Drowning-out crystallisation of benzoic acid: Influence of processing conditions and solvent composition on crystal size and shape

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**Abstract**

The aim of the present investigation is to increase the understanding of the role played by the solvent in inhibiting or enhancing crystal growth. Drowning-out crystallization experiments has been performed by the controlled addition of water or ethanol water mixtures to a saturated solution of benzoic acid in ethanol-water mixtures. Crystal habit controlling factors have been identified. Seeded crystallization experiments have been carried out to evaluate the effect of solvent composition on crystal habit at constant supersaturation. The solubility of benzoic acid in ethanol-water mixtures at the working temperatures has been determined.

Electro-zone sensing determinations and microscopic measurements are used to characterize the final crystalline product. It has been found that the shape of the benzoic acid crystals grown from ethanol-water solutions ranges from needles to platelets. Platy particles possess a predominant basal plane (001), bound by (010) and (100) faces, while needles are developed along the b-axis. Long needle-shaped particles have been produced at low initial bulk concentration and high ethanol concentration in the feed. Small platelets are obtained at high initial bulk concentrations and high water concentration in the feed.

The effect of solvent composition on the growth rate has been evaluated at constant supersaturation. Seed crystals are characterized by image analysis measurement both before and after each experiment. Length and width dimensions have been measured on the particle silhouette. The growth rate, the solid-liquid interfacial energy and the surface entropy factor for the (010) faces (length dimension) and (100) faces (width dimension) have been estimated. The interfacial energy and surface entropy factor decreases in the direction of increasing ethanol concentration due to increasing solubility.

The results suggest that at low ethanol concentration ($x_{\text{EtOH}} < 60\%$) growth proceeds by screw dislocation mechanism, and adsorption of ethanol molecules may reduce the growth rate. As the ethanol concentration increases above a critical value ($x_{\text{EtOH}} \geq 60\%$), the growth mechanism shifts to surface nucleation and the growth rate increases with increasing ethanol concentration. It has been suggested that the observed effect of the solvent composition on crystal habit is the result of two conflicting effects here referred as the kinetic and interfacial energy effects. High interactions of the pair ethanol-benzoic acid seem to be responsible of the growth retardation (kinetic effect) exerted by the solvent. On the other hand, increased ethanol concentration leads to reduce interfacial energy and increasing surface nucleation which might contribute to enhance growth kinetics.

**Keywords**: drowning-out crystallisation, solvent composition, benzoic acid, solubility, crystal growth, interfacial energy, surface entropy factor, growth mechanism, crystal shape distribution.

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Cover artwork by Jan Holmbäck: “Crystalberries”
To the light of my life
J³ Holmbäck

Y si durmieres?
Y si,
en sueños,
soñarás?
Y si,
en el sueño,
fuera al cielo
y allí tomaras
una extraña
y hermosa flor?
Y si,
al despertar,
tuvieras esa flor
en la mano?

Samuel Taylor Coleridge
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This thesis is based on the following papers, referred to by Roman numerals:


IV. González X. and Rasmuson, Å.C (1997), “Crystal habit of benzoic acid in a drowning-out crystallization process”, in Bremer international workshop on industrial crystallization (J. Ulrich, K Wangnick, eds), Universitätsdruckerei: Bremen, ISSN 1431.5149


VII. Holmbäck X. and Rasmuson Å.C. (2002), “Examination of the effect of solvent on crystal growth”, in the 15th International Symposium on Industrial Crystallization (ed by Prof. Angelo Chianese), Sorrento, Italy,
1 Introduction

Crystals of desired physical form and properties are required for a broad range of industrial applications such as in the production of specialty chemicals, catalysts, cosmetics, waxes, pharmaceuticals, food products, etc. The product size and shape may affect the rate at which materials can be processed, the agglomeration and mixing characteristics as well as the end use properties (e.g. bulk density, wettability, bioavailability, dispersability, etc). An undesired crystal shape can reduce the efficiency of the filtration step, alter the purity of the product, and create problems during drying, packaging, handling and storage.

Industrial production of crystalline particles under controlled operating conditions has become more and more important for targeted industrial purposes. Various areas are identified in which the control of crystal habit is a desirable long-term target (e.g. solids formulation, catalyst preparation, quality and efficiency of pharmaceutical products). Drowning-out crystallisation, affected by the addition of a water miscible organic liquid, forms the basis of several industrially important processes. It is commonly employed in the manufacture of pharmaceutical products, in the crystallisation of organic substances, for the preparation of pure inorganic substances and in the production of crystalline materials where high crystal yield and crystal purity are required. However, the drowning-out crystallisation possesses some characteristic features that can lead to the production of a large number of small particles with a high degree of agglomeration and marked secondary changes in the solid phase (Rousseau, R.W. et al 1987, Filipescue L., et al 1989 and Fleishmann W. et al 1984).

It has been reported that both crystal size and solid-liquid separation characteristics can be enhanced by a proper combination of the operating conditions and mixing mode. Namely, increasing precipitant addition rate, increasing precipitant concentration and higher agitation rates give rise to decreased mean particle size and coefficient of variation (Jones et al 1987, Nyvlt and Zacek 1986, and Charmolue and Rousseau 1990 and 1991). However, the significance of the growth environment on the relative growth rate of organic materials is not well understood at present (Davey and Garside 2000). The growth of crystals in a supersaturated solution is a complex process where surface adsorption, surface diffusion and integration into the crystal lattice are involved (Mersmann 2001). Much research work is still required to identify the controlling mechanism behind the effect of solvent on crystal growth (Lahav and Leiserowitz 2001).
1.1 Objectives and scope

The overall goal of the present investigation is to increase the general understanding of the role played by the solvent on the product size distribution and crystal shape.

In the present research work, the habit and size of benzoic acid drowned-out from different ethanol-water mixtures is studied. The influence of some process conditions (stirring rate, feeding profile, and feeding time, precipitant and bulk composition) on product characteristics has been investigated. Key habit controlling factors have been identified. In addition, seeded crystallization under controlled conditions has been carried out to investigate the effect of solvent on crystal growth and particle shape at constant supersaturation.
2 Literature review

Growth proceeds by volume and surface diffusion (Figure 2.1). Close to the interface, transport is restricted to molecular diffusion through a diffusion boundary layer. After the solute molecules have been transported from the bulk liquid phase to the interfacial region, they diffused onto the crystal surface before being integrated into the crystal lattice (surface diffusion step). During the surface integration step, bonds between the solute and solvent molecules are broken, freeing the solute to form bonds with the surface molecules, process known as desolvation. The partially desolvated growth unit enter into the adsorption layer of the face from where it may diffuse across the surface to a step and undergo further desolvation to enter a kink site position. The activation free energies associated with the desolvation, surface diffusion and surface integration steps are $\Delta G_{\text{desolv}}$, $\Delta G_{\text{diff}}$, and $\Delta G_k$, respectively (Davey et al 2000). The relative importance of desolvation, surface diffusion and surface integration depends on the structure of the surface and on solution properties. The solvent might affect crystal growth by its influence on the desolvation process (Meenan et al 2001). Strong interactions between the solute solvent at specific crystal faces might become the rate determining step to crystal growth (Berkovitch-Yellin 1985).

Figure 2.1. Surface structure and diffusional processes affecting crystal growth (Meenan et al 2001)
A change in crystal habit can be quantified by the relative rate at which the crystal face move outward in a direction normal to the face. The relative growth rate of the individual faces is influenced by both the internal crystal structure and external factors (e.g. the level of supersaturation, the solvent, temperature, and solution purity). Different crystal faces of the same crystalline material may exhibit different chemical properties arising from the specific arrangement of molecules in the crystal lattice and the corresponding portion of the molecule that is exposed at each face. Consequently, individual crystal faces may exhibit specific structural and chemical attributes that determine, among other things, their interaction with the environmentally determined properties (Meenan et al 2001, Davey and Garside 2000).

2.1 Influence of process conditions on product characteristics in a drowning-out crystallization process

It has been reported that both crystal size and solid-liquid separation characteristics can be enhanced by a proper combination of the operating conditions and mixing mode (Jones et al 1987). Percentage of recovery, crystal purity, crystal habit and degree of agglomeration has been found to be dependent on the process conditions (Charmolue et al 1991, Filipesce 1989, Bhatt et al 1986 and Fleischmann et al 1984, Rousseau et al 1987). Charmolue et al (1991) suggested that the crystal purity of L-serine crystals is linked to the habit and crystallization mode. Higher crystal purity was found for hexagonal crystals obtained from cooling crystallization than for needle-shaped particles crystallized by methanol addition.

It has been suggested that the micromixing process plays a relevant role in the precipitation process as concluded from the observation that the mean particle size decreases as the precipitant concentration was increased in the drowning-out crystallization of potash alum from aqueous solution using ethanol (Zacek et al 1984 and Mydlarz et al 1989). Indeed, it has been found that increasing stirring speed leads to increasing nucleation rate and decreasing growth rate. These effects are more pronounced at low stirring speed and low precipitant concentration (Nyvlt et al 1986). On the other hand, increasing precipitant concentration and higher precipitant addition rates causes higher levels of supersaturation that definitely favours nucleation rate over crystal growth and produces a large number of small crystals (Zacek et al 1984 and Charmolue et al 1991). In fact, it has been shown that the kinetic behaviour of fructose crystallization strongly depends on supersaturation, precipitant composition and temperature. Moreover, increased addition rates,
increased precipitant concentration and higher agitation rates give rise to decreased mean particle size and coefficient of variation (Jones et al 1987, Charmolue et al 1990 and Fleischmann et al 1984). It is then expected that programmed addition of precipitant controls the transient supersaturation and crystal growth rate, thereby improving the product crystal size distribution (Jones et al 1988). It is anticipated that, the metastable zone width would tend to decrease as the addition rate of the drowning-out agent is increased (Jones et al 1988 and Mullin et al 1989).

2.2 Influence of solvent effect on crystal growth and habit

The role played by the solvent in enhancing or inhibiting crystal growth is not clear at present (Lahav et al 2001). However, it has been reported that it depends on the supersaturation level, the prevailing growth mechanism, the molecular roughness and the atom types exposed at the surface (Davey 1978 and Meenan et al 2002). According to the existing literature (Berkovitch-Yellin 1985, Lahav et al 2001 and Mersmann 2001), the solvent may contribute to decrease growth rate due to a selective adsorption of solvent molecules or may enhance face growth rate by causing a reduction in the interfacial tension. The first mechanism has been referred to as the kinetic effect (Davey 1978 and Mersmann 2001) and has been attributed to a selective adsorption of solvent molecules at specific surface sites due to strong interactions between solute and solvent molecules (Meenan et al 2002 and Berkovitch-Yellin, 1985). The second mechanism referred to here as the interfacial energy effect is related to the influence of the solvent on the surface roughening which under certain circumstances may induce to a change in the growth mechanism (Davey 1978, Bourne 1980, Bourne et al 1976a and 1976b). The interfacial effect of the solvent has been attributed to a reduction of the interfacial energy and Gibbs free enthalpy to form nuclei (Mersmann 2001). Higher kink site incorporation rates, a change in the growth mechanism, and increasing growth rates might be promoted (Davey 1982, Berkovitch-Yellin 1985, Lahav et al 2001). However, the extent at which decreasing interfacial energies lead to increasing growth rates depends on the supersaturation level and the dominant growth mechanism (Davey 1978 and Mersmann 2001).

