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Publication Spotlight

Janssen Employs PAT to Overcome Oiling Out

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

ABSTRACT

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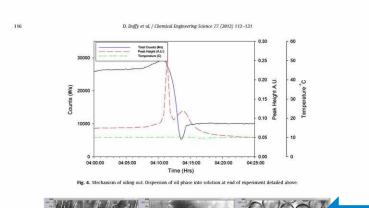
The oiling out and crystallization behavior of a pharmaceutical compound from acetone and w studied using a range of in-situ tools to qualitatively describe the oiling out phenomenon. Using peak height in the IR spectral region, the liquid phase concentration could be tracked during th liquid phase separation and also during the subsequent crystallization. This allowed the oi region of the system to be properly understood at a mechanistic level and also allowed minormentarion of a control technicue that would control the particle size over regular see © 2012 Elsevier Ltd. All right

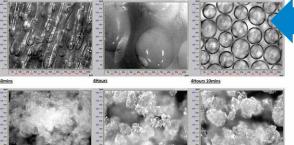
1. Introduction
The technique of crystallization is used extensively in the pharmaceutical, process and food industries as a method of isolation and purification of compounds. Cooling of a compound from a supersaturated solution has been the most common method of crystallization for the past 50 yr, although, anti-solvent, reactive and evaporative methods are also commonly employed. Research on cooling crystallizations has been extensive (Barrett et al., 2010; Fewer et al., 2007; Fewer et 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 exacerbared when, upon cooling of the API, a second liquid plase is formed containing oil droplets. This phenomenon is typically termed oling out on liquid-liquid demixing (Deneau and Steele, 2005). The tradicular of the plantaceutical industry in which the process is controlled by following operating trajectories, typically a temperature profile, can no longer be employed

* Corresponding author at: University College Dublin, Dublin 4, Ireland E-mail address: damian.duffy@ucd.ie (D. Duffy). 0009-2509/\$-see front matter © 2012 Elsevier Ltd. All rights res doi:10.1016/j.ces.2012.01.047

the solution will 'oil out', before undergoing crystallization

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 between the solution concentration and the saturation concentration. The size and shape of the final product crystals are assuably dependent on the superstantarian 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; Zolian, 2009), optical temperature profiles (Feng and Bergland, 2002), anti-solvent addition profiles (Yoo et al., 2009; Zolian, 2009), optical temperature profiles (Feng and Bergland, 2002), anti-solvent addition profiles (Yoo et al., 2007); Zolian, 3009), optimal temperature profiles (Feng and Bergland, 2002), anti-solvent addition profiles (Yoo et al., 2007); Zolian, at hese are extremely high supersaturations meaning there is very little time for crystall growth and controlling particle size and shape is extremely difficult (Kesow et al., 2008); In a typical cooling crystallization, the profiles (Woo et al., 2008); In a typical cooling crystallization, the profiles (Woo et al., 2008); In a typical solution where it desupersaturates towards the solubility curve and undergoes growth when cooled further to the isolation temperature.





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size

optimize product purity

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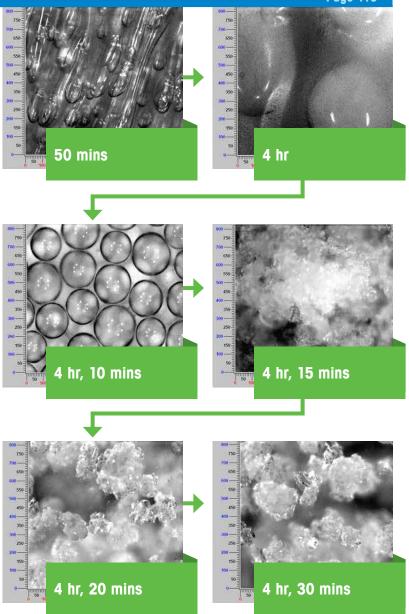
control crystal size

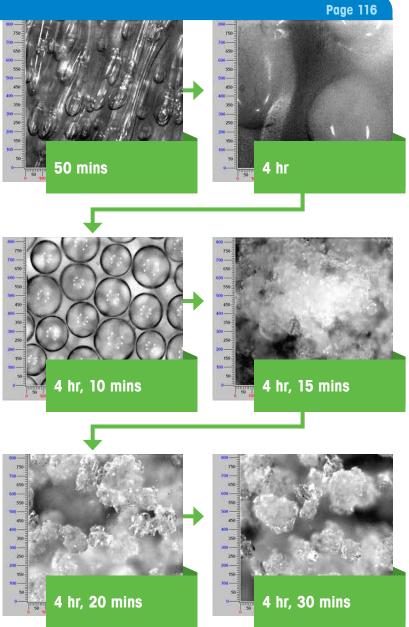
prevent

oiling out

ParticleView for Mechanistic Process Understanding

C PVM [ParticleView] images, from all experiments were used to quantify the effect of different experimental protocols



