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DEVELOPMENT OF PARTICLE SIZING METHOD OF IBUPROFEN CRYSTALS USING MALVERN MASTERSIZER LASER LIGHT SCATTERING TECHNIQUE

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ABSTRACT

During a study of the crystallization of the drug ibuprofen from ethanolic solutions, it was necessary to measure crystal size distributions. Ibuprofen is hydrophobic and shows a marked tendency to aggregate in contact with water, a possible suspending liquid. Further the ibuprofen crystals are plate shaped and are easily broken. A surfactant can be used to "wet" the ibuprofen crystals and reduce aggregation. With the liquid cell in the Malvern® laser light scattering sizer, there is agitation and ultrasound can be used. This paper describes experimental results to determine the extent of de-aggregation and breakage of crystals by agitation and ultrasound in the sizing. Ultrasound gives very rapid breakage of the crystals while the agitation gives only minor breakage.

Key words: Ibuprofen, Crystal size distribution, Hydrophobic, Plate shaped.

INTRODUCTION

A study was undertaken into the crystallization kinetics of the drug ibuprofen [2-(4-isobutyl-phenyl) propionic acid] from ethanolic solutions (Rashid, 2011). This involved measuring the solution supersaturations and the crystal sizes during an isothermal non-nucleating seeded batch crystallization. The real time solution supersaturation was measured directly using a refractometer. The most convenient technique for crystal size distribution measurement is laser light scattering and a Malvern® instrument (MasterSizer 2000) was used for this study. The aim of this paper is to discuss the development of a procedure for reproducible size measurements using the Malvern®.

Selection of suspending liquid

A suspending liquid was sought to suspend the ibuprofen crystals in the Malvern sizer. Ibuprofen is insoluble in water but very soluble in ethanol (Gracin & Rasmuson, 2002; Garzon & Martinez, 2004; Rashid et al., 2014). With laser light scattering using a suspending liquid, very low particle contents (typically ~ 100 ppm) are used to avoid secondary scattering. If the particle material has a high solubility in the saturated suspending fluid, it is susceptible to temperature changes. E.g. if ethanol saturated with ibuprofen were used as the suspending fluid a very small temperature rise (~ 0.001°C) would be sufficient to dissolve all the particles. The temperature of the suspension cell can rise due to suspension cell mixing and the cell

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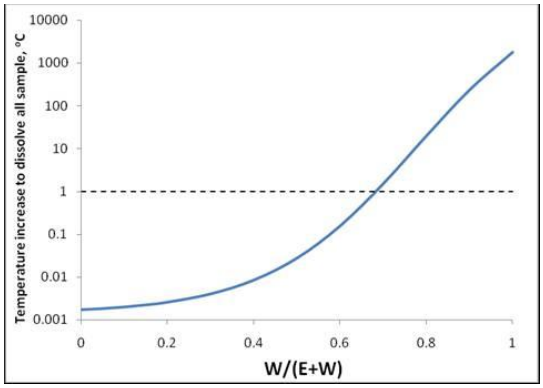

Figure 1: Predicted temperature rise to dissolve 100 ppm ibuprofen suspended in saturated aqueous ethanol at 1 atma pressure. The horizontal dotted line corresponds to 1°C rise. The horizontal scale is the mass fraction water in the ibuprofen free aqueous solvent.

being in an uncontrolled temperature enclosure close to electronics. Figure 1 shows the predicted temperature rise sufficient to dissolve 100 ppm of ibuprofen in various saturated aqueous ethanolic solutions. The calculations are based on solubility data (Rashid *et al.*, 2014). This shows that high ethanol (low water) content aqueous mixtures are not suitable as a suspending liquid.

To use aqueous ethanol as the suspending liquid, the solvent must contain > 80% water by wt. to prevent serious loss of crystal (and smaller sizes) in the Malvern cell due to temperature fluctuations.

