Molecular Modeling of Solid-Fluid interactions toward the prediction and control of Solid-phase properties: A drug recrystallization case study using the SAS process

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ABSTRACT

In the case of a drug recrystallization study, it is of the utmost importance to control the crystal habit and polymorphism of generated particles. Bioavailability and drug efficiency strongly depend on these properties of crystals. This study investigates a novel tool based on molecular modeling that aims to predict, control and optimize solid-phase material properties. Modeling solid-fluid interactions, at the atomic scale, between solvent molecules and crystal faces has allowed an efficient prediction of the structural properties of crystals.

The software presented allows the study of small molecules (as conventional drugs), macromolecules (as modern therapeutics like proteins and nucleic acids), crystalline materials, porous materials (as metal organic frameworks), *etc.* with up to 25000 non-hydrogen atoms. A crystalline solute can then be considered in its crystalline form, taking into account its possible polymorphism. Atoms positioning can be performed *ab-initio* by determining the most energetically favored structure or directly transcripted from X-Ray Diffraction patterns of monocrystals. For each generated crystal or material, the investigation of solid-fluid interactions can be performed by simulating adsorption and by an attachment energy calculation [1]. This approach may help for understanding various phenomena involved in processes such as crystallization and particle generation, gas storage and/or recovery, surface coating and impregnation, among others.

The case study presents an application to a drug crystallization process. The Sulfathiazole, a widely described drug model with five known polymorphic forms, has been recrystallized through the Supercritical AntiSolvent process, which allows the generation of powders in a given polymorphic form. Four solvents exhibiting different properties in terms of polarity and proticity have been used: acetone, acetonitrile, tetrahydrofuran and acetic acid. Generated crystals are observed with a Scanning Electron Microscope. In parallel of this experimental work, the modeling work is achieved by calculating interactions between each face of the Sulfathiazole crystals and the considered solvents. Attachment energy calculations have allowed the prediction of the solvent's effect on the crystal habit of Sulfathiazole.

Keywords : Crystallization, Supercritical AntiSolvent, molecular modeling, adsorption

INTRODUCTION

Molecular modeling is a growing field that offers a relevent line for the development or optimization of processes. Starting from the modeling of compounds at an atomic scale, those computational tools allow a rapid approximation of numerous data usually obtained throughout tedious experimental campaigns. Such tools are therefore well fitted to support and boost research and development steps, especially for the process engineering field, by limiting the number of "Trial and error" attempts in a screening approach, by orientating the investigation or even avoiding unfruitful combinations of solvent-solute in the case of crystallization, extraction or industrial cleaning, for example.

The presented case shows an application of molecular modeling to the crystallization field, and particularly to the crystallization into a pressurized fluid such as supercritical CO_2, pure or in a mixture with an organic solvent. This approach allows a better control of solid properties in terms of size, crystal habit and polymorphic form, as well as saving time and money by superseding long experimental campaigns. The studied solute is the Sulfathiazole, a well described drug compound that crystallizes into five different polymorphic forms. Full crystallographic data, derived from X-Ray Diffraction analysis and accessible online (Cambridge Crystallographic Data Centre (CCDC)), were used as a basis to perform the modeling part, that aims to predict crystal habit of Sulfathiazole grown in each specific growth environment (solvent + CO_2). To compare predicted results from molecular modeling, an experimental work has been conducted. Two different polymorphic forms have been selectively recrystallized from acetone, acetonitrile, tetrahydrofuran and acetic acid solutions by using the Supercritical AntiSolvent (SAS) process.

Solid-Fluid or Fluid-Fluid intermolecular interactions are usually computed in light of an application in a liquid phase. This study aims to compare the obtained results from the predictive work using usual models with generated crystals from a pressurized dense fluid to validate the feasibility of the predictive method to this case study and, therefore, to supercritical media in general.

