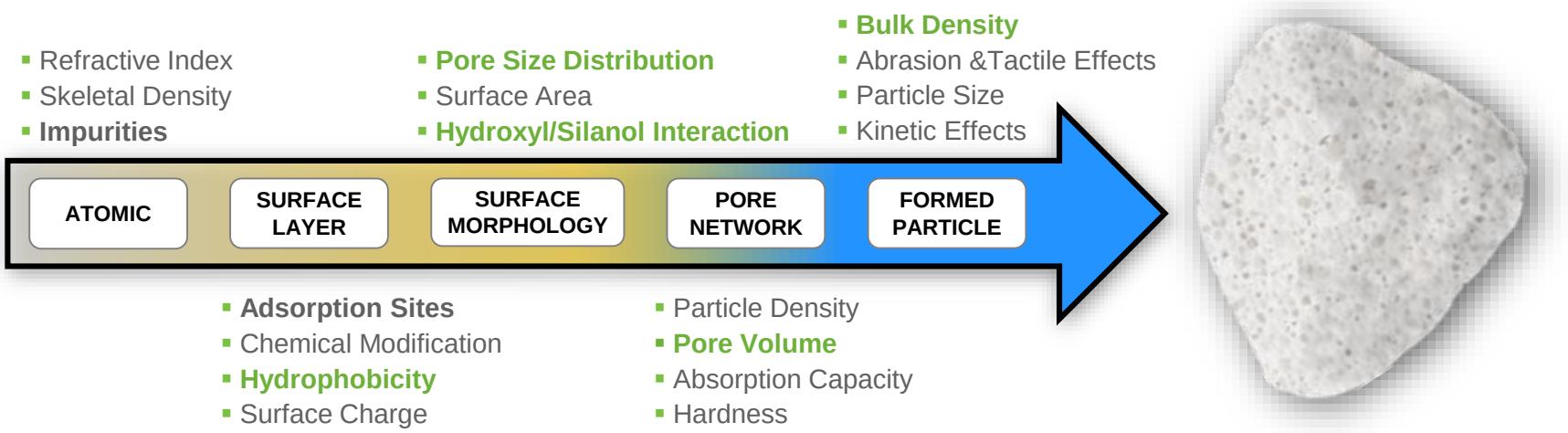
- In 1965 Grace receives Drug Master File for first pharmaceutical formulation using SYLOID® FP silica
- Today, SYLOID® FP silica is used numerous patented drug formulations including blockbusters such as Allegra®, Plavix®, and Depakote®
- In 1987 VYDAC® Biopurification Resin is patented in Epogen® process
- In 2001 Grace develops and commercializes paramagnetic particles for biopurification
- In 2011 Grace and Formac demonstrate first human trial of silica-based drug delivery
- In 2013 Grace launches new optimized particle SYLOID® XDP silica to be used as a liquisolid carrier in pharmaceutical formulations and nutritional supplements
- In 2016 Grace launches SILSOL® silica drug delivery technology

Grace Silica in Pharmaceutical Formulations

Grace's Particle Design Expertise

Elements of Silica Particle Design

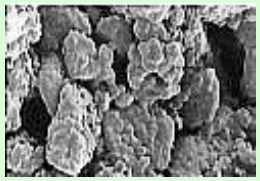
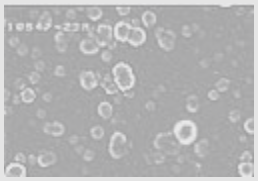
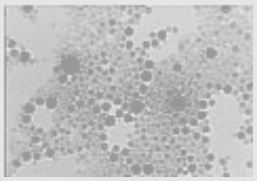
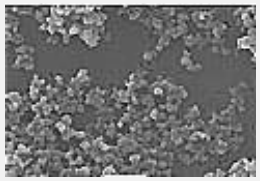
- Multiple Product Types
- Wide Range of Tunable Properties
- Fundamental Understanding of Particle Functionalities
- Experience in a Variety of Applications



Surface, pore, and particle properties can be tuned for specific applications

Not All Silicas Are The Same

GRACE

Silica Gel	Spherical Silica	Precipitated Silica	Colloidal Silica	Fumed Silica
3-Dimensional network of primary particles	Spray drying of silica slurry	Growing of primary particles; due to the presence of electrolytes, it comes to an agglomeration	Growth of primary particles excluding electrolytes; pH dependent	Pyrogenic process formation of aggregates and agglomerates
Pharma				**Pharma**
				
SYLOID® FP Silica **SYLOID® XDP** Silica **SILSOL®** Silica	**DAVISIL®** Sphere Silica **VYDAC®** Silica	**PERKASIL®** Silica Amorphous	**LUDOX®** Silica	AEROSIL® CABOSIL® AEROPERL®

Mesoporous
Porosity and its surface is developed intra-particle and always available
4-6 OH/nm^2 = providing better stability

Dust
Porosity inter-particle
2 OH/nm^2

Fumed (“colloidal”) silica is recognized as the industry standard, but there is a great deal of confusion in terminology