The mechanism at which solvent molecules are adsorbed on the surface is not clear at present. The Cabrera-Vermilyea model could be useful to increase the understanding of the effect of the solvent on the growth process (Meenan et al 2002 and Davey et al 1982). Three distinct adsorption sites could be identified: kink, step and ledge sites (Bourne 1980, Davey et al 1982, Davey 2000, Win et al 2000, and
Lahav et al 2001). Adsorption of solvent molecules onto the adsorption layer of a face (ledge sites), might lead to an increasing desolvation energy and a reduction of the surface flux to the steps with a subsequent reduction of the step velocity. Adsorption at the steps, which is hindered by the desolvation barrier, causes a reduction of the effective length along which kink sites may be formed. On the other hand, adsorption at the kink sites contributes to increase the activation energy for kink site entry ($\Delta G_k$), renders the kink site ineffective for crystal growth and leads to increasing inter-kink distance (Davey 1976).

Succinic acid crystals (Davey et al 1982) are taken as an example to explain the effect of solvent in the light of the Cabrera-Vermilyea model. Davey and co-workers reported that the (010) faces growth faster than the (100) faces. Examination of the surface chemistry of succinic acid crystals showed that the carboxylic acid group projects normally from the (100), but lie parallel to the (010) faces. In the case of the (100) faces, it is expected that the solvent molecules that arrives to the surface of the crystal, would be eventually adsorbed onto the ledge and fixed to the crystal lattice probably by hydrogen bonding interactions. Higher $\Delta G_{\text{diff}}$ and reduced surface flux to the step would cause a decrease in the step velocity and reduce the growth rate of the (100) faces. On the other hand, solvent molecules that enters into the adsorption layer of the (010) face would eventually be able to diffuse “two dimensionally” on the surface and probably be adsorbed at the steps or kink sites. A kink site that is poisoned by a solvent molecule would be ineffective for crystal growth. This type of adsorption might cause a significant increase in the inter-kink distance and prevent lateral step movement. It is believed that the adsorption at the ledge will more effectively reduce the step velocity than adsorption at the steps (Davey et al 1982).

A good example of the interfacial effect of the solvent on crystal interface structure is the one reported by Davey and co-workers on the growth kinetics of hexamethylene tetramine (HMT) crystallized from different solvents and solvent mixtures (Bourne and Davey, 1976; Bourne et al, 1978, Bourne 1980, Davey 1986). It was reported that the growth rate of the (110) face increased faster when water or water/acetone mixtures replaced ethanol as the solvent. Estimation of the surface entropy factor ($\alpha$-factor) suggests a change in the growth rate from a slow growth regime in ethanol to a fast growth regime in water. Decreasing surface diffusion and a direct integration to the crystal lattice were connected to a change in the growth mechanism. The observed effect was attributed to favourable interactions between the solute and the solvent at increasing solubility. It was suggested that increasing negative deviations from Raoult’s law not only increase solubility, but also decrease
the interfacial energy and the $\alpha$-values, thereby accelerating crystal growth (Bourne, 1980).

The kinetic effect of the solvent on crystal habit has been partially explained in terms of the relative polarity of the growing faces (Berkovitch-Yellin 1985 and Green et al 1996). Adipic acid crystal structure comprises chains of H-bonded molecules aligned along the a-axis (Davey et al 2000). Based on its crystal structure, it is expected that when growth occurs from an aqueous media the (100) surface might be covered by a layer of water molecules which occupies the H-bonding sites. On the other hand, when growth occurs from the vapour phase growth would be controlled by the internal lattice structure and the growth morphology could be predicted by the attachment energy model (Davey et al 2000, Berkovitch-Yellin 1985). It has been in fact reported that adipic acid crystals grown from aqueous solutions are platy with a dominant (100) basal plane while a needle-like morphology elongated along the a-axis has been experimentally found and predicted for crystals grown from the vapour phase (Davey et al 1992 and Berkovitch-Yellin, 1985).

It has been found that succinic acid crystals, which are actually structurally similar to adipic acid, grown from aqueous solutions are platy particles with a predominant basal plane (100) bounded by (111) and (011) faces, while needles with (100) and (010) planes were developed from isopropanol solutions (Davey et al 2000, and Van der Voort E. 1991). On the other hand, succinic acid crystals grown from the vapour phase have predominant (010) faces and smaller (100), (111), (110) and (011) faces. The observed effect of solvent on crystal habit could be partially explained by considering the polarity of succinic acid crystal (Green et al 1996, van der Voort E. 1991, Berkovitch-Yellin 1985 and Davey et al 2000). The following order of decreasing polarity of succinic acid faces has been reported by Berkovitch-Yellin 1985: (011)>(100)> (111)> (110)> (010). It is expected that the morphological importance (M.I.) of the (011), (100) and (111) faces will increase with increasing solvent polarity, while the M.I. of the (010) faces will decrease. However, the relatively high M.I. of the (010) faces developed from a solvent of intermediate polarity such as isopropanol could not be explained in these terms.
Recent studies, have suggested that strong adsorption of water molecules at a subset of sites and repulsion at the remaining set of sites might enhance growth rate by desolvating the surface and perpetuating its corrugation on a molecular level (Shimon et al 1990 and Lahav et al 2001). Lahav and co-workers reported that of (R,S)-alanine crystals grown in 80% methanol:water mixture grow faster at the +c amino end of the crystal than at the -c carboxylic end, suggesting that methanol binds stronger than water to the (001) faces. It was additionally reported that the dissolution of γ-glycine in both ethanol and methanol was notably faster along the amino end as compared to the carboxylic end. This suggests that effect of solvent on crystal growth can not easily be explained in terms of the binding potential of a face (Lahav et al 2001).
3 Fundamentals

The equilibrium condition in multi-component systems at constant temperature and pressure when the solvent does not enter the solid phase, establish that the fugacity of the undissolved solid, \( f^i_s \), is equal to that of the dissolved solute \( f^i_{\text{sat}} \). The fugacity of the dissolved solute can be conveniently expressed in terms of the activity coefficient at equilibrium conditions, \( \gamma_{\text{eq}} \), the mole fraction concentration of the solute in the solution (equilibrium concentration) \( x_{\text{eq}} \) and the standard state fugacity. The standard state fugacity can be defined as the fugacity of the pure solid solute in a sub-cooled or hypothetical liquid state below its melting point \( f_{i(scl)} \).

\[
\begin{align*}
\dot{f}_i^s &= \dot{f}_{i_{\text{sat}}} = \gamma_{\text{eq}}x_{\text{eq}}f_{i(scl)} \\
\end{align*}
\]  

(3.1)

If we rearrange the equation and express it in terms of the activity, the following expression is obtained:

\[
\begin{align*}
\dot{x}_{\text{eq}} &= \frac{\dot{f}_i^s}{f_{i(scl)}\gamma_{\text{eq}}} = \frac{\dot{\gamma}_i^s}{\gamma_{\text{eq}}} \\
\end{align*}
\]  

(3.2)

By using standard thermodynamics calculations (Walas, 1985), the activity of the pure solid phase can be determined (equation 3.4) and the solubility equation expressed as follows:

\[
\begin{align*}
\dot{x}_{\text{eq}} &= \frac{\dot{\alpha}_i^s}{\gamma_{\text{eq}}} \\
\dot{\alpha}_i^s &= \exp \left[ \frac{\Delta H(T_m)^f}{R} \left( \frac{1}{T_m} - \frac{1}{T} \right) - \frac{\Delta C_p}{R} \left( \ln \frac{T_m}{T} - \frac{T_m}{T} + 1 \right) \right] \\
\end{align*}
\]  

(3.3)

(3.4)

In this equation, the assumption that the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid can be regarded as constant has been made. It is customary to simplify equation (3.4) by considering that the heat capacity difference at the melting point is negligible. However, it has been shown both theoretically (Hildebrand et al 1970) and experimentally (Neau, et al 1997) that the heat capacity difference is closer to the entropy of fusion than to zero.
The fundamental dimensionless driving force for crystallisation (equation 3.6) can be expressed in terms of the concentration and the activity coefficient ratio as shown in equation 3.7 where $\gamma_{x}/\gamma_{eq}$ and $\gamma_{c}/\gamma_{eq}$ are the activity coefficient ratio on molar basis, $x$, and concentration basis, $c$, respectively.

$$\sigma_a = -\Delta \mu /RT$$

$$\sigma_a = \ln\left(\frac{\gamma_x}{\gamma_{eq}}\frac{x}{x_{eq}}\right) = \ln\left(\frac{\gamma_c}{\gamma_{eq}}\frac{c}{c_{eq}}\right)$$

### 3.1 **Interfacial energy**

The interfacial energy can be determined based on two main approaches: those based on the application of the classical nucleation theory (Mullin 2001) and those based on simplified thermodynamic models (Nielsen and Söhnel 1971; Bennema and Söhnel 1990; and Mersmann 2001). The Mersmann equation, derived on the basis of the Gibbs adsorption isotherm, correlates the crystal-solution interfacial energy with the natural logarithm of the equilibrium solubility (equation 3.8), where a value of 0.414 has been recommended for the constant $C$ (Mersmann 2001).

$$\gamma_{sl} = C kTV_m^{-2/3} \ln\left(\frac{c}{c_{eq}}\right)$$

Alternatively, Bennema and Söhnel (1990) proposed a model based on the regular solution theory where the interfacial energy, between a solid and its saturated solution, can be considered as a fraction of the enthalpy of dissolution (equation 3.9). The parameter $\xi_{\gamma r}$ in equation 3.9 depend on the particular crystalline face being considered and its roughness.

$$\gamma_{sl} = \xi_{\gamma r} \frac{\Delta H(T)_{diss}}{N_A V_m^{2/3}}$$
3.2 Surface entropy factor

The surface roughness, which refers to the order and the configuration of a surface at the molecular level, can be measured in terms of the surface entropy factor ($\alpha$–factor). The $\alpha$–factor which is originally proposed by Jackson and based on the Temkin-like block model (Figure 3.1) is in fact a surface roughness parameter and allows identification of likely growth mechanism based only on solute and solution properties (Bourne 1980, Meenan et al 2002, and Davey and Garside 2000).