MATERIALS AND METHODS

1 – Molecular modeling for the crystal habit prediction

At first, Sulfathiazole crystals were constructed at thermodynamic equilibrium using crystallographic data from the CCDC. The data files contain every atom position representing one crystal lattice, in addition of the crystal lattice parameters, therefore giving knowledge on molecular conformation and inter-reticular distances. For Sulfathiazole, the CCDC references are SUTHAZ01, SUTZAZ05, SUTZAZ02, SUTHAZ and SUTZAZ04, respectively for polymorphic form I, II, III, IV and V.

Once the crystalline atomic stacking is known, the next step is to determine the crystal habit. It is determined *in vacuo*, meaning that the growth environment and its potential influence on the crystal growth are not yet considered. A crystal is an object delimited by a set of plane faces, whose relative development will lead to a given habit. A crystal face can be indexed by Miller's indices, noted (hkl) where h, k and l should the lower integer possible. The area or size of each visible (hkl) face depends on the face's growth velocity, called the linear growth rate and noted V_{hkl}. A larger face's area implies a slower V_{hkl}, and *vice versa*. The set of all V_{hkl} allows the determination of the crystal habit. Two models are proposed for the calculation of V_{hkl}.

The first model is called BFDH model (Bravais, Friedel, Donnay and Harker [2]). The authors have observed that larger faces, the ones with the slower V_{hkl}, are connected through the longer inter-reticular distance d_{hkl}, which basically is the size of the crystal lattice in the (hkl) direction. This model therefore allows a fast and easy way to draw the crystal habit but gives an adequate description only when molecules forming the crystal are bonded to each other

through Van der Waals forces. If bonding forces such as hydrogen bonding or coulombic forces are existing in the crystal, the BFDH model does not fit for an accurate description of the crystal habit. Because Sulfathiazole crystals are partly bonded with hydrogen bonding [3], the BFDH model might be inaccurate.

The second and used model is called the attachment energy model, noted EATT. It has been proposed by Hartman and Perdok [4] then refined by Hartman and Bennema [5]. This model is based on thermodynamic fundamentals, and therefore considers that the crystal can exist and grow if each successive attachment of solute molecules releases an amount of energy, called the attachment energy. The sum of those released amount of energy gives the crystal energy, noted E_{cr} (kJ.mol^{-1}). It can be used as a quantification of the crystal stability. However, the attachment energy can vary from one (hkl) face to another, causing different linear growth rates. V_{hkl} is therefore proportional to the attachment energy on the (hkl) face, noted E_{att}^{hkl}, which can be estimated through molecular modeling [6]. For this purpose, a spherical cluster of solute molecules is considered in the crystal, with the actual conformation and molecular packing. A (hkl) slice is considered, parallel to the (hkl) face and with a thickness of d_{hkl}. The attachment energy of the central molecule of the (hkl) slice will be calculated from two interaction energy calculation. Firstly, the slice energy (E_{sl}) is calculated as the energy released from the interactions between the central molecule and other molecules included in the slice (Figure 1, red dotted double arrows). Secondly, the crystal energy is calculated as the energy released from interactions between the central molecule and every molecule in the cluster (Figure 1, blue double arrows). Therefore, E_{att}^{hkl} can be defined as:

$$E_{att}^{hkl} = \frac{1}{2}\left(E_{cr} - E_{sl}\right) \quad (1)$$

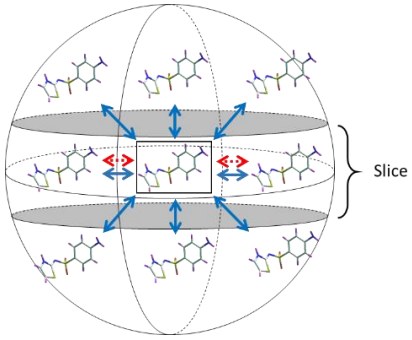


Figure 1. Computing (hkl) attachment energy from (⇠⇢) slice energy and (⇿) crystal energy. Arbitrary packing chosen for an easier illustration.

