PLIVA

Effect of application of ultrasonic power on the crystallization behavior of maleate salt of active pharmaceutical ingredient

Utjecaj ultrazvučnog zračenja na proces kristalizacije maleatne soli aktivne farmaceutske supstance

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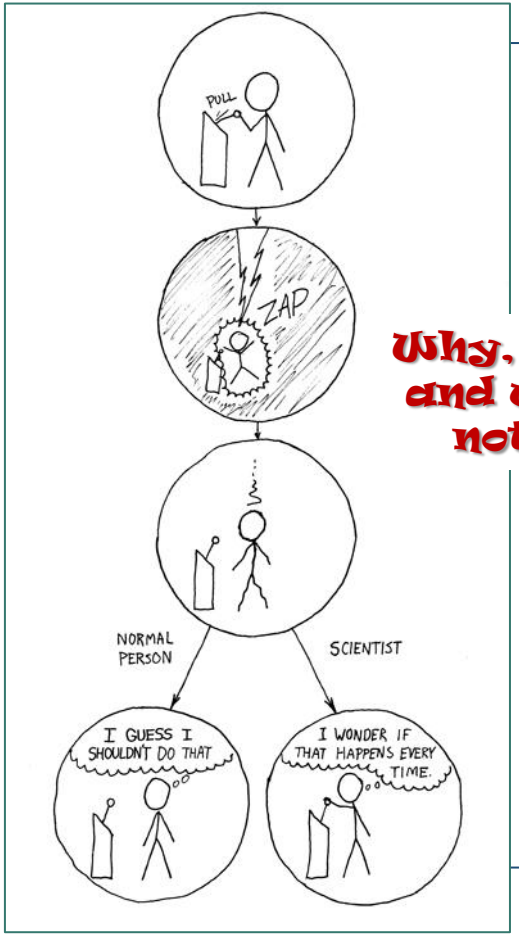
Scientific approach



Why, how and why not?

Science

- Literature researching → theoretical background
- Asking a question and developing an experiment to answer the question
- Analyzing results and data
- Communicating results to the scientific community via published papers

Collaboration of academia and industry to apply the results of research and to develop new techniques, products or practices…
Use the scientific approach for better control of manufacturing process by complete understanding of the process…

hand to hand

Industry

- Design, improvement and installation of integrated system of men, eqipment and materials
- Knowledge and skills in mathematical and physical science together with the principles and methods of engineering
- Using the engineering design process to create solutions to problem

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Crystallization process

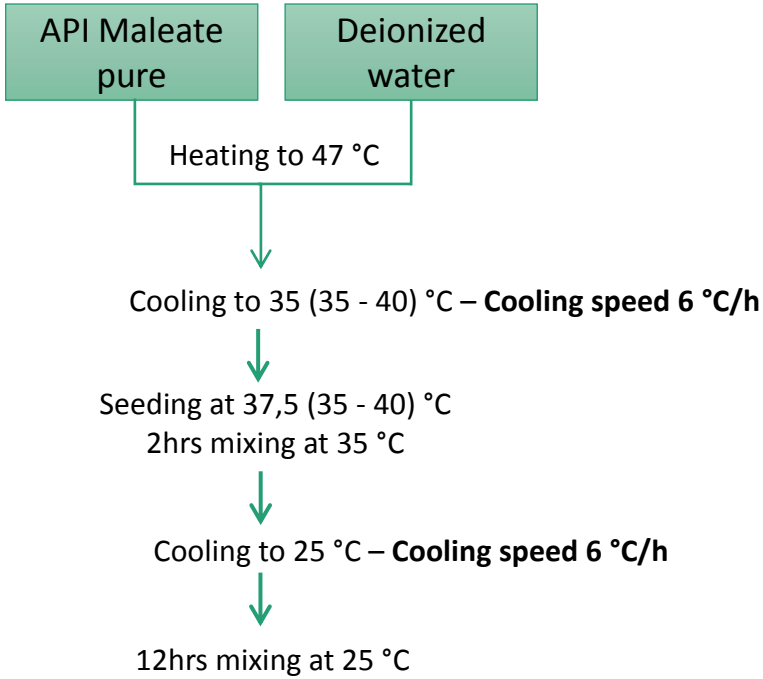
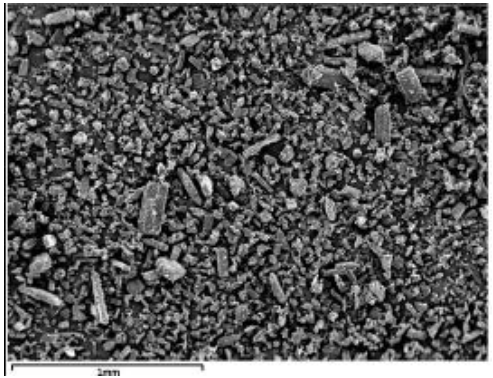


