Amitraz Solid Dosage Form

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Submitted in partial fulfilment of the requirements for the degree of Master of Science: Applied Science: Chemical Technology

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February 2006

Abstract

This study considered the use of urea eutectics as fast release solid dosage carrier forms for the acaricide N-methylbis (2,4-xylyliminomethyl) methylamine (Amitraz^{TM}).

Wettol D2 and Arkopal N090 were chosen as the wetting agent and dispersants respectively. Their optimum levels were determined as the surfactant concentrations that yielded a minimum in the dispersion viscosity of a concentrated (30% m/m) Amitraz suspension. The optimum dosage levels were found to be ca. 2% Arkopal N090 and ca. 1% Wettol D2.

Eutectic phase diagrams were obtained using the melting-cooling method. The components were ground together into a fine powder and heated in a glass tube immersed in a silicon oil bath. The liquid was allowed to cool down and solidify at ambient conditions. The time-dependant temperature change of the sample was tracked with a thermocouple. The data was captured in real time on a personal computer and analysed using an Excel spreadsheet programme.

The melt-cast method was used to prepare eutectic mixtures. They were characterised using DSC, DTA, XRD and Light Microscopy. The XRD peaks showed the presence of the two separate crystal structures for the eutectic mixture constituents.

The urea - $CaBr_2.2H_2O$ combination was initially considered as carrier for Amitraz. However, this eutectic system was found to be too hygroscopic. Small additions of PEG 6000 improved the tablet strength but decreased the dissolution rate.

Urea and acetamide formed a eutectic at ± 46^{o}C with a composition of ca. 40 % m/m urea. Unfortunately acetamide is a suspected carcinogen. Therefore the urea - 1,3-dimethylurea was selected as Amitraz carrier system instead. The eutectic mixture comprised 40% m/m urea and 60% m/m 1,3-dimethylurea, which melt at ± 56^{o}C.

The melt-press method was used to prepare Amitraz containing pellets measuring 5 mm thick and 33 mm ϕ and weighing about 5,0 g. It was possible to suspend Amitraz powder in the eutectic melt mixture provided it remained in powder form. However, when liquefied (by

melting), phase separation occurred. Thus the temperature of the eutectic mixture should be kept below the 80^{o}C melting point of Amitraz.

The dissolution tests were performed in a 10-liter Pyrex glass beaker with normal tap water (± 25^{o}C). The time taken for complete dissolution was measured with a stopwatch. These results were confirmed with turbidity tests. Starch-based super disintegrants were used in an attempt to enhance the dissolution rate of the pellets. Explotab® improved the dissolution rate of 30% and 40% m/m Amitraz formulations slightly. The best formulation obtained in this study had the following composition (in m/m): 30% Amitraz; 8% $CaCO_3$; 1 % Wettol D2; 2% Arkopal N090; 10% Explotab® and 49% urea – 1,3-dimethylurea eutectic. Such tablets disintegrated within 6,5 minutes when suspended in water.

Keywords: Solid dosage forms, Amitraz, Eutectic, Urea, 1,3-dimethylurea.

Acknowledgements

I would like to thank my heavenly Father for the great opportunity I had!!

Many thanks to Professor Walter W. Focke, my supervisor for his guidance patience and being such a big inspiration to me. You are greatly appreciated.

To my love Virgill Hine for always being there for me.

My dear mother and father, Dorothy and Terence Walbrugh, for being such great parents and always keeping me in their prayers. My sisters (Lorraine, Alicia and Therese) and brother Nicholas. To Poala, Chloe, Luke and Jordan, Hannah and Tamlyn. I love u guys. Uncle Frikkie and Koos.

Ernest Schay, from Bayer, is gratefully acknowledged for his assistance during the course of this study.

The financial and technical support of the following institutions:
University of Pretoria
Xyris Technology CC
THRIP programme of the Department of Trade and Industry
Bayer Health Sciences: Animal Health

To my colleaques and friends at the Institute of Applied Materials, especially Ollie. Thanks a million!!

Finally, I would like to dedicate this work to my belated brother, Rodney Walbrugh. You are dearly missed…

Table of contents

Pages

List of Figures

Pages

List of Tables

Pages

List of Symbols

Symbol	Description	Units
A	surface area of undissolved solid	m^2
C	solute concentration	mol/ℓ
C_s	solute concentration required to saturate solvent	mol/ℓ
G	dissolution rate	$mg/cm^2/h$
h	separation distance between particles	mm
k	dissolution rate constant	-
m	mass of solute passed into solution	mg
M	molecular weight	g/mol
M_L	molecular mass of solvent	g/mol
P	pressure	Pa
ρ_L	density of solvent	g/cm^3
pKa	logarithm of dissociation constant	-
r	radius of tube	mm
t	time taken for solute to pass into solution	s
Tg	glass transition temperature	K
V_{tot}	total potential energy	J
V_R	double layer repulsion energy	J
V_A	van der waals attraction energy	J
V_S	steric repulsion energy	J
W_a	work of adhesion	J
W_i	work of immersion	J
W_s	work of spreading	J
W_d	total work for dispersion	J
		J

Greek symbols

$\gamma_{S/L}$	interfacial free energy at the solid-liquid interface	N/m or J/m^2
$\gamma_{S/V}$	interfacial free energy at the solid-vapour interface	N/m or J/m^2
$\gamma_{L/V}$	interfacial free energy at the liquid-vapour interface	N/m or J/m^2
θ	contact angle	radians
ϕ	volume fraction polymer in adsorbed layer	-
ϕ	diameter	mm
κ	thickness of the double layer	mm
χ	Flory interaction parameter	-
ψ_o	Surface potential	J/m
δ	Distance	mm

Subscripts

L	liquid
s	solid

1. Introduction

Ticks are the most important ectoparasites of livestock in tropical and sub-tropical areas, and are responsible for severe economic losses both through the direct effects of blood sucking and indirectly as vectors of pathogens and toxins. Control of tropical tick-borne diseases still depends mainly on intensive tick control with acaricides (Jongejan, 1996).

One of the oldest methods for treating parasites on the surface of the skin of animals, especially sheep and cattle, is by way of dips. By totally immersing an animal, all areas are covered by the insecticides. Because of human health risks, certain dips containing benzene hexachloride, lindane, and arsenic have been banned in many countries. Following the ban of these products, organophosphates, e.g. diazinon, propetamphos, rotenone, Amitraz, as well as compounds from other chemical groups were introduced. However, these products are not without risk. Because of the large number of adverse reactions reported in the U.K. following use of organophosphates in dips, the sale of these products is restricted to individuals holding a certificate of competence. Formulations intended for use in dips vary from aqueous solutions to emulsifiable concentrates to wettable powders. Stability in the formulation as well as in the final dip solution is required. Photostability is also a requirement. There are no specific rules in formulating dip preparations except that the active ingredient must remain in a form that does not “oil out”, or separate from water in the dip tank (Hardee & Baggot, 1998: 209-210).

Amitraz is a triazapentadiene compound, a member of the amidine chemical family. Amitraz is a powerful compound that inhibits the tick from "feeding" on the animal, e.g. dog. The tick's sharp barbed mouthparts become paralyzed and cannot pierce the skin. This causes even attached ticks to detach (Jongejan, 1996)!

Currently, there are six active Amitraz product applications. Bee mite strip and cattle collar uses were recently voluntarily cancelled. Formulated Amitraz products include an emulsifiable concentrate, wettable powder, soluble concentrate, and impregnated material. The registered formulations include an unspecified solid formulation for manufacturing (97%), three emulsifiable concentrates (12.5% and two 19.8%), a wettable powder (50%), and

an impregnated dog collar/tag (9%). Amitraz products can be applied with aerial and ground equipment, including airblast sprayers and hand sprayers, using either dilute or concentrated solutions. There is also a 3-month dog collar (Rossi, 1998).

Purpose of the present study

Bayer produces Amitraz in the form of emulsifiable concentrates and wettable powders. They would like to move away from powders and liquids, as they can become a potential environmental problem. Bayer wants to produce a tablet with a 250ppm active content. The solid dosage should have ca. 20-40% mass/mass active ingredient, which disperses in a 10-litre drum of tap water within 3 - 5 minutes. The tablet should have a melting point of above 50^{o}C to avoid melting in tropical regions. The tablet cannot be pressed because this method has been patented. Bayer proposed using a melt extrusion or melt-cast method to produce the tablet.

The purpose of this investigation is to deliver Bayer a unique tablet capable of delivering the pesticide in the correct dosage.

The surfactants used for this investigation was Arkopal N090 and Wettol D2. It is the surface acting agents for Amitraz in Bayer's commercial wettable powder, named Milbitraz.

Urea was chosen as the inert carrier because of its high water solubility and low toxicity levels. Urea decomposes at its melting point; eutectic formation with another compound will reduce or increase its melting point. Potential eutectic forming compounds with urea were investigated.

The effect of super disintegrants on the dissolution rate of the solid dosage form was investigated.

2. Literature Review

2.1 Introduction

A solid dosage form is a drug delivery system that includes tablets, capsules, sachets, and pills, as well as bulk or unit-dose powders and granules (Banker & Rhodes, 1990: 355). Tablets and capsules currently account for the highest proportion of all drug presentations. The prominence and popularity they enjoy are attributable to the following factors:

- Simple and practical administration
- Good possibilities of controlling absorption, e.g. by the use of slow-release enteric coated forms
- Accuracy of dosage
- Good chemical, physical, and microbiological stability
- Rational manufacture and packaging
- Relatively low costs (Hess, 1985: 11)

Solid dosage forms can be produced in a wide range of variants. This means that it is possible to devise, for almost any active substance, a technically and bio-pharmaceutically optimal formulation which is compatible with the physical, chemical, and biological characteristics of the substance in question (Hess, 1985:11).

A ‘solid dispersion’ is the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method. Solid dispersions in water-soluble carriers were shown to improve the dissolution rate and bioavailability of a range of hydrophobic drugs compared to conventional dosage forms (Chiou & Riegelman, 1971).

2.2 Prefomulation

Preformulation involves studies to collect basic information on the physical and chemical characteristics of the drug substance to be prepared into pharmaceutical dosage forms. A physical and chemical description of a drug substance is important prior to dosage form development. Most of drug substances in use today occur as solid materials. These pure chemical compounds are either in a crystalline or amorphous form (Howard, 1985:87).

2.2.1 Microscopic Examination

Microscopic examination of the raw drug substance gives an indication of crystal structure, particle size and particle size range (Howard, 1985: 88).

2.2.2 Particle Size

The particle size distribution of the drug affects the following physical and chemical properties: drug dissolution rate, bioavailability, content uniformity, taste, texture, colour, stability, flow characteristics and sedimentation rates. The product formulator must establish as early as possible how the particle size of the drug substance may affect formulation and product efficacy. The methods available to evaluate particle size and distribution includes, sieving or screening, microscopy, sedimentation and stream scanning. Sieving and screening is the most widely used method for size analysis of powders in the range of 44 microns and greater. Optical microscopy is usually the first step in determination of particle size and shape for the new drug substance. Sedimentation utilizes the relation between rate of fall of particles and their size. Stream scanning determines the particle size distribution of powdered drug substances (Howard, 1985:88).

2.2.3 Partition Coefficient and Dissolution Constant

The degree of ionization or pK_a value of the drug is an important physical-chemical characteristic relative to evaluation of possible effects on absorption from various sites of administration. The dissociation constant or pK_a is usually determined by potentiometric titration (Howard, 1985: 89).

2.2.4 Polymorphism

The crystal or amorphous form of the drug substance is an important factor in formulation. Polymorphic forms have different physical-chemical properties including melting point and solubility. Polymorphic forms with drugs are relatively common. Drug molecules in the crystal form require more energy to escape from this form, compared to amorphous drug molecules. Therefore, the amorphous form of a compound is always more readily soluble than a corresponding crystal form. The changes in crystal characteristics can influence

bioavailability, chemical and physical stability and have important implications in dosage form process functions (Howard, 1985: 89).

2.2.5 Solubility

When the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. If the drug substance is acidic or basic, solubility may be influenced by changes in pH. Other techniques that can be used to improve the drug's solubility include complexation, micronization or solid dispersions. Surfactants are good wetting agents and solubilisers (Howard, 1985: 90).

2.2.6 Dissolution

A decrease in the drug's particle size or an increased solubility in the diffusion layer increases the drug's dissolution rate (Howard, 1985:90).

2.2.7 Dissolution Rates of Solid in Liquids

This action is composed of two consecutive stages:

1. An interfacial reaction results in the liberation of solute molecules from the solid phase,
2. Followed by transport of these molecules away from the interface into the bulk of the liquid phase under the influence of diffusion or convection (Aulton, 1988: 75).

The overall rate of mass transport that occurs during dissolution will be determined by the rate of the slowest stage. In the absence of a chemical reaction between solute and solvent then the slowest stage is usually the diffusion of dissolved solute across the static boundary layer of liquid that exists at a solid-liquid interface. The dissolution rate of a solid in a liquid may be described quantitatively by the Noyes-Whitney equation:

$$\frac{dm}{dt} = kA\left(C_s - C\right) \qquad (1)$$

Where m is the mass of solute that has passed into solution in time t, dm/dt represents the rate of dissolution, A is the surface area of the undissolved solid in contact with the solvent, C_s is

the concentration of solute required to saturate the solvent at the experimental temperature, C is the solute concentration at time t and k is the intrinsic dissolution rate or simply the dissolution rate constant

The factors that influence the dissolution rate are described in Table 2.1 (Aulton, 1988:76).

Table 2.1: Factors affecting in vitro dissolution rates of solid in liquids

Term in Noyes-Whitney equation	**Affected by**
A, surface area of undissolved solid	Size of solid particles Dispersibility of powdered solid in dissolution medium Porosity of solid particles
C_s, solubility of solid in dissolution medium	Temperature Nature of dissolution medium Molecular structure of solute Crystalline form of solid Presence of other compounds
C, concentration of solute in solution at time, t	Volume of dissolution medium Any process that removes dissolved solute from the dissolution medium
k, dissolution rate constant	Thickness of boundary layer Diffusion coefficient of solute in the dissolution medium

2.2.8 Stability

Evaluation of the physical and chemical stability of the pure drug substance is important for preformulation work. The stability studies conducted in the preformulation phase include solid-state stability of the drug alone, solution phase stability and stability in the presence of expected excipients. Knowledge of the drug's chemical structure allows the preformulation scientist to anticipate the possible degradation reactions. Chemically the most frequently encountered destructive processes are hydrolysis and oxidation. Hydrolysis is a solvolysis process in which drug molecules interact with water molecules to yield breakdown products of different chemical constitution. Oxidation involves the loss of electrons from an atom or

molecule. Each electron lost is accepted by some other atom or molecule, thereby accomplishing the reduction of the recipient. In drug product formulation steps are taken to reduce or prevent the occurrence of drug substance deterioration (Howard, 1985: 91).

2.3 Solid Dosage Forms

2.3.1 Powders, Granules and Sachets

A *powder* is a mixture of finely divided drugs and/or chemicals in dry solid form. This should be differentiated from the general use of the term "powder" or "powdered" which is commonly used to describe the physical state of a single chemical substance or a single drug (Howard, 1985: 117). Powder solid dosage forms consist either of pure pulverized active substance or of the active substance mixed with desiccant excipients such as talc, zinc oxide or starches (Hess, 1985: 38). The disadvantages of powders as a solid dosage form is the decomposition of hygroscopic, deliquescent, or aromatic materials and the time and expense required in the preparation of uniform individually wrapped doses of powders (Howard, 1985: 117).

Granules consist of powder particles, which have been aggregated to form a larger particle that is usually 2-4 mm in diameter (Aulton, 1988: 300). They are generally irregularly shaped and behave as single larger particles. Granules of various mesh sizes may be prepared depending upon the application. Granules are prepared by moistening the desired powder or blended powder mixture and passing the moistened mass through a screen of the mesh size that will produce the desired size granules. The larger particles thus formed are then dried by air or under heat. Granules may also be prepared by passing compressed masses of powdered material through a granulating machine. Granules are physically and chemically more stable than are the corresponding powders from which they were prepared (Howard, 1985: 123).

Sachets are active substances in powder mixture or granule form, which are used in high doses and difficult to compress. They must to given in accurate dosages. Single dosages are measured into sachets made of aluminium or coated papers (Hess, 1985: 14).

2.3.2 Capsules

The word capsule is derived from the Latin word‘capsula’ meaning a small box. In pharmacy the word capsule is used to describe an edible package made from gelatine, which is filled with medicines to produce a unit dose, mainly for oral use. There are two types of capsule, ‘*hard*’ and ‘*soft*’. The hard-gelatine capsule consists of two pieces, a cap and a body, which fit one inside the other (Figures 2.1). They are produced empty and are filled in a separate operation (Aulton, 1988: 322). Drugs which are difficult to compress into tablets are filled as a powder mixture or as granules into hard–gelatine capsules (Hess, 1985: 12).

Figure 2.1 Hard – Gelatine Capsule

The soft - gelatine capsule is manufactured and filled in one operation (Aulton, 1988: 322). Soft - gelatine capsules, in contrast to hard- gelatine capsules are pliable and completely sealed (Figure 2.2). They contain preparations in liquid or paste form (Hess, 1985: 12).

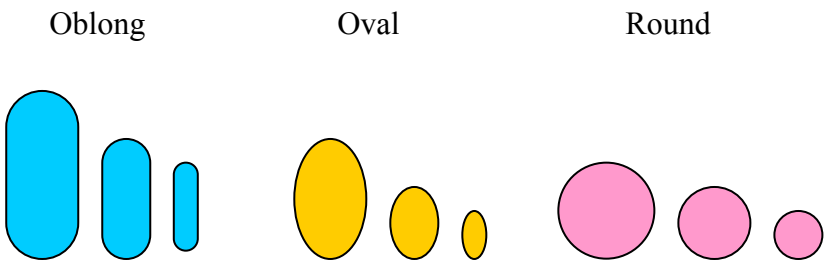

Figure 2.2 Shapes and Dimensions of Soft – Gelatine Capsules

2.3.3 Tablets

Compressed tablets are the most widely used of all pharmaceutical dosage forms. They are convenient, easy to use, portable, and less expensive than other dosage forms. They deliver a precise dose with a high degree of accuracy. Tablets can be made in a variety of shapes and sizes limited only by the tool and the die maker. Compressed tablets are defined as solid – unit dosage forms made by compaction of a formulation containing the drug and certain fillers or excipients, selected to aid in the processing and properties of the drug product. There are various types of tablets designed for specific uses or functions. Effervescent tablets are formulated to dissolve in water with effervescence caused by the reaction of citric acid with sodium bicarbonate or some other effervescent combination that produces effervescence in water. Suppositories can be made by compression of formulations using a specially designed die to produce the proper shape (Lieberman, Lachman & Schwartz, 1989: 131).

2.3.4. Evaluation of Tablets

Two types of test procedures are categorized: those that are requirements in an official compendium and those that, though unofficial, are widely used in commerce (Banker & Rhodes, 1990: 416).

Official Standards

Tests that are mandatory according to the United States Pharmacopoeia (USP) and The National Formulary (NF) will be discussed (Banker & Rhodes, 1990: 416).

Uniformity of Dosage Units

The uniformity of dosage units can be determined by two different general approaches: the weight variation between a specified number of tablets and the extent of drug content uniformity. The use of weight uniformity as a singular means of quantifying uniformity of dosage units is only permitted in cases where the tablet is uncoated and contains 50 mg or more of a single active ingredient that comprises 50% or more of the total tablet weight. Content uniformity in a USP test is designed to establish the homogeneity of a batch. Ten tablets are assayed individually after which the arithmetic mean and relative standard deviation (RSD) are calculated. USP criteria are met if the content uniformity lies within 85-

115% of the label claim and the RSD is not greater than 6% (Banker & Rhodes, 1990:416-417).

Disintegration Testing

The disintegration time of a tablet when immersed in some test fluid has been a requirement in most compendia for many years. The test consists of an apparatus in which a tablet can be introduced into each of six cylindrical tubes, the lower end of which is covered by a 0.025 $in.^2$ wire mesh. The tubes are then raised and lowered through a distance of 5.3-5.7 cm at a rate of 29-32 strokes per minute in a test fluid maintained at 37 ± 2°C. Continuous agitation of the tablets is ensured by this stroking mechanism and by the presence of a specially designed plastic disk, which is free to move up and down in the tubes (Banker & Rhodes, 1990: 416-417).

The tablets are said to have disintegrated when the particles remaining on the mesh (other than fragments of coating) are soft and without palpable core. A maximum time for disintegration to occur is specified for each tablet, and at the end of this time the aforementioned criteria must be met. The disintegration media required varies depending on the type of tablet to be tested. The disintegration time of the tablet may be affected by the amount of disintegrant used as well as the tablet processing conditions (Banker & Rhodes, 1990: 416-417).

Unofficial Tests

Mechanical Strength

Mechanical strength has been described by various terms, including friability, hardness, and fracture resistance, crushing strength, and flexure, or breaking strength. It is an important tablet property and plays a significant role in both product development and control (Banker & Rhodes, 1990: 417). Interpretation of this property is less straightforward than it first might appear. Anisotropy is almost certain to be present, and the ideal test conditions, employing closely defined uniform stresses are rarely met. The physical changes that occur during tablet compression are the formulation of interparticle bonds and a reduction in porosity resulting in an increased density. These factors are responsible for mechanical strength (Banker & Rhodes, 1990: 417).

Crushing Strength

The crushing strength is described as the minimum compression force, applied diametrically to a tablet, which fractures it. The force is transmitted to the tablet by means of a moving plunger. When a load is applied at 90°C to the longest axis (i.e. across the tablet's diameter), the load requirement to break the tablet is referred to as the diametrical strength. The load can also be applied across the tablet's thickness, in which case it is referred to as flexure or breaking strength Commercially available testers include, the Stokes (or Monsanto), Strong-Cobb, Pfizer, and Erwerka and Schleuniger (or Heberlein). (Banker & Rhodes, 1990: 417).

Abrasion

The crushing strength of a tablet gives an indication of its mechanical robustness, but it does not truly measure the ability of the tablet to withstand the handling it will encounter during processing and shipping. A test that can measure the resistance of the surface regions to abrasion or other forms of general "wear and tear" may be more appropriate in this regard. Tablets with a certain weight are subjected to a well-defined level of agitation in a fixed-geometry, closed container for a specific time. The tablets are reweighed, and abrasion resistance or friability is usually expressed as a percentage loss in weight (Banker & Rhodes, 1990: 417).

Porosity

The rate and efficiency of the initial disintegration and dissolution process markedly influence the bioavailability of the drug from tablets. Tablet formulators are always faced with a compromise situation. The tablet should be sufficiently hard to resist breaking prior to administration and yet soft enough to dissolve or disintegrate after administration. The major factors affecting both these properties is the structure of the tablet, in particular its density (or porosity) and the pore structure (Banker & Rhodes, 1990: 418).

Liquid Penetration

Liquid penetration into tablets can be used to study their pore structure. The rate of liquid penetration should also provide information on the disintegration/dissolution behaviour of a tablet on administration. These investigations are capable of forming a valuable link between physico-mechanical characteristics and in vivo performance (Banker & Rhodes, 1990: 418).

Near-Infrared Spectroscopy (NIR)

Near-infrared analysis is particularly useful because it is both rapid and non-destructive to the sample. This method has been used to measure:

- Sample composition and identification,
- Moisture content,
- Content uniformity,
- Homogeneity of mixing,
- Degradation products,
- Particle size

As researchers become more familiar with this method, its applications will undoubtedly grow (Banker & Rhodes, 1990: 418).

2.4 Solid Dispersions

The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting/fusion, solvent, or melting-solvent method (Chiou & Riegelman, 1971).

Solid dispersion systems (Figure 2.3) can be divided into six different categories (Chiou & Riegelman, 1971).

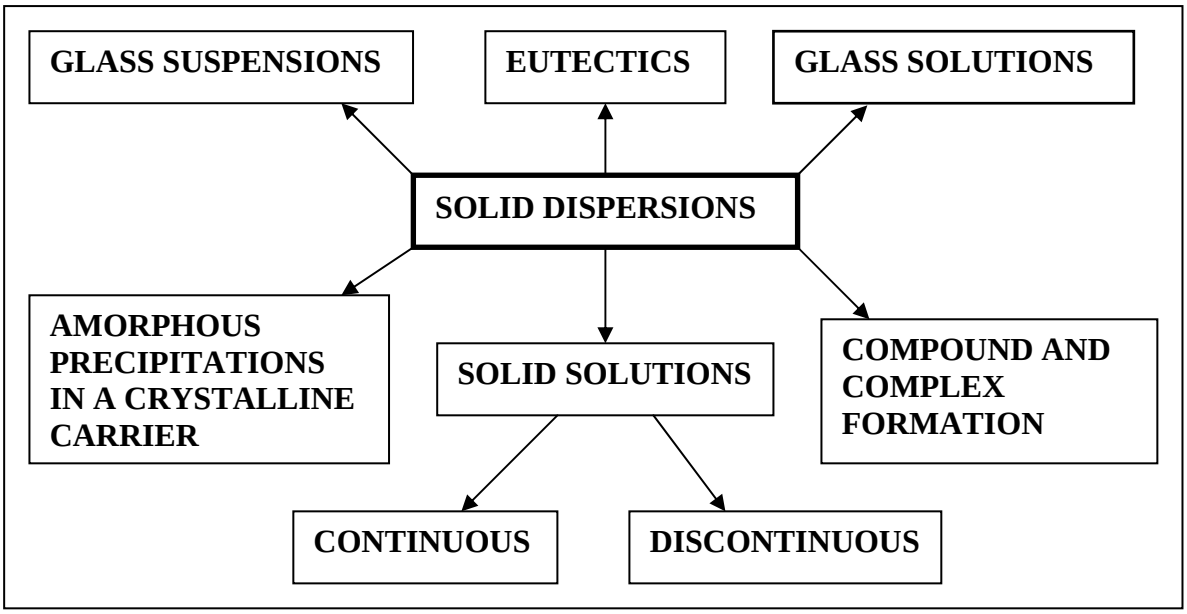

Figure 2.3 Categories of Solid Dispersions (Chiou & Riegelman, 1971)

2.4.1 Method of Preparation

Melting Method —The melting method involves heating a physical mixture of a drug and a water–soluble carrier until it melts. The molten mixture is mixed and then allowed to cool and solidify. The melting method can be used to prepare fast release solid dispersion dosage forms (Sekiguchi & Obi, 1961). The advantage of the melting method is its simplicity and low costs (Chiou & Riegelman, 1971).

Solvent Method – A physical mixture of two solid components is dissolved in a common solvent, followed by evaporation of the solvent (Mayersohn & Gibaldi, 1969). The advantage of the solvent method is the prevention of thermal decomposition of drugs and carriers because of the low temperature required for the evaporation of organic solvents. The disadvantages are the:

- Higher cost of preparation,
- Difficulty in completely removing liquid solvent,
- Possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug,
- Selection of a common volatile solvent, and
- Difficulty of reproducing suitable crystal forms (Chiou & Riegelman, 1971).

Melting–Solvent Method – This method involves dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the molten carrier without removing the liquid solvent. The advantage of this method is that it possesses both the melting and solvent method. The disadvantage is that it is limited to drugs with a low therapeutic dose, e.g., below 50 mg (Chiou & Riegelman, 1971).

2.4.2 Categories of Solid Dispersions

2.4.2.1 Eutectic mixtures

The eutectic mixture is prepared from the melting method, with the two compounds showing complete liquid miscibility and negligible solid–solid solubility. Thermodynamically this type of system is regarded as an intimately blended physical mixture of its two crystalline components (Findlay, 1951: 477).

The following factors may contribute to the faster dissolution rate of a hydrophobic drug dispersed in the eutectic:

1. Decrease in solid drug crystal size,
2. Presence of a hydrophilic carrier,
3. Absence of drug particle aggregation and agglomeration
4. Drug crystallizes in a metastable form (Chiou & Riegelman, 1971)

Decrease in solid drug crystal size. Law and co - workers (2002) have shown that the crystallization of the eutectic mixture, poly (ethyleneglycol) and fenofibrate 20 – 25% (w/w), resulted in the formation of an irregular microstructure in which fenofibrate crystals were found to be less than 10 μm in size. The decrease in fenofibrate crystal size resulted in an improvement in the dissolution rate. Decreasing the drug particle size of 10% (m/m) ketoprofen in a poly(ethyleneglycol) 6000 eutectic increased the dissolution rate (Margirit, Rodriguez & Cerezo, 1994). Molecular dispersion is responsible for the increased dissolution rate of the poly(ethyleneglycol) and hydroflumehiazide eutectic mixture (Corrigan, Murphy & Timoney, 1979).

Presence of a hydrophilic carrier. The reduced particle size, increased surface area, and the close contact between the hydrophilic carrier, Eudragit®, and hydrophobic drug, itraconazole may be responsible for the enhanced drug solubility (Jung *et al.,* 1999). The solubility of the hydrophobic drug, 17 β-estradiol hemihydrate, was also increased in the solid dispersion system prepared with water–soluble polyvinylpyrolidone. The reason for the higher dissolution rates for the system is because of the improved wettability of the drug. The water–soluble polymer surrounds the dispersed drug particles in the solid dispersion. The polymer dissolves readily in contact with the release medium and therefore results in a better wetting of the drug particles by the medium (Hülsmann *et al*., 2000).

Absence of drug particle aggregation and agglomeration. The absence of drug particle aggregation and agglomeration plays a very important role in increasing drug dissolution rates (Chiou & Riegelman, 1971).

Drug crystallizes in a metastable form. The metastable, crystalline form has a higher solubility, which leads to a faster dissolution rate according to the Noyes-Whitney equation (Chiou & Riegelman, 1971),

$$\frac{dm}{dt} = kA\left(C_s - C\right) \tag{2}$$

2.4.2.2 Solid Solutions

Solid solutions compared to liquid solutions are made up of a solid solute dissolved in a solid solvent. This system is called a mixed crystal because the two components crystallize together in a single homogeneous phase (Findlay, 1951). Goldberg, Gibaldi and Kanig (1965) showed that solid solution formation reduced the drug's "particle size" to its absolute minimum. Solid solutions can be classified according to two methods. One is their miscibility (continuous and discontinuous solid solutions) and two is the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous) (Leuner & Dressman, 2000).

Continuous and discontinuous solid solutions. In continuous solid solutions the components are miscible in all proportions. It can be concluded that the bonding strength between the two components is stronger than the bonding strength between molecules of each of the individual components (Leuner & Dressman, 2000). In discontinuous solid solutions the solubility of each of the components in the other component is limited (Leuner & Dressman, 2000).

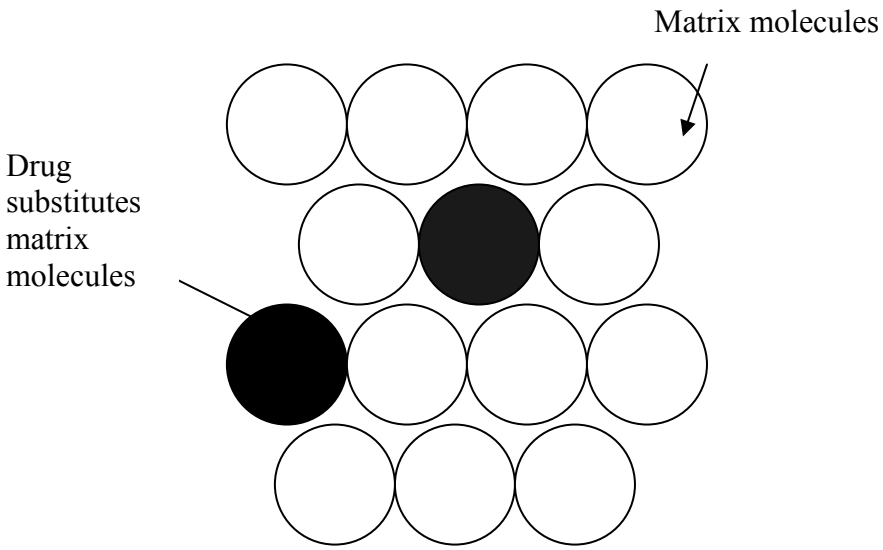

Figure 2.4 Substitutional Crystalline Solid Solution (Chiou & Riegelman, 1971).

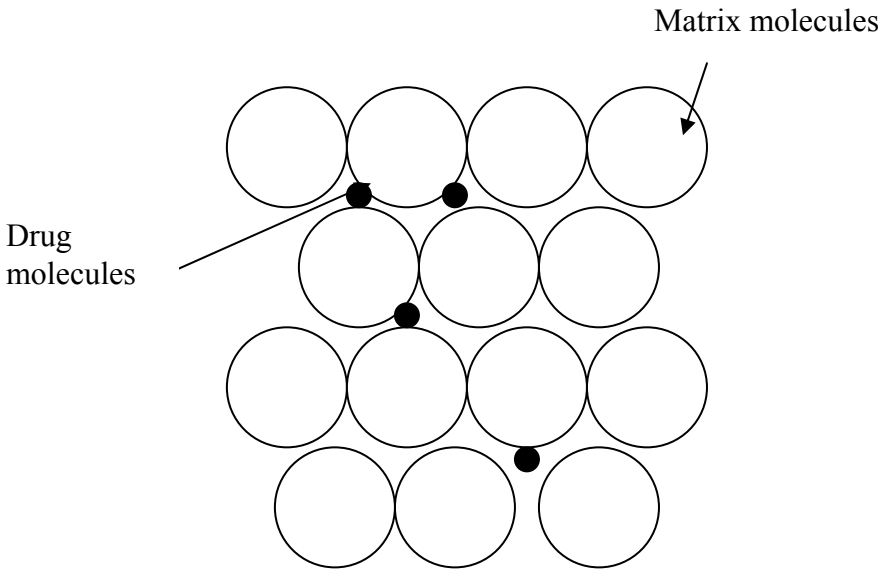

Figure 2.5 Interstitial Crystalline Solid Solution (Chiou & Riegelman, 1971).

Substitutional crystalline and interstitial crystalline solid solutions. The solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules (Figure 2.4 and 2.5) (Leuner & Dressman, 2000).

2.4.2.3 Glass Solutions

The glass solution is a homogeneous glassy system in which a solute dissolves in a glassy solvent. This system is usually characterized by transparency and brittleness below the glass-transition temperature, *Tg.* (Chiou & Riegelman, 1971).

2.4.2.4 Amorphous Precipitations in a Crystalline Carrier

In a eutectic mixture the drug and carrier crystallize out simultaneously. In amorphous precipitations the drug precipitates out in an amorphous form in the crystalline carrier. The amorphous form is the highest energy form of a pure drug, and it should produce faster dissolution rates than the crystalline form (Chiou & Riegelman, 1971).

2.4.3 Eutectic Mixture as a Fast Release Solid Dosage Form

2.4.3.1 Liquid-solid phase diagrams

Solid and liquid phases may both be present in a system at temperatures below the boiling point. See Figure 2.6 for a typical phase diagram (Atkins, 1998:204).

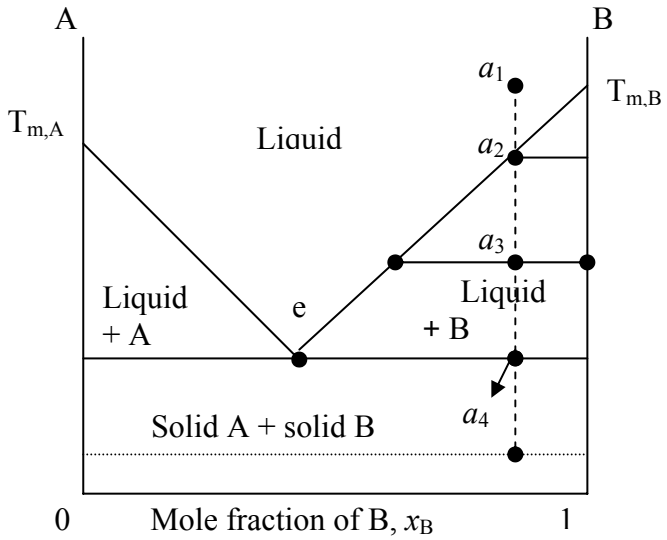

Figure 2.6 The Temperature-Composition Phase Diagram for Two Almost Immiscible Solids and Their Completely Miscible Liquids.

