# The crystallization of sulphadiazine by the solvent change method in turbulent conditions

Crystallization of organic compounds, by the solvent change method, has been examined by Packter (1959), Elworthy & Worthington (1971) and Riley (1972). The process of crystallization is critical in the preparation of powders with specific physical properties. This letter reports an extension of the work of Elworthy & Worthington (1971) to the crystallization of sulphadiazine by the solvent change method using a Silverson mixer to give agitation during a batch crystallization.

The sulphadiazine was added to water (1 litre) as a solution in dimethylformamide at 20° ± 1° using a controlled flow injector syringe. The Silverson mixer was used at 10 or 41 rev $s^{-1}$; the solutions of sulphadiazine (3, 9 or 15% w/v) were added below the surface at 0·38 or 12·9 $cm^3$ $min^{-1}$. After injection, the suspension which resulted was stirred gently for 60 min using a magnetic stirrer. The crystals were collected on a 0·22 μm Millipore filter, washed with water, dried and their particle size distribution determined microscopically.

The acicular crystals (length: breadth, 6:1) were assigned to size classes on the basis of their length. The mean particle length was calculated as $d_L = \Sigma nd/\Sigma n$, where d is the mean of the class length limits and n is the number of crystals in that class; for the smallest crystals, those below 0·7 μm, the mean size was assumed to be 0·48 μm.

Preliminary experiments showed that no change in crystal size distribution occurred between 30 min and 180 min after solution addition was complete.

There are several possible variables and so a series of crystallizations was carried out using two levels of theoretical supersaturation (Elworthy & Worthington, 1971) and the agitation rates, injection rates and concentrations of sulphadiazine solutions specified above. The results obtained are listed in Table 1.

A multiple regression analysis indicated that only a combination of agitation rate with solution concentration produced a significant effect on particle size. The results obtained at the lower level of supersaturation (5·5) were less clear cut than those produced with a theoretical supersaturation of 16·5. This is probably due to the fact that a supersaturation of 5·5 is close to the supersaturation at which nucleation is initiated in a solution (Strickland-Constable, 1968). Crystallizations were also carried out to determine the effect of changing the total volume of sulphadiazine solution

Table 1. *Results of particle size analyses carried out on batches of sulphadiazine crystals produced using the specified conditions.*

| Mean length of crystals produced using the specified conditions (μm) | | | | | | | |
|---|---|---|---|---|---|---|---|
| with sulphadiazine concentration % w/v | | | | | | | |
| 3 | | 9 | | 15 | | | |
| And agitation rate rev $s^{-1}$ | | | | | | | |
| 10 | 41 | 10 | 41 | 10 | 41 | Injection rate $cm^3$ $min^{-1}$ | Theoretical supersaturation |
| 5·1 | 5·7 | 6·8 | 6·2 | 4·0 | 7·0 | 0·38 | 5·5 |
| 6·2 | 5·2 | 3·4 | 4·0 | 4·1 | 6·0 | 12·9 | |
| 8·0 | 6·2 | 7·0 | 8·0 | 5·2 | 7·6 | 0·38 | 16·5 |
| 9·9 | 6·2 | 4·3 | 6·8 | 3·1 | 7·5 | 12·9 | |

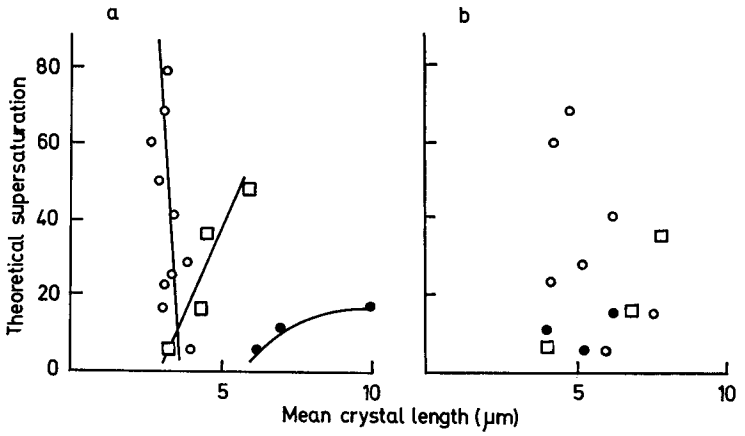


FIG. 1. Plots to show mean particle length of crystals obtained for different degrees of theoretical supersaturation. 1 (a) agitation 10 rev $s^{-1}$ 1 (b) agitation 41 rev $s^{-1}$. Sulphadiazine solutions, ○ 15%; □ 9%; ● 3% w/v.

added. The results obtained are summarized in Fig. 1a and b, for agitation rates of 10 and 41 rev $s^{-1}$ respectively.

These two plots illustrate two important points. Firstly, the results obtained in the more turbulent conditions are scattered, whereas those obtained at the lower agitation rate show definite trends. Secondly, using the 9 and 15% solutions the mean particle size obtained is greater under conditions of greater turbulence. With a concentrated (15% w/w – 83% saturated) solution of sulphadiazine nucleation occurs during the initial solvent mixing; before the total amount of drug added reaches the level required to saturate the total mixed solvents. Thus using 15% w/v solution nucleation occurs during the whole of the solution addition, whereas, with the 3% solution mixing precedes visible crystal growth. We therefore see that the total volume of solution added makes only a minor difference to the product size using the 15% sulphadiazine solution. Using the 3% and to a lesser extent the 9% solution of sulphadiazine the final product size increases with increase in the total volume of sulphadiazine solution added. This is clearly seen using the lower agitation rate. At the higher rate of agitation greater turbulence will mean faster mixing, more collision nucleation and some heating in the region of the mixer head. The combination of these factors gives the scattered results in Fig. 1 (b).

Thus, if one wishes to prepare crystals of a given size the agitation rate can be raised to a level where this is not possible. Also, in conditions of lesser turbulence the final product size of sulphadiazine crystals can be controlled by choice of the concentration and the total volume of solution used.

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March 28, 1973

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