Haiyan Qu

TOWARDS DESIRED CRYSTALLINE PRODUCT PROPERTIES:
IN-SITU MONITORING OF BATCH CRYSTALLIZATION

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Abstract

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The objective of industrial crystallization is to obtain a crystalline product which has the desired crystal size distribution, mean crystal size, crystal shape, purity, polymorphic and pseudopolymorphic form. Effective control of the product quality requires an understanding of the thermodynamics of the crystallizing system and the effects of operation parameters on the crystalline product properties. Therefore, obtaining reliable in-line information about crystal properties and supersaturation, which is the driving force of crystallization, would be very advantageous. Advanced techniques, such as Raman spectroscopy, attenuated total reflection Fourier transform infrared (ATR FTIR) spectroscopy, and in-line imaging techniques, offer great potential for obtaining reliable information during crystallization, and thus giving a better understanding of the fundamental mechanisms (nucleation and crystal growth) involved.

In the present work, the relative stability of anhydrate and dihydrate carbamazepine in mixed solvents containing water and ethanol were investigated. The kinetics of the solvent mediated phase transformation of the anhydrate to hydrate in the mixed solvents was studied using an in-line Raman immersion probe. The effects of the operation parameters in terms of solvent composition, temperature and the use of certain additives on the phase transformation kinetics were explored. Comparison of the off-line measured solute concentration and the solid-phase composition measured by in-line Raman spectroscopy allowed the identification of the fundamental processes during the phase transformation. The effects of thermodynamic and kinetic factors on the anhydrate/hydrate phase of carbamazepine crystals during cooling crystallization were also investigated.

The effect of certain additives on the batch cooling crystallization of potassium dihydrogen phosphate (KDP) was investigated. The crystal growth rate of a certain crystal face was determined from images taken with an in-line video microscope. An in-line image processing method was developed to characterize the size and shape of the crystals. An ATR FTIR and a laser reflection particle size analyzer were used to study the effects of cooling modes and seeding parameters on the final crystal size distribution of an organic compound C15. Based on the obtained results, an operation condition was proposed which gives improved product property in terms of increased mean crystal size and narrower size distribution.

Keywords: batch crystallization, anhydrate/hydrate, thermodynamic relative stability, solvent-mediated phase transformation, Raman spectroscopy, ATR FTIR, in-line monitoring, image analysis

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This thesis is based on the following papers, which are referred to in the text by Roman numbers I-V.


Associated publications:


Contribution of the author

The author carried out all of the experiments and the calibration of Raman spectra, made the necessary calculations, and interpreted the obtained results for publications I, II, III, and V. The author wrote the manuscripts together with the co-authors.
The author planned and performed the crystallization experiments in Paper IV. The calibration of ATR FTIR spectra in Paper IV was done by Dr. Kati Pöllänen. The interpretation of the operation parameter effects on the crystallization of C15 was completed by the author. The manuscript was written by the author together with the co-authors.
List of Symbols

\( a \)  Activity (eq. 2.4) [-]
\( a \)  Molecule diameter (eq. 2.23-2.24) [m]
\( a \)  Surface area occupied by one crystallization molecule (eq. 2.34) [m\(^2\)]
\( A \)  Nucleation constant (eq. 2.7 and eq. 2.11) [-]
\( A \)  Free energy of a solid (eq. 3.1) [J]
\( A' \)  Induction time constant (eq. 2.14-2.15) [-]
\( A' \)  Surface nucleation based crystal growth model parameter (eq. 2.21-2.23)
\[ m/s \]
\( A_B \)  Heat transfer area of a batch crystallizer [m\(^2\)]
\( B \)  BCF growth model parameter [m/s]
\( B' \)  Surface nucleation based crystal growth model parameter [-]
\( c \)  Concentration, arbitrary units
\( c \)  Velocity of light [m/s]
\( C_P \)  Heat capacity of the solution in crystallizer [J/(kg K)]
\( C_S \)  Seed loading, defined as the ratio of the seed mass and the theoretical yield of the crystallization [-]
\( \Delta C_i \)  Supersaturation of polymorph i [g/100g solution]
\( D_{surf} \)  Surface diffusion coefficient [m\(^2\)/s]
\( E \)  Internal energy of a solid [J]
\( f \)  Fugacity [Pa]
\( F \)  Shape factor ratio of the nuclei [-]
\( g \)  Overall order of the growth process [-]
\( G \)  Gibbs free energy (eq. 2.6-2.9, eq. 3.2-3.4, eq. 3.6-3.7) [J]
\( G \)  Linear crystal growth rate (eq. 2.26) [m/s]
\( H \)  Enthalpy [J]
\( \Delta H_d \)  Molar enthalpy of dissolution [J/mol]
\( \Delta H_f \)  Molar enthalpy of fusion [J/mol]
\( J \)  Nucleation rate (eq. 2.7 and 2.11) [#/m\(^3\) s]
\( J \)  Intrinsic dissolution rate (eq. 3.6), arbitrary units
\( k \)  
Boltzmann constant, \( 1.3805 \times 10^{-23} \ [\text{J/K}] \)

\( K \)  
Force constant of the bond between the atoms \([\text{m}^2 \text{g/s}^4]\)

\( k_d \)  
Mass transfer coefficient \([\text{m/s}]\)

\( k_D \)  
Rate constant for crystal dissolution \([\text{m/s}]\)

\( k_g \)  
Growth rate constant \([\text{mol}^{1/3}/(\text{m}^{2-3/5}\text{s})]\)

\( k_G \)  
Rate constant for crystal growth \([\text{m/s}]\)

\( K_h \)  
Anhydrate/hydrate equilibrium constant [-]

\( k_r \)  
Growth integration rate constant \([\text{kg}^{1/3}/(\text{m}^{2-3/5}\text{s})]\)

\( L \)  
Separation of active sites available for impurity adsorption \([\text{m}]\)

\( L_S \)  
Mean mass size of seed crystals \([\mu\text{m}]\)

\( L_P \)  
Mean mass size of product crystals \([\mu\text{m}]\)

\( m \)  
Mass flux density \([\text{kg/(m}^2\text{s)}]\)

\( M \)  
Mass of atoms \([\text{g}]\)

\( M_S \)  
Mass of the solution in crystallizer \([\text{kg}]\)

\( M_T \)  
Crystal concentration in suspension \([\text{m}^3/\text{m}^3]\)

\( n_i \)  
Number density of polymorph i \([1/\text{m}^3]\)

\( N_A \)  
Avogadro’s number, \( 6.032 \times 10^{23} \ [/\text{mol}]\)

\( P \)  
Vapor pressure \([\text{Pa}]\)

\( R \)  
Universal gas constant, \( 8.3143 \ [\text{J/(mol K)}] \)

\( r \)  
Radius of a nucleus (eq.2.6) \([\text{m}]\)

\( r \)  
Order of the integration process (eq. 2.16) [-]

\( r_{crit} \)  
Radius of critical size nucleus \([\text{m}]\)

\( S \)  
Supersaturation, \( c/c^* \) (eq. 2.9-2.11, eq. 2.14-2.15, eq. 2.17-2.18) [-]

\( S \)  
Entropy (eq. 3.1-3.2) \([\text{J/(mol K)}]\)

\( \Delta S_d \)  
Molar entropy of dissolution \([\text{J/(mol K)}]\)

\( \Delta S_f \)  
Molar entropy of fusion \([\text{J/(mol K)}]\)

\( t \)  
Time \([\text{s}]\)

\( t_{ind} \)  
Induction time \([\text{s}]\)

\( T \)  
Temperature \([\text{K}]\)

\( T_P \)  
Polymorphic or pseudopolymorphic phase transition temperature \([\text{K}]\)

\( U \)  
Overall heat transfer coefficient of a batch crystallizer \([\text{W/(m}^2\text{ K)}]\)
\( v \) Growth rate of crystal face (eq. 2.17-2.18, eq. 2.21-2.22) [m/s]
\( v \) Frequency [1/s]
\( V \) Step velocity in the presence of impurities [m/s]
\( V_m \) Molecule volume [m\(^3\)]
\( V_0 \) Step velocity in pure solution [m/s]
\( x \) Solubility of the solute in mole fraction [-]
\( x_s \) Mean displacement of the adsorbed units [m]

Greek Symbols

\( \alpha \) Surface free energy (eq. 2.6-2.15) [J/m\(^2\)]
\( \alpha \) Effectiveness factor of an impurity (eq. 2.33) [-]
\( \beta \) Correction factor (\( \approx 1 \) or < 1) [-]
\( \phi \) Heterogeneous nucleation factor [-]
\( \gamma \) Activity coefficient [-]
\( \gamma_{CL} \) Interfacial energy [J/m\(^2\)]
\( \gamma_e \) Edge free energy [J/m]
\( \Gamma \) Adsorption overage [mol/m\(^2\), or molecules/m\(^2\)]
\( \eta \) Effectiveness factor for crystal growth [-]
\( \mu \) Chemical potential [J/mol]
\( \nu \) Number of ions dissociating from a molecule [-]
\( \theta \) Contact angle(eq. 2.13) [degree]
\( \theta \) Number of adsorbed units based on the total number of adsorption sites Eq. 2.31) [-]
\( \sigma \) Relative supersaturation, \((c-c^*)/c^*\) [-]
\( \sigma_C \) BCF growth model constant [-]
\( \theta_{eq} \) Fractional coverage of active sites by adsorbed impurities on the crystal surface [-]
\( \tau \) Batch time constant for natural cooling mode [s]
\( \tau_B \) Batch time [s]
Subscripts

BCF Burton-Cabrera-Frank
B+S Birth and spread
crit Critical size
d Dissolution
exp Experimentally measured
f Fusion
hom Homogeneous nucleation
het Heterogeneous nucleation
I Interface value
i Initial
im Impurity
ind Induction
int Indefinitely fast diffusion condition
m Melting
max Maximum
o Final
Surf Surface
v Per unit volume
0 Without additive or impurity
I Respective polymorph
2 Respective polymorph
A Respective polymorphs
B Respective polymorph
P Phase transition
A-B Difference between polymorph A and B

Superscripts
* Equilibrium state, saturation

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ATR</td>
<td>Attenuated Total Reflection</td>
</tr>
<tr>
<td>BCF</td>
<td>Burton-Cabrera-Frank</td>
</tr>
<tr>
<td>B+S</td>
<td>Birth and Spread</td>
</tr>
<tr>
<td>CBZ</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>CBZA</td>
<td>Carbamacepine Anhydrous form III</td>
</tr>
<tr>
<td>CBZH</td>
<td>Carbamacepine Dihydrate</td>
</tr>
<tr>
<td>CSD</td>
<td>Crystal Size Distribution</td>
</tr>
<tr>
<td>CCD</td>
<td>Couple Charged Device</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene Diamine Tetra Acetic acid</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier Transform</td>
</tr>
<tr>
<td>HPMC</td>
<td>Hydroxypropyl Methylcellulose</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>NIR</td>
<td>Near Infrared</td>
</tr>
<tr>
<td>KAP</td>
<td>Potassium Acid Phthalate</td>
</tr>
<tr>
<td>KDP</td>
<td>Potassium Dihydrogen Phosphate</td>
</tr>
<tr>
<td>KPY</td>
<td>Potassium pyrophosphate</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td>PIA</td>
<td>Particle Image Analysis</td>
</tr>
<tr>
<td>PLS</td>
<td>Partial Least Squares</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>SLS</td>
<td>Sodium Lauryl Sulfate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>XRPD</td>
<td>X-ray Powder Diffraction</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 Background

Crystallization from solution is an important unit operation widely used in process industries for the production and purification of foods, pharmaceuticals, agrochemicals and other specialties. The objective of an industrial crystallization process is to produce crystals with a specified crystal size distribution, mean crystal size, crystal shape, purity, polymorphic and pseudopolymorphic phase. A well-designed and controlled batch crystallization process that yields crystalline product with the desired qualities can significantly benefit down-stream processes, like filtration and drying, in terms of robustness, operating simplicity, and cost-effectiveness.

For the crystallization of pharmaceutical ingredients, which are frequently capable of forming polymorphs and solvates, efficient control of the polymorphic and pseudopolymorphic phase of the crystals is very important. This is because different polymorphs and pseudopolymorphs possess different product properties, such as solubility and dissolution rate in a given solvent, density, chemical stability and morphology. Consequently, the polymorphic and pseudopolymorphic phase of the drug product significantly affects the bioavailability of the final dosage. The polymorphic and pseudopolymorphic phase of the crystals depend on the competitive nucleation and growth kinetics of the different polymorphs and pseudopolymorphs, and the phase transformation from the metastable form to the stable form. In order to obtain the desired polymorph or pseudopolymorph, both the thermodynamic relative stabilities and the crystallization kinetics of the forms have to be fully understood.

The properties of the crystal product are all determined by the kinetics of the fundamental processes involved in the crystallization, such as primary and secondary nucleation, crystal growth, attrition and agglomeration (Mersmann 2001, Mullin 2001). The operational parameters of the crystallization, such as supersaturation level, temperature, mixing conditions, solvent (or solvent composition), additives (or impurities) are the decisive factors for the process kinetics and therefore decide the final crystalline properties. The
thermodynamics of the crystallization system and the mechanism governing the effect of the operation parameters on the product properties have to be studied in order to achieve a controlled crystallization process. In-line information about the crystal properties and the supersaturation, which is the driving force of the crystallization, is very important for an understanding of the thermodynamics and the crystallization mechanism of the system. Recently developed advanced techniques offer great potential for obtaining reliable in-line information during crystallization, and therefore, allowing a better understanding of the fundamental mechanisms during the crystallization and thus a more efficient determination of the optimum operation parameters to gain the desired crystal product properties.

1.2 Objective and scope of the work

The aim of the work is to produce a systematic study of the thermodynamics and crystallization mechanism of the model compounds. Recently developed process analytical techniques, such as ATR FTIR (attenuated total reflection Fourier transform infrared) spectroscopy, laser reflection particle size analysis, in-line imaging, Raman spectroscopy, combined with novel data analysis methods were used to obtain in-line information concerning the properties of both the solution and the crystalline phase during crystallization. Pharmaceutical substances and other industrial important inorganic and organic compounds were studied.

The thesis consists of theoretical and experimental parts. In chapter 2, the basics of the thermodynamics and kinetics of crystallization processes are presented. The fundamentals of polymorphism and pseudopolymorphism of pharmaceutical substances are introduced in chapter 3. The principles of in-line monitoring of the crystal and the solution properties during crystallizations are presented in chapter 4. The results presented in publications I-II and V concerning the thermodynamics and kinetic study of an anhydrate/hydrate system in mixed solvents are explained and summarized in chapter 5. Chapter 6 discusses the effect of additives on the crystal growth, based mainly on the results presented in publication III. The experimental results given in publication IV concerning the study of the effect of operation parameters on the final crystal properties based on the in-line measurement of supersaturation and crystal size distribution are summarized in chapter 7. Finally, conclusions based on the present study and suggestions for future work are given in chapter 8.
2 Batch cooling crystallization and control of product quality

2.1 Solubility, supersaturation, metastable zone limit and nucleation

*Solubility and the driving force for crystallization*

Determining the solubility of a substance in a given solvent is usually the first step in the design of a crystallization process. The solubility of a substance in a solvent can be measured experimentally by determining the maximum amount of the substance that can be dissolved at a given temperature. Another approach to determine the solubility of a compound is to calculate the ideal solubility based on the thermal properties (temperature and enthalpy of fusion) of the compound and then incorporate the ideal solubility with the activity coefficient, which can be computed with activity coefficient models.

If the solution is an ideal solution, the solubility of a solute can be predicted from the van’t Hoff equation (Mullin 2001):

\[
\ln x = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R}
\]  

(2.1)

where \(x\) is the mole fraction of solute in the solution, \(\Delta H_f\) and \(\Delta S_f\) are the molar enthalpy and entropy of fusion, respectively.

In practice, very few solutions can be considered as ideal solutions. The solubility of a solute in a non-ideal solution can be predicted by expressing equation (2.1) as

\[
\ln x = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R} + \ln \gamma
\]  

(2.2)

where the key point of using this equation to predict the solubility is a reliable estimation of the activity coefficient \(\gamma\) of the solute.

If the solution exhibits non-ideal behavior, the solvent effect, i.e. the enthalpy and entropy of mixing, can be taken into account by replacing \(\Delta H_f\) with \(\Delta H_d\) (enthalpy of dissolution) and \(\Delta S_f\) by \(\Delta S_d\) (entropy of dissolution) (Beiny and Mullin 1987).

\[
\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R}
\]  

(2.3)
In practice, if the solubility of a substance in a given solvent is measured at different temperatures, the enthalpy and entropy of dissolution can be estimated by plotting the solubility data versus the reciprocal of absolute temperature using equation (2.3).

The fundamental driving force for crystallization is the difference in the chemical potential $\mu$ of a given substance in the supersaturated solution (state 1) and saturated solution (state 2) (Mullin and Sohnel 1977).

$$\Delta \frac{\mu}{RT} = \frac{\mu_1}{RT} - \frac{\mu_2}{RT} = \ln \left( \frac{a}{a^*} \right)$$ (2.4)

where $a$ and $a^*$ are the activity of the solute in the supersaturated and saturated solution respectively. In practice, this thermodynamic representation of the driving force of crystallization is difficult to utilize since the activity of a crystallizing substance at the saturated and supersaturated states is not always available. Therefore, the driving force of crystallization is usually expressed in terms of supersaturation. The relative supersaturation $\sigma$ is defined as follows:

$$\sigma = \frac{c}{c^*} - 1$$ (2.5)

where $c$ and $c^*$ are the concentration of the solute in the supersaturated and saturated solution respectively. However, the application of a concentration based driving force instead of the fundamental activity-based driving force is based on the assumption that the supersaturation is very low and the salts are non-dissociating salts (Myerson 2002). As a consequence, using concentration-based supersaturation might lead to significant errors in the analysis of crystal growth, especially for electrolyte solutions (Mullin and Sohnel 1997, Kim and Myerson 1996, Bohenek, et al. 1997, Mohan and Myerson 2002).

**Metastable zone limit and nucleation**

A prerequisite for the occurrence of a crystallization process is the production of a supersaturated solution. When the solution is supersaturated, the nucleation does not occur spontaneously before the supersaturation exceeds a certain level. This supersaturation level is referred to as the metastable zone width. A hypothetical solubility and metastable zone width for cooling crystallization is shown in Fig. 2.1. In principle, three different metastable zone widths exist with respect to the three different nucleation mechanisms: homogeneous
nucleation, heterogeneous nucleation, and secondary nucleation. In practice, the width of the metastable zone is influenced by the solution history (how it was made and stored), the employed cooling rate, and the presence of impurities, including dust and dirt. Therefore, the effective metastable zone width, which is much smaller than the true metastable zone width, is usually measured in the laboratory. Information about the metastable zone width is very important for understanding the nucleation behavior of a system, and the measured effective metastable zone is often used to define the working zone of industrial crystallization processes (Myerson 2002). A polythermal method for the measurement of the metastable zone width was proposed by Nyvlt (1968).

![Fig. 2.1 The solubility/supersolubility diagram. (Davey and Garside 2000).](image)

Classic nucleation theory is derived from a thermodynamic equation that defines the overall Gibbs free energy for forming a spherical particle with radius $r$ (Mullin 2001):

$$
\Delta G = 4\pi r^3 \Delta G_v + \frac{4}{3} \pi r^3 \Delta G_c
$$  \hspace{1cm} (2.6)

where $\Delta G_v$ is free energy change per unit volume. As $\Delta G$ is negative, the free energy of formation has a maximum value at the point $d\Delta G/dr = 0$. The rate of homogeneous nucleation can be expressed in the form of the Arrhenius equation:

$$
J = A \exp(-\Delta G_{crit} / kT)
$$  \hspace{1cm} (2.7)

According to the Gibbs-Thomson relationship:

$$
\ln S = \frac{2\alpha V_m}{kT}
$$  \hspace{1cm} (2.8)

If the above equations are combined, the following equations are obtained:

$$
\Delta G_{crit} = \frac{16\pi \alpha^3 V_m^2}{3(kT \ln S)^2}
$$  \hspace{1cm} (2.9)
\[ r_{\text{crit}} = \frac{2\alpha V_a}{kT \ln S} \]  
(2.10)

\[ J = A \exp \left( -\frac{16\pi \alpha^2 V_a^2}{3kT^3(\ln S)^2} \right) \]  
(2.11)

The nucleation is facilitated by the presence of foreign substances, since the free energy barrier is lower in a heterogeneous system. It has been found that the decrease in free energy depends on the contact angle of the solid phase:

\[ \Delta G_{\text{hom}} = \phi \Delta G_{\text{het}} \]  
(2.12)

\[ \phi = \frac{1}{4} (2 + \cos \theta)(1 - \cos \theta)^2 \]  
(2.13)

Secondary nucleation results from the presence of crystals in the supersaturated solution. The parent crystals have a catalyzing effect on the nucleation, consequently, nucleation happens at a lower supersaturation level than that for homogeneous and heterogeneous nucleation. The mechanisms and kinetics of secondary nucleation are poorly understood (Myerson 2002).

![Graph showing induction periods as a function of supersaturation for CaCO₃ precipitation at 25 °C showing regions of homogeneous and heterogeneous nucleation (Söhnel and Mullin 1988).](image)

In practice, the nucleation rate can be determined by observing the time elapsed between the creation of supersaturation and the formation of new nuclei, which is defined as the induction time. The induction time can be considered to be inversely proportional to the nucleation rate:
\[ t_{\text{ind}} = A' \exp \left( \frac{F \alpha^3 V^2 \phi}{k T (\ln S)^2} \right) \] (2.14)

or

\[ \ln t_{\text{ind}} = \ln A' + F \alpha^3 V^2 \phi (k^3 T^3 (\ln S)^2) \] (2.15)

where \( F \) is the shape factor ratio of the nuclei, \( \phi = 1 \) for homogeneous nucleation and \( \phi < 1 \) for heterogeneous nucleation. A plot of \( \log (t_{\text{ind}}) \) versus \( (\log S)^2 \) at a constant temperature is shown in Fig. 2.2, where it is clear that homogeneous nucleation happens at higher supersaturations and heterogeneous nucleation is observed at lower supersaturations.

### 2.2 Crystal growth

The habit of the crystals depends on the growth rate of the crystal faces, which also have a significant impact on the crystal purity. The nucleation and crystal growth control the final particle size distribution of the obtained product. Understanding crystal growth theory is very important for the design and development of industrial crystallization processes. Reviews of crystal growth theory can be found in the literature (Ohara and Reid 1973, Nyvlt et al. 1985).

