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**CRYSTALLIZATION KINETICS OF MEFENAMIC ACID
AND POLYMORPHISIM**

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ÖZET

**MEFENAMİK ASİDİN KRİSTALİZASYON KİNETİKLERİ
VE POLİMORFİZM**

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Bu tezde endüstride önemli bir yere sahip, en eski ayırma ve saflaştırma işlemlerinden kristalizasyon ve kristalizasyon kinetikleri ilaç sanayinde çok tüketilen Mefenamik Asit, (MA) için incelenmiştir. MA'ın adet düzensizliklerine bağlı ağrılarda ağrı kesici etkisi vardır. MA'ın hidrofobikliği ve yüzeylere yapışma eğilimi özellikleri granülleme ve tabletleme işlemlerinde büyük problemler yaratır. Kristal boyut dağılımı, yüzey alanı, çok biçimlilik ve kristalleşme adımları ilacın tesirini ve kristalizasyon sürecini etkileyen en önemli değişkenlerdir. Bu nedenle MA'ın yapısal karakteristik özellikleri spektrum ve kırınım yöntemleriyle incelenmiştir. MA'ın kristalizasyon süreci iki ayrı yöntemle, Garside ve Nüfus Denklik Model yaklaşımı ile modellenmiş ve deneysel ve model ile elde edilen derişimin zamana göre değişiminin uyumlu olduğu gözlenmiştir. Hesaplanan kristalizasyon kinetik parametreleriyle (b , k_b , g , k_g) kristal çekirdeklenme ve büyüme kinetikleri hesaplanmıştır. MA iğne şeklindeki küçük kristal yapısıyla kurutma ve eleme işlemlerini zorlaştırabilir ve kristal büyüme kinetikleri araştırılarak kristalizasyon işlemi kontrol altına alınıp istenen kalitede kristaller elde edilebilir.

Anahtar Sözcükler: Kristalizasyon, Mefenamik asit, Büyüme kinetikleri, Kristal Boyut Dağılımı, Nüfus Denklik Model Yaklaşımı

ABSTRACT

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Crystallization is an old separation and purification process and in this study, crystallization and crystallization kinetics were investigated for Mefenamic Acid, (MA) which has prevalent usage in drug formulation. MA is a high-dose, anti-inflammatory, analgesic agent used for pain in menstrual disorders. Some negative properties of MA, a high hydrophobicity and propensity to stick to surfaces, cause great problems during granulation and tableting. The crystal size distribution (CSD), crystal shape, polymorphic form and the crystallization steps are important factors that affect the quality and bioavailability of a drug. Characterization of MA was done by different analysis methods. Two different modeling approaches, Garside and Population Balance Equation Modeling were used to study the crystallization kinetics and kinetic model parameters (b , k_b , g , k_g) were predicted. The crystallization kinetic parameters of MA were calculated. The modeling results and the experimental data obtained are in good agreement. By using determined crystallization rate kinetics of MA, crystallization can be controlled to obtain desired quality of crystals.

Keywords: Crystallization, Mefenamic acid, Growth kinetics, Crystal size distribution, Population Balance Equation Model Approach

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TABLE OF CONTENTS

	<u>Pages</u>
ÖZET	V
ABSTRACT	VII
ACKNOWLEDGMENT	IX
LIST OF FIGURES	XVII
LIST OF TABLES	XXI
NOMENCLATURE	XXIII
1.0 INTRODUCTION	1
1.1 Pharmaceutics and polymorphism	5
1.2 Literature Survey on Characterization of Mefenamic Acid	7
1.2.1 Solubility studies	8
1.2.2 Morphology	15
1.2.3 Polymorphic Transition	17
1.2.4 Crystallography	20
1.2.5 Molecular Motion	22
1.3 Literature Survey on Crystallization Kinetics	25

TABLE OF CONTENTS (Continued)

	<u>Pages</u>
2.0 FUNDAMENTALS OF CRYSTALLIZATION	27
2.1 Crystal and Crystal Properties	27
2.2 Supersaturation And Metastable zone	29
3.0 NUCLEATION AND GROWTH KINETICS	33
3.1 Crystallization	33
3.2 Nucleation	34
3.1.1 Primary nucleation	35
3.1.1.1 Homogeneous nucleation	35
3.1.1.2 Heterogeneous nucleation	39
3.1.2 Secondary Nucleation	40
3.1.2.1 Initial breeding	41
3.1.2.2 Needle breeding and polycrystalline breeding	42
3.1.2.3 Collision breeding	43
3.1.2.4 Impurity concentration gradient	44
3.1.2.5 Fluid shear	45
3.2 Growth	45

TABLE OF CONTENTS(Continued)

	<u>Pages</u>
3.2.1 Theories based on thermodynamic properties	46
3.2.1.1 Theory of limiting faces	46
3.2.1.2 Theory of Kossel and Stransky	47
3.2.1.2 The solid on solid (SOS) model	49
3.2.2 Theories based on kinetics properties	49
3.2.2.1 Boundary layer theory	49
3.2.2.2 Surface diffusion model (BCF Model)	50
3.2.2.3 Bulk diffusion model	52
3.2.2.4 Combined bulk-surface diffusion	53
3.2.2.5 The kinematic theory	53
3.2.2.6 The diffusion layer model	54
3.2.2.7 The nuclei above nuclei (NAN) model	55
3.3 Nucleation Kinetics	57
3.4 Crystal Growth Kinetics	59
4.0 CRYSTAL SIZE DISTRIBUTION (CSD)	62
4.1 Measurement of Size Distribution	67

TABLE OF CONTENTS(Continued)

	<u>Pages</u>
5.0 POPULATION BALANCE EQUATION (PBE)	72
5.1 Population Balance Equation For Batch Crystallizers	72
5.1.1 Solution-side Information	73
5.1.2 Solid-side Information	75
6.0 DETERMINATION OF GROWTH RATE KINETICS	77
6.1 Method of Isolation for Crystal Growth	79
6.1.1 Direct Methods	79
6.1.2 Indirect Methods	83
6.1.2.1 Desupersaturation curve technique	83
6.1.2.2 The population balance equation (PBE) modeling approach	86
7.0 EXPERIMENTAL WORK	91
7.1 Determination of Polymorphic Structure of Mefenamic Acid	91
7.2 Crystal Size Distribution (CSD) Measurements	94
7.3 Estimation of ConcentrationProfile	95
8.0 RESULTS	98
8.1 Experimental Results	98

TABLE OF CONTENTS(Continued)

	<u>Pages</u>
8.1.1 Polymorphic structure of Mefenamic Acid	98
8.1.2 The crystal size distribution of Mefenamic Acid	108
8.1.3 Estimation of concentration profile	111
8.2 Modeling Results	113
8.2.1 Garside solution	113
8.2.2 The PBE modeling for seeded and unseeded crystallization	118
9.0 DISCUSSION AND CONCLUSION	123
10.0 FUTURE WORK	126
REFERENCES	128
RESUME	133

LIST OF FIGURES

<u>Figures</u>	<u>Pages</u>
1.1. Conformational changes in mefenamic acid between polymorph I and II	8
1.2. Dissolution profile of MA in ethanol, in 50% ethyl acetate in ethanol, and in ethyl acetate	10
1.3. Solubilities of MA and its complexes with alkanolamine in the ethanol-water mixture at various ratios	14
1.4. SEM photographs of MA sample	16
1.5. van't Hoff plot of MA form I and II	19
1.6. DSC thermogram of MA commercial samples and the USP reference standard sample	19
1.7. Powder X-ray patterns of commercial samples of MA and the USP reference standart	21
1.8. IR spectra of MA. A, Form I; B, Form II; C, Forms I and II after equilibration with ethanol	23
1.9. Infrared spectrum of mefenamic acid as received	24
2.1. The most common unit cells for crystals of drugs.	28
2.2. .The solutbility curve and metastable zone width for a batch cooling crystallization	32
3.1. The diagram represents the types of nucleation	35
3.2. Gibbs free energy diagram for homogeneous nucleation showing free energy change versus size of nucleus.	39
3.3. Kossel's model of crystal growth	48
3.4. Schematic representation of the Surface Diffusion Model (a) kinks, (b) steps, and (c) terrace	51
3.5. Schematic representation of the Diffusion Layer Model	54
3.6. Birth and Spread Model of crystal growth	57
4.1. A typical cumulative numbers oversize plot	64

LIST OF FIGURES (Continued)

<u>Figures</u>	<u>Pages</u>
4.2 A typical population density versus size plot	65
4.3 Set-up for crystal size distribution measurement by Lasentec (FBRM)	69
4.4 Photographs of Lasentec FBRM machine parts such as reactors, probes and stirrer	70
6.1 The techniques for determination of crystal kinetic data	78
6.2 Schematics representation of determination of the crystal growth kinetics by single crystal growth method.	82
6.3 Apparatus to measure the concentration profile on line	84
8.1 The SEM of MA crystal recrystallized from EA	98
8.2 Raman spectrum for Form I of MA recrystallized from EA	99
8.3 Raman spectrum for Form I of MA crystals recrystallized from Acetone	100
8.4 Raman spectrum for Form I of MA crystals recrystallized from DMS by slow cooling	100
8.5 Raman spectrum for Form I of MA crystals recrystallized from DMS by fast cooling	101
8.6 Raman spectrum for Form I of MA crystals recrystallized from DMA by slow cooling	101
8.7 Raman spectrum for Form I of MA crystals recrystallized from DMA by fast cooling	102
8.8 Raman spectrum for Form I of MA crystals recrystallized from DMF	102
8.9 Powder X-ray pattern of Form I of MA crystals recrystallized from Acetone.	104
8.10 Powder X-ray pattern Form I of MA crystals recrystallized from DMA slow cooling.	105

LIST OF FIGURES(Continued)

<u>Figures</u>	<u>Pages</u>
8.11 Powder X-ray pattern Form I of MA crystals recrystallized from DMA fast cooling	105
8.12 Powder X-ray pattern Form I of MA crystals recrystallized from DMS by slow cooling	106
8.13 Powder X-ray pattern Form I of MA crystals recrystallized from DMS by fast cooling	106
8.14 Powder X-ray pattern of Form II of MA crystals recrystallized from DMF	107
8.15 Powder X-ray pattern Form I of MA crystals recrystallized from EA	107
8.16 CSD results of MA and ethyl acetate solution with different end temperatures and cooling rates	108
8.17 The mean length and the crystal density of MA in the first experiment	109
8.18 The mean length and the crystal density of MA in the second experiment	110
8.19 The mean length and the crystal density of MA in the third experiment	110
8.20 Calibration curve for MA-EA solution	113
8.21 Desupersaturation curve for MA-EA solution at 25°C	114
8.22 The linear growth rate change for different g values	117
8.23 The mass growth rate change for different g values	117
8.24 The graphical representation of the four moments of equation of PBE of MA crystals	121
8.25 The agreements of the Garside and the PBE modeling approach to the experimental data	122

LIST OF TABLES

<u>Tables</u>	<u>Pages</u>
1.1 Methods for characterizing pharmaceutical solid polymorphs	7
1.2 Thermodynamic values calculated for Form I and II of MA	9
1.3 Physical properties of powder and spherical crystals of MA	12
1.4 Solubilities in various vehicles of MA and its complexes with alkanolamine at 32°C	13
1.5 Solubility of MA in ethyl acetate	15
1.6 Onset temperatures of DSC transition (First Peak) and melting points (Second Peak) of two manufacturers	18
1.7 DSC Melting characteristics of the MA complex(Mean±SD, n=3)	20
7.1 The amount of mefenamic acid and solvents for experimental analysis	93
7.2 Literature data for the calculations of the densitometer constant and kinetic parameters	97
7.3 Concentration values of MA-EA solution for calibration curve	97
8.1 The polymorphic behavior of MA crystals in different solvents	103
8.2 The relative intensity values and °2θ angles for the peaks obtained in powder X-ray diffractograms	104
8.3 Measured period values and calculated density values for MA-EA solution for calibration curve	111
8.4 Concentration of MA-EA sample solutions for desupersaturation curve	112
8.5 The calculated growth rate constants for different g values	116

LIST OF TABLES

<u>Tables</u>	<u>Pages</u>
8.6 The nucleation rate (μ_0) and the growth rate constants of MA for seeded crystallization	121
8.7 The crystallization kinetics parameters of MA for unseeded crystallization	122

NOMENCLATURE

Symbol	Description	Dimension
A	: Surface area of the crystals	$[\text{cm}^2]$
A_T	: Surface area of the seeds	$[\text{cm}^2/\text{g}_{\text{solv}}]$
a	: Mean distance between growth units in the crystal	$[\mu\text{m}]$
B	: Nucleation rate	$[\text{no.}/\text{m}^3\text{s}]$
B_s	: Nucleation rate	$[\text{g}_{\text{sol}}/\text{g}_{\text{solv}} \text{ sec}]$
C	: Concentration	$[\text{g}/\text{L}]$
ΔC	: Concentration driving force	$[\text{g}_{\text{sol}}/\text{g}_{\text{solv}}]$
$\Delta \dot{C}$ and $\Delta \ddot{C}$	: First and second derivatives of the desupersaturation curve	$[\text{g}_{\text{sol}}/\text{g}_{\text{solv}}]$
c_{eq}	: Equilibrium concentration of a saturated solution	$[\text{particle}/\text{ml}]$
d	: The average distance between adsorbed species in the boundary layer	$[\mu\text{m}]$
D	: Diffusion coefficient	$[\text{cm}^2/\text{sec}]$
E	: Activation energy of growth proces	$[\text{kJ}/\text{mol}]$
F	: Shape factor ratio	$[\text{g}_{\text{sol}}/\text{g}_{\text{solv}}]$
G	: Linear growth rate	$[\text{length}/\text{time}]$
h	: Step heigth	$[\mu\text{m}]$
h_i	: The distance of the i th plane from the centre of the crystal	$[\mu\text{m}]$
k_v	: Volume shape factor	$[-]$
k_a	: Surface shape factor	$[-]$

NOMENCLATURE(continued)

Symbol	Description	Dimension
k_b	Nucleation rate constant	
k	: Boltzmann constant	[erg/particle K]
k_g	: Linear growth rate constant	[cm/min(g _{sol} /g _{solv})]
K_g	: Mass growth rate constant	[g/min(g _{sol} /g _{solv})]
L	: Size of cluster	[μm]
$\bar{L}_0$	: Average size of the seeds	[μm]
l	: Linear rate of face growth perpendicular to the surface	[μm/sec]
MW	: Molecular weight	[g/mol]
M_T	: Suspension density	[g _{crystal} /g _{solv}]
n^*	: The solute particle numbers	
R	: Overall growth rate	[g/cm ² sec]
r	: Radius of cluster	[μm]
r^*	: Critical radius of a solute	[μm]
R_g	: Universal gas constant	kJ/mol K
s	: Number of cooperating spirals on the surface	[-]
T	: Temperature	K, °C
t	: Time	[min]
V_m	: Molecular volume	[μm ³]
W	: Weight of crystals	[g/g _{solv}]
σ	: The specific energy of i th plane	[erg/particle]
	: Supersaturation(ΔC-1)	[-]
γ	: Interfacial free energy	[erg/particle]

NOMENCLATURE(continued)

Symbol	Description	Dimension
μ_k	: k th moment of the crystal size distribution	[no cm ^k /(g _{solv})]
δ	: Thickness of the diffusion layer on the crystal surface	[μ m]
Ω	: Volume of the growth particle in the crystal	[ml]
t	: time	[sec]
u	: Step velocity	[length/time]
ρ	: Density	[g/cm ³]
g	: Growth power	[-]
b	: Nucleation power	[-]
<u>symbols</u>		
0	: Time zero	
Δ	: Difference	
j	: Number of moment	
β	: Area shape factor	
α	: Volume shape factor	

1.0 INTRODUCTION

Nowadays, crystallization from solution is a world-wide common process for separation or purification of substances. The field of application comprises nearly every industry branch, like pharmaceuticals, pigments, food, plastics etc. Despite the frequent implementation of crystallization in industrial processes and the knowledge of the positive influence of process control on economics and product quality, most crystallizers lack an efficient process control. The most important parameter for the control of a crystallization process is the supersaturation ΔC as the thermodynamic driving force.

For every substance, crystallizer and parameters describing the product quality are

- median crystal size
- crystal purity
- crystal size distribution
- specific surface area
- crystal morphology

In industrial point of view, crystal products must have high purity, a desired crystal size distribution (CSD) and crystal shape. Crystals with random CSD are not acceptable. To achieve a desired CSD, the supersaturation must be controlled through the cooling temperature and the agitation rate, among other factors.

Crystals are formed when nuclei appear and then grow. In the cooling crystallization process, the nucleation and crystal growth kinetics require supersaturation and it is attained by a change in temperature. The transfer of the molecules from the continuous phase (solution) to the solid phase is governed by nucleation and growth rates called as the crystallization kinetics.

Determination of the crystallization kinetics is important for the design and performance of the crystallizers. The crystallization kinetics must be determined experimentally. Continuous, batch, and single crystal experiments are performed to extract the crystallization kinetics. The steady state Mixed Suspension Mixed Product Removal (MSMPR) technique is the one of the early approaches. It analyzes the final particle size distribution of the slurry after reaching steady state conditions.

Batch crystallization has been widely used because its operation is simple and experimental data are easily generated. On the other hand modeling of the batch crystallization is not simple. The model includes independent variables as time and three space dimensions, and it is not clear. In general, batch runs are less time-consuming than MSMPR but require a more complex analysis because of the presence of experimental inaccuracies (death and birth of crystals).

In single crystal experiments, a large number of crystals should be investigated under a microscope to find the growth rate.

Cooling batch crystallization with seeding is used intensively to find the crystallization kinetics. This condition can be used for the parameter estimation of crystallization parameters under certain specified

conditions or finding the optimal cooling strategies and its effect on the final CSD.

Mefenamic Acid, (MA) which has prevalent usage in drug formulation. MA is a high-dose, anti-inflammatory, analgesic agent used for pain in menstrual disorders. Some negative properties of MA, a high hydrophobicity and propensity to stick to surfaces, cause great problems during granulation and tableting.

In this thesis, the characterization of MA was done by different analysis methods, scanning electron microscopy (SEM), Raman microscopy, and X-ray powder diffraction. Two different modeling approaches, Garside and Population Balance Equation Modeling were used to study the crystallization kinetics and kinetic model parameters (b , k_b , g , k_g) of MA were calculated.

This thesis contains nine chapters and in addition references are placed at the end of chapters. The description of each chapter is given in the following paragraphs.

Chapter 1 introduces to the background and purpose of the present study, the contribution of the previous studies of researchers about the characterization of Mefenamic acid and determination of crystallization kinetics, the present state of knowledge about the study topic, and the sequence of approach taken for the present study.

Chapter 2 gives brief information about the crystal and crystal properties that are the basic steps to understand crystallization. Also it includes description of the supersaturation and metastable zone which are

the most important parameters to control crystallization and crystal products quality.

Chapter 3 starts with a review of the basic crystallization theory. Then it discusses the main steps of crystallization and the available techniques for the calculation of crystallization kinetics. This section includes only theoretical background of the models of crystallization kinetics.

Chapter 4 presents the crystal size distribution (CSD) and the measurement techniques of CSD.

Chapter 5 explains the population balance equation (PBE) especially for the batch crystallizers. It discusses PBE into two sections as the solution-side and the solid-side information.

Chapter 6 elaborates determination of the crystal growth rate kinetics. The popular methods for calculation of the crystal growth kinetics which will be adopted in this study are presented.

Chapter 7 discusses the experimental part of this study which includes the identification of polymorphic behavior of MA crystals that recrystallized from different solvent and CSD measurements of MA crystals recrystallized from ethyl acetate with recent techniques of LASENTEC and the estimation of concentration profile.

Chapter 8 discusses the results of the experimental and modeling studies. The determination of crystallization kinetic parameters of MA with two different methods, Garside and PBE modeling method were explained by tables and figures.

Chapter 9 describes the discussions and conclusions of the present study and Chapter 10 includes recommendations for the future work.

The experimental part of this study was carried out at the crystallization laboratory of Illinois Institute of Technology, Chicago, USA. The experiments were done in the three months period. Crystallization has wide range of research areas and this is a valuable opportunity to introduce these researches and accomplishment experimental studies of this thesis.

This study was presented in two congresses as 20 minutes lectures, in an international congress and a national congress (Gökbel and Cesur, 2006 (a) and 2006 (b)). For the participation of the international congress, the financial support was given by TÜBİTAK.

1.1 Pharmaceutics and Polymorphism

Pharmaceutical drugs are commonly crystalline materials and are therefore subject to polymorphism. Polymorphism, the ability of a substance to exist in more than one crystalline form, is a significant phenomenon in the field of chemical engineering sciences, including pharmaceutical development. As a result of different arrangement and/or conformation, the polymorphic solids have different unit cells and hence exhibit different physical properties, including intermolecular interaction, crystalline disorder, and change in free energy, thermodynamic activity, solubility, dissolution rate, stability, and bioavailability. In addition, the change in the crystal structure often means a change in the external shape of the crystal, which is an important parameter in the industrial crystallization that has to be controlled.

These properties, in particular stability and solubility, have an impact on the development potential of a drug molecule and it is for this reason that an understanding of the solid-state of a drug molecule, including the identification of all possible forms and thorough characterization of the observed forms, is of prime importance within the pharmaceutical industry. Establishing the polymorphic behavior of a drug molecule early in development minimizes the number of unsuitable candidates progressed and reduces the risk of encountering issues later which may have major financial and time impact.

Polymorphism exhibits important problems that it is necessary to control conditions to obtain the desired polymorph and to prevent the transformation of the material to another polymorph. Materials that form polymorphs often transform from one form to another. This is known as the polymorphic transition.

In crystallization processes involving a material that displays polymorphism, it is quite common for an unstable polymorph to appear first and then transform into stable form. This observation is summarized by Ostwald's step rule, sometimes referred to as the "Law of Successive Reactions", which says that in any process, the state which is initially obtained is not the stable state but the least stable state is closest in terms of free energy change, to original state.

When a material has multiple polymorphs and one of the polymorphs is the stable form at all temperatures the system is known as *monotropic*. If different polymorphs are stable at different temperatures the system is known as *enantiotropic*.

A number of methods are currently employed for characterizing pharmaceutical solid polymorphs and polymorphic forms of drugs. Some of them are presented on **Table 1.1**.

By combining different methods it is possible to obtain more reliable results, but X-ray diffraction is the primary method and all other methods are the supporting methods.

Table 1.1 Methods for characterizing pharmaceutical solid polymorphs

Methods		Usage
Microscopy		morphology
X-ray powder diffraction (XRPD)		crystallography
Thermal analysis	Differential scanning calorimetry (DSC)	polymorphic transition
	Thermal gravimetric analysis (TGA)	
	Hot-stage microscopy	
Spectroscopy	IR	molecular motion
	Raman	
	Solid state NMR	
Densimeter		solubility studies
Nuclear magnetic resonance		chemical environment

1.2 Literature Survey on Characterization of Mefenamic Acid

Mefenamic acid [N-(2,3-xylyl) anthranilic acid] is a potent prostaglandin synthetase inhibitor that is widely used as a non-steroidal anti-inflammatory and analgesic–antipyretic drug. Mefenamic acid (MA) is used for relief of postoperative and traumatic inflammation and swelling, antiphlogistic analgesic treatment of rheumatoid arthritis, and

for antipyresis in acute respiratory tract infection arthritis. MA is available in the form of tablets, capsules, and a pediatric suspension (Adam et al., 2000).

Figure 1.1 shows the conformational structure of mefenamic acid. As seen in the figure, the carboxyl group, the ring containing it, and the bridging amino group are all coplanar resulting from resonance interactions and internal hydrogen bonding between the NH and the carboxyl group.

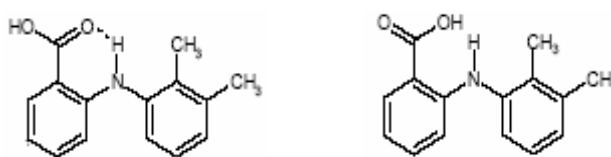


Figure1.1. Conformational changes in mefenamic acid between polymorph I and II (Gilpin and Zhou, 2005)

In most cases, the specifications of a drug include identification and purity, but the physicochemical drug properties does not described in drug literature. To facilitate tabletability, enhance dissolution rates, and develop a stable and reproducible dosage form, investigation of the physicochemical properties of mefenamic acid is necessary.

1.2.1 Solubility studies

Measurement of thermodynamic properties such as heats of solution, entropy and enthalpy relationships of polymorphs often aid in the proper selection of the desired crystalline modification of the drug. Anguiar and Zelmer, 1969 studied on the solubility and dissolution behavior of three polymorphs of chloramphenicol palmitate and two of mefenamic acid. The thermodynamic relationships involving the

transition of the metastable modifications to the stable one was also examined.

MA was reported to have two kinds of polymorphic forms, form I and II. Form I has prepared by acetone and form II by N, N-dimethyl formamide. The dissolution profiles of two polymorphs in dodecyl alcohol were investigated at 30°C, 40°C and 50°C. They found that the metastable polymorph II had higher saturation solubility than polymorph I, but in the dissolution media, polymorph II was unstable and was completely converted into polymorph I. The limiting step in the dissolution process was therefore attributed to poor solubility of polymorph I.

The heat of solutions and the thermodynamic values for the conversion from Form II to Form I were calculated and these data were summarized in **Table 1.2**.

Table 1.2 Thermodynamic values calculated for Form I and II of MA (Anguiar and Zelmer, 1969)

Form	Transition Temp. to Form I(°C)	Heat of Solution kcal/mol	ΔG_T at 30°C cal/mol ^a	ΔS_{303} e.s.u. ^a	ΔS_T e.s.u. ^a
I	-	6.7	-	-	-
II	89	5.7	-251	-2.6	-2.8

^a Calculated for the conversion to Form I.

The dissolution profile and solubility of two polymorphic forms of mefenamic acid were examined in solvent mixtures of ethanol-water and

ethyl acetate-ethanol by Romero et al, 1999. The solubility parameter (δ) was used to study the effect of polarity on the solubility behavior of two forms.

Both polymorphs had high dissolution rates in the less polar mixtures (ethyl acetate-ethanol) of lower solubility parameter values than in the mixture of higher solubility parameters (ethanol-water). Form II showed larger dissolution rates and saturation concentrations than Form I in all the solvents studied by Romero et al, 1999. The concentration dissolved of Form I increased with time and reached to the asymptotic region corresponding to equilibrium solubility in all solvent systems. **Figure 1.2** shows the dissolution profile of both polymorphs of MA in ethanol, ethyl acetate-ethanol mixture and ethyl acetate.