![Fig. 3.1 Roughening of a solid-liquid interface (Davey and Garside, 2000)](image)

The general expression for the $\alpha$–factor is given in terms of the edge energy for crystallization from solution (Bourne et al 1976a and Mersmann 2001):

$$\alpha_{hkl} = 4\gamma_e / kT = 4V_M^{2/3} \gamma_{sl} / kT$$

(3.10)

Equation 3.10 has been further developed by a number of authors (Bennema and Gilmer 1973, Bourne and Davey 1976, Bennema and Van der Eerden 1977, Human et al 1981 and Jetten et al 1984) giving rise to the model proposed by Bennema and Gilmer (1973):

$$\alpha_{hkl} = \frac{\xi_{hkl}}{\Delta H(T)_{diss}} \frac{\Delta H(T)_{diss}}{RT}$$

(3.11)

The parameters $\xi_{hkl}$ and $\Delta H(T)_{diss}$ in equation (3.11) represent the anisotropy factor and the enthalpy of dissolution, respectively. Calculation of the $\alpha$-factor therefore involves two steps. Namely, the calculation of the anisotropy factor, $\xi_{hkl}$, from crystallographic data and the calculation of the heat of dissolution from measured quantities:
1. The anisotropy factor $\xi_{hkl}$ can be determined based on the Hartmann-Perdock theory according to equation 3.12 where $E_{\text{latt}}$ and $E_{\text{hkl}}$ can be predicted by computer simulations (Bennema and Gilmer 1973):

$$\xi_{hkl} = \frac{E_{\text{latt}} - E_{\text{hkl}}}{E_{\text{latt}}} \quad (3.12)$$

2. The heat of dissolution can be estimated following the thermodynamic route suggested by Jetten et al 1984. In his model, the entropy of dissolution at the equilibrium temperature $T$ is estimated by assuming that the process of dissolution is thermodynamically equivalent to a process of melting followed by a process of mixing. A three-step process represented by equation (3.14) replaces the melting process at the working temperature

$$\Delta H(T)_{\text{diss}} = T \Delta S(T)_{\text{diss}} = T(\Delta S(T)_{\text{fus}} + \Delta S(T)_{\text{mix}}) \quad (3.13)$$

$$\Delta S(T)_{\text{fus}} = \int_{T_m}^{T_f} \frac{C_{p,s}}{T} dT + \frac{\Delta H(T_m)}{T_m} + \int_{T_m}^{T_f} \frac{C_{p,l}}{T} dT \quad (3.14)$$

The partial molar entropy of mixing is in the work of Jetten et al (1984) considered equal to the ideal mixing entropy based on the regular solution theory:

$$\Delta S(T)_{\text{mix}} = \Delta S(T)_{\text{mix}}^{\text{ideal}} = -R \ln x_{eq}(T) \quad (3.15)$$

If the difference between the heat capacity of the solid and the heat capacity of the melt ($\Delta C_p = C_{p,s} - C_{p,l}$) can be regarded as constant inside the temperature range, the heat of dissolution can conveniently be expressed as follows:

$$\Delta H(T)_{\text{diss}} = T \left[ \frac{\Delta H(T_m)_{\text{fus}}}{T_m} + \Delta C_p \ln \left( \frac{T_m}{T} \right) - R \ln x_{eq}(T) \right] \quad (3.16)$$

By introducing equation 3.16 into equation 3.11 the surface entropy factor based on Jetten et al model (1984) is obtained:
Granberg (2000) has proposed an alternative approach referred to here as Jetten’s modified model. In Jetten’s modified model deviations from the ideal solution are accounted for by including the excess entropy term into the calculations of the molar entropy of mixing (equation 3.18). The excess entropy in equation 3.18 is obtained by assuming that the combinatorial term in the UNIFAC model accounts for the entropic contributions of mixing (equation 3.19).

\[
\Delta S^{\text{mix}} = \Delta S(T)_{\text{ideal}}^{\text{mix}} + S^E
\]  

(3.18)

\[
S^E \approx -R\ln(\gamma^C)
\]  

(3.19)

Substituting equation (3.18) into equation 3.16, the model proposed by Granberg (2000) for the enthalpy of dissolution (equation 3.20) is obtained.

\[
\Delta H(T)_{\text{diss}} = T\left[\frac{\Delta H(T_m)^{\text{fus}}}{T_m} + \Delta C_p \ln\left(\frac{T_m}{T}\right) - R\ln(\gamma^C)\right]
\]  

(3.20)

\[
\alpha_{hkl} = \tilde{\alpha}_{hkl} \left[\frac{\Delta H(T_m)^{\text{fus}}}{RT_m} + \frac{\Delta C_p}{R} \ln\left(\frac{T_m}{T}\right) - \ln(\gamma^C x_{eq})\right]
\]  

(3.21)

Computer simulations carried out by Gilmer and co-workers (Gilmer et al 1972a and Gilmer and Bennema 1972b) have shown that the surface entropy factor can be successfully correlated to the controlling growth mechanism. Three main growth regimes have in fact been identified (Bourne 1980 and Mersmann 2001):

a. \(\alpha \leq 3.2\) (linear growth): The surface is molecularly rough with integration sites covering the entire face. Each growth unit reaching the surface in a supersaturated solution is integrated into the crystal lattice after a short diffusion distance.

b. \(3.2 \leq \alpha \leq 4\) (two-dimensional nucleation growth): As \(\alpha\) increases the interface becomes smoother, growth becomes more difficult, as energetically favourable sites are limited. Above a critical \(\alpha\)-value, two-dimensional surface nucleation must occur in order to create energetically favourable sites for growth units.
c. $\alpha \geq 4$ (spiral growth): As the $\alpha$-factor increases even further, the surface becomes even more flat and does not provide enough integration sites for the arriving growth units. The availability of steps is not sufficient for growth to occur continuously in a layer-by-layer mechanism at low supersaturation. The presence of screw dislocations terminating in the surface is required to allow growth at low supersaturation.

### 3.3 Growth mechanisms

#### 3.3.1 Screw dislocation mechanism

The Burton-Cabrera-Frank diffusion (BCF) model best describes the growth rate for flat surfaces ($\alpha > 4$) where surface nucleation is not sufficient for growth at low to moderate supersaturation. The BCF model is based on the addition of growth units to kink sites on an endless series of steps at equal distance apart created by the presence of screw dislocations at the surface (Fig. 3.2). Crystal growth occurs perpetually up a spiral staircase. The curvature of the spiral cannot exceed a certain maximum value, determined by the critical radius of a two-dimensional nucleus, $r^*_c$ (equation 3.24).

The spiral steps are characterized by the average distance between steps, $y_o$, and by the average distance, $x_o$, between neighbouring kinks in the steps (Bennema and Gilmer 1973 and Mersmann 2001): The relation between the edge energy, $\gamma_e$ and the square of the intermolecular distance $a$ in equation 3.22 can be approximated to the interfacial energy ($\gamma_e \approx \gamma_{sl} a^2$) and molecular volume ($a = v^{1/3}_m$) as proposed by Ohara and Reid (1973), Bennema and Gilmer (1973) and Mersmann (2001).

\[ y_o = 19r^*_c = \frac{19\gamma_e a}{\kappa T \ln S} \]  
\[ x_o = \exp(\gamma_e) \frac{1}{\kappa T \sqrt{S}} \]  

The rate of growth $G_{hl}$, perpendicular to a face in unit length per unit time is given by equation 3.24 for the BCF model. The parameter $h$ in equation (3.24) represents the step-height and can be assumed equivalent to one molecule diameter, $h \approx a$ (Bennema and Gilmer, 1973 and Mersmann 2001)
\[ G_{hkl} = \frac{v_{step} h}{y_o} = \frac{2\bar{D}_{surf} \Gamma^* f_o \sigma}{x_s} \tanh \left( \frac{y_o}{2x_s} \right) \frac{h}{y_o} \] (3.24)

Equation 3.24 can be re-written as:

\[ G_{hkl} = C_1 \frac{2x_s}{y_o} (S - 1) \tanh \left( \frac{y_o}{2x_s} \right) \equiv C_1 \frac{C_2 (S - 1) \ln S \tanh \left( \frac{C_2}{\ln S} \right)}{\sigma} \] (3.25)

The constant values \( C_1 \) and \( C_2 \) in equation 3.25 are defined as follows:

\[ C_1 = \frac{\bar{D}_{surf} \Gamma^* y_o}{x_s^2} \] (3.26)

\[ C_2 = \frac{19\gamma_\sigma a}{2\kappa T x_s} \] (3.27)

The BCF model changes from a parabolic to a linear growth law as the supersaturation increases. If \( \sigma \ll C_2 \), the hyperbolic tangent assumes unity, resulting in a parabolic law. All growth units arriving in a region of width \( 2x_s \) around a particular step have a chance of entering that step alone. On the other hand, if \( \sigma \gg C_2 \), the growth rate depends linearly on supersaturation. Any growth unit arriving on the surface has a chance of entering one of several steps (Bennema and Gilmer 1973).

Figure 3.2. Square spiral originating from a screw dislocation on a crystal face (Winn and Docherty, 1998)

### 3.3.2 Surface nucleation mechanism: Birth and spread model

As the supersaturation increases, there is a possible change in growth mechanism since surface nucleation becomes a source of much higher density of kink sites. Adsorbed growth units collide with each other and a monolayer island nucleus, referred as two-dimensional nucleus is created to start growth (Fig. 3.3).
The Birth and Spread model (B+S model) describes the dependence of growth rate on supersaturation:

\[ G_{hkl} = h v_{\text{step}}^{2/3} \beta_{\text{surf}}^{1/3} = A (S - 1)^{2/3} \left( \ln S \right)^{1/6} \exp \left( - \frac{B}{\ln S} \right) \]  \hspace{1cm} (3.28)

In equation 3.28, the step-height has been assumed equivalent to one molecule diameter. A and B constants are described by equation 3.29 and 3.30 whereas the step velocity and the two-dimensional nucleation rate are given in equation 3.31 and 3.32, respectively.

\[ A = \left( \frac{16}{\pi} \right)^{1/3} a^{1/6} D_{\text{surf}} (V_m \Gamma N_A)^{5/6} \left( \frac{\beta \Gamma^*}{x_s} \right)^{2/3} \]  \hspace{1cm} (3.29)

\[ B = \frac{\beta_{sl} \gamma_e a}{(kT)^2} = \frac{\pi}{3} V_m^{4/3} \left( \frac{\gamma_{sl}}{kT} \right)^2 \]  \hspace{1cm} (3.30)

\[ \nu_{\text{step}} = \zeta \frac{2V_m D_{\text{surf}} \Gamma^*}{x_s h} \]  \hspace{1cm} (3.31)

\[ B_{\text{surf}} = \frac{2}{\pi} (\Gamma N_A)^2 \nu \left( \frac{V_m}{h} \ln S \right)^{1/2} \exp \left( - \frac{B}{\ln S} \right) \]  \hspace{1cm} (3.32)

Figure 3.3 A schematic representation of the creation of nuclei on a surface for the B+S model (Davey and Garside 2000).
If the supersaturation is greater than $B$ in equation 3.30, the exponential term approaches unity and the creation of surface nuclei is not rate determining to crystal growth. On the other hand, if the supersaturation is much lower than $B$ or if the interfacial energy is low, the activation energy term becomes dominant. In this latter case, the growth will be controlled by the number of surface nuclei formed per unit area and time (Davey 1978).
4 Experimental work

The effect of some process conditions on the mean particle size and aspect ratio of benzoic acid crystals grown from ethanol-water mixtures is investigated. The experimental work could be divided into two distinct stages. In the first stage, the crystal habit controlling factors are identified (Paper I and II) and extensively explored (Paper III, IV and V) in three series of drowning-out crystallisation experiments. Since knowledge of the solubility is a prerequisite to the investigation of any crystallization process, the solubility for the system benzoic acid-ethanol-water (20.00 ± 0.02 °C and 25.62 ± 0.02 °C) has been determined (Paper V and VI). In the second stage, the effect of solvent composition on face growth rate and final crystalline shape has been investigated in more detail by constant supersaturation experiments (Paper VI and VII).

Material

Benzoic acid (benzene carboxylic acid) has the molecular formula C₆H₅COOH; a molar mass of 0.122 kg/mol, a crystal density of 1316 kg/m³ and a melting point of 395.525 K. Values of 17982.3 J/mol (Lin et al 1993) and 90600 J/mol (Colomina et al 1982) have been reported for the enthalpy of fusion and enthalpy of sublimation, respectively. The solubility of benzoic acid at 15 °C is 0.0029 g of benzoic acid/g solution and 0.3724 g of benzoic acid/g solution in pure water and ethanol (abs), respectively. Benzoic acid crystallizes in lustrous, white, monoclinic leaflets or needles and belongs to the prismatic class of crystals (Kirk-Othmer, 1979).

