INFLUENCE OF ANTISOLVENT ADDITION ON CRYSTALLIZATION KINETICS AND GRANULOMETRIC PROPERTIES OF FOSAMPRENAVIR CALCIUM

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Introduction

The focus of the pharmaceutical industry is the research and development of an active pharmaceutical ingredient (API) that can be successfully applied for preparing various drug dosage forms. API are complex organic compounds that tend to agglomerate, oiling out, or form hydrates and/or solvates during crystallization. Therefore, crystallization of the API is the first and critical step that needs to be taken to successfully prepare a drug formulation. By developing a controlled crystallization process, obtaining the desired size distribution, yield, form, and purity of crystals is possible. Crystallization can be carried out by various methods that affect supersaturation which is the main factor in the formation of crystals with defined crystal's properties. Addition of an antisolvent is potentially the best method to achieve controlled and unimodal crystal size distribution (CSD).

Experiment

The research investigates the antisolvent crystallization of fosamprenavir calcium used as an active ingredient for the treatment of HIV. In preliminary study, the width of the metastable zone same as the dependence of fosamprenavir calcium solubility on the added water content for the selected solvent mixture (80 wt% methanol and 20 wt% ethanol) was defined. At constant antisolvent addition rate, the influence of the initial concentration of the solution and a mass fraction of antisolvent on granulometric properties of obtained crystals were examined. Furthermore, a MatLab based program (CrySiV v.1.1) [2] was used for population balance modeling and subsequent simulation of experiments at 30 °C. Solubility parameters were estimated for a pre-defined solubility model and a simple kinetic model consisting of primary nucleation and crystal growth is proposed. Kinetic parameters were estimated by minimization of the objective function using high resolution finite volume algorithm. The objective function takes into account the differences between simulated and measured values of concentration profile during crystallization and final product CSD in equal proportions.

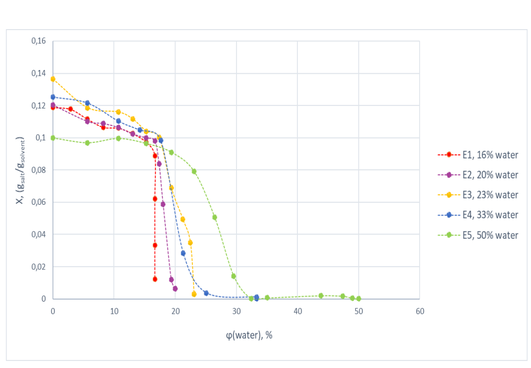
Results

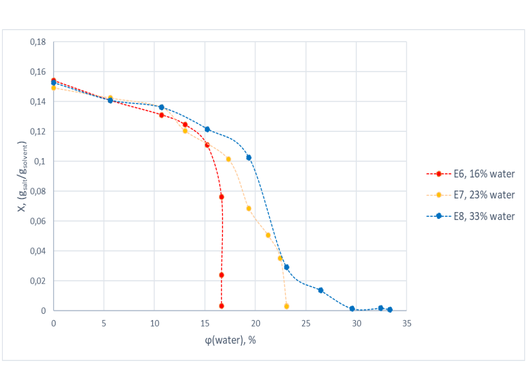
Finding a suitalbe antisolvent

GLASS	1	2	3	4	5
ANTISOLVENT	Water	Isopropyl alcohol	Ethyl acetate	Dichloromethane	Acetonitrile
CRYSTALS	+	-	-	-	-

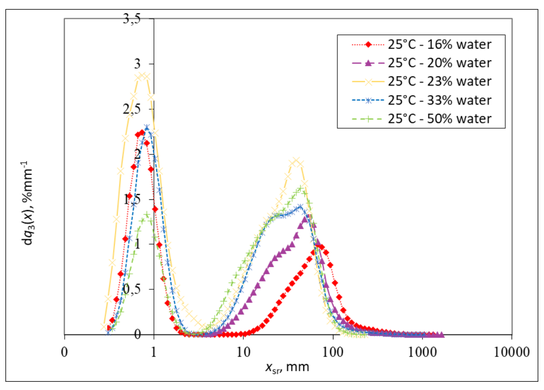
Batch crystallization process conditions