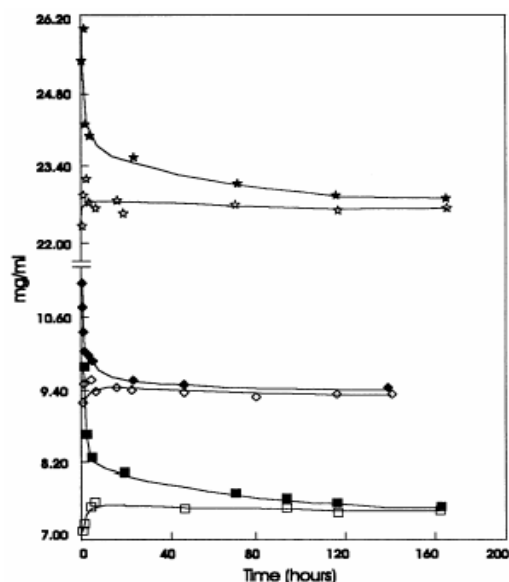


Figure 1.2 Dissolution profile of MA in ethanol, in 50% ethyl acetate in ethanol, and in ethyl acetate (open-Form I, filled-Form II)(Romero et al, 1999)

Tablet disintegration, and wet granulation is the first step for dissolution and is the wetting of the solid surface. Wetting is the

replacement of the air on the solid surface by a liquid. In the study of Adam et al, 2000, the wetting behavior and dissolution rates of MA taken from different companies with different lot numbers was characterized by adsorption of various solutions with different concentrations of sodium dodecyl sulfate (SDS) and Tween 80. Tween 80 solutions did not completely wet the solid surface at any practical concentration, while SDS solutions reached a nearly complete wetting. Dissolution was accelerated in SDS, in which the release rates reached a plateau after 15-20 min in each experiment, however dissolution rates in Tween 80 did not reach until the end of the measurements.

If the large amounts of poorly soluble drugs such as MA are formulated, the quality of a solid pharmaceutical preparation is influenced by the shape and size of drug crystals. Fine crystals improve the dissolution rate of poorly soluble drugs because of greater surface area. However, micronization can change drug powder properties such as wettability, compressibility, packability, and flow and thus prevent efficient powder packaging. So transformed the microcrystalline drug into an agglomerated form can be used in a crystallization process more beneficially. The resulting spherically agglomerated crystals then can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation. This provides direct tableting in which powders are simply mixed and compressed. Direct tableting generally is preferred because it saves time and reduces cost in comparison with the granulation technique.

Bhadra et al, 2004 prepared spherical crystals of MA with the ternary solvent system, which is partially miscible solvents, ammonia

water, acetone and chloroform and compared the physical properties of the spherical crystals with those of MA powder. The results of the study showed that the spherical crystals of MA had excellent flow properties and greater wettability than did the MA powder with the lower contact angle and surface tension. Spherical Crystallization also increased the aqueous solubility of MA as seen on **Table 1.3**.

The solubility study of Bhadra et al, 2004 showed that spherical crystals had good solubility in water as well as in other solvents because of decrease in crystallinity and increase in wettability of agglomerates of MA crystals. The dissolution rates of tablets of spherical crystals were higher than that of the tablets made from simple MA.

Table 1.3 Physical properties of powder and spherical crystals of MA (Bhadra et al, 2004).

Parameter	Powder	Spherical crystals
Particle size(μm)	74.93 $\pm$ 3.21	553.99 $\pm$ 15.26
Surface area(cm^2)	1.76 $\times 10^{-4}$	96 $\times 10^{-4}$
True density(g/cm^3)	1.1743 $\pm$ 0.094	0.9987 $\pm$ 0.086
Bulk density (g/cm^3)	0.615 $\pm$ 0.053	0.503 $\pm$ 0.045
Angle of repose	38.65 $^\circ$	29.40 $^\circ$
Density(g/cm^3)	0.9756 $\pm$ 0.25	0.9986 $\pm$ 0.15
Surface tension (dyne/cm)	55.76 $\pm$ 0.95	48.53 $\pm$ 0.85
Aqueous solubility (mg/ml)	0.18 $\pm$ 1.08	0.25 $\pm$ 1.92
Values are represented as mean $\pm$ SD, n=3		

To characterize the physicochemical properties of MA complexes with different salts such as propanolamine (P), diethanolamine (D), and triethanolamine (D) were studied by Fang et al, 2004 to increase the transdermal flux of MA. Salts are usually considered alternatives for drug delivery when the physicochemical characteristics of the parent drug

molecule are unsuitable for an adequate formulation. The use of different salt-forming counter ions can be cause of variations in the solubility, dissolution rate, and other pharmaceutical properties.

The solubilities of MA and its complexes in water, ethanol, isopropyl myristate (IPM), and 10% ethanol in isopropyl myristate (EI) system were determined at 32°C. The results are illustrated in **Table 1.4** and solubility of MA and its complexes in an ethanol-water mixed system is illustrated in **Figure 1.3**. This study demonstrated that MA and each alkanolamine formed an ion pair complex. The series of amine complexes had a lower melting point and higher solubility in water compared with pure MA.

Table 1.4 Solubilities in various vehicles of MA and its complexes with alkanolamine at 32°C (Fang et al, 2004)

Vehicle	MA	MA-P	MA-D	MA-T
Water	0.25 (6.98) ^a	1063 (9.53) ^a	15.7 (9.04) ^a	9.32 (9.13) ^a
Ethanol	58.6	807.7	28.3	59.3
IPM	12.3	4.02	0.04	4.49
EI system	47.2	42.7	4.14	15.3
^a Values in parentheses represent the final pH of the solutions				

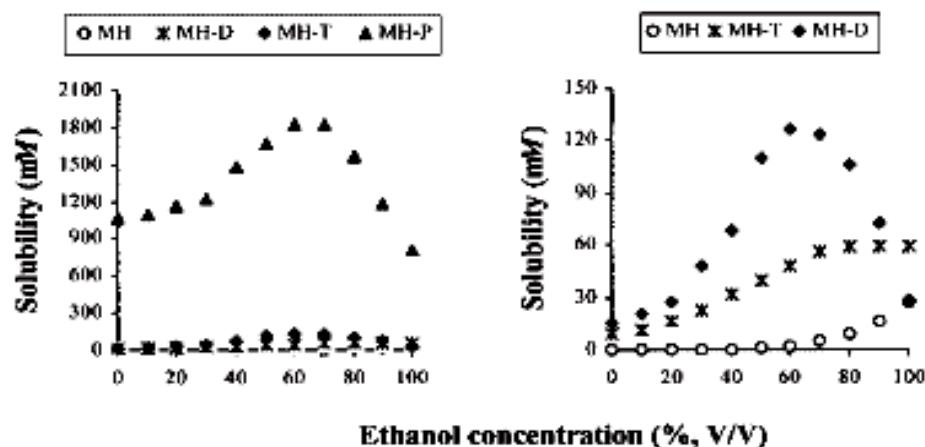


Figure 1.3 Solubilities of MA and its complexes with alkanolamine in ethanol-water mixture at various ratios (Fang et al, 2004).

In the study of Park et al, 2003, a technique for determining the solubility of both stable and metastable polymorphs was presented. The technique was developed during a study of the thermodynamic relationships, between the polymorphic forms of carbamazepine, glycine and mefenamic acid using differential scanning calorimeter (DSC).

Heat flow derivative curves are used in the solubility determination of metastable polymorphic form of the system. The saturation point and the solubility at known weight percentage were given by the peak of a heat flow curve. The solubility data was given in **Table 1.5**.

Apart from the high dose of MA, its inherent material characteristics, such as high hydrophobicity and propensity to stick to surfaces, pose great problems during granulation and tableting. Panchagnula et al, 2004 deal with the characterization of the solid state properties of commercial samples and the influence of crystallization parameters on the solid-state properties of MA.

Table 1.5 Solubility of MA in ethyl acetate (Park et al, 2003)

Form I			Form II		
Temp (°C)	Solubility		Temp (°C)	Solubility	
	w%	g _{sol} /g _{solv}		w%	g _{sol} /g _{solv}
26.17	1.04	1.051	33.26	1.97	2.010
37.93	1.59	1.616	39.66	2.50	2.564
43.45	2.13	2.176	44.95	2.91	2.997
50.62	2.74	2.817	52.20	3.59	3.724
57.74	3.46	3.584	58.06	4.18	4.362

Particle size distribution and surface area of the drug are important parameters that affect dissolution.

1.2.2 Morphology

The morphology of MA samples from different manufacturers was observed with the scanning electron microscope (SEM) by Adam et al, 2000 and Panchagnula et al, 2004.

The crystal habit of a drug can also affect the tableting process. Based on some literature the orthorhombic paracetamol exhibited better tableting than the monoclinic form due to the presence of parallel sliding planes. Thus, SEM can be used to describe the crystal habit of the different mefenamic acid batches (Adam et al, 2000). The scanning electron micrographs of mefenamic acid samples showed needle-shaped flat particles with or without sharp edged.

In SEM photographs (**Figure 1.4**), Panchagnula et al, 2004 observed different habits as needle shaped with rounded edges or plate shaped with angular edges and some aggregates. These crystal habit

differences could be due to crystallization conditions and method employed during bulk drug manufacturing.

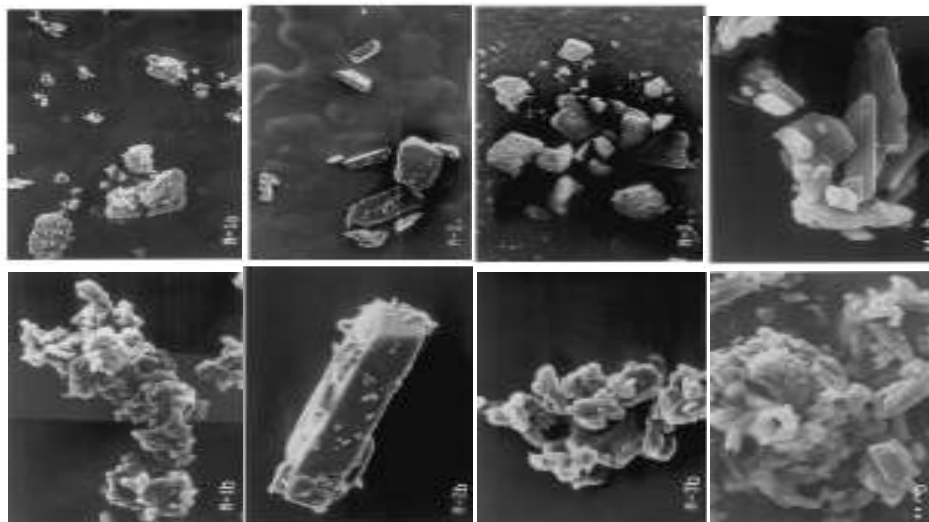


Figure 1.4 SEM photographs of MA sample (Panchagnula et al, 2004).

To alter the material characteristics, MA was recrystallized from three different solvents as tetrahydrofuran (THF), ethyl acetate (EA), and ethanol (EtOH) employing different conditions including agitation rate, cooling rate, and degree of supersaturation.

MA recrystallized from THF, EA, and EtOH had thin, plate-like crystals, flake and needle shaped, respectively. The differences were due to the preferential adsorption of solvent molecules on the crystal faces, which inhibits the growth from one face and produces elongated crystals. Varying process conditions of crystallization in EtOH also affected the crystal habit. Crystallization at slow cooling rate produced more symmetric crystals than the crystals formed with fast cooling rate; the

latter yielded needle shaped crystals. Beside this, the crystals obtained under stirring conditions were finer (Panchgnula et al, 2004).

1.2.3 Polymorphic transition

The conversion of one polymorph into another can occur as a function of time during processing and/ or storage depending on their thermodynamic relationship and stability. The polymorphic transitions can be either reversible or irreversible. During crystallization from different solvents, the metastable polymorph is often obtained first and then the stable form crystallizes at the expense of the dissolution of the less stable form. Therefore, a precise knowledge of the thermodynamic relationship and stability between different polymorphic forms is crucial in crystallization as well as formulation development.

To determine the transition temperature, Aguiar and Zelmer, 1969 used the van't Hoff plot method. The transition temperature and the enthalpy change ΔH for the transition of Form II to I was estimated to be about 89°C and -1031cal/mol, respectively.

Romero et al, 1999 showed that Form I displayed two endothermic peaks at 190 and 230.4°C which correspond to the transition from Form I to Form II and to the fusion of Form II, respectively. These results were different than other literature data depend on the heating rate. The molar enthalpy of fusion of form II was 38.243 kJ/mol at the fusion temperature 503.55 K.

Adam et al, 2000 studied with different commercial samples of MA to observe the polymorphic transition from Form II to Form I. The

samples were first heated to 225°C and cooled. After storage for one week at room temperature, the samples were heated for a second time to 300°C. The data of all onset temperatures are summarized in **Table 1.6**.

All DSC curves showed one endothermic peak during the first heating at onset temperatures ranging from 187°C to 205°C not the same with the literature. During the second heating, there appeared to be no difference between the batches. All curves showed an endothermic peak at an onset temperature of 230°C which is stated to be the melting point of polymorphic form II. Thus, the results indicated that, during a storage period of one week, Form II was not converted into Form I (Adam et al, 2000).

Table 1.6 Onset temperatures of DSC transition and melting points of two manufacturers (Adam et al, 2000).

Samples	Onset Temperatures of DSC Transition (°C)	Melting Points (°C)
I	187.52	231.29
II	194.94	231.51
III	195.35	231.48
IV	196.92	231.04
V	205.63	231.18
VI	200.82	230.95
VII	205.32	230.71

In the Park et al, 2003 study, the thermodynamic relationship between the two polymorphic forms of MA was determined by producing a van't Hoff plot of the solubility data.

By extending the trend line as represented in **Figure 1.5**, a transition point between Form II to Form I was determined to be at 87°C. Since this point was below the melting point of MA at 229°C, there was no enantiotropic relationship between the two polymorphic forms.

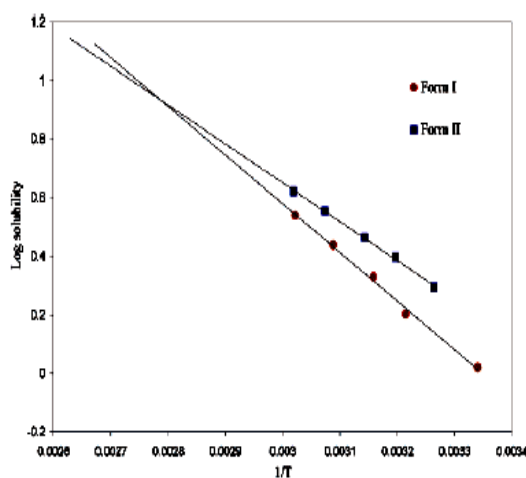


Figure 1.5 van't Hoff plot of MA Form I and II

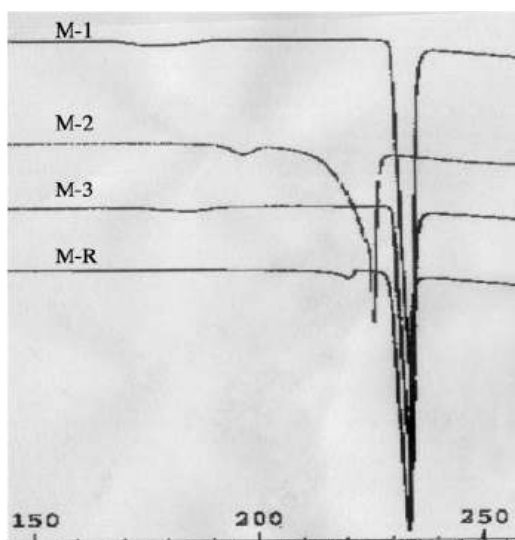


Figure 1.6 DSC thermogram of MA commercial samples and the USP reference standard sample (Panchagnula et al, 2004).

As shown in **Figure 1.6**, DSC curves had two endothermic peaks, which correspond to the transition of Form I to Form II and the melting of Form II, respectively. The onset temperature of the first endotherm varied from 167°C to 217°C among the commercial samples, whereas the heats of transition were similar (Panchagnula et al, 2004).

The second endotherm, melting of MA, is at 231 °C with exception of one sample. For one of the samples a shift was observed and the possibility of organic and inorganic impurities causing the shift in the melting point was ruled out by high performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS) and thin layer chromatography (TLC) by Panchagnula et al, 2004.

Table 1.7 summarizes the melting point and the enthalpy of fusion for MA and its alkanolamine (propanolamine-P, diethanolamine-D, triethanolamine-T) complexes. The melting point 231.2 °C was in good agreement with that in the literature. The shift in melting point and change in the molar enthalpy of fusion were the result of MA complexation with alkanolamine.

Table 1.7 DSC Melting characteristics of the MA complex (Mean $\pm$ SD, $n=3$)

MA complex	Peak(°C)	Enthalpy of Fusion(kJ/mol)
MA	231.2 $\pm$ 0.2	35.7 $\pm$ 2.0
MA-P	110.1 $\pm$ 0.3	45.2 $\pm$ 0.7
MA-D	168.7 $\pm$ 0.1	69.7 $\pm$ 3.2
MA-T	110.0 $\pm$ 0.1	59.8 $\pm$ 2.0

1.2.4 Crystallography

The commercial samples of MA studied by Adam et al, 2000, show differences between batches. The d values and relative intensities were almost the same, and there were no difference between batches. One additional peak observed at a theta angle of 27.57 (°2 θ) but that could not be related to one type of mefenamic acid.

The pXRD patterns of commercial MA samples (M-1, M-2, M-3 and M-R) are illustrated in **Figure 1.7**. All commercial samples showed same pXRD patterns that were consistent with that of M-R. However, a peak at 12.6 ($^{\circ}2\theta$) was more prominent in the spectrum of M-2 than in the spectra of the other samples. Furthermore, the relative intensity of peaks varied in all samples. These variations were attributed to the differences in crystal habit and size that resulted in preferred orientation of the crystals in the XRD sample holder.

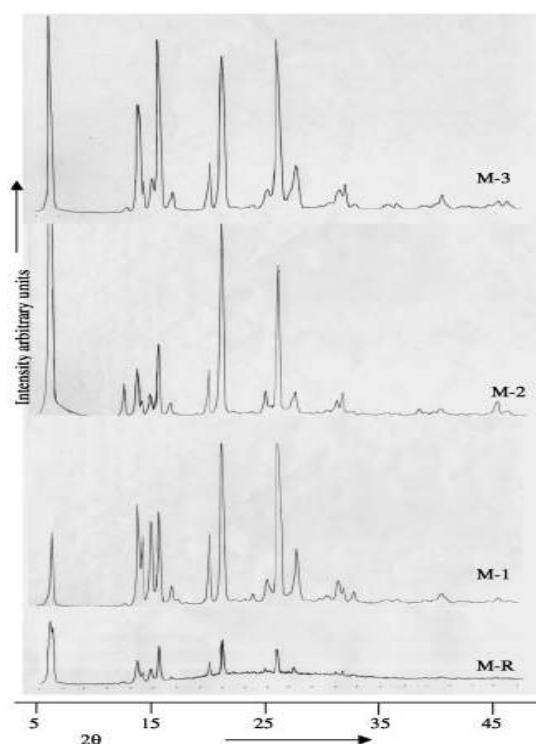


Figure 1.7 Powder X-ray patterns of commercial samples of MA and the USP reference standart

1.2.5 Molecular motion

Raman and near-infrared spectroscopy (NIR) measure fundamental vibrational modes and these techniques can be used to provide distinguishing fingerprints associated with each polymorphic form. These spectroscopic techniques complement one another with Raman measuring vibrational modes that change in polarizability and NIR measuring vibrational modes that change in dipole moment.

Although Raman and NIR spectroscopies can be used to provide a wealth of information on polymorphic form, vibrational spectroscopy does not provide information on crystal structure directly. For vibrational spectroscopy, the observations on crystal form must be first “qualified” by X-ray diffraction.

The crystal structure of the compound determines the electrostatic micro-environment of the functional groups and so this will vary between forms, for example through differences in hydrogen bonding (inter or intra-molecular) and the steric forces within the molecule may also alter due to conformational or crystal-packing changes. Therefore, the frequencies of some, or all, of the vibrational modes will probably differ between solid-state forms. In addition changes in symmetry, due to conformational or packing effects, can alter the appearance of the spectrum by causing band splitting or relative intensity changes.

The IR adsorption spectra of form I and II of MA showed characteristic differences in the detailed shape and intensities of some of the major absorption bands that can be used to identify each polymorph as shown in **Figure 1.8**. Specifically, in the region of wavenumber between 3350 and 3300 cm^{-1} , the -NH stretching frequency occurs at 3313 for Form I and at 3347 for Form II. In addition, Forms I and II had

different characteristic absorption peaks in the region $1600\text{--}400\text{ cm}^{-1}$ (Romero et al., 1999)

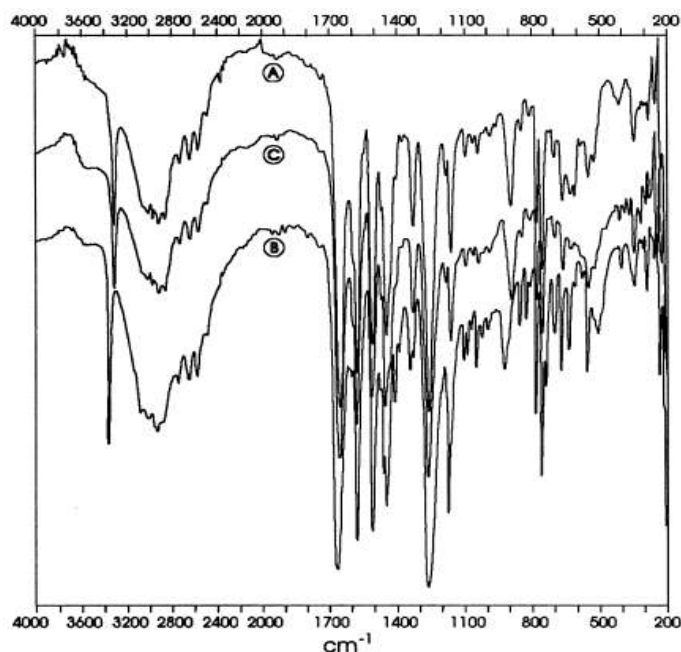


Figure 1.8 IR spectra of MA. A, Form I; B, Form II; C, Forms I and II after equilibration with ethanol (Romero et al, 1999).

After analysis of MA samples by Fourier Transform Infrared Spectroscopy, Panchagnula et al, 2004 was reported that all used samples were in form I.

Rates of polymorphic transition of MA from form I to form II was measured at different temperature using infrared method and activation energy for the process was calculated by Gilpin and Zhou, 2005. The value obtained using the infrared method is significantly smaller than the value of DSC reported previously. In order to explain the difference,

HPLC experiments were carried out to evaluate the potential loss of analyte due to sublimation when samples of MA were maintained at elevated temperatures in the DSC pans. Based on the study of Gilpin, 2005, the rate of analyte loss due to sublimation is the likely mechanism explaining the larger reported value for the activation energy of the polymorphic conversion of mefenamic acid obtained by DSC.

The infrared spectrum of MA is illustrated in **Figure 1.9**. The NH stretching band that occurs between 3300 and 3350 cm^{-1} can be used to identify two crystal form of MA. The band at about 3311–3312 cm^{-1} arises from the amino group internally hydrogen bonding with the carbonyl group and the band at about 3346–3347 cm^{-1} is from the NH stretch in the form II as seen in **Figure 1.1**.

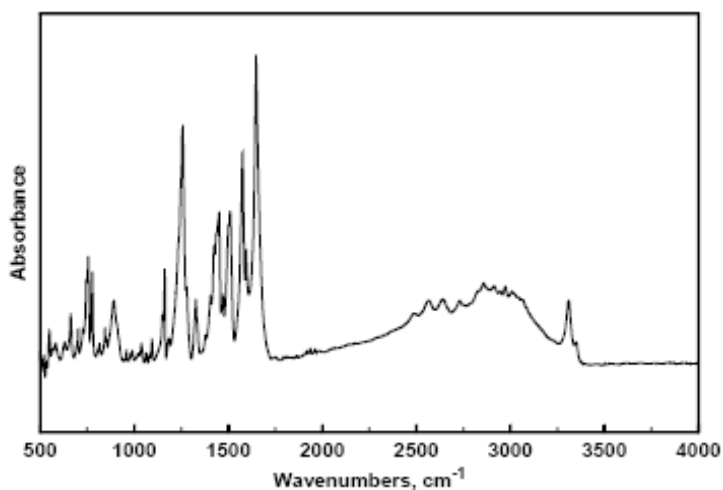


Figure 1.9 Infrared spectrum of mefenamic acid as received (Gilpin and Zhou, 2005)

1.3 Literature Survey on Crystallization Kinetics

Qui and Rasmuson, 1991(a) used concentration and final product CSD data to determine kinetic parameters for an aqueous succinic acid system. They simplified the population balance equation (PBE) to a first-order quasilinear equation system by assuming that the crystal growth rate could be expressed as a product of a function of supersaturation and a function of crystal size. They showed that applying evaluated kinetics in process simulation allowed for a reasonably accurate prediction of the product weight mean size.

Qui and Rasmuson, 1991(b) evaluated the kinetics from isothermal desupersaturation experiments by comparing polynomial fitting, initial derivatives and a non-linear parameter estimation method. In particular, this study referred to separating the volume diffusion resistance from the surface integration resistance.

Bohlin and Rasmuson, 1992 investigated the influence of growth rate dispersion on the product size distribution of batch cooling crystallization by computer simulations. The study includes three different growth rate activity distributions. For unseeded and seeded processes, the influence of the corresponding coefficient of variation was analyzed. They showed that the effect of growth rate dispersion on the crystal size distribution was significant at moderate dispersion. At high dispersion, even the actual shape of the growth rate activity distribution was important.

Mohameed et al, 2002 investigated three different cooling rate effects on the crystallization kinetics parameters and on the final mean

particle size of potassium chloride. They used the gravimetric method to measure the concentration of potassium chloride in the liquid phase as a function of time. A non-linear optimization method is applied to estimate the growth and nucleation rate parameters from unseeded batch cooling crystallization experiments. Their study suggested that the unseeded batch crystallization can produce reasonable mean particle sizes if an appropriate cooling rate is chosen.

