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Precipitation of Curcuminoids from Hydrotrope Solutions: Crystal Nucleation and Growth Kinetics from Batch Experiments

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ABSTRACT

Precipitation kinetics of curcuminoids from aqueous hydrotropic solutions of sodium cumene sulfonate was investigated in a laboratory-scale agitated vessel using acidic water (pH 3) as a precipitant. The time evolution of the crystal size distribution was used to deduce simultaneously the crystal growth kinetics. The transient population density curves were measured by a Coulter counter light scattering unit. The kinetic data from the experimental runs were correlated by a power law relative kinetic expression. Crystallization experiments using hydrotropic extracts of turmeric were also performed to compare the results with pure curcuminoids in the hydrotrope solutions. The results indicate

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slow crystal growth and thus formation of very fine crystals of curcuminoids in the range of 1 to 100 μm.

Key Words: Curcuminoids; Hydrotropy; Sodium cumene sulphonate; Nucleation kinetics; Crystal growth kinetics; *Curcuma longa*; Turmeric.

INTRODUCTION

Curcuminoids form the most important group of compounds present in turmeric rhizomes giving turmeric most of its colouring and medicinal properties. Conventionally, the curcuminoids have been extracted using polar organic solvents such as alcohols, acetone, etc. However, the presence of residual solvent in the final product may not be permitted, if the curcuminoids are to be processed and used for pharmaceutical formulations. Recently, we have shown the extraction of curcuminoids using aqueous hydrotropic solutions to be a feasible option without using any organic solvent.[1]

Hydrotropism is the phenomenon of increasing solubility of a normally insoluble or sparingly water-soluble organic substances in aqueous solutions in the presence of hydrotropes, which are themselves highly water soluble, amphiphilic organic salts. Typical examples of hydrotropes are the alkali and alkaline metal salts of benzoic and salicylic acids, alkyl substituted aromatic sulphonic acids, naphthalene sulphonic/carboxylic acids, and various hydroaromatic acids. The solubility of an organic compound in hydrotropic media is a strong function of the hydrotrope concentration and varies with the nature of an organic solute too. Although amphiphilic in structure, because of their short hydrophobic part as compared to that of a surfactant, hydrotropes do show a significant difference in their behavior when compared to surfactants. For example, a micellar solubilization in a surfactant solution is possible only in the presence of micelles, i.e., above the critical micelle concentration (CMC) of the surfactant. In the case of hydrotropes also, the solubility enhancement is appreciable only above a certain minimum hydrotrope concentration (MHC), but usually this concentration is very high, i.e., usually in molar region. A characteristic feature of hydrotropic solubility is its sigmoidal dependence on the hydrotrope concentration. When coupled with the requirement of very high concentration of the hydrotrope, it indicates a highly cooperative phenomena in the solution. The necessity of a minimum hydrotrope concentration and the sigmoidal solubility behavior in hydrotropic solubilization was generalized by Balasubramanian et al.[2] by their studies of solubilization of different sparingly soluble solutes in aqueous solutions of hydrotropes

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over a range of concentrations. Aromatic sulphonates seem to aggregate in a stack-like fashion in the aqueous solutions and solubilize the solute by a similar associative mechanism, perhaps involving intermolecular interactions that are specific in nature. Once considered as a prerequisite for the hydrotropic effect, the stack-like aggregation is, however, difficult to envisage for nonaromatic hydrotropes, such as sodium butyl monoglycol sulphate (Na-BMGS). The hydrotropic solubilization is also strongly dependant on the nature of the solute. In some cases, the aggregation of a hydrotrope is probably promoted further by the presence of solute molecules.[3]

Two characteristics of the hydrotropic solubilization seem to have great potential in the extraction of natural products. First, hydrotropes have an ability to differentiate among different organic constituents of a mixture, even among isomers. It is this ability of molecular recognition that should be applicable for selective extraction of a solute from a complex matrix of neutral raw material. Second, the recovery of the solute can be achieved by mere dilution of the extract by water. This provides an easy method for the extraction and recovery of usually water-insoluble and thermally labile products. The characterization of the precipitation process from hydrotrope solutions is of importance as crystal size distribution (CSD) affects filterability, washing and drying, and other physical properties, along with the recovery of the product.

Hydrotropic extraction is a very efficient process for the rapid extraction of certain organic compounds. Compounds such as curcuminoids, with aromatic rings and hydrophilic groups such as -OH, are extracted with a greater selectivity. Because of higher solubilization capacity, absence of any organic solvent residue in the final product, and the ambient conditions of the operations, hydrotropic extraction provides an easily scalable alternative to other methods of extraction of natural products, including supercritical fluid extraction. What is achieved with the pressure variation in the supercritical fluid extraction can be achieved by manipulation of concentration in the hydrotropic extraction. To have a complete process, the recovery of solute from hydrotropic solutions also needs an attention. The purpose of the present work was to study the precipitation of curcuminoids from their hydrotropic aqueous solutions by dilution with water. The study was aimed at developing crystal nucleation and growth rate expressions from the experiments using synthetic solutions and applying them to predict the crystal size distribution (CSD) of a product from actual turmeric extract under similar conditions. Such an analysis should be useful to identify the underlying principles and probably for better operation of the hydrotropic extraction of curcuminoids and/or other similar products.

