DICLOFENAC SALTS: THEIR SYNTHESIS, CHARACTERIZATION AND LYOPHILIZATION CAKE CHARACTERISTICS

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ABSTRACT

Lyophilization has become a more acceptable approach in developing potentially unstable chemical entities. For the purposes of this research, diclofenac, a very stable small molecule was chosen as the model. The goal of this research was two fold. First, different salts of diclofenac were prepared and characterized. The characterizations of the diclofenac salts included appearance, crystalline characteristics, melting point, DSC, TGA, solubility in water and different pH buffers, and assay by High Performance Liquid Chromatography (HPLC). Secondly, the salts were lyophilized to determine if the salts cation affected the physical characteristics of the lyophilization cake. Comparisons were be made between salts with monovalent cations versus divalent and trivalent cations and different sizes of cations. The resulting lyophilized cakes were analytically compared as to the lyophilization cake's appearance, reconstitution time, color and clarity of solution, percent moisture in the vial (Karl Fischer analysis) and assay by UV. This research demonstrated that the different salts of diclofenac do have an effect on the final lyophilization cake. The lyophilization cake appearance, reconstitution time, percent moisture and primary drying time were all affected by the different salts of diclofenac.

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DEDICATION

I would like to dedicate this to my children; Lauren and Evan, their smiles and laughter are what motivate me in all that I do.

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Introduction

Lyophilization, commonly known as freeze drying, is dehydration or the removal of water. Lyophilization was first extensively used in the pharmaceutical industry during World War II to preserve blood plasma. Plasma was spoiling due to the amount of time it took to ship to the battlefield. Lyophilization provided a preservation mechanism. Lyophilization has been developed as a preservation technique for products such as proteins, to highly oxidation sensitive products, and flowers (FTS, 1991). Lyophilized products must meet certain criteria in order to be considered successful. The criteria include, but are not limited to, appearance, reconstitution time, stability, and maintenance of the physical characteristics of the original substance (Bedu-Addo, 2004). The appearance of the cake must be aesthetically pleasing. For a pharmaceutical lyophilized product, the cake cannot appear to be deformed, melted, or not "elegant". The reconstitution time must be within acceptable time limits. A lyophilized product that requires extensive mixing or an extended reconstitution time is not considered acceptable. One of the main goals of lyophilization is to improve the stability of the product. If the stability is less than or equal to the original material, then the cost and time required to lyophilize do not make economic or scientific sense. In terms of maintaining the physical characteristics of the original material, if the material undergoes changes that affect the inherent efficacy or in vitro mechanisms of the material then lyophilization of the product does not make pharmaceutical sense. Elegance of the cake can be defined as a cake that has not collapsed (Costantino, 2004). Elegance also includes subjective observations about cake structure, texture, and color. If the cake is not elegant, reformulation of the product might be necessary.

Lyophilization has become a more acceptable approach in developing potentially unstable chemical entities. It allows the product to be protected from oxidation from a solvent

system and headspace in the vial. Lyophilization also moves the material in question from the liquid state to the solid state where it is likely to be stable for a longer term (Constantino, 2004).

The lyophilization process takes place through three basic steps, freezing, primary drying, and secondary drying. These steps are summarized in the following paragraphs.

The freezing step converts the material from liquid to solid state. The freezing step is important because it can affect the outcome of the final product (Beaty, 2007). The freezing rate of the sample solution can lead to a more optimized lyophilization cycle. Generally, the faster the solution freezes, the smaller the crystals, while the slower the solution freezes, the larger the crystals (Beaty, 2007). Crystal size can have a significant affect on how a product will lyophilize. Drying time can be increased if the small crystal size impedes the sublimation of the solvent out of the matrix (FTS, 1991).

Primary drying is the removal of free ice from the system by sublimation (FTS, 1991.) The sublimation of the ice is driven by a pressure difference between the vapor pressure of the water and the pressure of the condenser. This difference can be directly calculated by obtaining the vapor pressure of the water at a specific temperature from standardized tables (Weast, 1987) and subtracting the pressure of the condenser (FTS, 1991).

Secondary drying is the removal of adhered or bound water to the surface of the cake matrix. Removal of this water involves increasing the temperature of the product to provide the necessary energy to remove the water. Secondary drying takes place after the temperature of the product reaches 0°C (FTS, 1991).

Considering the phase diagram of water (Encarta, 2006), see Figure 1, the aqueous sample solution goes from the liquid phase to the solid phase during the freezing step. To remove the "solid" water by sublimation, two actions must take place; there must be a decrease

in pressure around the solid phase and the temperature of the solid phase must be increased until the ice sublimes. In a lyophilization chamber the pressure around the system is lowered using a vacuum pump and the temperature of the shelf in the lyophilizer is increased to provide the necessary temperature increase. After the free ice is removed from the sample, the shelf temperature of the lyophilizer is again increased to above 0°C. Secondary drying takes place at this point.

During the lyophilization cycle, the sample temperatures are monitored using a thermocouple placed in a sample vial. It is generally accepted that when the temperature of the product or lyophilization cake reaches the temperature of the shelf and then tracks the shelf temperature, primary drying is completed (FTS, 1991). For example, if the product temperature is reading -27°C when the shelf temperature is -20°C, it would be inferred that primary drying is not completed and more time should be allowed.

The goal of this research was two fold. First, different salts of diclofenac were prepared and characterized, see Appendix D for salt structures. The characterizations of the diclofenac salts included appearance, presence of crystalline structure, melting point, Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), solubility in water at different pH's, and assay by High Performance Liquid Chromatography

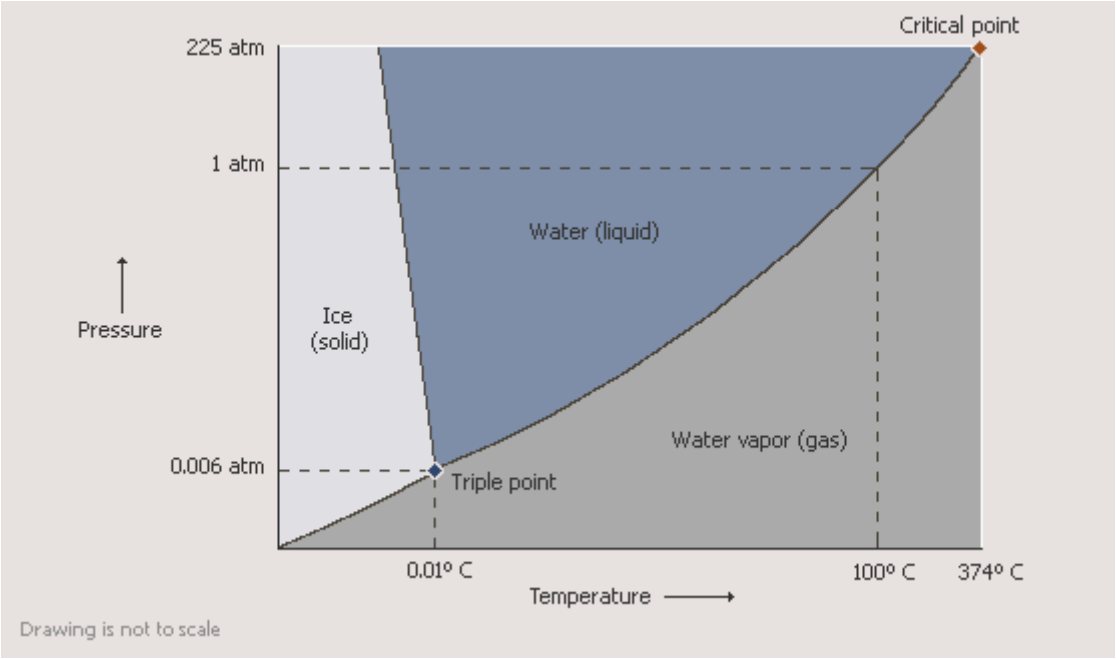

Figure 1. Phase Diagram of Water

(HPLC). Secondly, the salts were lyophilized to determine if the salts cation affected the physical characteristics of the lyophilization cake. Comparisons were be made between salts with monovalent cations versus divalent and trivalent cations and different sizes of cations. The resulting lyophilized cakes were analytically compared as to the lyophilization cakes appearance, reconstitution time, color and clarity of solution, percent moisture in the vial (Karl Fischer analysis) and assay by UV.

Experimental

Commercially prepared diclofenac salts were obtained through AAIPharma stocks and used throughout the research. Sodium diclofenac is the sodium salt of diclofenac. The sodium diclofenac, Lot 269/1 was manufactured by Secifarma. The potassium diclofenac, Lot DCPU003, was manufactured by Yung Zip Chemical Inc., Co. The first experiment was to prepare the free acid for use in possible synthetic routes to other salts of diclofenac. Sodium diclofenac was dissolved in water at a concentration of 7 mg/mL. When the sodium diclofenac was completely dissolved, it was titrated with an equal molar amount of hydrochloric acid. This solution was allowed to stir using a magnetic stir bar and plate for 10 minutes. Because the diclofenac free acid was not soluble in water, it immediately precipated out of solution (Khazaeinia, 2003). The free acid of diclofenac was a suspension in water while the resulting sodium and chloride ions remained in solution. The mixture was filtered using 0.45µm filter paper and a vacuum apparatus. The filtrate was washed with dilute HCl (0.001 N) and excess amounts of water to remove any excess sodium chloride and un-reacted sodium diclofenac. The powder was allowed to dry under a hood, collected and stored in a clear glass vial. The solubility of the free acid in methylene chloride was shown to be greater than 5 mg/mL.

Ammonia Diclofenac (NH_4D)

The preparation of NH_4D was done by reacting diclofenac free acid with ammonia. The reaction was completed by the ammonia deprotonating the free acid and allowing the positively charged ammonia group to form the salt complex. To aid in the dissolution of the free acid, the final concentration of the methylene chloride solution was 4.1 mg/mL. The free acid was dissolved into methylene chloride resulting in 1.4×10^{-2} moles per liter of diclofenac. Ten milliliters of a 1.0 N solution of ammonium hydroxide was slowly titrated into the solution using a class A pipette. The solution was mixed using a stir bar and stir plate. The solution turned to a milky white suspension within 30 seconds. The suspension was mixed for 10 minutes to allow for the reaction to go to completion. The suspension was transferred to a graduated cylinder and the water layer was removed using a disposable pipette. The suspension was transferred to petri dishes and placed in a fume hood. The methylene chloride was allowed to evaporate and the ammonium diclofenac was collected.

Tetrabutyl ammonium diclofenac was prepared and used in several lyophilization cycles. The salt was prepared by combining equal portions of diclofenac free acid with 0.4 M tetrabutyl ammonium hydroxide in water. The reactants were placed in a scintillation vial and mixed overnight using a stir bar and magnetic stir plate. It was predicted the diclofenac salt would be formed and water would be the only byproduct.

Metal Stock Solution Preparation

Several metal stock solutions were prepared to synthesize the different diclofenac salts for this research. In most cases, 1 molar stock solutions were prepared, however in the zinc solution, due to limited material, a 0.34 M solution was prepared. These solutions were prepared volumetrically in the laboratory and used throughout the research.

Magnesium Sulfate

The $MgSO_4$ (formula weight 120.4 g/mole), used in the preparation of the stock solution, was sourced from Sigma, lot 50K0248. A one molar solution was prepared by dissolving 12.0 g of $MgSO_4$ into 100 mL volumetric flask containing approximately 80 mL of Milli-Q water (in-house deionized water). The solution was mixed until the resulting solution was clear and colorless. The solution was filled to volume and mixed well.

Aluminum Chloride

The $AlCl_3$ hexahydrate (formula weight 241.43), used in the preparation of the stock solution, was sourced from Fisher, lot 028520. A one molar solution was prepared by dissolving 24.1 g of $AlCl_3$ into 100 mL volumetric flask containing approximately 80 mL of Milli-Q water. The solution was mixed until the resulting solution was clear and colorless. The solution was filled to volume and mixed well.

Zinc Sulfate

The $ZnSO_4$ heptahydrate (formula weight 287.5), used in the preparation of the stock solution, was sourced from Sigma, lot 128H14291. A 0.34 molar solution was prepared by dissolving 9.7 g of $ZnSO_4$ into 100 mL volumetric flask containing approximately 80 mL of Milli-Q water. The solution was mixed until the resulting solution was clear and colorless. The solution was filled to volume and mixed well.

Lead Nitrate

The $Pb(NO_3)_2$ (formula weight 331.2), used in the preparation of the stock solution, was sourced from Aldrich, lot 11113TU. A one molar solution was prepared by dissolving 33.1 g of $Pb(NO_3)_2$ into 100 mL volumetric flask containing approximately 80 mL of Milli-Q water. The

solution was mixed until the resulting solution was clear and colorless. The solution was filled to volume and mixed well

Copper Sulfate

The $CuSO_4$ (formula weight 249.7), used in the preparation of the stock solution, was sourced from Sigma, lot 4OK3704. A one molar solution was prepared by dissolving 24.9 g of $CuSO_4$ into 100 mL volumetric flask containing approximately 80 mL of Milli-Q water. The solution was mixed until the resulting solution was clear and royal blue. The solution was filled to volume and mixed well.

Metal Complex Preparation

The magnesium, zinc, copper, lead, and aluminum salts of diclofenac were prepared by combining a metal cation with solutions of sodium diclofenac. Because the magnesium, aluminum, zinc, copper and lead salts of diclofenac have limited solubility in water, they form a precipitate and fall out of solution. The salts were then collected and characterized.

A stock solution of 0.044 molar sodium diclofenac was prepared by dissolving 25.0 grams of sodium diclofenac in 1.8 liters of Milli-Q water. This solution was divided into sub lots that would be used to prepare the metal salts of diclofenac. Sodium diclofenac has a ratio of 1:1 between the sodium ion and the diclofenac ion. Using this information, the correct molar concentration of metal salt solution was calculated so that when titrated it could be expected that all of the diclofenac would be reacted to the intended metal salt. The amount of metal solutions used to titrate the diclofenac solution was calculated using Equation 1. The concentration of the lead and magnesium metal

solutions was one molar. The concentration of the sodium diclofenac solution was 0.044M, therefore the molar amount of the divalent metals needed to titrate the diclofenac solution was

0.022M. The calculated amount of metal solution used to titrate the solution was 8.8 mL. 9 mL of solution was added to provide an excess of the metal. The concentration of the zinc metal solution was 0.34 M, which required a titration volume of 25.9 mL for the correct molar equivalent ratio. To provide an excess, the solution was titrated with 27 mL of zinc metal solution, see Table 1 for the molar equivalents used in the salts preparation. The concentration of the aluminum salt solution was one molar. Due to aluminum being a trivalent metal, 0.015 moles of metal were needed to react all of the diclofenac in solution. 7 mL of solution were used to titrate the diclofenac.

The 400 mL aliquot of the sodium diclofenac in solution was stirred continuously using a stir bar and stir plate. The metal solution was slowly titrated into the diclofenac solution using a class A pipette. A white precipitate was immediately visible in the beaker. The suspension was allowed to stir for an additional ten minutes. The suspended solids were collected on filter paper using 0.45μm filter paper and vacuum filtration. The filter paper and collected solids were resuspended using Milli-Q water to "wash" the solids. The filter paper was then placed in a 40°C oven and dried overnight. This procedure was acceptable except for the lead diclofenac system, which passed through the filter paper. Two alternatives for collecting the lead diclofenac were explored. First,

Equation 1. Molar Equivalent Calculation

$V_1C_1 = V_2C_2$

V_1 = Initial volume
C_1 = Initial concentration
V_2 = Final volume
C_2 = Final concentration

$2Na^{+} + 2Diclofenac^{-} + Mg^{2+} + SO_4^{2-} \rightarrow MgD_2 \downarrow + Na_2SO_4$

$3Na^{+} + 3Diclofenac^{-} + Al^{3+} + 3Cl^{-} \rightarrow AlD_3 \downarrow + 3NaCl$

$2Na^{+} + 2Diclofenac^{-} + Zn^{2+} + SO_4^{2-} \rightarrow ZnD_2 \downarrow + Na_2SO_4$

$2Na^{+} + 2Diclofenac^{-} + Pb^{2+} + 2NO_3^{-} \rightarrow PbD_2 \downarrow + 2NaNO_3$

$2Na+ + 2Diclofenac - + Cu2+ + 2NO3- \rightarrow CuD2 \downarrow + 2NaNO3$

Figure 2. Reactions of the Diclofenac Salts Prepared

Table 1. Molar Ratios for Diclofenac Salt Preparation

Cation	Molar Ratio (Diclofenac to Metal) Theoretical	Molar Ratio (Diclofenac to Metal) Used
Magensium	2 : 1	2.05 : 1
Copper	2 : 1	2.05 : 1
Zinc	2 : 1	2.08 : 1
Lead	2 : 1	2.05 : 1
Aluminum	3 : 1	3.5 : 1

an aliquot of the lead diclofenac suspension was placed in a centrifuge tube. The sample was centrifuged at 3000 rotations per minute (RPM) for 30 minutes and the supernatant was poured off and the solids collected. The solids were dried in a 40°C oven overnight. The second approach was to filter an aliquot of the lead diclofenac system using a 0.22 μm filter and collect the solids. The centrifuge alternative was more effective and was used to process the lead diclofenac. Once the solids had dried, they were stored in amber glass bottles with black plastic tops.

Once all of the salts were prepared, they were evaluated visually for appearance, color, and crystallinity using an Olympus Microscope. Salt characterization included purity by HPLC analysis, evaluation of crystallinity, melting point, thermogravimetric analysis (TGA), differential calometric scanning (DSC), solubility in water and pH 4, 7, 8, and 10 buffers.

Appearance

The synthesized diclofenac salts were evaluated visually using an Olympus BH2 Microscope. The appearance, color, size and crystallinity of each powder were established. Slides were prepared using standard techniques with Cargille non-drying Immersion Oil for microscopy, Type A, lot 101376. Each diclofenac salt was assessed at 400X under normal light and crossed polarized light. Under normal light, the slide was inspected for particle size and quality. Each diclofenac salt was described using common identifying terms, such as square, cubic, needle, agglomerates, and color. A larger agglomerate or crystal was used to assess if the particulate showed birefringent light under the crossed polarized light. This would indicate whether or not the sample was crystalline.

Sample Purity

Sample purity was determined using a modified high performance liquid chromatography method in use at AAIPharma. The method was currently being used to test sodium diclofenac content in tablets. The method was modified so that the standard ratio was correct for the reconstitution of the lyophilized samples. The mobile phase was a combination of phosphate buffer and organic solvents, see Table 2 for mobile phase ratios. The buffer was prepared by dissolving 10.2 g of potassium phosphate into 1500 mL of water and then adjusting the pH to 3.0 using concentrated phosphoric acid. The final pH of the solution was 3.08. This buffer was mixed with acetonitrile and methanol; this solution was the mobile phase for the HPLC run. The diclofenac standard was prepared by dissolving 18.57 mg of sodium diclofenac in 250 mL of mobile phase. The purity of the sodium diclofenac being used for the standard preparation was assumed to be 100%.

The samples were injected on a Hewlett Packard® HP1100 high performance liquid chromatogram using an Altech Inertisil® ODS-2 column, 15 cm in length with an internal diameter of 4.6 mm and a 5 µm packing size. The mobile phase flow rate was 1.2 mL/minutes at ambient temperature. The injection volume was 10µL and the UV detector was set to 250 nm. The data acquisition system used was Millenium 32®, Version 4.0. A series of three standards were injected to establish system suitability.

Ksp Evaluation

The solubility product, Ksp, was determined by placing an excess amount of the diclofenac salt into a 10 mL clear glass vial and adding 5.0 mL of Milli-Q water. A stir bar was placed in the vial and the vial was sealed. The vials were stirred using a magnetic stir plate for a minimum of 48 hours. The resulting solution was filtered using a 0.45 µm Nylon filter and

collected in a glass test tube. The filtrate was analyzed by UV at 278 nm for amount of drug dissolved in the water (Pfeiffer, 1998). Using the calculated amount of diclofenac in the water (mg/mL), the Ksp of each salt was calculated. The standard for the Ksp testing was prepared by dissolving 26.01 mg of sodium diclofenac in 25 mL of water. The 1mg/mL solution was then diluted to a working concentration of 0.01 mg/mL. Using this standard, system suitability was determined by reading the standard and comparing the absorbance to previous runs and comparing multiple runs of the same standard. The samples were then diluted to appropriate concentrations and the samples were read. The mg/mL of diclofenac in solution was calculated and used to calculate total mg of diclofenac dissolved, which was then used to calculate the molarity and Ksp of each salt.

pH Solubility of Metal Salts

As part of the characterization of the new diclofenac salts, the solubility was determined in pH 4.0, 7.0, 8.0, and 10.0 buffers. Buffers were prepared using established buffer systems, see Table 3 for the buffer systems and actual pH. The pH meter used was calibrated using commercially available buffers at pH 4.0, 7.0, and 10.0. A series of stock solutions were prepared and then used to create the specific pH buffers. A 0.1M citric acid solution was prepared by dissolving 21.0 g of citric acid in water to 1L. A 0.2 M dibasic sodium phosphate solution was prepared by dissolving 28.4 g of the salt in water to 1L. The 0.2 M monobasic sodium phosphate solution was prepared by dissolving 27.6 g of salt in water to 1L. A 0.2 M sodium hydroxide solution was prepared by dissolving 8.0 g of sodium hydroxide pellets in water to 1L. A boric acid /

Table 2. Components of HPLC Mobile Phase Preparation

Component	Milliliters
Phosphate Buffer pH 3.0	450
Methanol	250
Acetonitrile	300

Equation 2. Example Ksp Equations

Sodium Diclofenac (s) $\rightleftharpoons$ Na^{+} (aq) + Diclofenac $^{-}$ (aq)

$Ksp = [Na^{+}]\,[Diclofenac^{-}]$

Magnesium Diclofenac (s) $\rightleftharpoons$ Mg^{2+} (aq) + 2Diclofenac^{-} (aq)

$Ksp = [Mg^{2+}]\,[Diclofenac^{-}]^{2}$

Table 3. pH Buffer Systems Used with Measured pH

pH of Buffer System to be Prepared	Buffer System Used	Measured pH of Buffer System	Buffers Ionic Strength
4	Citric Acid	4.01	NA
7	Sodium Phosphate	6.96	0.22
8	Sodium Phosphate	7.99	0.64
10	Sodium Hydroxide	9.84	0.09

potassium chloride solution was prepared by dissolving 12.4 g of boric acid and 14.9 g of potassium chloride in water to 1L (Dawson, 1978).

The pH 4 buffer was prepared by combining 61.45 mL of the citric acid solution with 38.55 mL of the dibasic sodium phosphate solution. The dilutions were completed using class A pipettes and an Ependorf pipette. The resulting solution was mixed well and the pH of the solution was 4.01.

The pH 7 buffer was prepared by combining 30.5 mL of 0.2M dibasic sodium phosphate solution and 19.5 mL of monobasic sodium phosphate and then diluting the solution to 100 mL with water. The solution was mixed thoroughly and the resulting pH was 6.96.

The pH 8 buffer was prepared by combining 47.35 mL of 0.2M dibasic sodium phosphate solution and 2.65 mL of monobasic sodium phosphate and then diluting the solution to 100 mL with water. The solution was mixed thoroughly and the resulting pH was 7.99.

The pH 10 buffer was prepared using 43.7 mL of the 0.2M sodium hydroxide solution and 50 mL of the boric acid/potassium chloride solution. The solution was mixed well with a resulting pH of 9.84.

Samples of each diclofenac salts were prepared by adding an excess amount of salt to a vial containing 10 mL of the appropriate pH buffer. The vials were labeled and sealed. The vials were then placed on a sample nutator and mixed by rocking back and forth for a minimum of 24 hours. The salts did not wet well and shaking the vials by hand was required to wet all of the diclofenac salt in the vial.

The final solutions were removed from mixing and filtered using syringes and 25 mm 0.45µm nylon syringe filters. This filter was chosen because AAIPharma had shown that these filters do not retain diclofenac during filtration (Pfeiffer, 1998). A small amount of the filtrate

was used to saturate the filter (approximately 0.5 mL) and the rest was collected in glass test tubes to be analyzed by UV spectrometry for diclofenac at wavelength 278 nm. The analysis was done by comparing absorbance readings of the samples to the absorbance of a 0.01 mg/mL standard that was prepared in the laboratory. The standard was prepared by dissolving 26.18 mg of sodium diclofenac into 25 mL of water. The solution was then diluted to the working concentration with the appropriate pH buffer. The working concentration of each salt in each pH buffer was established and the absorbance recorded. Using this absorbance, along with the dilution information, the mg/mL dissolved of each salt was calculated.

X-Ray Diffraction

Samples of ammonium, magnesium, lead, and aluminum diclofenac samples were run using Siemens Diffraktometer using Materials Data Incorporated Data Scan® 4 with Materials Data Incorporated Jade®, Version 7 printing software. The experiment was carried out by affixing a small amount of sample to the quartz zero-background sample plate and mounted in the instrument. The sample was then scanned from 2° to 40° at 0.05° intervals with a scan rate 2.4°/min and the refractance of the x-rays was measured (Stowell, 2002).

Melting Point Determination

The melting point of each salt was determined in the lab using a 9100 Electrothermal melting point apparatus. The melting point of each salt was estimated using the fastest ramp rate of the melting point apparatus. Once an estimate for each of the salts melting point was determined, the temperature ramp rate was slowed and a more specific melting point was determined. This work was compared to the evaluation of the salts by Differential Scanning Calorimetry.

TGA

Thermogravimetric analysis (TGA) of each salt was carried out in the physical characterization laboratory at AAIPharma. The TGA samples were analyzed using a Seiko® Instruments TG/DTA 220 with the Seiko software package, version 6.0. Individual samples of approximately 10 mg were analyzed from 30°C to 350°C with a ramp rate of 10°C per minute. The analysis of the TGA chromatograms was used to determine the amount of solvent loss from the salt complex (Mettler, 2001).

DSC

Differential Scanning calorimetry analysis of the diclofenac salts provided information on the possible formation of hydrates of the samples. The samples were analyzed using a Mettler Toledo® DSC821e instrument using STARe® software, version 6.01. The samples were heated from 30°C to 350°C with a ramp rate of 10.0°C per minute. The DSC provided chromatograms of the salts melting and recrystallizing characteristics (Mettler, 2001).

Equation 3. Calculation of mg/mL Diclofenac in pH Buffer Solubility Study

$$A = \frac{Area\ of\ Sample}{Area\ of\ Std} \times \frac{Std\ \ wt\,(mg) \times Purity}{Vol\ of\ Std\ \ (mL)} \times \frac{Dilution\ \ of\ Std}{Dilution\ \ of\ \ Sample}$$

$$B = \frac{Formula\ \ \ wt\,of\ Sample\ \ (mg)}{1\,mole\ \ of\ Sample\ \ D} \times \frac{1}{\frac{317000\ \ mg\ \ NaD}{1\,mole\ \ NaD}} \times \frac{MoleofD\ \ \ in\ Sample}{Mole\ \ of\ \ D\,in\,Std}$$

*A * B = mg/mL Diclofenac in pH Buffer System*

Area of Sample = Area of sample

Area of Std = Area of standard

Std wt = weight of standard in mg

Vol of Std = Volume of standard in mL

Dilution of Std = Dilution of standard in mL/mL

Dilution of Sample = Dilution of sample in mL/mL

Formula wt of Sample = Formula weight of sample diclofenac in mg

1 mole of Sample D = 1 mole of Sample Diclofenac

317000 mg NaD = Formula weight of sodium diclofenac in mg

Mole of D in Sample = Moles of diclofenac in sample preparation

Mole of D in Std = Moles of diclofenac in standard preparation

Crystal Analysis

A series of experiments were conducted with the intention of growing large single crystals that could be used for crystal analysis and photographic analysis (Boyle, 2004). Seven different solvent systems were chosen based on the above article and standard universal solvents for growing crystals. The solvents were prepared in bulk and individual samples were prepared by charging a small amount of diclofenac salt, approximately 5 mg, into a 5 mL clear glass vial. Two to three mL of solvent were charged to the vial and the diclofenac salt was dissolved in the solvent system. The vials were covered with parafilm and two small holes were pierced in the parafilm.

Lyophilization cycle experiments

The lyophilizer used for this research was an FTS Dura-Stop µp shelf system with a Dura-Dry µp condenser located in the Formulation Development laboratory of AAIPharma. The Dura-Stop µm shelf system had a 4.5 square foot of dryer with three separate shelves. The Dura-Dry µp condenser had a capacity of five liters at a temperature of -80°C. The vacuum pump had the capability of achieving a vacuum of approximately 25 mT. The data acquisition system for the lyophilizer was Lyoware® version 2.2. The software had the capability to program the system with different temperature ramp rates, temperature hold times, and operating pressures as needed for this project. The software could then provide numerical data of the lyophilization cycle along with a graphical representation of the data. These graphs provided an excellent

Table 4. Solvent Systems Used in the Crystal Growing Experiments

Solvents
Acetonitrile
Ethanol
Methanol
Acetone
50:50 Ethanol : Water
50:50 Methanol : Water
50:50 Acetonitrile : Water

overview of the cycle and were used extensively in evaluating the effectiveness of the lyophilization cycle.

Initial studies of sodium diclofenac and potassium diclofenac were prepared at 10 mg/mL in water with 2% w/v mannitol. The mannitol was used as a bulking agent (Kibbe, 2000). The bulking agent was used to provide mass for the formation of the lyophilization cake. The cake provides a measurable entity for comparison of the different diclofenac salts. The factors used in the comparisons included cake appearance, reconstitution time, and retained moisture. The appearance was a visual description of the lyophilization cake characteristics including texture, color and height. The samples were then analyzed for reconstitution time, clarity of solution, retained moisture by Karl Fischer, and assayed by UV analysis. The reconstitution time was determined by the time it took for the cake to completely dissolve leaving a clear solution. The definition for clarity of solution was found in the United States Pharmacopeia (USP 28, 2005). For a sample to meet the USP definition it must meet the following requirements. One, "the solid dissolves completely, leaving no visible residue as undissolved matter" and two, "The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water contained in a similar vessel and examined similarly" (USP 28, 2005). The retained moisture was determined by Karl Fischer testing. The Karl Fischer testing was completed using a Brinkmann, Metrohm 701 KF Titrono Karl Fisher apparatus, Hydranol Composite -2 as the titrant and methanol. The vials were reconstituted with a known volume of methanol and mixed well. The KF apparatus was calibrated using approximately 10 μL of water and blanked with methanol that had been dried with molecular sieves. Samples were then reconstituted with the dried methanol.