Mohameed et al., 2003 developed a model-based optimization strategy for optimal cooling profile of batch crystallization. They used the numerical method of lines to solve the batch crystallizer model by discretization of population density function over the size length.

Hu et al., 2004 proposed a new optimization-based identification approach for general batch cooling seeded crystallization of ammonium sulfate to overcome insufficient information on the CSD based on simplified population balance models such as the moment equations. The final-time CSD was directly used for identification. Consequently, size-dependent growth rates can be considered.

Hu et al., 2005 used the final product CSD, the reactor temperature profile, and the solute concentration profile for the estimation of the kinetic parameters of crystal nucleation and growth. They solved the PBE directly instead of reduction it to a set of ordinary differential equations (ODEs) or changing the PBE to simple forms under some assumptions, so it can be applied to cases size-dependent growth rate. The determination of optimal temperature profiles for the batch crystallizer was discussed.

2.0 FUNDAMENTALS OF CRYSTALLIZATION

2.1 Crystal and Crystal Properties

Crystals are solids with arranged atoms in a periodic repeating pattern that extends in three dimensions. While all crystals are solids, solids that have short-range rather than long-range ordering are non-crystalline. A non-crystalline solid is often called as an amorphous solid. Depending on the conditions of growth, solids can be formed as crystalline or amorphous, and also their three-dimensional structure or shape can be different under microscope.

Crystals are formed of unit cells with arranged molecules in a highly ordered fashion. The molecules of a unit cell are closely packed to each other with so little void space. Unit cells are often viewed as boxes and crystals as three-dimensional arrays of these boxes which are called as the crystal lattice. All crystals can be identified with seven classes of unit cells: triclinic, monoclinic, orthorhombic, tetragonal, hexagonal, rhombohedral and cubic. These classes are defined by the relationships between the individual dimensions (a , b , and c) and the individual angles (α , β , and γ) of the unit cell. Most common unit cells for drugs are triclinic, monoclinic and orthorhombic as shown in **Figure 2.1**.

From the industrial point of view, the term crystal habit or crystal morphology refers to the relative sizes of the faces of a crystal. The crystal habit is determined by the internal structure and external influences on the crystal such as the growth temperature, supersaturation history, and the presence of impurities.

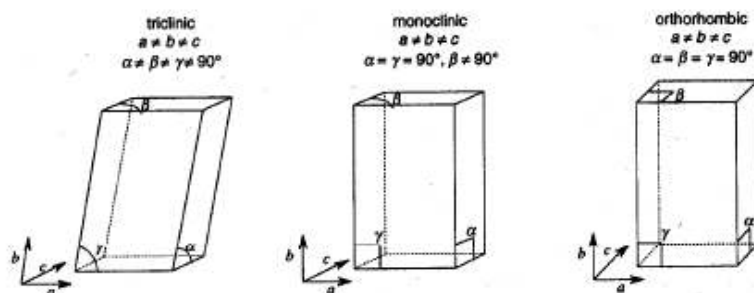


Figure 2.1 The most common unit cells for crystals of drugs.

The each individual crystal faces has their own growth-rate dependence on temperature and supersaturation, so changing the temperature and supersaturation history can affect the crystal habit. As consequence, crystals become more extreme in habit as supersaturation levels increase. Impurities operate by binding to growth sites, and thereby reducing the crystal growth rate. Since different crystal faces can have different characteristics due to the order of orientation imposed by the crystal lattice, specific impurities can bind effectively to some faces, but not others. These face-specific interactions result in modification of the crystal habit, and some impurities can have significant effects even at trace levels. Comparison of crystallization from pure and impure solutions may indicate whether or not significant habit modification is caused by the impurities in the test solutions.

Crystal habit affects the efficiency of downstream processes (such as filtering, washing and drying) and influences material properties such as bulk density and mechanical strength, which play a major role in storage and handling. The crystal habit also affects the flowability, agglomeration and mixing characteristics of particulates.

2.2 Supersaturation And Metastable zone

Solutions are formed by mixing two or more components such as adding and dissolving a solid substance. The amount of solute that can dissolve in a given amount of solvent depends on temperature. In most cases, if the temperature of the solvent increases, more solute dissolves. So, the resulting solution becomes increasingly “concentrated” until where no more solute can dissolve. The maximum amount of solute that can dissolve in a solvent at a given temperature is called *the solute solubility*. Solubility is, therefore, temperature dependent.

Saturation is defined as the state of a system where the solid is in equilibrium with the solution at a stated temperature and pressure. *Undersaturation* is the case when a solution is at lower concentration than the saturation value. *Supersaturation* refers to solutions that are at a higher concentration than the saturation value.

Supersaturation is the fundamental driving force for crystallization and can be expressed in dimensionless form as

$$\frac{\mu - \mu^*}{RT} = \ln \frac{a}{a^*} = \ln \frac{\gamma C}{\gamma^* C^*} \quad (2.1)$$

Where μ is the chemical potential, C is the concentration, a is the activity, γ is the activity coefficient, and $*$ represents the property at saturation. In most situations, the activity coefficients are not known and the dimensionless chemical potential difference is approximated by a dimensionless concentration difference

$$\sigma = C - \frac{C^*}{C^*} \quad (2.2)$$

This substitution is only accurate when $\gamma/\gamma^* = 1$ or $\sigma \ll 1$ so that $\ln(\sigma + 1) = \sigma$. Supersaturation is also often expressed as a concentration difference

$$\Delta C = C - C^* \quad (2.3)$$

And as a ratio of concentrations

$$S = \frac{C}{C^*} \quad (2.4)$$

The choice of supersaturation generation technique has a major influence on the possibility of achievement of the desired product specification and ease of the crystallizer operation. Supersaturation can be generated in a number of ways; the four most commons are as follows:

- Cooling; presuming the solubility increases with increasing temperature;
- Solvent evaporation;
- Drowning out; the addition of a non-solvent (anti-solvent) which is miscible with the primary solvent to make a solvent mixture in which the solute has reduced solubility;
- Chemical reaction; to form a less soluble product (the reaction might vary from addition or removal of a proton, through formation of a salt, to the coupling of two large molecules).

In working with materials of very steep solubility, such as hydrated salts, it is common to use cooling type crystallizers for very high overall yields and reduction of the overall energy requirements of the separation process. With materials that have a normal but moderate slope solubility curves, many choices are available including evaporative cooling, surface cooling, or constant temperature evaporation. With materials having flat or inverted solubility, evaporative crystallization should be used by considering the economics, the crystal phase desired, and the materials of construction available. If the product is quite soluble and the solubility varies little with temperature, then solvent evaporation or drowning out with an anti-solvent may be suitable choices.

The metastable zone width is another essential piece of information, which must be obtained. Effectively, this is the supersaturation level at which primary nucleation occurs in a crystal free solution. Also the metastable zone width is an important parameter to analyze the specifications of the products obtained from the industrial crystallization processes, such as product crystal size, crystal size distribution and crystal shape by its contribution to nucleation and crystal growth. The metastable zone width depends mainly on temperature, solution, cooling rate, presence of impurity, mechanical effects, etc.

The metastable zone width can be determined by slowly increasing the supersaturation in a crystal-free solution until primary nucleation occurs, and noting the equilibrium solubility level corresponding to the nucleation conditions. The metastable zone represents the region within which the supersaturation needs to be maintained for the crystallization to be controlled. Thus, if the metastable limit lies close to the solubility curve, then control of the crystallization is likely to be difficult.

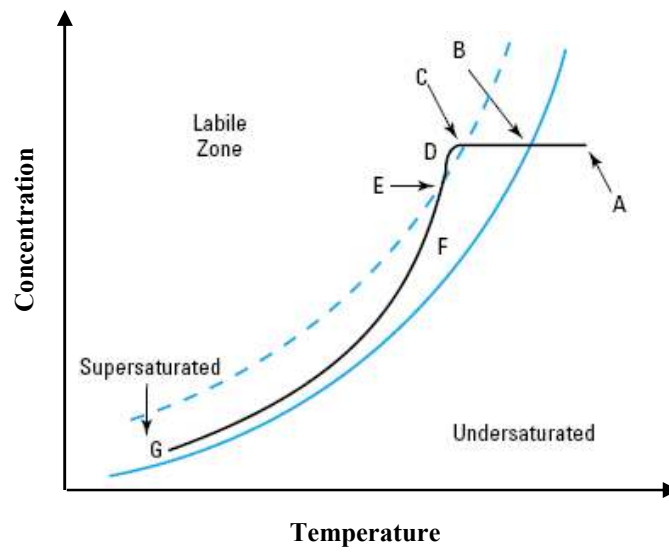


Figure 2.2. The solubility curve and metastable zone width for a batch cooling crystallization.

Figure 2.2 shows the solubility curve and metastable zone width for a batch cooling crystallization showing the trajectory of the operating points during unseeded operation. Point A indicates the initial charge that the solution is undersaturated. Now the solution is cooled until saturation point B. Point C represents the entrance of labile zone which nucleation starts. Rapid nucleation is seen in labile zone (D). After concentration decays the solution leaves the labile zone so during main cooling of batch (F) the growth of crystals can be seen until end point G.

3.0 NUCLEATION AND GROWTH KINETICS

3.1 Crystallization

Crystallization is one of the oldest separation processes. Crystallization is the formation of solid particles within a homogeneous phase, where the solid molecules are arranged in a repeating lattice structure.

Competing with distillation as a separation and purification technique, crystallization operates at low temperatures with low energy consumption and yields with high purifications in one-step. Also crystallization is a process by which a change of phase occurs to obtain crystalline product from a solution. Generally crystallization is referred as a process involving only liquid solutions, although in some cases it occurs out of melt or gaseous phases.

Crystallization is significant because it is widely used in many industries such as the pharmaceutical, fertilizer, dyes and pigments, biotech and other specialty chemicals industries. This technique must be performed in a controlled manner since it affects product quality. A product with uniform and narrow size distribution and large mean crystal size is often desired in industry. The industrial challenge is to produce crystals of the desired size and bulk density in the most economic manner.

Crystallization process consists of two basic steps called as nucleation and growth. Nucleation is the formation of crystal nuclei or stable crystalline phase in the crystallizing system. The increase in size of

this nucleus with layer by layer addition of solute is called growth. The crystalline solids subsequently grow to visible size. Analysis of industrial crystallization processes requires knowledge of both nucleation and crystal growth.

Nucleation and growth of the crystals are both rate processes and are defined as crystallization kinetics. The rates of nucleation and growth determine the characteristics of the ultimate product crystals. Both nucleation and crystal growth have supersaturation as a common driving force. If the solution is not supersaturated, crystals can neither form nor grow. The crystallization kinetics is, therefore, essentially governed by the level of supersaturation. In order to understand the crystallization process, especially its kinetics, the knowledge of supersaturation is important.

3.2 Nucleation

Nuclei formation takes place in several different ways as listed in **Figure 3.1**. The formation may originate from attrition, which is especially true for large crystals and occurs under macroscopic conditions because the resultant particles can visually be detected (Larson, 1984).

On the other hand, the formation of nuclei can also proceed in sub-microscopic range, such as in the homogenous nucleation process. The currently available equipment for nucleation process detection, particularly in sub-microscopic range, is usually not adequate; hence assumptions that nuclei have zero sizes are sometimes necessary.

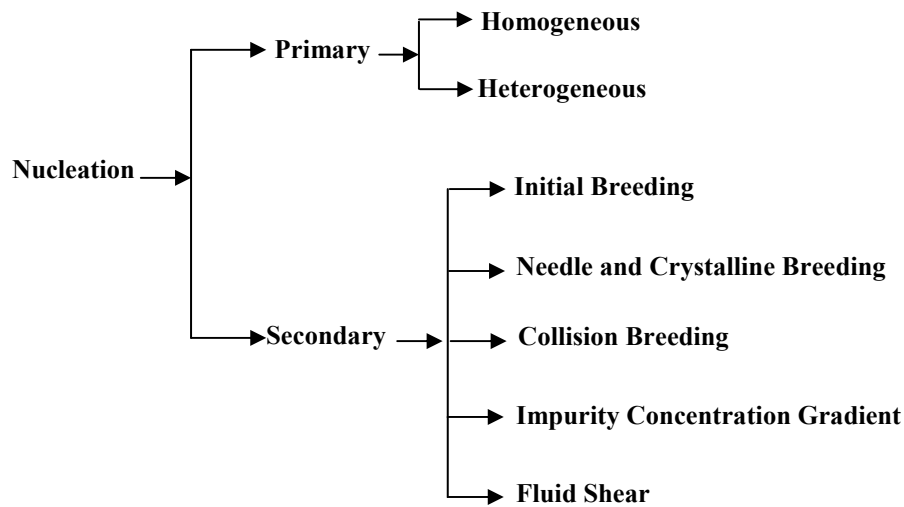


Figure 3.1 The diagram represents the types of nucleation.

3.2.2 Primary nucleation

Primary nucleation occurs in a crystallizing solution in the absence of solute crystals and usually takes place at relatively high supersaturation levels. Primary nucleation is divided in homogeneous and heterogeneous nucleation.

3.2.2.1 Homogeneous nucleation

Homogeneous nucleation is defined as formation of nuclei without any influence from solid material or impurities. Homogeneous nucleation occurs due to the effect of supersaturation only. As a supersaturated solution is not in equilibrium, there are fluctuations in local concentrations which give rise to the formation of small and unstable

molecular aggregates. These aggregates are called as clusters that are continuously forming and falling apart.

In a homogeneous nucleation mechanism there is no foreign surface present in the crystallizing solution to start the nucleation. Instead, the new phase formation takes place by statistical fluctuations of solutes entities, which form clusters. It is assumed that clusters are formed by an addition mechanism of growth units. As the addition mechanism continues, the cluster grows until reaching a critical size.

The attainment of critical size, however, is subject to the level of saturation of the crystallizing liquid. In undersaturated or just-saturated solutions, the number of clusters formed is equal to the number of clusters decayed away so the clusters will never reach a critical size. The clusters of the critical size can be formed in supersaturated solutions where the size is inversely dependent on the level of supersaturation. Since higher supersaturated solutions are less stable than low supersaturation, the critical size of the clusters is smaller than those low ones.

Thermodynamically, the Gibbs free energy, ΔG is the free energy change for the formation of nucleus in homogeneous nucleation. It is the sum of two opposing terms. The free energy change for the phase transformation, which means solute molecules attached and incorporated into a cluster, per unit volume, ΔG_{volume} , is negative and can be defined by **Eq.3.1**

$$\Delta G_{\text{volume}} = - \frac{k_v L^3}{V_m} \Delta \mu \quad (3.1)$$

Where, k_v is the volume shape factor (dimensionless), L is the size of cluster, V_m means molecular volume, and $\Delta\mu$ is chemical potential difference per solute molecule.

On the other hand, the free energy change for the formation of the nucleus surface, $\Delta G_{\text{surface}}$, is positive and can be defined by **Eq.3.2**.

$$\Delta G_{\text{surface}} = k_a L^2 \gamma \quad (3.2)$$

here, k_a is the surface shape factor (dimensionless), and γ is the interfacial free energy, erg/particle.

Since clusters are so small, a cluster can be assumed as a sphere and **Eq.3.1** becomes

$$\Delta G = -\frac{4\pi r^3}{3V_m} \Delta\mu + 4\pi r^2 \gamma \quad (3.3)$$

Where r is the radius of cluster in μm .

The critical radius of the cluster, r^* , can be calculated by minimizing the free energy equation above with respect to radius:

$$\frac{d(\Delta G)}{dr} = -\frac{4\pi r^2}{V_m} \Delta\mu + 8\pi r \gamma = 0 \quad (3.4)$$

$$r^* = \frac{2\gamma V_m}{\Delta\mu} \quad (3.5)$$

$$n^* = \frac{4}{3} \frac{\pi r^{*3}}{V_m} \quad (3.6)$$

Therefore, the solute particle numbers required to form a nucleus, n^* , is equal to

$$n^* = \left(\frac{2a\gamma}{3\Delta\mu} \right)^3$$

Where “a” is the surface area of a solute entity in the cluster surface.

The corresponding critical Gibbs free energy is then,

$$\Delta G^* = \frac{1}{3} 4\pi r^* \gamma \Rightarrow \Delta G^* = \frac{16\pi \gamma^3 V_m^2}{3\Delta\mu^2} = \frac{16\pi \gamma^3 V_m^2}{3k^2 T^2 (\ln \Delta C)^2} \quad (3.7)$$

The nucleation rate can be defined by using the Arrhenius type equation, as **Eq.3.8**

$$B_0 = A \exp\left(-\frac{\Delta G}{kT}\right) \quad (3.8)$$

In this case, ΔG is chosen as $\Delta G_{\text{critical}}$ and it is equal to ΔG^* . Therefore,

$$B_0 = A \exp\left(-\frac{16\pi \gamma^3 V_m^2}{3k^3 T^3 (\ln \Delta C)^2}\right) \quad (3.9)$$

From **Eq.3.9** can be seen that nucleation rate is a function of supersaturation, temperature and surface energy. The rate of nucleation will increase with increasing supersaturation and temperature. On the other hand, it will decrease if the surface energy is increasing. **Figure 3.2** represent a cluster radius (size of nucleus) greater than the critical size, r_c , is associated with decreasing free energy and therefore the nuclei will

survive to grow. Also **Figure 3.2** shows that the size of the critical nucleus increases with temperature.

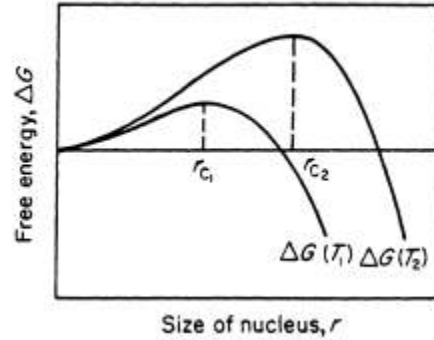


Figure 3.2 Gibbs free energy diagram for homogeneous nucleation showing free energy change versus size of nucleus.

3.2.2.2 Heterogeneous nucleation

Nucleation process that is catalyzed by foreign solid matter is called heterogeneous nucleation. Heterogeneous nucleation occurs in lower supersaturation than homogeneous nucleation. The occurrence of homogeneous nucleation requires a very high level of supersaturation and it is practically rare. Usually heterogeneous nucleation takes place before reaching conditions suitable for homogeneous nucleation.

Under heterogeneous conditions, the formation of nuclei needs less energy than that under homogeneous conditions. It has been postulated that the difference in energy requirement for both the two situations is related to the wetting angle, θ , between the foreign surface and the nucleus. The relationship is formulated in **Eq.3.10**.

$$\Delta G_{\text{homogeneous}} = \frac{(2 + \cos \theta)(1 - \cos \theta)^2}{4} \Delta G_{\text{heterogeneous}} \quad (3.10)$$

Eq.3.10 implies that under condition of complete wetting, that means θ is equal to zero; the energy required for homogeneous nucleation is zero, so spontaneous nucleation could take place.

A common example of heterogeneous nucleation is using a seed crystal (seeding). By adding seed crystals of a known polymorph to the solution it is possible to guide the crystallization process so that it produces crystals of the seeded polymorph. It is also possible to control the crystal size distribution and the start-point of the crystallization with seeding.

3.2.3 Secondary Nucleation

Secondary nucleation occurs under the influence of crystals or solid matter found in a supersaturated solution. The pre-existence of “parent” crystals are involved in the initiation of further nucleation by three mechanisms:

- Breakage
- Attrition due to collisions
- Removal of semi-ordered surface layers through fluid shear

Under most commercial operating conditions, all three mechanisms can be presumed to take place simultaneously, their relative importance varying, depending upon the local conditions in the crystallizer. Since all three have the same overall consequence of increasing the number of crystals present and since it is not possible to distinguish between crystals

formed by the separate mechanisms, these methods are usually combined under the overall category of secondary nucleation. All three mechanisms depend on the same principal variables such as supersaturation, the concentration of crystals in the slurry, and the agitation conditions.

In a stirred crystallizer especially when supersaturation level is not high, secondary nucleation is the most important source of nuclei. The extent of secondary nucleation is partly dictated by the area and roughness of the crystal surface.

When the surface is rough which implies that there are large numbers of dislocation points, the number of nuclei formed is high. Similarly, when the surface area is large, the more dislocation points is found by assuming that the density of dislocation points is constant, hence more nuclei will be born. This also implies that size dependent growth of crystals is dependent on the surface roughness. Large crystals have large surface areas and thus have more dislocation points. Practically, it is sufficient to assume that secondary nucleation must be dominant in stirred crystallizers. One reason is that crystal surfaces are always rough. Even smooth surfaces of a crystal are actually microscopically rough; hence, the possibility of secondary nucleation always exists. Another reason is that detachment of tiny fragment from the crystal surface is always induced by agitation or stirring in the crystallizer.

3.2.3.1 Initial breeding

If the level of supersaturation is relatively low, when a crystal is put into a supersaturated solution, a number of small crystalline particles (nuclei) is usually formed (Myerson, 2002). The appearance of these

nuclei can be caused by crystallite fragments that are detached from the surface of the “parent crystals” added into the supersaturated solution. The crystallite fragments might be formed during storage or when the crystal drying process takes place quickly. As the phenomenon occurs only at the time when the crystals are first put into the solution, the mechanism is called initial breeding. Initial breeding also called dust breeding due to the source of nuclei or crystallite fragments, which are likened to “dust” attached to the parent crystals (Myerson, 2002).

It is obvious that the mechanism of the initial breeding is not significantly affected by stirring because the detachment of the small crystallites from the parent crystals is relatively easy. Also level of supersaturation does not influence the initial breeding strongly due to the larger size of the detached crystals relative to that of clusters, thus it is very unlikely that the detached crystals will disintegrate. If there is no disintegration, then all crystallites will grow to become crystals.

Assuming that the same size of surface area of added crystals is attached by the same number of crystallites, it may be possible to relate nucleation rate with the surface area of the added crystals. The occurrence of initial breeding can be prevented or lessened by pretreating the parent crystals, such as by elutriation or washing. Initial breeding can be categorized as “apparent” secondary nucleation because there is no formation of completely new nuclei (Nývlt, 1985).

3.2.3.2 Needle breeding and polycrystalline breeding

In a solution with higher level of supersaturation, irregular growth of crystals is often found. This irregular growth appears as needles and these needle-shaped crystals attach at the ends of parent crystals causing

the roughening of crystals surfaces. Mixing or agitating the solution causes these needle-like fragments to break away and detach from the parent crystals.

If the level of supersaturation is even higher the needle-like fragments might grow and attach to each other forming aggregates or “polycrystals”. This form can be broken and detached from the parent crystals and hence the name polycrystalline breeding. The detachment will occur due to lowering of supersaturation or abrasion.

3.2.3.3 Collision breeding

If a crystallization process involves agitation, collision breeding takes place and crystals collide among themselves and/or with crystallizer internals. The collision breeding can occur even if the supersaturation level is low and the crystals have regular shape.

Collision breeding is an important incident for crystallization process with high slurry density. If slurry density is low and the crystals have small sizes, the collision breeding can be neglected because small crystals tend to follow the liquid streams and therefore do not collide either among themselves and/or with the stirrer or the crystallizer internals.

Collision breeding is generally differentiated into two types. First, attrition types, in which new crystals are formed from the fragments generated by the collision or impact. The process of attrition breeding will leave visible defects on the surface of the parent crystals and in some cases the parent crystals will become rounded. Attrition breeding is usually found in a system with intense agitation. Second, contact

nucleation, in which the mechanism does not leave macroscopic, defects on the surface of the parent crystals. The formation of nuclei in this process can either be caused by micro abrasion or from the adsorbed solute layer, which has not been crystallized.

Contact nucleation is probably the most important type of secondary nucleation in crystallization for the following reasons.

- For initial breeding to occur the crystals must have tiny fragments. Thus, initial breeding does not always take place.
- Crystallization will not produce needle breeding unless the level of supersaturation is reasonably high.
- In order for the attrition to happen, agitation in the crystallizer should be such as to cause strong collision among the suspended crystals and between the crystals and the crystallizer internals.

3.2.3.4 Impurity concentration gradient

The nucleation by this mechanism occurs when the process of crystallization proceeds in the presence of impurities (Myerson, 2002).

Impurities in the solution may be incorporated in the lattice or onto the surface of the growing crystals, thus creating a gradient of impurity concentration inside and along the width of the boundary layer. Further away from the crystal surface, the concentration gradient will be lower and this condition enhances the possibility of spontaneous nucleation.

3.2.3.5 Fluid shear

Agitation or movement of solution inside a crystallizer causes shearing flow and this is responsible for the breeding of nuclei. There are two sources of the nuclei, namely the dendritic crystallites and the boundary layer.

In a crystallizing solution with high supersaturation, on the surface of crystals may develop dendritic growth which due to shearing action within the solution will be broken and grow as nuclei. The second source of the nuclei is the boundary layer, which is removed by the shearing action of the fluid. In this case the removed layer will act as growth units.

3.3 Growth

After nucleation, the consequent crystallization step is the crystal growth. The nuclei grows larger by the deposition of solute molecules or growth units and these molecules break whatever bonds they have with the crystallizing or supersaturated solution and make new bonds with the crystals.

While the size and weight of the crystals increase, the solution concentration is depleting. The growth of crystals is determined by the rate of increase in the size of the surfaces. Different faces may grow at different rates and this condition dictates the final shape of crystals. The fastest growing faces will disappear while the slowest ones will remain, leaving the crystal bounded by the slowest growing faces.

The crystal growth rate can also be determined by the overall growth of the crystal. In this case, the usual method to be used to determine the change of the crystal mass per unit time (Nývlt, 1985). The theories are classified into two groups, that is, based on either thermodynamic or kinetics properties, as explained in the following sections.

3.3.1 Theories based on thermodynamic properties

3.3.1.1 Theory of limiting faces

The theory of limiting faces explains the relationship between the shape of a crystal and the surface energies of its individual planes. The growth of individual planes or faces of a crystal depends on the capability of the crystallization system to proceed towards a more stable equilibrium state. Specifically, the growth of individual planes depends on the specific surface energies of those planes. The Wulff theorem is generally used to calculate the specific surface energies as follows.

$$\frac{\sigma_1}{h_1} = \frac{\sigma_2}{h_2} = K = \frac{\sigma_i}{h_i} = K = \frac{\sigma_n}{h_n} = \text{constant} \quad (3.11)$$

Where σ_i is the specific energy of i^{th} plane, and h_i is the distance of i^{th} plane from the centre of the crystal.

