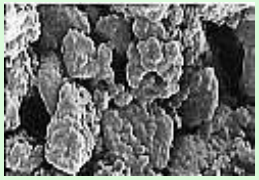
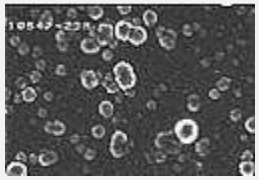
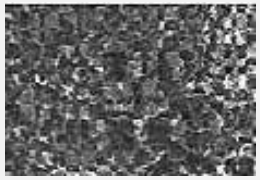
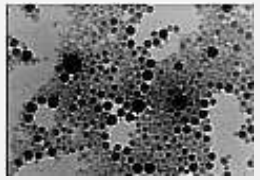
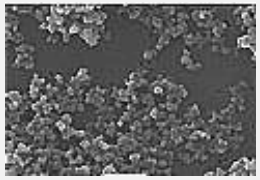
Grace® Silica Drug Delivery

GRACE

Talent | Technology | Trust™

1. Syloid FP Highlights 2015
2. Syloid XDP Highlights 2015
3. Grace SilSol Introduction

Not all Silicon Dioxides are the Same

Silica Gel	Spherical Silica	Precipitated Silica	Colloidal Silica	Fumed Silica
3-Dimensional network of primary particles; pH dependent **Pharma**	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**
				

Syloid® FP silica
Syloid® 3D silica
Syloid® XDP silica
SilSol™ 6 Silica

Tixosil® Silica
Sipernat® Silica
Perkasil® Silica

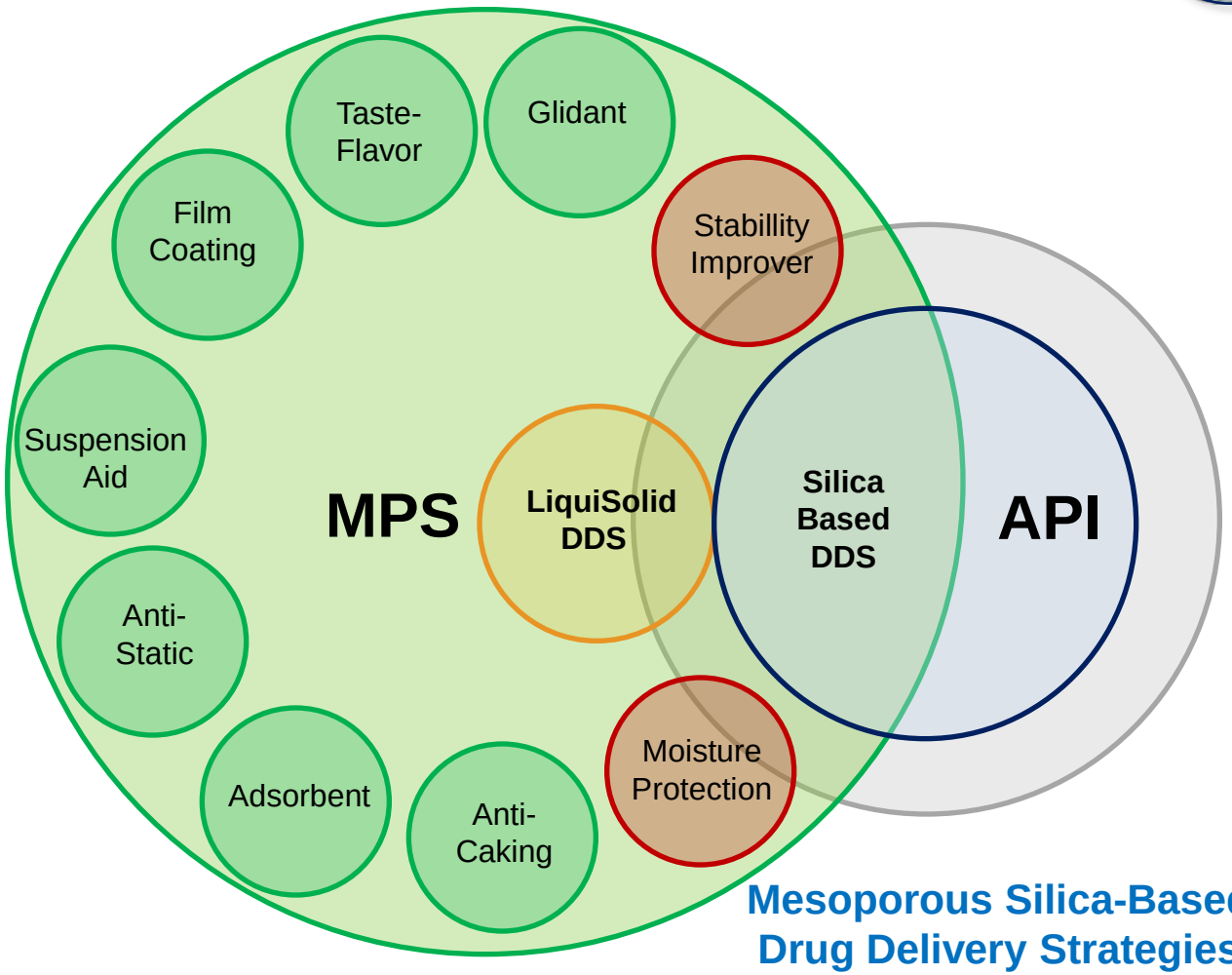
Aerosil® Silica
Aeroperl® Silica
Cab-o-sil® Silica

Mesoporous
Porosity and its surface is developed intra-particle and always available
4-6 OH/nm2 = providing better stability

Dust
Porosity inter-particle
2 OH/nm2

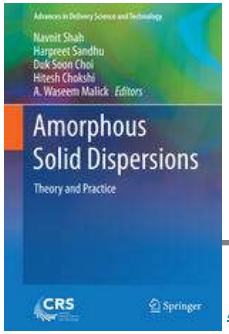
Fumed (“colloidal”) silica is recognized as the industry standard, but there is a great deal of confusion in terminology

The Strength of Silica based formulation strategies



Mesoporous Silica Based Excipient Strategies

Mesoporous Silica-Based Drug Delivery Strategies

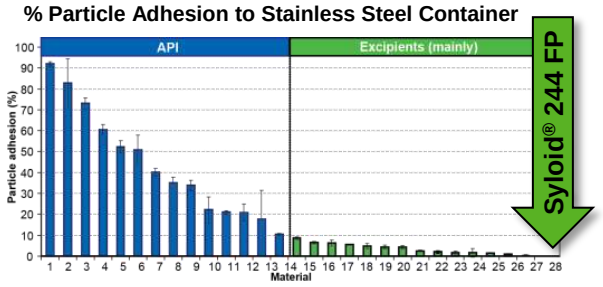


Advances in Delivery Science and Technology 2014, pp 665-693 Choudhari, Monsuur, Hoefer, McCarthy, Libanati

Micronized, Multi-functional, and Highly Porous

1. Smallest mesoporous silica : Syloid® AL-1FP/63 FP

- Increased Physical Stability of hygroscopic systems (API, Polymer, Natural Extract
- Intragranular Desiccant / Moisture control up to 80% RH
- Stabilise the water in your formulation to protect API
- High surface area 700m2/g provides monolayered water under all RH%. % AL1FP dependent on %RH and CRH of Actives (min. 5% up to 20%)



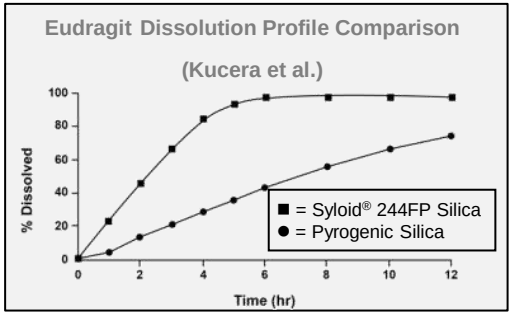
2. Intermediate mesoporous silica : Syloid® 244FP

- Wetting agent : ODT and for Maximum API release (pores stay available)
- Anti-tacking agent in coatings + Anitcacking for Waxi API
- During API premixing with 244FP providing optimum uniformity, lower friability, maximum API release and great Triboelectrostatic advantages

BIOGRUND FILMCOATING EXCELLENCE

- Improved suspension stability (replace or additional to talc)
- Helps prevents valve blockage
- Anti-tacking agent (replace or additional to talc)
- Increases wettability

If premixes are prefered : Biogrund as Bonulac, **Aquapolish-C** and Evonik as Readymix **Eudragit EPO** (mostly 10% 244FP used)



Glatt

- Granulation : Syloid is in general directly dispersed into the melt phase and works as an anti-tacking agent for the process. It can also be blended to the obtained granules for his anti-tacking and lubricant properties

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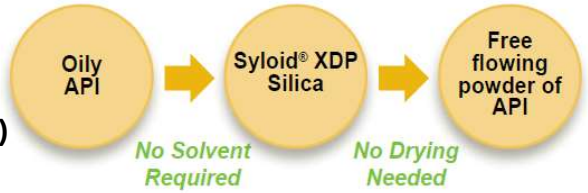
For over 40 years Syloid® FP multi-functional silicas have been used successfully in numerous pharmaceutical formulations

From Mesoporous Excipient to Drug Delivery System

3. Large Mesoporous silica for liquisolid : Syloid® XDP 3 Series

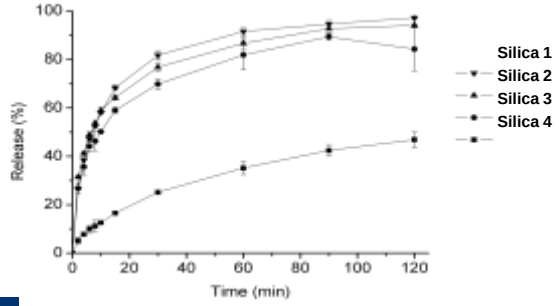
- Loading Oily API, SEDDS, … (3050 = Tablets, 3150 = Capsules)
- Optimized poresize for best density, volumetric capacity
- Optimized porevolume for maximum adsorptive capacity **(1.5:1 – liquid:silica)**
- Optimized porestructure for maximum release



4. Mesoporous silica for topical delivery : Syloid® 3D

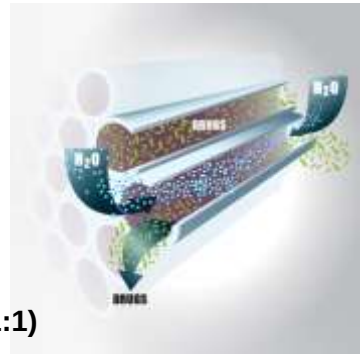
- Optimized particle size for skin feeling
- Optimized poresize for stability
- Improved concentration on the skin

Performance "tailorable" by using different silicas



5. Solvent based loading for BCS2 : SilSol 6 Series

- **Solvent based drug loading** (controlled poresize close to API size)



6. Dry strategy for BCS2 silica solid dispersions

- Mechanochemical activation by using the right friction "energy" between API/Silica **(ratio 1:1)**
- Large poresize silica providing access to internal surface area. (turning crystaline into amorphous)

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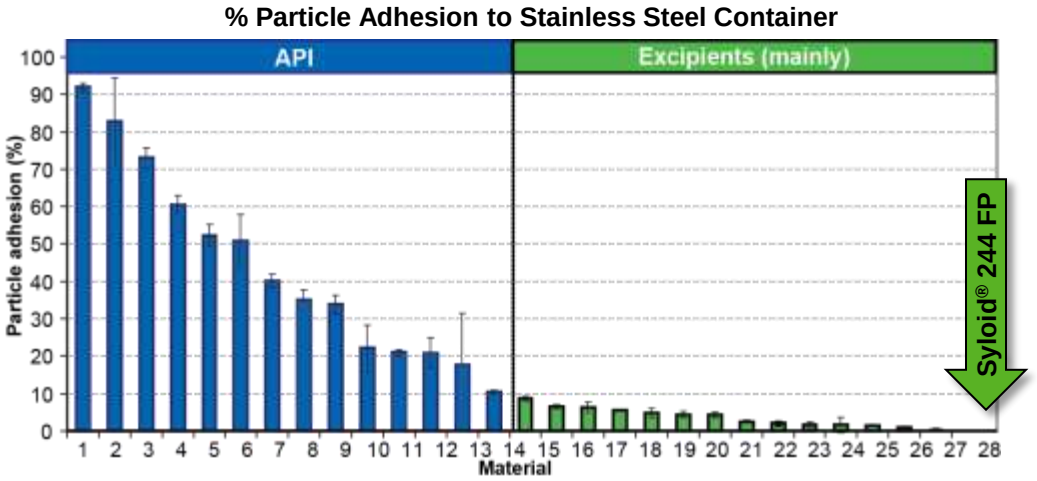
Flow Improvement

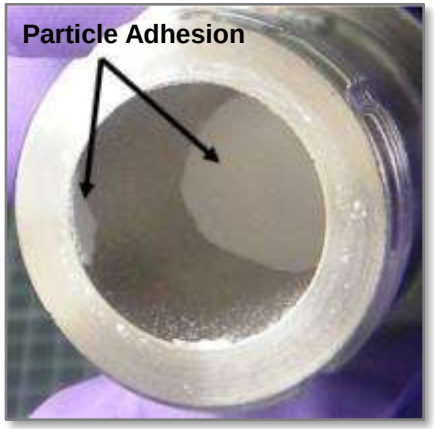
- Interparticulate attractions
- ***Tribo-electrostatic charge***
- Permanent electrostatic charge
- Ionised surfaces
- Presence of polar functional groups on the surface
- Molecular interatctions (dipole dipole, Van der Waals)
- Capillary forces (Wasburn's equation)



$$V_f = \frac{(\rho_p - \rho_f) \cdot g \cdot d2 \cdot \varepsilon 3}{150 \cdot n \cdot (1 - \varepsilon)}$$

ρ = density
d = diameter of particles
n = viscosity
g = gravity
ε = void of the particles

Stainless steel container prior to test



Post charging showing particle adhesion

Film Coatings

Syloid® FP Silica Benefits to Film Coatings

- Improved suspension stability (replace talc and add 2-3%)
- Helps prevents valve blockage
- Anti-tacking agent (replace talc)
- Increases permeability (AL1FP/244FP add 10 or more %)

Ingredient:	Parts by Weight:
EUDRAGIT® Acrylic Polymer	3,334 g
x	200 g
Syloid® 244 FP Silica	300 g
x	3,361 g

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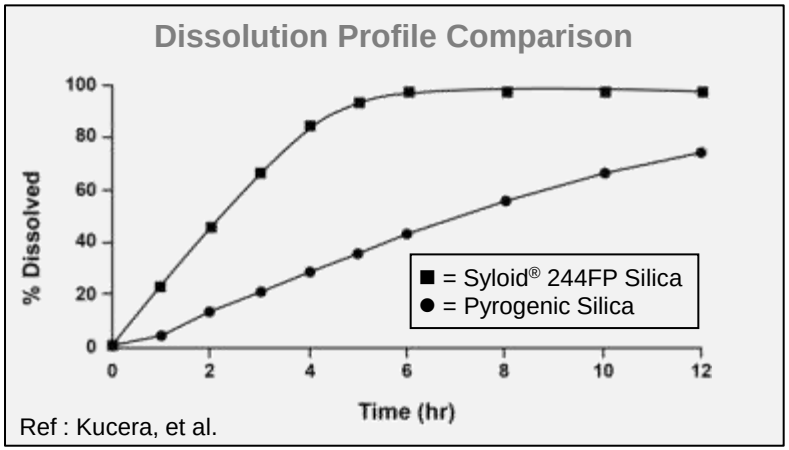
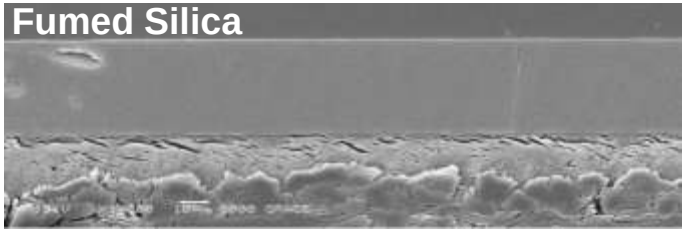
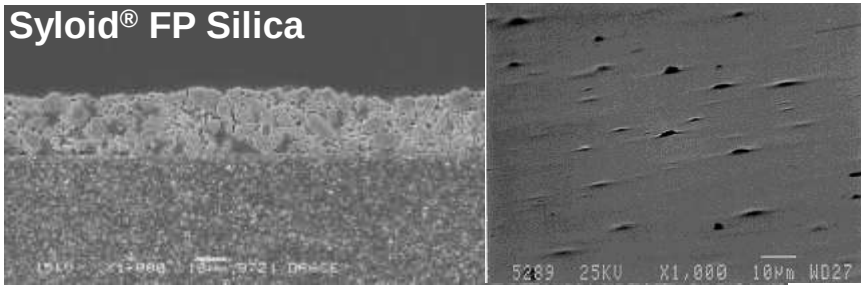
FILMCOATING EXCELLENCE