Mesoporous Silica Applications

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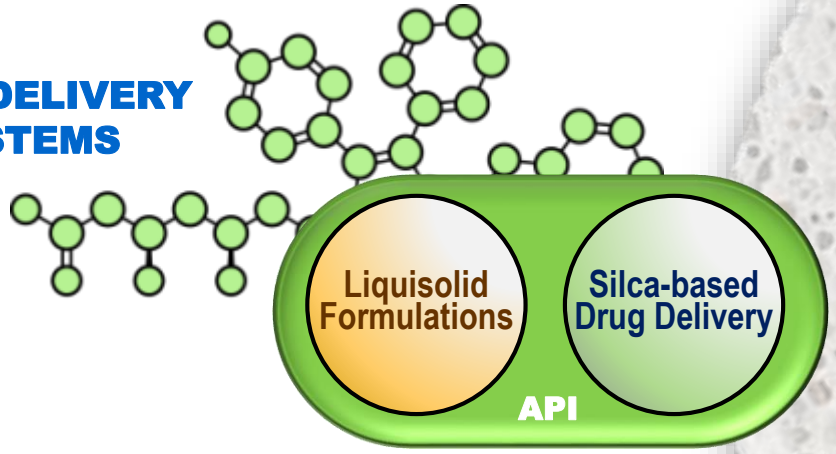
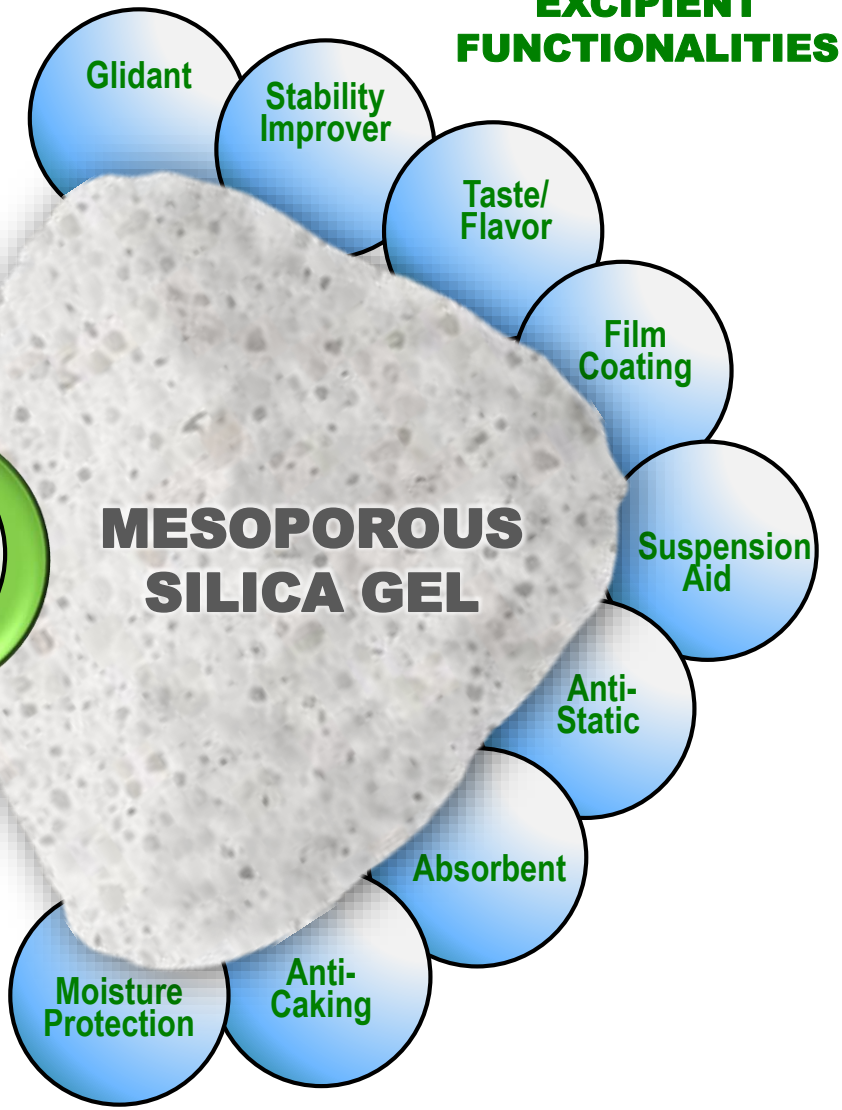
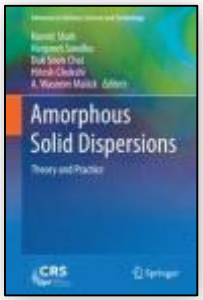
Silica particles can be engineered to impart a range of functionalities or even act as sophisticated delivery mechanisms

DRUG DELIVERY SYSTEMS



EXCIPIENT FUNCTIONALITIES





"Mesoporous Silica Drug Delivery Systems"
Choudhari, Monsuur, Hoefer, McCarthy, Libanati, 2014, pp 665-693

Advances in Delivery Science and Technology, Amorphous Solid Dispersions: Theory and Practice

The Versatility of Mesoporous Silica

Grace's Strategic Formulation Platforms

SYLOID® Silica Excipients

SYLOID® FP silica	SYLOID® XDP silica
Multifunctional Excipients	**Optimized Carriers**
▪ Static Reduction ▪ Film Coating ▪ Physical Moisture ▪ Chemical Moisture ▪ Anti-tacking ▪ Suspension Aid ▪ Glidant	▪ Liquisolids ▪ Lipid and Oils ▪ SEDDS ▪ PEG ▪ Melt Loading

SILSOL® Silica-based Drug Delivery

SILSOL® silica

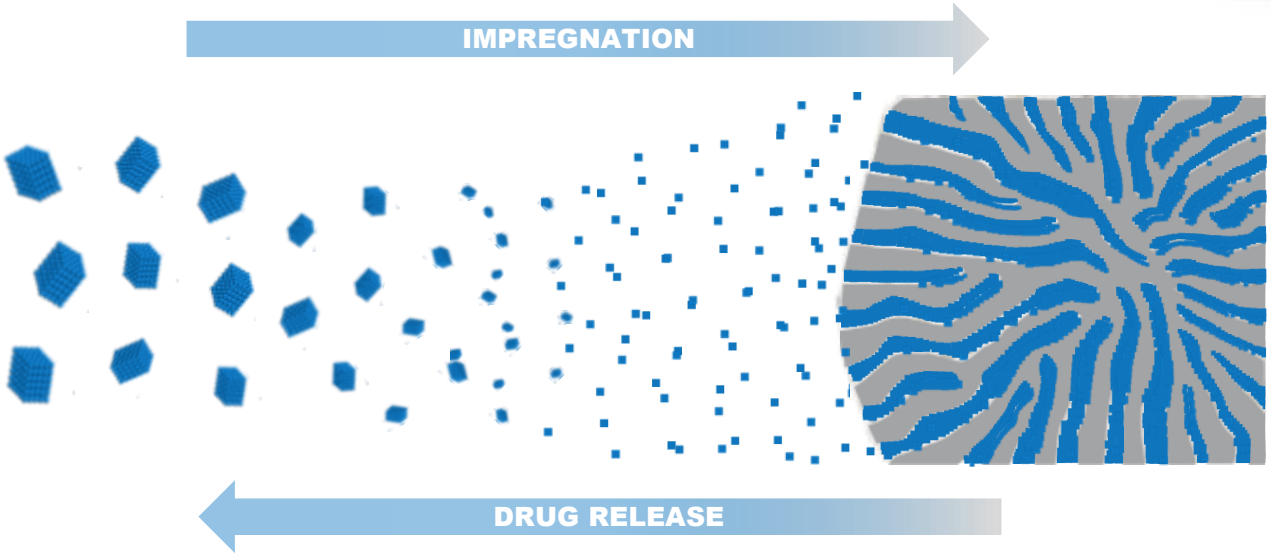
Solvent-based Amorphous Dispersions	Solvent-free Amorphous Dispersions
▪ Solubility Enhancement ▪ Amorphous Stability ▪ Immediate Release	▪ Solubility Enhancement ▪ Amorphous Stability ▪ Immediate Release

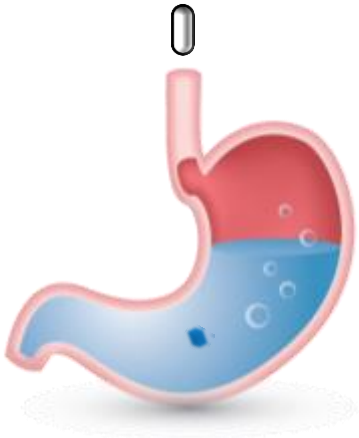
Technologies to address advanced formulation challenges

Fundamentals of Silica Drug Delivery

How it Works

- The internal mesopores of the hydrophilic silica material are impregnated with a concentrated drug solution
- A stable amorphous phase results from confinement of the API in pores of sub-critical dimensions and/or from the strength of the absorptive interaction (H-bonding)
- On contact with gastric fluids, the confined amorphous drug is rapidly released



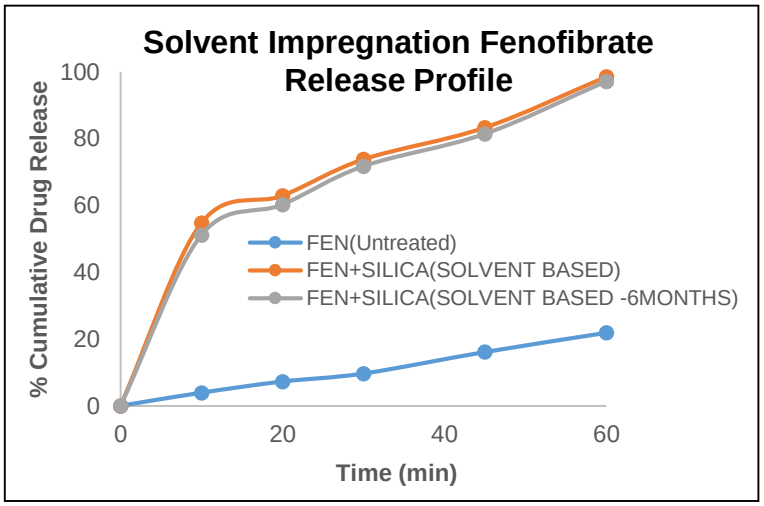


Mellaerts et al. Chem Commun (13):1375–1377 – 2007 and Van Speybroeck et al. 2009. J Pharm Sci 98(8):2648–2658.

