

DIHYDROERGOTAMINE MESYLATE MONOHYDRATE SOLID STATE CHARACTERIZATION FOR INHALATION FORMULATION: POLYMORPH SCREENING AND DETERMINATION OF AMORPHOUS CONTENT

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INTRODUCTION

A polymorph screening study and quantitative method development for determination of amorphous/crystalline content were executed as a part of comprehensive physical properties characterization of the drug substance dihydroergotamine mesylate monohydrate (DHEMM). MAP Pharmaceuticals is using a proprietary form of this drug substance to develop an inhalation suspension formulation for the treatment of migraine¹.

(1) POLYMORPH SCREENING: The presence of different polymorphs in drug formulations can significantly impact crucial drug product properties, such as bioavailability, solubility, stability, and efficacy². The FDA's regulatory guidelines require polymorph screening as part of drug substance characterization to assess the probability of forming new polymorphs either as part of the drug substance synthesis or in the generation of a stable formulation^{3,4}.

EXPERIMENTAL: To assess the DHEMM, a proprietary form of the drug substance (lot R06009804-006, also used as the control sample in analysis) was dissolved and subjected to recrystallization from 22 different solvent systems with widely varying degree of polarity (see Table 1). Crystals were successfully isolated from 11 solvent systems. The crystal samples were subsequently analyzed by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA) for polymorph evaluation.

Solvent System	Dielectric Constant*	Relative Polarity (1-polar, 3-nonpolar)	Crystal Yield [mg]
Methanol Evaporation	32.6	1	313
Methanol Ethanol	24.3	1	124
Methanol Stabilized with Cold Ethanol	24.3	1	225
Methanol - Butyl Alcohol	17.8	2	128
Methanol - Methyl Isobutyl Ketone	12.4	2	268
Methanol - Ethyl Ether	8.1	2	284
Methanol - Butyl Acetate	5.1	2	306
Methanol Octanol	3.4	3	252
Methanol - tert Butyl methyl ether	2.6	3	309
Methanol - tert butyl methyl ether (2)	2.6	3	319
Methanol/Ethanol Hexane	2	3	311
Methanol - Water	88	1	No Crystals
Methanol - Acetonitrile	37.5	1	No Crystals
Water - Acetonitrile	36.6	1	No Crystals
Water - Acetone	20.7	1	No Crystals
Ethanol - Acetone	20.7	1	No Crystals
Methanol - Dichloromethane	9.1	2	No Crystals
Methanol - Tetrahydrofuran	7.5	2	No Crystals
Methanol - Xylene	2.4	3	No Crystals
Methanol - Toluene	2.4	3	No Crystals
Ethanol - Toluene	2.4	3	No Crystals

* source http://www.clippercontrols.com/info/dielectric_constants.html#0

Table 1. List of Solvent Systems used for DHEMM Polymorph Screen

RESULTS

PXRD: Figure 1 shows representative examples of PXRD spectra for the control sample and for crystal samples isolated from methanol-ethyl ether, methanol/ethanol, methanol/ethanol-hexane solvent systems. Although microscopic images showed different shapes and sizes for the crystal samples, all 11 crystal samples yielded comparable PXRD patterns with characteristic peaks at 9, 10, 11.5, 13.5, 15.5, 17, 20, and 25 degree 2-Theta, with some differences observed in the relative intensities of the peaks.