The growth of crystals in supersaturated solutions is considered as a complex multi-step process. Two of these steps are considered to be the most significant for the crystal growth. First, the growth units are transported from the bulk solution to the crystal surface by diffusion and convection; then the units are incorporated into the crystal lattice through an integration reaction. Depending on the system, the flow condition, and the supersaturation, either the diffusion process or the integration process can be the rate controlling process. The crystal growth rate can generally be described with the following equation (Mersmann 2001):

\[ m = k_4 (c - c_i) = k_r (c_i - c^*) \gamma \] (2.16)

where \( k_d \) is the mass transfer coefficient and \( k_r \) is the reaction rate constant. If the integration reaction happens quickly, the rate of the crystal growth is determined by the diffusive-convective transport of the growth units. In such a case, the crystal growth rate at a given supersaturation increases with increasing temperature and mixing intensity in a stirred tank, and with decreasing crystal size.
When the diffusion step takes place rapidly, the rate of crystal growth depends on the rate of the integration process. In principle, the growth unit must find an energetically favorable site to integrate into the crystal lattice when it diffuses on the crystal surface. Such energetically favorable sites can be classified into kinks and steps, as shown in Fig. 2.3. Burton, Cabrera and Frank (BCF) proposed a crystal growth model, which interprets crystal surface growth as the addition of growth units to kink sites on an endless series of steps (Burton, et al. 1951). These spiral steps are characterized by the average distance $y_0$ between neighboring turns and by the average distance $x_0$ between neighboring kinks in the steps. The BCF model can be written as (Mersmann 2001)

$$v_{BCF} = \frac{2kT^*D_{ref}}{19x_k\gamma_{CL}} \left( \nu \ln S \right) \sigma \tanh \left( \frac{19V_m\gamma_{CL}}{2x_kT} \frac{1}{\nu \ln S} \right)$$

(2.17)

If the supersaturation is low, then $\ln S = \sigma$.

$$v_{BCF} = \frac{2kT^*D_{ref}}{19x_k\gamma_{CL}} \nu \sigma^2 \tanh \left( \frac{19V_m\gamma_{CL}}{2x_kT} \frac{1}{\nu \ln S} \right) = B \frac{\sigma^2}{\sigma_c} \tanh \left( \frac{\sigma_c}{\sigma} \right)$$

(2.18)

where

$$B = \frac{\Gamma^* D_{ref} V_n}{x_k^2}$$

(2.19)

$$\sigma_c = \frac{19V_m\gamma_{CL}}{2x_kTV}$$

(2.20)

Fig. 2.3 Energetically favorable sites for integration (Mersmann 2001).

If $\sigma \ll \sigma_c$, $\tanh(\sigma_c / \sigma)$ approximates unity, equation (2.18) denotes a parabolic relation between $v_{BCF}$ and $\sigma$ leading to $v_{BCF} \propto \sigma^2$. If $\sigma \gg \sigma_c$, $\tanh(\sigma_c / \sigma)$ approximates $\sigma_c / \sigma$, equation (2.18) denotes a linear relation between $v_{BCF}$ and $\sigma$ resulting in $v_{BCF} \propto \sigma$. The
parameters $\sigma_c$ and $B$ are complex functions of the system properties, and they are usually difficult to obtain experimentally.

A change in the crystal growth mechanisms is possible with increasing supersaturation, and surface nucleation becomes the source of much higher densities of kink sites, which causes an exponential dependence of the growth rate on supersaturation. In the surface nucleation crystal growth model it is considered that adsorbed growth units collide with each other and form clusters and finally nuclei. A stable nucleus of critical size forms when a sufficient number of growth units join together. Subsequently other growth units can join onto the corner of the nucleus so that crystal growth takes place over the entire surface area. Ohara and Reid (1973) have introduced three models for the surface nucleation based crystal growth mechanism.

\[ v = A' \sigma^P \exp \left( -\frac{B'}{\sigma} \right) \]  

(2.21)

where $P = 1/2$ for the mononuclear model, $P = 3/2$ for the polynuclear mechanism, and $P = 5/6$ for the birth and spread (B+S) model. The B+S model has been widely used in the modeling of crystal growth with the following expression:

\[ v_{B+S} = A' \sigma^{5/6} \exp \left( -\frac{B'}{\sigma} \right) \]  

(2.22)

where

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

(2.23)

\[ B' = \frac{\pi}{3} V_m a \left( \frac{Y_{cl}}{kT} \right)^2 \]  

(2.24)

where $a$ is molecule diameter, $\beta'$ is a correction factor. A very low growth rate results when $\sigma << B'$ and $\sigma >> B'$ yields a relationship of $Y = X^{5/6}$.

Generally speaking, the crystal growth rate follows the solid line in the scheme shown in Fig. 2.4. At low supersaturation levels, only imperfections, such as screw dislocations, act as possible integration sites. With increasing supersaturation, the formation of surface nuclei becomes more probable and new integration sites are possibly created by the B+S
mechanism. With further increase in supersaturation, the spreading of the nuclei continuously
roughens the crystal surface by a polynuclear mechanism, and the rough surface provides
enough favorable sites, making the crystal growth rate bulk diffusion controlled.

The BCF and B+S crystal growth models both give a good insight into the physics of crystal
growth. However, the parameters included in the models, such as surface diffusion
coefficient and kink densities, are difficult or impossible to determine or predict.
Furthermore, the crystal growth rate computed with the models is a single-face growth rate of
an ideal crystal, which is different from the overall growth rate of a crystal collective in an
industrial crystallizer. The BCF and B+S models are usually used to estimate parameters by
fitting the models to experimentally measured growth rates.

Fig. 2.4 Scheme of competing growth regimes with rising supersaturation (Mersmann 2001).

One of the crucial issues concerning the study of crystal growth rates is the prediction of the
different regimes of the diffusion-controlled and integration-controlled growth mechanisms.
In practice, it is difficult to divide systems into diffusion limited and integration limited
groups. The rate-limiting step (diffusion or integration) depends on the supersaturation.
Furthermore, the growth mechanism can be different for particles with different sizes. Small
particles under 100 μm often grow with an integration limited mechanism, while the rate-
limiting process for large particles can be totally diffusion controlled. The following simple
equation is often used to describe crystal growth:

\[ \dot{m} = k_s (\Delta c)^g \]  

(2.25)

In most cases, the crystal growth rate is limited by bulk diffusion and surface integration, and
thus the exponent \( g \) in equation 2.25 is in the range \( 1 < g < 2 \). An effectiveness factor \( \eta \) is
introduced to describe the relationship between the diffusion and integration rates in crystallization (Garside 1971):

$$\eta = \frac{G_{exp}}{G_{int}}$$  \hspace{1cm} (2.26)

where $G_{exp}$ is the experimentally measured growth rate and $G_{int}$ is the growth rate at an indefinitely fast diffusion condition.

### 2.3 Crystal attrition and agglomeration

In addition to the nucleation and crystal growth rate, the crystal size and habit are also influenced by the kinetics of some secondary processes, such as crystal breakage and attrition, and agglomeration. However, it is impossible to make a general prediction of agglomeration, attrition and breakage rates. Crystal attrition and breakage are initially caused by mechanical and fluid dynamic processes, such as crystal-rotor collision and crystal-crystal collision. Some of the attrition fragments can survive and grow in a supersaturated solution and thus contribute to the crystal size distribution in the crystallizer. The attrition of crystals mainly depends on the physical properties of the solid and the collision of the crystals, while the subsequent growth of the attrition fragments depends on both kinetic factors and the inner state of the fragments. The attrition of crystals can have a strong impact on the crystal size distribution (CSD) and the median crystal size. The effect of attrition on CSD and median crystal size depends on the type, geometry, and scale of the crystallizer, the operation conditions (specific power input, density difference between the solid and solution, solid concentration), the properties of the solution and the solid. The final crystal size can be supersaturation controlled if the attrition rates of the crystals are small at a given growth period (e.g., for small crystals with small collision velocities). The crystal size of the final product can also be attrition controlled if the crystallization is conducted at low supersaturation and the crystallizer is equipped with a high speed rotor which leads to high collision velocities. In most cases, it is difficult to distinguish between nucleation, growth and agglomeration for very small particles. The agglomeration kinetics is difficult to describe, because it depends on so many different parameters, such as the hydrodynamic conditions, the crystal growth kinetics, the particle properties (e.g., size, shape, and density), and the interactions between the particles or a particle with the solvent. There is no
fundamental theoretical approach to describe the agglomeration kinetics. Nevertheless, kinetic models for agglomeration exist in literature (Smoluchowski 1917).

2.4 Control of final crystal product properties by manipulating the operation parameters of batch cooling crystallization

The quality of a crystalline product is determined by the median crystal size, the crystal size distribution (CSD), the coefficient of variation (CV), the shape and the purity of the crystals. For pharmaceutical products, polymorphism and pseudopolymorphism of the product should also be taken into account, and this topic will be discussed in the next chapter. The median crystal size, CSD and CV depend on the rates of nucleation, crystal growth, agglomeration, and attrition. The kinetics of these processes all strongly depends on the supersaturation level and impurities (or additives) present in the crystallizer. For batch cooling crystallization, however, the supersaturation level is influenced not only by the cooling policy but also by the kinetics of the crystallization process and the presence of seed crystals.

2.4.1 Effect of cooling mode and cooling rate

In general, the cooling mode for crystallizations can be roughly classified into 3 groups: natural cooling, linear cooling, and programmed cooling (Fig. 2.5). Natural cooling means allowing cooling water at constant temperature to flow through the crystallizer jacket at a constant rate. The temperature profile in the crystallizer can be calculated as (Davey and Garside 2000):

$$\frac{T - T_w}{T_i - T_w} = \exp\left(-\frac{t}{\tau}\right)$$

(2.27)

where the batch time constant $\tau$ can be calculated from the overall heat transfer coefficient, the heat transfer area, and the mass and heat capacity of the solution as follows:

$$\tau = \frac{M \cdot C_p}{U A_g}$$

(2.28)

The natural cooling mode gives a very high cooling rate in the early stage of the crystallization because of the great temperature difference between the cooling water and the crystallizing solution. As a consequence, the supersaturation in the crystallizer rapidly
exceeds the metastable zone limit, generates un-controlled nucleation and produces a large amount of fine particles, which is usually not desired. Linear cooling describes the situation in which the cooling rate is constant throughout the crystallization process. The supersaturation can be kept within the metastable zone limit if an adequately low cooling rate is employed. However, the low cooling rate means long batch times and large crystallizer volume, which can be uneconomical for the whole process as a whole.

In order to get the desired CSD in batch crystallization, it is essential that the supersaturation is controlled to remain constant within the metastable zone, thus preventing uncontrolled nucleation during the crystallization. In other words, the generation rate of the supersaturation has to match the desupersaturation process through crystal growth. Much work has been done to compute the temperature-time profile to achieve such controlled crystallizations. The following simplified temperature-time profile has been proposed by Mullin and Nyvlt (1971) for substances with solubility roughly linearly dependent on temperature:

\[
\frac{T_i - T}{T_i - T_0} = \left( \frac{t}{\tau_B} \right)^n
\]  

(2.29)

where \(n=4\) for unseeded and \(n=3\) for seeded crystallizations. This programmed cooling mode allows a slow cooling rate in the beginning of the crystallization and an increased cooling rate at the late stage when the available crystal surface area for crystal growth is larger. Experimental results have confirmed that increased crystal size and a narrower crystal size distribution (CSD) can be obtained by applying a programmed cooling mode to batch crystallizations (Chung et al. 1999, Ma et al. 1999, Bohlin and Rasmuson 1992). However, the feasibility of programmed cooling depends on the nucleation and crystal growth kinetics, and the thermodynamic properties of the system, such as the solubility-temperature dependency, and the metastable zone width for primary and secondary nucleation. Programmed cooling gives a high cooling rate at the late stage of the crystallization, which might in some cases let the supersaturation level exceed the metastable zone width of the secondary nucleation and generate a large amount of fine particles. The effect of cooling strategies on the final crystal size distribution of an organic compound named C15 during unseeded and seeded crystallization from toluene has been studied (Qu et al 2005a). It was observed that the programmed cooling strategy reduced the initial supersaturation level for
unseeded crystallizations and thus produced larger crystals. Meanwhile, the relatively high supersaturation level at the late stage of the crystallization resulted in undesired secondary nucleation, which produced more fine particles and lead to a wider bimodal crystal size distribution. The result of this work will be further introduced in chapter 7 of the thesis.

Fig. 2.5 Different cooling modes for batch cooling crystallization.

2.4.2 Effect of seeding

In addition to the cooling mode, seeding is another variable that can be used to affect the CSD. Appropriate seeding can usually increase the average crystal size and provide better reproducibility from batch to batch. The seeding effect on the final crystal size distribution at different cooling modes has been studied by the research group of Kubota (Jagadesh et al. 1999, Kubota et al. 2001, Doki et al. 2002). A seed chart was developed in their work to determine the critical seed loading. Above this critical seed loading, the mean mass size of the product $L_P$ can be correlated with that of the seed $L_S$ with equation (2.30), indicating that secondary nucleation was suppressed.

$$\frac{L_P}{L_S} = \left(1 + \frac{C_S}{C_S}\right)$$  \hspace{1cm} (2.30)

It was also found that the critical seed loading was not significantly affected by the operation conditions of the crystallizer, such as cooling mode, mixing intensity, and supersaturation level. With sufficient seed loading, a cooling strategy with a higher cooling rate in the beginning of the crystallization could be preferred to produce the desired narrow crystal size distribution with increased mean crystal (Jagadesh et al. 1999, Qu et al. 2005a).
2.4.3 Effect of additives

Crystallization is frequently used as a purification process during which one component or a mixture of components is crystallized out. The trace components existing in the crystallization solution are either additives, which have been added intentionally for a specific purpose, or impurities, which usually come from up-stream unit operations (e.g. by-products, unreacted reactants, etc.). In general, the presence of components other than the crystallizing solute can change the solution properties, such as density, viscosity, diffusion coefficient, and the structure of the solution. Moreover, the additive or impurity can be adsorbed on certain faces of the crystals, thus changing the crystal surface or modifying the habit. The effects of the additives or impurities can principally be classified as thermodynamic effects and kinetic effects (Davey 1979). An important thermodynamic parameter in the crystal growth models that is changed significantly by the adsorption of additives or impurities is the interfacial energy. The thermodynamic effect of the additives can be investigated by determining experimentally the induction time of the crystallization system with and without additives (Chen et al. 1997, Westin and Rasmuson 2005). If the Langmuir adsorption isotherm is applied, the effect of the adsorbing species on the interfacial energy can be expressed with the following equation (Mersmann 2001):

$$\gamma_{CL,\text{ads}} = \gamma_{CL,0} - RT\ln\left(\frac{1}{1-\theta}\right)$$

(2.31)

The above equation generally predicts a decrease in the interfacial energy, and thus, increasing crystal growth rate with increasing adsorption of the additives. The parameters in equation (2.31) are face-specific, so the additive effect on the interfacial energy, and thus growth rate, is different for different crystal faces. The growth rate of one single face can be accelerated faster than others, consequently resulting in a notable modification of the crystal habit (Qu et al 2005b, Qu et al 2006a). The promotion effect of additives has been observed in many works (Fu et al. 1999, Yang et al. 1999, Podder 2002, Li et al. 2004), the mechanism is however, not fully understood. Kuznetsov et al (1998) investigated the effects of various organic additives on the growth kinetics of potassium acid phthalate (KAP) and potassium dihydrogen phosphate (KDP) crystals. It was observed that the effects of additives on the crystal growth rate strongly depend on the concentration of the additives; with increasing additive concentration, the growth rate increased to a maximum value and then started to
decrease. The significant promotion effect of additives cannot be explained solely by the thermodynamic effect described by equation (2.31). The authors explained the effect of the additives in terms of the conflicting tendencies of the kinetic and thermodynamic effects. At lower concentrations, the additives eliminated the competition between the adventitious impurities (usually high valent metal ions, like Fe$^{3+}$, Al$^{3+}$ and Mn$^{2+}$, which always exist in the raw material at very low concentrations) and the growth units by forming complexes with the adventitious impurities in the solution, which consequently increased the concentration of growth units adsorbed on the growing surface. However, when the additive concentration increased, the additive molecules may compete with the growth units and so reduce the step velocity. As a consequence, a peak value in the crystal growth rate appeared with increasing additive concentration. This conclusion has been verified by experimental results reported in the literature. Lu et al. (2001) detected an enhanced KDP growth unit layer with a Raman spectrometer at the crystal-solution interface boundary when ethylene diamine tetra acetic acid (EDTA) was present as an additive. The effect of EDTA on the growth rate of KDP crystals during batch cooling crystallization was studied with an in-line video microscope (Qu et al 2006a). It was found that the presence of EDTA increased the density of the adsorbed crystallizing solute molecules on the surface of the crystal, and consequently increased the crystal growth rate. The results of this work will be further discussed in chapter 6. Both research groups found that the promotion impact of EDTA was more remarkable on the prismatic face of the KDP crystals, and the crystal habit was greatly modified by the additive. This can be explained by the surface structures of KDP crystal faces. The prismatic (100) faces of a KDP crystal are terminated by a layer of K$^+$ and H$_2$PO$_4^-$ group while the pyramidal (101) faces are ended by a layer of K$^+$ (de Vries et al. 1998, de Vries et al. 1999). The incorporation of adventitious impurity ions, like Fe$^{3+}$, Al$^{3+}$ and Cr$^{3+}$, on the prismatic face is more favorable. Therefore, formation of the complexes by the chelating agent EDTA and the impurity ions gives a more significant promotion effect on the prismatic faces.

The kinetic effect of additives has been intensively studied in the literature both theoretically and experimentally. In many cases, additives that affect crystal growth can also influence nucleation in a similar way. In other words, a growth inhibitor usually increases the metastable zone width, and a growth promoter decreases it. As an example, it was found that the admixture Fe$^{3+}$, Al$^{3+}$ and Mn$^{2+}$ increased the metastable zone width of ammonium
chloride (Chianese et al. 1996), and these ions also inhibited the growth of potassium dihydrogen phosphate (KDP) and ammonium dihydrogen phosphate crystals (Mullin et al. 1970, Rashkovich and Kronsky 1997). The most widely accepted mechanism for the retarding effect of the additives on the crystal growth is based on the adsorption of the additives. It has been proposed that the adsorption of the additives at different sites onto the growing crystal surfaces hinders the movement of the steps on the crystal surface. Davey and Mullin (1976) derived the following equation to describe the step velocity in the presence of impurities, assuming that the rate of surface diffusion of growth units to the steps is reduced by impurities adsorbed on the flat faces between the steps:

$$\frac{V}{V_0} = 1 - \theta_{eq}$$  \hspace{1cm} (2.32)

where $\theta_{eq}$ is the fractional coverage by adsorbed impurities on the surface.

Later the equation was modified by Kubota and Mullin (1995) by introducing the effectiveness factor $\alpha$ to take into account the effectiveness of a given impurity for growth suppression (Kubota and Mullin 1995, Kubota et al. 1999).

$$\frac{V}{V_0} = 1 - \alpha \theta_{eq}$$  \hspace{1cm} (2.33)

with

$$\alpha = \frac{\gamma_a \sigma}{kT \ell_a}$$  \hspace{1cm} (2.34)

Following this principle, Sangwal (1999) introduced a theoretical expression relating step velocities and face growth rates with impurity concentration and supersaturation for adsorption at kinks and surface terrace.

The additive effects on crystal growth have also been investigated by applying molecular modeling techniques (Myerson and Jang 1995, Lu and Ulrich 2004, Pino-Garcia and Rasmuson 2004). The surface bounding energy, defined as the interaction energy between an additive molecule and a specific crystal face, was computed for adipic acid faces with various alkanoic acids (Myerson and Jang 1995). It was observed that the inhibiting effect of the additives predicted by the surface binding energy calculation was in good agreement with the measured additive effect on the metastable zone width.
2.4 Summary

Industrial crystallization takes place in multi-phase and multi-component system. The median crystal size, CSD and CV are determined by the kinetics of the processes involved in the crystallization: primary and secondary nucleation, crystal growth, attrition, and agglomeration. The operation parameters of the crystallization have a strong impact on the kinetics of these processes.

Supersaturation is the driving force of both nucleation and crystal growth, and thus has a significant influence on the properties of the final product. The interdependence of the supersaturation and crystal properties is complicated. On the one hand, the supersaturation level inside the crystallizer determines the rate of the nucleation and growth of the crystals, which can subsequently decide the crystal size distribution in the crystallizer. On the other hand, the supersaturation level depends on the generating rate of the supersaturation (e.g. the cooling rate in cooling crystallization) and the desupersaturation rate through nucleation and crystal growth, which strongly depends on the specific crystal surface area determined by the crystal size distribution. Usually it is desired to operate the crystallizer at a constant supersaturation level within the metastable zone during the whole crystallization process. This can be implemented by using optimized operation conditions to ensure the generating rate of the supersaturation matches the desupersaturation rate throughout the whole process.

Among the many controllable parameters, cooling strategy, seeding parameters, and the use of additives are frequently selected as the optimizing variables to attain a desired crystallization product. Programmed cooling is usually preferred to obtain narrower crystal size distribution and larger crystal size. Appropriate seeding strategy, which means the specific surface area of the seed crystals is adequate for the consumption of the supersaturation through crystal growth, can effectively suppress secondary nucleation and thus minimize the quantity of fine particles in the crystalline product. The presence of additives can exert a strong effect on the solubility of the solute, the metastable zone width, nucleation, and the growth kinetics of the crystals. The effects of additives on the crystal growth are usually face-dependent, and as a consequence, the morphology of the crystals could be significantly modified. The inhibiting effect of additives is often explained by the
adsorption of the additives onto the growing crystal surfaces, thus hindering the movement of the steps. Promoting effects of additives have also been reported, the mechanism is however still not fully understood. Generally the mechanism of this promoting effect is mainly attributed to the ability of the additives to form complexes with the adventitious impurities in the system.