The isopleth e corresponds to the eutectic composition, the mixture with lowest melting point. Consider the two-component liquid of composition a_1. The changes that occur may be expressed as follows (Atkins, 1998:205).

(1) $a_1 \rightarrow a_2$. The system enters the two-phase region labelled 'Liquid + B'. Pure solid B begins to crystallize out of solution (Atkins, 1998: 205).

(2) $a_2 \rightarrow a_3$. More of solid B forms and the remaining liquid becomes richer in A. The relative amounts of the solid and liquid phases (which are in equilibrium) are given by the lever rule. (See Appendix A). At this stage there are roughly equal amounts of each. The

liquid phase is richer in A than before (its composition is given by b_3) because some B has been deposited (Atkins, 1998: 205).

(3) $a_3 \rightarrow a_4$. At the end of this step, there is less liquid than at a_3, and its composition is given by e. The liquid now freezes to give a two-phase system of pure B and pure A (Atkins, 1998: 205).

2.4.3.2 Eutectics

The isopleth at *e* in Figure 2.6 corresponds to the *eutectic* composition, the name coming from the Greek words for 'easily melted'. A liquid with the eutectic composition freezes at a single temperature, without previously depositing solid A or B. A solid with the eutectic composition melts, without change of composition, at the lowest temperature of any mixture (Atkins, 1998: 205).

Solutions of composition to the right of *e* deposit B as they cool, and solutions to the left deposit A: only the eutectic mixture (apart from pure A or pure B) solidifies at a single definite temperature without gradually unloading one or other of the components from the liquid (Atkins, 1998: 205). The situation is defined by the Gibbs Phase Rule: F = C – P + 2. With two components (C = 2) and three phases in equilibrium (P = 3) there is one degree of freedom (F = 1).

Although a simple eutectic solid is a two-phase system, it crystallizes out in a nearly homogeneous mixture of microcrystals. The two microcrystalline phases can be distinguished by microscopy and structural techniques such as X-ray diffraction (Atkins, 1998: 206).

Thermal analysis is a very useful practical way of detecting eutectics. It can be illustrated by considering the rate of cooling down the isopleth through a_1 in Figure 2.6. The liquid cools steadily until it reaches a_2, where B starts to deposit (Figure 2.7). The cooling rate is now slower because the solidification of B is exothermic, i.e. it releases heat. When the remaining liquid reaches the eutectic composition, the temperature remains constant (F' = 0) until the whole sample has solidified: this region of constant temperature is the *eutectic halt* (Atkins, 1998: 206).

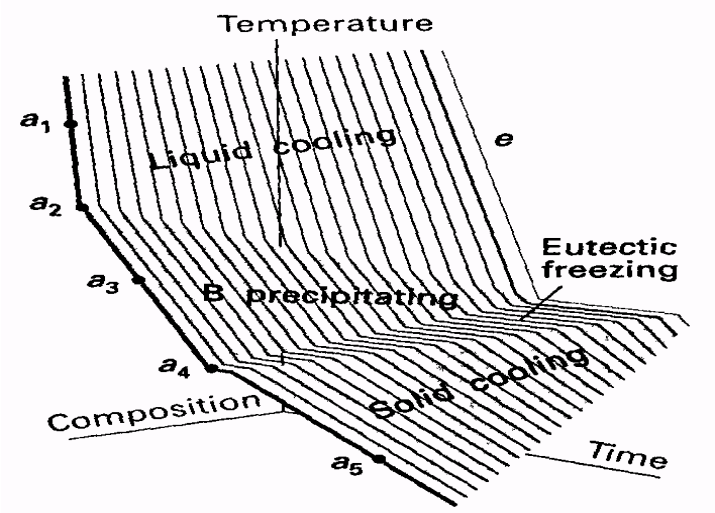

Figure 2.7 The Cooling Curves For The System Shown in Figure 2.6.

For isopleth a the rate of cooling slows at a_2 because solid B deposits from solution. There is a complete halt at a_4 while the eutectic solidifies. This halt is longest for the eutectic isopleth, e. The eutectic halt shortens again for compositions beyond e (richer in A) (Atkins, 1998).

If the liquid has the eutectic composition e initially, it cools down steadily to the freezing temperature of the eutectic, where there will be a long eutectic halt as the entire sample solidifies (like freezing of a pure liquid) (Atkins, 1998: 206).

Monitoring the cooling curves at different overall compositions gives a clear indication of the structure of the phase diagram. The points at which the rate of cooling changes define the solid-liquid boundaries. The longest eutectic halt gives the location of the eutectic composition and its melting temperature (Atkins, 1998: 206).

2.4.4 Carriers for Solid Dispersions

2.4.4.1 Polyethyleneglycol (PEG)

Polyethylene glycols are made from the monomer, ethylene oxide. The molecular weight falls in the range 200 to 300 000. Polyethylene glycols with molecular weights of 1500 – 20 000 are usually used for solid dispersions and solutions. The viscosity increases as the molecular weight increases. Their solubility in water is good but normally decreases with increasing

molecular weight. An advantage of PEG's for the formation of solid dispersions is that they have good solubility in most organic solvents, their melting points is relatively low for the manufacture of solid dispersions from the melting method (Leuner & Dressman, 2000).

Influence of the PEG chain length. The dissolution rate of PEG samples decreases as the molecular weight is increased The decrease in dissolution rate with increasing molecular weight corresponds with a decrease in diffusion coefficients, Table 2.2 (Corrigan *et.al*., 1979).

Table 2.2 Properties of PEG samples at 37^{o}C (Corrigan, 1986)

Molecular weight, g/mol	Diffusion coefficient, cm^2/s	Dissolution rate, $mg/cm^2/h$
1000	3.82×10^{-6}	1018.2
4000	3.10×10^{-6}	649.2
6000	2.47×10^{-6}	486.0
20000	-	259.7

The diffusion properties of the PEG's are the dominant factor in determining the dissolution rate of the pure polymer samples (Bailey & Koleske, 1976: 48). In polymers, dissolution is dependent on diffusion within the swollen surface layer and on the thickness of this swollen layer. Increasing the polymer chain length reportedly decreases the velocity of dissolution due to increased entanglement of the macromolecules. A relationship between molecular weight and dissolution rate is,

$$G = kM^{-A} \tag{3}$$

This equation shows that increased molecular weight leads to a reduced dissolution rate. Where G is the dissolution rate, M the molecular weight, k and A are constants (Ueberreiter, 1968: 219; Asmussen & Ueberreiter, 1962).

Corrigan (1986) showed that, when the drug is present in a low drug/polymer ratio (20% and lower in the case of phenobarbitone), the dissolution rate is dependent on the properties of the carrier. The dissolution rate of PEG 6000 solid dosages is also carrier dependent for the systems with 2% phenylbutazone and 15% paracetamol (Dubois & Ford, 1985).

Further studies indicated that the dissolution rate increases with a decrease in PEG molecular weight (Ford & Steward, 1986; Shah, Chen & Chow, 1995). For other drug/carrier systems, the influence of the carrier molecular weight on the dissolution characteristics of the solid

dispersion varies widely. For 5% sulphamethoxydiazine drug concentrations and PEG (6000 and 20 000) solid dispersions, the dissolution rate increases with the molecular weight of the polymer. Above 5% drug content there is no difference in the dissolution rate between the two polymers (Salib & Ebian, 1978). Solid dispersions of ibuprofen with PEG 4000, 6000 and 20000 also showed increasing dissolution rates with increasing molecular weight (Mura, Liquori & Bramanti, 1978). Anguiano-Igea and co-workers (1995) showed that the dissolution rate of clofibrate with PEG 10 000 and 20 000 increased with an increase in polymer molecular weight.

Influence of the drug/PEG ratio. A solid dispersion of naproxen in PEG 6000 resulted in a faster dissolution when a 5% or 10 % naproxen loading is used than when a 20%, 30% or 50% loading is used. X-ray diffraction results indicated that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline (Lin & Cham, 1996). It can be concluded that if the percentage of the drug is too high, it will form small crystals within the dispersion medium rather than being molecularly dispersed. If the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and a large increase in the solubility and release rate of the dug (Leuner & Dressman, 2000).

2.4.4.2 Polyvinylpyrrolidone (PVP)

Polyvinylpyrrolidone is made from the monomer vinylpyrrolidone. PVP with molecular weights ranging from 2 500 to 3 000 000 are commercially available. The glass transition temperature of a given PVP sample is not only dependent on its molecular weight but also on the moisture content. For this reason PVP's have only limited application for the preparation of solid dispersions by the hot melt method. PVP's are suitable for the preparation of solid dispersions by the solvent method because of its good solubility in organic solvents (Leuner & Dressman, 2000). PVP's have good water solubility and can improve the wettability of the dispersed compound (Itai, Nemoto, Kouchiwa, Murayama & Nagai, 1985).

Influence of the PVP chain length. An increase in the PVP chain length leads to a reduction in aqueous solubility and an increase in viscosity. This property is a disadvantage for fast release solid dispersions (Walking, 1994: 392-399). The release rate of drugs was lowered when PVPs of higher molecular weights were used as carriers for solid dispersions (Simonelli, Metha & Higuchi, 1969; Kassem, Zaki, Mursi & Tayel, 1979; Jachowicz, 1987).

Drug/PVP ratio. Solid dispersions prepared with high proportions of PVP showed higher drug release rates than those with high proportions of drug (Torrado's & Cadorniga, 1996).

2.4.4.3 Polyvinylalcohol (PVA), Crospovidone (PVP-CL), Polyvinyl-pyrrolidone-polyvinylacetate copolymer (PVP-PVA)

These polymers belong to the polyvinyl group. Polvinylalcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are water-soluble and crospovidone swells when dispersed in water (Leuner & Dressman, 2000). PVP, HPMC and PVA increased the dissolution rate of nifedipine solid dispersions. The solid dispersions prepared with PVA dissolved 20 times faster than the pure drug whereas HPMC and PVP yielded even better results (Suzuki & Sunada, 1998). PVP/PVA copolymers have shown to increase the drug release rate from solid dispersions (Leuner & Dressman, 2000). An increase in the PVP/PVA content could lead to a decrease in the release rate of the drug. The reason for this was attributed to high viscosity in the diffusion boundary layer adjacent to the dissolving surface (Moneghini, Carcano, Zingone & Perissutti, 1998). Crospovidone increased the dissolution rate of furosemide by a factor of 5.8 in comparison with a physical mixture of the components (Shin, Oh, Lee, Choi & Choi, 1998).

2.4.4.4 Cellulose derivatives

Cellulose is a natural occurring polysaccharide from the plant kingdom. This material consists of high molecular weight unbranched chains, in which the saccharide units are linked by β-1,4-glycoside bonds. Cellulose can be derivatized through the process of alkylation to form methyl-(MC), hydroxypropyl-(HPC), hydroxypropylmethyl-(HPMC) and many other semi-synthetic types of cellulose. Another possibility for derivatization is the esterification to yield, for example, cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP) (Leuner & Dressman, 2000).

Hydroxypropylmethylcellulose (HPMC). The molecular weight of HPMC ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol. Typical HPMC's are mixed ethers of cellulose, in which 16.5%-30% of the hydroxyl groups are methylated and 4%-32% are derivatized with hydroxypropyl groups (Harwood & Johnson,

1994: 220-232). HPMC improved the dissolution rate of the poorly soluble drug nivaldipine in a solid dosage form (Sekiguchi & Obi, 1961).

Hydroxypropylcellulose (HPC). Hydroxypropylcellulose has good solubility in water, ethanol, methanol and chloroform. It has a average molecular weight range from 37 000 to 1 150 000 (Harwood & Johnson, 1994: 223-228). The release rate of flurbiprofen was improved as the proportion of HPC was increased when lower molecular weight HPC's were used as carrier (Yuasa *et al.*, 1994).

2.4.4.5 Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are produced from the polymerization of acrylic and methacrylic acid. They are glassy polymers and are mostly used as coatings to modify the release of drugs from solid dosages (Leuner & Dressman, 2000). These polymers are normally referred to their trade name, Eudragit®. Eudragit® E is often used to improve the dissolution rate of solid dispersions since it is soluble in buffer solutions at a pH<5 and swells at higher pH's. Solid dispersions of itraconazole prepared with pH-dependent hydrophilic polymers, AEA® and Eudragit®E100, resulted in greater increases in drug solubility over those prepared with pH-independent hydrophilic polymers, PEG 20000, PVP, Poloxamer®188 and HPMC (Jung *et.al*., 1999). Moneghini, Carcano, Zingone and Perissutti (1998) showed that Eudragit®E did not improve the dissolution rate of atenolol solid dispersions.

2.4.4.6 Urea

Urea is used as a fertiliser and is an end product of human protein metabolism. It has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 part in 1 part. It also exhibits good solubility in many common organic solvents (Leuner & Dressman, 2000). Goldberg and co-workers (1966) have shown that faster dissolution rates of chloramphenicol can be achieved when prepared with urea as the carrier. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 (Okonogi *et al.*, 1997). The faster dissolution rate of acetaminophen from its physical mixture with urea can be explained by the solubilization effect of urea for the drug (Goldberg *et al.*, 1966). Urea increased the dissolution rate of phenytoin, however, in this case PEG 6000 was far more efficient (Jachowicz, 1987).

2.4.4.7 Sugars and polyols

Sugars and their related compounds are highly water-soluble and have few, if any, toxicity problems. They are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic. Sugars and polyols have poor solubility in most organic solvents, making it difficult to prepare co-evaporates (Leuner & Dressman, 2000). Sorbitol improved the dissolution rate of nitrofurantoin (Ali & Gorashi, 1984) and ursodeoxycholic acid (Okonogi *et.al*., 1997).

2.4.4.8 Emulsifiers

Emulsifying agents improve the release behaviour of many insoluble drugs. Their mode of action includes improving the wetting properties of the drug and solubilizing it. Emulsifiers are usually used in combination with another carrier because of their potential toxicity problems (Leuner & Dressman, 2000). The dissolution rate of solid dispersions of naproxen with PEG 4000, 6000 and 20 000 can be improved by the incorporation of sodium lauryl sulphate or Tween® 80 (Mura *et al.*, 1999).

2.4.4.9 Organic acids and their derivatives

Succinic acid and citric acid have also been used as carriers in solid dispersions to enhance the dissolution rate of griseofulvin (Chiou & Riegelman, 1969; Goldberg *et al*., 1966).

2.4.5 Characterizarion of Solid Dispersions

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. A combination of two or more methods is required to study its complete picture. The methods are:

- Thermoanalytical methods
- Differential thermal analysis
- Differential scanning calorimetry
- X-ray diffraction
- Infrared spectroscopy
- Dissolution test (Chiou & Riegelman, 1971).

2.4.5.1 Thermoanalytical method

Cooling – Curve method

The physical mixtures of various sample compositions are heated until a homogeneous melt is obtained. The cooling temperature of the mixture is then recorded as a function of time. The phase diagram can be drawn from a series of time - temperature curves (Findlay, 1951: 477; Moore, 1963).

2.4.5.2 Differential Thermal Analysis (DTA)

Differential thermal analysis measures the difference between the temperature of a test sample and a reference sample that has no phase transitions in the temperature range of interest. The data are plotted as the temperature difference between the reference and test sample (Walas, 1985: 539).

2.4.5.3 Differential Scanning Calorimetry (DSC)

This technique includes examining the characteristics of the system as a function of temperature. Differential scanning calorimetry (DSC) is the most highly regarded method. DSC measures the quantitative changes in energy in the system, e.g. endothermic and exothermic phase transformations. The method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy requiring phase transition occurs in the test sample, extra heat is applied to the sample so that its temperature increases at the same rate as in the reference (Leuner & Dressman, 2000).

2.4.5.4 X-Ray Diffraction (XRD)

X-ray diffraction measures the intensity of the x-ray diffracted or reflected from the sample as a function of diffraction angles (Nuffield, 1966). When an X-ray beam is applied to a sample, interference bands can be detected. A characteristic fingerprint region in the diffraction pattern reflects the crystallinity in the sample. It is possible to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which the drug is at least partly present in the crystalline form (Leuner & Dressman, 2000). In eutectic systems, diffraction peaks of each crystalline compound can be found in the diffraction spectra (Rai & Rai, 1998).

2.4.5.5 Infrared Spectroscopy

Changes in bonding between functional groups can be detected with IR spectroscopy (Leuner & Dressman, 2000).

2.4.5.6 Dissolution – Rate Method

The goal of preparing a solid dispersion is to improve the dissolution characteristics of a drug, the results of the release rate experiments are important in assessing the success of the approach. Individual dissolution tests are performed on the drug, carrier and physical mixtures of the two. The results are compared to help indicate the mechanism by which the carrier improves the dissolution of the pure drug (Leuner & Dressman, 2000).

2.5 Formulation Aids

Solid dosage formulations must meet requirements for manufacturing, dosage uniformity, stability, timely drug release, and bioavailability. Most drug substances do not inherently have such properties and must be formulated with other pharmaceutical ingredients, i.e. excipients (McCarty, s.a.). In the preparation of solid dosages,

- Diluents or fillers are commonly added to increase the bulk of the formulation,
- Binders to cause the adhesion of the powdered drug and pharmaceutical substances,
- Antiadherents or lubricants to assist the smooth tableting process,
- Disintegrating agents to promote tablet break-up after administration,
- Coatings to improve stability, control disintegration, or to enhance appearance (Howard, 1985: 83).

2.5.1 Surfactants

Surfactants are surface-active agents that are used to disperse a hydrophobic drug as a colloidal dispersion. (Banker *et al*, 1990: 517) They are often employed as emulsifying agents, solubilising agents, and suspension stabilisers or as wetting agents in dosage forms. The release of poorly soluble drugs from tablets and capsules may be increased by the inclusion of surfactants in their formulations. The surfactant reduces the solid/liquid interfacial tension, permitting the fluid to wet the drug more effectively and to come into more intimate contact with the solid dosage forms (Aulton, 1988: 163).

2.5.2 Diluents

Diluents or 'bulking agents' are inert substances, which are added to the active ingredient in sufficient quantity to make a reasonably sized tablet. The main diluent is lactose; it has a pleasant taste, rapidly dissolves in water, absorbs very little moisture and is fairly neutral in reaction. Other diluents include dicalcium phosphate, starch, microcrystalline cellulose, dextrose, sucrose and mannitol (Aulton, 1988: 309).

2.5.3 Adsorbents

Adsorbents are used to convert liquids into solids before blending it with the other ingredients in preparing solid dosages. The adsorption is a surface phenomenon and is influenced by the available surface area on the solid. The most efficient adsorbents are small particles. The most commonly used adsorbents are the silica's, microcrystalline celluloses, starches and carbonates (McCarty, s.a.).

2.5.4 Binders/Adhesives

Binding agents are added to tablet formulations to add cohesiveness to powders, providing the necessary bonding to form solid dosages. When choosing a binder its compatibility with the other tablet components should be considered. The binder must impart sufficient cohesion to the powders to allow for normal processing. Allow the tablet to disintegrate and the drug to dissolve in the desired medium. Examples of common tablet binder ingredients are glucose, acacia, gelatine, syrup and starch (Lieberman *et. al*., 1989: 105).

2.5.5 Lubricants

The function of lubricants is to reduce friction and prevent the material from sticking to the tooling. Lubricants are typically fine powders that coat particles and tooling during tableting and encapsulation. In general, water-insoluble lubricants, like magnesium stearate, are more efficient than the water-soluble ones (McCarty, s.a.).

2.5.6 Glidants

Glidants improve the flow properties of powders during processing. The mechanisms responsible for enhancing flow include reducing surface roughness, interparticle friction, cohesive forces, electrostatic forces, and acting as moisture scavengers. The most commonly

used glidant is silica; others include talc, cornstarch and microcrystalline cellulose (McCarty, s.a.).

2.5.7 Disintegrants

Disintegrants facilitate the break-up of a tablet or capsule when placed in an aqueous environment. They facilitate tablet break-up by wicking the water into the tablet and by swelling, the combination of these actions being best. Pregelatinized starch typifies disintegration by swelling, while microcrystalline cellulose typifies wicking. Combining these materials will produce a rapidly disintegrating tablet. Sodium starch glycolate, cross-linked polvinylpyrrolidone and croscarmellose sodium are considered super-disintegrants due to the low amounts needed. Calcium and sodium carboxymethylcellulose, low-substituted hydroxypropylcellulose and alginic acid and its sodium salt, are less commonly used disintegrants. These disintegrants can also act as dry binders, at the same level of use as for disintegration. The common use levels for the disintegrants are given in Table 2.3. (McCarty, s.a.).

Table 2.3. Disintegrants Use Levels

Disintegrant	**Use Level**
Alginic acid	1-5% tablets and capsules
Calcium carboxymethylcellulose	5-15% tablets and capsules
Croscarmellose sodium	0.5-5% tablets, 10-25% capsules
Cross-linked polyvinylpyrrolidone	2-5% tablets
Low-substituted hydroxypropylcellulose	10-15% tablets
Microcrystalline cellulose	5-15% tablets
Pregelatinized starch	5-10% tablets
Sodium alginate	2.5-10% tablets
Sodium starch glycolate	2-4% tablets, 4-8% capsules

The Superiority of the Super-Disintegrants. Visavarungroj and Remon (1990) have shown the superiority of the super- disintegrants over the crosslinked-modified starches. The tablets containing super-disintegrants showed better disintegrating properties over all starch samples investigated. An increase in tablet hardness did not alter the disintegration time of the tablets containing super-disintegrants. Sodium starch glycolate was found to have a 217% increase in

perimeter diameter on wetting and crosslinked polyvinylpyrrolidone a 19% increase in perimeter diameter (Wan & Kanneganti, 1989). Perisutti and co-workers (2003) found a remarkable increase in drug dissolution by adding crosslinked polyvinylpyrrolidone to tablets prepared from the melt granulation method. However, Debunne, Vervaet and Remon (2002) found carboxymethyl cellulose to be a better disintegrant than sodium starch glycolate for the drug, piroxicam.

Effect of sodium starch glycolate's chemical structure on disintegration efficiency. Starch does not swell much in water because of the inter- and intra-molecular hydrogen bonds between the polysaccharide macromolecules, resulting in a rigid structure. Carboxymethylation of starch introduce anionic, strongly hydrophilic groups, which allows it to swell when it is brought into contact with water. An increase in the degree of substitution (increasing electrostatic repulsion) leads to increased rate of tablet disintegration, a gradual increase of cold water solubility and an increased viscosity. Carboxymethylated starch does not facilitate the disintegration of solid dosages. This is because during initial liquid penetration into the tablet an impenetrable viscous barrier is created, which inhibits further water uptake. The introduction of covalent crosslinking bonds improves the disintegration time of the solid dosages. The water uptake capability of carboxymethylated starches is strongly increased at low degrees of crosslinking and decrease at higher degrees of crosslinking. The proper combination of carboxymethylation and crosslinking of potato starch enable the production of sodium starch glycolate with optimal disintegration properties. The presence of sodium chloride, a by-product of the carboxymethylation reaction has a marked effect on the disintegration. The sodium chloride content can be reduced by purification of the sodium starch glycolates (Bolhui, Van Kamp & Lerk, 1984).

The chemical compositions of three sodium starch glycolate products, Explotab®, Primojel® and Vivastar® P were investigated by Edge and co-workers, (2002). Their studies suggest that Primojel® and Explotab® exhibit different chemical compositions to Vivastar® P. The chemical differences may reflect the different manufacturing processes used.

Effect of fillers on disintegration. The water uptake does not alone influence the disintegration time of tablets containing disintegrants. It is the influence of excipients individually and the resultant effect of excipients in combination, that produces a correlation between water penetration into and disintegration of tablets (Wan & Kanneganti, 1989).

Water-soluble fillers tend to dissolve rather than disintegrate, while insoluble fillers produce rapid disintegration. Super-disintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system (Bathia, Desai and Sheth, 1978; Johnson, Wang, Gordon and Chowhan, 1991; Sheen and Kim, 1989).

Crosslinked cellulose, a new tablet excipient provides excellent disintegration and binding properties when used in tablets at levels 10-20%. Crosslinked cellulose is water-insoluble, but is highly absorbent. The properties of crosslinked cellulose were not affected by the solubility of the filler used in the formulation, as in the case of the superdisintegrants. The mechanism of disintegration is governed first by the capillarity, then by the mechanical phenomenon, the breaking up of interparticulate bonds. Tablet disintegration depends on solubility of the filler and/or any formulated ingredient as well as the water uptake of the disintegrating agent. The effect of the filler solubility is, the more soluble the filler, the longer is the disintegration of the tablet. This effect can be explained by the dissolution of the water-soluble filler, increasing the void space of the tablet, then it becomes more difficult for the disintegrant to push against the insoluble remaining matrix, but crosslinked cellulose draws more water to saturate the increased void space, in order to exert the necessary pressure to break apart the granules, thus increasing tablet disintegration (Chebli & Cartilier, 1998).

2.6 Packaging and Storage of Solid dosages

The type of packaging selected depends to a large extent on dispensing customs; certain types tend to predominate in certain countries. Blister packs are preferred in central Europe whereas the English-speaking countries prefer glass or plastic packs. Aluminium strip packs have gained good acceptance in the tropics (Hess, 1985:24).

2.6.1 Blister packs

Blister packs are made from plastic or aluminium laminated foils sealed with an aluminium covering foil. Each drug has an individual cup (Figure 2.8), which, in the case of perforated blister strips, can also be detached as an individual dose. The moisture sensitivity of the dosage form will determine the impermeability of the aluminium foil to water vapour. Additional sealing in aluminium foil may be considered necessary in some cases (Hess, 1985:24).

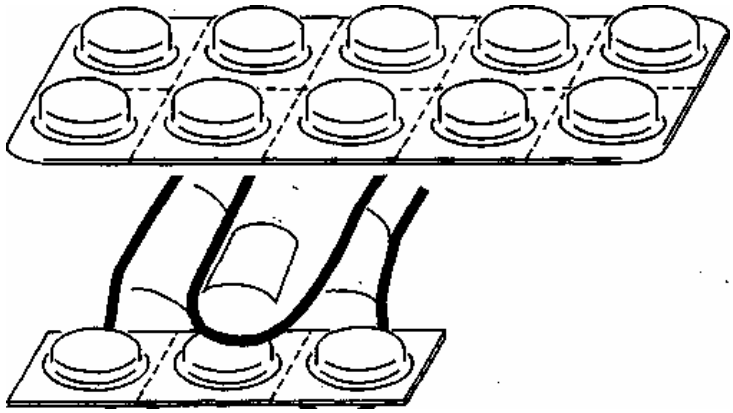

Figure 2.8: Perforated Blister Pack

2.6.2 Strip packs

Strip packs (Figure 2.9) are made from two sealed laminated aluminium foils. The two foils are sealed only in the marginal zone around each individual tablet. Strip packs are used primarily for samples, but it is also employed for individually packed effervescent tablets in tropical countries (Hess, 1985:24).

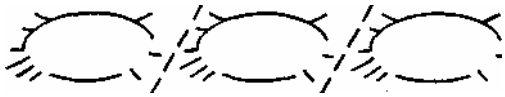

Figure 2.9: Strip Pack

2.6.3 Glass bottles

Brown glass bottles are not being used anymore because of their weight. They are replaced with packs, which are more convenient to produce each dose unit separately. *Plastic containers* are used where relatively big packs are required (Hess, 1985: 25).

2.6.4 Drying agents

A drying agent is a chemical compound that is included in the package to keep the solid dosage form dry. It absorbs the water from the atmosphere surrounding the solid dosage. The drying agent usually employed is silica gel, sometimes mixed with a so-called molecular sieve, which remains active even at very low levels of atmospheric humidity. Silica gel can take up an amount of water equivalent to as much as 40% of its own weight; the molecular sieve is inorganic silicon (Hess, 1985: 25).

The physical and chemical changes that can occur if storage instructions are ignored are shown in Table 2.4.

2.7 Dispersion of Powders in Liquids

The *dispersion process* is the incorporation of a powder into a liquid medium such that the final product consists of fine particles distributed throughout the medium. Fine particles dispersed in liquids is normally termed colloidal if at least one dimension of the particles lies between 10 Å (1 nm) and 10^4 Å (1 μm) (Parfitt, 1973).

The three stages of the dispersion process are:

- Wetting of the powder
- Breaking up of agglomerates and aggregates to form colloidal particles
- Stabilization of the dispersion (Parfitt, 1973).

2.7.1 Wetting of powders

The liquid must wet the external surfaces of the powder and also displace air from the internal surfaces between the particles in the clusters (Parfitt, 1973). The total process can be described as a sequence of three steps shown in Figure 2.10.

Table 2.4. Drugs Storage Issues (Hess, 1985).

Storage instruction	**Dosage form**	**Possible changes**
Protect from heat	Tablets, coated tablets, lacquered tablets	Disintegration (sintering, change in pore structure) → slower release of active substance
	Slow-release forms	Structural alterations → changes in release of active substance
	Solutions	Decomposition of active substance
	Suspensions	Change in crystal structure → changes in release of active substance
	Suppositories	Decomposition of active substance
	Ointments, creams	Decomposition of active substance Crystal growth → slower release of active substance
Protect from moisture	Slow-release forms	Structural changes → changes in release of active substance
	Enteric coated forms	Hydrolysis of film coating → loss of resistance to gastric juice
	Hard-gelatine capsules	Aggregation of contents → slower release of active substance
	Soft-gelatine capsules	Leakage of contents
	All solid dosage forms	Hydrolysis of active substance (decomposition)
Protect from light	Solutions	Decomposition of active substance Discoloration

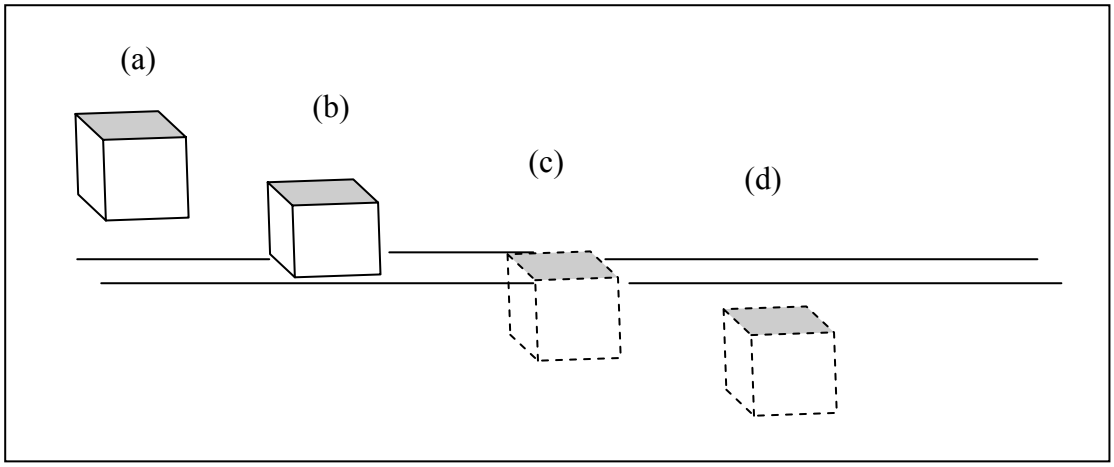

Figure 2.10 The Process of Wetting a Cube Immersed in a Liquid (Parfitt, 1973).

Adhesional wetting. When a plane of solid (S) surface is brought into contact with a plane of liquid (L) surface, unit surface area of each phase disappears to form unit area of the new solid-liquid interface. The work W_a involved in moving from (a) to (b) under isothermal conditions (decrease in free surface energy) was given by Dupre as (Parfitt, 1973):

$$W_a = \gamma_{S/L} - (\gamma_S + \gamma_{L/V}) \tag{4}$$

Immersional wetting. The total immersion of a unit area solid surface into a liquid (from (b) to (c) above) involves exchange of solid-vapour for solid-liquid interfaces without any change in the extent of the liquid surface. The immersional work is given by (Parfitt, 1973):

$$W_i = 4\left(\gamma_{S/L} - \gamma_{L/V}\right) \tag{5}$$

Spreading wetting. When a liquid spreads over a plane solid surface (from (c) to (d) above), every unit area of solid surface that disappears equivalent areas of liquid surface and solid-liquid interface are formed. The work involved is (Parfitt, 1973):

$$W_S = (\gamma_{S/L} + \gamma_{L/V}) - \gamma_{S/V} \tag{6}$$

Values of γ_S, $\gamma_{S/V}$ and $\gamma_{S/L}$ are not readily accessible by experiment, but they are related by the Dupre equation for contact angle equilibrium (often referred to as Young's equation) (Parfitt, 1973):

$$\gamma_{S/V} = \gamma_{S/L} + \gamma_{L/V} \cos\theta \tag{7}$$

Young's equation evaluates the wetting functions in terms of the measurable quantities $\gamma_{L/V}$ and θ, where θ is the contact angle (Figure 2.11) between the solid and liquid phases (Parfitt, 1973).

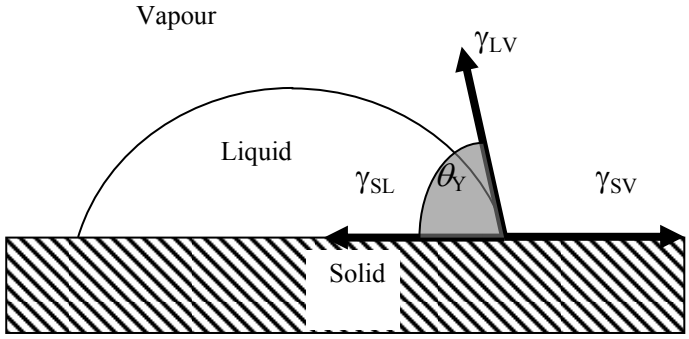

Figure 2.11 Contact Angle Of Liquid And Solid

In this equation the vapour refers to that of the liquid, i.e. the system is at equilibrium with the vapour at its saturated vapour pressure. It is important to remember that equation (8) only applies to a system at equilibrium and for which $\gamma_{L/V}$ and θ have their equilibrium values (Parfitt, 1973).

The process is spontaneous, i.e. when the appropriate W is negative. When W is positive then work must be expended on the system for the process to take place.

Spontaneous adhesion: $W_a < 0$, if $\theta < 180$

$$W_a = \gamma_{S/L} - (\gamma_{L/V} + \gamma_{S/V}) = -\gamma_{L/V}(\cos\theta + 1) \tag{8}$$

Spontaneous immersion: $W_i < 0$, if $\theta < 90$

$$W_i = 4\gamma_{S/L} - 4\gamma_{S/V} = -4\gamma_{L/V}\cos\theta \quad (9)$$

Spontaneous spreading: $W_s < 0$, if $\theta = 0$

$$W_S = (\gamma_{S/L} + \gamma_{L/V}) - \gamma_{S/V} = -\gamma_{L/V}(\cos\theta - 1) \quad (10)$$

Work must be done to achieve spreading at larger values of this angle (Parfitt, 1973).

The total work, W_d, for the dispersion process is given by the sum of the three separate stages,

$$W_d = W_a + W_i + W_s = 6\gamma_{S/L} - 6\gamma_{S/V} = -6\gamma_{L/V}\cos\theta \quad (11)$$

The addition of surface-active agents ensures that θ is often close to zero and spontaneous dispersion is common. When θ is zero or close to zero it is normal to say that the liquid wets the surface; non-wetting means that $\theta > 90^o$. From equation (8) (Parfitt, 1973):

$$\cos\theta = (\gamma_{S/V} - \gamma_{S/L})/\gamma_{L/V} \quad (12)$$

If $\theta > 90^o$ a decrease in $\gamma_{L/V}$ will reduce θ and hence improve wetting. The addition of a surface-active agent usually causes a reduction in $\gamma_{L/V}$ and if adsorbed a decrease in $\gamma_{S/L}$. Both effects lead to a better wetting. The change in $\gamma_{S/V}$ is probably negligible in most cases so that the dominating factor in wetting is normally $\gamma_{L/V}$, the surface tension of the liquid phase (Parfitt, 1973).

The penetration of liquid into the channels of the agglomerates can be estimated from the pressure P required to force a liquid into a tube of radius r, which is

$$P = -2\gamma_{L/V}\cos\theta / r \quad (13)$$

Penetration is only spontaneous (P negative) when $\theta < 90^{o}$. If θ is not zero then, using equation (8),

$$P = -2(\gamma_{S/V} - \gamma_{S/L})/r \quad (14)$$

The important requirement is that $\gamma_{S/L}$ should be made as small as possible since $\gamma_{S/V}$ is virtually constant. However, if θ is zero then $\gamma_{L/V}$ should be large (Parfitt, 1973).

