PHARMACEUTICAL CRYSTAL ENGINEERING IN MICROFLUIDIC EMULSIONS

Arpad I. Toldy[1], Abu Zayed Md. Badruddoza[2], Lu Zheng[2], T. Alan Hatton[1,3], Rudiyanto Gunawan[4], Raj Rajagopalan[1,2] and Saif A Khan[1,2*]

[1]Singapore-MIT Alliance, SINGAPORE
[2]National University of Singapore, SINGAPORE
[3]Massachusetts Institute of Technology, USA
[4]ETH Zürich, SWITZERLAND

ABSTRACT

In this paper, we present a crystallization platform that couples capillary microfluidics-based emulsion generation with evaporative crystallization for the production of monodisperse spherical agglomerates of glycine, a model molecule for API crystallization studies. This platform enables us to produce exquisitely uniform spherical agglomerates (SAs) in industrially relevant size ranges. Furthermore, on-line high-speed imaging provides valuable and hitherto unmatched insights into crystallization dynamics within emulsion droplets. We show that our system can be extended to other analogous molecules in a straightforward fashion. We also discuss several crucial aspects of crystallization dynamics that could extend our system's applicability to industrially relevant solutes.

KEYWORDS

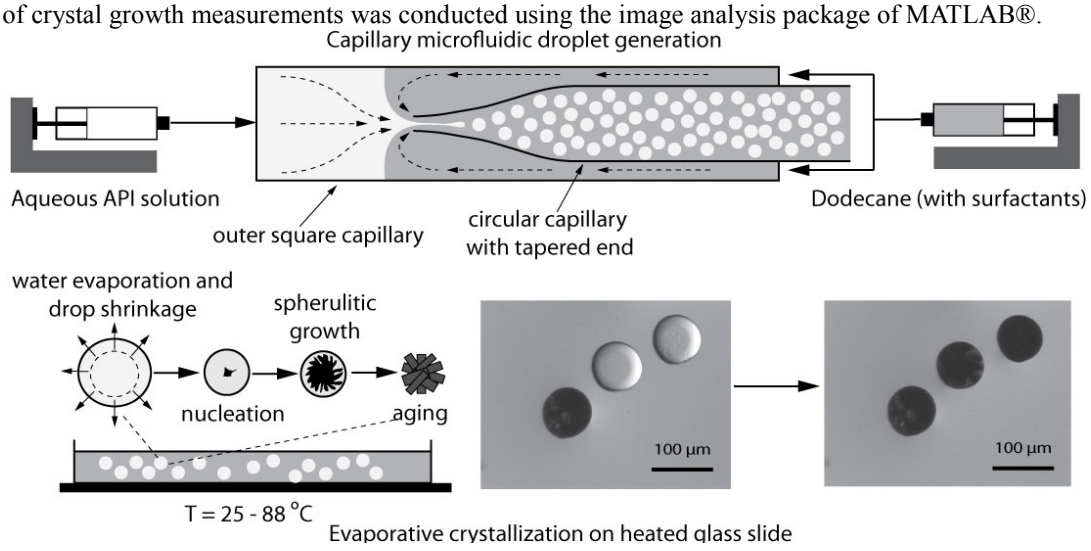
Spherical crystallization, Capillary microfluidics, Pharmaceuticals.

