Quantitative Measurement of Indomethacin Crystallinity in Indomethacin-Silica Gel Binary System Using Differential Scanning Calorimetry and X-ray Powder Diffractometry

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ABSTRACT

Differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRPD) methods were developed for the quantitative analysis of the crystallinity of indomethacin (IMC) in IMC and silica gel (SG) binary system. The DSC calibration curve exhibited better linearity than that of XRPD. No phase transformation occurred in the IMC-SG mixtures during DSC measurement. The major sources of error in DSC measurements were inhomogeneous mixing and sampling. Analyzing the amount of IMC in the mixtures using high-performance liquid chromatography (HPLC) could reduce the sampling error. DSC demonstrated greater sensitivity and had less variation in measurement than XRPD in quantifying crystalline IMC in the IMC-SG binary system.

KEYWORDS: Differential scanning calorimetry, X-ray powder diffractometry, crystallinity, quantitative analysis, indomethacin, silica gel, amorphization.

INTRODUCTION

It is well known that solid-state phase transformation could occur in the formulations due to processing (granulation, drying, milling, compression, etc.) or drug-excipient(s) interaction.[1-4] Such phase transformation could affect the properties (dissolution, bioavailability, stability, etc.) of the final products. Therefore, the development of qualitative and quantitative analytical methods to identify the cause and monitor the phase transformation in the formulations is essential for the quality control of the final products.

Different quantitative analytical methods have been developed to measure the crystallinity of one compound in the mixtures. For simple binary systems such as amorphous-polymorph or polymorph-polymorph mixtures of the same compound, the most frequently used quantitative methods include Fourier-transformed Raman (FT-Raman),[5,6] near-infrared (NIR),[7] solid state nuclear magnetic resonance (NMR),[8] Fourier-transformed infrared (FTIR),[9] and X-ray powder diffraction (XRPD).[10] However, in the pharmaceutical industry, active compounds typically are in admixture with several excipients. As systems become more complicated (more excipients involved), the interference introduced by excipients makes more difficult the development of proper quantitative methods to determine the crystallinity of compounds. Attempts have been made to quantitatively measure the crystallinity of drugs in the presence of 1 or 2 excipients using NIR spectroscopy[11] or XRPD.[12] Quantitative XRPD methods have also been developed to measure the crystallinity of drugs in the complete formulation blends including fillers and a lubricant[13] and attempts have also been made for the tablets.[14]

Differential scanning calorimetry (DSC) is often used as a qualitative method to study amorphous and polymorph materials in pharmaceutical mixtures.[15-17] Quantitative crystallinity estimation using DSC has been reported, and crystallinity has been calculated by the difference between the heat released for crystallization and the heat required for fusion of the sample divided by the estimated heat of fusion of a 100% crystalline sample.[18,19] The limitation of such crystallinity estimation is that amorphous material in the mixtures recrystallizes during DSC measurement and the amount of crystalline measured by DSC includes both the original crystalline in the sample and the crystalline transformed from amorphous during DSC measurement. The exact amount of crystalline transformed from amorphous during DSC heat process is hard to determine. The estimated crystallinity reported in these studies is based on several assumptions such as the heat of crystallization and heat of fusion are the same at different temperatures and this may not be true. Therefore, DSC may not be a good quantitative method to estimate crystallinity in the mixtures if phase transformation happened during measurement. Other analytical methods should be considered in such a situation. There have been increased interests in using porous adsorbents to improve the dissolution rate of poorly water-soluble drugs either by simple mixing or solid dispersion,[20-22] and DSC has been routinely used as a

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qualitative method to study such phase transformation in crystalline drugs/porous adsorbents mixtures.[23-25] Here, we report the development of quantitative methods using both DSC and XRPD to measure the crystallinity of indomethacin (IMC) in mixtures with the adsorbent, silica gel (SG). The results obtained by these 2 methods were also compared. Since crystalline IMC lost some of its crystallinity after mixing with SG, the quantitative estimation of IMC crystallinity by DSC was verified to confirm that no phase transformation of IMC occurred during DSC measurements.

