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## Effect of Manufacturing Methods Used in the Stability of Amorphous Solid Solutions and Predictions to Test them

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EFFECT OF MANUFACTURING METHODS USED IN THE STABILITY OF  
AMORPHOUS SOLID SOLUTIONS AND PREDICTIONS TO TEST THEM

BY

KAORU TOMINAGA

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

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2013

DOCTOR OF PHILOSOPHY DISSERTATION

OF

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## ABSTRACT

With the advent of combinatorial chemistry and high throughput screening of drug molecules, poorly water soluble molecules have been entering the development stage as new drug candidates. The poor aqueous solubility of these molecules is one of the limiting factors for them to succeed as a new drug product. This had led to converting these drugs in most cases are crystalline to amorphous solid dispersion with use of amorphous polymers to improve the solubility.

Although amorphous solid dispersion of a poorly water drug can improve the solubility, careful selection of polymer is a necessity in order to stabilize the high energy nature of the amorphous solid dispersion. Miscibility of a drug and a polymer is important. With specific interaction between the drug and the polymer, the dispersion can remain miscible much longer. Another factor that needs to be considered when formulating an amorphous solid dispersion is the amount of drug that is incorporated into the polymer. Over saturating the polymer with the drug can cause instability of the dispersion and crystallization may occur which will lead to reduced solubility.

In this work, effects of processing method, polymer selection and the drug concentrations for the preparation of amorphous solid dispersion as well as prediction of drug-polymer miscibility have been studied. Hot melt extrusion (HME), rotary evaporation (Rot) and spray drying (SD) processing methods used in the study with

Eudragit E 100 (EPO), HPMCAS LF and PVPVA 64 polymers. Drug concentration was another factor that was explored.

The objective of this dissertation were: (1) to prepare amorphous solid dispersion of nifedipine with polymers (2) to characterize the solid dispersions (3) to determine the factors which contributes to successful amorphous solid dispersion (4) to evaluate prediction methods used to study drug and polymer miscibility and solubility (5) to use a thermodynamic prediction model to determine solubility of nifedipine at room temperature.

In the first manuscript, amorphous solid dispersions of nifedipine and polymers were prepared. Physical and chemical characterizations of the solid dispersions indicated solid dispersions prepared with EPO polymer were unstable although intrinsic dissolution rates (IDR) of those samples had higher rates than those prepared with HPMCAS LF or PVPVA 64 polymers. The instability was explained by the lack of specific hydrogen bond interaction while the high IDR was explained by the low glass transition temperature ( $T_g$ ) of the polymer. With lower  $T_g$ , molecular mobility would be higher and therefore the drug could dissolve at a faster rate. ANOVA analysis of factorial design showed all factors (process, polymer and drug concentration) affected the IDR. Further optimization of experiments may be necessary to determine the dominant factor for improving IDR.

In the second manuscript, we have calculated three different ways to calculate the Flory-Huggins interaction parameter,  $\chi$ . Although using melting point depression approach and solubility parameter of a drug and a polymer are common to estimate the

miscibility of the two, there were assumptions that needed to be addressed. We have modified the melting point depression approach by calculating a better estimate of volume fractions needed to calculate the interaction parameter.

In the third manuscript, we have taken a recently published thermodynamic prediction model, which can estimate the stable drug concentration that can be incorporated into an amorphous solid dispersion at room temperature, to predict the solubility of nifedipine with EPO, HPMCAS LF and PVPVA 64 polymers in amorphous solid dispersions prepared by HME, Rot and SD processes. The predictions showed less stable nifedipine concentration could be incorporated into HME processed solid dispersions than samples prepared by Rot or SD processes. Overall, nifedipine-PVPVA 64 solid dispersion prepared by SD method was predicted to incorporate nifedipine concentration up to 30 % w/w.

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## **PREFACE**

This dissertation has been prepared in the manuscript format as outlined in the formatting guideline provided by the Graduate School of University of Rhode Island. The entire dissertations were divided into three manuscript sections.

**Manuscript 1:** Evaluation of Processing Method, Polymer Selection and Drug Load on Amorphous Solid Dispersion of Nifedipine

**Manuscript 2:** Testing the use of “heat of fusion” in calculations of interaction parameter ( $\chi$ ) in Flory-Huggins and its comparison with the use of melting point depression and solubility parameters

**Manuscript 3:** A Study of Stability Prediction of the Nifedipine Solid Dispersions Prepared with Hot Melt Extrusion, Spray Drying and Rotary Evaporation

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## MANUSCRIPT 1

Evaluation of Processing Method, Polymer Selection and Drug Load on Amorphous Solid Dispersion of Nifedipine

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## **Abstract**

**Purpose:** To evaluate the characteristics of amorphous solid dispersions of nifedipine processed with hot melt extrusion (HME), rotary evaporation (ROT) and spray drying (SD) at 5, 10, 20 and 40% w/w drug loadings, to determine the differences involved in the final products.

