ELSEVIER

International Journal of Pharmaceutics 201 (2000) 79–88

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Relations between crystallisation conditions and micromeritic properties of ibuprofen

I. Nikolakakis *, K. Kachrimanis, S. Malamataris

Laboratory of Pharmaceutical Technology, School of Pharmacy, University of Thessaloniki, Thessaloniki 54006, Greece

Received 29 September 1999; received in revised form 13 March 2000; accepted 13 March 2000

Abstract

The effects of solvent, cooling rate and type of methacrylic polymer (Eudragit®) on the micromeritic properties (size, elongation ratio, roundness and fullness ratio), the temperature change in the crystallisation liquid, the crystal yield and the extent of agglomeration of ibuprofen crystals have been compared. Twenty batches of crystals were prepared and Latin square experimental design was applied with four levels for each factor. It was found that crystal yield (Y) is related to the extrapolated point of maximum rate of temperature-deviation (T_d) with a logarithmic-type equation [$Y = 34.45 \ln T_d - 28.00$] and to the area under the curve of temperature-deviation versus time (AUC) with a polynomial equation including cooling rate [$Y = 19.95\text{AUC} - 1.57\text{AUC/CR} + 63.00$]. Crystal size is affected by the cooling rate and analysis of variance (ANOVA) showed that elongation ratio and fullness ratio of single crystals ($P = 0.05$ and 0.05), as well as roundness and fullness ratio of agglomerates ($P = 0.05$ and 0.1), are affected by the solvent. Post hoc statistical analysis of the solvent effects on the shape of crystals and agglomerates (Tukey's HSD multiple pairwise comparison test of means) indicated that their significance lies in the different polarity and may be attributed to interactions of solvent (acetone) with the growing crystal faces. Extent of crystal agglomeration was found to be inversely proportional to the ratio of elongation ratio/circle equivalent diameter of the single crystals.

Keywords: Crystallisation; Eudragit polymers; Ibuprofen; Micromeritic properties

1. Introduction

Crystallisation conditions influence the physicochemical and micromeritic properties of crystals and efforts are being made towards the production of drugs and excipients with preselected or desired properties by controlling the process of crystal formation (nucleation and growth). In this context, for the case of ibuprofen, the effects of cooling rate and solvent polarity have been investigated (Gordon and Amin, 1984; Ludlam-Brown et al., 1990; York, 1992; Chen, 1993) and alterations of the crystal habit were found. Also, crystal alteration of ibuprofen has been noticed due to the presence of Eudragit® S100 polymer (Kachrimanis et al., 1998).

* Corresponding author. Tel.: +30-31-997635; fax: +30-31-997652.

E-mail address: yannikos@pharm.auth.gr (I. Nikolakakis)

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00398-7

Ibuprofen is a drug for which changes in size, shape and agglomeration of crystals, as well as addition of various types of Eudragit® copolymers are essential for improvement of flow, compaction and release and for optimizing its formulations. In general, flow is improved by the formation of spherical particles, compaction by friable, fragmenting agglomerates and release by small particles of narrow size distribution leading in the development of continuous and uniform coating. Therefore, it is thought of interest to describe and monitor in more detail the crystallisation of ibuprofen performed under different solvents, cooling rates and presence of Eudragit® polymers and compare the effect on the micromeritic properties.

In the present work it is attempted to monitor the temperature changes in the crystallisation solution of ibuprofen and furthermore to establish possible correlations between them, the crystal yield and the micromeritic properties of the final product obtained under different crystallisation conditions.

2. Materials and methods

2.1. Materials

Crystalline ibuprofen was used (USP grade, from Boots Pharmaceuticals, Nottingham, UK, supplied by Vianex, Athens, Greece). The polymers used were four methacrylic copolymers in powder form (Eudragit® S100, L100, RS and RL, supplied by Röhm Pharma, Darmstadt, Germany). Absolute ethanol (Merck, Darmstadt, Germany), methanol (Carlo Erba Montedison Group, Italy), acetone (Riedel de Haen, Seelze, Germany) and isopropanol (Lab Scan, Dublin, Ireland), all analytical grade, were used as solvents.

2.2. Crystallisation

Certain amounts of Eudragit® copolymer (50 mg) and ibuprofen (50 g) were dissolved in 50 g solvent and kept under constant stirring (200 rpm) and constant temperature (40°C), in crystallisation vessels immersed in a water bath. The solutions were subsequently cooled down to 10°C, at the selected cooling rate, using a digital programmable temperature controller (PolyScience model 9510, refrigerated circulator, USA) and the crystals formed were collected by filtration, dried at 40°C under vacuum and kept in closed amber glass jars. Instead of pure acetone and isopropanol, mixtures 8:2 or 2:8 w/w of these two solvents were used, because of solubility problems of Eudragit® RS in isopropanol and of Eudragit® S100 and L100 in acetone.