INTRODUCTION

Emulsion-based crystallization to produce spherical crystalline agglomerates (SAs) is an attractive route to control crystal size and morphology during the downstream processing of active pharmaceutical ingredients (APIs) [1-3]. However, conventional methods of emulsification in stirred vessels pose several problems that limit the utility of emulsion-based crystallization, the most important two being the polydispersity of the SAs obtained and the lack of possibility to conduct meaningful on-line observation of the crystallization process. In our recently published study, we use capillary microfluidics coupled with off-chip evaporative crystallization to overcome both these issues: microfluidic droplet generation enables us to achieve unprecedented uniformity of SAs, while on-line stereomicroscopic observation provides valuable insight into the crystallization process [4]. In this study, as an extension to our previous work, we present detailed analyses of the crystallization process on two distinct scales: (i) on the global scale, nucleation probability analysis shows that although it is often assumed that microfluidic droplets can be treated as isolated miniature batch crystallizers [5], this assumption is not necessarily valid for emulsion-based crystallization (ii) on the single SA scale, the distinctly linear growth rate obtained from high-speed imaging suggest that crystal growth within the droplets resembles spherulitic crystallization from melts [6-7]. We analyze how processing conditions influence, and ultimately, set the limits for spherical crystallization from microfluidic emulsions. We also show that our system can be extended to other analogous molecules in a straightforward fashion.

EXPERIMENTAL SECTION

Our experimental setup is shown in Figure 1. Emulsions of saturated glycine or L-alanine solutions in dodecane (loaded with 2% w/w% of a 7:3 mixture of Span-20 and Span-80 [2]) are generated in a common concentric capillary microfluidic device [8]. We use syringe pumps (Harvard PhD 2000) to infuse the two phases at different flow rates in order to control droplet size. These emulsions are then dispensed on heated glass slides maintained at surface temperatures varying from 25 to 88 °C. Crystal nucleation and growth is observed and imaged by high speed cameras (Basler pI640 or Vision Research Phantom EX2) mounted on a microscope (Leica MZ16). Image analysis of crystal growth measurements was conducted using the image analysis package of MATLAB®.



978-0-9798064-5-2/µTAS 2012/$20©12CBMS-0001

Figure 1. Schematic of our experimental setup and the crystallization process. Emulsion generation is performed in concentric microfluidic glass capillaries, where a square capillary (ID=1 mm) houses a tapered round capillary (OD= 1 mm). The two ends of the square capillary function as inlets and the round capillary functions as an outlet. The emulsions thus generated on a heated glass slide, where crystallization occurs. The two micrographs show typical droplets and formed (but un-aged) spherical agglomerates.

RESULTS AND DISCUSSION

Droplet shrinkage is followed by nucleation events within individual droplets. Once a nucleus is formed within a droplet, crystal growth is very rapid (<0.1 s) and occurs linearly along radially advancing fronts at speeds of the order of 1 mm/s, similar to spherulitic crystal growth from impure melts. The spherulitic aggregate thus formed ages to yield the final SA morphology. Overall crystallization times are of the order of minutes, as compared to hours in conventional batch processes [2]. This process enabled us to produce the most uniform SAs reported to date, with narrow, nearly monodisperse size distributions and complete absence of extremes in particle size (Figure 2(a-d)). We have also successfully applied our method to the crystallization of L-alanine - a glycine analogue with an extra methyl group. Extending this method to other pharmaceutically relevant molecules will require selection and optimization of an appropriate emulsion system in which the molecule of interest is strictly localized within the dispersed phase.

CRYSTALLIZATION DYNAMICS: NUCLEATION

By observing arrays of crystallizing droplets on the glass slide via optical microscopy, we could track droplet shrinkage and nucleation over time (a sample set of data is provided in Figure 2(e)). It can be seen that nucleation is preceded by the complete shrinkage of the droplets, and the two phenomena can essentially be decoupled from each other (this can be observed under most conditions used during our experiments). From the nucleation data we estimate the probability of no nucleation within a droplet (P) over time (t). In a conventional crystallizing system this would follow a Poissonian exponential decay ($P(t) = \exp[-t/\tau]$). Interestingly, in our case, the probability of no nucleation observed follows a compressed exponential decay process ($P(t) = \exp[(-t/\tau)^{\beta}]$ under all conditions (a sample set of data is provided in Figure 2 (f)). This suggests that the presence of formed SAs enhances nucleation rate. While changes in crystallization conditions (temperature, droplet size) can change the time constant (τ) and the compressed exponent (β) – for example at higher temperatures crystallization times drop drastically – the general observation holds for all conditions and for both solutes investigated in this study.