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In the last decade, some research dealt with the precipitation of a dissolved solute from hydrotrope solutions, as there has been an increasing recognition of the importance of crystallization kinetics in the design and performance assessment of the products. Precipitation of salicylic acid from aqueous solutions of sodium salicylate by dilution as well as by reactive precipitation using sulphuric acid,[4] precipitation of nitrochlorobenzenes from Na-BMGS solutions,[5] separation of naphthols,[6] and of chlorobenzoic acids[7] are some of the reports dealing with crystallization from hydrotrope solutions. However, none of these studies dealt with the extraction from a complex plant matrix or crystallization of naturally occurring compounds from the actual extract.

The following report is the part of extraction process developed in our laboratory for the extraction of curcuminoids from turmeric rhizomes using hydrotropy. We report on crystal nucleation and growth kinetics for the precipitation of curcuminoids from hydrotropic solutions of pure curcuminoids as well as from hydrotropic extracts of turmeric. In both the cases, the rates were compared for the effects of different parameters. The method of s-plane analysis was followed to simultaneously deduce growth and nucleation kinetics expressions.[8]

POPULATION BALANCE AND MOMENT EQUATIONS

In a perfectly mixed semibatch crystallizer, with an assumption of negligible crystal breakage and agglomeration with time, the population balance equation for size independent growth rate is

$$\left(\frac{\partial n}{\partial t}\right) + G\left(\frac{\partial n}{\partial L}\right) = 0 \tag{1}$$

where G is the size independent overall linear growth rate and n is the population density.

For an unseeded semibatch crystallizer, the relevant boundary conditions to the population balance equation are

$$n(L,0) = 0 \tag{2}$$

and

$$n(0,t) = \frac{B}{G} \tag{3}$$

where B is the nucleation rate at near zero size.

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The moment transformation of the population balance equation, Eq. (1), with respect to size yields

$$\frac{d\mu_0}{dt} = B \tag{4}$$

$$\frac{d\mu_1}{dt} = \mu_0 G \tag{5}$$

$$\frac{d\mu_2}{dt0} = 2\mu_1 G \tag{6}$$

$$\frac{d\mu_3}{dt} = 3\mu_2 G \tag{7}$$

with boundary conditions

$$\mu_j = 0 \tag{8}$$

at $n(L,0) = 0$ and $j = 0, 1, 2, 3$.

The variation of crystal size in a semibatch crystallizer starting from $L = 0$ at $t = 0$ as the initial condition can be represented as

$$\frac{dL}{dt} = G \tag{9}$$

The population balance, Eq. (1), coupled with concentration profile in the hydrotrope solution through the set of moment equations and appropriate boundary conditions, mathematically represents the precipitation of a solute in a semibatch crystallizer.

s-Plane Analysis

The method of s-plane analysis can be used to determine both the growth and nucleation rates, from experimental transient population density curves. It is often advantageous to estimate model parameters in Laplace transform domain rather than in time domain.[8] The experimentally determined population density can be converted into the Laplace transformed response with respect to size as

$$n(s,t) = \int_0^\infty n(L,t)\exp(-sL)dL \tag{10}$$

By taking the Laplace transform with respect to size, the transformation of the population balance equation can be obtained

$$\frac{dn(s,t)}{dt} + G[sn(s,t) - n(0,t)] = 0 \tag{11}$$

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Although G and $n(0,t)$ are functions of t, they can be assumed as constant over a small time interval of t and $t + \Delta t$ and that parameters have average values over this interval. Using the zero initial condition with regard to the initial size distribution for N crystals, Eq. (1) reduces to

$$\frac{dn(s,t)}{dt} + Gsn(s,t) - B = 0 \tag{12}$$

Transforming the derivative in Eq. (12) into differentials gives the following working equation

$$\frac{\Delta n(s,t)}{\Delta t} = -Gsn(s,t) + B \tag{13}$$

where $\Delta n(s,t)$ is the difference between the Laplace transformed population density at any time t and Δt and $n(s,t)$ is the average of these quantities.

A plot of the time rate of change of the Laplace transformed population density $n(s,t)$ against the product of the Laplace transform variable s, and the average Laplace transformed population density $n(s,t)$ over the optimal range of the Laplace transform variable s, yields a straight line with slope $= -G$ and intercept $= B$. One of the obvious advantages of using the Laplace domain is that the sensitivity to experimental errors in the determination of the experimental response is greatly reduced provided that a suitable value of s is used. The Laplace transform variable s was constrained by $s_f L_2 = I$, where L_2 is mean particle size. The nucleation and growth rates represent the average value over the time interval, and so, all other state variables incorporated in the kinetic correlation should correspond to the average time.

EXPERIMENTAL METHODS

A series of experiments was performed to study the precipitation of curcuminoids from aqueous solutions of sodium cumene suphonate (Na-CuS). Standard curcuminoids and dry *Curcuma longa* rhizomes were obtained from M/s. Cancore Flavours and Extracts Ltd, Kochin, Kerala (India). Na-CuS was purchased from M/s. Navdeep Chemicals, Mumbai, and purified by recrystallization. Other chemicals, like hydrochloric acid and sodium hydroxide, or solvents for analysis, like methanol, ethanol, and chloroform (all AR grade), were purchased locally and were used as such.

The solubility of pure curcuminoids at pH 3 in aqueous Na-CuS solutions was determined by the addition of pure standard curcuminoids to

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aqueous solutions of different hydrotrope concentrations and stirring the suspension using a magnetic stirrer in a constant temperature bath at 30°C for 10 hours. The concentration of curcuminoids was determined by analysing the hydrotrope solutions using UV-Visible spectroscopy at wavelength 423 nm.