Materials and Methods

Materials

IMC (≥99%) was purchased from Sigma (St Louis, MO) in its γ-crystalline form. This has been confirmed by our DSC and XRPD analysis. α-Form crystalline IMC was prepared from γ-form crystalline IMC using method reported by Otsuka et al.[25] DSC and XRPD analysis confirmed the substance prepared to be α-form crystalline IMC. Amorphous IMC was prepared by melting γ-form crystalline IMC in a 2-inch aluminum foil pan and quench-cooling the melt in liquid nitrogen. The glassy amorphous IMC was ground in a mortar and pestle. Powders with particle size <74 μm were collected by sieving through a No. 200-mesh screen. Polar light microscopy and XRPD confirmed the collected samples to be amorphous. Silica gel with pore sizes of 40Å was purchased from Aldrich (St Louis, MO). Acid-washed glass beads were purchased from Sigma.

DCS analysis

Samples were analyzed with a Perkin Elmer DSC-7 (model 7719, Boston, MA) apparatus at a scan rate of 5°C/min under a flow of dry N_2 gas (50 mL/min) from 25°C to 170°C. Samples were sealed in the aluminum Dupont pans.

XRPD analysis

A Rigaku Geigerflex X-ray diffractometer (model 4037V1, Tokyo, Japan) with Ni filtered Cu-Kα radiation was used under the following experiment conditions: voltage, 40kV; current 40mA; divergence slit, 1/2°; scatter slit, 1/2°; receiving slit, 0.3mm; receiving slit, monochrometer, 0.6 mm; scanning speed, 3.0 degree/min; scanning range, 3 to 50 degree (2θ).

High-Pressure Liquid Chromatography Analysis

The amount of IMC in the mixtures analyzed by DSC was measured by HPLC to reduce the potential errors from inhomogeneous mixing as well as sampling since only a very small amount of sample was used (4-7 mg). After DSC study, the sample pan was cut open using a scissors, and IMC in the mixture was extracted out by 10 mL of phosphate buffer (pH 6.8). After dilution, sample was analyzed by an Agilent HP1100 system (Palo Alto, CA) with a Supelcostil C_{18} column. Absorbance was measured by a UV detector at 254 nm, and the mobile phase consisted of 0.01M phos phate buffer in 40% acetonitrile and 60% H_2O.

Preparation of Mixtures for Calibration Curves

Mixtures of γ-form crystalline IMC and fumed silica were prepared for the XRPD calibration curve. However, large variation in the measurement of the total peak areas of the diffraction peaks was found due to the difficulty of achieving mixing homogeneity because of the fluffy nature of fumed silica. Therefore, an alternative material was used to prepare the mixtures for the calibration curve. Acid-washed glass beads (GB) (60-200 μm) that are nonporous amorphous materials and did not cause phase transformation of γ-form crystalline IMC as confirmed by DSC study were used to prepare the γ-form crystalline IMC-GB mixtures for XRPD calibration curve. Different known amounts of γ-form IMC (5%-100% in the mixtures) were mixed with GB in 60-cc high-density polyethylene (HDPE) bottles by a T2C Turbula shaker-mixer at 62 rpm for 15 minutes. Five independent samples from each mixture were analyzed by both XRPD and DSC. XRPD calibration curve was prepared by plotting the relative total peak areas versus the percentage crystalline IMC in the mixtures.

DSC calibration curve was prepared using different known amounts (0.05-5 mg) of pure γ-form IMC. The areas under the melting endotherm around 162°C were calculated and plotted versus the amounts of γ-form crystalline IMC to obtain the calibration curve.

Preparation of Mixtures With Unknown Amount of Crystalline IMC

IMC and SG were mixed at different known ratios in 60-cc HDPE bottles by a T2C Turbula shaker-mixer at 62 rpm for 15 minutes. Crystalline to amorphous phase transformation of IMC occurred during the mixing as confirmed by both DSC (reduced melting peak and XRPD (reduced total diffraction peak area) studies. Crystalline IMC remaining in these mixtures were quantitatively measured by both DSC and XRPD. Data were the means of 3 independent measurements. Results from DSC and XRPD measurements were compared.

Instrument Reproducibility and Method Error

Instrument reproducibility of XRPD was determined by measuring the crystallinity of one IMC-SG sample (30:70) 10 times without removing the sample. Method error of

XRPD was estimated by measuring the crystallinity of 5 independent samples of IMC-SG mixture (30:70).