Solvent vs. Solvent-free

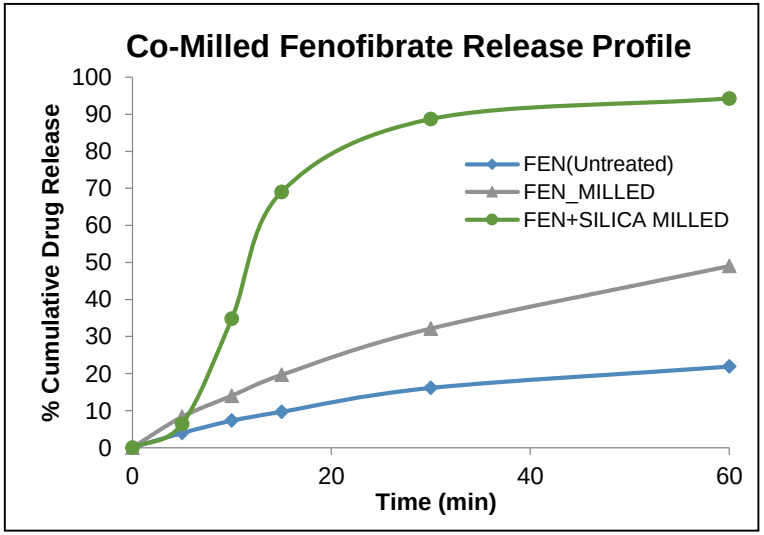
Solvent-based Strategies

- Pore structure and particle size optimized to provide stable amorphous dispersions
- Robust, scalable processing to load silica
- A number of commercially available drying technologies possible
- Works with most poorly soluble compounds
- Solvent handling capability is an important consideration



Solvent-free Strategies

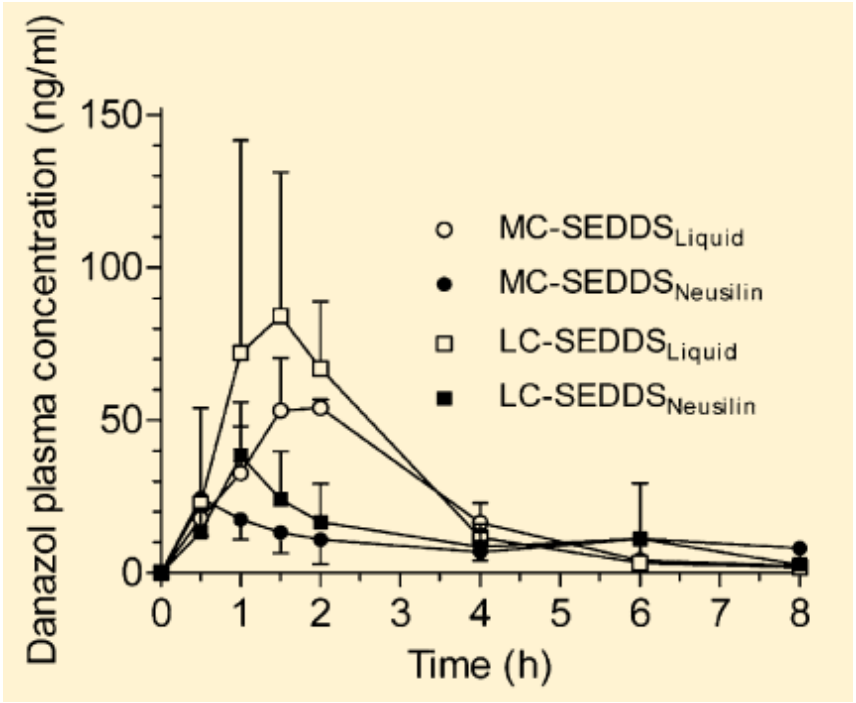
- Type of silica, pore structure and particle size optimized to provide stable amorphous dispersions
- Robust, scalable co-milling technologies available
- APIs with good H-bonding ability desired
- Critical material attributes and critical process parameters defined
- Next generation: combine hot melt extrusion, mesoporous silica technologies for optimal bioavailability



Liquisolid Drug Delivery

Where did it all start? Why was there a need for a new carrier ?

"Incomplete Desorption of Liquid Excipients Reduces the *in Vitro* and *in Vivo* Performance of Self-Emulsifying Drug Delivery Systems Solidified by Adsorption onto an Inorganic Mesoporous Carrier"



Michiel Van Speybroeck - *Mol. Pharmaceutics*, **2012**, *9* (9), pp 2750–2760

Liquisolid Systems Today

Liquisolid systems are of interest today not only for NCEs but also in particular for reformulation and life cycle management

Challenges with SEDDS and Liquids

- Difficult to handle
- Unstable - limited shelf life
- Limited capsule compatibility
- Storage temperature must be controlled to prevent degradation
- Inefficiencies of filling causes waste