Benzoic acid is found in natural constituent of many balsam-resins. It is contained in benzoin, liquidambar, balsams of Tolu and Peru, and other resinous bodies. Small amounts of benzoic acid also occur naturally in fruits and berries. For example, ripe berries of some Vaccinium species contain up to 2 mg/g of benzoic acid (Nationalencyclopedin, 1990). Benzoic acid is destructive to bacterial forms of life, and equally as valuable as salicylic acid in arresting putrefaction. Benzoic acid and benzoates are employed in a wide range of preservative applications and medical uses because of its effective combination of bactericidal and bacteriostatic action with non-toxicity and tastelessness. Its major medicinal use is in the treatment of disorders of the urinary tract when caused by alkaline urine. It is also of great use in cosmetics, resin preparation, plasticizer, in the production of caprolactan, etc.
4.1 Influence of process conditions on product characteristics: stage one

Solubility determination

The solubility of benzoic acid in water-ethanol mixtures in the range from 30 to 90 % by weight of ethanol (on solute free basis) has been experimentally determined by analytical (Paper V) and gravimetrical methods (Paper VI). The temperature chosen for determination were 20.00 ± 0.02 °C and 25.60 ± 0.02 °C for the analytical and gravimetrical methods, respectively.

The experimental set-up consisted of a thermostat water bath that stands on a serial magnetic stirrer. Erlenmeyer flasks provided with Teflon-coated magnetic stirrers, filled with an ethanol-water mixture and an excess of benzoic acid are used to prepare the saturated solutions. The flasks are covered and sealed with parafilm to prevent evaporation losses. The benzoic acid-ethanol-water solutions are equilibrated under constant stirring conditions at the selected temperature for at least 72 hours. When equilibration has been reached, the agitation is stopped and the excess of solid benzoic acid is allowed to settle down for at least 4 hours. Samples are taken from the clear solution and the concentration is determined according to the method selected.

In the analytical method, the sample density is determined by a high precision density-meter (Anton Paar, model 602) and the equilibrium concentration obtained from calibration charts (Paper V). In the gravimetrical method, the samples are weighed, and placed in a vacuum oven at 25 °C until a constant dry mass residue is obtained (Paper VI).

Drowning-out crystallization experiments

Apparatus

A jacketed, 1 L, glass crystallizer having 100 mm internal diameter is used. Four stainless steel baffles, 2 mm thick and 10 mm wide are attached to the walls. Agitation is provided by a six blade turbine of stainless steel. A piston pump is used to transfer the drowning-out agent from the stock vessel to the semi-batch crystallizer. The feed pipe is an L-shaped glass tube with 1.5 mm internal diameter. The feeding point outlet is located in the impeller outflow stream, 35 mm from the bottom of the vessel.
Procedure

Drowning-out crystallisation of benzoic acid has been performed by the controlled addition of a liquid precipitant to a saturated solution of benzoic acid in ethanol-water mixture at 20 °C. Pure water or ethanol-water mixtures of varying composition are employed as liquid precipitant. Higher supersaturation generation rates are achieved by increasing the water content in the liquid precipitant or the ethanol content in the bulk. The influence of different process variables on the crystal size distribution, mean particle size and particle shape were investigated. The experimental work has been divided into three experimental series where a set of different process conditions and starting-up procedures has been chosen for evaluation.

Experimental series number one and two have been carried out to explore the influence of agitation rate, total feeding time, feeding profile and ethanol bulk concentration on the mean particle size and crystal shape (Paper I and II). In the experimental series number three (Paper III, IV and V), a wide range of ethanol bulk concentrations is explored to evaluate the influence of solvent composition, and rate of supersaturation generation on product characteristics. Different precipitant addition rates (150, 301, 602, 902 and 1805 ml/h), increasing ethanol content in the liquid precipitant (0, 10 and 20 wt % of ethanol on solute free basis) and varying ethanol bulk concentrations (30, 40, 50, 60, 70, 80 and 90 wt % of ethanol on solute free basis) were evaluated.

Electrozone sensing determinations and microscopic measurements were employed to evaluate the influence of process conditions on crystal size distribution and general particle appearance, respectively (Paper I and II). Among 100 to 150 particles were counted and sized under an Olympus microscope. Particle length, particle width, and total number of particles free or in an aggregate were recorded. The mean particle length ($L_a$), mean particle width ($L_b$); aspect ratio ($MLW$), projected area diameter ($d_{eq}$), median size ($X_M$), mean size ($L_{43}$) and percentage of aggregation ($p_A\%$) are used to characterize the final crystalline product.

The percentage of aggregation is determined by dividing the total number of crystals contained in aggregates by the total number of particles that have been counted ($p_A\% = \frac{N(A)}{N} * 100$). The feed rate is either increasing (IF) or decreasing with time (DF), following a second order relation (Figure 4.1).
Influence of solvent composition on crystal growth: stage two

Apparatus
The experiments are performed in a 1 L, flat-bottomed jacketed, glass crystalliser (100 mm internal diameter) equipped with four vertical baffles (2 mm thick and 10 mm wide) attached to the crystalliser walls. A three-blade marine-type propeller of stainless steel (\(\Phi=5\) cm), placed 2 cm from the bottom, provides agitation (400 rpm). The batch crystalliser temperature is kept constant (25.6 ± 0.02 °C) by a heating and refrigerator circulator (Julabo MH/FP35).

Crystal growth experiments
The effect of solvent composition on face growth rate and final crystalline shape has been investigated with the aid of Image Analysis determinations (Paper VI and VII). A total of twenty-seven growth experiments have been performed where the supersaturation and solvent composition has been kept constant. At least six solvent compositions (30 %, 40 %, 50 %, 60 %, 70 % and 80 %) and three supersaturation levels (0.008, 0.012 and 0.016) have been evaluated under constant stirring (400 rpm) and temperature control (25.60 ± 0.02 °C).

A saturated solution of benzoic acid in an ethanol-water mixture (30 %–80 % wt of ethanol in solute free basis) is prepared and kept under constant stirring and temperature control (25.6 ± 0.02 °C) during at least 12 hours in a thermostatic bath. Once equilibrium conditions have been attained, a predefined amount of distilled filtered water is manually added to the solution to create an initial supersaturation (0.008, 0.012 and 0.016). The bath temperature is then raised to 30 °C and kept
constant for at least 24 hours. The solution is finally transferred to the crystalliser which is initially kept at 30°C, then the temperature is raised to 35 °C to dissolve the nuclei that could have been formed during the starting-up procedure. Fifteen minutes later the temperature is decreased down to the working temperature (25.6 °C) at a low cooling rate (0.1 °C/min) to avoid primary nucleation. Once the desired temperature is attained, a known amount ($M_{c,0}=0.001$ g) of seed crystals (Figure 4.2) carefully selected from a narrow sieve fraction (0.255-0.355 mm) is added to the supersaturated solution and allowed to grow during a time period $t_c$. When the growth time is completed, the agitation is stopped and the seed crystals are allowed to settle down to the bottom of the crystalliser. The supernatant solution is sucked out and the remaining solution is vacuum filtered to recover the seeds. The filtering system is isolated to avoid further growing by evaporation. The crystals are then dried in a desiccator and their final mass ($M_{c,o}$) determined by weighing.

Shape and size are characterised by image analysis. The image analysis set-up consists of a transmitted light microscope equipped with a CCD monochrome camera and a motorised stage connected to a stationary computer. The image acquisition process begins by opening the communication links between both the CCD camera and the motorised stage that is remotely controlled by the stationary computer. Between 100 to 150 seed crystals, carefully selected from a narrow sieve fraction (0.255-0.355 mm) were weighed and deposited on a glass slide provided with a reference frame. Rather uniform illumination of the scanned area was achieved by using normalised transmitted light. A professional image analysis software (Image-Pro-Plus 4.0) and an Excel program were used for the determination of the shape descriptors. The software handles the analogue image and converts it to a digital image on 256 grey-levels. Features of interest are identified, counted, measured, classified and exported to an Excel file.

Primary parameters are computed on the particle silhouette: surface $S$, perimeter $P$, particle length $L_a$ and particle width, $L_b$. Secondary parameters, equivalent diameter, $d_{eq}$ (equation 4.1), aspect ratio, $MLW$, also known as elongation ratio (equation 4.2) are calculated. The projected area diameter, $d_{eq}$, is the diameter of a circle having the same area as a projection of the crystal perpendicular to the plane of greatest stability: When the dimension $L$ in equation 4.3 is replaced by the length or the width, the face growth rate can be estimated. Cumulative size and shape distributions are obtained and the number averaged projected area diameter and aspect ratio of the product particles of each experiment are reported (Paper V).
\[ d_{eq} = \frac{\sum (A L_a L_b)}{N}^{1/2} \]  

(4.1)

\[ MLW = \frac{L_a}{L_b} \]  

(4.2)

\[ G_{sd} = \frac{(\Delta L)}{t_c} / 2 \]  

(4.3)

Figure 4.2 Photomicrographs of the initial seeds (sieve range 0.255-0.355 mm) for the growth experiments
5 Results and Evaluation

5.1 Solubility and activity coefficients

Tables I and II list the experimental results over the solubility of benzoic acid in 9 ethanol-water mixtures at 20.00 ± 0.02 °C and 25.62 ± 0.02 °C, respectively. The solubility is reported in mole fraction and represents the mean value obtained from a set of n measurements performed on the same sample. The best estimate of the standard error s.e.m. is also reported and involves the accuracy of the apparatus and the number of measurements (95% confidence level). In Figure 5.1, the mole fraction solubility of benzoic acid in ethanol-water mixtures is plotted as a function of the solvent composition (ethanol wt fraction on solute free basis) at two distinct temperatures (20.00 ± 0.02 °C and 25.62 ± 0.02 °C).