High purity indium metal was used to calibrate the DSC instrument. The starting melt temperature and heat of melting of different runs were compared for the reproducibility of DSC instrument. Method error of DSC mainly came from 2 sources. One is from inhomogeneous mixing and small sampling size (4-7 mg) in DSC study. Since the sample size is so small in DSC study, the actual amount of crystalline IMC in the mixture could deviate from the theoretical amount due to errors in sampling. Such deviation could be substantial and lead to a large variation in quantifying the crystallinity of IMC among samples. This error could be reduced by analyzing the amount of IMC in the mixtures using HPLC. Another error comes from the possible phase transformation of IMC during the heating processing. This error could limit the application of DSC as a quantitative method. In order to use DSC as a quantitative analytical method for measuring the crystallinity of IMC in IMC-SG mixtures, it is important to prove that phase transformation of IMC does not happen during DSC measurement. In this study, IMC-SG (30:70) mixture was prepared. Half of the sample was put in an oven (Isotemp Oven, model 750G, Fisher Scientific, Pittsburgh, PA), and the other half was used as control. The temperature of the oven was manually increased from 21°C to 155°C at a rate of 5°C/min to mimic the heating process of DSC experiments. The crystallinity in the heat-treated and untreated samples was determined by both DSC and XRPD. Data are the means of 5 independent measurements.

Results and Discussion

DSC Calibration Study

Figure 1 shows the DSC calibration curve by plotting the areas under the melting endotherm versus the amount of pure γ-form crystalline IMC used. Linear regression of the data produced a straight line going through the origin with an $r^2 = 1$. This indicates that the area of melting peak is directly correlated to the quantity of the γ-form crystalline IMC in the sample pan. When the area under melting endotherm is adjusted by the amount of γ-form crystalline IMC, heat of fusion of γ-form crystalline IMC is generated. In this study, the heat of fusion of γ-form crystalline IMC is obtained from the slope of the calibration curve and it is 105.6 J/g, which is similar to the reported value.[26]

The limit of detection was estimated by calculating 3 standard deviations and the limit of quantitation was estimated by calculating 10 standard deviations. The standard deviation was calculated from 10 independent pure crystalline IMC samples. The standard deviation of the 10 measurements was 0.3% giving a limit of detection of 0.9% and a limit of quantitation of 3%.

The amount of crystalline IMC in IMC-GB mixtures was determined by DSC. The crystallinity of IMC is defined as the percentage of crystalline IMC remaining in the mixtures compared with the initial crystalline IMC (assumed to be 100% crystalline). Five independent samples from each mixing ratio were analyzed and peak area was calculated for each sample.

To predict the crystallinity of IMC (γ-form) in the mixtures by DSC, following equation was used:

$$Crystallinity\ of\ IMC = \frac{A}{Wt \times S} \times 100\%, \qquad (1)$$

where, A is the area under the melting endotherm; Wt is the amount of IMC in the mixture (as measured by HPLC); and S is the slope of DSC calibration curve.

Table 1 shows the results of crystallinity of γ-form IMC in IMC-GB mixtures predicted by DSC using the theoretical amounts of IMC in the mixture and the amounts of IMC determined by HPLC. It was clear that predicting crystallinity using HPLC-determined amounts of IMC has less variation among samples since it reduced the errors associated with mixing and sampling. This was true for all mixtures except for 100% crystalline sample, where predicted crystallinity using theoretical amount of IMC in the mixtures showed less variation than crystallinity predicted using HPLC-determined amount of IMC. This finding indicates that HPLC analysis could introduce new error, probably during sample preparation. Crystallinity predicted using the amount of IMC determined by HPLC showed smaller SD and percentage relative standard deviation (RSD) values in the measurements, indicating that HPLC analysis-introduced error is much less than the error associated with mixing and sampling. From Table 1, the predicted crystallinity for mixtures with various mixing ratio is ~100%. In DSC profiles, only one melting endotherm was found at around 162°C