The saturated solutions of curcuminoids in Na-CuS for the precipitation experiments were prepared by adding solid curcuminoids to 2.0 mol/dm^3 Na-CuS solutions and the suspension was stirred using a magnetic stirrer for 10 hours and filtered with a filter of pore size of 0.4 μm.

The precipitation experiments were conducted in 1.0 dm^3 glass vessel provided with a flat lid having four entry holes for the impeller, thermometer, diluent addition, and sampling. A 6-blade pitched turbine impeller of 5.0-cm diameter was mounted at the central axis with a clearance of about 2.0 cm from the bottom. The temperature within the crystallizer was maintained constant at 30°C by using a water bath. An acidic water solution, with pH adjusted to 3 by addition of 1.0 mol/dm^3 hydrochloric acid, was kept at constant temperature of 30°C and was pumped using a peristaltic pump to the crystallizer at a predefined rate.

The product crystal size distribution (CSD) was determined using Coulter counter light scattering unit (Model LS 230) using a small volume module. The measurements were made in the size range of 0.4 to 2000 μm.

In a typical experiment, 50 cm^3 of 2.0 mol/dm^3 Na-CuS solution saturated with curcuminoids was charged into crystallizer. The precipitant (acidic water) addition rate was fixed to the desired value at the beginning of the run. Several samples (around 1.0 to 5.0 cm^3 each) were collected from the crystallizer at predefined time intervals. About 0.5 cm^3 of the sample was used to measure the CSD, whereas, the rest of the sample was filtered immediately using a syringe filter with a pore size of 0.4 μm. The clear solution was analyzed for the dissolved curcuminoids content.

Nine experimental runs were performed by varying the diluent addition rate, stirring speed, and the diluent addition point. In the first three runs, the stirring speed was kept constant at 100 rpm and the diluent addition rate was varied from 2.0 to 5.0 to 7.5 cm^3/min. In the next three runs, the stirring speed was kept constant at 200 rpm with the same diluent addition rates. In all six runs, the diluent was added directly at the surface. The next three runs were performed at a stirring of 200 rpm, for the same range of dilution rates, keeping the diluent addition point just below the plane of the impeller blade near the center of the vessel.

In a separate set of experiments, turmeric extracts in Na-CuS were prepared by extracting turmeric raw material using a 2.0 mol/dm^3 solution of Na-CuS.[9] Three extracts were prepared in three different batches using fresh raw material and hydrotrope solutions each time. The turmeric extracts

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were charged into the crystallizer for the crystallization experiments. Three runs were performed using the extracts (Run 10, 11, and 12). The crystallization kinetics of the precipitation of curcuminoids from the extracts was studied at a stirring speed of 200 rpm and diluent addition rate of 5.0 cm^3/min with the diluent addition at surface. The samples (around 1.0 to 5.0 cm^3 each) were withdrawn from the crystallizer at predefined time intervals. About 0.5 cm^3 of the sample was used to measure the CSD using the Coulter counter light scattering unit, whereas, the rest of the sample was filtered immediately using a syringe filter with a pore size of 0.4 μm. The clear solution was then analyzed for the curcuminoids content in the solution using high performance thin layer chromatography (HPTLC). The precipitated curcuminoids were also analyzed using HPLTC to determine the purity of the precipitated curcuminoids with respect to time.

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ANALYTICAL METHODS

The HPLTC analysis was performed on 10 cm × 10 cm HPLTC silica gel 60 F_{254} plates from Merck KGaA, Darmstadt, Germany. The extracts were applied as 0.5-cm bands using a Desaga applicator, Model AS 30, Desaga, Heidelberg, Germany. The separation was performed using chloroform–ethanol (95%) and glacial acetic acid (94:5:1, v/v) in a previously saturated thin layer chromatography chamber for 15 minutes. The plates were developed to a distance of 7.0 cm. The plates were then dried in air and scanned using a Desaga densitometer CD60 and Desaga software CD60 at wavelenght 423 nm.

In the spectrophotometric method, UV-visible spectrophotometer HITACHI (Model U-1100) Hitachi, Japan, was used with quartz cuvettes of 1.0-cm path length. The absorbance was recorded at a wavelength of 423 nm.

RESULTS AND DISCUSSION

A solute dissolved in a hydrotrope solution can be recovered by its simple dilution with water, as the solute solubility is a strong function of the hydrotrope concentration. The supersaturation for the precipitation of curcuminoids was achieved by the dilution of the solution using acidic water in the present studies as it was found separately that the precipitation was very slow at neutral pH and could take a very long time. Whereas by adjusting the pH of solution below the pKa of curcuminoids,

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the precipitation occurs at faster rates in acidic media and, therefore, the crystallization was investigated at pH 3.