The samples were mixed for approximately 30 seconds and then allowed to settle on the bench. A portion of the sample/methanol mixture was then injected into the KF apparatus and titrated with the Hydranol composite-2 solution. For most pharmaceutical lyophilized preparations, the percent water content for the lyophilized cake should be less than 3% (Nakhla, 2005). The percent moisture per vial was calculated using Equation 4.

Initially, water would be the solvent system for all of the formulations in the study. This proved impossible because most of the salts used in this study did not dissolve to the proposed concentration in water. Because the solvent must sublime in order to be a feasible lyophilization solvent and the study required currently available pharmaceutically acceptable solvents, only ethanol and tert-butyl alcohol were used along with water. Initial lyophilization cycle experiments were carried out using 20 mL
type 1 clear glass vials with 20 mm finish. The stoppers were West 4432/50 grey butyl rubber lyophilization stoppers.

Results

Salt Characterization Appearance Results

The ammonium diclofenac (NH_4D) was a white fine powder. The particles were non-descript under normal light conditions. The particle size ranged from fines to greater than 200 μm. The samples did produce birefringence when exposed to crossed polarized light.

The magnesium di-diclofenac (MgD_2) was a white to off white powder. The particles were non-descript under normal light conditions. The particle size ranged from fines to greater than 200 μm. The samples did produce birefringence when exposed to crossed polarized light.

Equation 4. Calculation for % Moisture by Karl Fischer Analysis

$$= \frac{KF\ Factor(mg/mL) \times \langle VStd(mL) - VBlank(mL) \rangle \times \mathrm{Re}constitutionVol(mL)}{Sample\ wt(mg) \times InjectionVol(mL)} \times 100\%$$

KF Factor (mg/mL) = Standardization Value in mg/mL

VStd (mL) = Volume of tritrant used for sample in mL

VBlank (mL) = Volume of titrant used for blank in mL

Reconstitution Vol (mL) = Reconstitution volume of sample in mL

Sample wt (mg) = weight of sample in mg

Injection Vol (mL) = volume of sample analyzed in mL

Table 5. Lyophilization Cycle used to Evaluate 0.2% Mannitol versus 0.5% Mannitol Bulking Concentration

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT
2.5	-40	120	Ambient
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT			
0.6	0	120	225
0.1	27	120	225
0.0	27	NA	1100

The zinc di-diclofenac (ZnD_2) was a white granular powder with a crystalline appearance. The particle size of the crystals was approximately 200 μm in size. The crystals were square with a cross moving from corner to corner in the crystal. The crystals did not show height in any of the slides assessed. The samples did produce birefringence when exposed to crossed polarized light.

The lead di-diclofenac (PbD_2) was a fine white powder with many agglomerates ranging in size from fines to greater than 200 μm. The sample did not show any birefringence when viewed under crossed polarized light.

The aluminum tri-diclofenac (AlD_3) formed a sticky white to off white mass. The sample required additional drying before a slide could be prepared. The particle size of the samples was very small, less than 2.0 μm in size. The sample contained agglomerates that were larger in size.

The copper di-diclofenac (CuD_2) formed two different substances. The first was a light green powder and the second an emerald green crystal structure. The emerald green crystals were observed to be approximately 200 μm in size. The shape of the emerald green crystal was determined to be six sided flat cubic crystal (Crystal Shapes, 2000). The light green powder was measured at approximately 80-120 μm. Using the data from the DSC, it was determined that the two materials were different hydrates of the copper salt. The light green material was a hexahydrate salt while the emerald green crystals were the dihydrate.

Crystal Growth Analysis

Although the experiments were continued for over 6 months, no acceptable single crystal was formed. Several crystal cluster groups were formed but were judged inappropriate for use in crystal analysis. Only a few crystals were marginal for use and all were of the free acid form and

not one of the salt complexes used in this research. Additional work in this area would be appropriate to continue this research.

X ray diffraction

The X-ray diffraction chromatogram compared intensity in counts compared to 2-Theta (degrees), see Appendix E for raw data. A chromatogram that showed sharp, high intensity peaks represented a compound with strong crystalline characteristics. Zinc Diclofenac and copper diclofenac were not analyzed due to the crystalline structure being visually observed. The zinc crystal structure were square flat plates with no observable height. The copper diclofenac crystals were emerald green in color, six sided cubic, and flat in shape. The results of this analysis show that the ammonia diclofenac, magnesium diclofenac, and the lead diclofenac have some crystalline properties. The aluminum diclofenac did not show any sharp, high intensity peaks. Using this information, the aluminum diclofenac might be able to be dissolved and recrystallized but in its current physical state, it was not crystalline, see Table 6 for a summary of the results.

HPLC Assay Results

This method of analysis was successful because the samples dissolved easily into the mobile phase using only mechanical shaking and sonication. With a run time of only 25 minutes, the analysis time was acceptable for routine use in the analytical laboratory. The peak shape was excellent with no fronting or tailing, see Figure 3 for a chromatography example. The three standards reproduced with an average of 277209.4 area counts and a relative standard deviation of 0.3 %. The results of the assay for the aluminum, zinc, lead, and copper salts were acceptable because they were with in 90 to 110 % of the expected assay value, see Table 7. The

magnesium salt result, 80.0%, was lower than expected. Upon completion of the TGA data, a reason for the 80% recovery was determined. The magnesium salt had a water content of approximately 20%. The magnesium diclofenac weight percent decreased from 99.9% to 78.7% at 100°C. The 80% assay result was then accounted for by hydration of the salt.

The results for the ammonia assay were explained by the reaction of the free acid not going to completion. Because the free acid was lighter in weight than the reacted ammonium, any "contamination" of the product from free acid diclofenac would cause the calculated purity to be higher than 100%. Further investigation of the assay result demonstrated that the maximum difference that could be accounted for by a 100% free acid contamination would be 105.7%. Published data reports that the ammonium diclofenac has the potential to degrade to ammonia gas and the free acid form of diclofenac (Fini, 2005). The DSC data for the ammonium diclofenac supported this hypothesis. The plot exhibited a drifting baseline that was accounted for by the off gassing of ammonia. The exotherm at approximately 100°C was attributed to a recrystallization due to loss in solvent, and the large exotherm at approximately 169° could be the recrystallization of the free acid form of diclofenac due the loss of ammonia from the system. The ammonium salt characterization was completed but due the potential loss of the ammonia calling into question the results, the ammonium salt was

Table 6. Results of X-Ray Diffraction Scans of Diclofenac Compounds

Compound	X-Ray Scan Results
Ammonia Diclofenac	Sharp, High Intensity Peaks
Magnesium Diclofenac	Sharp, High Intensity Peaks
Aluminum Diclofenac	No Peaks Observed.
Lead Diclofenac	Sharp, High Intensity Peaks

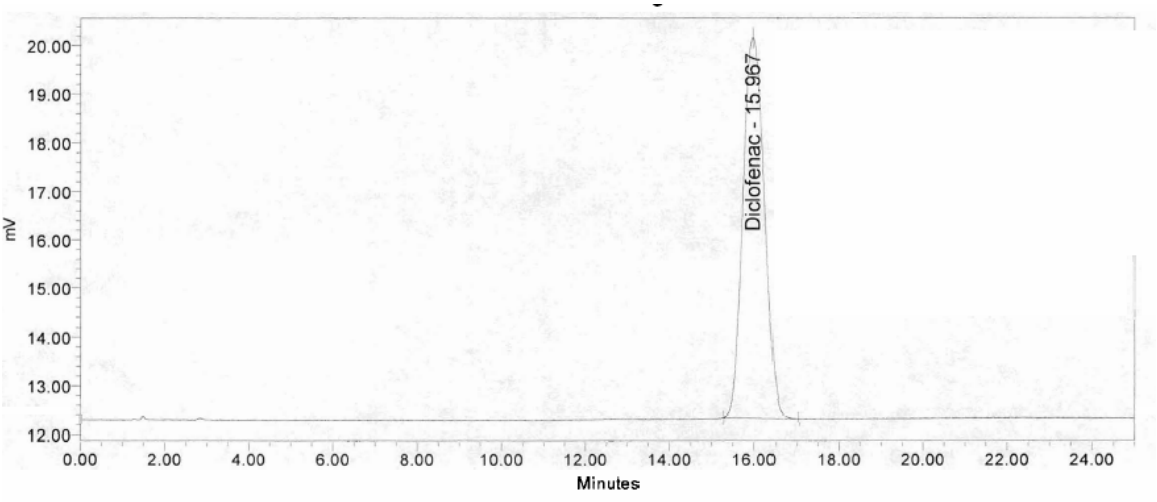

Figure 3. Example Sample Chromatography of Sodium Diclofenac

Table 7. Salt Purity Results from HPLC Analysis

Diclofenac Salt	Percent Assay % LC	Percent Assay (%LC) Corrected for % Solvent Loss
Ammonia	111.8	NA
Magnesium	80.0	102.0
Aluminum	98.1	98.4
Zinc	92.2	100.4
Lead	95.7	96.8
Copper	91.8	104.3

not used in the final lyophilization studies. Several experiments were conducted using a tetrabutyl ammonium diclofenac. However, due lack of crystal formation of the material for the characterization studies, the experiments were not completed. Additional research could be explored using this salt

.Melting Point DSC and TGA Results

The DSC provided scans of the salts thermal events, such as melting (Mettler, 2001). The analysis of the TGA chromatograms was used to determine the amount of solvent loss in the salt complex (Mettler, 2001). The laboratory determined melting points closely reflected the melting points determined by DSC, see Table 9. TGA printouts and DSC thermograms are found in Appendix B and C respectively. No additional cleanup procedures were used to prepare samples for either the TGA or DSC analysis. The samples were also not dried to constant weight before analysis took place. The TGA analysis established that all of the synthesized diclofenac salts (the sodium and potassium salts were commercially obtained) contain some solvent. Water was the only solvent used during the synthesis and therefore any solvent loss was attributed to water loss, see Table 8 for a summary of solvent loss.

The TGA for sodium diclofenac showed a loss of less than 2% by weight up to 250°C. The DSC for sodium diclofenac was similar to published DSC thermogram (Florey, 1990). The scan displayed an inflection at approximately 280°C which relates to a melt with decomposition. The melting point range for sodium diclofenac has been reported as 283-285°C (Florey, 1990). Published data was also found that contradicts the conclusions drawn by Florey. The data suggests that the melt and decomposition, described by Florey, are the decomposition of diclofenac to form new chemical entities

Table 8. Weight Loss by percent attributed to solvent loss in synthesized Diclofenac salts.

Salt Cation	Weight loss by Percent
Sodium	0.9
Potassium	0.0
Magnesium	21.3
Copper	12.0
Zinc	8.2
Lead	1.2
Aluminum	0.2

Table 9. Melting points determined in Laboratory using 9100 Electrothermal Melting Point Apparatus.

Salt	Approximate Melting point °C (Onset)	Melting Point from DSC °C	Literature Values °C
Diclofenac Free Acid	NA	NA	156-158 (Budavari, 1996)
Sodium Diclofenac	284	285	283-285 (Budavari, 1996)
Potassium Diclofenac	290	285	278-283 (Yung, 2002)
Ammonium Diclofenac	Not completed	166	Approximately 170 (Fini, 2005)
Magnesium Diclofenac	257	275	291 (Fini, 2005)
Zinc Diclofenac	255	250	NA
Copper Diclofenac	183	219	NA
Lead Diclofenac	189	180	NA
Aluminum Diclofenac	Melted with Decomposed at 180	175	NA

and then degradation of the oxidation byproducts (Tudja, 2001). The DSC spectra for the sodium, potassium, magnesium, zinc, lead, and aluminum salts all exhibit some inflection between 260 and 280°C. These inflections could be explained by the degradation of diclofenac to form new chemical entities. Ammonia and copper do not indicate any inflections in the DSC baseline between 260 and 280°C. Further research would be necessary to determine if the inflections in the DSC of the salts presented in this research directly correlate to the conclusions put forth by Tudja.

The DSC for potassium diclofenac also agreed with published DSC thermograms and the correlating melting points (Fini, Dec. 2001). The material exhibits a decomposition and melt at approximately 278°C to 282°C. The reported melting point range for potassium diclofenac was 278-283°C (Yung Zip, 2002). Using these two commercially available materials as references, the remaining samples were then analyzed by TGA and DSC.

The TGA for magnesium diclofenac confirmed the assay result of 80.0% in that the material lost approximately 21.2% of its weight during the analysis. The TGA instrument also measures DTA or differential thermal analysis. DTA and DSC data should correspond. The DSC chromatograph displays several endotherms between 70 and 120°C. These results indicate a loss in solvent. Because of the 20 % loss in weight being attributed to loss in solvent, the multiple peaks would be explained by lower and higher energy bound solvent being lost. The chromatogram also displays a exotherm at approximately 180°C. This indicates a recrystallization of the complex into a more stable form. There is a final endotherm and melt at approximately 260-275°C.

There are two crystalline forms of the copper diclofenac (Bob Whittle, personal conversation). The first form contains approximately 9% by weight solvent. After the loss of

this solvent at 100-117°C the material exhibits an exotherm at 176°C, which indicates a recrystallization to a more stable structure. The material then loses an additional 3% by weight before the material exhibits an endotherm at 219°C which indicates a melt and degradation of the material. Additional DSC experiments on the copper diclofenac were also carried out. Scans were obtained showing the original temperature ramp rate to approximately 185° C and then the sample was cooled to 30°C before the temperature was again ramped up to 350°C. The experiment demonstrated that the endotherm/solvent loss at approximately 100°C was completed and the recrystallization at 176°C was not degradation.

The DSC and TGA for zinc diclofenac correlate in that both indicate an endotherm at approximately 100°C, a solvent loss. The DSC and DTA show evidence to a recrystallization at 181°C to a new structure before a final melt and degradation at 262°C. The DSC was also analyzed using the same type of ramping then cooling of the samples as the copper diclofenac. Again the DSC demonstrated that the solvent loss at 100°C was complete and the exotherm at 181° was a recrystallization and not a degradation of the sample. The TGA data indicates a total loss of 8 percent by weight which correlates with the assay value of 95.7%. The DSC derived melting point of the zinc diclofenac was 250°C.

The lead diclofenac TGA data demonstrated that the material did not lose any adhered solvent until the temperature was in excess of 170°C. The weight of the sample lost approximately 20% as the temperature increased through 300°C. The DSC and DTA data indicate a strong endotherm between 170 and 220°C with several distinct peaks. A 20% weight loss indicates approximately 10 water molecules were displaced. This could account for the multiple peaks in the endotherm between 170 and 220°C. The DSC and DTA also exhibit an exotherm followed by an endotherm between 300 and 340°. This would indicate that the

material recrystallized into a more stable form and then melted. The melting point result correlates to the loss in solvent at approximately 180°C and was experimentally found to be 189°C.

The aluminum diclofenac original TGA data did not compare with the assay value obtained earlier. The assay value, 92.2%, did not correlate to the 60% loss in weight according to the TGA data. The DSC also exhibited a large endotherm at approximately 90-120°C. The preparation of the material included a drying step after collection on filter paper. The salt was then transferred to clear glass vial with screw top for storage. The assay analysis was completed using the material after the drying step. The TGA and DSC analysis was completed later. The hypothesis was that the material was hygroscopic and had adsorbed water during the time between the assay and the TGA and DSC analysis. To support this hypothesis and to acquire meaningful TGA and DSC data, the aluminum diclofenac was dried in an oven at 105° C for 16 hours. The salt was removed from the oven and allowed to cool in a desiccator. The DSC and TGA analysis were reanalyzed using the dried material and the results were more in line with the original assay data. The TGA exhibited a loss of approximately 0.2 percent by weight. The DSC and DTA both correlate to the TG data in that there were no endotherms observed at 100°C which would indicate losses in solvent. Based on this data, the assay value of 92.3% LC was acceptable, however for future work, the aluminum diclofenac should be dried before use.

Solubility in Water and pH Buffers

The Ksp values for each salt were calculated using the results from the maximum solubility in water experiment, see Table 12 for results. The solubility of sodium diclofenac in water was determined to be 18.7 mg/mL. The pH of the water used was approximately 6. This value correlates with the result published by Kincl (Kincl, 2004). Using the assay results

(mg/mL), the molarity of each solution and the Ksp of each salt was calculated. It was evident by the decreasing Ksp values that the solubility of the salt decreased in water as the size of the cation increased. In the pH buffers, all of the diclofenac salts exhibited no solubility at pH 4. The salts were diluted to the concentration of the working standard and no spectra were visible. To confirm this result, the stock solution was then assayed. Again, there were no visible spectra observed for each of the salts. The pH 7, 8, and 10 buffer solubility samples were collected and analyzed by UV spectrometry. The results are listed in Table 10 and for sodium diclofenac, compare favorably with published results of solubility in pH buffered systems (Kincl, 2004). The differences in solubility results between water and the pH buffer systems have been reported to be a function of both pH and ionic strength (Kincl, 2004). Initially, the results indicated that at pH 7, the solubility of the salt was dependent on its cation valence and size, however upon statistical evaluation revealed no significant difference ($P<0.05$). Among the divalent cations, the solubility appeared to decrease as the size of the cation increased, but again were all approximately the same after the variance of the results were accounted for and no trends were noted ($P<0.05$). It was evident that the copper cation demonstrated a slightly higher solubility than the other +2 cations. A possibility for the increase in solubility of copper diclofenac could be that the copper diclofenac salt recovered was in two different forms which were physically distinct, one an emerald green crystalline matrix and also a light green structure that did not appear to be crystalline. The calculation of water content from the TGA scan show one form of the copper salt contains six waters while the other form contains only two water molecules. The emerald green crystals contained two water molecules (Bob Whittle, personal communication) as AAI had completed crystal structure analysis of copper di-diclofenac. It was possible that one structure has a greater rate of solubility than the other salts. Lead salts are well known to be

minimally soluble in water. As there was only one trivalent cation used in this research, no trending could be observed except that its solubility was less than that of either the single valent or divalent cations. The different diclofenac salts solubility increased, in almost all cases, as the pH of the buffer increased. The possible trend in solubility of the salts decreasing as the cation ion size increase was not as distinguished at the higher pH. The pKa of diclofenac has been reported as 4.0 (Florey, 1990). The increase in solubility can be attributed to the disassociation of the salt at the higher pH.

Table 10. Solubility of Diclofenac Complexes at pH 7, 8, and 10.

Cation	pH 7 Buffer mg/mL	pH 8 Buffer mg/mL	pH 10 Buffer mg/mL
Na	1.04	4.01	4.14
K	0.89	4.38	4.06
NH_4	0.61	1.44	1.49
Mg	1.35	1.42	0.69
Cu	1.60	3.49	3.01
Zn	1.26	1.71	1.61
Pb	1.21	1.17	0.34
Al	0.57	0.91	1.01

Table 11. Atomic Radii of Metals Used to Formulate Diclofenac Salts

Cation	Atomic Radii (Å) (Weast, 1986)
Na	0.97
K	1.33
NH_4	1.43
Mg	0.66
Cu	0.72
Zn	0.74
Pb	1.20
Al	0.50

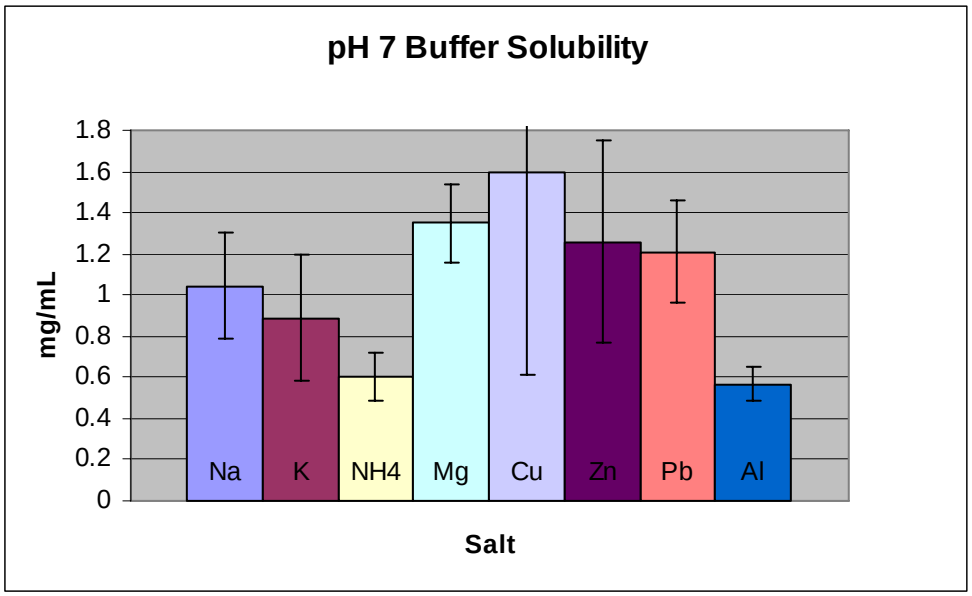

Figure 4. Solubility of Diclofenac Complexes at pH 7

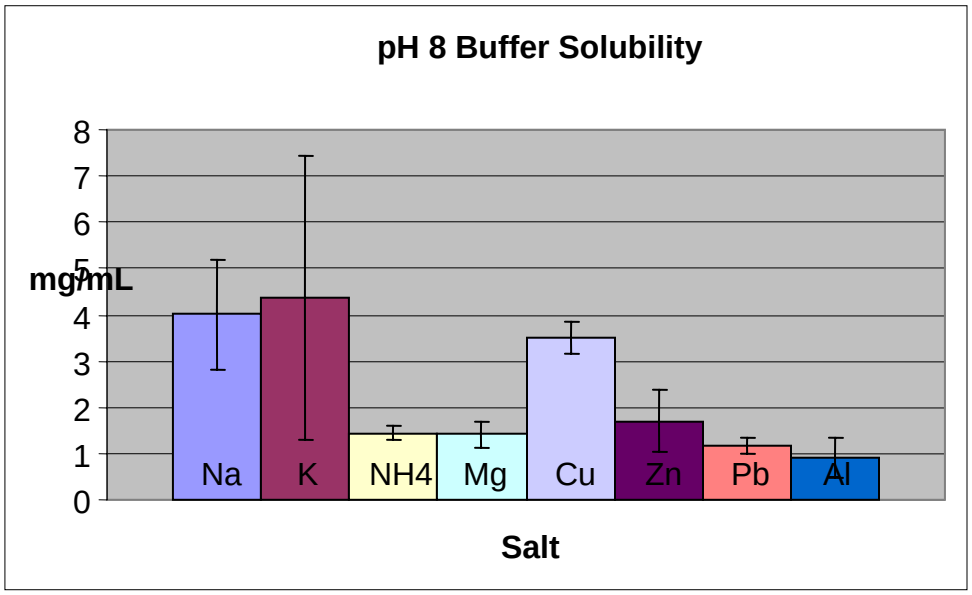

Figure 5. Solubility of Diclofenac Complexes at pH 8.

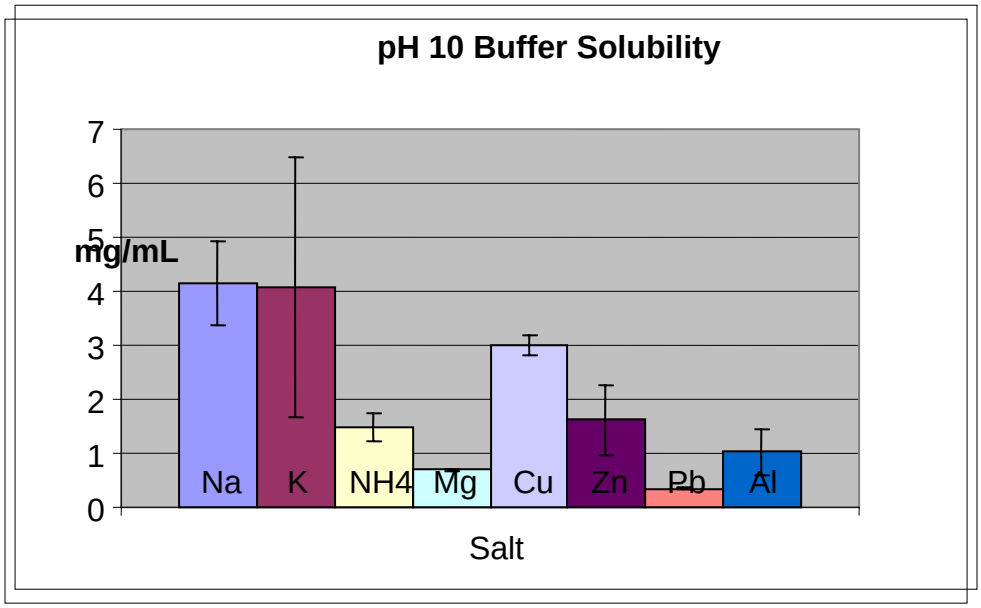

Figure 6. Solubility of Diclofenac Salts at pH 10

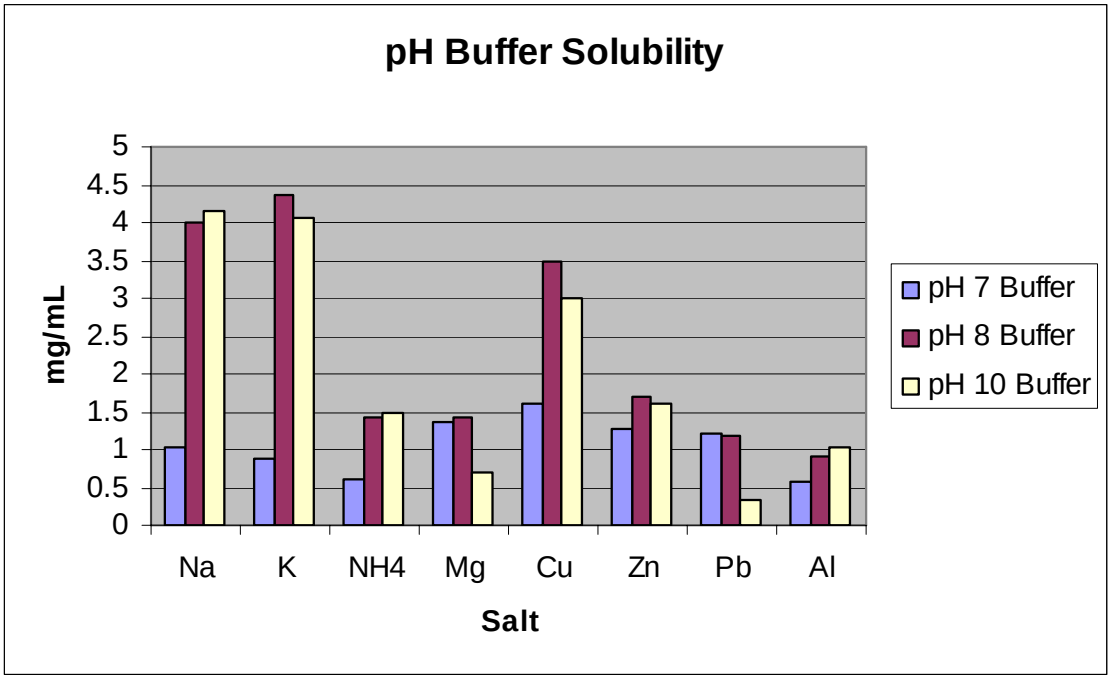

Figure 7. Comparison Graph of Solubility of Diclofenac Salts in pH 7, 8, and 10 Buffer

Table 12. Solubility of Diclofenac Complexes in Water with Calculated Ksp Values

Salt	Solubility in Water (mg/mL)	Calculated Ksp
Na	18.7	$3.45 X10^{-3}$
K	35.0	$1.08 X 10^{-2}$
NH_4	0.272	$7.17 X 10^{-10}$
Mg	2.18	$1.79 X 10^{-7}$
Cu	0.269	$2.81 X 10^{-10}$
Zn	0.470	$1.55 X 10^{-09}$
Pb	0.330	$3.47 X 10^{-10}$
Al	0.030	$8.50 X 10^{-17}$

Lyophilization

Using the metal salts prepared for this research, samples were prepared with a goal of 10 mg of diclofenac per mL of solution. It was determined that water could not be used for all of the proposed salts due to their limited solubility. Several different solvent concentrations of water and ethanol and water and t-butyl alcohol were explored. Although the solvents increased the concentration of the solution in most cases to the desired concentration, the lyophilization cycle had to be changed in order to successfully lyophilize the samples. Several cycles were run in the laboratory but all resulted in poor cake formation or the cycle parameters caused the cake to "pop". Popping was caused by un-sublimed solvent melting due to increased shelf temperature and then boiling due to the lowered pressure. The boiling caused the cake to disintegrate and pop out of the vial. Many different experiments were carried out with very limited success at maintaining intact cakes. When cakes were formed, the appearance did not have any common characteristics with the cakes when water was used as the solvent.

The goal of the research was to determine if the different salts of diclofenac would cause physical differences in the cake formation during lyophilization. With several different solvent systems and different lyophilization cycles for each solvent, it was becoming very difficult to make any direct comparisons. Therefore the target concentration of 10 mg/mL diclofenac was reduced to a target concentration of 0.15 mg/mL diclofenac. This change allowed for a consistent aqueous solvent system and the use of the same lyophilization cycle for all salts. A single solvent system using the same lyophilization cycle allowed for a direct comparison of the cake properties between the different salts. Initial experiments were conducted using only mannitol at 0.2 and 0.5% in water as control samples. Using the control samples, both the cycle

and the correct concentration of mannitol could be evaluated, see Table 5 for lyophilization cycle. The control samples were prepared and filled at both the 0.2% w/v and 0.5% w/v concentrations. The goal of the experiment was to obtain cake stability at lower mannitol concentrations. Use of a lower concentration of mannitol, as compared to 2.0% w/v used in earlier experiments, allowed for subtle differences in cake properties to be more evident and not masked by the larger concentration of mannitol. It was necessary to use enough mannitol so that the cake would stand the lyophilization process and not disintegrate into powder in the vial. The 0.2% w/v mannitol lyophilization cakes did not provide the cake stability needed for this research and was not used in further tests. The 0.5% w/v mannitol sample did demonstrate the necessary cake robustness and was used for all of the subsequent lyophilization runs.