Control of crystal size and shape during crystallization is a very complex process. Usually the kinetic models for nucleation and crystal growth cannot be applied directly for the prediction of the nucleation and crystal growth rate. Furthermore, it is impossible to make a general prediction of crystal attrition and breakage, and agglomeration rate. Control of the crystal product properties requires an understanding of the thermodynamics of the system, and the mechanisms of both nucleation and crystal growth. Identification of the factors that affect the crystallization kinetics, and the dependency of the process kinetics on the operation conditions of the crystallization also need to be known.
3 Polymorphism and pseudopolymorphism of pharmaceutical substances

3.1 Fundamentals of polymorphism and pseudopolymorphism

3.1.1 Thermodynamics of polymorphism

Polymorphism is often defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (Bernstein 2002, Brittain 1999). Different polymorphs of a compound may have distinct mechanical, thermal, physical and chemical properties, such as compressibility, melting point, solubility, crystal habit, and stability, and therefore the polymorphic form strongly impacts on the bioavailability, filtration, and tabletting process of the compound. Based on the thermodynamic principle, the relative stability of the polymorphs depends on their free energies; the form with the lowest free energy will be the most stable. The transformation of the less stable polymorph to the more stable polymorphs is driven by the difference between the free energies of the polymorphs. However, kinetic factors can prevent this transformation.

The free energy of a solid phase can be represented with the Helmholtz equation (Grant 1999):

\[ A = E - TS \]  \hspace{1cm} (3.1)

where \( E \) is the internal energy, \( T \) is the absolute temperature, and \( S \) is the entropy. Equation (3.1) can also be presented in a more familiar form on the basis of the Gibbs free energy by replacing \( A \) with the Gibbs free energy \( G \), and the internal energy \( E \) with enthalpy \( H \):

\[ G = H - TS \]  \hspace{1cm} (3.2)

The Gibbs free energy difference between different polymorphs can be described as the ratio of the fugacity \( f \), and for ideal systems the fugacity can be approximated by the saturated vapor pressure \( p \).

\[ \Delta G = RT \ln \left( \frac{f_2}{f_1} \right) \approx RT \left( \frac{P_2}{P_1} \right) \]  \hspace{1cm} (3.3)
where the number 1 and 2 denote the respective polymorphs. The fugacity is proportional to the thermodynamic activity \(a\), which can be assumed to be proportional to the solubility \(c\) of the polymorphs in a given solvent.

\[
\Delta G = RT \ln \left( \frac{a_1}{a_2} \right) \approx RT \left( \frac{c_2}{c_1} \right)
\]  

(3.4)

Since the most stable polymorph under defined conditions of temperature and pressure has the lowest Gibbs free energy, it also has the lowest value of fugacity, vapor pressure, thermodynamic activity, and solubility in any given solvent. Based on the above mentioned thermodynamic relationship between the polymorphs, the solubility ratio of two polymorphs reflects the Gibbs free energy difference of the two polymorphs and should thus be independent of the solvent. Also the enthalpy and entropy of transition, and the transition temperature of the two polymorphs should be independent of the solvent.

Fig. 3.1 Energy versus temperature of an enantiotropic dimorphic system (Gu and Grant 2001).

A typical energy versus temperature diagram is shown in Fig. 3.1. The polymorphs A and B may be related either enantiotropically (Fig. 3.1 a) or monotropically (Fig. 3.1 b). At absolute zero the second term in the right side of equation (3.2) equals zero, and the Gibbs free energy
equals the enthalpy, which means the most stable polymorph must have the lowest enthalpy. When the temperature is higher than absolute zero, the entropy term will contribute to the Gibbs free energy. The way in which the Gibbs free energy changes with the temperature may differ, depending on the behavior of the entropy term. The stability relationship of polymorphs is determined by the transition temperature, \( T_P \), at which the free energy of the polymorphs is identical. For an enantiotropic system, the transition temperature is between 0 K and the lower melting temperature; while a monotropic system has a hypothetical transition temperature above the melting points of the two forms.

One of the most important issues in the characterization of polymorphs is to determine the transition temperature between the polymorphs. Both theoretical derivate and experimental approaches for the estimation of the transition temperature of polymorphs have been introduced in the literature and they are summarized below:

**Solubility extrapolation method.** For this method, the solubility of the polymorphs in a given solvent is measured at several temperatures. The free energy difference between the polymorphs, \( \Delta G \), is evaluated from the solubility ratio of the polymorphs and the transition temperature \( T_P \) is estimated by extrapolating the \( \Delta G \) versus \( 1/T \) plot, which is usually linear (Higuchi and Grant 1990, Grant et al. 1984). The transition temperature can also be evaluated by plotting the solubility (in molar fraction units) versus the reciprocal of absolute temperature; the intercept of the solubility lines represents the transition temperature where the two polymorphs have equal solubility, and therefore equal free energy (Ghosh and Grant 1995, Park et al. 2003, Luk and Rousseau 2006, Qu et al. 2006b, Qu et al. 2006d).

**Heat of solution and solubility method.** This method was introduced by Gu and Grant (2001). In this method, the enthalpy difference between the polymorphs A and B is estimated from their heat of solution at a given temperature \( T \):

\[
\Delta H_{B-A} = \Delta H_A - \Delta H_B
\]  (3.5)

The free energy between the polymorphs can be calculated from the solubility data \( c_A \) and \( c_B \), or the intrinsic dissolution rates \( J_A \) and \( J_B \):

\[
\Delta G_{B-A} = RT \ln \frac{\gamma_A c_B}{\gamma_A c_A} \approx RT \ln \frac{c_B}{c_A} \approx RT \ln \frac{J_B}{J_A}
\]  (3.6)

The entropy difference between A and B at temperature \( T \) can then be calculated:
\[
\Delta S_{B,A} = \frac{\Delta H_{B,A} - \Delta G_{B,A}}{T} \quad (3.7)
\]

If the heat capacity difference of the polymorphs is negligible, and thus the values of \(\Delta H_{B,A}\) and \(\Delta S_{B,A}\) are independent of temperature, the transition temperature can then be estimated as:
\[
T_p = \frac{\Delta H_{B,A}}{\Delta S_{B,A}} = \frac{\Delta H_A - \Delta H_B}{T} - R \ln \frac{c_A}{c_B} \quad (3.8)
\]

**Suspension method.** The transition temperature between the polymorphs can be measured by suspending polymorph mixtures in a solvent at a given temperature. The transition temperature can be determined by analyzing the polymorphic composition of the harvested solids at various times. It has been shown by Gu and Grant (2001) that the transition temperature estimated from the heat of solution and solubility is in good agreement with the values measured with the suspension method for the polymorphs of sulfamerazine.

**Differential scanning calorimetry (DSC) method.** The transition temperature can be obtained from the melting data measured by DSC (Yu 1995) by the following equation:
\[
T_p = \frac{\Delta H_{A,B}}{\Delta S_{A,B}} = \frac{\Delta H_{m_A} - \Delta H_{m_B} + 0.003 \cdot \Delta H_{m_A} \cdot (T_{m_B} - T_{m_A})}{T_{m_A} - T_{m_B} + 0.003 \cdot \Delta H_{m_A} \cdot \ln \frac{T_{m_B}}{T_{m_A}}} \quad (3.9)
\]

However, the obtained transition temperature depends on the transition rate. As a result, the transition temperature determined from the melting data is often much higher than that estimated from the solubility data. Furthermore, the apparent transition temperature shown in the DSC curve is influenced by many other external factors, such as the heating rate, the crystallinity of the crystals, particle size, thermal conductivity of the samples, and the polymorphic purity of the samples (Gu and Grant 2001).

### 3.1.2 Thermodynamics of hydrates

Solvates are frequently referred to as pseudopolymorphs, which are defined as the crystals formed by the same substance crystallized with different amounts or types of solvent molecules (Bernstein 2002). Hydrate, which is the most commonly encountered solvate, has received more and more attention in the last decade due to its potential impact on the
development process of drug products and dosage form performance. Substances may undergo hydration or dehydration depending on changes in environment conditions during the processing and even storage of the product. The incorporation or removal of the water molecules to or from the crystal lattice can both lead to distinct internal structural changes. Ultimately, the structural change induced by hydration or dehydration will be reflected as altered physical and chemical properties of the pharmaceutical ingredients, such as dissolution rate, solubility, bioavailability, tableting properties, and stability. Dehydration can also result in an amorphous form which is chemically labile and may be subsequently oxidized (Morris 1999).

Polymorph and hydrate systems have many similarities, and thus are often discussed together. Both polymorphic forms and hydrate systems (anhydrate/hydrate, lower/higher hydrate state) have different crystal structures and thus exhibit different x-ray powder diffraction patterns, thermograms (DCS or TGA), infrared spectra, Raman spectra, dissolution rate and solubility, etc. The transition between polymorphic forms and hydrate forms may both happen as a function of temperature and/or pressure, and can also be solution mediated. It is possible to get both polymorphic and anhydrate/hydrate transition during processing and storage of the drug product.

However, a hydrate is usually not referred to as a polymorph because there are significant differences between polymorphs and hydrates. First of all, polymorphs are different crystal structures of the same molecules, while in hydrates different amounts of water molecules are cooperated into the crystal structure. In other words, the anhydrate and hydrate, or the hydrates with different hydration state, have unequal molecular formula. Furthermore, the hydration state of a hydrate system depends on temperature, pressure and the water activity above the solid, while generally the polymorphic transition is only affected by the temperature and pressure, with the exception of the solution mediated transformation mechanism.

Hydrates are classified into the following three groups according to the water arrangement in the crystal structure (Morris 1999):
Class 1: Isolated site hydrates. In the molecular structure of hydrates in this group the water molecules are isolated from direct contact with other water molecules by intervening drug molecules. This structure yields sharp DSC endotherms and narrow TGA weight loss range, and sharp O-H stretching frequencies in the infrared spectrum.

Class 2: Channel hydrates. Hydrates in this class contain water in the lattice channel, where the water molecules lie next to other water molecules of adjoining unit cells along an axis of the lattice, forming “channels” through the crystal.

Class 3: Ion associated hydrates. Hydrates in this group contain metal ion coordinated water. The interaction of metal ions and water can be very strong and results in high dehydration temperature.

Grant and Higuchi (1990) have established the following relationship to describe the equilibrium between a hydrate and an anhydrate:

\[
A^{(\text{solid})} + m\text{H}_2\text{O} \leftrightarrow A \cdot m\text{H}_2\text{O}^{(\text{solid})}
\]

where \( K_h \) is the equilibrium constant for the process, and \( a[A \cdot m\text{H}_2\text{O}^{(\text{solid})}] \), \( a[A^{(\text{solid})}] \) and \( a[\text{H}_2\text{O}] \) are the thermodynamic activities of the hydrate, the anhydrate and water. \( m \) is the number of water moles taken up by one mole of the anhydrate. When \( a[\text{H}_2\text{O}] > \{a[A \cdot m\text{H}_2\text{O}^{(\text{solid})}]/[a[A^{(\text{solid})}]K_h]\}^{1/m} \), the hydrate is the more stable form. The anhydrous form will be more stable in the inverse situation. If the pure solids of anhydrate and hydrate are taken as the standard states (i.e., with unity activity), then Equation (3.9) can be simplified as: \( K_h = a[\text{H}_2\text{O}]^{-m} \). Thus, the hydration state of a hydrate depends on the water activity in the surrounding medium.

For an anhydrate/hydrate system, the value of the solubility ratio and Gibbs free energy difference of the anhydrate and hydrate forms strongly depend on the water activity in the solvent, and the system is defined by temperature, pressure and water activity in the solvent. The anhydrate/hydrate transition is both solvent and temperature dependent in organic solvent-water mixtures (at ambient pressure). It is essential to understand the thermodynamics of the anhydrate/hydrate system and the mechanisms of the transformation in solvent mixtures in order to control the phase of the crystalline product. The influence of
water activity in organic solvent and water mixtures on the hydration state of drug compounds at room temperature has been reported in the literature (Grant and Higuchi 1990; Ghosh and Grant 1995; Zhu et al., 1996; Zhu and Grant 1996). Zhu et al. (1996) studied the influence of water activity in organic solvent and water mixtures on the anhydrate/monohydrate phase of theophylline at 25°C. They found that solvent composition corresponding to $a[H_2O] = 0.25$ was the transition point; if the water activity was higher than 0.25, the monohydrate was the stable form, and the anhydrate was more stable if water activity was lower than 0.25. The dependency of the transition point water activity of anhydrate/dehydrate carbamazepine on temperature has been investigated by measuring the solubility data of the anhydrate/dihydrate forms in various water-ethanol mixtures at different temperatures (Qu et al. 2006b). It was found that the transition point water activity increased with increasing temperature. The results of this work will be further discussed in chapter 5.

Table 3.1 Types of most important phase transitions during processing of pharmaceuticals (Morris 2001).

<table>
<thead>
<tr>
<th>Basic process</th>
<th>State of aggregation</th>
<th>Specific process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transformations (one component)</td>
<td>Solid-solid</td>
<td>Polymorphic transformations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crystallization of the amorphous form and vice versa</td>
</tr>
<tr>
<td></td>
<td>Solid-liquid-solid</td>
<td>Incongruent melting (melting followed by crystallization of a more stable form)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution–mediated polymorphic transformations</td>
</tr>
<tr>
<td>Physical interactions (multicomponent)</td>
<td>Solid-solid</td>
<td>Eutectic reaction</td>
</tr>
<tr>
<td></td>
<td>Solid-liquid-solid</td>
<td>Formation of a molecular compound or a solid solution (including solvate formation)</td>
</tr>
<tr>
<td></td>
<td>Solid-solid or Solid-liquid-solid</td>
<td>Hydrate formation in humid air</td>
</tr>
<tr>
<td>Physical decomposition (multicomponent)</td>
<td>Solid-solid or Solid-liquid-solid</td>
<td>Desolvation</td>
</tr>
</tbody>
</table>
3.2 Process-induced phase transformation of active pharmaceutical ingredients

In the last two decades, more and more emphasis has been placed on the characterization and control of the crystal form of active pharmaceutical ingredients throughout manufacturing processes. It has been recognized that changes in crystal form may ultimately affect dosage form performance (Morris et al. 2001). During processing of the ingredients, some stress might be exerted on the system, which could be induced by thermal, mechanical, or interaction with a second factor. The stress can induce a phase change either from the thermodynamically stable form to a metastable form or in the opposite direction. The most important phase transitions during the processing of pharmaceutical ingredients are summarized in Table 3.1. A review of the theoretical approaches of the physical transformations of pharmaceutical ingredients can be found in the literature (Morris 2001).

3.3 Controlling the formation of polymorphs and solvates during crystallization of pharmaceutical products

Control of the formation of polymorphs and solvates is one of the most important issues in the pharmaceutical industry. Approximately half of all active pharmaceutical ingredients are capable of forming polymorphs or solvates (Beckmann 2000). Crystallization is widely used in the pharmaceutical industries for the production and purification of products. Usually the stable form is desired as the final product, however, the more soluble metastable form is occasionally selected if the stable form has insufficient solubility to attain the desired healing effect of the final dosage (Singhai and Curatolo 2004). The goal of the crystallization is to produce a certain solid state form with good reproducibility from batch to batch. For a polymorphic system, the phase of the crystal product is determined by the competitive nucleation and crystal growth of the polymorphs, and the transformation from the metastable forms to the stable form. In order to control the polymorph of the crystallization product, the crystallization mechanism of the polymorphs in each elemental process and the dependence of the crystallization behavior of the polymorphs on the operation parameters have to be understood.
3.3.1 Nucleation and growth of crystals in polymorphic system

Based on classical nucleation theory, molecular clusters or molecular aggregates are formed before the nucleation happens. Control of aggregate formation is very important for polymorphic system crystallization; since different polymorph nuclei are grown from different aggregates in a supersaturated solution (see Fig. 3.2). The existence of aggregates before nucleation has been verified both with experiments (Williams-Seton et al. 1999) and with molecular simulation (Anwar and Boateng 1998). Davey et al. (2001) investigated the dependence of the aggregate on solvent for 2, 6-dihydroxybenzoic acid in two organic solvents. Both the measured extinction coefficients of the solutions and the molecular simulation results suggest that the formation of the aggregates is strongly related to the solvent. Dimer formation is favored in toluene while polymeric aggregates are preferred in chloroform. The dimer and polymeric aggregates grow into polymorphic form 1 and form 2, respectively. Therefore, the solvent is dominant for this system to obtain the desired polymorph. Understanding the relationship between molecular clusters and nucleation during crystallization also makes it possible to design tailor-made additives, which can selectively inhibit the crystallization of the more stable polymorph and therefore lead to stabilization of the metastable phase (Davey et al. 1997).

![Diagram of nucleation of polymorphic forms](image)

Fig. 3.2 Nucleation of polymorphic forms (Bernstein 2002)

The occurrence of nucleation for a particular polymorph is the consequence of competition between kinetic and thermodynamic factors. For example, if aggregate 2 nucleated crystals grow much faster than those from aggregate 1, then polymorph 3 might be the obtained form even if polymorph 1 is the thermodynamically most stable. If the kinetic and thermodynamic factors are nearly equal, then two or more polymorphs can be obtained simultaneously.
Ostwald formulated the experimental observations as Ostwald’s rule, that is, when leaving an unstable state, the system does not seek out the most stable state, rather the nearest metastable state which can be reached with loss of free energy (Ostwald 1897). Ostwald’s rule states that in the case of a compound capable of crystallizing in several forms, it will be the least stable form which is produced first by spontaneous crystallization, followed successively by forms of increasing stability. It has been shown that this rule has no general proof, and the nucleation behavior strongly depends on the crystallizing system and the operation conditions (Davey et al. 1997, Kitamura 2002).

The operation parameters of crystallization, such as the solvent, temperature range, supersaturation level, mixing condition, presence of additives or impurities, and the seeding parameters, all have an effect on the polymorphic form of the crystal product. The controlling factors of the crystallization of polymorphs are schematically demonstrated in Fig. 3.3 (Kitamura 2002). Depending on the particular crystallizing system, one or more parameters can be dominant. Generally speaking, the stable form is usually obtained under thermodynamic conditions, e.g. a slow cooling or slow evaporating, and thus the thermodynamic equilibrium is nearly maintained during the process. On the other hand, kinetic conditions (for example, rapid cooling in a cooling crystallization) will result in a metastable polymorph in crystallization (Bernstein 2002). However, this cannot be used as a
general rule in the design of a crystallization process, since exceptions are frequently observed (Kitamura 2004).

![Diagram](image)

Fig. 3.4 Polymorphic system of two enantiotropically related polymorphs I and II. (solid lines: solubility of the forms; dashed lines: metastable zone limits of the polymorphs; x: transition point) (Modified from Threlfall 2000).

Many experimental studies have been performed on the subject of the effects of operation parameters on the obtained crystalline polymorphic phase during crystallization. Kitaruma et al (2006) reported that the polymorphism of an enzyme inhibitor named BPT was strongly dependent on the solvent. Only the stable form was crystallized out from acetonitrile regardless of the supersaturation level and cooling rate. The seeding effect on the polymorphic phase of efloclimbe from a mixed solvent has been investigated (Teychene et al. 2004). It was found that seeding was not always a reliable way to produce the preferred polymorph even though the solubility of the two forms was very close to each other. Beckmann (2000) performed a systematic study of the seeding effect on the polymorphism of the final product. It was concluded that the reliability of the seeding strategy depends on the thermodynamic properties of the polymorphs, such as solubilities and metastable zone limits. It has been shown that tailor-made additives can be very effective for controlling the polymorphic phase of the crystallization product (Torbeev et al. 2005, Sonoda et al. 2006, Doki et al. 2004). It was observed that a dissolved additive with stereochemistry similar enough to that of the unwanted polymorph is adsorbed on the surface of the unwanted
polymorph crystals or the corresponding clusters, which can then suppress the nucleation and growth of the unwanted crystal form.

A theoretical analysis of the mechanism of the influence of operation parameters on polymorph formation was proposed by Threlfall (2000) based on competition of the thermodynamic and kinetic factors during crystallization. A polymorphic system of two enantiotropically related polymorphs was taken as an example, as shown in Fig. 3.4. Various situations while cooling an undersaturated solution to a supersaturated solution were considered as follows:

- If the cooling starts from A to A1, the solution concentration will reach the solubility of form I and then pass through its metastable zone limit. If the cooling rate is controlled and the concentration remains below the form II solubility, then the only form obtained from crystallization is form I. By assuming that the activity coefficient of form I and form II is equal regardless of the solvent, the solubility ratio of form I and form II is then solvent independent (see equation 3.6). This means the solvent has no effect on the polymorph of the outcome crystals in this situation.

- If the cooling of the solution starts from B, it is possible to initiate the crystallization by seeding of polymorph I at B1. It is obvious that only polymorph I can be obtained. Therefore, for any crystallization operating at the area jkxn, which is between the solubility curve of form I and form II, the crystal product must consist entirely of the stable form I, and the solvent has no influence on the polymorph of the outcome crystals.

- The situation is different if the solution is cooled from C to C1 rapidly. The solution concentration passes through the metastable zone limit of both form I and form II. The polymorphic phase of the product will depend on the relative nucleation and growth kinetics of form I and form II. In such a case, the solvent is influential because it can accelerate the nucleation of a particular polymorph by favoring the corresponding molecular aggregate formation (Davey et al. 2001). Additives may also play a significant role in determining the product polymorph following a similar mechanism to the solvent effect.

- When a solution is cooled from concentration D to D1 located in the area klmx, which is within the metastable zone of both forms and near the transition point
between the two forms, this will again result in kinetic controlled crystallization. It is also possible to obtain a mixture of form I and form II in this region. Both the solvent and the seeding is significant in determining the obtained polymorphic form of the product. Other operation parameters that influence nucleation kinetics can all be dominant. As this region is around the transition temperature, the temperature usually has very little effect on the polymorphic phase of the crystals, and the thermodynamic driving force of the phase transition from the metastable form to the stable form is small.

- If the cooling of the solution starts from concentration E, the situation is similar to that when the cooling starts from B with the stable form II instead of form I. The seeding dominates and polymorph II can reliably be produced by seeding. The kinetic factors have no effect on the polymorphic form of the product.
- Cooling the solution from concentration F can only produce form II because the concentration will not reach the solubility of form I.

### 3.3.2 Solvent-mediated phase transformation of polymorphs and anhydrate/hydrate

In addition to the nucleation and growth kinetics of the polymorphs, solvent-mediated phase transformation plays an important role in determining the polymorphic phase of the final crystal product. According to Ostwald’s rule (Ostwald 1897), the metastable form is crystallized out first in a polymorphic crystallization system, and subsequently it transforms into the stable form. Control of the transformation process is critical in order to ensure that the desired polymorph is produced. However, pharmaceutical solids are designed to come into contact with solvents in the early stages of development (for example, crystallization) and during processing of the product, such as wet granulation, spray-drying, freeze-drying, etc.) (Rodriguez-Hornedo and Murphy 1999).

