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The particle-size of sulphadiazine produced by a solvent-change method

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The factors affecting the particle-size of sulphadiazine produced by a solvent-change method of crystallization have been studied. The most important variables appear to be the degree of turbulence in the pipeline mixer used for the crystallization process, and the concentration of drug in the dimethylformamide injection solution. Mechanisms which can account for these, and other features of this crystallization method, are presented.

The *in vivo* absorption of a number of drugs is limited by their dissolution rate and with such materials reduction in particle-size can result in improved physiological availability (Fincher, 1968). Of the various methods used to obtain drugs in fine-particle form, the application of controlled crystallization brought about by solvent-change, has already been described (U.S. Patent Number 2,908,612, 1959; Lees, 1969). Factors affecting the particle-size of crystals produced by such methods, however, have received little attention and the report of Packter (1959), working with mechanically stirred solutions, appears to be the only one giving results for the crystallization of organic compounds. The solvent-change method has been adapted industrially as described in British Patent Number 899,667 (1962) for the production of fine-particle griseofulvin. In this case the mixing of solvent and non-solvent is carried out in a pipeline mixer and the process is termed "line-mixing". The present investigation reports studies on the factors affecting the particle-size of sulphadiazine produced by injection of a solution in dimethylformamide (DMF) into water flowing through a pipeline mixer.

MATERIALS AND METHODS

Materials. The sulphadiazine used was B.P. quality. Dimethylformamide was distilled under reduced pressure and gave $n_{25}^{D} = 1{\cdot}4283$ ($n_{25}^{D} = 1{\cdot}4294$, Dawson, Golben & others, 1952 and $n_{25}^{D} = 1{\cdot}4269$ Ruhoff & Reid, 1937). The water used in the pipeline mixer was deionized by passage through a mixed-bed ion-exchanger.

Apparatus

The apparatus (Fig. 1) consisted of a device giving a constant flow rate of water, a mixing tube and a means of injecting a solution of sulphadiazine in DMF, into the water flowing along the tube.

The constant-head device was a reservoir fitted with overflow and replenishment tubes, the latter carrying deionized water pumped from a bulk tank. Flow from the reservoir to the mixer was controlled by a tap fitted at the reservoir base.

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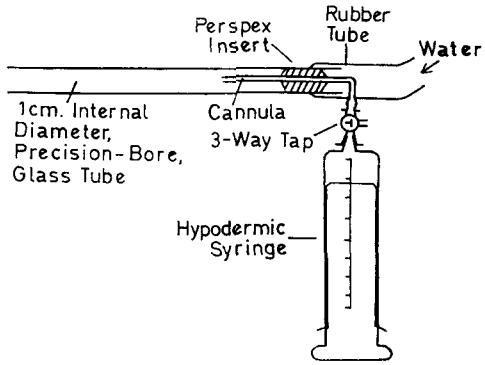

FIG. 1. Diagram of the pipeline mixer.

The mixing tube was 1 cm internal diameter, precision-bore, Pyrex glass tubing. The tubing was supported by brass angle-pieces secured to a movable horizontal beam which allowed the tube to be moved when the reservoir was raised or lowered. The beam was on a slide which was adjustable so that the tube was maintained horizontal. The tube assembly used for crystallization experiments made under turbulent flow conditions measured 193 cm in length from the position of the injector needle tip. That used for non-turbulent flow was 444 cm long.

The injector unit comprised a hypodermic syringe held in a Tufnol cradle, fitted with a screw drive propelled by a constant speed motor. The motor speed was controlled through a 50 KΩ helical wire-wound potentiometer fitted with a multi-turn indicating dial. The syringe was connected by way of a three-way tap to a cannula, which was bent to allow insertion into the inside of the mixing tube. The cannula had an internal diameter of 1·13 mm, and the portion within the tube was 13·5 cm long, measured from the point of entry, which was by puncture of the rubber tubing joining the mixing tube to the reservoir. The cannula was located centrally in the mixing tube by means of a small Perspex insert.