If a certain face releases a large amount of energy it will experience the fastest growth and vice versa. Hence, the face will either grow bigger or disappear. The face with the slowest linear growth rate determines the final shape of the crystal.

3.3.1.2 Theory of Kossel and Stransky

Kossel and Stransky (Nývlt, 1985; Mullin, 2000; Myerson, 2002) suggested that crystals grow by a repetitive process of incorporation of growth units onto a plane, because a plane is the least energetically favorable site. However, once an initial species or growth unit has incorporated onto the plane, many other growth units will rapidly cover the plane and eventually form a completely new plane layer on top of the previous plane.

According to the Kossel model a mononuclear layer with a smooth surface (P') is attached on a smooth surface of crystal (P). The end of the layer P' is an incomplete line with at least one kink (K). This kink site has the highest binding energy and is the most favorable position for the incorporation of a unit molecule from the solution phase. The deposition of a growth unit upon a crystal face is assumed to take place by the following steps as shown in **Figure 3.3**:

- (i) transport of a growth unit to the crystal surface (A) and adsorption on the surface,
- (ii) diffusion on the surface in a two-dimensional way to reach the step (B),
- (iii) one-dimensional diffusion along the step to a kink site (C), and
- (iv) desolvation of the molecule.

Then, the slow process of finding an initial growth unit to attach to the newly formed plane follows and the same process repeats. Thus, there is fluctuation of growth. The theory also assumes that crystals have no imperfection on their surfaces and that their shapes are regular. Kossel

and Stransky proposed that the amount of energy liberated during the incorporation of a growth unit, e.g. an ionic species, onto a crystal plane depends on its position relative to the plane. Four equations were formulated.

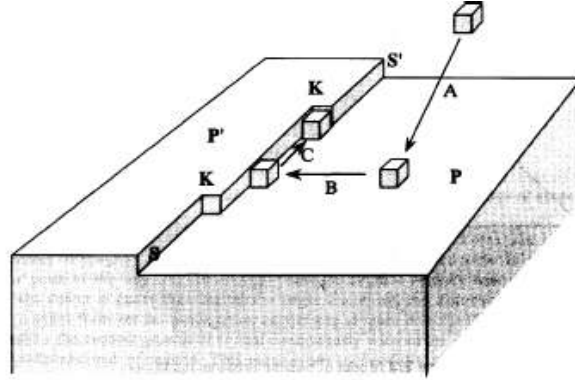


Figure 3.3 Kossel's model of crystal growth.

$$E_H = 0.8738 \, e^2/r \quad (3.12)$$

$$E_R = 0.2470 \, e^2/r \quad (3.13)$$

$$E_K = 0.0903 \, e^2/r \quad (3.14)$$

$$E_P = 0.0660 \, e^2/r \quad (3.15)$$

Where, **E** refers to the amount of energy liberated, **e** is the elementary charge and **r** the ion distance. The subscripts **H**, **R**, **K**, and **P** refer to the position of the growth unit relative to the crystal plane. **H** is the half-central position. **R** represents the unit is located in a corner of a completed plane. **K** is the unit is added at the edge of a completed plane and **P** shows the unit is added in the centre of a completed plane.

3.3.1.3 The solid on solid (SOS) model

The SOS model (Nývlt 1985) explains that crystal growth mechanism is dependent on the roughness of the crystal surface. The rougher the surface the easier the growth units attach themselves to the surface. In this regard the similarity between the SOS Model and the Kossel and Stransky Theory is evident. Furthermore, in both theories a crystal is seen to consist of regularly structured repetitive units. During growth process, the solid species in the boundary layer are in contact with the liquid phase. The SOS model assumes that during crystal growth, the liquid phase in contact with the surface of the crystal could become solid particles. The total number of particles in the phase layer, N , is then calculated using the following equation:

$$N = N_{ns} + N_{nf} \quad (3.16)$$

Where N_{ns} and N_{nf} are the total number of the solid species and the liquid species respectively

3.3.2 Theories based on kinetics properties

3.3.2.1 Boundary layer theory

The theory is advanced by Volmer (Nývlt 1985) and is an important breakthrough of crystal growth based on kinetic theory. As opposed to previous theories, Volmer considered the existence of a boundary layer, which strongly adheres to the crystal surface.

Depending on its energy level, a growth unit can either move back to the mother phase, stay in the boundary layer, or be adsorbed onto the crystal surface. Thus, it is predicted that unless the growth unit or species has high energy, it will stay in the boundary layer or be adsorbed onto the surface of the crystal. The rate at which the species moves is determined by the coefficient of surface self-diffusion of the species, **D**, as **Eq.3.17**:

$$D=d^2/4t \quad (3.17)$$

here, *d* is the average distance between adsorbed species in the boundary layer in μm and *t* represents the mean time period spent by the particle in the position corresponding to the potential valley.

3.3.2.2 Surface diffusion model (BCF Model)

This surface diffusion model was developed by Burton, Cabrera and Frank; hence the name of theory is also shortened as the BCF model (Nývlt 1985; Myerson 2002). The Surface Diffusion Model does not recognize the existence of boundary layer; instead it explains that the species of growth moves directly from the bulk of the solution to the crystal surface. It then moves over the surface and attaches itself to the most energetically favorable growth sites. In terms of energy level there are three regions, as depicted in the following **Figure 3.4**.

The crystal surface structure affects significantly the rate of crystals growth. As a growth site, the crystal surface is generally classified into three regions as shown in **Figure 3.4**. The first region is the terrace that appears as flat surface. The terrace is atomically smooth and has a low energy. An atom, a molecule or a growth unit has only one side to attach

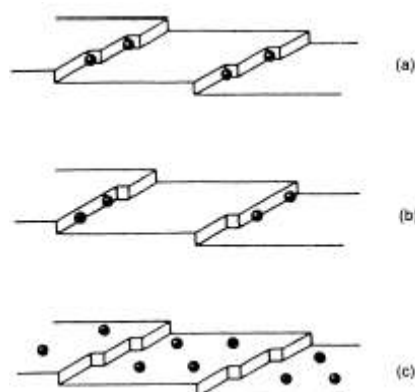


Figure 3.4 Schematic representation of the Surface Diffusion Model (a) kinks, (b) steps, and (c) terrace.

on the surface. Therefore, a terrace is an unfavorable site for a growth unit attachment.

The second region, step separates flat terraces. A growth unit attached onto the step has two-side attachment. One side is attached to the terrace and the other is attached to the step. Thus, the probability of attachment is greater than that on the terrace.

If a particular step cannot grow completely along the terrace, it gives rise to yet another region called a kink. It can be seen that a kink is the most favorable site for attachment due to the three sides that belong to it. Kinks have the highest bonding energy and offer the most favorable sites for unit growth or particle integration. Thus, consistency can be seen among all modes so far discussed, in that the face of a crystal is the most difficult surface onto which a growth unit can stick it. This theory, however, did not explain how kinks, steps or terraces are formed. The

growth rate equation of the BCF model is represented by **Eq.3.18** as follow

$$R = A\sigma^2 \tanh\left(\frac{B}{\sigma}\right) \quad (3.18)$$

Where R is the mass crystal growth rate, σ represents the supersaturation and A, B are temperature dependent constants.

3.3.2.3 Bulk diffusion model

Where the concentration gradient is usually small and negligible, the surface diffusion model is more suitable for crystallization from vapor phase (Nývlt 1985). For a solution crystallization where the concentration gradient in the solution phase is greater than in the vapor phase crystallization, it seems logical to assume that the bulk diffusion can be a controlling factor. In order to adsorb onto the crystal surface, the growth units need to move from bulk of the solution through a layer, which adheres to the crystal surface. Hence, the thickness of the layer plays an important role. Consequently, all factors that affect the thickness of such layer must be considered. **Eq.3.19** describes a relationship for the linear growth rate, l :

$$l = \frac{s.B.k.T.c_{eq}.\Omega}{4\gamma} . b. \left[\frac{1}{1 + \frac{B.a}{D} \ln \frac{c.\delta}{b.a} \sinh \frac{b}{c}} \right] \quad (3.19)$$

where, l is the linear rate of face growth perpendicular to surface with unit of $\mu\text{m}/\text{sec}$, s is number of corresponding spirals on the surface and dimensionless, B is a complex factor characterizing the rate of incorporation of the growth particle into the step, k represents Boltzmann constant in units of $\text{erg}/\text{particle}$. K . c_{eq} is the equilibrium concentration of

a saturated solution, Ω is volume of the growth particle in the crystal, α is mean distance between growth units in the crystal, D is diffusion coefficient and δ is thickness of the diffusion (unstirred) layer on the crystal surface, μm

3.3.2.4 Combined bulk-surface diffusion

This theory considers all the factors that exist in both and surface diffusion theories (Nývlt 1985). It explains that all these factors exert resistance to the incorporation of species of growth onto the crystal surface and that the resistance dictates the growth rate.

3.3.2.5 The kinematic theory

In the surface diffusion model, the growth sites, whether they are surfaces, steps or kinks, are considered as composed of regular distribution of mono-atomic steps. In the kinematic theory, these growth sites are considered as irregular, thus there is no crystal surface that is absolutely smooth (Nývlt 1985). The kinematic theory considers both lattice defects and surface roughness as the controlling factors for crystal growth.

The surface roughness affects crystal growth by affecting the layer movement, and hence, the rate of the crystal growth can be defined as **Eq.3.20**.

$$u=q/n \quad (3.20)$$

where, u is step velocity, q is step flux or it represents the number of steps passing a given point per unit time, n is the step density or the number of steps per unit length in a given area.

3.3.2.6 The diffusion layer model

The Diffusion Layer Model describes the crystal growth mechanism as consisting of two consecutive steps, that is, diffusion of growth units towards the crystal surface followed by integration or adsorption onto surface (Nývlt 1985; Mullin 2000; Myerson 2002).

Diffusion layer model is represented as in Figure 3.5 schematically and C_b is the concentration in the bulk of solution. C_i is the concentration at the interface. The concentration at saturated condition is denoted as C^* .

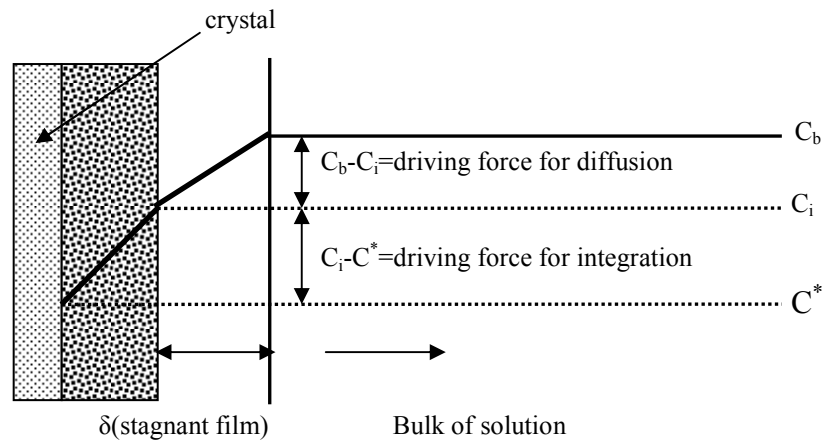


Figure 3.5 Schematic representation of the Diffusion Layer Model

The diffusion rate of a growth unit into surface can usually be represented by the following equation:

$$\frac{dm}{dt} = DA \frac{C_b - C_i}{\delta} \quad (3.21)$$

Where, dm/dt is the diffusion rate, A is the surface area of crystal, cm^2 .

3.3.2.7 The nuclei above nuclei (NAN) model

In the nuclei above nuclei (NAN) model, a nucleus is assumed as a shape and thus of two dimension on a flat surface (Nývlt, 1985; Myerson, 2002). The NAN model is also known as the Two Dimensional Growth Theory. If the crystallizing solution has a constant supersaturation, bulk diffusion does not occur. Two dimensional nuclei form on the crystal surface and then they grow sideways. However, this theory is somewhat indefinite in describing the growth rate of nuclei, and three models are advanced as mono nuclear, poly nuclear and birth and spread.

Mono Nuclear Model explains that the rate of growth of nuclei is extremely fast. The rate of crystal growth, G , is defined simply as:

$$G = h.A.I \quad (3.22)$$

Where, h is the step height in the unit of μm , A is the crystal surface area in the unit of μm^2 , I is the rate of formation of a critical nucleus per unit surface area per unit time.

Poly Nuclear Model define that the rate of growth is zero or that the two dimensional nuclei once formed do not grow at all. In other words,

there have to be a large number of nuclei, which sit next to each other until they cover the entire layer. The rate of crystal growth is represented by **Eq.3.23**.

$$G=J.\pi.h. r_c^2 \quad (3.23)$$

Where, J is a constant factor.

The (B/S) Model has a finite constant rate and is independent of the size. In reality, the Mono Nuclear Model is not adequate because it contradicts the experimental data (Myerson, 2002). According to the Mono Nuclear Model large faces grow faster than small faces which in reality the opposite occurs. The Poly Nuclear Model is not adequate either, because it expected that a certain supersaturation level, the growth rate, G, will achieve a maximum and decline afterwards, the condition, which has not been experimentally observed. In reality, G, always increases with supersaturation. In the (B/S) Model, G, increases with both supersaturation and temperature. It can be assumed that the spread of the nuclei on the crystal surface could be dependent on the level of supersaturation as well as on the temperature.

The crystal growth according to the (B/S) Model is expressed as follows:

$$G=h. J^{1/3} (v^*)^{2/3} \quad (3.24)$$

Where, v^* is the rate of the spread of the nucleus.

All the three models have disadvantages, which make them difficult to be considered as adequate models. The following reasons can

be put forward. First, in all of the three models, the growth process is assumed to be a non-continuous. Second, at a low supersaturation, the calculated growth rates obtained are much lower than that of the experimental data.



Figure 3.6 Birth and Spread Model of crystal growth

The Two Dimensional Model is not widely accepted due to the fact that dislocation-free crystals are very rare. Instead, the “spiral mechanism” theory dominates.

3.4 Nucleation Kinetics

Formation of new crystals may result from any one, or a combination, of homogeneous, heterogeneous and secondary nucleation mechanisms or by attrition. In an industrial crystallization practice secondary nucleation usually has a predominant influence (Tavare, 1987). Secondary nucleation is a complex phenomenon and is not well understood as a general theory for the prediction of nucleation rates does not exist. Several correlations based on the power law model have been found to explain most of the experimental data satisfactorily. **Eq.3.25** defines the power law from the Becker-Doering relationship.

$$B = k_b \mu_k^j \Delta C^b \quad (3.25)$$

The nucleation rate, B , is normally given in units of $\text{no}/\text{m}^3\text{s}$. The nucleation rate constant k_b may be a function of many other variables, in particular temperature, hydrodynamics, presence of impurities and perhaps some crystal properties, and the effect of these might be incorporated in the rate equation using suitable functional forms. The power law term μ_k^j represents the k th moment of the crystal size distribution present in the crystallizer. Normally use of the third moment, i.e. slurry concentration or magma density, is found to be suitable in accounting for secondary nucleation effects. In the industrial crystallizer, most of the nuclei are generated by contact with the crystallizer environment. Thus **Eq.3.25** with $k=3$ can satisfactorily be used to represent nucleation rate in industrial situations.

$$B = k_b M_T^j \Delta C^b \quad (3.26)$$

A power law term of energy input per unit suspension volume, impeller tip speed or stirrer speed, representing a measure of the fluid mechanics effect on secondary nucleation, may be incorporated in **Eq.3.25**. It is sometimes also convenient to express the nucleation rate in terms of solute mass deposition per unit mass of solvent as

$$B_s = k_b M_T^j \Delta C^b \quad (3.27)$$

Typical values of b lie between ~ 0.5 and 2.5 for secondary nucleation rates and higher (up to 10 or so) for primary nucleation. In cases where secondary nucleation is dominant most values of j are close to unity suggesting the dominance of collisions between crystals and stirrer or vessel walls rather than between two crystals. When primary nucleation mechanism is significant the influence of particle concentration on the nucleation rate will be absent. Primary nucleation

rates can also be increased by the mechanical energy inputs to the systems but may not be reduced by reduction in contact energy.

3.5 Crystal Growth Kinetics

There are several ways to describe the crystal growth rate. First, the growth rate is measured as a change in some dimensions with time, and this is known as the linear growth rate. As crystals have more than one face, the linear growth rate must be specific to a particular face. It is usually meant to be the growth rate of a certain face in the direction normal to that face. This can be difficult decision because different faces of a crystal might grow at different rates, so that from one particular crystal several different growth rates may be obtained. This solution can be useful for the fundamental study of crystal growth such as a crystallographic study where growth of different faces of a crystal needs to be compared.

Second, the crystal growth rate can also be measured by observing the change in the characteristic dimension with time. As is well known each type of crystal has its own characteristic dimension, such as spherical, plate-like, needle-like etc. For example, if the crystal is spherical in shape the characteristic dimension is its diameter. Thus the growth rate can be determined as the change in diameter over a certain length of time (Nývlt 1985).

The development and operation of the industrial crystallization processes can be made significantly easier if some data on the kinetics of crystal growth are available. This information can be incorporated in

process models, can be used in process and crystallizer design, and can shed light on the observed behavior of the system.

The crystal growth theories provide a theoretical basis for the correlation of experimental crystal growth data and the determination of kinetic parameters from the data to be used in models of industrial crystallization processes. For engineering purposes in crystallizer design and assessment the simple empirical power law relationship expressing the rate of mass deposition as given by

$$R = \frac{1}{A} \frac{dW}{dt} = K_g \Delta C^g \quad (3.28)$$

Size dependence of the growth rate constant may be attributed to hydrodynamic environments surrounding the growing crystal or crystal surface or shape characteristics and may be expressed by one of several models, this being a simple power law term as in the Bransom growth rate model. It is more convenient to express the overall linear growth rate instead of mass deposition **Eq.3.28** as

$$G = \frac{dL}{dt} = k_g \Delta C^g \quad (3.29)$$

Eq.3.29 employs a linear crystal growth velocity (length/time) with **Eq.3.28** employs a mass rate of crystal growth (mass/area. time). The constant in **Eqs.3.28** and **3.29** can be related each other through the expression

$$K_g = 3 \frac{\alpha}{\beta} \rho k_g \quad (3.30)$$

The power g in the growth equations does not depend on the form of the equation used and is normally a number between 1 and 2.

In general, the overall rate constants K_g and k_g depend on temperature, crystal size, hydrodynamic situation and presence of impurities and are usually fit to the Arrhenius equation to obtain a general expression for growth rate as a function of temperature. The Arrhenius equation can be written as

$$k_g = A \exp(-E_G/R_g T) \quad (3.31)$$

Where A is a constant and E_G is the activation energy. The activation energy can be used to obtain information of whether the rate-controlling step is diffusion or surface integration (Nývlt 1985). A complete crystal growth expression that include both the effect of temperature and supersaturation on the growth rate would, therefore, be written as

$$G = A \exp(-E_G/R_g T) \Delta C^g \quad (3.32)$$

There are a number of experimental methods that can be used to obtain the crystal growth rate data needed to obtain kinetics. Unfortunately, unless great care is taken, these methods can provide very different results for the same system at the same supersaturation.

4.0 CRYSTAL SIZE DISTRIBUTION (CSD)

Although historically, pharmaceutical production involves the manufacture of the finished product using batch processes, followed by laboratory testing and analysis to verify its quality, modern process engineering and manufacturing science achieves high levels of quality through the use of online process monitoring and control. For the pharmaceutical industry, this is an opportunity to lower manufacturing cycle times and end-product variability, which can result in a shorter time-to-market and a reduced likelihood of product failures.

The main measures of the quality of the crystal product are the crystal size distribution, crystal shape, and polymorphic form. The size and shape of the crystals formed will have a strong effect on the processability, with smaller particles and non-spherical particles are more difficult to flow, filter, and process. Shape can also be important in applications such as pharmaceuticals wherein different crystal faces have different dissolution rates, leading to variation in bioavailability for crystals of different shapes. Fine particles have much higher surface area and can collect impurities at the surface. The solubility of different polymorphic forms can differ and dissolution rates will also depend on crystal size and polymorphic form. The critical variables that affect the final quality can be divided into thermodynamic and process variables.

Size distribution can relate to performance during filtration and drying, the product bulk density, powder flow properties, and the ease of formulation. To change the crystal-size distribution, it is necessary to change the relative nucleation and growth rates. This may be done by adjusting the supersaturation history. In general, nucleation rates increase

more rapidly than growth rates with increasing supersaturation. Thus, operation at low supersaturation tends to favor growth of large crystals, whereas high supersaturation close to the metastable limit favors formation of many nuclei resulting in small crystals.

If the crystal size is too small, it should be considered to add seed crystals to a just supersaturated solution, rather than relying on primary nucleation to initiate the process. The seed loading and supersaturation generation rate can be optimized through trial and error, although the biggest difference is likely to be between seeded and unseeded crystallization. A particularly difficult problem is the uneven distribution of supersaturation. If supersaturation generation is highly localized, as in the case of drowning out or reaction, then the variation in the supersaturation environments within the crystallizer will have a significant effect on the relationship between nucleation and growth, and may be an indicator of potential scale-up problems.

Crystalline product obtained from a crystallization process can be characterized with respect to size and shape and it is always found that the crystals vary in size and that no two individual crystals have perfectly identical shape. Therefore one of the main characteristics of crystalline product is the crystal size distribution (CSD). For non-crystalline or agglomerate product the CSD is termed particle size distribution (PSD).

CSD is best presented crystal size versus the amount of crystals. In addition, the crystals should have unit size, which is representative of their shape. For example, if the crystals are spherical, it is logical to represent the size as the crystal diameter. For other shapes, a characteristic dimension of the crystals is used.

The concept of particle size and its measurement is both very simple and complex. In the specific case of size definition for crystallization, it resorts to single linear dimension to establish size. Crystals do not occur in single sizes, but have distributions. Two types of crystal size distribution are normally considered, the density distribution and the cumulative distribution. The density distribution is defined as

$$\int_0^{\infty} f(L)dL = 1 \quad (4.1)$$

Where $f(L)dL$ denotes the fraction of particles in the size range between L and $L+dL$. **Eq.4.1** is written in normalized form, which results in the integral being equal to one. The second type of size distribution is the cumulative distribution defined as

$$F(L) = \int_0^L f(L)dL \quad (4.2)$$

The density distribution has arbitrary units of no./size.volume while the cumulative distribution has arbitrary units of no./volume.

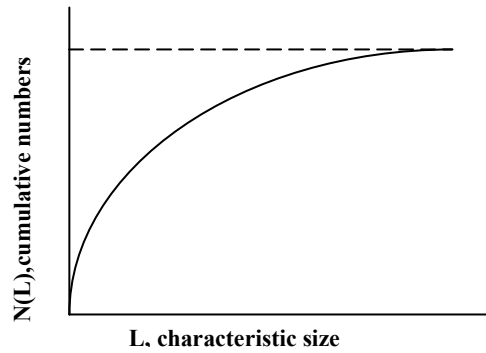


Figure 4.1 A typical cumulative numbers oversize plot.

If the type of data usually encountered in the analysis of crystallizers is considered, the relative importance of the two distributions becomes more apparent. A typical cumulative oversize plot is shown in **Figure 4.1**. Such a plot would be constructed by summing the number of particles greater than zero. In this condition, a single characteristic dimension to describe each particle can be used. This will be determined by the method of size measurement. The transformation from the numbers data, N , to population density, n , is then defined by

$$n = \left. \frac{dN}{dL} \right|_L \quad (4.3)$$

A population density distribution plot is shown in **Figure 4.2**. Typical units for n and N are $\text{no}/\text{m}^3 \cdot \text{m}$ and no/m^3 , respectively.

The relationship between the number distribution, $N(L)$, and the number density distribution, $n(L)$, can be thought of as a transform. Specifically, **Eq.4.3** can be used to transform in one direction while **Eq.4.4** can be used for the reverse transformation.

$$N(L) = \int_0^L n(L) dL \quad (4.4)$$

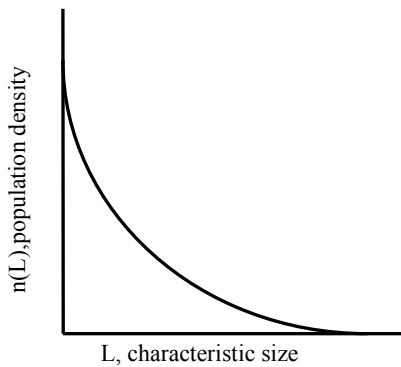


Figure 4.2 A typical population density versus size plot

This is very important in a practical sense because we measure distribution in the integral domain, i.e., $N(L)$. $n(L)$ is not directly measured but it is calculated. The conventional approach to use of the population balance utilizes $n(L)$; therefore, transformed experimental data is considered.

Many important properties of the crystal size distribution (CSD) can be calculated utilizing the population density. The total number of particles per unit volume, N_T , is

$$N_T = \int_0^{\infty} n(L) dL \quad (4.5)$$

In a similar fashion, the total area of the size distribution per unit volume, A_T , is

$$A_T = \int_0^{\infty} k_a L^2 n(L) dL \quad (4.6)$$

where k_a is the area shape factor that relates the area of a particle to the square of the characteristic dimension. A third property is the total mass per unit volume, M_T , which is also referred to as the suspension density. M_T is calculated

$$M_T = \rho k_v \int_0^{\infty} L^3 n(L) dL \quad (4.7)$$

Here, ρ is the density of the solid and k_v is the volumetric shape factor that relates the volume of a particle to its characteristic dimension cubed.

Eqs.4.5, 4.6, and 4.7 can be used in a different manner upon changing the limits of integration. If the upper limit of integration is changed to L instead of ∞ , the number [shown in **Eq.4.4**], area and mass distribution are obtained and these are very important in specifications based on mass distribution. Furthermore, this relationship can be used to convert from $M(L)$ to $n(L)$ when working with sieves.