Lyophilization cycle development was completed over a series of lyophilization runs by analyzing the graphs of the shelf temperature versus the thermocouple temperature, which reads the temperature of the cake in a vial. The optimum cycle would allow the thermocouple date to approach the shelf temperature during the primary drying portion of the lyophilization cycle. As the thermocouple temperature reaches the shelf temperature, it indicates that the free ice has been removed. Several lyophilization runs were completed before the initial cycle parameters were established. Cycles that did not meet the minimum acceptable cake parameters resulted in cakes that melted back into solution. This was caused by ice remaining in the vial and after the ice melted, there was enough water to re-dissolve the mannitol and diclofenac salt. See Table 13 for the cycle parameters used for the samples described in this research. After the samples from each lyophilization cycle were analyzed, the cycle's primary drying and secondary drying times were evaluated and changed to achieve a drier and more pharmaceutically acceptable cake. Appendix A contains the lyophilization cycle parameters along with the graphical

representations and numerical printout from the five lyophilization cycles discussed in this research.

The percent moisture was determined by Karl Fischer. There were a series of five runs completed once the salt concentration, mannitol concentration and cycle parameters were established. The cycles were essentially the same except for primary drying time and in the last run the secondary drying time was also increased.

The appearance evaluation considered the cake height, color, and consistency. The consistency would be defined as crystalline with a floss like structure similar of cotton candy. The color for all samples except the copper diclofenac was white. The copper diclofenac has a slight green tint to the cake. This was consistent with the color of the stock copper diclofenac solution. The cakes consistency showed some variance in amount of crust and adherence to the vial wall between the different salt versions of diclofenac, however all the cakes displayed a crust on top of the cake with the body of the cake appearing to be floss like. Due to the small amount of bulking agent, 0.5% mannitol, the structure of the cake was not very stable. Manipulation of the vial caused

Table 13. Lyophilization Cycle Used for Samples Described in Research

Rate °C/min	Final Temperature °C	Hold Time (hours)	Pressure mT	Step Definitions
0.2	-40	2	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	16	225	Primary Drying
0.1	27	12	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing

the cake structure to fail, leaving only a fine white powder in the vial, see Table 14 for a summary of the cake heights.

Reconstitution time of the samples did not vary in the total time it took to completely dissolve, but there were differences in the way that the cake dissolved. The reconstitution time for all samples was less than 30 seconds, see Table 15 for reconstitution times. Cakes that contained a more substantial crust dissolved from the top of the cake to the bottom whereas the lighter, more finely divided cake would dissolve from the bottom of the vial upwards through the cake. The copper and zinc lyophilization cakes had the most prominent crusts of the samples. This crust formation was hypothesized that it could be caused by the concentration of the diclofenac salt from the loss in solvent/water as the sample froze. The diclofenac salt would concentrate at the top of the vial because the vial freezes from the bottom to the top.

All samples met the criteria for clarity of solution. Once the sample was reconstituted, the samples were allowed to sit on the bench top for several minutes before being observed. All samples were clear with no visible residue when compared to an equal volume of Milli-Q water. This was important in that the lyophilization cakes must dissolve completely to be correctly assayed for diclofenac content.

The Karl Fischer analysis was completed and the results are summarized in Table 16. The results demonstrate that during the earlier lyophilization runs, there were differences between the salts in the percent water remaining in the vial. At 16 hours of primary drying, the copper salt had lowest amount of retained moisture at 2.3% and the potassium salt contained the highest amount of retained moisture at 4.7%. This range of 2.4% moisture demonstrates there are differences in how the cakes are drying in the

Table 14. Lyophilized Cake Heights

Primary Drying Time Secondary Drying Time	16 Hours 12 Hours	24 Hours 12 Hours	36 Hours 12 Hours	48 Hours 12 Hours	48 Hours 24 Hours
Cake Height (cm)					
Control	0.5	1.5	2.0	2.0	2.0
Na	2.0	1.8	2.0	2.0	2.0
K	2.0	1.8	1.8	2.0	2.0
TBAD	2.0	2.0	2.0		
Mg	1.0	1.8	2.0	2.0	2.0
Zn	1.6	1.8	1.8	2.0	2.0
Cu	1.8	2.0	2.0	2.0	2.0
Pb		1.8	2.0	2.0	2.0
Al	1.0	1.8	2.0	2.0	2.0

Table 15. Lyophilized Cake Reconstitution Time

Cation	Recon Time Seconds
Control	10
Sodium	5
Potassium	10
Magnesium	< 5
Zinc	20
Copper	10
Aluminum	<5
Tetrabutyl ammonium	<2.5

lyophilizer. At 24 hours of primary drying the range in moisture levels has fallen to 1.4%. As the lyophilization cycle's primary and secondary drying were extended, the percent moisture levels for all salts converged at approximately one percent. For the longest primary and secondary drying lyophilization cycle, the range in retained moisture was 0.45%, see Figure 8 for a bar graph of the percent moisture levels during the five lyophilization cycles. In terms of the research, it was a noteworthy discovery in that there were observable differences between the different salts. However in terms of a pharmaceutical application, no lyophilization cake of a small molecule would be left at the higher percent moisture levels. It was also noted that the two observable crystalline salts, zinc and copper, dried to a greater degree than the other samples. This ability to dry more quickly, even at the shorter primary drying times could be related to the crystalline structure of the active. As the water is removed and the diclofenac salts and mannitol become solid cake, the larger crystals of the zinc and copper could be providing channels for the moisture to move more freely in. For development of future lyophilization cycles, it would be worth considering the size and molecular weight of the salt along with its physical structure when developing the initial conditions for a lyophilization cycle.

It is noted that the sample volume changed from 2 mL injected to 5 mL injected for the two 48 hour primary drying runs. This change was due to the reduced amount of moisture in the lyophilization cake. The additional sample size increased the accuracy of the analysis.

Table 16. % Moisture by Karl Fischer for Lyophilization Cakes

Primary Drying Time Secondary Drying Time	16 Hours 12 Hours	24 Hours 12 Hours	36 Hours 12 Hours	48 Hours 12 Hours	48 Hours 24 Hours
Sample Size	2 mL	2 mL	2 mL	5 mL	5 mL
	Percent Moisture per Vial				
Control	NA	1.61	1.31	0.51	0.60
Na	4.18	2.51	3.02	1.17	0.77
K	4.70	2.81	3.41	0.95	0.93
TBAD	2.85	1.96	1.44		
Mg	4.45	2.19	1.17	0.69	0.78
Zn	2.97	1.69	0.2	1.03	0.82
Cu	2.32	1.41	0.17	0.65	0.95
Pb		2.04	1.09	1.51	1.05
Al	2.5	2.04	0.93	1.24	0.94

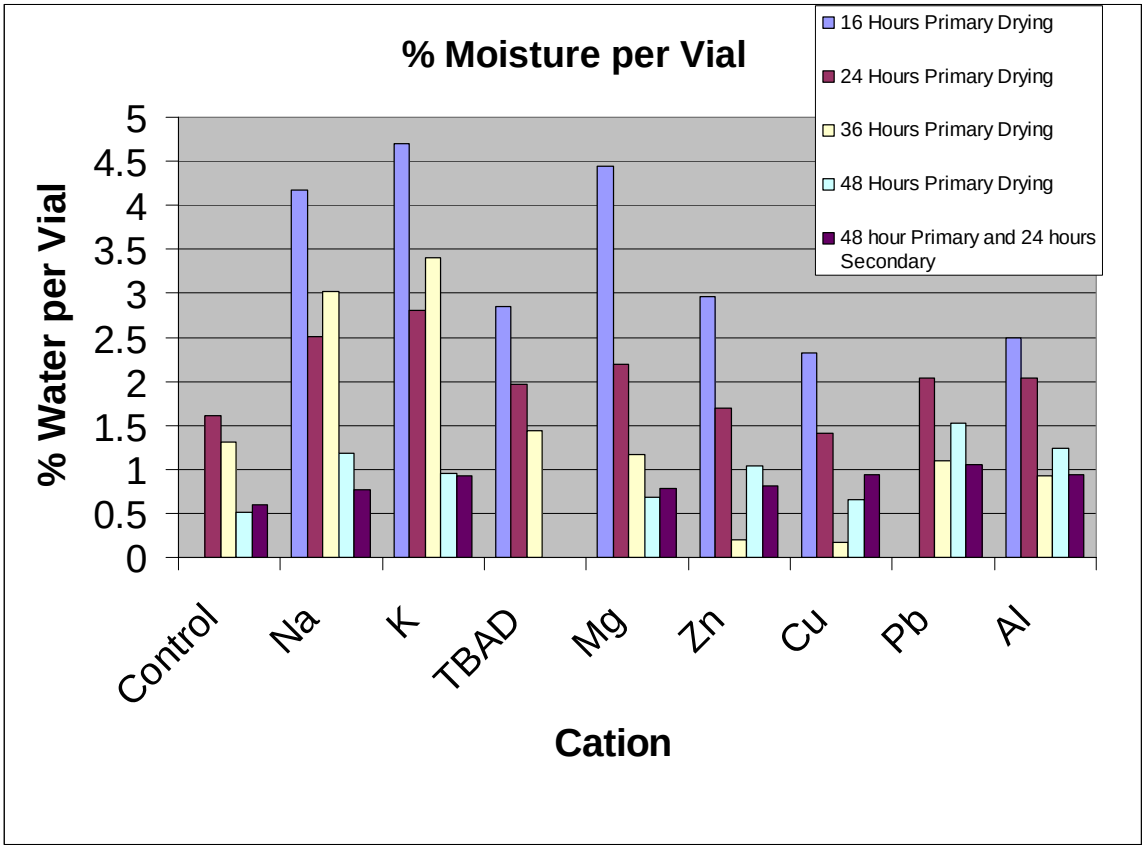

Figure 8. Graph Summarizing % Moisture by Karl Fischer for Lyophilization Runs

The assay testing was used to demonstrate that the lyophilization cycle did not cause loss of the diclofenac salt during the cycle. The stock solutions and reconstituted lyophilization samples were analyzed by UV for diclofenac content. Analysis of both the stock solution and the reconstituted samples demonstrated that the lyophilization cycle did not cause any loss in diclofenac concentration.

Conclusions

Several non-commercially available diclofenac salts were successfully prepared and characterized using standard laboratory testing including purity assay, melting point, crystallinity determination, TGA, DSC, solubility in water and pH buffers 4, 7, 8, and 10. The solubility data demonstrated that the diclofenac salts solubility was pH dependent with a higher solubility at pH 10 versus pH 4. The data suggests the solubility of the diclofenac salts may decrease as the size of the cation increases in each of the valence categories, however statistical interpretation of the data using regression analysis showed no trends among each of the different cations ($P<0.05$). Ionic strength also plays a strong role in solubility. Of the +2 cations, the copper salt did show a slightly higher solubility versus the other +2 cations. The copper has two different crystalline forms and one could have a much larger solubility and skew the results. The different crystalline structures of copper diclofenac could be separated and individually characterized to provide more a comprehensive solubility curve. A correlation could not be derived from the solubility of the sodium, magnesium, and aluminum cations, in that their atomic numbers are in sequence and they represent + 1, +2 and +3 cations. Statistical analysis demonstrated that there were no trends in the solubility data other than solubility generally decreased as atomic number increased. Atomic radii did not affect the solubility in any of the experiments. Statistical

analysis of the solubility results when compared to the atomic radii showed no trends at a confidence level of greater that 90%.

A lyophilization cycle was established over a series of experiments until minimum lyophilization cake criteria were met. The lyophilization cake minimum criteria included a formed cake that did not melt back and a cake that had some basic tolerance for the process. The cycle was then used to prepare lyophilization cake samples that could be directly compared to one another. The experiments demonstrated that differences could be seen between the different salts of diclofenac in the earlier lyophilization runs. There were differences in cake heights during the cycles with shorter primary drying times. These differences were explained as cake melt back from residual water. There were also differences noted in the residual moisture in the lyophilized cakes. The percent moisture differences ranged from approximately 2.3% in short primary drying runs and decreased to less than 0.5% with the longest primary drying run. It was noted that as the drying times were increased to achieve a pharmaceutically acceptable percent moisture, the differences in residual moisture were not as great. The lyophilized cake appearances were consistent between all of the salts except for copper. All the cakes were white with a brittle crust and a floss like interior, the copper salts lyophilization cake was pale green in color with the same physical characteristics as the other cakes. All samples met the criteria for the USP test for clarity of solution. All of the reconstituted solutions including the copper, were clear with no visible particulates visible.

This research demonstrated that the different salts of diclofenac do have an effect of the final lyophilization cake. The lyophilized cake's appearance, reconstitution time, percent moisture and primary drying time were all affected by the different salts of diclofenac.

This data demonstrates that in choosing a new salt for a lyophilized product, solubility in the chosen solvent system will determine the final concentration of product in the vial. Although this data did not demonstrate any overall increase in solubility due to a cation affect, the salts solubility profile was pH dependent. Understanding the new salts solubility profile provides the correct information on predicting the maximum allowable concentration and therefore provides the first step in formulation of a new lyophilized product. Understanding the physical characteristics of the salt can provide information on how the product will lyophilize. Based on this research, a larger more defined crystal could decrease the primary drying time versus a smaller less defined crystalline salt. It was hypothesized that the larger crystal provided channeling in the lyophilized cake, allowing for shorter primary drying times. Lyophilization cycle development was shown to be dependent on the fill volume, bulking agent concentration, and the cakes ability to transmit moisture. Defining the fill volume for a new salt would provide basic information on the amount of primary drying necessary to dry the product to an acceptable moisture level. Using all of this information together provides a framework for formulation and development of a new lyophilized product.

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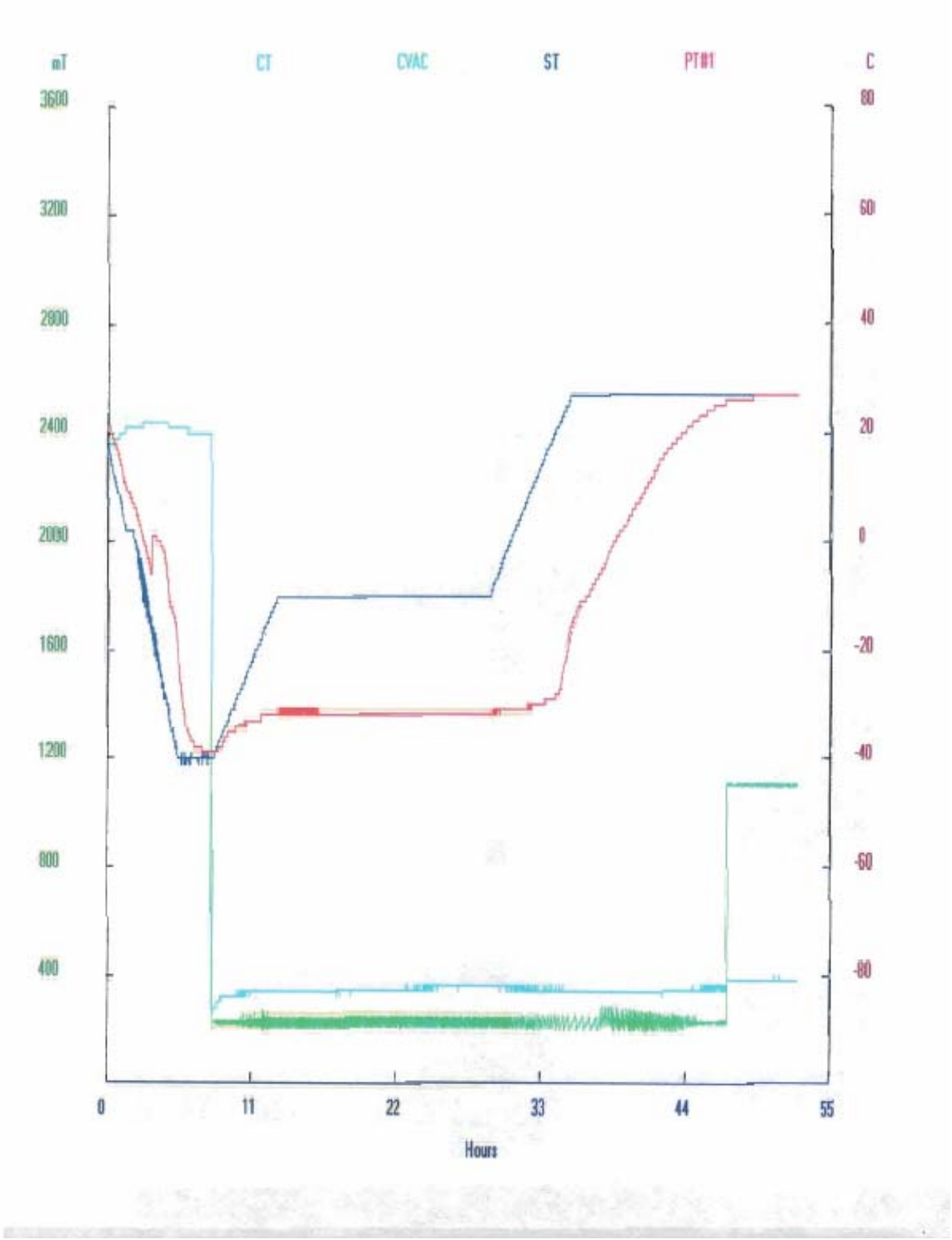
Appendix A

Lyophilization Cycle Raw Data

Run 09-18-2005 16 Hours Primary Drying

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT	Step Definitions
0.2	-40	120	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	960	225	Primary Drying
0.1	27	720	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing


mT
CT
CVAC
ST
PT#1
C
3600
3200
2800
2400
2000
1600
1200
800
400
80
60
40
20
0
-20
-40
-60
-80
0
11
22
33
44
55
Hours

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER						PRODUCT TEMPERATURES deg.C							
			STEP TIME		CVAC		SHELF									
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1	17	3HHH	0	0	0		3HHH	18	18	21							
30	19	3HHH	1	0	0		3HHH	12	12	19							
60	20	3HHH	1	0	0		3HHH	6	6	14							
90	21	3HHH	1	30	8		3HHH	2	2	10							
120	21	3HHH	2	0	0		3HHH	0	0	6							
150	21	3HHH	2	0	0		3HHH	- 6	- 8	2							
180	22	3HHH	2	0	0		3HHH	-12	-14	- 3							
210	22	3HHH	2	0	0		3HHH	-18	-16	1							
240	22	3HHH	2	0	0		3HHH	-24	-24	- 0							
270	22	3HHH	2	0	0		3HHH	-30	-29	- 6							
300	21	3HHH	2	0	0		3HHH	-36	-36	-13							
330	21	3HHH	2	120	8		3HHH	-40	-40	-24							
360	21	3HHH	2	120	38		3HHH	-40	-40	-34							
390	20	3HHH	2	120	68		3HHH	-40	-40	-37							
420	20	3HHH	2	120	98		3HHH	-40	-40	-38							
450	20	3HHH	F	30	8		3HHH	-40	-40	-39							
480	-86	355	P		9		409	-40	-40	-39							
510	-85	149	a	0	0	225	223	-37	-37	-38							
540	-84	135	a	0	0	225	224	-34	-34	-36							
570	-84	141	a	0	0	225	230	-31	-31	-35							
600	-84	139	a	0	0	225	231	-28	-28	-34							
630	-83	134	a	0	0	225	227	-25	-25	-33							
660	-83	121	a	0	0	225	209	-22	-22	-33							
690	-83	123	a	0	0	225	212	-19	-19	-33							
720	-83	166	a	0	0	225	267	-16	-16	-32							
750	-83	135	a	0	0	225	230	-13	-13	-32							
780	-83	136	a	0	0	225	232	-10	-10	-32							
810	-83	128	a	960	27	225	220	-10	-10	-31							
840	-83	120	a	960	57	225	209	-10	-10	-31							
870	-83	146	a	960	87	225	247	-10	-10	-32							
900	-83	135	a	960	117	225	230	-10	-10	-31							
930	-83	126	a	960	147	225	218	-10	-10	-31							
960	-83	120	a	960	177	225	209	-10	-10	-32							
990	-83	142	a	960	207	225	234	-10	-10	-32							
1020	-83	144	a	960	237	225	244	-10	-10	-32							
1050	-83	138	a	960	267	225	235	-10	-10	-32							
1080	-83	132	a	960	297	225	226	-10	-10	-32							
1110	-83	125	a	960	327	225	216	-10	-10	-32							
1140	-83	126	a	960	357	225	208	-10	-10	-32							
1170	-83	138	a	960	387	225	234	-10	-10	-32							
1200	-83	121	a	960	417	225	211	-10	-10	-32							
1230	-83	139	a	960	447	225	235	-10	-10	-32							
1260	-83	118	a	960	477	225	205	-10	-10	-32							
1290	-83	127	a	960	507	225	219	-10	-10	-32							
1320	-83	136	a	960	537	225	232	-10	-10	-32							
1350	-83	147	a	960	567	225	246	-10	-10	-32							
1380	-83	119	a	960	597	225	207	-10	-10	-32							
1410	-83	126	a	960	627	225	217	-10	-10	-32							
1440	-83	128	a	960	657	225	220	-10	-10	-32							
1470	-83	131	a	960	687	225	224	-10	-10	-32							
1500	-83	129	a	960	717	225	222	-10	-10	-32							
1530	-82	126	a	960	747	225	217	-10	-10	-32							

Run # 01

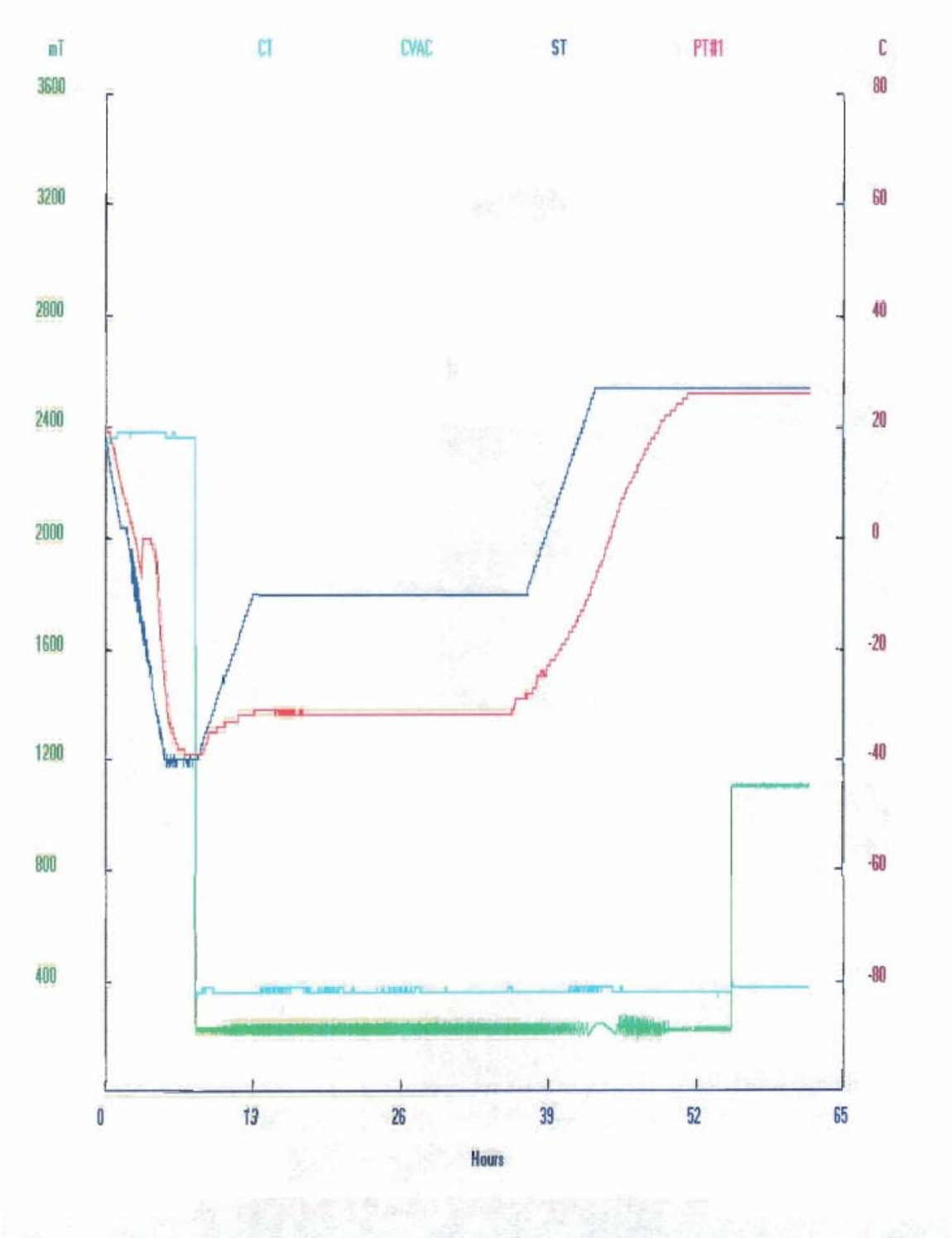
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1560	-82	122	a	960	777	225	211	-10	-10	-32							
1590	-82	117	a	960	807	225	205	-10	-10	-32							
1620	-82	145	a	960	837	225	245	-10	-10	-32							
1650	-82	137	a	960	867	225	233	-10	-10	-32							
1680	-82	131	a	960	897	225	224	-10	-10	-32							
1710	-82	126	a	960	927	225	217	-10	-10	-32							
1740	-82	122	a	960	957	225	212	-10	-10	-32							
1770	-82	136	b	0	0	225	220	- 7	- 7	-32							
1800	-82	130	b	0	0	225	223	- 4	- 4	-31							
1830	-82	132	b	0	0	225	226	- 1	- 1	-31							
1860	-83	118	b	0	0	225	206	2	2	-31							
1890	-83	126	b	0	0	225	217	5	5	-31							
1920	-83	120	b	0	0	225	209	8	8	-31							
1950	-83	136	b	0	0	225	231	11	11	-30							
1980	-83	136	b	0	0	225	232	14	14	-30							
2010	-83	122	b	0	0	225	211	17	17	-29							
2040	-83	128	b	0	0	225	220	20	20	-29							
2070	-83	121	b	0	0	225	211	23	23	-25							
2100	-83	135	b	0	0	225	230	26	26	-19							
2130	-83	137	b	720	17	225	232	27	27	-14							
2160	-83	132	b	720	47	225	225	27	27	-12							
2190	-83	126	b	720	77	225	218	27	27	-10							
2220	-83	126	b	720	107	225	217	27	27	- 8							
2250	-83	131	b	720	137	225	223	27	27	- 6							
2280	-83	142	b	720	167	225	242	27	27	- 3							
2310	-83	125	b	720	197	225	215	27	27	- 0							
2340	-83	126	b	720	227	225	216	27	27	2							
2370	-83	134	b	720	257	225	227	27	27	4							
2400	-83	114	b	720	287	225	198	27	27	6							
2430	-83	122	b	720	317	225	209	27	27	8							
2460	-83	139	b	720	347	225	234	27	27	10							
2490	-83	115	b	720	377	225	198	27	27	12							
2520	-83	153	b	720	407	225	233	27	27	15							
2550	-83	139	b	720	437	225	233	27	27	16							
2580	-83	133	b	720	467	225	224	27	27	18							
2610	-83	126	b	720	497	225	212	27	27	19							
2640	-83	139	b	720	527	225	228	27	27	21							
2670	-83	142	b	720	557	225	227	27	27	22							
2700	-83	148	b	720	587	225	228	27	27	23							
2730	-82	149	b	720	617	225	228	27	27	23							
2760	-82	151	b	720	647	225	225	27	27	24							
2790	-82	155	b	720	677	225	223	27	27	25							
2820	-82	158	b	720	707	225	219	27	27	26							
2850	-81	1106	c	999	17	1100	1105	27	27	26							
2880	-81	1119	c	999	47	1100	1098	27	27	26							
2910	-81	1136	c	999	77	1100	1098	27	27	26							
2940	-81	1129	c	999	107	1100	1105	27	27	26							
2970	-81	1123	c	999	137	1100	1092	27	27	27							
3000	-81	1133	c	999	167	1100	1098	27	27	27							
3030	-81	1136	c	999	197	1100	1105	27	27	27							
3060	-81	1136	c	999	227	1100	1105	27	27	27							
3090	-81	1126	c	999	257	1100	1098	27	27	27							

Run # 01

RUN	CONDENSER	TRAY-DRYER													
TIME		STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
3120	-81	1123	c	999	287	1100	1092	27	27	27							
3150	-81	1126	c	999	317	1100	1105	27	27	27							

Run 10-06-2005 24 Hours Primary Drying

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT	Step Definitions
0.2	-40	120	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	1440	225	Primary Drying
0.1	27	720	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing


mT
CT
CVAC
ST
PT#1
C
3600
3200
2800
2400
2000
1600
1200
800
400
80
60
40
20
0
-20
-40
-60
-80
0
13
26
39
52
65
Hours

