International Journal of Pharmaceutical Research and Innovation, Vol. 8, 2015, 8-10

COMPARATIVE STUDY ON THE EVALUATION OF THE GROWTH RATE COEFFICIENT FOR IBUPROFEN IN ETHANOL BY *IN-SITU* PAT AND CONVENTIONAL TECHNIQUES.

Abdur Rashid[1*], Ted White[2], Tony Howes[2], Jim Litster[3] and Ivan Marziano[4]

[1]Department of Pharmaceutics, College of Pharmacy and Dentistry, Buraidah Private Colleges, AL-Qassim, Kingdom of Saudi Arabia.

[2] School of Chemical Engineering, The University of Queensland, Brisbane, QLD - 4072, Australia.

[3] School of Chemical Engineering, Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 479 07-2100, USA.

[4] Chemical Research & Development, Pfizer Worldwide Research and Development, Sandwich, Kent CT13 9 NJ, United Kingdom.

ABSTRACT

The growth rate of ibuprofen crystals in ethanol at 25 (± 0.1)°C was measured in two laboratories by two methods. In one, *in-situ* Process Analytical Techniques (**PAT**) a Mettler Toledo Focused Beam Reflectance Measurement (**FBRM**) particle analyser and a Fourier Transform Infrared Spectroscopy (**FTIR**) unit for concentration measurement were used. In the second, a conventional Malvern laser light scattering sizer and a refractometer for concentration measurement were used. Results from both techniques indicate that the growth kinetics were first order, i.e. **n** = 1 for growth rate $\mathbf{G = k_G s^n}$. For **n** = 1, the **PAT** based method gives $\mathbf{k_G'}$ = 27 (± 8%) µm/min/unit of **I/E** with size taken as a root mean square average chord length. The conventional techniques gave $\mathbf{k_G}$= 13 (± 15%) µm/min/unit of I/E with size now the volume equivalent size. The errors shown are the 95% uncertainty. The reason for the different $\mathbf{k_G}$ values are attributed to differences in the measurement system. FBRM data indicates that the root mean square average chord length / median volume equivalent size ~ 2.0 (± 17%) for ibuprofen crystals, with this ratio generally considered an indicator for aspect ratio.

Keywords: Crystallization, Ibuprofen, Kinetics, **PAT**.

INTRODUCTION

In order to design an isothermal batch crystallizer for producing ibuprofen particles of controlled size, it is necessary to know the crystal growth rates. These were measured in two laboratories by two methods by the same investigator. The results are compared here.

METHODOLOGY AND RESULTS

The growth kinetics of the pharmaceutical ibuprofen [2-(4-isobutyl-phenyl)-propionic acid] crystallizing from ethanol (Figure 1) were determined by conventional batch crystallization means at The University of Queensland [1]. During a batch, solution supersaturations were determined by refractive index and the crystal size distribution by a Malvern MasterSizer/E. The Malvern reports size as the volume equivalent size. Ibuprofen was found to show **GRD** (growth rate dispersion), hence the size was characterised by the volume median size **L**. The growth rate is described as **G = dL/dt** where **t** is time. This may be correlated against the operating supersaturation (expressed as **s** = **ΔI/E = I/E – I*/E**, where **I** and **E** are the masses of ibuprofen and ethanol and **I*/E** is the solubility value). A special fitting routine [2] was used to evaluate the results. The results showed (Figure 2and3) that the growth kinetics were first order, i.e. $\mathbf{G = k_G\, s}$, where $\mathbf{k_G}$ is the growth rate coefficient. At 25 ^{o}C, $\mathbf{k_G}$ (with 95% error) was found to be 13 (± 15%) µm/m in/unit of I/E [1].

Corresponding author:

***Email:** rashid.uq@gmail.com*

The opportunity arose to repeat the measurements using a **PAT** (Process Analytical Techniques) crystallization unit at Pfizer laboratories, Sandwich, UK. Supersaturations were measured using **FTIR** (Fourier Transform Infrared Spectroscopy), which was calibrated for ibuprofen in ethanol. Need to describe calibration procedure or reference a paper which does. Chord sizechanges were monitored using a Mettler Toledo **FBRM** (Focused Beam Reflectance Measurement). This instrument measures the distribution of chord lengths encountered by a revolving laser spot. The root mean square average chord length was taken as a characteristic measure and it was assumed that this measure was related to mean crystal size. The **FTIR** supersaturations and the **FBRM** root mean square chord lengths for one trial are shown in Figures 4 and 5. The fitting routine was again used to find the crystal growth kinetics as **G'** = $\mathbf{k_G'}$ **s** for which $\mathbf{k_G'}$ at 25 °C was 27 (± 8%) (chord measure in µm) /min/unit of I/E. Including replicates, the average ratio $\mathbf{k_G'}$ **/** $\mathbf{k_G}$was determined as ~ 2.0 (± 17%). This suggests that the root mean square average chord length is twice the volume median size (with size as the volume equivalent size) of the ibuprofen crystals.

