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Controlling the dissolution rate of APIs by formulation on porous nano- and microcarriers

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CHOBOTIX CHEMICAL ROBOTICS

THE PROBLEM

- New active pharmaceutical substances (APIs) are poorly soluble in crystalline form.
- This lowers the APIs bioavailability and requires higher API dosage to be used.
- This is countered with various means, f.x. micronization or various ways of amorphization such as formulating the API in polymer matrix or solid dispersion or by hot melt extrusion.
- However, usually these techniques suffer from low effectivity or are patent protected.
- Thus new methods of formulation of poorly soluble APIs are desired.

THE PURPOSE OF THE WORK

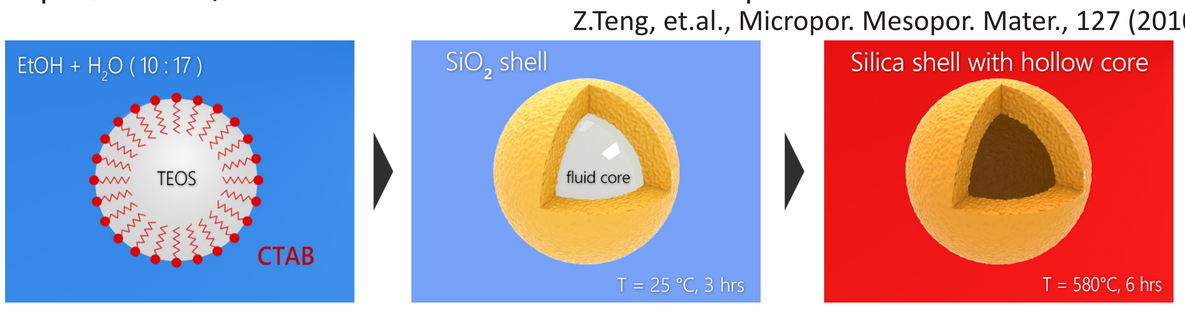
- Explore the possibilites of using porous micro- and nanocarriers for stabilizing APIs in amorphous form.
- Substances cannot crystallize inside the confined space of pores, if the pore diameter is small enough (generaly below 10 nm).
- Test sorption abilities of various porous silica particles with various morphology.
- Small nanoparticles should increase the dissolution rate due to their small size and high surface area.
- Large hollow particles could slow down the dissolution rate of well soluble APIs (transport through the particles shell is limited by the diffusion, if the API is also deposited inside the hollow core).

SYNTHESIS OF THE PARTICLES

NANOPARTICLES

- 0.5 ml of tetraethyl orthosilicate was added to a mixture of 25.5 ml of water and 15 ml of ethanol under stirring. Then 0.08 (5mM - hollow particles) or 0.16 g (10mM - dense particles) of centrimonium bromide was added and after that 0.5 ml of NH_4OH was stirred in and the reaction mixture was stirred for 3 hours. Resulting particles were centrifuged (6000rpm, 5 mins) and dried at 90°C. Calcination is possible.