**Two-step phase transformation**

In principle, solvent-mediated phase transformation is a two-step process, first the metastable form is dissolved and subsequently the stable form crystallizes out. Depending on the relative kinetics of the dissolution of the metastable form and the crystallization of the stable form, the transformation can be dissolution controlled or crystallization controlled (Cardew and
Davey 1985, Davey and Cardew 1986). Usually the solvent-mediated phase transformation process starts from slurry consisting of the metastable solid phase and the saturated solution with respect to the metastable form. As soon as the nuclei of the stable form are formed in the slurry, the growth of these nuclei will consume the supersaturation and the solution becomes undersaturated with respect to the metastable form. The dissolution of the metastable form is thus driven by the undersaturation, which produces the supersaturation for the crystallization of the stable form. The expected supersaturation-time profile during the phase transformation is shown in Fig. 3.5. The plateau supersaturation \( \sigma_p \) simply represents the point at which the dissolution rate of the metastable form and the growth rate of the stable form crystals are balanced. The maximum supersaturation \( \sigma_{12} \) is defined as:

\[
\sigma_{12} = \frac{x_1 - x_2}{x_2}
\]  

(3.10)

where \( x_1 \) and \( x_2 \) are the solubility of the metastable and stable forms at the transformation temperature, respectively.

The desupersaturation profile strongly depends on the relative kinetics of the dissolution and crystal growth. By assuming linear dissolution kinetics (with rate constant \( k_D \)) and parabolic growth kinetics (with rate constant \( k_G \)), the desupersaturation profiles of growth-controlled and dissolution-controlled phase transformation can be predicted as shown in Fig. 3.6. If the dissolution rate of the metastable form is much faster than that of the crystallization of the stable form, the plateau supersaturation will be close to the maximum obtainable supersaturation \( \sigma_{12} \) (the concentration of the solution is close to the solubility of the
metastable form). The decrease in the supersaturation starts at a very late stage of the transformation. On the other hand, if the crystallization rate of the stable form is much faster, then the supersaturation starts to decrease at the onset of the crystallization of the stable form. The plateau supersaturation $\sigma_p$ will be much lower than the maximum obtainable supersaturation $\sigma_{12}$.

![Graph](image)

Fig. 3.6 Expected desupersaturation profiles for growth and dissolution controlled phase transformation ($k_D$ and $k_G$ are the rate constant for metastable phase crystal dissolution and stable phase crystal growth, respectively) (Davey and Cardew 1986).

The solvent-mediated polymorphic transformation can be simulated by a model including both population balance equations and kinetic equations. The population balance and kinetic equations that have been used in the modeling of the phase transformation of L-glutamic acid in aqueous solution are presented in Table 3.2 (Ono et al. 2004b). The kinetics of the fundamental processes during the transformation, such as the dissolution of the metastable $\alpha$ form, and the secondary nucleation and growth of the stable $\beta$ form, were taken into account in the modeling. The parameters of the kinetic equations, $k_{\beta,b}$, $k_{\alpha,\beta}$, and $k_{\beta,\beta}$, can be estimated from the in-line measured solid phase composition, solution concentration and particle size distribution (Ono et al. 2004b, Schöll et al. 2006).
Table 3.2 The population balance and kinetic equations for the phase transformation of L-glutamic acid ($n$: number density; $C$: concentration, $L$: particle size; $t$: time; $G$: growth rate).

<table>
<thead>
<tr>
<th>Population balance equations</th>
<th>$\Delta C_i &gt; 0$</th>
<th>$\frac{\partial n_i (L,t)}{\partial t} + \frac{\partial}{\partial L} \left[ n_i (L,t) \cdot G_i \right] = 0$</th>
<th>$\Delta C_i &lt; 0$</th>
<th>$\frac{\partial n_i (L,t)}{\partial t} + \frac{\partial}{\partial L} \left[ n_i (L,t) \cdot G_i \right] = 0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinetic equations</td>
<td>$\beta$ form growth rate: $G_\beta = k_{\beta} \cdot L^z \cdot \frac{\Delta C_\beta}{100}$</td>
<td>$\alpha$ form dissolution rate: $D_\alpha = k_{\alpha} \cdot \frac{\Delta C_\alpha}{100}$</td>
<td>$\beta$ form secondary nucleation rate: $B_\beta = k_{\beta} \cdot \frac{\Delta C_\beta}{100} \cdot M_{\beta}$</td>
<td></td>
</tr>
</tbody>
</table>

### Solvent-mediated phase transformation of anhydrate/hydrate

In principle, there are many similarities between the fundamental mechanism of solvent-mediated anhydrate/hydrate transformation and that of polymorphic transformation. Both processes consist of the dissolution of the metastable form and the crystallization of the stable form. Two-step polymorphic phase transformation theory can also be applied to the study of solvent-mediated anhydrate/hydrate transformations (Qu et al. 2006c, Qu et al. 2007, Murphy et al. 2002). The effect of lattice disorder on the phase transformation from anhydrous to dihydrate carbamazepine in aqueous solution has been investigated by Murphy et al. (2002). It was reported that grinding changed the rate controlling step from crystallization of the dihydrate form to the dissolution of the anhydrous form. The crystallization rate of the dihydrate form increased significantly due to the fact that the surface nucleation of the dihydrate was facilitated on the surface of the freshly ground anhydrous crystals and amorphous solids.

Despite the above-mentioned similarities between polymorphic phase transformation and anhydrate/hydrate transformation, it should be noted that anhydrate/hydrate transformation is not a true polymorphic transformation. For a polymorphic transformation, the nucleus of the stable form consists of only one component and no solvent molecules are incorporated into the crystal lattice. The nucleation of a hydrate is a two-component system, for which the evaluation of the free energy of nuclei formation is different from that of a one component system. The ratio in which the different molecules are incorporated into the cluster and the way they affect each other have to be taken into account (Mersmann et al. 2001). Therefore,
the classical nucleation theory presented in chapter 2 is not applicable for hydrate nucleation. Hydrate crystallization is still not well understood either kinetically or thermodynamically. An anhydrate/hydrate transformation mechanism has been proposed in the literature (Qu et al. 2006c) by correlating the transformation rate with the deviation of the water activity in the mixed solvent from the equivalent water activity (defined as the water activity at which the anhydrate and hydrate have the same solubility). It was found that the anhydrate/hydrate transformation mechanism was better described by this water activity based correlation than by conventional supersaturation-based crystal growth model. This work will be discussed later in chapter 5.

Dependency of solvent-mediated phase transformation rate on operation parameters

The solvent-mediated phase transformation of pharmaceutical substances has been investigated by many authors (Starbuck et al. 2002, Wang et al. 2000, Hu et al. 2005, Ferrari et al. 2003). The solvent-mediated phase transformation of L-glutamic acid in aqueous solutions has been studied using an in-line Raman immersion probe (Ono et al. 2004a, Ono et al. 2004b, Schöll et al. 2006). It was shown that the crystallization of the stable β form was the rate controlling step. In many cases the increasing transformation rate was caused by an increased plateau supersaturation level that drove the phase transformation and controlled the crystallization rate of the stable form. This usually resulted from the enhanced solubility difference between the metastable and stable forms. It has been observed that the transformation rate of L-glutamic acid from α to β form increased with increasing temperature. This increased transformation rate was explained by the increasing solubility difference between the two forms with increasing temperature. In addition, the temperature dependent growth rate of the β form also contributed to the increasing of the transformation rate (Ono et al. 2004a, Ono et al. 2004b). The solvent effect on the polymorphic phase transformation was investigated by Gu et al. (2001). It was found that the solvent that gives higher solubility usually gives a faster phase transformation rate. On the other hand, the phase transformation can be retarded if a solvent giving low solubility is selected. A similar phenomenon was observed for the phase transformation of glycine in mixed solvents (Ferrari et al. 2003). It was shown that the phase transformation was controlled by the dissolution of the metastable form, and the transformation time was significantly reduced by increasing the
The presence of additives may have a distinct influence on the phase transformation due to either the thermodynamic or kinetic effect. The additives that can be used to influence the phase transformation of pharmaceutical products are either tailor-made additives or some excipient materials. Mukuta et al. (2005) observed that tailor-made additives can retard the solvent-mediated phase transformation from the metastable to the stable form of an active pharmaceutical ingredient. The retarding effect was explained by the additive’s ability to disrupt the nucleation and crystal growth of the stable form and at the same time the additive increased the solubility of the stable form, which consequently reduced the supersaturation, the driving force of the phase transformation. Modifying both crystal structure and morphology by tailor-made additives has recently been reported by Kwon et al. (2006). The effect of surfactants on the anhydrate/hydrate transformation has been intensively studied, because surfactants are usually used in the solubilization and absorption of drugs and lipids in the gastrointestinal tract. The effect of surfactants on the transformation of anhydrous to dihydrate carbamazepine in pure water has been investigated in the literature (Luhtala et al. 1990, Luhtala 1992a, Luhtala 1992b). It was observed in their work that polysorbate 80 and poloxamer 184 inhibited phase transition while sodium lauryl sulfate (SLS) and benzalkonium chloride accelerated the phase transition. The mechanism of the promoting effect of sodium lauryl sulfate and sodium taurocholate (STS) on the solvent-mediated transformation of carbamazepine in water solution was thoroughly explored by Rodriguez-Hornedo and Murphy (2004). It was found that the surfactants had no effect on the solubility of carbamazepine below the critical micelles concentration (cmc), and the solubility of carbamazepine increased linearly with the surfactant concentration above the cmc. Both surfactants enhanced the solvent-mediated phase transformation and changed the rate-controlling step from crystallization of dihydrate carbamazepine (CBZH) to the dissolution of anhydrous carbamazepine (CBZA). It was observed that the surface-mediated nucleation of CBZH was facilitated by the presence of SLS, which probably resulted from the adsorption of SLS at the CBZA crystal-solution interface and solubilization of CBZ in these adsorbed assemblies. This solubilization can lead to high interfacial concentration of CBZ on the surface of the dissolving CBZA crystals and offers a high driving force for the
crystallization of CBZH on the CBZA surface. The promoting effect of STS was explained by the fact that the surfactant assemblies can act as templates for the nucleation and growth of CBZH crystals. In addition to surfactants, cellulose and polymers have also been widely reported to have effects on the dissolution and phase transformation of pharmaceutical compounds. Hydroxypropyl methylcellulose was reported as an inhibitor for the phase transition from anhydrate to hydrate (Otsuka et al. 2000) and as a promoter for the dissolution of anhydrous carbamazepine (Mitchell et al. 2003). The strong inhibiting effect of Hydroxypropyl methylcellulose (HPMC) on the solvent-mediated phase transformation of CBZA to CBZH in ethanol-water mixtures was observed by Qu et al. (2007). The mechanism of the inhibiting effect was mainly due to the thermodynamic effect. The presence of HPMC selectively increased the solubility of CBZH and consequently reduced the solubility difference between CBZA and CBZH. This resulted in a decreased supersaturation during the phase transformation. It was found that the effect of HPMC on the nucleation and growth kinetics of CBZH crystals was not pronounced. Polymers, such as polyethylene glycol and povidone, could increase the solubility and dissolution rate of carbamazepine by preparing solid dispersion of the drug compound and the polymers (Nair et al. 2002). The effect of certain excipients on the kinetics of vapor phase induced phase transformation between hydrates and anhydrates was investigated by Salameh and Taylor (2006). It was observed that both mannitol and polyvinylpyrrolidone K12 enhanced the dehydration of carbamazepine dihydrate and theophylline monohydrate. For the transformation from anhydrates to hydrates, polyvinylpyrrolidone K12 showed a promoting effect on the hydration process of anhydrous carbamazepine, but it retarded the transformation of anhydrous theophylline. The effect of the excipients on the phase transformation was explained by attempting to relate the effects with the properties of the excipients in terms of physical state, chemical composition, and the possibility of specific drug-excipient interaction. It was concluded that the mechanism of the excipient effects on the phase transformation was complex and was still not fully understood.

3.4 Summary

Most active pharmaceutical ingredients are capable of forming polymorphs and pseudopolymorphs. Polymorphism results from the existence of two or more crystalline
phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Pseudopolymorphs, which are also referred to as solvates, are defined as the crystals formed by the same substance crystallized with different amounts or types of solvent molecules in the lattice. Different polymorphs or pseudopolymorphs have different crystal structures and thus exhibit different x-ray diffraction patterns, thermograms (DCS or TGA), infrared spectra, Raman spectra, dissolution rate and solubility, etc. The crystal morphology is usually different for different polymorphs or pseudopolymorphs, which causes different powder flow characteristics, compressibility, and filterability for the different forms. As a consequence, polymorphism and pseudopolymorphism strongly impact not only on the performance of the final dosage but also the processing efficiency of the drug product. The relative stability of the polymorphs depends on temperature and pressure, while the relative stability of the anhydrate/hydrate depends on the temperature, pressure, and the water activity in the surrounding medium.

Crystallization is widely used for the production and purification of pharmaceutical products. The objective of a crystallization process is to produce a certain solid state form with good reproducibility from batch to batch. The polymorphic phase of the crystal product during crystallization is determined by the competitive nucleation and crystal growth of the polymorphs, and the transformation from the metastable forms to the stable form. In order to control the polymorph of the crystallization product, the crystallization mechanism of the polymorphs in each elemental process and the dependence of the crystallization behavior of the polymorphs on the operation parameters have to be understood. Depending on the operation supersaturation level with respect to the solubilities and metastable zone widths of the polymorphs, the dominating factor for the determination of the polymorphic phase can be either thermodynamic factors that mainly depend on the temperature, or kinetic factors that are driven by external conditions such as the solvent, seeding, mixing, and additives.

The solvent-mediated phase transformation plays an important role in determining the polymorphic phase of the final crystal product. The solvent-mediated polymorphic or pseudopolymorphic transformation consists of two steps, first the metastable form is dissolved and subsequently the stable form crystallizes out. The process can be dissolution controlled or crystallization controlled, depending on the relative kinetics of the dissolution
and the crystallization steps. The rate controlling step can be changed by using additives, or altering the surface properties of the metastable form crystals. The solvent that gives higher solubility usually gives a faster phase transformation rate. The presence of additives can affect the phase transformation rate due to either kinetic or thermodynamic effects. The phase transformation rate can be significantly increased if the additives promote the nucleation and growth kinetics of the stable form. On the other hand, the additives can retard the phase transformation by reducing the solubility difference between the polymorphs or pseudopolymorphs.

The polymorphic and pseudopolymorphic phase of active pharmaceutical ingredients has to be controlled throughout the whole manufacturing process. This requires an understanding of the thermodynamics of the polymorphic and pseudopolymorphic system, and the mechanism of the process-induced phase transformation of the active pharmaceutical ingredients has to be comprehended.
4 Process analytical technology for in-line monitoring of batch crystallization

4.1 Monitoring of solute concentration during crystallization

As the thermodynamic driving force of crystallization, supersaturation has a tremendous influence on the mechanisms of nucleation, crystal growth, and agglomeration, which will subsequently determine the properties of the crystalline product. Product quality control requires keeping the supersaturation at an optimum level, which is usually within the metastable zone, throughout the crystallization process. For batch cooling crystallization, the cooling mode should be appropriate so that the supersaturation generation rate should match the desupersaturation rate by crystal growth. Nevertheless, it is possible to operate a batch crystallizer following a predetermined optimized cooling mode that is decided based on the nucleation and crystal growth kinetic data for a particular system. However, nucleation and crystal growth kinetic data are not always available for industrial crystallization systems. Furthermore, the measured kinetic data are often highly sensitive to operation conditions such as mixing intensity and the presence of impurities, and thus can fail to accurately predict the crystallization processes when the operation conditions are altered from batch to batch. Real time information of supersaturation allows the possibility of ensuring the crystallizer is operating at the most appropriate supersaturation level and therefore the desired product quality can be obtained with good reproducibility from batch to batch.

The supersaturation level during crystallization can be obtained by measuring the solute concentration during crystallization when the solubility and temperature of the system are already known. The concentration of the solution can be determined by measuring some variables that can be easily related to the solution concentration. Various techniques have been reported in the literature for the in-line measurement of supersaturation, however most of them have restrictions and are not suitable for industrial applications. In-line density measurement is a conventional method to obtain concentration data during crystallization (Qui and Rasmuson 1994). The main restriction of this method is that the accuracy of the measurement is sensitive to the presence of various concentrated impurities, which are frequently encountered in industrial crystallizations. The requirement of a crystal-free solution sample means an external sampling loop is needed, and this could bring operational
difficulties in practice. It has been reported that reliable concentration data can be obtained by measuring the electric conductivity of the solution (Hlozny et al. 1992, Jagadesh et al. 1996). However, the method is not applicable for most organic compounds as they are usually not electric conductors. In addition, undesirable fouling on the conductivity cell caused by crystallization can induce large measurement errors. The presence of impurities is another potential problem that can ruin the measurements (Lewiner et al. 2001a). The ultrasonic technique works on the principle that the spread velocity of ultrasonic waves through a liquid at a certain temperature depends on the density of the liquid and its adiabatic compressibility (Omar and Ulrich 1999a). It has been shown that for some selected solute-solvent systems the concentration profile can be determined by monitoring the ultrasonic velocity and temperature of the solution (Omar and Ulrich 1999b). Since the density and the adiabatic compressibility change in opposite ways with the changing of temperature, some substances may show only a minor change or theoretically no change in the ultrasonic velocity during cooling crystallization. The applicability of the method to industrial practice has yet to be tested. Calorimetry is a theoretically straightforward method, however, only a few applications of calorimetry have been reported for the in-line monitoring of supersaturation during crystallization. The main difficulty is the weakness thermal effects involved during the crystallization phenomenon (Fevotte and Klein 1996).

Attenuated total reflection Fourier transform infrared (ATR FTIR) spectroscopy is a novel method for the in-line monitoring of supersaturation during crystallization. The method was originally introduced by Dunuwila et al. (1994) for the in-line monitoring of supersaturation during crystallization. The method has attracted more and more attention and has been successfully applied to the study and optimization of crystallization processes. A closed-loop supersaturation control for a batch crystallizer has been developed based on ATR FTIR spectroscopy (Grön et al. 2003). As a novel technique, it has numerous advantages over other in-line concentration measurement techniques: the measurement is not affected by the crystals in the suspension and thus no sampling procedure is needed; it provides information about many species in the suspension, including the crystallizing solute and impurities; it is widely applicable for a wide range of solute-solvent systems. The principle of ATR spectroscopy is shown in Fig. 4.1. It is based on the total reflection of infrared radiation when an optically denser (higher refractive index) internal reflection element is brought into
contact with an optically rarer (lower refractive index) solution sample. The incidence infrared radiation is introduced to the internal reflection element at a certain angle ($\theta$) that causes a total reflection of the radiation to take place at the interface of the ATR element and the solution sample. The absorption of the sample causes the attenuation of the internally reflected radiation, which is then transmitted to the detector to obtain the absorption spectrum. The measured spectra are a function of the solution concentration and the temperature. The penetration depth ($d_p$) is related to the wavelength ($\lambda$) and the angle ($\theta$) of the incidence radiation, the refractive index of the reflection element ($\eta_1$) and the sample ($\eta_2$) by the following equation (Lewiner et al. 2001a):

$$d_p = \frac{\lambda}{2\pi\eta_1\left[\sin^2\theta - (\eta_2 / \eta_1)^2\right]^{1/2}}$$

The penetration depth decreases with increasing incidence angle, decreasing incidence radiation wavelength and decreasing refractive index ratio ($\eta_2 / \eta_1$). The refractive indices at 1000 cm$^{-1}$ of commonly used ATR elements (for example, ZnSe or AMTIR crystal) are within 2-4. The penetration depth for most solution samples is usually within several micrometers, and thus the measurement can be considered to be within the liquid phase. As a consequence, the technique is insensitive to the solid particles present in the suspension. This is a significant advantage for the in-line monitoring of supersaturation during crystallization, since the problems connected with sample taking and filtering devices are avoided.

Fig. 4.1 Principle of the ATR sensor (modified from Lewiner et al. 2001a).

The reliability of the concentration data resulting from ATR FTIR spectra data depends on appropriate setting up and operating conditions of the system and the prediction performance of the calibration model. Spectrum variation can be caused by any mechanical change to the
system because the penetration depth ($d_P$) depends on the incidence angle ($\theta$). Imperfect mixing in the crystallizer is another potential problem which can induce measurement errors. Various calibration methods have been reported in the literature. The calibration model can be created by correlating the height of the selected characteristic peaks or the area under the selected peaks, or the ratio of the height or area of the selected peaks, with the temperature and the solute concentration by a model equation containing certain parameters (Dunuwila and Berglund 1997, Lewiner et al. 2001a, Lewiner et al. 2001b, Feng and Berglund 2002, Groen and Roberts 2004). The value of the parameters is then estimated by fitting the equation with data taken from calibrating solution samples with known solute concentrations. However, this ordinary least squares (OLS) calibration is not always robust because of the strong correlations within the data. The multivariable chemometric methods can be used to handle the highly correlated data to construct the calibration model. A variety of chemometric techniques, such as orthogonal signal correction (OSC), principle component analysis (PCA), partial least squares (PLS), can be used for the pretreatment of the spectra data and to construct the calibration model. Robust procedures for generating a calibration model using chemometric methods have been reported in the literature for the ATR FTIR monitoring of supersaturation during crystallization process (Pöllän et al. 2005, Fujiwara et al. 2002, Togkalidou et al. 2001, Togkalidou et al. 2002, Zhou et al. 2006). It has been shown by Qu et al (2005a) that the temperature effect on the spectra was rather small in the crystallization of an organic compound C15.

4.2 Monitoring the crystal properties during crystallization

4.2.1 Monitoring of crystal size and shape

The crystal size and shape often represent very important properties of the crystalline product, since they determine not only the end-use functional properties but also the downstream processing and handling efficiency of the product. Difficulties in filtration, grinding, granulating, powder flowing, and storage of the product are frequently related to the size and shape of the crystals. Tremendous efforts have been made to model and control crystal size distribution and the shape of the crystal. A review of the process control and modeling of CSD has been presented by Rawlings et al. (1993). Theoretical research work on this topic
has also led to the development of software aimed at modeling the crystal shape. For example, the software system CERIUS-2 has been developed to calculate the attachment energies and the relative growth rate of the crystal faces. However, it is very difficult to predict the shape of crystals grown in industrial crystallizers because minor changes in supersaturation, cooling rate, mixing conditions, and impurities in the feed can have a great impact on the nucleation and growth of the crystal faces, and thus the crystal size and shape. For these reasons, in-line techniques need to be developed that can offer real time monitoring of the crystal size and shape throughout the whole crystallization process.