Table 1. Process conditions in a standard procedure

C [g/L]	210,0
Water [v/w]	4,80
wt (seeds) [%]	0,52
Drying temperature [°C]	40
LOD [%]	0,3
Yield [%]	90,0

Nucleation point = 39 – 41 °C

Granulometric properties of targeted crystal and crystal obtained from Pilot experiments



TARGET

API-1.7

Experiment	D_{10} / µm	D_{50} / µm	D_{90} / µm
TARGET	/	/	60-90
28201215	14	43	125
API 1.1	16	54	171
API 1.6	14	49	138
API 1.7	14	42	111
API 1.8	10	28	97*
API 1.9	12	36	92
API 1.10	10	29	69
API 1.11	13	36	106*
API 1.12	17	84	531*
API 1.13	14	54	159
API 1.14	13	42	105
API 1.15	13	43	188*
API 1.18	26	91	651,3
API 1.19	13	30	84
API 1.20	13	33	163
* presence of agglomerates			

SYSTEM CHARACTERIZATION BY FBRM MEASUREMENTS

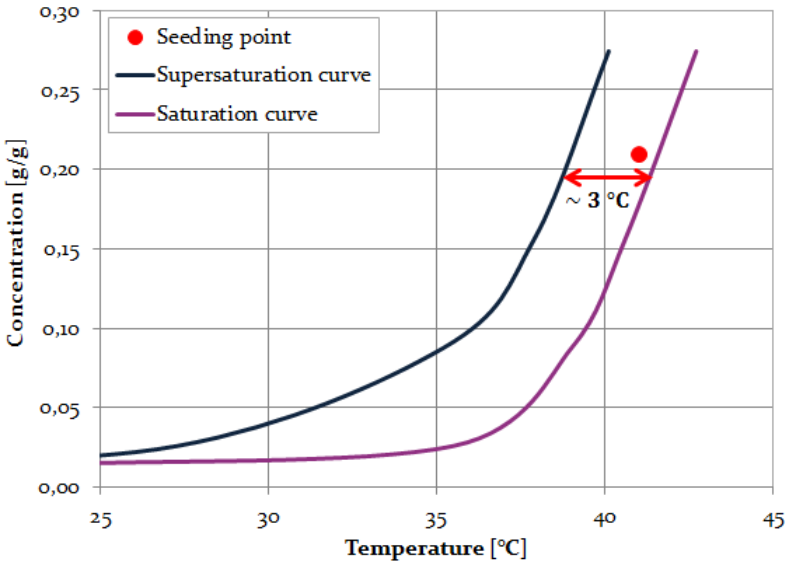


Figure 1. Metastable zone width for the system of maleate salt of the API / water

