DRUG AMORPHOUS SOLID DISPERSIONS USING MESOPOROUS SILICA PARTICLES – FORMULATION APPROACHES AND PROCESS SCALE-UP

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Why drugs in porous particles?

- Drugs (APIs) loaded inside the pores stay amorphous
- Max pore size is 20x the diameter of API molecule
- Amorphous state provides faster dissolution rates
- Oral formulation option for BCS class II and IV APIs
- Mesoporous particles enhance disintegrant efficiency

Silica particles and their scale-up

Nano particles (SiNano)

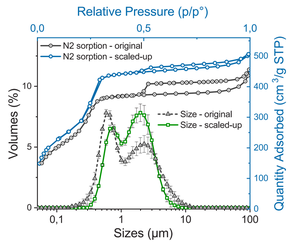
TEOS + CTAB in H_2O + EtOH mix
- reaction initiated by ammonia

c_{CTAB} and c_{EtOH} affects the shell thickness and porosity

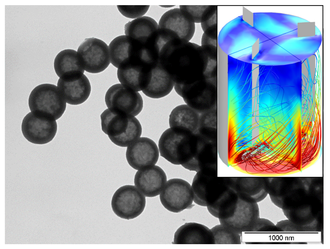
600 d.nm, 1040 m^2/g, 0.6-0.8 cm^3/g, pores 2-3 nm

40 fold volume based scale-up achieved - 4g / batch

Chem. Eng. J. 334, 1135-1147 (2018)



PSDs and N2 adsorption isotherms of silica nano-particles from original synthesis and from scale-up



TEM image of silica nano-particles prepared using the original synthesis and visualisation of CFD model used for scale-up development

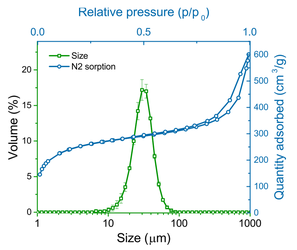
Micro particles (SiMicro)

TEOS + Octylamine (1:1 v/v)
- reaction initiated by water + EtOH (3:1 v/v)

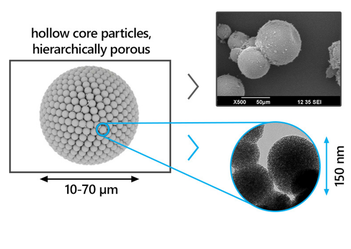
formation of micro-spheres with hierarchical mesoporous network, 10-70 µm, 980 m^2/g, 0.8 cm^3/g, 6-10 nm

production of 10 g / batch achieved

Micropor. Mesopor. Mater. 274, 61-69 (2019)



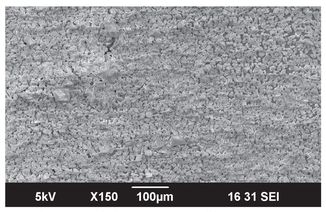
PSD and N2 adsorption isotherm of silica micro-particles with hierarchical porous structure



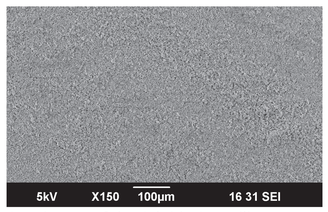
Scheme, SEM and TEM image of the micro-particles.

Chosen commercial silica excipients

Merck Parteck® SLC 500	Grace Syloid® 72 FP
13 µm, 510 m^2/g, 0.8 cm^3/g, 2-20 nm	6 µm, 340 m^2/g, 1.1 cm^3/g, 5-60 nm



SEM image of the SLC 500 silica



SEM image of the Syloid 72 FP silica

There are several methods of loading APIs into porous particles

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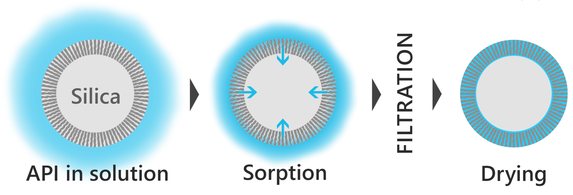
Solvent immersion (adsorption equilibrium)

when API is at least sparingly soluble in low polar solvents or soluble in more polar solvents, lowest crystallinity

Int. J. Pharm. 555, 19-27 (2019)