2.7.2 Breaking up the aggregates and agglomerates to form colloidal particles

High mechanical energy is required to break down aggregates completely, to the point where the surface of each primary particle is available to the wetting liquid. Agglomerates are held together by weak forces, they normally require less energy to be broken down. Many factors are involved in the powder achieving its particular state, so that knowledge of its manufacture and/or storage conditions is necessary for the problem of breaking the bonds between particles in the clusters (Parfitt, 1973).

2.7.2.1 The adsorption of surface active agents

The adsorption of surface active agents (Figure 2.12) at the solid - liquid interface is dependent on the structure of the surface active agent and the nature of the solid and liquid. The nature of the adsorption is largely controlled by three factors:

- The chemical nature of the species being adsorbed, including the nature of the head group (anionic, cationic, non-ionic, etc.) and that of the hydrophobe (length and nature of the chain, degree of branching, etc.)
- The nature of the solid surface onto which the surfactant is being adsorbed (highly charged, nonpolar, etc.) and
- The nature of the liquid environment (in water the pH, electrolyte content, temperature, additives, etc.).

A slight change in one of these or other factors can result in a major change in the adsorption characteristics of the system (Kissa, 1999).

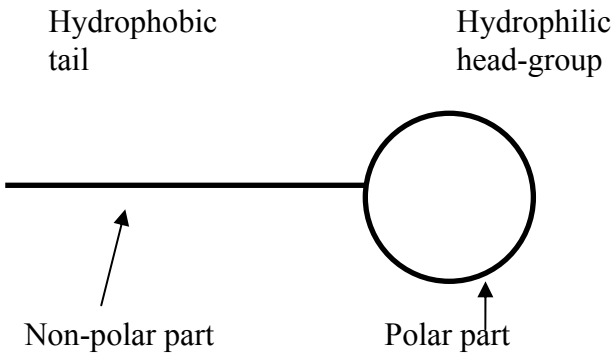

Figure 2.12 Schematic Surfactant Molecule

2.7.3 Dispersion Stabilisation

Dispersions are stable if there is no change in the total number of particles with time. The three reasons why instability may occur,

- The large interfacial energy is reduced by crystallization into larger particles
- Sedimentation under gravity
- Kinetic phenomena, Brownian motion cause particles to collide and stick to each other because of adhesion (Kissa, 1999).

The mechanisms to prevent inter-particle collisions are discussed below.

2.7.3.1 Particle interactions

When particles approach each other at close range, the following interactions are involved,

- London – Van der Waals attraction
- Coulombic attractive/repulsive force
- Repulsive forces resulting from solvation and adsorbed layers (Kissa, 1999).

London-Van der Waals attraction. Electromagnetic interactions from permanent, transient or induced dipoles in particles create London-Van der Waals attractive forces. The attractive potential between two identical, spherical particles is a function of the properties of the particles, the medium and the separation distance of the particles, according to the relation, (Kissa, 1999).

$$V_A = \frac{C}{12h} \tag{15}$$

Coulombic repulsion. The Coulombic repulsive force results from the overlap of the electrical double layers that surround polar particles in high dielectric constant media as they approach each other at close range. The distance at which the repulsive forces become significant increases with the thickness of the double layer (1/κ). The force increases with the surface potential (ψ_o), according to equation: (Kissa, 1999).

$$V_R = V_R\left\{\Psi_o \exp\left(-\kappa / h\right)\right\} \tag{16}$$

Steric interaction. Polymer chains attached to the particle suface require long, highly soluble, chain segments that extend to a distance (δ) into the solvent. These chains hinder the close approach of two particles. Steric repulsion is limited over inter-particle distances less than s = 2δ . An approximate inter-particle potential is given by:

$$V_S = \pi\rho_1 RT\phi^2\left(0.5-\chi\right)\left(2\delta - s\right)/M_L \tag{17}$$

The Flory interaction parameter χ is both temperature and solvent dependent. Low values of χ indicate high solvation of chain segments. The chains take up extended configurations corresponding to a swollen state. The theta condition applies when the value of χ equals 0.5. This corresponds to incipient collapse of the chains and precipitation of the polymer (Kissa, 1999).

2.7.3.2 The total interaction energy

The total potential energy V_{tot} for the system is given by the sum of the double layer repulsion (V_R) and the van der Waals attraction (V_A) forces. The form of the resulting potential energy against distance relationship will be dependent upon the relative magnitudes of the two forces. V_R decreases exponentially with distance while V_A shows an approximate inverse relationship with the square of the distance. Attraction predominates at short distances. Otherwise the form of the V_{tot} curve depends to a large extent on the V_R term. Figure 2.13 illustrates the type of plot we might expect for particles of radius 0.1-1μm in an aqueous system containing about

0.01M of 1:1 electrolyte for which the range of attractive and repulsive forces are similar (Parfitt, 1973).

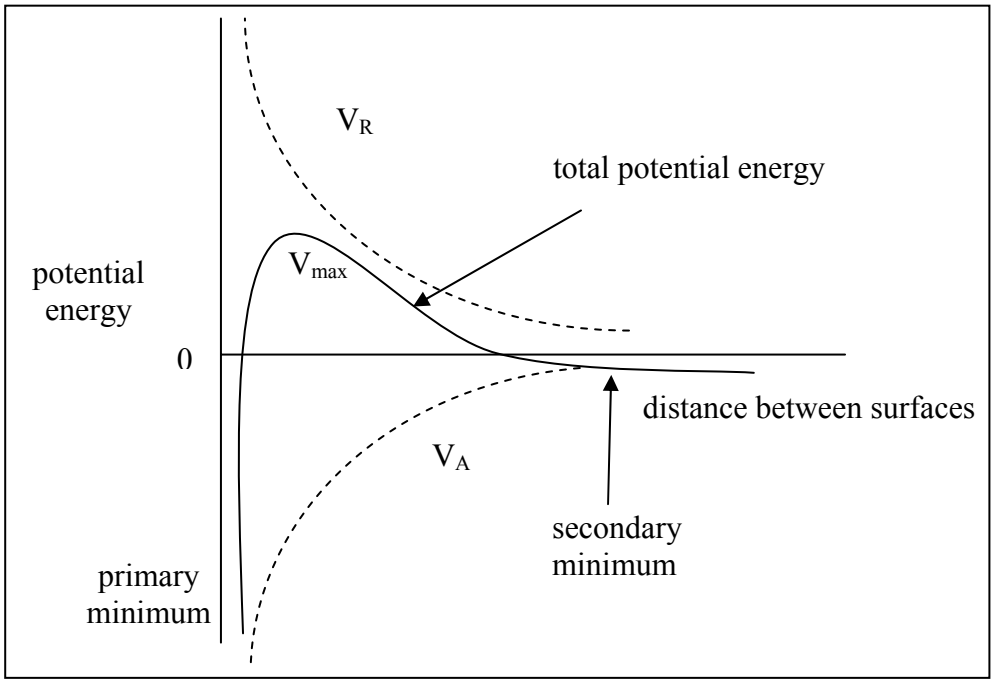

Figure 2.13 Potential Energy Curves For The Interaction Of Two Charged Surfaces.

Three important characteristics are shown in Fig 2.13 and these are directly related to flocculation behaviour.

- The potential energy barrier must be surmounted before the particles make lasting contact in the primary minimum. Provided the barrier is considerably larger than the thermal energy of the particles, relatively few will make contact and the system should be stable.
- But if the secondary minimum is of depth > *kT* then the particles would flocculate with a liquid film between them in the cluster. Since both the attractive and repulsive forces are approximately proportional to the particle radius, the secondary minimum should become increasingly significant with increasing particle size, and particularly so with parallel plates. The effect will also increase with increasing electrolyte concentration, which reduces the energy barrier, which again would promote flocculation. Systems which have flocculated into the secondary minimum tend to be reversible, i.e. they can be readily re-dispersed (peptised) with shaking; those in the primary minimum need considerably more energy to re-disperse (Parfitt, 1973).

The effect of reducing the electrolyte concentration (increasing $1/\kappa$ at constant ψ_o) on the total potential energy is shown in Figure 2.14 and illustrates the difference between dispersions in aqueous and non-aqueous solutions of a surface active agent of the same stoichiometric concentration (Parfitt, 1973).

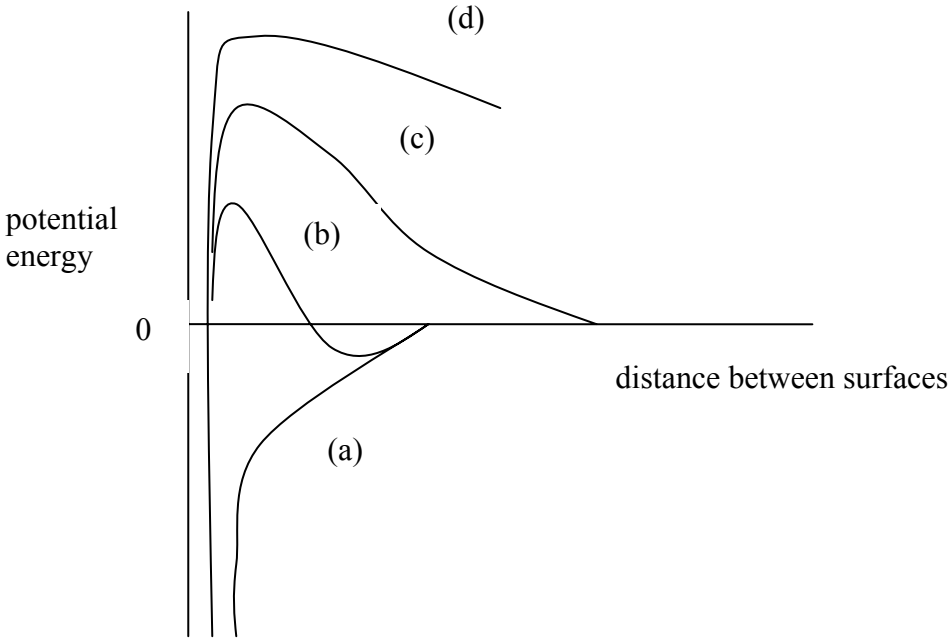

Figure 2.14: Influence Of Electrolyte Concentration On The Total Potential Energy Of Interaction Ot Two Spherical Particles Of Radius 1000 Å In Aqueous Media. (a) $1/\kappa = 10^{-7}$ cm, (b) $1/\kappa = 10^{-6}$ cm, (c) $1/\kappa = 10^{-5}$ cm, (d) $1/\kappa = 10^{-4}$ cm (Parfitt, 1973).

3. Experimental Design

3.1 Raw materials

3.1.1 Urea (H_2NCONH_2)

Urea is used as a commercial fertiliser to promote crop protection by supplying nutrients to plants (Watson, 2000). Urea is the compound chosen for use as the main ingredient for the inert carrier. It is inexpensive and it has high water solubility (1193g/liter). Urea is a slightly basic compound with a pH of 7.2 and a molecular weight of 60.06 g/mol. It also has a very

low toxicity. Urea [57-13-6] prils were supplied by Sigma-Aldrich (Cat. No. U270-9), and dried over silica gel (Promark Chemicals).

The problem with urea is it decomposes at its melting point of ca. 132ºC – 134^{o}C. This problem can be overcome by using a suitable urea eutectic to lower the melting point (Ozawa, 1985). The following were tried as eutectic formers for urea:

$CaBr_2.nH_2O$ [71626-99-8]**.** $CaBr_2.nH_2O$ is very soluble in water. Sigma-Aldrich (Cat. No. 23,374-9] supplied this compound. It is very hygroscopic and has to be stored in a sealed container. $CaBr_2.nH_2O$ was dried over silica gel (from Promark Chemicals) and then hydrated with 2 moles of water per molecule $CaBr_2$. It was tested to form a eutectic with urea.

PEG 6000 and 4000 $(-CH_2CHOH-)_n$. Urea forms inclusion compounds with polyethylene glycols. These show higher melting points than the two compounds. The inclusion compounds do not form eutectics but monotectics. Polyethylene glycols improve the solubility of active substances for pharmaceutical usage (Brandstatter *et al*., 1994).

Acetamide (CH_3CONH_2) [60-35-5]**.** Urea 40% m/m and Acetamide 60% m/m forms a eutectic at 55^{o}C (Bokhovkin *et al.*, 1976). Acetamide was supplied by Sigma-Aldrich (Cat. No.12,263-7). It has a melting point of 80^{o}C and a molecular weight of 59.07 g/mol. Acetamide was dried over silica gel (Promark Chemicals). This eutectic mixture is not approved for industrial use because of the high toxicity levels.

1,3-Dimethylurea ($CH_3NHCONHCH_3$). Urea 40% m/m and 1,3-Dimethylurea 60% m/m forms a eutectic at ±56^{o}C. This eutectic mixture is very hygroscopic and has to be sealed from the atmosphere. It was dried over silica gel (Promark Chemicals). 1,3-Dimethylurea [96-31-1] was supplied by Sigma-Aldrich (Cat. No. D19, 045-4).

3.1.2 Amitraz ($C_{19}H_{23}N_3$)

The acaricide N-methylbis (2,4-xylyliminomethyl) methylamine (Amitraz^{TM}) is the pesticide to be delivered as a solid dispersed drug. It is a pale yellow powder with a melting point of 86-87^{o}C and a molecular weight of 293.4 g/mol. Amitraz is a very weak base and is unstable

in acid solution. It undergoes hydrolysis to ultimately yield 2,4-dimethylformanilide and methylamine (Corta *et al*., 1999). See Appendix B for details of the hydrolysis reaction.

Amitraz has a very low solubility in water (less than 1mg/liter). The solubility in xylene is 666g/litre, in acetone 500g/litre and in methanol 23.8g/litre. Methanolic solutions are also unstable, but solutions in dimethylformamide or isopropanol are less so (FAO, 1980). Amitraz is relatively heat stable in neat form and in dry inert solvents such as xylene or toluene (FAO, 1980).

The pesticide used in these experiments was pure Amitraz with an average particle size of 60 μm (Appendix C), supplied by Bayer and a milled powder blend with 21% m/m calcium carbonate. The particle size of the latter was about 99% smaller than 38 μm.

3.1.3 Wettol D2 (sodium naphthalenesulfonic acid-formaldehyde-polycondensate)

Wettol D2 is the dispersant that was chosen as the primary wetting agent. It is a brownish powder with a melting point of 280^{o}C. Its solubility in water is approximately 400g/litre at 20^{o}C. Bayer supplied Wettol D2.

3.1.4 Arkopal N090 (Nonylphenol-ethoxylate 9)

Arkopal N090 is the surfactant that was chosen as the dispersant for Amitraz. It is a clear viscous liquid at room temperature with a density of 1 in water. The optimum dosage Arkopal N090 was determined for Amitraz.

3.1.5 Calciumcarbonate ($CaCO_3$)

Calcium carbonate improves the milling process for Amitraz. Calcium carbonate also stabilises Amitraz in suspension. The $CaCO_3$ buffers the pH of the water at ca. pH = 10 (George *et.al* 1998). Bayer supplied the $CaCO_3$ as a milled mixture with Amitraz.

3.1.6 Super disintegrants – Sodium starch glycolate, Croscarmellose sodium, Crospovidone and Kollidon

These compounds are used in the pharmaceutical industry as super disintegrants. They improve the dissolution rate of tablets and capsules (McCarthy, 2003).

Sodium starch glycolate (STG). STG, NF, JPE, Type A Ph.Eur., Type A BP (Explotab®) was supplied by Penwest Pharmaceutical Co (Lot No: E9568X) obtained via Chempro. STG, NF/BP (Explotab® low pH) was supplied by Edward Mendell Co (Lot No: E4800). STG, Ph.Eur. (Type A), USP/NF (Vivastar® P) was supplied by J. Rettenmaier & Söhne (Batch No: 2111034188). The properties of the three types of sodium starch glycolate used in the present study are listed in Table 3.1.

Table 3.1. Physical Properties Of Different Types Of Sodium Starch Glycolate

Property	Explotab®	Explotab® low pH	Vivastar® P
Appearance	White powder	White powder	White powder
Particle size	35-55 µm	106 µm	106 µm
pH	6.6	6.8	5.8
Sodium chloride	3.6 %	4.6%	4.5%
Sodium glycolate	0.5%	0.54%	<2%

Croscarmellose sodium. Vivasol® was supplied by J. Rettenmaier & Sohne (Batch No: 3211041005). The particle size range is between 45 µm and 75 µm. The pH is 6 and the degree of substitution, 0.79. The sodium chloride and sodium glycolate content is less than 0.5%. Jonhson et. al. (1991) has shown that hygroscopic excipients decrease the efficiency of croscermellose sodium.

Crosslinked Polyvinylpyrrolidone (1-Ethenyl-2-pyrrolidinone homopolymer). Crospovidone® [9003-39-8] was supplied by BASF and obtained via the CSIR. It has a pH of 5-8 and a particle size distribution of 50% greater than 50 µm and maximum of 1% greater than 250 µm.

3.2 Experimental Methods

3.2.1 Selection of Dispersant

Viscosities versus surfactant concentration measurements were performed to determine the optimum additive dosages for a concentrated 30% m/m Amitraz suspension. Dispersions were prepared in distilled water at room temperature (25 ± 2°C) using an Ultra Tarrax T25 high shear mixer. Mixing was maintained for ± 5 min. The viscosity was measured with a Brookfield Digital Viscometer Model DV-II at a speed of 60 rpm using Spindle No. 3. After

addition of surfactant, the suspension was mixed with the high shear mixer for ± 2 minutes before the viscosity was measured. Readings were taken for surfactant concentrations in the range ca. 0 - 10%. The optimum surfactant level for wettable powder was determined from the minimum in the viscosity vs. composition plots.

3.2.2 Melting-Cooling Method for Eutectic Characterization

Cooling curves were obtained with the melting-cooling method. All experiments were performed in a hood.

Urea and the eutectic forming component were ground together with a mortar and pestle. The physical mixture was then heated in a glass tube immersed in a silicon oil bath on a hot plate. The mixture was continuously stirred until a homogeneous liquid formed. The sample tube was then transferred to and inserted into a Pyrex beaker.

The liquid was allowed to cool down and solidify at ambient conditions. The time-dependant temperature change of the sample was tracked with a thermocouple. The data was captured in real time on a personal computer. The data was analysed using an Excel spreadsheet programme.

3.2.3 Melting – Cast/Press – Dissolution Method

Melt-Casting. Trial formulations were molten in a glass tube. The urea and eutectic former were first melted. Discs measuring 5 mm thick and 35 mm ϕ were cast using O-rings placed on polyester foil. This resulted in disks weighing about 5,0 g. Different ratios of disintegrant were added to the molten eutectic and cast to the same dimensions as above.

Melt-Press. Amitraz and excipients were added to the molten eutectic mixture. Thereafter it was weighed into a polypropylene tube and pressed with a load of 180 kg into disks measuring 5 mm thick and 35 mm ϕ. This resulted in disks weighing about 5,0 g. It was possible to suspend Amitraz in the eutectic melt mixture provided it remained in powder form. However, when liquefied, the system tended to phase separate. Thus the temperature of the eutectic mixture should be kept below the melting point of Amitraz, i.e. 80^{o}C. The Load Cell used is a 25835 Sub 100 kN, from Load Cell Services Pty. Ltd. The HBM Digitalizer DA

24, Equipment number: 13035 displayed the digital values. The data was acquired from the HBM KWS 3037, factory number: 97086.

Figure 3.1 Schematic Of Cooling Curve Measurement Setup.

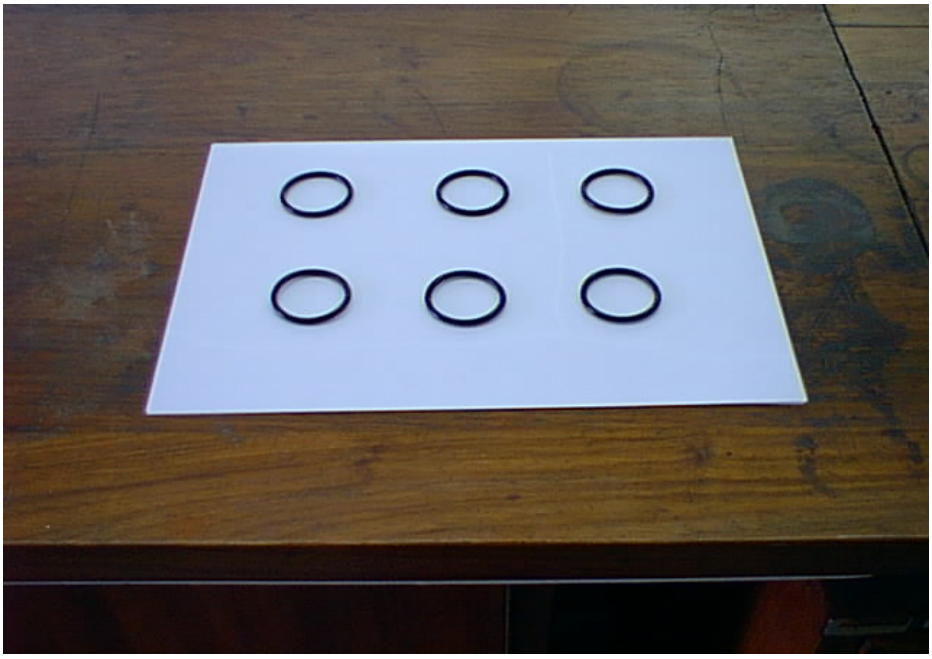

Figure 3.2 Schematic Of Cast Setup.

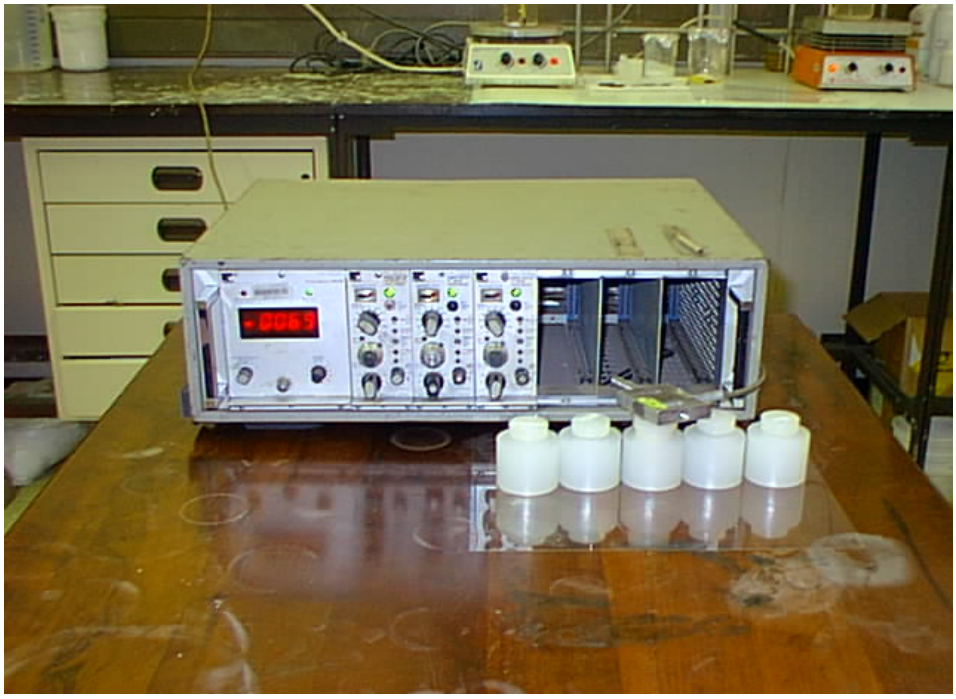

Figure 3.3 Schematic Of Press Setup.

Dissolution. The time of complete dissolution was measured as follows. A disk was placed into a large beaker containing 10 litre of tap water at room temperature (± 25^{o}C). The water was stirred with a 60 mm magnetic stirrer bar at a speed of 50 rpm. The dissolution of the tablet was followed by visual inspection. The time taken for complete dissolution was measured with a stopwatch.

3.2.4 Characterisation of Compounds and Solid Dispersion

Particle Size Analysis. The average particle size of pure Amitraz was determined with the Mastersizer 2000, Malvern Instruments using distilled water as the liquid medium.

X-Ray Powder Diffraction Analysis (XRD). Phase identification was carried out by XRD analysis performed on a Siemens D-501 automated diffractometer Cu Kα (1.5406 Å) operated at 40 kV and 40 mA. This machine is equipped with a divergence slit of 1^{o}, a receiving slit of 0.05^{o}. The sample was scanned from between 3 to 70^{o}, on a 2θ-scale with a counting time of 1.5 s at room temperature.

Figure 3.4 Schematic Of Dissolution Measurement Setup.

Thermal Analysis (DTA/TGA). A Mettler Toledo A851 simultaneous TGA/SDTA machine was used for the thermal and gravimetric analysis. The TGA and DTA graphs were obtained with nitrogen as purge gas at a scanning rate of 5^{o}/min from 25^{o}C – 250^{o}C. Samples weighing 15 mg were used and the experiments were performed in 70µl alumina crucibles with lids.

Differential Scanning Calorimetry (DSC). A Perkin Elmer DSC 7 was used to determine the eutectic point of the urea – 1,3-dimethylurea mixtures. The samples were heated to 110^{o}C with a heating rate of 10^{o}/min and purged with nitrogen gas.

Light Microscopy. A Nikon Digital Camera DXM 1200 No: 00401 were used to capture the crystallization of the eutectic mixture and the individual compounds.

Turbidity Test. The dissolution time of the drug from the solid dosage forms was determined with a Turbidimeter Model 2100A from Hach Chemical Company. The standard used was a 10 NTU, Cat No: 2480.

4. Results and Discussion

4.1 Selection of Dispersant

The experimental results obtained for a 30% m/m Amitraz suspension are reported in Figures 4.1 – 4.4. They suggest an optimum Arkopal N090 dosage of ca. 2% and Wettol D2 of ca.1%.

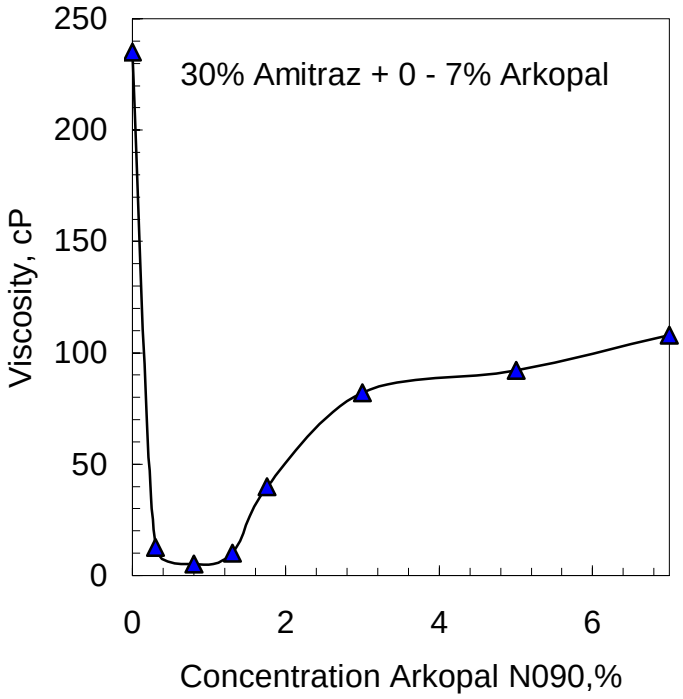

Figure 4.1 The Effect Of Arkopal N090 On The Viscosity of a 30% m/m Amitraz Suspension.

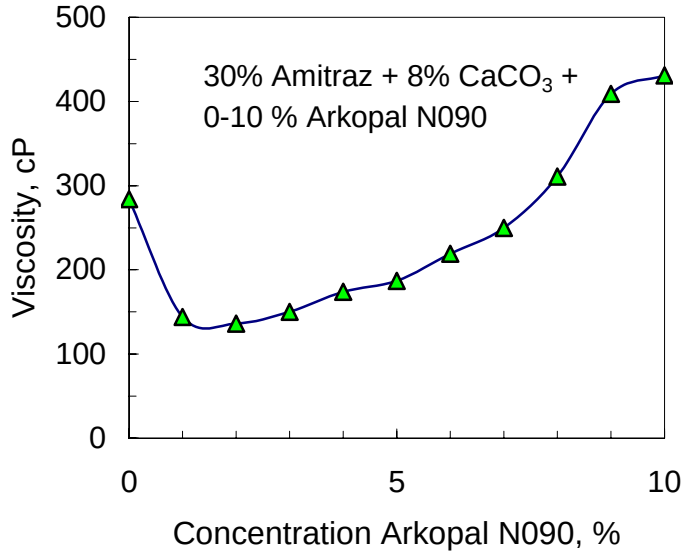

Figure 4.2 The Effect of Arkopal N090 on the Viscosity of a 30% m/m Amitraz + 8% $CaCO_3$ suspension

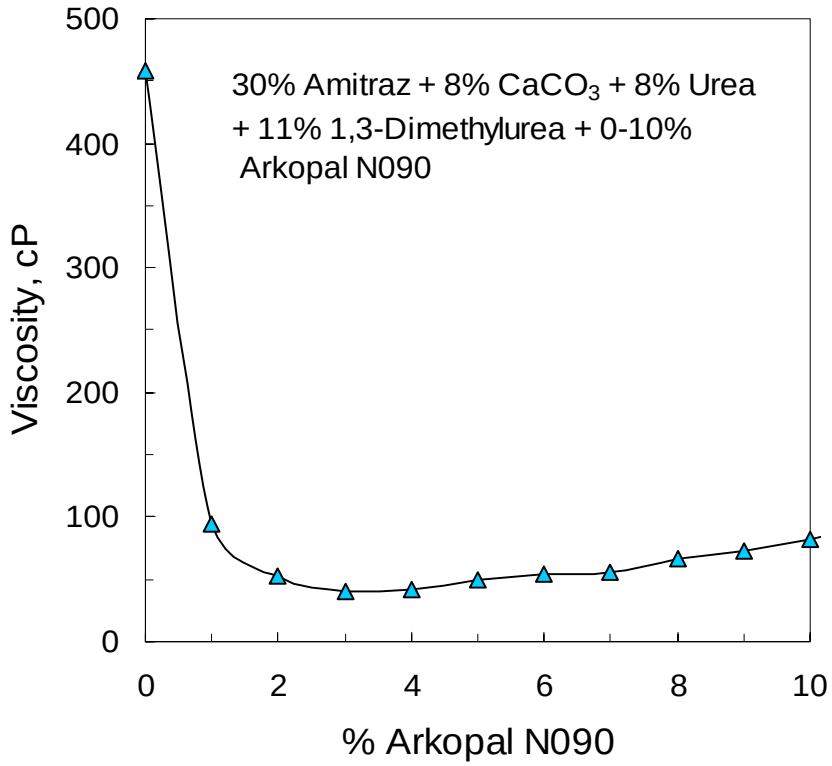

Figure 4.3 The Effect of Arkopal N090 on the Viscosity of a 30% m/m Amitraz + 8% $CaCO_3$ + 8% Urea + 11% 1, 3-Dimethylurea Suspension

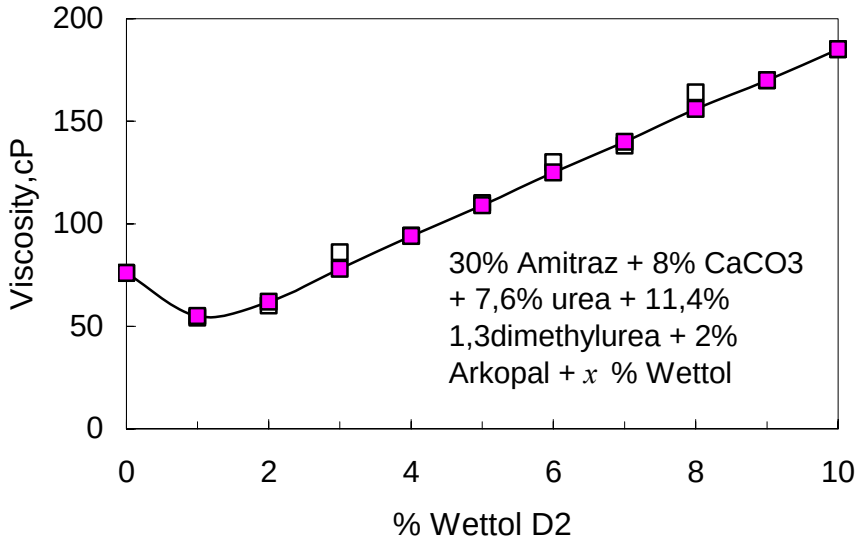

Figure 4.4 The Effect of Wettol D2 on the Viscosity of a 30% m/m Amitraz + 8% $CaCO_3$ + 8% Urea + 11% 1, 3-Dimethylurea + 2% Arkopal N090 Suspension

4.2 Melting – Cooling Method for Eutectic Characterisation

4.2.1 Urea – $CaBr_2.2H_2O$ Mixture

The preliminary experimental results shown in Figure 4.5 indicate that urea and $CaBr_2.2H_2O$ forms a eutectic at ± 57°C with a composition of ca. 70 % Urea.

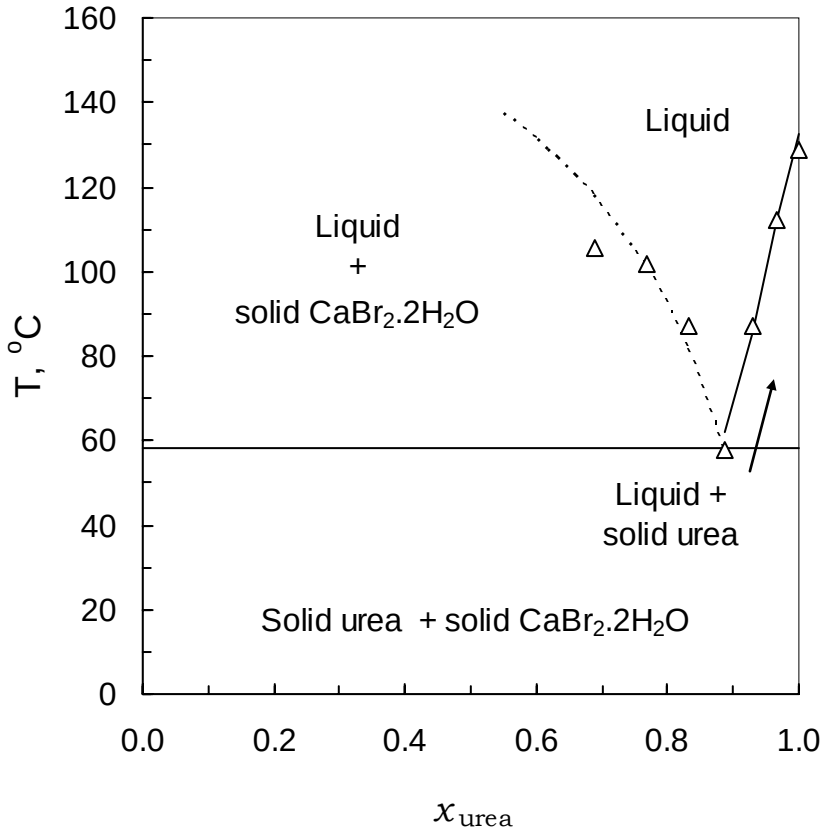

Figure 4.5 Liquid-Solid Phase Diagram of Urea-$CaBr_2.2H_2O$ System

The cooling curves for each composition are presented in Appendix D, Figure 1. The DTA results of urea and $CaBr_2.2H_2O$ (Appendix E, Figure 1 and 2) indicate a sharp dip in temperature for urea at 135°C. The $CaBr_2.2H_2O$ compound loses water in the temperature range of 52 – 194°C.

Pure urea forms a tetragonal crystal structure (Appendix F, Figure 1). The XRD results (Appendix F, Figure 2) indicate the presence of monoclinic $CaBr_2.6CO(NH_2)_2$ crystals at the eutectic point. However the DSC results (Appendix G, Figure 1) show two melting endotherms. This implies that the sample was not pure. Note that Durski (1972) prepared $CaBr_2.4CO(NH_2)_2$ crystals using the solvent evaporation method.

Addition of small amounts of PEG 6000 improved the tablet strength of the Urea-$CaBr_2.2H_2O$ mixture but decreased the dissolution rate of the eutectic.