Three different instruments can be considered the most promising for in-line measurement of crystal size distribution: the ultrasonic attenuation spectrometer, the focused laser beam reflectance (or backscattering) measurement sensor, and the in-line imaging probe. Ultrasonic attenuation spectroscopy is suitable for measuring crystal sizes in the range 0.1-1000 μm in slurries with high solid concentration (Mougin et al. 2003a, Mougin et al. 2003b). The main obstacle to applying the technique to industrial environments is the complexity of the relationship between the ultrasonic attenuation spectra and CSD. This complex relationship makes the technique sensitive to any change in the physical properties of both the liquid and solid medium, which is frequently encountered in crystallization processes. The back scatter CSD measurement instrument works on the principle of active laser beam scattering. The configuration and the measurement principle of the focused beam reflectance method (FBRM) are shown in Fig. 4.2 (Ruf et al. 2000). A laser beam rotating at high speed is propagated into the suspension through a sapphire window. The laser beam hits a particle and it is reflected and propagated back to the probe. The chord length is calculated as the product of the measured crossing time and the beam velocity. The measured chord length distribution (CLD) is a function of the number, size and shape of the particles (Barrett and Glennon 1999). Several models have been developed to convert the measured chord length distribution into particle size distribution (Heath et al. 2002, Ruf et al. 2000, Nere et al. 2006). The application of a focused laser beam reflectance measurement probe to the in-line monitoring of crystallization processes includes detecting the onset of nucleation and thus characterizing the metastable zone width (Tähti et al. 1999), and monitoring the crystal growth or agglomeration (Devarakonda et al. 1999, Loan et al. 2002). It has been shown that a focused laser beam reflectance measurement probe can be used to monitor the evolution of
the CSD during crystallization (Qu et al. 2005a). Control of fines suspension density was accomplished by controlling the count rate of fine particles measured by the FBRM probe (Tadayyon and Rohani 2000).

Fig. 4.2 Measurement principles of FBRM probe. (a) FBRM probe; (b) chord length measurement; (c) histogram of the chord length counts (Ruf et al. 2000).

The in-line imaging technique possesses a unique advantage over the other two approaches; the in-line imaging probe can simultaneously monitor both crystal size and shape during the crystallization. The ability to capture sequences of in-line digital images at high speed and with ready availability make the instrument very attractive for real time monitoring and control of the crystal size and shape. However, images taken with an in-line video microscope are usually of poorer quality than those from off-line instruments, because of the high level of noise caused by the hydrodynamics in the crystallizer and the continuous movement of the particles. The in-line imaging technique has been limited to qualitative applications due to the lack of appropriate image analysis algorithms that are sufficiently accurate, fast, robust, and tolerant to the quality of the in-line images. Typical qualitative applications of in-line imaging include the characterization of the metastable zone width of the crystallizing substance (Barett and Glennon 2002, Tähti et al. 1999) and visual observation of the polymorphic and pseudopolymorphic transformation (Calderon et al. 2005a, Qu et al. 2005c, Wang et al. 2006). Recently, a novel image analysis method based on edge-detection particle segmentation has been developed, which offers the possibility of performing quantitative measurement of crystal size and shape during crystallization processes (Calderon et al. 2005b, Qu et al. 2005b, Qu et al. 2006a). Edge-detection based
particle segmentation can overcome the difficulties in processing in-line images caused by the high background noise level and the vague edge of the particles. The quantitative growth rate of the crystal faces of KDP was obtained from in-line images (Qu et al. 2006a). The results of this work will be presented in more detail in Chapter 6.

4.2.2 Monitoring of the polymorphic and pseudopolymorphic phase of the crystals

Basic theory and principles of Raman spectroscopy

Infrared absorbance and Raman scattering spectroscopes can both detect vibrations in molecules and are widely used to identify chemical structures and physical forms. The substances can be recognized and quantified from characteristic spectral patterns, which can be considered as the ‘fingerprints’ of the molecules (Smith and Dent 2005). Despite the many similar applications of these two spectroscopes, the basic principle of infrared and Raman spectroscopy is different.

In infrared spectroscopy, infrared energy covering a range of frequencies is directed onto the sample. If the frequency of the incident radiation matches that of a vibration, the infrared energy at this frequency is absorbed and the molecules are promoted to a vibrational excited state. In other words, the absorption of infrared happens only at the frequencies where the energy of the incident radiation matches the energy difference between the ground and excited states. The loss of this frequency of radiation from the beam after it passes through the sample is then detected. Unlike infrared absorption spectroscopy, Raman spectroscopy uses a single frequency of radiation to irradiate the sample. The incident light then interacts with the molecule and causes distortion of the electron cloud round the nuclei and could also induce motion of the nuclei. A short-lived ‘virtual state’ is then formed and the radiation scattered from the molecule may gain or lose one vibrational unit of energy, which is detected by the spectroscopy. As shown in Fig. 4.3, Rayleigh scattering happens only if electron distortion is involved, in such a case, the energy change of the scattered photons is very small and usually can not be detected. Raman scattering occurs when nuclei motion is involved and therefore energy is transferred from the incident photons to the molecule or in the reverse direction. Since most molecules at room temperature are present at the lowest vibrational level \( m \), during the Raman scattering process the energy is transferred from the
incident photons to the molecule, which is then promoted to a higher energy excited vibrational state \( n \). This scattering process is called Stokes scattering. Anti-Stokes scattering refers to the situation where the molecules are present at an excited energy state \( n \) and the energy is transferred from the molecule to the scattered photons. Stokes Raman scattering is much more commonly encountered in practice than anti-Stokes scattering.

Fig. 4.3 Rayleigh and Raman scattering processes (the upward arrows represent the incident energy and the downward arrows represent the scattered energy) (Smith and Dent 2005).

The differing work principles of infrared absorption and Raman scattering spectroscopy give rise to a general selection rule: Infrared energy is usually absorbed by polar groups and hence asymmetric vibrations cause higher infrared intensities; in contrast, radiation is more effectively scattered in the Raman effect by symmetric vibrations and nonpolar groups, thus the more symmetrical ones give higher Raman intensities. Another consequence of the different work principle of infrared and Raman spectroscopy is that the vibrational spectroscopic information obtained from Raman and IR analysis regarding the same sample is complementary. Bands due to the stretching vibrations of symmetrical groups, which are usually infrared inactive, may be observed by using Raman spectroscopy. The opposite situation is also often true, which means that the Raman inactive bands (asymmetric groups) may be observed by using infrared spectroscopy (Socrates 2000).

The phenomenon of inelastic scattering of light (Stokes and anti-Stokes scattering in Fig. 4.3) was first experimentally observed by Raman and Krishnan in 1928 and since then it has been referred to as Raman spectroscopy. Raman also received the Nobel Prize in physics for his work on the scattering of light and the discovery of the Raman Effect two years later. Raman
scattering is inherently a weak process since only one in every $10^6$-10$^9$ photons is Raman scattered. In principle, the intensity of the Raman scattering is related to the power of the laser used to excite the scattering, the square of the polarizability of the molecule analyzed and the fourth power of the frequency chosen for the exciting laser (Smith and Dent 2005). A straightforward choice for obtaining higher scattering intensity is to increase the laser power or use a higher frequency, for example, to work in the UV region. However, the risk of sample degradation increases for UV excitation due to the fact that UV radiation is absorbed by many compounds and the energy of the photons in the UV region is high. Visible laser or near infrared laser are usually chosen for the excitation. The main disadvantage of using visible excitation is the fluorescence of the samples. High power densities are usually delivered to very small samples using modern laser and microscopy techniques in order to obtain sufficient scattering intensity of Raman spectroscopy.

It is possible to assign the vibrations of a molecule to the peaks in the Raman spectrum. The basic principle of this vibration assigning is Hook’s law, which defines the relationship between frequency, the mass of the atoms involved in the vibration and the bond strength for a diatomic molecule (Smith and Dent 2005):

$$v = \frac{1}{2 \pi c} \sqrt{\frac{K}{\mu}}$$

(4.2)

where $c$ is the velocity of light, $K$ is the force constant of the bond between the atoms A and B, and $\mu$ is determined by the mass of A and B:

$$\mu = \frac{M_A M_B}{M_A + M_B}$$

(4.3)

Hook’s equation provides a basic idea about the approximate order of the energies of specific vibrations. The vibrational frequency of a bond is expected to increase with bond strength and to decrease with the increase of the mass of the atoms involved. As an example, the C-H vibrations lie around 3000 cm$^{-1}$, while C-F vibrations are at 750 cm$^{-1}$. However, many factors may influence the precise frequency of a molecular vibration, such as the impact coming from other groups in the molecule, or vibrational coupling. More detailed work about assigning vibrations to spectral peaks requires knowledge about the effect of group vibrations on the spectra and is beyond the scope of this work. Reference Raman spectra data for common functional groups is available from the literature (Socrates 2001).
Raman spectroscopy has evolved rapidly as a technique to identify chemical structures and physical forms. The most commonly used Raman instruments are dispersive and FT spectrometer (Smith and Dent 2005, Laserna 1996). The former uses a visible laser for excitation and a dispersive spectrometer and CCD (couple charged device) for detection. The latter employs an NIR laser for excitation and an interferometer-based system which utilizes an FT program to produce the spectra (shown in Fig. 4.4). A microscope can be integrated with the Raman spectrometer, which offers many advantages for sample analysis. Fig. 4.5 shows a typical arrangement of Raman microscopy. It can look at very small samples or small parts of samples to detect only very minute amounts of materials. A relatively low laser power can be used because it is focused at a very small spot, thus giving high power density. This arrangement also provides the possibility to obtain profiles along X, Y (surface plane) and Z (depth) dimensions of the samples. One drawback of Raman microscopy is that a non-representative spectrum may be obtained when the diameter of the laser beam spot through the microscope is small compared with the particle size in the sample. The homogeneity of the samples has to be checked in this case. Another useful interface between the sample and spectrometer is a fiber optic. The fiber probe may be immersed into a liquid sample or a solid-liquid suspension (for example, during crystallization) to collect information about the molecules or the physical forms of both the solid and liquid phase. Indeed, the use of fiber optics has extended the application of Raman spectroscopy in chemical plants significantly. The main problem with the use of fiber optics is that the laser light excites Raman scattering
from the fiber optic material itself while passing through the fiber. This can be overcome by using a multi-mode cable in which the laser is launched down some fibers on the outside and collected through a single central fiber. One arrangement of a multi-mode cable probe is shown in Fig. 4.6.

![Diagram of Raman spectrometer and microscope](image)

**Fig. 4.5** Raman spectrometer and microscope using a visible laser, notch filter, spectrometer and CCD detector.

![Diagram of fiber optic probe end](image)

**Fig. 4.6** Fiber optic probe end (Lewis and Edwards 2001).

The application of Raman spectroscopy to pharmaceutical study

The identification of polymorphs and solvates is one of the most important issues in pharmaceutics. Crystal structure is different for different polymorphs, which can then give rise to differences in the pattern of molecule vibrations. Incorporation of the solvent molecules into the crystal lattice can result in a more significant difference in the crystal
structure and hence considerable altering in the vibrational modes of the molecules. Therefore, both infrared absorption and Raman scattering spectroscopy can be used to characterize the different polymorphs and solvates for pharmaceutical compounds (Al-Zoubi et al. 2002, Brittain 1997, Bugay 2001, Stephenson et al. 2001).

IR spectroscopy has been reported as a routine characterization method to analyze polymorphic and solvates mixtures in both qualitative and quantitative ways (Aaltonen et al. 2003, Al-Zoubi et al. 2002, Gilpin and Zhou 2005, Jasti et al. 1995). Typically, the substances are intimately mixed with potassium bromide and are then compressed into a pellet. The compression of the substances may sometimes induce solid-state phase transitions. Depending on the differences in the crystal structure of different polymorphs, the difference in the spectra for different polymorphs can range from very slight to significant. Databases have vast numbers of infrared spectra that can easily be referred to.

Recently, Raman spectroscopy is becoming more and more popular in the pharmaceutical industry for the analysis of a wide range of materials. It provides vibrational spectroscopic information that is complementary to that obtained from IR analysis. Compared with traditional IR, Raman spectroscopy has several advantages:
1. A very small sample amount is needed, and no special sample preparation procedure is required.
2. It is applicable for the analysis of multi-component systems.
3. It can be easily integrated with fiber optics or immersion probes to implement in-line monitoring of a unit operation process, such as crystallization.
4. It is relatively insensitive to aqueous media; this eliminates the disturbance of the solvent when Raman spectroscopy is applied to the in-line monitoring of crystallization, where water is the most commonly used solvent.
5. It is capable of collecting information about both the liquid and solid phase. For example, simultaneous monitoring of both the polymorphic or pseudopolymorphic phase of the crystals and the concentration of the mother liquor during crystallization can be implemented by Raman spectroscopy.
Raman spectroscopy can be used in the pharmaceutical analytical laboratory in a variety of ways. CCD-Raman spectroscopy has been used to quantitatively analyze the crystallinity of lactose (Niemelä et al. 2005, Murphy et al. 2005). Findlay and Bugay reported a quantitative FT-Raman analysis of two different polymorphs of a developmental pharmaceutical compound (Findlay and Bugay 1998). FT-Raman spectroscopy was reported to be an appropriate technique to study the conversion kinetics of carbamazepine polymorphs to the dihydrate form in aqueous suspension (Tian et al. 2006a). An excellent application of FT-Raman spectroscopy to the characterization of the polymorphic compositions of several commercial drug products was presented by Auer et al (2003). It was found that commercial drug products may contain also metastable polymorphs. The paper highlighted the advantages of Raman spectroscopy, and presented Raman spectroscopy as a fast and efficient technique that is very suitable for the identification of crystals forms in drug products during both processing and storage even when the used excipients are not known.

One of the main difficulties associated with the utilization of Raman spectroscopy for quantitative analysis is collecting a Raman spectrum which is truly representative of the concentration of the solid mixtures. The principle errors arise from the inhomogeneity of the mixture samples, which can be caused by large particle size, great density difference between the polymorphic forms, or the distinctly different morphologies of the substances (Roberts et al. 2002). The particle size of the polymorphic substances affects the Raman spectra significantly, especially when the sampling volume of the spectrometer is small with respect to the particle size. Roberts et al. reported that for a FT-Raman spectrometer focused on an approximate 100 µm spot, variation of the Raman spectra can be minimized by preparing the samples with particles smaller than 125 µm. The homogeneity of mixing of the samples can be improved by a slurry technique (Bugay et al. 1996) or by utilizing a rotating sample holder (Langkilde et al. 1997, Rantanen et al. 2005). It is very important to increase the total sampling volume of the spectrometer. This can be realized by averaging a large number of spectra taken from the same sample. It was found that analysis error can be significantly decreased by collecting spectra at a series of grid points on a tablet surface (Bell et al. 2004).

The ability to perform in-line monitoring during processing of drug and food compounds is the unique advantage that Raman spectroscopy possesses over the other analysis techniques.
The application of in-line Raman monitoring for solid-state phase transformation during fluidization of theophylline monohydrate has been reported in a recent paper (Aaltonen et al. 2006b). The dehydration profiles of the hydrate were obtained by combining Raman spectroscopy and the partial least squares regression (PLS) calibration algorithm. The kinetics of the solid-phase transformation of carbamazepine polymorphs in an isothermal chamber has been studied using in situ FT-Raman spectroscopy (O’Brien et al. 2004). In situ measurement of solvent-mediated phase transformation during dissolution testing was reported by Aaltonen et al. (2006a). In-line monitoring of the concentrations of both solvent and impurity in filter cake during filtrating and cake washing of sucrose has also been accomplished by Raman spectroscopy (Louhi-Kultanen et al. 2006).

Integration of the immersion probe with a Raman spectrometer offers the possibility of in-line monitoring of the solid and liquid phase during crystallization. The issue has been addressed by many research groups (Wang et al. 2000, Starbuck et al. 2002, Ono et al. 2004a, Ono et al. 2004b, Hu et al. 2005, Schöll et al. 2006, Qu et al. 2006c). Hu et al. presented an excellent application of a Raman in-line probe to crystallization processes. The authors utilized Raman spectroscopy to study the crystallization of flufenamic acid. Simultaneous measurement of both the desupersaturation profile in the solution phase and the polymorphic form composition in the solid phase was done (Hu et al. 2005). In the study, the solute dissolved in the solution, and the solid form I and form III of flufenamic acid all exhibit characteristic peaks which do not interfere with each other. Thus, two separate calibration models were set up to correlate Raman spectra with the concentration in the liquid phase and the polymorphic form composition in the solid phase.

It is very important to have a reliable and robust calibration model for the in-line quantitative measurement. The calibration spectra can be taken with the immersion probe from prepared slurries. The advantage of this calibration method is that the homogeneity mixing of the solid mixtures can be improved and the environment of spectra collecting is identical for calibration and real measurement. However, solvent-mediated phase transformation may occur and induce large errors in the calibration (Ono et al. 2004a). The calibration model can also be generated from spectra taken from the dry powder mixture. This is referred to as an off-line calibration model. The main difficulty with this method is obtaining representative
spectra from all dry powder mixtures. This issue has been discussed above in the section about the quantification of solid samples using Raman spectroscopy. It was found that the effect of the particle size on the prediction performance of the calibration model can be minimized by applying appropriate procedure to collect the spectra (Qu et al. 2006c).

In addition to appropriate collecting of the Raman spectra, the selection of the calibrating variables and the algorithm can both contribute to the prediction performance of the calibration model. Depending on the difference between the spectra of the studied substances, the peak height, peak area, or the peak position may be selected as the variable to set up the calibrating line to correlate the Raman spectra with the composition of the mixtures. Both single variable methods and multi-variable methods, such as the partial least-squares regression (PLS) method, can be used to set up the calibration model. Rantanen et al. (2005) investigated the factors contributing to the quantification of anhydrate/hydrate powder mixtures of several pharmaceutical compounds. They draw the conclusion that the prediction performances of the two methods, single variable methods and multi-variable methods, were comparable due to the fact that the analytical peak was large relative to the total variation over the extended spectra used for the multivariable analysis.

4.3 Summary

In-line monitoring of supersaturation and crystalline phase properties is motivated by concerns about crystal product quality control and the complexity of the dependence of the crystal properties on the operation conditions of the crystallization. ATR FTIR spectroscopy has been applied to the in-line monitoring of supersaturation for determination of the optimum operation conditions and for the closed-loop control of the supersaturation level throughout the crystallization process. The performance of the calibration model is crucial for the reliability and accuracy of the predicted supersaturation data. The ordinary least squares method and chemometric methods have been reported in the literature. The advantages and limitations of the technique have been reviewed in this chapter.

In-line crystal size and shape characterizing instruments include the ultrasonic attenuation spectrometer, the focused laser beam reflectance (or backscattering) measurement sensor,
and the in-line imaging probe. All the instruments and techniques have advantages and disadvantages when applied to the industrial environment. In-line imaging offers the possibility of simultaneous monitoring of crystal size and shape. A novel digital image analysis algorithm has been proposed by replacing the pixel intensity ‘thresholding’ method with edge-detection for the particle segmentation. There have been demonstrations of the application of this new image analysis technique to the determination of the growth rate of crystal faces from in-line images. Nevertheless, the utilization of the in-line imaging technique is still in the developmental stage, and further exploration is needed regarding both improvements to the technical performance of the instrument and improvements to the image processing method.

Infrared absorbance and Raman scattering spectroscopes can both detect vibrations in molecules and are widely used to identify polymorphism and pseudopolymorphism of pharmaceutical substances. However, the measurement principles of the two instruments are different. The ability to perform in-line monitoring during the processing of drug compounds is the unique advantage that Raman spectroscopy possesses over the other analysis techniques. The application of in-line Raman monitoring has been reported for solid-state phase transformation and solvent-mediated phase transformation during the manufacturing and processing of active pharmaceutical ingredients. The calibration of the Raman spectra plays an important role in the in-line utilization of the technique. There are many issues that have to be taken into account when setting up the calibration model, such as the sampling statistics in collecting the calibrating spectra, the treatment of the obtained spectra data, and the mathematical model used in correlating the spectra with the solid phase composition. It is clear that Raman spectroscopy has great potential for the characterization of chemical structure and solid phase in various multi-component systems. Recently developed in-line process analytical technology combined with sophisticated data treatment algorithms offer the possibility of gaining a deeper understanding of the mechanism of the processes, and the chance to effectively determine the optimum operation conditions to obtain a desired product quality.
5 Thermodynamic and kinetic study of an anhydrate/hydrate system in mixed solvents using in-line Raman spectroscopy

5.1 Introduction

Crystallization from solution is a central unit operation for the production and purification of active pharmaceutical ingredient (API). Many pharmaceutical crystalline products can exist as more than one solid-state, which possess different crystal structures or contain different numbers of solvent molecules in the crystal lattice. The former is referred to as polymorphs and the latter is referred to as solvates (or pseudopolymorphs). Different polymorphs or solvates of a compound may have distinct mechanical, thermal, physical and chemical properties, such as compressibility, melting point, solubility, crystal habit, and stability. Therefore the solid-state of the product strongly impacts on the bioavailability, filtration, and tableting process of the compound. A certain solid-state has to be selected as the final form to be isolated and supplied to market. The selection of the final form depends on many factors. The thermodynamically stable form is usually preferred since it minimizes the risk of alteration of the solid-state, and thus bioavailability during the storage and delivering of the product. However, the metastable form can also be selected for different reasons, such as a faster dissolution rate, a better separation of impurities in the crystallization step (Chemburkar et al. 2000), shorter processing time, ease of crystallization (Beckmann et al. 1998), or a preferred crystal habit that offers the desired powder flow or compaction properties to facilitate the tablet manufacturing (Brittain 1999). It should be noted that the selection of the metastable form as the final dosage form unavoidably brings a certain risk and additional efforts have to be made to ensure that thermodynamically driven phase transformation does not occur during the manufacturing, storage, and delivery processes. The advantages and the unavoidable risks have to be carefully balanced when selecting a metastable form as the final product form (Muller et al. 2006). Whether the stable form or the metastable form is selected, in both cases control of the solid-state is required and a batch crystallization process that yields crystalline product with the desired quality and reproducibility is needed. The thermodynamic relative stabilities of the solid forms and the kinetics of the phase transformation at various surrounding medium conditions (temperature,
humidity for solid-vapor systems, solvent or solvent composition for solid-liquid systems) have to be fully understood.