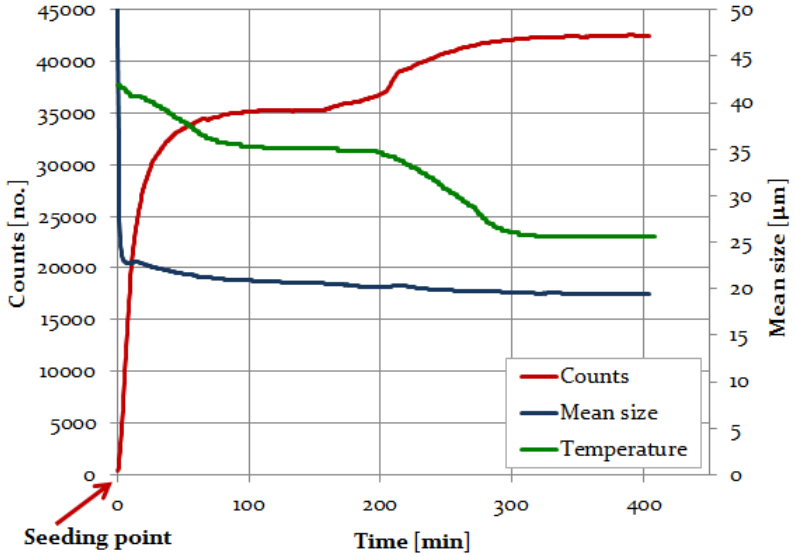


Figure 2. FBRM measurement data for experiment API-1.7. (FBRM G600Ex, Mettler Toledo)

Influence of ultrasound on crystal granulometic properties (API maleate / toluene)

Table 2. Process conditions in experiments in which ultrasound impact was investigated

Influence of the ultrasound on granulometry (API / toluene)		
Concentration [g/g]	0.08	API-1.7.-A-duration
Ultrasound frequency/power [kHz/W]	24 / 400	
Ultrasound amplitude (A) [%]	30, 40, 50, 60	
Ultrasound duration [min]	2.5, 5.0	
Type of irradiation	Continuous / pulsed	

Influence of ultrasound on crystal granulometic properties (API maleate / toluene)

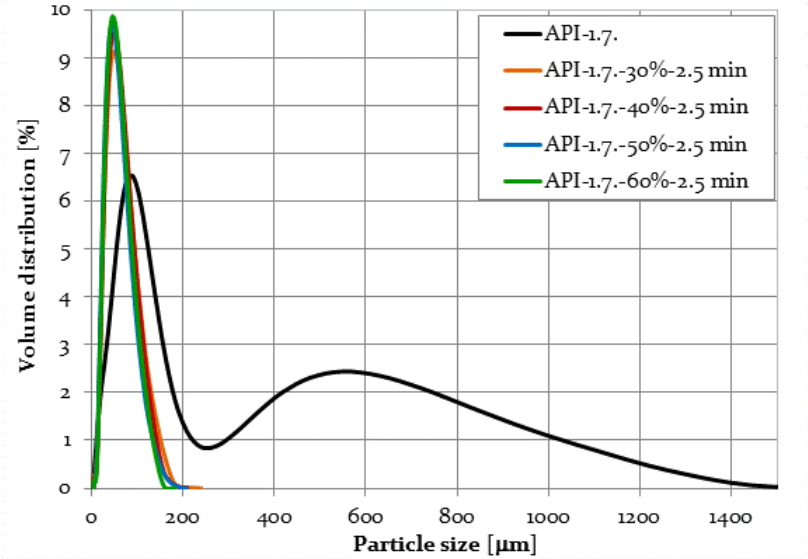


Figure 3. PSD obtained by suspension treatment with continuous ultrasound irradiation of variable amplitudes during 2.5 min