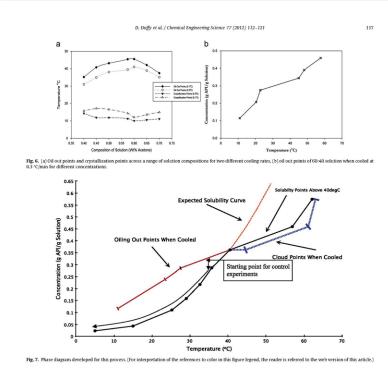




total counts/s and also IR peak height. The peak height is seen to increase for a very brief period of time before decreasing again as nucleation occurs. The very short initial increase in the peak height seen here is believed to be the FTIR detecting the solid phase. The two curves are extremely similar in shape and support the use of both tools as very good instruments for qualitative measurement and process understanding. The peak height decreases to a value of 0.05 A.U. and the FBRM counts/s remain constant at approximately 10.000. The PVM images shown in fig. 5 support this explanation as the oil phase can be seen to be dispersed into solution before rapid nucleation of crystals. Crys-allization was also detected by a very small decrease in reactor temperature due to the exothermic event. What is also very interesting to note is that the crystallization was note is that the crystallization was normally be expected. As such, supersaturation is at an ext high value giving further explanation to the speed at nucleation occurs following the dispersion of the oil layer.

4.2.2. Effect of cooling rate and solvent composition on oil phase formation and subsequent crystallization The effect of cooling rate was investigated on the points at which oiling out was seen to occur and also the point at which the second second second second second second second second second which oiling out was seen to occur and also the point at which the second seco ere dispersed into solution before rapi was investigated across a range of il droplets v ization. This

wn in Fig. 6(a) are the points where these two aspects of



nts at which the second layer was formed. The slower onus at which the second adjet was tormed. The shower grate of Ω^{-1} (rim) was seen to observe the same trend as or standard cooling crystallizations where nucleation is seen ure arditre (Barrett and Glemon, 2002) as opposed to the cooling rate of Ω^{-2} (rim). Cooling large the same figure are the at which dispersion of the oil droplets/crystallization were to occur. The trend is not as distinguishable as that for the out points but it can be seen that there is a still a noticeable oiling out points but it can be seen that there is a still a noticeable difference when crystallization occurs using the two different cooling rates although the change across the compositions is less obvious. Crystallization seems to occur near the isolation tem-perature where supersaturation is extremely high and as such, is quite unpredictable in when it occurs. Shown in Fig. 6(b) is the oiling out points for a solution composition of 60:40 acetone and water (v(v) across a series of concentrations when it is cooled from a saturated solution at 0.3 °C/min. The relationship was found to be approximately linear.

note is that the crystallization perature and not during the

4.3. Investigation of phase diagram and identification of a metastable zone

Shown in Fig. 7 is the phase diagram developed for the process. Again, a solution containing 60:40 (V/V) acetone and water was used and the solubility data up to 33° C was obtained using the method proposed by Barrett and Glennon (2002). The dashed red line indicates the solubility curve that would be expected in a standard cooling crystallization. However, as indicated by j annotation on the figure, the solubility data was found to erratic above 35 °C. Typically, above this point, a transient phase was formed before complete dissolution of the API. Wh solution of the API did occur, the FBRM total counts/ ere seen to be approaching zero and the peak height was s veel off, consistent with the literature. When this occurre as taken as the point of dissolution although it could be al s not a solubility point at all but a point of disper-ned phase diagram reveals that oiling out canno that this is

Featured in this paper:



ParticleView

ParticleView utilizes real time microscopy and image analysis to help scientists understand hidden crystallization mechanisms and solve challenging problems.

C...PVM [ParticleView] allowed the oil region to be better understood. The process was seen to observe five stages,







dissolution,

oiling out,

coalescence of oil droplets,



dispersion

and nucleation.

This led to the selection of a region where controlled seeded crystallizations could be performed and any undesirable separation could be prevented. **J**

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