Hydrates are the most frequently encountered solvates, since water or mixtures of water and organic solvents are often used in the manufacturing and processing of drug products. Approximately one third of active pharmaceutical substances are capable of forming hydrates. Hydrates and polymorphs are frequently discussed together because they have a lot of similarities. Both polymorphs and anhydrate/hydrate forms possess different crystal structures and exhibit different X-ray powder diffraction patterns, thermograms (differential scanning calorimetry or thermal gravimetric analysis), infrared and Raman spectra, solubility and dissolution rate in a given solvent, density, chemical stability, etc. On the other hand, anhydrate/hydrate forms are not true polymorphs. Unlike the relative stability of different polymorphic modifications depending only on the pressure and temperature, the relative stability of anhydrate/hydrate forms also strongly relies on the water activity in the surrounding medium. Yet, water and water-organic solvents mixtures are frequently used in the crystallization of pharmaceutical compounds to get higher yield. This stresses the importance of studying the thermodynamic properties of anhydrate/hydrate systems in mixed solvents. The effective control of the anhydride/hydrate state of the crystalline product requires an understanding of how the relative stability of the anhydrate/hydrate depends on temperature and water activity in the solvent, the mechanism of the solvent-mediated phase transformation, the effects of operation conditions (for example, temperature, solvent composition, mixing, presence of additives) on the phase transformation, as well as the crystallization mechanisms, such as the nucleation and crystal growth of the anhydrate and hydrate.

The objective of the present work is to conduct a systematic study of the thermodynamics and crystallization of the anhydrous and hydrate form of a model compound, carbamazepine, in mixed solvents. The work consists of four stages. Firstly, the thermodynamic properties of the anhydrate/dihydrate carbamazepine in ethanol-water mixtures, such as the relative stability, and enthalpy and entropy of dissolution, were estimated by plotting the measured solubility data according to the van’t Hoff equation. Secondly, the solvent-mediated phase transformation of anhydrous to dihydrate carbamazepine in ethanol-water mixtures was
studied using an in-line Raman immersion probe. The effects of operation conditions in terms of temperature and solvent composition on the phase transformation kinetics were investigated. Thirdly, the effects of certain additives on the phase transition from anhydrous to dihydrate carbamazepine in an ethanol-water mixture were studied. Finally, the feasibility of applying a Raman immersion probe for simultaneous monitoring of both the anhydrate/hydrate composition of the crystal phase and the concentration of the mother liquor during cooling crystallizations was explored. The results of this work are presented in papers I, II and VI.

5.2 Materials, equipment and methods

Materials
Carbamazepine (CBZ), an antiepileptic drug, was selected as the model compound in this work (Fig. 5.1). Four polymorphs and a dihydrate, as well as other solvates of CBZ, have been reported in the literature (Krahn and Mielck 1987; Rustichelli et al., 2000, Harris et al. 2005). Among them, the anhydrous form III (P-monoclinic form), which is the thermodynamically stable form at room temperature, and the dihydrate form are the most commonly encountered forms. They will be referred to as CBZA (anhydrous form III) and CBZH (dihydrate form) in this work. Carbamazepine was used as received from Orion Corporation (Finland) and Hawkings Pharmaceutical (USA). Based on the XRPD pattern (measured in Division of Pharmaceutical Technology, Helsinki University) and DSC trace (Fig. 5.2), it was pure form III (CBZA). The dihydrate form (CBZH) was prepared by cooling crystallization from a 61 mol-% ethanol aqueous solution. Analytical grade ethanol from Altia Corporation and deionized water were used as solvents. The additives were obtained from the Sigma-Aldrich Chemical Company.

![Fig. 5.1 Structure of carbamazepine](image-url)
Fig. 5.2 Differential scanning calorimetry curve of CBZA raw material (heating rate 10 K/min)

**Equipment.**

Raman spectra were collected with a LabRam 300 Raman spectrometer from Horiba Jobin Yvon. The system employed an external cavity stabilized single mode diode laser at 785 nm. The Raman spectrometer was interfaced with an optical microscope when analyzing powder samples, and an immersion probe sealed with a sapphire window for in-line suspension monitoring. The laser light was focused into the solid or the solid-liquid suspension using the optical microscope or the immersion optic, respectively. Backscattered Raman light was collected by the interfacial device and transmitted back to the spectrometer for analysis. The acquisition conditions were optimized so that a spectrum was captured with an exposure time of 5 s and 20 s for measurement of dry solid samples and the solid-liquid suspension respectively, with 3 accumulations, unless otherwise specified.
Table 5.1 Assignment of Raman bands to molecular vibrations for CBZA and CBZH (O’Brien et al. 2004, Socrates 2001) (υ: stretch, δ: bend, ρ: rocking)

<table>
<thead>
<tr>
<th>CBZA (cm⁻¹)</th>
<th>CBZH (cm⁻¹)</th>
<th>Approximate description of vibrational mode</th>
<th>CBZA (cm⁻¹)</th>
<th>CBZH (cm⁻¹)</th>
<th>Approximate description of vibrational mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>169</td>
<td>172</td>
<td>Torsion</td>
<td>792</td>
<td>791</td>
<td></td>
</tr>
<tr>
<td>183</td>
<td></td>
<td>Lattice vibration</td>
<td>873</td>
<td></td>
<td>υ (C-N-C)</td>
</tr>
<tr>
<td>254</td>
<td>259</td>
<td>Lattice vibration</td>
<td>950</td>
<td></td>
<td>δ (C-H) aromatic</td>
</tr>
<tr>
<td>272</td>
<td></td>
<td>Lattice vibration</td>
<td>988</td>
<td>967</td>
<td>υ (C-N)</td>
</tr>
<tr>
<td>332</td>
<td>330</td>
<td>Lattice vibration</td>
<td>1025</td>
<td>1029</td>
<td>δ (C-H) aromatic</td>
</tr>
<tr>
<td>375</td>
<td>383</td>
<td>Lattice vibration</td>
<td>1042</td>
<td>1045</td>
<td>δ (C-H) aromatic</td>
</tr>
<tr>
<td>390</td>
<td>392</td>
<td>Lattice vibration</td>
<td>1117</td>
<td>1118</td>
<td>ρ (NH₂)</td>
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<tr>
<td>413</td>
<td>413</td>
<td>Lattice vibration</td>
<td>1161</td>
<td>1161</td>
<td>υ (C-C) ring/(C-N-C) asymmetric</td>
</tr>
<tr>
<td>454</td>
<td>446</td>
<td></td>
<td>1205</td>
<td>1206</td>
<td>υ (C-C) ring</td>
</tr>
<tr>
<td>470</td>
<td>470</td>
<td></td>
<td>1222</td>
<td>1221</td>
<td>υ (C-N) amide III</td>
</tr>
<tr>
<td>537</td>
<td></td>
<td>δ aromatic</td>
<td>1251</td>
<td>1260</td>
<td>υ (C-N) amide III</td>
</tr>
<tr>
<td>545</td>
<td>547</td>
<td>δ aromatic</td>
<td>1309</td>
<td>1310</td>
<td>δ (CH) non-aromatic</td>
</tr>
<tr>
<td>582</td>
<td>580</td>
<td>δ (O-C-N)</td>
<td>1414</td>
<td>1408</td>
<td>υ (C=C)/ δ (CH)</td>
</tr>
<tr>
<td>620</td>
<td>626</td>
<td>δ (O-C-N) ring</td>
<td>1489</td>
<td>1493</td>
<td>υ (C=C) symmetric, aromatic/ υ (C-N) amid III</td>
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<tr>
<td>646</td>
<td>647</td>
<td>δ (O-C-N) ring/ δ (C=O)</td>
<td>1565</td>
<td>1567</td>
<td>υ (C=C) aromatic</td>
</tr>
<tr>
<td>698</td>
<td>699</td>
<td>δ aromatic</td>
<td>1600</td>
<td>1600</td>
<td>υ (N-H) amide II</td>
</tr>
<tr>
<td>723</td>
<td>718</td>
<td>υ (C-N-C) amide</td>
<td>1624</td>
<td>1625</td>
<td>υ (C=C) non-aromatic</td>
</tr>
</tbody>
</table>
Fig. 5.3 Raman spectra of CBZA and CBZH
Characterization of CBZA and CBZH by Raman spectroscopy

The Raman spectra of CBZA and CBZH are shown in Fig. 5.3. The assignment of Raman bands to molecular vibrations for CBZA and CBZH is summarized in Table 5.1 (O’Brien et al. 2004, Socrates 2001). A calibration model was generated to correlate the Raman spectra with the CBZA/CBZH fraction in the slurry. The details of the calibration have been presented in paper II.

5.3 Results and discussion

5.3.1 Thermodynamic properties of the anhydrate/hydrate system

The solubility of CBZA and CBZH was measured gravimetrically in five solvent mixtures with different ethanol water fractions. It was observed that the solubility of CBZ in pure ethanol was much higher than that in pure water. At a certain temperature, CBZ solubility exhibits a maximum value in an ethanol-water mixture having a certain composition. The solubility of CBZH and CBZA were plotted on a semi-logarithmic scale against the reciprocal of the absolute temperature for specified solvent systems according to van’t Hoff equation. As an example, the solubility of CBZA and CBZH in the ethanol-water mixture containing 39 mol% of water is plotted in Fig. 5.4. The enthalpy and entropy of dissolution of both forms were obtained from the slope and the intercept with y-axis of the resulting trend line. The solubility of CBZA and CBZH, and the obtained enthalpy and entropy of dissolution for both forms in the solvent mixtures have been presented in paper I. The system exhibits enantiotropic behavior in the studied temperature range. For a certain solvent composition, the thermodynamically stable form must have a lower solubility than the metastable form. The intercept of the extrapolation of the solubility of the two forms represents the point at which the solubility of CBZA and CBZH are identical, and thus the CBZA and CBZH are in equilibrium. This point is referred to as the transition temperature in the specified solvent mixture. For any given solvent composition, there exists a temperature corresponding to the transition point. If the temperature is higher than the transition point, CBZA is the stable form; CBZH is the stable form if the temperature is lower than the transition point.
Grant and Higuchi (1990) have introduced the equilibrium constant $K_h$ to describe the equilibrium between a hydrate and an anhydrate. It was deduced that the hydration state of a hydrate depends on the water activity in the surrounding medium. For the solid-liquid system studied in the present work, the hydration state of the CBZ solid depends on the water activity in the mixed solvents. As shown in Fig. 5.5, the ethanol-water mixtures are non-ideal solutions for which the activity value of water at various compositions can be found from the literature ((D’Avila and Silva 1970, Pemberton and Mash 1978). The solubility of CBZ in the studied temperature range is in the range of 0.3 - 2 mol%, so it is assumed that the water activity in the ternary system is not affected by the dissolved CBZ. This assumption was verified by determining the activity of water from vapor pressure data for both ethanol-water mixtures and ethanol-water-CBZ mixtures. The obtained results confirmed that the influence of the dissolved CBZ on water activity can be neglected. The water activity corresponding to the transition point in terms of the water/ethanol mole fraction and temperature can be obtained from the ethanol-water binary mixture data. As shown in Fig. 5.6, the smaller the water activity, the lower the temperature needed to attain the equilibrium between CBZA and CBZH.

![Graph](image_url)

Fig. 5.4 Solubility of CBZA (solid symbols) and CBZH (open symbols) in ethanol-water mixtures containing 39 mol% of water.
Fig. 5.5 Water activity in ethanol-water binary mixtures (a) (D’Avila et al. 1970); (b) (Pemberton et al. 1978) (The polynomial fit of the data is shown as the curve Poly.).

Fig. 5.6 Transition points of CBZA/CBZH in terms of water activity and temperature (Qu et al. 2006b) (The transition points were obtained in terms of solvent composition and temperature from the CBZA/CBZH solubility in five different solvent mixtures containing 31.1 mol%, 39.0 mol%, 46.0 mol%, 52.3 mol%, and 64.9 mol% of water. The water activity of the corresponding transition points were then obtained from the data shown in Fig. 5.5).
5.3.2 Kinetics of the solvent-mediated anhydrate/hydrate phase transformation

The solvent-mediated phase transformation from CBZA to CBZH was studied by performing experiments at different operation conditions in terms of solvent composition and temperature. The experiments were conducted in a 1 liter jacketed glass crystallizer equipped with an impeller and thermostat. The Raman probe was inserted into the crystallizer to get in-line monitoring of the solid form composition. The concentration of CBZ in the solution was measured gravimetrically by off-line sampling. The methods and the results of this study have been presented in paper II.

Solvent-mediated phase transformation is a complex process due to the fact that several mechanisms are involved in the transformation, such as the dissolving of the metastable form, primary heterogeneous nucleation and secondary nucleation of the stable form, and growth of the stable form crystals. Comparison of the solute concentration profile and the solid-phase composition measured with a Raman in-line probe allows identification of the mechanisms during the phase transformation. It was observed that as soon as the CBZA solid was added to the solution, the solute concentration in the solution phase increased from the solubility of CBZH to a plateau very quickly. The solute concentration remained at this plateau until the phase transformation was almost completed. This indicated that the dissolution rate of CBZA was fast and nucleation and growth of CBZH was the rate-controlling step for the phase transformation.

The effects of temperature and solvent composition on the transformation were studied by performing the transformation experiments at different solvent compositions and temperatures. The experimental conditions and the corresponding phase transformation profile measured by Raman spectroscopy are shown in Fig. 5.7. All experiments were carried out at temperatures lower than the transition temperatures. The lower the temperature, the more deviation from the transition temperature, and the greater the difference between the solubility of CBZA and CBZH. The large solubility difference resulted in the fast dissolution and high supersaturation level achieved during the phase transformation. As a consequence, the induction time decreased and the phase transformation rate increased with the lowering of the temperature.
Fig. 5.7 The experimental conditions and the phase transformation profile measured with in-line Raman spectroscopy (the experimental conditions of the data series in (b) and (c) are presented in (a) with the same marker).
The dependency of the transformation rate on the supersaturation level is different for the solvents containing different fractions of water (shown in Fig. 5.8). It was found that the transformation rate increased more dramatically with increasing supersaturation in the solvent containing 52.3 mol% of water. This suggests that in addition to the supersaturation level, the water activity in the solvent also plays an important role in the nucleation and crystal growth of hydrates. The relatively higher water activity in the solvent containing 52.3 mol% of water facilitated the nucleation and crystal growth of CBZH. The fundamental mechanism of crystallization of anhydrate and hydrate also supports this observation. For the crystallization of an anhydrate, solute molecules solely experience the phase change from solution to solid through nucleation and crystal growth. The crystallization of a hydrate is more complicated due to the fact that the water molecules have to be incorporated with the solute molecules to form the growth unit cell of the hydrate crystalline. Therefore, both supersaturation level and water activity should be taken into account in the study of hydrates crystallization.

The solvent effect on the transformation of CBZA to CBZH was studied by observing the crystal morphology of CBZH crystallized in pure water and in an ethanol-water mixture. As shown in Fig. 5.9, since the solubility of CBZH is very low in pure water, a whisker-like growth of CBZH occured due to the high local supersaturation during the transformation. A similar observation has been reported for CBZH and other water non-soluble hydrates by Luhtala (1990), Tian et al. (2006a), Nordhoff and Ulrich (1999). The local supersaturation of
CBZH was significantly decreased by its enhanced solubility in the ethanol-water mixture, and thus the shape of the CBZH crystals from the ethanol-water mixture was modified into columnar.

Fig. 5.9 Morphology of CBZH crystals transformed in pure water (left) and ethanol-water mixture containing 39 mol% of water (right) at 10°C (images were taken with a MTS PIA in-line imaging probe).
5.3.3 Effects of additives on the anhydrate/hydrate phase transformation

Additives have been proved to be one of the most influential factors modifying the polymorphic or solvation state, and the morphology of crystals. For pharmaceutical industries, the additives are either tailor-made additives having a similar molecular structure to that of the crystallizing compound, or excipients, such as surfactants, polymers, and carbohydrates, which are usually needed in drug formulation. In the present work, five different excipients were selected as additives based on the review of the literature: sodium lauryl sulfate (SLS), polyethylene glycol 6000 (PEG), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and D-mannitol. They have been reported to have an effect on the dissolution of drug compounds, or the solid-phase or solvent-mediated phase transformation between anhydrate and hydrate. In this work, effects of the additives on the phase transition from anhydrous (CBZA) to dihydrate (CBZH) carbamazepine in an ethanol-water mixture containing 39 mol% of water were studied. A Raman in-line probe was used to obtain the real time transformation rate during the transformation. The Raman spectra were collected with 45 s exposure time and 2 accumulations. The results are presented in paper V.

As shown in Fig. 5.10, the most influential additive was HPMC, which strongly inhibited the phase transformation from CBZA to CBZH. The mechanism of the effects of the additives on the phase transition was studied by investigating the influence of the additives on the solubility of CBZA and CBZH, and on the cooling crystallization of CBZH. It was found that HPMC exhibited a remarkable effect on the solubility of CBZ. It selectively increased the solubility of CBZH but had no effect on the CBZA solubility (shown in Fig. 5.11). Furthermore, the promoting effect of HPMC on the CBZH solubility was temperature dependent. The CBZH solubility was increased by 27.6% and 21.2%, at 10°C and 15°C respectively. When the temperature was at 20°C, this promoting effect was not visible at all. In order to understand this behavior, the dependency of the solubility difference of CBZA and CBZH on temperature and solvent composition has to be recalled. As was shown in section 5.3.1 Fig. 5.4, for the solvent containing 39 mol% of water, CBZH exhibits a lower solubility than CBZA at temperatures lower than the transition point (24.7°C). The solubility difference between CBZA and CBZH was greater when the temperature was decreasing. The promoting effect of HPMC also intensified with decreasing temperature. When the
temperature increased towards the transition point, the solubility difference between CBZA and CBZH reduced, and so did the promoting effect of HPMC. This observation indicates that regardless of the significant promoting effect of HPMC on the solubility of CBZH, the thermodynamic relative stability of CBZA and CBZH is still governed by the water activity in the solution and the temperature. The transition point of CBZA and CBZH in the solvent containing 39 mol% of water remained unchanged at 24.7°C. The inhibiting effect of HPMC on the phase transformation from CBZA to CBZH at temperatures lower than the transition point is due to the fact that the solubility difference of CBZA and CBZH was decreased dramatically by the presence of HPMC. This resulted in a reduced supersaturation level, which is the driving force of the crystallization of CBZH during the phase transformation, and therefore retarded the phase transformation.

Fig. 5.10 Additive effects on the phase transformation kinetics in solvent containing 39 mol% of water at 10°C (up) and 15°C (down). (Qu et al. 2007)
The effects of the additives on the cooling crystallization of CBZH were studied and the results can be found in paper V. It was observed that only SLS showed a slight promotion effect on the nucleation and crystal growth of CBZH by decreasing the metastable zone width and increasing the size of the final CBZH crystals. The effects of all the other additives during cooling crystallization were not significant.

Fig. 5.11 Effect of HPMC on the solubility of CBZA and CBZH in the solvent containing 39 mol\% water.

5.3.4 Simultaneous in-line monitoring of crystal and mother liquor properties during batch cooling crystallization

The crystallization of active pharmaceutical ingredient (API) capable of forming hydrate from aqueous solutions is very complex due to the fact that various mechanisms are involved during the process, such as the nucleation and crystal growth of the anhydrate and hydrate, and the phase transformation between them. The anhydrate/hydrate phase of the final product is determined by the thermodynamic properties of the anhydrate and hydrate, and their crystallization kinetics. The supersaturation level usually has a strong impact on the crystallization kinetics of the anhydrate and hydrate phases and therefore influences the purity of the crystalline product. The interpretation of the crystallization kinetics versus supersaturation is more complicated in an anhydrate/hydrate system. Any specified solute
concentration gives rise to different supersaturation levels with respect to the anhydrate and hydrate, since the solubility of the anhydrate and hydrate is different (except at the transition point). To understand the crystallization mechanism and to achieve the effective product quality control, it is of great importance to execute the in-line monitoring of both the solute concentration in the solution phase and the anhydrate/hydrate composition of the crystals throughout the whole crystallization process.

Raman spectroscopy is suitable for in-line monitoring of batch crystallization of anhydrate/hydrate systems, because the Raman spectra contain information about both the solution phase and the solid phase. One successful application has been reported by Hu et al. (2005). The authors set up two standard curves, one based on a series of flufenamic acid solutions over a certain concentration range for the prediction of solute concentration, and the other based on the polymorphic mixtures dispersed in aqueous solutions for the prediction of the polymorphic fraction in the solid phase. During the crystallization process, the solute concentration and the polymorphic fraction in the solid phase both changed with time. A prerequisite for using the ex situ calibration curves to predict simultaneous solute concentration and solid phase composition is that the selected variables (height of the characteristic peaks of the polymorphic forms and the solute) do not interfere with each other.

As shown in Fig. 5.12, the solution spectrum has a broad peak at 365 cm$^{-1}$, which is the only one that is not interfered with by the solid phase specific peaks. The CBZA and CBZH solid phase exhibit distinct peaks at 272 cm$^{-1}$, and 383 cm$^{-1}$ (marked with arrows in the figure). The heights of these peaks were selected as the characteristic variable of dissolved CBZ in solution, and the solid phase CBZA and CBZH, respectively. The simultaneous monitoring of both the anhydrate/hydrate phase of the crystals and the concentration of the mother liquor was implemented by interpreting the Raman spectra. It is possible to set up an ex situ calibration model to correlate the Raman spectra peak heights with the solute concentration and solid phase composition (Hu et al. 2005). However, accurate calibration can be a complicated task due to the fact that both the solution and solid phases are sampled by the Raman probe, and the resulting spectra contain the contribution of both components. For example, the height of the solute peak at 365 cm$^{-1}$ for a clear solution must be higher than
that for a suspension containing both solution and solid CBZA or CBZH phases, even though the solute concentration in the solution phase is identical for the suspension and the clear solution. For an accurate calibration model, the effect of pure CBZA and CBZH, as well as the mixtures of CBZA and CBZH, on the solute specific peak height has to be taken into account. This requires a large amount of calibrating spectra data and sophisticated data modeling work. For reasons of simplicity and efficiency, ex situ calibration curves to predict the solute concentration and solid phase composition were not created in this work. Instead, the height of the characteristic peak of CBZ solute was used to show the desupersaturation profile during the whole crystallization process. The specific-peak heights of CBZA and CBZH were plotted against time to demonstrate the change in the amount of CBZA and CBZH crystals during crystallization and phase transformation. In order to eliminate the effect of the Raman spectrometer laser power variation from day to day, all peak heights were scaled based on their minimum and maximum heights in one experiment.

