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Cocrystallization induced by compressed CO_2 as antisolvent: Simulation of a batch process for the estimation of nucleation and growth parameters

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ABSTRACT

A mathematical model describing the GAS antisolvent process applied to cocrystal formation has been developed with the aim of estimating nucleation and growth parameters that are critical issues in crystallization in general. The estimates are obtained by fitting the particle sizes distribution predicted by the model to experimental data. The investigated system was naproxen + nicotinamide that assembled as cocrystals when recrystallized by adding CO_2 to acetone solution. The concentration of naproxen + nicotinamide in the liquid phase was calculated from the experimental data of the quaternary system. Particle formation was described by primary and secondary nucleations and a growth rate driven by diffusion. The population balance equation was solved by the standard method of moments assuming a log-normal distribution. Particles of NPX_2:NCTA cocrystals of 40–80 μm mean size were experimentally produced and the experimental size distributions were well fitted by the proposed cocrystallization model.

1. Introduction

Fabrication of cocrystals in the pharmaceutical sector is a new strategy for modifying the macroscopic behavior of a drug like its dissolution rate or its stability [1,2]. Cocrystals are multicomponent assemblies of two compounds held together by non-covalent interactions such as hydrogen-bonding, ion pairing, van der Waals attractive forces [3,4]. So far, the formation of new cocrystal is screened mostly by mecanochemical techniques such as grinding or solvent assisted grinding [5,6] but to be developed at industrial scale, fabrication of cocrystal should be realized by more scalable techniques such as solution crystallization [1]. The choice of the appropriate solvent, of the pathway to produce the desired form through the multicomponent solid–liquid phase equilibrium diagrams, and of the mechanism to induce nucleation and control the desaturation kinetics of the process are the critical issues to examine in cocrystallization [7]. Most cocrystal fabrications in solution are carried out by cooling the API-coformer solution or slurry in order to supersaturate the solution [8,9]. Variation of initial composition allows for varying the crystallization pathway and yields, according to the classical ternary diagram with one cocrystal system, pure cocrystals, API or coformer crystals, or a mixture of cocrystals and one of the homocrystals [10].

Crystallization assisted by CO_2, and especially using CO_2 as an antisolvent has emerged years ago as an alternative route for a better control of the particle size. Applications of compressed CO_2 to cocrystal fabrication have been only marginally investigated, using techniques of rapid expansion of supercritical solution [11], supercritical fluid enhanced atomization [12], contacting [13], or antisolvent cocrystallization [14–17]. As pointed out by Ober and Gupta, a number of unique advantages and opportunities exist when using GAS cocrystallization for pharmaceutical cocrystal engineering: a reduced thermal and mechanical stress on the API compared to grinding processes, a reduced use of organic solvent use compared to traditional solution-based processes in favor of the environmentally benign CO_2, the facile recycling of the original organic solvent by simple depressurization, and a possible manipulation of the molecular recognition events that occur

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during cocrystal formation by analogy with the crystal manipulation documented for single species. Previous examples aimed at proving the feasibility of the CO_2-assisted cocrystallization, but in absence of thermodynamic data, they remain a case-by-case approach whose kinetic aspects of the cocrystallization cannot be derived neither. In order to strengthen the understanding of cocrystallization in CO_2 medium, and more specially of cocrystallization induced by the addition of CO_2 as antisolvent, we have designed a set-up and methodology for measuring the concentration of API + coformer mixtures in equilibrium with a solid phase in various CO_2 + solvent mixtures, which allows for representing the quaternary data relevant for the cocrystallization [18]. As a next step, the determination of kinetics parameters, i.e. nucleation and growth rates, is now investigated. In conventional crystallization carried out by solution cooling or antisolvent addition, the typical method used to extract kinetic orders uses the experimental particle size distribution fitted with a crystallization model that comprised a population balance equation with corresponding crystallization kinetics and a solubility model. The accounting of more or less complex mechanisms for nucleation (homogeneous or heterogeneous primary nucleation, secondary nucleation), growth (by diffusion, absorbed layer) or bi-dimensional population model [19] yield different degree of sophistication of the modeling. Computational fluid dynamics could be also coupled to the population balance equation to numerically investigate the effect of micro- and macro-mixing [20]. CO_2-antisolvent process has been developed in two variants, known as SAS (Supercritical Antisolvent) in which the solution is injected in a continuous flow of CO_2, and the GAS version (Gaseous Anti-Solvent) in which CO_2 is added to a solution, generally under stirring, until a desired pressure is obtained. The complete simulation of SAS, i.e. coupling the hydrodynamics of the mixing, the solubility and the nucleation/growth kinetics has been already developed but only in case of single species crystallization [21–23]. Aiming at developing meaningful simulation of cocrystallization by SAS, we propose to first obtain realistic nucleation and growth orders for the cocrystal through the use and the modeling of the GAS process under the assumption of well-mixed reactor generally employed in traditional crystallization model [24]. Hence, a model of GAS will lead to a simpler understanding of how particles form although the model could be useful as well to control the particle size distribution of produced cocrystals. Among literature, only few studies have dealt with both the thermodynamics and the crystallization kinetics of GAS. The pioneer work from Muhrer et al. [25] modeled the process by solving phase equilibria and population balance equation and used the Parsival software to solve the partial differential equations (generalized finite-element scheme with a self-adaptative grid). The equilibrium composition of the liquid phase at equilibrium with the gas and the solid phase was computed from experimental thermodynamic data. Both primary and secondary nucleations were accounted for particle formation and a general empirical correlation was adopted for the growth rate. The values of parameters in the nucleation and growth rate models were not regressed by fitting with experimental crystallization data but were chosen so as to be physically realistic. The objective was to specifically clarify the various effects of the CO_2 addition rate observed in literature in relation with settled ranges of the secondary nucleation parameter α''. By similar approach and assumptions, several authors [26–29] compared experimental particle size distribution and predictive data in order to numerically extract the nucleation and growth parameters. More specifically, Dodds et al. [26] evaluated two different equations for the secondary nucleation, the surface dependent expression used by Muhrer et al. [25], or an empirical one commonly used in crystallization. The solid–liquid interfacial tension that is an important parameter in crystallization was expressed as function of the solute concentration in the solid and the liquid phases. Bakhbakhi [29] and lately Esfandiari and Ghoreishi [27,28] focused on solving the population balance equation by using a combination of the Crank–Nicholson implicit method and of the Lax–Wendroff explicit one.