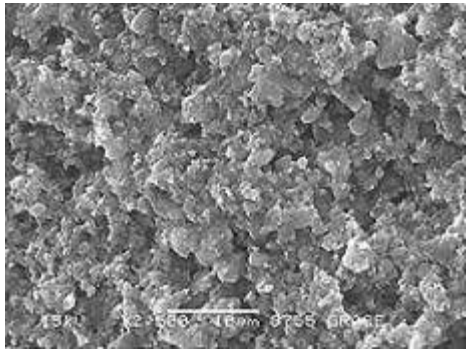




Wetting agent / Poreformer

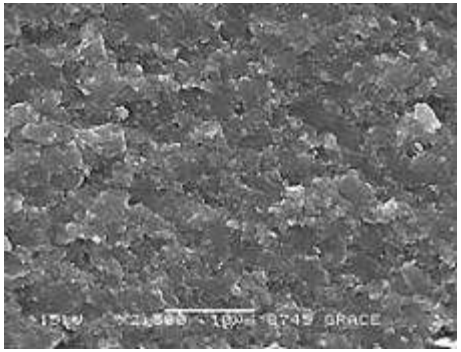
Sublingual, ODT , ODMT, ODF, Effervescent:

LOWER Compression Force

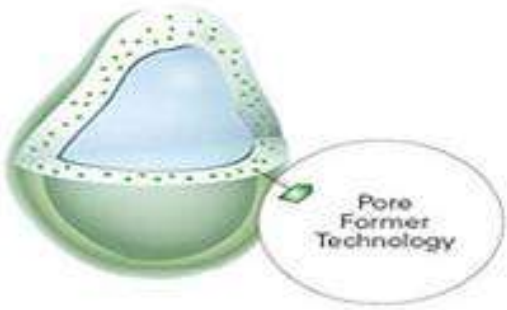


MORE Pore Availability

HIGHER Compression Force



LESS Pore Availability



- Often problems with tablet hardness
- **High porosity is needed : Aiding the disintegration**
- Anti-static agent
- **Protection from pre-activity**
- Improve water adsorption
- Improve mechanical stability
- **In ODT's compression forces are lower ! SyloidFP pores remain intact.**

Ethypharm : The permeabilising agent allows the creation of a hydrophilic network which facilitates the penetration of saliva and hence assists the disintegration of the tablet.

Effervescent tablet

- **Effervescent tablets are designed to break in contact with water, releasing carbon dioxide in the process.**
- **They contain sodium bicarbonate and an acid. The carbonate creates CO2 and H2O, and water stimulates further breakdown (autocatalytic)**
- **So it is of the utmost important to keep these tablets as dry as possible:**
  - packaging (dessicant in the cap)
  - inside the tablet (Syloid® 244 FP)
- **Note: as Syloid® 244 FP will not dissolve, it can only be used for dispersions (cloudy appearance)**

Syloid® FP silicas can help to preserve effervescent tablets by reducing water activity

Medicated chewing gum

- **Medicated chewing gum application**
- **Cafosa: gum in powder form, Spain**

Alternative procedure: premix of Oil + Syloid® 244 FP

Using too much silicon dioxide can cause a dry mouth sensation, so there was a need for a highly efficient glidant at low concentrations

CAFOSA
A subsidiary of Mars, Incorporated

EXAMPLE FORMULA:
Dimenhydrinate 20 mg
Compressed gum

Dimenhydrinate	**0,02%**	Silicon Dioxide	0,90%
HEALTH IN GUM	**95,00%**	Liquid Flavour	0,60%
Powder Flavour	1,80%	Intense Sweeteners	0,18%
Lubricant	1,50%		

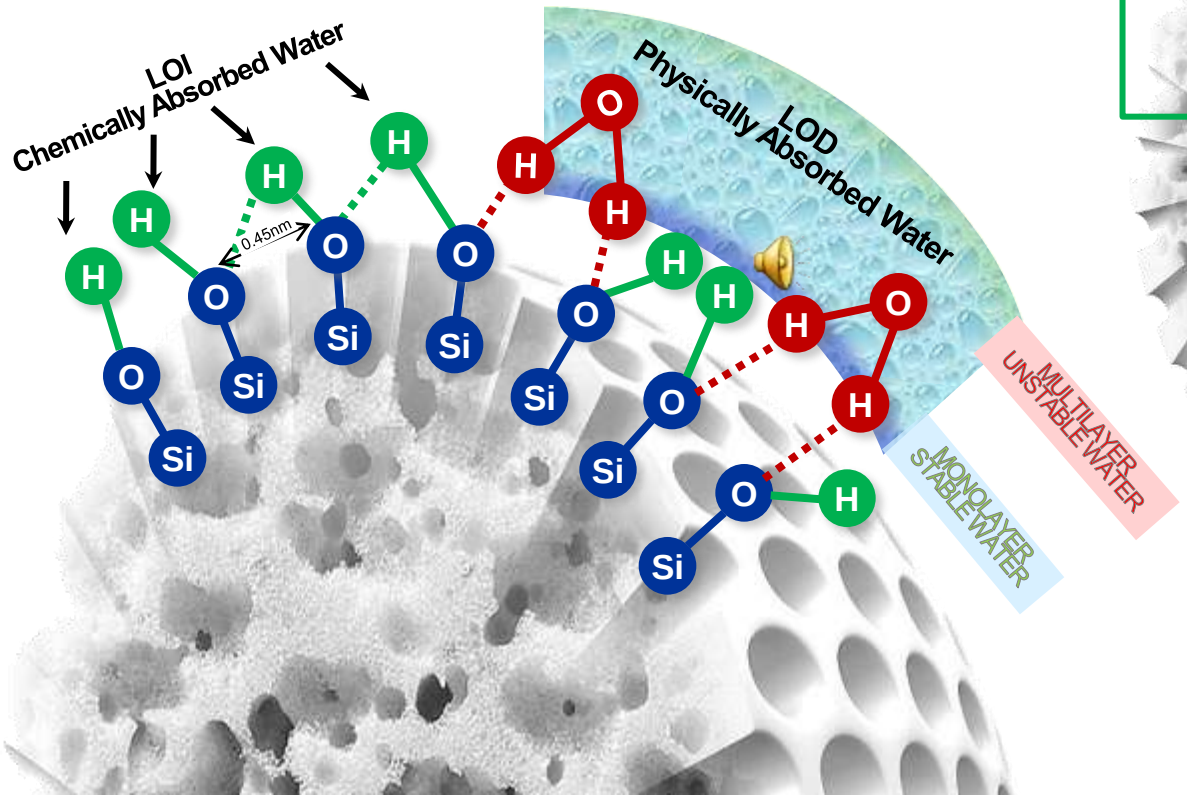
Very hygroscopic drug

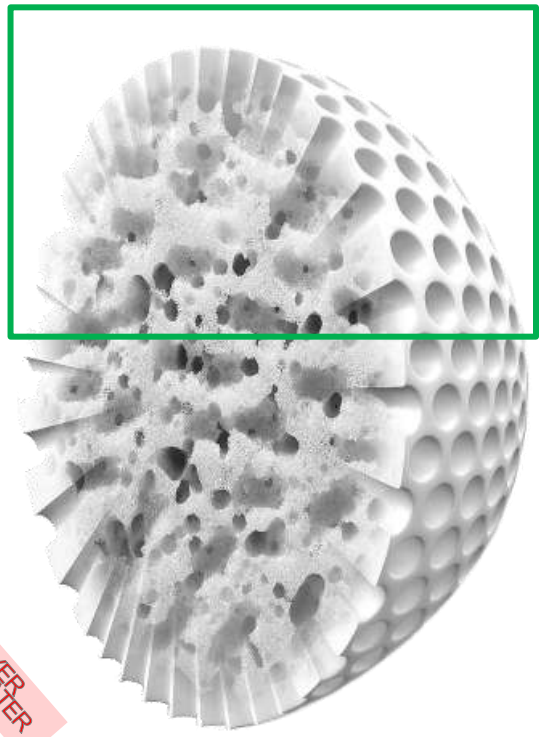
1. Definition: Very hygroscopic drug is the one whose mass increases by ≥ 5% when stored below 60% RH for 1 week time.
2. Problems of very hygroscopic drugs during tablet formulation.
    1. Chemical stability: For some drug, absorbed moisture may interact with drug, hydrolyze it and decreases its potency. Obtained byproducts may be toxic and not acceptable. **Use Syloid® AL1FP**

    2. Physical stability - Processability: Absorbed moisture may reduce the processability of the formulation e.g. flow property of powder blend, content uniformity of drug in powder blend, weight variation & hardness of tablets etc. **Use Syloid® 244FP or Syloid® XDP3050**

Moisture Protection - AL1FP

Syloid Silica gel = 4-6 OH/nm² + SA 700m²/g
Aerosil Fumed silica = 2 OH/nm² + SA of 200m²/g





Can we consider also amorphous systems and their moisture sensitivity ?

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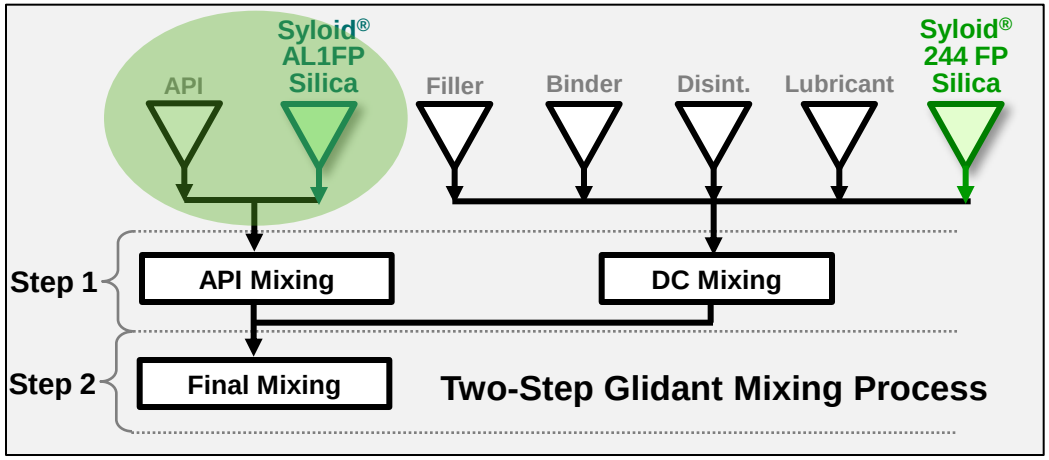
1. Improve Chemical stability – AL1FP

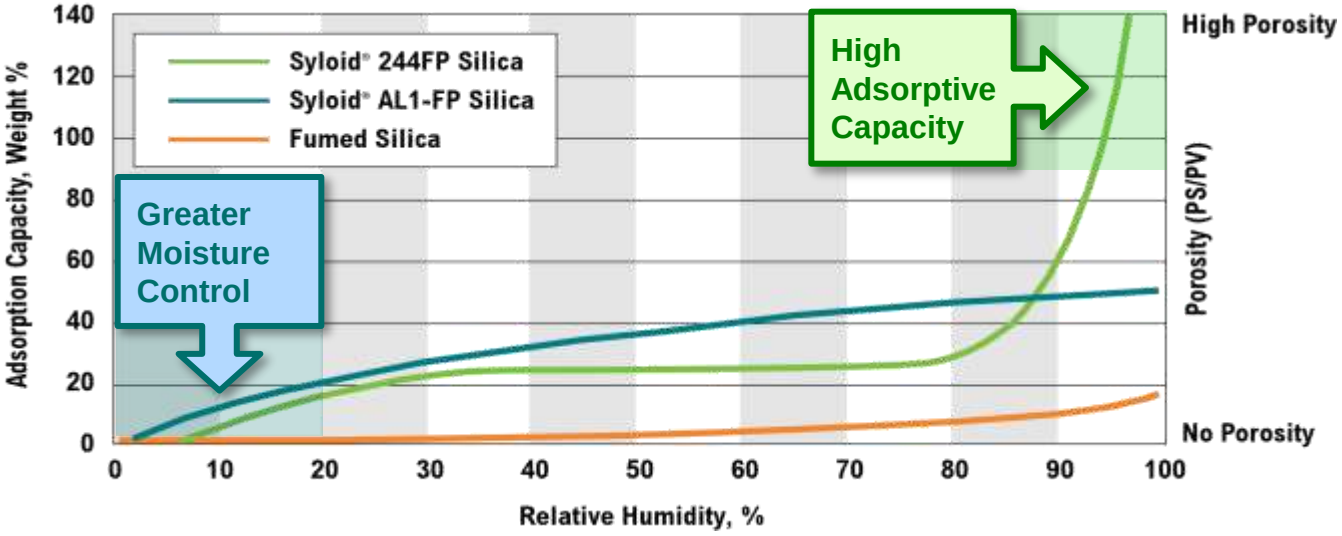
Porous Silica Can Improve your stability usingTwo-Step Mixing:

- Improves **chemical stability**

244FP in excipient part :

- Improves **flow properties**
- Improves **anticaking**
- Improves homogeneity, **uniformity**
- Improves **tablet hardness**

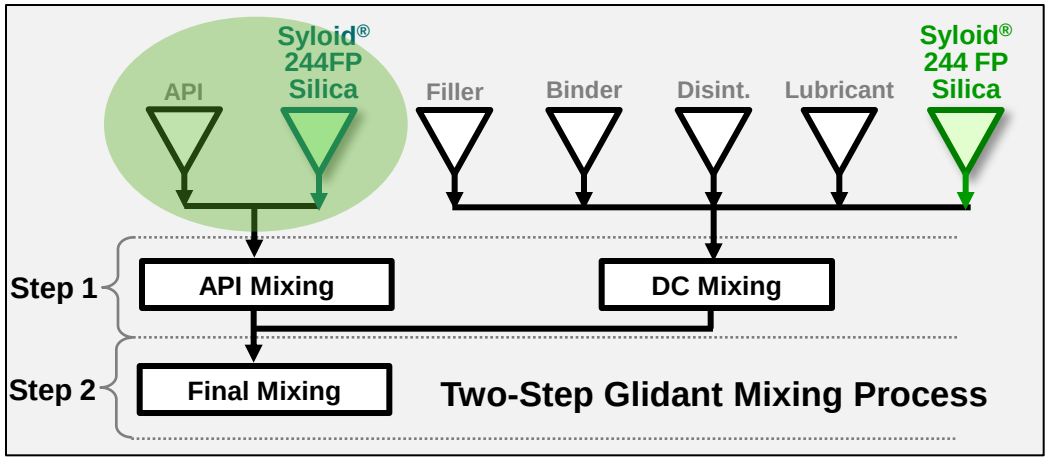


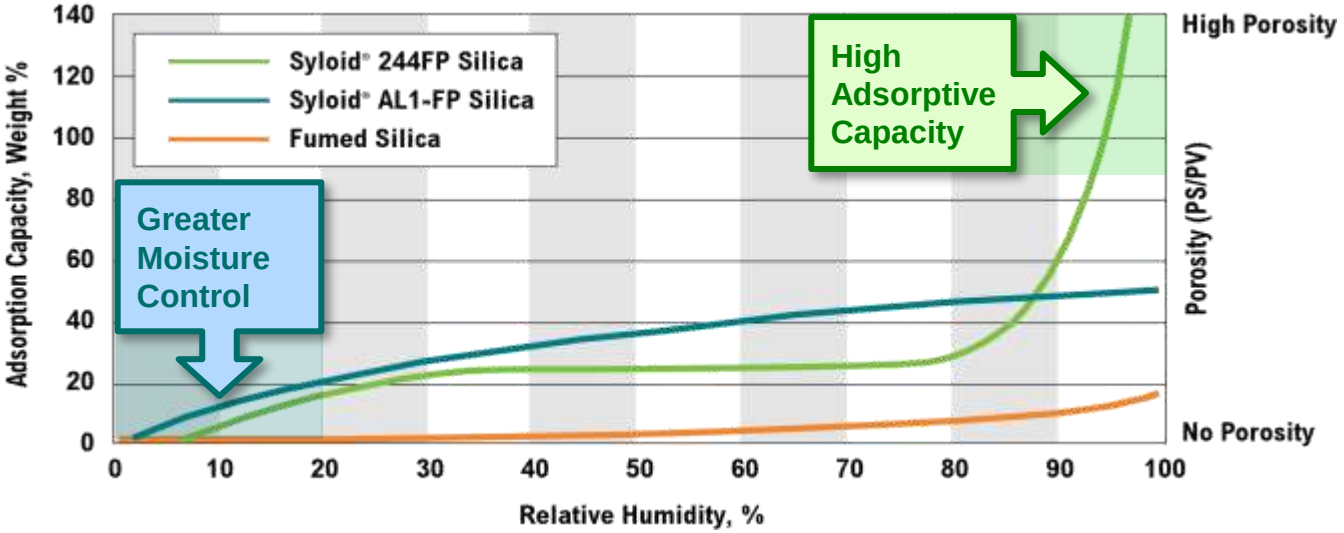


2. Improve Physical stability – 244FP

Porous Silica Can Improve your stability usingTwo-Step Mixing:

- Improves **physical stability**
- Improves **flow properties**
- Improves **anticaking**
- Improves homogeneity, **uniformity**
- Improves **tablet hardness**

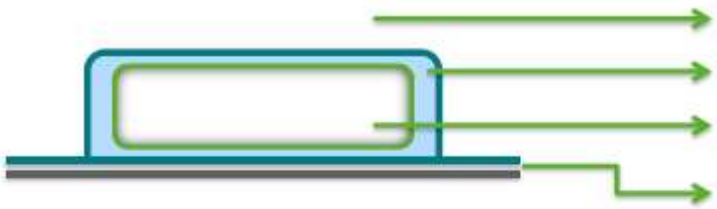




Chem. Pharm. Bull. **57**(7) 647—652 (2009)

Moisture : How much AL1FP or 244FP do I need ?