Z.Teng, et.al., Micropor. Mesopor. Mater., 127 (2010) pp.67-72

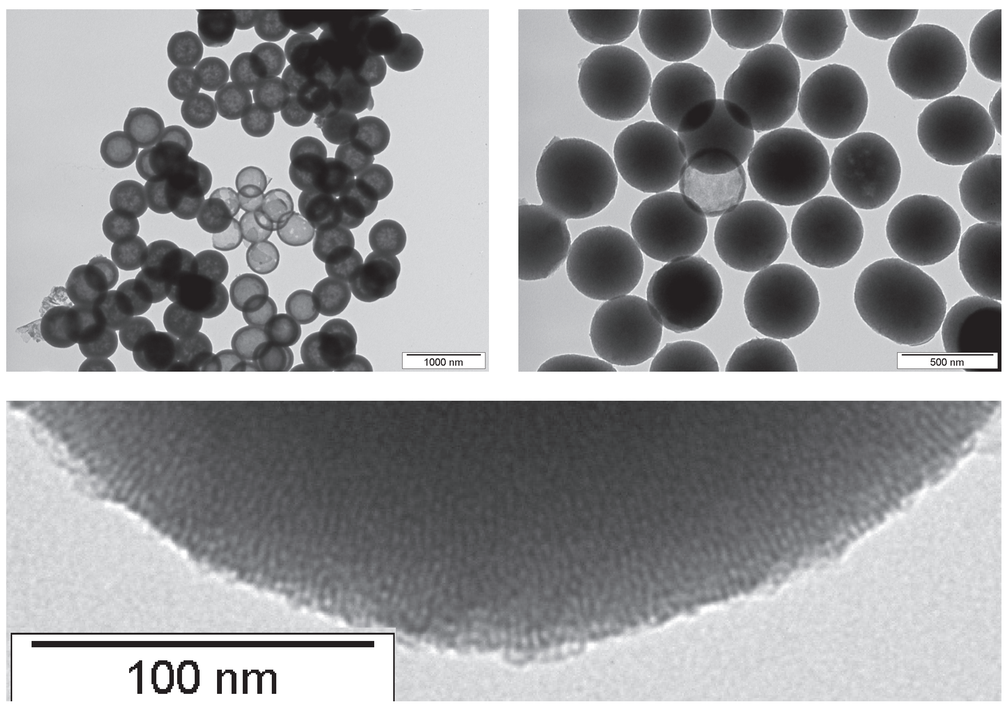


MICROPARTICLES

- 10 ml of tetraethyl orthosilicate was mixed with 10 ml of octylamine and the mixture was stirred for three minutes. Then 100 ml of water acidified with 0.2 ml of nitric acid was quickly added. The resulting microparticles were collected after additional 3 minutes of stirring by centrifugation, were washed with water and acetone, dried and calcined at 580 °C for 6 hours. Additionaly the particles can be sieved to obtain narrower size distributions.

X.Cheng, et.al., Micropor. Mesopor. Mater., 98 (2007) pp.41-46

CHARACTERIZATION OF PARTICLES



TEM images. **Top left**: Silica made with 5mM of CTAB. **Top right**: Silica made with 10mM of CTAB. **Bottom**: Detail of the pores (3.1 nm).

LOADING THE PARTICLES WITH APIs

- A well soluble API (API-W) and a class 2 poorly soluble API (API-P) were used to test the silicas ability to sorb and store substances.
- Sorbed from concentrated solutions. 10 mg of particles dispersed in 1 ml of the API solution. The dispersion was shaken in a sealed vial for at least 24 hours at 25 °C to ensure the equilibrium was reached.

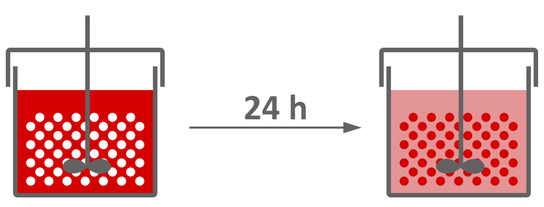
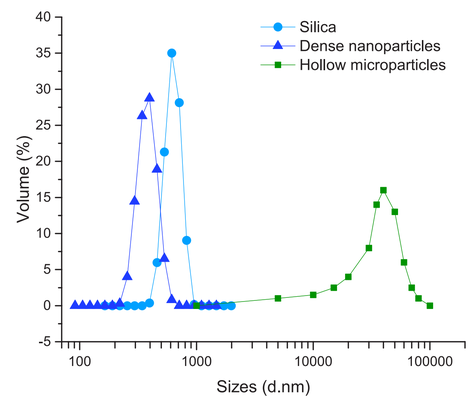
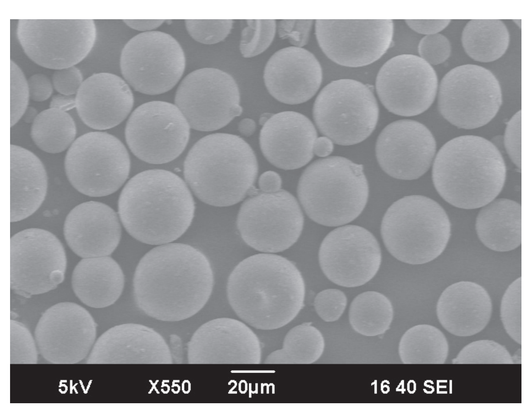


Table 1: Relative amounts of APIs loaded into the particles using sorption from concentrated solution.