The solubility data of curcuminoids in Na-CuS solution at pH 3 at 30°C are shown in Figure 1. The points indicate the experimental value, while the solid line is a result of smooth fitting of the data in a polynomial function,

$$S = 0.9041C_S^2 - 0.3359C_S + 0.0277 \tag{14}$$

Although, usually an exponential relation is used for representing the solubility in hydrotropic solutions, we preferred the polynomial function, in an empirical manner, for better representation in the subsequent calculations. The solubility of curcuminoids is a strong function of the

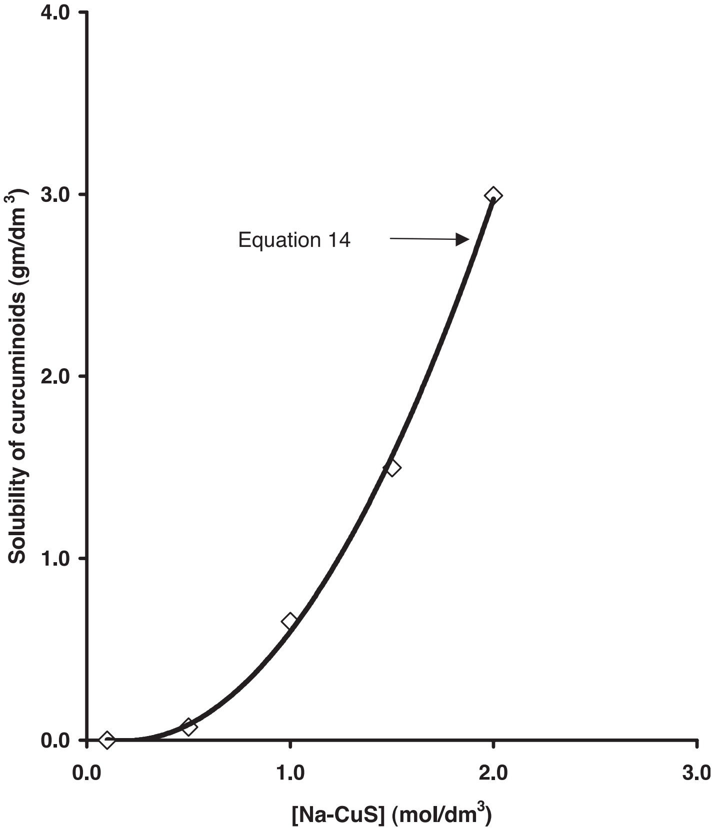

Figure 1. Solubility of curcuminoids in Na-CuS solution at pH 3.

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hydrotrope concentration as shown by the significant increase beyond the 0.5 mol/dm^3 concentration of Na-CuS, which reaches to 3.1 gm/dm^3 in 2.0 mol/dm^3 Na-CuS solution. It must be noted that curcuminoids are otherwise almost insoluble in water.

By comparing the experimentally determined concentrations in the aqueous Na-CuS solution with the solubility calculated from Eq. (14), the supersaturation values were estimated for each precipitation run wrt time (Figure 2). The supersaturation curves are strongly influenced by the diluent, i.e., water, addition rate, which is consistent with similar studies reported earlier.[4] Comparatively smoother supersaturation curves were obtained at the slow diluent addition rate of 2.0 cm^3/min. The supersaturation curves became sharper at higher diluent addition rates of 5.0 or 7.5 cm^3/min. The effect of stirring speed on the supersaturation was not very significant, in the range of 100 to 200 rpm. Also, no effect of the diluent addition point, both at the surface of suspension or below the impeller, was observed on the supersaturation curves. The slow precipitation rate of curcuminoids from the solution is relatively unaffected by the degree of mixing, at least in the range of agitation speed studied. Tavare and Gaikar[4] reported similar observations for precipitation of salicylic acid from hydrotropic media. The supersaturation (Δc) is the main driving force for the nucleation and growth rates of the crystals, it was further kinetically correlated with the growth and nucleation rates along with stirring speed (N) and suspension density (M_T). A precise measurement of supersaturation, however, would be difficult considering the process and the measurement techniques employed.

The CSD data obtained from the light scattering technique were used to calculate the growth and nucleation rates by the method of *s*-plane analysis. Some typical population density curves for a crystallization run are shown in Figure 3. The population density curves are binodal curves. Under the experimental conditions, a possibility of agglomeration of smaller crystals does not exist and the small hump in the population density curve at higher particle size may be attributed to such an agglomeration effect.[10] The curves indicate a distribution containing more of the finer size crystals than large size crystals. Although the crystals showed the growth with time, the continuous addition of diluent also results in formation of newer nuclei as the number density of the smaller crystals increased with time during the entire course of dilution. If the dissolved solute is located in different regions of microphase of the hydrotrope aggregates, the solute would tend to precipitate as fine crystal, rather than grown by mass transfer from one region to another. This could be an excellent method for preparation of ultrafine particles. The nucleation and growth rates determined by this parameter estimation technique represent average values over an average