RESULTS continued

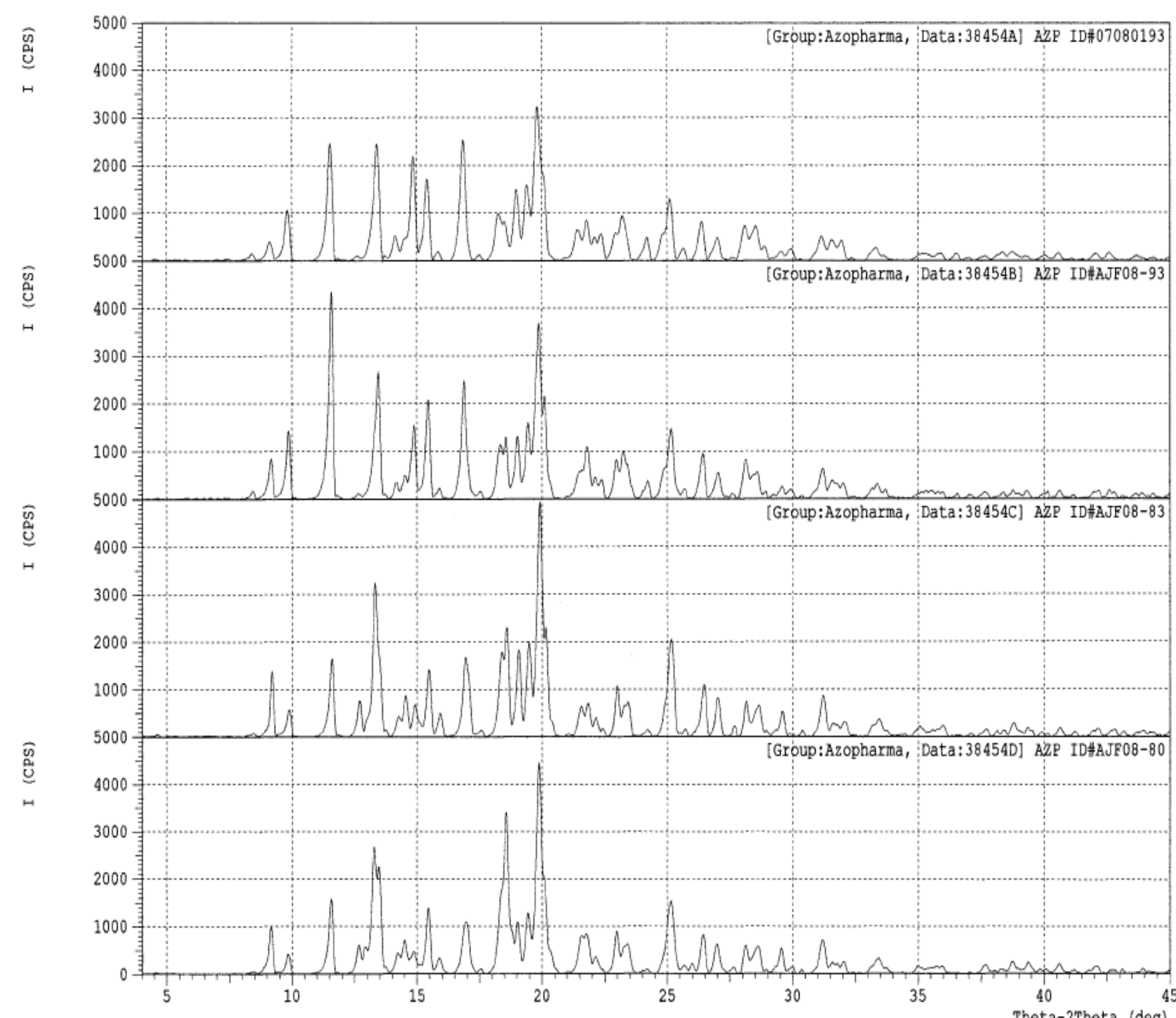


Figure 1. PXRD profile for the control sample (top) and isolated crystal samples (methanol-ethyl ether, methanol/ethanol, methanol/ethanol-hexane in descending order)

Thermal Analysis: Both DSC and TGA curves for all 11 crystal samples yielded comparable profiles with that of the control sample. Figure 2 shows the DSC curve for crystal sample isolated from methanol by evaporation (polar system) and from methanol-ethyl ether (non-polar system). Both samples show an initial broad peak with minimum around 82°C, which can be attributed to dehydration. The samples also show a main peak with melting point onset temperature of 231°C and 232°C. The melting points for all 11 crystal samples ranged from 228°C to 235°C. For comparison, the melting point from 20 unique drug substance lots ranged from 228.5°C to 234.8°C with a mean of 231.9°C.

