EFFECT OF SOLVENT SELECTION ON DRUG LOADING AND AMORPHISATION IN MESOPOROUS SILICA PARTICLES

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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 II and IV APIs
- Mesoporous particles enhance disintegrant efficiency

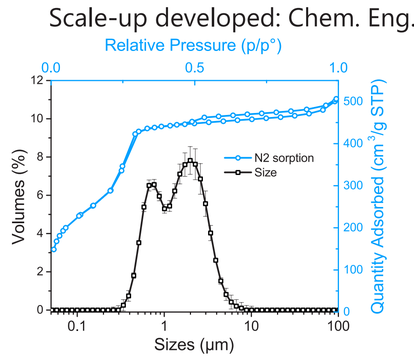
Silica prepared by an emulsion method from TEOS

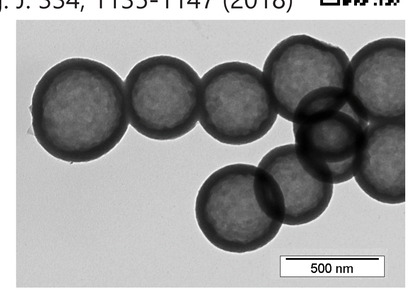
Scale-up developed: Chem. Eng. J. 334, 1135-1147 (2018)

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 cm^3/g, pores 3 nm

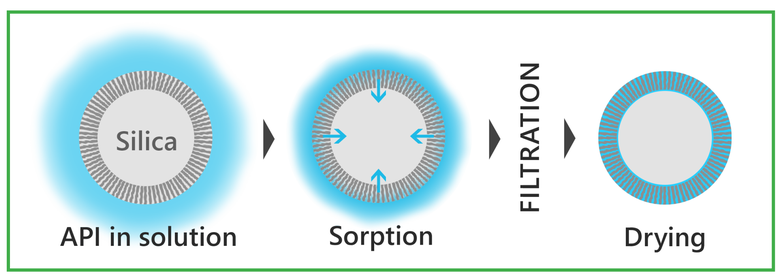




There are several methods of loading APIs inside particles

Solvent immersion (adsorption equilibrium)

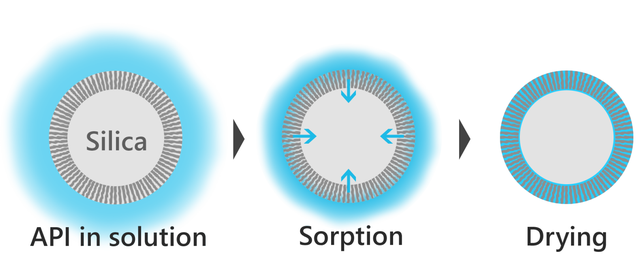
when API is at least sparingly soluble in low polar solvents or soluble in more polar solvents, lowest crystallinity



the method used in this work

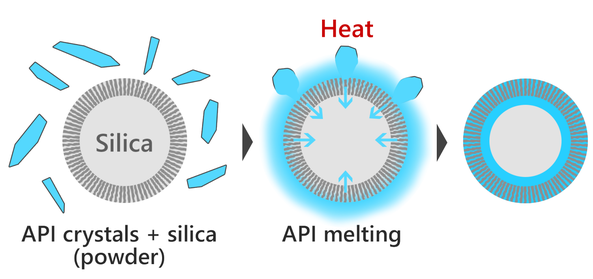
Solvent evaporation / incipient wettnes

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



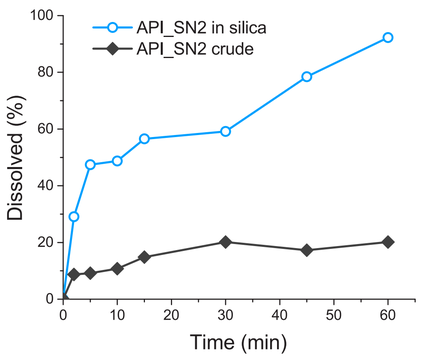
API melt loading

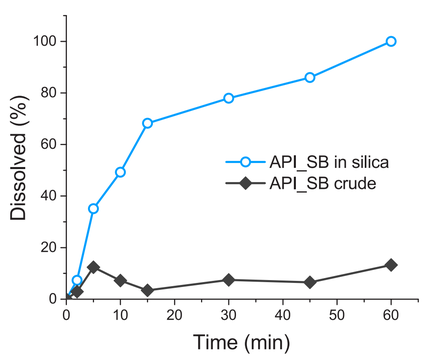
when API degrades above the melting point, solvent free - for insoluble APIs, risk of partial crystallinity



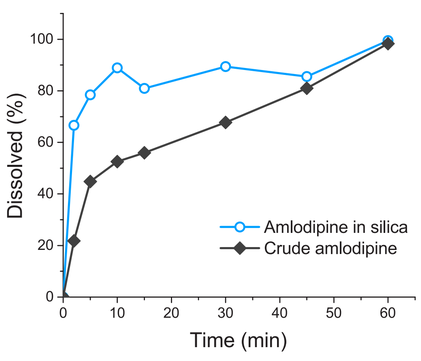
		achieved loading [w_{API}/w_{silica} %] (solvent used [mg/ml])
Fast dissolving APIs:		
Ibuprofen	weak acid	**25** (DCM 20), **41** (MeOH 65)
Lacosamide	neutral	**43** (DCM 20)
Abacavir sulphate	weak base	**39** (H_2O 32), **83** (H_2O 64)
Slow dissolving APIs:		
Valsartan	weak acid	**35** (DCM 20), **14** (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)

