Tuning process parameters for the heterogeneous nucleation of active pharmaceutical ingredients on excipients

R. Arribas-Bueno, C. M. Crowley, B. K. Hodnett, S. Hudson and P. Davern

Synthesis and Solid State Pharmaceutical Centre,
Department of Chemical Sciences, Materials and Surface Science Institute,
University of Limerick, Limerick, Ireland

For correspondence: Raquel.ArribasBueno@ul.ie

Keywords: heterogeneous nucleation, active pharmaceutical ingredients, excipients, tuning, process, parameters, acetaminophen.

Abstract

It is known that chemical and physical compatibility between a heterosurface and the crystallizing molecule promotes heterogeneous nucleation. In this work acetaminophen (AAP), α/β-Lactose (α/β-Lac) and methanol (MeOH) are selected as the model API, excipient and solvent, respectively. The excipient – suspended in a supersaturated solution of AAP in MeOH – was used as a heterogeneous surface (‘seed’), and parameters influencing the heterogeneous nucleation of the AAP such as (a) AAP solution/excipient contact time, (b) AAP supersaturation, and (c) AAP to excipient loading are tuned to demonstrate how the nucleation rate and degree of crystallization can be manipulated to control the particle size and the balance between nucleation and growth.

1. Influence of contact time on the crystallization of AAP from MeOH solutions in the presence of α/β–Lac

The API/excipient contact time had a pronounced influence on the crystallization of AAP from a supersaturated MeOH solution in the presence of α/β-Lac in terms of the extent of desupersaturation produced (Figure 1). As such, ca. 20% desupersaturation occurred within the first 30 minutes (at $S=1.25$, $T_{cry}=15 \degree C$) when α/β-Lac was present. Thereafter, the % desupersaturation rose to ca. 80% after 2 hours. In contrast, during induction time measurements performed under the same conditions of $S$ and $T_{cry}$ but in the absence of α/β-Lac, crystallization of AAP was not observed for up to 2 hours.

Over time, AAP particles nucleated on the α/β-Lac surface and then grew uniformly producing small AAP particles (<15 µm) in a robust manner such that the particle size distribution (PSD) remained constant over a wide variety of contact times.

2. Influence of supersaturation on the crystallization of AAP from MeOH solutions in the presence of α/β-Lac

The desupersaturation profile (Figure 2) initially rises to a maximum of ca. 89% corresponding to supersaturations in the range 1.4 – 1.5. Beyond this, there is a fall-off in desupersaturation to 67.6% at $S=1.64$. This is likely due to the comparatively larger quantities of α/β-Lac particles required at higher supersaturations resulting in a poorer mixing of these

Figure 1. (a) Desupersaturation of AAP-MeOH solutions in the presence of suspended α/β-Lac: influence of the contact time (hours) on the % desupersaturation (■), and the mean AAP particle size (◊); (b) SEM micrographs of α/β-Lac particles following contact with a supersaturated AAP-MeOH solution for 1.5 h. $S = 1.25$, maximum attainable AAP loading (% w/w) = 26%

Figure 2. Desupersaturation of AAP-MeOH solutions in the presence of suspended α/β-Lac: influence of the supersaturation ($S$) on the % desupersaturation (■), and (b) the mean AAP particle size (◊). Contact time = 2h, maximum attainable AAP loading (% w/w) = 26%
thicker suspensions. Indeed, the driving force provided by higher supersaturations appears to have had only a limited influence on the range of AAP particle sizes obtained. The range remained quite consistent regardless of the supersaturation used, with small particles (< 15 µm) predominating at all supersaturation levels examined. This suggests that the available surface area of α/β-Lac (as defined by the constant maximum attainable AAP loading of 26% w/w at each supersaturation) was sufficient to facilitate an initial surge of heterogeneous nucleation of AAP which thereafter transitioned to crystal growth in a broadly uniform manner during the remainder of the 2 hours.

3. Influence of the maximum attainable AAP loading (% w/w) on the crystallization of AAP from MeOH solutions in the presence of α/β-Lac

![Maximum Attainable AAP Loading](image)

Figure 3. Desupersaturation of AAP-MeOH supersaturated solutions in the presence of suspended α/β-Lac: influence of the maximum attainable AAP loading (% w/w) on the % desupersaturation (■), and (b) the mean AAP particle size (◊). Contact time = 2h, S = 1.25

This study illustrated that a degree of control may be exercised over the particle size of AAP crystals produced via heterogeneous nucleation onto the surface of suspended particles of α/β-Lac. In particular, the crystallization process showed good robustness over quite a broad intermediate range of maximum attainable AAP loadings (from 26 % to 68 %) in terms of the desupersaturations obtained and AAP crystal particle sizes produced. It is observed that at high maximum attainable AAP loadings, larger AAP crystals are formed; this may be due to the relative paucity of excipient surfaces at these high maximum attainable AAP loadings, leading to a reduced number of available nucleation sites, thus encouraging more crystal growth.

4. Conclusions

By varying the API supersaturation, the maximum attainable API loading and the API/excipient contact time for supersaturated solutions and suspended excipients particles, it has been shown that there are optimal ranges for supersaturation and maximum attainable API loading capable of producing consistently small API particles at high levels of desupersaturation. This highlights the importance of tuning process parameters for heterogeneous nucleation in the presence of solid excipient carrier particles.

5. References


Acknowledgments

This publication has emanated from research conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre, funded by Science Foundation Ireland (SFI) under Grant Numbers 12/RC/2275, as well as support from the Bernal Institute and the Department of Chemical Sciences, both at the University of Limerick.