Determination of dessicant mass required



External RH

Mass of Water trapped in air in blister

Mass of Water in tablet

Mass of water diffusing : W V T R trough packaging

1. **Water content of the trapped air [g H2O/cm3]**

   M air = (Vblister – Vtablet) x water content

2. **Water content of the tablet [g H2O/Tablet]**

   M tab = weight loss (or KF at storage conditions)

3. **Water vapour transmission rate [g H2O/m2/day]**

   WVTR supplied by company (aggressive conditions) or Weight of tablet before and after storage

4. **Water capacity of the desiccant [wt.%]**

   Use water adsorption capacity tabel for max loading

Can a Moisture Calculator be developped ?

Pharmaceutical Application Calculator

API = Active Pharmaceutical Ingredient

Tablet Properties

Mass	600	mg
Density	1,5	g cm^{-3}
API Quantity	10	mg
Water Content	1	wt.-%
Water Vapor Transition Rate	2,922	mg cm^{-2} a^{-1}
Tablet Volume	0,4	cm^3
Water Quantity	6	mg

Blister Dimensions

Height	0,5	cm
Length	1,7	cm
Width	0,5	cm
Volume	0,425	cm^3
Surface	3,9	cm^2

Storage Conditions

Temperature	25	°C
Pressure	980	mbar
Relative Humidity	50	%
Required Storage Time	1	a
Critical API rel. Humidity	30	%

Silica Gel

Total Water Quantity	17,37873	mg
Adsorption Capacity	26,15128	wt.-%
Total Quantity	66,45458	mg

Filling Conditions

Temperature	25	° C
Pressure	1013,25	mbar
Relative Humidity	45	%

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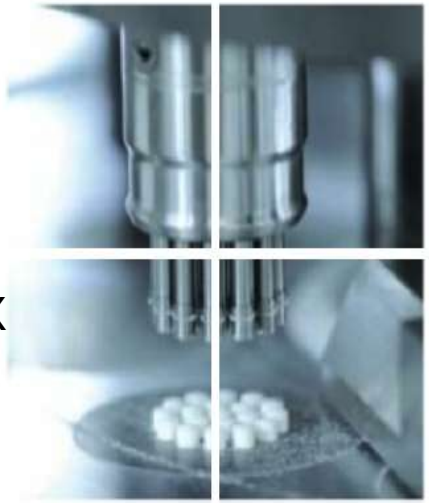
Materials Technologies

Paediatrics – EU is trendsetter

- Stability
- Dosing (mini-tablets, dry syrups, …)
- Taste acceptance

Grace Mesoporous Silica :



- safe excipients (5.3g/kg BW/day)
- used over 40 years, FDA, DMF and first IPEC GMP 2010 !
- used in dry suspensions (stability, flow and flavor addition)
- used in many ODT and extented into Sublinguals
- monograph compliant and already used in paediatric AMOX
- used in medicated chewing gum (CaFoSa)
- low dose / minitablets
    - 2 step mixing strategy provides better uniformity
- improved solubility = less API required
- new strategies avialable where there is no need for organic solvents

EuPFI : Children are no small adults

Syloid® XDP Silica
Pharmaceutical Excipient

A Silica-Based Carrier Optimized for Liquisolids & Lipid-based Formulations

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Liquisolid Systems Today (LBDDS)

Currently, there are limitations to LBDD Systems and carriers that limit their use or effectiveness

Limitation of SEDDS and liquidsToday:

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

Limitation of Carriers Today:

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

Liquisolid Systems are of interest today not only for NCE's but also in particular for reformulation and life cycle management

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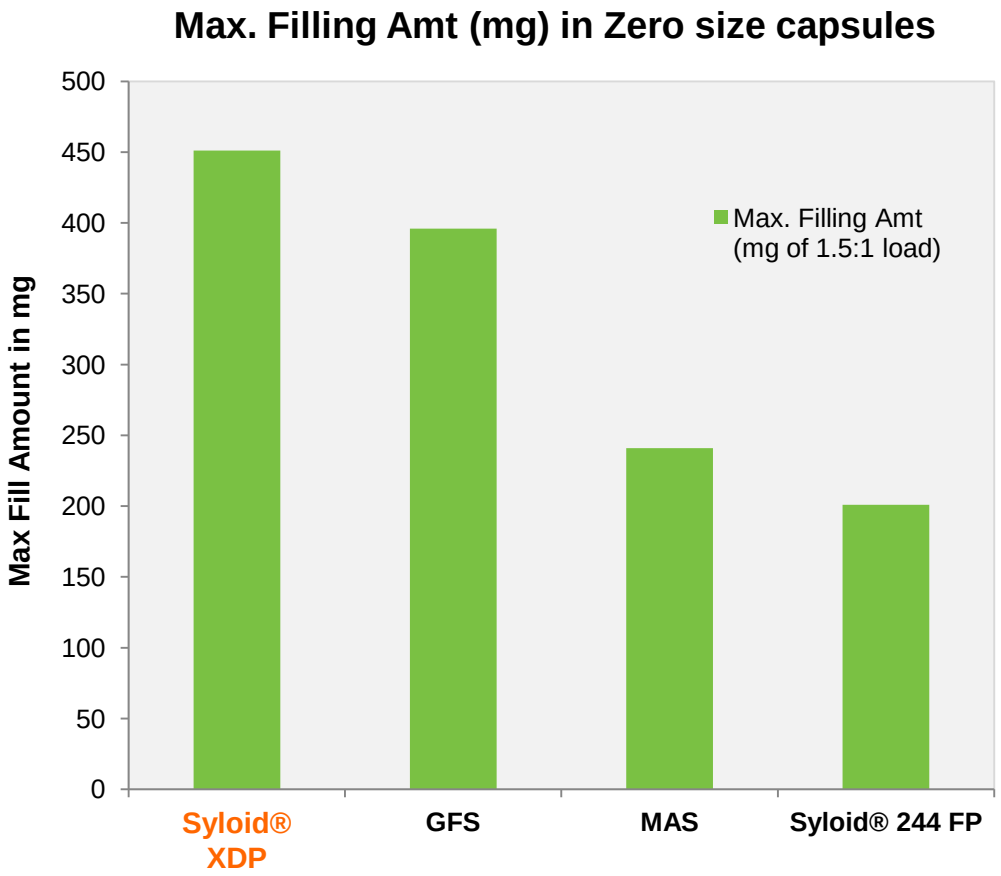
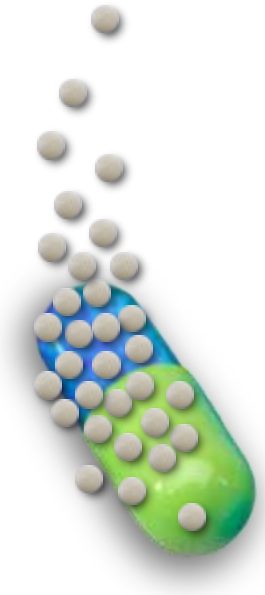
Volume & Density





Syloid® XDP carrier gives maximum filling amount per capsule

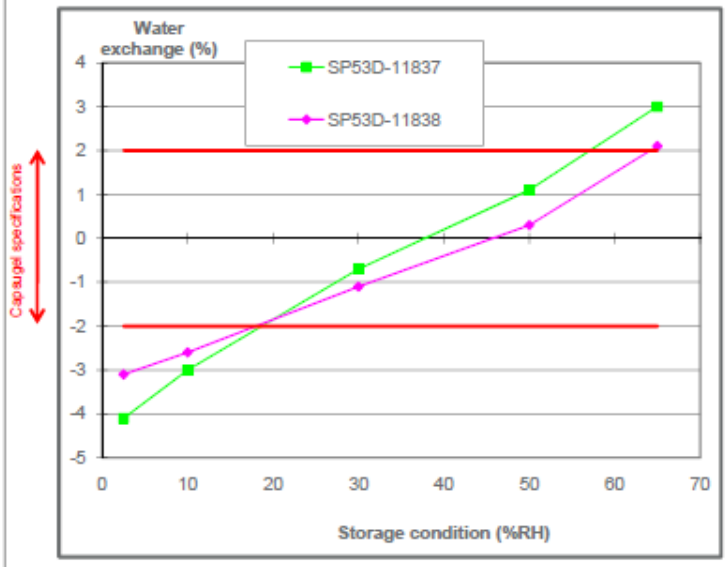
Objective

Evaluate the compatibility of 2 products developed by Grace with Capsugel capsules according to Capsugel Standard Operating Instructions

- **Hygroscopicity testing**
- **Mechanical resistance testing**
- **Desagregation testing**

Hygroscopicity testing – HPMC cap

Results after 2 weeks storage



Conclusion for gelatin capsules

➢ **Hygroscopicity testing:**

- Water exchange at low humidity conditions (< 25%RH) are out of Capsugel recommendations for both products
- No deformation or alteration of gelatin capsules observed for both products in all conditions

➢ **Mechanical robustness testing:**

- No alteration of mechanical properties of gelatin capsules observed with both products

➢ **Disintegration testing**

- Total disintegration time is conform to EP 2.9.1 monograph with total disintegration time below 30 min

➡ Products SP53D-11837 and SP53D-11838 are considered compatible with gelatin capsules when stored under standard storage conditions (35%RH – 65%RH)

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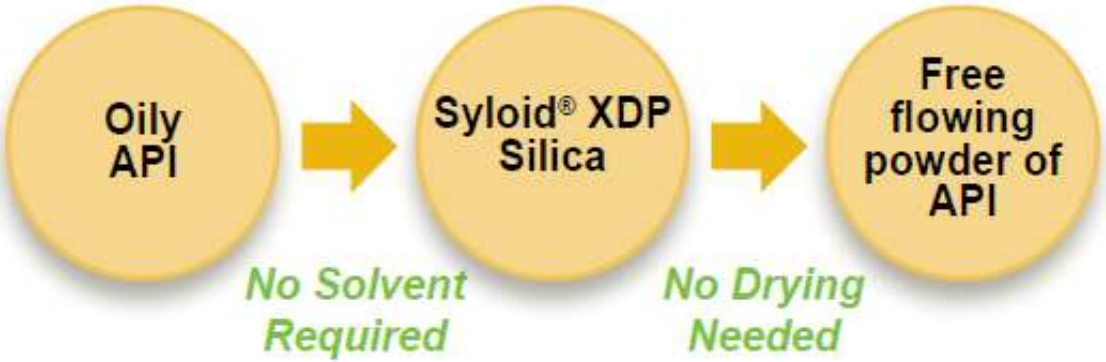
Loading procedure for most lipids



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

Simple liquid to solid transformation

1:1.5 ratio is used for capsules

1:1 ratio is used for tablets due to deformation of pores

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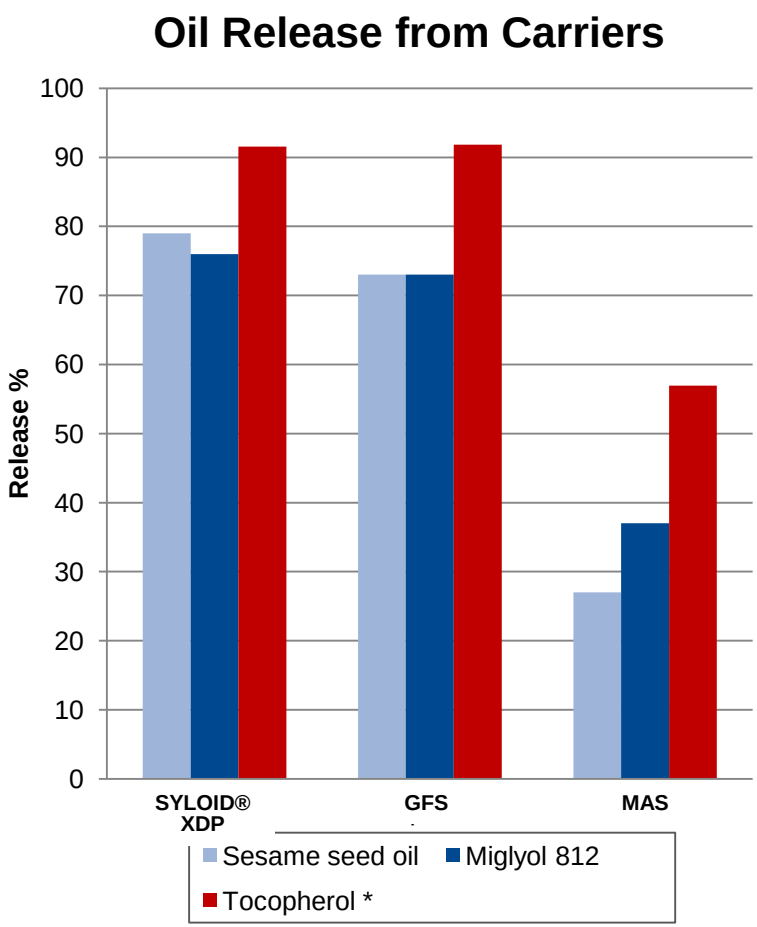
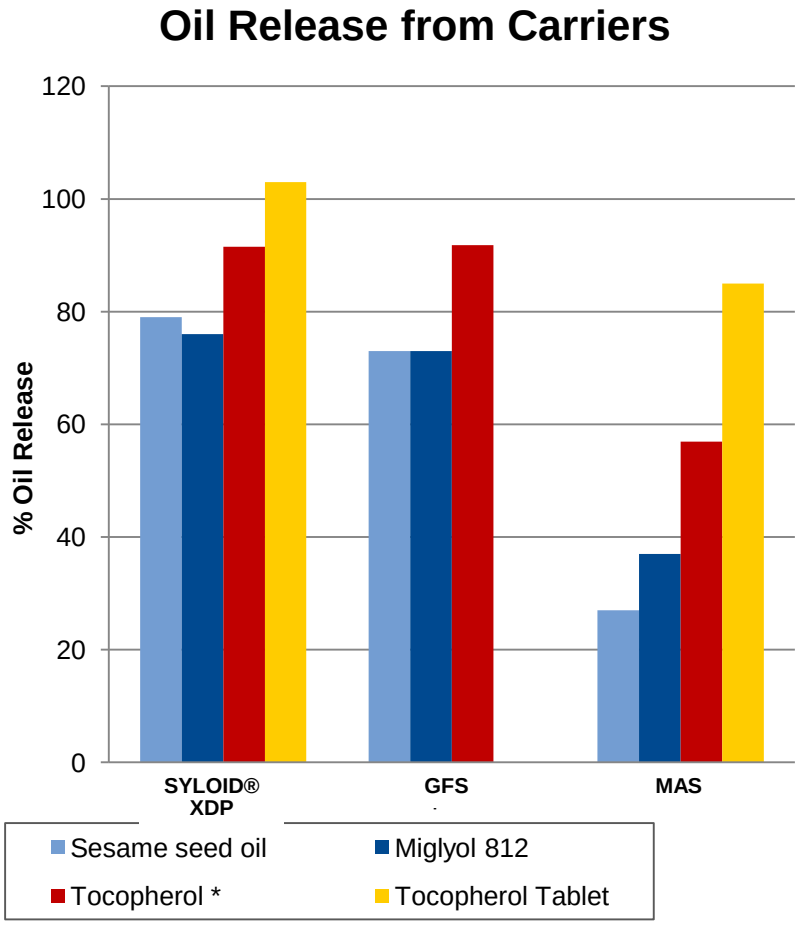
Solid Carriers – Oil Release - NO surfactant