Similarly, Figure 3 shows TGA curves for samples from polar (methanol by evaporation) and non-polar (methanol-ethyl ether) solvent systems. These samples show similar mass loss profile due to degradation between 240°C and 300°C, which is comparable to the control sample profile.

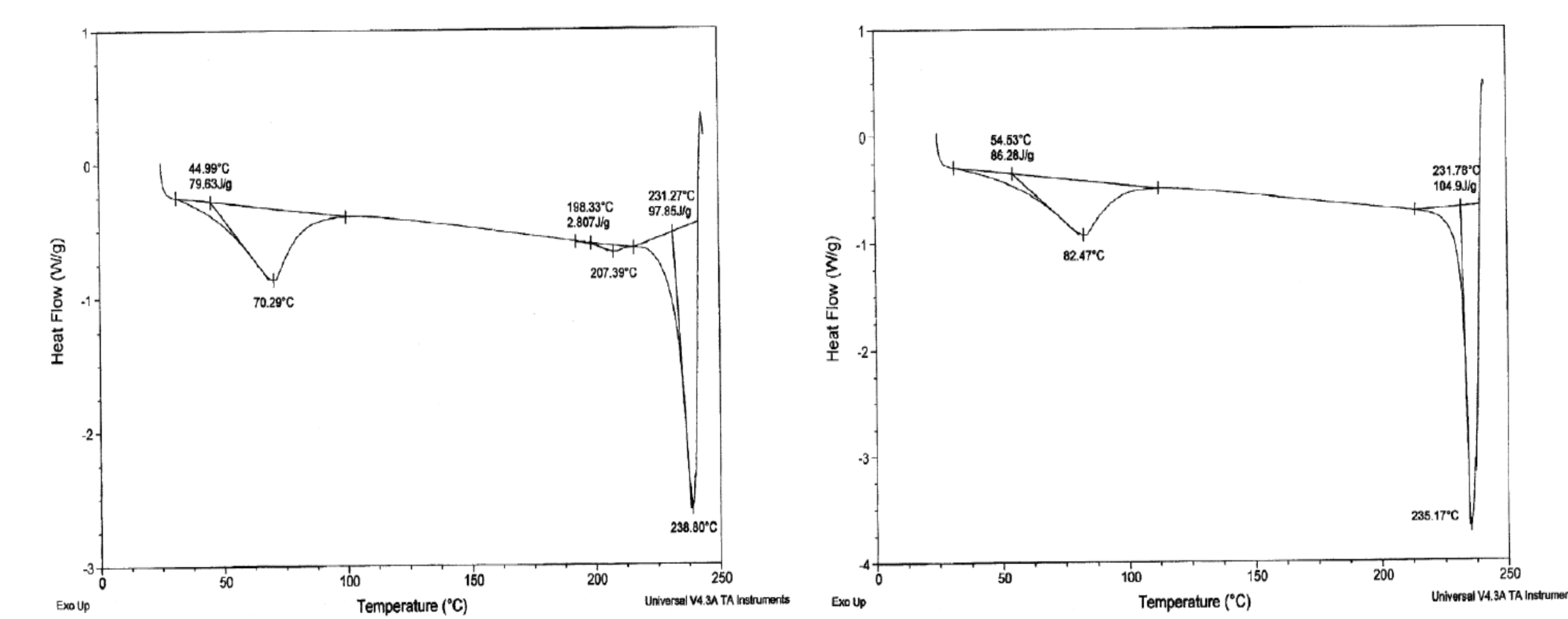


Figure 2. DSC profile for crystals obtained from polar and non-polar solvent system