The crystal yield (Y) was calculated from the weight of crystals expressed as percentage of ibuprofen dissolved initially (50 g). The extent of crystal agglomeration, defined as the weight of the greater than 300 μm fraction, expressed as percentage of the total weight of crystalline product, was determined by sieving of each dried batch. The choice of 300 μm cut off size was based on scanning electron microscopic (SEM) assessment of the crystalline product which indicated that primary crystals were smaller and agglomerates greater than this size, Fig. 1. A very thin coat of carbon was applied to samples of crystals before examination in a scanning electron microscope (JSM 840A, JEOL, Japan).

2.3. Temperature monitoring

Temperature in the crystallisation liquid was measured and recorded throughout the cooling period with an accuracy of ± 0.01°C. This was achieved by the use of Pt 100 thermistors connected to an electronic polymeter (Handyscope, Tie Pie Engineering, The Netherlands) and a computer equipped with a suitable software program for the capture and analysis of data in digital form. Data for 320 points were collected from each crystallisation experiment and graphs of temperature versus time were plotted. Fig. 2 presents typical plots for two parallel crystallisation vessels. The one with and the other without drug (reference vessel). The data were simultaneously harvested through different channels of the polymeter and further processed by using the Microsoft Excel program. The point at which the tangent of the plot (with drug) forms the greatest

angle with the reference plot, T_m, was determined. Then the extrapolated point, T_d, was obtained as the intersection of the vertical passing from T_m, and the linear (programmed) cooling plot. T_d is the programmed cooling temperature which corresponds to maximum rate of temperature deviation in the crystallisation liquid and is considered as indication of maximum crystallisation rate. Also, the area confined between the curves of measured and programmed temperature versus time (AUC) was calculated by using the trapezoidal rule.

2.4. Experimental design and statistical analysis

A standard Latin square design (4×4) with three factors (cooling rate, polymer type and solvent type) at four levels each was used, assuming no interaction (Steel and Torrie, 1981). The rows corresponded to the cooling rates, the columns to the polymers and the treatments to the solvents. Each treatment occurred only once in each row and column, and each cell corresponded to a particular combination of factors. In addition, four batches were prepared in polymer free solutions (reference batches).

For statistical analysis of the experimental design (ANOVA and Tukey's HSD multiple pairwise comparison of means) the SPSS 8.0 statistical software was used. For non-linear model fitting and residual analysis, as well as for the graphical presentation of results the SigmaPlot 4.0 software (SPSS Inc. Chicago, IL) was used.