Syloid® XDP carrier gives the best release profile

For MAS the more hydrophilic the better the release

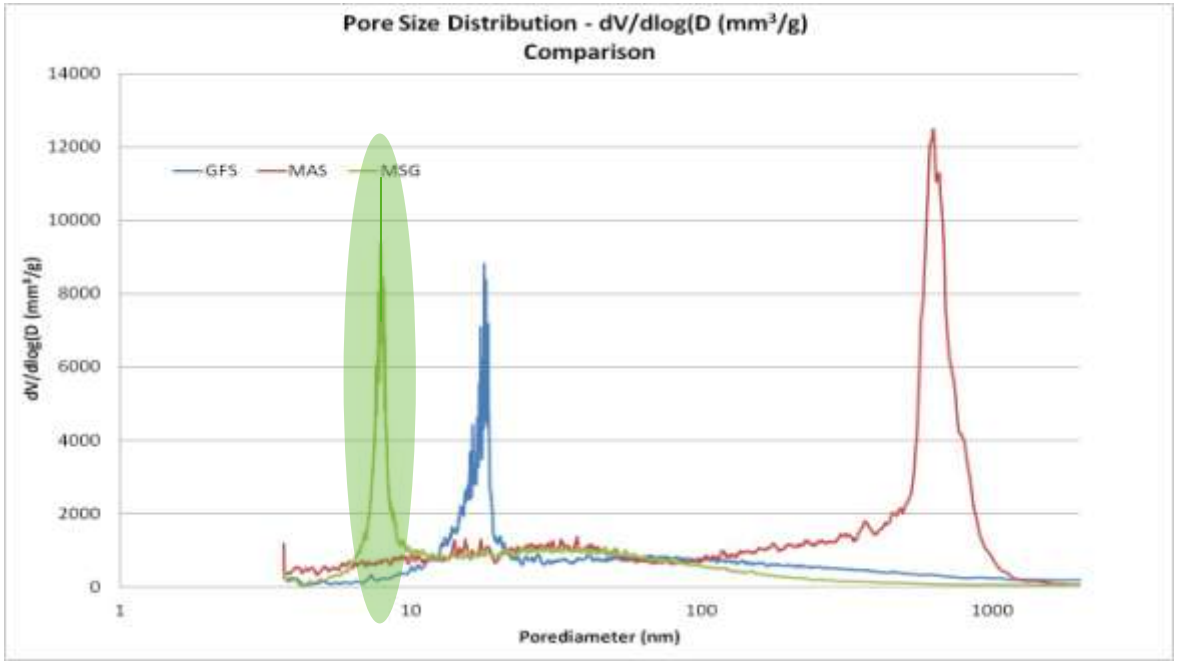
JPS, 1014, DOI 10.1002/jps.23970 : confirming incomplete desorption with different actives and surfactants

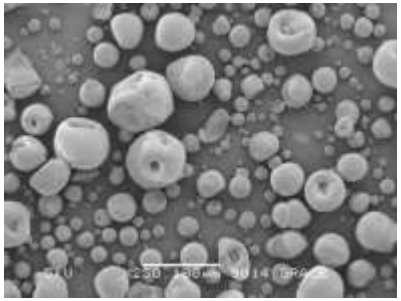
Incomplete Desorption of Liquid Excipients Reduces the *in Vitro* and *in Vivo* Performance of Self-Emulsifying Drug Delivery Systems Solidified by Adsorption onto an Inorganic Mesoporous Carrier Michiel Van Speybroeck *Mol. Pharmaceutics*, **2012**, *9* (9), pp 2750–2760

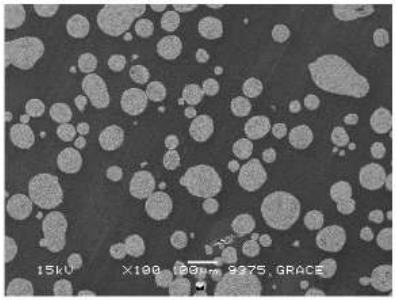
23

Optimised Poresize and pore-structure

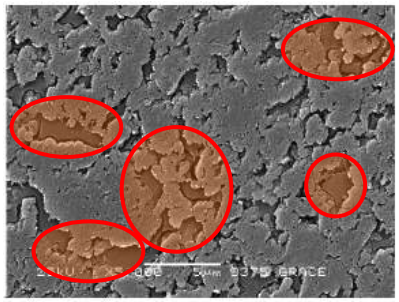
Syloid® XDP Silica

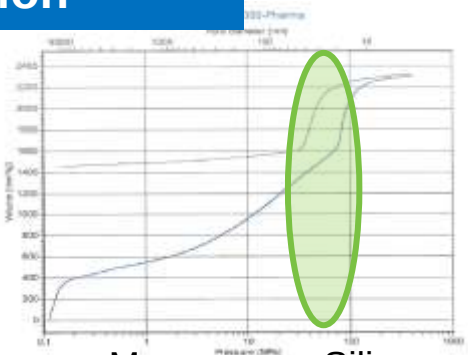






Avoid Bottleneck pores / Macropores
Will result in incomplete desorption





Macroporous Silica

Mesoporous Silica

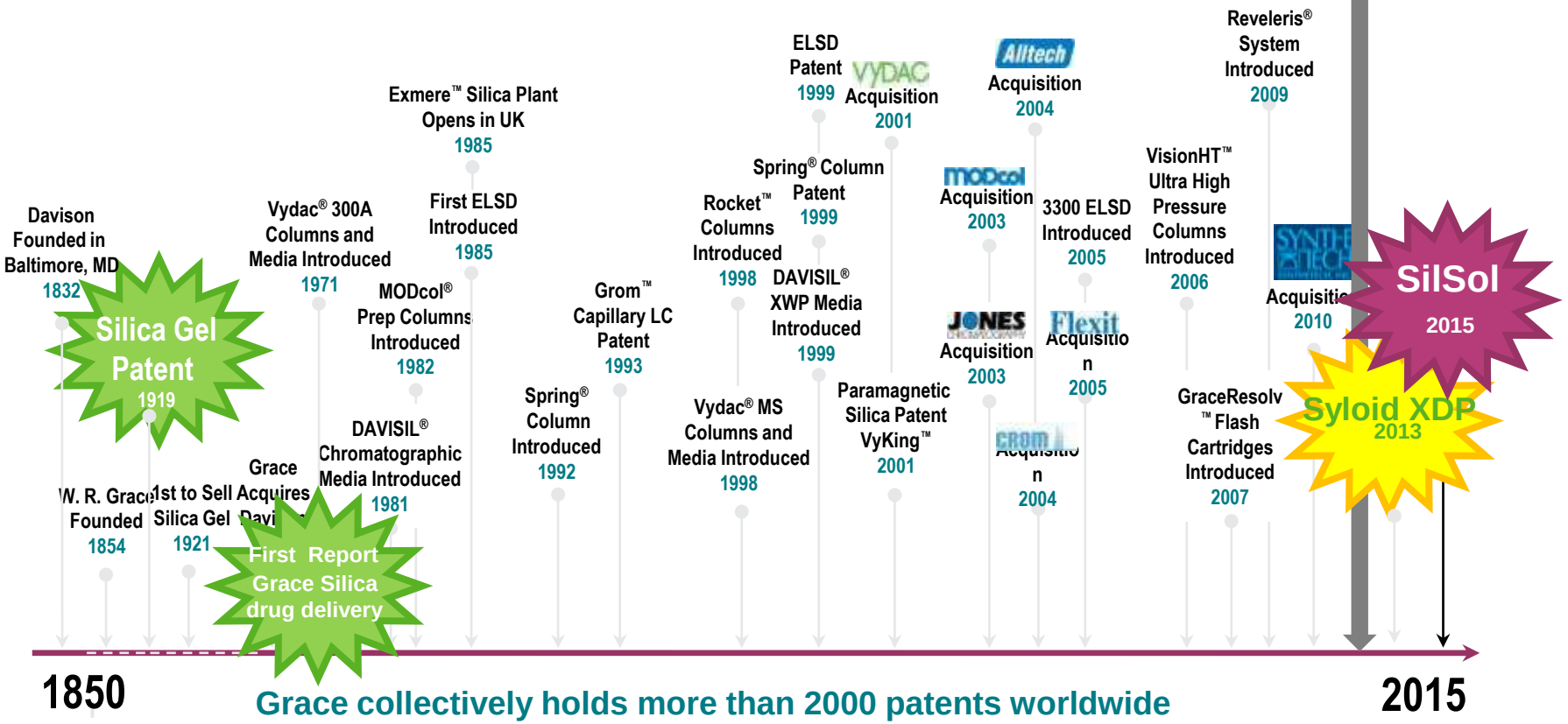
GRACE

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

Grace® Silica Drug Delivery

170 Years of Innovation From Discovery to Delivery

2011 Formac and Grace Form Strategic Global Partnership



Grace collectively holds more than 2000 patents worldwide

Grace® Silica Drug Delivery

Following a multi-year collaboration with Formac Pharmaceuticals; Grace is proud to announce the first Silica in "Grace® Silica-based Drug Delivery Platform" being named "*SilSol™ 6035 Mesoporous Silica Gel*"

The Grace® Silica Drug Delivery Platform Offers Five Major Benefits

Enhanced bioavailability – Through the formulation of amorphous drugs
Stability – Through design of the pores, the amorphous API is stabilized within the pores
Pharmacopeia acceptance – GMP manufactured silica conforms to global monographs
Scalability – Grams to tons quantities under Excipient GMP manufacture
FDA compliance – Material is listed on the FDA inactive ingredient database

The Platform Advantage—Simplicity

Compared to other bioavailability enhancing techniques such as particle size reduction, complexation, lipid-based systems and polymer-based solid dispersions, the Grace® platform introduces techniques that are often easier to screen, less complex to make, and require less time when scaling up.

- Suitable for NCE, life cycle management, reformulations, and repositioning
- Applicable to a broad range of compounds (including all BCS2 poorly solubles)
- Easy and cost effective introduction into established manufacturing units
- Generate stable formulations

Grace® Silica Drug Delivery

The Grace® Silica Drug Delivery Platform was engineered to bring together advanced silica technologies with challenging active pharmaceutical ingredients (APIs) to help more effectively formulate a large class of poorly soluble but otherwise promising compounds.
The Grace® platform gives pharmaceutical developers a new drug delivery option for enhanced bioavailabilty of BCS2 (poorly soluble) compounds. BCS2 compounds account for 40 percent of the APIs on the market today, 70 to 80 percent of pharmaceuticals active in the pipeline and those that have been shelved due to solubility issues. In total, BCS2 compounds represent an estimated market opportunity of $5 billion.

The Grace Silica Advantage

Grace® silicas have been used in pharmaceutical formulations since the 1960's and we continue to innovate today. This new Silica Drug Delivery Platform combines our expertise in silica materials, novel application methods, and patent pending technologies to accelerate the screening and development of solubility enhancing solid dispersions, with the added benefit of doing so with compendial, scalable, and available silicas.

Grace® Silica Drug Delivery

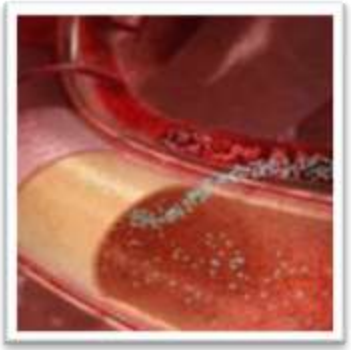
Oral delivery is preferred route for drug administration

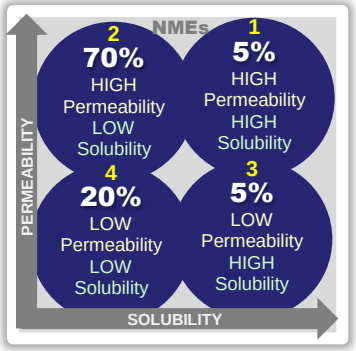
High number of all development candidates fail due to biopharmaceutical reasons

BCS classification: ***(Amidon et al.,1995)***

- **Class I**: HIGH permeability and HIGH solubility
  Formulation independent
- **Class II: HIGH permeability but LOW solubility**
  Formulation dependent
- **Class III**: LOW permeability but HIGH solubility
  Dependent on barrier properties
- **Class IV**: LOW permeability and LOW solubility
  Formulation and barrier properties dependent

70% of the compounds in pharmaceutical R&D pipelines are poorly soluble

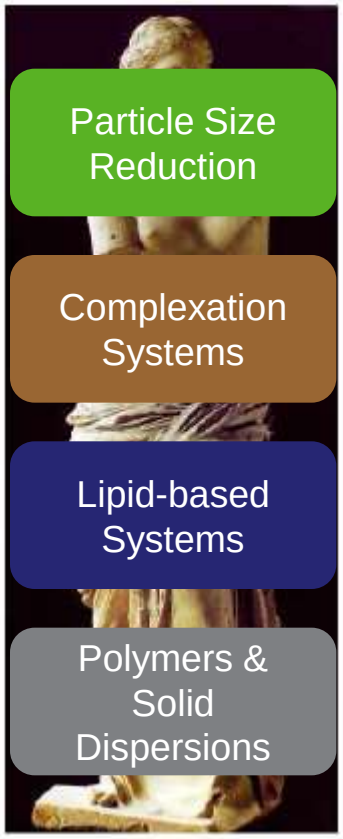




GRACE

Grace® Silica Drug Delivery

Most used advanced solubilization strategies



- **Each technology approach has disadvantages**
- **No one technology works on all components**
- **Number of poorly soluble compounds increases**

Need for new strategies

Marble = 10 000 x more soluble then many NCE

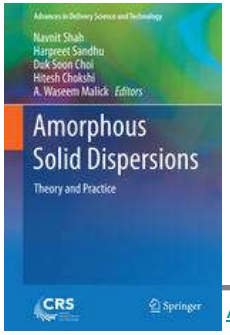
Grace® Silica Drug Delivery

Solvent based methods

- Solvent Immersion
- Solvent Drying
- Incipient Wetness / Impregnation
- Spray Drying
- SuperCritical Fluid

Solvent-free (dry) methods

- Melt Mixing
- Co-Milling/Grinding
- Microwave Assisted Loading
- Loading during synthesis of silica
- New High shear force strategies



GRACE

Selection of the right loading strategy

In a comparison study of three different drug loading methods, Mellaerts et al. investigated the location of ibuprofen and itraconazole in SBA-15 by means of N_2 physisorption, thermogravimetric analysis (TGA), DSC, diffuse-reflectance UV, and X-ray photoelectron spectroscopy (XPS). Here, the authors conclude that the effectiveness of the loading method is strongly compound dependent, which ultimately also affects the drug release (Figure 1-9) [97]. These data emphasize the great need for extensive research regarding the compound dependency of intrapore molecular organization and release kinetics depending on the drug loading method.

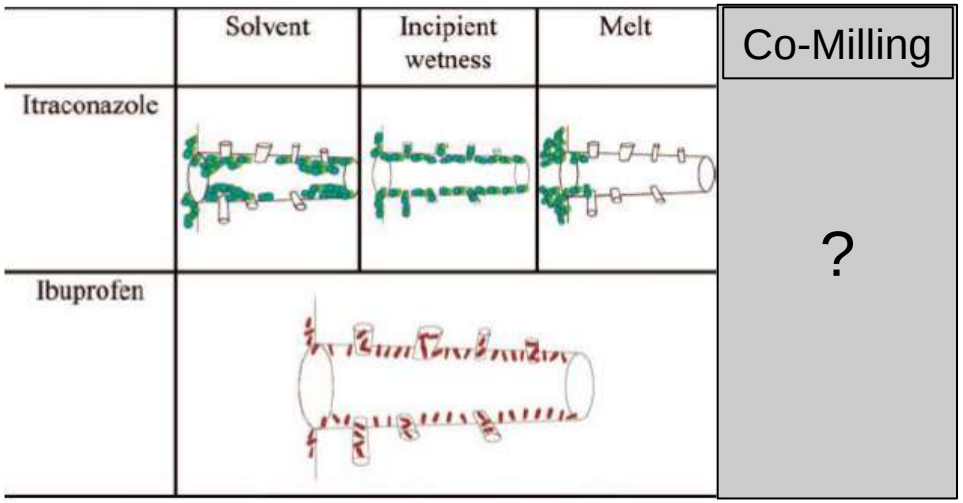


Figure 1-9. Physical state of itraconazole and ibuprofen in SBA-15 following three different drug loading methods [97].