With the EATT model, slow growing faces, the ones with the larger final area, are having the lower E_{att}. For a given crystal with a given crystal energy, predominant faces are therefore having the higher slice energy.

After having modeled *in vacuo* crystals with the EATT model, the third and last step of this modeling work aims to consider the influence of the growth environment regarding the crystal habit. Each probable face of *in vacuo* modeled crystals are put in contact with one solvent molecule through an adsorption simulation. Indeed, depending on the affinity between the (hkl) surface and the solvent, intermolecular interactions can lead to growth hindering and may modify the crystal habit. A calculation is performed for each crystal face and for each solvent, each case giving an interaction energy, noted E_i.

2 – Crystal generation with Supercritical AntiSolvent process

In parallel of the modeling work, an experimental campaign has been set to generate Sulfathiazole crystals. Among all different crystallization processes that use supercritical CO_2 , the SAS process was chosen. Unlike RESS (Rapid Expansion of a Supercritical Solution) or PGSS (Particles from Gas Saturated Solution), the crystallization step occurs at constant

conditions of pressure, temperature and fluid composition with the SAS process. In other words, the crystallization step occurs in a steady state, which is suitable for comparing experimentally generated crystals with EATT model. Furthermore, SAS process is preferred for the treatment of CO_2 poorly soluble components, such as Sulfathiazole (solubility in the order of 10^{-7} mol/mol in pure supercritical CO_2 [7]). The SAS process has allowed a successful recrystallization of Sulfathiazole with control on its polymorphic form, particle size and size distribution.

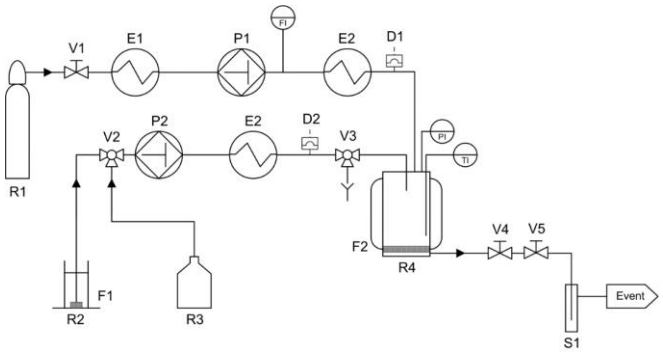


Figure 2. Flow diagram of the SAS process set-up. E1 and E2: heat exchangers; V1: valve; V2 and V3: 3-ways valves; V4 and V5: depressurizing valves; P1 and P2: high pressure liquid piston pumps; D1 and D2: bursting discs, F1: solvent frit filter; F2: glass fiber filter; S1: solvent trap; R1: CO2 pressurized bottle; R2: organic solution tank; R3: pure solvent tank; R4: crystallization double-jacket autoclave.

The experiment starts with a parallel injection of pure CO_2 and pure solvent, in order to stabilized the composition within the crystallization autoclave (60 mm inner diameter, 480 mL) at target pressure (100 bar) and temperature (313 K). Then, the pure solvent feed is swapped with the organic solution feed, containing the solute solubilized in the organic solvent. The jet of organic solution is atomized thanks to a capillary tube with an internal diameter of 127 µm. At this moment, the crystallization occurs thanks to the antisolvent behavior of CO_2, enhanced with a retro-diffusion effect of the CO_2 into the solvent rich phase and the solvent into the CO_2 rich phase. The obtained microparticles accumulate onto a glass microfiber filter with pores size of 1.2 µm at the bottom of the autoclave. After that the desired amount of organic solution has been injected, the organic solution flow is stopped but the CO_2 flow is maintained to renew the fluid content of the autoclave and wash/dry the generated powders. Then, after the pressure being dropped to atmospheric pressure, the powder is collected and analyzed by ^{13}C nuclear magnetic resonance to determine whether the powder is pure in one polymorphic form and by Scanning Electron Microscopy (SEM) to observe the crystal habit and compare it with the modeling results.