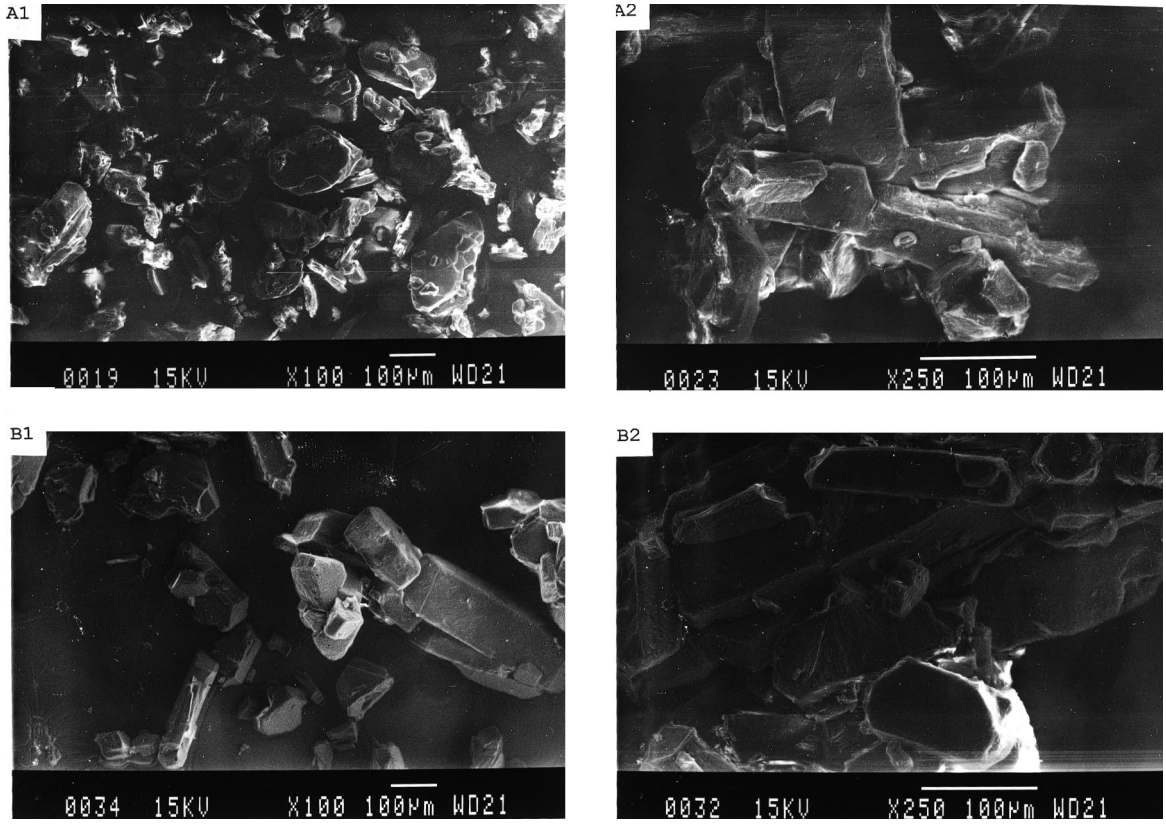

Fig. 1. Scanning electron photomicrographs of the largest and smallest single crystals (1) and of the corresponding agglomerates (2) prepared in methanol without polymer (A) and in ethanol containing Eudragit® RS (B), at cooling rates 0.291°C/min (A) and 0.073°C/min (B).

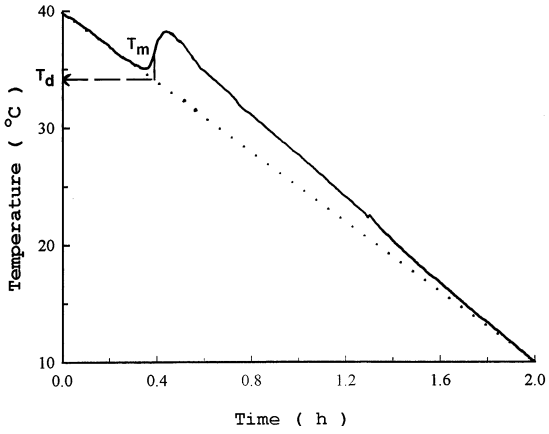

Fig. 2. Typical plots of temperature in the crystallisation solution versus time, in presence (solid line) or in absence (dotted line) of ibuprofen, with methanol and Eudragit® S100, at a cooling rate of 0.291°C/min.

2.5. Micromeritic properties

Size of single crystals and agglomerates was evaluated as circle equivalent diameter (CED), by using an image processing and analysis system (Quantimet 500, Leica, Cambridge, UK) and was expressed as geometric mean diameter by weight. At least 500 crystals or 200 agglomerates were measured in four optical fields of samples dispersed in saturated paraffin oil. Also, mean values and standard deviations of the elongation ratio (Heywood, 1947), the roundness or reciprocal sphericity or surface factor (Hausner, 1966) and the fullness ratio or solidity (Russ, 1999) were determined. The selected parameters are defined as follows:

$$\text{Elongation ratio} = \frac{\text{maximun Feret diameter}}{\text{minimum Feret diameter}}$$

where the measurements of the two Feret diameters are not necessarily at right angles to each other.

$$\text{Roundness} = \frac{\text{perimeter}^2}{4 \times \pi \times 1.064}$$

where 1.064 is an instrument dependent factor, correcting the perimeter for the effect of the corners produced by the digitisation of the image.

$$\text{Fullness ratio} = \left(\frac{\text{area}}{\text{convex area}}\right)^{1/2}$$

where convex area is the area of the polygon circumscribing the particle projection, formed by tangents to its boundary.

These shape parameters assume a value of 1 for a sphere. Fullness ratio is mainly related to surface irregularity, elongation ratio to crystal geometry and roundness to both of them.

3. Results and discussion

In Table 1 are given the results of the micromeritic properties of single crystals and those of crystal agglomerates (in brackets) together with the crystal yield and extent of crystal agglomeration, for all the crystallisation conditions applied.