**Methods:** Amorphous solid dispersion of nifedipine with Eudragit E 100 (Polymethyl methacrylate), HPMCAS LF and PVPVA 64 were prepared via hot melt extrusion, rotary evaporation and spray drying processes. The solid dispersions were analyzed with DSC, FT-IR, PXRD and the intrinsic dissolution rates (IDR) were determined.

**Results:** NIF-EPO samples prepared by HME and SD showed the highest IDR. However, analytical characterizations of the same samples show unstable amorphous solid dispersion. To keep the molecular mobility of the amorphous solid dispersion to a minimum to inhibit recrystallization, a system such as NIF-PVPVA 64 may give a better stable amorphous solid dispersions.

## **Keywords**

Amorphous, Process Methods, Solid Dispersion, Intrinsic Dissolution Rate, Polymer

## **Introduction**

Amorphous solid dispersions are one of the forms used in the pharmaceutical industry to manipulate poorly water soluble drug molecules; to improve their solubility in aqueous media and to achieve higher level of bioavailability. In an amorphous solid dispersion, the hydrophobic drug is dispersed in an amorphous hydrophilic polymer carrier by different means. The action of the polymer is twofold: to stabilize the

amorphous state of the drug and to improve the dissolution of the drug (1-5, 11). In some cases, the use of polymer have shown to prevent precipitation of the drug from a supersaturated solution created as the result of higher solubility of the amorphous form compared to the crystalline one. (6, 7)

In the literature, the effects of processing methods on the final product properties are rarely mentioned; for example, etravirine was processed by two different methods; via film casting, and solvent evaporation and the effects of methodologies used on the final solid dispersions were compared (7).

Weuts *et al.*, studied the changes occurred in the melt and the spray dried powder and they found that melting process provided a higher miscibility and longer stability whereas the spray drying method was not sufficient to produce stable products (8).

Patterson *et al.* mentioned the differences in the drug properties obtained by quench cooling and ball milling methods. However, the effects of each method used, were different on each of the drugs used for testing (9).

Amorphous solid dispersion can be prepared by several methods such as physical manipulation (i.e. milling) (9, 10), precipitation from solvents (11), melting (9, 12, 13) and solvent removal (11,13). The two most commonly used amorphous processing methods in the pharmaceutical industry are melting (fusion) and solvent removal. The fusion method employs high temperatures to melt both the drug and the polymer together; disperse the drug molecules throughout the polymer matrix and quench cool the mixture by either extruding the mixture or by placing the molten mixture in an ice bath or liquid nitrogen. The solvent removal method can produce an amorphous solid

dispersion by dissolving a poorly water soluble drug and a polymer in the same organic solvent. In most cases a type of alcohol is used as a solvent and then the solvent is removed by evaporation, lyophilization, vacuum drying or supercritical condition respectively.

Comparison of the effects of the processing methods, including the effects of different polymers used on the final products has been studied very little. We believe that the methods that we have selected will produce products of different characteristics. The reasoning behind this can be, for example, to investigate the differences in the rate of solvent evaporation for rotary evaporation compared to spray drying. In spray drying the solvent can evaporate from the droplets of drug-polymer combination in “milliseconds” which can lead to a successful solid dispersion (13). The typical evaporation capacity of the rotary evaporation and spray-drying differs since rotary dryer can have evaporation rate of 30-80 kg H<sub>2</sub>O/ h·m<sup>3</sup> compared to spray dryer which has 1-3 kg H<sub>2</sub>O/ h· m<sup>3</sup> (17).

Janssens *et al.* compared spray dried amorphous solid dispersion of itraconazole to film casted samples (11). The crystallization temperature of itraconazole reported for the two processing methods showed that the onset of crystallization for the film casted samples were lower which meant that the solid dispersions prepared by this process gave less stable products by influencing the crystallization behavior of the drug in the polymer.