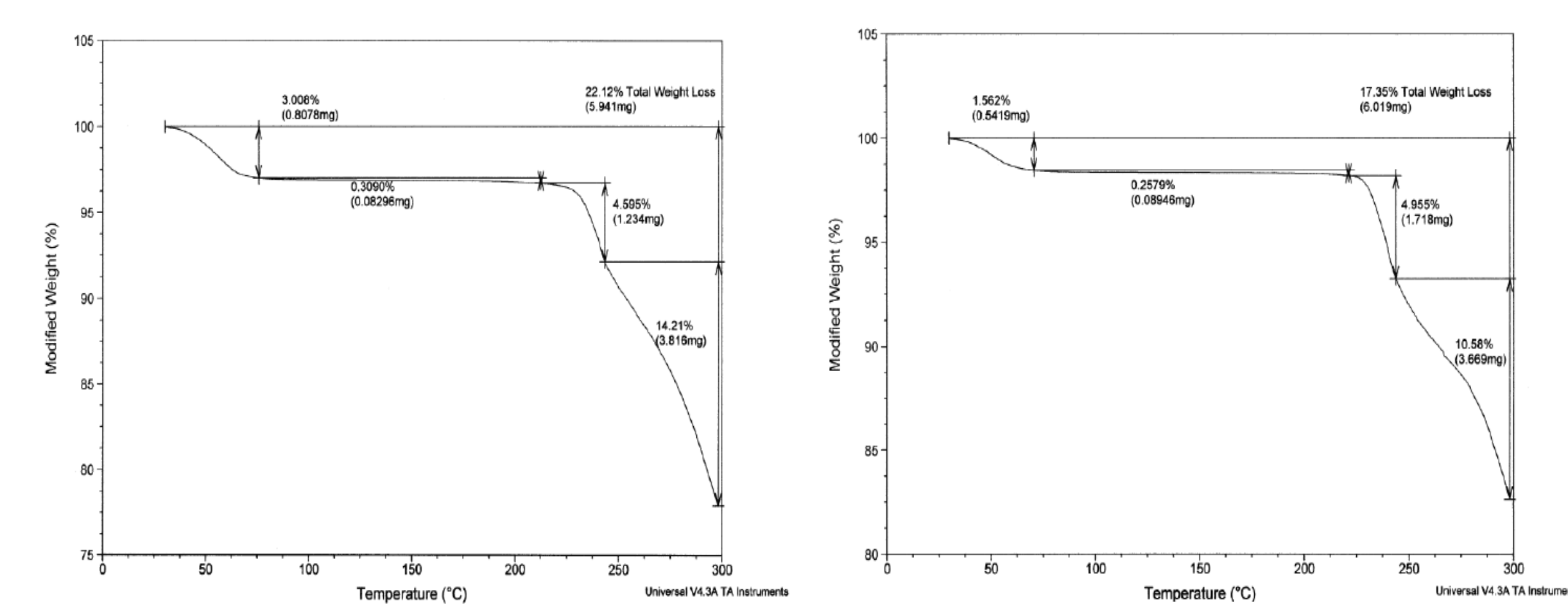


Figure 3. TGA profile for crystals obtained from polar and non-polar solvent system

RESULTS continued

(2) AMORPHOUS/CRYSTALLINE CONTENT QUANTITATION: Crystallinity is another solid state attribute that, if varied significantly, may impact the DHEMM product performance. The objective of this work was to develop a quantitative PXRD method using Shimadzu XRD-6000, X-Ray Powder Diffraction System and Kratos XRD-6000 V4.1 software.

EXPERIMENTAL: Approximately 200 mg ground sample of the proprietary DHEMM form (lot 07080017) was used to obtain PXRD patterns. A sample of the same lot was used to prepare an amorphous sample by dissolving in methanol and spray-drying. For the purpose of quantification, the PXRD patterns were scanned using the Bragg-Bretano configuration within the range of 5.0-40.0°. Quantification of the data was performed by loading the raw data (pattern) into the Kratos Percent Crystallinity window, utilizing the parameters outlined in Table 2 below.