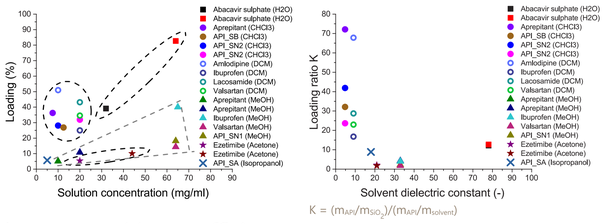


Fast dissolving APIs:		achieved loading [w_{API}/w_{silica}] (from solution of [mg/ml])
Ibuprofen	weak acid	**25 %** (DCM 20), **41 %** (MeOH 65)
Lacosamide	neutral	**43 %** (DCM 20)
Abacavir sulphate	weak base	**39 %** (H_2O 32), **83 %** (H_2O 64)
Slow dissolving APIs:		
Valsartan	weak acid	**35 %** (DCM 20), **14 %** (MeOH 64)
API_SA	weak acid	**6 %** (Isopropanol 5)
Ezetimibe	neutral	**5 %** (Acetone 20), **10 %** (Acetone 44)
API_SN1	neutral	**18 %** (MeOH 64)
API_SN2	neutral	**28 %** ($CHCl_3$ 10), **32 %** ($CHCl_3$ 20)
Amlodipine	weak base	**52 %** (DCM 10), **45 %** (DCM 20)
Aprepitant	weak base	**5 %** (MeOH 10), **11 %** (MeOH 20), **36 %** ($CHCl_3$ 7.5)
API_SB	weak base	**27 %** ($CHCl_3$ 12.5)

all samples with SiNano

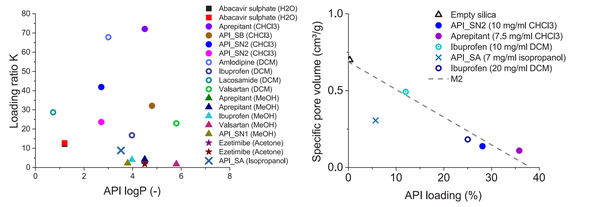
The loading depends on:

solution concentration, and solvent polarity...



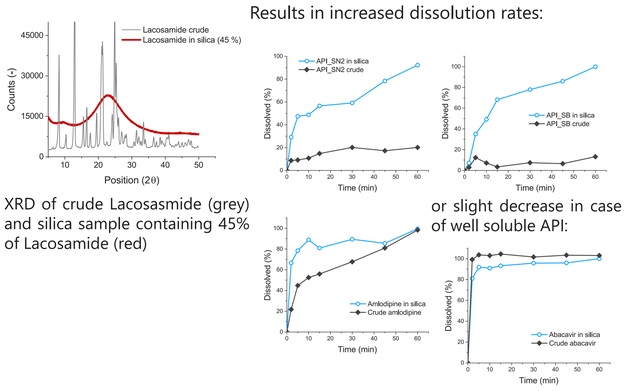
...but not partition coefficient.

The level of loading is observable on the pore volume:



Minimal/no crystallinity in all samples:

Results in increased dissolution rates:

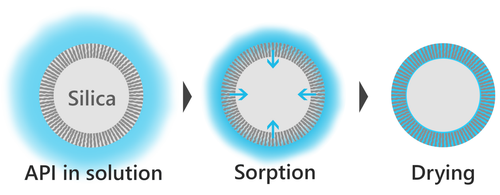


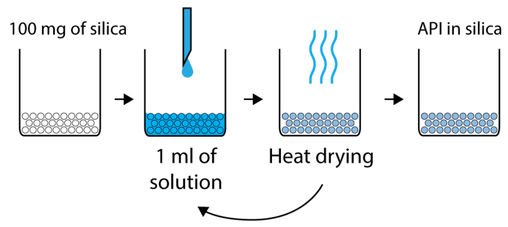
XRD of crude Lacosasmide (grey) and silica sample containing 45% of Lacosamide (red)

or slight decrease in case of well soluble API:

Solvent evaporation / incipient wettnes

when API is at least sparingly soluble in any volatile solvent, higher loadings, risk of crystallization at very high loading

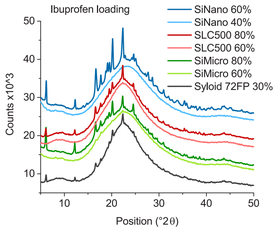




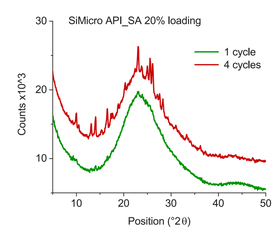
Loading solutions concentration was altered to achieve 2, 5, 10 and 20 % loadings in 1 cycle.

Higher loadings (>20 %) were achieved using multiple cycles.