4.2.2 Urea – PEG 6000 Mixture

Urea and PEG 6000 form a monotectic and a eutectic at low urea to PEG 6000 mass ratios (Kuhnert *et al*., 1995).

4.2.3 Urea – Acetamide Mixture

The preliminary experimental results shown in Figure 4.6 indicate that urea and acetamide forms a eutectic at ± 46°C with a composition of ca. 40 % urea.

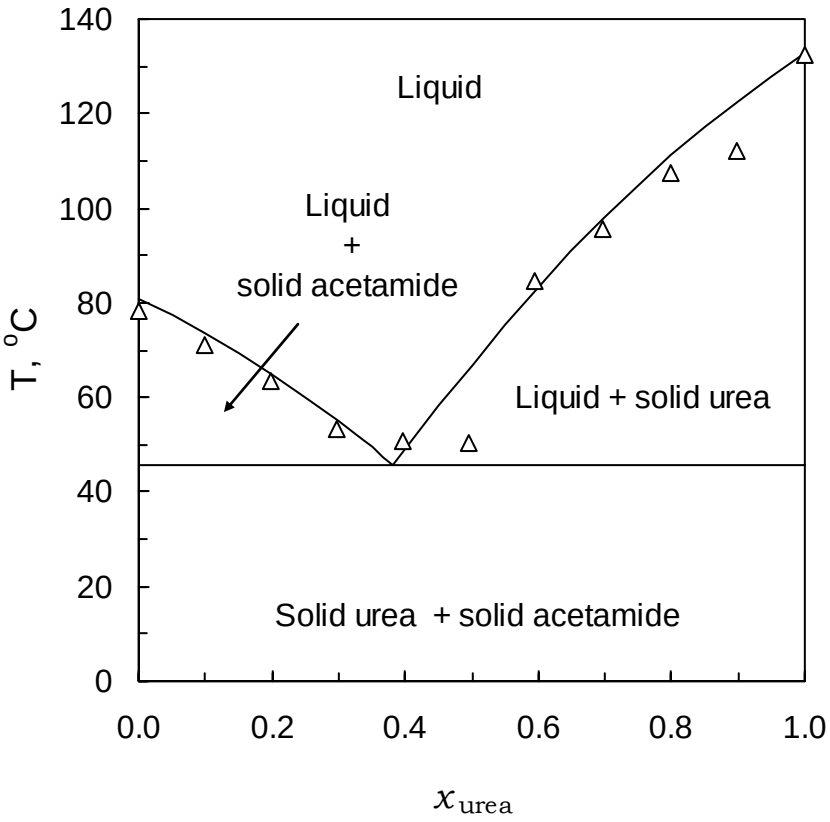

Figure 4.6 Liquid-Solid Phase Diagram of Urea-Acetamide System

Cooling curves were obtained for each composition (Appendix C, Figure 2). Bokhovkin (1964) showed the melting point of ca. 40% urea eutectic mixture is at 55°C. The slight difference in results might be because of purity differences in the used chemicals or a difference in the test conditions.

4.2.4 Urea-1, 3-Dimethylurea Mixture

The preliminary experimental results shown in Figure 4.7 indicate that urea and 1,3-dimethylurea form a eutectic at ± 56°C with a composition of ca. 40% urea.

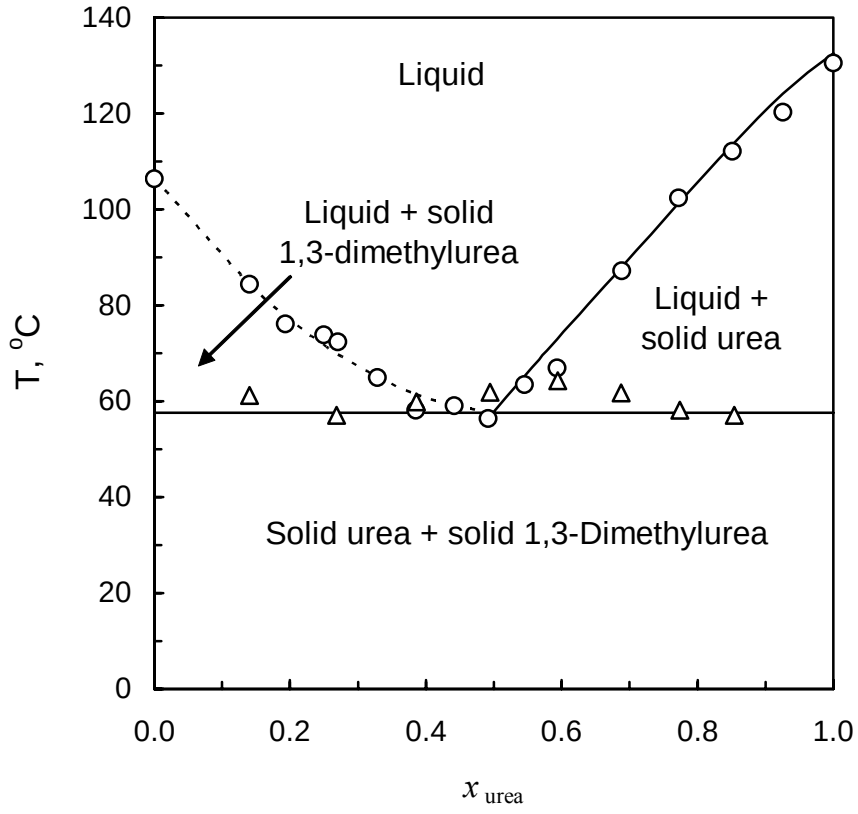

Figure 4.7 Liquid-Solid Phase Diagram of Urea - 1, 3-Dimethylurea System

Cooling curves were obtained for each composition (Appendix C, Figure 3). The DTA graph shows that there is a dip in temperature for 1,3-dimethylurea at 102.45°C (Appendix E, Figure 3). However, DSC results indicate the eutectic point to be at ± 60°C (Appendix F, Figure 2-10). The reason for the shift in the eutectic point might be related to the forced crystallization of the compounds in the DSC instrument. Light microscopy reveals separate crystals of the two compounds (Appendix H). This implies that urea and 1,3-dimethylurea crystallize as separate crystals when cooled to room temperature. XRD confirms the presence of two separate crystals (Appendix E, Figure 4). Urea (Appendix F, Figure 1) crystallizes as tetragonal crystals and 1,3-dimethylurea (Appendix F, Figure 3) crystallizes as orthorhombic crystals.

4.3 Melting – Cast/Press – Dissolution Method

4.3.1 Melting - Cast - Dissolution

4.3.1.1 Urea, 1,3-Dimethylurea and Eutectic Mixture

The effect of tablet size on dissolution time for urea, 1,3-dimethylurea and the eutectic mixtures is shown in Figure 4.8. Several large discs (35 mm ϕ and ca. 5 mm thick) were cast for each of the compositions tested. Test specimen samples were prepared by repeatedly cutting the discs in two halves.

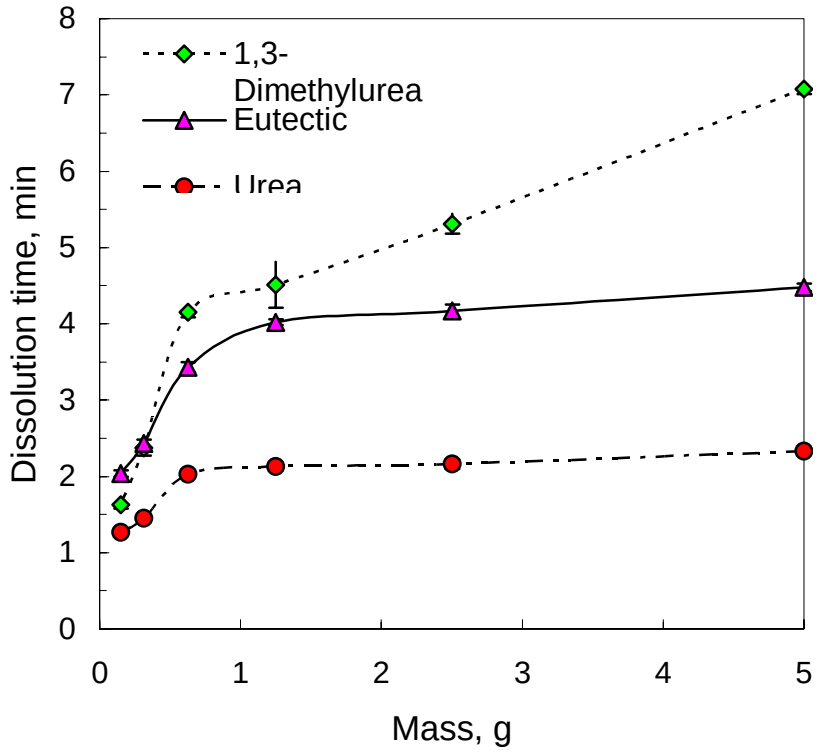

Figure 4.8 The Effect of Tablet Size on the Dissolution Time of Urea, 1,3 Dimethylurea and the Eutectic Mixture

The dissolution time for the eutectic mixture and pure urea approaches a plateau value above a sample mass of 1 gram. Urea having the fastest dissolution time of ±2 minutes followed by the eutectic mixture of ±4 minutes. The dissolution time of 1,3-dimethylurea is affected by tablet size.

4.3.1.2 Eutectic mixture and Disintegrants

Sodium starch glycolate (Explotab®) have shown to be the best disintegrant for the eutectic mixture (Figure 4.9).

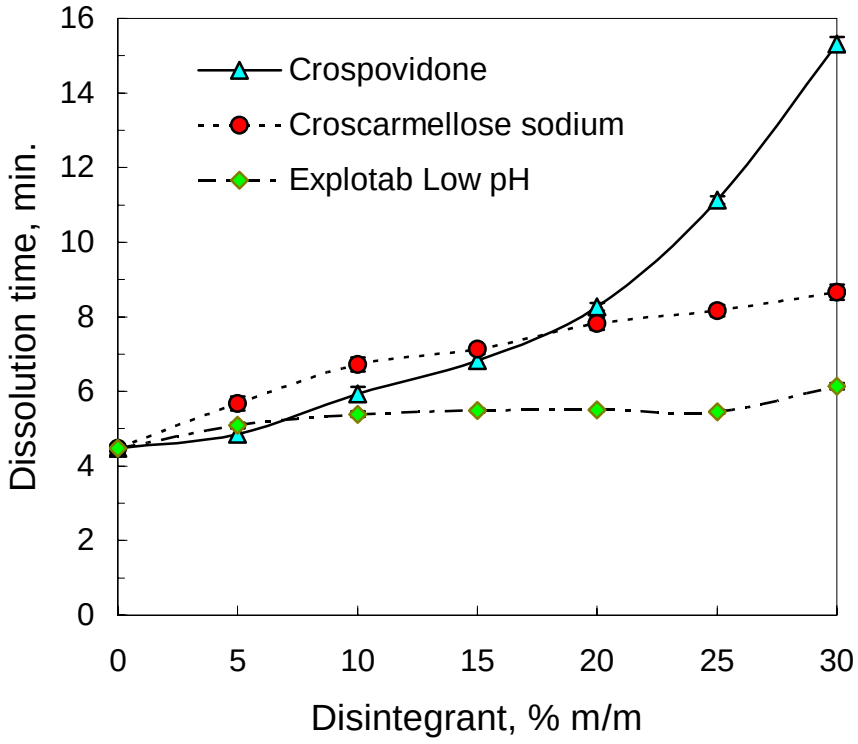

Figure 4.9 The Effect of the Disintegrants on the Dissolution Time of the Eutectic Mixture

Explotab® reduced the hygroscopicity of the eutectic mixture without having a significant effect on its dissolution rate. It is an amorphous compound (Appendix F, Figure 5) and might form a clathrate with the eutectic mixture (Appendix F, Figure 6). The DTA results (Appendix E, Figure 4) show that Explotab® starts losing water at 32^{o}C. A dip in temperature at 62^{o}C was observed for the 85% m/m eutectic and 15% m/m Explotab® mixture (Appendix E, Figure 5). This disintegrant was considered as a potential excipient for the final formulation. Addition of disintegrants to the eutectic mixture improved its hardness greatly. This was most obvious for crospovidone and croscaremellose sodium. The strong adhesive forces these disintegrants form can be the reason for the reduced dissolution rate.

4.3.2 Melting - Press - Dissolution

4.3.2.1 Eutectic mixture, Amitraz and Excipients

The excipients mentioned above are $CaCO_3$, Arkopal N090 and Wettol D2. Their ratios in the formulation are: 8% $CaCO_3$, 1%- Wettol and 2%-Arkopal to 30% m/m Amitraz.

The dissolution time of Amitraz was increased when used as a solid dispersion in the eutectic mixture (Figure 4.10).

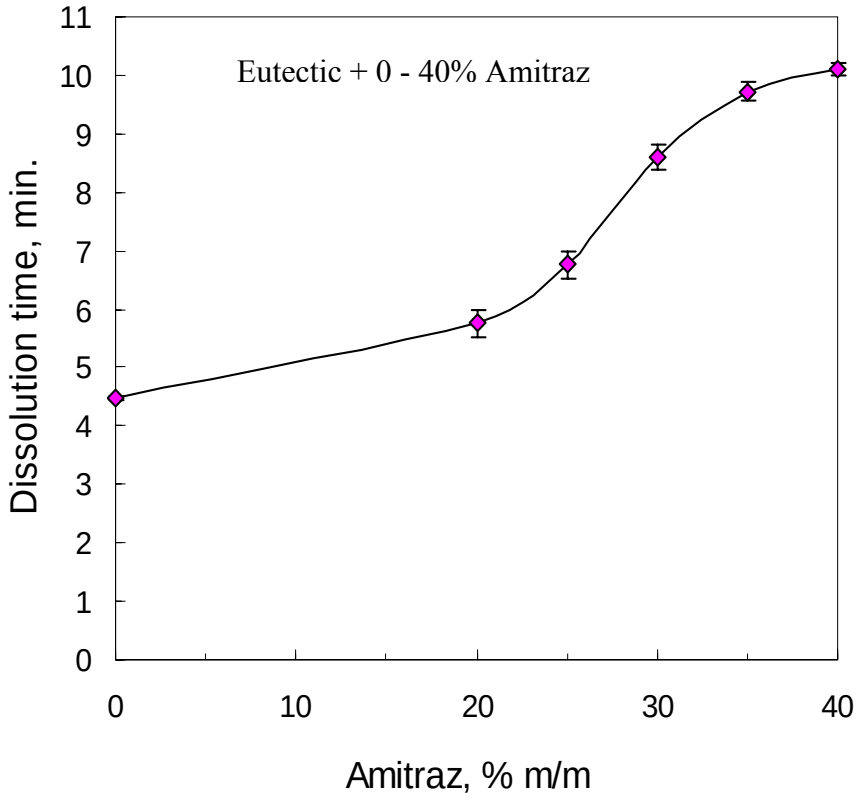

Figure 4.10 The Effect of the Eutectic Mixture as a Carrier on the Dissolution Time of Amitraz. All Samples Contained ca. 8% $CaCO_3$, 1%- Wettol and 2%-Arkopal to 30% m/m Amitraz

The dissolution time increased as the Amitraz content increased. The reason for this may be because of agglomeration of the insoluble drug in the soluble matrix. As the drug percentage increases in the formulation, the soluble matrix may be insufficient to encapsulate all the drug particles. It is also possible that the Amitraz powder might have melted during the sample preparation: The DTA graph shows a dip in temperature for pure Amitraz at 82^{o}C (Appendix E, Figure 6) and forms a crystal structure according to Appendix F, Figure 7.

20% Amitraz

The dissolution time of the solid dosage form was confirmed with a Turbidity test (Figure 4.11).

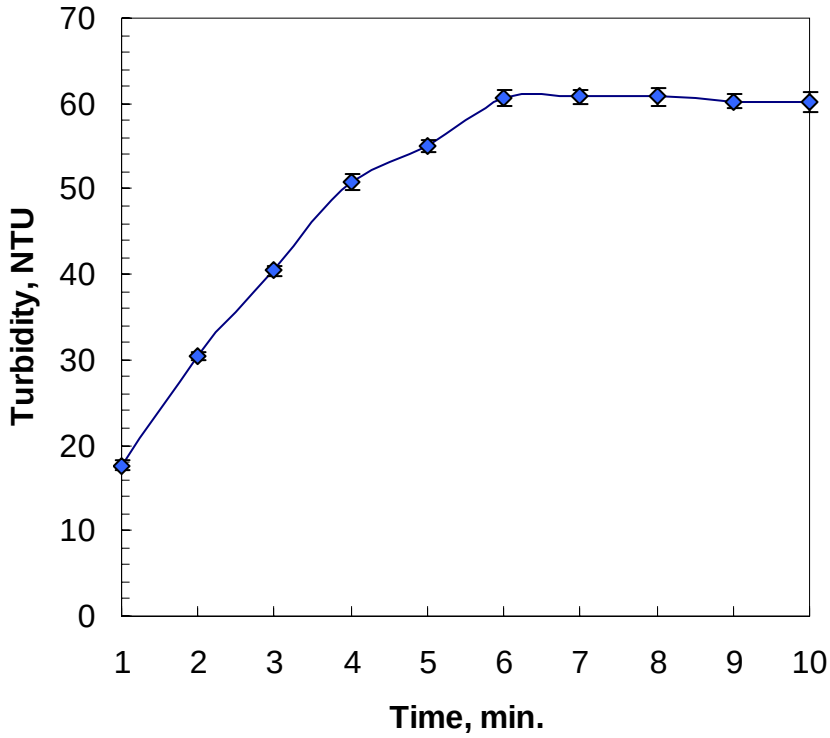

Figure 4.11 The Change in Turbidity as a Function of Time

The turbidity increase as Amitraz is released from the solid dosage form and reaches a constant value at ±6 minutes. This dissolution time corresponds to the dissolution tests performed with the 10-litre beaker and stopwatch.

The DTA graph shows two endothermic peaks for the solid dosage form (Appendix E, Figure 7). The eutectic mixture starts melting at 66^{o}C followed by Amitraz at 82^{o}C. The XRD pattern (Appendix F, Figure 8) shows the presence of urea, 1,3-dimethylurea and Amitraz crystals.

30% Amitraz

The DTA graph shows 3 endothermic peaks, 63^{o}C for the eutectic mixture and 81^{o}C for pure Amitraz (Appendix E, Figure 8). The peak at 144.70^{o}C might be the decomposition of urea.

The XRD pattern (Appendix F, Figure 9) shows the presence of the components of the eutectic mixture and pure Amitraz crystals.

40% Amitraz

The DTA graph shows 3 endothermic peaks, 61°C for the eutectic; 81°C for Amitraz and 169°C might be due to urea decomposing (Appendix E, Figure 9). The three distinct crystals of the 3 main compounds: urea, 1,3-dimethylurea and Amitraz can be seen from the XRD pattern (Appendix F, Figure 10).

Appendix F, Figure 11 compares all the above patterns. The Amitraz peak (12) increases with the addition of % m/m Amitraz to the formulation.

4.3.2.2 Eutectic mixture, Amitraz, Sodium starch glycolates and Excipients

Mixed results were obtained for the 20% m/m Amitraz with the different sodium starch glycolates (Figure 4.12).

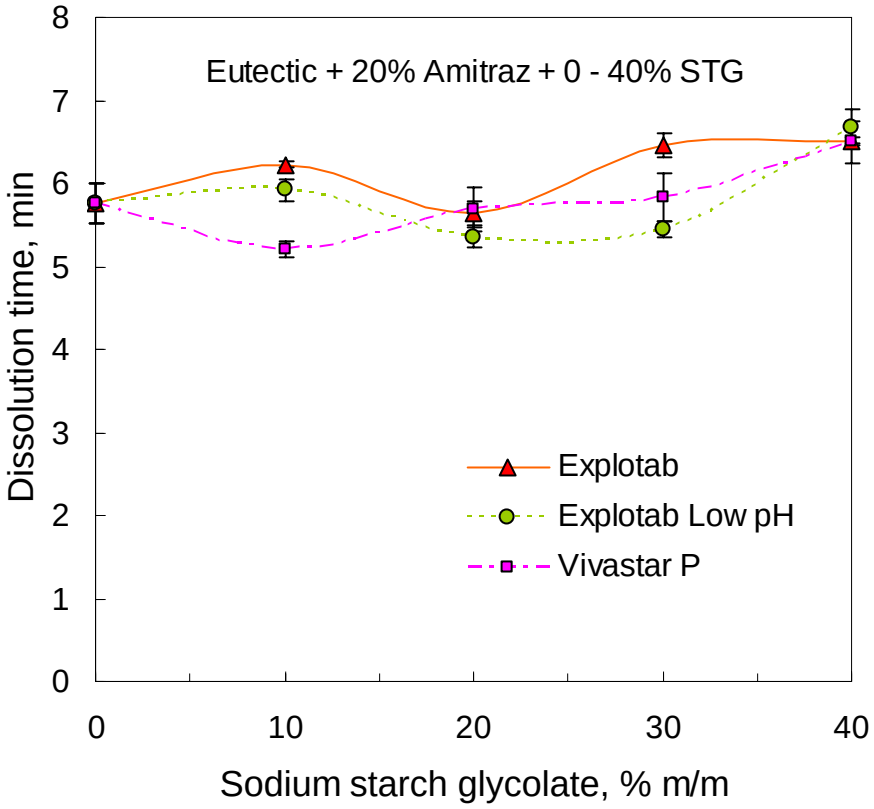

Figure 4.12 The Effect of Different Sodium Starch Glycolate's on the Dissolution Time of a 20% m/m Amitraz Solid Dispersion. All Samples Contained ca.5% $CaCO_3$, 0.6 %- Wettol and 1%-Arkopal

All three disintegrants are based on sodium starch glycolate chemistry. The results show that they have little effect on dissolution times.

For this solid dispersion system it might be concluded that the eutectic depresses the efficiency of sodium starch glycolate. Sheen and Kim (1989) showed that super-disintegrants have a greater effect on disintegration time in an insoluble or partially soluble system. The eutectic mixture, which is the dominant component in this system, is very water-soluble. It dissolves in the water and leave holes in the solid dispersion. The sodium starch glycolate are surrounded by these holes, and it becomes more difficult for the disintegrant to push against the insoluble remaining matrix for improved dissolution (Chebli and Cartilier, 1998).

The 10 and 20% m/m disintegrant improved the dissolution rate of the 30% m/m Amitraz solid dosage (Figure 4.13).

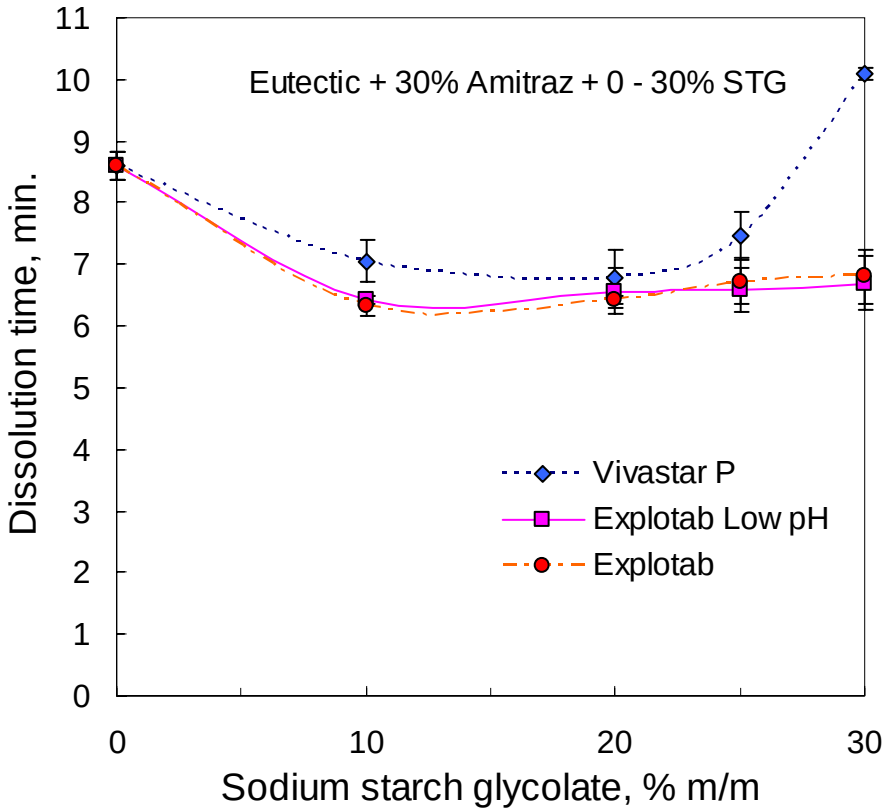

Figure 4.13 The Effect of Different Sodium Starch Glycolate's on a 30% m/m Amitraz Solid Dispersion. All Samples Contained ca.8% $CaCO_3$, 1 %- Wettol and 2%-Arkopal

This can be explained by the increased amount of the insoluble drug particles in the solid dosage form. The disintegrant can effectively absorb water and exert a swelling force against the insoluble particles for improved dissolution. The Explotab®'s showed slightly better results then Vivastar®P. The dissolution time was improved from ±9 minutes to ±6.30 minutes.

The Explotab® again showed improved dissolution for the 40% m/m Amitraz solid dosage form (Figure 4.14).

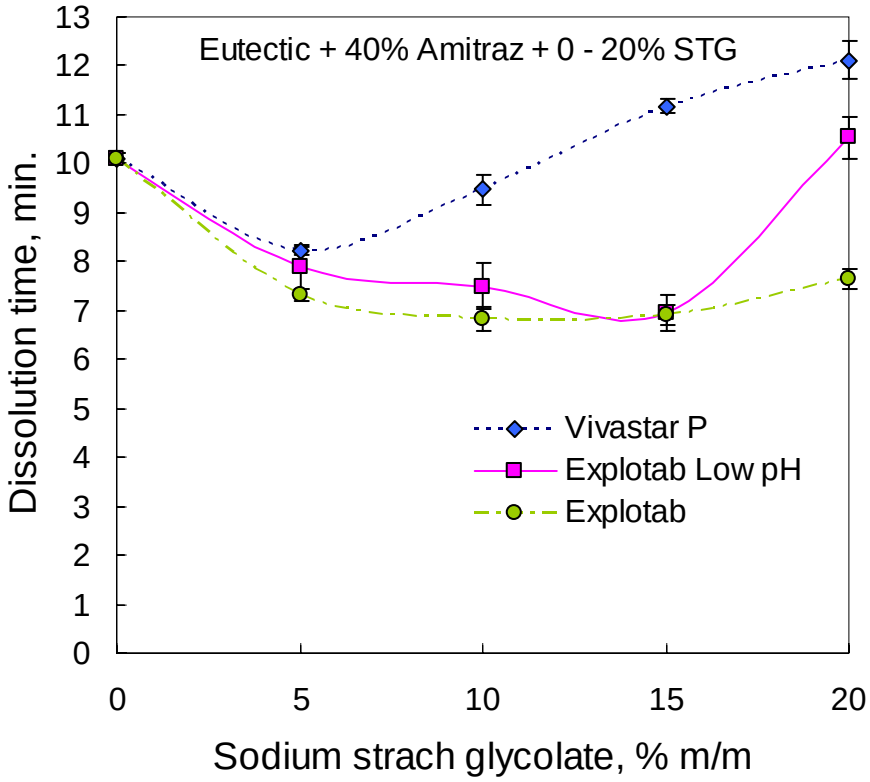

Figure 4.14 The Effect of Different Sodium Starch Glycolate's on a 40% m/m Amitraz Solid Dispersion. All Samples Contained ca.11% $CaCO_3$, 1 %- Wettol and 3%-Arkopal

The dissolution time was improved from ±10 minutes to ±7 minutes.
This can also be explained by the increased insoluble particles, which improves the effectiveness of the disintegrant. At high levels of disintegrant the adhesive forces or viscosity might be dominating the dissolution rate, therefore a lower dissolution rate.

5. Conclusions and Recommendations

Solid urea - 1,3-dimethylurea mixtures were prepared using the melting cooling method. The eutectic mixture contains 40% m/m urea and melts at ±56°C. Discs measuring 5 mm thick were prepared by casting. The dissolution time for the urea - 1,3-dimethylurea eutectic mixture itself was ±4 min for a 5 g disc. The dissolution of Amitraz improved when this mixture was used as carrier.

The Amitraz powder that was used in this study contained 22% calciumcarbonate. The latter acts as grinding agent during pulverization and also has a stabilizing effect on the active. Wettol D2 proved to be a good wetting agent and Arkopal N090 was a suitable dispersant for Amitraz in aqueous medium. The optimum levels of the dispersant and wetting agent for a 30% m/m Amitraz aqueous suspension were determined as 2% Arkopal N090 and 1% Wettol D2 using viscosity versus surfactant concentration measurements. The urea - 1,3-dimethylurea eutectic mixture was found to be a suitable solid state carrier for the active Amitraz powder with its associated excipients. Solid pellets, weighing ca. 5 g, were prepared by melt pressing. Amitraz solid dosages containing 20 and 30 and 40% m/m active were prepared. It was found that melting of the active must to be avoided.

Addition of sodium starch glycolate-based super disintegrants were explored in an attempt to decrease the tablet disintegration time. Vivastar® did not improve the dissolution rate of the 30 and 40% m/m Amitraz solid formulations. However, Explotab® improved the dissolution rate of these formulations. The presence of high levels of soluble fillers (urea and 1,3-dimethylurea) appears to impair the action of the super disintegrant. The dissolution time of the 30% m/m Amitraz solid dosage improved from 9 min to 6,5 min and the 40% m/m solid dosage from 10 min to 7 min.

The best formulations contained 30 or 40% m/m Amitraz and 10 and 15% m/m Explotab. The reason for this might be as follows: The insoluble Amitraz particles create a rigid barrier for the soluble disintegrants to push against and exert their disintegrating action. When too much disintegrant is present, it prevents rapid ingress of water to the inside of the tablet and the disintegration is retarded.

Future work could consider the use of hydrogel formulations to decrease the dissolution time.

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Appendices

Appendix A: Lever Rule

Lever Rule. The point in the two-phase region of a phase diagram indicated not only qualitatively that both liquid and vapour are present, but represents quantitatively the relative amounts of each. To find the relative amounts of two phases *a* and *b* that are in equilibrium, we measure the distances l_a and l_b along the horizontal tie line, and then use the lever rule (Figure 13).

$$n_a l_a = n_b l_b$$

where n_a is the amount of phase *a* and n_b the amount of phase *b*. In the case illustrated in Figure 13, because $l_b \approx 2l_a$, the amount of phase *a* is about twice the amount of phase *b*.

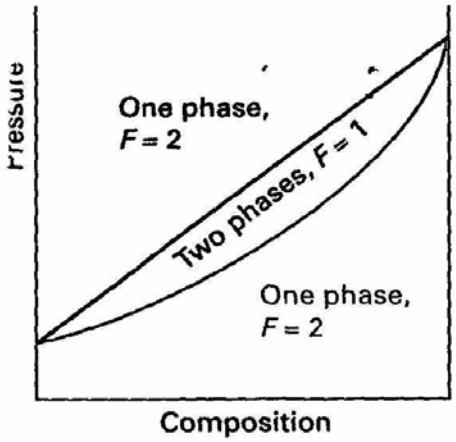


Figure 13: The lever rule. The distances l_a and l_b are used to find the proportions of the amounts of phases (Atkins, 1998).

Appendix B: Hydrolysis of Amitraz

Amitraz is unstable in the whole pH range, undergoing faster hydrolysis at acidic pH values (at pH < 2 the degradation is almost instantaneous). The nature of the degradation products depends on the pH. At very acidic pH's the main degradation product is BTS 24868, at less acidic pH's the main products are BTS 27271 and BTS 27919 and at basic pH BTS 27919 is

the principal hydrolysis compound. Some of these residues have toxicological importance, as in the case of BTS 27271 and BTS 24868.

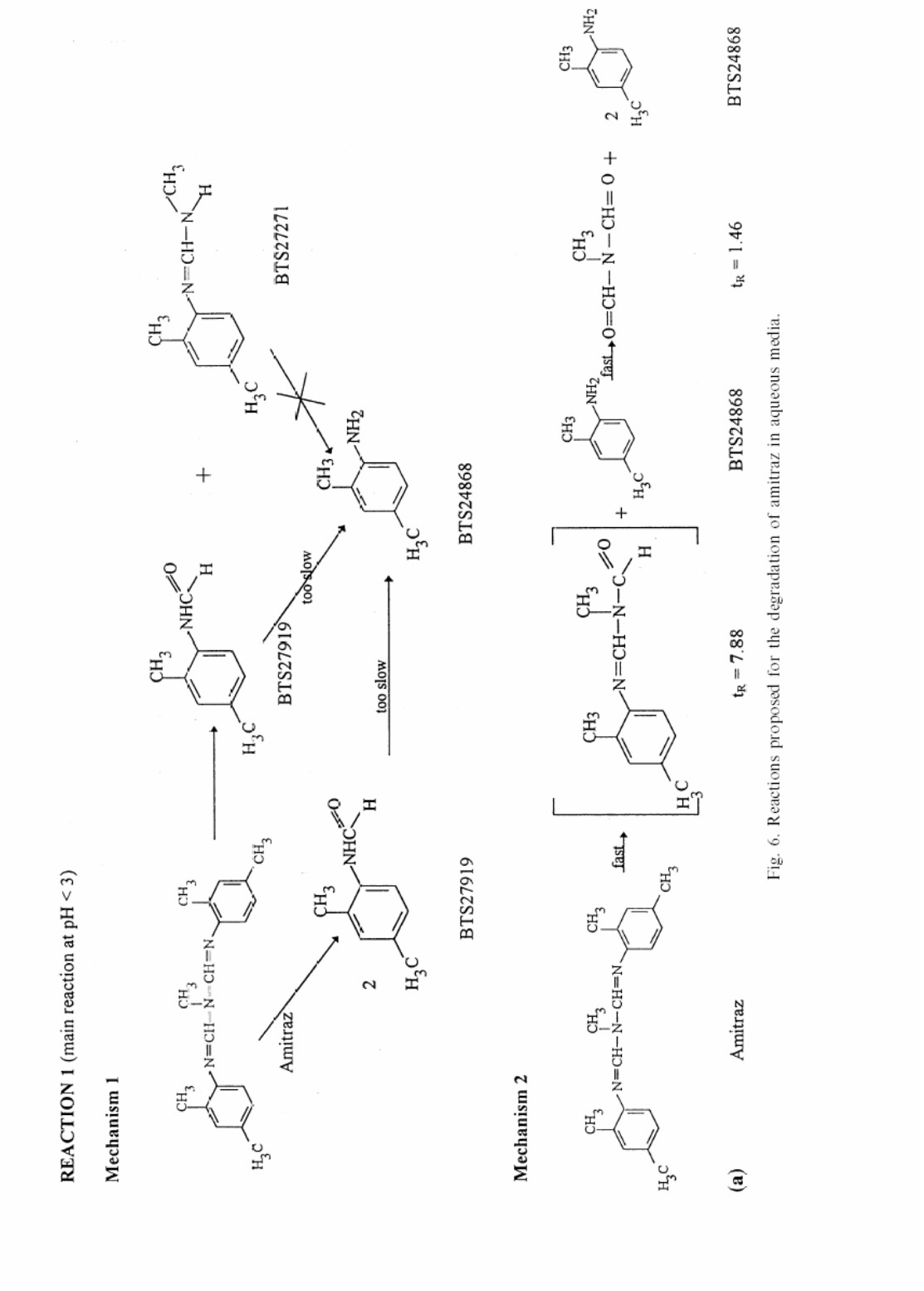
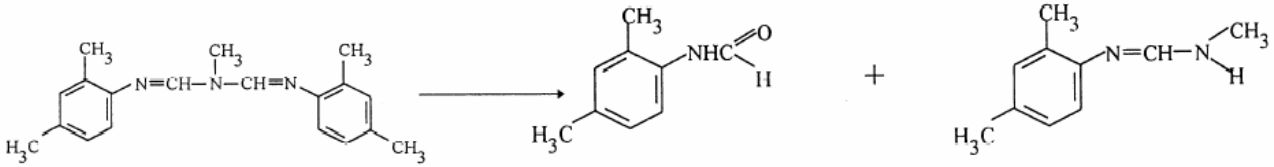
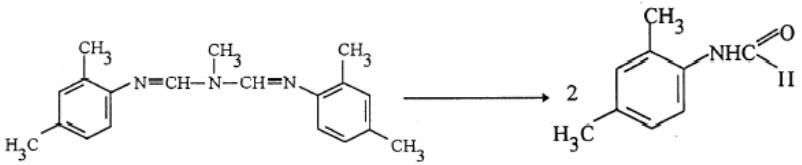


Fig. 6. Reactions proposed for the degradation of amitraz in aqueous media.