Table I Solubility of benzoic acid in ethanol-water mixtures at 20 °C

<table>
<thead>
<tr>
<th>Xeto (wt fr)</th>
<th>Xba 20.0°C (mole fr)</th>
<th>± s.e.m</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.0066</td>
<td>6.1E-04</td>
<td>2</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0133</td>
<td>6.7E-04</td>
<td>3</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0315</td>
<td>2.5E-04</td>
<td>3</td>
</tr>
<tr>
<td>0.60</td>
<td>0.0484</td>
<td>4.7E-05</td>
<td>2</td>
</tr>
<tr>
<td>0.70</td>
<td>0.0742</td>
<td>4.4E-05</td>
<td>3</td>
</tr>
<tr>
<td>0.80</td>
<td>0.1111</td>
<td>2.4E-04</td>
<td>4</td>
</tr>
<tr>
<td>0.90</td>
<td>0.1369</td>
<td>5.0E-04</td>
<td>4</td>
</tr>
</tbody>
</table>

Table II. Solubility of benzoic acid in ethanol-water mixtures at 25.6 °C

<table>
<thead>
<tr>
<th>Xeto (wt fr)</th>
<th>Xba (25.6°C)</th>
<th>± s.e.m</th>
<th>γeq (mole fr)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.30</td>
<td>0.0073</td>
<td>5.6E-05</td>
<td>36.3</td>
<td>4</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0216</td>
<td>8.3E-05</td>
<td>12.3</td>
<td>13</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0433</td>
<td>1.2E-04</td>
<td>6.1</td>
<td>11</td>
</tr>
<tr>
<td>0.60</td>
<td>0.0709</td>
<td>2.3E-04</td>
<td>3.7</td>
<td>12</td>
</tr>
<tr>
<td>0.65</td>
<td>0.0862</td>
<td>7.3E-05</td>
<td>3.1</td>
<td>4</td>
</tr>
<tr>
<td>0.70</td>
<td>0.1013</td>
<td>1.8E-04</td>
<td>2.6</td>
<td>11</td>
</tr>
<tr>
<td>0.80</td>
<td>0.1318</td>
<td>3.8E-04</td>
<td>2.0</td>
<td>7</td>
</tr>
<tr>
<td>0.85</td>
<td>0.1452</td>
<td>3.9E-04</td>
<td>1.8</td>
<td>5</td>
</tr>
<tr>
<td>0.90</td>
<td>0.1593</td>
<td>6.3E-04</td>
<td>1.7</td>
<td>15</td>
</tr>
</tbody>
</table>

In Figure 5.1, the mole fraction solubility of benzoic acid in water-ethanol mixtures is plotted as a function of the solvent composition (ethanol wt fraction on solute free basis) at both temperatures 20.0 ± 0.02 °C (analytical method) and 25.6 ± 0.02 °C (gravimetric method). As can be seen, the solubility increases both with increasing temperature and increasing ethanol concentration.
The UNIFAC group contribution model ($\ln \gamma = \ln \gamma^c + \ln \gamma^R$) has been used to predict the activity coefficient $\gamma_{eq}$ on molar basis. In the UNIFAC model, molecules are broken down into functional groups and the whole mixture is treated as a mixture of groups. The functional groups in benzoic acid molecule are identified as 6 aromatic CH-groups and 1 COOH. The interaction parameters needed for the calculations were obtained from Hansen et al (1991) and Fredenslund and Sorensen (1994). All the UNIFAC calculations have been carried out with the aid of a computer program written in Visual Fortran 5.0 and based on the UNIFAC group contribution model equation proposed by Fredenslund et al 1977 (Gracin et al 2002).

The experimental molar activity coefficient of benzoic acid, $\gamma_{eq}^{exp}$ (Table II) is calculated from equation 3.3 and compared with the one predicted by the UNIFAC model. As shown in Figure 5.2, the activity coefficient obtained from the UNIFAC predictions is a good approximation to the one obtained experimentally. The enthalpy of fusion at the melting point (17982.3 J/mol) required for the calculation of the activity in equation 3.4 was retrieved from Lin et al (1993). The heat capacity difference in this equation has been approximated to the heat capacity difference at the melting point by following the simplification suggested by Neau et al (1997). The linear dependency of benzoic acid heat capacity on the temperature for both the melted and the solid phase is shown in Figure 5.3 (Andrews et al 1926). The activity coefficient ratio as a function of the solvent composition is shown in Figure 5.4. It is
observed that the activity coefficient ratio approaches unity as the supersaturation decreases. Therefore the activity coefficient ratio has been approximated to unity.

![Graph showing activity coefficient ratio as a function of solvent composition.]

Figure 5.2 Predicted and experimentally activity coefficient as a function of the solvent composition.

![Graph showing linear heat capacity relationship for melt and solid.]

Figure 5.3. Linear heat capacity relationship for the melt and the solid (Andrews et al, 1926)
Figure 5.4 Activity coefficient ratio as a function of the solvent composition at constant driving force.

### 5.2 Drowning-out crystallization experiments

The experimental results obtained from series one is reported in Table III. The final crystalline product obtained from experimental series one (Paper I) is characterised as needles that decrease significantly in size as the ethanol bulk concentration, \(Y_2\), is increased from 50 % to 90 % wt regardless of the feeding profile, \(Y_1\) (Figure 5.5 and 5.6). No significant effect of process conditions on particle shape (\(MLW\)) and aggregation percentage (\(p_A\%\)) was encountered. However, the mean particle length (\(MPL\)) significantly decreases as the ethanol concentration was increased.

#### Table III Experimental results from series one

<table>
<thead>
<tr>
<th>Run</th>
<th>Y1</th>
<th>Y2</th>
<th>(L_{43}) (µm)</th>
<th>MPL (µm)</th>
<th>MLW</th>
<th>(p_A)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>DF</td>
<td>90</td>
<td>38,3±1,0 [2]</td>
<td>71,80±7,0 [2]</td>
<td>8,3±1,0 [2]</td>
<td>76,0±0,1 [2]</td>
</tr>
</tbody>
</table>
Figure 5.5 Photographs of product particles from the evaluation of feed profile and ethanol concentration on product characteristics in series one: (a) Run 1A (DF/50% etoh), and (b) Run 4A (IF/90%).

Figure 5.6. Influence of process variables on crystal size distribution (series one): (a) Influence of the feeding profile and (b) Influence of the ethanol bulk concentration.
In experimental series two (Paper II), the key process parameters influencing the mean particle size and habit of benzoic acid crystals have been identified. In Figure 5.7, the regression coefficients for the $2^3$ experimental design have been determined by using PLS regression. The scientific software Codex® 2.5 developed by SumIT System AB (Stockholm, Sweden) has been used for these determinations. The results have revealed that the ethanol concentration exerts the most significant influence on mean size and aspect ratio. The mean particle size and aspect ratio actually decrease as the ethanol concentration is increased. On the other hand, it has been found that by increasing the feeding time the mean particle size tends to decrease while the aspect ratio increases. A rather weak influence of agitation speed on aspect ratio has been encountered.

![Regression coefficients for series two: (a) mean size and (b) aspect ratio.](image-url)
Three types of drowning-out experiments have been carried out in series number three (Paper IV and V). In experiments type I, pure water is added at constant feed rate (5.0 g/min) to saturated bulk solutions having different ethanol concentration. In experiments type II, the ethanol concentration in the feed is varied, but the feed rate is constant (10.0 g/min) as well as the initial bulk solution composition (90 ethanol wt %). In experiments type III, the feed rate is altered, but the feed is always pure water and the initial bulk solution composition is unchanged (60 ethanol wt %). In Figure 5.8, the influence of ethanol bulk concentration (experiments type I) on the mean projected area diameter ($d_{eq}$), the mean particle length ($L_a$), the mean particle width ($L_b$) and the mean aspect ratio ($MLW$) is plotted. The influence of ethanol feed concentration and feed rate on product characteristics are plotted in Figure 5.9 (a) and (b), respectively.

Figure 5.8. Influence of the ethanol bulk concentration on the product characteristics

The effect of process conditions on particle size and shape can be summarized as follows. Increasing ethanol bulk concentration or decreasing ethanol concentration in the feed leads to decreasing aspect ratio (range 1.3 to 10.2) and decreasing mean size (range 69 to 218 µm). On the other hand, increasing feed rate results in increasing aspect ratio and decreasing mean size. The crystal habit moves from needle-like particles to platelets by increasing the ethanol bulk concentration, decreasing the ethanol feed concentration or decreasing the feed rate (Figure 5.9).
Figure 5.9. Influence of the feed rate (a) and ethanol feed concentration (b) on the product characteristics.
Influence of solvent composition on crystal growth

It has been found that benzoic acid crystals grown from ethanol-water mixtures range from needles to platelets depending on the process conditions. Single crystal x-ray diffraction measurements have revealed that platy particles possess a predominant basal plane (001), bound by (010) and (100) faces, while needles are developed along the b-axis (Paper V). The effect of solvent composition on the rate of the (100) and (010) faces has been studied. A total of twenty-seven growth experiments have been performed where supersaturation and solvent composition has been kept constant (Paper VI).
The influence of ethanol concentration on the rate of the (010) and (100) faces estimated according to equation (4.3) is plotted in Figure 5.11 at constant supersaturation. Supersaturation is here defined according to equation 3.5 where the activity coefficient ratio has been approximated to unity ($\gamma/\gamma_{eq} = 1.0$) based on the UNIFAC predictions (Figure 5.4). The experimental results suggest that the face growth rate depends on both the solvent composition and the prevailing supersaturation (Figure 5.11). Furthermore, it is observed that the (010) faces grow faster than the (100) faces (Figure 5.10) leading to higher median aspect ratio.
(Figure 5.12), higher growth rate ratios (Figure 5.13) and more elongated particles (Figure 5.14) as the ethanol concentration increases at constant supersaturation. Further details about the determination method employed for the determination of the crystal shape distributions are given in Paper V.

Figure 5.12. Effect of the ethanol concentration on the particle shape distributions at constant supersaturation \( \ln S = 0.008 \)

Figure 5.13. Effect of the ethanol concentration on Growth rate ratio at constant driving force
Figure 5.14. Influence of the supersaturation at constant ethanol concentration: (a) 30 %, (b) 40 %, (c) 50 % and (d) 70 % EtOH at three different supersaturations (0.008, 0.012 and 0.016)
6 Structural information and morphology of benzoic acid crystals

The structural information of benzoic acid crystals have been experimentally determined (Paper V). It has been found that benzoic acid crystals grown from ethanol-water solutions are needles or platelets depending on the prevailing conditions in the crystalliser. As mentioned in Section 5.3 single crystal x-ray diffraction measurements have revealed that needles are developed along the b-axis, while platelets possess a basal plane (001), bound by the (010) and (100) faces. The surface chemistry for the (010) faces (length dimension) and (100) faces (width dimension) has been predicted in order to examine the surface polarity. The theoretical morphology of benzoic acid crystals has been predicted based on the Bravais-Fiedel-Donnay-Harker and the attachment energy models (Paper V). The commercial package Cerius² (1995) developed by BIOSYM/Molecular simulations has been used in these predictions.

6.1 Crystal structure of benzoic acid crystals

Benzoic acid crystallises in a monoclinic structure with space group P21/c and four molecules ($Z=4$) in the unit cell (Figure 6.1). The benzoic acid molecule forms hydrogen-bonded dimers, which are lying in the <010> plane and held together by CH---O interactions (Berkovitch Yellin 1985, Sim et al 1955 and Feld et al 1981). The unit cell dimensions $a=5.4957$ Å, $b=5.1235$ Å, $c=21.9005$ Å and $\beta=97.375^\circ$ have been determined by single crystal x-ray diffraction by Karl Törnros at Stockholm university, 1995 (Paper V). A nice agreement with the values retrieved from the Cambridge Structural Database and data previously reported in the literature is obtained (Grimbergen et al 1996, Sim et al 1955 and Feld et al 1981).
6.2 Surface chemistry

The molecular arrangement for the (010) and (100) faces of the benzoic acid crystal is shown in Figure 6.2 (a) and (b), respectively (Paper V). The dotted lines represent the surface plane which is perpendicular to the plane of the paper sheet. The surface chemistry predictions of the (010) face suggest that the carboxylic acid group is well oriented to have a strong affinity for water molecules (hydrophilic face). On the other hand, the (100) faces exposes alternating layers of C-H- and carboxylic acid groups and so, is less hydrophilic than the (010) faces (Berkovitch-Yellin, 1985). It is expected that the (010) faces would interact strongly with hydrogen bonding solvents such as water. The growth rate of the (010) face would be slowed down when benzoic acid crystals are grown in a strongly hydrogen bonding solvent due to increasing desolvation energy. Conversely, the (100) faces which show a weak hydrogen bonding potential would be less affected by variations in the hydrogen bonding potential of the solvent (Berkovitch-Yellin, 1985).