Particles	API	Loaded (%, mg API/mg silica)	API molar weight	Solution concentration (mg/ml)
Hollow nanoparticles	API-W 1	18.2	~1250	5
	API-P 1	31.6	~500	10
Dense nanoparticles	API-P 1	44.9	~500	10
Hollow microparticles	API-W 2	46.7	~200	10

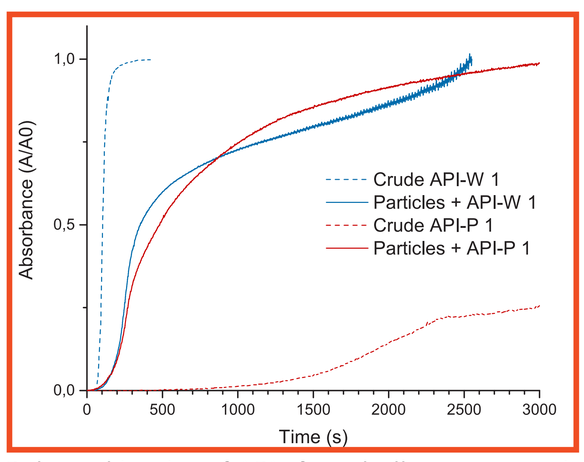




Left: Dynamic and static light scattering size distribution of all three types of prepared particles. **Right:** SEM image of obtained hollow microparticles.

RELEASE OF APIs FROM PARTICLES

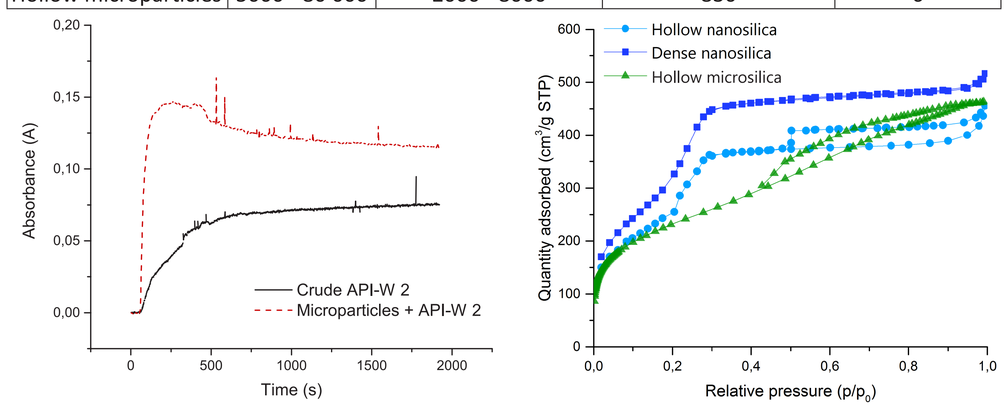
- Custom made dissolution setup was assembled to measure release kinetics of APIs from the particles using a standard UV-VIS spectrophotometer and a flow-through cell.
- The dissolution took place in a 100 ml stirred vessel. The sampling was secured by a tubing loop going through the cuvette and equipped with a pump. The suction was equipped with a filter to prevent the particles from interfering with the measurement. The inner volume of the loop including the cuvette was about 3 ml.



Release kinetics of APIs from hollow nanoparticles.

Table 2: Particles characteristics obtained by DLS/SLS, image analysis, nitorgen sorption and BJH

	Size (d.nm)	Shell thickness (nm)	BET surf. area (m^2/g)	Pore size (nm)
Hollow nanoparticles	650	50	990	3
Dense nanoparticles	400	-	1150	3
Hollow microparticles	5000 - 80 000	2000 - 8000	830	6



Left: Release kinetics of API-W 2 from hollow microparticles (only shells loaded, not cores). **Right:** Nitrogen sorption isotherms of all three types of prepared particles.

FORMULATION OF LOADED PARTICLES AND SLUGGING

- Dry hollow nanoparticles loaded with API-P1 were mixed with excipients and slugged into small 200 mg tablets to test if the nanoparticles can be successfully formulated.

Formulation:

- Loaded nanoparticles
- MCC PH 101
- Lactose anhydrous
- SLS
- Croscarmellose
- Magnesium stearate

Slugs:

- 6 mm Oblong punch
- 16 mm pour height
- 9 kN press force
- Hardness: 129 N
- Breakup: 17 seconds

Right: Dissolution profile of the slugged nanoparticles containing API-P 1 obtained from a standard dissolution test in phosphate buffer (pH 6.8).

CONCLUSIONS

- Prepared and characterized hollow and dense highly porous nanoparticles and hollow microparticles.
- Achieved high loading rates with all types of nanoparticles with both well and poorly soluble APIs.
- Poorly soluble API's dissolution rate was significantly increased when sorbed in the particles.
- Loaded nanoparticles were successfully formulated and pressed into slugs with good dissolution properties.

FUTURE WORK

- Conduct release experiments with microparticles with filled cores - see if the the diffusion through the shell can noticably hinder the dissolution rate.
- Use some of the commercially available silica particles (MCM, Sylloid) - compare them to the nanoparticles used in this work.
- Conduct experiments with more APIs

ACKNOWLEDGEMENT

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