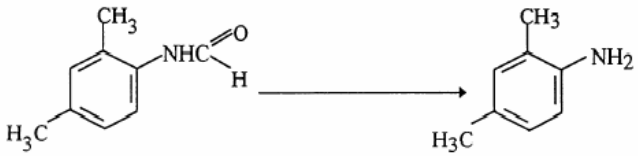
REACTION 2 (main reaction at 3 < pH< 6)



REACTION 3 (main reaction at basic pH)



REACTION 4



(b) BTS27919 BTS24868

Fig. 6. (*Continued*)

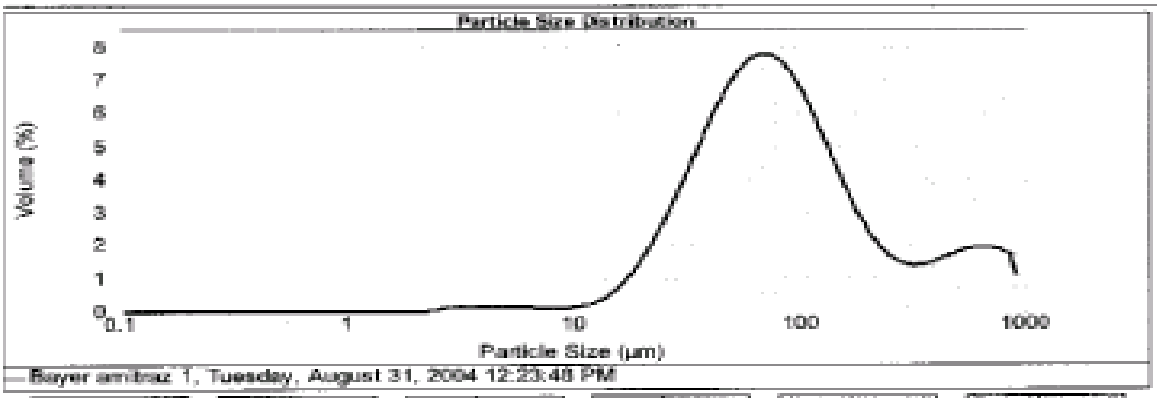
Appendix C: Particle Size

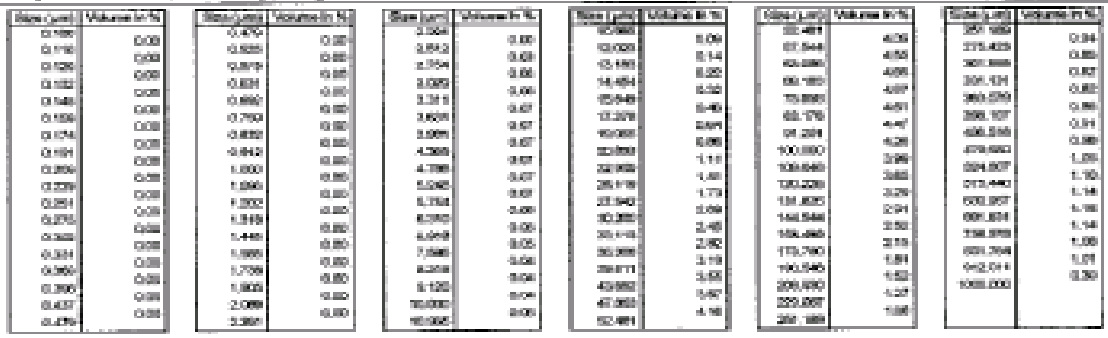
!004 09:35 8125296216 SGT:MOTSEPE PAGE 02/14

MASTERSIZER 2000

Result Analysis Report

Name: nitrac 1	**SOP Name:** Am8921	**Measured:** Tuesday, August 31, 2004 12:23:48 PM	
Source & type: Pretoria	**Measured by:** me	**Analysed:** Tuesday, August 31, 2004 12:23:49 PM	
bulk lot ref:	**Result Source:** Measurement		
Name:	**Accessory Name:** Hydro 2000MU (A)	**Analysis model:** General purpose	**Sensitivity:** Normal
RI:	**Absorption:** 0	**Size range:** 0.100 to 1000.000 um	**Obscuration:** 12.94 %
ant Name:	**Dispersant RI:** 1.330	**Weighted Residual:** 0.320 %	**Result Emulation:** Off
tration: %Vol	**Span :** 4.625	**Uniformity:** 1.26	**Result units:** Volume
Surface Area: m²/g	**Surface Weighted Mean D[3,2]:** 57.228 um	**Vol. Weighted Mean D[4,3]:** 145.549 um	
30.225 um	d(0.5): 78.495 um	d(0.9): 391.252 um	

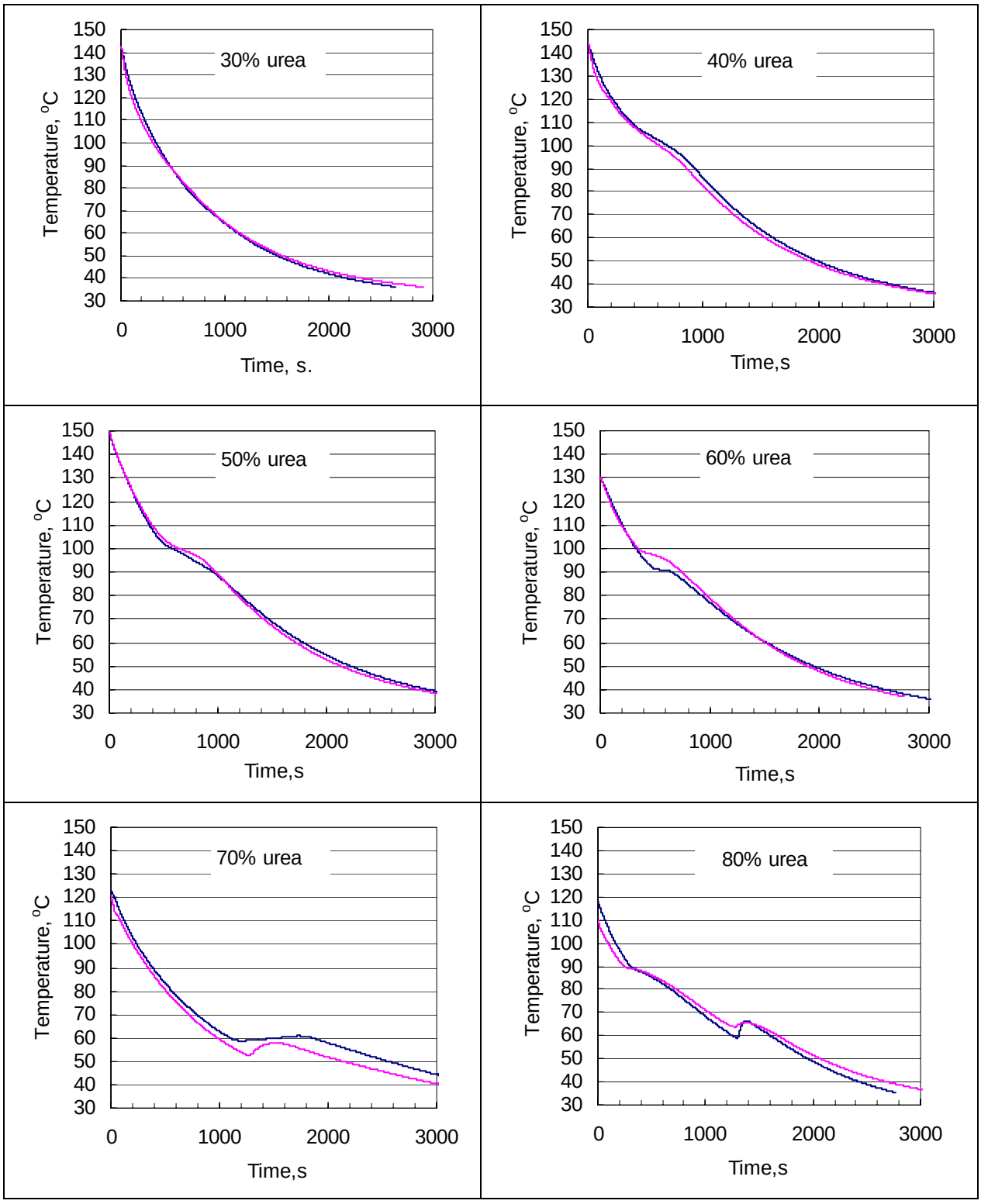


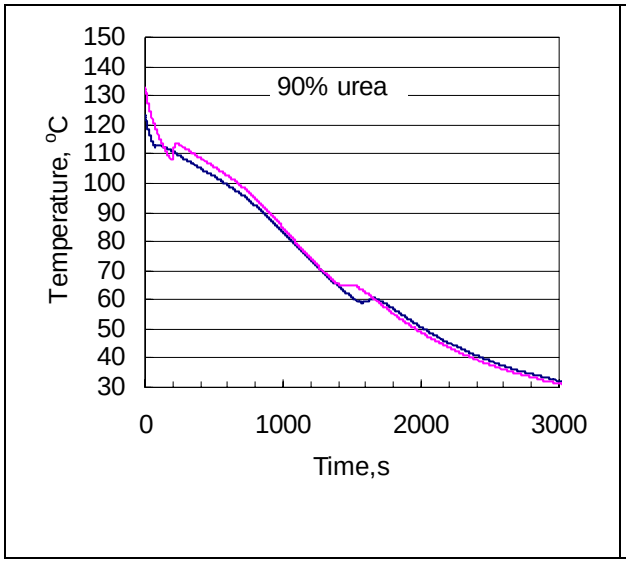


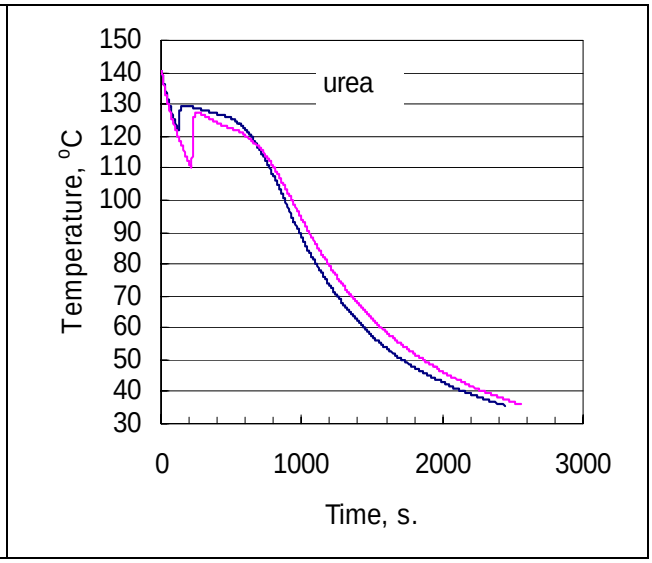
er notes:

Appendix D: Cooling Curves

Figure 1: Cooling curves for Urea-$CaBr_2.2H_2O$ mixtures

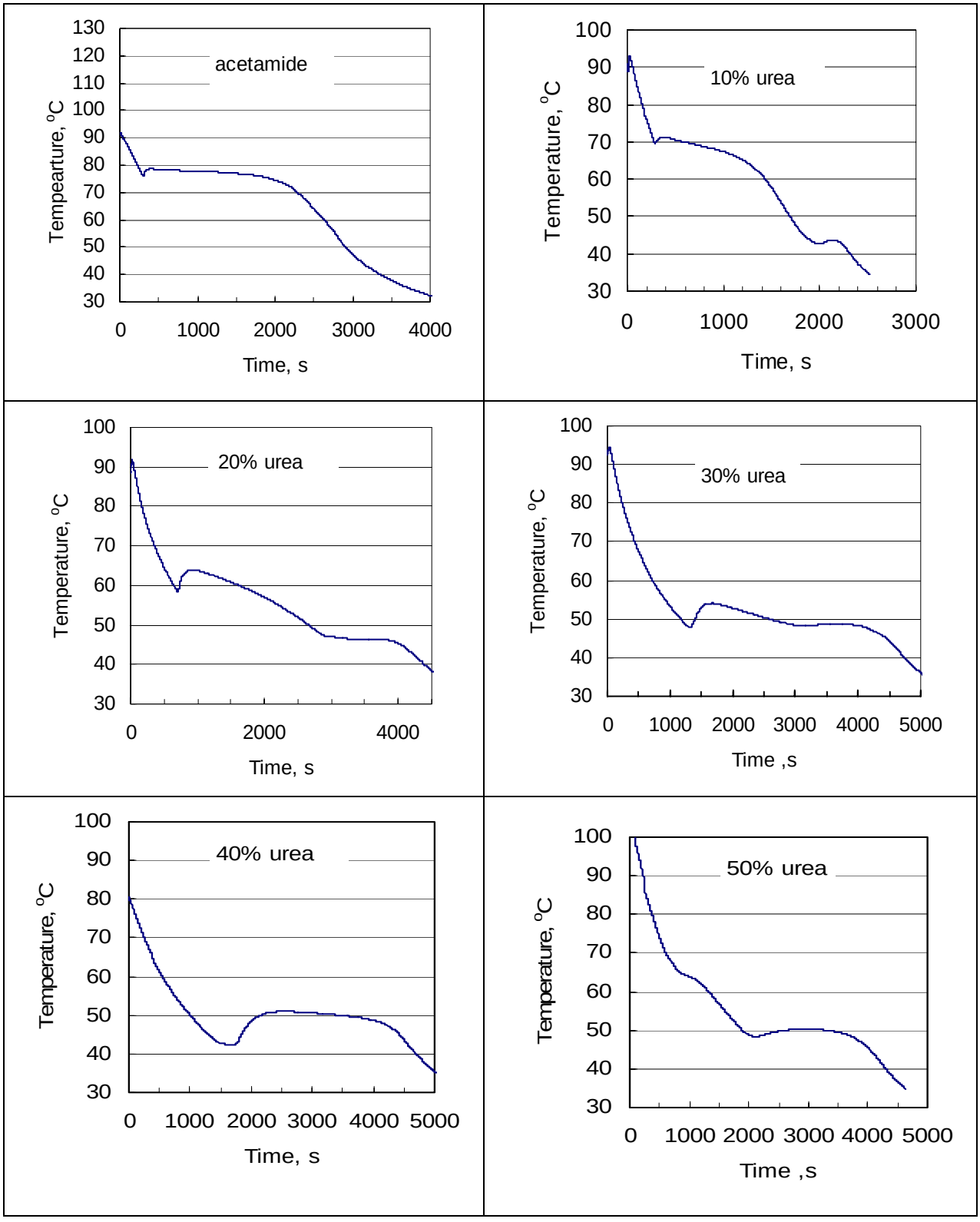


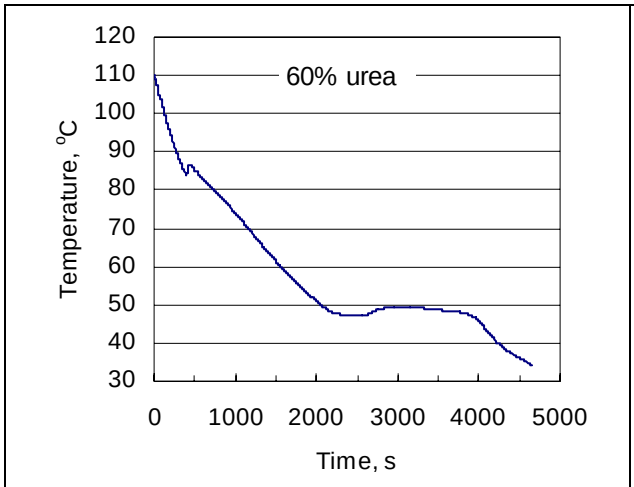

150
140
130
120
110
100
90
80
70
60
50
40
30
Temperature, °C
90% urea
0
1000
2000
3000
Time,s

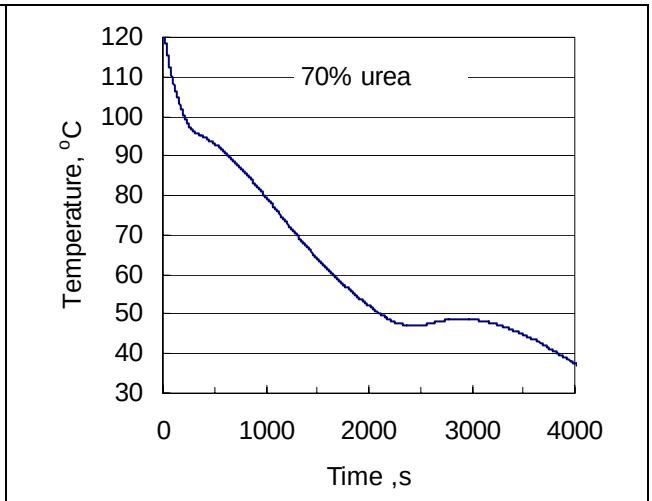

150
140
130
120
110
100
90
80
70
60
50
40
30
Temperature, °C
urea
0
1000
2000
3000
Time, s.

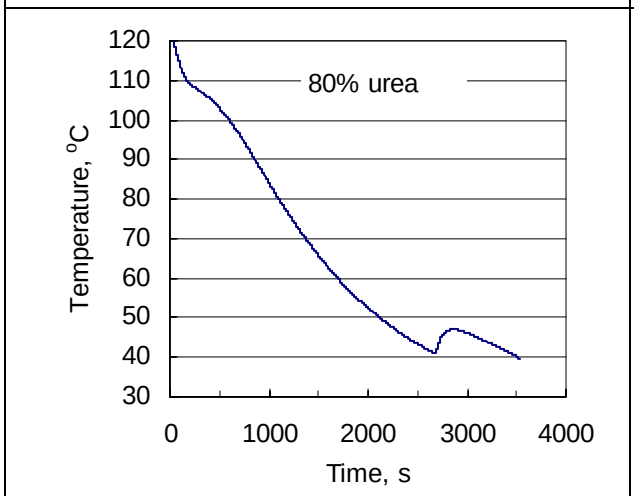
Appendix D

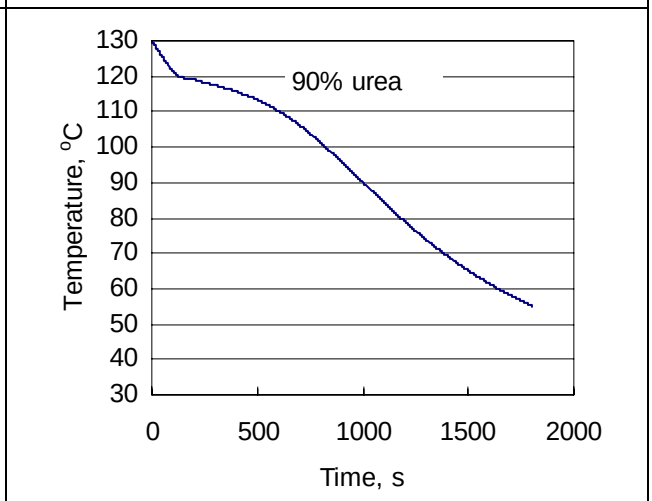
Figure 2: Cooling curves for Urea-Acetamide mixtures

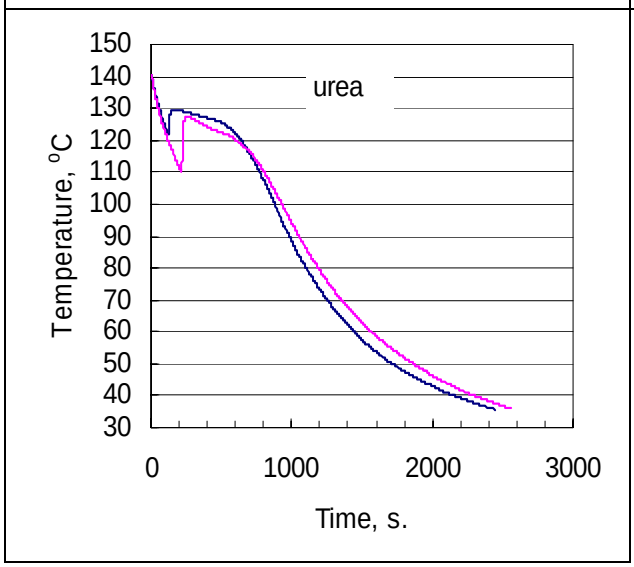



60% urea
Temperature, °C
Time, s


70% urea
Temperature, °C
Time ,s

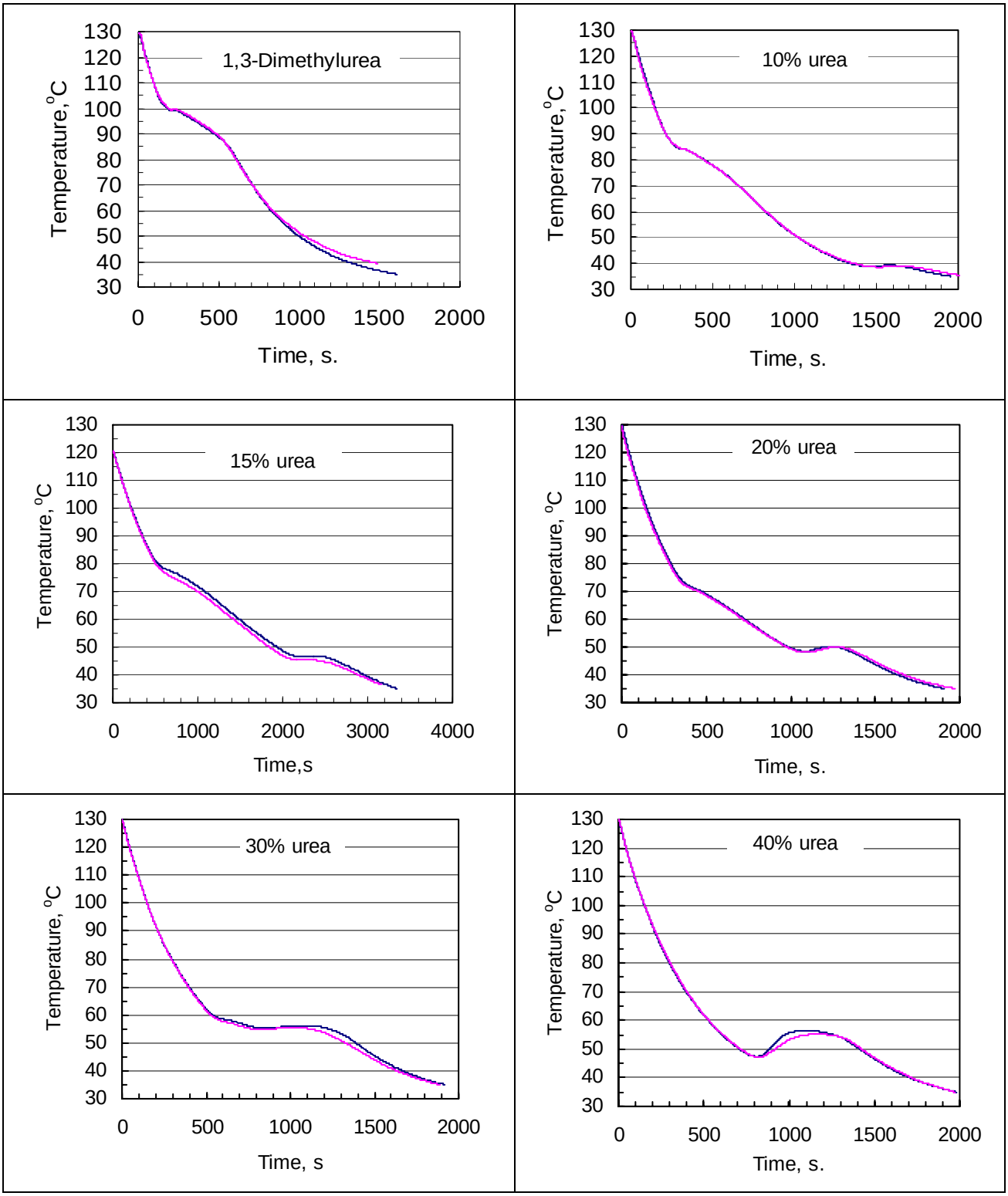

80% urea
Temperature, °C
Time, s

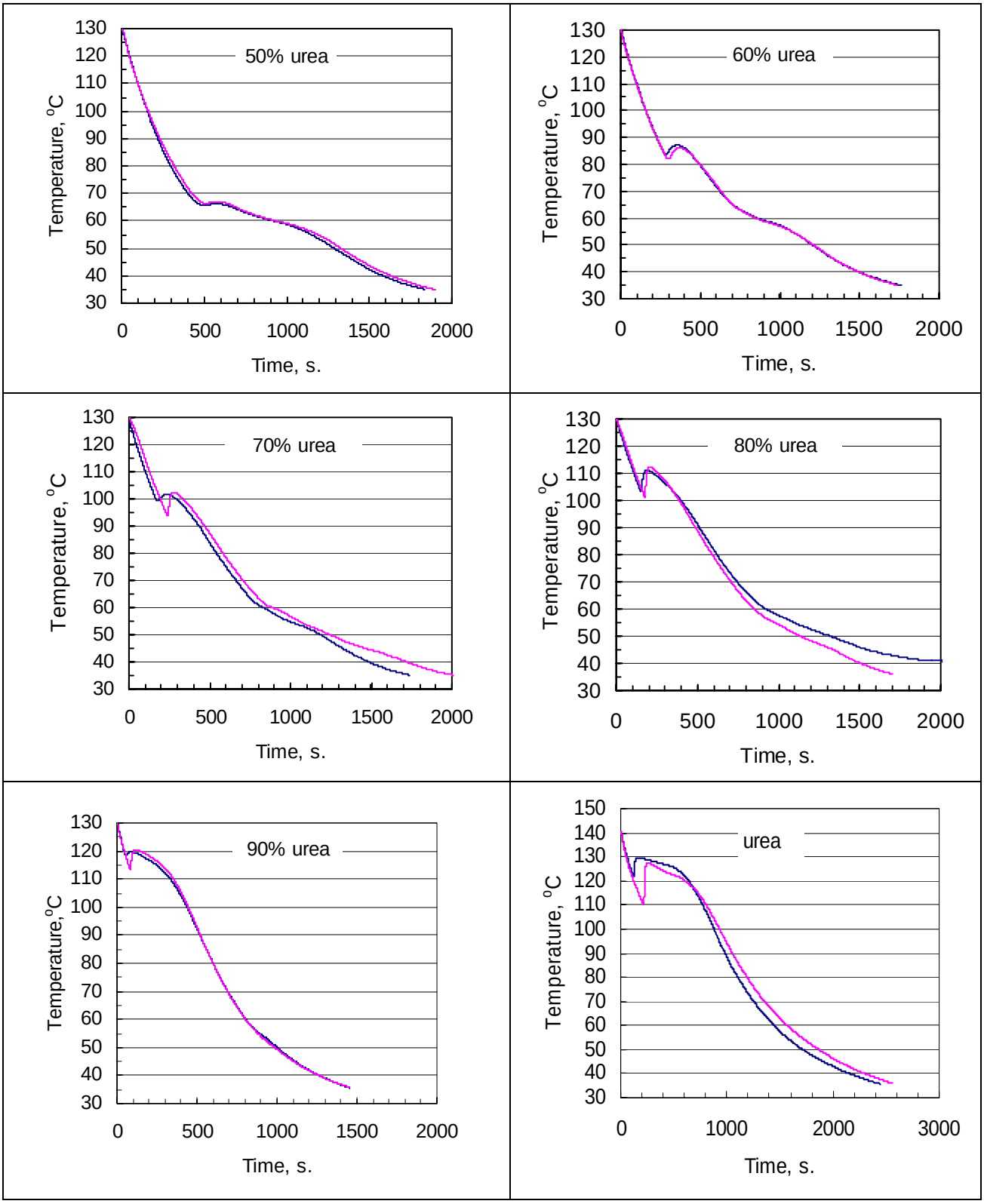

90% urea
Temperature, °C
Time, s


urea
Temperature, °C
Time, s.

Appendix D

Figure 3: Cooling curves for Urea-1,3-Dimethylurea mixtures




50% urea
60% urea
70% urea
80% urea
90% urea
urea
Temperature, °C
Time, s.