From the data presented in Table 1, and by averaging the diameter values for each cooling rate it appears that the crystal size is affected by the cooling rate. The mean values of circle equivalent diameter (CED) for the three faster rates seem to be similar, between 189 and 197 μm but markedly lower, 149 μm, is the mean value for the slower cooling rate (0.073°C/min). Cooling is known to affect the rate of growth and the size of crystals, through its effect on supersaturation. The crystal size generally decreases at high degree of supersaturation (fast cooling) due to incomplete growth of a large number of small crystals (Mullin, 1993). However, incomplete growth may also be the case at very low degree of supersaturation (slow cooling) due to the very long time required to complete growth.

The extent of crystal agglomeration, Table 1, could not be related to any of the crystallisation conditions studied, and this can be attributed to the complexity of the agglomeration. Agglomeration is known to increase with supersaturation because increased supersaturation leads to a higher number concentration of particles. High supersaturation also may increase the rate of binding of the primary aggregates into agglomerates, because it affects the crystal size and the type of the predominant crystal faces, or the crystal

Table 1
Micromeritic properties, crystal yield and extent of crystal agglomeration of the crystallisation products[a]

Solvent	Cooling rate (°C/min)	Eudragit type	Crystal yield (%)	Extent of agglomeration (%)	Diameter (μm) mean ± SD	Elongation ratio	Roundness	Fullness ratio
Methanol	0.291	none	89.0	56.6	231 ± 80	1.76 (1.50)[b]	1.55 (1.88)[b]	0.90 (0.87)[b]
Methanol	»	S100	92.8	25.3	227 ± 55	1.80 (1.41)	1.57 (1.72)	0.90 (0.90)
Ethanol	»	L100	75.6	39.4	179 ± 50	1.68 (1.48)	1.55 (1.65)	0.90 (0.90)
Acet/Isop.	»	RS	58.2	55.9	162 ± 46	1.75 (1.35)	1.64 (1.80)	0.89 (0.90)
Isopr/Acet.	»	RL	58.2	49.9	213 ± 58	1.59 (1.41)	1.63 (1.81)	0.91 (0.89)
Ethanol	0.145	None	73.8	59.4	227 ± 68	1.85 (1.45)	1.52 (2.16)	0.89 (0.87)
Methanol	»	L100	92.4	37.3	161 ± 47	1.67 (1.51)	1.46 (1.63)	0.90 (0.90)
Ethanol	»	S100	71.0	58.7	187 ± 56	1.69 (1.54)	1.51 (1.82)	0.90 (0.88)
Acet/Isop.	»	RL	62.0	54.7	215 ± 59	2.10 (1.47)	1.76 (2.37)	0.86 (0.84)
Isopr/Acet.	»	RS	54.4	61.3	224 ± 62	1.60 (1.43)	1.48 (1.66)	0.91 (0.90)
Acet/Isop.	0.097	None	56.6	49.2	199 ± 55	1.85 (1.47)	1.58 (2.04)	0.88 (0.86)
Methanol	»	RS	36.8	65.3	186 ± 43	1.40 (1.48)	1.76 (1.83)	0.91 (0.88)
Ethanol	»	RL	61.2	60.4	220 ± 59	1.65 (1.52)	1.54 (2.05)	0.89 (0.87)
Acet/Isop.	»	S100	59.8	56.4	183 ± 46	1.84 (1.52)	1.57 (2.05)	0.89 (0.86)
Isopr/Acet.	»	L100	53.4	56.2	166 ± 31	1.51 (1.47)	1.51 (1.69)	0.90 (0.90)
Isopr/Acet.	0.073	None	50.0	36.8	173 ± 41	1.81 (1.39)	1.54 (1.68)	0.89 (0.89)
Methanol	»	RL	46.6	64.9	165 ± 43	1.42 (1.38)	1.37 (1.60)	0.93 (0.90)
Ethanol	»	RS	48.8	36.6	131 ± 34	1.64 (1.61)	1.51 (1.66)	0.90 (0.89)
Acet/Isopr.	»	L100	59.6	46.3	150 ± 42	1.77 (1.77)	1.60 (1.93)	0.88 (0.87)
Isopr/Acet.	»	S100	56.0	49.8	149 ± 40	1.63 (1.44)	1.59 (1.78)	0.91 (0.88)

[a] Standard deviation: for elongation ratio, 0.25–0.53; for roundness, 0.13–0.403; and for fullness ratio, 0.025–0.050 ($n = 500$ for single crystals and $n = 200$ for agglomerates).