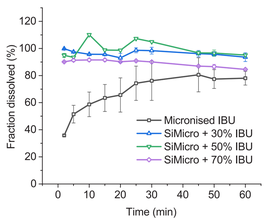
Fast diss. APIs:	Highest non-crystalline loading [w_{API}/w_{silica}]
Ibuprofen	**60 %** (Si-Micro, SLC500), **40 %** (Si-Nano), **20 %** (Syl72FP)
Lacosamide	**40 %** (Si-Micro)
Slow diss. APIs:	
Valsartan	**60 %** (Si-Micro)
API_SA	**20 %** (Si-Micro, SLC500), **10 %** (Syl72FP)
Ezetimibe	**120 %** (Si-Micro, Si-Nano)
API_SN2	**50 %** (Si-Micro, Si-Nano), **30 %** (SLC500, Syl72FP)
Amlodipine	**60 %** (Si-Micro)



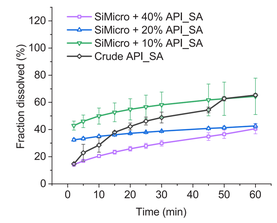
Silica morphology affects highest achievable non-crystalline loading



Higher number of loading cycles result in higher crystallinity



Increased dissolution rate remains even with high evaporation loadings

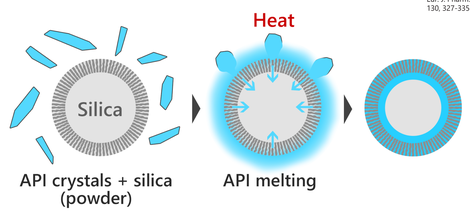


With too high recrystallisation of the API the dissolution improvement is lost

API melt loading

when API degrades above the melting point, solvent free - for insoluble APIs, risk of partial crystallinity

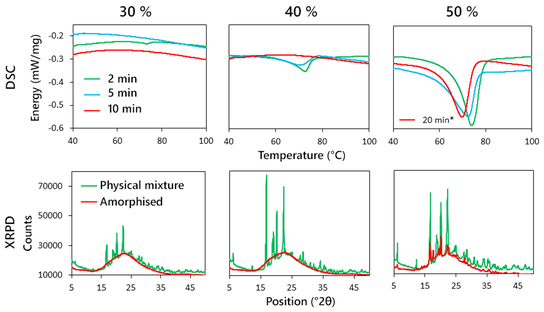
Eur. J. Pharm. Biopharm. 130, 327-335 (2018)



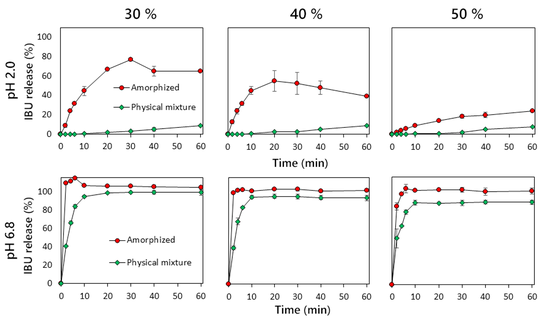
Ibuprofen loaded into silica microparticles using heated fluidized bed.

Mixture of Ibuprofen crystals and aggregates (<100 µm) of SiMicro at 30, 40 and 50% IBU content, fluidized for 2, 5 and 10 minutes.

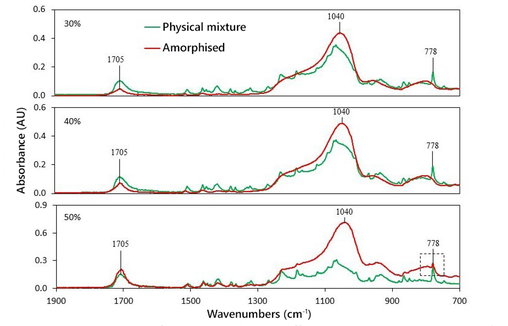
Suitable for industrial scale-up.



Maximum achievable loading with complete amorphization was **40%** of ibuprofen when fluidized for 10 min.



Dissolution rates greatly improved for all samples in both acidic and neutral pH compared to crude ibuprofen

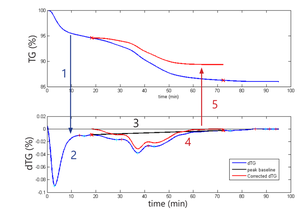


Amorphisation observable on FT-IR as well through the absence of the 778 cm^{-1} band in the amorphised samples.

Determination of loading by corrected TGA

Simultaneous evaporation of H_2O, silanol groups and API

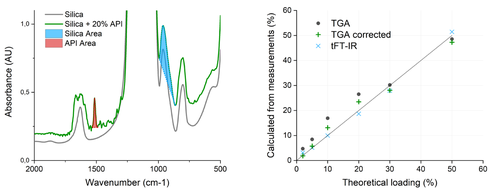
1) TGA measurement, **2)** Derivation of TG
3) Baseline of the API evaporation valley in dTG
4) Subtraction of the baseline from dTG
5) Reconstruction of TG from the corrected dTG



or by transmission FT-IR using KBr pellets

200 mg of dry KBr + 1-2 mg of silica containing API - pressed into pellets

Ratio of API band area vs. silica band area plotted for various API contents



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