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1	17	3HHH	F	1	1		3HHH	18	18	20							
30	18	3HHH	1	0	0		3HHH	12	12	18							
60	18	3HHH	1	0	0		3HHH	6	6	13							
90	19	3HHH	1	30	9		3HHH	2	2	9							
120	19	3HHH	2	0	0		3HHH	0	0	5							
150	19	3HHH	2	0	0		3HHH	-6	-3	1							
180	19	3HHH	2	0	0		3HHH	-12	-10	-4							
210	19	3HHH	2	0	0		3HHH	-18	-16	0							
240	19	3HHH	2	0	0		3HHH	-24	-23	-0							
270	19	3HHH	2	0	0		3HHH	-30	-31	-4							
300	19	3HHH	2	0	0		3HHH	-36	-37	-19							
330	18	3HHH	2	120	9		3HHH	-40	-39	-30							
360	19	3HHH	2	120	39		3HHH	-40	-40	-36							
390	18	3HHH	2	120	69		3HHH	-40	-40	-38							
420	18	3HHH	2	120	99		3HHH	-40	-40	-39							
450	18	3HHH	F	30	9		3HHH	-40	-40	-39							
480	-81	272	P		10		333	-40	-40	-39							
510	-81	143	a	0	0	225	223	-37	-37	-39							
540	-81	139	a	0	0	225	230	-34	-34	-36							
570	-82	131	a	0	0	225	222	-31	-31	-35							
600	-82	129	a	0	0	225	219	-28	-28	-34							
630	-82	135	a	0	0	225	228	-25	-25	-34							
660	-82	135	a	0	0	225	229	-22	-22	-33							
690	-82	126	a	0	0	225	217	-19	-19	-33							
720	-82	137	a	0	0	225	232	-16	-16	-32							
750	-82	129	a	0	0	225	223	-13	-13	-32							
780	-82	144	a	0	0	225	246	-10	-10	-32							
810	-82	138	a	1440	28	225	236	-10	-10	-31							
840	-81	130	a	1440	58	225	224	-10	-10	-31							
870	-81	122	a	1440	88	225	213	-10	-10	-31							
900	-82	139	a	1440	118	225	225	-10	-10	-32							
930	-81	137	a	1440	148	225	233	-10	-10	-31							
960	-82	124	a	1440	178	225	216	-10	-10	-31							
990	-81	145	a	1440	208	225	247	-10	-10	-32							
1020	-81	130	a	1440	238	225	224	-10	-10	-32							
1050	-81	126	a	1440	268	225	218	-10	-10	-32							
1080	-82	124	a	1440	298	225	216	-10	-10	-32							
1110	-82	120	a	1440	328	225	210	-10	-10	-32							
1140	-82	125	a	1440	358	225	208	-10	-10	-32							
1170	-81	142	a	1440	388	225	243	-10	-10	-32							
1200	-82	133	a	1440	418	225	228	-10	-10	-32							
1230	-82	123	a	1440	448	225	215	-10	-10	-32							
1260	-82	118	a	1440	478	225	207	-10	-10	-32							
1290	-82	147	a	1440	508	225	248	-10	-10	-32							
1320	-82	136	a	1440	538	225	232	-10	-10	-32							
1350	-82	127	a	1440	568	225	220	-10	-10	-32							
1380	-82	118	a	1440	598	225	208	-10	-10	-32							
1410	-82	145	a	1440	628	225	247	-10	-10	-32							
1440	-82	133	a	1440	658	225	228	-10	-10	-32							
1470	-82	122	a	1440	688	225	213	-10	-10	-32							
1500	-81	148	a	1440	718	225	249	-10	-10	-32							
1530	-81	133	a	1440	748	225	228	-10	-10	-32							

Run # 01

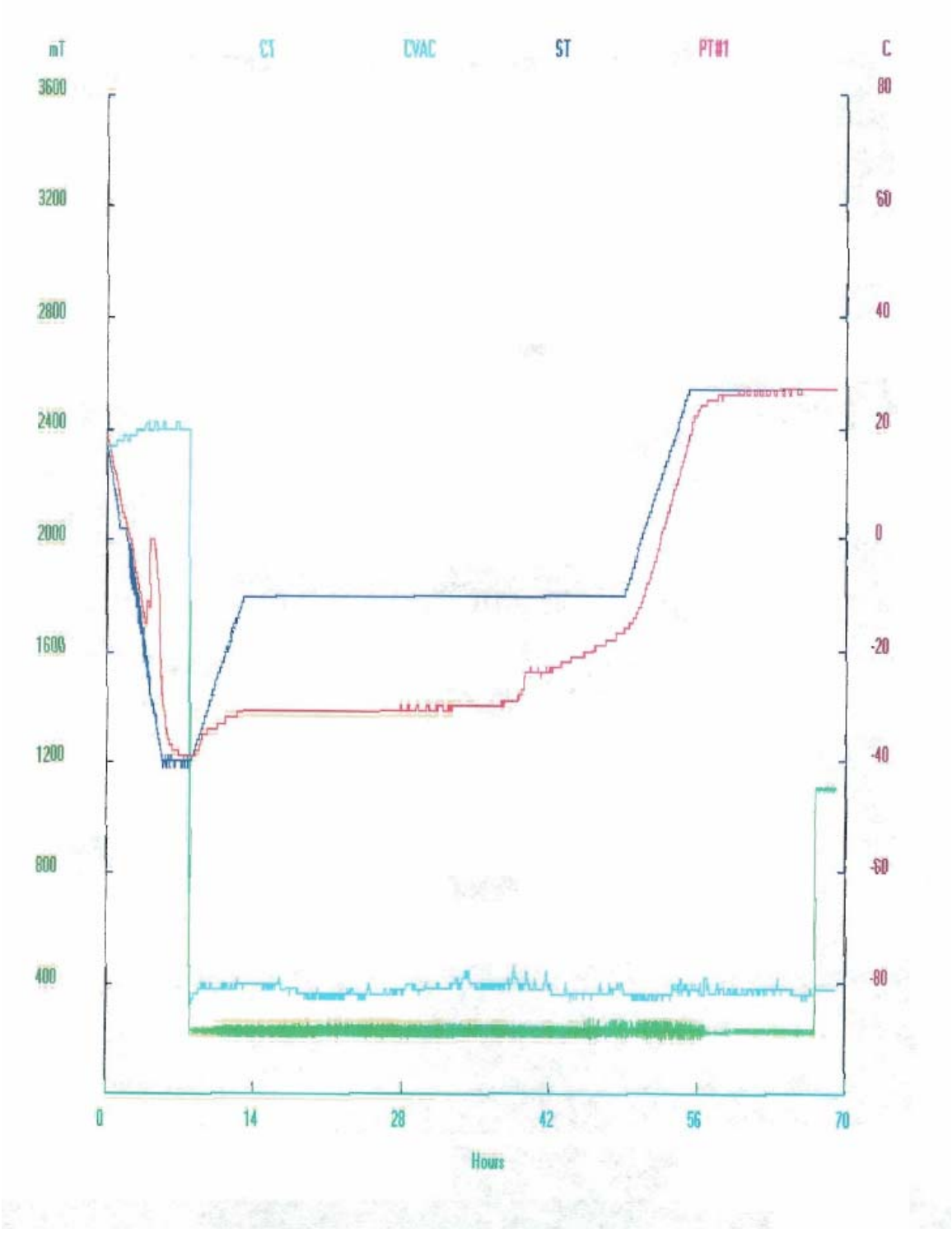
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1560	-82	121	a	1440	778	225	211	-10	-10	-32							
1590	-81	144	a	1440	808	225	245	-10	-10	-32							
1620	-82	127	a	1440	838	225	220	-10	-10	-32							
1650	-81	116	a	1440	868	225	204	-10	-10	-32							
1680	-82	135	a	1440	898	225	231	-10	-10	-32							
1710	-82	121	a	1440	928	225	212	-10	-10	-32							
1740	-82	144	a	1440	958	225	245	-10	-10	-32							
1770	-82	127	a	1440	988	225	220	-10	-10	-32							
1800	-81	138	a	1440	1018	225	224	-10	-10	-32							
1830	-82	133	a	1440	1048	225	228	-10	-10	-32							
1860	-82	119	a	1440	1078	225	208	-10	-10	-32							
1890	-82	138	a	1440	1108	225	234	-10	-10	-32							
1920	-82	121	a	1440	1138	225	212	-10	-10	-32							
1950	-82	141	a	1440	1168	225	240	-10	-10	-32							
1980	-82	123	a	1440	1198	225	214	-10	-10	-32							
2010	-82	139	a	1440	1228	225	236	-10	-10	-32							
2040	-82	118	a	1440	1258	225	206	-10	-10	-32							
2070	-82	130	a	1440	1288	225	223	-10	-10	-32							
2100	-82	144	a	1440	1318	225	244	-10	-10	-32							
2130	-81	117	a	1440	1348	225	205	-10	-10	-32							
2160	-82	123	a	1440	1378	225	212	-10	-10	-31							
2190	-82	127	a	1440	1408	225	218	-10	-10	-29							
2220	-82	130	a	1440	1438	225	223	-10	-10	-28							
2250	-82	127	b	0	0	225	219	- 7	- 7	-28							
2280	-82	137	b	0	0	225	221	- 4	- 4	-26							
2310	-82	117	b	0	0	225	206	- 1	- 1	-25							
2340	-82	135	b	0	0	225	231	2	2	-23							
2370	-82	136	b	0	0	225	232	5	5	-22							
2400	-82	121	b	0	0	225	211	8	8	-20							
2430	-82	124	b	0	0	225	215	11	11	-19							
2460	-81	146	b	0	0	225	245	14	14	-17							
2490	-82	117	b	0	0	225	205	17	17	-15							
2520	-81	142	b	0	0	225	242	20	20	-13							
2550	-82	137	b	0	0	225	222	23	23	-11							
2580	-81	136	b	0	0	225	232	26	26	- 8							
2610	-81	143	b	720	18	225	244	27	27	- 5							
2640	-81	141	b	720	48	225	240	27	27	- 3							
2670	-81	132	b	720	78	225	225	27	27	0							
2700	-82	117	b	720	108	225	204	27	27	4							
2730	-82	132	b	720	138	225	225	27	27	7							
2760	-82	141	b	720	168	225	239	27	27	9							
2790	-82	132	b	720	198	225	209	27	27	11							
2820	-82	142	b	720	228	225	240	27	27	13							
2850	-82	128	b	720	258	225	216	27	27	15							
2880	-82	131	b	720	288	225	220	27	27	17							
2910	-82	130	b	720	318	225	218	27	27	19							
2940	-82	137	b	720	348	225	222	27	27	21							
2970	-82	144	b	720	378	225	229	27	27	22							
3000	-82	143	b	720	408	225	221	27	27	23							
3030	-82	158	b	720	438	225	228	27	27	24							
3060	-82	166	b	720	468	225	229	27	27	25							
3090	-82	168	b	720	498	225	223	27	27	26							

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
3120	-82	182	b	720	528	225	230	27	27	26							
3150	-82	178	b	720	558	225	221	27	27	26							
3180	-82	191	b	720	588	225	232	27	27	26							
3210	-82	189	b	720	618	225	227	27	27	26							
3240	-82	197	b	720	648	225	232	27	27	26							
3270	-82	198	b	720	678	225	232	27	27	26							
3300	-82	192	b	720	708	225	227	27	27	26							
3330	-81	1136	c	999	18	1100	1105	27	27	26							
3360	-81	1133	c	999	48	1100	1098	27	27	26							
3390	-81	1143	c	999	78	1100	1105	27	27	26							
3420	-81	1133	c	999	108	1100	1098	27	27	26							
3450	-81	1136	c	999	138	1100	1098	27	27	26							
3480	-81	1143	c	999	168	1100	1105	27	27	26							
3510	-81	1143	c	999	198	1100	1105	27	27	26							
3540	-81	1136	c	999	228	1100	1098	27	27	26							
3570	-81	1139	c	999	258	1100	1105	27	27	26							
3600	-81	1136	c	999	288	1100	1092	27	27	26							
3630	-81	1136	c	999	318	1100	1098	27	27	26							
3660	-81	1139	c	999	348	1100	1098	27	27	26							
3690	-81	1136	c	999	378	1100	1105	27	27	26							
3720	-81	1136	c	999	408	1100	1098	27	27	26							

Run 10-16-2005 36 Hours Primary Drying

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT	Step Definitions
0.2	-40	120	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	2160	225	Primary Drying
0.1	27	720	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing


mT
CT
CVAC
ST
PT#1
C
3600
3200
2800
2400
2000
1600
1200
800
400
80
60
40
20
0
-20
-40
-60
-80
0
14
28
42
56
70
Hours

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1	16	3HHH	F	1	1		3HHH	18	18	19							
30	17	3HHH	1	0	0		3HHH	12	12	15							
60	18	3HHH	1	0	0		3HHH	6	5	10							
90	18	3HHH	1	30	11		3HHH	2	2	5							
120	18	3HHH	2	0	0		3HHH	- 0	- 0	2							
150	19	3HHH	2	0	0		3HHH	- 6	- 9	- 2							
180	20	3HHH	2	0	0		3HHH	-12	-13	- 7							
210	20	3HHH	2	0	0		3HHH	-18	-18	-14							
240	20	3HHH	2	0	0		3HHH	-24	-25	-12							
270	21	3HHH	2	0	0		3HHH	-30	-30	- 0							
300	20	3HHH	2	0	0		3HHH	-36	-36	-13							
330	20	3HHH	2	120	11		3HHH	-40	-40	-32							
360	20	3HHH	2	120	41		3HHH	-40	-40	-37							
390	20	3HHH	2	120	71		3HHH	-40	-40	-38							
420	20	3HHH	2	120	101		3HHH	-40	-40	-39							
450	20	3HHH	F	30	11		3HHH	-40	-40	-39							
480	-83	169	P		12		236	-40	-40	-39							
510	-82	138	a	0	0	225	218	-37	-37	-39							
540	-81	138	a	0	0	225	230	-34	-34	-36							
570	-80	125	a	0	0	225	214	-31	-31	-35							
600	-80	127	a	0	0	225	218	-28	-28	-34							
630	-81	134	a	0	0	225	228	-25	-25	-33							
660	-80	132	a	0	0	225	226	-22	-22	-33							
690	-80	129	a	0	0	225	222	-19	-19	-32							
720	-81	136	a	0	0	225	222	-16	-16	-32							
750	-79	143	a	0	0	225	245	-13	-13	-31							
780	-81	122	a	0	0	225	214	-10	-10	-31							
810	-80	133	a	2160	30	225	229	-10	-10	-31							
840	-80	143	a	2160	60	225	246	-10	-10	-31							
870	-80	120	a	2160	90	225	211	-10	-10	-31							
900	-80	132	a	2160	120	225	228	-10	-10	-31							
930	-80	145	a	2160	150	225	246	-10	-10	-31							
960	-81	123	a	2160	180	225	216	-10	-10	-31							
990	-79	141	a	2160	210	225	243	-10	-10	-31							
1020	-81	134	a	2160	240	225	230	-10	-10	-31							
1050	-81	133	a	2160	270	225	230	-10	-10	-31							
1080	-81	124	a	2160	300	225	217	-10	-10	-31							
1110	-82	146	a	2160	330	225	249	-10	-10	-31							
1140	-82	142	a	2160	360	225	244	-10	-10	-31							
1170	-83	129	a	2160	390	225	223	-10	-10	-31							
1200	-83	126	a	2160	420	225	208	-10	-10	-31							
1230	-83	131	a	2160	450	225	226	-10	-10	-31							
1260	-82	145	a	2160	480	225	241	-10	-10	-31							
1290	-82	122	a	2160	510	225	214	-10	-10	-31							
1320	-82	133	a	2160	540	225	228	-10	-10	-31							
1350	-82	142	a	2160	570	225	244	-10	-10	-31							
1380	-82	148	a	2160	600	225	248	-10	-10	-31							
1410	-81	116	a	2160	630	225	205	-10	-10	-31							
1440	-83	119	a	2160	660	225	209	-10	-10	-31							
1470	-83	120	a	2160	690	225	211	-10	-10	-31							
1500	-81	122	a	2160	720	225	213	-10	-10	-31							
1530	-82	138	a	2160	750	225	236	-10	-10	-31							

Run # 01

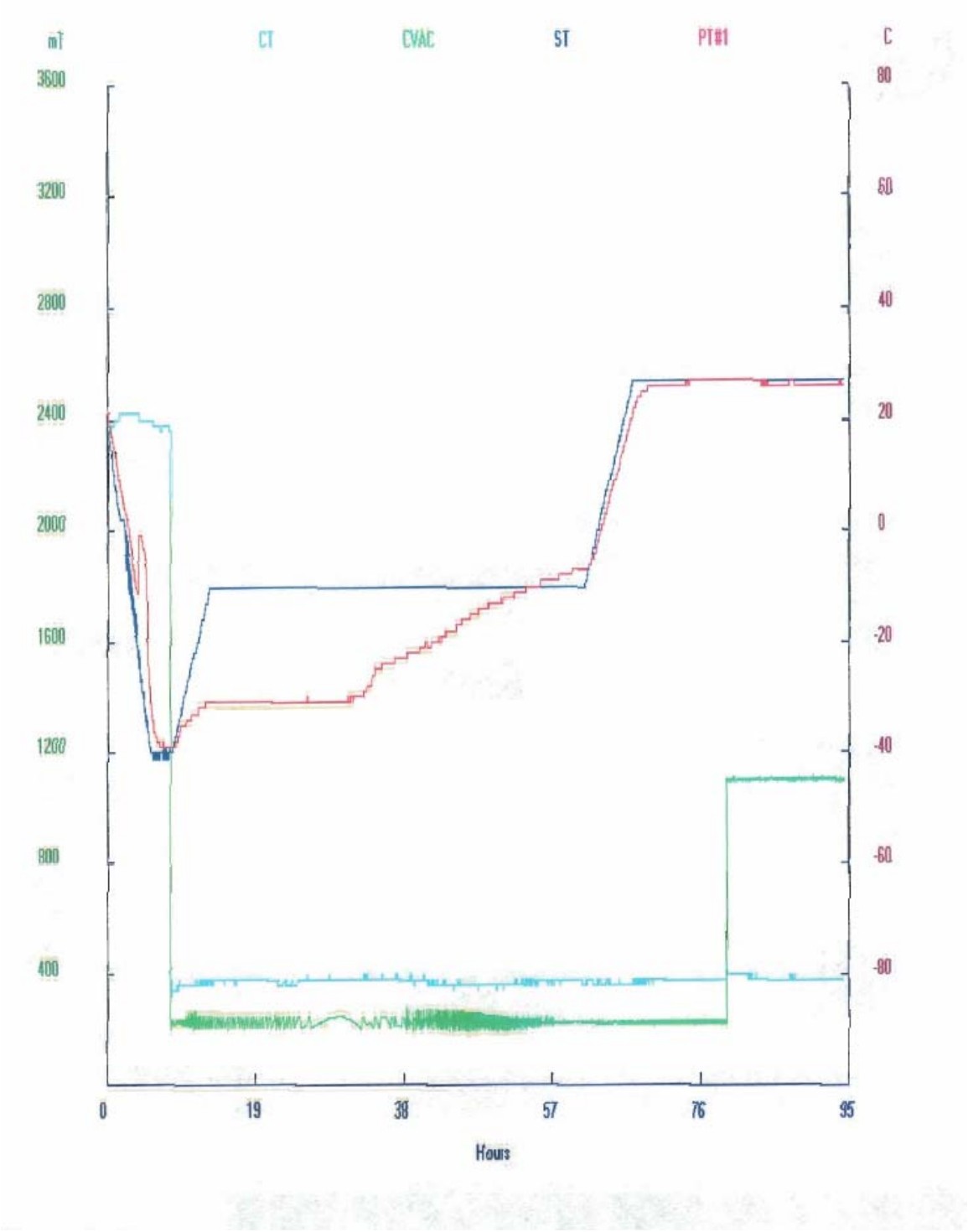
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1560	-82	128	a	2160	780	225	223	-10	-10	-31							
1590	-81	144	a	2160	810	225	247	-10	-10	-31							
1620	-82	136	a	2160	840	225	225	-10	-10	-31							
1650	-81	123	a	2160	870	225	216	-10	-10	-31							
1680	-82	123	a	2160	900	225	216	-10	-10	-31							
1710	-80	122	a	2160	930	225	214	-10	-10	-30							
1740	-80	130	a	2160	960	225	225	-10	-10	-31							
1770	-81	124	a	2160	990	225	217	-10	-10	-30							
1800	-81	123	a	2160	1020	225	215	-10	-10	-31							
1830	-81	115	a	2160	1050	225	204	-10	-10	-30							
1860	-81	115	a	2160	1080	225	204	-10	-10	-31							
1890	-80	128	a	2160	1110	225	222	-10	-10	-30							
1920	-81	136	a	2160	1140	225	233	-10	-10	-31							
1950	-81	120	a	2160	1170	225	210	-10	-10	-31							
1980	-80	136	a	2160	1200	225	233	-10	-10	-30							
2010	-81	119	a	2160	1230	225	209	-10	-10	-30							
2040	-79	133	a	2160	1260	225	228	-10	-10	-30							
2070	-80	128	a	2160	1290	225	222	-10	-10	-30							
2100	-81	118	a	2160	1320	225	207	-10	-10	-30							
2130	-81	129	a	2160	1350	225	223	-10	-10	-30							
2160	-81	144	a	2160	1380	225	246	-10	-10	-30							
2190	-80	119	a	2160	1410	225	210	-10	-10	-30							
2220	-81	130	a	2160	1440	225	224	-10	-10	-30							
2250	-80	140	a	2160	1470	225	241	-10	-10	-30							
2280	-80	134	a	2160	1500	225	220	-10	-10	-29							
2310	-79	120	a	2160	1530	225	211	-10	-10	-29							
2340	-79	125	a	2160	1560	225	218	-10	-10	-28							
2370	-81	129	a	2160	1590	225	224	-10	-10	-26							
2400	-79	134	a	2160	1620	225	229	-10	-10	-24							
2430	-81	131	a	2160	1650	225	225	-10	-10	-24							
2460	-81	121	a	2160	1680	225	207	-10	-10	-24							
2490	-80	129	a	2160	1710	225	223	-10	-10	-24							
2520	-81	127	a	2160	1740	225	220	-10	-10	-24							
2550	-82	125	a	2160	1770	225	217	-10	-10	-23							
2580	-82	121	a	2160	1800	225	210	-10	-10	-22							
2610	-81	122	a	2160	1830	225	208	-10	-10	-22							
2640	-82	141	a	2160	1860	225	240	-10	-10	-21							
2670	-82	125	a	2160	1890	225	216	-10	-10	-21							
2700	-82	142	a	2160	1920	225	241	-10	-10	-21							
2730	-82	142	a	2160	1950	225	241	-10	-10	-20							
2760	-82	143	a	2160	1980	225	244	-10	-10	-20							
2790	-82	136	a	2160	2010	225	232	-10	-10	-19							
2820	-81	137	a	2160	2040	225	233	-10	-10	-19							
2850	-82	122	a	2160	2070	225	212	-10	-10	-18							
2880	-81	117	a	2160	2100	225	205	-10	-10	-18							
2910	-81	124	a	2160	2130	225	215	-10	-10	-17							
2940	-81	124	b	0	0	225	214	-10	-10	-17							
2970	-82	136	b	0	0	225	230	- 7	- 7	-15							
3000	-83	132	b	0	0	225	216	- 4	- 4	-14							
3030	-82	125	b	0	0	225	216	- 1	- 1	-12							
3060	-83	129	b	0	0	225	212	2	2	- 9							
3090	-83	125	b	0	0	225	215	5	5	- 6							

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
3120	-82	138	b	0	0	225	229	8	8	- 3							
3150	-82	148	b	0	0	225	250	11	11	0							
3180	-82	123	b	0	0	225	213	14	14	3							
3210	-83	116	b	0	0	225	202	17	17	7							
3240	-81	136	b	0	0	225	226	20	20	10							
3270	-80	157	b	0	0	225	257	23	23	14							
3300	-81	134	b	0	0	225	224	26	26	18							
3330	-81	162	b	720	20	225	256	27	27	21							
3360	-81	135	b	720	50	225	211	27	27	23							
3390	-82	157	b	720	80	225	252	27	27	24							
3420	-80	146	b	720	110	225	227	27	27	25							
3450	-82	151	b	720	140	225	227	27	27	25							
3480	-80	151	b	720	170	225	227	27	27	26							
3510	-81	155	b	720	200	225	224	27	27	26							
3540	-81	160	b	720	230	225	220	27	27	26							
3570	-82	166	b	720	260	225	218	27	27	26							
3600	-82	186	b	720	290	225	222	27	27	26							
3630	-82	185	b	720	320	225	223	27	27	27							
3660	-81	181	b	720	350	225	218	27	27	27							
3690	-81	192	b	720	380	225	231	27	27	27							
3720	-81	185	b	720	410	225	222	27	27	26							
3750	-81	194	b	720	440	225	232	27	27	26							
3780	-81	193	b	720	470	225	231	27	27	27							
3810	-81	194	b	720	500	225	232	27	27	27							
3840	-81	186	b	720	530	225	224	27	27	26							
3870	-81	192	b	720	560	225	230	27	27	27							
3900	-81	182	b	720	590	225	218	27	27	27							
3930	-82	183	b	720	620	225	219	27	27	26							
3960	-82	182	b	720	650	225	217	27	27	27							
3990	-82	190	b	720	680	225	226	27	27	27							
4020	-82	194	b	720	710	225	231	27	27	27							
4050	-81	1126	c	999	20	1100	1098	27	27	27							
4080	-81	1129	c	999	50	1100	1098	27	27	27							
4110	-81	1133	c	999	80	1100	1098	27	27	27							
4140	-81	1139	c	999	110	1100	1105	27	27	27							

Run 02-19-2006 48 Hours Primary Drying

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT	Step Definitions
0.2	-40	120	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	2880	225	Primary Drying
0.1	27	720	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing


mT
CT
CVAC
ST
PT#1
C
3600
3200
2800
2400
2000
1600
1200
800
400
80
60
40
20
0
-20
-40
-60
-80
0
19
38
57
76
95
Hours

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1	19	3HHH	F	1	1		3HHH	20	20	22							
30	19	3HHH	1	0	0		3HHH	14	14	18							
60	20	3HHH	1	0	0		3HHH	8	8	14							
90	21	3HHH	1	30	0		3HHH	2	2	9							
120	21	3HHH	2	0	0		3HHH	2	2	5							
150	21	3HHH	2	0	0		3HHH	-4	-7	2							
180	21	3HHH	2	0	0		3HHH	-10	-12	-3							
210	21	3HHH	2	0	0		3HHH	-16	-16	-8							
240	21	3HHH	2	0	0		3HHH	-22	-22	-1							
270	20	3HHH	2	0	0		3HHH	-28	-29	-3							
300	20	3HHH	2	0	0		3HHH	-34	-34	-9							
330	20	3HHH	2	120	0		3HHH	-40	-40	-29							
360	19	3HHH	2	120	30		3HHH	-40	-40	-36							
390	19	3HHH	2	120	60		3HHH	-40	-41	-38							
420	19	3HHH	2	120	90		3HHH	-40	-40	-39							
450	19	3HHH	F	30	0		3HHH	-40	-40	-39							
480	18	3HHH	P		1		3HHH	-40	-39	-39							
510	-83	148	a	0	0	225	222	-38	-38	-39							
540	-83	141	a	0	0	225	229	-35	-35	-38							
570	-82	129	a	0	0	225	222	-32	-32	-35							
600	-82	124	a	0	0	225	215	-29	-29	-35							
630	-82	136	a	0	0	225	227	-26	-26	-34							
660	-82	130	a	0	0	225	224	-23	-23	-33							
690	-82	127	a	0	0	225	221	-20	-20	-33							
720	-82	128	a	0	0	225	222	-17	-17	-32							
750	-82	121	a	0	0	225	208	-14	-14	-32							
780	-82	120	a	0	0	225	212	-11	-11	-31							
810	-81	119	a	2880	19	225	211	-10	-10	-31							
840	-81	125	a	2880	49	225	219	-10	-10	-31							
870	-81	117	a	2880	79	225	207	-10	-10	-31							
900	-81	145	a	2880	109	225	247	-10	-10	-31							
930	-81	137	a	2880	139	225	224	-10	-10	-31							
960	-81	135	a	2880	169	225	232	-10	-10	-31							
990	-82	121	a	2880	199	225	214	-10	-10	-31							
1020	-81	121	a	2880	229	225	213	-10	-10	-31							
1050	-81	140	a	2880	259	225	240	-10	-10	-31							
1080	-81	119	a	2880	289	225	211	-10	-10	-31							
1110	-81	139	a	2880	319	225	239	-10	-10	-31							
1140	-81	121	a	2880	349	225	213	-10	-10	-31							
1170	-81	135	a	2880	379	225	232	-10	-10	-31							
1200	-81	143	a	2880	409	225	238	-10	-10	-31							
1230	-81	114	a	2880	439	225	204	-10	-10	-31							
1260	-81	125	a	2880	469	225	207	-10	-10	-31							
1290	-81	140	a	2880	499	225	241	-10	-10	-31							
1320	-82	128	a	2880	529	225	222	-10	-10	-31							
1350	-82	139	a	2880	559	225	239	-10	-10	-31							
1380	-82	143	a	2880	589	225	244	-10	-10	-31							
1410	-82	121	a	2880	619	225	207	-10	-10	-31							
1440	-82	116	a	2880	649	225	206	-10	-10	-31							
1470	-81	141	a	2880	679	225	242	-10	-10	-31							
1500	-81	115	a	2880	709	225	204	-10	-10	-31							
1530	-81	120	a	2880	739	225	211	-10	-10	-31							