[b] Results for crystal agglomerates (in brackets)

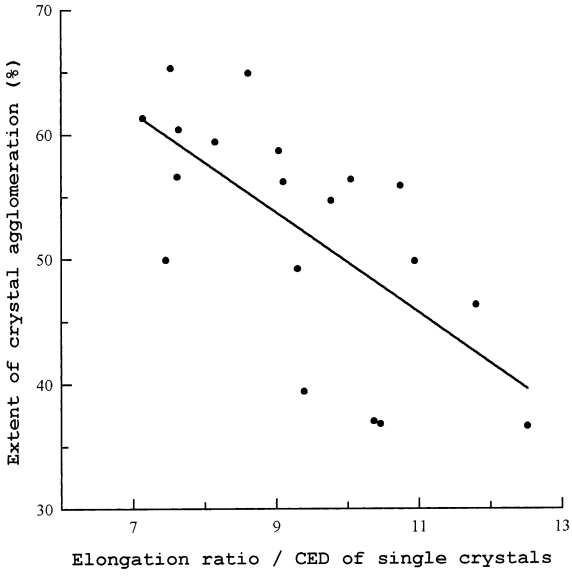

Fig. 3. Extent of crystal agglomeration (%) versus the ratio of elongation ratio/circle equivalent diameter (CED) of single crystals.

habit and surface irregularity (Granberg et al., 1999). Therefore, correlation of the extent of crystal agglomeration with the shape factors of single crystals was attempted and showed some dependence on elongation and fullness ratio but with very low correlation. A better linear relationship was obtained when extent of crystal agglomeration was plotted against the ratio elongation ratio/circle equivalent diameter (Fig. 3), which despite of the low coefficient of determination, $R^2 = 0.442$, was significant at $P = 0.01$. Such relation indicates an increase of agglomeration with decreasing elongation and increasing crystal size.

In Table 2 are listed the results of analysis of variance (ANOVA) for the shape parameters determined. $F_{(3,6)}$ is the ratio of the variance due to certain factor (crystallisation condition, d.f. = 3) over the variance due to experimental error (d.f. = 6) and P is the error probability. The application of the experimental design was based on the assumption of additivity of responses, or, in the absence of interaction between the factors (Steel and Torrie, 1981). In order to test this assumption, the Tukey's additivity test was used as adopted for Latin square design (Tukey, 1949, 1955). This procedure involves the split of total experimental error (d.f. = 6) into error due to non-additivity (d.f. = 1) and residual error (d.f. = 5), the calculation of F-statistic (mean square of non-additivity/mean square of residual) and comparison of the result with the corresponding value of F-distribution ($F_{(1,5)}$ obtained from standard textbooks, which is 6.61 for $P = 0.05$ and 4.06 for $P = 0.1$). The calculated values of F-statistic were found between 0.1–1.7, for all the cases presented in Table 2. Therefore, it can be inferred that the interaction is not significant, compared to the main effects of the crystallisation conditions on the shape parameters.

The results of ANOVA (Table 2), show that the type of solvent affects the elongation ratio and the fullness ratio of the single crystals, at probability level $P = 0.05$, and the roundness and fullness ratio of crystal agglomerates at $P = 0.05$ and $P = 0.10$, respectively. For the three shape parameters for which the effects are significant at $P = 0.05$

Table 2
Analysis of variance of the Latin square experimental design for the shape parameters determined

Results	Cooling rate		Polymer		Solvent	
	$F_{(3,6)}$	P	$F_{(3,6)}$	P	$F_{(3,6)}$	P
Elongation ratio	1.540	0.298	0.991	0.458	4.956	0.046
» »[a]	1.605	0.284	1.201	0.387	1.401	0.331
Roundness	0.371	0.777	0.204	0.890	0.696	0.587
» »[a]	1.618	0.282	2.675	0.141	5.377	0.039
Fullness ratio	0.722	0.574	0.278	0.840	4.944	0.046
» »[a]	1.810	0.246	1.810	0.246	3.524	0.089

[a] Results of crystal agglomerates.

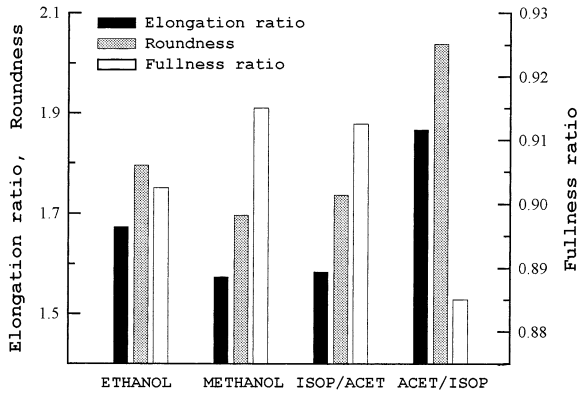

Fig. 4. Effect of solvent type on the mean values of elongation ratio and fullness ratio of single crystals and roundness of agglomerates.

level, the multiple pairwise comparison of means was used [Tukey's HSD (honestly significant difference) test], in order to distinguish the solvents with significantly different means. The results of this analysis showed that methanol with high (32.6) polarity (Martin et al., 1993) and acetone/isopropanol (8:2 w/w), with low (20) polarity (calculated according to Sokolowski (1980)), produce crystals with significantly different shape parameters ($P = 0.05$).