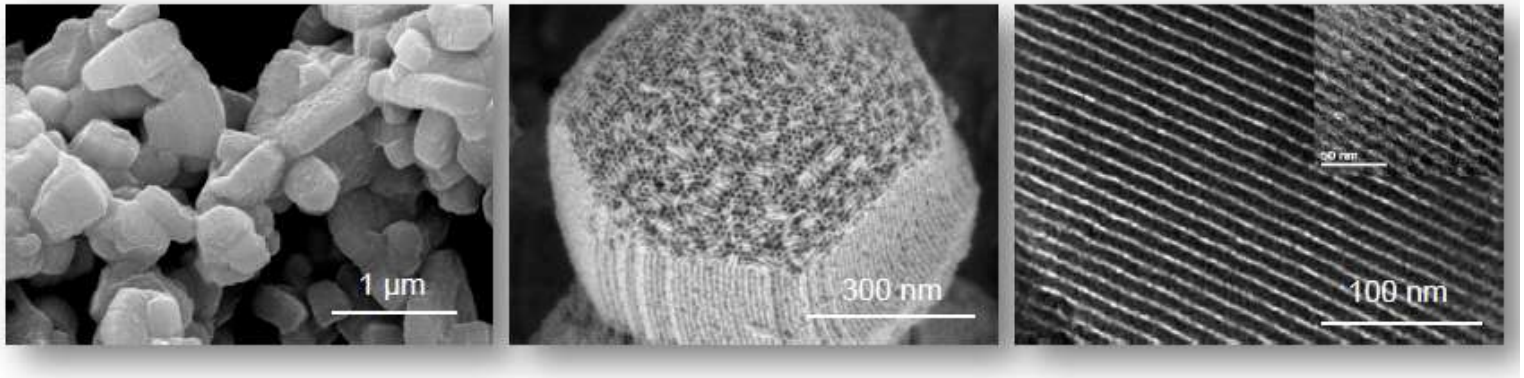
Mellaerts et al. Chem Commun (13):1375–1377 - 2007

Van Speybroeck et al. 2009. J Pharm Sci 98(8):2648–2658.

Where did it all start ? MCM - SBA

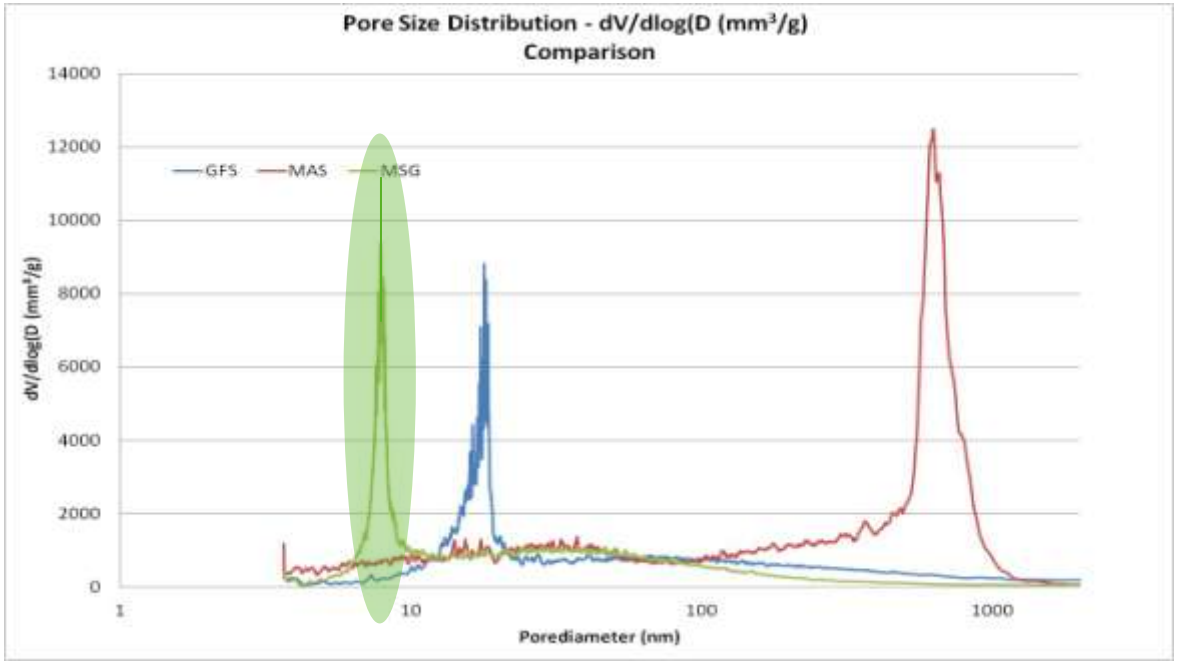
Mesoporous silica

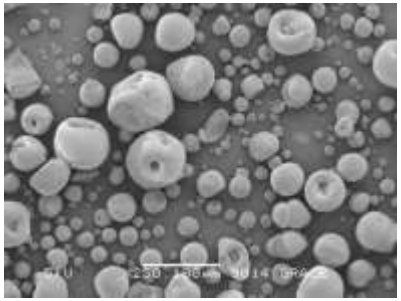
Formac pharmaceuticals

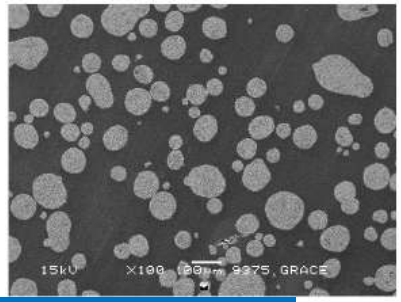


- Silica: silicon dioxde, SiO_2
- Mesoporous: exhibiting pores with diameter between 2-50 nm (IUPAC definition)
- High internal pore volume: up to 1,5 cm^3/g
- High surface area: up to 1000 m^2/g
- Ability to synthesise materials with different porosity characteristics (pore size, pore size distribution, pore volume, surface area)

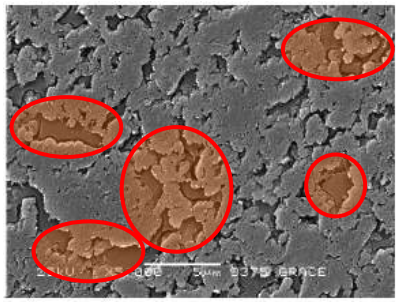
Optimised Poresize and pore-structure

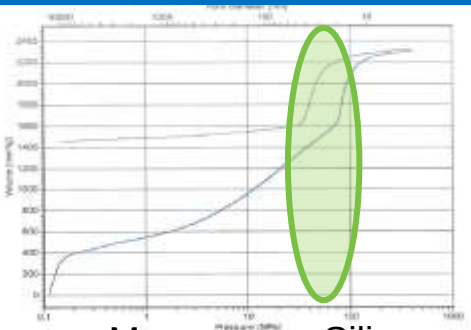






Avoid Bottleneck pores / Macropores (loading + stability problems)
Will result in incomplete desorption and recrystalisation !





Macroporous Silica

Mesoporous Silica

GRACE

Grace® Silica Drug Delivery

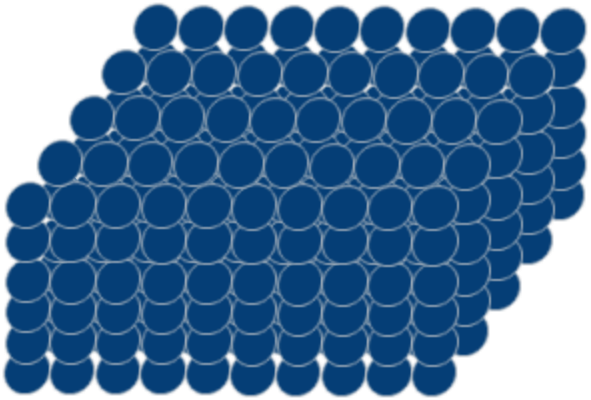
The **Grace® Silica Drug Delivery Platform** can be used with both solvent impregnation and solvent-free techniques to create amorphous solid dispersions.

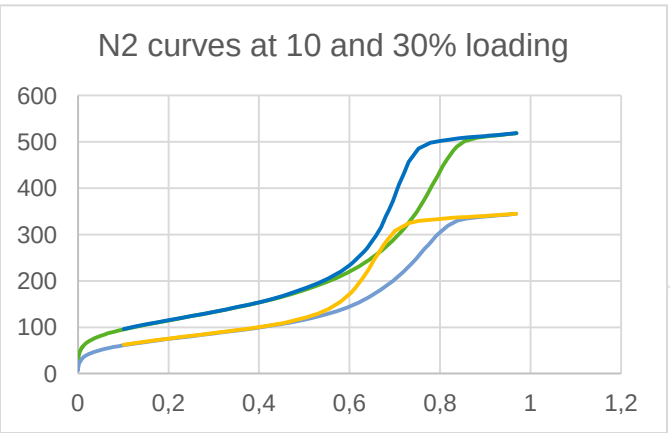
Through molecular engineering, Grace can modify the pore size and surface characteristics of silica to accommodate various API molecules. The net result is enhanced bioavailability with stability.

Solvent Techniques	Solvent Free Techniques
1. Crystalline API, which is difficult for the body to absorb, is dissolved in a volatile solvent to create a solution of amorphous API	1. Crystalline API, which is difficult for the body to absorb, is mixed with specifically engineered silica
2. Grace silica material is impregnated with the API-solvent solution.	2. The mixture is milled or compressed to introduce energy into the mixture
3. The API is deposited into the silica's mesopores	3. The energy creates an amorphous form of the API and breaks down the silica particle so more of the surface can interact with the API
4. The solvent is then evaporated from the particles.	4. Equilibrium is created to form a new particle that suppresses the re-crystallization of the API
5. Silica pores suppress the tendency of the API molecule to re-crystallize.	5. The amorphous API is released from the particles and becomes available in the gastrointestinal system.
6. The amorphous API is released from the pores and becomes available in the gastrointestinal system.	

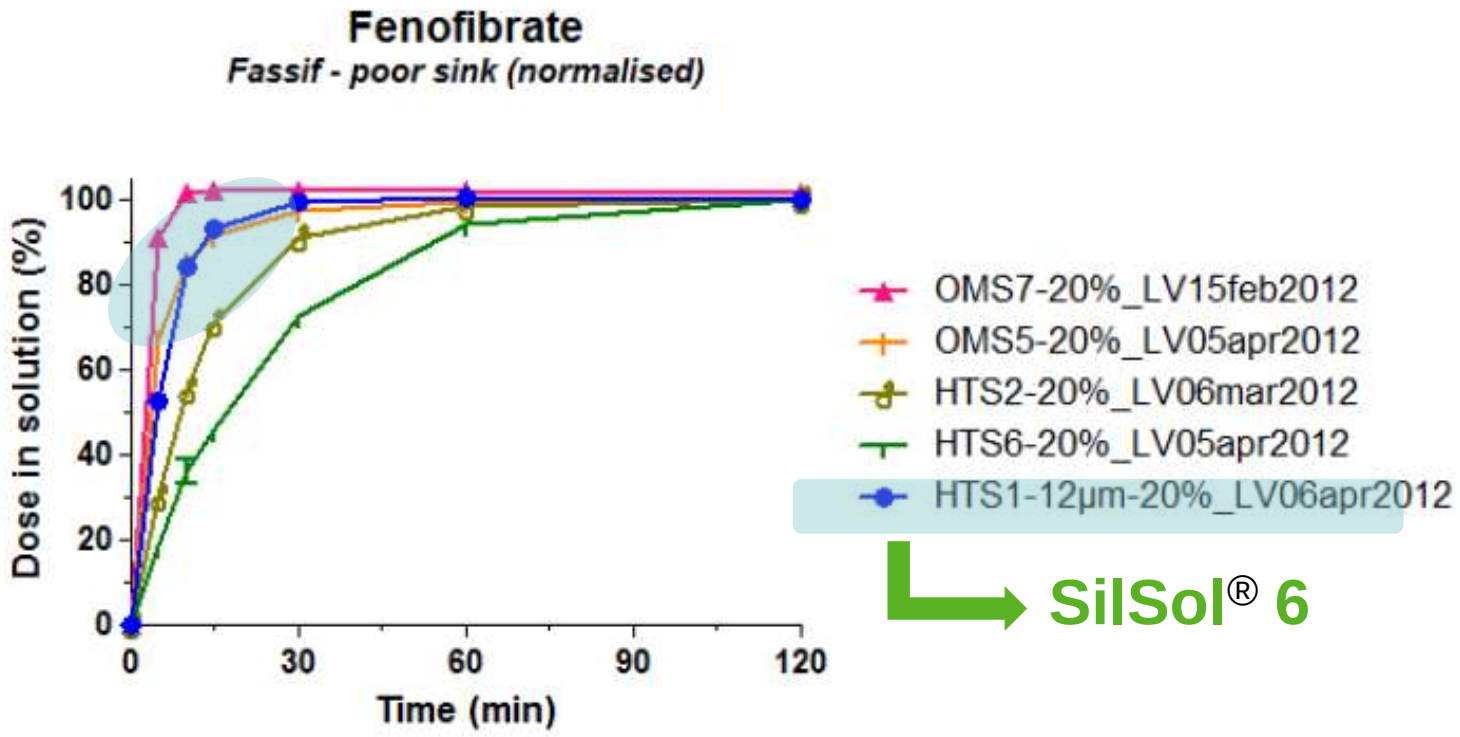
Dissolution-Enhancing Effect of Mesoporous Silicas

API Dissolved in Organic Solvent and Loaded into Silica





Ordered vrs Non-ordered Optimised PSD
Influence of poresize

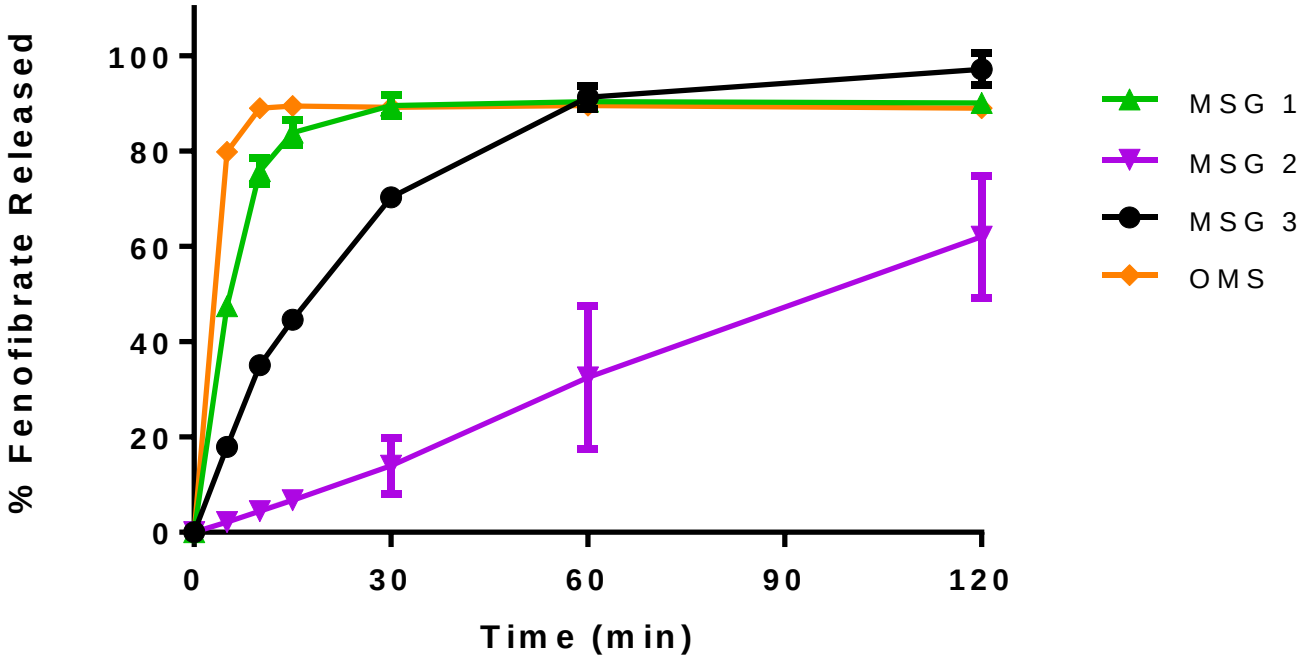


HTS 1 (SilSol® 6) selected as closest to OMS (ordered)

Van Speybroeck M et al, 2010 - Eur J Pharm Sci 41(5):623–630 (On OMS only)

Ordered vrs Non-ordered Optimised PSD

Influence of Particle size



Potential use in Controlled Release

Courtesy by W. R. Grace – Formac Pharmaceuticals

Grace® Silica Drug Delivery

From Solvent based to Dry Strategy ?