Instrument Settings		Kratos Software Settings	
X-ray tube: Cu Ka, 40 kV, 30 mA		Lorentz Correction:	
Slits:		Theta M 13.3000 deg	
Divergence Slit	1.00 deg	Amorphous Peak	
Scatter Slit	1.00 deg	Parameter K	1.0000
Receiving Slit	0.30 mm	Auto/Manual	Auto
Scanning:		Pitch	28 points
Scan Range	5.0-40.0 deg	Width	5 points
Scan Mode	Continuous	Loop	38 times
Step Size	0.02°		
Scan Rate	1°/min		

Table 2. Instrument and software settings

The method assumes that only the two forms of DHEMM, crystalline and amorphous, are present in analyzed samples. Figure 4 shows the PXRD pattern for 100% amorphous and 100% crystalline DHEMM samples.

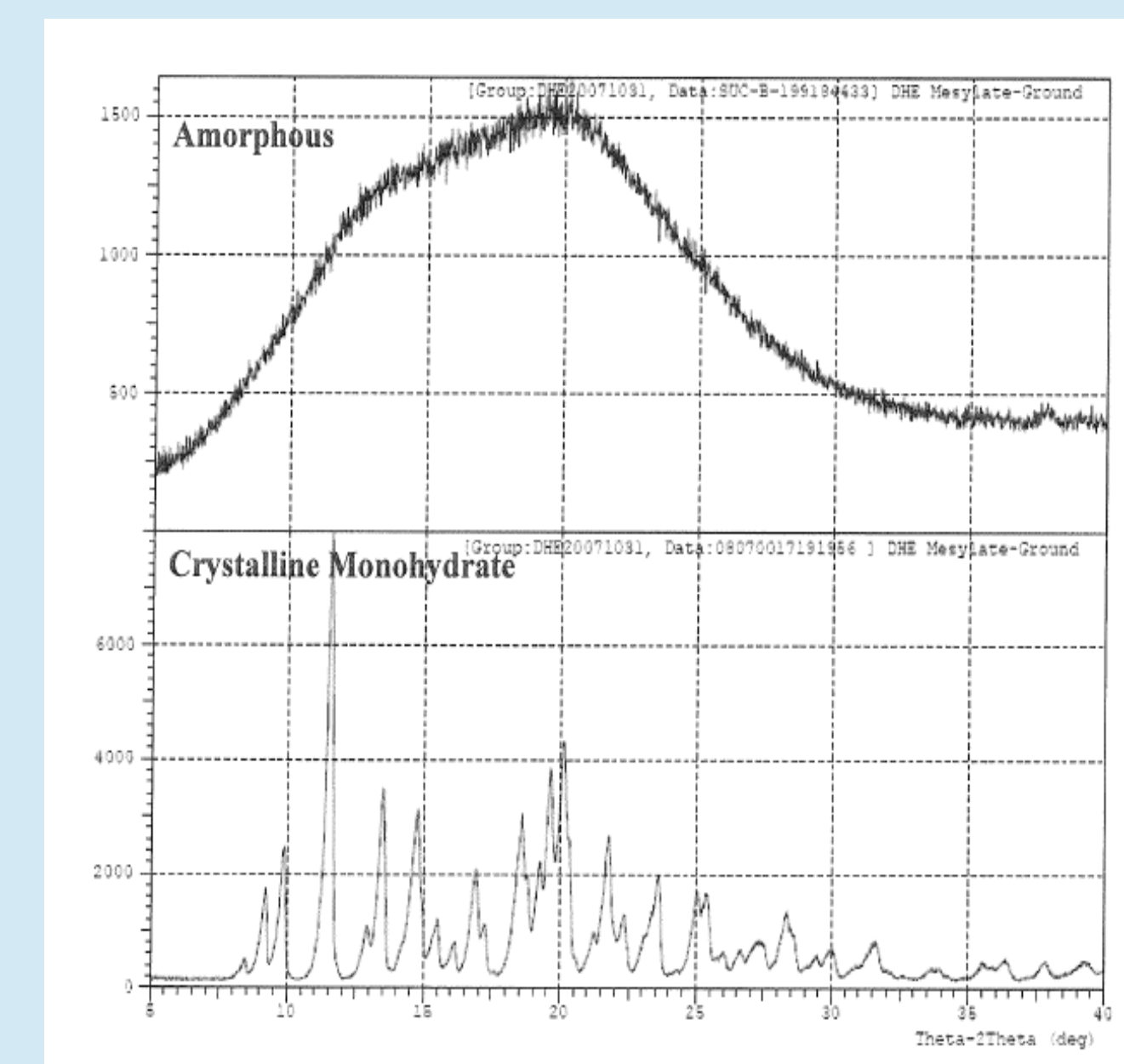


Figure 4. PXRD profile for amorphous and crystalline DHEMM

Test samples were prepared by mixing the amorphous and crystalline forms of DHEMM in seven ratios to produce mixtures with crystallinity between 66 and 97 Wt%. The method was evaluated for accuracy, precision and linearity.

Amorphous (mg) (lot SUC-B-198)	Crystalline (mg) (lot 07080017)	Amorphous (Wt%) (lot SUC-B-198)	Crystallinity (Wt%) (lot 07080017)
68	133	34	66
51	151	25	75
34	166	17	83
51	200	20	80
10	190	5	95
6	195	3	97
26	225	10	90

Table 3. Sample set prepared for method evaluation

RESULTS continued