In this study, amorphous solid dispersions of nifedipine (NIF), which is a calcium channel blocker, used for the treatment of high blood pressure and to control angina, with three different polymers, Eudragit E 100 [Poly(butyl methacrylate-co-(2-demethylaminoethyl) methacrylate-co-methyl methacrylate)], HPMCAS LF (hydroxypropylmethylcellulose acetate succinate), PVPVA 64 (polyvinyl pyrrolidone vinyl acetate) coprecipitates. They were prepared by using hot melt extrusion (HME), spray drying (SD) and rotary evaporation (Rot). The processed formulations were analyzed for physical, thermal and chemical properties by using modulated differential scanning calorimetry (MDSC), Fourier transform infrared spectroscopy (FT-IR), powder X-ray diffraction (PXRD). The intrinsic dissolution rates were also measured to relate properties obtained with the solubility of the final product.

## **MATERIALS AND METHODS**

### **MATERIALS**

The API (Active pharmaceutical ingredient) used was, nifedipine (NIF) purchased from RIA International (East Hanover, NJ). Eudragit E-100 (EPO) polymer which was kindly provided by Evonik (Parsippany, NJ), HPMCAS LF from Shin-Etsu Chemical Co., Ltd (Biddle Sawyer Corp, New York, NY) and PVPVA 64 was purchased from BASF (Florham Park, NJ).

Methylene chloride was used as the solvent in both spray drying and rotary evaporation processes as received. For processing NIF with HPMCAS LF, methanol was used because HPMCAS LF does not dissolve in methylene chloride. Both solvents were purchased from Sigma-Aldrich Co. (St. Louis, MO).

Fig. 1-1 shows the chemical structures of the drug and the polymers and Table I lists the physical-chemical properties of the drug and the polymers.

## **METHODS**

### **Hot Melt Extrusion (HME)**

Physical mixtures of NIF and EPO were prepared using a mortar and pestle with drug loadings of 5, 10, 20 and 40 % w/w. The mixture was then extruded using Haake Minilab micro compounder (Thermo Scientific, Waltham, MA). The extruded material was ground and sized through a # 40 sieve. A diagram of a hot melt extruder is shown in Appendix 1, Fig IA-1

In this machine, the physical mixture went into the extruder through the funnel on the left hand side and softened with the temperature applied and extrudes out from the flush hole. The extrusion screw speed was set to 50 RPM throughout the experiments and no shear force was additionally applied to the mixture.

### **Rotary Evaporation (Rot)**

The same physical mixtures prepared for HME were used for rotary evaporation. Physical mixtures of 5-10 grams were dissolved in 50-100 mL of methylene chloride, for EPO and PVPVA 64 respectively. The solvents were removed by using a rotary evaporator apparatus (Büchi Rotavapor from Büchi (New Castle, DE). The rotary evaporator was set to approximately 30 RPM for all experiments conducted. The

samples were collected by removing the foamy film formed on the walls of the flask with a metal spatula and ground by using a mortar and pestle. The particles were sized through a # 40 sieve.

### **Spray Drying (SD)**

A Mini Spray Dryer B-290 (Büchi, New Castle, DE) attached to Inert Loop B-295 cooling block was used in the spray drying experiment to manufacture amorphous solid dispersion of nifedipine prepared with three different polymers respectively. A solution of NIF and polymer in methylene chloride (methanol in the case when HPMCAS LF) was used as the polymer matrix having drug loads ranging from 5-40% w/w. A solid content of 3 to 5% w/w solid content were used in order to adjust the workability of the sample.

In Appendix I, the geometry of the spray dryer is shown in Fig. IA-2.

In this spray dryer, the solution is atomized from (1) while nitrogen is continuously supplied from (2). The atomized droplets are dried in the heated chamber (3) and are collected in the collection vessel through cyclone in (4). Smaller particles are removed from the nitrogen flow by a filter located in (5) and the gas flows out to (6) to be condensed to collect the solvent.

In our experiments, the pump speed was set to 24%, inlet temperature to 75 °C, and aspirator to 90% on the control panel. The two-fluid nozzle was used to allow compressed air to disperse the pumped liquid into fine droplets. An electronic heater was used to heat the nitrogen gas which would dry the droplets to evaporate the solvent. The droplets would continue to dry in the spray cylinder and, a cyclone

created, separated the particles into the collection container or into the outer filter.

Aspirator located at the end of the spray dryer was used to generate the nitrogen flow and to collect the used solvent into the cooling block.

Materials collected were transferred into an amber colored vial and were kept in desiccators until further analysis.