Water could be considered as the suspending liquid, but there is a further problem. Ibuprofen is hydrophobic and crystals prefer to stick to other ibuprofen crystals rather than be wetted by water. Thus adding ibuprofen crystals to water gives aggregates rather than the well dispersed particles necessary for sizing.

Figure 2 illustrates the results of adding ibuprofen crystals to saturated aqueous ethanol solutions with high water contents. For water contents ≤ 88 wt % the crystals are well dispersed. Above that water content, the crystals are not wetted and form aggregates. Thus to use aqueous ethanol as the suspending fluid the water content of the solvent should lie between 80 and 88 %. This is a very restrictive range.

Detergent and agitation

To reduce aggregation a detergent could be added to the aqueous solution. This might coat the ibuprofen crystals and make them more liable to be wet by water. A domestic household detergent (Morning Fresh, Cussons, Australia), which is described as a detergent blend (Morning Fresh, 2010) was used and found to be quite effective. Ibuprofen was well dispersed in water with the addition of a few drops of detergent.

Also agitation or ultrasound addition would minimize aggregation. The Malvern must use agitation to keep the crystals suspended and ultrasound is optionally available for particle dispersion. But there is a further problem. The ibuprofen crystals are thin flat plates in shape and are prone to breakage. Ultrasound or agitation may break crystals altering the size distribution.

For simplicity it was decided to use tap water with the addition of detergent as the suspending liquid. The aim of the investigation here is to determine,

- The quantity of detergent to be added,
- The effect of suspension cell agitation on crystal breakage and
- The effect of ultrasound on crystal breakage.

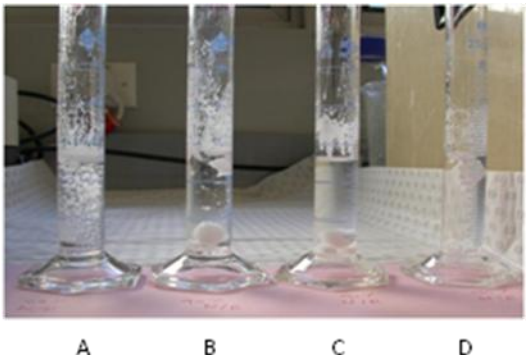

Figure 2: Ibuprofen crystals added to saturated aqueous ethanol solutions. A: 88% w/w water - ethanol, B: 90% water – ethanol, C: 92% water-ethanol, D: 95% water - ethanol. Ignore the upper white layers which are crystals adhering to the glass above the liquid level. Aggregates are clearly seen at the bottom of B, C and D.

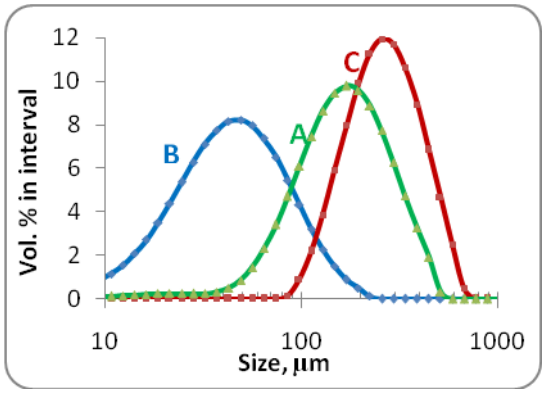

Figure 3: Malvern size distributions of three test samples A, B and C.

EXPERIMENTAL

All measurements were made using a Malvern MasterSizer 2000 (Malvern®, UK) with 0.5 L of water (with detergent) in a 0.6 L suspension beaker. The stirrer speed was 2000 rpm, which was adequate to give good suspension of the crystals to an apparent uniform concentration. Once the instrument was zeroed, sufficient crystal sample was added to the beaker to give the required light obscuration. It took

a minute or so for the particles to be fully wetted and dispersed. Measurements were taken at various times after sample addition.