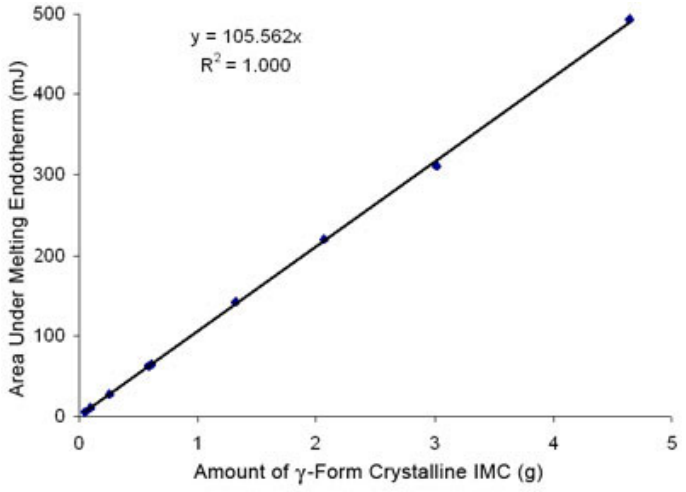

Figure 1. DSC calibration curve of γ-form crystalline IMC.

Table 1. Results of Crystallinity of γ-Form IMC in IMC-GB Mixtures as Predicted by DSC Using Theoretical Amount of IMC in the Mixtures and Using Actual Amount of IMC as Determined by HPLC (n = 5)*

% IMC in Mixture	Predicted Crystallinity (using theoretical IMC) Mean (SD, %RSD)	Predicted Crystallinity (using actual IMC) Mean (SD, %RSD)
5	102.1 (8.4, 8.2)	99.2 (2.1, 2.2)
10	99.8 (5.7, 5.7)	99.4 (2.0, 2.0)
20	98.6 (6.7, 6.8)	99.3 (1.5, 1.5)
30	99.8 (3.6, 3.6)	100.0 (2.0, 2.0)
50	98.9 (4.9, 4.9)	99.2 (1.3, 1.3)
70	101.8 (5.3, 5.2)	100.0 (1.8, 1.8)
90	101.1 (3.7, 3.7)	99.8 (1.5, 1.5)
100	100.5 (0.3, 0.3)	100.2 (1.2, 1.2)

*IMC indicates indomethacin; GB, glass beads; DSC, differential scanning calorimetry; HPLC, high-performance liquid chromatography; and %RSD, relative standard deviation.

for all IMC-GB samples analyzed. This finding indicates that γ-form crystalline IMC remained as γ-form and no phase transformation occurred in IMC-GB mixtures during the study. Therefore, IMC-GB mixtures could be used to validate the DSC calibration curve.

Figure 2 shows the correlation between the predicted crystalline IMC in IMC-GB mixtures obtained using DSC calibration curve and the actual crystalline IMC in the IMC-GB mixtures as determined by HPLC. A straight line going through the origin with an $r^2 = 1$ and a slope of 1.0 was found. This study has validated the DSC calibration curve. It has shown that DSC method could accurately predict the crystalline IMC in the mixtures.

XRPD Calibration Study

Figure 3 shows the XRPD profiles of GB, SG, amorphous IMC, pure α-form crystalline, pure γ-form crystalline IMC, and IMC-GB (50:50) mixture. SG and GB are amorphous and show similar "amorphous halo" patterns as amorphous IMC. The diffraction pattern of IMC-GB shows a combined diffraction pattern of pure γ-form crystalline IMC and GB. It is assumed that GB did not interfere with the XRPD analysis and its background diffraction was negligible if the diffraction peak areas are integrated above the amorphous halo curve.

Figure 4 shows the XRPD calibration curve of IMC-GB mixtures by plotting the percentage total peak area above the "amorphous halo" versus the theoretical percentage crystalline IMC (γ-form) in the mixtures. It is assumed that the total peak area of 100% crystalline γ-form IMC is 100%. Linear regression of the data produced a straight line going through the origin with an $r^2 = 0.989$ and a slope of 0.935.

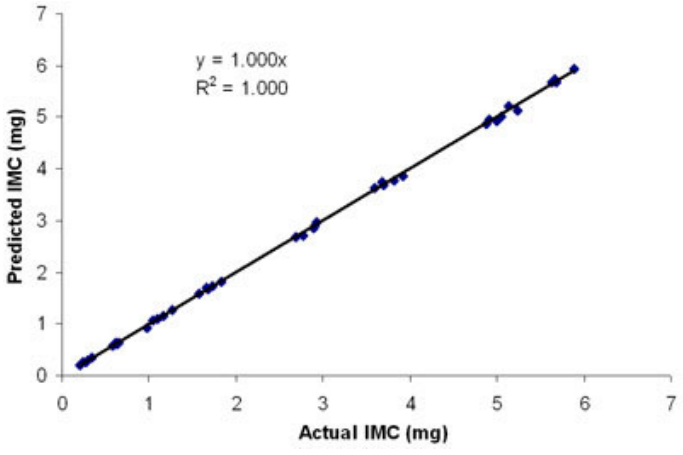

Figure 2. Correlation between predicted amount of crystalline IMC in IMC-GB mixtures obtained using DSC calibration curve and actual amount of IMC in IMC-GB mixtures as determined by HPLC.