## **Methods Used for Analytical Tests**

### **Modulated differential scanning calorimetry (MDSC)**

NIF-polymer samples were thermally analyzed with a MDSC instrument Q2000 (TA Instruments, New Castle, DE). Samples to be scanned were weighed (6- 8 mg) and placed in to aluminum pans with lids. Heating was controlled throughout the measurement and the samples were heated from room temperature up to 20- 30°C above the melting point of the pure drug at a rate of 5°C/ minute unless noted otherwise. The samples were kept at the highest temperature for two minutes and then cooled down to -50°C at -50°C/minute cooling rate. The samples were kept at the lowest temperature for a maximum of 2 minutes and then heated up to 20-30 °C above the melting point of the drug.

### **Fourier transform-infrared spectroscopy (FT-IR)**

FT-IR used was Nicolet 6700 FT-IR spectrometer (Thermo Scientific, Waltham, MA) to collect infrared spectra. The FT-IR was equipped with Smart Orbit ATR (Attenuated Total Reflection) objective lens with a diamond crystal in reflection mode. OMNIC software program was used to analyze the data.

### **Powder X-ray diffraction (PXRD)**

PXRD was performed by using X-ray diffraction obtained with Bruker D8 XRD. The samples were analyzed using Cu, K  $\alpha$  radiation to determine the crystalline or amorphous phases of the drugs. The X-Ray pattern was collected in the angular range of  $1 < 2\theta < 40^\circ$  in the step scan mode (step width  $0.02^\circ$ , scan rate  $1^\circ$ / per minute).

### **Intrinsic dissolution rate determination (IDR)**

Dissolution studies using solid dispersions samples obtained, which contained 5, 10, 20 and 40% w/w NIF and the three polymers respectively, were prepared by HME, Rot and SD, were conducted to determine the intrinsic dissolution rates. USP II apparatus with an amber vessel was used for the study. Fig. IA-3 in Appendix I shows the setup of an intrinsic dissolution vessel with a die, containing a drug compact exposing a single surface to the dissolution media at the bottom. Approximately 200 mg of sample was weighed and compressed in a disk with a press using 2000 lbs. force with 5 second dwelling time. Dissolution media used in the experiments were 500 mL of 0.1 N hydrochloric acid with pH of 1.2 for NIF-EPO samples. Phosphate buffer with pH6.8 was used for all other samples. Temperature used was  $37^\circ\text{C}$ . IDR was determined using the initial linear profile of the dissolution plot. The  $3 \times 3 \times 4$  factorial design of experiments were analyzed with a general linear model of ANOVA to determine the effects of processing methods, polymer choice and drug concentration on IDR.

## **RESULTS**

### **Products Obtained with Hot Melt Extrusion (HME)**

In HME, we observed significant changes at the –NH stretch and the C=O of the ester groups with the wavelength changing at  $3318\text{ cm}^{-1}$  and at  $1676\text{ cm}^{-1}$  peaks which agrees with previous reporting (23) that indicate hydrogen bond interaction with NIF-HPMCAS LF and NIF-PVPVA 64 samples occurred, see Figs. 1-2 and 3. No significant interaction was present with NIF-EPO samples. The peak at  $3318\text{ cm}^{-1}$  which is associated with the –NH moiety, shifts to a lower wave number and the peak broadening and shift to a higher wave number of the C=O have been linked to hydrogen bonding interaction between nifedipine and polymer solid dispersions (24, 25).

According to the DSC thermograms, HME process creates amorphous solid dispersions up to 20 % drug concentrations for all polymers and up to 40 % drug concentration for NIF-PVPVA 64 solid dispersions. With NIF-EPO and NIF-HPMCAS LF samples, at 40 % drug concentration, melting endotherms were observed, see Figs. 1.4 and 1.5. Although all the samples prepared by HME process had one  $T_g$  which are shown in Table II, suggesting a one-phase amorphous solid dispersion, a melting endotherm seen at  $161\text{ }^\circ\text{C}$  which was preceded with a recrystallization peak of the NIF-EPO sample indicated thermal instability; crystallization of NIF was not apparent in the XRD data, Fig. 1- 6. There was also a melting endotherm that was observed at  $165\text{ }^\circ\text{C}$  of the NIF-HPMCAS LF sample at 40 % drug concentration, which was not preceded by a recrystallization peak. This may

suggest that there were small nifedipine clusters in the solid dispersion that did not convert to amorphous form that had melted while the sample was heated in the DSC instrument, see Fig. 1- 7. They were too small to be detected by the XRD.