In Situ Amorphisation at point of equilibrium
Details under CDA

Drug Mechanochemical Activation
I. Colombo et al. - JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 98, NO. 11, NOVEMBER 2009

Planinsek O, Kovacic B, Vrecer F. 2011. Carvedilol dissolution improvement by preparation of solid dispersions with porous silica. Int J Pharm 406(1–2):41–48 (comparing milled CAR with SD silica)

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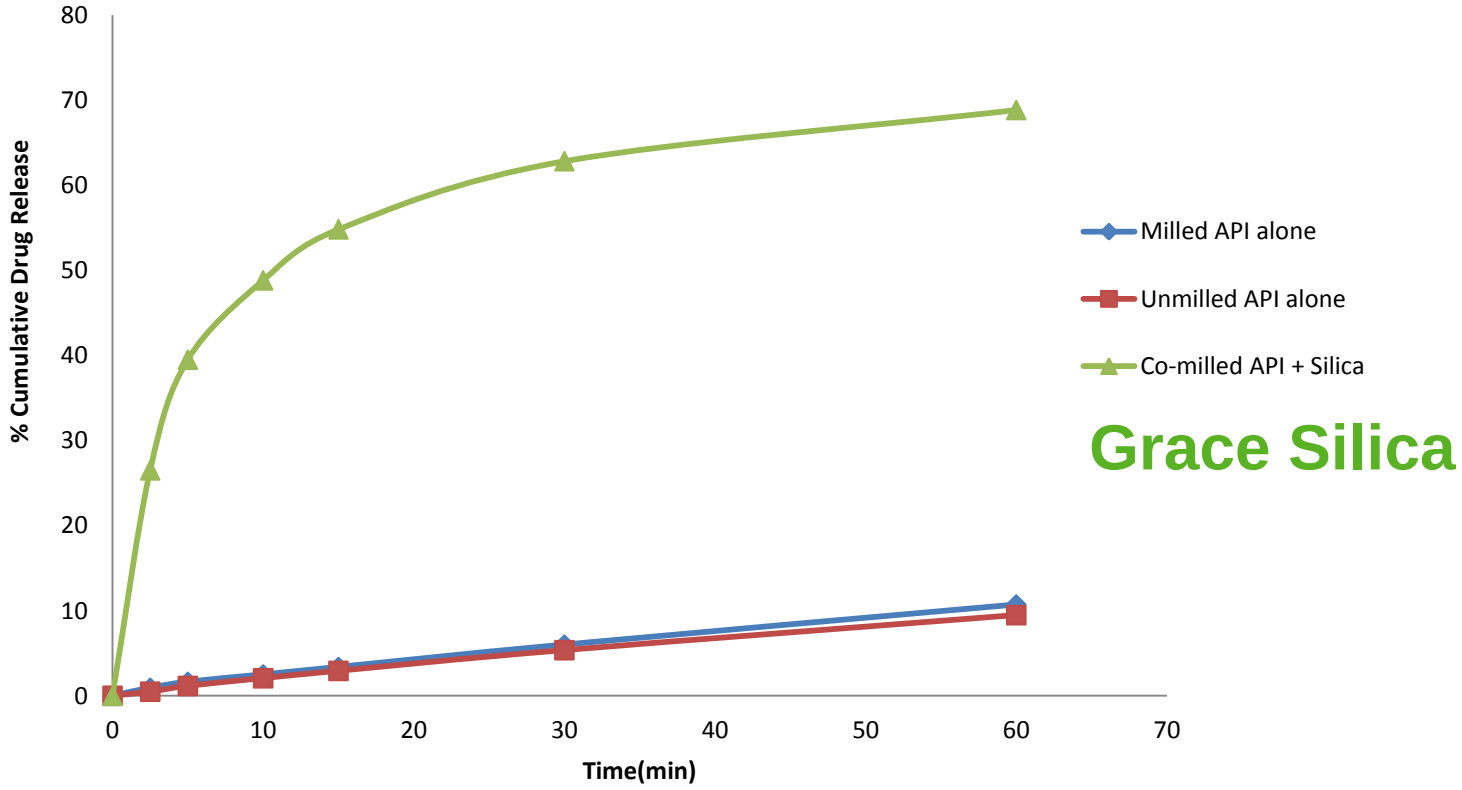
Grace® Silica Drug Delivery

Is it the silica providing the dry amorphisation



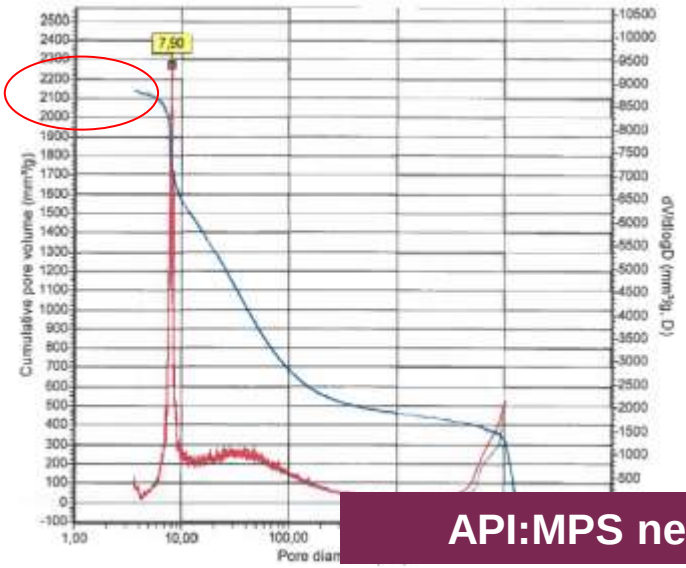
API alone milled does not provide the improvement in dissolution

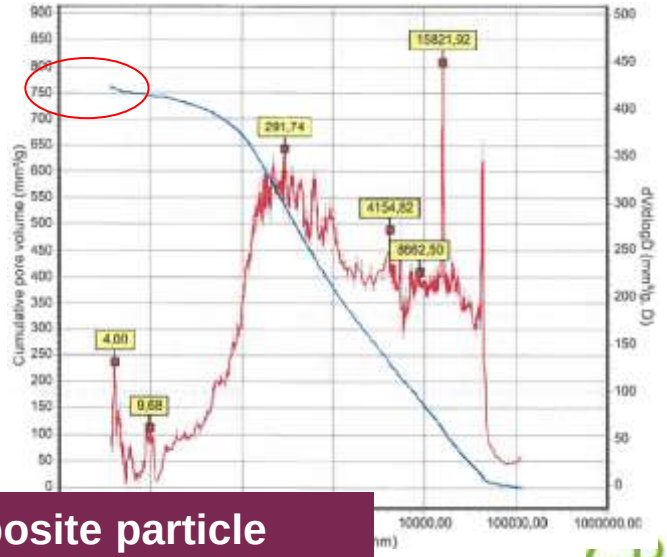
Xiaohong Pan et al. Drug Development and Industrial Pharmacy, 34, 221-231, 2008

Grace® Silica Drug Delivery

Grace silica 50 as is

Grace Silica 50 after 30HZ 60min





API:MPS new composite particle

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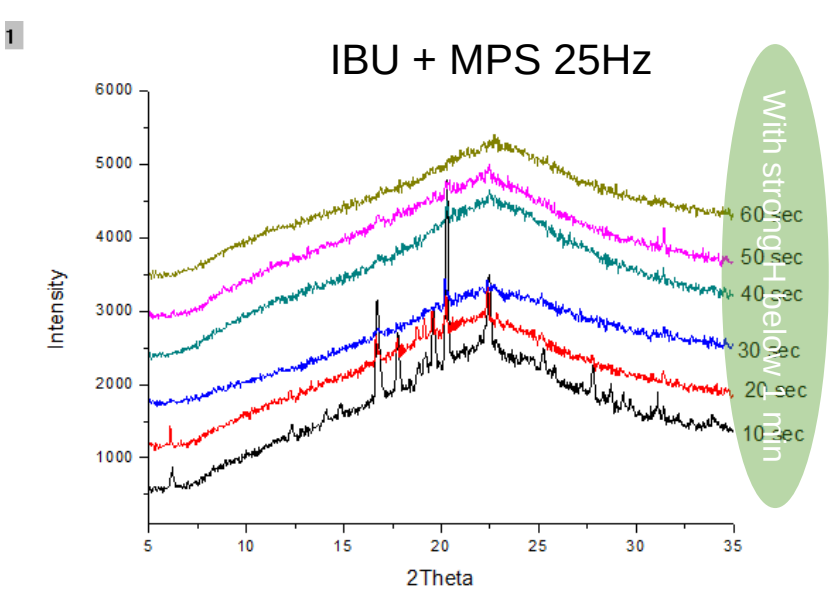
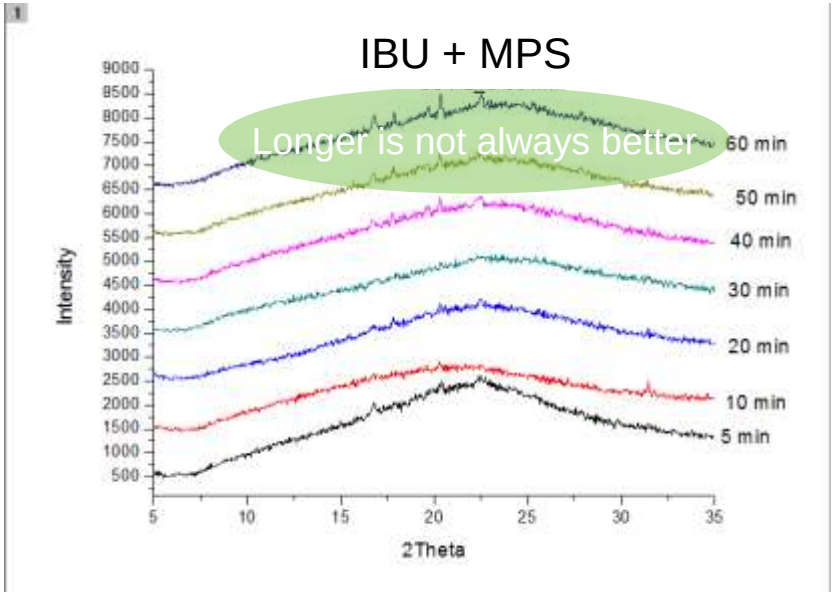
Grace® Silica Drug Delivery

Intensity + Residence/Contact Time
Can we reduce the amorphisation time ?





Energy transfer 'saturation' taking place ?

Hüttenrauch et al. - Pharm Res. 1985 302-306

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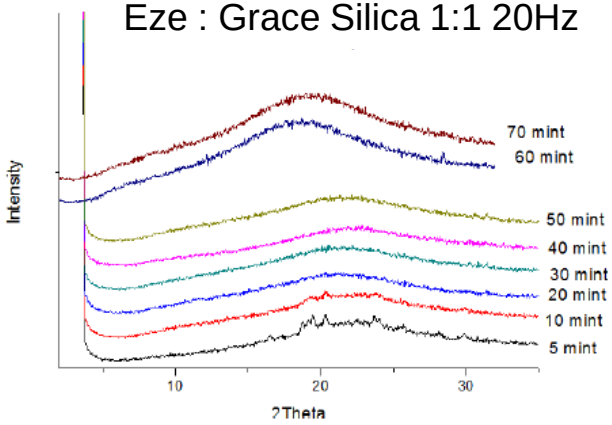
Grace® Silica Drug Delivery

Ezetimibe as is

Eze : Grace Silica 1:1 20Hz



Grace Silica 50 as is

Eze : Grace Silica 1:1 20min 20Hz

API:MPS new composite particle

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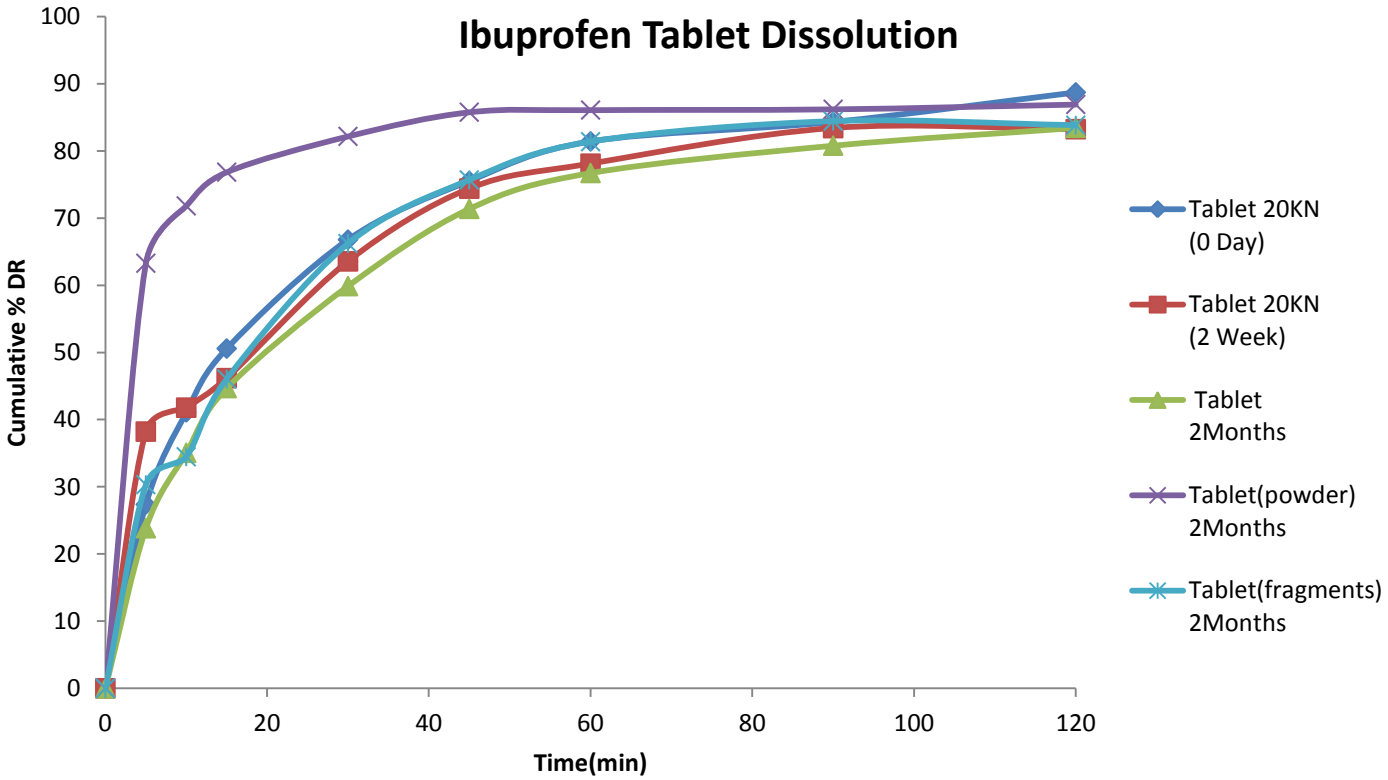
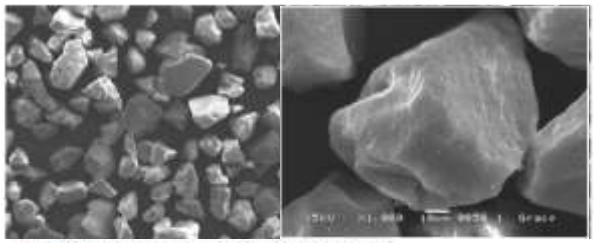
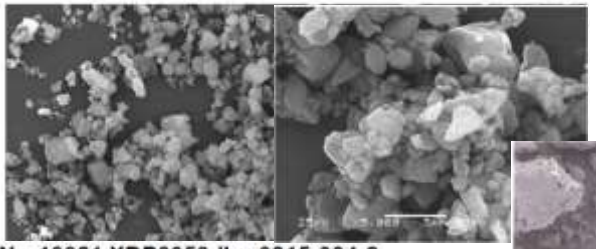
Shelflife and Release change on crushed tablet