In operation, the water flow down the mixing tube was first established and this was followed by simultaneously operating the three-way tap (previously closed to prevent access of water to the syringe) and the syringe drive, to inject drug (sulphadiazine) solution into the mixing tube. The water flow rate was calibrated by collecting and measuring volumes issuing from the mixer over timed intervals. Calibration of injector flow rates was by weighing quantities of solutions collected over timed intervals, direct from the cannula which was withdrawn fom the mixing tube. The weights were converted to volumes using the density figures:—

% w/v sulphadiazine in DMF	3	5	6	7·5	9	10	12	15
Density (g/cm³) ..	0·9599	0·9672	0·9709	0·9763	0·9821	0·9856	0·9930	1·0036

Syringe flow-rate calibrations were made in duplicate over a range of potentiometer dial settings using 3, 6, 9, 12 and 15% w/v sulphadiazine in DMF solutions. The figures obtained showed a maximum variation about the mean of approximately 3% for a given dial setting, using different sulphadiazine concentrations, and the variation occurred randomly. Viscosity differences of the solutions did not appear to effect the flow rates.

To check that injector flow rates were not significantly modified when the cannula was positioned in the water stream of the crystallizer, a volume of mixed liquids was collected over a timed interval. The sulphadiazine concentration in the mixture was determined by dissolving the precipitated drug in a suitable volume of DMF and assaying an appropriately diluted sample spectrophotometrically. The calculated value for injector flow rate was in good agreement with that given by the calibration method described.

Collection and treatment of samples

Crystals were examined microscopically soon after collection from the mixer, 1 h after mixing and at later times. Except for cases of very low supersaturation arising from solutions of low concentration being injected, no significant change in the particle-size of crystalline suspensions obtained from the mixer occurred subsequent to storage for 1 h. Assays performed on suspension filtrates (passing an 0·2 μm membrane filter) at similar times indicated crystallization to be virtually complete after 1 h. Except where indicated, all crystal samples were obtained from slurries stored for 1 h before the commencement of filtration. Production and storage of slurries was at 20°.

Crystals were collected on 0·2 μm membrane filters using vacuum. This pore-size filter was chosen so that all particles, down to at least those just visible under the microscope (about 0·2 μm when using white light, Edmundson, 1967) would be retained. After washing with a small amount of water, the samples were sucked as dry as possible, and drying completed at 40° in a vacuum, over phosphorus pentoxide.

Particle-size measurement

The particle-size of crystalline products has been evaluated by a microscope method and by an air-permeability method. Because of the pronounced anisometry of the sulphadiazine crystals it was not possible to use the microscope method (British Standard 3406: Part 4: 1963) to obtain an estimate of the projected area of particles. Instead, the eyepiece graticule was used to size particles in terms of their length. Due to the hydrophobic nature of the drug, and the need to use a mountant of reasonable viscosity to prevent Brownian movement of fine particles, samples were suspended in light liquid paraffin containing 3% Span 80 (Honeywill-Atlas Ltd.). Sizing was carried out in other respects in accordance with the British Standard method: a minimum count of 1000 particles was made for each sample, with adjustment of the suspension concentration so that not less than 96 fields were counted for the most frequently occurring particle-size. The results have been used to give cumulative number-percent undersize-frequency curves and the arithmetic length-number mean, d_{ln} ($= \Sigma nd/\Sigma n$).

Surface area measurements were made on the crystalline samples using the Rigden air permeability method (Rigden, 1943) to the results of which a slip-flow correction was applied (Rigden, 1947). The Rigden apparatus was modified by use of an accurately machined powder cell allowing formation of plugs from 50 mg samples. Plugs, compressed to a porosity of 0·5, were prepared by applying even pressure on both plungers simultaneously, a process found to give the most reproducible results. Calculations were based on a density of sulphadiazine of 1·505, measured using a 50 ml density bottle.

Calculation of the theoretical degree of supersaturation

The theoretical degree of supersaturation, with reference to sulphadiazine, of pipeline mixtures after complete mixing was calculated as the ratio C'/C_S, where C' is the total concentration of sulphadiazine present and C_S is the equilibrium solubility of sulphadiazine in the pipeline solvent mixture. Values of C_S for solvent compositions in deionized water at 20° are:—

DMF (% v/v)	0	0·25	0·5	0·75	1·0
Sulphadiazine (% w/w) ..	0·00455	0·00475	0·00488	0·00510	0·00525

Values for intermediate solvent compositions were obtained by graphical interpolation.