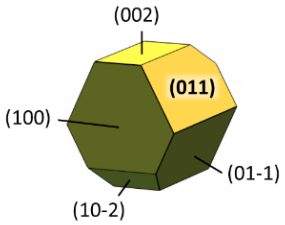
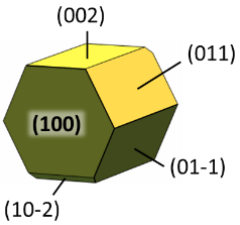
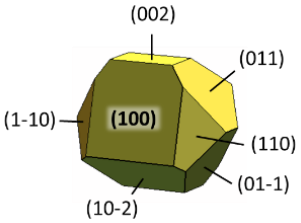
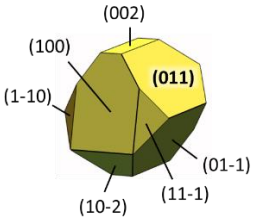
RESULTS

1 – Modeling results

Sulfathiazole crystal parameters and molecular conformation data picked up from CCDC database have allowed a complete modeling of crystal habits (Table 1) with both EATT and BFDH models for polymorphic forms IV and I. Form IV has a monoclinic lattice composed by 4 asymmetric units of 1 molecule. Form I also has a monoclinic lattice, that is composed by 8 molecules (4 asymmetric units of 2 molecules).

In vacuo crystal habits are presented alongside calculated data that has allowed their modeling *i.e.* E_{cr}, E_{att} and d_{hkl}. A first result highlights that Form IV is more stable than Form I, giving that the crystal building has released a greater amount on energy (158 ± 5 kJ.mol^{-1} for all simulated form IV against only 139 ± 4 kJ.mol^{-1} for all simulated form I). SUTHAZ is therefore a more stable form than SUTHAZ01, which is in accordance with experimental observation. This approach can therefore be used to predict relative stability of polymorphic forms of new compounds at thermodynamic equilibrium.

Table 1. Crystal habit computed for forms IV and I of Sulfathiazole with both EATT and BFDH models.

	(hkl)	E_{att} (kJ.mol^{-1})	d_{hkl} (Å)	EATT model	BFDH model
Form IV (SUTHAZ) P21/c, Z = 4 E_{cr} = - 156 kJ.mol^{-1}	0 1 1	-30,3	7,49		
	1 0 0	-31,2	8,22		
	0 0 2	-35,8	7,76		
	1 0 -2	-39,3	5,83		
Form I (SUTHAZ01) P21/c, Z = 8 E_{cr} = - 133 kJ.mol^{-1}	1 0 0	-22	10,03		
	1 0 -2	-31,6	7,55		
	1 1 0	-36,2	7,99		
	0 0 2	-37,7	8,10		
	0 1 1	-40,8	10,24		

Crystal habits of both forms I and IV are not in a perfect accordance between EATT and BFDH models, highlighting existing hydrogen bonding forces. However, for both models and both polymorphic forms, the predominant faces are always the same: (011) and (100) are the most predominant faces, (002) and (10-2) are also developed. Named faces have their E_{att} close to one another, this results in crystal habits of an equant or isometric type. Results obtained solely from the EATT model are considered for the next step of calculations, corresponding to the adsorption simulation calculations.

Calculations of interactions between solvent and crystal faces have been performed with CO_2, acetone, acetonitrile, tetrahydrofuran and acetic acid. Results are presented in the Table 2. Furthermore, an illustration of the system after an adsorption simulation of an acetone molecule is given in the Figure 3. The figure shows that each face of a given crystal is unique, with two major characteristics, that is its chemical composition and its surface roughness. The later may cause small enough solvent molecules to be "deeply" adsorbed (at an atomic scale), involving stronger interaction energies and thus increases the probability of the face's growth to be slowed down. Figure 3(b) shows that SUTHAZ's (002) face is irregular, with a noticeable roughness. Smaller solvents such as acetone are therefore deeply adsorbed which may imply strong interactions (see Table 2).