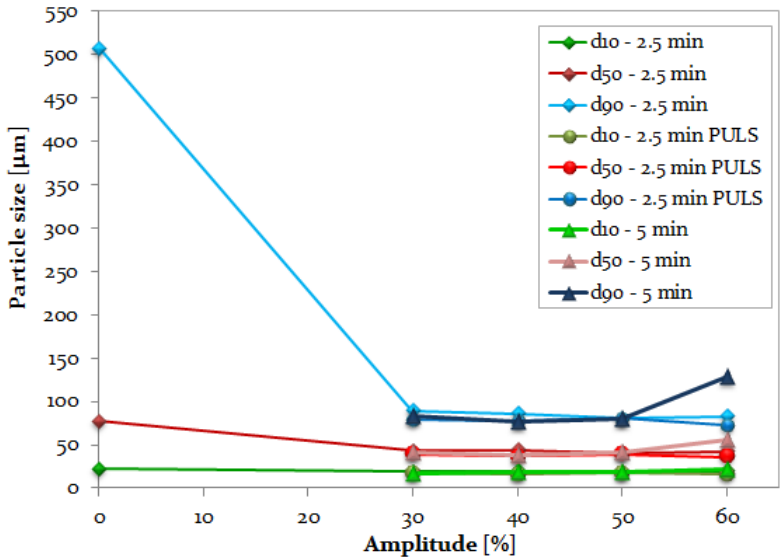
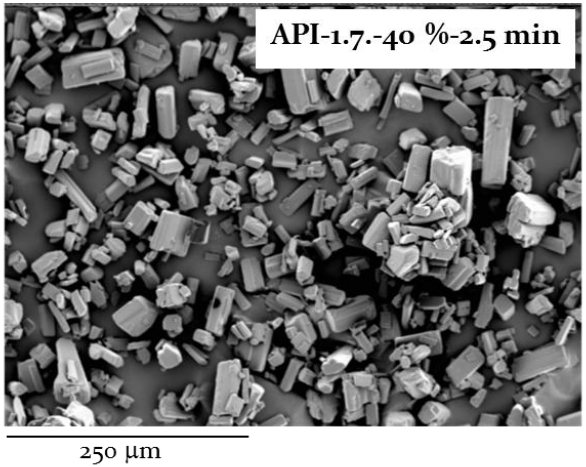
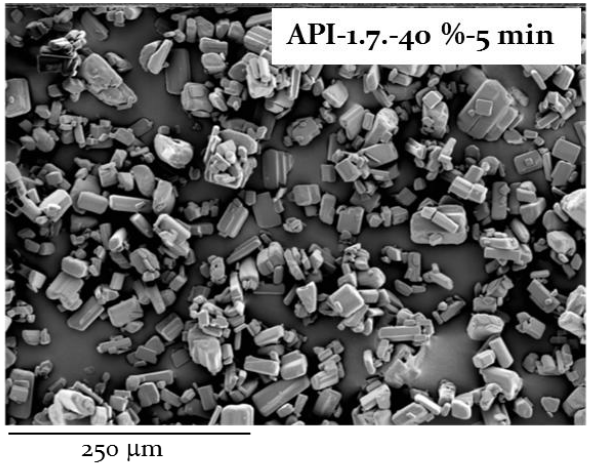
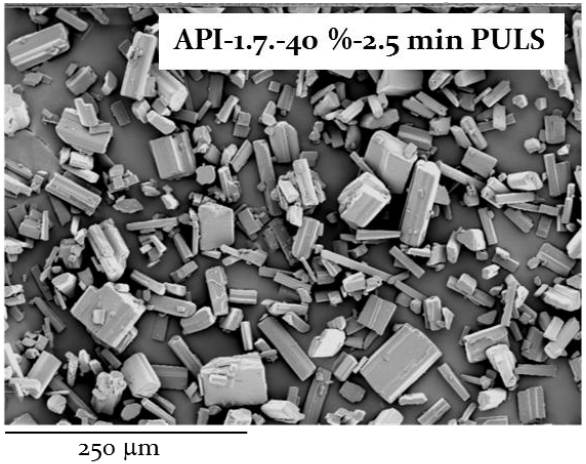


Figure 4. Influence of ultrasonic irradiation on *d*10, *d*50 and *d*90 values for variable times, amplitudes and irradiation type