RESULTS AND DISCUSSION

Crystallization conditions and particle-size data for water flow rates, of 6200, 3100, and 620 ml/min are given in Tables 1–3. The first part of the reference number used to identify each sample indicated the % w/v of sulphadiazine in the DMF solution injected.

Table 1. *Crystallization conditions and particle-size data.* Water flow 6200 ml min^{-1}.

Reference number*	Drug solution flow (ml min^{-1})	Theoretical degree of supersaturation,† SS	d_{1n}, μm, from microscope	Specific surface area from air permeability method $m^2\ g^{-1}$
15/1	4·3	2·27	$0·7_5$	insufficient sample
15/2	8·6	4·48	$0·9_1$	12·7
15/3	17·2	8·78	$0·9_1$	12·2
15/4	25·0	12·60	1·0	10·8
12/1	5·4	2·27	0·9	insufficient sample
12/2	7·7	3·22	1·0	10·3
12/3	10·8	4·48	1·2	8·9
12/4	15·4	6·32	1·2	9·5
12/5	21·6	8·73	1·2	9·6
12/6	25·0	10·00	1·5	8·7
9/1	7·7	2·41	2·0	6·4
9/2	10·8	3·36	2·5	6·3
9/3	15·4	4·74	3·0	5·7
9/4	21·6	6·55	3·4	5·6
9/5	25·0	7·52	3·3	5·6
6/1	10·8	2·24	4·1	insufficient sample
6/2	13·6	2·79	7·0	1·7
6/3	15·4	3·15	7·6	1·9
6/4	19·1	3·88	7·4	1·8
6/5	21·6	4·36	8·3	1·4
6/6	25·0	5·00	8·5	1·3
3/1	15·4	1·57		
3/2	21·6	2·18		See footnote†
3/3	25·0	2·50		

* The first part of the reference number is the % w/v of sulphadiazine in the injection solution.

† $SS = \dfrac{\text{Weight of sulphadiazine contained in 100 ml pipeline mixture before crystallization}}{\text{equilibrium saturation solubility of sulphadiazine in pipeline mixed solvent}}$

‡ Crystals collected after 24 h storage at 20° in case of sample 3/3. No crystals visible in 3/1 and 3/2 after 24 h storage.

The data, together with previously published information on the solubility of sulphadiazine in mixtures of water and DMF (Elworthy & Worthington, 1968), have been used to interpret the effects of turbulence and other factors on the particle-size of sulphadiazine produced by solvent change.

Table 2. *Crystallization conditions and particle-size data.* Water flow 3100 ml min^{-1}.

Reference number*	Drug solution flow (ml min^{-1})	Theoretical degree of supersaturation,† SS	d_{ln}, μm, from microscope	Specific surface area from air permeability method (m^2 g^{-1})
15/5	2·15	2·27	$0{\cdot}9_5$	10·5
15/6	4·3	4·51	$0{\cdot}9_5$	11·7
15/7	8·6	8·58	1·0	10·5
15/8	17·2	16·97	1·2	9·3
15/9	25·0	23·88	1·3	8·9
12/7	2·7	2·25	1·5	8·6
12/8	5·4	4·48	1·5	8·2
12/9	10·8	8·74	1·6	8·1
12/10	15·4	12·22	1·6	8·1
12/11	21·6	16·24	1·8	7·5
12/12	25·0	18·95	1·4	9·1
9/6	3·85	2·42	2·5	6·8
9/7	7·7	4·74	2·8	6·7
9/8	10·8	6·55	2·7	6·6
9/9	15·4	9·14	2·5	6·6
9/10	21·6	12·46	2·6	6·5
9/11	25·0	14·21	2·7	6·6
6/7	5·4	2·24	3·4	4·8
6/8	7·7	3·15	3·6	4·6
6/9	10·8	4·36	3·7	4·2
6/10	13·6	5·42	4·6	3·6
6/11	16·7	6·54	5·3	2·9
6/12	19·1	7·43	6·7	2·4
6/13	25·0	9·42	3·7	4·2
3/4	7·7	1·57		
3/5	10·8	2·17		
3/6	15·4	3·04		See footnote §
3/7	21·6	4·13		
3/8	25·0	4·69		

*† See Table 1.
§ Crystals collected after 24 h storage at 20°. Crystals too large for microscope sizing and insufficient in quantity for air permeability method.

Table 3. *Crystallization conditions and particle-size data.* Water flow 620 ml min^{-1}.