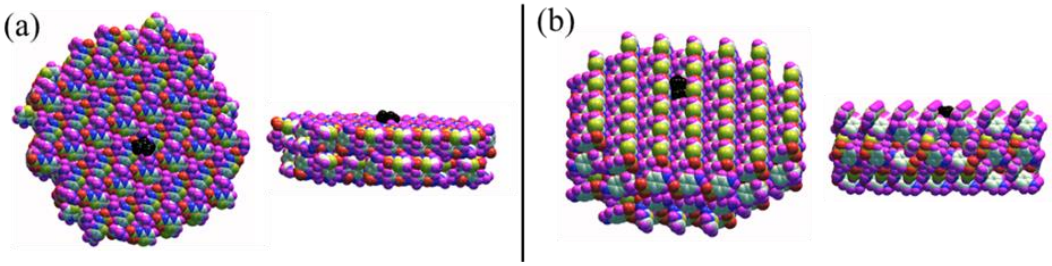


Figure 3. Adsorption simulation of an acetone molecule on (a) the (100) face and (b) the (002) face of SUTHAZ.

As shown in Table 2, this work highlights a negligible adsorption effect of carbon dioxide on both Sulfathiazole forms I and IV. The effect of CO_2 is therefore not considered, and only organic solvents effect can be investigated. Among them, acetonitrile is the one with the lowest likelihood of modifying the crystal habit, also for both Sulfathiazole forms I and IV, because interaction energies are mainly lower than attachment energies for each (hkl) face. Acetone and Tetrahydrofuran both have strong interactions with already predominant (slow-growing) faces, *i.e.* faces (011) and (002) of form IV and faces (100), (10-2) and (110) of form I. By slowing

down the predominant faces, acetone and tetrahydrofuran shall modify the crystal habit and form a flattened crystal, with most likely a strongly developed (002) face (from IV) and (100) face (form I). Lastly, for both forms, acetic acid strongly interacts with each of the most probable faces. This avoid crystal habit predictions, but may increase the range of operating conditions where metastable form I can be obtained, by hindering the form transition from form I to form IV.

Table 2. Attachment energies and interaction energies with solvents for polymorphic form IV and I of Sulfathiazole. Bold values: E_i lower than E_{att} for a given (hkl) face.

Solute	(hkl)	E_{att} (kJ.mol^{-1})	E_i (kJ.mol^{-1})				
			CO_2	Acetone	Acetonitrile	Tetrahydrofuran	Acetic acid
SUTHAZ Form IV	0 1 1	-30.3	-25.7	**-33**	-22.4	**-34.4**	**-51.9**
	1 0 0	-31.2	-22.3	-30	-20.3	**-32.2**	**-48.1**
	0 0 2	-35.8	-30.7	**-40.5**	-28.6	**-42.7**	**-53.3**
	1 0 -2	-39.3	26.9	-33.7	-24.1	-33.1	**-50.2**
SUTHAZ01 Form I	1 0 0	-22	**-24.9**	**-29.8**	**-22.5**	**-28.4**	**-48.5**
	1 0 -2	-31.6	-25.9	**-36.4**	-22.7	**-35.4**	**-51.9**
	1 1 0	-36.2	-26.7	**-41.8**	-29.2	**-40.9**	**-54.8**
	0 0 2	-37.7	-27.6	**-37.9**	-25.1	**-38.5**	**-51.5**
	0 1 1	-40.8	-30.2	**-41.4**	-27.8	-40.8	**-54**