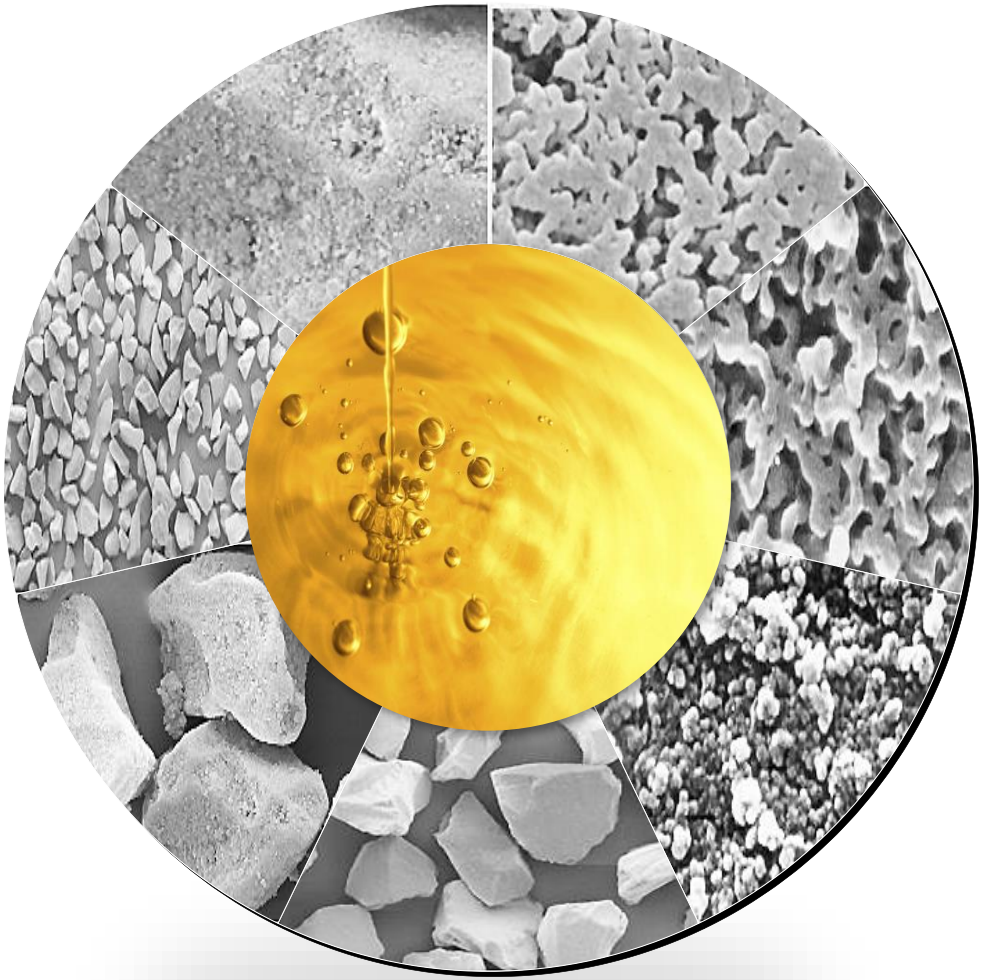
Limitations of most carriers

- Poor loadability characteristics
- Low volume and density
- Potential interaction with the drug (MAS)
- Desorption problems or low release profiles
- Monograph + freedom to operate limitation

There is a need for more effective carriers!

Introducing SYLOID® XDP Silica

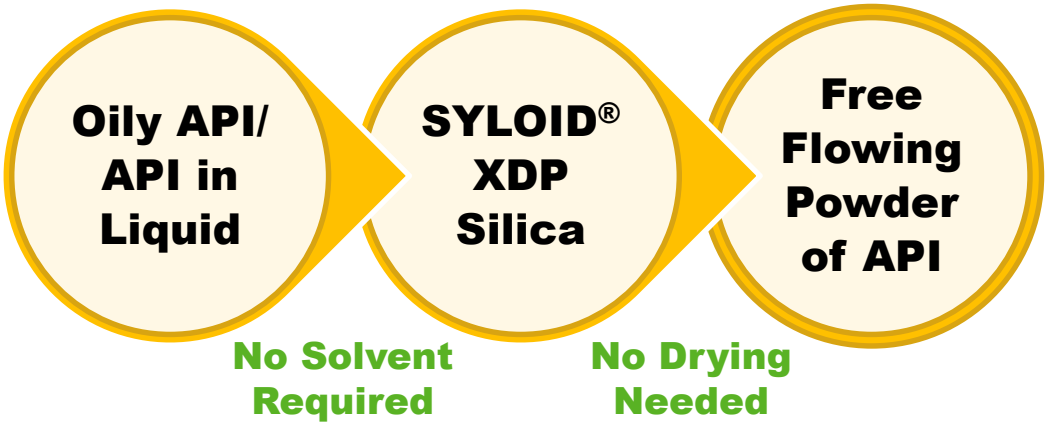
A grade of Grace® silica designed specifically for liquid and oil-based formulations



Experience the benefits of large particles with true internal porosity

- More API per particle
- Smaller dosage forms
- More efficient release of API
- A novel platform to extend product life-cycle by transforming liquid dosage forms into solids

Loading Procedure for Lipid/Liquisolids



- Most carriers requires the use of solvents to load the lipid to reduce viscosity, followed by drying.
- The morphology of SYLOID® XDP silica was designed to promote effective absorption and desorption of lipids.
- Oils can penetrate pores of SYLOID® XDP silica without the use of solvents and no surfactant needed.

Simple liquid to solid transformation
1.5:1 ratio is used for capsules 1:1 ratio is used for tablets due to deformation of pores