The ibuprofen crystal samples were dried final products produced by batch crystallization growth studies (Rashid, 2011). Rashid (2014) also shows a micrograph of typical crystals. The materials are identified as samples **A**, **B** and **C**. Figure 3 shows their size distributions, as determined subsequently by the preferred sizing procedure. In discussion in this paper, the material size will be indicated by the volume median size of the distribution, D[v,0.5]. The relative spreads did not alter much in the sizing tests.

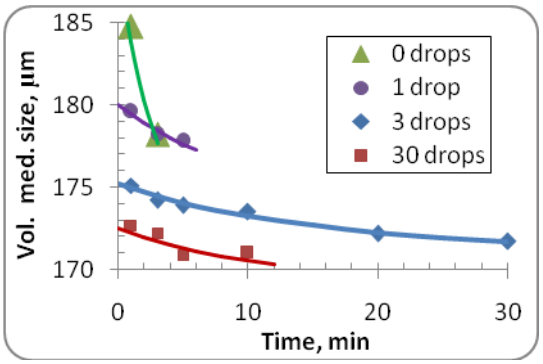

Figure 4: Effect of detergent addition on measured volume median size for sample A.

Amount of detergent

Figure 4 shows the effect on the measured median size of the amount of detergent added to 0.5L of water with sample **A**. With no detergent and with 1 drop (~ 0.05 ml) of detergent the cell agitation was insufficient to disperse all of the sample for sizing) and un-wetted crystals still remained on the surface after 1 minute. Three drops of detergent (to 0.5 L; ~ 300 ppm) proved adequate. The three drop results have been followed through to 30 minutes in the instrument, but sizings are usually completed after but a few minutes. Over 30 minutes with three drops the volume median size drops by 3.6 µm, which is acceptable. So detergent addition with at least 300 ppm of detergent will be adopted hereafter.

Effect of ultrasound and agitation

The Malvern instrument allows ultrasound (nominal intensity range from 0 to 20) to be used to disperse particles in suspension. Figure 5 shows the result of tests with sample **A** with different levels of ultrasound on the measured median size. The upper

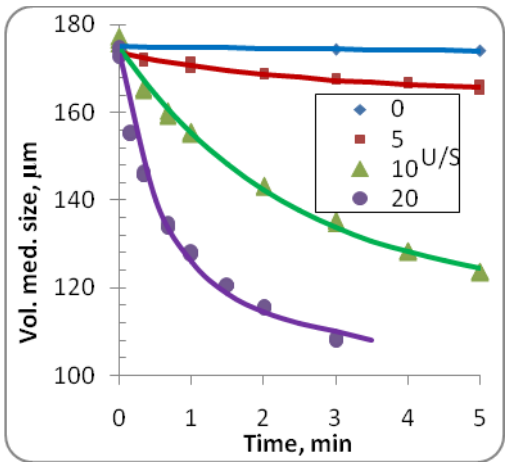

Figure 5: Effect of ultrasound level on measured median size for sample A. Ultrasound U/S = 0 is agitation alone.

line (no ultrasound; agitation only) is that shown on Figure 4. Note the change in time and size scales. Ultrasound at any level obviously breaks the crystals and is unacceptable.

To quantify the effect of ultrasound, the estimated decreases in size in the first 10 seconds have been evaluated and are shown in Table 1 for sample **A** and later samples.

Other samples

The results in Figure 5 are for one sample (**A**). To check if the effects are similar for other samples, a finer sample (**B**) and a coarser sample (**C**) were tested. The results corresponding to Figure 5 are shown as Figures 6 and 7. The size decreases in the first 10 seconds are given in Table 1. The effect of ultrasound at level 20 is similar. Figure 7 shows a repeat test for an ultrasound level of 20 and there is good repeatability. It is desirable to have a sizing procedure that changes size by less than 1 percent

Table 1: Decrease in size in first 10s for various ultrasound conditions.