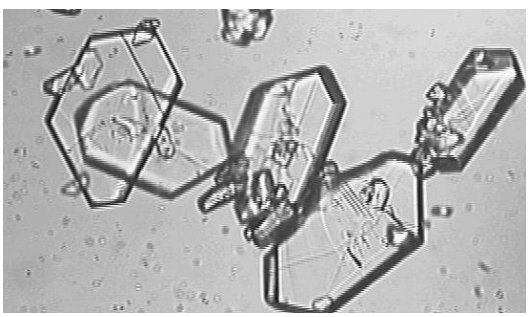

Figure 1: Ibuprofen crystals grown from ethanol.

CHORD SIZE MEASUREMENT VS. PARTICLE SIZE MEASUREMENT

The **FBRM** measure is very convenient, simple and *in situ*. There is considerable interest in relating the **FBRM** output to conventional measures of size, especially for crystals. Algorithmshave been described (e.g [3]) which first generates the resulting chord length distribution for a single randomly oriented non-rentrant crystal of a given size and shape. This is then used to generate the particle size distribution for an assemlage of particles given the measured chord length distribution. The calculation is much easier if all

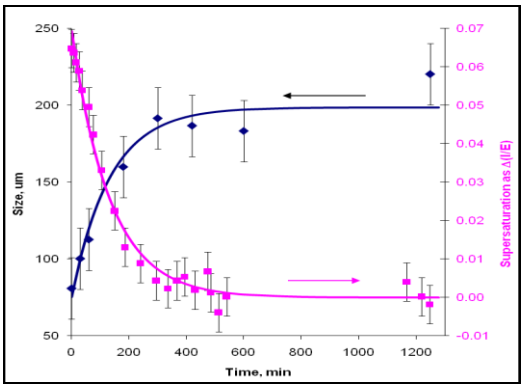

Figure 2: Particle size and supersaturation as function of time for ibuprofen crystallization at 25 °C.

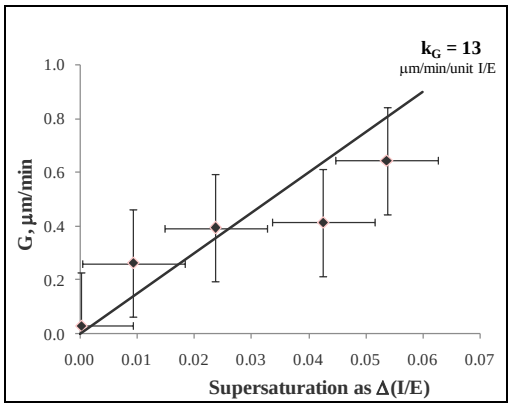

Figure 3: Growth rate plotted as a functionof supersaturation s [as Δ(I/E)]

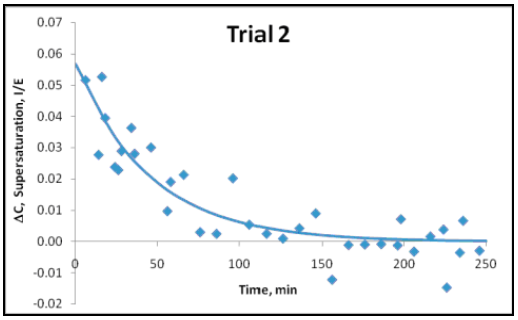

Figure 4: Supersaturations from FTIR for trial 2.

particles have the same shape. However, in realist the relationship between chord size and particle size is complex, and depending to a large extent on the aspect ratio of the particles. For this reason, establishing a correlation between chord size and

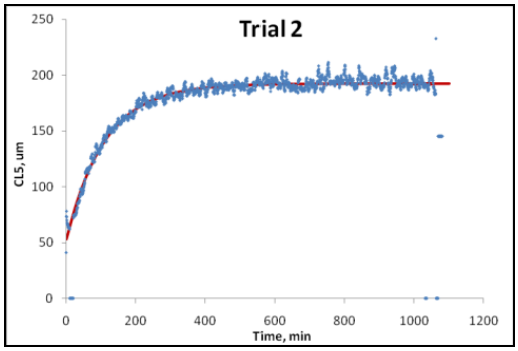

Figure 5: Root mean square chord lengths for trial2.

particle size measurements remains a fertile area in particle research, see for instance [4].

CONCLUSIONS

Comparison of the growth kinetics for ibuprofen from ethanol suggest that the root mean square average chord length (from the FBRM) is about twice the volume median size (with size as the volume equivalent size) from conventional laser diffraction-based particle sizing.

ACKNOWLEDGEMENTS

The authors would like to thank Pfizer Global Research and Development(PGRD), UK for financial support.

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