The mean values of the significantly affected shape parameters, Fig. 4, show that methanol results in crystals with the lowest elongation ratio and the highest fullness ratio, or in the most symmetrical and smooth crystals. Furthermore, it results in agglomerates with the lowest value of roundness or highest sphericity. On the contrary, crystals produced from acetone/isopropanol (8:2 w/w) have the highest elongation ratio and the lowest fullness ratio, and therefore are most asymmetrical and rough and the value for the roundness of the agglomerates is highest. Microscopic examination of the crystallisation products confirmed the above changes of crystal shape, which are in agreement with those observed by York (1992), during the crystallisation of ibuprofen in hexane, a solvent of very low polarity (1.9). The great elongation of single crystals produced from acetone/isopropanol (8:2 w/w) can be attributed to physico-chemical interactions of the low polarity solvent with the hydrophobic faces of the growing ibuprofen crystals. Similarly, their increased surface irregularity can be ascribed to incomplete crystal growth due to the aforementioned interactions. Furthermore, the effect of solvent type on the roundness of agglomerates may be exerted through its effect on crystal elongation, which affects the arrangement and packing of single crystals in the agglomerates.

The results of Tukey's HSD test also showed that the solvents employed can be organized in two homogeneous subsets, one comprised of methanol, ethanol and isopropanol/acetone (8:2 w/w) and the other of ethanol, isopropanol/acetone (8:2 w/w) and acetone/isopropanol (8:2 w/w). The solvents ethanol and isopropanol/acetone (8:2 w/w) that overlap between the two subsets produce crystals of intermediate shape parameter values, Fig. 4. Considering polarity values, this is expected for ethanol with intermediate (25) polarity but not for isopropanol/acetone with a relatively lower (19) polarity than the solvent acetone/isopropanol (polarity 20). It seems that isopropanol may form hydrogen bonds with the carboxylic groups of ibuprofen and the combination of low polarity with greater ability for hydrogen bonding, reduces interactions with the hydrophobic ibuprofen crystal faces, resulting in intermediate shape parameter values for the case of isopropanol/acetone (8:2 w/w).

In Table 3 are given representative results of the extrapolated points of maximum rate of temperature-deviation, T_d, and of area under the temperature–time curve, AUC, for the crystallisations corresponding to ethanol. The case of ethanol was selected because it is a common solvent in the two homogeneous subsets mentioned above. From Table 3, it can be seen that irrespectively of polymer type, faster cooling rates result in higher T_d values and that the presence of Eudragit® S100 and L100 causes an increase in T_d, as compared with the reference (polymer-free) crystallising solution. On the contrary, the presence of RS and RL causes a reduction in T_d. Also, in Table 3 are given results of T_d and AUC for the crystallisations corresponding to Eudragit® S100, the polymer causing the higher increase in T_d. It is seen that the change in T_d is greater between different solvents than between different

Table 3
Extrapolated points of maximum rate of temperature deviation in the crystallising solution, T_d, and area under the temperature deviation versus time curve, AUC, for certain solvent (ethanol) and different polymers, and for certain polymer (S100) and different solvent, irrespectively of cooling rate

Solvent	Eudragit® polymer	Cooling rate (°C/min)	T_d (°C)	AUC (°C h)
Ethanol	–	0.145	15.52	2.03
Ethanol	L100	0.291	18.08	1.10
Ethanol	S100	0.145	20.15	1.72
Ethanol	RL	0.097	12.98	0.79
Ethanol	RS	0.073	12.38	2.27
Methanol	S100	0.291	34.00	2.78
Acetone/Isop.	S100	0.097	12.18	1.59
Isopropanol/Acet.	S100	0.097	14.31	1.53

polymers and T_d decreases in the order: methanol > ethanol > acetone/isopropanol (8:2 w/w).

The values of AUC, given in Table 3, seem to be related to those of T_d for different solvents, but not for different polymers. The relationship between AUC and T_d for different solvents but the same polymer (S100), irrespectively of cooling rate, is shown in Fig. 5. It appears to be a logarithmic or power model with coefficient of determination $R^2 = 0.969$ and significant at $P = 0.0001$ (ANOVA, F-test), where R^2 is the variation explained by the model. This means that the solubility of ibuprofen in the different solvents, and, consequently, the different degrees of supersaturation achieved with the fixed quantities of solvent and ibuprofen employed, are responsible for the above relationship. Furthermore, taking into account that the presence of polymers causes smaller changes in T_d than the nature of solvent, it is expected for the AUC value to be affected by the cooling capacity of the temperature controller and consequently by the cooling rate applied.