Appendix E: TGA/DTA results

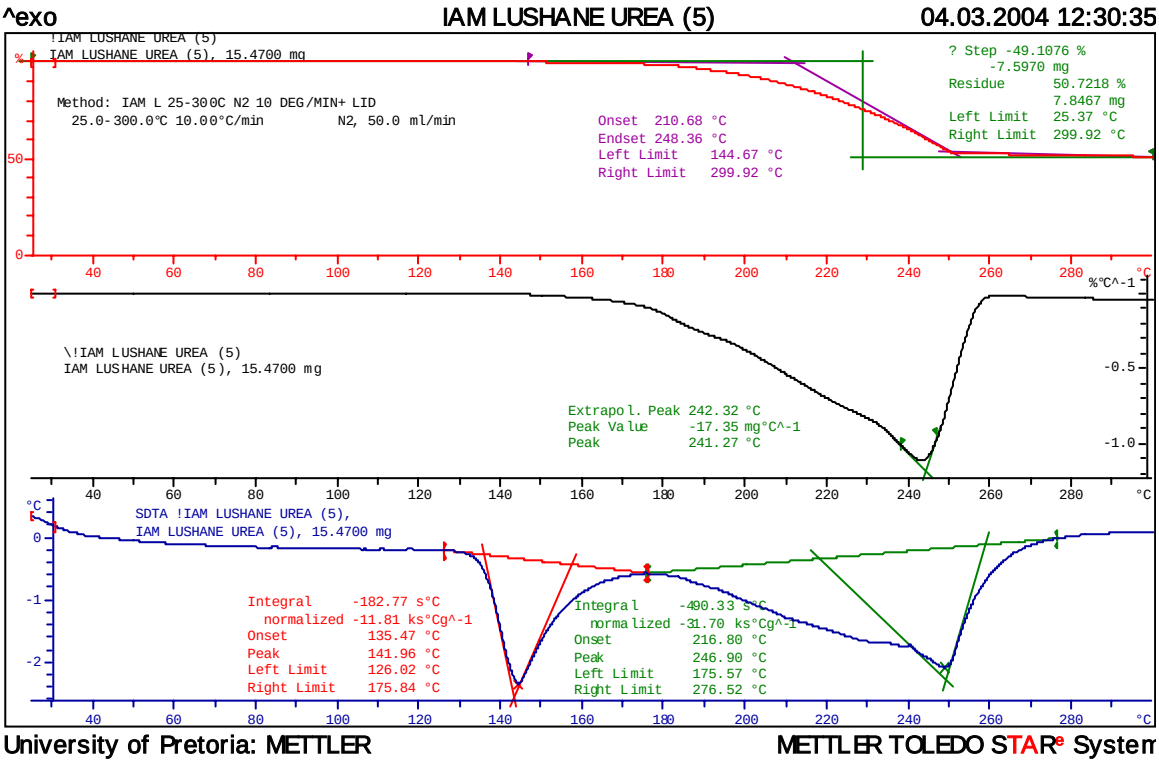


Figure 1: TGA/DTA curve of pure urea

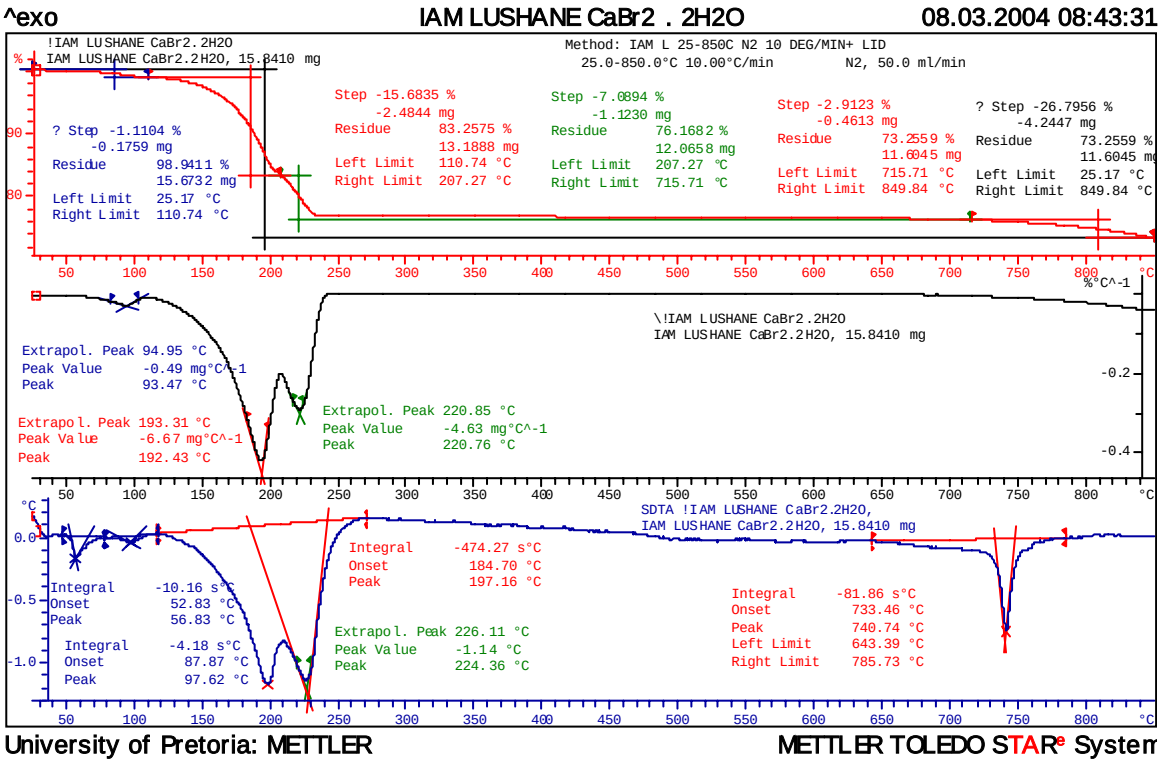


Figure 2: TGA/DTA curve of $CaBr_2.2H_2O$

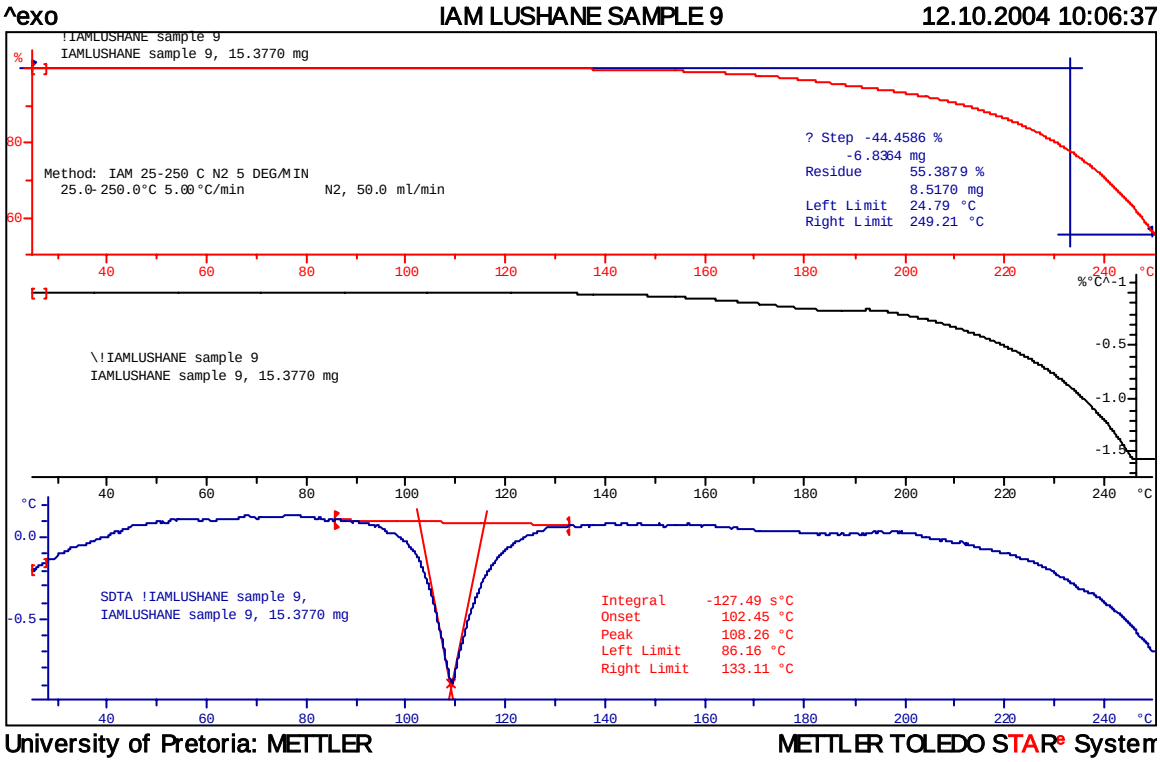


Figure 3: TGA/DTA curve of 1,3-dimethylurea

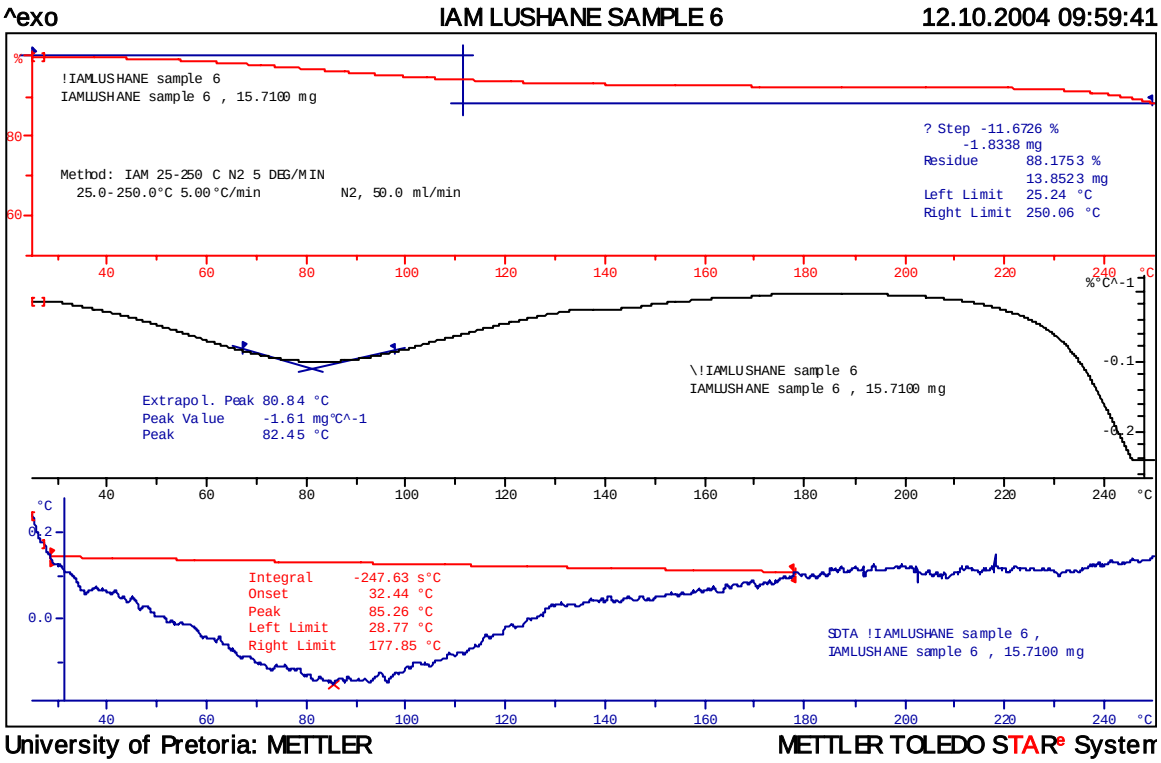


Figure 4: TGA/DTA curve of Explotab®

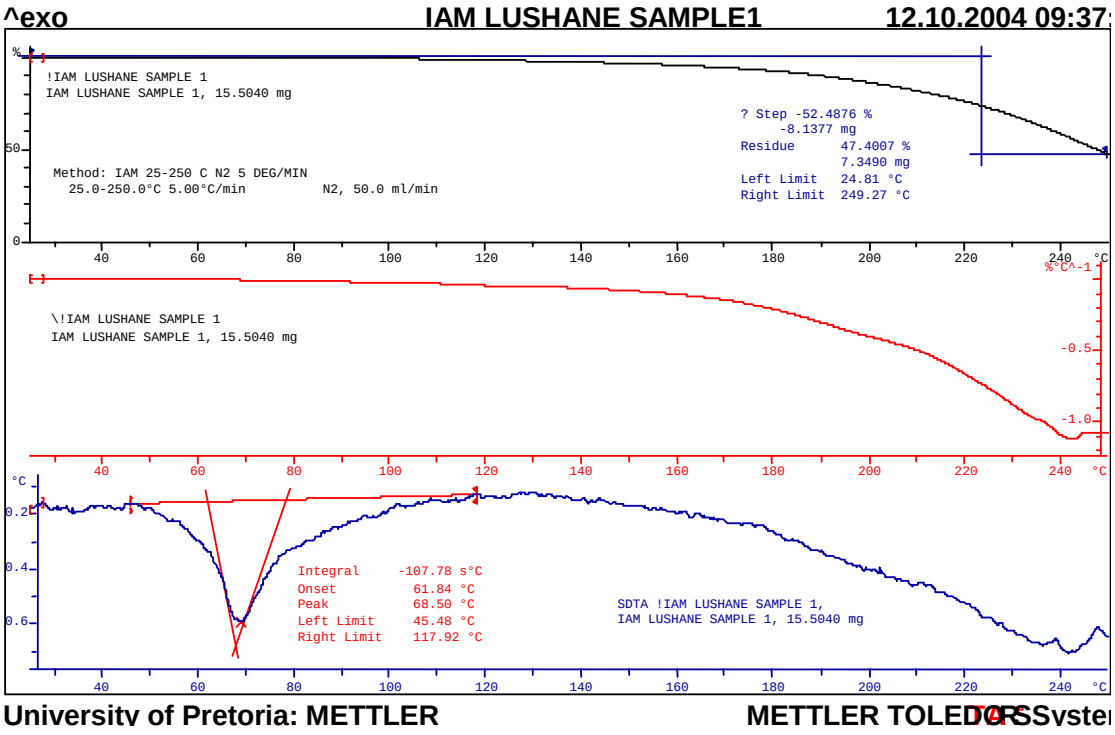


Figure 5: TGA/DTA curve of 85% m/m eutectic mixture and 15% m/m Explotab®

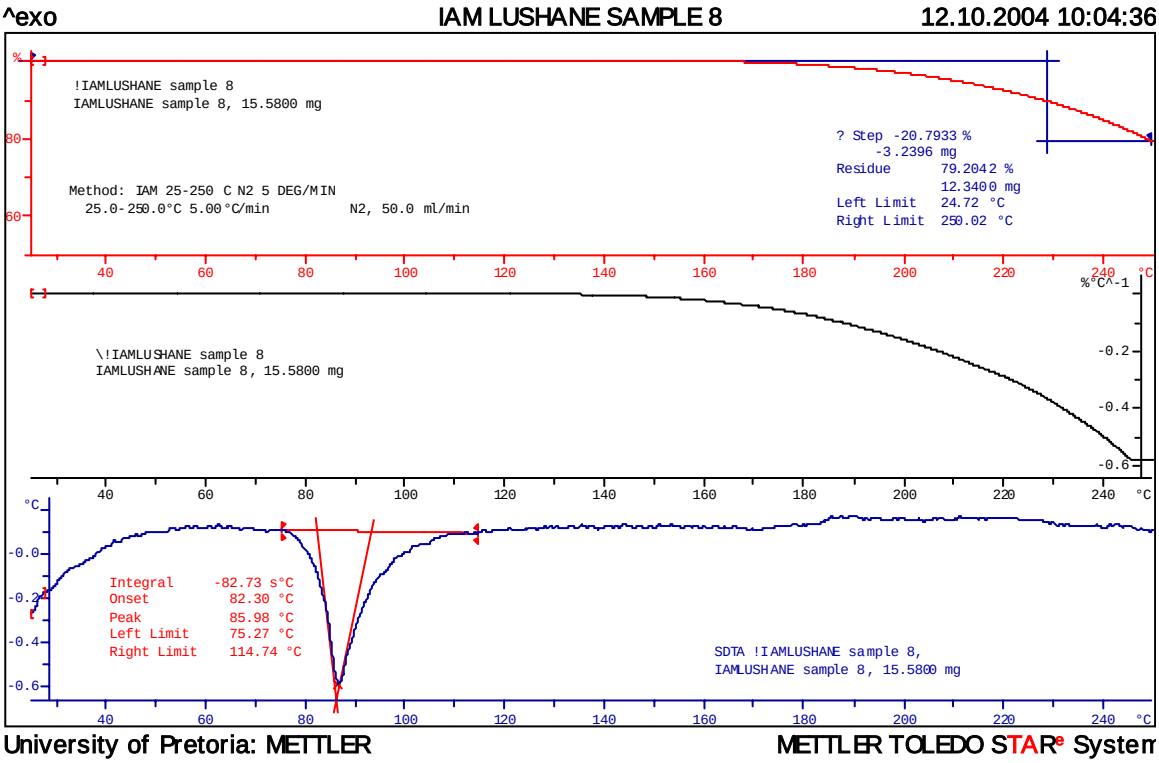


Figure 6: TGA/DTA curve of pure Amitraz

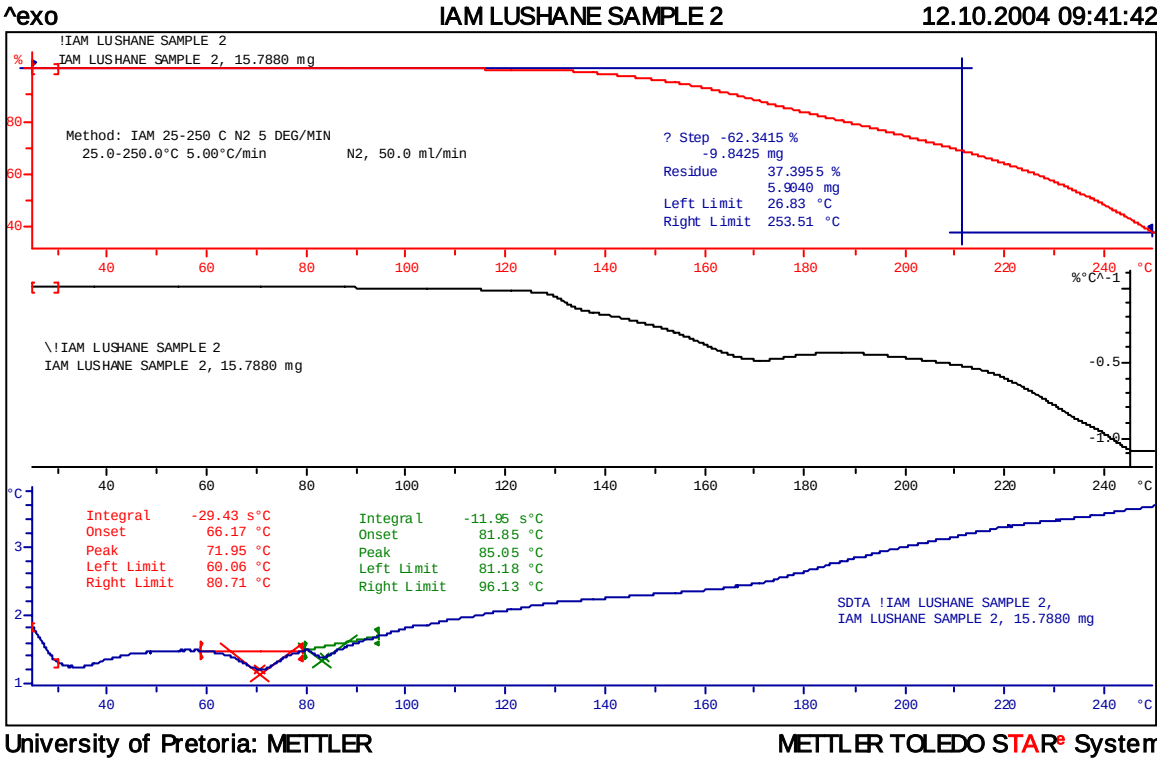


Figure 7: TGA/DTA curve of 20% m/m Amitraz + 72% m/m eutectic mixture + excipients

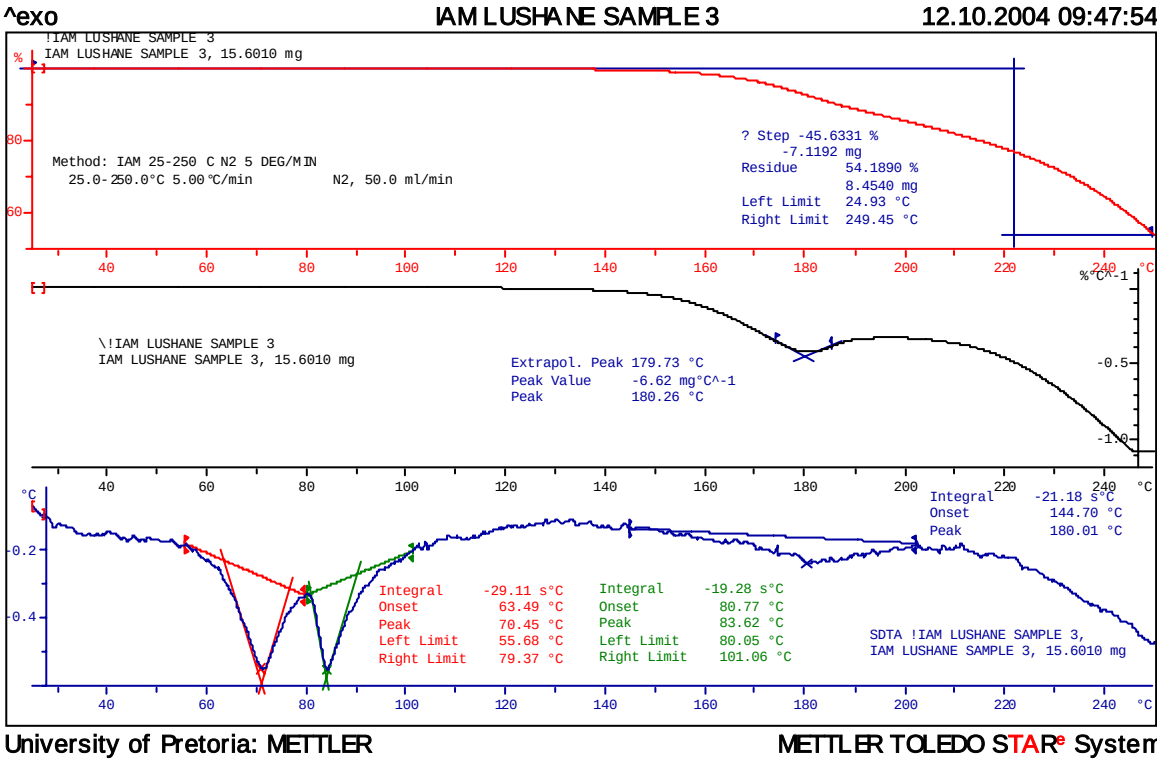


Figure 8: TGA/DTA curve of 30% m/m Amitraz + 59% m/m eutectic mixture and excipients

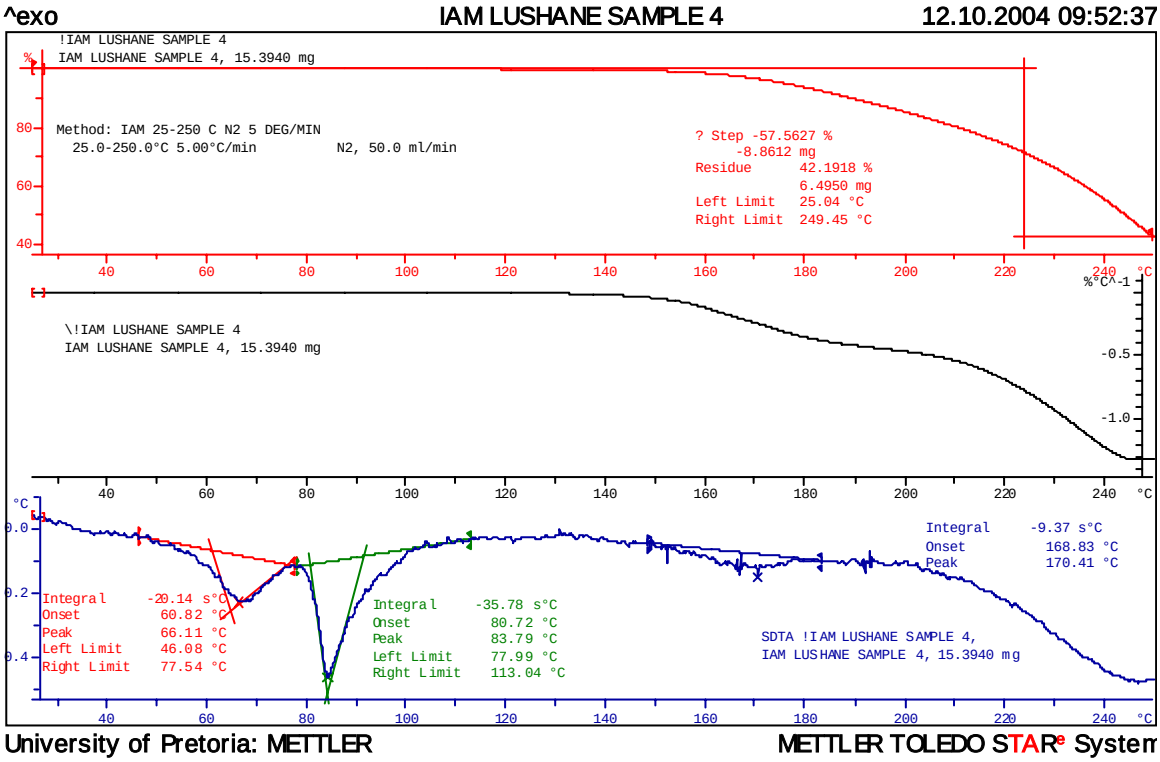


Figure 9: TGA/DTA curve of 40% m/m amitaz + 45% m/m eutectic mixture and excipients