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1560	-81	146	a	2880	769	225	247	-10	-10	-31							
1590	-81	120	a	2880	799	225	211	-10	-10	-31							
1620	-81	123	a	2880	829	225	216	-10	-10	-31							
1650	-81	128	a	2880	859	225	222	-10	-10	-31							
1680	-81	134	a	2880	889	225	230	-10	-10	-31							
1710	-81	138	a	2880	919	225	237	-10	-10	-31							
1740	-81	139	a	2880	949	225	238	-10	-10	-31							
1770	-81	141	a	2880	979	225	243	-10	-10	-31							
1800	-81	142	a	2880	1009	225	244	-10	-10	-31							
1830	-81	142	a	2880	1039	225	243	-10	-10	-31							
1860	-81	139	a	2880	1069	225	239	-10	-10	-31							
1890	-81	134	a	2880	1099	225	230	-10	-10	-30							
1920	-81	126	a	2880	1129	225	219	-10	-10	-30							
1950	-81	117	a	2880	1159	225	206	-10	-10	-30							
1980	-80	136	a	2880	1189	225	233	-10	-10	-29							
2010	-81	128	a	2880	1219	225	222	-10	-10	-28							
2040	-81	122	a	2880	1249	225	214	-10	-10	-26							
2070	-81	138	a	2880	1279	225	236	-10	-10	-25							
2100	-81	135	a	2880	1309	225	222	-10	-10	-25							
2130	-81	146	a	2880	1339	225	246	-10	-10	-24							
2160	-81	134	a	2880	1369	225	229	-10	-10	-24							
2190	-81	142	a	2880	1399	225	243	-10	-10	-24							
2220	-80	135	a	2880	1429	225	232	-10	-10	-23							
2250	-81	122	a	2880	1459	225	213	-10	-10	-23							
2280	-81	137	a	2880	1489	225	234	-10	-10	-23							
2310	-81	140	a	2880	1519	225	219	-10	-10	-22							
2340	-81	128	a	2880	1549	225	221	-10	-10	-22							
2370	-81	135	a	2880	1579	225	230	-10	-10	-22							
2400	-81	164	a	2880	1609	225	262	-10	-10	-22							
2430	-81	136	a	2880	1639	225	231	-10	-10	-21							
2460	-82	129	a	2880	1669	225	222	-10	-10	-21							
2490	-82	127	a	2880	1699	225	221	-10	-10	-20							
2520	-82	151	a	2880	1729	225	236	-10	-10	-20							
2550	-82	127	a	2880	1759	225	220	-10	-10	-19							
2580	-81	140	a	2880	1789	225	239	-10	-10	-19							
2610	-82	122	a	2880	1819	225	204	-10	-10	-18							
2640	-82	165	a	2880	1849	225	267	-10	-10	-18							
2670	-82	124	a	2880	1879	225	214	-10	-10	-18							
2700	-81	149	a	2880	1909	225	252	-10	-10	-17							
2730	-82	137	a	2880	1939	225	231	-10	-10	-16							
2760	-82	128	a	2880	1969	225	219	-10	-10	-16							
2790	-82	133	a	2880	1999	225	227	-10	-10	-15							
2820	-82	120	a	2880	2029	225	208	-10	-10	-15							
2850	-82	119	a	2880	2059	225	208	-10	-10	-15							
2880	-82	146	a	2880	2089	225	245	-10	-10	-14							
2910	-82	148	a	2880	2119	225	248	-10	-10	-14							
2940	-82	146	a	2880	2149	225	246	-10	-10	-13							
2970	-82	153	a	2880	2179	225	246	-10	-10	-13							
3000	-82	135	a	2880	2209	225	230	-10	-10	-13							
3030	-82	142	a	2880	2239	225	238	-10	-10	-13							
3060	-82	136	a	2880	2269	225	229	-10	-10	-12							
3090	-82	117	a	2880	2299	225	203	-10	-10	-12							

Run # 01

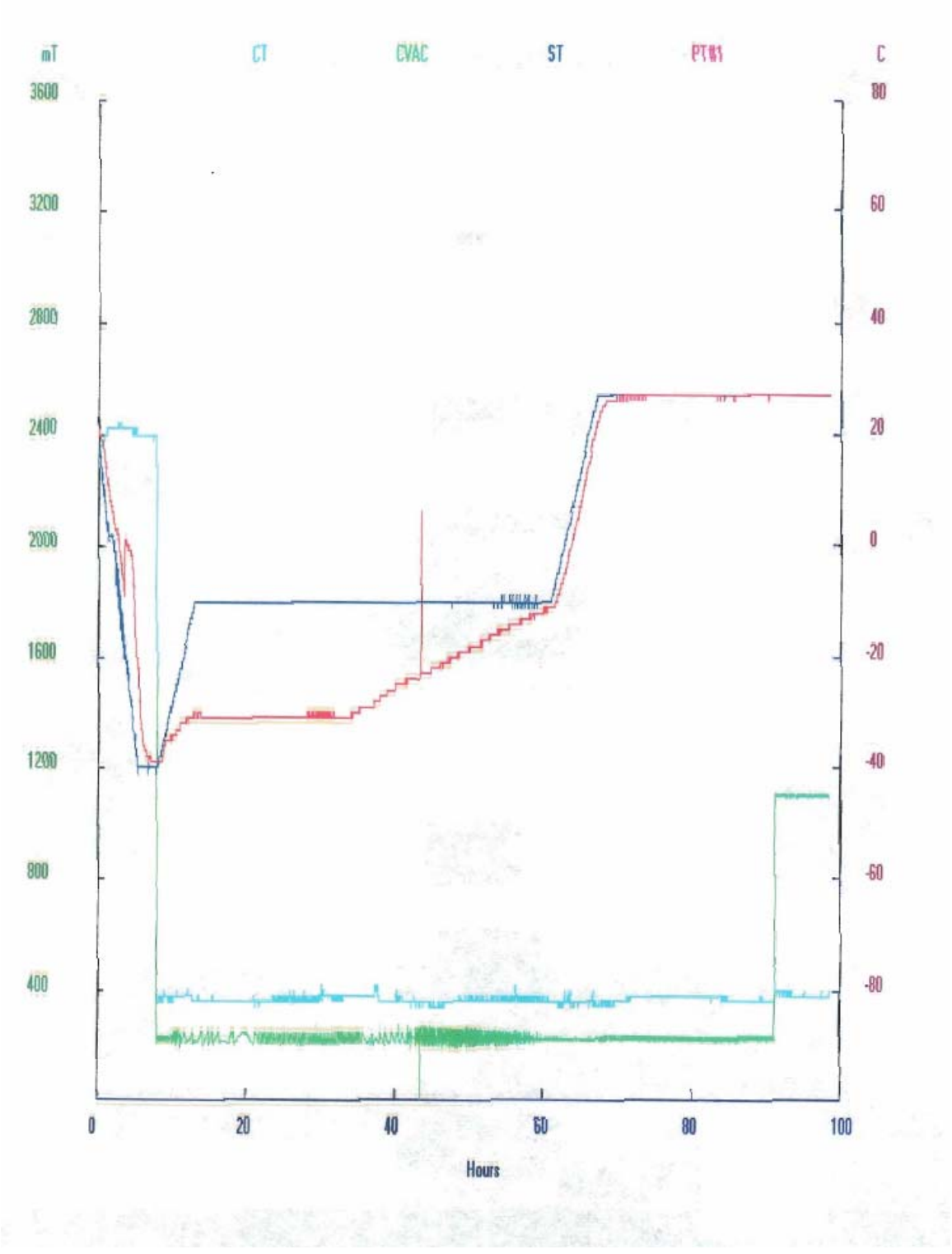
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
(mins)	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
3120	-82	139	a	2880	2329	225	215	-10	-10	-12							
3150	-82	146	a	2880	2359	225	240	-10	-10	-11							
3180	-82	132	a	2880	2389	225	207	-10	-10	-11							
3210	-82	149	a	2880	2419	225	234	-10	-10	-11							
3240	-81	129	a	2880	2449	225	216	-10	-10	-10							
3270	-81	123	a	2880	2479	225	208	-10	-10	-10							
3300	-82	133	a	2880	2509	225	219	-10	-10	-10							
3330	-81	135	a	2880	2539	225	222	-10	-10	-10							
3360	-81	138	a	2880	2569	225	225	-10	-10	- 9							
3390	-81	141	a	2880	2599	225	227	-10	-10	- 9							
3420	-81	135	a	2880	2629	225	219	-10	-10	- 9							
3450	-81	137	a	2880	2659	225	221	-10	-10	- 9							
3480	-81	138	a	2880	2689	225	221	-10	-10	- 8							
3510	-81	138	a	2880	2719	225	219	-10	-10	- 8							
3540	-81	151	a	2880	2749	225	225	-10	-10	- 8							
3570	-81	152	a	2880	2779	225	228	-10	-10	- 8							
3600	-81	147	a	2880	2809	225	224	-10	-10	- 7							
3630	-81	155	a	2880	2839	225	226	-10	-10	- 7							
3660	-82	149	a	2880	2869	225	223	-10	-10	- 7							
3690	-81	155	b	0	0	225	227	- 8	- 8	- 7							
3720	-81	155	b	0	0	225	223	- 5	- 5	- 5							
3750	-82	156	b	0	0	225	226	- 2	- 2	- 4							
3780	-81	162	b	0	0	225	227	1	1	- 1							
3810	-82	150	b	0	0	225	219	4	4	1							
3840	-81	161	b	0	0	225	227	7	7	4							
3870	-82	155	b	0	0	225	220	10	10	6							
3900	-82	167	b	0	0	225	227	13	13	9							
3930	-82	161	b	0	0	225	219	16	16	11							
3960	-82	165	b	0	0	225	219	19	19	14							
3990	-82	177	b	0	0	225	228	22	22	17							
4020	-82	184	b	0	0	225	229	25	25	20							
4050	-82	182	b	720	9	225	226	27	27	22							
4080	-81	190	b	720	39	225	230	27	27	24							
4110	-82	190	b	720	69	225	230	27	27	25							
4140	-81	180	b	720	99	225	218	27	27	25							
4170	-81	185	b	720	129	225	222	27	27	26							
4200	-81	185	b	720	159	225	221	27	27	26							
4230	-81	189	b	720	189	225	222	27	27	26							
4260	-81	191	b	720	219	225	228	27	27	26							
4290	-81	185	b	720	249	225	221	27	27	26							
4320	-81	194	b	720	279	225	231	27	27	26							
4350	-81	185	b	720	309	225	222	27	27	26							
4380	-81	194	b	720	339	225	231	27	27	26							
4410	-81	184	b	720	369	225	220	27	27	26							
4440	-81	189	b	720	399	225	225	27	27	26							
4470	-81	193	b	720	429	225	229	27	27	27							
4500	-81	196	b	720	459	225	230	27	27	27							
4530	-81	185	b	720	489	225	221	27	27	27							
4560	-81	192	b	720	519	225	228	27	27	27							
4590	-81	196	b	720	549	225	230	27	27	27							
4620	-81	191	b	720	579	225	222	27	27	27							
4650	-81	191	b	720	609	225	222	27	27	27							

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
4680	-81	193	b	720	639	225	222	27	27	27							
4710	-81	196	b	720	669	225	230	27	27	27							
4740	-81	194	b	720	699	225	230	27	27	27							
4770	-80	1129	c	999	9	1100	1098	27	27	27							
4800	-80	1123	c	999	39	1100	1105	27	27	27							
4830	-80	1133	c	999	69	1100	1105	27	27	27							
4860	-80	1123	c	999	99	1100	1105	27	27	27							
4890	-80	1123	c	999	129	1100	1098	27	27	27							
4920	-81	1129	c	999	159	1100	1105	27	27	27							
4950	-81	1129	c	999	189	1100	1105	27	27	27							
4980	-81	1126	c	999	219	1100	1105	27	27	27							
5010	-81	1129	c	999	249	1100	1105	27	27	27							
5040	-81	1129	c	999	279	1100	1105	27	27	27							
5070	-81	1129	c	999	309	1100	1105	27	27	27							
5100	-81	1129	c	999	339	1100	1112	27	27	26							
5130	-81	1123	c	999	369	1100	1098	27	27	26							
5160	-81	1129	c	999	399	1100	1105	27	27	26							
5190	-81	1126	c	999	429	1100	1098	27	27	26							
5220	-81	1133	c	999	459	1100	1105	27	27	26							
5250	-80	1129	c	999	489	1100	1098	27	27	27							
5280	-81	1126	c	999	519	1100	1098	27	27	26							
5310	-81	1126	c	999	549	1100	1098	27	27	26							
5340	-81	1123	c	999	579	1100	1098	27	27	26							
5370	-81	1126	c	999	609	1100	1098	27	27	26							
5400	-81	1126	c	999	639	1100	1098	27	27	26							
5430	-81	1133	c	999	669	1100	1105	27	27	26							
5460	-81	1136	c	999	699	1100	1098	27	27	26							
5490	-81	1129	c	999	729	1100	1098	27	27	26							
5520	-81	1136	c	999	759	1100	1105	27	27	26							
5550	-81	1133	c	999	789	1100	1098	27	27	26							
5580	-81	1133	c	999	819	1100	1098	27	27	26							
5610	-81	1133	c	999	849	1100	1105	27	27	26							
5640	-81	1133	c	999	879	1100	1105	27	27	26							

Run 04-03-2006 48 Hours Primary Drying 24 Hours Secondary Drying

Rate °C/min	Final Temperature °C	Hold Time (minutes)	Pressure MT	Step Definitions
0.2	-40	120	Ambient	Freezing
Evacuate the chamber Fore line Pressure = 135 mT Chamber Pressure = 185 mT				
0.1	-10	2880	225	Primary Drying
0.1	27	1440	225	Secondary Drying
0.0	27	NA	1100	Vial Sealing


mT
CT
CVAC
ST
PT%1
C
3600
3200
2800
2400
2000
1600
1200
800
400
80
60
40
20
0
-20
-40
-60
-80
0
20
40
60
80
100
Hours

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1	17	3HHH	F	1	1		3HHH	18	18	21							
30	19	3HHH	1	0	0		3HHH	12	12	18							
60	20	3HHH	1	0	0		3HHH	6	7	14							
90	21	3HHH	1	30	8		3HHH	2	2	9							
120	21	3HHH	2	0	0		3HHH	0	0	6							
150	21	3HHH	2	0	0		3HHH	-6	-8	2							
180	22	3HHH	2	0	0		3HHH	-12	-15	-3							
210	21	3HHH	2	0	0		3HHH	-18	-19	-8							
240	21	3HHH	2	0	0		3HHH	-24	-25	-0							
270	21	3HHH	2	0	0		3HHH	-30	-29	-2							
300	20	3HHH	2	0	0		3HHH	-36	-36	-15							
330	20	3HHH	2	120	8		3HHH	-40	-40	-27							
360	20	3HHH	2	120	38		3HHH	-40	-40	-35							
390	20	3HHH	2	120	68		3HHH	-40	-40	-37							
420	20	3HHH	2	120	98		3HHH	-40	-40	-38							
450	20	3HHH	F	30	8		3HHH	-40	-40	-39							
480	-80	376	P		9		426	-40	-40	-39							
510	-82	153	a	0	0	225	232	-37	-37	-39							
540	-81	135	a	0	0	225	225	-34	-34	-36							
570	-81	130	a	0	0	225	222	-31	-31	-35							
600	-81	140	a	0	0	225	233	-28	-29	-34							
630	-81	157	a	0	0	225	252	-25	-25	-34							
660	-81	138	a	0	0	225	234	-22	-22	-33							
690	-81	129	a	0	0	225	223	-19	-19	-32							
720	-81	117	a	0	0	225	206	-16	-16	-31							
750	-81	127	a	0	0	225	221	-13	-13	-31							
780	-82	116	a	0	0	225	206	-10	-10	-30							
810	-82	121	a	2880	27	225	213	-10	-10	-30							
840	-82	137	a	2880	57	225	234	-10	-10	-31							
870	-82	119	a	2880	87	225	210	-10	-10	-31							
900	-82	144	a	2880	117	225	247	-10	-10	-31							
930	-82	137	a	2880	147	225	235	-10	-10	-31							
960	-82	125	a	2880	177	225	219	-10	-10	-31							
990	-82	138	a	2880	207	225	230	-10	-10	-31							
1020	-82	122	a	2880	237	225	214	-10	-10	-31							
1050	-82	119	a	2880	267	225	209	-10	-10	-31							
1080	-82	141	a	2880	297	225	230	-10	-10	-31							
1110	-82	138	a	2880	327	225	230	-10	-10	-31							
1140	-82	131	a	2880	357	225	226	-10	-10	-31							
1170	-82	142	a	2880	387	225	242	-10	-10	-31							
1200	-82	147	a	2880	417	225	248	-10	-10	-31							
1230	-82	133	a	2880	447	225	227	-10	-10	-31							
1260	-82	120	a	2880	477	225	210	-10	-10	-31							
1290	-82	141	a	2880	507	225	239	-10	-10	-31							
1320	-82	136	a	2880	537	225	231	-10	-10	-31							
1350	-82	117	a	2880	567	225	205	-10	-10	-31							
1380	-82	135	a	2880	597	225	229	-10	-10	-31							
1410	-82	141	a	2880	627	225	230	-10	-10	-31							
1440	-81	131	a	2880	657	225	224	-10	-10	-31							
1470	-82	117	a	2880	687	225	204	-10	-10	-31							
1500	-82	136	a	2880	717	225	232	-10	-10	-31							
1530	-81	118	a	2880	747	225	206	-10	-10	-31							

Run # 01

RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
1560	-81	134	a	2880	777	225	228	-10	-10	-31							
1590	-82	129	a	2880	807	225	213	-10	-10	-31							
1620	-82	132	a	2880	837	225	226	-10	-10	-31							
1650	-82	147	a	2880	867	225	246	-10	-10	-31							
1680	-81	122	a	2880	897	225	213	-10	-10	-31							
1710	-81	135	a	2880	927	225	230	-10	-10	-30							
1740	-81	144	a	2880	957	225	244	-10	-10	-31							
1770	-82	132	a	2880	987	225	213	-10	-10	-31							
1800	-82	119	a	2880	1017	225	207	-10	-10	-31							
1830	-80	121	a	2880	1047	225	211	-10	-10	-31							
1860	-81	125	a	2880	1077	225	216	-10	-10	-30							
1890	-81	128	a	2880	1107	225	220	-10	-10	-30							
1920	-81	133	a	2880	1137	225	226	-10	-10	-31							
1950	-81	136	a	2880	1167	225	231	-10	-10	-31							
1980	-81	138	a	2880	1197	225	234	-10	-10	-31							
2010	-81	131	a	2880	1227	225	225	-10	-10	-31							
2040	-81	133	a	2880	1257	225	227	-10	-10	-31							
2070	-81	128	a	2880	1287	225	221	-10	-10	-30							
2100	-81	125	a	2880	1317	225	215	-10	-10	-30							
2130	-81	130	a	2880	1347	225	223	-10	-10	-29							
2160	-81	138	a	2880	1377	225	236	-10	-10	-29							
2190	-81	119	a	2880	1407	225	210	-10	-10	-29							
2220	-81	127	a	2880	1437	225	212	-10	-10	-29							
2250	-79	123	a	2880	1467	225	216	-10	-10	-28							
2280	-82	120	a	2880	1497	225	209	-10	-10	-27							
2310	-82	128	a	2880	1527	225	221	-10	-10	-27							
2340	-82	137	a	2880	1557	225	234	-10	-10	-26							
2370	-82	116	a	2880	1587	225	205	-10	-10	-26							
2400	-82	135	a	2880	1617	225	230	-10	-10	-26							
2430	-82	144	a	2880	1647	225	244	-10	-10	-25							
2460	-81	117	a	2880	1677	225	205	-10	-10	-25							
2490	-82	127	a	2880	1707	225	220	-10	-10	-24							
2520	-82	122	a	2880	1737	225	212	-10	-10	-24							
2550	-82	134	a	2880	1767	225	229	-10	-10	-24							
2580	-82	158	a	2880	1797	225	264	-10	-10	-24							
2610	-82	140	a	2880	1827	225	234	-10	-10	-23							
2640	-82	142	a	2880	1857	225	237	-10	-10	-23							
2670	-82	118	a	2880	1887	225	207	-10	-10	-23							
2700	-83	163	a	2880	1917	225	260	-10	-10	-22							
2730	-83	117	a	2880	1947	225	204	-10	-10	-22							
2760	-83	113	a	2880	1977	225	198	-10	-10	-22							
2790	-83	122	a	2880	2007	225	203	-10	-10	-21							
2820	-82	121	a	2880	2037	225	210	-10	-10	-21							
2850	-82	155	a	2880	2067	225	243	-10	-10	-21							
2880	-82	130	a	2880	2097	225	221	-10	-10	-20							
2910	-82	124	a	2880	2127	225	205	-10	-10	-19							
2940	-81	145	a	2880	2157	225	244	-10	-10	-19							
2970	-82	147	a	2880	2187	225	245	-10	-10	-19							
3000	-82	125	a	2880	2217	225	213	-10	-10	-19							
3030	-82	134	a	2880	2247	225	225	-10	-10	-18							
3060	-82	127	a	2880	2277	225	216	-10	-10	-18							
3090	-82	125	a	2880	2307	225	214	-10	-10	-18							

Run # 01

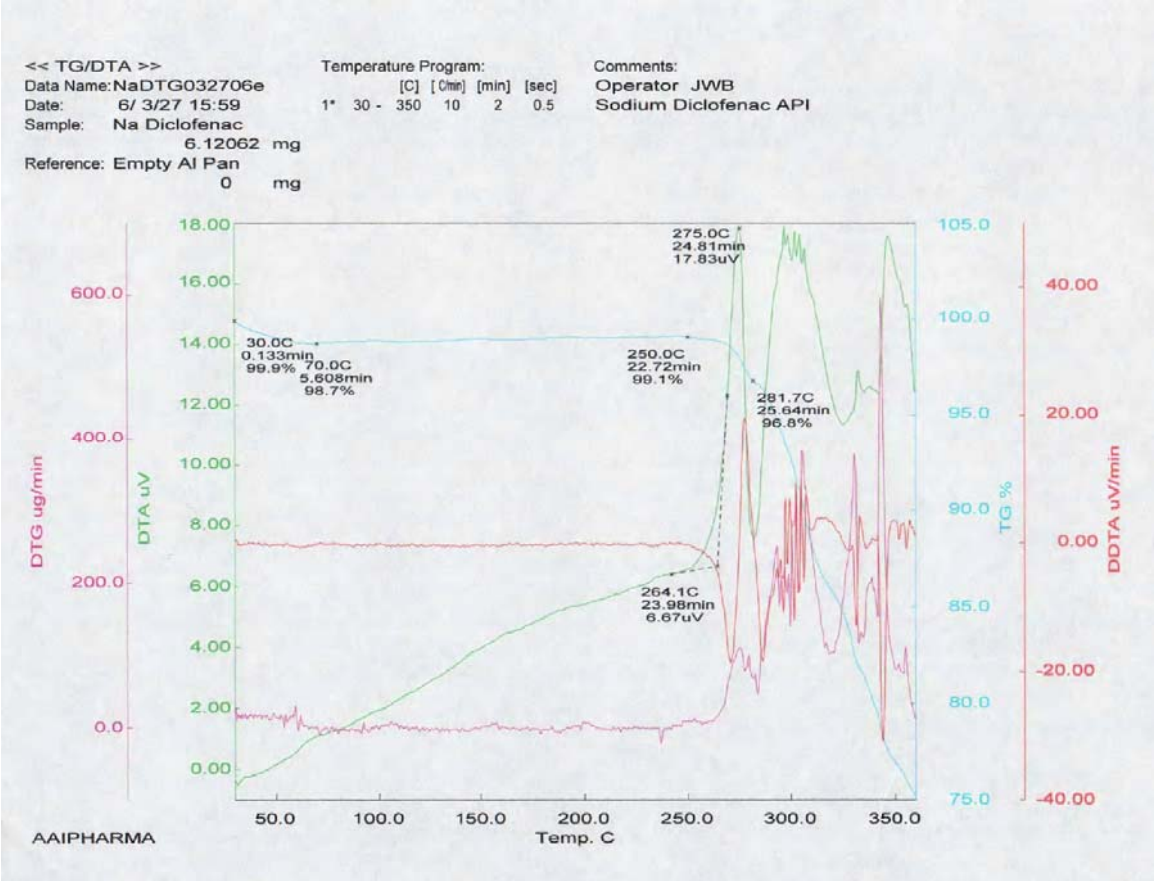
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME		CVAC		SHELF		PRODUCT TEMPERATURES deg.C							
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
3120	-82	115	a	2880	2337	225	200	-10	-10	-17							
3150	-82	122	a	2880	2367	225	209	-10	-10	-17							
3180	-82	156	a	2880	2397	225	251	-10	-10	-16							
3210	-82	121	a	2880	2427	225	209	-10	-10	-16							
3240	-82	153	a	2880	2457	225	244	-10	-10	-16							
3270	-81	151	a	2880	2487	225	246	-10	-10	-15							
3300	-82	132	a	2880	2517	225	221	-10	-10	-15							
3330	-81	133	a	2880	2547	225	224	-10	-10	-14							
3360	-82	149	a	2880	2577	225	240	-10	-10	-14							
3390	-81	126	a	2880	2607	225	213	-10	-10	-14							
3420	-81	131	a	2880	2637	225	219	-10	-10	-14							
3450	-81	139	a	2880	2667	225	228	-10	-10	-13							
3480	-81	145	a	2880	2697	225	234	-10	-10	-13							
3510	-81	137	a	2880	2727	225	224	-10	-10	-12							
3540	-81	141	a	2880	2757	225	227	-10	-10	-12							
3570	-81	139	a	2880	2787	225	225	-10	-10	-12							
3600	-82	134	a	2880	2817	225	218	-10	-10	-11							
3630	-82	136	a	2880	2847	225	221	-10	-10	-12							
3660	-82	140	a	2880	2877	225	226	-10	-10	-11							
3690	-82	144	b	0	0	225	229	- 7	- 7	-11							
3720	-82	139	b	0	0	225	223	- 4	- 4	- 9							
3750	-83	143	b	0	0	225	222	- 1	- 1	- 6							
3780	-81	139	b	0	0	225	221	2	2	- 4							
3810	-82	144	b	0	0	225	225	5	5	- 1							
3840	-82	141	b	0	0	225	221	8	8	2							
3870	-82	140	b	0	0	225	220	11	11	5							
3900	-82	145	b	0	0	225	223	14	14	8							
3930	-82	156	b	0	0	225	227	17	17	11							
3960	-82	160	b	0	0	225	229	20	20	15							
3990	-82	149	b	0	0	225	219	23	23	18							
4020	-83	168	b	0	0	225	229	26	26	21							
4050	-83	173	b	1440	17	225	230	27	27	23							
4080	-83	178	b	1440	47	225	230	27	27	25							
4110	-83	184	b	1440	77	225	230	27	27	26							
4140	-82	184	b	1440	107	225	225	27	27	26							
4170	-83	195	b	1440	137	225	232	27	27	26							
4200	-82	189	b	1440	167	225	227	27	27	27							
4230	-82	191	b	1440	197	225	229	27	27	27							
4260	-82	185	b	1440	227	225	223	27	27	27							
4290	-81	194	b	1440	257	225	231	27	27	27							
4320	-81	191	b	1440	287	225	225	27	27	26							
4350	-81	181	b	1440	317	225	220	27	27	27							
4380	-81	187	b	1440	347	225	226	27	27	27							
4410	-81	190	b	1440	377	225	230	27	27	27							
4440	-81	191	b	1440	407	225	230	27	27	27							
4470	-81	189	b	1440	437	225	228	27	27	27							
4500	-81	189	b	1440	467	225	228	27	27	27							
4530	-81	188	b	1440	497	225	227	27	27	27							
4560	-81	187	b	1440	527	225	225	27	27	27							
4590	-81	181	b	1440	557	225	218	27	27	27							
4620	-81	192	b	1440	587	225	231	27	27	27							
4650	-81	181	b	1440	617	225	218	27	27	27							