Sample	Size, µm	U/S level	Decr. in size, µm
A	175	0	0.1
		5	0.8
		10	5.7
		20	18.0
B	49	0	0.05
		20	9.8
C	255	0	0.26
		20	22.2

over say 3 minutes and thus any use of ultrasound is undesirable. The effect of cell agitation (No U/S) is small but acceptable.

As a final demonstration of the effects of agitation and ultrasound on ibuprofen crystal breakage, Figure 8 shows for sample **A** and an extended sizing period, the intermittent use of ultrasound at level 20 followed by no ultrasound. The sharp decrease in median size with ultrasound and generally the minor change in size with no ultrasound is clear.

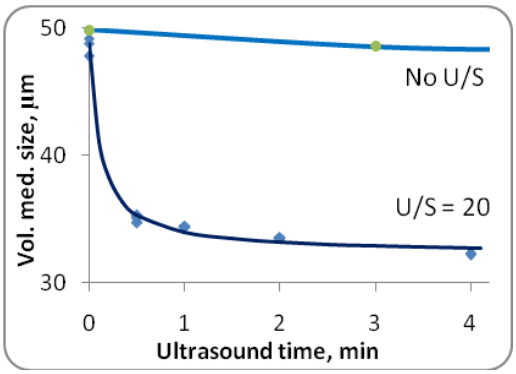

Figure 6: Effect of ultrasound level on measured median size for sample B.

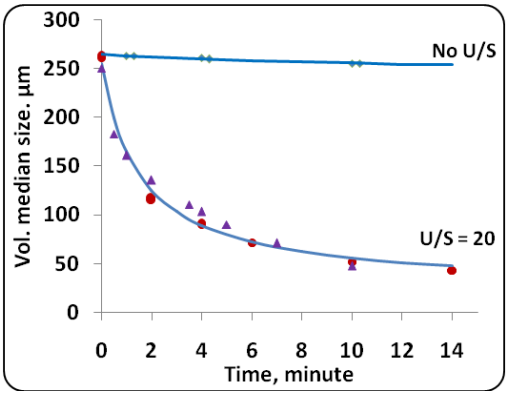

Figure 7. Effect of ultrasound level on measured median size for sample C.

Selected sizing procedure

Based on the above results, the procedure adopted for sizing ibuprofen crystals was,

i) to use water as the suspension liquid with at least 300 ppm of household detergent,
ii) to agitate at 2000 rpm and
iii) not to use ultrasound.

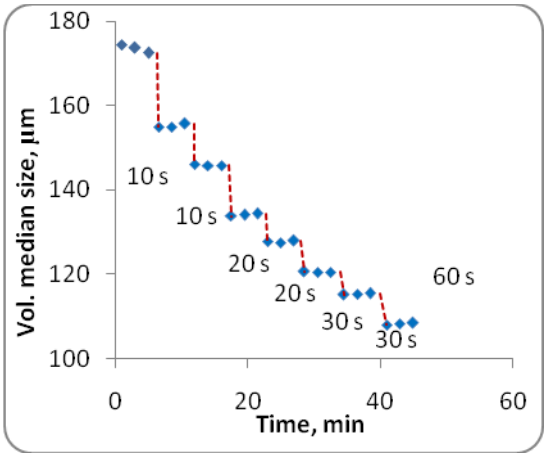

Figure 8: Effect of intermittent ultrasound use (at level 20) for sizing sample A.

This procedure worked satisfactorily for sizings for the growth rate studies (Rashid *et al.*, 2011).

CONCLUSIONS

Sizing ibuprofen crystals must overcome three problems, ibuprofen is highly soluble in most non-aqueous solvents, the crystals aggregate in water and they are prone to breakage.

Experiments have been described to assess the effects of these problems.

Based on these measurements, a sizing procedure using water with > 300 ppm of detergent and no ultrasound was adopted and found satisfactory.

ACKNOWLEDGEMENT

The authors thank Pfizer Ltd., United Kingdom for financial support for the overall project.

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