In this work, a similar approach was used to model a case of cocrystallization, on the grounds of our preliminary results on the successful formation of naproxen and nicotinamide cocrystals by GAS [30]. The modeling of the GAS cocrystallization proposed in this work accounts for the two key aspects of the process: (1) the liquid–vapor equilibrium of solvent and antisolvent and its effect on equilibrium concentration of naproxen and nicotinamide in the liquid phase, and (2) the particle formation via primary and secondary nucleations and growth of the cocrystal. The population balance equation was solved with the standard method of moments assuming a log-normal distribution. The phase equilibria of the mixture are modeled by the Peng Robinson equation of state and the supersaturation was calculated through the solubility of the species obtained experimentally [18]. A minimization algorithm was used to determine the nucleation and growth parameters by comparison with experimental size data. It is worthwhile noting that although the theoretical background for GAS modeling is similar to previous works, this is the first example of GAS modeling applied to the formation of cocrystal, for which the phase equilibria of API + coformer mixture in CO_2 + solvent is accounted for, together with the supersaturation ratio expressed through the solubility product.

2. Experimental

Experimental set-up and procedure applied to cocrystal fabrication were previously described [30]. Briefly, the set-up is a 0.49 L vessel equipped with an impeller whose end, fitted with a Rushton turbine, plunged into the solution to allow for dispersing the antisolvent CO_2 directly into the solution. The solution consisted in 40 mL of acetone in which naproxen and nicotinamide were dissolved in a molar ratio of 2:1, respectively. Three global concentrations were investigated, ranging from 50 to 120 mg/mL. Temperature was fixed at 310 K and the stirring rate was 500 rpm. CO_2 was introduced into the vessel by an ISCO pump (Model 260D, Teledyne Isco, USA). Two introduction rates were investigated, 20 g/min and 3 g/min. Thanks to the sapphire windows of the vessel, the precipitation could be visualized and the corresponding pressure and amount of CO_2 recorded. Once the desired pressure of 10.0 MPa was attained, the formed CO_2-solvent solution was drawn down at the vessel bottom whilst fresh CO_2 was introduced by a LEWA pump (EM1, Lewa, Germany) at 25 g/min for 90 min to further eliminate the residual solvent. At the vessel bottom, filters held back the produced particles. At the end of the period, the vessel was depressurized through the exit line and particles were collected, weighed and characterized.

The morphology of produced powders was documented by optical microscopy (Olympus SZX12 and camera ColorView U-CMAD3). The particle size distributions were measured by laser diffraction using a Mastersizer 2000 (Malvern) equipped with a low volume circulation unit. Silicon oil was used as dispersion medium. Powder X-ray diffraction analysis and spectroscopy (ATR-FTIR) of produced powders evidenced the formation of naproxen:nicotinamide cocrystals only [30]. Moreover, no amorphous phase was found in the recovered powders.

As for materials, naproxen ((+)-(S)-2-(6-methoxynaphtalen-2-yl) propanoic acid, 98%, NPX) and nicotinamide (pyridine-3-carboxamide, 99.5%, NCTA) were purchased from Sigma Aldrich (France), whereas carbon dioxide (CO_2, 99.5%) and acetone (99.5%, Scharlau) were supplied from Air Liquide (France) and Atlantic Labo ICS (France), respectively.