Reference number*	Drug solution flow (ml min^{-1})	Theoretical degree of supersaturation,† SS	d_{ln}, μm from microscope	Specific surface area from air permeability method (m^2 g^{-1})
15/10	0·5	2·64	1·7	8·0
15/11	1·1	5·71	1·6	8·6
15/12	2·5	12·56	1·8	7·6
9/12	1·1	3·41	3·2	5·4
9/13	2·5	7·53	3·8	4·3
9/14	5·4	15·17	4·4	3·4
3/9	2·5	2·51		See footnote §
3/10	15·4	12·02	8·1	1·5

*† See Table 1,
§ Crystals collected after 24 h storage at 20°. Crystals too large for microscope sizing and insufficient in quantity for air permeability method.

The effect of turbulence on particle size

The rate at which mixing of the two fluid streams takes place in the pipe must be largely influenced by the degree of turbulence existing in the fluids as they pass down the mixing tube. The principal consequence of mixing is that a fluid of changed

solvent power for sulphadiazine is produced, giving a mixture supersaturated with respect to the drug. The speed at which supersaturation increases will depend on the speed of mixing and on the rate of the competing process of crystallization, the latter bringing about relief of supersaturation. The effects of turbulence are seen by comparing samples derived from mixtures of similar theoretical supersaturation but prepared under different mixing conditions, as for example in Table 4, extracted from

Table 4. *The effect of turbulence on particle-size.*

Reference number	Water flow (ml min^{-1})	Drug solution flow (ml min^{-1})	Reynolds number	Theoretical degree of supersaturation after complete mixing	d_{1n}, μm	Specific surface area (m^2 g^{-1})
15/1	6200	4·3	13 155	2·27	$0·7_5$	—
15/2	6200	8·6	13 155	4·48	$0·9_1$	12·7
15/5	3100	2·15	6577	2·27	$0·9_5$	10·5
15/10	620	0·5	1315	2·64	1·8	7·6
6/3	6200	15·4	13 155	3·15	7·6	1·9
6/8	3100	7·7	6577	3·15	3·6	4·6
6/5	6200	21·6	13 155	4·36	8·3	1·4
6/9	3100	10·8	6577	4·36	3·7	4·2

Tables 1–3 for clarity. In the first four entries, the results for sample number 15/2 are included in Table 4 in support of the single size measurement available for sample number 15/1, for which a surface area figure in excess of 12·7 m^2g^{-1} is predicted. The results indicate that an increase in turbulence decreases the sulphadiazine particle-size. The size of the effect is not as large as was expected since, with non-turbulent flow conditions, materials of substantial specific surface area result. This may be explained by the large decrease in the solubility of sulphadiazine in passing from pure DMF, to DMF containing a relatively low percentage of water. As a result, only the partial mixing of the incoming sulphadiazine-DMF solution with the water stream gives rise to high supersaturations and in consequence high nucleation rates, causing production of fine-particle products. Classical crystallization theory indicates that the crystallization process is a balance of the consecutive and concurrent stages of nucleation and crystal growth. Nucleation shows a high order dependence on supersaturation, whereas crystal growth shows an approximately linear relation (see for example Van Hook, 1961; Schoen, 1961). High supersaturations therefore favour the formation of small particle-size products.

The same effect, a decrease in particle-size with increased turbulence, is shown with the 12% w/v sulphadiazine injection solutions. For 6% solutions the effect is reversed, as shown by the second four entries in Table 4. Here, for equivalent theoretical supersaturations, the system with the lower Reynolds number produced crystals of smaller particle-size. The difference in viscosity of sulphadiazine solutions of low and high concentration was thought to be a possible means of explaining this effect. Viscosities of drug-DMF solutions at 20°, measured using an M2 viscometer (British Standard 188: 1957), were found to be:—

Sulphadiazine in DMF (% w/v)..	0	3	9	15
Viscosity (cP)	$0·90_3$	$0·98_3$	$1·26_9$	$1·69_7$

Two levels of mixing are recognized (Brodkey, 1966): (i) "scale of segregation", which is a measure of the size of unmixed portions of the pure compounds, (ii)

"intensity of segregation", which describes the effect of molecular diffusion on the mixing process, and is a measure of the difference in concentration between the neighbouring portions of fluid. The increased solution viscosity (see above) of high concentrations of sulphadiazine in DMF may, by molecular diffusion, slow the reduction of intensity of segregation although this may not show as an effect on particle-size because of the high supersaturations achieved with partial mixing. The lower viscosity of weaker solutions enables complete mixing to be more rapidly achieved.