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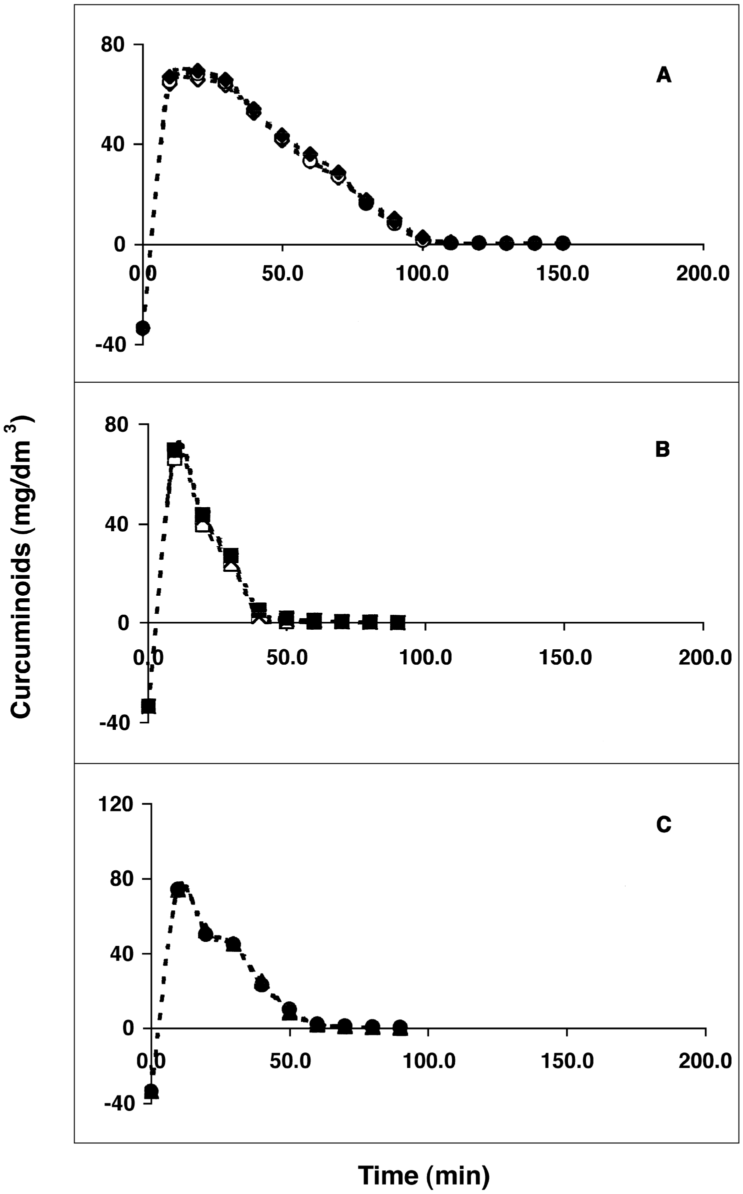

Figure 2. Super-saturation curves (pure curcuminoids). A. ◇ Run 1; ○ Run 4; ◆ Run 7. B. □ Run 2; × Run 5; ■ Run 8. C. △ Run 3; ● Run 6; ▲ Run 9.

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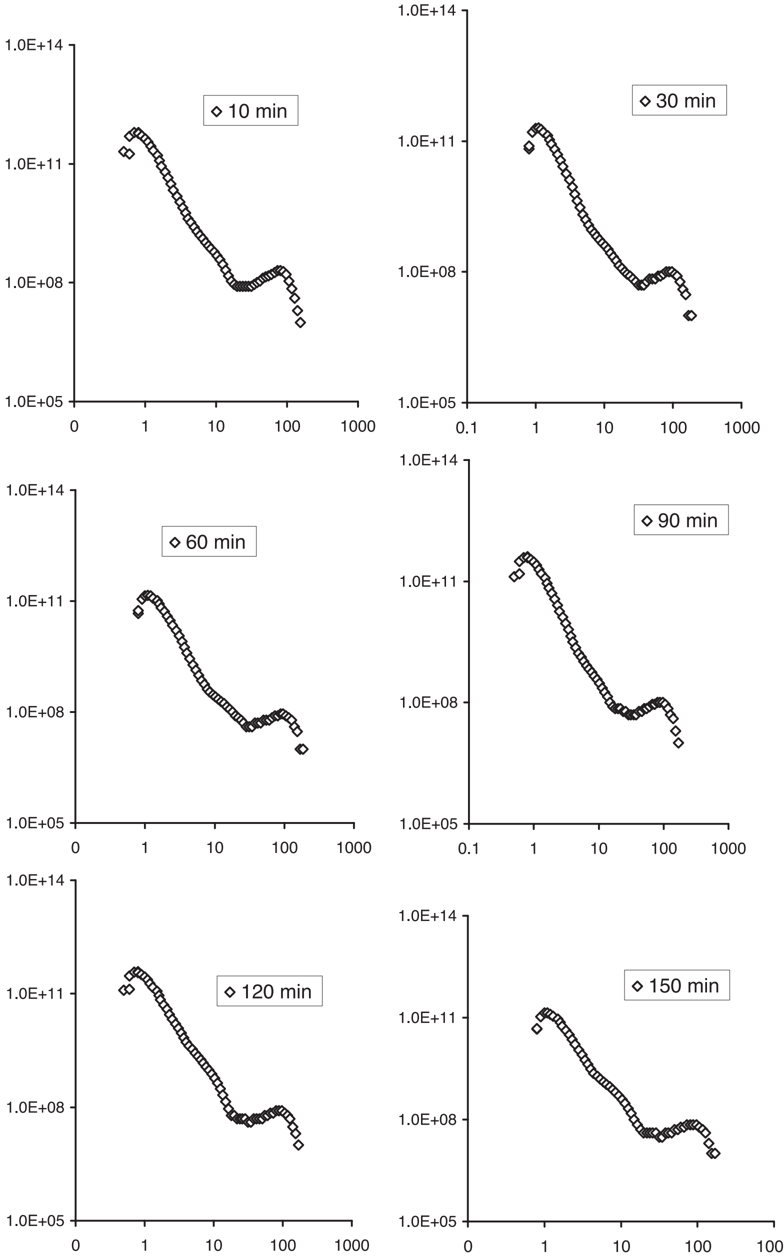

Figure 3. Typical population density curves (run 4, flow rate: 2.0 cm^3/min). *x* Axis; size of particles, µm; *y* Axis: population density of particles (number of particles/dm^3).