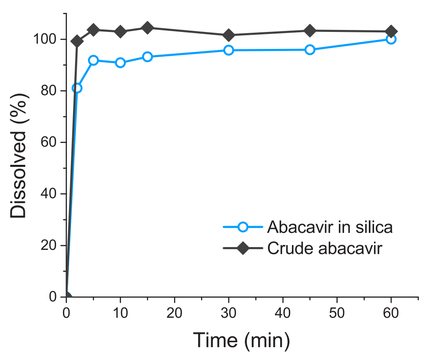
Dissolution rates are greatly improved





For well soluble APIs, the dissolution rate can be slower:

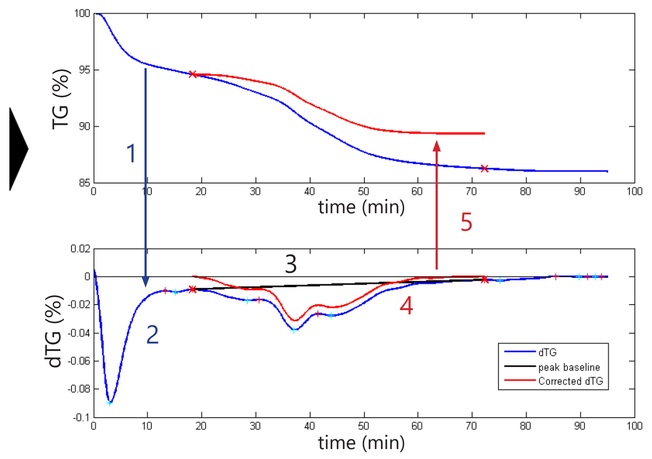




Determination of loading by corrected TGA

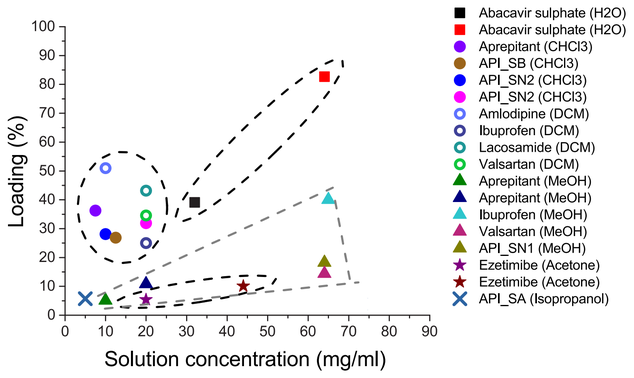
Simultaneous evaporation of H_2O, silanol groups and API

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

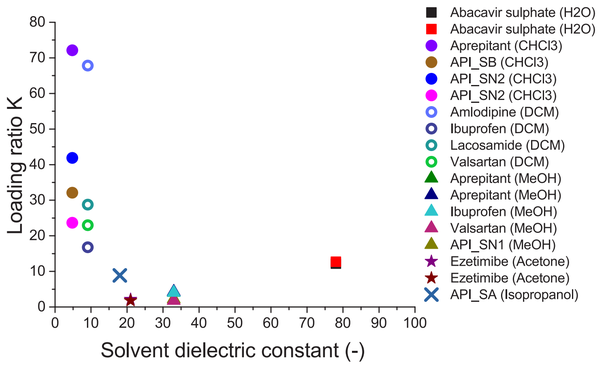


The loading depends on:

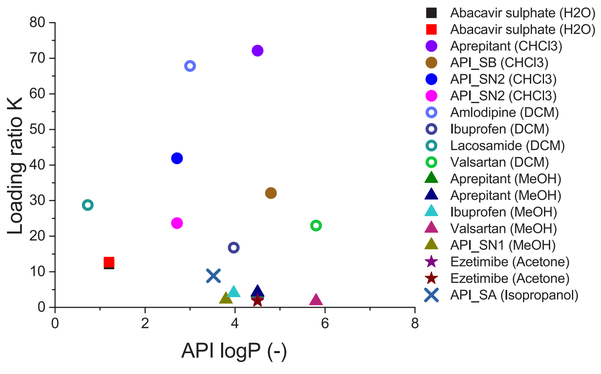
the solution concentration...



...and also on the solvent polarity...

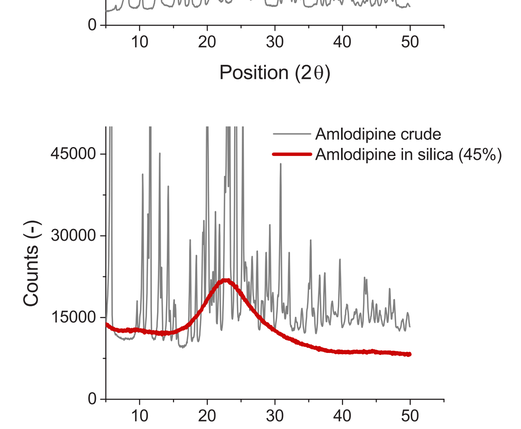


...but not on the API partition coefficient.



$K = (m_{API}/m_{SiO_2})/(m_{API}/m_{solvent})$

The level of loading is observable on the pore volume:



No crystals on XRPD

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CHOBOTIX CHEMICAL ROBOTICS

Read more about this work in the paper:

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

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