Mean size can also be defined through use of the population density. For example, if it desired to calculate the number based mean size, it can be found from

$$\bar{L}_{1,0} = \frac{\int_0^{\infty} L n(L) dL}{\int_0^{\infty} n(L) dL} = \int_0^{\infty} L n(L) dL / N_T \quad (4.8)$$

A more common mean size is that based on mass which is

$$\bar{L}_{4,3} = \frac{\int_0^{\infty} L^4 n(L) dL}{\int_0^{\infty} L^3 n(L) dL} \quad (4.9)$$

In fact, any weighting of mean size can be used in addition to **Eqs.4.8** and **4.9** through use of the recursion

$$\bar{L}_{i+1,i} = m_{i+1} / m_i \quad (4.10)$$

Where m_i is the i th moment of the size distribution defined as

$$m_i = \int_0^{\infty} L^i n(L) dL \quad (4.11)$$

4.1 Measurement of Size Distribution

There are two common major classes of sizing techniques practice: mass-based and number-based. The mass-based techniques include classical sieving procedures. Sieves are used by measuring the mass retained on a series of screens of progressively smaller size when moving from the top to the bottom of the stack. If the conversion of sieve data to population density data is necessary, the following equation should be used

$$n = \frac{\Delta m}{k_v \rho \bar{L}^3 (\Delta L)} \quad (4.12)$$

Where Δm is the weight retained on a sieve, k_v is the volumetric shape factor defined earlier, ρ is the particle mass density, $\bar{L}$ is the mean size of the sieve on which the particles are retained and the sieve above it in the stack, and ΔL is the size difference between the two sieves just discussed.

Other techniques also based on a mass are sedimentation and light scattering/diffraction. In each case, including sieves, there will be some difficulty in measuring small particles in the presence of larger particles. This will manifest itself in poor estimation of the small size population density, a shortcoming that will become more obvious when nucleation rates are determined from crystal size distribution measurements.

A second class of measurement techniques, based on particle number, overcomes some of the problems associated with mass-based techniques. Electronic zone sensing sometimes referred to as the “Coulter Principle”, permits simultaneous particle size and number measurement. Particles are sized by suspending them in an electrolyte and drawing them through an aperture tube through which a current is passed. As particles pass through the aperture, a change in conductivity occurs and an electrical pulse is created, the magnitude of which is proportional to the volume of the particles. Typically, the size reported is the equivalent spherical diameter and the diameter of a sphere with the same volume as the particle measured.

The electronic zone-sensing technique has been widely used as both a research and quality control tool. The major shortcoming of the

technique is the requirement of an electrolyte solution in which to suspend the particles without causing dissolution. Other problems such as electrical noise and coincidence can usually be overcome by the choice of appropriate experimental conditions.

More recently, there has been in-process techniques developed. Focused Beam Reflectance Measurement (FBRM®) uses an immersion probe and is capable of in situ measurement of particle chord length. Obscuration measurement can also be used as an in line size measurement. Acoustic size measurement is also emerging as in-process technique that permits use in heavy slurries that are difficult to measure using optical techniques. Set-up and pictures of Lasentec FBRM for crystal size distribution measurement is represented in **Figure 4.3** and **4.4** respectively.

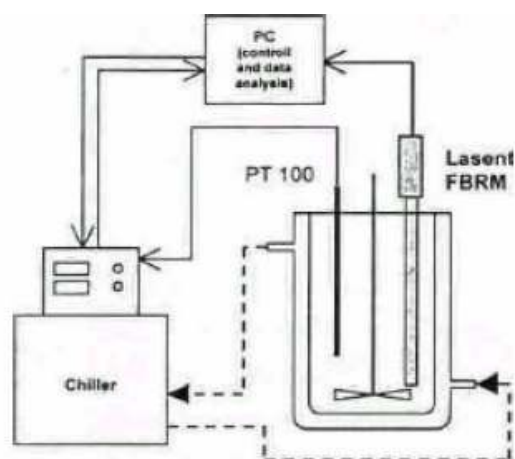


Figure 4.3 Set-up for crystal size distribution measurement by Lasentec (FBRM)



Figure 4.4 Photographs of the Lasentec FBRM machine parts such as reactors, probes and the stirrer

Microscopy can also be employed as a number-based sizing technique. The major shortcoming is the requirement of counting individual particles. Even with use of image analysis techniques, this shortcoming makes it difficult to acquire sufficient counts so as to be statistically significant. Another shortcoming is the two-dimensional nature of the sizing technique. While the third dimension can sometimes be inferred by shadowing techniques, only two dimensions are directly measured. The main considerations in choosing a sizing technique are usually cost and convenience. Irrespective of the technique chosen, it is imperative that the practitioner is aware of the strength of technique and shortcomings.

Traditional methods for determining a particle size distribution, such as dynamic light scattering, require removal of a sample from the process. However, there are several methods that have the potential to characterize the particle size distributions in situ. These include diffusing wave spectroscopy (DWS), turbidity, and frequency-domain photon migration (FDPM) that rely on the multiple scattering of light (useful for any non-transparent suspension), methods that correct for multiple

scattering (cross-correlation dynamic light scattering), and methods that use time variance of reflectance to measure a chord length distribution. Other physical properties that can be related to particle size include acoustic attenuation of sound waves (signal is proportional to the density difference between particles and solvent), electro acoustic effects, and spectroscopic methods such as NIR that are sensitive to particle size and chemical composition.

Essentially all indirect measurements of particle size measure a signal that is an integration of a size dependent weighting function over the particle size distribution. A reported particle size distribution only results from solution of an inverse problem to find the optimal distribution. Alternatively the result of the measurement can be considered as a fingerprint of a particular size distribution. For online monitoring in a process, this level of accuracy maybe sufficient as the measurement can be compared with that of a desired state through a calibration process. Chemometric methods can be employed to build correlations of signal with process conditions or outcomes. Where direct imaging of the process is possible, the direct determination of a size distribution is preferable.

5.0 POPULATION BALANCE EQUATION (PBE)

A complete crystallization process requires three types of conservation laws. The material balances are the first conservation law to calculate the yield or production rate. The second is the enthalpy balance to calculate energy requirement. Thirdly, the population balance is needed to calculate the crystal size distribution (CSD). The third balance is unique to crystallization and other particulate processes. The population balance equation (PBE) depends on crystal size distribution developed over time under certain crystallization parameters such as supersaturation of the solution, crystallization temperature, residence time, chemical composition of the solution etc.

Briefly, PBE provides two ways to determine crystallization kinetics, nucleation and growth rates. Firstly, if a set of crystallization operating conditions was applied with obtained experimental CSD, then a set of the kinetic parameters of the crystallization process can be estimated. Secondly, given a set of the crystallization kinetics equations, the desired CSD can be estimated.

5.1 Population Balance Equation For Batch Crystallizers

Batch crystallizers are used extensively in the chemical industry, particularly for the manufacture of many expensive fine chemicals and pharmaceuticals. They are generally useful in small-scale operations, especially when working with chemicals systems, which are difficult to handle due perhaps to their highly viscous or toxic properties. They are simple, flexible, require less investment and generally involve less process development.

Tavare, 1987 outlines the advances that have been made in experimental data reduction and analysis techniques which can be used to characterize the crystallization kinetics and crystal size distribution in batch crystallizers. The review helps as a starting point in the rational design, understanding and better utilization of batch crystallizers.

During this study, the crystallization of pharmaceuticals was investigated and experimental work was carried out for the measurement of the crystallization kinetic parameters and the crystal size distribution. In pharmaceutical crystallization processes usually batch crystallizers are operated. Therefore, the population balance equation for batch crystallizers systems will be considered.

Usually two types of information can be made available from seeded isothermal batch experiment, the solution-side information in representing the supersaturation-time variation and the solid-side information depicting the population density as a function of time and size. If only the solution-side information is available then two processes, nucleation and growth are generally assumed competitive and the nucleation rate is expressed in terms of solute mass deposition per unit mass of solvent. In many cases nucleation may be assumed negligible (Tavare, 1987).

5.1.1 Solution-side Information

For a constant volume isothermal batch crystallizer with no generation of supersaturation a supersaturation balance can be written as

$$-\frac{d\Delta C}{dt} = B_s + A_T R = k_B M_T^j \Delta C^b + K_g A_T \Delta C^g \quad (5.1)$$

Assuming constant crystal shape factors and negligible breakage and agglomeration the magma density, crystal surface area, average size and slurry voidage are defined as

$$M_T = M_{T0} [W/W_0] \quad (5.2)$$

$$A_T = A_{T0} [W/W_0]^{2/3} \quad (5.3)$$

$$\bar{L}_T = \bar{L}_0 [W/W_0]^{1/3} \quad (5.4)$$

$$\varepsilon = 1 - [W/\rho_c V] \quad (5.5)$$

Where

$$W = W_0 + (\Delta C_0 - \Delta C)S \quad (5.6)$$

The initial values M_{T0} and A_{T0} can be evaluated from the initial weight and size of seed crystals through the expressions

$$A_{T0} = \frac{FW_0}{\rho_c \bar{L}_0 S} \quad (5.7)$$

$$M_{T0} = \frac{W_0}{S} \quad (5.8)$$

5.1.2 Solid-side Information

In the solution-side representation, the supersaturation is assumed as continuous. During isothermal batch run, a seeded crystallizer however contains two types of crystals as occurred nuclei and seed crystals, so the general solution to the population balance equation should comprise one part representing the population density of the seeds and the other subsequently generated nuclei. These crystals are distinguished as the seeds, S crystals and the nuclei, N crystals; their respective number densities being continuous functions of the size and time (Tavare, 1987).

For a perfectly mixed batch crystallizer in which crystal breakage and agglomeration are negligible the population balance equation for size independent growth rate is (Randolph and Larson, 1971)

$$\frac{\partial n}{\partial t} + G \frac{\partial n}{\partial L} = 0 \quad (5.9)$$

where n is the population density.

The boundary condition for the nuclei, the population density can be represented by the relation obtained from **Eqs.3.26** and **3.30**

$$n(t,0) = n^0 = \frac{B}{G} = K_R M_T^j G^{i-1} \quad (5.10)$$

where i is the relative kinetic order given by $i=b/g$ and

$$K_R = k_b / k_g^i$$

The first four moment equations for N crystals obtained by moment transformation of the population balance, **Eq.5.9**, with respect to size are

$$\frac{d\mu_0}{dt} = B \quad (5.11)$$

$$\frac{d\mu_i}{dt} = iG\mu_{i-1} \quad \text{for } i = 1, 2, 3 \quad (5.12)$$

In a batch crystallizer the rate of solid deposition per unit mass of solvent on the S crystals alone is

$$\frac{dW_s}{dt} = \frac{3W_{s0}L_s^2G}{L_{s0}^3S} \quad (5.13)$$

While that for the N crystals will be

$$\frac{dW_N}{dt} = k_v\rho_c \frac{d\mu_3}{dt} = \frac{3k_v\rho_c}{k_a} A_N G \quad (5.14)$$

The supersaturation balance for this configuration can therefore be written as

$$-\frac{d\Delta C}{dt} = \frac{dW_s}{dt} + \frac{dW_N}{dt} = \frac{3W_{s0}L_s^2G}{L_{s0}^3S} + \frac{3k_v\rho_c A_N G}{k_a} \quad (5.15)$$

The population balance equation coupled with this supersaturation balance equation through the set of moment equations represent mathematically the batch crystallizer configuration generally used for the determination of the crystallization kinetics of a solute.

6.0 DETERMINATION OF GROWTH RATE KINETICS

There are significant uncertainties associated with the crystallization kinetics and this is a challenge in controlling crystallization. Part of the difficulty is that the kinetic parameters can be highly sensitive to small concentrations of contaminating chemicals, which can result in kinetic parameters that vary over time. Also, many crystals are sufficiently fragile that the crystals break after formation, or the crystals can agglomerate or have erosion or other surface effects that are difficult to characterize. Another significant source of uncertainty in industrial crystallizers is associated with mixing. Although crystallization models usually assume perfect mixing, this assumption is rarely true for an industrial-scale crystallizer.

Numerous techniques have been devised to measure and analyze crystal growth and, to a far lesser extent, nucleation. The experimental techniques developed to extract crystallization kinetic parameters as depicted in **Figure 6.1** are based on phenomenological models.

The classical approach to establish crystallization kinetics is to isolate the growth and nucleation processes and determine their kinetics separately by direct and/or indirect methods under different hydrodynamic conditions.

The kinetics for secondary nucleation can be measured either by measuring the width of the metastable zone, the induction time or by counting the number of nuclei formed. One of the methods for the determination of nucleation rates is by measuring the maximum possible

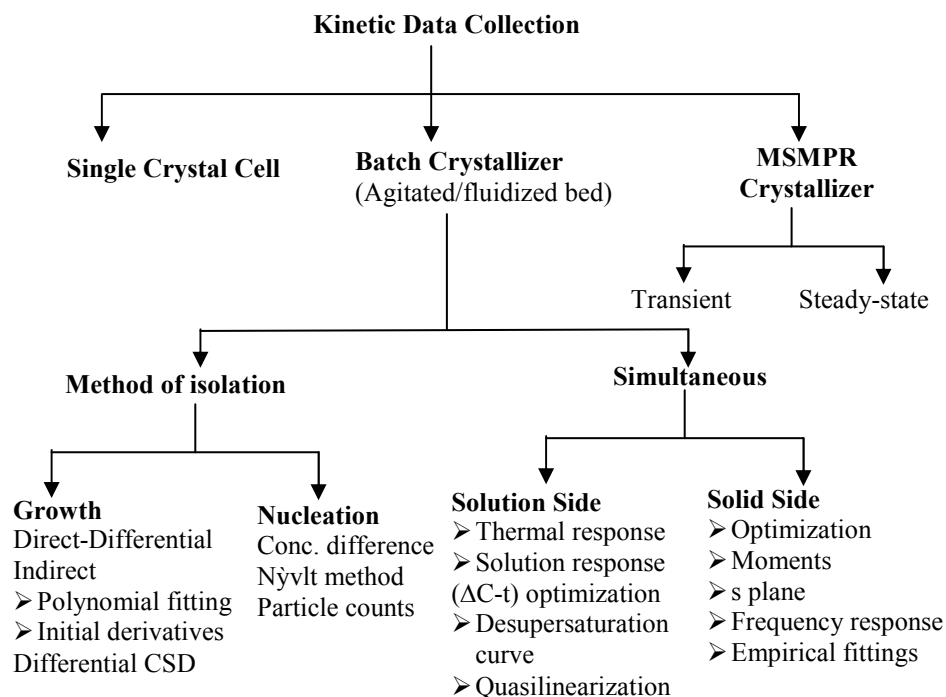


Figure 6.1 The techniques for determination of the crystallization kinetics data

supercooling that can be obtained in a saturated solution when it is cooled at different rates (metastable zone width measurement). The polythermal experiment is carried out in a jacketed crystallizer cooled by a circulating water/ethylene-glycol bath accurate to $\pm 0.1^\circ\text{C}$. The temperature can be increased or decreased at a constant rate by programmed controller. The crystallizer is fitted with an accurate thermometer $\pm 0.1^\circ\text{C}$ to read the solution temperature (Myerson, 2002).

The rate of nucleation can also be determined by observing the time elapsed between the creation of supersaturation and the formation of a new phase. This time interval is defined as the induction time and is a function of the solution temperature and supersaturation. The formation

of a new phase can be detected in several different ways such as by the appearance of crystals or by changes in properties as turbidity or refractive index of the solution (Myerson, 2002).

6.1 Method of Isolation for Crystal Growth

Techniques used to measure crystal growth rates can be divided into two main groups. Direct methods to characterize crystal growth include single crystal studies; measurement of weight gain or movement of a distribution of seeds suspended in supersaturated solution. In an indirect method supersaturation depletion is measured.

6.1.1 Direct Methods

In experiments in which single crystals are grown, the goal is to allow the crystal to grow at a known supersaturation without any nucleation occurring. This implies, therefore, that the supersaturation used in these experiments must be small. In addition, seed crystals must be prepared that can be used in the experiments.

A common method, to prepare seed crystals, is to make a saturated solution at any temperature above the room temperature and then allow the solution to cool without the stirring. The resulting crystals are then examined under a microscope and the one of the desired size showing discernible faces are used. In some systems this method produces very large crystals. In those cases, a gentle agitation will reduce the size obtained.

The rate of crystal growth is affected by the boundary thickness. The boundary layer thickness is affected by the relative velocity between the crystal and the solution. In order to prevent diffusion from controlling the crystal growth rates in single crystal experiments, all methods employ some means to create a velocity between the growing crystal and the solution (Myerson, 2002).

Weighting the seed crystal at the beginning of the experiment and the product crystal at the end of the experiment is the simplest way to measure crystal growth in single crystal experiments. The linear growth rates can also be obtained this way by measuring the crystal dimension before and after the experiment through a microscope. By use of a traveling microscope or cathetometer, the growing crystal can be observed during the experiment and the growth of a particular dimension or face can be observed.

Pumping solution past a crystal is an alternate method that is quite similar to the circulation method. In this method, the crystal is suspended from a rod in a chamber. As previously mentioned, the measurement of growth is the same. This method is more difficult to use for several reasons. First, pumping of the solution tends to increase the chance of nucleation, as does the presence of the various tubing and connections. Second, the lines must be kept at the desired temperature or material will crystallize in the lines (Myerson, 2002).

A third single crystal growth method involves rotating the crystal instead of moving the liquid. The experiment can be done simply by attaching a seed crystal to a rod that is inserted into a variable speed agitator. A more complex sample preparation method known as the rotating disk method involves fixing the crystal in a Teflon epoxy disk

with a particular face exposed. The advantages of the rotating disk are the well defined geometry and hydro-dynamics (Nývlt, 1985)

Determining the crystal growth kinetics of a particular material using one of the single crystal growth methods just described involves conducting a series of experiments at different supersaturation at a given temperature. The resulting data at each supersaturation are used with **Eqs.3.28** or **3.30** to obtain the parameter k_g (or K_g) and g . Normally this means that the $\ln$ of G is plotted versus the $\ln$ of ΔC and a least squares fit is performed. The slope of this line will be g and the intercept $\ln k_g$. The schematic representation of the measurement is shown on **Figure 6.2**.

The entire process can then be repeated at a different temperature to determine the effect of the temperature on the crystal growth kinetics. The well-defined flow or stirring rates is important to conduct these experiments. Usually in measurements of this method, it is desired to minimize the effect of bulk diffusion so that surface integration is the rate-controlling step. This is normally done in practice by measuring the growth rate as a function of flow rate (or stirring speed) at a given supersaturation. If mass transfer is controlling, the growth rate will increase with increase flow rate. This is continued until a point is reached where no observable increase in growth rate is noted with increasing flow rate. A flow rate in this range is then used for all additional experiments. One of the assumptions done in experiments is that the size of the crystal does not affect its growth rate. This is often known as a McCabe ΔL law. This is a good first assumption but it is not necessarily true (Myerson, 2002).

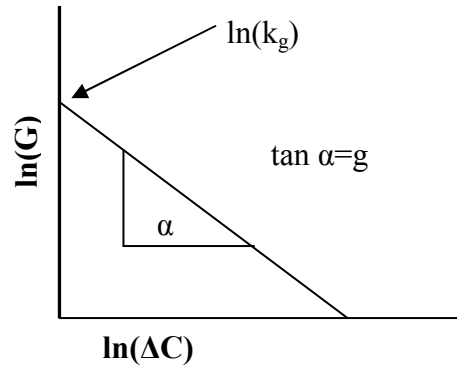


Figure 6.2 Schematic representation of the determination of the crystal growth kinetics by the single crystal growth method.

The environment in an industrial crystallizer where many crystals are growing in a suspension is very different than single crystal growth experiments. A laboratory method known as a fluidized bed crystallizer, attempts to measure the growth rates of a number of crystals. In this method, solution is circulated through a crystallizer in which seed crystals are suspended by the flowing fluid. The flow is such as no settling of the crystal and flowing out of the crystallization vessel. As in single crystal growth experiments, if the mass of solute depositing on the growing crystals are small enough, the system can be considered to be at constant supersaturation. By using seed crystals of the same initial size, the final size and mass of the crystals can be used to obtain an average growth rate (Myerson, 2002).

The most common method for obtaining crystal growth kinetics involving suspensions involves the use of a continuous mixed suspension, mixed product removal (MSMPR) crystallizer operating at steady state. By using the population balance concepts developed and described by Randolph and Larson (1971), growth rates can be obtained.

6.1.2 Indirect Methods

Indirect methods are used for the estimation of both the growth and the nucleation kinetics, because all of the direct measurement techniques are time consuming. Also determination of kinetics parameters requires a significant number of experiments to obtain sufficient data.

Most of the indirect methods are based on the measurement of the solution concentration versus time in a seeded isothermal batch experiment. This is often called the desupersaturation curve since the concentration and solubility can be used to calculate the supersaturation of the system versus time.

6.1.2.1 Desupersaturation curve technique

The desupersaturation technique involves the preparation of a saturated solution of known concentration in a batch crystallizer or other vessel where the temperature can be controlled. The vessel should be equipped with a stirrer. With the stirrer on, the temperature of the solution is lowered to several degrees for obtaining the supersaturated solution.

The solution must remain clear with no crystals present at the lower temperature. Seed crystals of the solute of known mass and size or size distribution are added to the solution. Since the solution is supersaturated, these crystals will grow, causing a decline in the concentration at the solution that is measured as a function of time. This is done by taking samples and using one of a number of concentration measurement techniques. The density meter is one of the concentration measurement methods.

Figure 6.3 shows the apparatus to measure the desupersaturation curve online. Solution is continuously pumped from the crystallizer to a ceramic cross flow filter. Clear solution is obtained in a small side stream that returned to the crystallizer (Myerson, 2002).

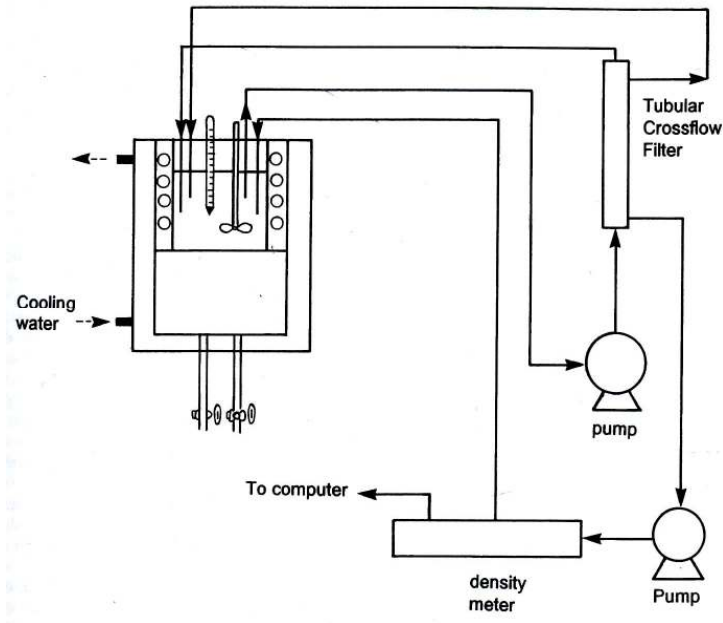


Figure 6.3 Apparatus to measure the concentration profile on line (Myerson, 2002)

The direct measurement of the crystal weight change enables the overall growth rate to be determined as **Eq.6.1** at a particular temperature, crystal size and supersaturation level. This may be correlated in terms of the operating variables.

$$R = \frac{\Delta W}{A_T \Delta t} \quad (6.1)$$

If the experiment results of supersaturation are empirically fitted into a fourth order polynomial in time as

$$\Delta C = a_0 + a_1 t + a_2 t^2 + a_3 t^3 + a_4 t^4 \quad (6.2)$$

The desupersaturation rate at a point is

$$\frac{d\Delta C}{dt} = a_1 + 2a_2 t + 3a_3 t^2 + 4a_4 t^3 \quad (6.3)$$

When a model crystallizer is operated isothermally with a negligible mass deposition in nucleation and no generation of supersaturation, the supersaturation balance **Eq.5.1** at any time in a batch operation is given by **Eq.6.4**.

$$R = -\frac{1}{A_r} \frac{d\Delta C}{dt} \quad (6.4)$$

Using **Eqs.6.2-6.4** and **5.3-5.6** values of growth rate, supersaturation, average size and slurry voidage at a particular time may be obtained.

The growth rate kinetics can be estimated by a number of methods from the desupersaturation curve obtained during batch-seeded isothermal experiments. The simplest of these methods was developed by Garside et al., 1982 and involves using the first two derivatives of a second order polynomial fitting of an initial portion of a desupersaturation curve at time zero. It is assumed in the method that the concentration change is due only to crystal growth with no nucleation occurring. Using this analysis, the power g and constant k_g of the crystal growth rate equation of **Eq.3.28** can be obtained from the equations of **6.5** and **6.6**.

$$g = \frac{2F\Delta C_0}{3\rho L_0 \bar{A}_{T0}} + \frac{\Delta C_0 \Delta \ddot{C}_0}{\Delta \dot{C}_0^2} \quad (6.5)$$

$$K_g = \frac{-\Delta \dot{C}_0}{\bar{A}_{T0} \Delta C_0^g} \quad (6.6)$$

Where ΔC_0 is the supersaturation at time zero, $\Delta \dot{C}_0$ and $\Delta \ddot{C}_0$ are the first and second derivatives of the desupersaturation curve at time zero, respectively. F is the shape factor ratio and equals to β/α . $\bar{L}_0$ represents the average size of the seeds, A_{T0} denotes the surface area of the seeds at time zero.

The derivatives $\Delta \dot{C}_0$ and $\Delta \ddot{C}_0$ are usually obtained by fitting the desupersaturation curve to the 2nd order polynomial form of **Eq.6.7**

$$\Delta C = a_0 + a_1 t + a_2 t^2 \quad (6.7)$$

So that $\Delta C_0 = a_0$, $\Delta \dot{C}_0 = a_1$, and $\Delta \ddot{C}_0 = 2a_2$. Although it is quite simple, the results obtained from this method are quite sensitive to measurement errors since the method relies on derivatives.

6.1.2.2 The population balance equation (PBE) modeling approach

The estimation technique is based on a model for seeded batch cooling crystallization and optimization method which minimizes the difference between experimental data and those predicted by the model. The mathematical model comprises a population balance equation for crystal size distribution and a mass balance equation which relates the total mass of crystals to the concentration change of the solution.

As mentioned in the Population Balance Equation part of the this study, for a perfectly mixed batch crystallizer of constant volume, in which crystal breakage, agglomeration and crystal growth rate dispersion are assumed to be negligible, PBE for size independent growth rate is

$$\frac{\partial n(L,t)}{\partial t} + G \frac{\partial n(L,t)}{\partial L} = 0 \quad (6.8)$$

Subject to the boundary and initial conditions:

$$n(0,t) = n^0 = \frac{B}{G^0} \quad (6.9)$$

$$n(L,0) = n_s \quad (6.10)$$

Where n_s denotes the population density distribution of the seeds, which are added at $t=0$, and G^0 is the growth rate of nuclei.