Grace® Silica Drug Delivery



Nr. 10060 XDP3050-Ibu 0815-034-1



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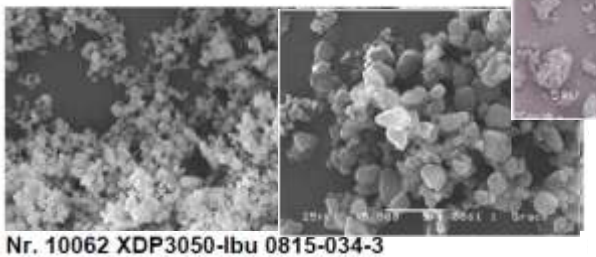

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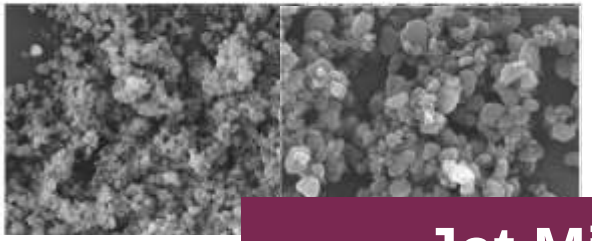
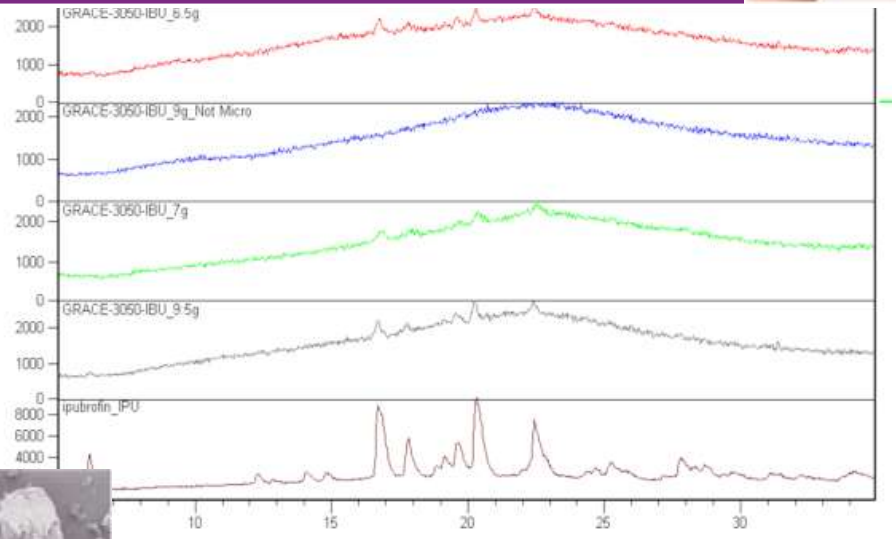
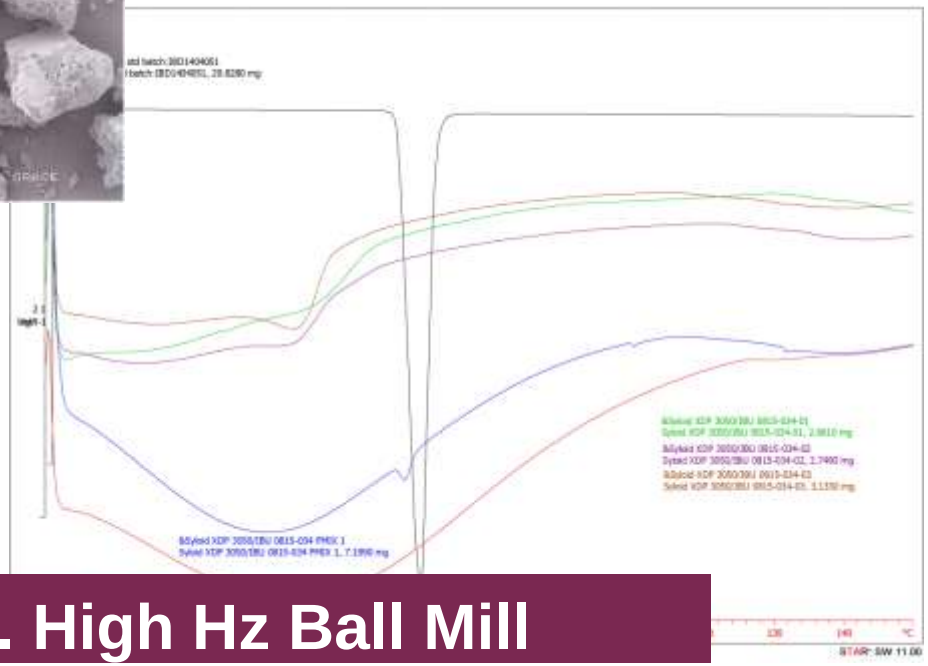






Jet Mill vrs. High Hz Ball Mill

Grace® Silica Drug Delivery

Vapor-Phase-Mediated Mass Transfer: Spontaneous Amorphization

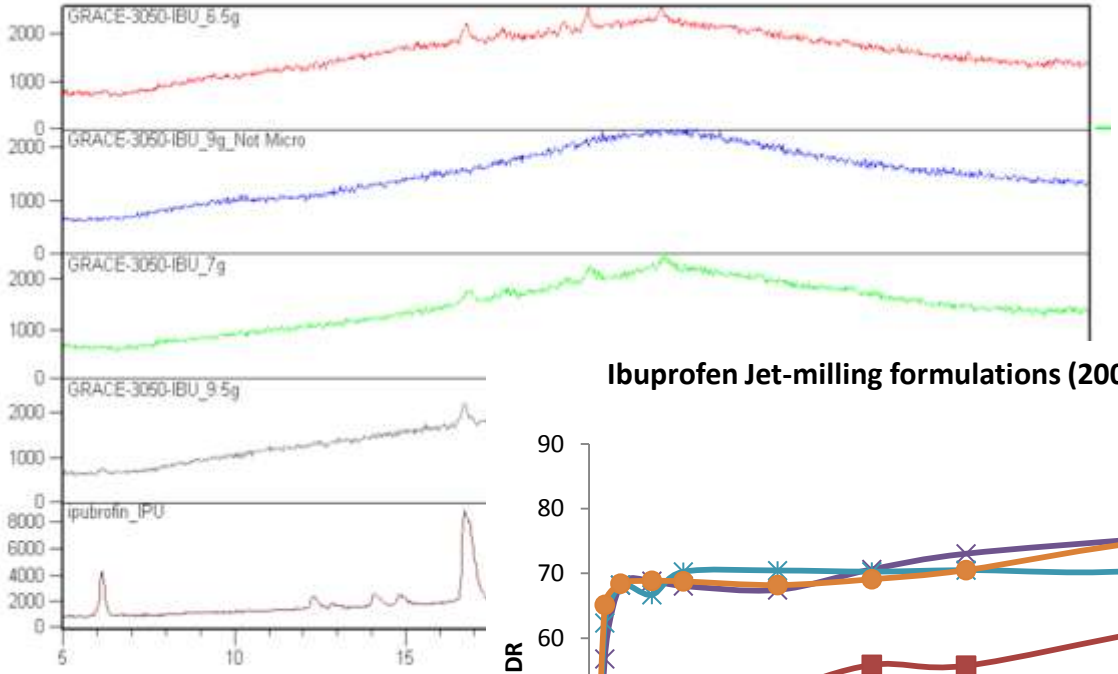
In a vapor-phase-mediated amorphization process, neither organic solvent nor grinding is necessary. This type of phase transformation was first observed by Nakai *et al.98 Physical mixtures of CPG (7-nm mean* pore diameter) with a crystalline organic compound (benzoic acid, ethyl *p-aminobenzoate, or benzophenone)* were prepared and stored. As a control experiment, the same physical mixtures, but using nonporous glass beads instead of CPG, were also prepared and stored. The authors noted an anomalous behavior of the organic molecules mixed with CPG, that is, disappearance
of melting endotherms and X-ray diffraction peaks. These changes were not observed with the mixtures using nonporous glass beads. The authors speculated that the organic compounds diffused into the pores of CPG and lost their crystallinity; however, further analysis was not performed to characterize this unusual amorphization phenomenon.
Konno *et al.99 reported that when a physical mixture* of Neusilin R *and a crystalline organic compound* (naphthalene or benzoic acid) or a medicinal compound (phenacetin or aspirin) at 4:1 (w/w) ratio was prepared and stored, model compounds became amorphous during storage, verified using PXRD

In order
to understand the pathway of this unusual phase transformation, the authors prepared physical mixtures using a series of structurally homologous organic compounds (*o-, m-, and p-hydroxybenzoic acid* and *o-, m-, and p-chlorobenzoic acid). Not only did* these compounds become amorphous, but the rate of amorphization also correlated with the vapor pressure of the guest compound, with faster amorphization occurring for compounds having higher vapor pressure. Furthermore, amorphization was accelerated under reduced pressure. Because molecules in the vapor state had longer mean free paths under reduced pressure than under atmospheric pressure, amorphization was suggested to be facilitated by the vapor phase, that is, sublimation of compounds from the crystalline state, followed by adsorption onto the surface of Neusilin R *.More importantly, because there* was no energy input during phase transformation, the amorphization process took place spontaneously.

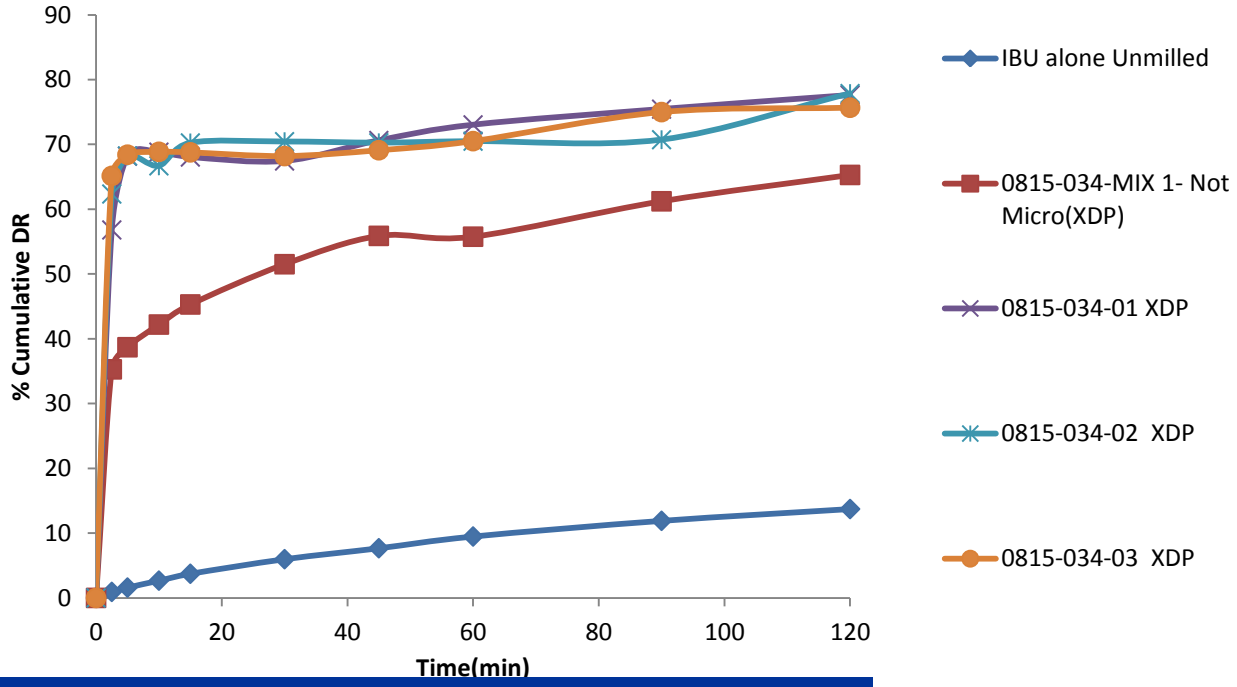
JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 101, NO. 2, FEBRUARY 2012

Bogner et al. JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 100, NO. 7, JULY 2011 (4-5days amorphisation time)

Grace® Silica Drug Delivery



Ibuprofen Jet-milling formulations (200mg dose in 900ml dissolution media)

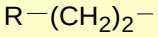
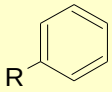
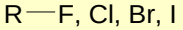
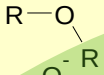
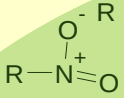
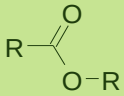
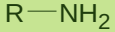
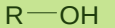
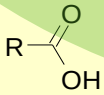


Energy transfer 'saturation' taking place ?

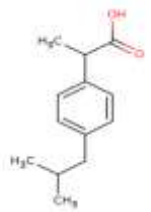
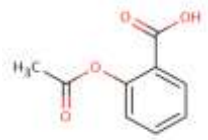
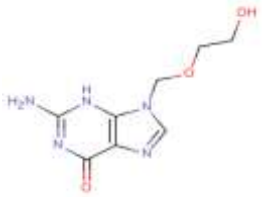
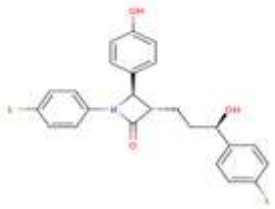
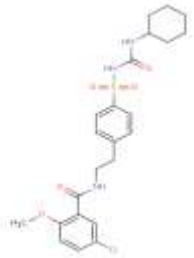
Hüttenrauch et al. - Pharm Res. 1985 302-306

Selection of the right loading strategy

Functional Group Polarity Comparisons

Polarity	Functional Group	Structure	Bonding Types	Intermolecular Forces Displayed
Low	Methylene		σ	London
	Phenyl		σ , π	London
	Halide		σ	London, Dipole-Dipole
	Ether		σ	London, Dipole-Dipole, H-bonding
	Nitro		σ , π	London, Dipole-Dipole, H-bonding
	Ester		σ , π	London, Dipole-Dipole, H-bonding
	Aldehyde		σ , π	London, Dipole-Dipole, H-bonding
	Ketone		σ , π	London, Dipole-Dipole, H-bonding
	Amino		σ , π	London, Dipole-Dipole, H-bonding, Acid-base chemistry
	Hydroxyl		σ	London, Dipole-Dipole, H-bonding
High	Carboxylic Acid		σ , π	London, Dipole-Dipole, H-bonding, Acid-base chemistry

GRACE

S No	Drug Name	Structure	Properties	Response to comilling	H-Bonding Tendency
1	**Ibuprofen**		1. Insoluble in water 2. pKa= 4-5 3. Melting Point = 75 C 4. Crystalline nature	**Excellent**	**1. Easily can form H-bonding with Hydrophilic substances**
2	**Aspirin**		1. Limited solubility in water 2. pKa= 3-4 3. Melting Point 135 C 4. Crystalline nature	**Good**	**1. Easily can form H-bonding with Hydrophilic substances**
3	**Acyclovir**		1. Limited water Solubility 2. pKa= 2.27 & 9.25 3. Melting Point =255 C 4. Crystalline nature	**Good**	**1. Easily can form H-bonding with Hydrophilic substances**
4	**Ezetimibe**		1. Insoluble in water 2. pKa= 9.5 3. Melting Point = 163 C 4. Micronized crystalline nature	**Poor**	**1. Difficult to form H-bonding with Hydrophilic substances 2. Aromatic rings makes it non-polar**
5	**Gliburide**		1. Insoluble in water 2. pKa= 4 3. Melting Point = 169 C 4. Crystalline nature	**Poor**	**1. Difficult to form H-bonding with Hydrophilic substance 2. Aromatic rings makes it non-polar**

Examples via Melt + Extrusion

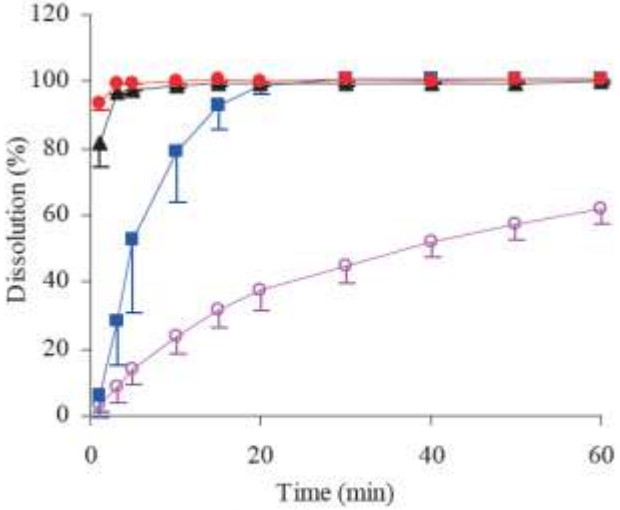


Fig. 7. Dissolution profiles of (○) original IMC, (■) physical mixture of IMC and silica (1:1), and solid dispersion of IMC and silica (1:1) prepared at (▲) 150 and (●) 160˚C.