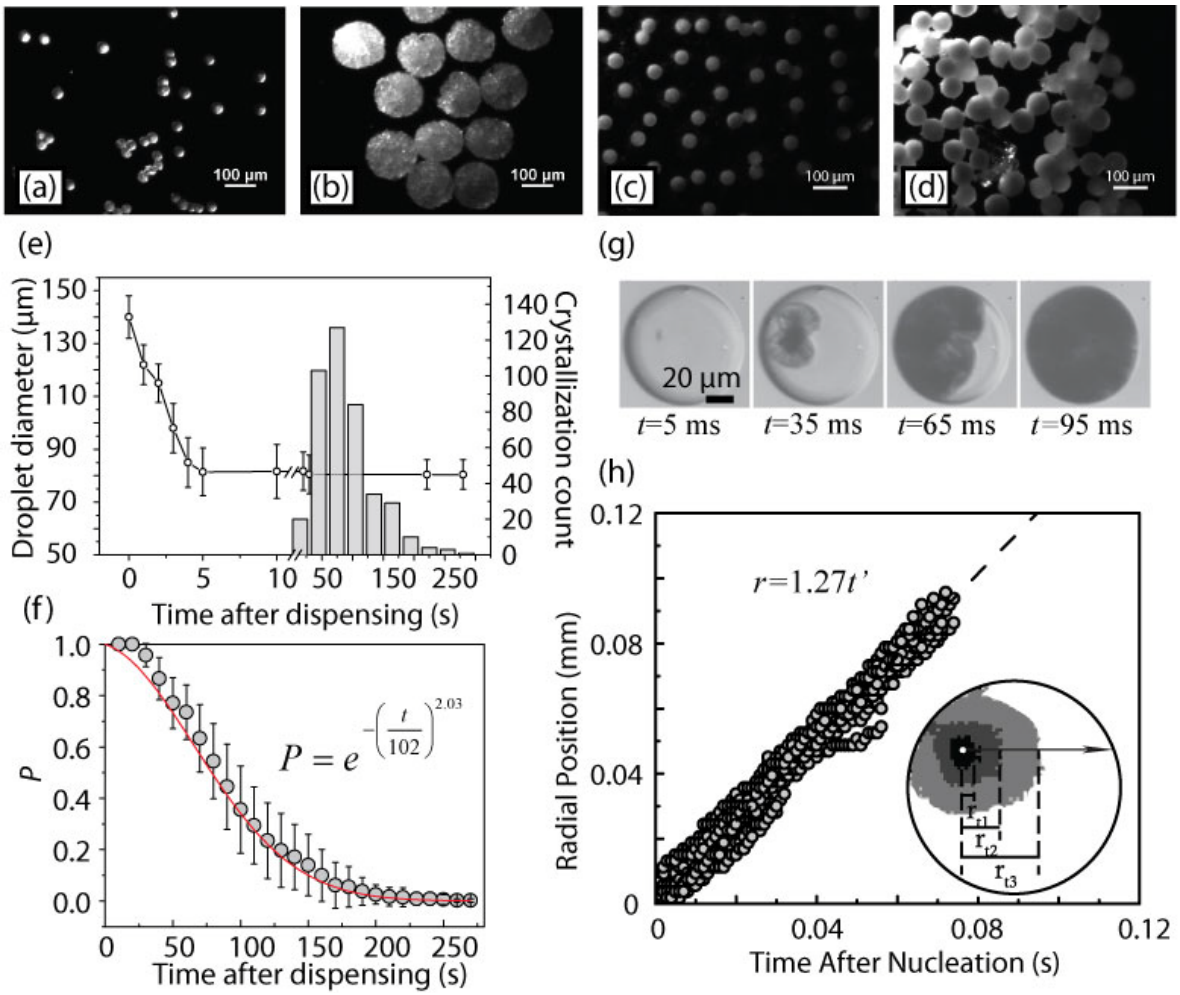


Figure 2: (a-b) uniform SAs of glycine for two representative sizes; (c-d) uniform SAs of L-alanine for two representative sizes; (e) Droplet size vs. time (shrinkage dynamics) with an overlayed histogram indicating nucleation in a population of droplets of ~140 µm of initial size; (f) nucleation statistics for a population of ~80 µm spherical agglomerates: the probability of no nucleation within a droplet vs. time after dispensing on the glass slide. (g) the formation of a ~85 µm SA after the nucleation event (h) crystal growth rate measurement (tracking the distance of the crystal front from the nucleation origin over time) for a 110 µm SA in several growth directions.

CRYSTALLIZATION DYNAMICS: GROWTH

In order to gain insight into the crystal growth mechanism in this system, high speed videos of crystallizing droplets were recorded and analyzed to obtain crystal growth rates in several directions [4]. Figure 2(g) shows an image sequence of a representative forming spherical agglomerate, whereas Figure 2(f) shows representative results for our image analysis process. It has been observed that crystal growth in most cases is linear in all directions, which is a characteristic of spherulitic growth from polymeric or metallic melts under extreme supersaturation conditions [6-7]. This observation also stands for both materials investigated and for most conditions explored, although under some conditions we can observe instances of anisotropic (but still linear) growth, which has also been shown to occur in spherulitic processes [9]. The detailed investigation of spherulitic crystallization in water-in oil emulsions is under way, and is expected to provide guidelines for the design of industrially relevant spherical crystallization processes.

CONCLUSIONS