2 – Experimental results

SAS process has allowed a selective generation of Sulfathiazole powders that are pure in one polymorphic form. A list of operating conditions that have allowed the recrystallisation of pure powders of Sulfathiazole, in terms of polymorphic form, is presented in the Table 3. As for the modeling part, the considered organic solvents are acetone, acetonitrile, tetrahydrofuran and acetic acid. With each solvent, fluid flow rates (CO_2: 2 to 21 g.min^{-1}; organic solution: 0.19 to 3.04 mL.min^{-1}) as well as Sulfathiazole concentration in the organic solvent (60 % of Sulfathiazole solubility [9], up to 70 % in the case of 1 % w/w into acetonitrile) have been varied to generate different polymorphic forms of Sulfathiazole. With those conditions, solvent/CO_2 molar ratio was varied from 3.4 % (corresponding to a supercritical monophasic environment) up to 20 % (liquid monophasic environment). Only pure form I, pure for IV and mixtures of both (not presented) were obtained. Pure form I were generally obtained at higher fluid flow rates, corresponding to higher mixing conditions. Supersaturation reaches higher

Table 3. Operating conditions producing pure polymorphic forms of STZ

# exp.	Solvent	CO_2 flow (g.min^{-1})	Organic solution flow (mL.min^{-1})	Solution concentration wt %	Solv/CO_2 ratio mol %	Polymorphic form
1	Acetone	21	3	1.8 %	8.2 %	I
2		10	1.9		11 %	IV
3		5	0.42		4.8 %	IV
4		2	0.19		5.5 %	IV
5	Acetonitrile	21	1.9	1.0 %	7.3 %	I
6		21	1.35		5.2 %	IV
7		21	1.9	0.81 %	7.3 %	IV
8		21	1.35		5.2 %	IV
9	Tetrahydrofuran	8	3.04	0.67 %	20 %	I
10		21	1.9		4.8 %	IV
11		21	1.35		3.4 %	IV
12	Acetic acid	12	1.9	0.48 %	12 %	I
13		15	1.17		5.9 %	I
14		5	0.31		4.7 %	I

levels quicker, therefore involving higher nucleation frequencies, explaining the presence of the metastable form. Lastly, the most stable form (form IV) has not been observed when acetic acid was used as solvent, even at lower fluids flow rates. This observation is in accordance with modeling predictions.
SEM photographs of samples obtained with experiments #2, #6, #10 for form IV and #1, #5, #9 and #12 for form I are respectively presented in Figure 2 (form IV) and Figure 3 (form I).