The accuracy results are presented in Table 4. The mean recovery and error for all 7 samples was 101.3% and 2.5%, respectively. Two samples, Sample 3 and 5 have significantly higher errors (7.3 and 4.9%, respectively) than the remaining five. Further investigation is necessary to determine the cause. The precision data presented in Table 5 show an overall intermediate precision of 2.10%. The linearity fit shown in Figure 5 has correlation coefficient of 0.9164.

Sample Number	Gravimetric Weight Percent	Weight Percent Determined by XRPD					% Recovery	Abs. Error	
		Run 1	Run 2	Run 3	Mean	Std. Dev.			%RSD
1	66.14	66.96	71.20	67.13	68.43	2.400	3.508	103.5	2.3
2	74.76	73.75	75.80	77.44	75.66	1.849	2.443	101.2	0.9
3	82.89	88.08	90.51	91.91	90.17	1.938	2.149	108.8	7.3
4	79.74	81.34	79.38	77.35	79.36	1.995	2.514	99.5	0.4
5	89.68	84.92	85.80	83.67	84.80	1.070	1.262	94.6	4.9
6	94.88	94.34	96.30	95.79	95.48	1.017	1.065	100.6	0.6
7	96.93	97.63	98.35	97.95	97.98	0.361	0.368	101.1	1.1

Table 4. Accuracy for DHEMM crystalline/amorphous content

	Measured Percent Crystallinity	
	Analyst 1	Analyst 2
Mean (n=6)	86.31	88.06
Std. Dev.	2.038	1.185
%RSD	2.361	1.346
Total of 12 Analyses		
Mean (n=12)	87.18	
Std.Dev.	1.83	
%RSD	2.10	

Table 5. Intermediate Precision (6 replicates) for DHEMM crystalline/amorphous content