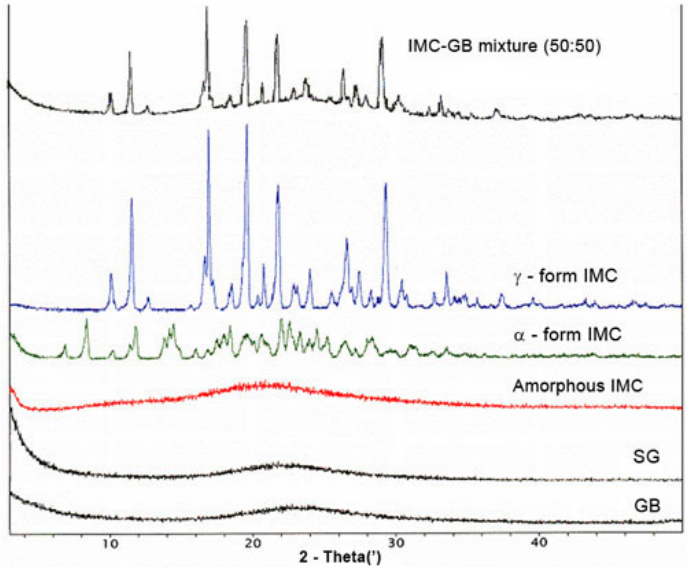

Figure 3. XRPD patterns of GB, SG, amorphous IMC, α-form IMC, γ-form IMC, and IMC-GB mixture (50:50).

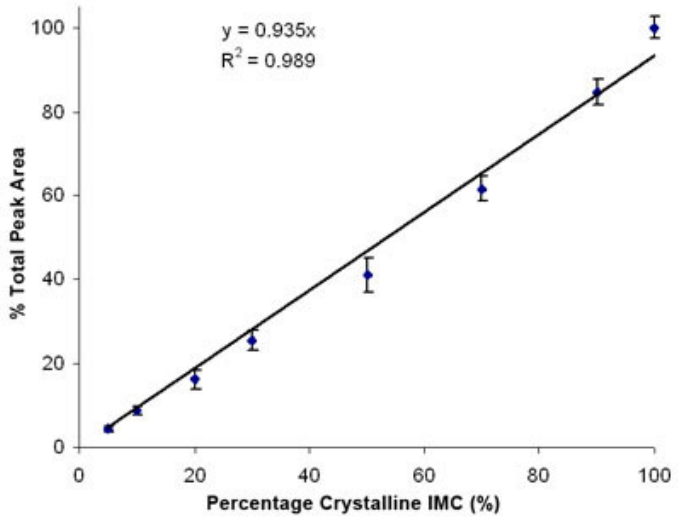

Figure 4. XRPD calibration curve.

The crystallinity of IMC is defined as the percentage crystalline IMC remaining in the mixtures compared with the initial crystalline IMC (assumed to be 100% crystalline). To predict the crystallinity of IMC (γ-form) in the mixtures by XRPD, following equation was used:

$$Crystallinity\ of\ IMC = \frac{A}{A_0 \times S \times P} \times 100\%, \qquad (2)$$

where, A is total peak areas above the "amorphous halo" of diffraction pattern; A_0 is total peak area of pure γ-form crystalline IMC; *P* is the initial percentage crystalline IMC (γ-form) in the mixture; S is the slope of XRPD calibration curve.

Table 2 shows the results of crystallinity of γ-form IMC in IMC-GB mixtures predicted by XRPD. From DSC study, we knew no phase transformation of γ-form crystalline IMC occurred in the IMC-GB mixtures. Therefore, the crystallinity of IMC in the mixtures at all mixing ratio should be around 100%. However, the predicted crystallinity for most of the mixtures was lower than 100% and large variation in the measurements were found, especially in mixtures with low levels of IMC. Such large variation could due to following reasons: (1) preferred orientation of crystalline IMC in the samples; (2) increased difficulty of achieving mixing content uniformity as the levels of IMC in the mixtures decreased; (3) increased interference of GB in the mixtures as the levels of IMC decreased.