The crystal yield (Y) of the representative crystallisation conditions (Table 3) plotted against T_d, Fig. 6, shows that it increases with T_d, particularly at lower T_d values. This demonstrates that the effect of the width of the metastable zone has greater impact on crystal yield when crystallisation occurs at lower temperature. The relationship between crystal yield and T_d, derived from regression analysis of the results given in Table 3, can be described with a linear equation of logarithmic type:

$$Y = 34.45 \ln T_d - 28.00 \quad (1)$$

with coefficient of determination $R^2 = 0.845$ and significant at $P = 0.01$ (ANOVA, F-test), that might be useful for the prediction of crystal yield by following temperature changes in the crystallisation liquid.

Considering the parameters of Y and AUC, a relation between them could be established only after involvement of the reciprocal-cooling rate (1/CR) as an independent variable. This is ex-

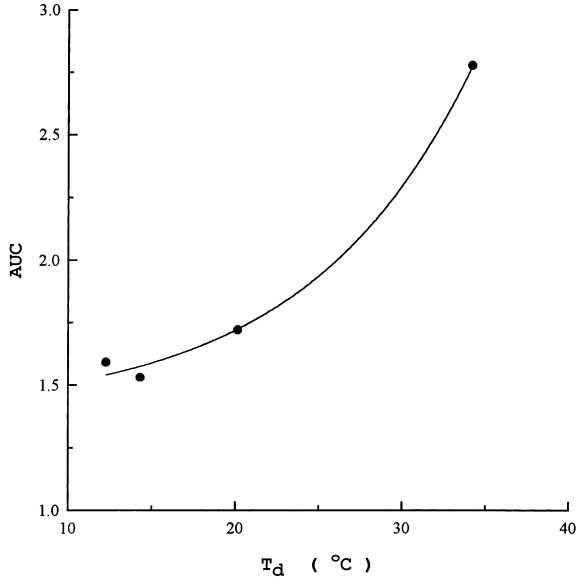

Fig. 5. Area under the curve (AUC) versus point of extrapolated maximum rate of temperature deviation, T_d, in presence of Eudragit® S100, for different solvents and irrespectively of cooling rate.

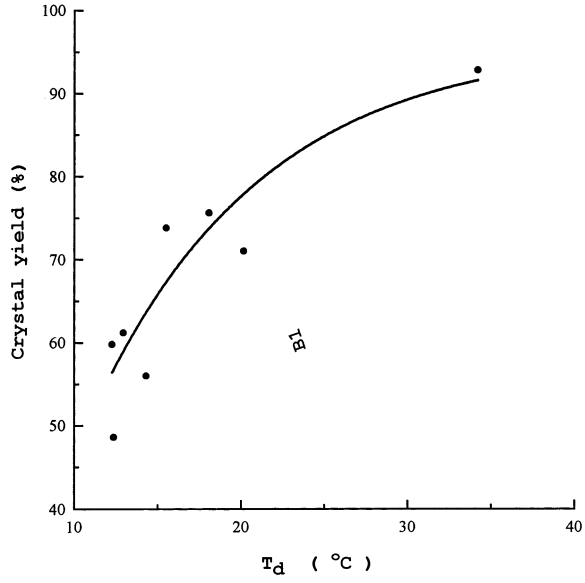

Fig. 6. Plot of crystal yield (%) versus point of extrapolated maximum rate of temperature deviation, T_d.

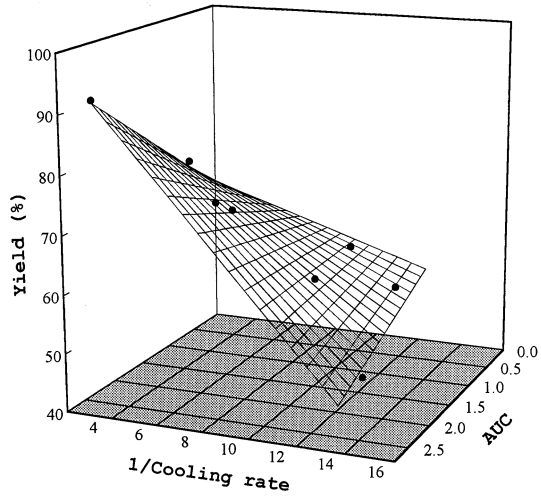

Fig. 7. Scatter plot and response surface for crystal yield versus AUC and 1/Cooling rate.