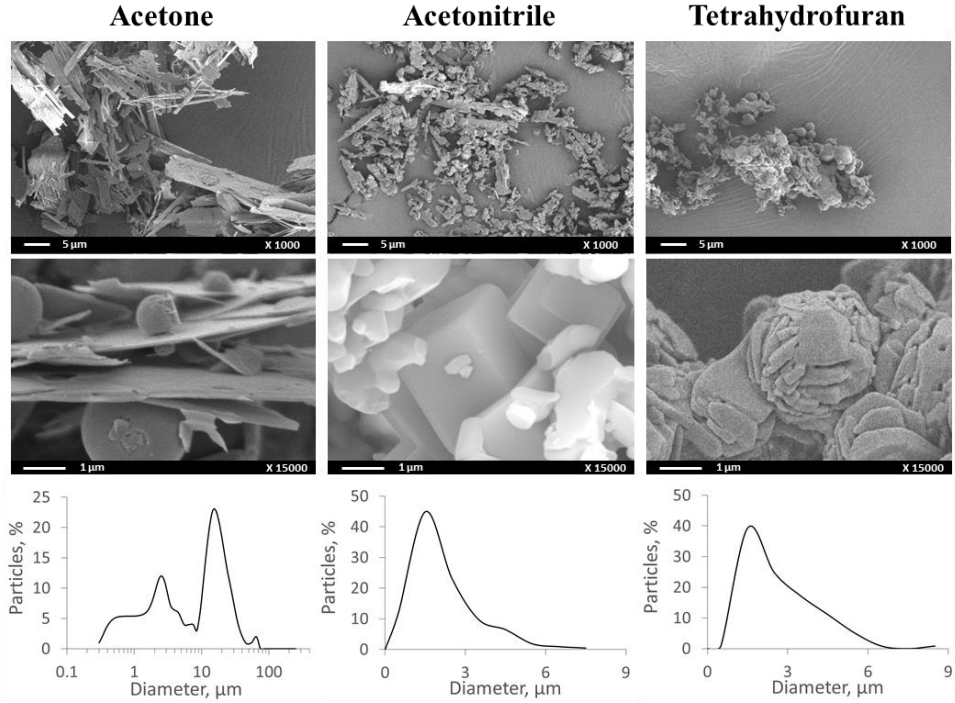


Figure 2. SEM observation of powder samples from Exp. #2, #6, #10 (pure Sulfathiazole form IV)

When the most stable form is obtained, the growth environment plays an important role regarding the crystal habit. When acetone is used as solvent, plate-like or leave-like crystal habit was obtained, with higher crystal size and more attrition due to fragility of generated crystals. This is in accordance with the predicted results, the predominant face shall therefore correspond to the (002) face that has been strongly hindered by solvent adsorption. When acetonitrile was used, obtained crystals were isometric with a crystal habit close to the one predicted *in vacuo*. This experimental observation also matches with the modeling results because acetonitrile does not preferentially adsorb and interact strongly enough to modify the Sulfathiazole crystal habit. Lastly, when tetrahydrofuran was used, agglomerated small plate-like crystals where obtained. As mentioned in the modeling part, Sulfathiazole crystals grown in tetrahydrofuran should have a relative development close to the one grown in acetonitrile, which is the case. However, another behavior is highlighted in this sample: a droplet drying crystallization mechanism, leading to spherical clusters of crystals.
In contrast with form IV, observed samples from form I show a rather low effect of solvent adsorption. Two different crystal habits can be observed: a hexagonal plate-like habit, obtained when acetone and acetonitrile were used, and an acicular needle-like habit, obtained when tetrahydrofuran and acetic acid were used. Crystals are not exhibiting clear delimitating faces due to crystallization conditions being too far from thermodynamic equilibrium (intense mixing conditions). Such incompletely grown crystals cannot directly be correlated with crystal habits at thermodynamic equilibrium.