The limit of detection was estimated by calculating 3 standard deviations and the limit of quantitation was estimated by calculating 10 standard deviations of 10 independent pure crystalline IMC samples. The standard deviation of the 10 measurements was 1.9% giving a limit of detection of 5.7% and a limit of quantitation of 19%. Compared with DSC method, XRPD is less sensitive, less accurate, and has larger variations in the measurements.

Instrument Reproducibility and Method Error

Instrument reproducibility of XRPD was estimated by scanning the same sample (IMC-SG [30:70] mixture) 10 times without removing it from the sample holder. The crystallinity of these 10 measurements was between 44.4% and 45.2% with a standard deviation of 0.3 and percentage RSD of 0.7%. The method error mainly comes from mixing homogeneity and preferred orientation of crystalline particles during the preparation of the powder bed. It was estimated by measuring the crystallinity of 5 independent samples of IMC-SG (30:70) mixture. The crystallinity of these 5 samples was between 40.3% and 47.6% with a standard deviation of 3.0% and percentage RSD of 7.0%.

Instrument reproducibility of DSC was checked by comparing the starting melting temperature and heat of melting of high purity indium metal of different runs. The starting melt temperature and heat of melting are consistent in different runs. This indicates that DSC instrument is functioning properly and generates reproducible data. The method error of DSC was mainly from 2 sources: (1) mixing homogeneity and sampling and (2) possible phase transition during

Table 2. Results of Percentage and Crystallinity of γ-Form IMC in IMC-GB Mixtures as Predicted by X-ray Powder Diffractometry (n = 5)*

% IMC in Mixture	% IMC Predicted Mean (SD, %RSD)	Predicted Crystallinity Mean (SD, %RSD)
5	4.6 (0.8, 16.7)	92.6 (15.5, 16.7)
10	9.4 (1.0, 10.9)	94.5 (10.3, 10.9)
20	17.4 (2.5, 14.1)	86.9 (12.3, 14.1)
30	27.4 (2.6, 9.5)	91.3 (8.7, 9.5)
50	44.1 (3.6, 8.1)	89.9 (8.9, 8.1)
70	66.2 (3.1, 4.7)	94.5 (4.5, 4.7)
90	90.7 (3.3, 3.6)	100.8 (3.6, 3.6)
100	105.3 (2.6, 2.4)	105.3 (2.5, 2.4)

*Abbreviations are explained in the footnote to Table 1.

DSC heating process. HPLC analysis of the amount of IMC in the mixture reduced the mixing homogeneity and sampling errors. However, HPLC analysis could also introduce new error, probably during sample preparation.

The major issue of using DSC as a quantitative method to measure the crystallinity of a compound comes from the possible phase transformation (between crystalline and amorphous or between one polymorph and another) during the analysis. In order to use DSC as a quantitative method to estimate the crystallinity of IMC in IMC-SG mixtures, it is important to prove that there was no phase transformation of IMC in the mixtures during DSC analysis. This is done by comparing the crystallinity of IMC in IMC-SG samples with and without heat treatment. Figure 5 shows the DSC profiles of IMC-SG mixtures with and without heat treatment. Only one melting endotherm was observed at around 162°C for all samples with and without heat treatment, indicating that the crystal material in the mixtures is γ-form crystalline IMC. The percentage crystalline IMC remaining in the mixtures without heat treatment was found to be 41.7% (± 2.3%) of the original amount. The percentage crystalline IMC remaining in the mixtures with heat treatment was 42.7% (± 2.2%). There is no significant difference in crystallinity between the samples with and without heat treatment. Similar results were found in XRPD analysis. Every major peak of the XRPD diffraction pattern matched the profile of the γ-form of IMC described in the *Analytical Profiles of Drug Substances*.[26] Although IMC lost some of its crystallinity in the mixtures, it is not due to the heat treatment. Part of the crystalline IMC converted to its amorphous form during the mixing with SG. It is interesting to notice that no glass transition temperature was found in DSC profiles, although part of the IMC in the mixtures is amorphous. This is probably due to the formation of hydrogen bonding between the amorphous IMC and SG, which prevents the crystallization of amorphous IMC in the IMC-SG mixtures (details will be discussed in another article). From this study, it is concluded that phase transformation of IMC did not happen in IMC-SG mixtures during the heating process of DSC. DSC is a valid quantitative method for measuring the crystallinity of IMC in IMC-SG mixtures.