A more probable explanation for the reversed effect with 6% injection solutions and the less turbulent water flow lies in the relative speeds of mixing and nucleation. At the higher water flow, mixing may outpace the speed of nucleation. Lower degrees of supersaturation are reached as a result of dilution rather than by immediate crystallization. In these circumstances nucleation will be less favoured and larger crystals formed. With the slower mixing associated with the lower water flow of 3100 ml min^{-1}, more nucleation will be possible before dilution reduces supersaturation and smaller crystals will result.

With the intermediate strength, 9% w/v, sulphadiazine solution, the effect appears transitional between that for the concentrated solutions and that for 6% w/v sulphadiazine-DMF solution (Table 5).

Table 5. *The effect of turbulence on particle-size.*

Reference number	Water flow (ml min^{-1})	Sulphadiazine solution flow (ml min^{-1})	Reynolds number	Theoretical degree of supersaturation after complete mixing	d_{1n}, μm	Specific surface area (m^2 g^{-1})
9/4	6200	21·6	13 155	6·55	3·4	5·6
9/8	3100	10·8	6577	6·55	2·7	6·6
9/12	620	1·1	1315	3·41	3·2	5·4
9/13	620	2·5	1315	7·53	3·8	5·3

With 3% sulphadiazine-DMF solutions, crystallization was slow and gave large crystals. A significant yield of crystals could be obtained for sample 3/3, for example, only after 24 h storage. In this case, a theoretical degree of supersaturation of 2·5 existed and the effects contrast with those obtained for samples 15/1 and 15/5 where a slightly lower theoretical degree of supersaturation gave a yield of small crystals within 1 h of mixing. Owing to the sparse yield of crystals and the difficulty of applying the microscope method to large-particle materials, quantitative information is not available for the crystal size of most samples produced using 3% solutions. The rate of crystallization in some of these samples was monitored by assaying 0·2 μm membrane filtrates of pipeline mixtures that had been stored, and results are shown in Table 6. These suggest that for sample 3/1 the supersaturation conditions achieved at any stage are insufficient to promote nucleation. With sample 3/2 the supersaturation reached is either too transient or too low to allow more than slight nucleation: crystals are seen after 4 days. Conditions used for sample 3/3 gave crystals visible after 24 h. The effects are again explicable in terms of the relative rates of mixing, nucleation and crystal growth, and of the supersaturations possible during mixing. When low concentration solutions are used, the extent of mixing, in terms of the solvent composition, must be considerable before any supersaturation

Table 6. *The rate of decrease of sulphadiazine in solution in pipeline prepared mixtures using* 3% *w/v sulphadiazine in DMF and a water flow of* 6200 *ml min*$^{-1}$.

Reference number	Rate of injection of sulphadiazine solution (ml min^{-1})	Theoretical degree of supersaturation after complete mixing	0·2 μm membrane filtrate assays % w/w sulphadiazine 1 h	24 h	4 days	24 days
3/1	15·4	1·57	$0{\cdot}0072_4$	$0{\cdot}0072_1$	$0{\cdot}0072_0$	$0{\cdot}0072_0$
3/2	21·6	2·18	0·0102	$0{\cdot}0099_7$	$0{\cdot}0085_8$	$0{\cdot}0060_0$
3/3	25·0	2·50	0·0119	0·0100	$0{\cdot}0070_3$	$0{\cdot}0055_7$

occurs. Because of this, the high local supersaturations possible in the early stages of mixing using high concentration solutions, cannot be realized. Consequently nucleation is limited, growth conditions prevail, and large crystals result.

A further factor, that may accentuate some of the effects described, is the phenomenon of "collision breeding" (Lal, 1966). By this means fresh nuclei are produced by collision of crystals under turbulent conditions. The effect is increased by an increase in supersaturation because of the decrease in critical cluster size with increase in supersaturation (Walton, 1965).