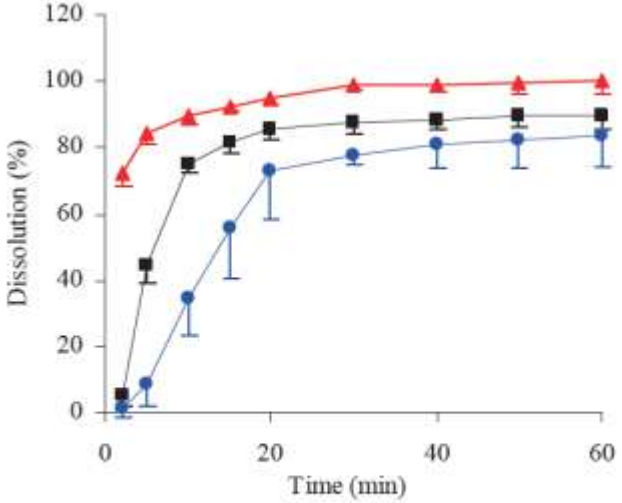


Fig. 8. Dissolution profiles of (●) original RPD, (■) physical mixture of RPD and silica (1:1), and (▲) solid dispersion of RPD and silica (1:1).

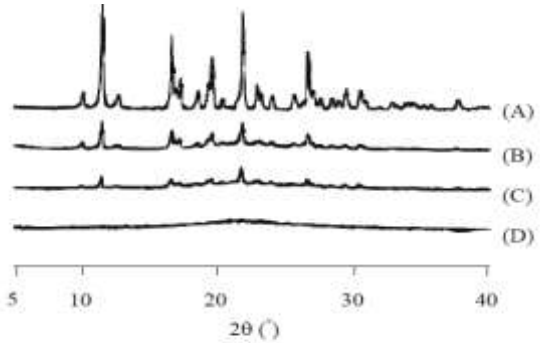


Fig. 1. Powder X-ray diffraction patterns of (A) original IMC, (B) physical mixture of IMC and silica (1:1), and solid dispersion of IMC and silica (1:1) prepared at (C) 150 and (d) 160˚C.

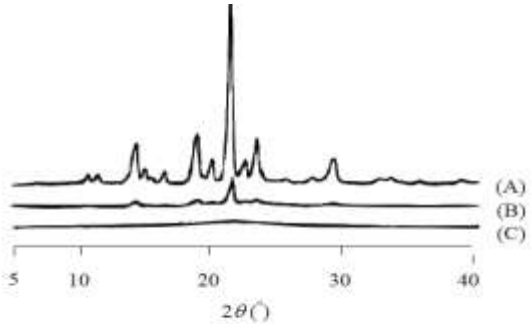
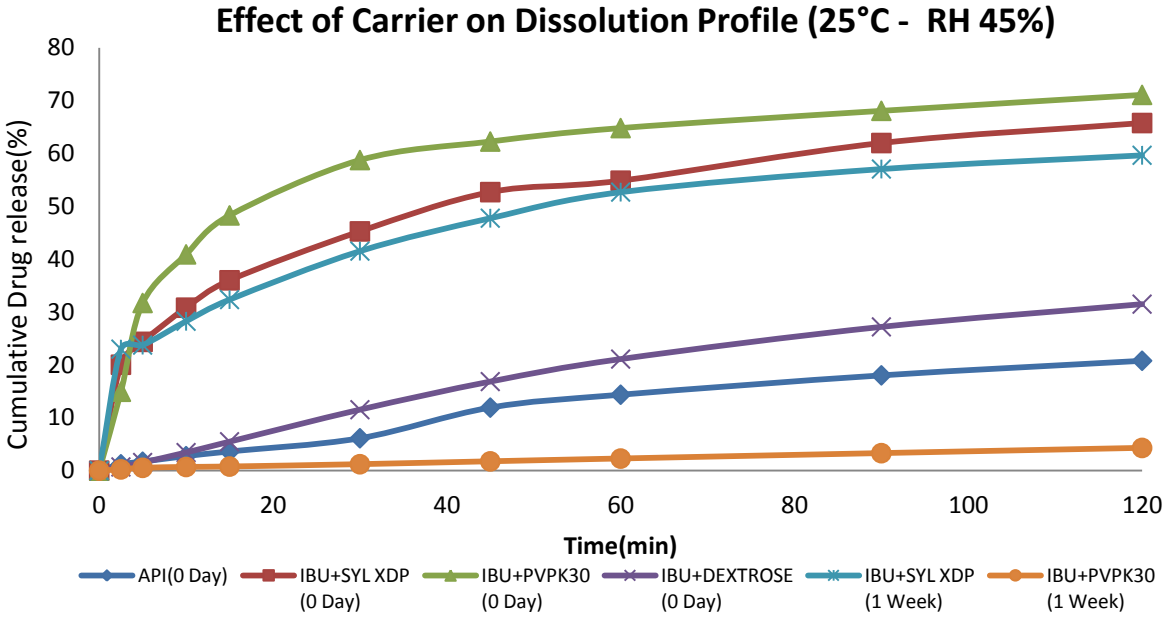


Fig. 3. Powder X-ray diffraction patterns of (A) original RPD, (B) physical mixture of RPD and silica (1:1), and (C) solid dispersion of RPD and silica (1:1).

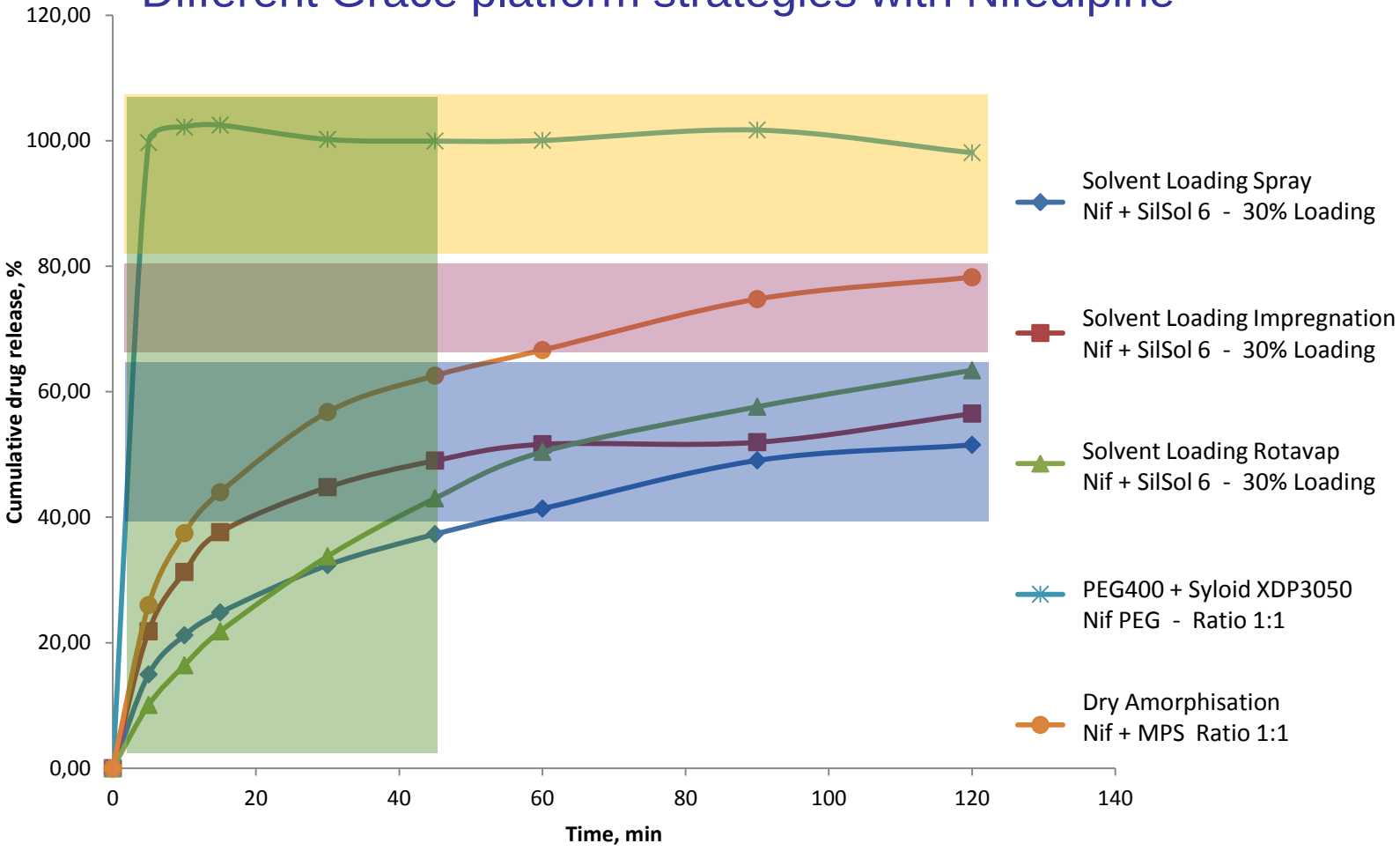
Yohei Hoashi et al. 2011 : a twin-screw kneader with hydrophilic porous silica as a completely solvent-free method

Effect of Carrier (25°C - RH 45%)



Grace® Silica Drug Delivery

Different Grace platform strategies with Nifedipine



Grace® Silica Drug Delivery

Ternary systems can be considered

Example : API – PVP and Grace Silica !

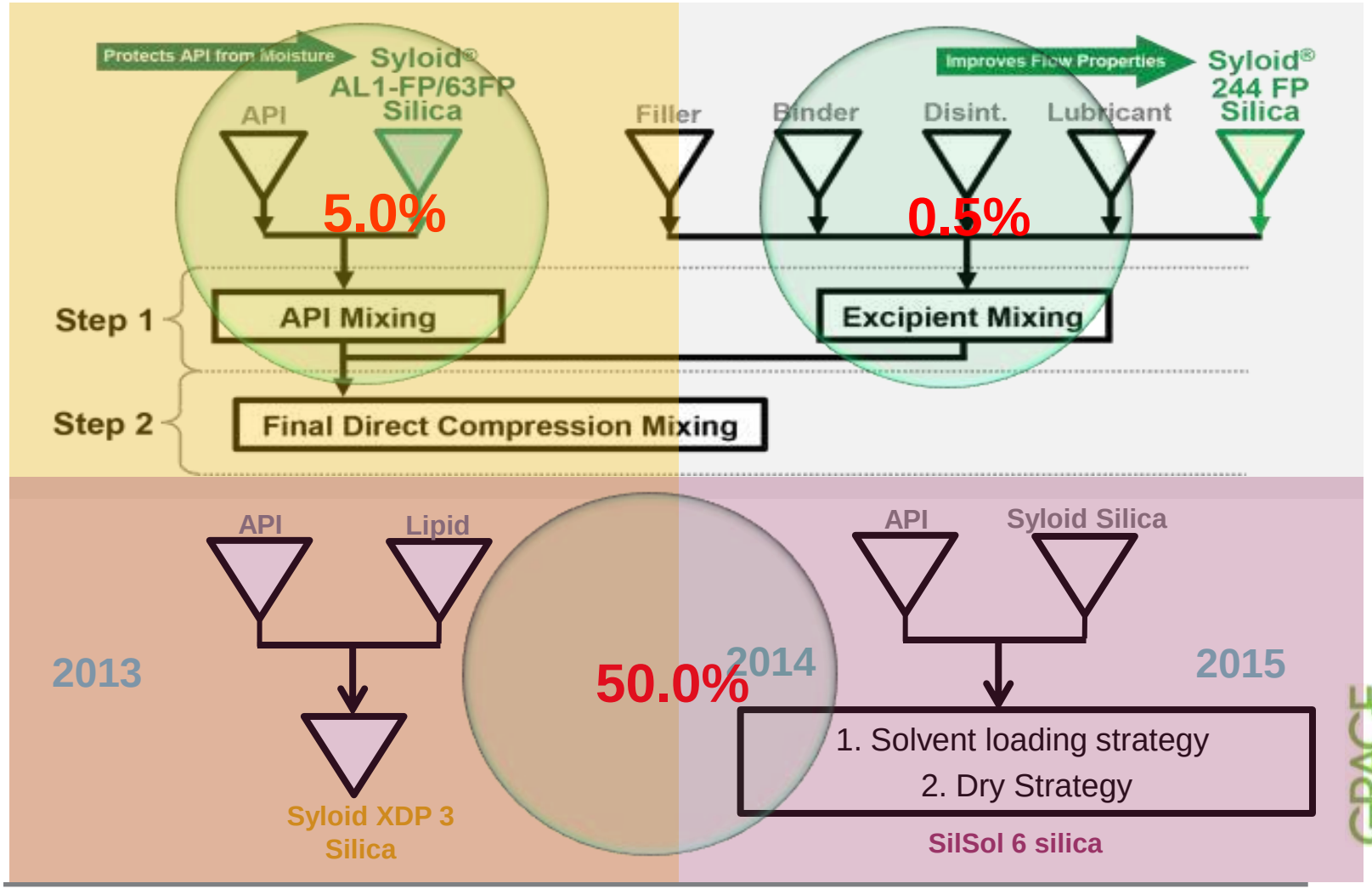
Depending on the API respons to mechanochemical activation : Grace Silica providing

- Improved amorphisation (SilSol)
- Improved stability to highly hygroscopic polymer systems.
- Avoiding reagglomeration after micronisation creating a microenvironment where solubility is high ! (SilSol)
- Improving anti-plasticizing properties (Syloid)

SilSol™ solubility advantage, Syloid® processing advantage

Grace® Silica Drug Delivery

Stability + Solubility improvement (Physical vs. Chemical)



% represent starting conditions

Grace® Silica Drug Delivery

Is there a future for MPS in BioPh ?

Biopharma

Challenges for Therapeutic Peptides Part 2: Delivery Systems

By Rodney Lax at PolyPeptide Group and Christopher Meenan at Araya Biosciences

The first part of this article (*IPT* 42, page 54) discussed some of the challenges facing peptides as a class of therapeutic agents and suggested that a more holistic approach that addressed bioavailability, stability, route of administration and cost of goods would improve the chances of success. In this second part, the authors turn their attention to novel drug delivery platforms and how these can add value to a peptide product – although ultimately it will be the health insurance companies that decide whether this 'added value' is worth paying for.

- **Oral Administration : The holy grail of peptide delivery**
- **New oral platforms : Trojan Horse (XDP3, SilSol, Silica based drug delivery)**
- **Limitations : Stability, degradation and Bioavailability**

Silicone :

Proteins can easily be incorporated into these matrices and their folding has been demonstrated to be substantially unaffected by entrapment while their stability is increased

Proteins embedded whitin the structure remain firmly trapped and no leakage occurs

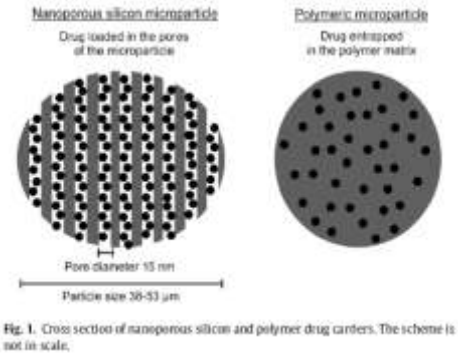


Fig. 1. Cross section of nanoporous silicon and polymer drug carriers. The scheme is not in scale.

Nanostructured porous silicon microparticles enable sustained peptide (Melanotan II) delivery - Miia Kilpeläinen EJPB

Riikka Laitinen, Thomas Rades et al. *Emerging trends in the stabilization of amorphous drugs*

- SyloidFP silica : the amorphous state of the drug was retained even after 3 months at 40°C and 70% RH, was not the case for silicone (complete degradation problems)
- Pure silanol interactions (Hydrogen bond formation)
- High Surface area, high silanol %

Silicon dioxide :

- high biocomatibility is observed
- targeted drug delivery
- site specific DDS (cancer research)
- to prevent aggregation in aqeous media, hydrophilic peptide based valves have been designed

Mesoporous silica nanoparticles for cellular and nuclear targeted drug delivery – Alexander Kros

Grace® Silica Drug Delivery

Grace® Formulation Strategies Platform

Excipient	Grace® Silica Drug Delivery	
Syloid® FP	**Syloid® XDP**	**SilSol™**
Avoid Charging Filmcoating Moisture protection Physical + Chemical Anti-tacking Suspension Aid Anti-caking	**Max Desorption** Liquisolid Wax Lipids + Oils SEDDS PEG MADG	**Optimum PSD** Amorphisation Solvent loading Milling Equilibrium Dry Milling Dry Extrusion Micronisation