The mass balance models the solute concentration in the continuous phase. Since the solute concentration is one of the few parameters of crystallization that may be measured experimentally, the mass balance provides a connection between the model and experiment that may be used to identify kinetic model parameters for a specific system.

Under the assumption of constant volume during crystallization, the mass balance is

$$\frac{dC}{dt} = -3\rho_c k_v h_0^\infty \int_0^\infty G n L^2 dL \quad (6.11)$$

Where C is the mass of solute per mass of solvent, ρ_c is the crystal density, k_v is the volume shape factor converting L^3 to actual crystal

volume, and h is a constant factor converting solvent mass to slurry volume.

The simplified form of the energy balance for the batch crystallizer is

$$\rho V C_p \frac{dT}{dt} = -3\Delta H_c \rho_c k_v V \int_0^\infty G n L^2 dL = -UA(T - T_f(t)) \quad (6.12)$$

Where c_p is the specific heat of the slurry, ΔH_c is the heat of crystallization, U is the overall heat transfer coefficient, V is the volume of crystallizer, A is the surface area available for heat transfer, and $T_f(t)$ is the time dependent temperature of the coolant in the jacket. For this study the energy balance was not considered because the system is isothermal and no temperature change observed.

The other constitutive equations required are the nucleation rate and the growth rate given as **Eq.3.25** and **3.29**.

$$B = k_b \Delta C^b \quad (3.25)$$

$$G = k_g \Delta C^g \quad (3.29)$$

With these equations the model is completely defined. The parameters k_b , b , k_g , g are inferred from experimental data.

The PBE is solved using the method of moments. The i^{th} moment of the PBE is defined as

$$\mu_i = \int_0^\infty n(L,t) L^i dL \quad (6.13)$$

The first four moments are required for the general batch crystallizer model.

$$\frac{d\mu_0}{dt} = B \quad (6.14)$$

$$\frac{d\mu_1}{dt} = \mu_0 G \quad (6.15)$$

$$\frac{d\mu_2}{dt} = 2\mu_1 G \quad (6.16)$$

$$\frac{d\mu_3}{dt} = 3\mu_2 G \quad (6.17)$$

The initial conditions are:

$$\mu_i(0) = 0 \quad \text{for } i = 1, 2, 3, 4 \quad (6.18)$$

$$C(0) = C_0 \quad (6.19)$$

$$T(0) = T_0 \quad (6.20)$$

Numerical solution of Mefenamic acid crystallization kinetics can be investigated and by using the mass balance, the energy balance and the moments of PBE, the model can be solved. MathCAD is the one of ordinary differential equation solver. This routine has an advantage of solving stiff systems.

Optimization provides an intuitive approach to parameter estimation for non-linear batch systems. The approach uses a nonlinear optimization routine to generate successive guesses of the kinetics parameters. For each guess, the dynamic model equations describing the process are solved and the resulting measurement predictions are compared with data according to an optimization criterion. Generally, the

criterion is a measure of the prediction errors. The model equations are solved implicitly by a non-linear equation integrator each time the optimizer provides a parameter guess.

The optimal sets of parameters are found by solving the nonlinear optimization problem:

$$\min_p \Phi(\dot{C}, C; p) \quad (6.21)$$

In which

$$p^T = [g, k_g, b, k_b] \quad (6.22)$$

Where $\dot{C}$ is solute concentration calculated from the model.

The objective function, Φ , is formulated as the summed squared error between experimental measurements, C , and the model predictions, $\dot{C}$. The objective function in terms of the least square estimations takes the form:

$$\Phi = \sum_{i=1}^m (\dot{C}_i - C_i)^2 \quad (6.23)$$

Where m is the number of experimental time records.

The crystallization kinetics of MA were calculated by using two different method, the desupersaturation curve technique with Garside solution and PBE modeling approach, the more detailed information and experimental procedure is given the experimental work and results sections.

7.0 EXPERIMENTAL WORK

The polymorphic form, crystal shape and crystal size distribution are the main criteria for the quality of the crystal product. The size and shape of the crystals have a strong effect on the processability. Shape can also be important in pharmaceuticals wherein different crystal faces have different dissolution rates and variable bioavailability.

In most cases, the specifications of a drug include identification and purity, but the physicochemical properties are also necessary for drug development in pharmaceutical industry. Since the polymorphic content of pharmaceuticals is affected on the development of drugs, such as dissolution rate and bioavailability, characterization of polymorphic forms is very important for design of pharmaceuticals.

In this section, the experimental study on the characterization of MA polymorphs in different solvents, the crystal size distribution of MA-EA solution and the crystallization kinetics of MA are described. This section also includes the experimental set-ups.

7.1 Determination of Polymorphic Structure of Mefenamic Acid

Mefenamic acid obtained from the Aldrich Chemical Co. with purities >99% was used in the present study. To analyze the polymorphic forms of mefenamic acid, different solutions of mefenamic acid were prepared with high performance liquid chromatography (HPLC) grade solvents of N, N-dimethylformamide (DMF), acetone, N, N-dimethylacetamide (DMA), and Dimethylsulfoxide (DMS).

Firstly, four samples of 0.5g, 1g, 2g and 3g mefenamic acid in 20ml of DMF were prepared for Form II and three samples of 100mg, 200mg, and 500mg mefenamic acid in 20ml of A were made for Form I.

These samples were put in a sonic-heater within a water bath. The samples were heated and mixed by vibration. Nearly all samples dissolved when the water temperature reached to 50°C. After observing the complete solution, the sonic-heater was turned off and samples were left in the water bath overnight and allowed for slow cooling.

At the beginning of the experiment, the water temperature was measured again. It was 25 °C. Since there was no published solubility data of MA in DMF and A, reasonable results were not obtained from all solutions. After this trial, 1g of MA in DMF and 500mg of MA in A were chosen as suitable to analyze. The crystals obtained from other samples, for example with higher concentration than these solutions, agglomerated and did not have good quality crystals to analyze. For this purpose, 2g of MA in DMF were examined and the result of the crystal quality was reasonable. In other solutions of lower concentrations (0.5g and 1g), no crystals were observed so it can be concluded that these solutions were either saturated or undersaturated.

Different solutions were prepared with DMA and DMS. As solution with A and DMF, no published data in literature for solubility of MA in DMA and DMS were found. So firstly solutions of 0.5g, 1g, 2g, and 3g of MA in 20 ml of DMA and DMS were prepared by the same procedure as mentioned above. But after waiting for a night, there were no crystals observed. So these concentrations were not enough to reach the supersaturation. For other trial solutions 4g and 5g of MA in 20 ml of DMA and DMS were prepared.

The complete solubility was observed at 65° C, which was a higher value than the first experiment. In this experiment, different from the first experiment with A and DMF, two types of cooling are examined first slow cooling, the sample is left in the water bath of the sonic heater as in the first experiment and allowed to cool and second the sample is removed from the sonic heater and allowed to cool outside allowing the evaporation of the solvent.

The suitable amounts of MA and solvents and the polarity of solvents for analysis are summarized in **Table 7.1**. The scanning electron microscope, Raman microscope and X-ray diffraction were used to analyze the MA crystal samples obtained.

Table 7.1 The amount of mefenamic acid and solvents for experimental analysis

MA Solution Amount	Solvent Polarity
1g MA+20ml DMF	6.4
500mg MA + 20ml A	5.1
4g MA+ 20ml DMA	8.3
4g MA + 20ml DMS	7.2
500mg MA+ 20ml EA	4.4

Raman microscope is not enough to recognize the forms of mefenamic acid therefore X-ray Diffraction should be used. All samples firstly were tested by Raman spectroscopy and then X-ray powder diffraction was used for exact identification of polymorphic forms of mefenamic acid recrystallized from different solvents. All spectrum results were given in Results section.

7.2 Crystal Size Distribution (CSD) Measurements

After the characterization of MA, the crystal size distribution of MA-EA solution was investigated. For this purpose the Lasentec FBRM was used. The solubility data was obtained from literature as $2.755 \text{ g}_{\text{sol}}/100 \text{ g}_{\text{solv}}$ at 50°C .

A mixture was prepared with 0.804g MA and 29.2g EA. This mixture was poured into the reactor of the Lasentec. After the stirrer and probe were mounted, the experimental data were collected by the computer on-line. For the first experiment the mixture was mixed and heated for 10 min to 50°C . When it reached 50°C the mixing continued for another 30 min to assure complete mixing was achieved, the solution was cooled at a rate of $1^{\circ}\text{C}/\text{min}$ to 20°C . These procedures can be followed on the computer. At the end of 140 min, the crystal size distribution data were obtained.

The experiment was repeated two more times. In the second experiment the solution was cooled to 35° by $0.5^{\circ}\text{C}/\text{min}$. The cooling rate for the last experiment was again $0.5^{\circ}\text{C}/\text{min}$ but the end temperature 20°C . During the experiment, stirring rate was constant. All experimental steps and crystallization process were watched on-line on the computer and the results were saved. The final product CSD, the mean length and the crystal density as a function of time were observed during experiments. The graphical representations were illustrated in Result section.

7.3 Estimation of concentration profile

In the present study, the crystallization kinetic parameters of Mefenamic Acid were determined by two different methods, Garside and the PBE modeling methods. For both methods, the concentration profile was necessary. So the experimental set-up was prepared for estimation of concentration profile of MA-EA solution in isothermal batch cooling vessel (crystallizer).

A 250 ml saturated MA-EA solution was prepared at 30°C in a batch vessel with a jacket to control the temperature. The vessel equipped with a stirrer. By stirring, a clear solution was obtained. After that, the temperature of the solution was lowered to 25°C to make the solution supersaturated. The solution was remained clear with no crystals present at the lower temperature and a supersaturated solution was obtained. Size distribution of seed crystals were measured by Lasentec FBRM for calculations and added to the solution. 1% seed means that 0.0034g of seed crystal was used. Since the solution was supersaturated, the crystals grew. So, a decline in the concentration of the solution was measured as a function of time.

The 2 ml sample was taken every minute through the experiment. These samples were filtered and the concentration change of the solution was measured by a densitometer. It was very difficult to measure the density because of the manual feeding of the samples into the machine. Air bubble occurrence had a negative affect on the measured density values, so the sample should be introduced without any air bubble.

The density determination was based on measuring the period of oscillation of vibrating U-shaped sample tube, which was filled with sample liquid.

The measuring principle of the instrument was based on the change of the natural frequency of a hollow oscillator when filled with different liquids or gases. For the determination of the densitometer constant, k , in **Eq.7.1**, two calibration measurements of samples of know density were necessary. **Eq.7.1** represents the difference of densities of two samples as follow;

$$\rho_1 - \rho_2 = k(TP_1^2 - TP_2^2) \quad (7.1)$$

For estimation of density of an unknown sample **Eq.7.1** is arranged as **Eq.7.2**.

$$\rho_x = k(TP_x^2 - TP_{water}^2) + \rho_{water} \quad (7.2)$$

To determine the densitometer constant, k , measurements were done at 30°C with air and the distilled water. After a sufficient time for the proper temperature equilibration, the period TP was read for the sample tube filled with air. Double distilled water was now introduced by means of the supplied syringe into the tower entrance part of the sample tube. The filling of the sample tube can be observed when the illumination for the sample tube is turn on. Temperature equilibration could be conveniently followed over several read out cycles the TP-value becomes constant ± 1 , indicating complete temperature equilibration.

TP values obtained for air and water and by using **Eq.7.1**, the k -value was calculated. The calculations were given in the Results section.

Table 7.2 was represented the data required for calculations. This table also included the literature data for further calculation of determination of crystallization kinetics of MA

Table 7.2 Literature data for calculations of densitometer constant and kinetics

MW_{MA} , kg/kmol	241.29
MW_{EA} , kg/kmol	88.1
$\rho_{EA@ 25^{\circ}C}$, g/cm ³	0.902
$\rho_{air@ 30^{\circ}C}$, g/cm ³	0.00117
$\rho_{water@ 30^{\circ}C}$, g/cm ³	0.99565
F	4.2
P_{MA} , g/cm ³	1.1743
L_0 , μm	65.53
k_v	10
h	1.2

For conversion of the density values to the concentration, a calibration curve was necessary. In order to draw a calibration curve, three samples were prepared with different known concentrations as given in **Table 7.3**. The calculated density values and calibration curve were presented in the Results section.

Table 7.3 Concentration values of MA-EA solution for calibration curve

Weight of MA (g)	Weight of EA (g)	Concentration (g _{MA} /g _{EA})
0.18	17	0.010588
0.16	17	0.009412
0.14	17	0.008235

8.0 RESULTS

This study included two parts as experimental and modeling study. In the experimental study, the characterization and identification of polymorphic behavior of MA, the CSD measurement of MA crystals in MA-EA solution and the estimation of concentration profile for calculations of crystallization kinetic parameters of MA were given. In the modeling study, the nucleation and growth kinetic parameters of MA were determined. So the results section was divided in two sub-sections as the experimental results and modeling results.

8.1 Experimental Results

8.1.1 Polymorphic structure of Mefenamic Acid

The scanning electron micrographs (SEM) of MA recrystallized from EA are presented in **Figure 8.1**. They show needle-shaped flat particles. The smaller particles are agglomerated, and some of them adhered to larger ones. All particles are sharp edged and seem to laminate. Also particles were characterized by a wide crystal size distribution.



Figure 8.1 The scanning electron micrographs of MA crystallized from EA.

Raman spectrogram of MA crystals recrystallized from EA is illustrated in **Figure 8.2**. The following figures represent the polymorphic form of the MA crystals in different solvents. There are no published Raman spectrogram results in the literature, but if they are compared with the other spectroscopic results published, it might be concluded that the crystals are in form I of mefenamic acid. In order to be confident, all results were rechecked with X-ray powder diffraction.

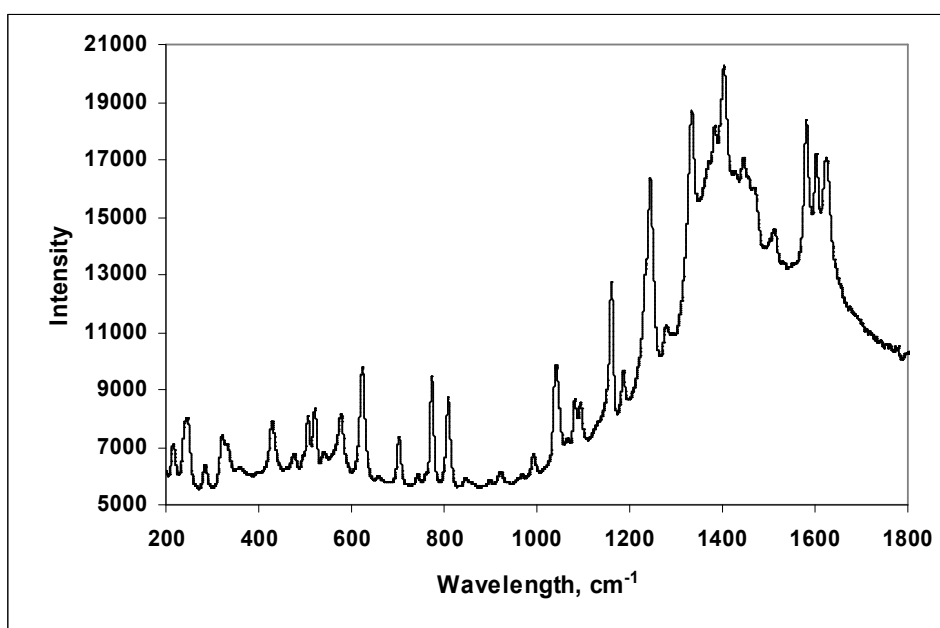


Figure 8.2 Raman spectrum for Form I of MA crystals recrystallized from EA.

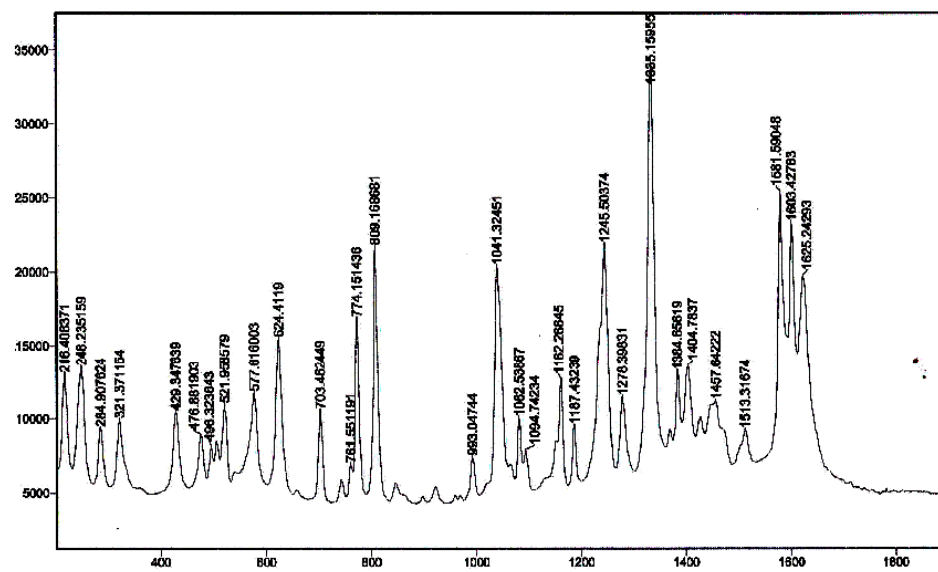


Figure 8.3. Raman spectrum for Form I of MA crystals recrystallized from Acetone.

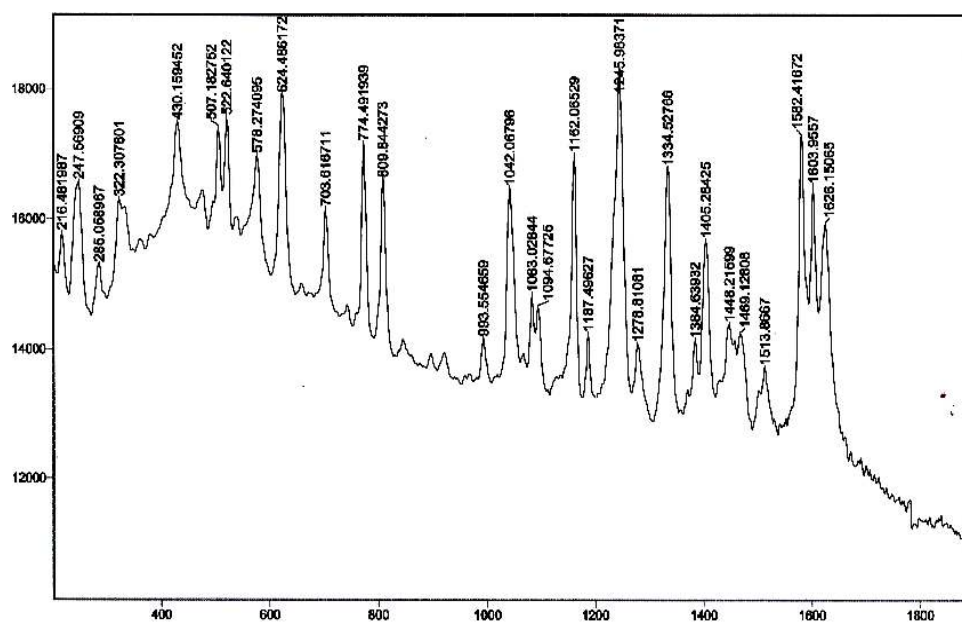


Figure 8.4. Raman spectrum for Form I of MA crystals recrystallized from DMS by slow cooling

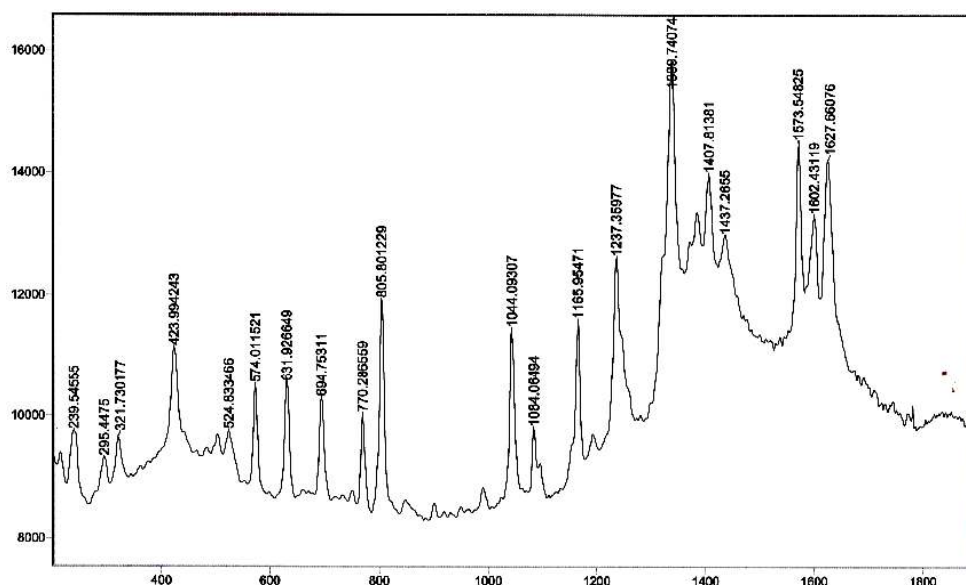


Figure 8.5. Raman spectrum for Form I of MA crystals recrystallized from DMS by fast cooling.

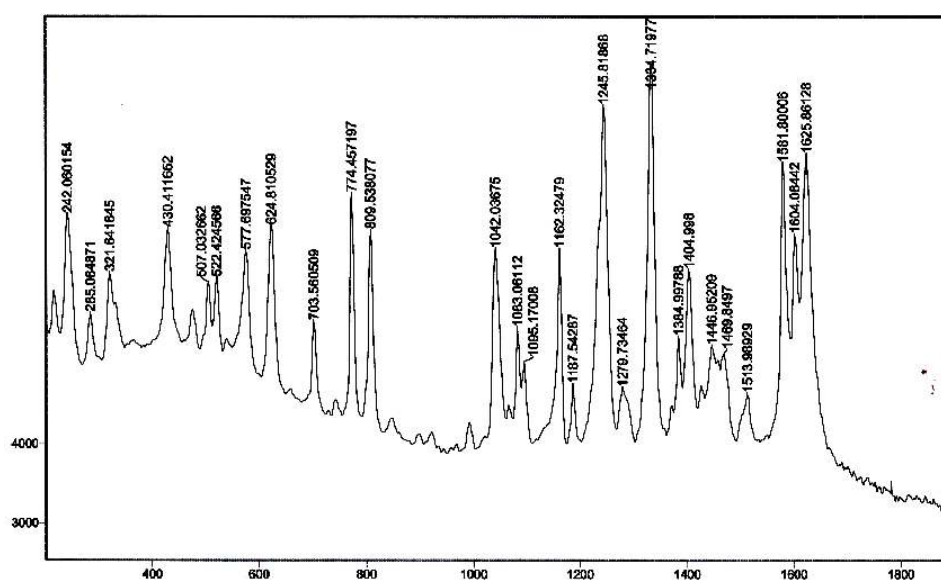


Figure 8.6. Raman spectrum for Form I of MA crystals recrystallized from DMA by slow cooling.

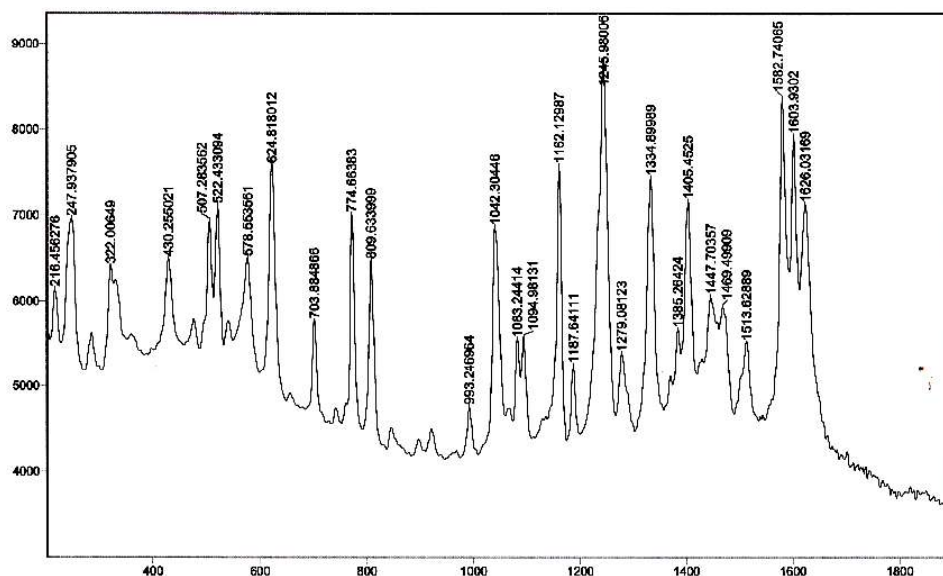


Figure 8.7. Raman spectrum for Form I of MA crystals recrystallized from DMA by fast cooling.

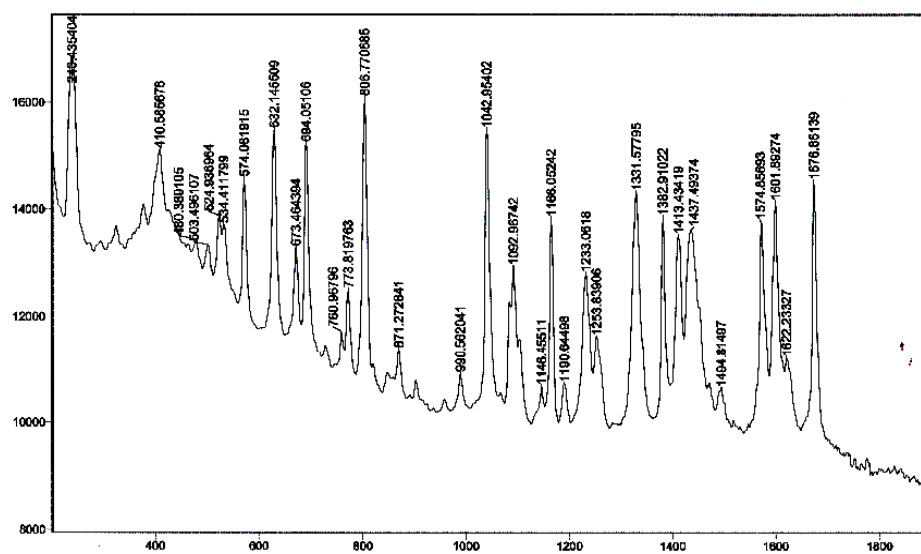


Figure 8.8. Raman spectrum for Form II of MA crystals recrystallized from DMF.