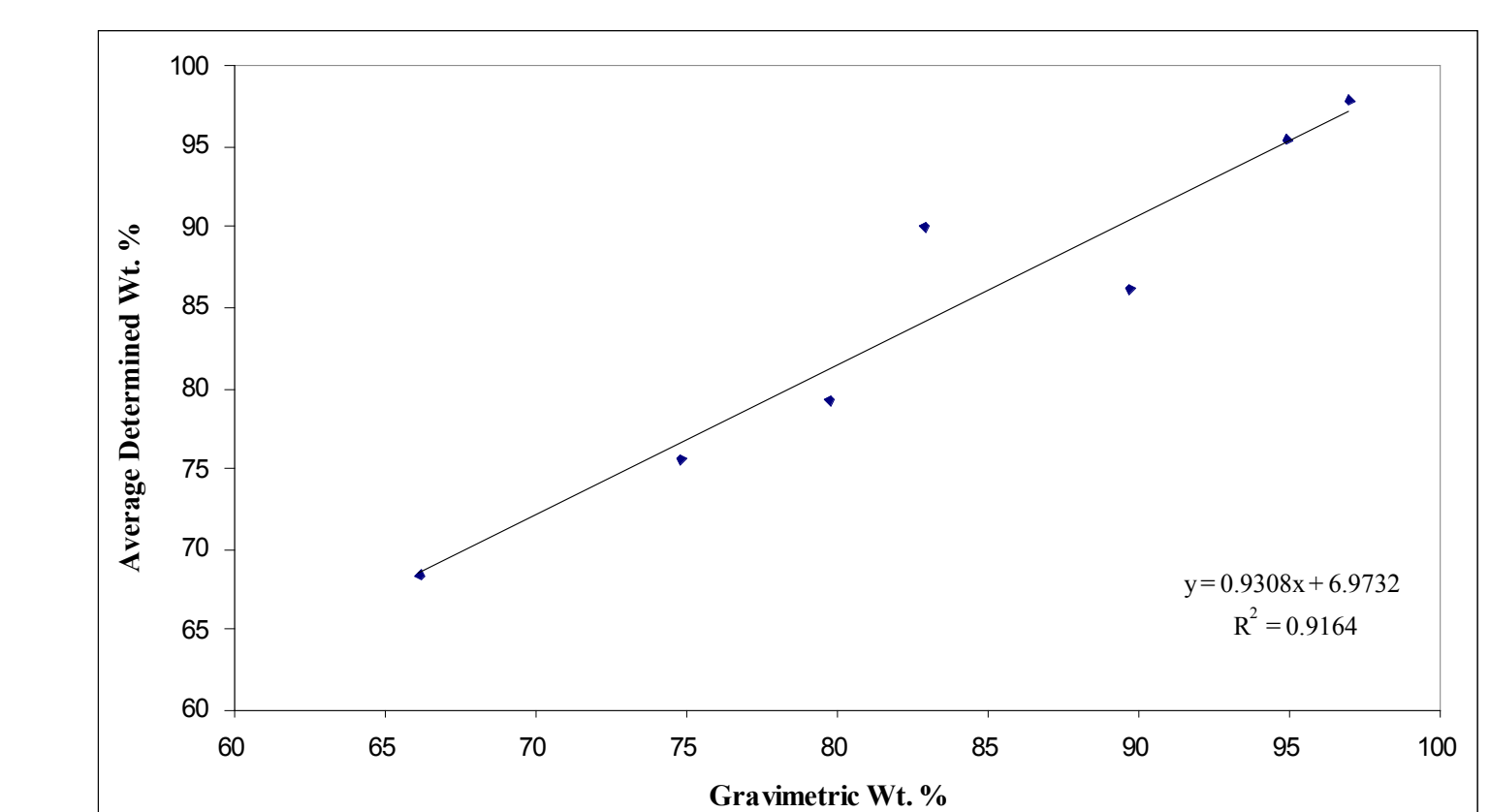


Figure 5. A plot of average vs. actual Wt% of crystalline DHEMM

CONCLUSION

POLYMORPH SCREEN: Although different solvent systems yielded crystals of varying size and shapes, the PXRD data indicated that all crystal samples were of the same polymorphic form. The PXRD patterns of new crystal samples were consistent with that of the sample control. The small melting point variations were caused by method variability and possibly by differing amounts of impurities or amorphous content in each crystal sample. These observations suggest that a new polymorphic form of DHEMM is not formed and, therefore, the probability of introducing a new polymorph into the suspension formulation for the migraine pMDI product is very low, particularly with a highly controlled solvent system and crystallization process currently used for particle formation.

CRYSTALLINITY: The PXRD method showed capability to predict the sample crystallinity on the average to within 2.5% of the actual crystalline content with linear fit showing R2 of 0.9164. Two samples out of the seven, the 89.7 and 82.9 Wt% appeared as outliers, with absolute errors of 4.9 and 7.3%, respectively. An investigation will be necessary to understand the outlier cause and potentially further improve method accuracy.

- References
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