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time interval. In a small number of cases, incorrect parameter estimates (e.g., negative rates) were predicted. Such predictions may be attributed to several reasons, such as inaccuracies associated with taking representative samples and in measuring the population density curves as the important ones. It is important to note that the method of *s*-plane is usually insensitive to the noise levels associated with both the experimental observations and the numerical techniques used for integral evaluations.

Kinetic Correlation

Growth rate G and nucleation rate B obtained from all the experimental runs using the successive population density curves were correlated by power law kinetic expressions in terms of the observable variables as

$$G = k_g N^{m'} \Delta c^g \tag{15}$$

and

$$B = k_r N^{m''} M_T^j G^i \tag{16}$$

The values of the model parameters[8] in Eqs. (15) and (16) were estimated by the least-squares multiple linear regression analysis of the data from 40 observations (from 9 experimental runs) together and are reported in Figures 4 and 5.

Although the fit showed significant relative error (∼50 to 60%), the quality of correlation can be assessed from Figures 4 and 5. Figure 4 shows a large scatter in the growth kinetics correlation, which can be attributed to uncertainties associated with estimation of the variables and, in particular, with Δc. Also, a high exponent on the stirring speed in the nucleation correlation, Eq. (16), is probably due to the insignificant variation of this parameter during the experimental program. In general, the range over which the variables have been investigated is rather small and this might have contributed to the uncertainties associated with parameter estimates. However, the usefulness of these estimated parameters could be judged from the prediction of the CSD from these values for precipitation from actual turmeric extract of curcuminoids from aqueous hydrotrope solutions.

The data obtained from the precipitation experiments using the aqueous extracts were also analyzed using the *s*-plane method. The nucleation and growth rate kinetics were measured. The supersaturation curves for Runs 10, 11, and 12 are shown in Figure 6. The comparison between the precipitation of curcuminoids from pure curcuminoids solutions and the extracts were done by comparing the growth rates obtained for the extracts

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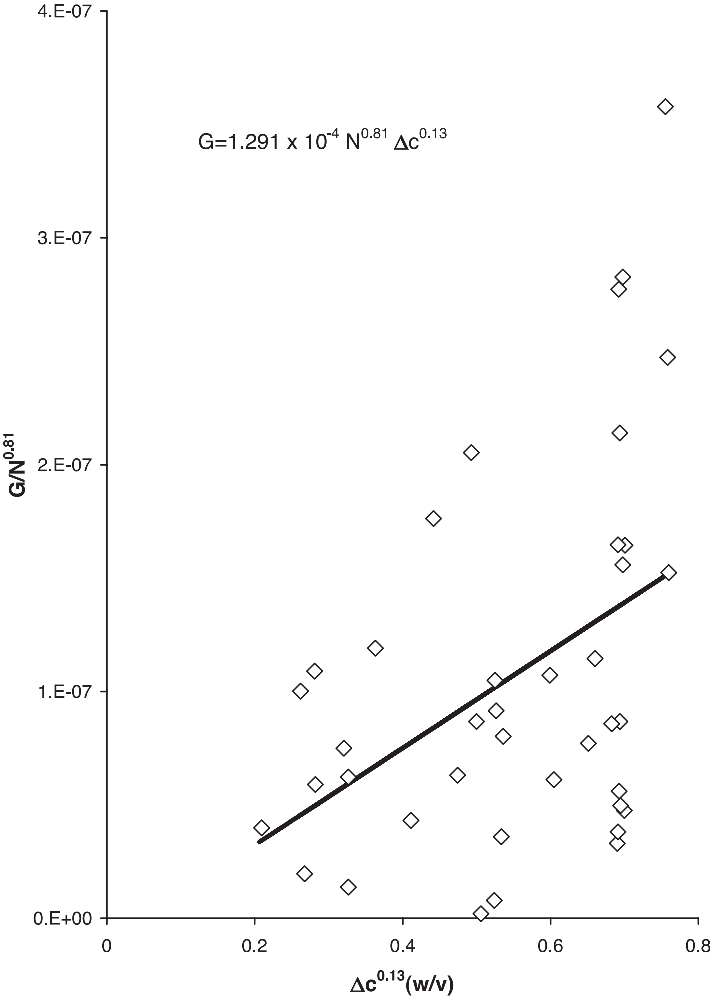

Figure 4. Relative kinetic correlation, Eq. (15).

and the expected growth and nucleation rates calculated from Eqs. (15) and (16) using experimental M_T and Δc values. The CSD can be estimated using these growth and nucleation rates. The values showed an excellent fit and actual CSD was predicted with a good accuracy (Figure 7).

This is the first report of study of the precipitation of a natural phytochemical from an actual hydrotropic extract. In the previous studies,[4–8] the precipitation studies from hydrotropic solutions were conducted either for