Volumetric Absorptive Capacity

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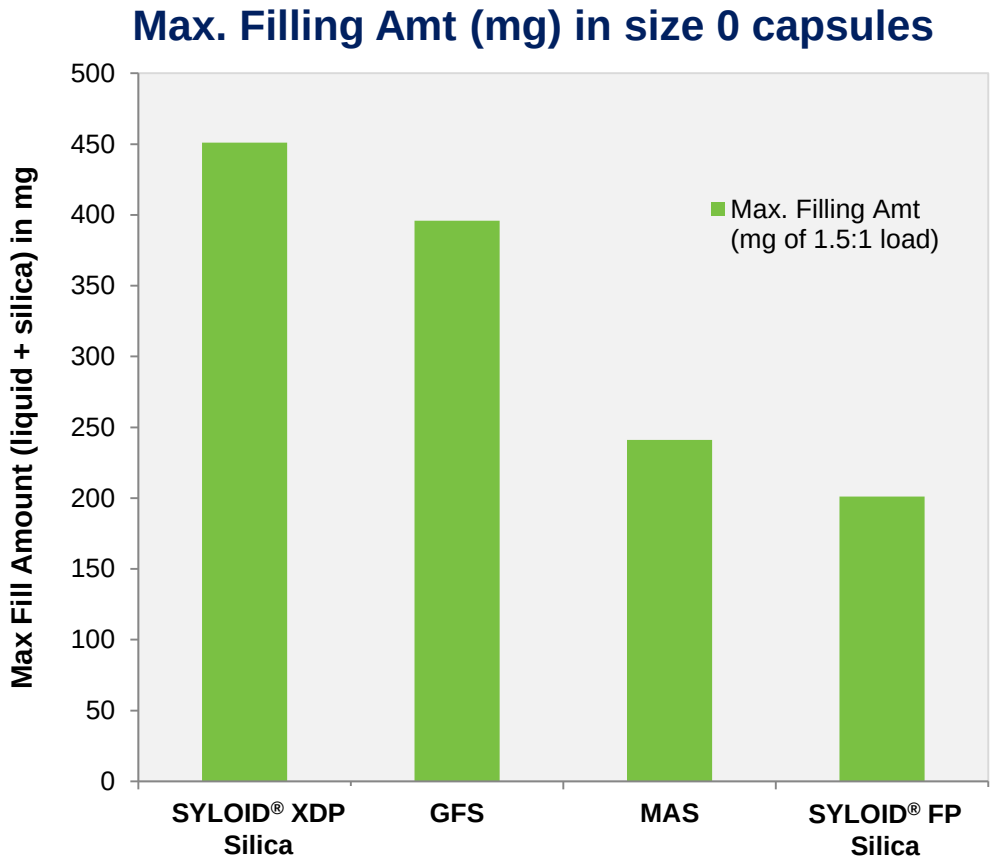
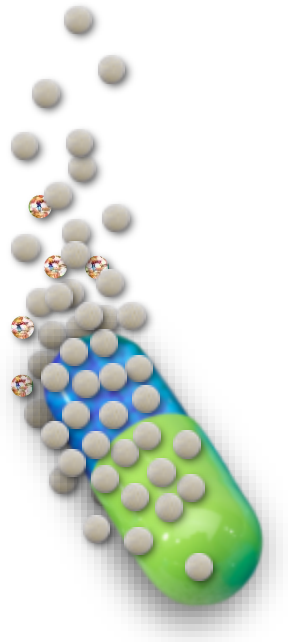
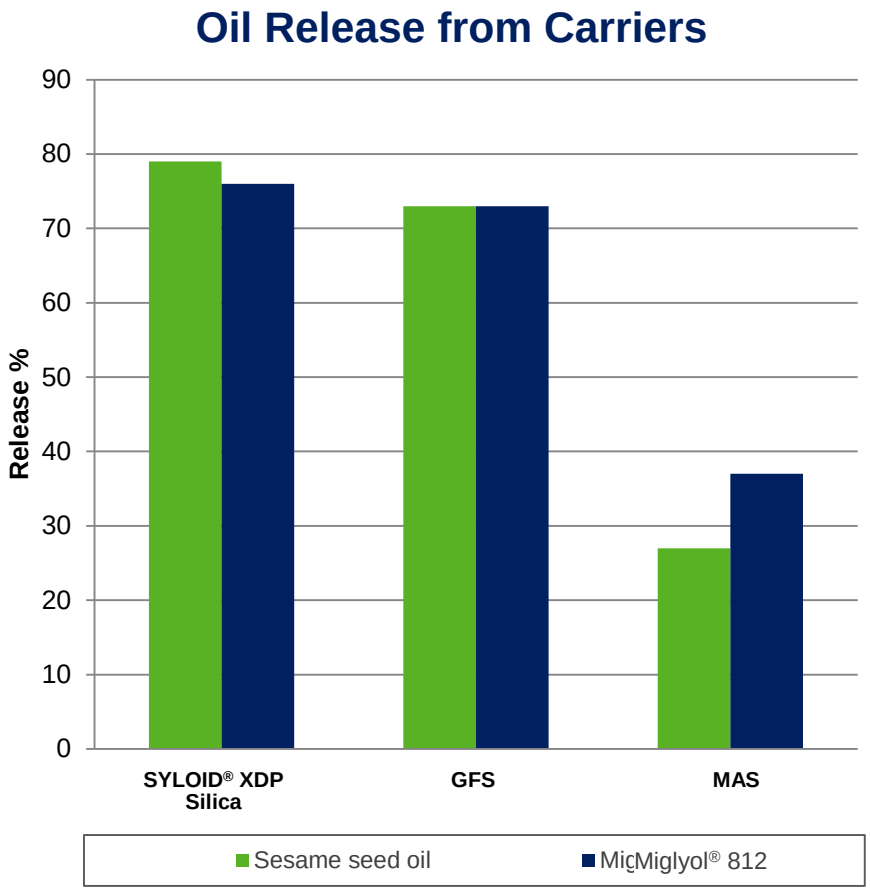
12 carriers and over 30 oils, lipids, surfactants, co-surfactants were tested

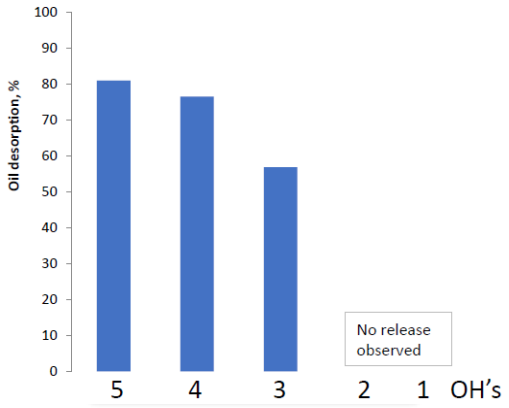




SYLOID® XDP silica carrier gives maximum filling amount per capsule

Solid Carriers: Oil Release – NO Surfactant

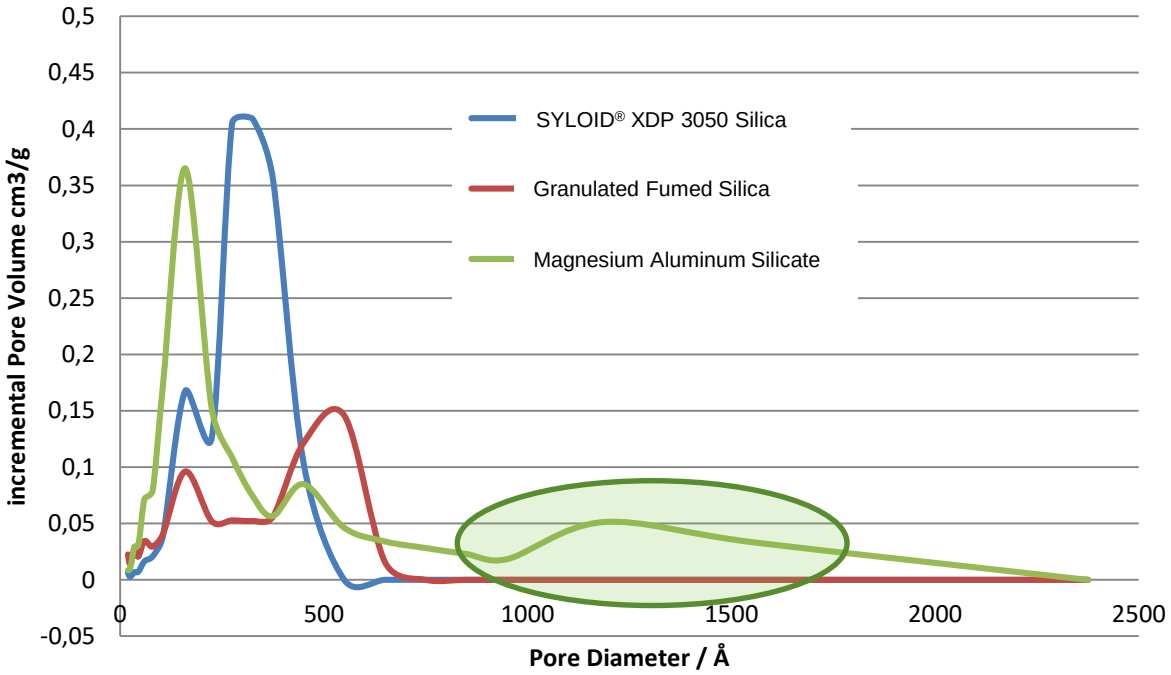


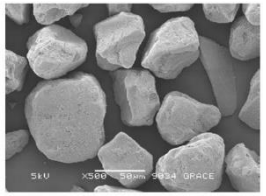


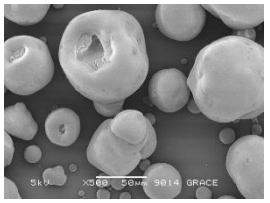
Incomplete Desorption of Liquid Excipients Reduces the in Vitro and in Vivo Performance of Self-Emulsifying Drug Delivery Systems Solidified by Adsorption onto an Inorganic Mesoporous Carrier Michiel Van Speybroeck *Mol. Pharmaceutics, 2012, 9 (9), pp 2750–2760*