Figures 8.9- 8.15 represent the X-ray powder diffraction results of MA recrystallized from Acetone, DMF, DMS, DMA, and EA.

MA crystals obtained from these solvents compared with the literature data obtained by Aguiar and Zelmer, 1969. If the diffractogram has a characteristic peak between 5 and 10°, it means that the crystals are in Form I otherwise they are in Form II. The polymorphic behavior of MA crystals in these solvent were summarized in **Table 8.1**.

The relative intensity values and °2θ angles for the peaks obtained in powder X-ray diffractograms are given in **Table 8.2**.

Table 8.1 The polymorphic behavior of MA crystals in different solvents

Solvents	Polymorphic Structure
Acetone	Form I
DMS	Form I
DMA	Form I
EA	Form I
DMF	Form II

Table 8.2 The relative intensity values and $^{\circ}2\theta$ angles for the peaks obtained in powder X-ray diffractograms

$^{\circ}2\theta$	d(Å)	A	DMF	DMA_F	DMA_S	DMS_F	DMS_S	EA
6.33	13.95	100.00	11.46	100.00	100.00	100.00	100.00	100.00
13.66	6.48	-	27.79	-	-	-	-	-
13.81	6.41	56.25	-	44.03	33.64	35.41	34.88	7.82
14.33	6.18	26.95	44.83	35.37	25.23	30.95	26.30	-
15.16	5.84	30.99	12.99	31.77	28.41	33.93	23.86	-
15.89	5.57	45.44	49.44	46.19	32.73	37.80	36.50	6.31
16.86	5.25	16.40	13.27	-	22.50	28.27	12.74	-
17.97	4.93	-	100.00	-	-	-	-	-
21.40	4.15	82.16	11.87	59.93	55.68	52.68	53.30	15.00
26.42	3.37	62.50	12.85	50.53	50.00	49.69	50.28	6.97
27.84	3.20	23.05	12.29	23.11	23.63	25.30	19.81	-
31.37	2.85	17.32	15.23	22.03	12.51	19.64	11.81	-
32.01	2.79	16.37	10.33	21.29	15.23	16.07	10.31	-
32.99	2.71	11.20	8.10	20.94	10.91	16.96	7.53	-

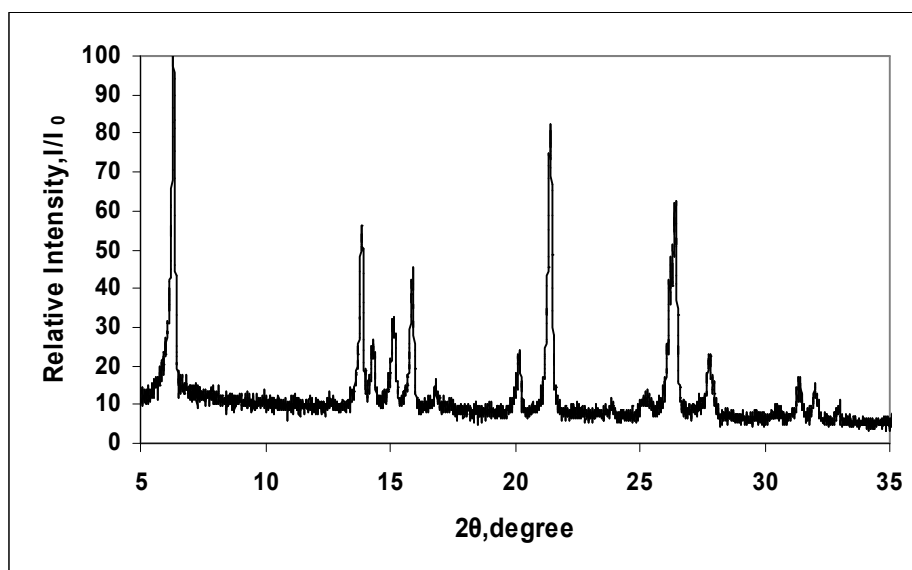


Figure 8.9 Powder X-ray pattern of Form I of MA crystals recrystallized from Acetone.

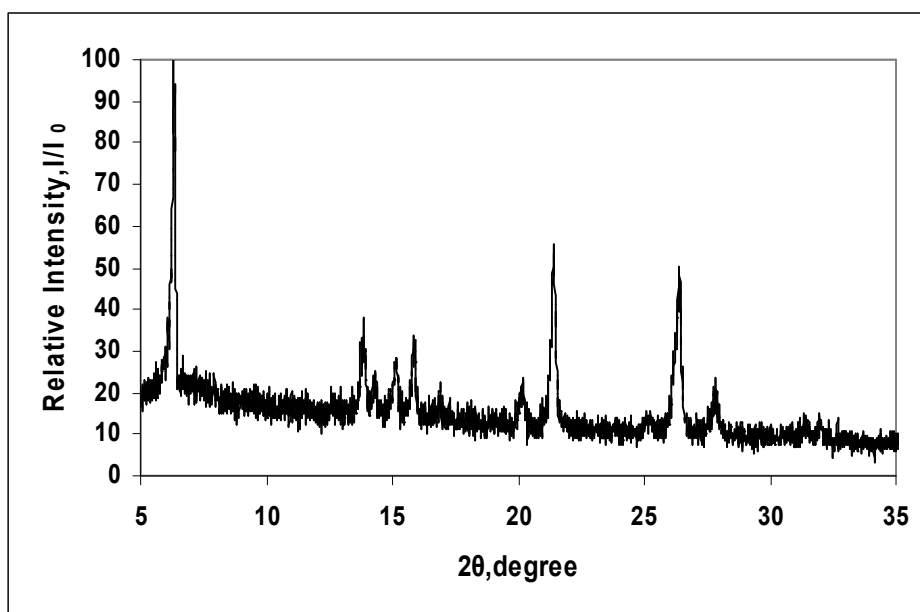


Figure 8.10 Powder X-ray pattern Form I of MA crystals recrystallized from DMA slow cooling.

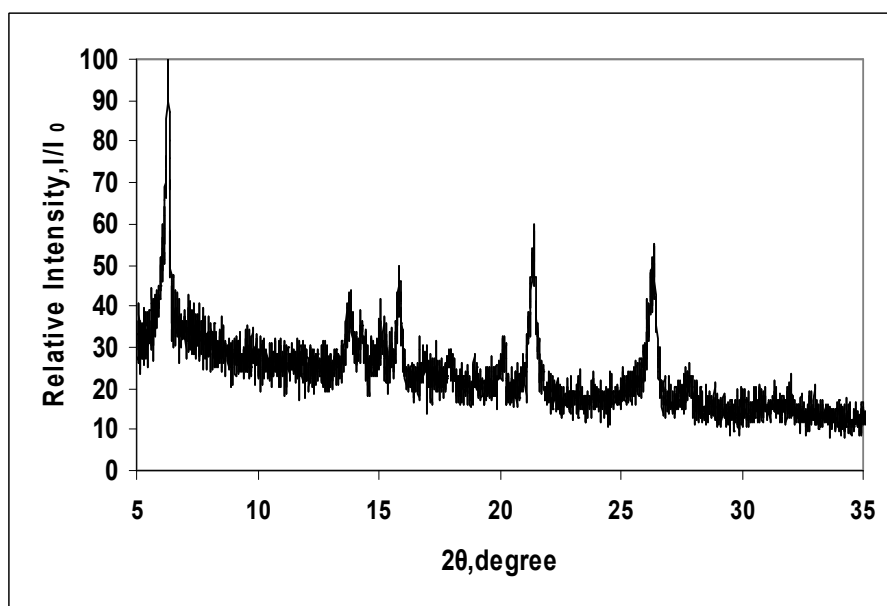


Figure 8.11 Powder X-ray pattern Form I of MA crystals recrystallized from DMA fast cooling.

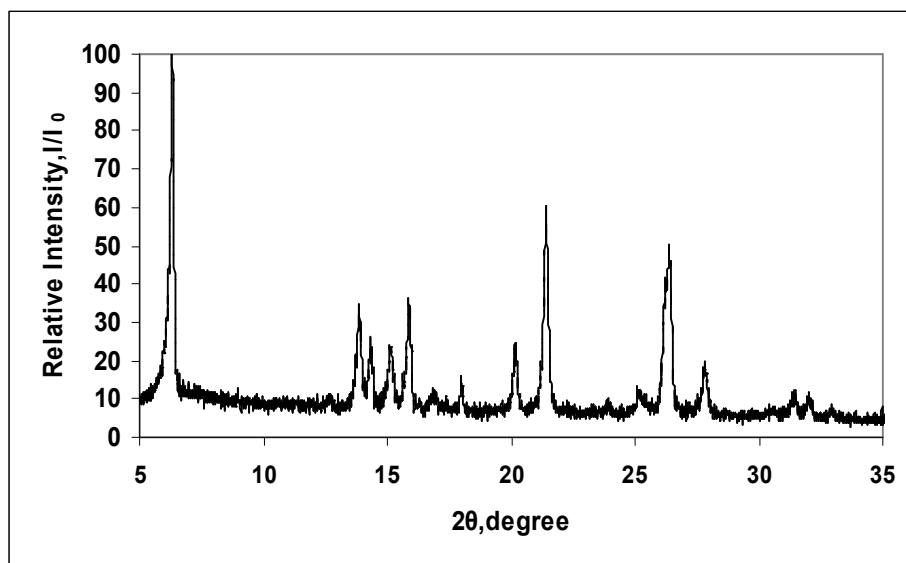


Figure 8.12 Powder X-ray pattern Form I of MA crystals recrystallized from DMS by slow cooling.

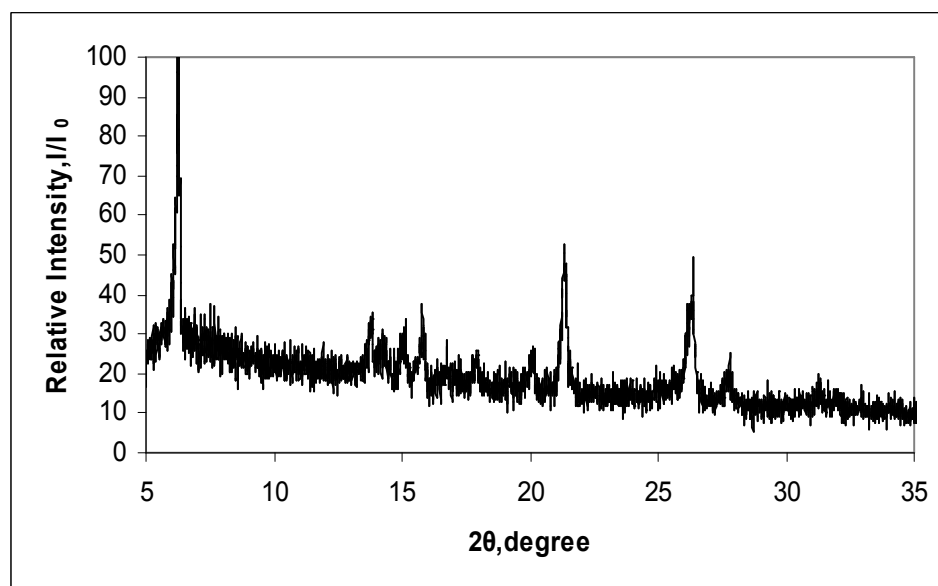


Figure 8.13 Powder X-ray pattern Form I of MA crystals recrystallized from DMS by fast cooling.

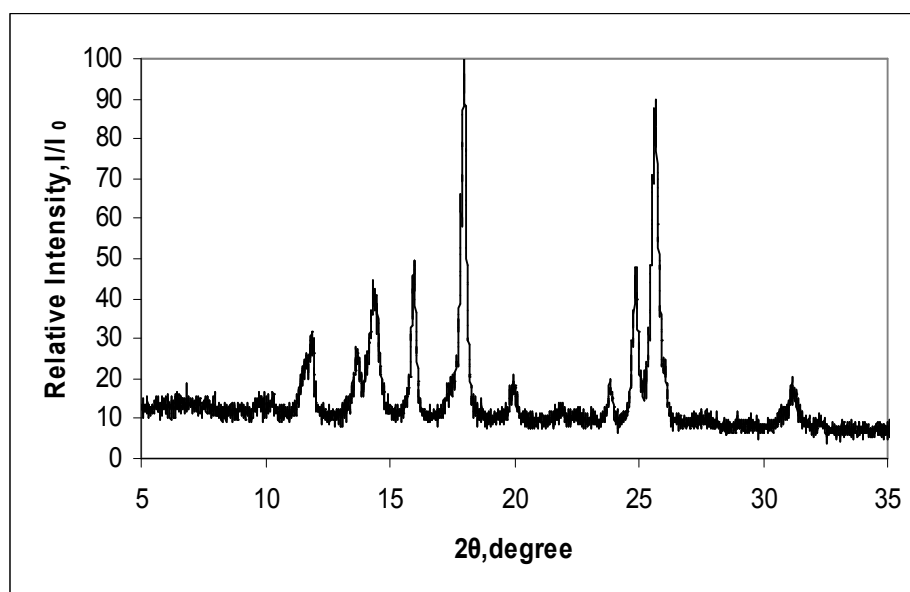


Figure 8.14 Powder X-ray pattern of Form II of MA crystals recrystallized from DMF.

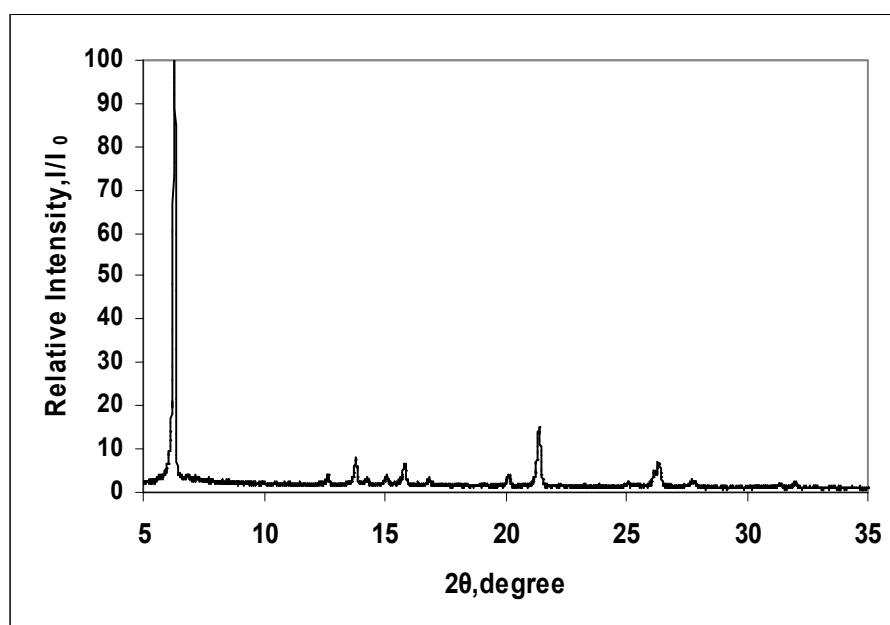


Figure 8.15 Powder X-ray pattern Form I of MA crystals recrystallized from EA.

8.1.2 The crystal size distribution of Mefenamic Acid

The CSD results of MA in EA solution obtained with different experiments were given in **Figure 8.16**. In the first experiment, the cooling rate was 1K/min and the end temperature for the crystallization was 20°C. The results were reasonable but the crystal size distribution curve wider than the last experiment. The difference was not very big but if the curve was wide this showed the crystal size distribution is in a large range. So it could be a problem during filtration and drying as mentioned earlier. The result of second experiment (0.5 K/min and $T_{\text{end}}=35^{\circ}\text{C}$) was not uniform; it could be caused of insufficient probe signals or impurities.

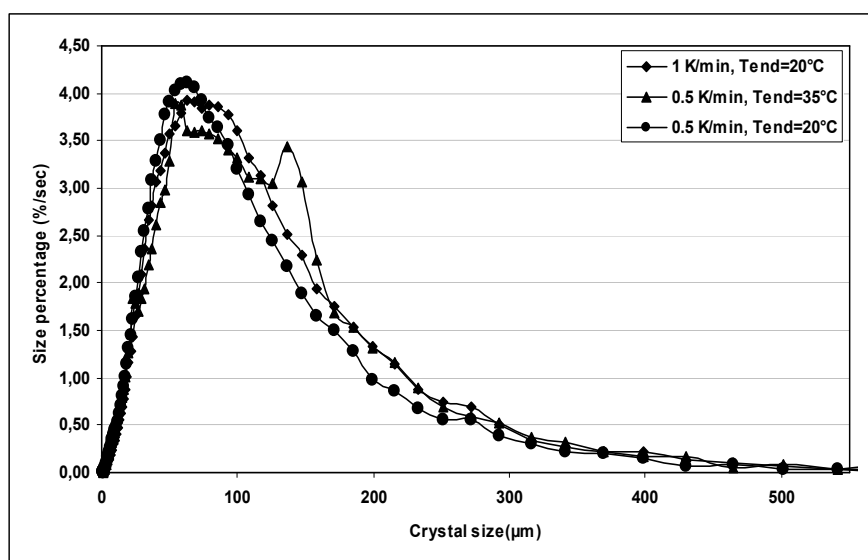


Figure 8.16 CSD results of MA and ethyl acetate solution with different end temperatures

Figure 8.17-8.19 represented the mean length and the crystal density of MA crystals in different crystal size intervals during the crystallization for three experiments, respectively. In the first experiment, the mean length changed between 50-90 microns. During crystallization,

while the crystal density of 1-50 microns of MA was decreasing as a function of time, the crystal density of 40-100 microns and 100-315 microns of MA crystal increased.

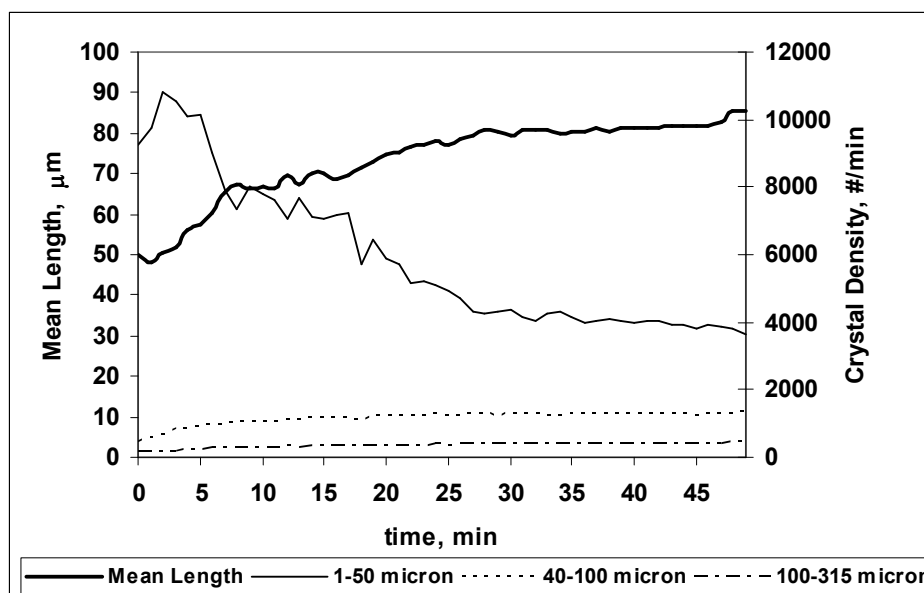


Figure 8.17. The mean length and the crystal density of MA in the first experiment

In the second and third experiments, the mean length changed between 10-90 microns. The crystal density of 1-5 microns, 5-50 microns and 50-215 microns increased up to 7 min and after that while the crystal density of 1-5 microns and 5-50 microns were decreasing 50-215 microns crystal density increased.

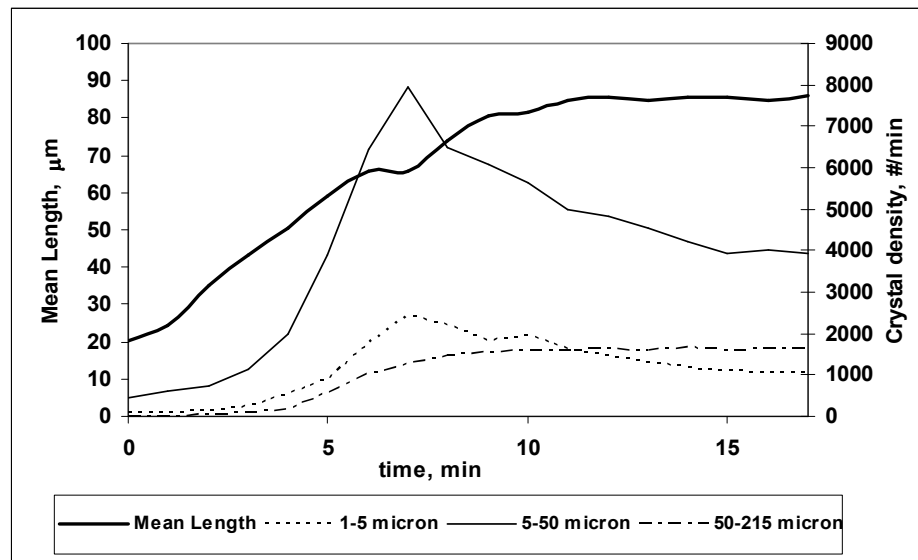


Figure 8.18. The mean length and the crystal density of MA in the second experiment

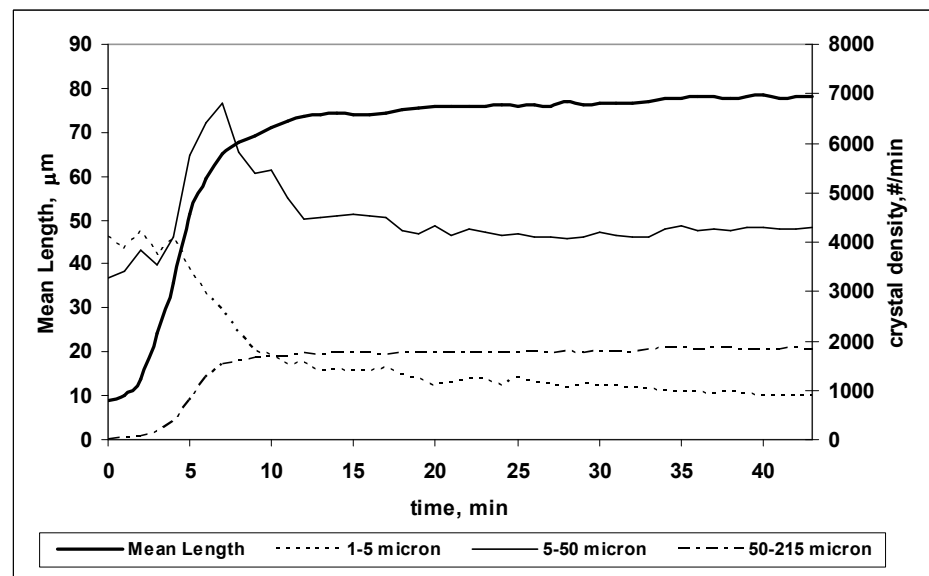


Figure 8.19. The mean length and the crystal density of MA in the third experiment

8.1.3 Estimation of concentration profile

To calculate the densitometer constant, k , the following calculations were done.

$$TP_{air} = 1.83085 \quad \Rightarrow \quad TP_{air}^2 = 3.363868$$

$$TP_{water} = 2.550513 \quad \Rightarrow \quad TP_{water}^2 = 6.505117$$

$$\rho_{air} - \rho_{water} = k(TP_{air}^2 - TP_{water}^2)$$

$$0.00117 - 0.99565 = k(3.363868 - 6.505117) \Rightarrow k = 0.316589$$

After obtaining the constant, k , for the calibration curve, three sample solutions were prepared with designated amounts on **Table 8.3**. By using **Eq.7.2** the solution densities were calculated.

$$\rho_{solution} = k(TP_{solution}^2 - TP_{water}^2) + \rho_{water}$$

$$\rho_{solution} = 0.316589(6.185492 - 6.505117) + 0.99565$$

$$\Rightarrow \rho_{solution} = 0.894461 \text{ g/cm}^3$$

Table 8.3 Measured period values and calculated density values for MA-EA solution for calibration curve

TP _{solution}	TP _{solution} ²	ρ _{solution}
2.487065	6.185492	0.894461
2.486788	6.184115	0.894024
2.486363	6.182001	0.893355

By using the density values on **Table 8.4**, to convert the density to the concentration, the calibration curve was drawn as **Figure 8.20**.