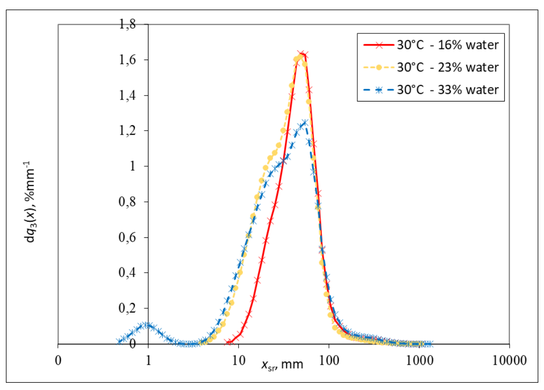
NAME OF THE EXPERIMENT	E1	E2	E3	E4	E5	E6	E7	E8
Mass of salt, g	9,7	9,7	9,7	9,7	9,7	12,6	12,6	12,6
Solvent	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)	MetOH-EtOH (80:20)
Volume of solvent, mL	100	100	100	100	100	100	100	100
Volume of antisolvent, mL	20	25	30	50	100	20	30	50
Volume fraction of antisolvent, %	16	20	23	33	50	16	23	33
T, °C	25°C	25°C	25°C	25°C	25°C	30°C	30°C	30°C
Stirrer speed, rpm	500	500	500	500	500	500	500	500
Process duration	3 min 30 sec	4 min 10 sec	5 min	8 min 20 sec	16min 40sec	3min 30 sec	5 min	8min 20 sec

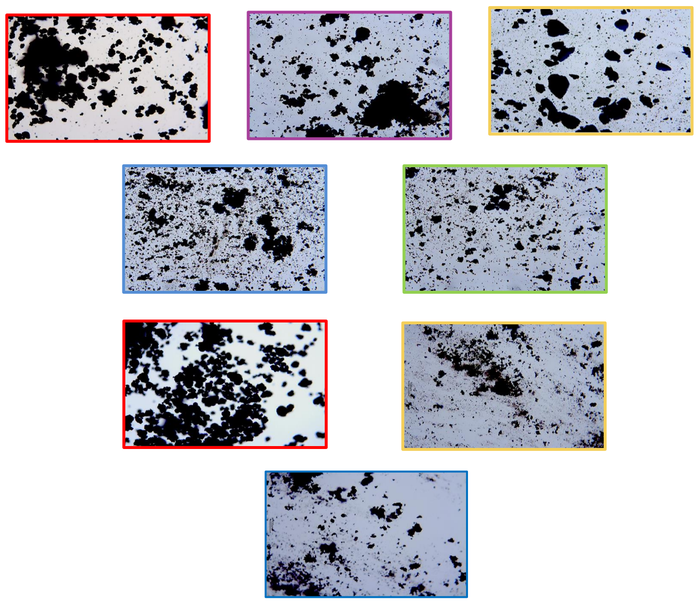




Granulometric properties







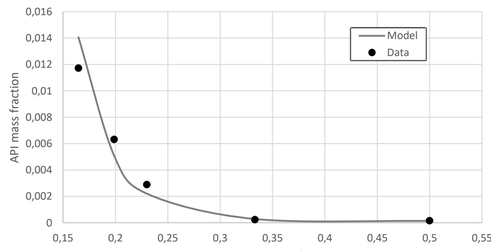
Population balance modeling for experiment E6

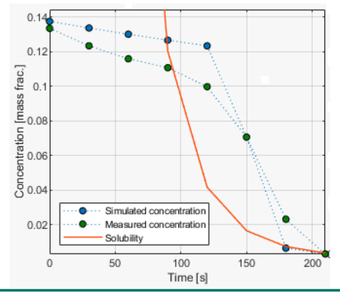
Solubility: $C_s = e^{[a_1+a_4A+a_5\exp(A)]}$

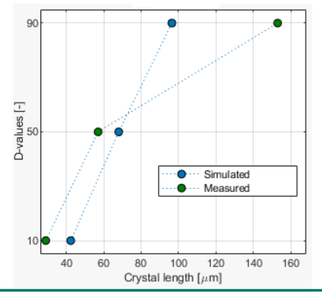
Nucleation: $B = k_n\sigma^n$

Growth: $G = k_g\sigma^g$

Solubility of API, 30 °C







Parameter	Meaning	Nominal
k_n	Primary nucleation rate constant	1.4632* 10^7
n	Primary nucleation supersaturation exponent	5.1590
k_g	Growth rate constant	0.8161
g	Growth supersaturation exponent	0.8504
a1	Solubility model parameter	-77.172
a4	Solubility model parameter	-124.937
a5	Solubility model parameter	79.289

Conclusion

After determining the metastable zone width for different solvents, the mixture of methanol-ethanol (80:20) was chosen for the crystallization process while water was used as anti-solvent.
Nucleation starts with 16 vol% water added to the solutions when the concentration curves indicate a significant decrease.
The increase of the saturation temperature favoured the granulometric properties of the formed crystals.
The crystal size distributions obtained from most experiments show a bimodal form caused by secondary nucleation or crystal agglomeration.
Population balance modelling has been used to estimate kinetic parameters of nucleation and crystal growth.

References

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[2] B. Szilágyia, Z. K. Nagy, Graphical processing unit (GPU) acceleration for numerical solution of population balance models using high resolution finite volume algorithm, Computers and Chemical Engineering (2016.), DOI: (http://dx.doi.org/10.1016/j.compchemeng.2016.03.023)

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