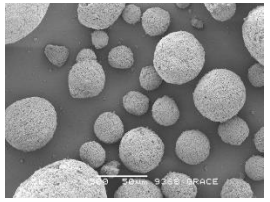
SYLOID® XDP silica carrier gives the best release profile
For MAS the more hydrophilic the better the release

Optimized Pore Size and Pore Structure

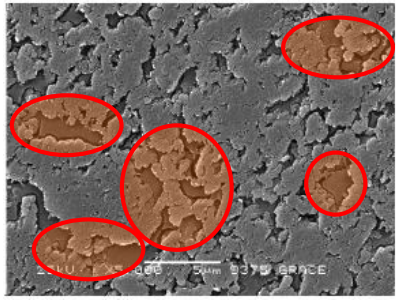


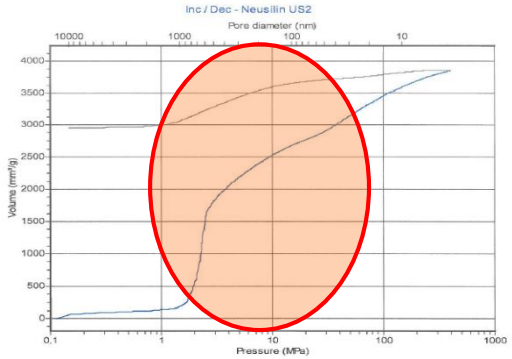

SYLOID® XDP Silica


Granulated Fumed Silica (GFS)

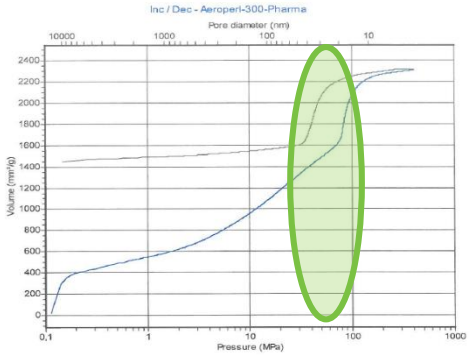

Magnesium Aluminum Silicate (MAS)

Bottleneck pores / Macropores result in incomplete desorption





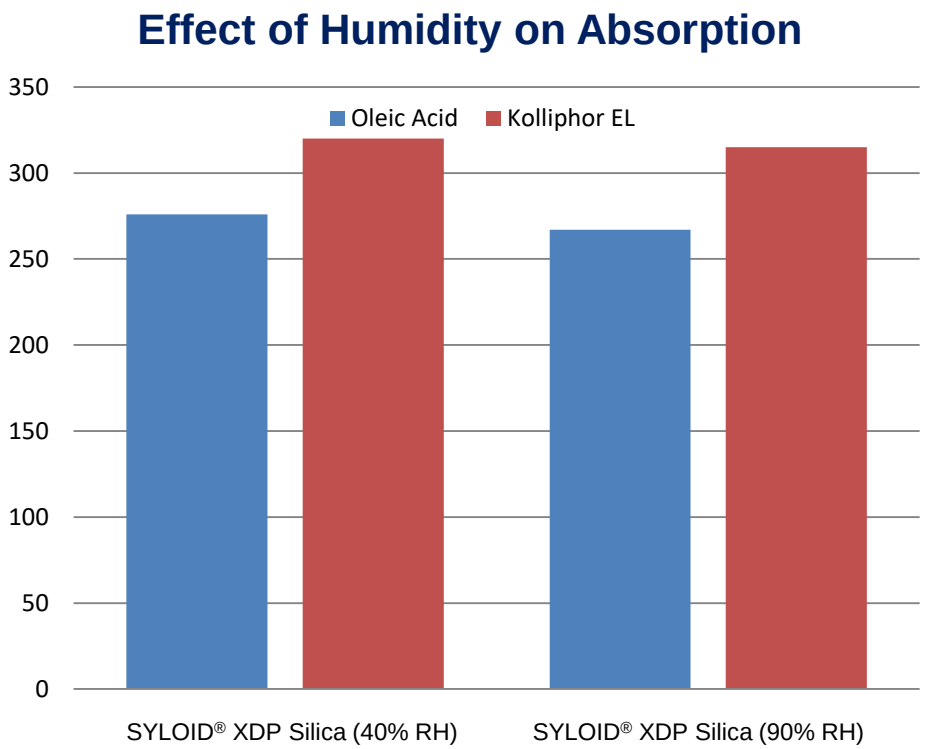
Macroporous Silica



Mesoporous Silica

Choudhari; Monsuur et al. DOI 10.2478/mesbi-2014-0004 Comparative evaluation of porous silica based carriers for liquisolids

Humidity - Effect on Absorption



Carrier	Initial LOD (%)	LOD, 90% RH after 2 days (%)	Max Oil Adsorption, *initial* (g/100g)	Max Adsorption, 90% RH after 2 days (g/100g)	Decrease (%)
MAS	3.34%	21.93%	363	336	**7.43%**
GFS	4.72%	10.58%	328	309	**5.79%**

EJPB 84 (2013) 172-182 : confirming humidity uptake and potential precipitation of incorporated lipophilic drug with MAS

Humidity has negligible effect on MPS adsorption capacity

Case Studies

Glyburide from Liquid SEDDS to LiquiSolid

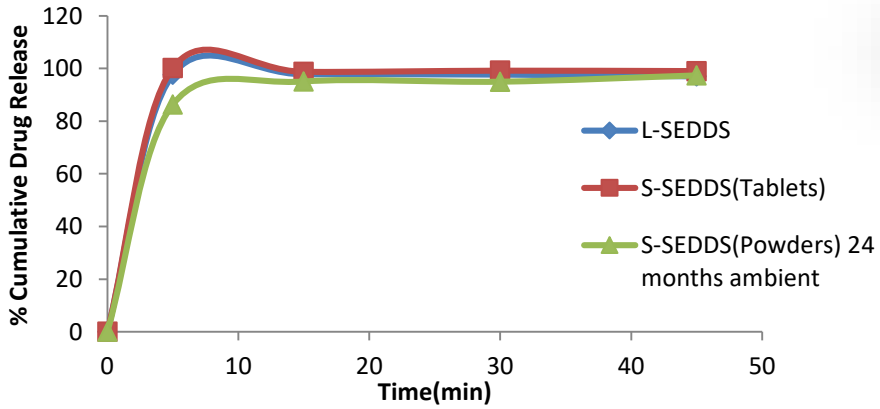
Liquid-SEDDS (old)	
Ingredient	% Composition
No co-solvent	0%
Capryol™ 90 (oil Phase)	15%
Tween 20 (Surfactant)	30%
Transcutol® HP (Co Surfactant)	54,40%
Drug(Glyburide) (API)	0,60%

Refor-mulate

Liquid-SEDDS (new)	
Ingredient	% Composition
N-methyl Pyrrolidone (co-solvent)	10%
Labrafac™ lipophile WL 1349 (oil Phase)	10%
Cremophor® EL (Surfactant)	40%
Labrasol® (Co Surfactant)	37,00%
Drug(Glyburide) (API)	3,00%