Appendix F: XRD Spectra

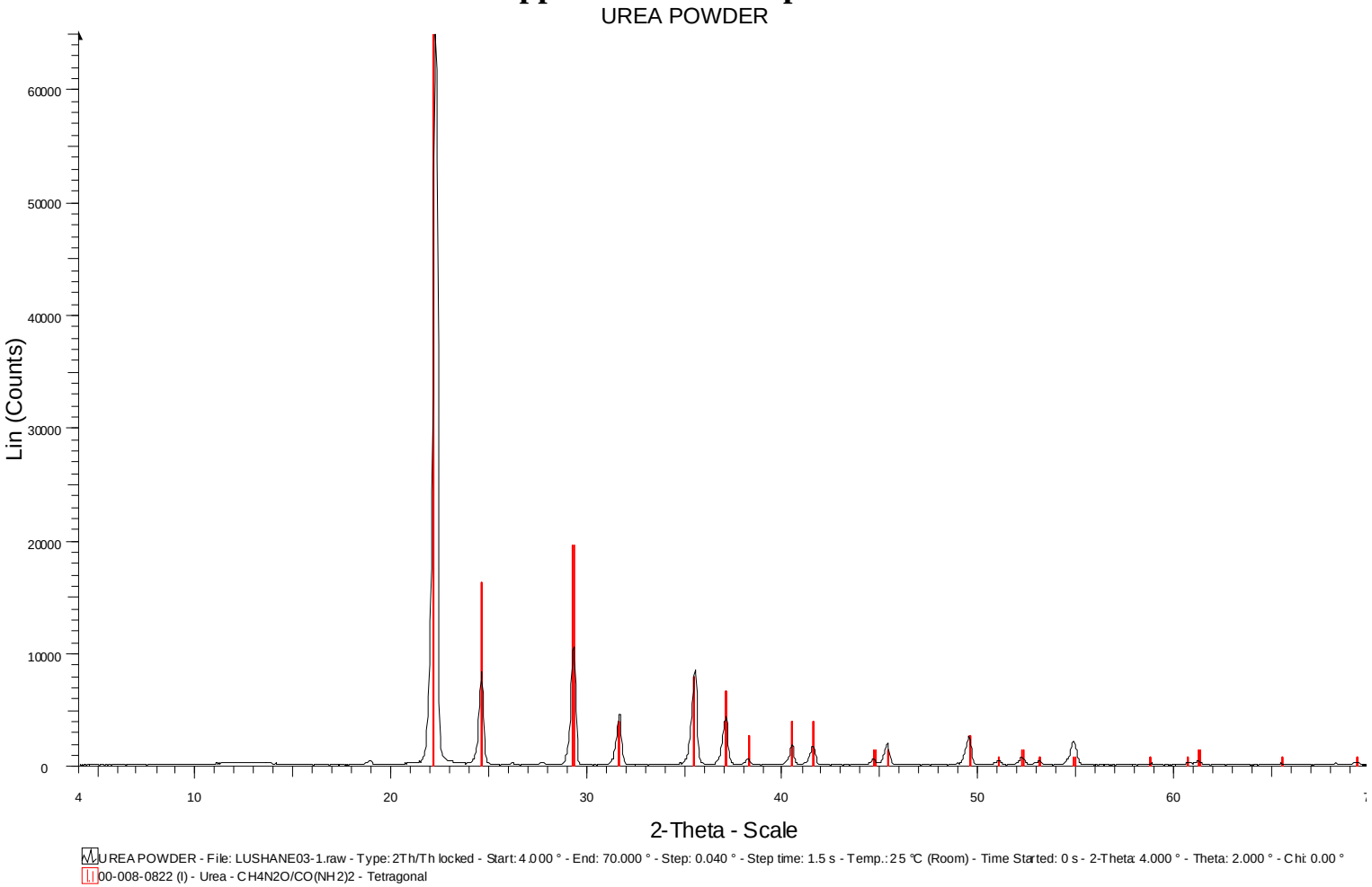


Figure 1: XRD spectra of pure urea

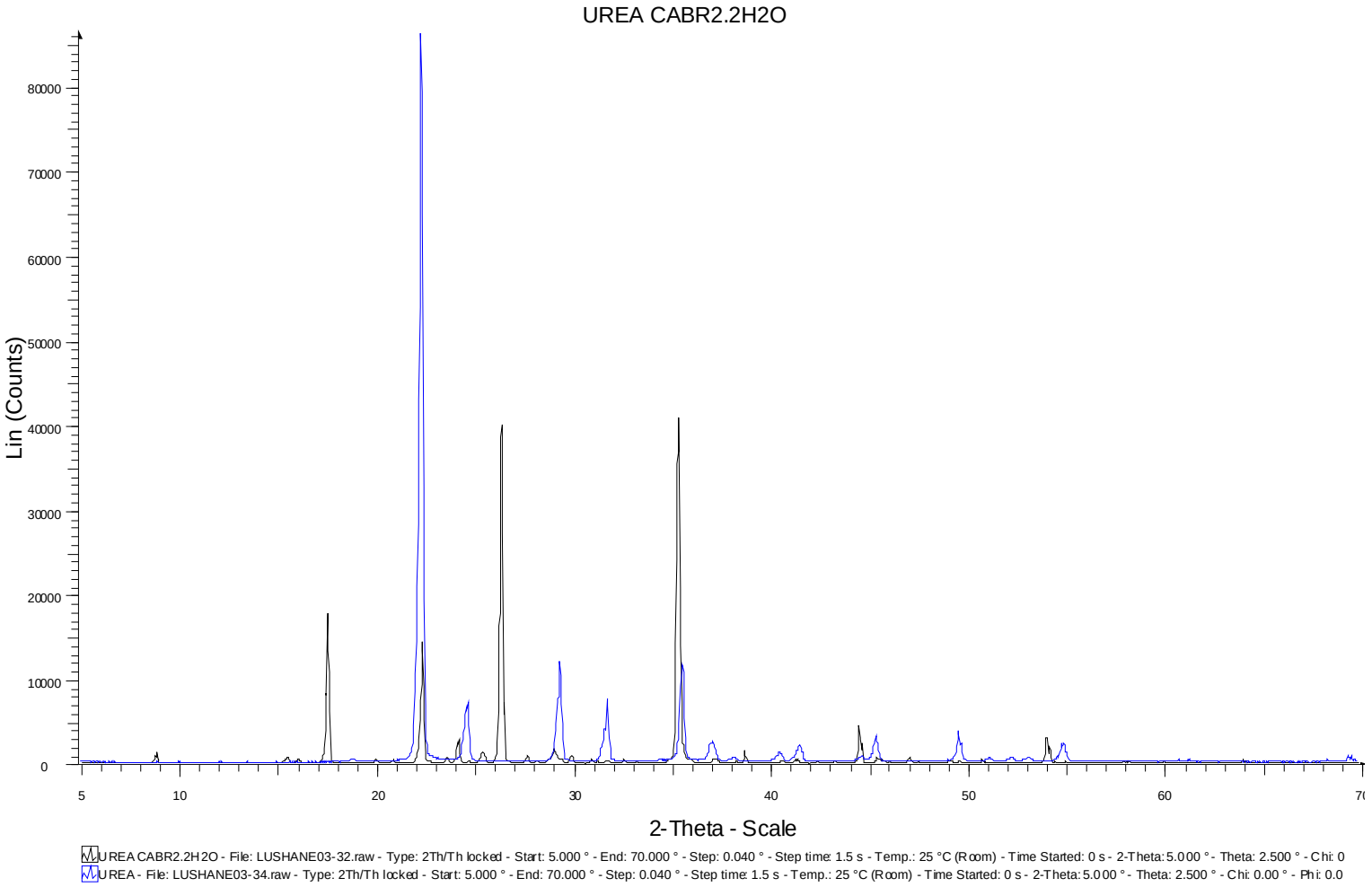


Figure 2: XRD spectra of urea and $CaBr_2.2H_2O$ eutectic mixture

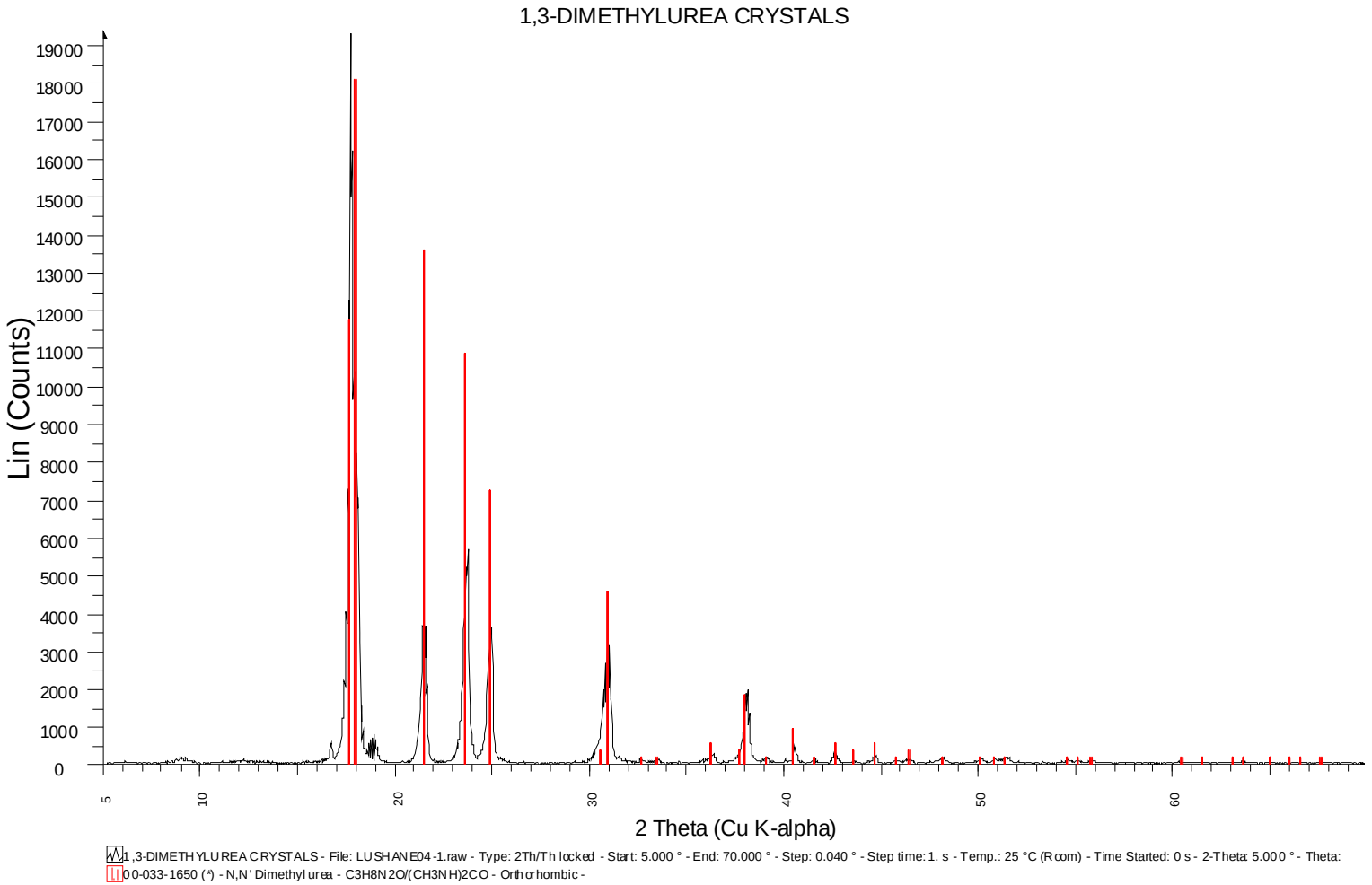


Figure 3: XRD spectra of pure 1,3-dimethylurea

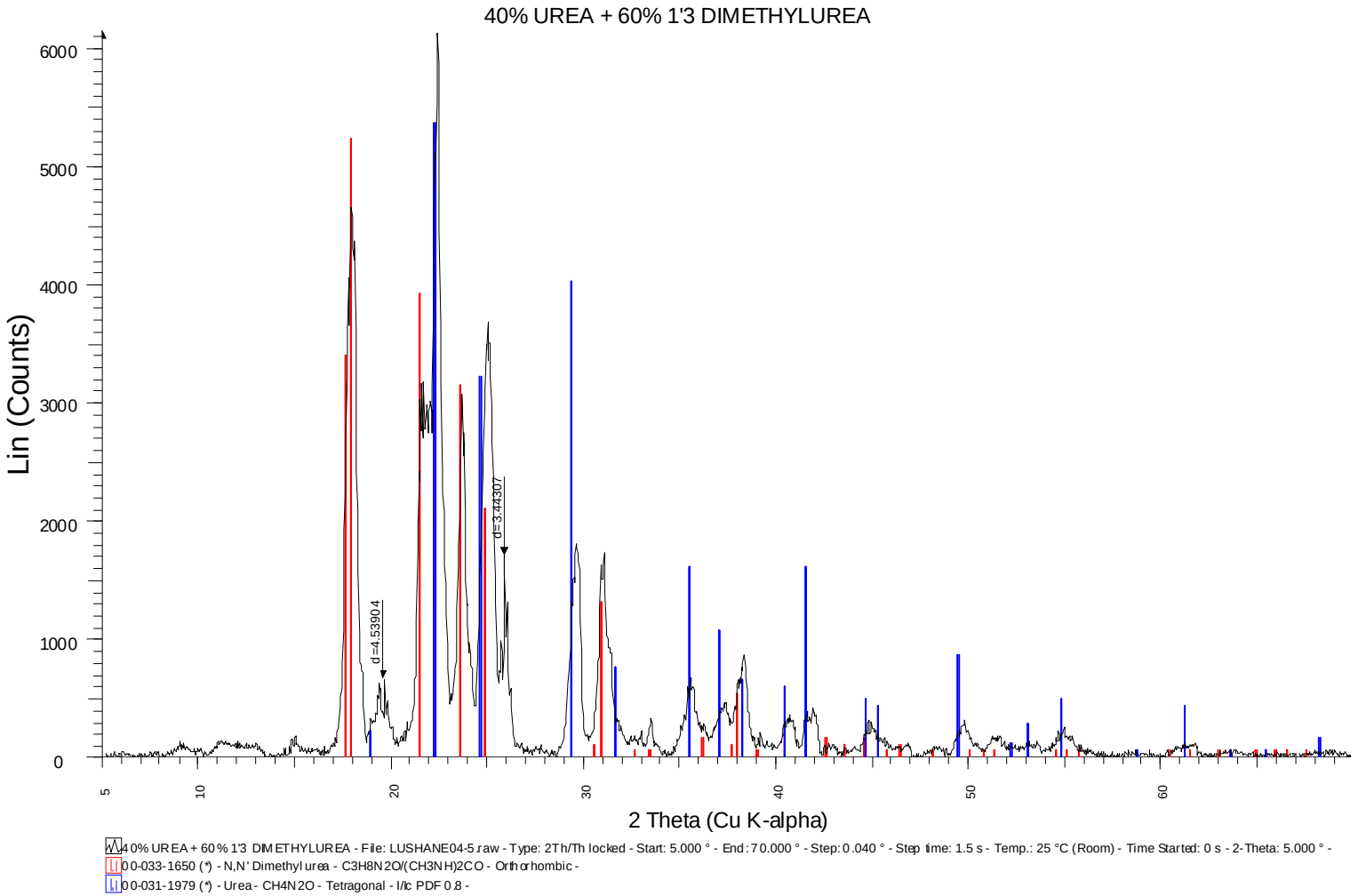


Figure 4: XRD spectra of 40% m/m urea and 60% m/m 1,3-dimethylurea mixture

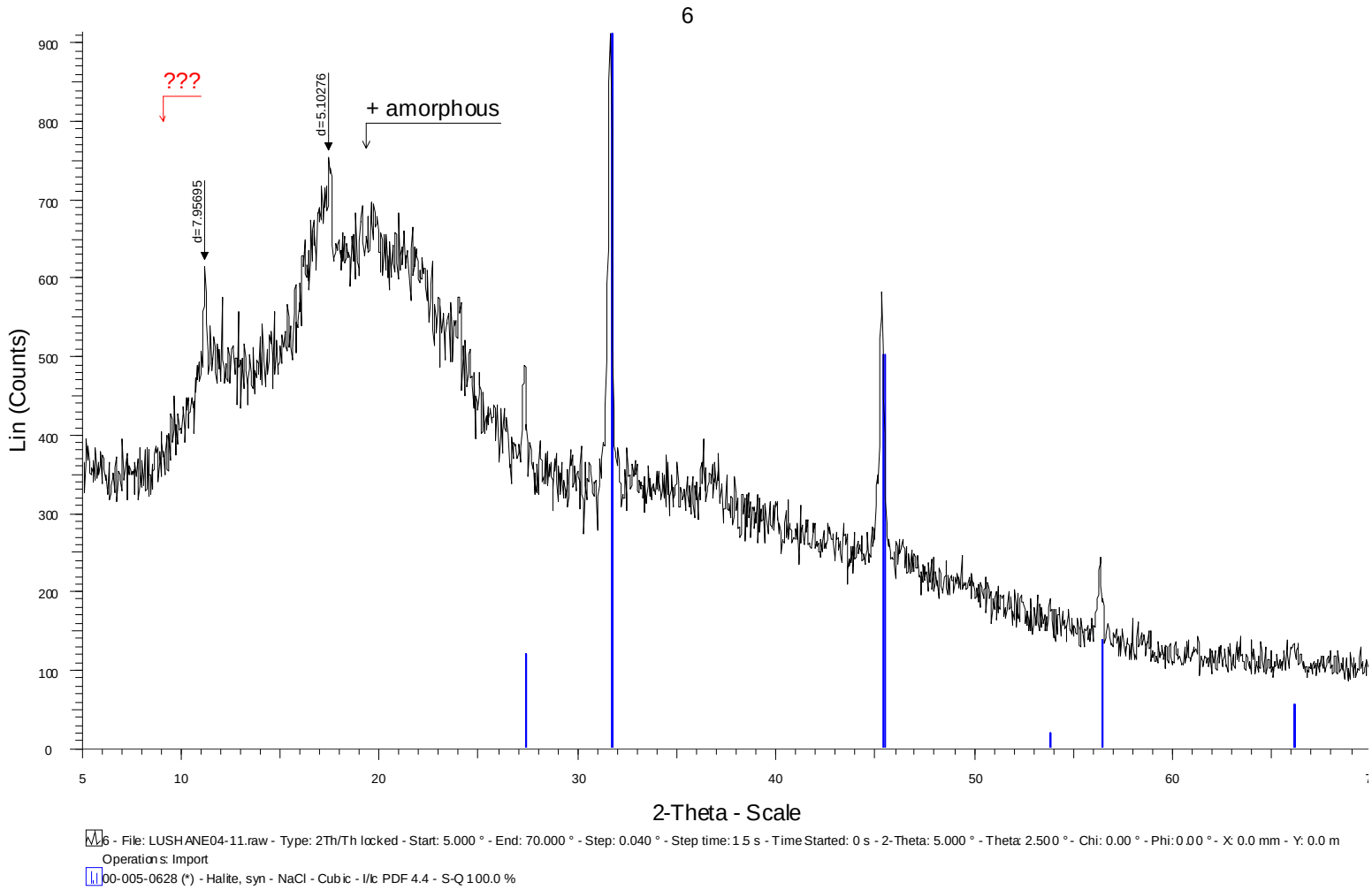


Figure 5: XRD spectra of Explotab®

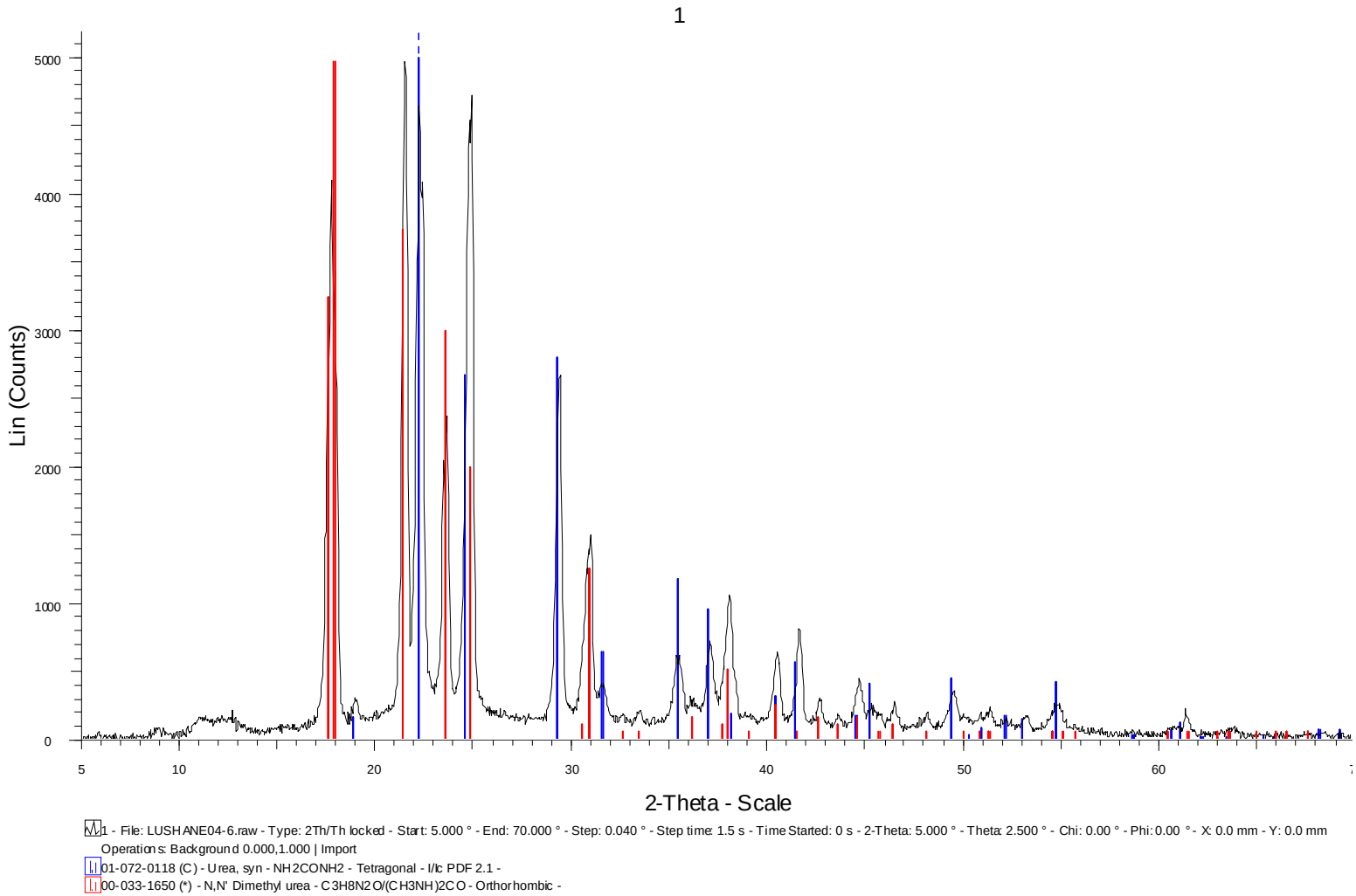


Figure 6: XRD spectra of 85% m/m eutectic mixture and 15% m/m Explotab®

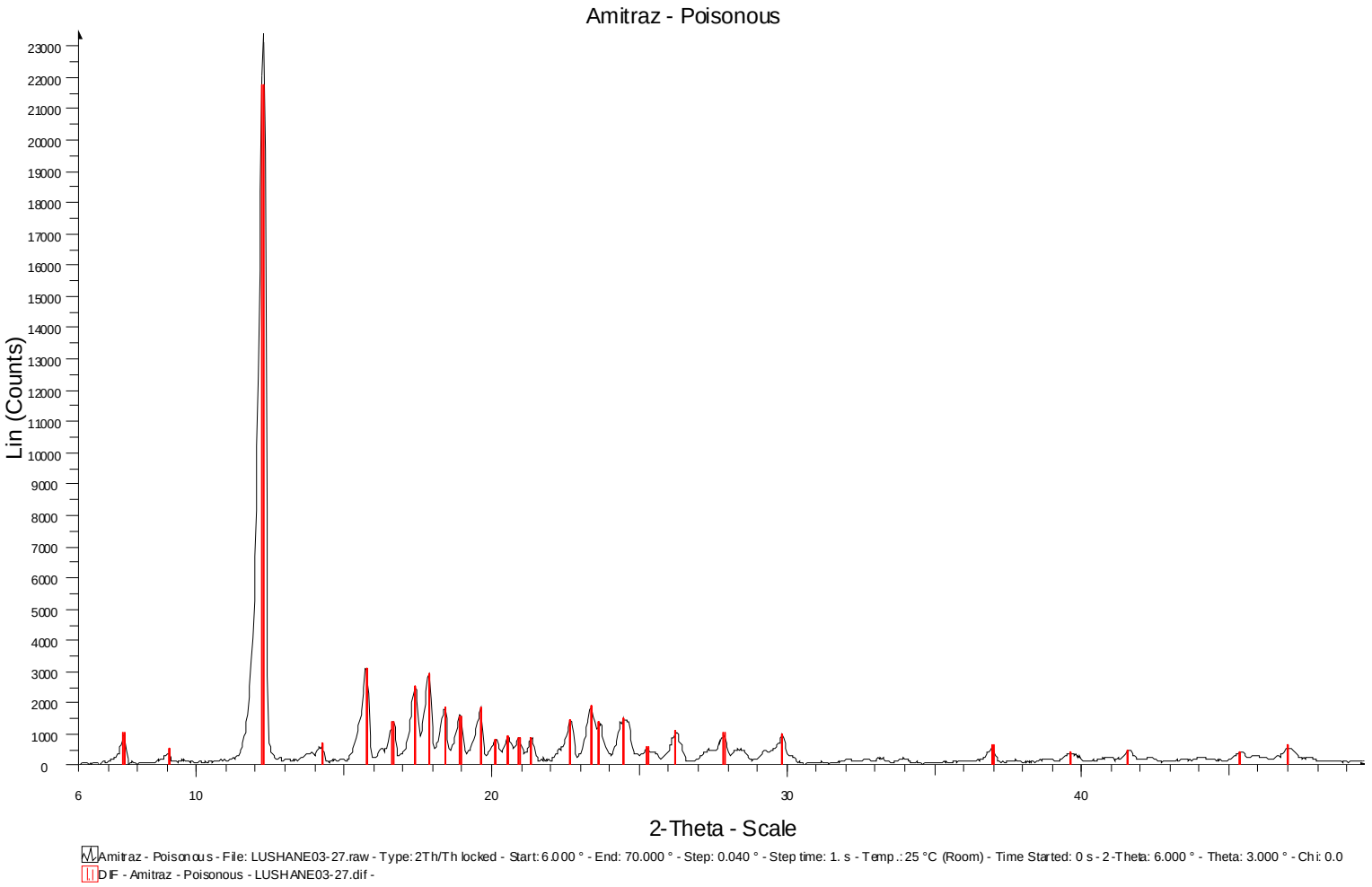


Figure 7: XRD spectra of pure Amitraz

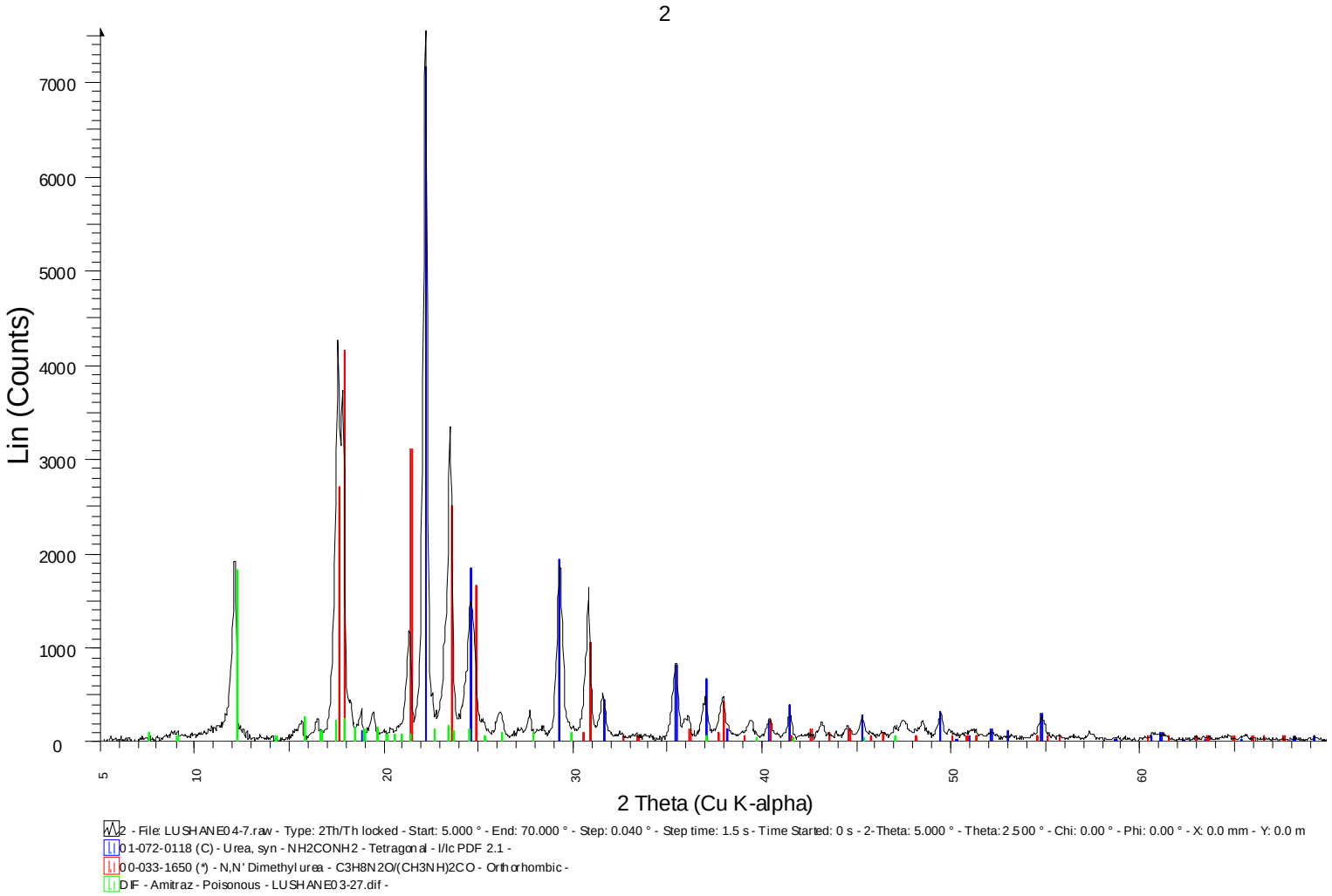


Figure 8: XRD spectra of 20% m/m Amitraz + 72% m/m eutectic mixture + excipients

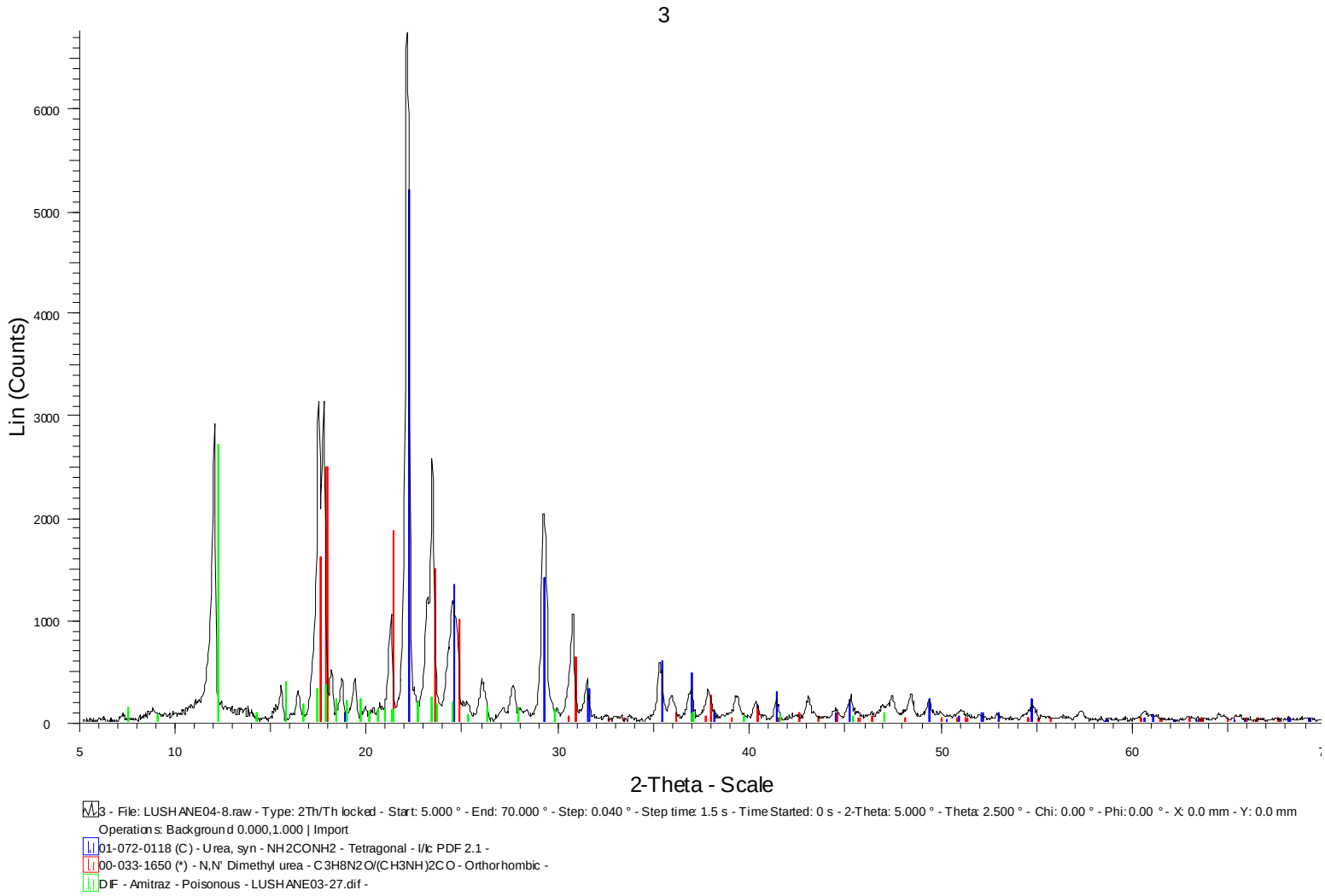


Figure 9: XRD spectra of 30% m/m Amitraz + 59% m/m eutectic mixture + excipients

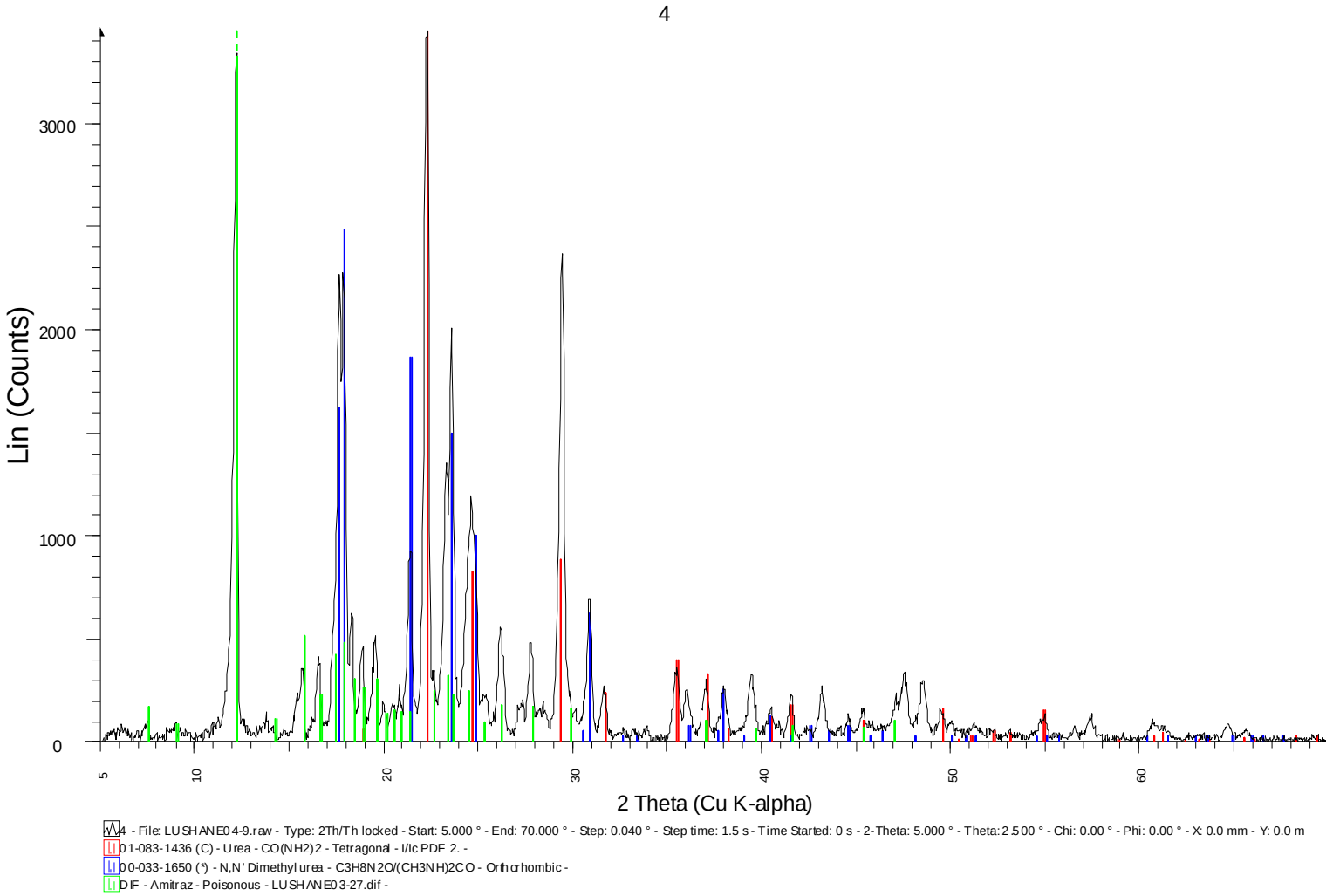


Figure 10: XRD spectra of 40% m/m Amitraz + 45% m/m eutectic mixture + excipients