6.3 Theoretical morphology

The Bravais-Friedel-Donnay-Harker (BFDH) model is used as an initial approach for identifying the likely faces that dominates the crystal habit. In the BFDH model, the morphology of a crystal is determined by the morphological importance (M.I.) of its various faces, which is derived from the interplanar distance $d_{hk0}$, corrected for the
extinction condition of the space group (Donnay and Harker 1937). The higher the M.I. of a face, the larger is its size and the higher the frequency of occurrence. Or in simpler terms, the slowest-growing and most influential faces are the closest-packed and possess the lowest Miller indices (Meenan et al 2001).

Figure 6.2. Surface chemistry predictions of benzoic acid crystal relevant faces: (a) face (010) and (b) face (100) (Holmbäck and Rasmuson 1999)

From the initial approach the theoretical morphology is further refined by the attachment energy model to predict the centre-to-face distance based on the assumption that there is a direct proportionality between the growth rate of a face (hkl) and the calculated attachment energy, $E_{att}^{hkl}$. The attachment energy model based on the further developed Periodic Bond Chain (PBC) theory (Hartman and Perdok 1955; Berkovitch-Yellin 1985) provides a tool for the calculation of the M.I. of a crystal face. In this theory, the various faces are classified according to the number of PBC vectors as F (flat) faces, S (stepped) faces, and K (kinked) faces which are parallel to at least two, one, and none PBC vector, respectively. F-faces are the morphologically most important faces and therefore
determine the crystal morphology. The attachment energy model may fail for solution-grown crystals where the solute-solvent interactions at the various crystal-solution interfaces may have a pronounced influence on the shape of the crystal (Davey et al 1982, Saska and Myerson 1990, Davey 1992, Van der Voort 1991 and Green et al 1996).

According to Hartman and Perdok theory, the attachment energy of a growth slice is calculated by assuming that the oncoming layer has an identical structure to a similar slice in the bulk. The crucial relation is therefore between the layer energy, $E_{sl}$, which is the energy released when a new layer is formed, and the attachment energy, $E_{att}$, which is defined as the energy per molecule released when a new layer is attached to the crystal face. The attachment energy controls the growth rate perpendicular to the layer while the slice energy measures the stability of the layer. The working hypothesis is that the morphological importance of a crystal face decreases with increasing attachment energy. In another words, the face with the lowest attachment energy will be the slowest growing and thus the morphologically most important.

The attachment energy predictions were obtained by using the Dreiding 2.21 force field, the charge equilibration approach and a dielectric constant of 1.0 (vacuum). The benzoic acid molecule is always hydrogen bonded to another benzoic acid molecule in the crystal structure (Berkovitch-Yellin 1985). Dimer molecules are considered as growth units. The reliability of the energy lattice predicted from the molecular modelling calculations can be estimated based on the equation ($\Delta H_{sub} = E_{latt} - 2RT$) proposed by Davey et al 1992 and William-Seton et al 1999. In the model proposed by Berkovitch-Yellin (1985), the enthalpy of sublimation is directly estimated from the attachment energy calculations ($\Delta H_{sub} \approx E_{latt}$). The molecular modelling calculations yield a sublimation enthalpy of -96.4 KJ/mol if the correction factor is included and -91.4 kJ/mol if excluding the correction factor. The experimental enthalpy of sublimation is $\Delta H_{sub} = -90.6$ kJ/mol as reported by Colomina et al 1982. A relative error of 0.9 % is obtained between the predicted crystal lattice and the one reported in the literature when the correction factor is neglected (Berkovitch-Yellin 1985).
Figure 6.3 shows the "theoretical form" of benzoic acid crystals as obtained from the (a) BFDH and (b) attachment energy models. The morphological importance (M.I) of the various faces in the attachment energy model is given as follows: (002) > (10-2) > (011) > (11-1) > (110). A key feature when comparing both morphologies is that the attachment energy morphology (Figure 6.3b) is more elongated along the b-axis than the BFDH morphology (Figure 6.3a). The presence of a strong hydrogen-bonding network along the b-direction leads to the observed elongation of the attachment energy morphology.
7 Discussion

7.1 Influence of process conditions on product characteristics at varying supersaturation

In semi-batch drowning-out crystallisation the mean particle size and crystal shape are expected to be dependent on the supersaturation. The rate of supersaturation generation has been managed by increasing the feed rate, decreasing the ethanol concentration in the feed or increasing the ethanol concentration in the bulk. Increasing rate of generation of supersaturation is expected to result in stronger nucleation and hence in a product where the crystal size is smaller, and this is in accordance with our experimental results. The influence of supersaturation on nucleation provides a reasonable explanation to the influence of process variables on the product mean size in the case of crystallisation of benzoic acid from water-ethanol mixtures. However, concerning the crystal shape both supersaturation and the solvent composition, seem to be of importance. In series I, the average MLW initially decreases at increasing ethanol concentration in the bulk, and gradually levels off into an almost constant value. Increasing ethanol concentration in the bulk leads to that the supersaturation generation rate increases. However, besides the experiment at 30 % ethanol the product mean size steadily decreases at increasing ethanol concentration in the bulk, which means that also the total crystal surface area for consumption of supersaturation increases. In series II, the increasing ethanol concentration in the feed reduces the rate of supersaturation generation but the simultaneously increasing size tends to counteract this. In series III, an increasing feed rate increases the supersaturation generation rate but again the size decreases which leads to a higher consumption rate. Hence, the influence of supersaturation on crystal shape cannot be easily resolved.

7.2 Influence of solvent composition on crystal growth at constant supersaturation

The effect of solvent on crystal growth is discussed by investigating two distinct and conflicting effects referred here as the interfacial energy effect and the kinetic effect, respectively. The interfacial energy and the surface entropy factor have been chosen to quantify the interfacial effect. This selection has been made based on the fact that decreasing interfacial energy brings about a reduction in the critical nucleus size and a subsequent roughening of the face involved (Mersmann 2001). The surface entropy factor which measures the roughness at a molecular level is used to assess
the effect of solvent on the growth mechanism (Davey 1982, Meenan et al 2001). It is evident that a proper prediction of the enthalpy of dissolution is required for the estimation of both the interfacial energy (equation 3.9) and the surface entropy factor (equation 3.10 and 3.11). The kinetic effect of the solvent on the growth of benzoic acid crystals has been analysed in terms of the existing theories.

7.2.1 Enthalpy of dissolution

The enthalpy of dissolution (equation 3.13) is estimated according to equations 3.16 (Jetten et al 1984) and equation 3.20 (Granberg 2000). In equation 3.16, the entropy of dissolution at the equilibrium temperature T is estimated by assuming that the process of dissolution is thermodynamically equivalent to a process of melting followed by a process of mixing. In equation 3.20, the system has been modelled as a nonideal solution by including the excess free energy term in the calculation of the entropy of mixing. In all equations, the heat capacity difference has been approximated to the heat capacity difference at the melting point by following the simplification suggested by Neau et al (1997). A value of 20.6 cal/mole has been considered for the heat capacity difference at the melting point (Figure 5.3). The results from the models mentioned above are compared with the values predicted by either neglecting the heat capacity difference or approximating it to the entropy of fusion at the melting point according to Hildebrand’s approach (equation 7.1).

\[
\Delta H(T)_{diss} = T\left[ \Delta S(T_m) \frac{f_{iss}}{T} \left( 1 - \ln \frac{T_m}{T} \right) - R \ln x_{eq} T \right]
\]  

(7.1)
The results obtained from the estimation of the enthalpy of dissolution are shown in Figure 7.1. It observed that enthalpy of dissolution estimated by approximating the heat capacity difference to the entropy of fusion (equation 7.1) are lower (14.9-22.1 kJ/mol) than the ones obtained by neglecting the effect of the heat capacity difference (18.8-25.9 kJ/mol). The enthalpy of dissolution obtained from equations 3.16 and 3.20, are 11.6-18.8 kJ/mol and, 10.4-15.4 kJ/mol respectively. It has been reported that the enthalpy of dissolution of organic compounds dissolved in organic solvents lies often in the range from 5 and 20 kJ/mol (Mullin, 1993). It has been suggested that Jetten’s modified model provides a good estimate of the enthalpy of dissolution when deviations from ideal behaviour are significant (Granberg 2000). However, based on the UNIFAC predictions (Figure 5.4) the benzoic acid-ethanol-water system is modelled as an ideal solution. The use of Jetten et al model (equation 3.16) is supported for the estimation of the enthalpy of dissolution of the system under investigation.
7.2.2 Interfacial energy

The solid-liquid interfacial energy has been estimated by using both the Mersmann (equation 3.8) and the Bennema (equation 3.9) model. Some vagueness in the estimation of the constant value \( C \) (equation 7.2) in both models has been reported by Mersmann, (2001). A value of 0.414 has been obtained by Mersmann (1990) when estimated from the crystal geometry. Nielsen and Söhnle (1971) and Bennema et al (1990) reported a value of 0.272 and 0.70, respectively when \( C \) was determined experimentally. The value of \( \xi_\gamma \) found by Bennema et al (1990) was 0.248 which is actually a close approximation to the theoretical value \( \xi_\gamma = 1/4 \) in the Kossel model when a cubic closest packing is considered for the (111) faces. However, the theoretical value in the Kossel model for the (100) faces \( \xi_\gamma = 1/3 \) is slightly higher whereas the one for the (010) faces is somewhat lower, \( \xi_\gamma = 1/6 \). Even though, there are some uncertainties in the estimation of the value of \( C \) the derivation method based on the crystal geometry has been recommended as a good estimation of the interfacial energy (Mersmann 2001).

\[
\frac{\gamma_{sl} V_m^{2/3}}{kT} = C \ln\left(\frac{C}{C_{eq}}\right) = \xi_\gamma (C - \ln x_{eq}) \tag{7.2}
\]

It has been found that the solid-liquid interfacial energy tend to decrease as the ethanol concentration increases (increasing solubility). The interfacial energy \( \gamma_{sl} \) derived from equation 3.9 is in the range 22.4-36.1 mJ/m\(^2\) and 11.2-18.0 mJ/m\(^2\) for the (100) and (010) faces, respectively. The enthalpy of dissolution in equation 3.9 has been determined by following the thermodynamic route proposed by Jetten et al (1984) according to equation 3.16. Equation 3.8 (Mersmann approach), provides an estimate of the interfacial energies that range from 8.1 to 21.2mJ/m\(^2\). Experimental evidence suggests that the interfacial energy estimated by using Mersmann model is best compared with that obtained from induction time measurements (Åslund 1994). However, a face-specific estimation of the interfacial energy (Bennema model) is more suitable to predict the effect of the growing environment on the surface perfection of a crystal. It is expected that the face growth rate will tend to increase due to decreasing interfacial energy at increasing ethanol concentration. It might then be anticipated that the (010) faces, which have a lower interfacial energy, would grow faster than the (100) faces due to a roughening effect of the solvent. The experimental results have shown that the growth rate along the b-direction is always higher than the growth rate along the a-direction which causes an elongation of the particles as the ethanol concentration increases (Figure 5.11 and 5.14).
7.2.3 Surface entropy factor

The surface entropy factor is estimated in order to characterize the surface roughness and identify the growth regime. The model proposed by Bennema et al. (1973) has been employed (equation 3.11). In that model, the anisotropy factor, $\xi_{hkl}$, has been estimated based on the Hartmann-Perdock theory (equation 3.12). Molecular modelling simulations (Cerius²) have been carried out for the prediction of the anisotropy factor (Paper VII). The values reported for the (010) and (100) faces are $\xi_{010} = 0.28$, and $\xi_{100} = 0.61$, respectively. The heat of dissolution in equation 3.11 has been estimated according to the model proposed by Jetten et al. (11.6-18.7 kJ/mol). The surface entropy factor (equation 3.17) obtained varies from 2.8-4.6 and 1.3-2.2 for the (100) and (010) faces, respectively.