Table 8.4 Concentrations of MA-EA sample solutions for the desupersaturation curve

Time (min)	TP _{sample}	TP ² _{sample}	ρ_{sample} (g/cm ³)	Concentration (g _{sol} /g _{solv})
0	2.491867	6.209401	0.9020	0.07622
1	2.491638	6.208260	0.9017	0.07058
2	2.491460	6.207373	0.9014	0.06634
3	2.491172	6.205938	0.9009	0.05978
4	2.491017	6.205166	0.9007	0.05640
5	2.490841	6.204289	0.9004	0.05268
9	2.490474	6.202461	0.8998	0.04534
10	2.490450	6.202341	0.8998	0.04488
11	2.490748	6.203826	0.9003	0.05076
12	2.490667	6.203422	0.9001	0.04912
13	2.490585	6.203014	0.9000	0.04750
15	2.490106	6.200628	0.8993	0.03855
16	2.489917	6.199687	0.8990	0.03529
17	2.489867	6.199438	0.8989	0.03445
18	2.489846	6.199333	0.8988	0.03410
19	2.489837	6.199288	0.8988	0.03395
20	2.489506	6.197640	0.8983	0.02872
21	2.489501	6.197615	0.8983	0.02864
22	2.489464	6.197431	0.8982	0.02808
23	2.489262	6.196425	0.8979	0.02515
24	2.489288	6.196555	0.8980	0.02552
26	2.489528	6.197750	0.8983	0.02905
29	2.489023	6.195235	0.8975	0.02190
30	2.488998	6.195111	0.8975	0.02158
31	2.489054	6.195390	0.8976	0.02231
32	2.489097	6.195604	0.8977	0.02288
34	2.488711	6.193682	0.8971	0.01803
35	2.488730	6.193777	0.8971	0.01825

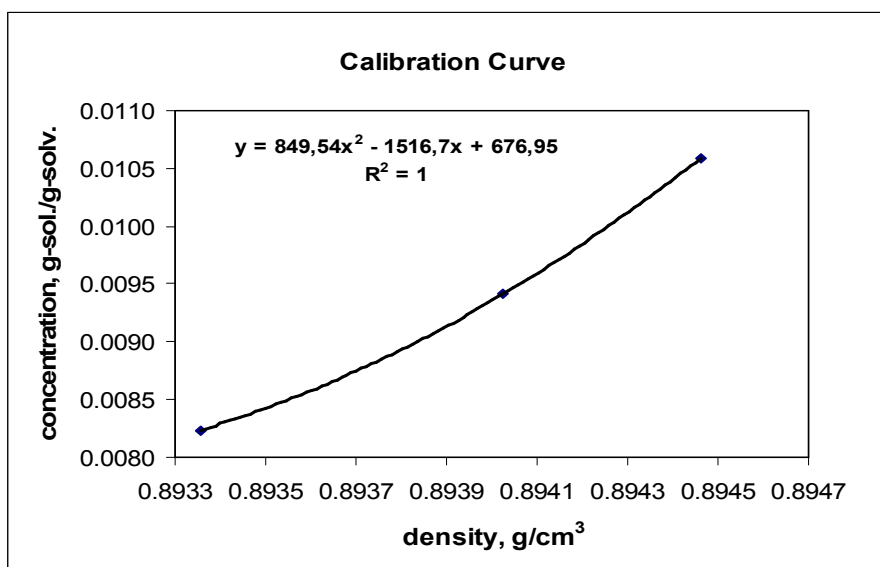


Figure 8.20 Calibration curve for MA-EA solution

8.2 Modeling Results

8.2.1 Garside solution

As mentioned previously Garside Method can be used for rough estimations of the crystallization kinetic parameters. By using the calibration curve (See **Figure 8.20**), the concentration of MA-EA solution were calculated and given as **Table 8.4** previously. The desupersaturation curve was drawn and a second order line fitted to the experimental data as illustrated in **Figure 8.21**.

The simplest method of Garside, 1982 was used for the calculations of the crystal growth rate constant and power of MA crystallization process.

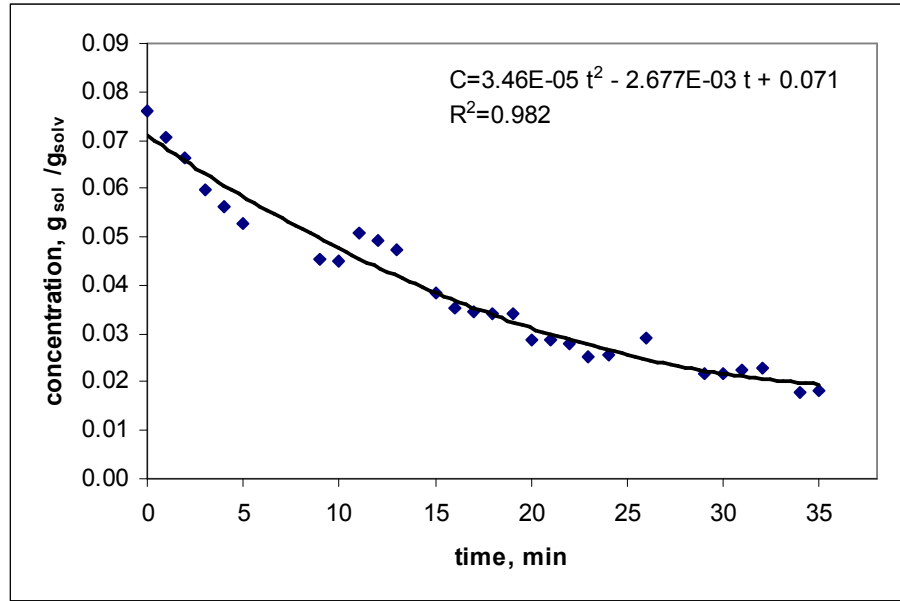


Figure 8.21 Desupersaturation curve for MA-EA solution at 25°C

For Garside solution the crystal growth rate power, g , was assumed as 1, 2, 2.5, 3, and 3.5 and all calculation was repeated in MathCAD. Firstly, experimental concentration (See **Table. 8.4**) values introduced to the program. A second order line equation as a function of time was defined as **Eq.8.1** and for fitting an optimization problem was solved to the MathCAD. This function was expressed as **Eq.8.2** and this objective function was minimized.

$$C(t_{\text{exp}}, a_0, a_1, a_2) = a_0 + a_1 t_{\text{exp}} + a_2 t_{\text{exp}}^2 \quad (8.1)$$

$$SSE(a_0, a_1, a_2) = \sum (C_{\text{exp}} - C(t_{\text{exp}}, a_0, a_1, a_2))^2 \quad (8.2)$$

Initial guess for parameters,

$$a_0 = 0, \quad a_1 = 0, \quad a_2 = 0 \quad \text{and} \quad SSE(a_0, a_1, a_2) = 0$$

And a_0 , a_1 , and a_2 values were calculated by MathCAD. After that the $\bar{A}_{T0}$ value was calculated by assuming different g values. For each assumptions, $\bar{A}_{T0}$, the growth rate constants, K_g and k_g was given on **Table 8.5**. In the following calculations, the growth rate constants K_g and k_g were calculated for g equaled to 1.

$$\Delta C = a_2 t^2 + a_1 t + a_0$$

$$\Delta C = 3.46 \times 10^{-5} t^2 - 2.677 \times 10^{-3} t + 0.071$$

$$\Delta C_0 = a_0 \Rightarrow \Delta C_0 = 0.071 g_{sol} / g_{solv}$$

$$\Delta \dot{C}_0 = a_1 \Rightarrow \Delta \dot{C}_0 = -2.677 \times 10^{-3} g_{sol} / g_{solv}$$

$$\Delta \ddot{C}_0 = 2a_2 \Rightarrow \Delta \ddot{C}_0 = 2 \times 3.46 \times 10^{-5} = 6.92 \times 10^{-5} g_{sol} / g_{solv}$$

Firstly, the crystal growth rate power, g , of MA was assumed as 1 and in the further calculation g was assumed as 2, 2.5, 3, and 3.5 and the results were given on the **Table 8.5**.

$$g = \frac{2F\Delta C_0}{3\rho L_0 \bar{A}_{T0}} + \frac{\Delta C_0 \Delta \ddot{C}_0}{\Delta \dot{C}_0^2}$$

$$\Rightarrow 1 = \frac{2 \times 4.2 \times 0.071}{3 \times 1.1743 \times 65.53 \times \bar{A}_{T0}} + \frac{0.071 \times 6.92 \times 10^{-5}}{(-2.677 \times 10^{-3})^2}$$

$$\Rightarrow \bar{A}_{T0} = 25.735 \text{ cm}^2 / g_{solv}$$

$$K_g = \frac{-\Delta C_0}{A_{T0} \Delta C_0^g}$$

$$K_g = \frac{-(-2.677 \times 10^{-3})}{25.735 \times 0.071} = 1.468 \times 10^{-3} \text{ g/cm}^2 \text{ min} [g_{sol} / g_{solv}]$$

$$K_g = 3 \frac{\alpha}{\beta} \rho k_g \Rightarrow k_g = \frac{F K_g}{3 \rho} = \frac{4.2 \times 1.468 \times 10^{-3}}{3 \times 1.1743}$$

$$k_g = 2.055 \times 10^{-3} \text{ cm/min} [g_{sol} / g_{solv}]$$

Table 8.5 The calculated crystal growth rate constants for different g values.

g	$\bar{A}_{T0},$ (cm ² /g _{solv})	K _g , [g/cm ² min(g _{sol} /g _{solv})]	k _g , [cm/min(g _{sol} /g _{solv})]
1	25.735	1.468x10 ⁻³	2.055x10 ⁻³
2	12.879	0.041	0.029
2.5	10.305	0.194	0.109
3	8.589	0.876	0.409
3.5	7.363	3.839	1.536

Linear and mass growth rate of MA crystals were illustrated on the **Figures 8.22** and **8.23**, respectively. For linear growth rate, while the g value was increasing, there was a decrease in the linear growth rate. Also during crystallization time, the linear growth rate was decreasing because of the decrease in the concentration difference.

In the mass growth rate in 5 min. interval while g value was increasing the mass growth rate increasing but after 5 min. this changed oppositely. It means that when the g value increased a decrease seen in the mass growth rate.

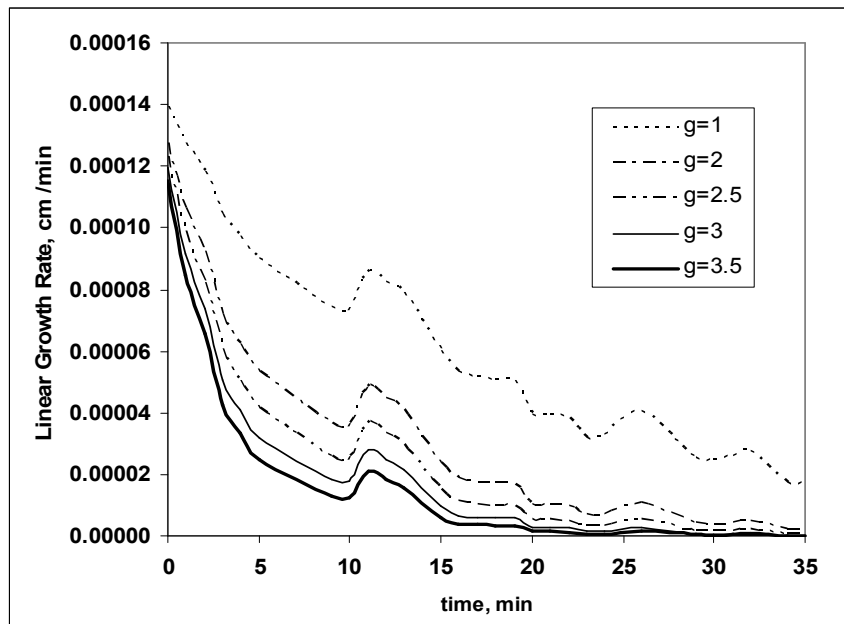


Figure 8.22 The linear growth rate change for different g values.

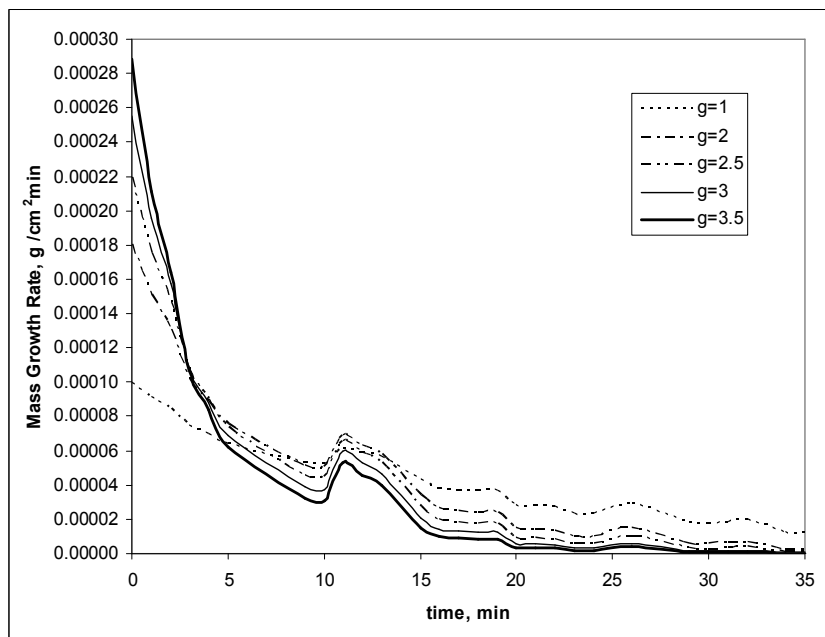


Figure 8.23 The mass growth rate change for different g values

8.2.2 The PBE modeling approach for seeded and unseeded crystallization

As mentioned previous section PBE modeling approach includes the population balance equation, the mass balance and the energy balance. The PBE can be solved different methods, in this study the method of moments was chosen. Ordinary differential equations and algebraic equations of this model were solved in the optimization problem. For solutions MathCAD was used.

The mass balance equation (**Eq.6.11**) was defined as **Eq.8.3** and the moments of equation of PBE (**Eq.6.14-6.17**) were introduced in MathCAD as **Eq.8.4-8.7**. Since the experiment was carried out in an isothermal batch vessel, in model identification the energy balance equation was not considered in solution. **Eq.8.8** and **8.9** represented the initial and boundary conditions.

$$\frac{d}{dt} C(t) = -3\rho_c .k_v .h.k_g (C(t) - C^*)\mu_2(t) \quad (8.3)$$

$$\frac{d}{dt} \mu_0(t) = k_b (C(t) - C^*)^b \quad (8.4)$$

$$\frac{d}{dt} \mu_1(t) = K_g (C(t) - C^*)^g \mu_0(t) \quad (8.5)$$

$$\frac{d}{dt} \mu_2(t) = 2K_g (C(t) - C^*)^g \mu_1(t) \quad (8.6)$$

$$\frac{d}{dt} \mu_3(t) = 3K_g (C(t) - C^*)^g \mu_2(t) \quad (8.7)$$

In this study the PBE modeling approach was solved in two different ways as seeded and unseeded crystallization. The zeroth moment of the PBE equaled to the nucleation rate. For seeded crystallization, the nucleation was not considered. The zeroth moment taken the big values to represents the nucleation (e.g for $g=1$, $\mu_0=2.05 \times 10^5$). The initial and boundary conditions for seeded crystallization,

$$\mu_i(0) = 0 \quad \text{for } i = 1, 2, 3 \quad (8.8)$$

$$C(0) = 0.07622 \, g_{sol} / g_{solv} \quad (8.9)$$

As initial and boundary conditions for unseeded crystallization,

$$\mu_i(0) = 0 \quad \text{for } i = 0, 1, 2, 3 \quad (8.10)$$

The model solution was continued up to 35 min the end of the experimental measurements of concentration of MA. Also time interval divided to 100 parts. So the model solution was done 100 times for every minute measurement. The saturation concentration at 25°C is $0.009888 \, g_{sol} / g_{solv}$.

The optimization problem with ordinary differential equations was identified to the MathCAD as,

$$\begin{pmatrix} C \\ \mu_0 \\ \mu_1 \\ \mu_2 \\ \mu_3 \end{pmatrix} = \text{Odesolve} \left[\begin{pmatrix} C \\ \mu_0 \\ \mu_1 \\ \mu_2 \\ \mu_3 \end{pmatrix}, t, t_f, 100t_f \right] \quad (8.11)$$

$$T = 0, \frac{t_f}{100t_f} \dots t_i \text{ and } i = 0 \dots 28 \quad (8.12)$$

During concentration measurements some unreasonable data were observed and during this model approached these data were not considered so there are twenty eight i values. For the graphical representation the following equation was used.

$$C_{Model_i} = C(T_{exp_i} + 5) \quad (8.13)$$

For the solution of the optimization problem the objective function was defined as,

$$\Phi = \left[\sum_{i=1}^N (C_{exp,i} - C_{model,i})^2 \right] + \left(\frac{1}{N} \right) \left[\sum_{i=1}^N \left(\frac{C_{model,i} - C_{exp,i}}{C_{exp,i}} \right) \right] \quad (8.14)$$

As in the Garside solution the growth rate power, g , was assumed as 1, 2, 2.5, 3 and 3.5 and same growth rate constants were used. For seeded crystallization, the nucleation was eliminated and best agreement was predicted for the zeroth moment of the PBE. But for unseeded crystallization the nucleation was considered and by changing the nucleation rate constant k_b and power b , the best prediction was done. The calculated kinetic parameters for MA by MathCAD were given on **Table 8.6** and **8.7** for seeded and unseeded crystallization of MA, respectively.

The first four moments of the PBE were calculated and investigated for unseeded crystallization. **Figure 8.24** graphically showed the solution of the first four moment of the PBE of MA crystallization.

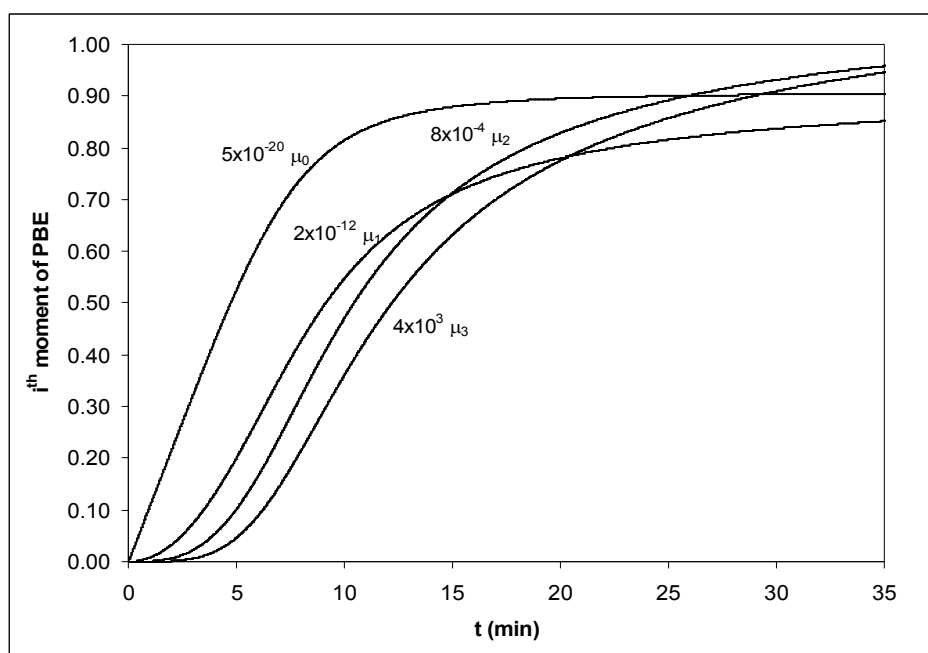


Figure 8.24 The graphical representation of the first for moment of the PBE of MA crystals.

As seen from figure, the curve increased suddenly in 5 min. and continued constantly and it meant that the nucleation occurred in 5 min. This nucleation time was added the system as seen in **Eq.7.13**.

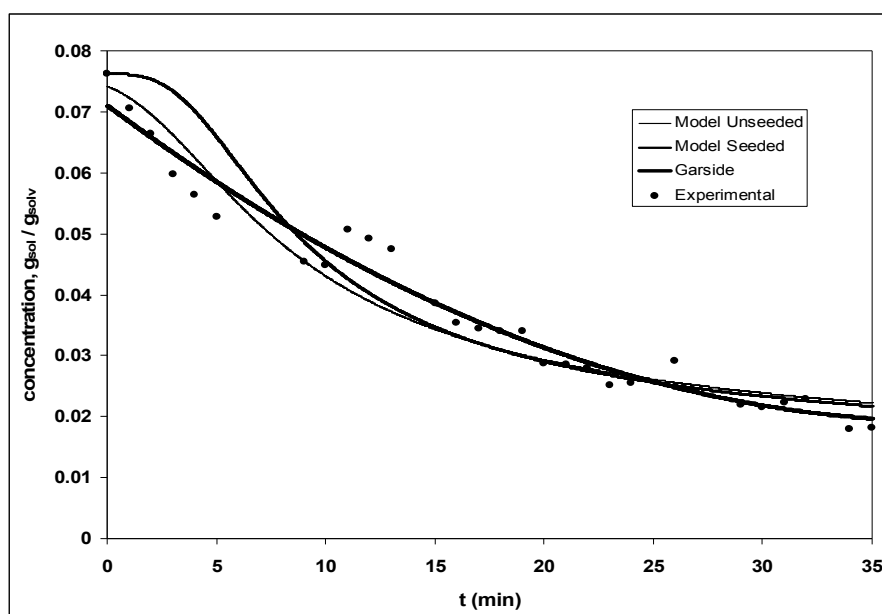
Table 8.6 The nucleation rate (μ_0) and growth rate constants of MA for seeded crystallization

g	K_g , [g/cm ² min(g _{sol} /g _{sol} v)]	k_g , [cm/min(g _{sol} /g _{sol} v)]	μ_0	Φ
1	1.468×10^{-3}	2.055×10^{-3}	2.0×10^5	0.17
2	0.041	0.029	8.8×10^5	0.08
2.5	0.194	0.109	4.35×10^6	0.10
3	0.876	0.409	9.6×10^6	0.12
3.5	3.839	1.536	7.4×10^6	0.18

Table 8.7 The crystallization kinetic parameters of MA for unseeded crystallization

g	K_g, [g/cm²min(g_{sol}/g_{solv})]	b	k_b, [#/g.min(g_{MA}/g_{EA})]	Φ
1	1.468×10^{-3}	4.46	5.86×10^9	0.22
2	0.041	4.52	3.6×10^{10}	0.08
2.5	0.194	4.80	2.3×10^{11}	0.09
3	0.876	5.60	5.0×10^{12}	0.12
3.5	3.839	6.30	6.2×10^{13}	0.15

As consequence, **Figure 8.25** represents the fitting of all solution methods such as Garside method and the PBE modeling approach for seeded and unseeded crystallization of MA crystallization in EA. The best fit was obtained in the model solution with without seed crystals.

**Figure 8.25** The agreements of the Garside and the PBE modeling approach to the experimental values.

9.0 DISCUSSION AND CONCLUSION

- Firstly the polymorphic forms of MA are characterized and identified by SEM, Raman microscopy and X-ray powder diffraction.
- The mefenamic acid crystals recrystallized from DMA, DMS, Acetone and EA have the polymorphic Form I of MA. The crystals obtained from solutions with DMF show the structure of Form II. The solubility, dissolution rate and bioavailability of different polymorphic forms can differ.
- Mefenamic acid crystals show needle-shaped flat particles. The smaller particles are agglomerated, and some of them adhered to larger ones. Agglomeration and small particles can be a problem during filtration and drying. Also these particles negatively affect the product bulk density, powder flow or the ease of formulation.
- For CSD measurement Lasentec FBRM recent measurement technique is used. Three experiments are done. The CSD is investigated under different cooling rates such as 0.5°C/min and 1°C/min and the crystallization end temperature are changed as 25 and 30°C. A narrow size distribution is obtained which is a desired condition for filtration and drying processes of the crystallization. The mean lengths are changed between 10-90 microns.
- After characterization of some solid-state of MA the next step is estimation of the crystallization kinetics parameters to control crystallization and to obtain desired product with suitable size, shape and polymorphic form.

- To determine the kinetic parameters two methods are chosen, the desupersaturation curve technique and the PBE modeling approach. Both methods need the desupersaturation curve, a concentration versus time profile during crystallization. So the experiments to obtain the concentration profile are carried out.
- MA is crystallized in an isothermal batch crystallizer with seed crystals. The density is measured for every minute samples by the densitometer. For densitometer the device constant firstly calculated by calibration of machine with air and the distilled water as 0.316589. And by using calibration curve the density measurements converts to the concentration values and a profile as a function of time is drawn.
- Firstly, the desupersaturation curve technique with the solution of Garside method for the estimation of the growth kinetics can be used for quick estimation of kinetics parameters to design the process and modeling purposes, because the experiments are fast and the data are easy to obtain, but they do not supply very accurate kinetics data. Also it is very sensitive to experimental conditions and errors.
- In Garside solution g values are assumed as 1, 2, 2.5, 3 and 3.5 and $\bar{A}_{T0}$ values are calculated as 25.735, 12.879, 10.305, 8.589 and $7.363\text{cm}^2/\text{g}_{\text{solv}}$ respectively. Also the mass growth rate constants, K_g are calculated as 1.468×10^{-3} , 0.041, 0.194, 0.876, $3.839[\text{g}/\text{cm}^2\text{min}(\text{g}_{\text{sol}}/\text{g}_{\text{solv}})]$.
- The second method is the PBE modeling approach for seeded and unseeded crystallization of MA. The parameters of the growth and nucleation rates have been successfully estimated for Mefenamic Acid using the non-linear optimization. For solution in MathCAD, both

Runge-Kutta explicit methods and implicit methods were used but no difference observed. So in our system the equations were not stiff but some literature published concluded that the solution based on the stiff equations.

- Both Garside and the PBE modeling approach are compared and it can be concluded that both methods are in good agreements with the experimental data as desired.
- The development and operation of industrial crystallization processes can be made significantly easier if some data on the kinetics of crystal growth are available. This information can be incorporated in process models, can be used in process and crystallizer design, and can shed light on the observed behavior of the system.

10.0 FUTURE WORK

- Further studies on Mefenamic Acid with variable-temperature X- ray diffraction, single crystal X-ray diffraction, DSC, and FTIR shall provide more insight on the polymorphs and their relative stability. Experimental data can be used to estimate kinetic parameters of MA for the process of crystallization of different cooling and agitation profiles.
- Also, the other important research subjects are the thermal conversion of MA from its Form I to the Form II in different solvents and solubility studies at different temperatures.
- In order to control the crystallization process, the key properties of the mefenamic acid such as nucleation and growth rate, induction time, width of metastable region, and morphology are required in the laboratory and industry. Beside this, these process properties are depend on operation conditions and variables like solubility, impurities, mixing, solvent and supersaturation. A crystallization process can be dominated by nucleation or growth. The choice can be directed by manipulation of the key variables such as supersaturation, seeding and crystal surface area, CSD and purity etc.
- For the crystallization of MA, experiments can be repeated without seed crystal with different stirring rate at different temperature. If the experiments are done at different temperatures, the temperature dependence of the kinetic rate constant can be found and the kinetic power, g assumptions can be proved. Also the effect of mixing can be observed.

- The method of moments to reduce the PBE to a set of ordinary differential equations or changed the PBE to the simple forms under some assumptions, so their applications are limited to cases such as size-independent growth rate and no fines dissolution. So, the final-time CSD can be used directly for identification of kinetic parameters of MA.
- Also different solution methods can be used and their reliability and precision can be analyzed. For example, a mathematical model for the linear growth rate can be developed, using transient CSD data, the solution concentration curve, and suspension density of crystallization process. This prevents the effect of the shape factors on the linear growth rate.

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RESUME

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