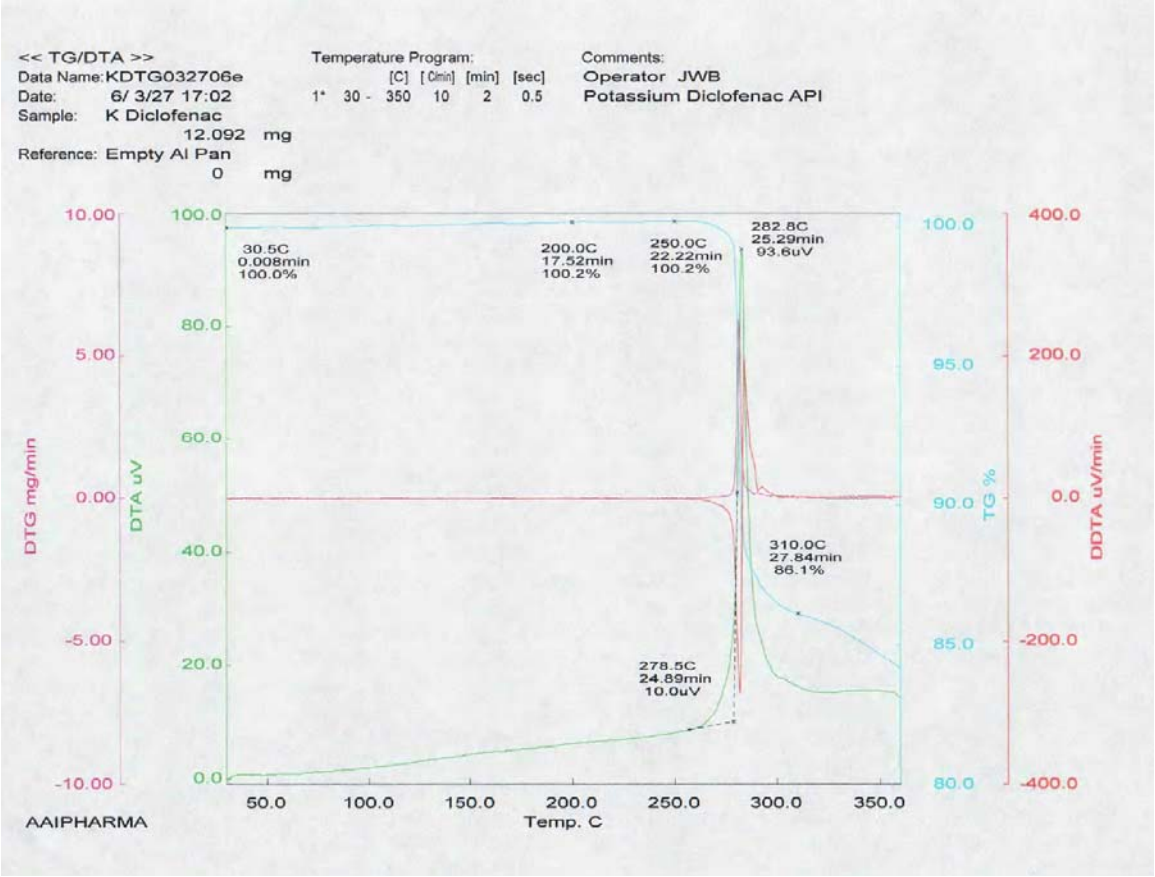
Run # 01

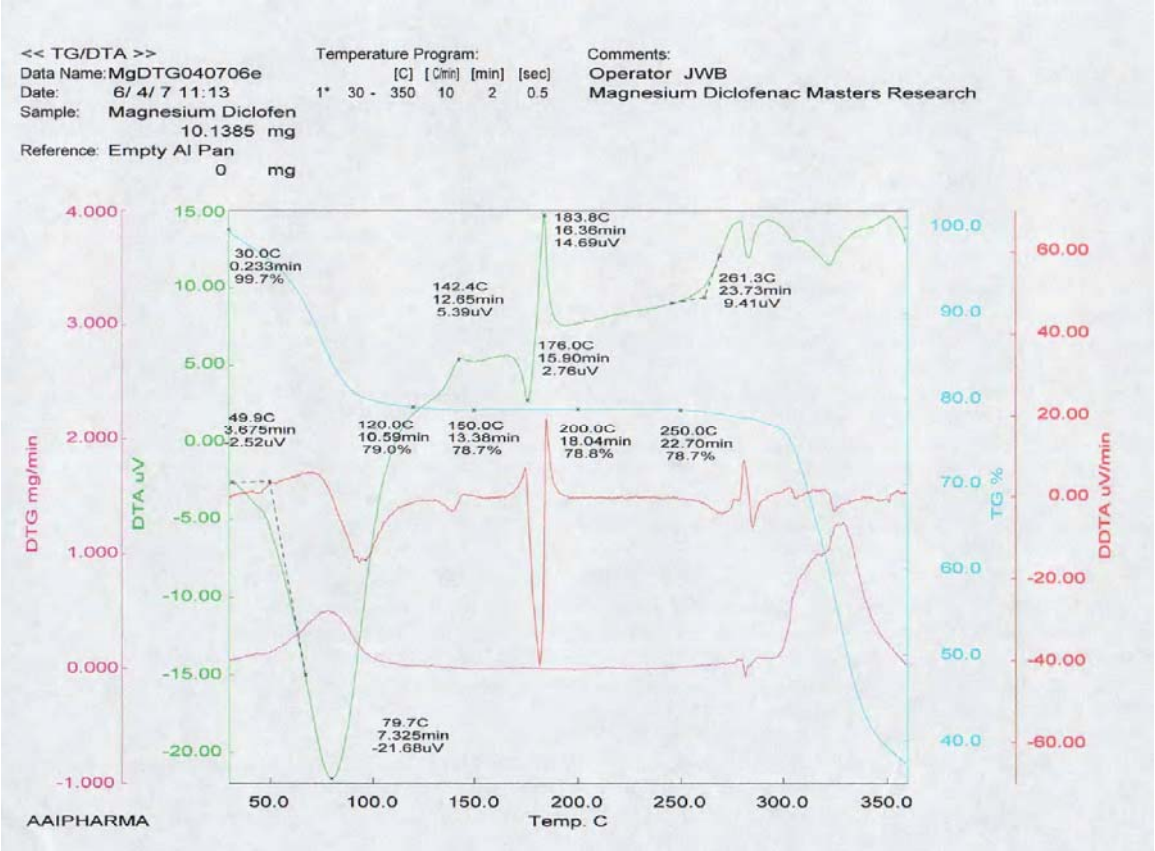
RUN TIME	CONDENSER		TRAY-DRYER													
			STEP TIME			CVAC		SHELF		PRODUCT TEMPERATURES deg.C						
mins	CT	FVAC	#	SP	RDG	SP	RDG	SP	RDG	#1	#2	#3	#4	#5	#6	#7	#8
4680	-81	184	b	1440	647	225	222	27	27	27							
4710	-81	184	b	1440	677	225	222	27	27	27							
4740	-81	184	b	1440	707	225	221	27	27	27							
4770	-81	184	b	1440	737	225	221	27	27	27							
4800	-81	182	b	1440	767	225	219	27	27	27							
4830	-81	182	b	1440	797	225	219	27	27	27							
4860	-81	181	b	1440	827	225	218	27	27	27							
4890	-81	194	b	1440	857	225	231	27	27	27							
4920	-81	189	b	1440	887	225	226	27	27	27							
4950	-81	183	b	1440	917	225	219	27	27	27							
4980	-81	192	b	1440	947	225	229	27	27	27							
5010	-81	189	b	1440	977	225	227	27	27	27							
5040	-81	192	b	1440	1007	225	229	27	27	27							
5070	-81	194	b	1440	1037	225	232	27	27	27							
5100	-82	190	b	1440	1067	225	227	27	27	27							
5130	-82	182	b	1440	1097	225	217	27	27	26							
5160	-82	194	b	1440	1127	225	229	27	27	27							
5190	-82	188	b	1440	1157	225	223	27	27	27							
5220	-82	183	b	1440	1187	225	218	27	27	27							
5250	-82	185	b	1440	1217	225	220	27	27	27							
5280	-82	185	b	1440	1247	225	218	27	27	27							
5310	-82	193	b	1440	1277	225	227	27	27	27							
5340	-82	192	b	1440	1307	225	227	27	27	27							
5370	-82	192	b	1440	1337	225	227	27	27	27							
5400	-82	194	b	1440	1367	225	230	27	27	27							
5430	-82	187	b	1440	1397	225	220	27	27	27							
5460	-82	188	b	1440	1427	225	222	27	27	27							
5490	-80	1143	c	999	17	1100	1098	27	27	27							
5520	-80	1146	c	999	47	1100	1098	27	27	27							
5550	-80	1143	c	999	77	1100	1098	27	27	27							
5580	-80	1139	c	999	107	1100	1098	27	27	27							
5610	-80	1146	c	999	137	1100	1098	27	27	27							
5640	-81	1139	c	999	167	1100	1098	27	27	27							
5670	-81	1139	c	999	197	1100	1098	27	27	27							
5700	-81	1143	c	999	227	1100	1098	27	27	27							
5730	-81	1143	c	999	257	1100	1098	27	27	27							
5760	-81	1139	c	999	287	1100	1098	27	27	27							
5790	-81	1143	c	999	317	1100	1105	27	27	27							
5820	-81	1143	c	999	347	1100	1105	27	27	27							
5850	-81	1150	c	999	377	1100	1098	27	27	27							
5880	-81	1150	c	999	407	1100	1105	27	27	27							
5910	-81	1143	c	999	437	1100	1098	27	27	27							

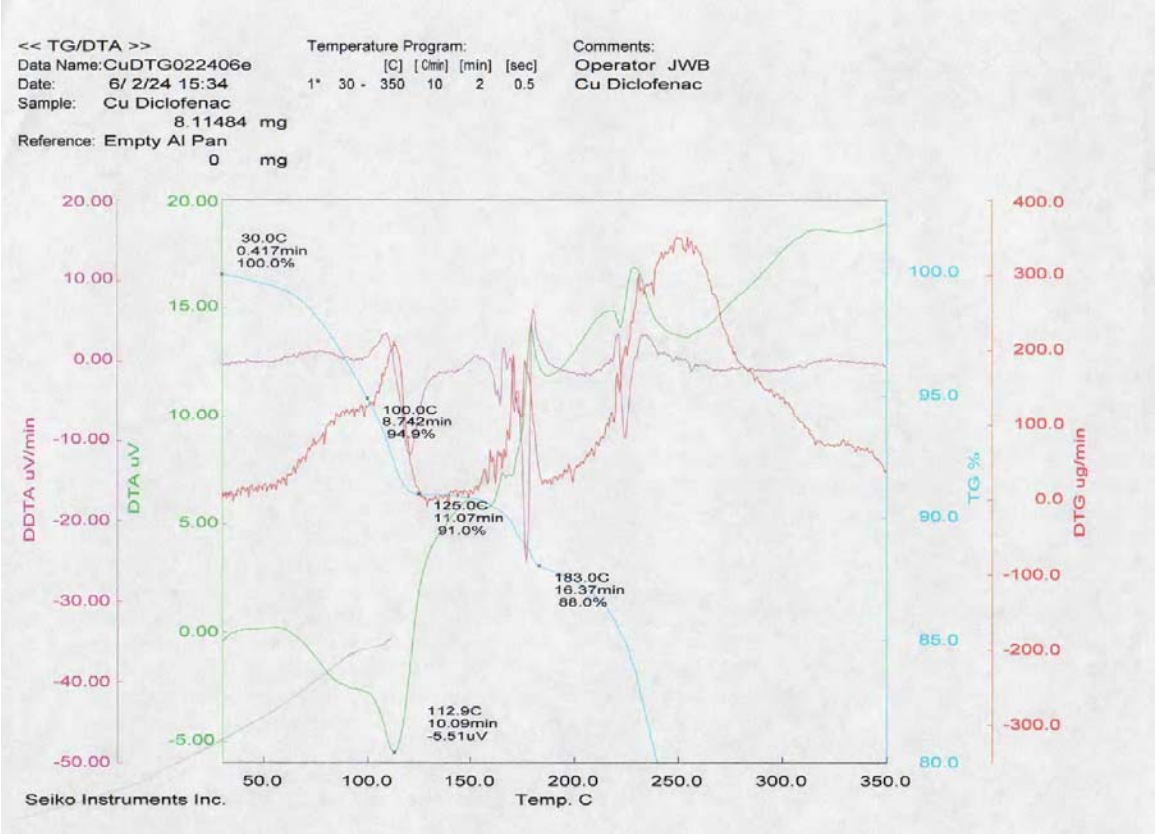
Appendix B

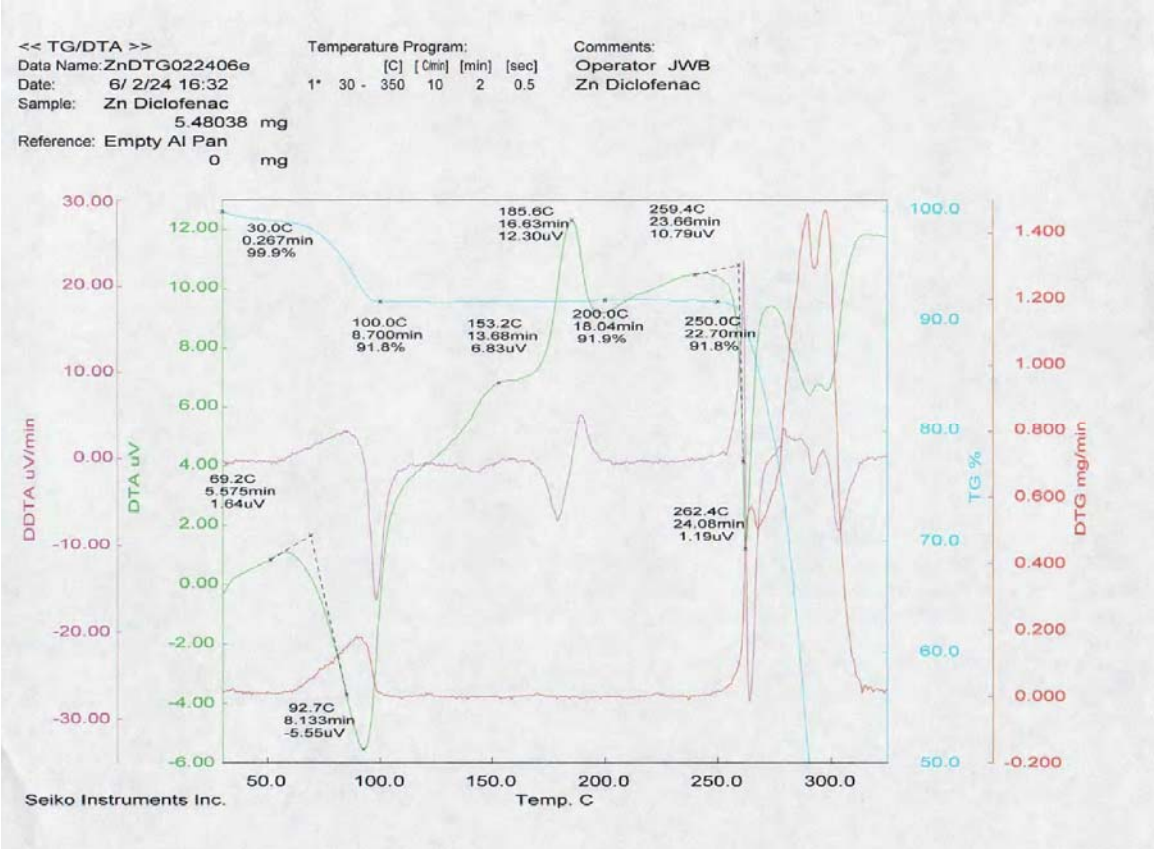
TGA Printouts

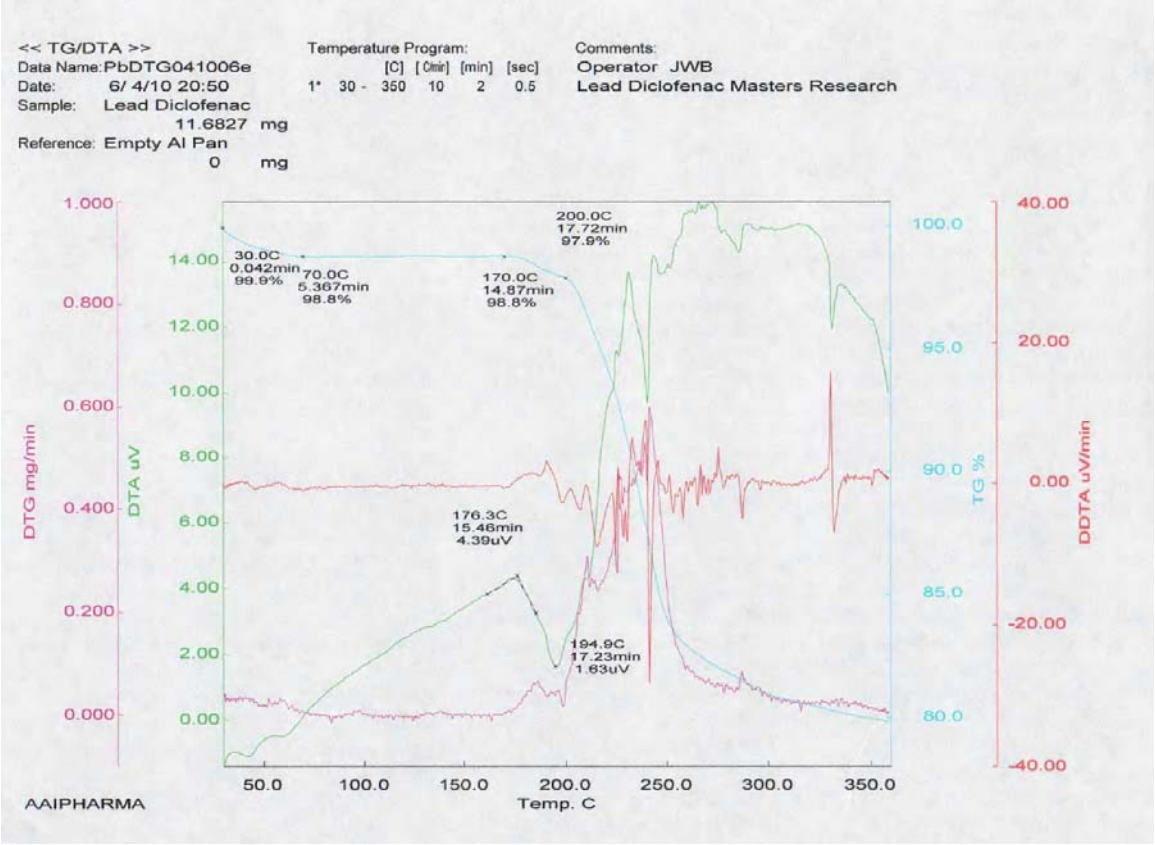

<< TG/DTA >>
Data Name: NaDTG032706e
Date: 6/ 3/27 15:59
Sample: Na Diclofenac
6.12062 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Sodium Diclofenac API
275.0C
24.81min
17.83uV
30.0C
0.133min
99.9%
70.0C
5.608min
98.7%
250.0C
22.72min
99.1%
281.7C
25.64min
96.8%
264.1C
23.98min
6.67uV
DTG ug/min
DTA uV
TG %
DDTA uV/min
Temp. C
AAIPHARMA

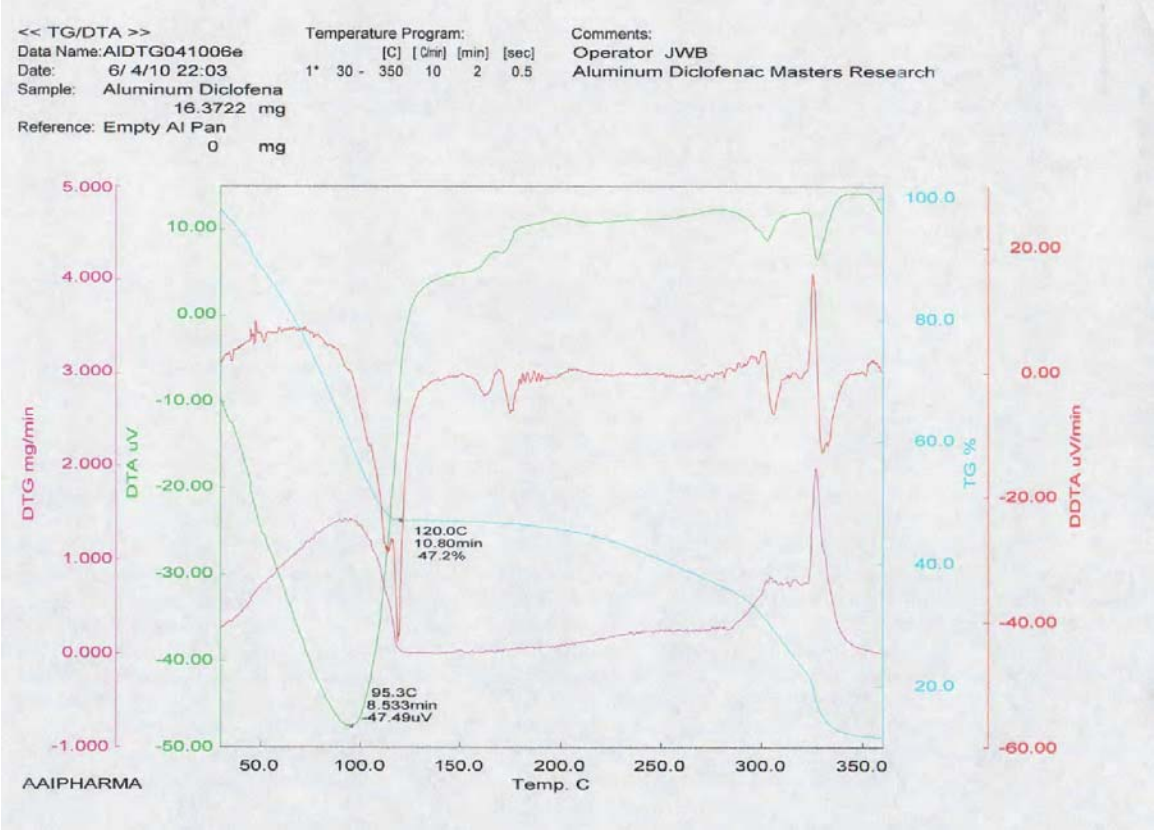

<< TG/DTA >>
Data Name: KDTG032706e
Date: 6/ 3/27 17:02
Sample: K Diclofenac
12.092 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Potassium Diclofenac API
30.5C
0.008min
100.0%
200.0C
17.52min
100.2%
250.0C
22.22min
100.2%
282.8C
25.29min
93.6uV
310.0C
27.84min
86.1%
278.5C
24.89min
10.0uV
DTG mg/min
DTA uV
TG %
DDTA uV/min
Temp. C
AAIPHARMA


<< TG/DTA >>
Data Name: MgDTG040706e
Date: 6/ 4/ 7 11:13
Sample: Magnesium Diclofen
10.1385 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Magnesium Diclofenac Masters Research
30.0C
0.233min
99.7%
142.4C
12.65min
5.39uV
183.8C
16.36min
14.69uV
261.3C
23.73min
9.41uV
176.0C
15.90min
2.76uV
49.9C
3.675min
-2.52uV
120.0C
10.59min
79.0%
150.0C
13.38min
78.7%
200.0C
18.04min
78.8%
250.0C
22.70min
78.7%
79.7C
7.325min
-21.68uV
DTG mg/min
DTA uV
TG %
DDTA uV/min
Temp. C
AAIPHARMA


<< TG/DTA >>
Data Name:CuDTG022406e
Date: 6/ 2/24 15:34
Sample: Cu Diclofenac
8.11484 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Cu Diclofenac
30.0C
0.417min
100.0%
100.0C
8.742min
94.9%
125.0C
11.07min
91.0%
183.0C
16.37min
88.0%
112.9C
10.09min
-5.51uV
DDTA uV/min
DTA uV
TG %
DTG ug/min
Temp. C
Seiko Instruments Inc.

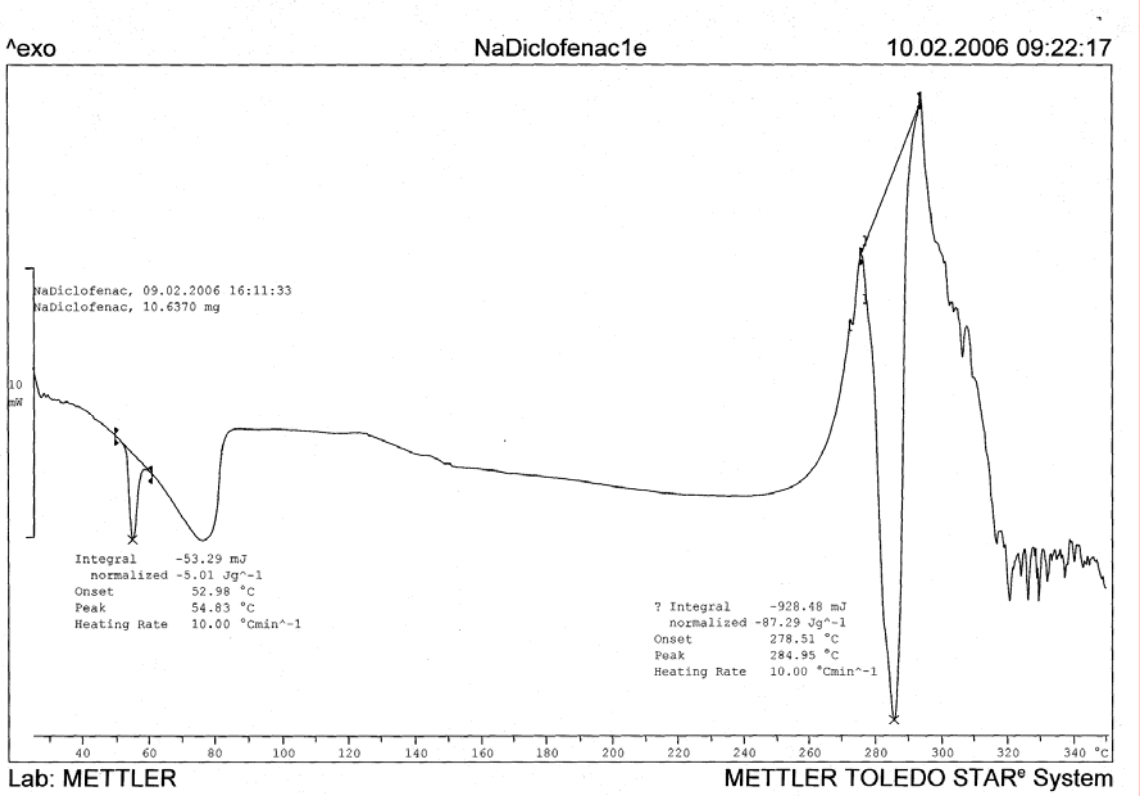

<< TG/DTA >>
Data Name: ZnDTG022406e
Date: 6/ 2/24 16:32
Sample: Zn Diclofenac
5.48038 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Zn Diclofenac
30.0C
0.267min
99.9%
100.0C
8.700min
91.8%
153.2C
13.68min
6.83uV
185.6C
16.63min
12.30uV
200.0C
18.04min
91.9%
259.4C
23.66min
10.79uV
250.0C
22.70min
91.8%
69.2C
5.575min
1.64uV
92.7C
8.133min
-5.55uV
262.4C
24.08min
1.19uV
DDTA uV/min
DTA uV
TG %
DTG mg/min
Temp. C
Seiko Instruments Inc.

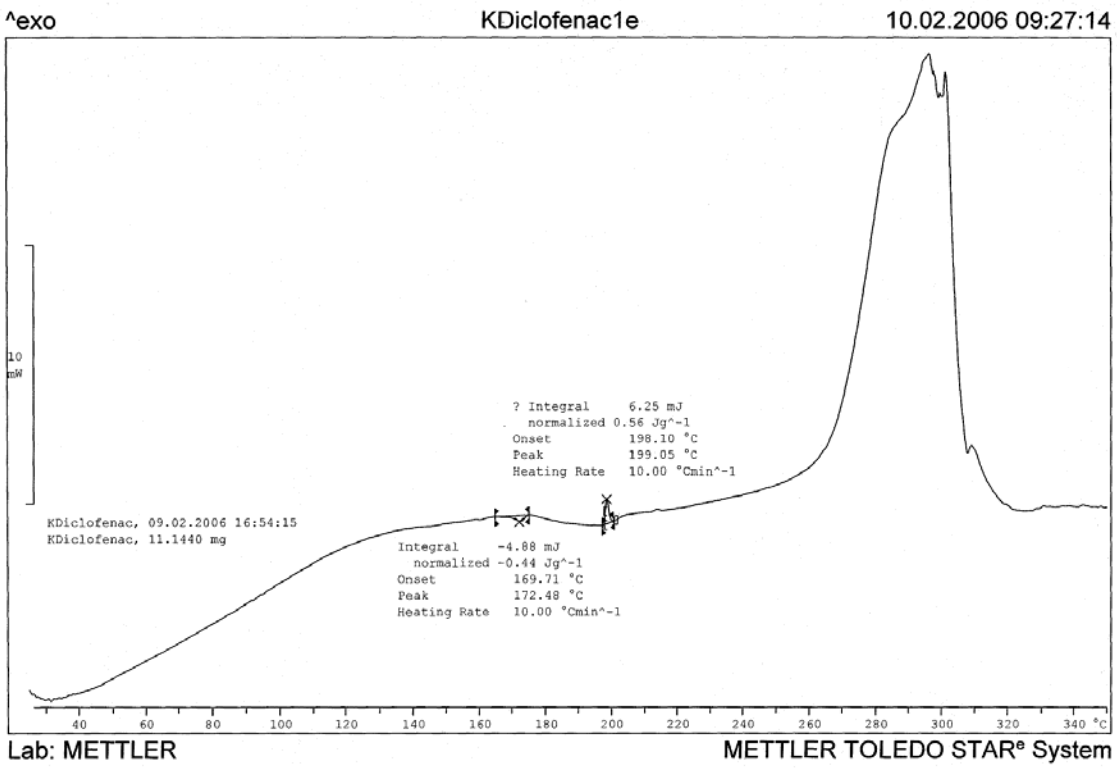

<< TG/DTA >>
Data Name: PbDTG041006e
Date: 6/ 4/10 20:50
Sample: Lead Diclofenac
11.6827 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Lead Diclofenac Masters Research
30.0C
0.042min
99.9%
70.0C
5.367min
98.8%
170.0C
14.87min
98.8%
200.0C
17.72min
97.9%
176.3C
15.46min
4.39uV
194.9C
17.23min
1.63uV
DTG mg/min
DTA uV
TG %
DDTA uV/min
Temp. C
AAIPHARMA

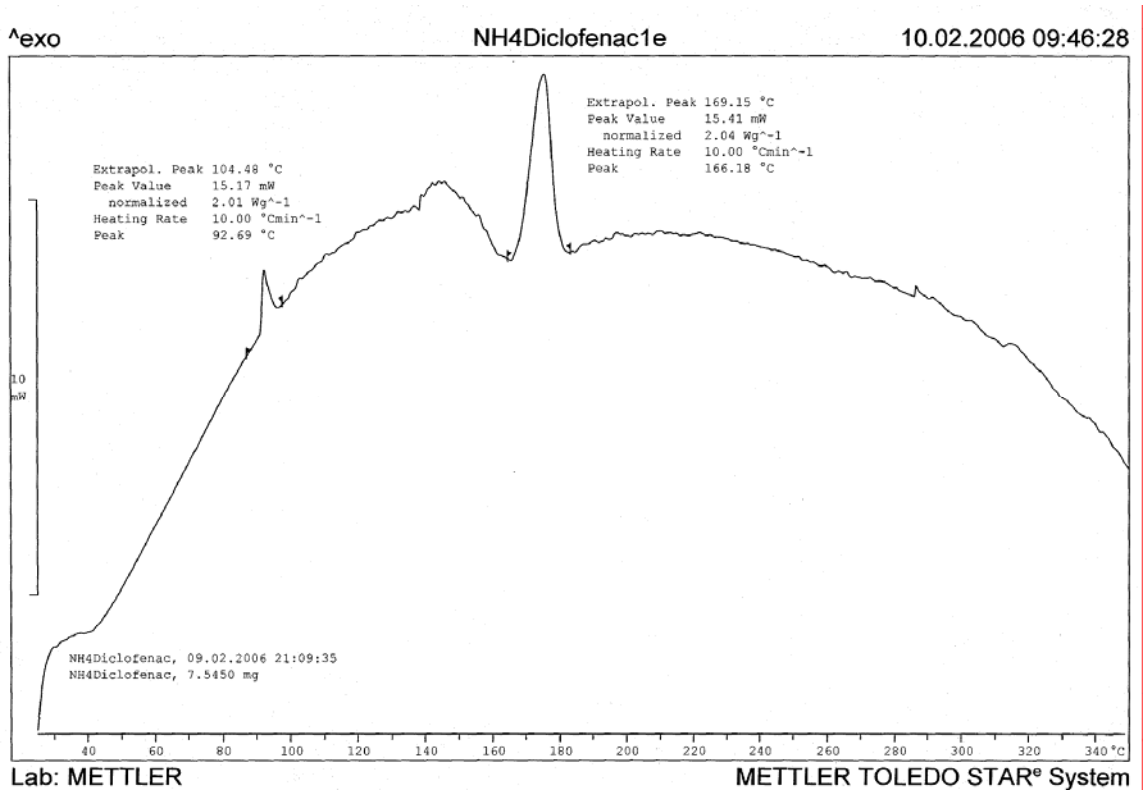

<< TG/DTA >>
Data Name:AIDTG041006e
Date: 6/ 4/10 22:03
Sample: Aluminum Diclofena
16.3722 mg
Reference: Empty Al Pan
0 mg
Temperature Program:
[C] [C/min] [min] [sec]
1* 30 - 350 10 2 0.5
Comments:
Operator JWB
Aluminum Diclofenac Masters Research
120.0C
10.80min
47.2%
95.3C
8.533min
-47.49uV
DTG mg/min
DTA uV
TG %
DDTA uV/min
Temp. C
AAIPHARMA