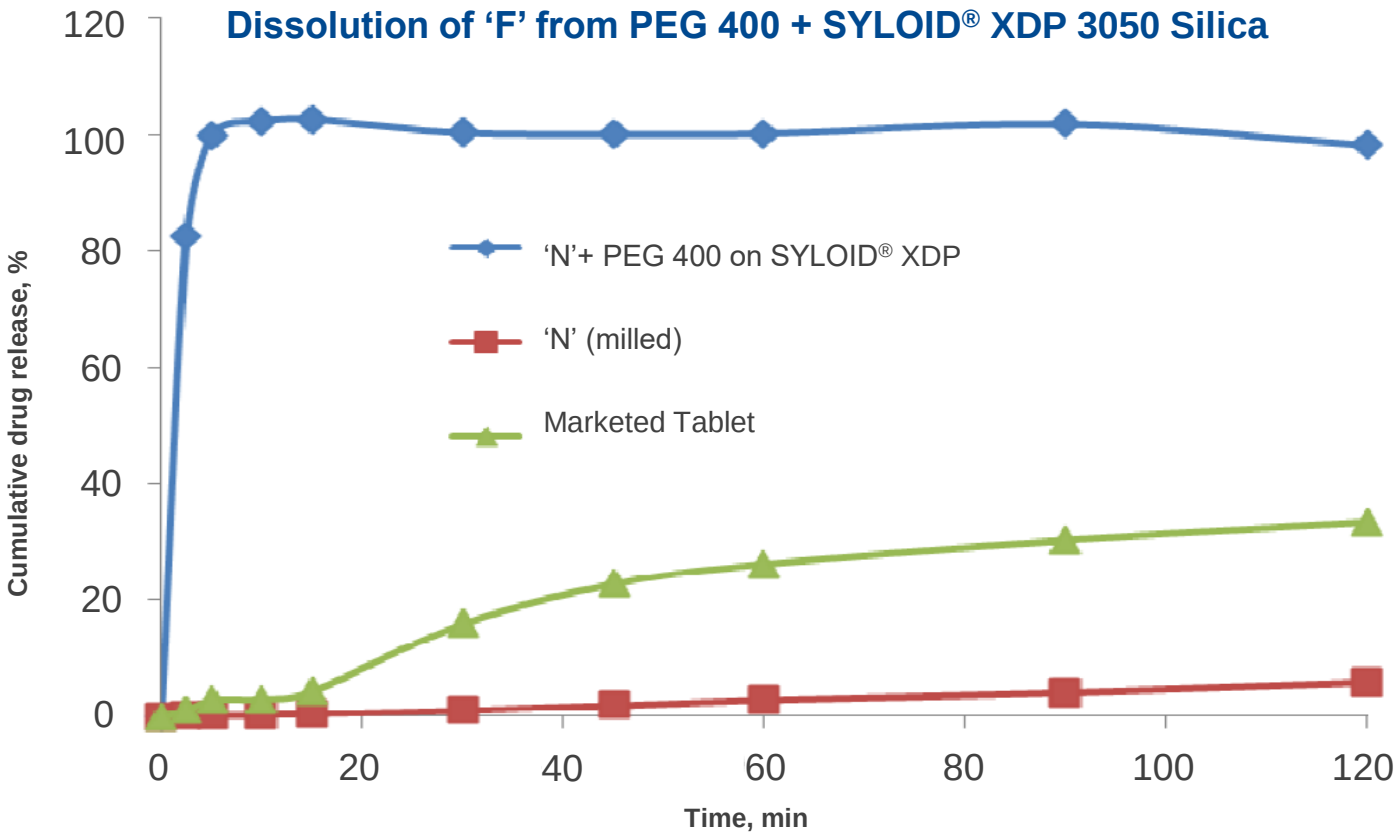
Load on silica

Glyburide release comparison for different formulations



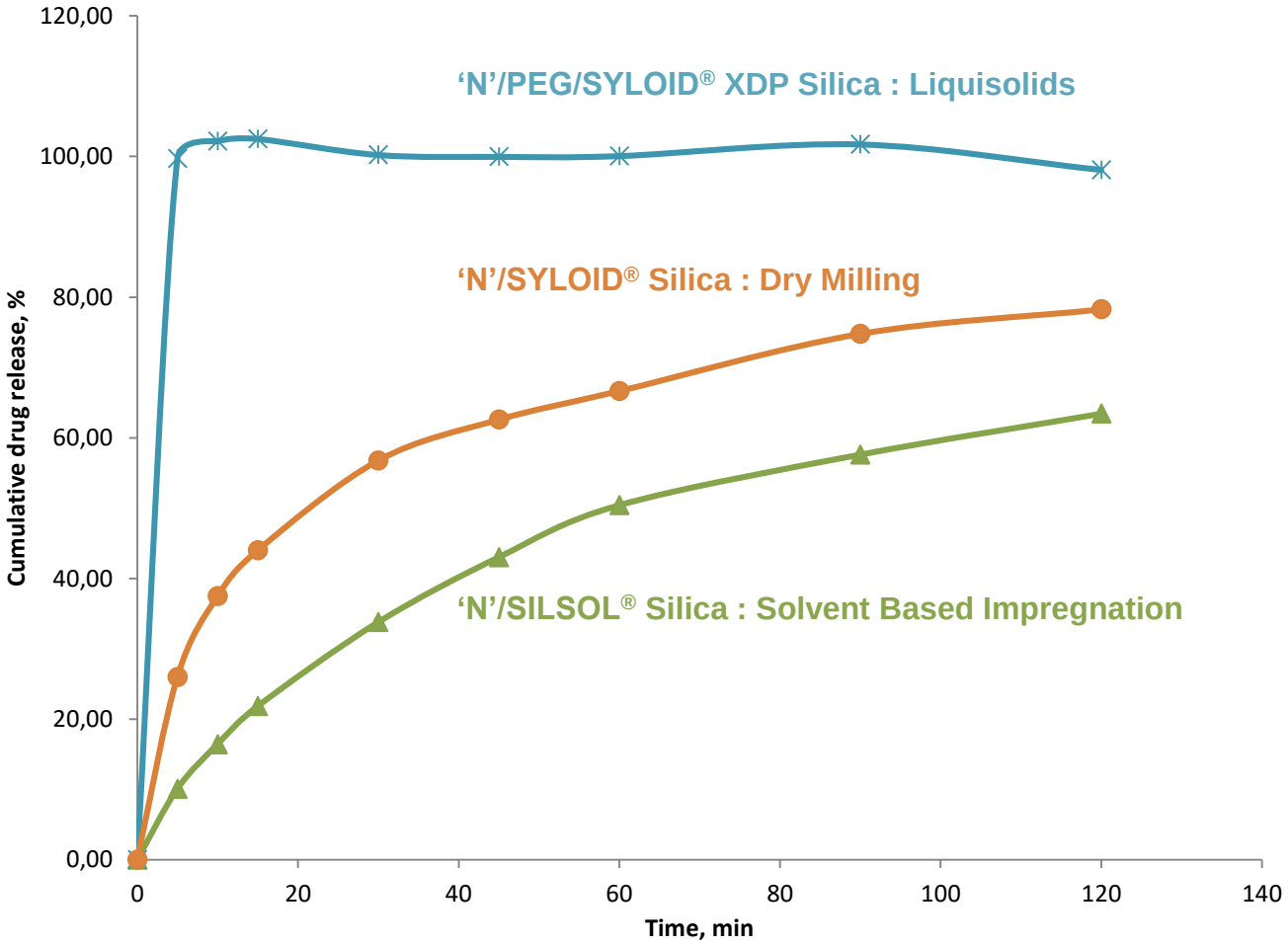
Optimization of L-SEDDS required for same dosage strength. Liquid - and Solid-SEDDS have same release!