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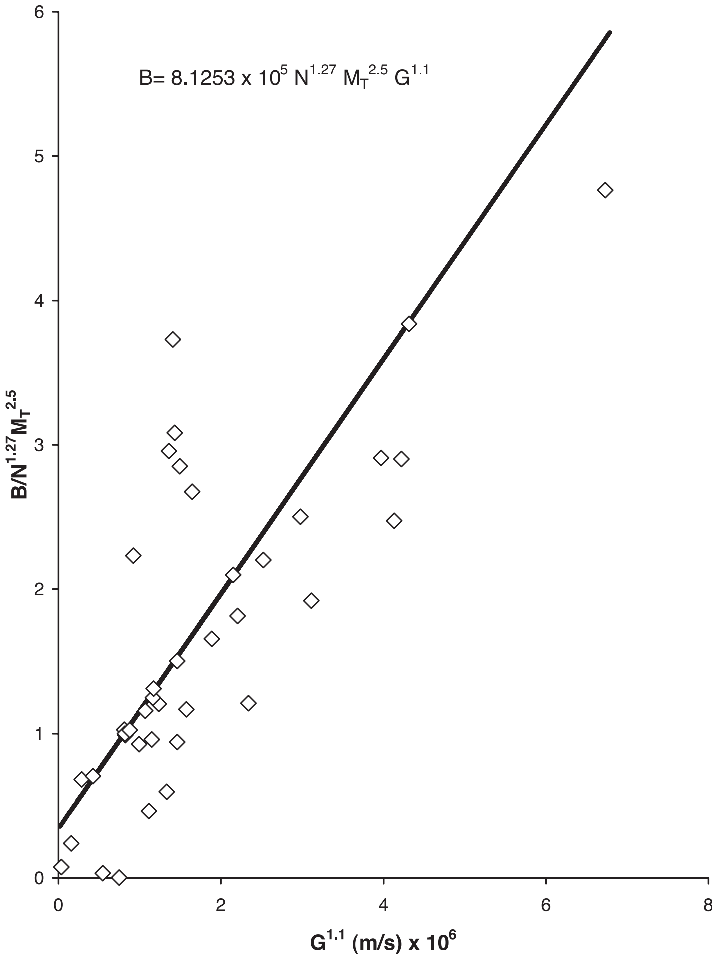

Figure 5. Relative kinetic correlation, Eq. (16).

separation of close boiling isomeric compounds from their synthetic binary mixtures or with solutions containing pure compounds. The molecules studied were not bulky and unknown impurities were absent, unlike in the present investigation. The specific effects of diluent addition rate were observed since it directly effects the supersaturation in crystallizer but the diluent addition point was not important.

The lower solubility of curcuminoids increases the relative uncertainties in the determination of supersaturation, which affects the further

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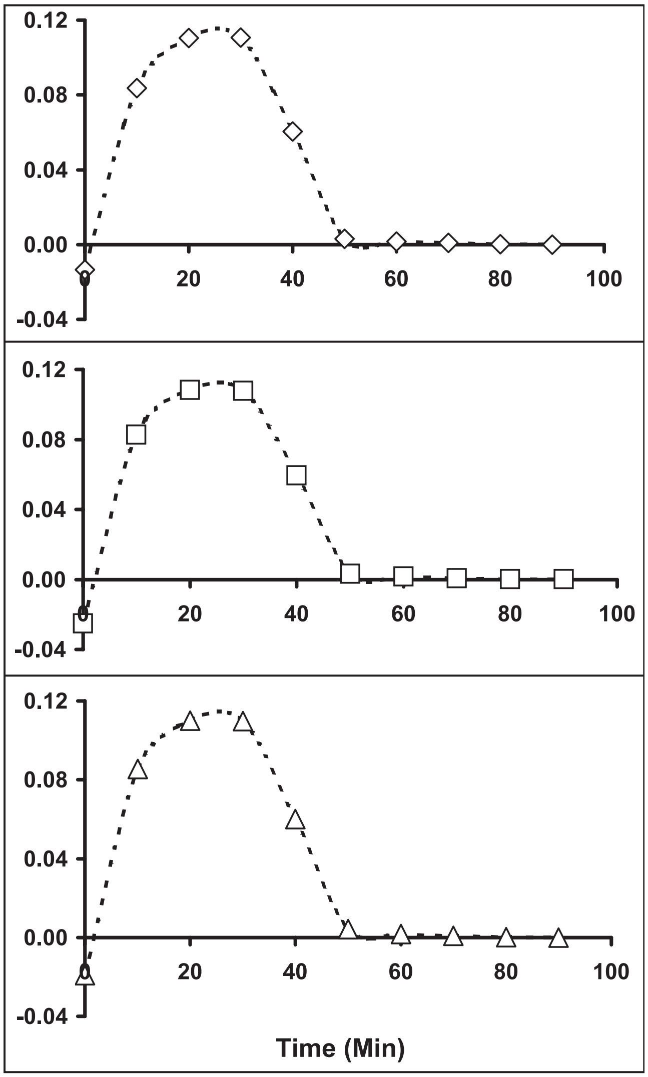

Figure 6. Supersaturation curves (turmeric extract solutions, flow rate 5.0 cm^3/min).

kinetics correlation of the data. As the turmeric extracts were used directly, other unknown impurities were also present along with the curcuminoids in the extract. No considerable difference was, however, observed in the purity of the recovered curcuminoids (Figure 8). The overall purity remained around 92%, showing no significant change with time.