The surface entropy factors obtained from equation 3.17 for the (010) faces are compared with those obtained by using equation 3.10. In equation 3.10, the surface entropy factor is a function of the interfacial energy according to the model proposed by Bourne and Davey (1976a). The interfacial energy in equation 3.10 has been estimated based on Bennema model (equation 3.9). The enthalpy of dissolution in equation 3.9 has been estimated by following the model proposed by Jetten et al., and Granberg, equations 3.16 and 3.20, respectively. The surface entropy factors estimated from equation 3.10 and equation 3.17 are plotted as function of the solvent composition in Figure 7.2. It is observed that the surface entropy factors obtained from equation 3.10 are higher than the ones obtained from equation 3.17 regardless of the model employed for the determination of the enthalpy of dissolution. It has been reported that the attachment energies of a \{hkl\} slice is lower than the vacuum attachment energy when the solvent has to be removed from the surface (Horst et al 1999). This suggests that the anisotropy factor estimated from the vacuum attachment energy might be lower than the one estimated from an interactive solvent. It is believed that equation 3.17 is suitable for the estimation of the surface entropy factor when the attachment energy model provides a good prediction of the growth morphology. Alternatively, it is believed that equation 3.10 provides a good estimate of the surface entropy factor when the interfacial energy predictions are reliable. Although the attachment energy model predicts an elongation of the morphology along the b-axis, the \{100\} and \{010\} faces that are present in the crystals grown from ethanol-water solutions are completely absent in the predicted morphology (Figure 6.3a/b). Equation 3.10 is recommended for the calculation of the surface entropy factor for solution growth.
The results suggest (Figure 7.2) that increasing ethanol concentration leads to a transition in the growth mechanism for the (010) faces from a slow growth regime at low ethanol concentration to an intermediate growth regime ($\alpha \leq 3.2$) at high ethanol concentration. This suggests that as the ethanol concentration increases above a critical value ($x_{\text{EtOH}} \approx 60\%$) surface nucleation becomes a source of favourable sites even at low supersaturation (Mersmann 2001). On the other hand, the results suggest that the surface entropy factors predicted for the (100) faces are always in the region of slow growth regime regardless of the solvent composition and supersaturation explored. In another words, any increase in the solubility due to increasing ethanol concentration might not lead to a change in the growth mechanism for the (100) faces (Gilmer et al 1972a, Gilmer and Bennema 1972b, Davey et al 1982). Under these circumstances, the mainly source of favourable integration at low supersaturation is the presence of spiral dislocations on the surface. The observed effect of solvent composition on growth rate is comparable to the reported influence of salt concentration on crystal growth mechanism (Plomp et al 1998 and Yu et al 2001).

Figure 7.2 Surface entropy factors (SEF) as a function of the solvent composition.
7.2.4 Solvent effect

According to the surface entropy factor estimations, two distinct growth mechanisms could be identified: screw dislocation at low ethanol concentration (slow growth regime) and surface nucleation at high ethanol concentration (intermediate growth regime). The BCF diffusion model (equation 3.25) and the B+S model (equation 3.28) are used to describe the growth rate inside the slow regime ($\alpha > 4$) and intermediate region ($3.2 \leq \alpha \leq 4$), respectively (Bennema and Gilmer, 1973, Bourne 1980, Mersmann 2001). The effect of solvent on growth rate is examined through estimation of the parameters $B$ (equation 3.30) and $C_2$ (equation 3.27). It is observed that the constant $C_2$ in the BCF model (equation 3.27) depends on both the edge energy ($\gamma_e \approx \gamma_{sl} a^2$) and the mean diffusion distance on the surface, $x_s$, but it is independent of supersaturation. $C_2$ can be estimated by assuming that $x_s$ can be equated to the intermolecular distance $a$ ($a = \nu_m^{1/3}$) as suggested by Bennema and Gilmer (1973). The estimated value of $C_2$ is in the range 7.4-11.9. The parameter $B$ for the B+S model is estimated according to equation 3.30. Values of $B$ between 0.6-0.8 have been obtained. The interfacial energy in equations 3.27 and 3.30 has been estimated according to Bennema model (equation 3.9) for the (010) faces where $\Delta H_{dis}$ has been obtained according to the model proposed by Jetten et al, 1984 (equation 3.16).

Based on the estimation of the parameter $B$ and $C_2$, it is found that the hyperbolic tangent (equation 3.24) assumes unity whereas the exponential term (equation 3.28) is close to zero. The growth rate for the BCF and B+S models is estimated by minimizing the quadratic difference between the simplified model equations and the growth rate for the (010). A precision of $1 \times 10^{-9}$ and a tolerance of 5% were used in these calculations. In Figure 7.3, the estimated growth rates for the (010) are plotted as function of the supersaturation ($S-1)\ln S$ for some representative ethanol concentrations. Based on these results, it is reasonable to suggest that when growth proceed by surface nucleation ($x_{EtOH} \geq 60\%$) the growth rate may increase due to decreasing interfacial energies and increasing two-dimensional nucleation rate (Bennema and Gilmer, 1973, Bourne 1980, Mersmann 2001 and Davey 1978). However, solvent adsorption may lead to conflicting effects when growth proceeds by screw dislocation ($x_{EtOH} \leq 60\%$). The growth rate might either decrease due to a delay in the step velocity or increase caused by an increased step density (Davey 1978, Davey 1982, Berkovitch-Yellin 1985, Lahav et al 2001, Mersmann 2001).
Figure 7.3. Experimental and predicted rate of growth as a function of the supersaturation for the (010) face

The effect of solvent on the step density for the (010) faces (BCF model) is examined by estimating the average distance between steps, $y_o$ (equation 3.22). The interfacial energy employed in this equation is the one estimated (11.2-18.0 mJ/m$^2$) based on the model proposed by Bennema (equation 3.9). In Figure 7.4, the density of steps and the interfacial energy for the (010) faces are plotted as a function of the solvent composition at constant supersaturation. The results reported in Figure 7.4 suggest that the step density $1/y_o$ increases with increasing ethanol concentrations due to decreasing interfacial energies. Based on this estimation, it is reasonable to expect that if the interfacial effect of the solvent dominates over the kinetic effect, the growth rate should increase as the ethanol concentration increases at constant supersaturation. However, the experimental results have shown that the growth rate decreases despite a decrease in the interfacial energy when the growth proceeds predominantly by screw dislocation mechanism. This observation suggests that the kinetic effect of the solvent may dominate over the interfacial energy effect when growth proceeds by screw dislocation.
The kinetic effect of the solvent could be interpreted in terms of the selective adsorption of water molecules on specific faces (Davey et al. 1982 and Davey 1992). It has been suggested that the adsorption of solvent molecules onto a growing surface is controlled by the hydrogen bonding potential of the face (Berkovitch-Yellin 1985 and Green et al. 1996). The surface chemistry predictions for the (010) face (section 6.2) suggest that the (010) faces interact strongly with a high polarity solvent such as water. Based on the adsorption mechanism theory proposed by Davey and co-workers (Davey 1976 and Davey et al. 1982), it is expected that water molecules that arrive to the (010) faces would be absorbed at the ledge while adsorption at the steps may eventually occur onto the (100) face. It means that water molecules that arrive to the (010) face would eventually be bound onto the adsorption layer of the surface which would contribute to increase the desolvation energy and decrease the step velocity. On the other hand, water molecules that arrive at the (100) face would be able to diffuse two-dimensionally before being eventually adsorbed at the steps. Adsorption at the step might contribute to increase the average distance between neighbouring kinks and hence decrease the step velocity (Davey et al. 1976). It is expected that adsorption at the ledge would be more effective in
inhibiting growth rate than adsorption at the steps (Davey 1982). However, the experimental results actually show the opposite trend (Figure 5.11). Decreasing growth rates have been reported at increasing ethanol concentration when growth proceeds by screw dislocation \( \chi_{\text{EtOH}} \leq 60 \% \). It has been suggested that the effect of solvent on crystal growth can not easily explained just in terms of the hydrogen bonding potential of a face (Shimon et al 1990 and Lahav et al 2001).

As previously mentioned, (R,S)-alanine crystals in an 80% methanol:water mixture grow faster at the +c amino end of the crystal than at the -c carboxylic end, suggesting that methanol blocks solute access to the pockets in a corrugated face more effectively than water (Shimon et al 1990 and Lahav et al 2001). This effect was explained in terms of the relay mechanism which suggest higher growth rate in aqueous solution for a “corrugated face” than for a “smoother face”. There is further experimental evidence that makes us to believe that ethanol molecules are more effective than water as growth retardation factor. Davey and co-workers reported that stronger adsorption of isopropanol molecules with the growing faces of succinic acid crystals leads to higher growth kinetics in water than in isopropanol. This effect was explained in terms of the solution chemistry of succinic acid crystals (Davey et al 1982). It was shown that succinic acid does not interact strongly with the three-dimensional water molecules; rather it prefers to form intra- and inter-molecular hydrogen bonds. Conversely, a higher interaction between the succinic acid molecule and isopropanol leads to higher solubility and slight negative deviations from Raoult’s law.

Simple inspection of the surface chemistry of the (010) and (100) suggest the more corrugated nature of the (010) faces (Figure 6.2). Figure 5.1 shows that the solubility of benzoic acid is higher in ethanol than in water. It has been reported that benzoic acid crystals form almost coplanar hydrogen-bonded dimers which are stacked along the b-direction (Berkovitch-Yellin, 1985). It might then be expected that benzoic acid crystals are more open to ethanol molecules and might interact more strongly than with water. Adsorption of ethanol molecules onto the growing faces may block access of solute molecules to the pockets (Figure 6.2) more effectively than water. The experimental evidence (Figure 5.11) suggests that the growth rate tends to decrease as the ethanol concentration increase at low supersaturation despite a decrease in the interfacial energy when growth proceeds by screw dislocation.
8 Conclusions

The effect of process conditions on product characteristics have been studied under two distinct operating modes. In the first case, the rate of supersaturation generation has been managed by increasing the feed rate, decreasing the ethanol concentration in the feed or increasing the ethanol concentration in the bulk. In the second case, the effect of solvent composition was investigated at constant supersaturation (seeded crystallization experiments). The experiments performed at varying rate of supersaturation generation have shown that the crystal habit of benzoic acid crystals depend on both the supersaturation and the solvent composition. Decreased mean particle size ($d_{eq}$) correlates well with increasing rate of supersaturation generation. At constant feed rate, high initial bulk concentration (0.4678 g/g solvent) and high water concentration in the feed give rise to the formation of small platelets. On the other hand, long needle-shaped particles are produced at low initial concentration and low water concentration in the feed. Big platelets and small needle-shaped particles have been produced at low feeding rates (150 m/h) and high feeding rates (1805 ml/h), respectively.