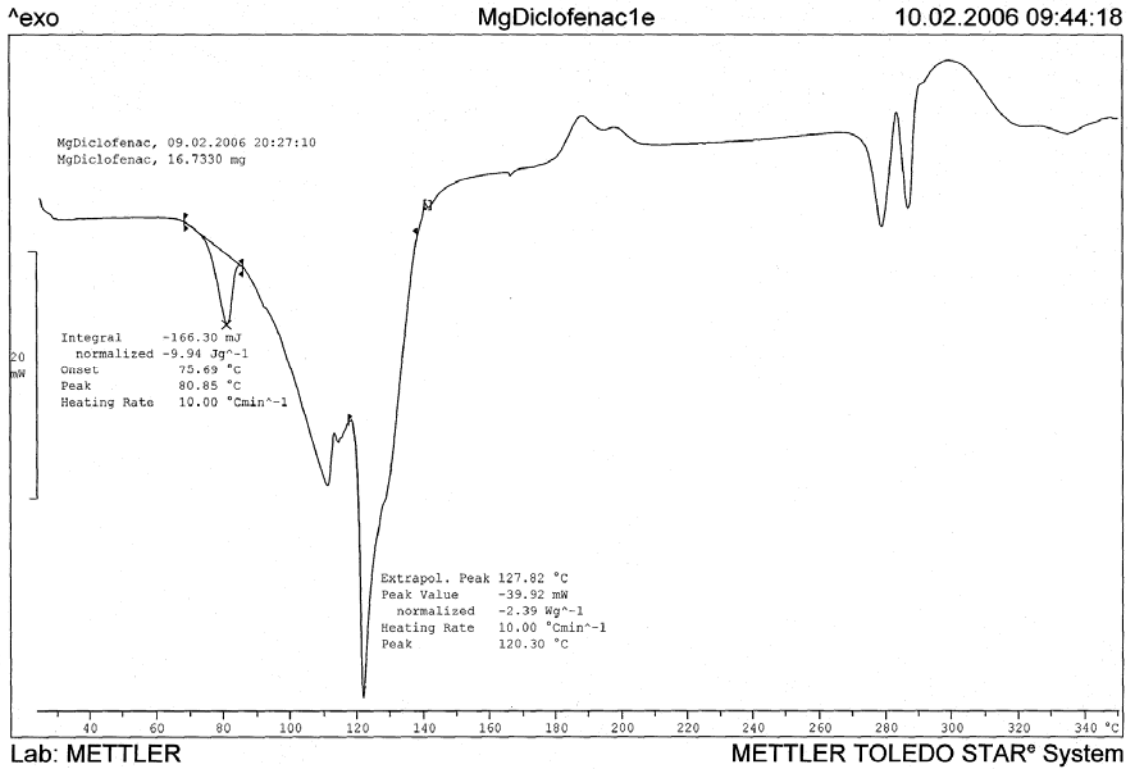
Appendix C

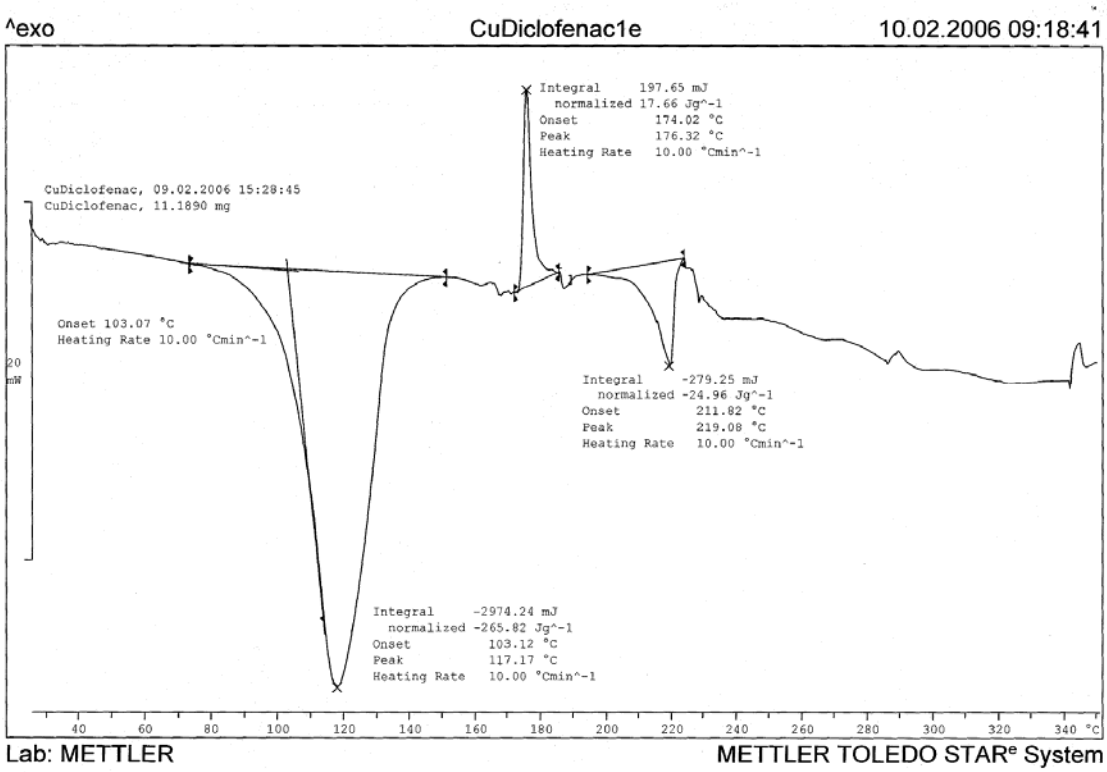
Differential Scanning Calorimetry

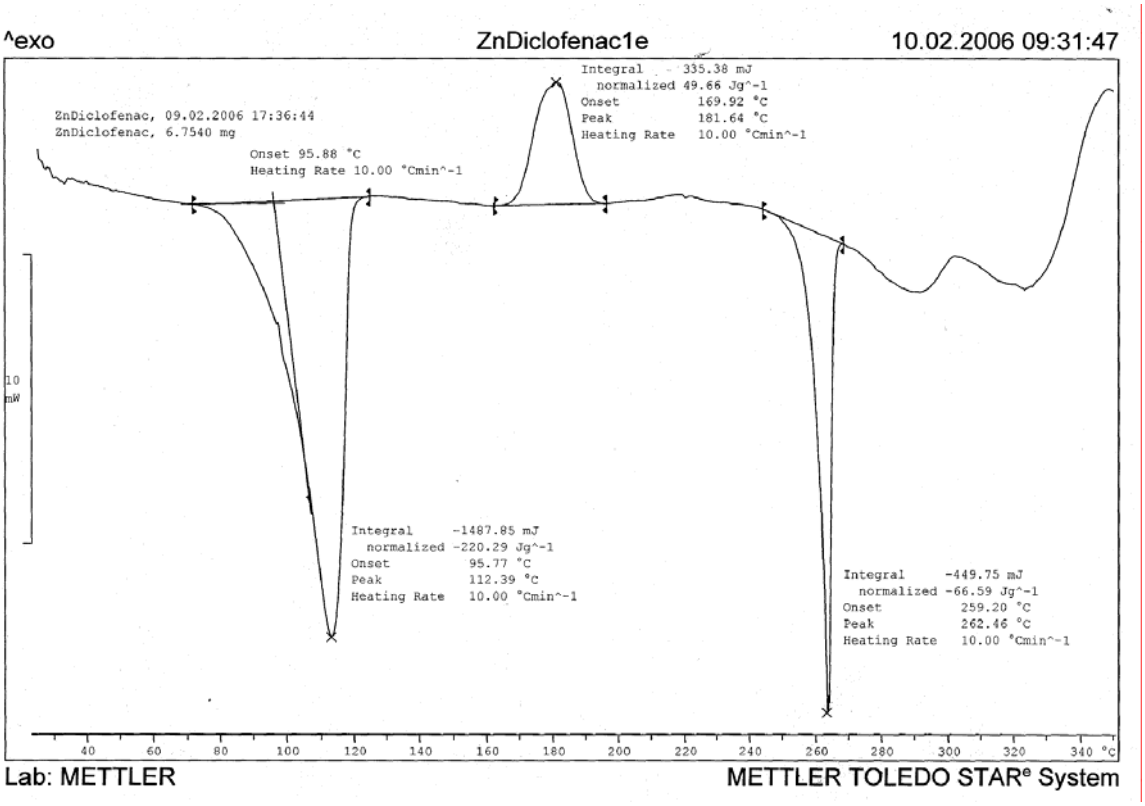

^exo
NaDiclofenac1e
10.02.2006 09:22:17
NaDiclofenac, 09.02.2006 16:11:33
NaDiclofenac, 10.6370 mg
10
mW
Integral -53.29 mJ
normalized -5.01 Jg^-1
Onset 52.98 °C
Peak 54.83 °C
Heating Rate 10.00 °Cmin^-1
? Integral -928.48 mJ
normalized -87.29 Jg^-1
Onset 278.51 °C
Peak 284.95 °C
Heating Rate 10.00 °Cmin^-1
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System

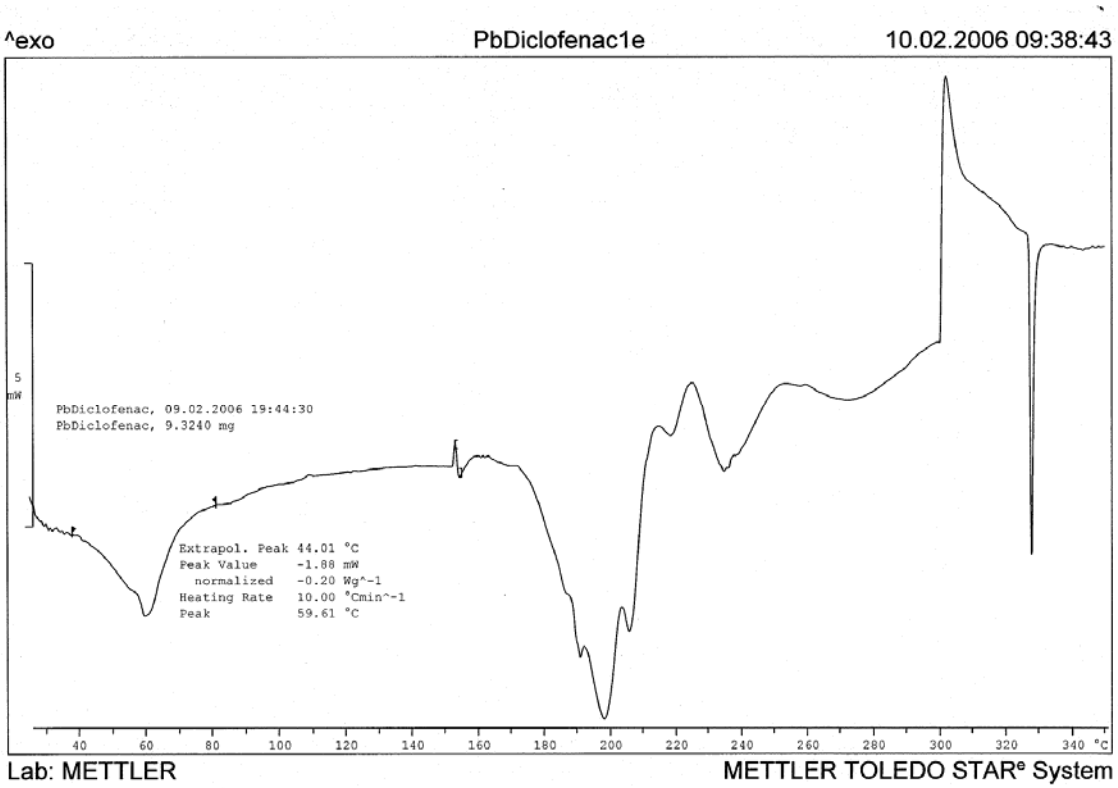

^exo
KDiclofenac1e
10.02.2006 09:27:14
10
mW
? Integral 6.25 mJ
normalized 0.56 Jg^-1
Onset 198.10 °C
Peak 199.05 °C
Heating Rate 10.00 °Cmin^-1
KDiclofenac, 09.02.2006 16:54:15
KDiclofenac, 11.1440 mg
Integral -4.88 mJ
normalized -0.44 Jg^-1
Onset 169.71 °C
Peak 172.48 °C
Heating Rate 10.00 °Cmin^-1
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STAR^e System

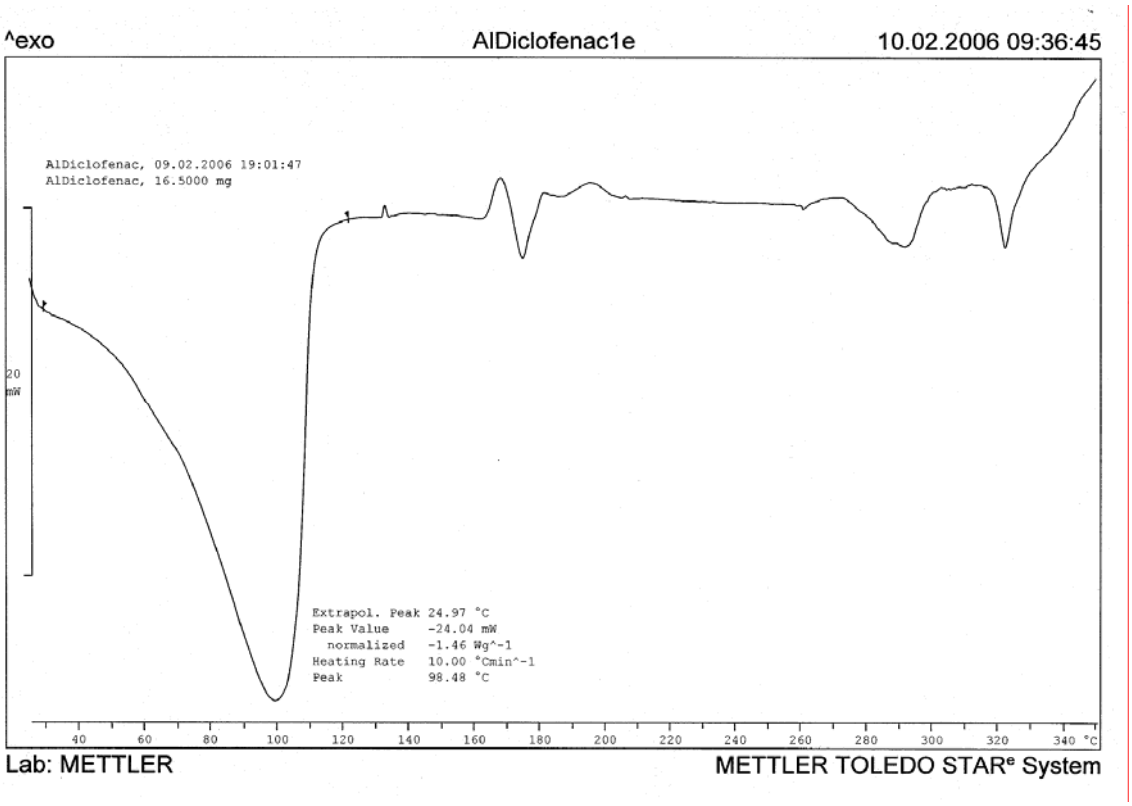

^exo
NH4Diclofenac1e
10.02.2006 09:46:28
Extrapol. Peak 104.48 °C
Peak Value 15.17 mW
normalized 2.01 Wg^-1
Heating Rate 10.00 °Cmin^-1
Peak 92.69 °C
Extrapol. Peak 169.15 °C
Peak Value 15.41 mW
normalized 2.04 Wg^-1
Heating Rate 10.00 °Cmin^-1
Peak 166.18 °C
10 mW
NH4Diclofenac, 09.02.2006 21:09:35
NH4Diclofenac, 7.5450 mg
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System


^exo
MgDiclofenac1e
10.02.2006 09:44:18
MgDiclofenac, 09.02.2006 20:27:10
MgDiclofenac, 16.7330 mg
Integral -166.30 mJ
normalized -9.94 Jg^-1
Onset 75.69 °C
Peak 80.85 °C
Heating Rate 10.00 °Cmin^-1
20 mW
Extrapol. Peak 127.82 °C
Peak Value -39.92 mW
normalized -2.39 Wg^-1
Heating Rate 10.00 °Cmin^-1
Peak 120.30 °C
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System


^exo
CuDiclofenac1e
10.02.2006 09:18:41
Integral 197.65 mJ
normalized 17.66 Jg^-1
Onset 174.02 °C
Peak 176.32 °C
Heating Rate 10.00 °Cmin^-1
CuDiclofenac, 09.02.2006 15:28:45
CuDiclofenac, 11.1890 mg
Onset 103.07 °C
Heating Rate 10.00 °Cmin^-1
20 mW
Integral -279.25 mJ
normalized -24.96 Jg^-1
Onset 211.82 °C
Peak 219.08 °C
Heating Rate 10.00 °Cmin^-1
Integral -2974.24 mJ
normalized -265.82 Jg^-1
Onset 103.12 °C
Peak 117.17 °C
Heating Rate 10.00 °Cmin^-1
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System


^exo
ZnDiclofenac1e
10.02.2006 09:31:47
Integral 335.38 mJ
normalized 49.66 Jg^-1
Onset 169.92 °C
Peak 181.64 °C
Heating Rate 10.00 °Cmin^-1
ZnDiclofenac, 09.02.2006 17:36:44
ZnDiclofenac, 6.7540 mg
Onset 95.88 °C
Heating Rate 10.00 °Cmin^-1
10 mW
Integral -1487.85 mJ
normalized -220.29 Jg^-1
Onset 95.77 °C
Peak 112.39 °C
Heating Rate 10.00 °Cmin^-1
Integral -449.75 mJ
normalized -66.59 Jg^-1
Onset 259.20 °C
Peak 262.46 °C
Heating Rate 10.00 °Cmin^-1
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System

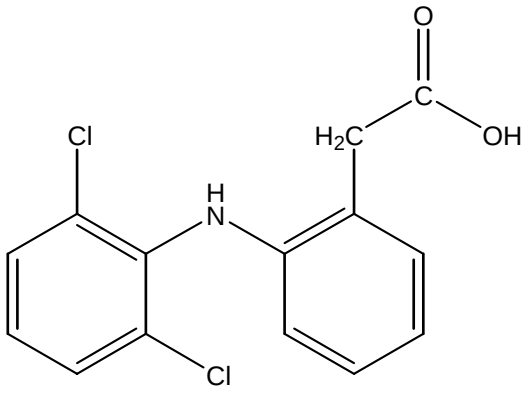

^exo
PbDiclofenac1e
10.02.2006 09:38:43
5
mW
PbDiclofenac, 09.02.2006 19:44:30
PbDiclofenac, 9.3240 mg
Extrapol. Peak 44.01 °C
Peak Value -1.88 mW
normalized -0.20 Wg^-1
Heating Rate 10.00 °Cmin^-1
Peak 59.61 °C
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STARe System


^exo
AlDiclofenac1e
10.02.2006 09:36:45
AlDiclofenac, 09.02.2006 19:01:47
AlDiclofenac, 16.5000 mg
20
mW
Extrapol. Peak 24.97 °C
Peak Value -24.04 mW
normalized -1.46 Wg^-1
Heating Rate 10.00 °Cmin^-1
Peak 98.48 °C
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
Lab: METTLER
METTLER TOLEDO STAR^e System

Appendix D

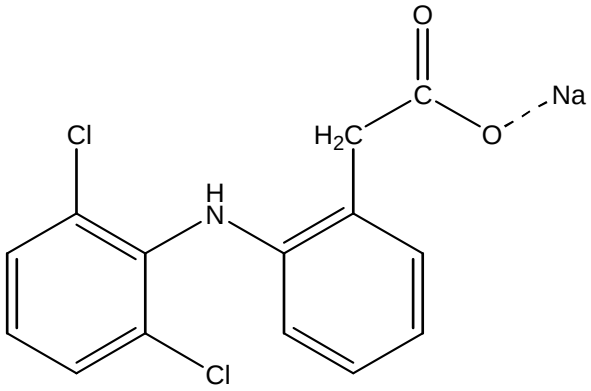
Diclofenac Salt Structures

Diclofenac Free Acid



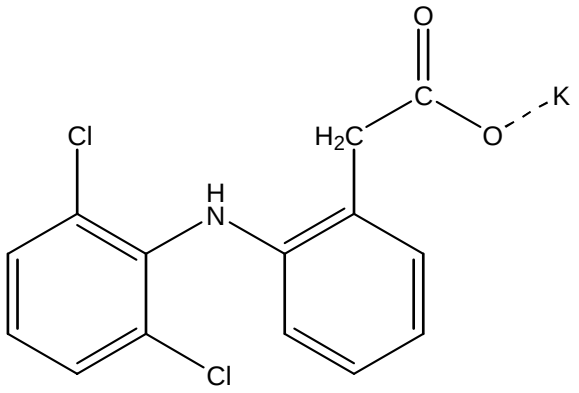
$C_{14}H_{11}Cl_2NO_2$
Exact Mass: 295.02
Mol. Wt.: 296.15
C, 56.78; H, 3.74; Cl, 23.94; N, 4.73; O, 10.80

Sodium Diclofenac



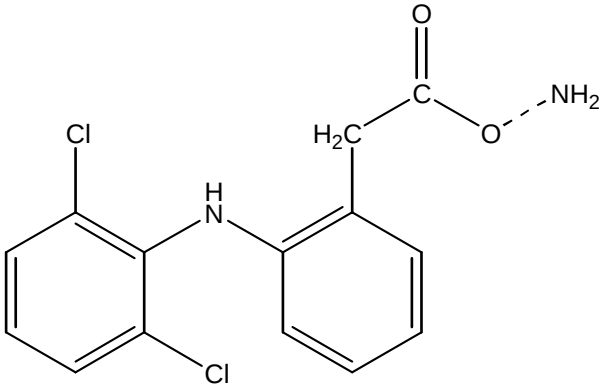
$C_{14}H_{10}Cl_2NNaO_2$
Exact Mass: 317.00
Mol. Wt.: 318.13
C, 52.86; H, 3.17; Cl, 22.29; N, 4.40; Na, 7.23; O, 10.06

Potassium Diclofenac



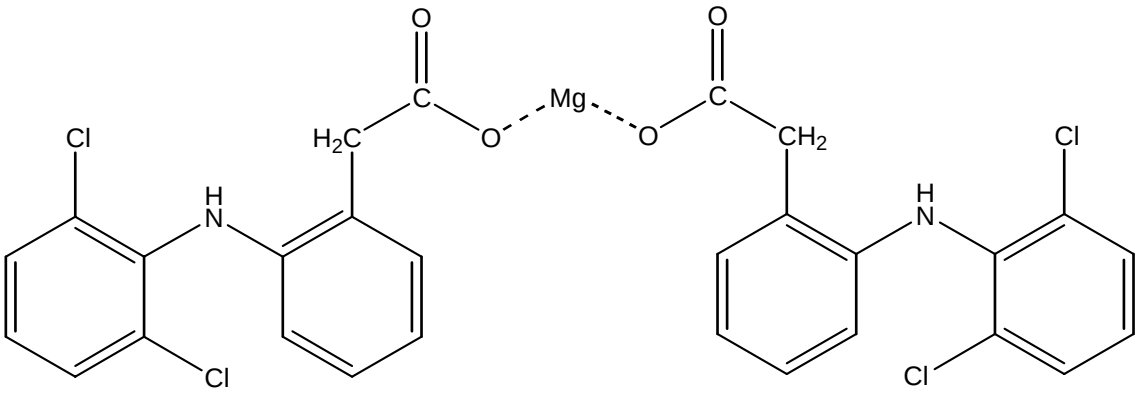
$C_{14}H_{10}Cl_2KNO_2$
Exact Mass: 332.97
Mol. Wt.: 334.24
C, 50.31; H, 3.02; Cl, 21.21; K, 11.70; N, 4.19; O, 9.57

Ammonium Diclofenac



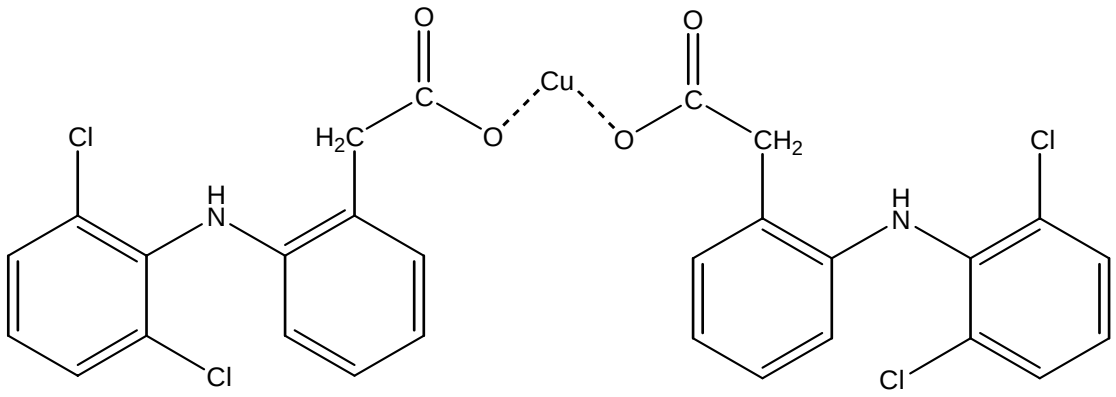
$C_{15}H_{16}Cl_2N_2O_2$
Exact Mass: 326.06
Mol. Wt.: 327.21
C, 55.06; H, 4.93; Cl, 21.67; N, 8.56; O, 9.78

Magnesium Diclofenac



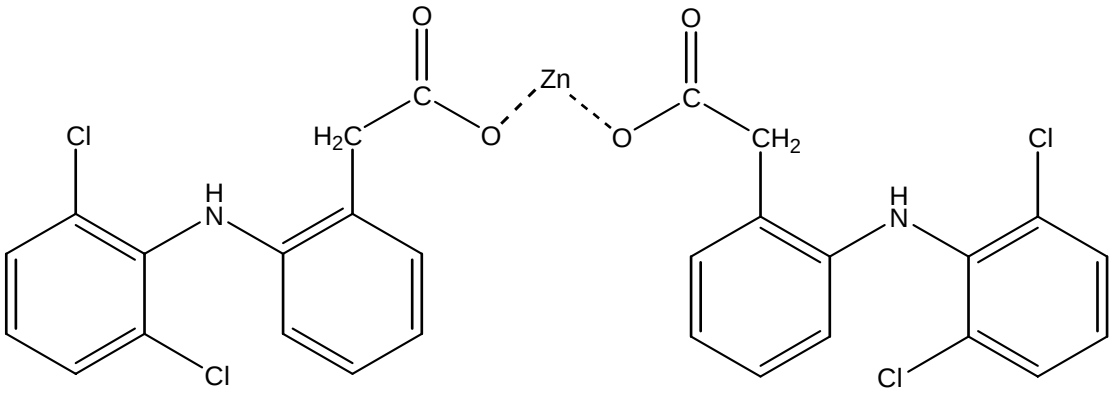
$C_{28}H_{20}Cl_4MgN_2O_4$
Exact Mass: 612.00
Mol. Wt.: 614.59
C, 54.72; H, 3.28; Cl, 23.07; Mg, 3.95; N, 4.56; O, 10.41

Copper Diclofenac



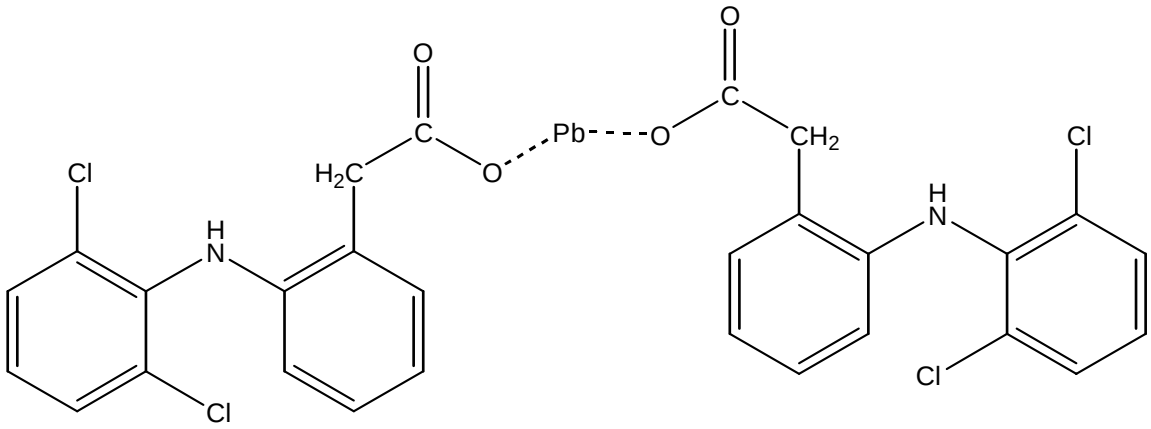
$C_{28}H_{20}Cl_4CuN_2O_4$
Exact Mass: 650.96
Mol. Wt.: 653.83
C, 51.44; H, 3.08; Cl, 21.69; Cu, 9.72; N, 4.28; O, 9.79