Influence of ultrasound on crystal granulometic properties







Magnification: 200 x

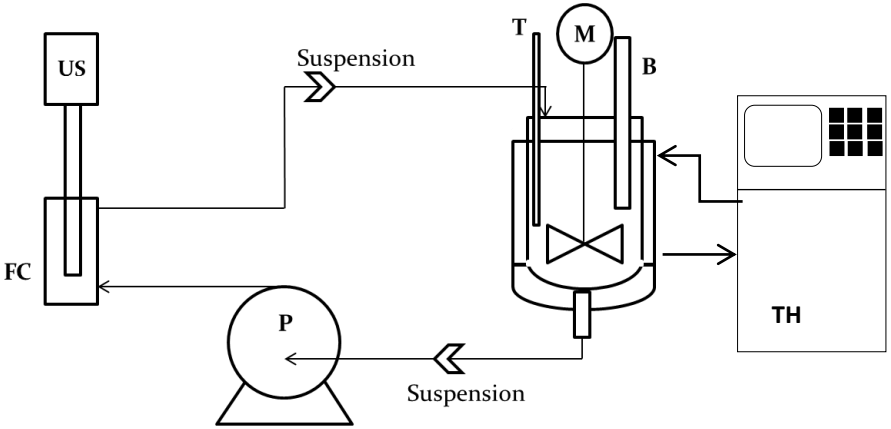
Figure 5. SEM pictures of the samples obtained by treatment the suspension with 40 % ultrasound amplitude for variable time and irradiation type

Sonocrystallization

Table 3. Process conditions in sonocrystallization experiments

Sonocrystallization (API / water)		
Ultrasound amplitude [%]	40	
Cooling crystallization / type of irradiation	Continuous suspension flow	API-1.18.
	Batch / continuous	API-1.19.
	Batch / puls, 50%	API-1.20.

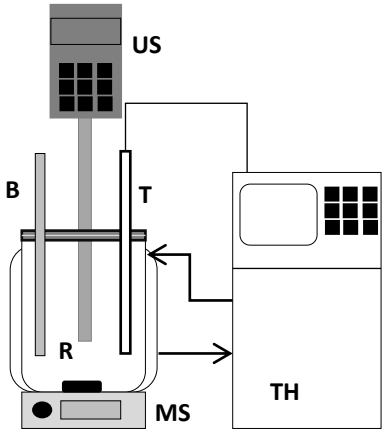
CONTINUOUS SUSPENSION FLOW + SONOCRYSTALLIZATION (Exp. API-1.18)



B – baffle; FC – flow cell; M – mixer; P – pump; T – temperature probe; US – ultrasonic processor (UP400St Hielscher, 400 W, 24 kHz)

Figure 6. A schematic diagram of the equipment for the continuously irradiated suspension using flow cell, experiment API-1.18.

BATCH SONOCRYSTALLIZATION (Exp. API-1.19, API-1.20)



B – baffle; MS – magnetic stirrer; R – double jacketed reactor; T – temperature probe; TH – thermostat; US – ultrasonic processor (UP 400St Hielscher, 400 W, 24 kHz)

Figure 7. A schematic diagram of the equipment for the batch sonocrystallization, experiment API-1.19., API-1.20