The batch crystallizations were performed in a 1-liter crystallizer equipped with a thermostat and overhead mixer. The original solution was prepared by dissolving a certain amount of CBZ crystals in 700 g ethanol-water mixture containing 39 mol% of water. Two different cooling strategies, stepwise cooling and cooling-heating, and the effect of one surfactant SLS (with concentration 0.5 g/100 g solvent) were studied. Suspension samples were taken during the experiments, and after filtration, the solute concentration in the solution phase was measured gravimetrically. Optical images of the solid crystals were taken to study the morphology of the crystals.
Fig. 5.12 Raman spectra of dissolved CBZ, solid form CBZA and CBZH (the CBZ solution spectrum was taken from a clear CBZ solution with concentration 11.76 g CBZ/100 g solvent; CBZA and CBZH solid spectra were taken with pure dry powder of CBZA and CBZH, respectively).

**Crystallization with stepwise cooling mode and the effect of SLS**

The crystallization with stepwise cooling mode consisted of 4 steps (see Fig. 5.13 and Fig. 5.14). In step 1, the solution saturated at 48.6°C was first cooled down from 55°C to 35°C. As shown in Fig. 5.13 (a), for pure CBZ crystallization, the solute specific peak (at 365 cm⁻¹) height remained unchanged until the temperature was decreased to 37°C. This suggests that the temperature effect on the solute specific peak height is negligible. Decrease of the solute peak height and increase of the CBZA solid peak (at 272 cm⁻¹) height started simultaneously at 37°C, indicating the onset of CBZA nucleation. Based on the previous work, the transition point of CBZA/CBZH in ethanol-water mixture containing 39 mol% of water is 24.7°C, thus the crystallized CBZA was the thermodynamically stable form at a temperature higher than the transition point. A similar phenomenon can be observed from Fig. 5.14 (a) for the crystallization of CBZA with SLS. However, the nucleation of CBZA was delayed to step 2, when the temperature had already been lowered to 35°C. In step 2, the suspension was then kept at 35°C for 30 minutes. For pure CBZ crystallization, the rate decrease of the solute peak height and the rate of increase of the CBZA solid peak height both slowed down, suggesting a slower CBZA crystallization rate during this isothermal step of the process. This slower trend in the decrease of the solute peak height and the increase of the CBZA peak
height can hardly be observed in Fig. 5.14, where SLS was used as an additive. This is probably because the supersaturation level in step 2 was higher when SLS was present due to the delayed CBZA nucleation. When the suspension was subsequently cooled down from 35°C to the final temperature of 17°C in step 3, the CBZA crystallization continued as the solute peak height decreased, and the CBZA peak height increased to a maximum value. Observing the optical images of the crystals taken at 26°C without or with SLS, it can be seen that only pure CBZA was present at this time (Fig. 5.15 (a) and (b)). The decrease of the CBZA peak height at a late stage of step 3 indicates that the phase transformation from CBZA to CBZH was initiated. By comparing the scaled CBZA peak height in step 3, shown in Fig. 5.13 (b) and Fig. 5.14 (b), it is clear that for the pure CBZ system, the phase transformation started at the end of step 3, but for the experiment with SLS, the phase transformation started earlier. The images of the crystals taken at the end of step 3 (Fig. 5.15 (c) and (d)) also support this observation. For the pure CBZ system, the appearance of CBZH crystals can hardly be observed at the end of step 3, while when SLS was used the presence of CBZH crystals is rather evident at the same time. This suggests that SLS promoted the phase transformation from CBZA to CBZH. This observation is in agreement with the results of other research groups (Rodriguez-Hornedo and Murphy 2004). It was reported that the surface nucleation of CBZH was significantly facilitated by the presence of SLS. Step 4 is an isothermal process in which the temperature was kept at 17°C for 100 minutes and the phase transformation from CBZA to CBZH continued. At the end of the batch, both CBZA and CBZH specific peak heights were inclining towards stable, which means the completion of the phase transformation. The crystal samples taken at the end of the batches were analyzed with Raman microscopy and indicated that the CBZH fraction was over 95%. The images in Fig. 5.15 (e) and (f) also show that mainly CBZH exists at the end of the experiments.

Information provided by the in-line Raman spectra lead to a better understanding of the whole crystallization process. The comparison of the scaled peak height with respect to the solute, CBZA and CBZH solid phase, and the optical images taken during the experiment allow identification of the fundamental mechanisms involved in the whole process, such as the primary nucleation of CBZA, the dissolution of CBZA and the crystallization of CBZH. The consistency between the in-line Raman spectra and the optical images is evidence that
SLS enhanced the phase transformation of CBZA to CBZH due to its promoting effect on the crystallization of CBZH.

![Graph](image)

Fig. 5.13 Experimental results for the cooling crystallization of pure CBZ with stepwise cooling mode. (a) CBZ solubility, off-line measured concentration of CBZ solute in solution and the scaled solute specific peak height, and (b) the scaled distinct peak heights of solid phase CBZA and CBZH.

As shown in Fig. 5.13 (a) and Fig. 5.14 (a), the agreement between the scaled Raman spectra peak height with respect to CBZ solute as a function of time and the off-line measured CBZ solute concentration data is good during the cooling steps 1-3. However, a significant discrepancy between the off-line measured concentration and Raman solute peak height revolution was observed in step 4. The off-line measured solute concentration remained
almost constant during this step, while the Raman spectra intensity decreased all the time. A possible explanation for this discrepancy is that the decreasing of the Raman spectra intensity is due to the increased CBZH crystal phase. As has been discussed above, the Raman probe was sampling both the liquid and solid phase in the suspension, and the solute peak height depends not only on the solute concentration in the solution phase, but also on the fraction of the solid phase (CBZA or CBZH), and the effect of the solid phase CBZA and CBZH on the intensity of the solute peak could be different.

Fig. 5.14 Experimental results for the cooling crystallization of CBZ with SLS (0.5 g/100 g solvent) as an additive with stepwise cooling mode. (a) CBZ solubility, off-line measured concentration of CBZ solute in solution and the scaled solute specific peak height, and (b) the scaled distinct peak heights of solid phase CBZA and CBZH.
A cooling-heating mode was utilized to investigate the crystallization of CBZH from solution and the dehydration of CBZH. As shown in Fig. 5.16-5.17, the solution saturated at $35^\circ$C. Crystallization with cooling-heating mode and the effect of SLS
was cooled from 40°C to 15°C in step 1. The crystallization of CBZH was encountered at 20.5°C for both the pure CBZ and CBZ with SLS systems, indicated by a similar dramatic decrease of the solute peak height and increase of the CBZH peak height. This probably implies that the presence of SLS has no effect on the primary nucleation of CBZH. Comparing the increasing profile of CBZA in Fig. 5.13 (b) with that of CBZH in Fig. 5.16 (b), it can be seen that the crystallization kinetics of CBZH was much faster than CBZA. Step 2 was an isothermal process, where the suspension was kept at 15°C for 40 minutes. The gradual decrease of the solute peak height and increase of the CBZH peak height during this step probably suggested that the supersaturation was consumed mainly by the growth of CBZH crystals. In the beginning of step 3, 35 g CBZH crystals were added to the system and heating was performed from 15°C to 34°C. The decrease of the CBZH peak height demonstrated the dissolution of CBZH, meanwhile no presence of CBZA can be observed during the steps 1-3. Images of the crystal samples (Fig. 5.18 (a) and (b)) taken at the end of step 2 showed the presence of only CBZH crystals. Step 4 consists of an isothermal process at 34°C and a subsequent heating to 35°C. The CBZA peak height started to increase at the beginning of step 4, indicating the onset of crystallization of CBZA. The peak height of CBZA and CBZH evolved to a stable value at the end of the process, which means that the transformation of CBZH to CBZA was completed. This can be confirmed by the images of the crystals taken at the end of the process, shown in Fig. 5.18 (c) and (d). The off-line measured solute concentration in step 4 exhibited a very high supersaturation level with respect to the solubility of CBZA. This implied that the solubility of the metastable form CBZH was much higher than that of the stable form CBZA. The decrease of the solute concentration started at the late stage of step 4, when the phase transformation of CBZH to CBZA was almost finished. It could be concluded that the rate controlling step of the phase transformation from CBZH to CBZA was the crystallization of CBZA.

It is worth noting the disagreement between the scaled solute peak height from Raman spectra and the off-line measured solute concentration in step 3 and 4. Although the first increasing and subsequent decreasing trend of the solute concentration in step 3 and 4 was reflected by the Raman spectra, the increase in the solute concentration caused by the dissolution of CBZH crystals was significantly under-estimated by the Raman spectra. This is possibly because of the relatively high solid concentration in the suspension in step 3,
including the 35 g CBZH crystals added to the system at the beginning of step 3 and the CBZH crystals crystallized out during step 1 and 2. Since both the solid and liquid phases are sampled by the Raman probe, the intensity of the solute specific peak was significantly reduced by the presence of the crystal phase.

Fig. 5.16 Experimental results for the cooling crystallization of pure CBZ with cooling-heating mode. (a) CBZ solubility, off-line measured concentration of CBZ solute in solution and the scaled solute specific peak height, and (b) the scaled distinct peak heights of the solid phase CBZA and CBZH.
Comparing Fig. 5.16 and Fig. 5.17, it can be observed that the effect of SLS on the primary nucleation of CBZH and the solvent-mediated phase transformation of CBZH to CBZA was not significant. Nevertheless, the presence of SLS improved the Raman spectra by diminishing the scattering of the spectra. This improvement is especially obvious in the cooling-heating crystallizations, where the variation of the spectra was reduced from around ±15% to around ±5% when SLS was present. The diminishing effect of SLS on the spectra data scattering can also be observed in the stepwise cooling crystallizations. However, the
mechanism of this spectra improvement is still not clear. One possible explanation could be that the SLS changed the property of the interface between the Raman probe surface and the suspension, and consequently prevented the fouling on the probe surface. The signal/noise ratio of the spectra collection was then intensified.

(a) pure CBZ, at the end of step 2, T = 15°C  (b) with SLS, at the end of step 2, T = 15°C

(c) pure CBZ, at the end of the batch  (d) with SLS, at the end of the batch

![Images of crystals taken at different steps of cooling-heating crystallizations of pure CBZ and CBZ with SLS.](image)

Fig. 5.18 Optical images of the crystals taken at different steps of cooling-heating crystallizations of pure CBZ and CBZ with SLS.

**Effect of thermodynamic and kinetic factors on the crystallization of CBZA and CBZH**

During the crystallization of an anhydrate/hydrate system, the appearance of the anhydrate or the hydrate over the other phase depends on the thermodynamic properties of the anhydrate and hydrate, such as the solubility and metastable zone width, and the nucleation and growth kinetics of both phases. As shown in Fig. 5.19 (a), when the solution was cooled from point 1 to point 2, the solution became supersaturated with respect to both CBZA and CBZH.
However, the supersaturation with respect to CBZA was higher than that with respect to CBZH, since at this temperature CBZH is the less stable form and possesses a higher solubility. The nucleation of CBZA was driven out at this point by the thermodynamic factor. On the other hand, the concentration at point 2 was still within the metastable zone of CBZH, and no CBZH was detected at this time. The supersaturation was consumed by the nucleation and growth of CBZA crystals as the cooling proceeded to point 3. During the isothermal step at 35°C, the concentration passed through the CBZH solubility. The solution at point 4 was undersaturated with respect to CBZH but supersaturated with respect to CBZA. In principle, any undetectable fine CBZH nuclei that possibly formed during the previous cooling process will dissolve at this point. Cooling from point 4 to point 5 gave rise to a supersaturated solution with respect to both CBZA and CBZH. Further cooling from point 5 to point 6 shifted the thermodynamic stable form from CBZA to CBZH. From point 5 to point 6, the supersaturation with respect to CBZH was higher than that for CBZA, but the growth of the existing CBZA crystals was driven by the kinetic factor during this stage. The thermodynamic driven heterogeneous nucleation of CBZH happened at point 6. The supersaturation was consumed by the crystallization of CBZH. The concentration decreased and passed through the CBZA solubility, which subsequently lead to the dissolution of CBZA crystals. Finally, the transformation from CBZA to CBZH was completed at the CBZH solubility at point 7.

The effect of thermodynamic and kinetic factors on the crystallization of CBZ with cooling-heating mode can be interpreted from Fig. 5.19 (b). When the solution was cooled from point 1 to point 2, the concentration passed through the solubility of both CBZA and CBZH. Meanwhile, this cooling process also shifted the thermodynamic stable form from CBZA to CBZH. At point 2, the nucleation of CBZH was driven by the thermodynamic factor, since the supersaturation with respect to CBZH was higher than that with respect to CBZA. The nucleation and growth of CBZH crystals consumed the supersaturation and caused the concentration to pass through the solubility of CBZA at point 4 and 5. During the heating process, the CBZH crystals dissolved, leading to the increase in the concentration along the CBZH solubility curve to point 6. At this point, the solution was highly supersaturated with respect to CBZA. The nucleation of CBZA was driven out by the thermodynamic factor. The
phase transformation from CBZH to CBZA was finished when the concentration finally reached the CBZA solubility at point 7.

Fig. 5.19 Solubility of CBZA (solid symbols) and CBZH (open symbols) in the ethanol-water mixture containing 39 mol% of water, and the solute concentration during crystallization with stepwise cooling mode (a) and cooling-heating mode (b). (The dash lines are the extrapolation of the measured solubility curve of CBZA and CBZH, they are considered as the metastable form solubility of CBZA and CBZH at the temperatures where they are metastable. The solute concentrations were measured with off-line sampling. The temperature profiles are shown in Fig. 5.13 and Fig. 5.16).

As a conclusion, the thermodynamic factor seems to be dominant in the studied CBZA/CBZH crystallization process. The homogeneous nucleation of CBZA or CBZH in the early stage of the process and the heterogeneous and second nucleation (or phase transformation) at the late stage were both driven by the thermodynamic factor.
5.4 Summary

The research work of this chapter is motivated by the fact that the anhydrate/hydrate phase of active pharmaceutical ingredients significantly affects the thermal, physical and chemical properties of the product. As a consequence, the anhydrate/hydrate phase of the crystal product has to be controlled in order to achieve the desired product quality. This chapter concentrated on the study of the thermodynamic properties of anhydrous (CBZA) and dihydrate carbamazepine (CBZH), the mechanism of the solvent-mediated phase transformation between CBZA and CBZH, and the crystallization of CBZA and CBZH in ethanol-water mixtures. Raman spectroscopy was proved to be a powerful tool to identify the solid form of CBZA and CBZH, and to quantify their mixtures in both dry powder or suspension. The in-line information provided by the Raman spectrometer is valuable for understanding the fundamental processes involved in the CBZA/CBZH crystallization, and this information is very important for the optimization of the crystallization to obtain the desired hydration state of the crystalline product.

Knowledge about the thermodynamic relationship between the anhydrate and hydrate is a prerequisite in the development of the manufacturing process. The thermodynamic relative stability of CBZA/CBZH and their other thermodynamic properties in ethanol-water mixtures, such as the enthalpy and entropy of dissolution, were estimated by plotting the measured solubility data according to the van’t Hoff equation. The CBZA and CBZH showed an enantiotropic relationship in the mixtures and temperature ranges studied. It was found that at a certain temperature, there was an equilibrium water activity value at which CBZA and CBZH were in equilibrium. This equilibrium water activity value depends significantly on the temperature. The lower the temperature, the smaller water activity value needed to attain equilibrium between CBZA and CBZH. These equilibrium conditions in terms of water activity and temperature were referred to as the transition points between CBZA and CBZH.

Any deviation from the equilibrium conditions will lead to solvent-mediated phase transformation, either from CBZA to CBZH when the water activity is higher than the equilibrium water activity, or from CBZH to CBZA if the water activity is lower than the
equilibrium value. The solvent-mediated phase transformation between CBZA and CBZH was a two-step process, consisting of the dissolution of the metastable form and the crystallization of the stable form. It was found that for both CBZA transforming to CBZH or CBZH transforming to CBZA, the crystallization of the stable form was the rate-controlling step. The phase transformation experiments of CBZA to CBZH were conducted with different operation parameters in terms of solvent composition and temperature. The transformation rate depended on both solvent composition and temperature. The influence of the operation parameters on the transformation rate can be interpreted as the effects of the solvent and supersaturation on the crystallization kinetics. Another interpretation was proposed in the present work by correlating the deviation of the water activity from the equilibrium value to the rate of phase transformation. It was observed that the correlation of the water activity deviation and the phase transformation rate was independent of solvent composition and temperature.

The presence of additives can significantly influence the anhydrate/hydrate phase of the crystals during crystallization, due to either thermodynamic or kinetic effects. The solubility of the anhydrate/hydrate could be affected by the additives, and the crystallization kinetics of the forms may be altered. The effects of 5 different additives, sodium lauryl sulfate (SLS), polyethylene glycol 6000 (PEG), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and D-mannitol, on the phase transition from anhydrous (CBZA) to dihydrate (CBZH) carbamazepine in an ethanol-water mixture containing 39 mol% of water were studied. It was observed that HPMC exhibited a strong inhibiting effect on the phase transformation. This inhibiting effect was due to the fact that HPMC selectively increased the solubility of CBZH but has no effect on CBZA solubility. As a consequence, the solubility difference of CBZA and CBZH decreased dramatically. This resulted in a reduced supersaturation level during the phase transformation. The effects of additives on the cooling crystallization of CBZH were also investigated. It was found that SLS was the only additive which showed a slight promotion effect on the nucleation and crystal growth of CBZH by decreasing the metastable zone width and increasing the size of the final CBZH crystals.
The feasibility of using Raman spectroscopy to obtain simultaneous in-line monitoring of both solution phase concentration and anhydrate/hydrate composition in the solid phase was studied. The in-line Raman spectroscopy provided useful information about both the solution and solid phase during the crystallization of the CBZA/CBZH system. The onset of the primary nucleation of CBZA or CBZH from the solution could be clearly identified from the in-line measured solute peak height profile. The initiating of the phase transformation could be easily observed from the solid phase monitoring. The kinetics of the crystallization of CBZA and CBZH, and the phase transformation could be followed. Raman spectroscopy was proved to be a powerful tool for the in-line monitoring of the anhydrate/hydrate crystallization process. The information obtained from the Raman spectroscopy lead to improved understanding of the process and it offers great potential for optimization of the process and the control of the crystalline quality.
6 In-line imaging technique for the study of additives effects on the crystallization of KDP from solution

6.1 Introduction

Control of the size and morphology of the crystals is very important for industrial crystallization. These particle properties significantly affect the filterability, powder flow characteristics, dissolution rate, and handling in milling and grinding. The size and morphology of crystals can easily be affected by any minor change in the operation conditions, and therefore in-line monitoring of the crystallization would be very valuable. However, only a few techniques can be considered appropriate for in-line monitoring of crystal size and morphology. In-line imaging is a powerful tool for this purpose. Nevertheless, the application of this technique has been limited by difficulties in the analysis of the in-line images. Compared with off-line images, the images taken with an in-line microscope exhibit stronger background intensity variation and vaguer particle edge. This characteristic of in-line images causes difficulties for the traditional image analysis method, which usually identifies the particles by the difference in pixel intensity, termed ‘thresholding’.

The growth mechanism of the faces of potassium dihydrogen phosphate (KDP) crystals has been intensively studied in the literature (Mullin and Amatavivadhana 1967, Alexandru et al. 1996, Alexandru 1999, Alexandru and Antohe 2003). The effect of additives on the growth rate of single KDP crystals has been reported in several papers. The inhibiting agents include high valent ions (Alexandru and Antohe 2003) and some compounds which have similar molecule structure with KDP (Fu et al. 1999). In recent years, it has been reported that some chelating agents, such as ethylene diamine tetra acetic acid (EDTA), could promote the growth of KDP crystal significantly (Lu et al. 2001). However, most authors attributed the promoting effect solely to the fact that the chelating agent can reduce the chemical activity of high valent metal ions, the mechanism of the promotion effect on KDP crystallization is not clearly understood.
The objective of the present work is to study the effects of two additives, ethylene diamine tetra acetic acid dipotassium salt (EDTA) and potassium pyrophosphate (KPY), on the crystallization of KDP in seeded batch crystallization. The thermodynamic and kinetic effects of the additives were investigated by determining the solubility, induction time, metastable zone width, desupersaturation rate, and crystal growth rate. The crystal growth rate of a certain crystal face was determined from in-line images taken with a MTS Particle Image Analysis (PIA) video microscope. A novel image analysis algorithm based on edge-detection particle segmentation was developed in the present work. Finally, the mechanism of the promotion effect of EDTA was further analyzed with a 2D nucleation growth model.

The results of this work have been presented in paper III.

6.2 Materials, equipment and methods

Materials and equipment
Analytical grade chemicals were used in the present work. The natural habit of KDP is shown in Fig. 6.1. The shape is a tetragonal prism in combination with a tetragonal bipyramid. A MTS particle image analysis (PIA) 4000 LUT mode video microscope was used to collect in-line images during batch crystallization.

Fig. 6.1 Natural habit of KDP crystals (Mullin and Amatavivadhana 1967).

Methods
The crystallization experiments were performed in a 1-liter crystallizer. Details about the experiments can be found in paper III.
In-line image from PIA

Segmentation of the particles by edge detection

Morphological closing

Filling of the closed ranges

Morphological opening

Removal of the particles touching the image border

Removal of the overlapped ‘pseudo-particles’

Removal of the small particles

Removal of the spherical air bubbles

Saving the size and shape factor of the particles in the database matrixes

If the number of the images is less than 400, then go to the next image

If the number of the images is equal to 400, then go to the computing step

Computing the size distribution and the mean size based on the length and width of the particles

Fig. 6.2 Schematic of the image analysis procedure
A new image analysis algorithm was developed in the present work to replace the image analysis software provided with the PIA analyzer. The main difference between the old software and the new algorithm lies in the mechanism used for the identification of the particles. The old software detects the particles based on the pixel intensity value. A ‘threshold’ of the pixel intensity is defined, if the pixel intensity is higher than the ‘threshold’ value, this pixel is treated as being in the particle range. The new algorithm on the other hand detects the edge of the particles by the local maximum of the absolute value of the first derivative of the smoothed image intensity function (Caldern De Anda et al. 2005). The new algorithm was also complemented with procedures for removing particles that are partly shielded by the image border, and ‘pseudo-particles’ caused by the overlapping of the particles. The image analysis procedures are shown in Fig. 6.2. Some examples of the original and treated images are given in Fig. 6.3.