Zinc Diclofenac



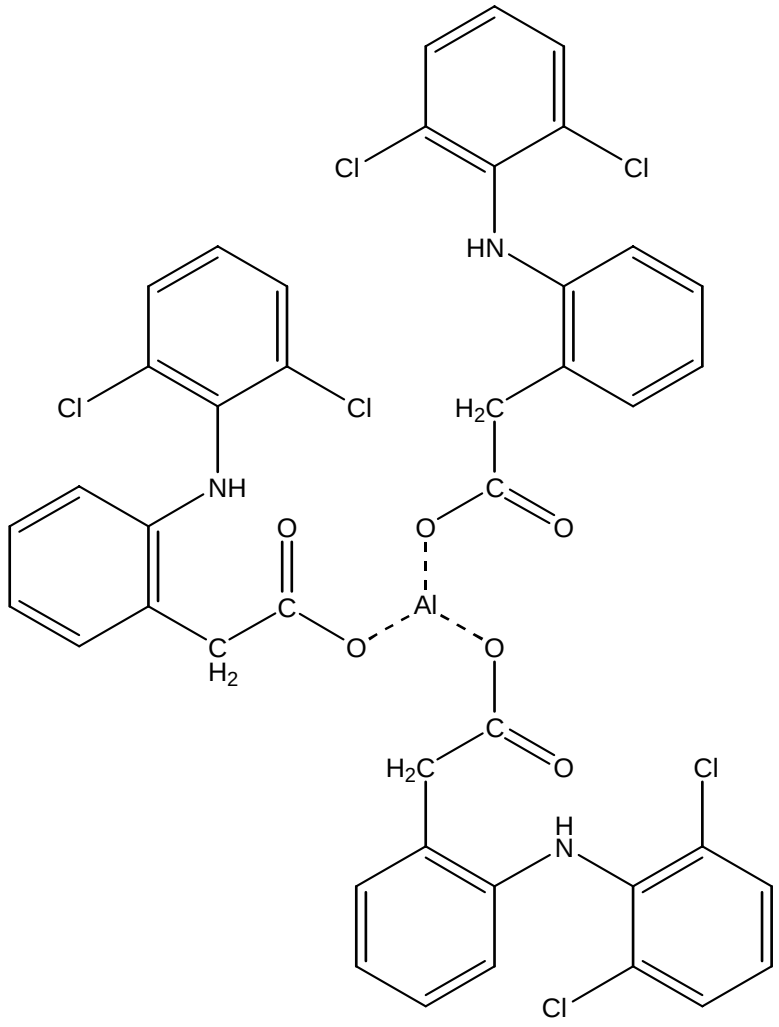
$C_{28}H_{20}Cl_4N_2O_4Zn$
Exact Mass: 651.95
Mol. Wt.: 655.67
C, 51.29; H, 3.07; Cl, 21.63; N, 4.27; O, 9.76; Zn, 9.97

Lead Diclofenac



$C_{28}H_{20}Cl_4N_2O_4Pb$
Exact Mass: 795.99
Mol. Wt.: 797.48
C, 42.17; H, 2.53; Cl, 17.78; N, 3.51; O, 8.02; Pb, 25.98

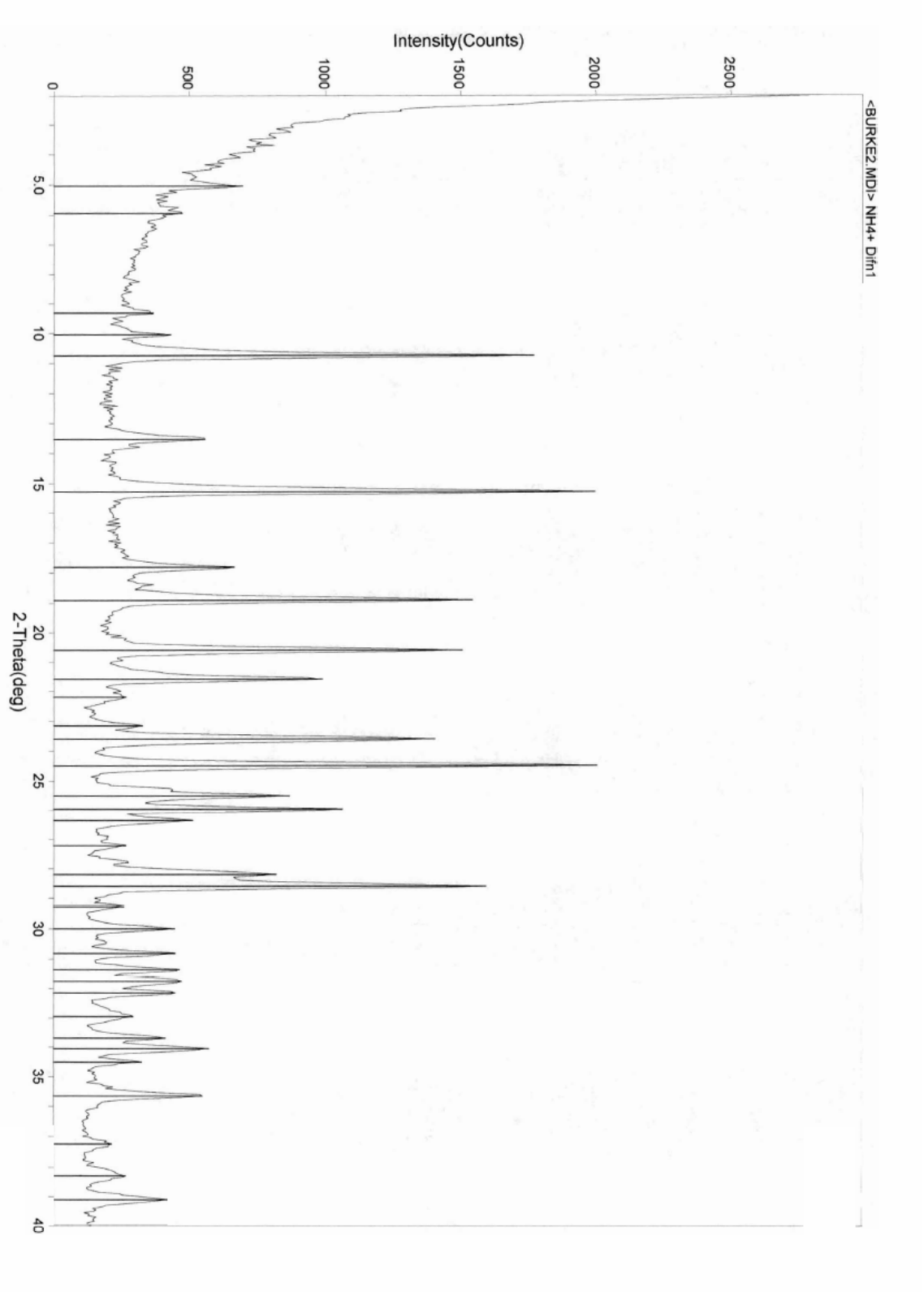
Aluminum Diclofenac



$C_{43}H_{34}AlCl_6N_3O_6$
Exact Mass: 925.04
Mol. Wt.: 928.44
C, 55.63; H, 3.69; Al, 2.91; Cl, 22.91; N, 4.53; O, 10.34

Appendix E

X-Ray Diffraction Chromatography


Intensity(Counts)
0
500
1000
1500
2000
2500
5.0
10
15
20
25
30
35
40
2-Theta(deg)
<BURKE2.MDI> NH4+ Diffn1

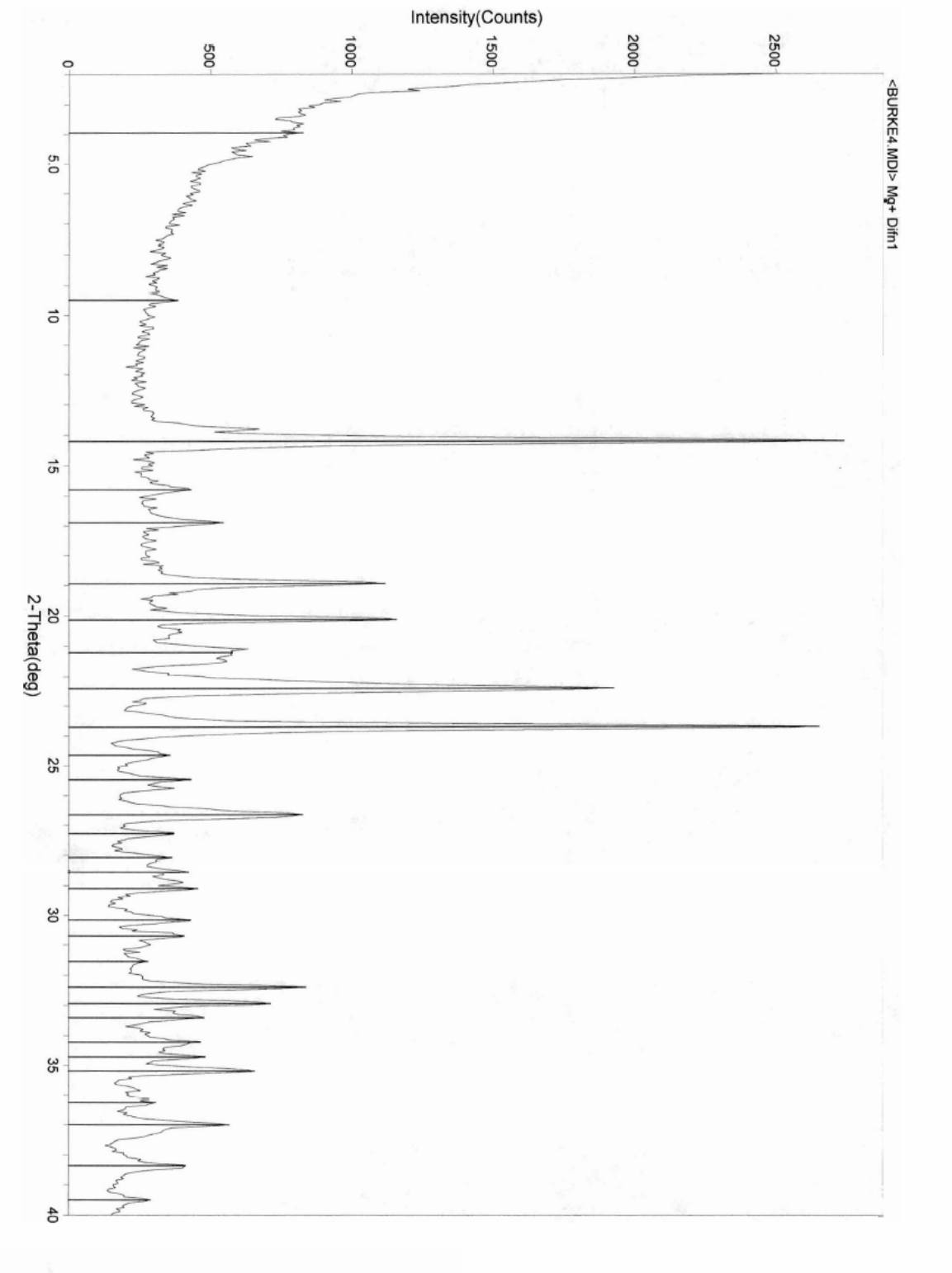
<BURKE2.MDI> NH4+ Difn1 [JADE - Peak List Report]

Scan Parameters: Range = 2.0-40.0/0.05, Slew = 2.4(d/m), Max-I = 2842, Anode = CU Date: 11-30-04@10:39

Search Parameters: Filter = 15(pts), Threshold = 3.0(esd), Peak-Cutoff = 0.3%, 2-Theta Zero Offset = 0.0(deg)

Note: Intensity data from raw counts, Summit peak location, Wavelength for computing d-spacing = 1.540562<CU, K-alpha1>

#	2-Theta	d(A)	h	k	l	BG	Peak	P%	Area	A%	FWHM	Size(A)	#
1	5.047	17.4964				467	227	12.3	35	8.7	0.122	>1000	1
2	5.941	14.8651				377	93	5.0	17	4.1	0.139	>1000	2
3	9.318	9.4835				242	119	6.5	20	4.8	0.129	>1000	3
4	10.045	8.7989				291	137	7.4	17	4.0	0.094	>1000	4
5	10.753	8.2208				264	1506	81.8	307	76.7	0.163	>1000	5
6	13.533	6.5374				201	354	19.2	113	28.2	0.255	523	6
7	15.285	5.7919				207	1790	97.2	400	100.0	0.178	>1000	7
8	17.811	4.9757				268	395	21.4	87	21.8	0.176	>1000	8
9	18.895	4.6927				252	1291	70.1	275	68.7	0.170	>1000	9
10	20.599	4.3082				213	1292	70.1	283	70.8	0.175	>1000	10
11	21.589	4.1128				195	791	42.9	175	43.8	0.177	>1000	11
12	22.195	4.0019				135	127	6.9	48	11.8	0.297	343	12
13	23.156	3.8379				135	188	10.2	45	11.2	0.191	>1000	13
14	23.602	3.7665				163	1241	67.4	322	80.6	0.207	746	14
15	24.489	3.6319				163	1842	100.0	388	97.1	0.168	>1000	15
16	25.500	3.4902				153	716	38.9	237	59.2	0.264	406	16
17	25.958	3.4297				168	893	48.5	211	52.7	0.188	>1000	17
18	26.353	3.3792				168	342	18.6	85	21.1	0.197	814	18
19	27.214	3.2742				158	103	5.6	16	3.9	0.122	>1000	19
20	28.202	3.1616				164	656	35.6	219	54.8	0.267	391	20
21	28.598	3.1188				151	1442	78.3	393	98.4	0.218	575	21
22	29.257	3.0500				163	92	5.0	10	2.5	0.085	>1000	22
23	29.994	2.9768				165	278	15.1	54	13.5	0.155	>1000	23
24	30.817	2.8990				197	248	13.5	40	9.9	0.128	>1000	24
25	31.356	2.8505				274	186	10.1	26	6.5	0.111	>1000	25
26	31.752	2.8158				176	292	15.9	105	26.1	0.286	347	26
27	32.147	2.7821				161	284	15.4	70	17.4	0.195	715	27
28	32.947	2.7163				151	138	7.5	40	9.8	0.228	499	28
29	33.687	2.6583				189	220	11.9	50	12.4	0.179	905	29
30	34.054	2.6306				147	423	23.0	112	28.0	0.211	572	30
31	34.508	2.5970				207	113	6.1	14	3.3	0.092	>1000	31
32	35.643	2.5168				127	419	22.7	122	30.4	0.232	472	32
33	37.253	2.4117				108	98	5.3	28	7.0	0.227	486	33
34	38.296	2.3483				124	135	7.3	46	11.4	0.269	371	34
35	39.103	2.3017				138	278	15.1	78	19.4	0.223	494	35
@	End-of-List												


Intensity(Counts)
0
500
1000
1500
2000
2500
2-Theta(deg)
5.0
10
15
20
25
30
35
40
<BURKE4.MDI> Mg+ Difn1

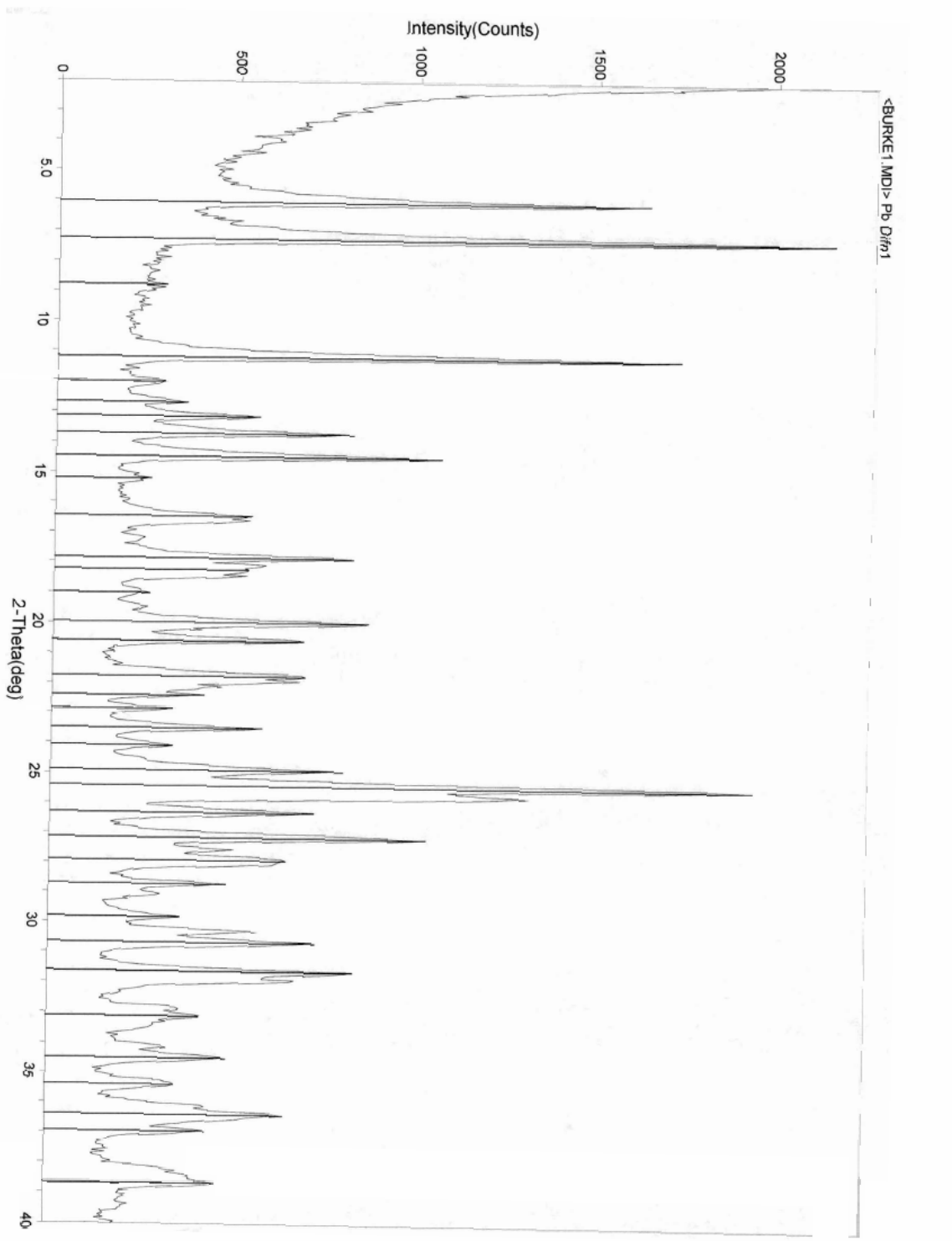
<BURKE4.MDI> Mg+ Difn1 [JADE - Peak List Report]

Scan Parameters: Range = 2.0-40.0/0.05, Slew = 2.4(d/m), Max-I = 2745, Anode = CU Date: 11-30-04@11:18

Search Parameters: Filter = 15(pts), Threshold = 3.0(esd), Peak-Cutoff = 0.3%, 2-Theta Zero Offset = 0.0(deg)

Note: Intensity data from raw counts, Summit peak location, Wavelength for computing d-spacing = 1.540562<CU, K-alpha1>

#	2-Theta	d(A)	h	k	l	BG	Peak	P%	Area	A%	FWHM	Size(A)	#
1	3.953	22.3324				701	124	5.0	15	2.1	0.095	>1000	1
2	9.486	9.3157				282	99	4.0	16	2.3	0.124	>1000	2
3	14.199	6.2325				271	2474	100.0	656	96.0	0.212	>1000	3
4	15.792	5.6070				263	165	6.7	37	5.4	0.178	>1000	4
5	16.901	5.2416				269	273	11.0	64	9.4	0.187	>1000	5
6	18.947	4.6799				293	823	33.3	224	32.8	0.218	740	6
7	20.131	4.4073				312	844	34.1	170	24.8	0.160	>1000	7
8	21.198	4.1878				326	250	10.1	104	15.2	0.332	290	8
9	22.403	3.9652				264	1665	67.3	565	82.8	0.271	398	9
10	23.707	3.7500				202	2454	99.2	683	100.0	0.222	598	10
11	24.648	3.6088				180	174	7.0	54	7.8	0.245	472	11
12	25.461	3.4954				183	245	9.9	49	7.1	0.158	>1000	12
13	26.654	3.3417				202	622	25.1	201	29.4	0.258	418	13
14	27.281	3.2663				200	168	6.8	28	4.0	0.131	>1000	14
15	28.085	3.1745				254	106	4.3	17	2.4	0.122	>1000	15
16	28.546	3.1244				161	262	10.6	105	15.3	0.318	301	16
17	29.102	3.0659				208	245	9.9	48	6.9	0.155	>1000	17
18	30.155	2.9612				214	214	8.6	50	7.2	0.183	951	18
19	30.699	2.9100				232	173	7.0	36	5.2	0.164	>1000	19
20	31.550	2.8334				216	59	2.4	7	0.9	0.082	>1000	20
21	32.405	2.7606				296	540	21.8	101	14.8	0.149	>1000	21
22	32.942	2.7167				314	396	16.0	76	11.0	0.152	>1000	22
23	33.404	2.6802				331	144	5.8	22	3.1	0.118	>1000	23
24	34.218	2.6183				289	173	7.0	29	4.2	0.131	>1000	24
25	34.708	2.5825				331	148	6.0	21	3.0	0.109	>1000	25
26	35.189	2.5483				278	377	15.2	76	11.0	0.160	>1000	26
27	36.248	2.4762				195	109	4.4	25	3.6	0.178	857	27
28	36.996	2.4278				177	388	15.7	121	17.6	0.248	421	28
29	38.366	2.3442				152	258	10.4	89	13.0	0.276	359	29
30	39.502	2.2794				165	121	4.9	23	3.3	0.148	>1000	30
@	End-of-List												


Intensity(Counts)
0
500
1000
1500
2000
<BURKE1.MDI> Pb Diffn1
5.0
10
15
20
25
30
35
40
2-Theta(deg)

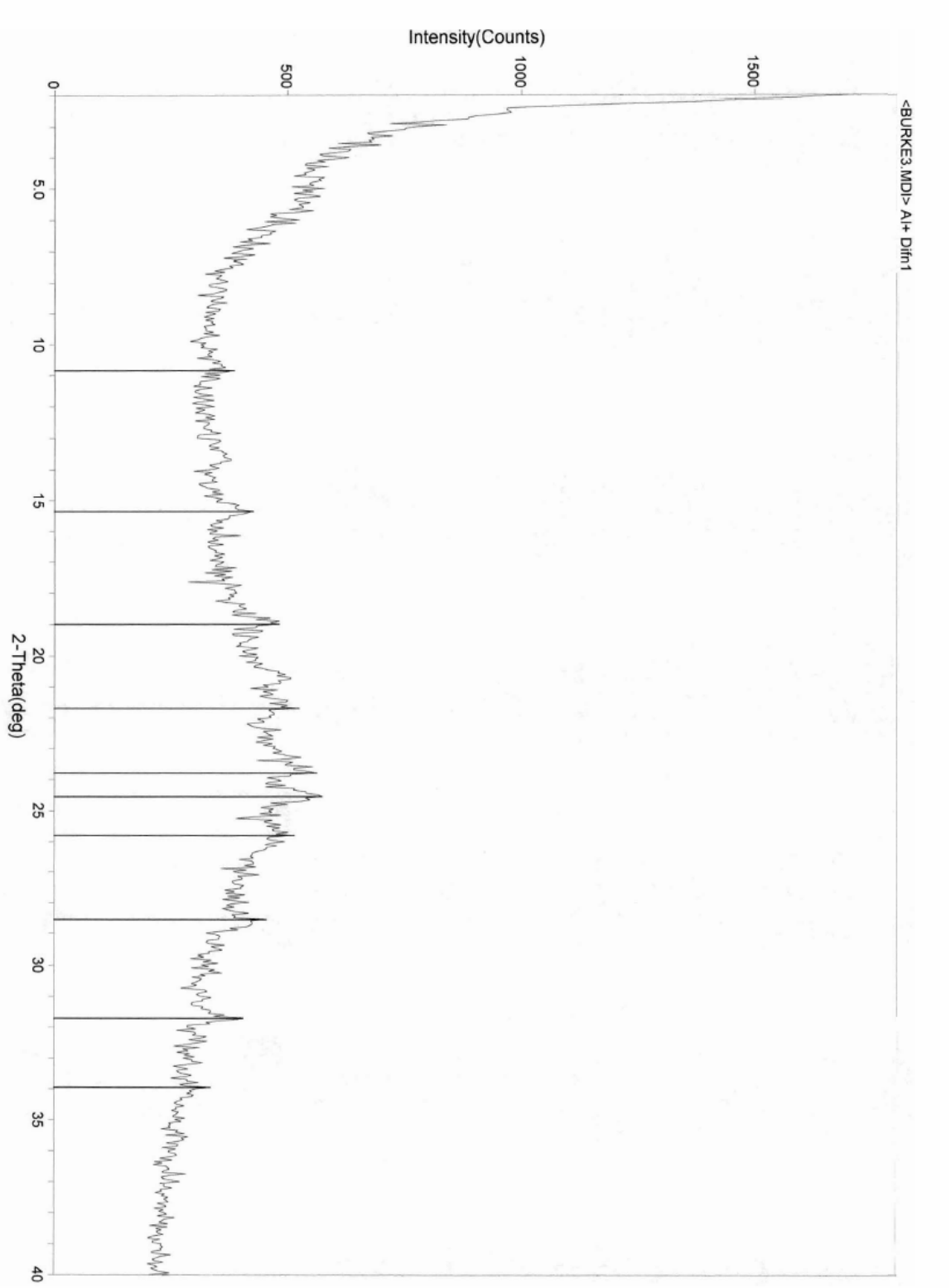
<BURKE1.MDI> Pb Difn1 [JADE - Peak List Report]

Scan Parameters: Range = 2.0-40.0/0.05, Slew = 2.4(d/m), Max-I = 2167, Anode = CU Date: 11-30-04@10:17

Search Parameters: Filter = 15(pts), Threshold = 3.0(esd), Peak-Cutoff = 0.3%, 2-Theta Zero Offset = 0.0(deg)

Note: Intensity data from raw counts, Summit peak location, Wavelength for computing d-spacing = 1.540562<CU, K-alpha1>

#	2-Theta	d(A)	h	k	l	BG	Peak	P%	Area	A%	FWHM	Size(A)	#
1	6.048	14.6005				420	1226	66.8	273	64.1	0.178	>1000	1
2	7.246	12.1900				333	1834	100.0	425	100.0	0.185	>1000	2
3	8.755	10.0921				244	55	3.0	6	1.2	0.076	>1000	3
4	11.187	7.9026				199	1542	84.1	336	79.0	0.174	>1000	4
5	12.020	7.3566				203	96	5.2	18	4.0	0.142	>1000	5
6	12.686	6.9721				275	88	4.8	10	2.2	0.085	>1000	6
7	13.141	6.7316				324	241	13.1	39	9.0	0.127	>1000	7
8	13.698	6.4591				296	531	29.0	99	23.2	0.148	>1000	8
9	14.451	6.1245				217	857	46.7	194	45.6	0.181	>1000	9
10	15.200	5.8243				184	79	4.3	17	3.8	0.165	>1000	10
11	16.462	5.3805				199	347	18.9	132	30.9	0.303	346	11
12	17.848	4.9656				207	624	34.0	176	41.3	0.225	682	12
13	18.250	4.8571				218	321	17.5	174	40.9	0.432	207	13
14	18.999	4.6673				204	61	3.3	7	1.6	0.088	>1000	14
15	19.959	4.4448				308	569	31.0	134	31.3	0.187	>1000	15
16	20.578	4.3125				151	545	29.7	134	31.4	0.196	>1000	16
17	21.752	4.0825				177	526	28.7	238	56.0	0.361	258	17
18	22.406	3.9647				316	104	5.7	10	2.2	0.073	>1000	18
19	22.875	3.8845				200	136	7.4	21	4.7	0.118	>1000	19
20	23.503	3.7820				194	391	21.3	82	19.1	0.166	>1000	20
21	24.089	3.6914				201	134	7.3	23	5.3	0.134	>1000	21
22	24.902	3.5727				199	616	33.6	196	45.9	0.253	440	22
23	25.398	3.5040				537	1423	77.6	327	76.8	0.183	>1000	23
24	26.308	3.3849				297	436	23.8	92	21.6	0.168	>1000	24
25	27.147	3.2821				207	842	45.9	241	56.5	0.228	530	25
26	27.903	3.1948				203	454	24.8	191	44.8	0.335	281	26
27	28.707	3.1072				192	298	16.2	59	13.9	0.158	>1000	27
28	29.821	2.9936				238	126	6.9	20	4.5	0.121	>1000	28
29	30.657	2.9138				205	536	29.2	150	35.3	0.224	528	29
30	31.614	2.8278				163	687	37.5	202	47.5	0.235	475	30
31	33.100	2.7042				180	243	13.2	129	30.2	0.422	211	31
32	34.497	2.5978				164	335	18.3	101	23.6	0.239	452	32
33	35.392	2.5341				170	186	10.1	58	13.4	0.245	431	33
34	36.401	2.4661				171	491	26.8	256	60.2	0.416	215	34
35	36.947	2.4309				158	284	15.5	79	18.4	0.220	514	35
36	38.650	2.3276				159	312	17.0	208	48.9	0.533	164	36
@	End-of-List												


Intensity(Counts)
0
500
1000
1500
5.0
10
15
20
25
30
35
40
2-Theta(deg)
<BURKE3.MDI> Al+ Difn1

<BURKE3.MDI> Al+ Difn1 [JADE - Peak List Report]

Scan Parameters: Range = 2.0-40.0/0.05, Slew = 2.4(d/m), **Max-I = 1720, Anode = CU** **Date: 11-30-04@11:01**

Search Parameters: Filter = 15(pts), Threshold = 3.0(esd), Peak-Cutoff = 0.3%, 2-Theta Zero Offset = 0.0(deg)

Note: Intensity data from raw counts, Summit peak location, Wavelength for computing d-spacing = 1.540562<CU, K-alpha1>

#	2-Theta	d(A)	h	k	l	BG	Peak	P%	Area	A%	FWHM	Size(A)	#
1	10.847	8.1496				312	72	63.7	8	26.0	0.086	>1000	1
2	15.355	5.7658				337	88	77.9	17	56.4	0.153	>1000	2
3	18.993	4.6686				392	88	77.9	12	39.1	0.106	>1000	3
4	21.699	4.0922				444	79	69.9	9	27.2	0.082	>1000	4
5	23.796	3.7361				465	97	85.8	12	39.6	0.097	>1000	5
6	24.549	3.6233				460	113	100.0	30	100.0	0.211	683	6
7	25.795	3.4509				434	79	69.9	10	31.0	0.094	>1000	7
8	28.558	3.1230				366	87	77.0	10	32.7	0.090	>1000	8
9	31.707	2.8197				294	110	97.3	20	65.6	0.142	>1000	9
10	33.951	2.6383				266	68	60.2	7	22.1	0.078	>1000	10
@	End-of-List												