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In situ monitoring, control and optimization of a liquid–liquid phase separation crystallization

D. Duffy [a,c,*], N. Cremin [b], M. Napier [b], S. Robinson [b], M. Barrett [a,c], Hongxun Hao [a,c], Brian Glennon [a,c]

[a] University College Dublin, Dublin 4, Ireland
[b] Janssen Pharmaceutical, Little Island, Co. Cork, Ireland
[c] Solid State Pharmaceutical Cluster, University of Limerick, Limerick, Ireland

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ABSTRACT

The oiling out and crystallization behavior of a pharmaceutical compound from acetone and water was studied using a range of in-situ tools to qualitatively describe the oiling out phenomenon. Using a single peak height in the IR spectral region, the liquid phase concentration could be tracked during the liquid–liquid phase separation and also during the subsequent crystallization. This allowed the oiling out region of the system to be properly understood at a mechanistic level and also allowed for the implementation of a control technique that would control the particle size over regular seeding and maintain supersaturation at a constant level.

1. Introduction

The technique of crystallization is used extensively in the pharmaceutical, process and food industries as a method of isolation and purification of compounds. Cooling of a compound from a supersaturated solution has been the most common method of crystallization for the past 50 yr, although, anti-solvent, reactive and evaporative methods are also commonly employed. Research on cooling crystallizations has been extensive (Barrett et al., 2010; Chew et al., 2007; Fevotte and Klein, 1996) but there are still a disproportionate number of problems associated with understanding and controlling the process, particularly when scaled up from lab to plant (Jones, 1974). A huge number of factors have to be controlled such as supersaturation, particle size, mixing intensity, product purity among others (Rohani, 2009). The difficulty in controlling these factors is only exacerbated when, upon cooling of the API, a second liquid phase is formed containing oil droplets. This phenomenon is typically termed oiling out or liquid–liquid demixing (Deneau and Steele, 2005). The traditional approach of the pharmaceutical industry in which the process is controlled by following operating trajectories, typically a temperature profile, can no longer be employed as the solution will 'oil out', before undergoing crystallization giving very impure product and unsatisfactory crystal size. A situation arises where the crystallization process has to be sufficiently understood and controlled to avoid this oiling out region and produce a product of consistent quality.

The fundamental driving force from crystallization from solution is the difference in the chemical potential between the solution and the solid phase, which is typically expressed as supersaturation, which is the difference between the solution concentration and the saturation concentration. The size and shape of the final product crystals are usually dependent on the supersaturation profile achieved during the crystallization (Lewiner et al., 2002). A huge number of publications have dealt with cooling and anti-solvent crystallizations as these are the two most common methods employed, from supersaturation control (Chew et al., 2007; Nonoyama et al., 2006), to particle size control (Yu et al., 2006; Zoltan, 2009), optimal temperature profiles (Feng and Berglund, 2002), anti-solvent addition profiles (Woo et al., 2009) and model free methods (Abu Bakar et al., 2009; Fujiwara et al., 2005). Typically, in crystallizations that undergo oiling out, the crystallization takes place at extremely high supersaturations meaning there is very little time for crystal growth and controlling particle size and shape is extremely difficult (Kiesow et al., 2008). In a typical cooling crystallization, the product nucleates from a supersaturated solution where it desupersaturates towards the solubility curve and undergoes growth when cooled further to the isolation temperature.

* Corresponding author at: University College Dublin, Dublin 4, Ireland.
E-mail address: damian.duffy@ucd.ie (D. Duffy).

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However, in a cooling crystallization that undergoes oiling out, before the onset of nucleation, the solution becomes cloudy due to the formation of this second liquid phase (oiling out) (Bonnett et al., 2003). Depending on the position of the liquid–liquid miscibility gap, different crystallization conditions can be obtained (Bonnett et al., 2003). Regions exist where the system will be stable, unstable and metastable where an energy barrier would have to be overcome for phase separation to occur. Liquid–liquid phase separations can be considered to be either thermodynamically stable or metastable. If the liquid–liquid phase separation is metastable, the liquid–liquid phase separation region lies below the solubility line and within the metastable zone for crystallization. However, in the stable case, a part of the liquid–liquid phase region lies above the solubility line. The thermodynamically stable case was discussed by Svard et al. (2007) by studying the binary system water–vanillin. They observe that vanillin crystals in a saturated aqueous solution disappear and a second liquid phase emerges when the temperature is raised above 51 °C. It has been suggested by Bonnett et al. (2003) that with all crystallization processes there is inevitably a metastable zone in which nucleation is unlikely and hence in which the supersaturated solution has significant stability. The metastable case proposed by Bonnett et al. (2003) says that a liquid–liquid phase boundary lies below the liquidus but just inside the metastable zone, thus, a supersaturated solution may be prone to liquid–liquid phase separation before the onset of crystal formation. Both phases would naturally have to have the same solute chemical potential as they are in equilibrium with each other and hence would have to have the same supersaturation.