With laminar flow conditions, mixing takes place largely through molecular diffusion, but to some extent by convection. In the pipeline mixer a "core" of unmixed solution is evident for much of the length of the tube. Consequently, crystallization occurs in the region surrounding the core where diffusion has taken place to give a change in solvent characteristics. The core becomes coated with crystalline material which gradually separates into the bulk of the surrounding, largely aqueous, fluid. Concentrated solutions give materials of slightly larger particle-size than those produced at comparable theoretical degrees of supersaturation under turbulent flow conditions. However, the materials are small in particle-size compared to those resulting from injection of weaker solutions, even under turbulent conditions. It seems that because mixing is much less rapid with laminar flow, the 15% sulphadiazine solutions give reduced nucleation rates, although the high supersaturations resulting from small degrees of mixing still have an overwhelming influence. With the concentrated drug solution, material nucleated around the core may grow rapidly because of the higher concentration gradient from the underlying concentrated solution. With dilute solutions large crystals are produced, an effect again explicable by the low local supersaturations achievable with such mixtures. The absence of collision breeding will also emphasize the effect.

The effect of theoretical mixture supersaturations on particle-size

Numerous workers have shown the dependence of crystal number and size on the concentration of solute in excess of solubility. Although von Weimarn's work (von Weimarn, 1925) has been subject to some criticism (Kolthoff, 1932), the usefulness of the principles he deduced has been upheld by Cartwright, Newman & Wilson (1967). It is suggested that the theoretical mixture supersaturation figure is not reached in the pipeline because significant and often substantial crystallization occurs before mixing is complete. Nevertheless, the amount of drug available for crystallization per unit of volume of mixed fluids should be a factor influencing the overall process, and therefore the characteristics of the final crystalline product.

In a series of experiments in which water flow and strength of sulphadiazine solution are kept constant (for example samples 12/1 to 12/6, 9/1 to 9/5 and 9/12 to 9/14), the general trend is for an increase in average particle size, as final supersaturation increases. This result is the reverse of von Weimarn's findings; however von Weimarn was studying the precipitation of barium sulphate produced by reaction, rather than crystallization by solvent-change. In the present work, increasing theoretical mixture supersaturation was brought about by raising the speed of injection of sulphadiazine–DMF solution. This may affect the speed of mixing of the fluids in the tube; it will also affect the flow characteristics of the liquid leaving the cannula. Calculation of the Reynolds number for fluid flowing in the cannula, shows that this is streamline for all the injection rates used. It is possible that with small volumes, turbulent water flow breaks up the incoming fluid into smaller portions in a given time, than it does at faster injection rates. The lower scale of segregation would give higher supersaturations more rapidly, causing increased nucleation and smaller particle-size products.

Table 7. *The effect of the concentration of sulphadiazine in the DMF injection solution on particle-size.*

Reference number	% w/v sulphadiazine in DMF solution	Water flow (ml min^{-1})	Theoretical degree of supersaturation	d_{ln}, μm	Specific surface area (m^2 g^{-1})
15/2	15	6200	4·48	$0{\cdot}9_1$	12·7
12/3	12	6200	4·48	1·2	8·9
9/3	9	6200	4·74	3·0	5·7
6/5	6	6200	4·36	8·3	1·4
15/6	15	3100	4·51	$0{\cdot}9_5$	11·7
12/8	12	3100	4·48	1·5	8·2
9/7	9	3100	4·74	2·8	6·7
6/9	6	3100	4·36	3·7	4·2
15/12	15	620	12·56	1·8	7·6
9/13	9	620	7·53	3·8	4·3
9/14	9	620	15·17	4·4	3·4
3/10	3	620	12·02	7·9	1·5

The effect of the concentration of sulphadiazine in the DMF solution on particle-size

The effects on particle size of samples prepared under similar conditions of turbulence and theoretical mixture supersaturation, but using different strength solutions, are compared in Table 7. For any specified level of turbulence and theoretical mixture supersaturation, increasing the concentration of sulphadiazine solution brings about a decrease in particle-size: the effect is evident for both turbulent and non-turbulent fluid flow in the pipeline. With high concentration solutions, high local supersaturations exist in the earliest stages of mixing, causing high nucleation rates. Also the higher diffusion gradients existing with more concentrated solutions will facilitate more rapid mixing at the molecular level, and rapidly reduce the intensity of segregation. Table 7 also summarizes results for similar theoretical mixture supersaturations.

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