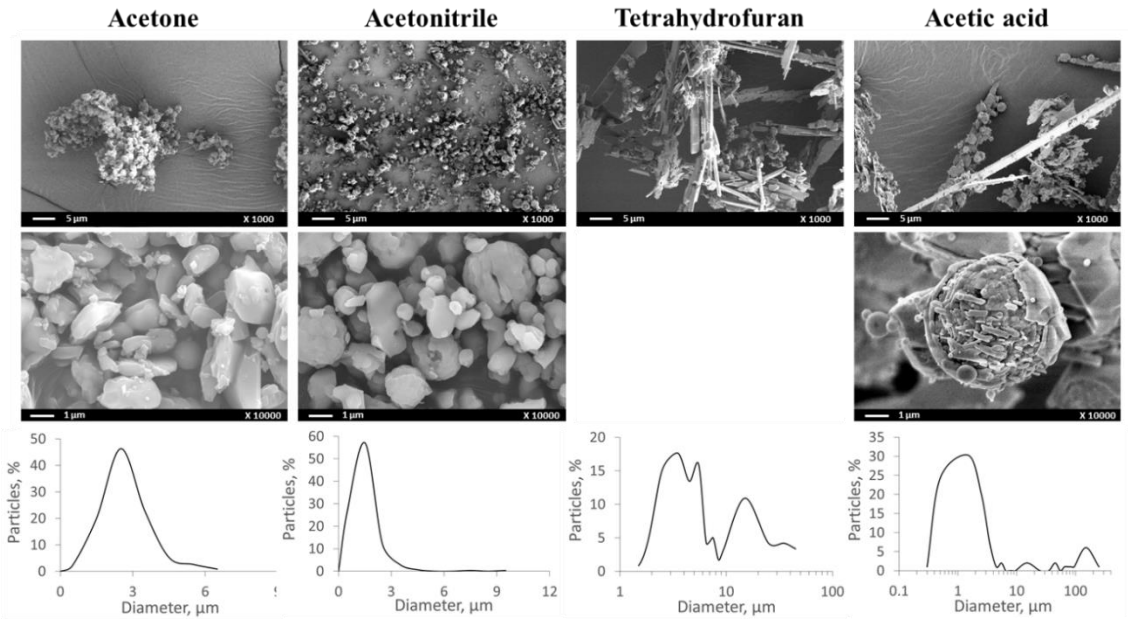


Figure 3. SEM observation of powder samples from Exp. #1, #5, #9 and #12 (pure Sulfathiazole form I)

CONCLUSIONS

This study has presented a feasibility study that confirms the strong potential of molecular modeling in the case of crystallization in a supercritical medium. More precisely, a case study mixing the attachment energy molecular modeling followed by adsorption simulations and the SAS process using different organic solvents at various operating conditions has allowed a better understanding of the crystallization mechanisms occurring in pressurized fluids. Operating conditions allowing a selective crystallization of a given polymorphic form of Sulfathiazole has been identified. Generated crystals have been observed and correlated with modeling predictions with a good agreement for the most stable form (form IV), obtained at moderate mixing conditions. Furthermore, relative stability of Sulfathiazole has been discussed, with an important consideration on the acetic acid case, blocking phase transition due to strong intermolecular interactions with Sulfathiazole crystals.

REFERENCES

[1] P. Hartman, The attachment energy as a habit controlling factor, J. Cryst. Growth. 49 (1980) 166–170. doi:10.1016/0022-0248(80)90077-9.

[2] J.D.H. Donnay, D. Harker, A new law of crystal morphology, Extanding the law of Bravais, Am. Mineral. 22 (1937) 446–467.

[3] N. Blagden, R.J. Davey, H.F. Lieberman, L. Williams, R. Payne, R. Roberts, R. Rowe, R. Docherty, Crystal chemistry and solvent effects in polymorphic systems Sulfathiazole, J. Chem. Soc. Faraday Trans. 94 (1998) 1035–1044. doi:10.1039/A706669D.

[4] P. Hartman, W.G. Perdok, On the relations between structure and morphology of crystals. I, Acta Crystallogr. 8 (1955) 49–52. doi:10.1107/S0365110X55000121.

[5] P. Hartman, P. Bennema, The attachment energy as a habit controlling factor, J. Cryst. Growth. 49 (1980) 145–156. doi:10.1016/0022-0248(80)90075-5.

[6] G. Pèpe, S. Fery-Forgues, P. Jouanna, Predicting crystal structure and habit of organic micro-crystals by experimentally assisted molecular modelling (EAMM). The case of n-octylamino-NBD, J. Cryst. Growth. 333 (2011) 25–35. doi:10.1016/j.jcrysgro.2011.07.035.

[7] A. Kordikowski, M. Siddiqi, S. Palakodaty, Phase equilibria for the CO2 + methanol + sulfathiazole system at high pressure, Fluid Phase Equilibria. 194–197 (2002) 905–917. doi:10.1016/S0378-3812(01)00649-5.

[8] Á. Munroe, Å.C. Rasmuson, B.K. Hodnett, D.M. Croker, Relative Stabilities of the Five Polymorphs of Sulfathiazole, Cryst. Growth Des. 12 (2012) 2825–2835. doi:10.1021/cg201641g.

[9] S. Clercq, A. Mouahid, P. Gérard, E. Badens, Investigation of crystallization mechanisms for polymorphic and habit control from the Supercritical AntiSolvent process, J. Supercrit. Fluids. (2017). doi:10.1016/j.supflu.2017.11.025.