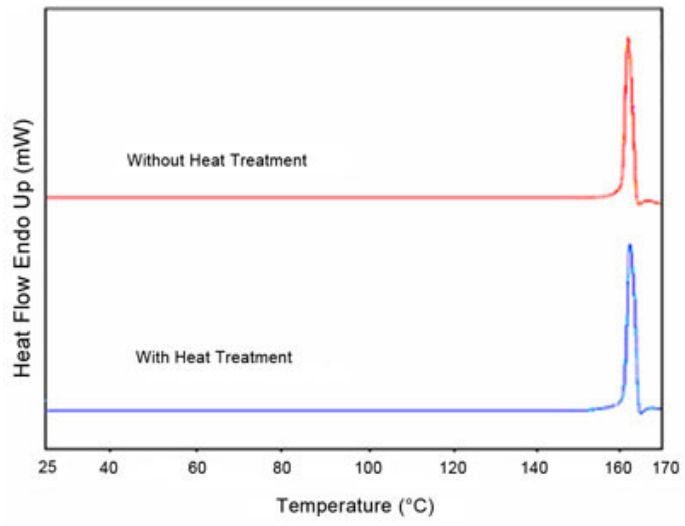

Figure 5. DSC profiles of IMC-SG (30:70) mixtures with and without heat treatment.

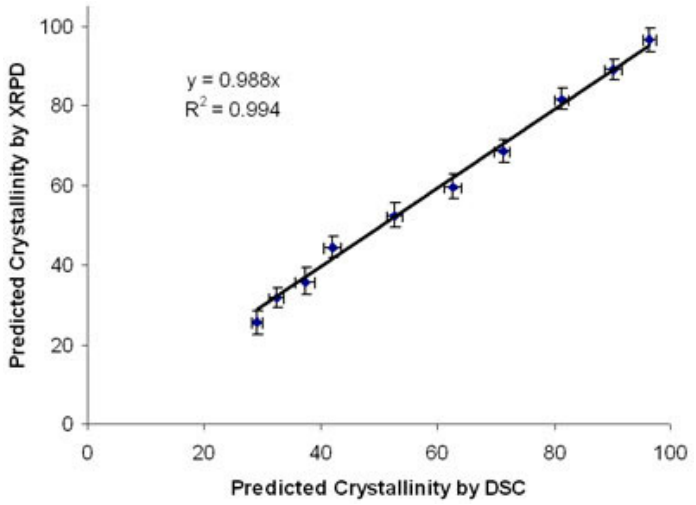

Figure 6. Correlation between predicted crystallinity of IMC in IMC-SG mixtures as measured by DSC and XRPD.

IMC-SG Mixtures With Unknown Amount of Crystalline IMC

From both DSC and XRPD studies, only γ-form crystalline IMC exists in the mixtures since only one melting peak at ~162°C was found in all the samples in DSC study and all the diffraction peaks match the profile of γ-form crystalline IMC in XRPD study. Figure 6 compares predicted crystallinity of IMC in IMC-SG mixtures measured by DSC and XRPD. A good correlation between the predicted crystallinity of IMC as determined by DSC and XRPD was found. However, the variation in the measurements was much less in DSC study than in XRPD study. Therefore, DSC is a preferred quantitative method for measuring the crystallinity of IMC in IMC-SG mixtures. XRPD could be used as a secondary quantitative method or a qualitative method for IMC-SG mixtures.

CONCLUSIONS

This study has demonstrated that no phase transformation of IMC occurred in IMC-SG mixtures during the DSC heating process and has validated DSC as a quantitative method that could be used to determine the crystallinity of IMC in IMC-SG mixtures. The major source of variation in the DSC measurements comes from inhomogeneous mixing and

sampling, which could be reduced by analyzing the amount of IMC in the mixtures using HPLC. The quantitative evaluation of crystallinity of IMC in IMC-SG mixtures by DSC was found superior to the XRPD method with better sensitivity and less variation in the measurements.

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