In conclusion, we present the first microfluidic platform for production of spherical agglomerates of API crystals, with unprecedented uniformity in size. This system also enabled us to gain several valuable insights into the nucleation dynamics and formation mechanism of SAs. We believe that these insights will enable the design of microfluidic emulsion-based crystallization processes for a wide range of APIs. Therefore, the work presented here paves the way for microfluidics-based continuous spherical crystallization processes that could drastically reduce downstream energy costs, thus leading to more sustainable pharmaceutical production and formulation processes.

REFERENCES

[1] Yoshiaki Kawashima et al., *Spherical Crystallization: Direct Spherical Agglomeration of Salicylic Acid Crystals During Crystallization,* Science 216(4), pp. 1127-1128, (1982).

[2] Keith Chadwick et al., *Crystallisation from Water-in-Oil Emulsions As a Route to Spherical Particulates: Glycine and the Hydrochloride Salts of Glutamic Acid and Ephedrine,* Organic Process Research & Development 13(6), pp. 1284-1290, (2009).

[3] M. Nocent et al., *Definition of a Solvent System for Spherical Crystallization of Salbutamol Sulfate by Quasi-Emulsion Solvent Diffusion (QESD) Method,* Journal of Pharmaceutical Sciences 90(10), pp. 1620-1627, (2001).

[4] Arpad I. Toldy et al., *Spherical Crystallization of Glycine from Monodisperse Microfluidic Emulsions,* Crystal Growth & Design Article ASAP, (2012).

[5] Philippe Laval et al., *Microfluidic Droplet Method for Nucleation Kinetics Measurements,* Langmuir 25(3), pp. 1836-1841, (2009).

[6] H. D. Keith and F. J. Padden, *A Phenomenological Theory of Spherulitic Crystallization,* Journal of Applied Physics 34(8), pp. 2409-2421, (1963).

[7] Nigel Goldenfeld, *Theory of Spherulitic Crystallization,* Journal of Crystal Growth 84, pp. 601-609, (1987).

[8] A.S. Utada et al., *Dripping, Jetting, Drops, and Wetting:The Magic of Microfluidics,* MRS Bulletin 32, pp. 702-708, (2007).

[9] László Gránásy et al., *Growth and Form of Spherulites,* Physical Review Letters E 72, pp. 011605-1-15, (2005).

CONTACT

* S. A. Khan, Tel: +65-6516 5133, E-mail: chesakk@nus.edu.sg