6.3 Results and discussion

Thermodynamic effects of the additives
The thermodynamic effects of the additives were studied by investigating the effect of the additives on the solubility, metastable zone width of KDP, and by measuring the induction time of the system to determine the surface free energy $\alpha$. The obtained results are shown in paper III Fig. 4-5. It was found both additives had a slight effect on the solubility of KDP. KPY increased and EDTA decreased the metastable zone width of KDP. This suggests that KPY has a inhibiting and EDTA has a promoting effect on the nucleation of KDP. The induction time measurement indicated that EDTA decreased the surface free energy of the KDP crystallization system.

Kinetic effects of the additives
It was observed that both additives modified the habit of KDP crystals significantly (shown in Fig. 6.4). However, the mechanism was different. KPY changed the KDP crystals into an octahedral shape due to the selective adsorption of the KPY molecules to the prismatic face of KDP crystals. The growth of the prismatic face of KDP crystals was strongly retarded by KPY. EDTA increased the growth rate of both prismatic and pyramidal faces, and the promoting effect was more remarkable on the prismatic face. This can be explained by the
surface structures of KDP crystal faces. The prismatic faces of KDP crystal are terminated by a layer of K$^+$ and K$_2$PO$_4^-$ group while the pyramidal faces are ended by a layer of K$^+$ (de Vries et al. 1998, de Vries et al. 1999). Incorporation of the adventitious ions of impurities, like Fe$^{3+}$, Al$^{3+}$ and Cr$^{3+}$, to the prismatic face is more favorable. The EDTA molecules present in the solution can form complexes with the impurities ions. Therefore, the presence of EDTA gives a more significant promotion effect on the prismatic faces.

Fig. 6.3 Original and treated images of KDP crystals.
The crystal size distribution of KDP during the crystallization was obtained from the in-line image analysis. The growth rate of both the length and width of the crystals was then deduced. The two-dimensional nucleation crystal growth model was used to describe the growth of the KDP crystals with and without additives. The crystal growth rate obtained from the in-line image analysis and the fitted growth model can be found in paper III Fig. 12.

6.4 Summary

The effect of two additives on the crystallization of KDP was studied. The in-line imaging technique proved to be a powerful tool to provide simultaneous monitoring for both the size and shape of the crystals. Integrated with an appropriate image analysis method, the in-line imaging technique can be used to study crystallization kinetics in a quantitative way. The two additives studied in the present work both modified the crystallization behavior significantly due to both thermodynamic and kinetic effects. KPY exhibited a strong inhibiting effect on the nucleation of KDP and the growth rate of the prismatic face. EDTA changed the surface free energy of the KDP-water system. Furthermore, the presence of EDTA enhanced the density of adsorbed solute molecules on the surface of the crystal, consequently increasing the crystal growth rate.
7 Seeding and cooling mode effects in batch cooling crystallization: In-line monitoring of supersaturation and crystal size distribution

7.1 Introduction

The quality and performance of fine chemicals is determined by properties of the product, such as the physical form, chemical purity, mean crystal size and size distribution. The particle properties of the crystalline product also influence the efficiency of down-stream operations, including filtration and drying. Usually larger mean crystal size and narrow distribution are desired, with good reproducibility from batch to batch. In principle, the particle size distribution of the product is a function of the supersaturation level in the crystallizer. In order to obtain the desired particle properties, the supersaturation level in the crystallizer should be kept constant within the metastable zone width during the whole process. A proper supersaturation level that can promote crystal growth relative to nucleation and meanwhile can maintain an economically reasonable batch time is preferred. This requires the crystallization to be operated in such a way that the generating of the supersaturation by cooling matches the consuming rate of the supersaturation through crystal growth. It is possible to compute the optimized cooling profile for a cooling batch crystallization based on the solubility, and the nucleation and crystal growth kinetics of the crystallizing substance. However, kinetic data for a particular industrial crystallization system is not always available. Furthermore, the parameters of the kinetic models are sensitive to the operation conditions of the crystallization and can fail to predict the real supersaturation level in the crystallizer.

Conventionally, most batch cooling crystallizers are operated by applying a preset cooling profile. There are three cooling modes that are commonly employed in crystallizations: natural cooling, linear cooling, and controlled cooling. The natural cooling mode allows cooling water at constant temperature to flow through the crystallizer jacket at a constant rate. This results in an extremely high cooling rate in the early stage and rapidly decreased cooling rate towards the end of the batch. The linear cooling mode applies a constant cooling rate during the whole process. The controlled cooling mode exhibits a convex profile and it was proposed by Mullin and Nyvlt (1971) for substances with solubility roughly linearly
dependent on temperature. The controlled cooling mode produces a slow cooling rate in the early stage and the cooling rate increases gradually as the crystallization proceeds. It has been proved that the controlled cooling mode can produce increased crystal size and narrower crystal size distribution (CSD) for some crystallization systems (Chung et al. 1999, Ma et al. 1999, Bohlin and Rasmusson 1992). However, the controlled cooling mode gives a high cooling rate at the late stage of the crystallization and this can sometimes bring problems by causing the supersaturation level to exceed the metastable zone limit, and consequently lead to secondary nucleation at the late stage. This is obviously not preferred since a large amount of fine particles can be generated.

In addition to the cooling profile, seeding is another efficient way to improve particle properties and reproducibility from batch to batch. The seeding effect on the final crystal size distribution at different cooling modes has been studied by the research group of Kubota (Jagadesh et al. 1999, Kubota et al. 2001, Doki et al. 2002). It has been shown that with sufficient seed loading, a cooling strategy with a higher cooling rate in the beginning of the crystallization could be preferred to produce the desired narrow crystal size distribution with increased mean crystal.

The application of on-line supersaturation and crystal size distribution measurement offers great potential to determine the optimized operation conditions, such as the cooling profile and seeding parameter, to obtain the desired product property. The method does not require kinetic models for a particular system, and is advantageous for the control and optimization for cooling batch crystallizations. The objective of the present work was to study the effects of the various cooling modes and seed loading on the final product properties by in-line monitoring of solute concentration and crystal size distribution. An ATR FTIR spectrometer was used to measure the concentration of the solute, and MTS PSyA laser reflection analyzer to measure the crystal size distribution. The results of the study have been presented in paper IV.
Table 7.1 Operation parameters for the batch cooling crystallization of C15 from toluene
(Initial temperature 75 °C, final temperature 25 °C, batch time 5 hours).

<table>
<thead>
<tr>
<th>Runs</th>
<th>Cooling mode</th>
<th>Seed concentration (Seed mass/theoretical yield)</th>
<th>On-line analyzer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run1</td>
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<td>FTIR</td>
</tr>
<tr>
<td>Run2</td>
<td>Linear</td>
<td>0</td>
<td>FTIR</td>
</tr>
<tr>
<td>Run3</td>
<td>Controlled</td>
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<td>FTIR</td>
</tr>
<tr>
<td>Run4</td>
<td>Linear</td>
<td>2%</td>
<td>FTIR</td>
</tr>
<tr>
<td>Run5</td>
<td>Linear</td>
<td>2% (unsifted seeds)</td>
<td>FTIR</td>
</tr>
<tr>
<td>Run6</td>
<td>Linear</td>
<td>4%</td>
<td>FTIR</td>
</tr>
<tr>
<td>Run7</td>
<td>Controlled</td>
<td>4%</td>
<td>FTIR</td>
</tr>
<tr>
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<td>0</td>
<td>FTIR and PsyA</td>
</tr>
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<td>Linear</td>
<td>0</td>
<td>FTIR and PsyA</td>
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<td>Run26</td>
<td>Step-mode1</td>
<td>2%</td>
<td>FTIR and PsyA</td>
</tr>
</tbody>
</table>
7.2 Materials, equipments and methods

Materials
The crystallization material used in the present work was referred to as C15, which was an acidic aromatic compound containing 15 carbon atoms. Technical grade toluene was selected as the solvent. The C15 material was used as received from the manufacturer without further purifying. The seed crystals were produced by sieving the raw C15 material. The fraction under 50 µm-sized mesh was taken as seed crystals.

Equipment
The crystallizations were carried out in a baffled 1-liter glass reactor, which was equipped with a programmed thermostat and a Pt-100 temperature sensor. A pitched-blade impeller with four blades was used to provide mixing and the rotation speed was kept at 500 rpm in all runs. A condenser was installed to the reactor to recover the evaporated solvent. Both ATR FTIR and MTS PSyA probes were inserted directly to the reactor. The crystal size distribution of the final product was analyzed with a Coulter LS 130 laser diffraction analyzer.

Methods
Before the crystallization experiments, the ATR FTIR spectrometer was calibrated by collecting the spectra for the C15 solutions with certain concentrations and at certain temperatures. The model for deriving C15 concentration from the measured spectra was generated with partial least squares (PLS) method. The calibration algorithm has been presented by Pöllänen et al (2005). The operation parameters of the cooling crystallization are summarized in Table 7.1. Five different cooling modes were studied in this work. Among them, the controlled cooling mode was adopted from Mullin and Nyvlt (1971). The stepwise cooling modes were created to resemble the natural cooling mode, which gives a rapid cooling rate at the early stage and a decreased rate towards the end of the batch. The cooling profiles used in this study are shown in Fig. 7.1.
7.3 Results and discussion

Effect of cooling mode on the supersaturation and final CSD for unseeded crystallizations

The supersaturation level during the batch crystallization was calculated from the in-line measured concentration of C15 with ATR FTIR and the solubility data. The solubility of C15 in toluene was measured with the ATR FTIR and the gravimetric method. The supersaturation level during the unseeded crystallization with different cooling modes is shown in Fig. 7.2. The supersaturation increased as the cooling proceeded, until it reached a maximum level corresponding to the metastable zone limit and then primary nucleation occurred. Comparing the supersaturation profile produced with the different cooling profiles, it is obvious that the slower the cooling rate, the lower the supersaturation level where the nucleation happened. It can be observed that the stepwise mode2 and mode3 produced an extremely high initial supersaturation level, which was subsequently consumed rapidly, probably mainly by the primary nucleation of C15. However, the initial supersaturation level produced by step mode1 was at a similar level with that in linear cooling, and it is much lower than that for step mode2 and mode3, although the stepwise mode1, mode2 and mode3 gave the same cooling rate in the early stage of the process, which was much rapid than that of the linear cooling mode (see Fig. 7.2). One possible reason could be that the nucleation of the experiment with stepwise mode1 was facilitated by some unexpected dust or impurity particles. The controlled cooling mode on the other hand, gave slow cooling at the beginning, and the nucleation occurred at a much lower supersaturation level. The nucleation was significantly delayed with respect to time compared with the other cooling profiles. After the nucleation, the supersaturation level remained quite stable at a level close to the solubility curve for the stepwise cooling modes. However, the supersaturation level increased gradually to a second peak value when the controlled cooling mode was applied. This probably implies that the supersaturation generating rate was too high with respect to the consuming rate of supersaturation through crystal growth due to the rapid cooling rate at the late stage. The effect of the cooling mode on the final CSD is shown in Fig. 7.3. It can be observed that the controlled cooling mode produced a very wide size distribution with a greater amount of large crystals. The amount of fine crystals was reduced by applying stepwise cooling mode1.
Fig. 7.1 Cooling profiles of the crystallization of C15.

Fig. 7.2 Supersaturation level for the unseeded crystallization of C15 with different cooling modes.

Fig. 7.3 Crystal size distribution of C15 produced by unseeded crystallizations with different cooling profiles (measured with a Coulter LS 130 laser diffraction analyzer).
**Effect of seed loading on the supersaturation level and final CSD**

The effect of seed loading on the supersaturation level for different cooling modes is shown in Fig. 7.4-7.6. It can be observed that the decrease in the supersaturation occurred right after the seeding. The decrease in the supersaturation depended on the seed loading. The seeding obviously narrowed the crystal size distribution for all cooling modes (shown in Fig. 7.7-7.9). The mechanism of the seeding effect could be the initial breeding effect, which means a large number of small nuclei was created by seeding. Comparing the CSD produced by different cooling modes and seed loadings, it can be seen that the stepwise cooling mode 1 with 2% seed loading was the most favorable operation condition to obtain improved particle properties in terms of larger mean crystal size and narrower size distribution.

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**Fig. 7.4 Effect of seed loading on the supersaturation level for controlled cooling mode**

**Fig. 7.5 Effect of seed loading on the supersaturation level for the linear cooling mode**
Fig. 7.6 Effect of seed loading on the supersaturation level for stepwise mode

Fig. 7.7 Effect of seed loading on the crystal size distribution of C15 for the controlled cooling mode (measured with a Coulter LS 130 laser diffraction analyzer).

Fig. 7.8 Effect of seed loading on the crystal size distribution of C15 for the linear cooling mode (measured with a Coulter LS 130 laser diffraction analyzer).
Fig. 7.9 Effect of seed loading on the crystal size distribution of C15 for stepwise cooling mode1 (measured with a Coulter LS 130 laser diffraction analyzer).

The CSD measured with an in-line PSyA analyzer was presented in paper IV. It was observed that the PSyA analyzer can be used to obtain in-line monitoring of the evolution of the CSD. The count rate of the analyzer reflected the nucleation rate to some degree. However, the resolution of the analyzer was too low to be used to study the effect of operation parameters on the crystal product properties.

7.4 Summary

In this chapter, the effects of various cooling modes and seed loadings on the properties of the final crystal product were studied using in-line measurement of supersaturation and crystal size distribution. ATR FTIR provided reliable supersaturation profile throughout the crystallization. For the crystallization of C15 from toluene, stepwise cooling with a rapid cooling rate at the early stage and a slower cooling rate at the late stage was preferred to reduce the amount of fine particles. Seeding was an effective way to narrow the size distribution. The stepwise cooling mode combined with sufficient seed loading can produce C15 crystals with improved properties in terms of larger mean crystal size and narrower size distribution.
8 Summary and Conclusions

The present work was motivated by general product quality control considerations for industrial batch crystallization processes: the crystalline product has to be produced with the desired particle size distribution, crystal shape, purity, polymorphic and pseudopolymorphic phase. These properties are determined by the kinetics of the fundamental processes involved in the crystallization, e.g. primary and secondary nucleation, and crystal growth of all present polymorphs and pseudopolymorphs, which all strongly depend on the operation conditions of the crystallization. Consequently, the industrial crystallizations are usually operated by controlling easily measurable process variables, like temperature and seeding parameters. However, such a control approach is not sensitive to any variations in the feed composition or impurities. The employment of in-line monitoring techniques can assure that the desired product quality is obtained in the presence of such disturbances. The in-line monitoring of the process also offers an efficient way for the optimization of industrial crystallizations.

In the present work, a systematic study was performed on the thermodynamics and kinetics of crystallization processes, the fundamental factors for the control of the properties of the final crystalline product. Several in-line techniques, such as ATR FTIR spectroscopy, Raman spectroscopy, and an in-line imaging approach, were applied to explore the mechanism of the process and the effect of the operation conditions on the properties of the crystals. Using these advanced in-line techniques, both the liquid phase properties (solute concentration or supersaturation) and crystal phase properties (crystal size and shape, pseudopolymorphic phase) were measured. The work consists of 3 main themes.

The first theme was the study of an anhydrate/hydrate system in mixed solvents using an in-line Raman spectrometer. The underlying thermodynamics of the anhydrate/dihydrate forms of carbamazepine in mixed solvents of ethanol and water, and the mechanism of the solvent mediated phase transformation between the anhydrate (CBZA) and dihydrate (CBZH) were investigated. It was found that the relative stability of CBZA and CBZH in ethanol-water mixtures depended on the temperature and the water activity in the solvent. The CBZA and CBZH system exhibited an enantiotropic relationship. For any given solvent composition (i.
e. water activity), there existed a temperature value corresponding to the transition point, where the solubility and thus stability of CBZA and CBZH was identical. These transition points in terms of temperature and water activity can be determined from the solubility data. The model hydrate used in this work was carbamazepine dihydrate, which belongs to the group of channel hydrates. In the future, further investigation can be made on the dependence of the relative stability of anhydrate/hydrate on temperature and water activity in mixed solvents for the hydrates that belong to other groups, isolated site hydrates and ion associated hydrates. This will lead to a better understanding of the role of water associated into the crystal structure of the hydrates.

Any deviation from the transition point will lead to solvent-mediated phase transformation, either from CBZA to CBZH when the water activity is higher than the transition point water activity or from CBZH to CBZA if the water activity is lower than the transition point. The solvent-mediated phase transformation was a complicated process due to the several mechanisms involved in the process, such as the dissolution of the metastable phase, primary and secondary nucleation, and the growth of the stable phase. The kinetics of the whole process is determined by the one that possesses the lowest kinetics. For the phase transformation from CBZA to CBZH in ethanol-water mixtures, it was observed that the nucleation and growth of CBZH crystals was the rate controlling step. The phase transformation kinetics can be influenced by many parameters, such as temperature, fraction of water in the mixed solvent, and the presence of additives. It was found that the impact of these operation parameters on the phase transformation kinetics was mainly due to their effects on the solubility difference of CBZA and CBZH. The solubility difference between CBZA and CBZH caused the supersaturation during the phase transformation, and therefore determined the crystallization rate of CBZH. In addition to the supersaturation level, the crystallization rate of CBZH was found also to depend on the water activity in the mixed solvent. Since conventional nucleation and crystal growth modeling are based on the crystallization of anhydrous substances, the role of water activity in the crystallization of hydrates needs to be further explored in the future. A new mechanism for hydrate crystallization could be proposed by taking both the supersaturation and water activity into account.
The effect of thermodynamic and kinetic factors on the crystallization of CBZ was studied by performing un-seeded cooling crystallizations of CBZA and CBZH from an ethanol-water mixed solvent followed by a solvent-mediated phase transformation. The thermodynamic factor seems to be dominant in the studied CBZA/CBZH crystallization process. At temperatures higher than the transition point, the stable form CBZA was crystallized out through homogeneous nucleation, which was driven by the higher supersaturation level with respect to the stable form. At temperatures lower than the transition point, however, CBZH crystallized out as the stable form following a similar mechanism. The subsequent phase transformation from CBZA to CBZH or from CBZH to CBZA was also driven by the thermodynamic factor.

Raman spectroscopy was applied as the main method for the identification and quantification of the solid anhydrate/hydrate mixtures. Raman spectroscopy proved to be a powerful tool for the in-line monitoring of the solid phase composition during crystallization. It is of great importance to obtain in-line measurement of supersaturation during the crystallization of polymorphic or pseudopolymorphic crystallization processes. A given solute concentration usually leads to different supersaturation levels with respect to the polymorphs or pseudopolymorphs due to their different solubility. The feasibility of using Raman spectroscopy to obtain simultaneous in-line monitoring of both liquid phase concentration and anhydrate/hydrate composition in the solid phase was also studied in the present work. The onset of the primary nucleation of CBZA or CBZH from solution can be clearly identified from the in-line measured spectra. The initiation of the phase transformation can be easily observed from the solid phase monitoring. The kinetics of the crystallization of CBZA and CBZH, and the phase transformation can be followed. However, the resolution of the Raman spectroscopy data for the measurement of solute concentration is restricted by the fact that both the solid and liquid phase are sampled by the Raman probe. Usually the more condensed solid phase has a more significant effect on the resulting spectra. This requires a calibration model that allows for the splitting of the contribution of the solid phase from that of the solute in the solution. This can cause large number of samples to be analyzed in the calibration and can demand sophisticated spectra modeling. A better alternative tool for the in-line measurement of solute concentration is ATR FTIR spectroscopy, which is not interrupted by the presence of the crystals in the suspension. In the future, the combination of
ATR FTIR and Raman spectroscopy may provide more accurate and valuable information about the liquid and solid phase during polymorphic and pseudopolymorphic system crystallizations. This will improve understanding of the mechanism of the process and furthermore will lead to more efficient control of the process and the crystalline product quality.

The second theme of this work was in-line image analysis for the study of the effects of additives on the batch cooling crystallization of KDP. The in-line imaging technique is a powerful tool for the in-line monitoring of both crystal size and morphology during crystallization. The main obstacle for the in-line application of this technique is the lack of an appropriate image analysis algorithm which has sufficient tolerance for the quality of the in-line images. A new image processing algorithm based on edge-detection particle segmentation was developed and applied to the study of the effects of two additives, ethylene diamine tetra acetic acid (EDTA) and potassium pyrophosphate (KPY), on the crystallization of KDP in seeded batch crystallization. The growth rate of the KDP faces was obtained from the in-line image analysis. It was observed that the habit of KDP crystals was significantly modified by KPY and EDTA due to different mechanisms. KPY changed the KDP crystals into an octahedral shape because the KPY molecules were selectively adsorbed on the prismatic face of the KDP crystals. The growth of the prismatic faces was strongly retarded by KPY. EDTA increased the growth rate of both prismatic and pyramidal faces due to both thermodynamic and kinetic effects. The presence of EDTA decreased the surface free energy of the KDP crystallization system. At the same time, EDTA can eliminate the competition between the adventitious impurities (usually high valent metal ions, like \( \text{Fe}^{3+}, \text{Al}^{3+} \) and \( \text{Mn}^{2+} \)) and the KDP growth units by forming complexes with the adventitious impurities in the solution. By fitting the crystal growth rate to the 2-dimension (2D) nucleation crystal growth model, it was shown that EDTA increased the concentration of KDP growth units adsorbed on the growing surface. In the future, the in-line imaging technique can be applied to the study of polymorphic and pseudopolymorphic systems. Visual observation of the morphology of the different polymorphs or pseudopolymorphs during crystallization could be attained.
The third theme of the work was to study the effects of the various cooling modes and seed loading on the final product properties by in-line monitoring of solute concentration and crystal size distribution. ATR FTIR spectroscopy provided accurate supersaturation data during the crystallization, while the resolution of the MTS PSyA laser reflectance particle analyzer was unsatisfactory. For the studied C15-toluene crystallization system, a stepwise mode with rapid cooling at the early stage and appropriate seeding was preferred to obtain the improved crystal particle properties in terms of larger mean size and narrowed size distribution.

In situ monitoring of the properties of the solution phase and the crystal phase during batch crystallization has been studied in the present work. A more comprehensive understanding of the thermodynamics and kinetics of the crystallization process is achieved by using the in situ measurement approaches. This also leads to more effective optimization of the crystallization process and better controlling of the crystalline produce quality.
References