pected due to changes in the cooling capacity of the temperature controller at the different cooling rates. By initial transformation of the independent variables to fit a linear model and by fitting subsequently the so obtained linear regression coefficients into a nonlinear iteration computer program, a first order polynomial equation with interaction term was derived as the best fitting model:

$$Y = 19.95\text{AUC} - 1.57\text{AUC/CR} + 63.00 \quad (2)$$

The adjusted coefficient of determination was $R_a^2 = 0.955$, and the model was significant at $P = 0.001$ (ANOVA, F-test). Ra^2 was chosen as a more strict measure of the goodness of fit, taking into account the number of data and the number of independent variables. The above equation is graphically presented in Fig. 7 as scatter plot and response surface. The surface curvature indicates interaction between AUC and cooling rate. Also, it is seen that crystal yield is little affected by AUC, at the lowest cooling rate applied, but it increases with AUC at cooling rates greater than 0.097°C/min (corresponding to $1/\text{CR} < 8$). Therefore, yield can be maximized by crystallising ibuprofen at fast cooling rates from solvents giving high AUC values, like methanol.

4. Conclusions

In conclusion we can say that the extrapolated point of maximum rate of temperature deviation, T_d, the crystal yield, Y, and the micromeritic properties, for ibuprofen crystallised in presence of low (1‰ w/w) concentration of Eudragit® polymers, are mainly controlled by the solvent and cooling rate. The polymer presence has a smaller effect. Particularly, the crystal yield (Y) is related to T_d with a logarithmic type equation and to the area under the curve of temperature-deviation versus time (AUC) with a polynomial equation including the reciprocal of cooling rate in the interaction term. Therefore, higher crystal yield and crystal growth can be achieved with fast cooling rates and solvents giving high AUC values like methanol. The shape and the surface irregularity of single crystals, as well as surface irregularity and roundness of crystal agglomerates are affected significantly by the solvent due to its polarity and interactions with hydrophobic faces of the growing crystals. Extent of agglomeration is inversely proportional to the ratio of elongation ratio/circle equivalent diameter of the single crystals.

References

Chen, J., 1993. Process for enhancing the flow characteristics of ibuprofen. US Patent 5191114, 2 March.

Gordon, R.E., Amin, S.I., 1984. Crystallization of ibuprofen. US Patent 4476248, 9 October.

Granberg, R.A., Bloch, D.G., Rasmuson, A.C., 1999. Crystallisation of paracetamol in acetone–water mixtures. J. Cryst. Growth 198–199, 1287–1293.

Hausner, H.H., 1966. Characterisation of the powder particle shape. Planseeber. Pulvermetall. 14, 75–84.

Heywood, H., 1947. The scope of particle size analysis and standardization. Inst. Chem. Eng. Suppl. 25, 14–24.

Kachrimanis, K., Ktistis, G., Malamataris, S., 1998. Crystallisation conditions and physicomechanical properties of ibuprofen — Eudragit S100 spherical crystal agglomerates prepared by the solvent-change technique. Int. J. Pharm. 173, 61–74.

Ludlam-Brown, I., York, P., Maclaine, J.Q., 1990. The role of crystallisation conditions in the control of final product character. In: Proceedings of the Fourth AAPS Meeting, Las Vegas.

Martin, A., Bustamante, P., Chun, A.C., 1993. Physical Pharmacy, fourth ed. Lea and Febiger, Philadelphia, p. 87 214–215.

Mullin, J.W., 1993. Crystallisation, third ed. Butterworth–Heinemann, Oxford, pp. 180–181.

Russ, J.C., 1999. The Image Processing Handbook. CRC Press LLC, Boca Raton, FL, pp. 553–555.

Sokolowski, D.T., 1980. Solution and phase equilibria. In: Osol, A. (Ed.), Remington's Pharmaceutical Sciences, 16th ed. Mack Publishing Company, Pennsylvania, pp. 214–215.

Steel, R.G.D., Torrie, J.H., 1981. Principles and Procedures of Statistics, 2nd ed. McGraw–Hill, New York, pp. 230–231.

Tukey, J.W., 1949. One degree of freedom for non-additivity. Biometrics 5, 232–242.

Tukey, J.W., 1955. Reply to query. Biometrics 11, 111–113.

York, P., 1992. Crystal engineering and particle design for the powder compaction process. Drug Dev. Ind. Pharm. 18, 677–721.