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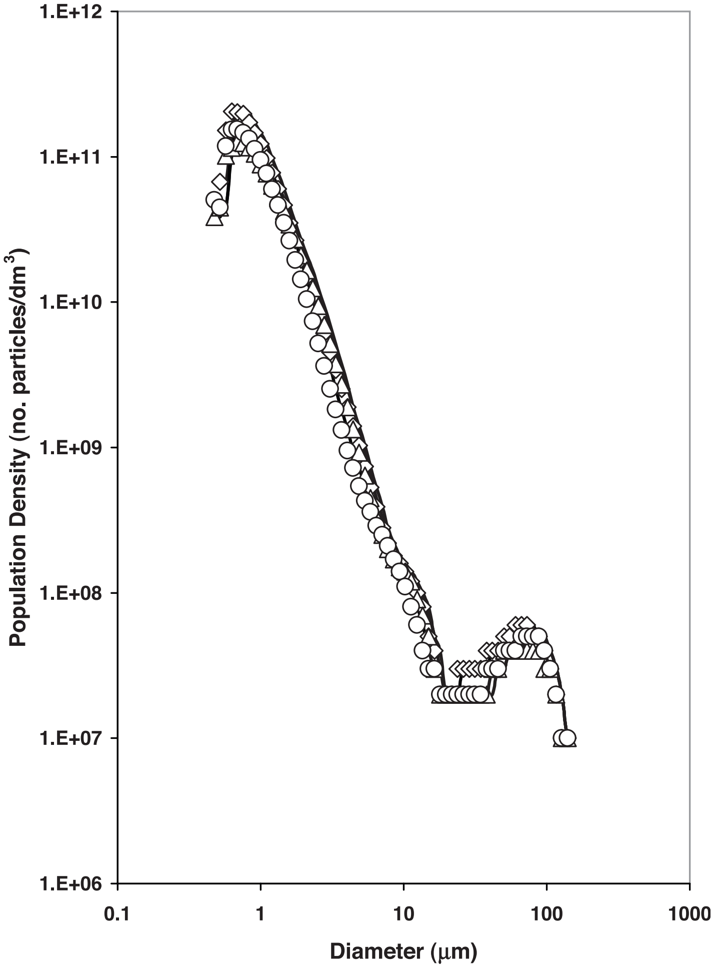

Figure 7. Comparison between the experimental and calculated CSDs for precipitation of curcuminoids from the extract. ◇ Experimental CSD Run 10, time 90 min, — predicted CSD Run 10, time 90 min; △ experimental CSD Run 11, time 90 min, — predicted CSD Run 11, time 90 min; ○ experimental CSD Run 12, time 90 min, — predicted CSD Run 12, time 90 min.

The precipitation rate of curcuminoids from either the pure curcuminoids solution or the extract was not high compared to the mixing speed. It also showed slower growth rates and higher nucleation rates, resulting in finer particles. Also, the CSD observed over time did not vary to a large extent and a constant pattern was observed for the population

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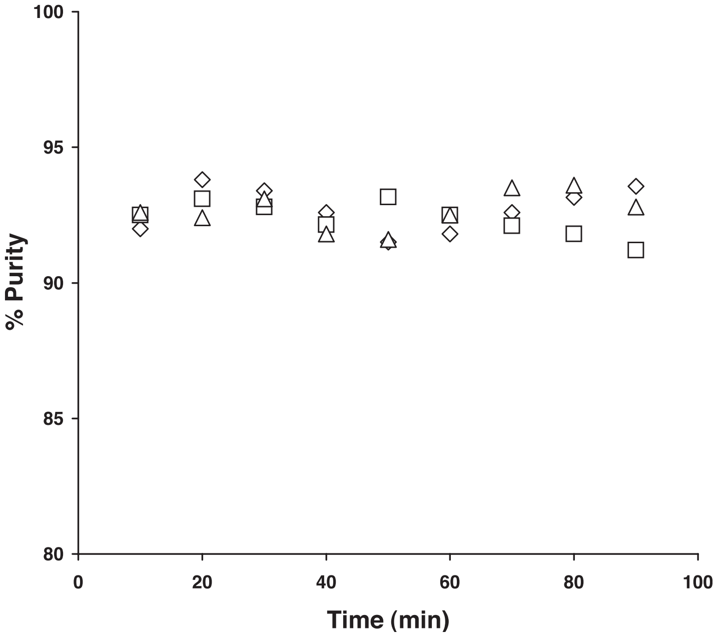

Figure 8. Purity of precipitated curcuminoids. ◇ Run 10; □ Run 11; △ Run 12.

density curve even over a sufficiently long time period. Also the time-invarient purity of the recovered curcuminoids from the extracts indicates no effect of impurities on the nucleation or growth of crystals in the present system.

CONCLUSION

The nucleation and growth rates of precipitation of curcuminoids from hydrotrope solutions can be simultaneously estimated using laboratory-scale batch crystallization. The method based on Laplace transform domain was found to be suitable for this purpose. The experiments with turmeric extracts are comparable with the results obtained from pure curcuminoids. The purity of precipitated curcuminoids from extracts was constant and the effect of impurities on the precipitation of curcuminoids was not significant. The precipitation from the aqueous hydrotrope solutions showed higher nucleation rates as compared to the crystal growth rates, leading to finer crystals in the product.

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NOTATIONS

B	nucleation rate (no/dm^3)
C_s	hydrotrope (Na-CuS) concentration (mol/dm^3)
Δc	supersaturation (gm/dm^3)
g	growth order in Eq. (15)
G	growth rate (m/s)
i	relative kinetic order in Eq. (16)
j	exponent of slurry density in Eq. (16)
k_g	growth rate coefficient in Eq. (15)
k_r	relative rate coefficient in Eq. (16)
L	crystal size (m)
m', m''	exponents of stirrer speed in Eqs. (15) and (16)
M_T	magma density (g/dm^3)
n	population density (number of particles/dm^3)
N	stirring speed (rev/min)
s	Laplace transform variable wrt/size (m^{-1})
S	solubility of curcuminoids (g/dm^3)
t	time (s)
μ_k	k^{th} moment of the crystal size distribution

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