API ‘N’ Release from MPS Loaded Formulation



AP019_Syloid XDP carrier for PEG_ N_Final_HR.pdf, GRACE, © 2015

API ‘N’ – MPS Loading Strategies



Different loading strategies provide different release profiles

Capsule Compatibility Study

Objective

- Compatibility of SYLOID® XDP silica (empty and loaded) with Gelatine and HPMC capsules.
- Tested as per Capsugel® Standard Operating Instructions

Conclusion

- Hygroscopicity: SYLOID® XDP silica compatible with capsules stored under standard conditions being %RH 25-65 at 15-25°C
- Mechanical Robustness: No deformation or alteration of mechanical properties
- Disintegration testing: Conform to EP 2.9.1 monograph (total disintegration < 30min)

Table 7: Disintegration of MSG and Cremophor® EL loaded MSG capsules (after 3 weeks, at 40°C, 75%RH)

MSG	Gelatin capsules	Opening time, min	<2
		Total disintegration time, min	<11
	Vcaps® Plus HPMC capsules	Opening time, min	<3
		Total disintegration time, min	<9
Cremophor® EL loaded MSG	Gelatin capsules	Opening time, min	<3
		Total disintegration time, min	<11
	Vcaps® Plus HPMC capsules	Opening time, min	<2
		Total disintegration time, min	<11
MSG is mesoporous silica gel			

Choudhari, Monsuur et al. Comparative evaluation of porous silica based carriers for lipids and liquid drug formulations - De Gruyter Open 2015

IVIVC Challenge

Next Step: Guidance LFCS - IVIVC

Schematic Representation of Lipid Formulation Classification System

Type I Lipid-based Formulations
Oils without surfactants

Type II Lipid Formulations
Oils and water insoluble surfactants

Type III Lipid Formulations
Oils and water soluble surfactants and co-solvents

Type IV Lipid-based Formulations
Water soluble surfactants and co-solvents (oil-free)

When high HLB > 40% in the liquisolid

Table 1. Lipid formulation classification system according to Pouton [7]

Excipient in formulation	Content of formulation (%, w/w)				
	Type I	Type II	Type IIIA	Type IIIB	Type IV
Oils: triglycerides or mixed mono and diglycerides	100	40–80	40–80	<20	–
Water-insoluble surfactants (HLB < 12)	–	20–60	–	–	0–20
Water-soluble surfactants (HLB > 12)	–	–	20–40	20–50	30–80
Hydrophilic co-solvents (e.g. PEG, or propylene glycol)	–	–	0–40	20–50	0–50

For Type 3 and 4 + high HLB IVIVC is a challenge

Kuentz, M. Lipid-based formulations for oral delivery of lipophilic drugs, Drug Discov Today: Technol (2012), doi:10.1016

IVIVC for Liquisolids requires Lipolysis for high HLB

European Journal of Pharmaceutical Sciences 119 (2018) 219–233

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journal homepage: www.elsevier.com/locate/ejps

Review

Drug permeability profiling using cell-free permeation tools: Overview and applications

Philippe Berben[a], Annette Bauer-Brandl[b], Martin Brandl[b], Bernard Faller[c], Gøril Eide Flaten[d], Ann-Christin Jacobsen[b], Joachim Brouwers[a], Patrick Augustijns[a,*]

Gastrointestinal lipolysis of lipid-based excipients intended for the oral drug delivery of poorly water-soluble drugs

OCL VOL. 17 N° 4 JUILLET-AOÛT 2010

Sylvie FERNANDEZ[1,2]
Frédéric CARRIÈRE[2]
Vincent JANNIN[1]

[1] Gattefossé SAS, 36, chemin de Genas, 69804 Saint-Priest, France <vjannin@gattefosse.com>
[2] Laboratoire d'enzymologie interfaciale et de physiologie de la lipolyse, CNRS UPR 9025, 31, chemin Joseph-Aiguier, 13402 Marseille cedex 20, France

Abstract: Labrasol® and Gelucire® 44/14 are lipid-based excipients used for the oral drug delivery of poorly water-soluble drugs. These macrogolglycerides are composed of acylglycerols and PEG esters, potential substrates of digestive lipases. We developed an in vitro method to simulate the gastrointestinal lipolysis of these excipients and to evaluate the impact of lipolysis in vivo. At the end of the gastric phase, the composition of both excipients was significantly modified underlining the importance of gastric lipolysis in vivo. We also studied the influence of excipients' lipolysis on the solubilization of a poorly water-soluble drug, cinnarizine, in aqueous phase. Gastrointestinal lipolysis of Labrasol® was a prerequisite to maintain cinnarizine in aqueous solution, whereas the lipolysis of Gelucire® 44/14 did not affect the cinnarizine solubilization.

Key words: oral drug delivery, gastrointestinal lipolysis, poorly water-soluble drugs, macrogolglycerides, lipases, lipid-based formulations

Solubility enhancement increases with increasing lipophilicity of the compounds and with increasing concentration of the micelles in solution.

From K Valko Physicochemical and Biomimetic Properties in Drug Discovery, Wiley, 2014

This finding supposes that in vivo Labrasol® lipolysis is a prerequisite to prevent cinnarizine form precipitation and keep the drug in supersaturation in the gastrointestinal milieu.

From Gattefosse, Vincent Jannin

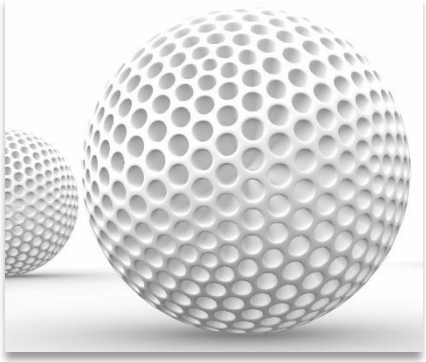
Quote: "There is a lipolysis in the intestine. It may be possible that some digestions (decomposition) of the lipid delivery system is going on in vivo, that might help to release the drug from the formulation. This also could explain that the bioavailability in vitro is worse than in vivo. Maybe we should add some enzymes in the dissolution media too. It might explain the HLB cutoff too."

Klara Valko worked for 20+ years at GSK implementing IAM (Immobilized Artificial Membrane) prediction chromatography on 1M+ compounds.

Conclusion

Selection of the right carrier is critial

- Critical Material Attributes (CMA) being :
- Absorptive capacity in combination with density
  - Volumetric Absorptive Capacity
- Optimum processing conditions / free flow
- Desorptive capacity
  - Pore size + porestructure (Bottleneck)
  - Number of silanol groups on the silica



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What does Grace provide?

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  - Manufactured to EXCiPACT® standards
- Know-how on loading techniques and analysis
- Application examples and data
- License to practice Grace IP with the purchase of our silica

Thank you for your time.

Questions?

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Fred Monsuur
New Business Development
and TCS Manager, Excipients

Grace GmbH & Co. KG
In der Hollerhecke 1
67547 Worms / Germany
www.grace.com

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