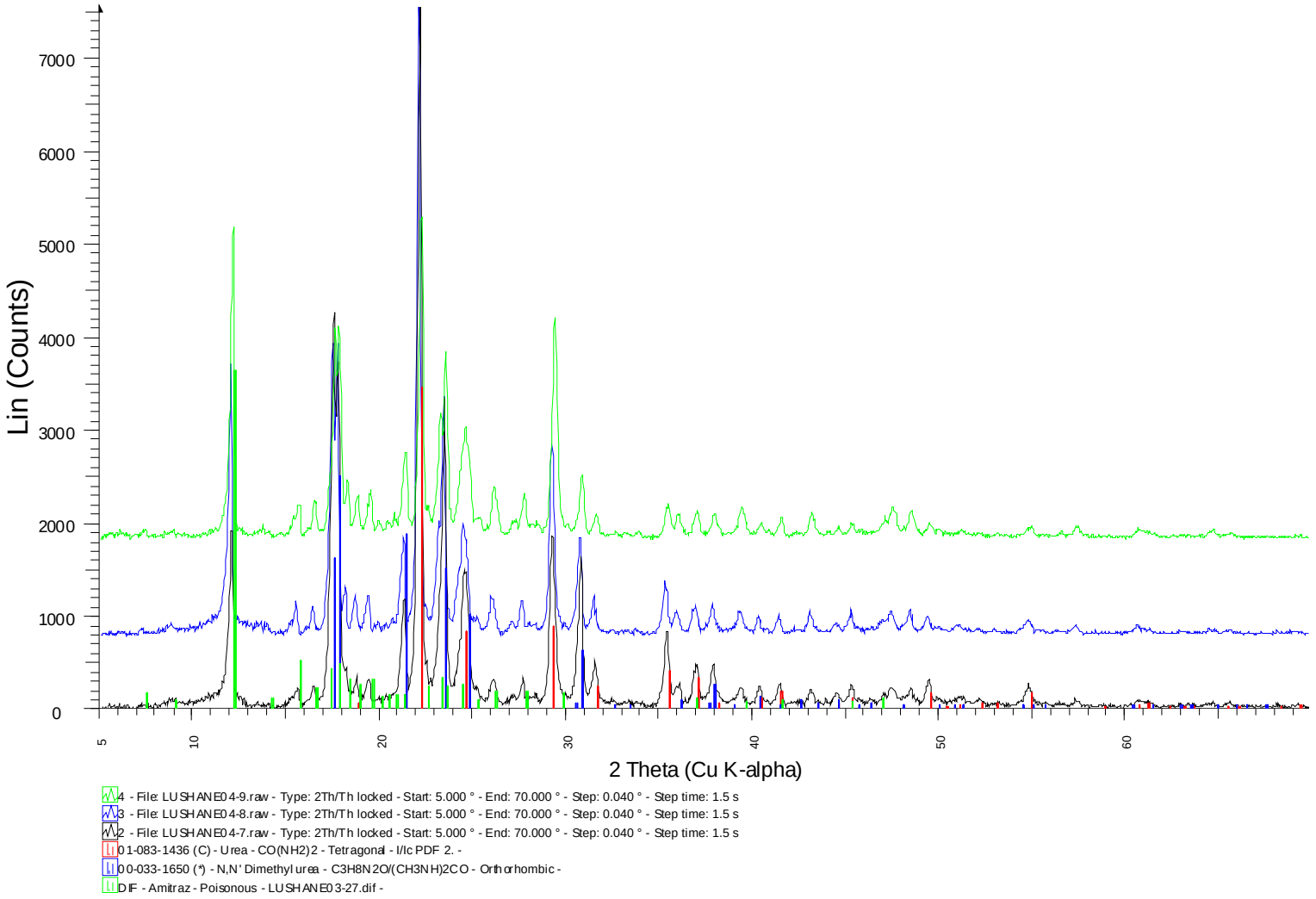


Figure 11: XRD spectra of 20%, 30% and 40% m/m Amitraz mixtures

Appendix G: DSC traces

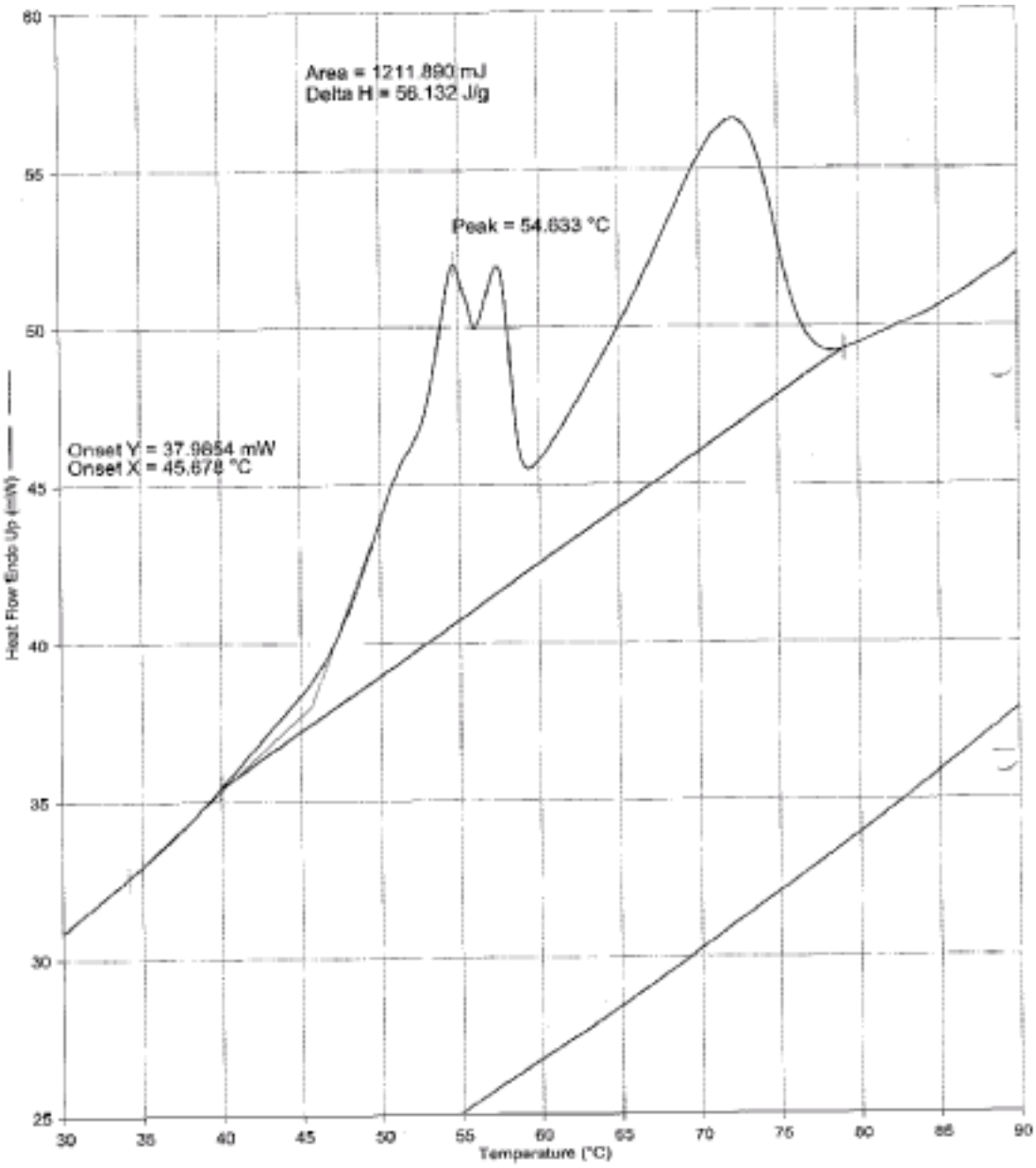


Figure 1: DSC traces for the 70% m/m urea + 30% m/m $CaBr_2.2H_2O$ mixture

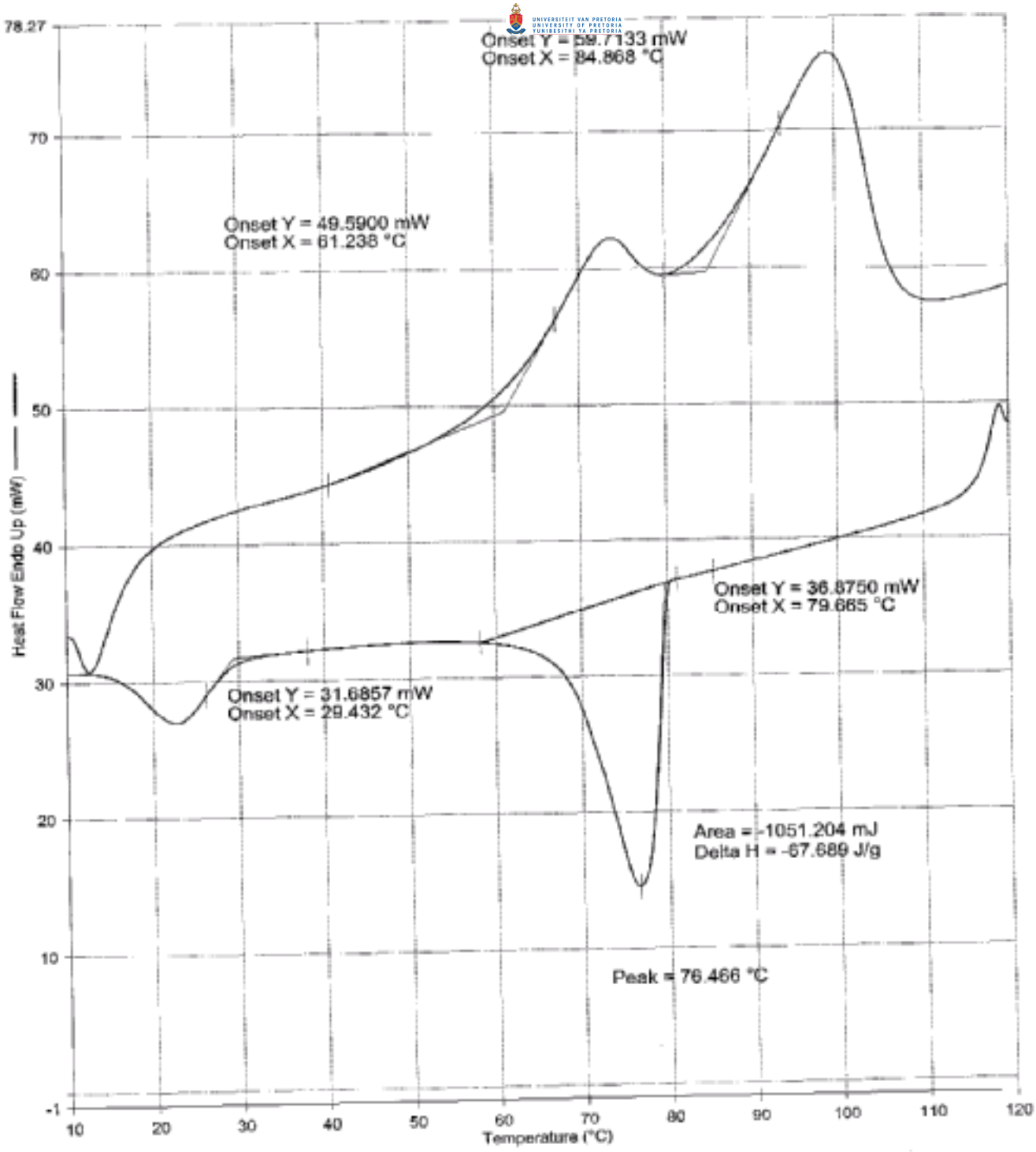


Figure 2: DSC traces for the 10% m/m urea + 90% m/m 1,3-dimethylurea mixture

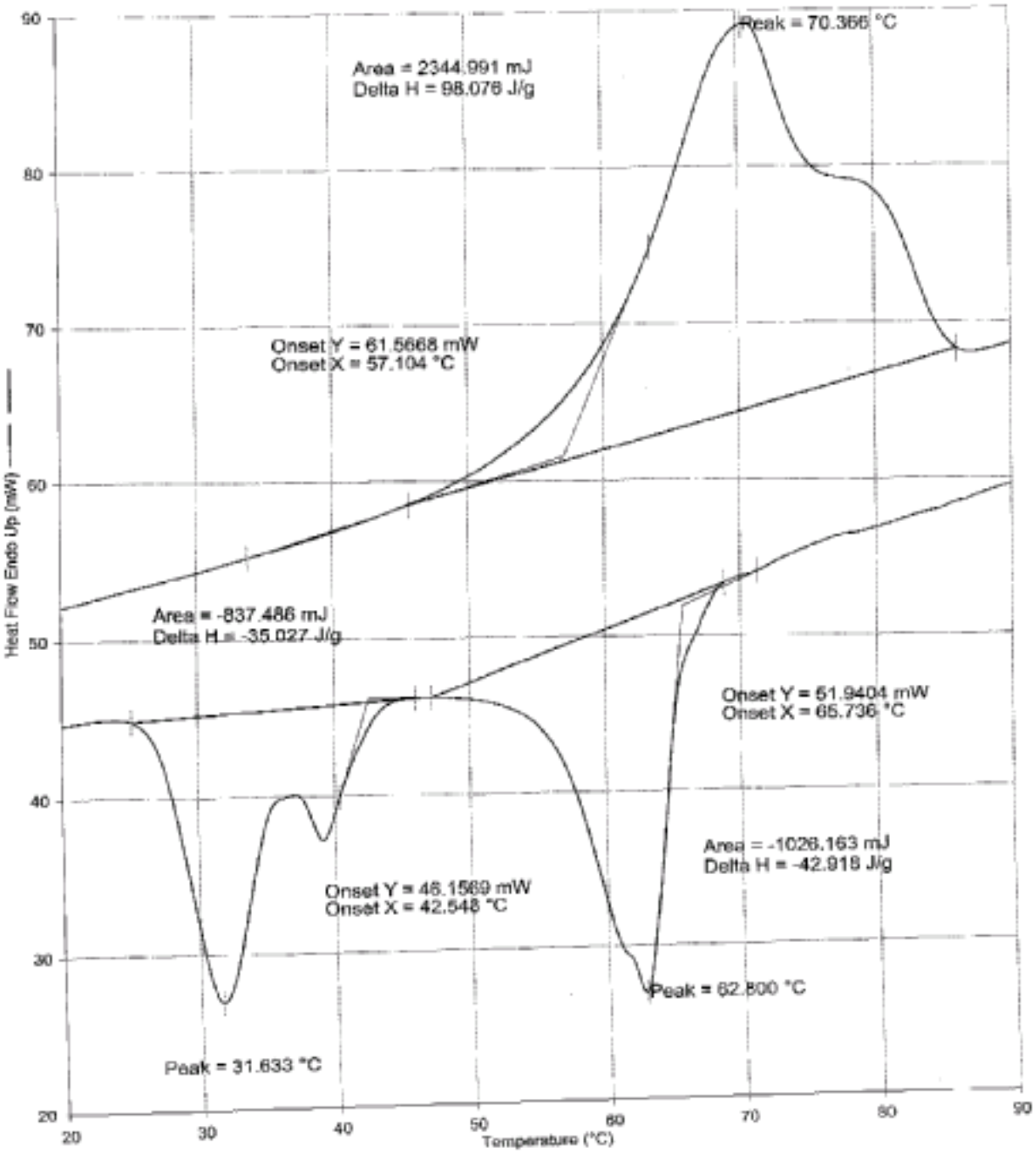


Figure 3: DSC traces for the 20% m/m urea + 80% m/m 1,3-dimethylurea mixture

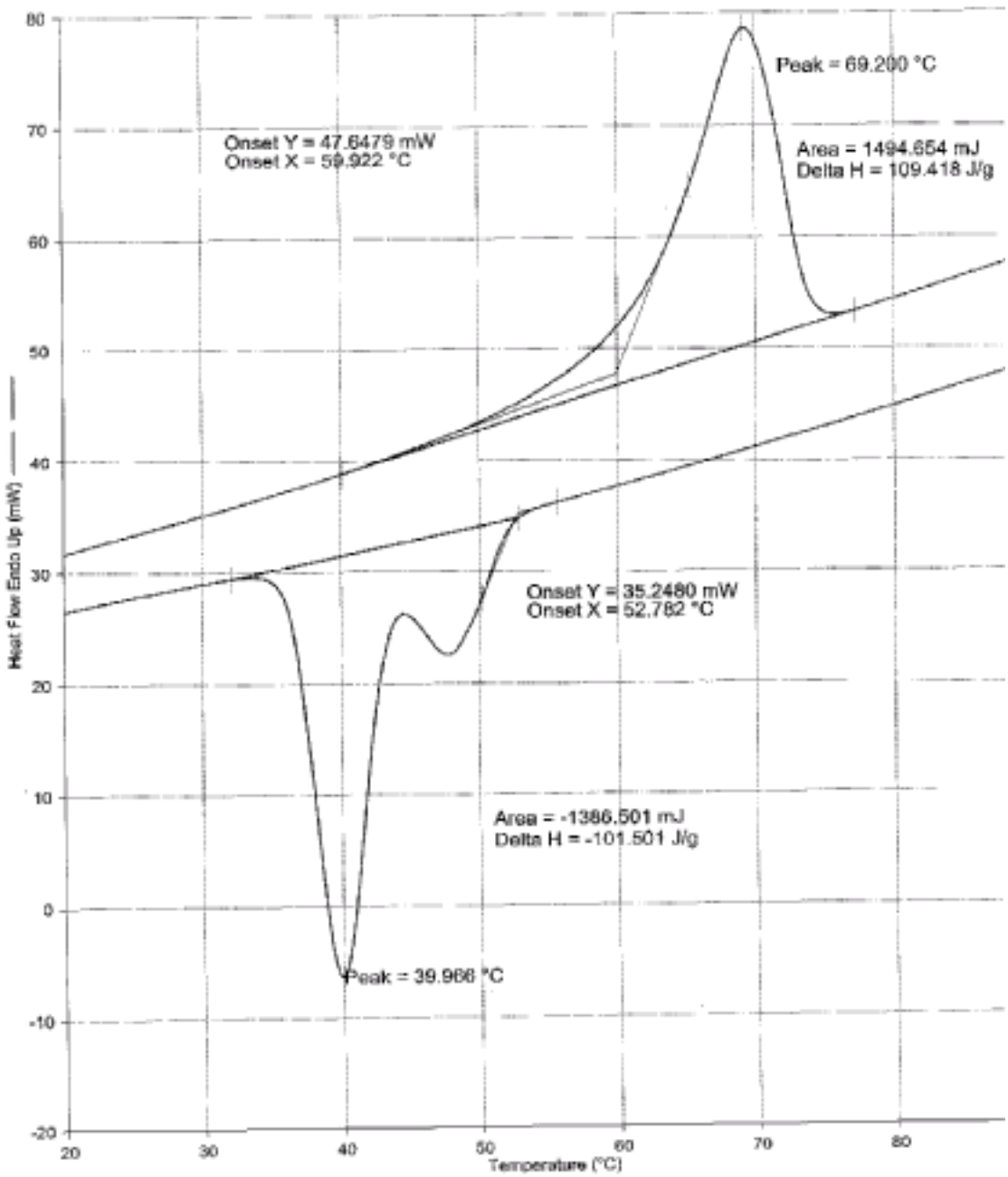


Figure 4: DSC traces for the 30% m/m urea + 70% m/m 1,3-dimethylurea mixture

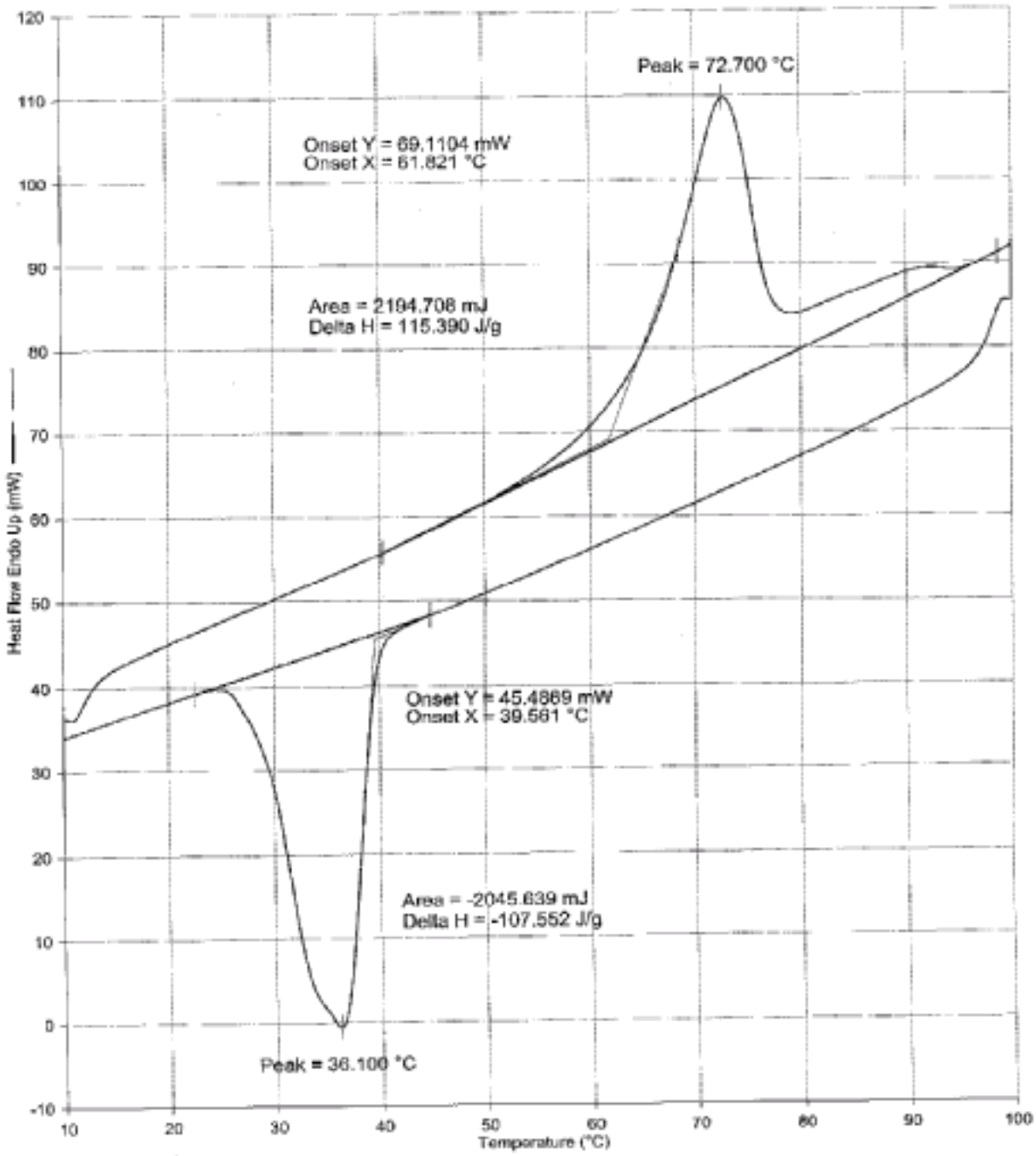


Figure 5: DSC spectra of 40% m/m urea + 60% m/m 1,3-dimethylurea mixture

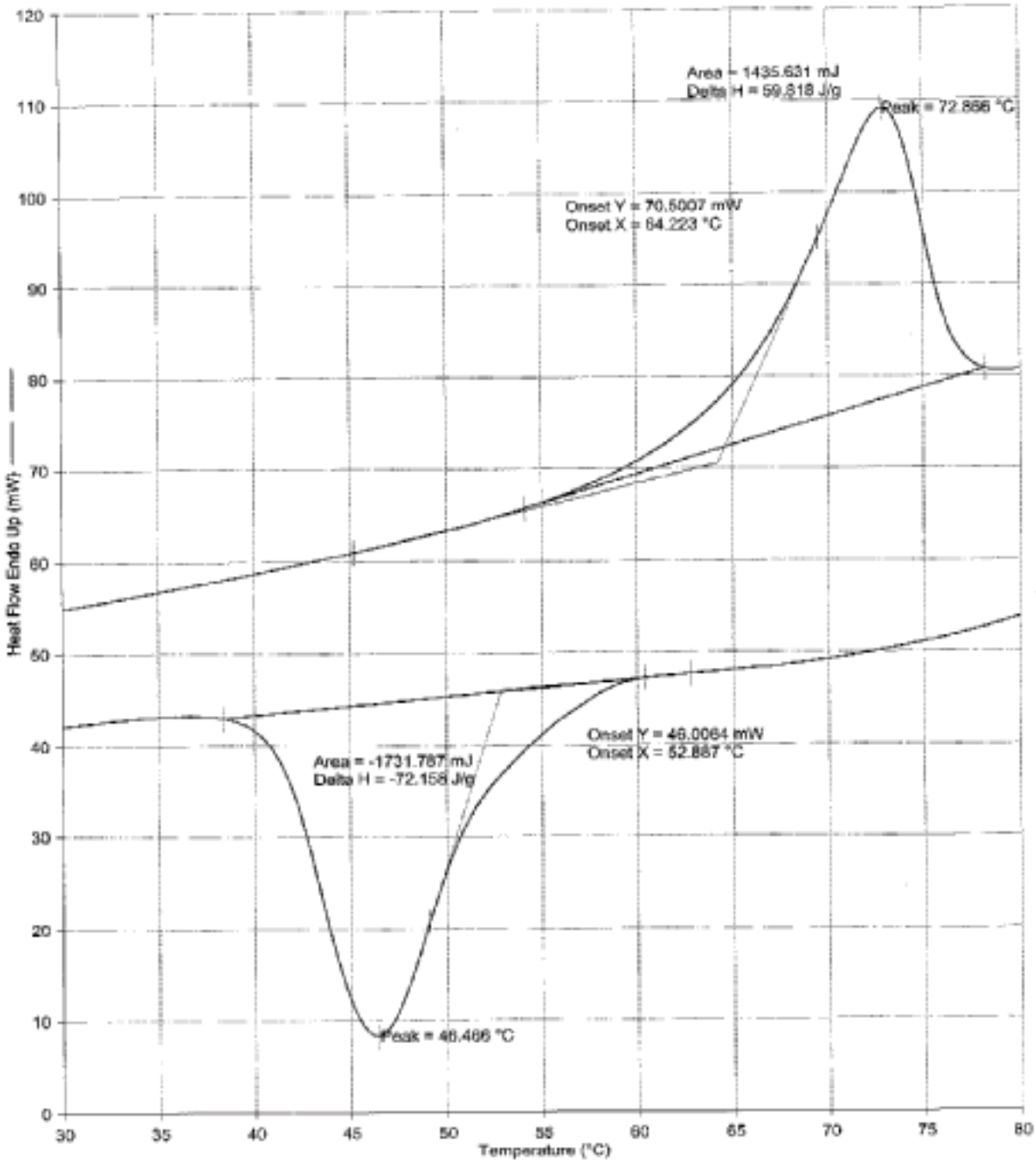


Figure 6: DSC traces for the 50% m/m urea + 50% m/m 1,3-dimethylurea mixture

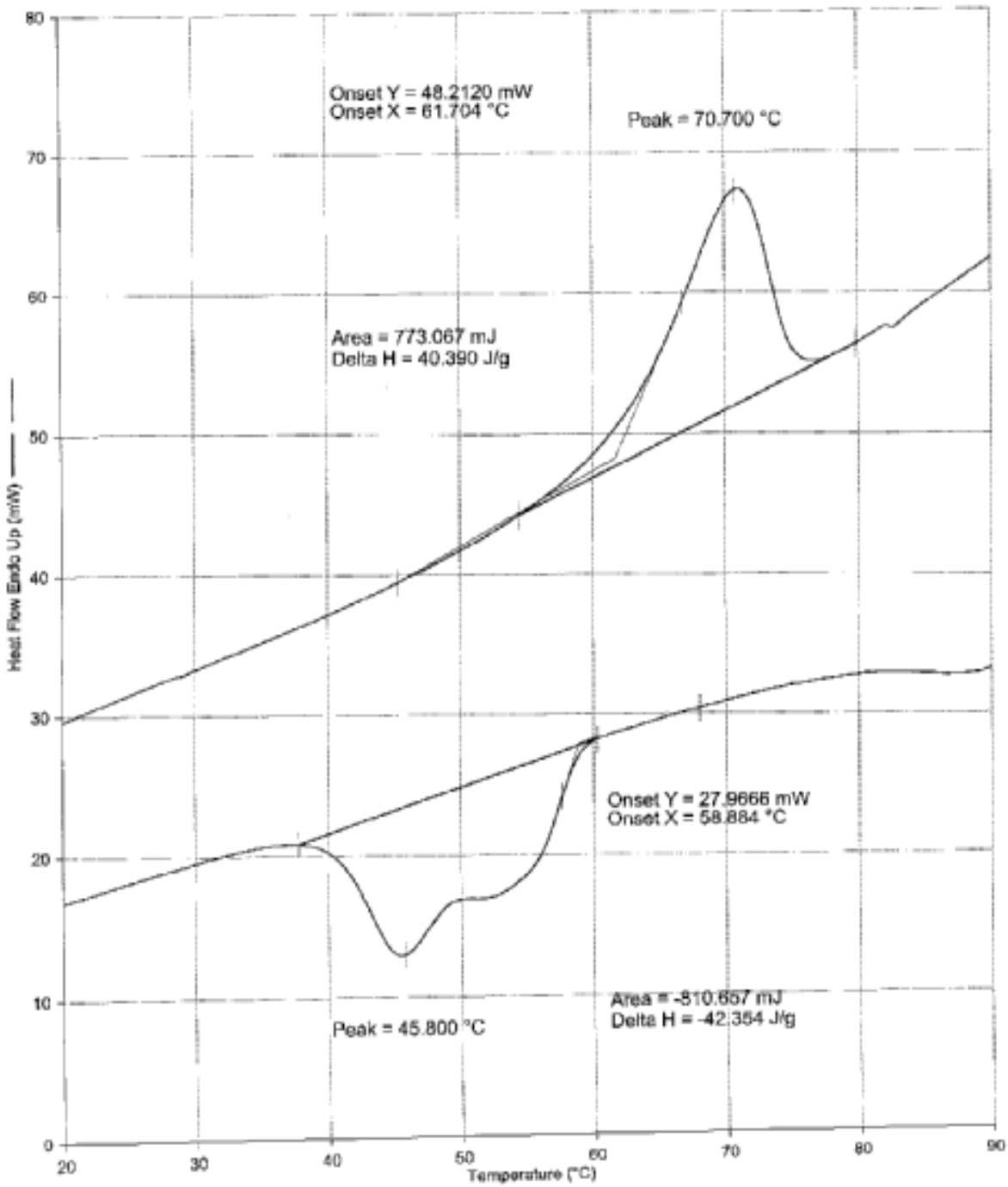


Figure 7: DSC traces for the 60% m/m urea + 40% m/m 1,3-dimethylurea mixture

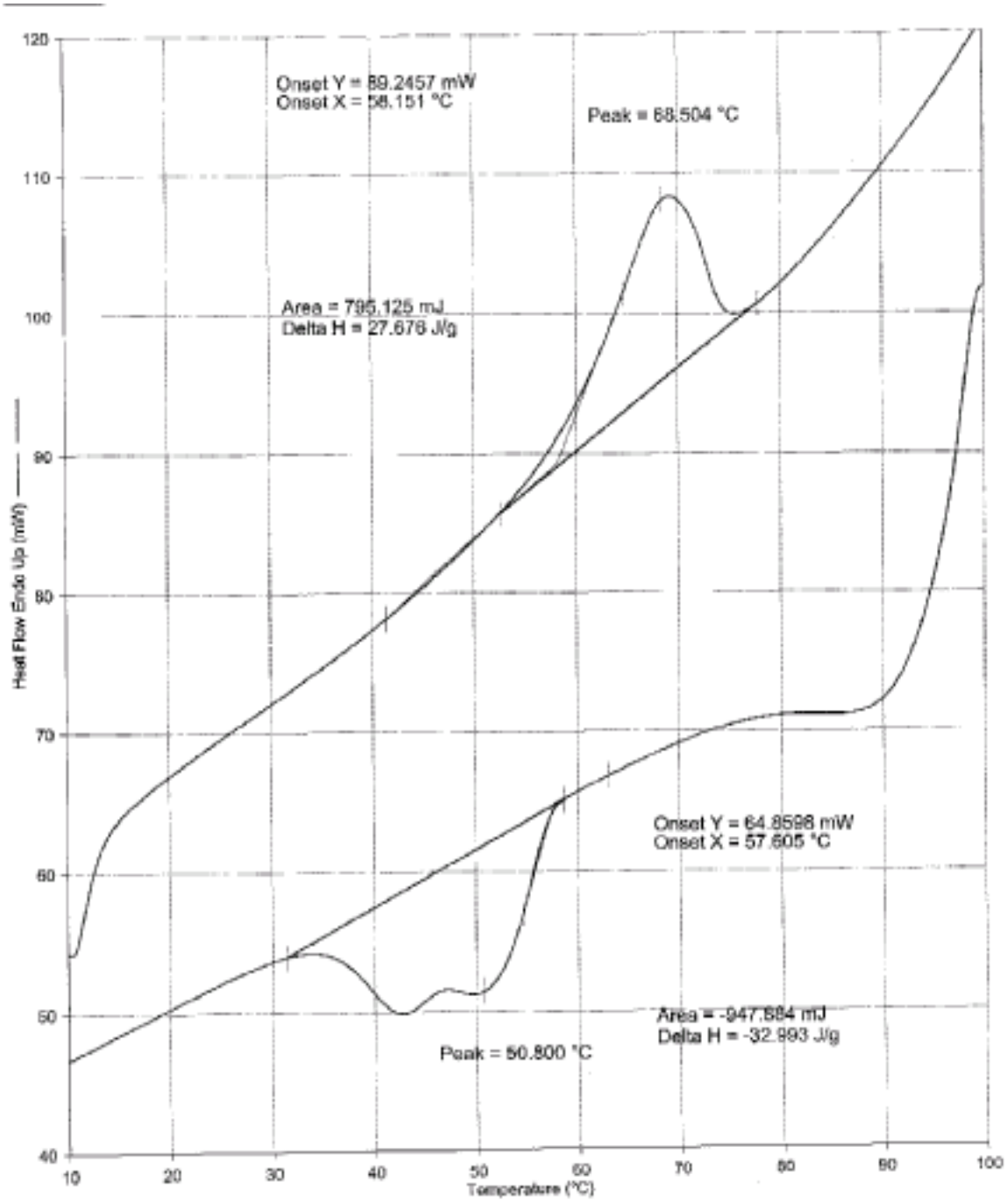


Figure 8: DSC traces for the 70% m/m urea + 30% m/m 1,3-dimethylurea mixture

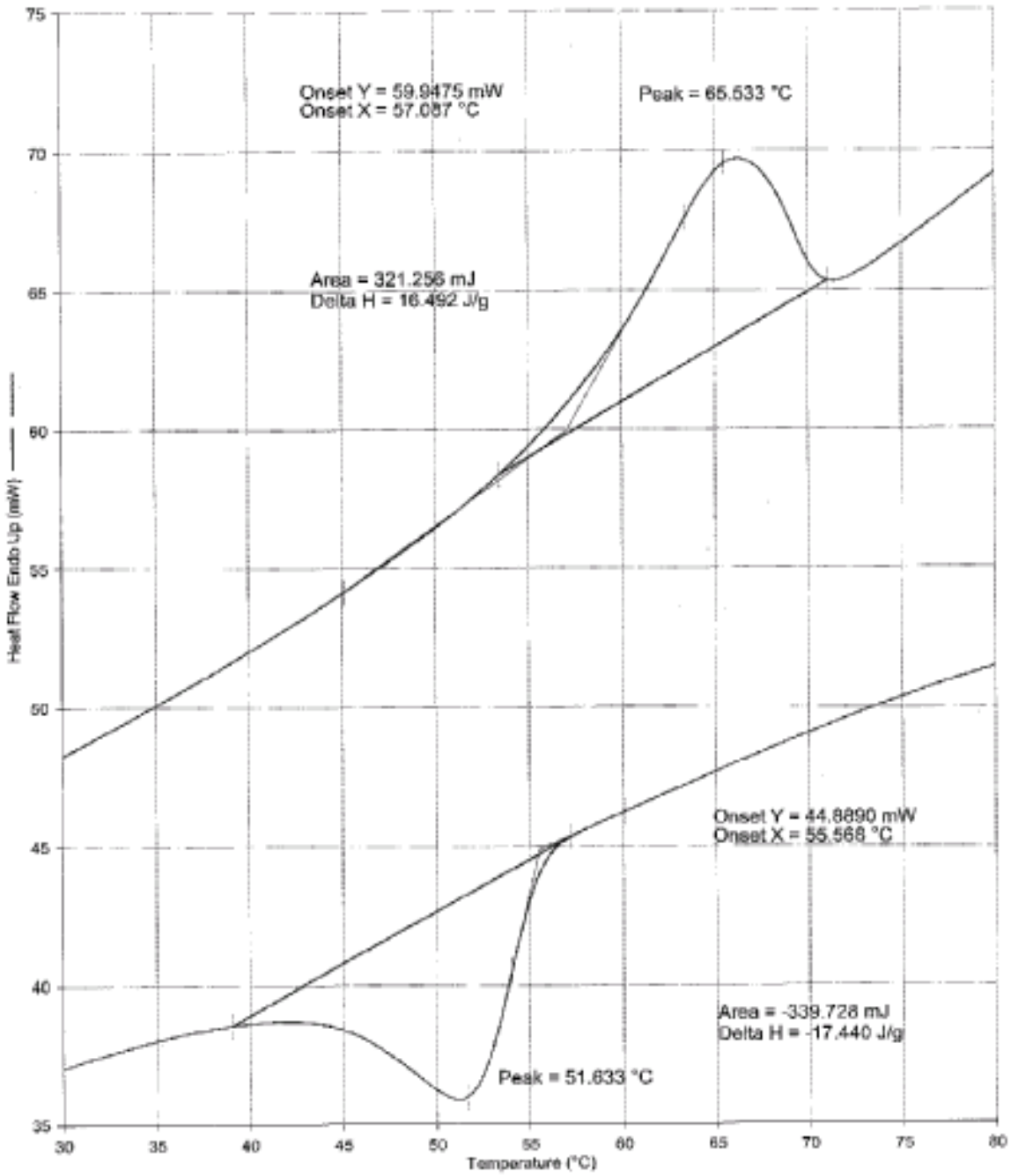


Figure 9: DSC traces for the 80% m/m urea + 20% m/m 1,3-dimethylurea mixture

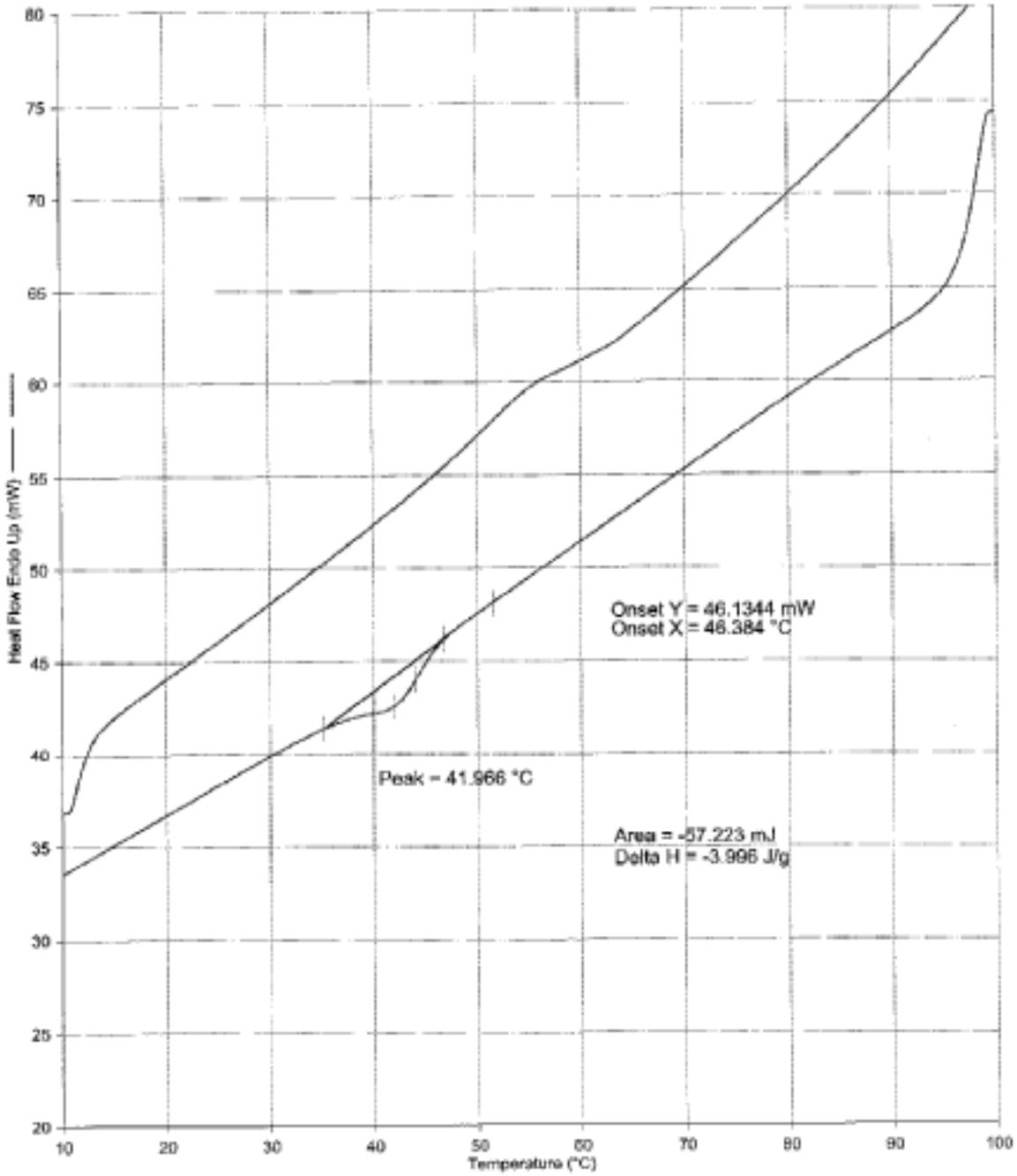


Figure 10: DSC traces for the 90% m/m urea + 10% m/m 1,3-dimethylurea mixture

Appendix H: Light Micrographs

Figure 1: Pure1,3-dimethylurea crystals

Figure 2: Pure urea crystals

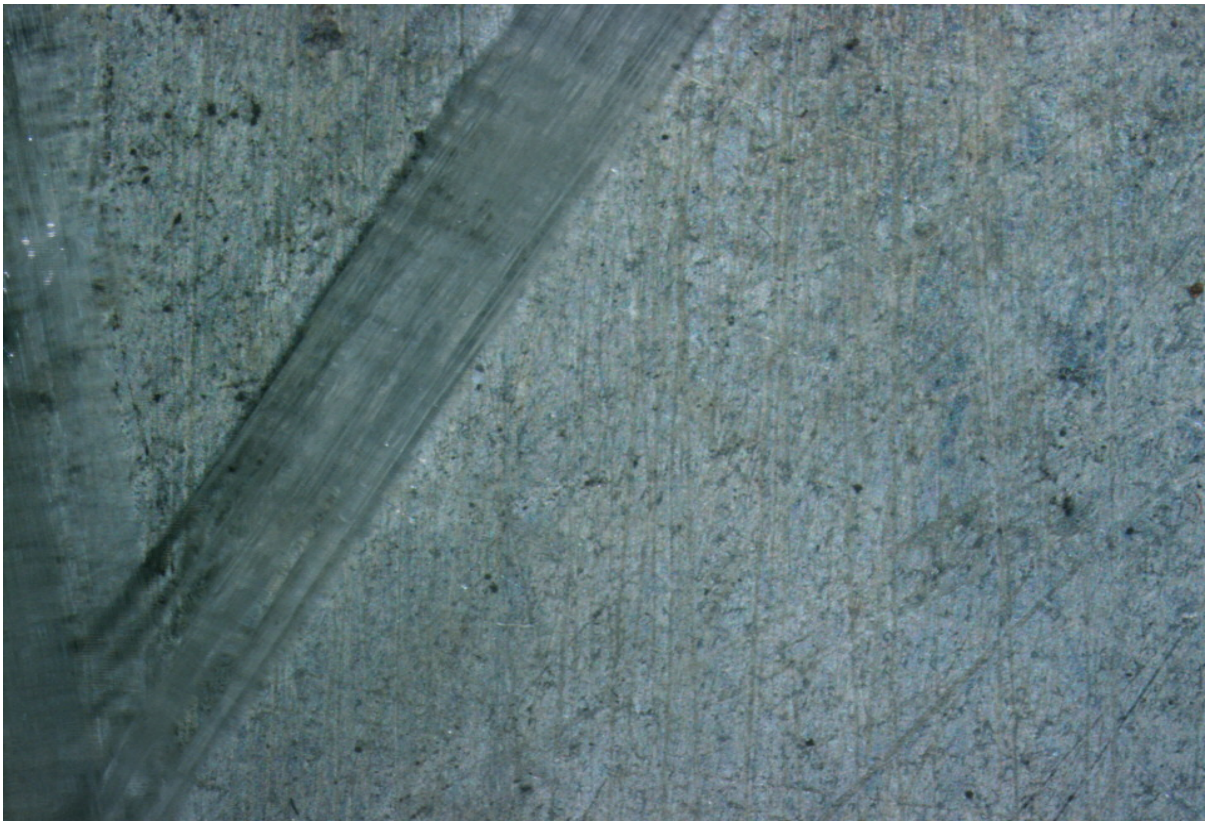


Figure 3a: Eutectic mixture crystals

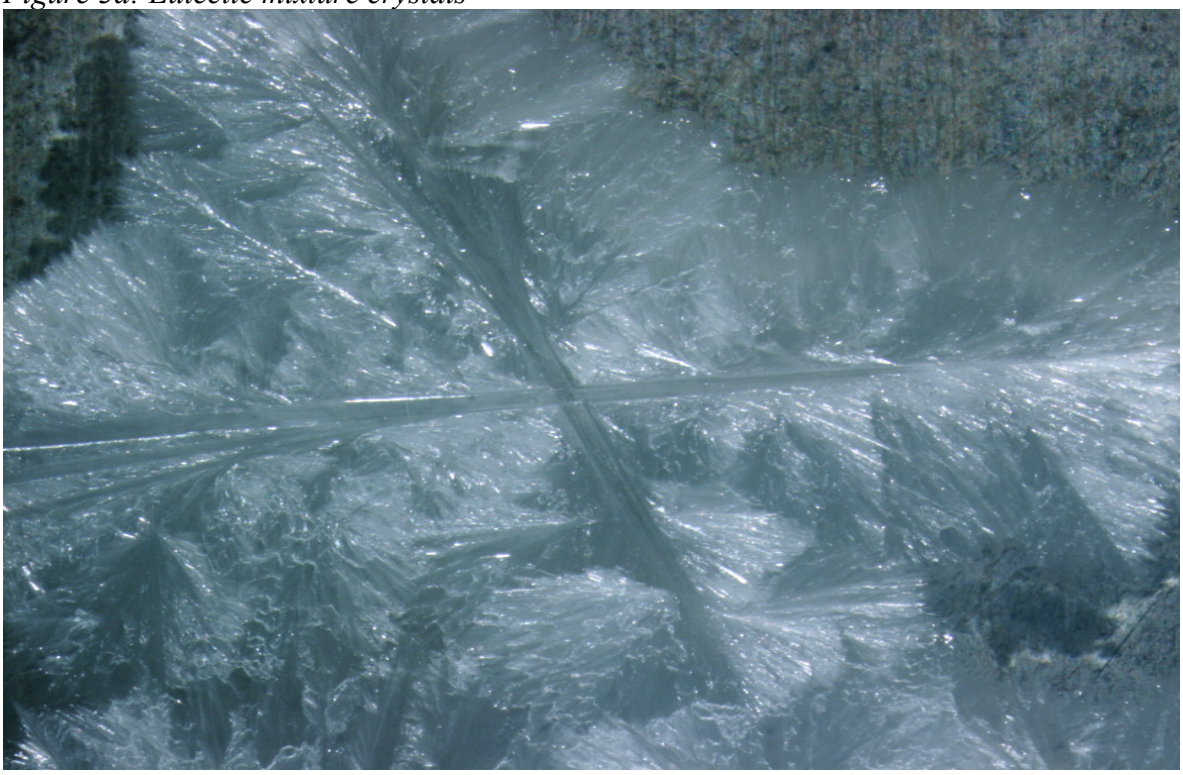


Figure 3b: Eutectic mixture crystals

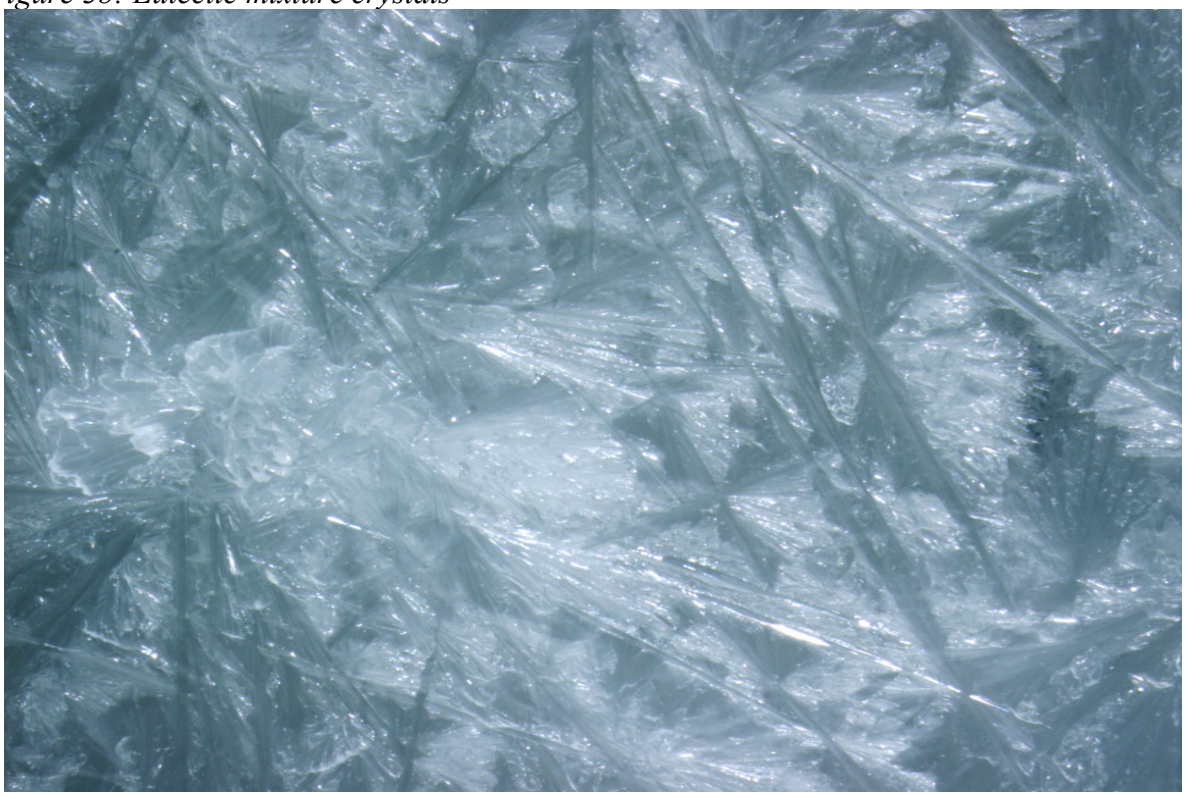


Figure 3c: Eutectic mixture crystals