At constant supersaturation, the results have suggested that at low ethanol concentration ($x_{EiOH}<60 \%$) growth proceeds by screw dislocation mechanism, and adsorption of solvent molecules may reduce the growth rate. As the ethanol concentration increases above a critical value ($x_{EiOH}\geq60 \%$), the growth mechanism shifts to surface nucleation and the growth rate increases with increasing ethanol concentration. It was found that increasing ethanol concentration (increasing solubility) lead to decreasing interfacial energies, 11.2-18.0 mJ/m$^2$ and increasing surface roughness, $3.1< \alpha$-factor$<5.0$ for the (010) faces. The aspect ratios were in the range 1.4-3.6 and tend to increase with increasing ethanol concentration. It is believed that the effect of solvent composition on growth rate is the result of two conflicting effects, one tending to increase growth rate (interfacial energy effect) and the other tending to decrease growth rate (kinetic effect).

The results suggest that the interfacial energy effect becomes dominant when growth proceeds by surface nucleation. This is supported by the fact that the growth rate in the B+S model tends to increase with decreased interfacial energies and increased two-dimensional nucleation rates. On the other hand, the kinetic effect may dominate when the growth is controlled by both the kinetic of the step movement and the steps density. The kinetic effect of the solvent has been
explained in terms of a selective adsorption of solvent molecules on specific crystal faces. It has been suggested that the interaction between the solute and the solvent depends on both the hydrogen bonding potential of a face and the surface topography. It has been proposed that the observed decrease in growth rate (kinetic effect) when growth proceeds by the screw dislocation mechanism is the result of strong interaction between the ethanol molecules and the growing surface. The selective adsorption of ethanol at specific surface sites has been supported by the relay mechanism theory proposed by Shimon et al (1990) and Lahav et al (2001). It is suggested that the effect of solvent on crystal growth depends on the supersaturation level, the prevailing growth mechanism, on the surface chemistry and topography.

The present study has shown that mean particle size and crystal habit could be managed by a proper combination of the process conditions. The experimental results have revealed that the quality of the product obtained from a drowning-out crystallization process can be successfully improved. The Cabrera-Vermilyea model could be useful to explain the effect of solvent on crystal habit. Surface chemistry predictions have been found to be a valuable tool to evaluate the solvent effect on crystal growth. Image Analysis measurements has been proved to be a valid technique for the evaluation of the effect of solvent on face growth rates.

The role played by the solvent on growth rate and crystal habit is a very complex process. No simple mechanism could be used to explain the effect of solvent on growth rate. However, the results presented could help to clarify the role played by the solvent in inhibiting or enhancing crystal growth.
9 Notations

Latin symbols

\( A \) \quad B+S parameter
\( a \) \quad intermolecular distance (m)
\( \dot{a} \) \quad activity (-)
\( \dot{a}^s \) \quad activity in solid phase (-)
\( B \) \quad B+S parameter
\( B_{\text{surf}} \) \quad nucleation rate on the surface (m\(^{-3}\)s\(^{-1}\))
\( C_1 \) \quad BCF model parameter
\( C_2 \) \quad BCF model parameter
\( C \) \quad constant in equation 3.8 and 7.3
\( c_{\text{eq}} \) \quad solubility in equation 3.8 (mole/m\(^3\) of solution)
\( c_s \) \quad concentration of the solute in the solid phase, \( \rho/M_v \) (mol/m\(^3\))
\( C_p \) \quad Heat capacity (J/mol K)
\( C_{p,l}^f \) \quad Heat capacity of the liquid phase at the melting point (J/mol K)
\( C_{p,s}^f \) \quad Heat capacity of the solid phase at the melting point (J/mol K)
\( d_{\text{eq}} \) \quad mean projected area diameter (\( \mu \)m)
\( d_m \) \quad molecular diameter (m\(^2\))
\( D_{\text{surf}} \) \quad Surface diffusion coefficient (m\(^2\)/s)
\( \text{DF} \) \quad decreased feed profile (Figure 4.1)
\( \Delta C_p \) \quad Heat capacity difference (J/mol K)
\( \Delta H(T)_{\text{diss}} \) \quad Enthalpy of dissolution (J/mol)
\( \Delta H(T)_{\text{fus}} \) \quad Enthalpy of fusion (J/mol)
\( \Delta H(T_m)_{\text{fus}} \) \quad Enthalpy of fusion at the melting point (J/mol)
\( \Delta H_{\text{sub}} \) \quad Enthalpy of sublimation (J/mol)
\( \Delta S(T)_{\text{diss}} \) \quad Entropy of dissolution (J/mol K)
\( \Delta S(T)_{\text{fus}} \) \quad Entropy of fusion (J/mol K)
\( \Delta S(T_m)_{\text{fus}} \) \quad Entropy of fusion at the melting point (J/mol K)
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta S(T)^{mix}$</td>
<td>Entropy of mixing (J/mol K)</td>
</tr>
<tr>
<td>$\Delta S(T)^{mix}_{\text{ideal}}$</td>
<td>Entropy of mixing of an ideal solution (J/mol K)</td>
</tr>
<tr>
<td>$E_{\text{latt}}$</td>
<td>Total lattice energy (J/mol)</td>
</tr>
<tr>
<td>$E_{hkl}^{\text{att}}$</td>
<td>Attachment energy (J/mol)</td>
</tr>
<tr>
<td>$E_{hkl}^{\text{sl}}$</td>
<td>Slice energy (J/mol)</td>
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<td>$f_i$</td>
<td>fugacity (-)</td>
</tr>
<tr>
<td>$f_o$</td>
<td>surface occupied by one growth unit in the crystal</td>
</tr>
<tr>
<td>$G_{hkl}$</td>
<td>Face growth rate (m/s)</td>
</tr>
<tr>
<td>$G_{\text{ratio}}$</td>
<td>The ratio of the growth rate along the b- and a-direction for the (010) and (100) faces, respectively</td>
</tr>
<tr>
<td>$h$</td>
<td>Step height (m)</td>
</tr>
<tr>
<td>IF</td>
<td>increased feed profile (Figure 5.1)</td>
</tr>
<tr>
<td>$k_{\text{lin}}$</td>
<td>Rate constant (m/s)</td>
</tr>
<tr>
<td>$L$</td>
<td>characteristic dimension of a crystal</td>
</tr>
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<td>$L_a$</td>
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</tr>
<tr>
<td>$L_b$</td>
<td>mean measured width (µm)</td>
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<tr>
<td>$L_{43}$</td>
<td>mean size (µm)</td>
</tr>
<tr>
<td>$\ln S_a$</td>
<td>Dimensionless supersaturation in terms of the activity(-)</td>
</tr>
<tr>
<td>$\ln S$</td>
<td>Dimensionless supersaturation in terms of the concentration (-)</td>
</tr>
<tr>
<td>$M$</td>
<td>seed crystals mass (g)</td>
</tr>
<tr>
<td>$M_w$</td>
<td>molecular weight (0.122 kg/mol)</td>
</tr>
<tr>
<td>$MLW$</td>
<td>aspect ratio or elongation ratio (-)</td>
</tr>
<tr>
<td>$MPL$</td>
<td>mean particle length, L_b</td>
</tr>
<tr>
<td>$MPW$</td>
<td>mean particle width, L_a</td>
</tr>
<tr>
<td>$N_A$</td>
<td>Avogadro constant ($6.023 \times 10^{23}$ 1/mol)</td>
</tr>
<tr>
<td>$p_A$</td>
<td>percentage of aggregates</td>
</tr>
<tr>
<td>$R$</td>
<td>Gas constant (8.314 J/mol K)</td>
</tr>
<tr>
<td>$r_c^*$</td>
<td>critical radius of a 2D nucleus (m)</td>
</tr>
<tr>
<td>$S$</td>
<td>Supersaturation ratio, $x/x_{eq}$ (-)</td>
</tr>
<tr>
<td>$S^e$</td>
<td>Excess entropy (J/mol K)</td>
</tr>
</tbody>
</table>
\( T \) \hspace{1cm} \text{Temperature (K)}

\( T_m \) \hspace{1cm} \text{melting point (K)}

\( t_c \) \hspace{1cm} \text{crystallization time (s)}

\( \bar{v} \) \hspace{1cm} \text{mean velocity (m/s)}

\( v_{\text{step}} \) \hspace{1cm} \text{mean step velocity (m/s)}

\( V_m \) \hspace{1cm} \text{molecular volume, } M_v/\rho N_A \text{ (m}^3\text{)}

\( x \) \hspace{1cm} \text{concentration (mole fraction)}

\( x_{\text{eq}} \) \hspace{1cm} \text{solubility (mole fraction)}

\( x_{\text{EtOH}} \) \hspace{1cm} \text{ethanol wt concentration}

\( x_M \) \hspace{1cm} \text{median size}

\( x_o \) \hspace{1cm} \text{average distance between neighboring kinks (m)}

\( x_s \) \hspace{1cm} \text{mean displacement of adsorbed units (m)}

\( y_o \) \hspace{1cm} \text{step length in spiral growth (m)}

\( w \) \hspace{1cm} \text{mass concentration (g of solute/100 g solvent)}

\textbf{Greek symbols}

\( \alpha_{hkl} \) \hspace{1cm} \text{Surface entropy factor (-)}

\( \beta' \) \hspace{1cm} \text{Correction factor (-)}

\( \beta_{2D} \) \hspace{1cm} \text{2D shape factor}

\( \xi \) \hspace{1cm} \text{Retardation factor for a linear step (-)}

\( \xi_{hkl} \) \hspace{1cm} \text{Surface anisotropy factor (-)}

\( \xi_\gamma \) \hspace{1cm} \text{fraction in equation 3.9 (-)}

\( \gamma \) \hspace{1cm} \text{Activity coefficient (-)}

\( \gamma_e \) \hspace{1cm} \text{Edge energy (J/m)}

\( \gamma^C \) \hspace{1cm} \text{Activity coefficient combinatorial term (-)}

\( \gamma^R \) \hspace{1cm} \text{Activity coefficient residual term (-)}

\( \gamma_{sl} \) \hspace{1cm} \text{Interfacial energy between a solid and a liquid (J/m}^2\text{)}

\( \gamma^X \) \hspace{1cm} \text{Activity coefficient on molar basis}

\( \gamma_{eq}^X \) \hspace{1cm} \text{Activity coefficient at equilibrium on molar basis}
\( \gamma_o \) retardation factor for a kink (-)

\( \frac{\gamma^c}{\gamma^c_{eq}} \) Activity coefficient ratio on concentration basis

\( \frac{\gamma^x}{\gamma^x_{eq}} \) Activity coefficient ratio on molar basis

\( \mu \) Chemical potential (J/gmol)

\( \Delta \mu \) Chemical potential driving force (J/gmol)

\( \kappa \) Boltzmann constant, \( R/\bar{N}_A \) (1.38 X 10^{-23} J/K)

\( \sigma_a \) relative supersaturation in terms of the activity (-)

\( \sigma \) relative supersaturation in terms of the concentration

\( \rho \) density (kg/m^3)

\( \rho_{sl} \) linear density of steps (1/y_o)

\( \Gamma_i \) Surface concentration (moles/m^2)

\( \Gamma^* \) Equilibrium concentration of surface adsorbed units on the surface (moles/m^2)

\( \tau_{sl} \) Surface tension (J/m^2)

**Subscripts**

EtOH ethanol

hkl Miller index

dr dried mass residue

v sample vials

o initial solution

t Teflon septum

l liquid phase

s solid phase

sat saturated
scl hypothetical liquid state (sub-cooled liquid)
cα initial seeds crystals
cω final seeds crystals
eq equilibrium
s solute in the solid phase
sup supersaturated
m melting point

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