Previous work has been carried out on systems which exhibit LLPS. According to Veesler et al. (2006), a full understanding of the phase diagram is a crucial step in completely controlling crystallization parameters like temperature, supersaturation and solution composition. The authors observed a LLPS that lies inside the metastable zone and hinders both primary and secondary nucleation. When primary nucleation did occur, it was observed inside the droplets producing quasi-spherical particles. An interesting case study was presented by Lafferrere et al. (2004) who used a turbidity probe and an FBRM to monitor seeding experiments and made similar observations about how a LLPS hinders nucleation and ultimately affects the process. They also make the point that depending on the point of seeding in the phase diagram, inside or outside the LLPS region, the crystallization mechanisms and kinetics are different.

In recent years, crystallization process characterization and development has made rapid advancement through the use of process analytical technologies (PAT). Further PAT initiatives, launched by the Food and Drug Administration (FDA), have seen these PAT tools become integral to the better understanding of crystallizations, and their subsequent optimization and scale-up (Chow et al., 2008). This has meant that key crystallization characteristics such as supersaturation and product dimension can be examined in situ resulting in better process design and a much higher level of understanding. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectroscopy has emerged as the primary instrument for the assessment of supersaturation and Focus Beam Reflectance Measurement (FBRM) for particle size measurement during both cooling and anti-solvent crystallization processes (Yu et al., 2006). This has opened up the possibility of feedback control-based crystallization design and operation. Many papers have been presented on both the use of ATR-FTIR for supersaturation assessment (Dunuwila et al., 1994; Mersmann and Loffelmann, 1999) and feedback control methodologies (Liotta and Sabesan, 2004). These methods typically rely on chemometric calibration methods which are both difficult to carry out and require a certain level of experience which is extremely limiting to its progression in industrial environments.

In this paper, the ATR-FTIR is used to track peak heights, which are specific to the API to gain an understanding of the oiling out and crystallization of a pharmaceutical API from a solvent mixture so that it could be studied, understood and controlled. Oiling out was seen to follow a number of steps when cooled from a supersaturated solution. A novel, calibration free, seeded control method was then implemented to avoid this phase separation and give consistent particle size and prevention of oiling out. It also allowed for the development of optimal temperature profiles that could be used for the scale-up of this crystallization.

2. Supersaturation tracking method

Knowledge of the supersaturation during any crystallization is of absolute importance. Typically, the application of IR spectroscopy is based on establishing a relationship between the individual peak heights in the systems IR absorption spectrum through chemometric techniques like PLS. These give an accurate measurement of the concentration and in turn, an accurate measurement of the supersaturation once the solubility information has also been obtained as the supersaturation is generally reported as the difference between the actual dissolved concentration and the corresponding saturated concentration at a specific temperature. Generally, for crystallization process, the supersaturation is maintained within the metastable region during the course of the batch (Zhou et al., 2006). The major drawback is that accurate chemometric calibration and validation is needed to get an accurate concentration measurement at any point during the batch, and the accuracy of the calibration must be well within the supersaturation levels encountered in the batch. In the approach adopted here, a characteristic peak height, specific to the solute of interest, is tracked directly at any given temperature. The peak height corresponding to the saturated solution at the same temperature is also measured, so that the supersaturation at any point in the batch is given in terms of the difference in peak height.

So, at any temperature, T_j, the concentration of a given solute i as a function of the characteristic peak height (PH), i.e.

$$C_{ij} = C_i(T_j) = f_{ij}(PH_{ij}, T_j) \tag{1}$$

Similarly, the solubility is given by

$$C^*_{ij} = C^i_i(T_j) = f_{ij}(PH^*_{ij}, T_j) \tag{2}$$

Therefore, the supersaturation is given by

$$\Delta C_{ij} = C_{ij} - C^*_{ij} = f_{ij}(PH_{ij}, T_j) - f_{ij}(PH^*_{ij}, T) \tag{3}$$

At any given temperature, the supersaturation will be directly proportional to the difference in peak height at that temperature, i.e.

$$\Delta C_{ij} = g_{ij}(PH_{ij} - PH^*_{ij}) \tag{4}$$

By applying this method, the supersaturation level can be maintained at a near constant level, within the metastable zone. The supersaturation, expressed in terms of the difference between peak height, will be efficiently described, since the temperature effect on both peaks will be identical, and therefore, irrelevant for the difference between both.

3. Experimental methods

Solution concentrations between 0.19 and 0.33 g API/g solution were made up with saturation temperatures between 31 °C and 65 °C for the solvent system studied. API crystallizations were carried out using both linear and cubic cooling rates, both