Comparison of PSDs obtained by different sonocrystallization processes

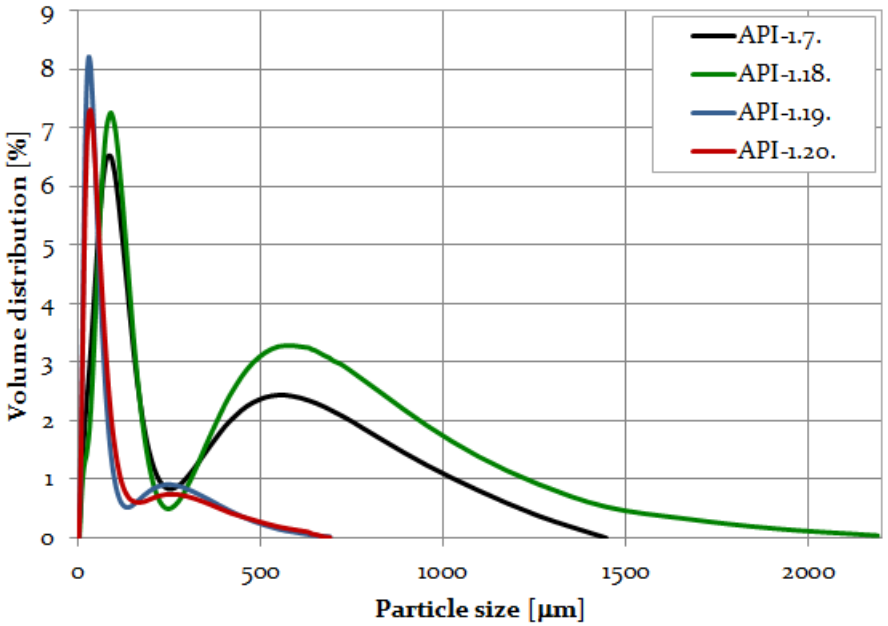


Figure 8. Particle size distributions obtained by sonocrystallization in a flow cell, batch continuous and batch pulsed sonication process

Repeating the same cooling crystallization, this time with constant ultrasonic irradiation (API-1.19. and API-1.20.), nucleation occured at 43 °C versus 40 °C in the absence of ultrasound (API-1.7.).

As the system crystallizes very fast, constant exposure of the suspension to sonication prevents dominant crystal growth keeping crystals very compact and uniform.

This way of process providing ensures high yield, desired granulometric properties without negative impact on chromatographic purity.

Comparison of crystal granulometric properties obtained by different sonocrystallization processes

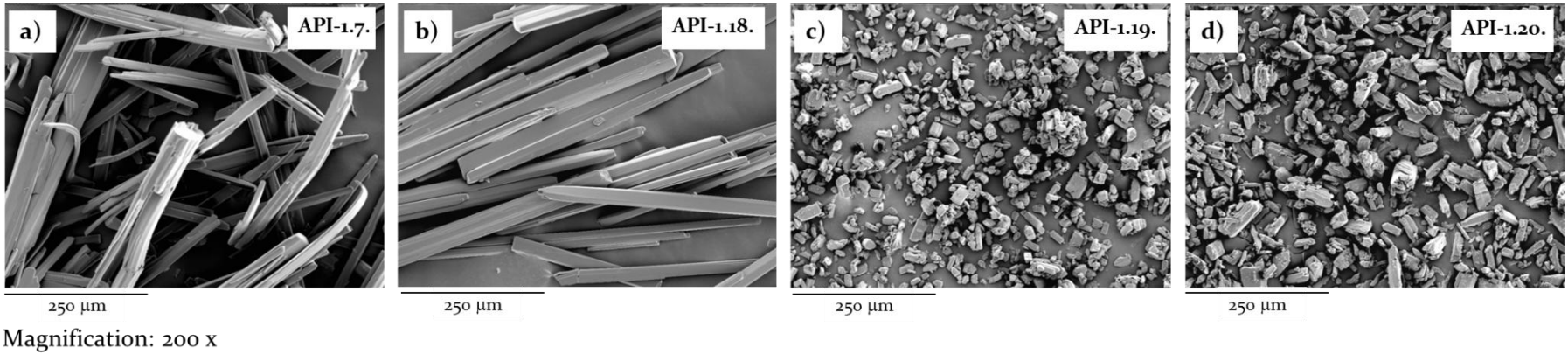


Figure 9. SEM pictures of initial crystal and crystals obtained by different sonocrystallization processes

CONCLUSION

- The application of ultrasound to crystallization of maleate salt of API is a promising method for obtaining product of desired properties

- Continuous ultrasonic irradiation (*A* = 40 %) has afforded improved crystal granulometric properties and time saving costs

- Many of industrial products could be greatly benefited by the development and application of sonocrystallization since it could be a solution for the systems which tend to achieve crystals of minimal size and narrow size distribution

Engineering is the conscious application of science to the problems of economic production. – H.P. Gilette, 1910.


THANK YOU FOR YOUR
ATTENTION
ANY QUESTION?