The findings from the XRD can suggest the possible limitation of high-angle x-ray diffraction. The presence of the melting endotherm may be the result of applied heat resulted in an unstable amorphous solid dispersion by the DSC, which caused recrystallization of the drug.

When the dissolution rates of the samples obtained with HME were investigated (Table III ), it is seen that the increasing dissolution rates are obtained with increasing drug concentrations with EPO and HPMCAS LF. This is an expected finding.

However, with PVPVA 64 polymer, dissolution rates are not following the same path. The reason may be that the high solubility of PVPVA 64 in water compared to EPO and HPMCAS LF. When the polymer engulfing the nifedipine molecules in a solid dispersion dissolves immediately, it exposes the drug molecules to the dissolution medium resulting high concentration of drug, which may be the reason of rapid crystallization and precipitation resulting lower intrinsic dissolution rate.

### **Products obtained with Rotary evaporation (Rot)**

Rotary evaporation also caused hydrogen bonding of nifedipine with; HPMAS and PVPVA 64, see Figs. 1-8 and 1-9. However, the DSC data, with PVPVA 64, Fig 1-10, demonstrates the presence of two glass transition temperatures. The first appears at 89.05 °C and the second at 125.57 °C. Although the X-ray diffractions showed amorphous product at all drug concentrations, shown in Fig. 1-11, the DSC data may

indicate the presence of two amorphous phases, one being the drug-rich, the other being the polymer rich regions since the change in the glass transition temperatures have shifted from a lower temperature to a higher one that is closer to the glass transition temperature of the polymer. Occurrence of two glass transition temperature regions could be the result of phase separation of the amorphous solid dispersions. This was suggested by Rumondor *et al.* (16).

In the DSC spectrogram, 20 % NIF-EPO sample showed a melting endotherm at 147.07 °C which suggests that there are crystalline nifedipine present in the solid dispersion, see Fig. 1- 12. In 40 % NIF-EPO sample, also a similar melting endotherm is present, at 150.99 °C, Fig. 1-13. The melting endotherm is accompanied with a recrystallization peak which suggests that it is a combination of crystalline nifedipine and unstable amorphous nifedipine that reverted to the crystalline form.

The XRD results for the NIF-EPO solid dispersions confirm the presence of crystalline nifedipine at 40 % drug concentration Fig. 1- 14. Sample prepared with HPMCAS LF polymer exhibited a melting endotherm at 40 % nifedipine concentration at 163.31 °C, Fig. 1- 15. This melting endotherm indicates the presence of undissolved nifedipine that had melted during the DSC scan. This crystalline nifedipine was also detected in the XRD spectrogram in Fig 1-16.

The intrinsic dissolution rates calculated , increase up to 20 % NIF-EPO samples and decrease about 50 times for 40 % drug concentration Table I.III. The presence of

both undissolved and unstable amorphous nifedipine could be the cause for the reduced dissolution rate.

For NIF-HPMCAS LF samples, there is a linear relationship between the drug concentration and the IDR. With increase in the drug concentration, the IDR will also increase even at 40 % drug concentration which contains crystalline nifedipine. The reason for not seeing the reduction in the IDR at 40 % drug concentration, maybe the result of HPMCAS LF's ability to inhibit precipitation of amorphous drug in dissolution media.

For PVPVA polymer, dissolution rates appear to be random and not consistent with increasing drug concentration. As explained earlier, the two glass transition regions seen in Fig. 1- 10, the possible phase separated nifedipine may be the cause for inconsistent trend.

### **Products Obtained with Spray Drying (SD)**

Spray dried samples showed no interaction between nifedipine and EPO but showed strong interaction between nifedipine and PVPVA 64 at  $2937\text{ cm}^{-1}$  and  $1698\text{ cm}^{-1}$ .

Similar interactions were seen given in Fig 1-8 and 1- 9. Samples prepared with EPO were amorphous up to 20 % drug concentration, according to the DSC thermogram which showed melting endotherm at  $150.67^\circ\text{C}$  accompanied by a recrystallization peak, Fig. 1- 17. This recrystallization was not apparent in the XRD diffractograms shown in Fig. 1- 18.

NIF-HPMCAS LF sample containing 40 % nifedipine also exhibited a melting endotherm at 159.04 °C shown in Fig 1-19. This melting was not preceded with recrystallization of the amorphous drug. In the XRD spectrograms, shown in Fig 1-20, all of the samples demonstrated amorphous characteristics.

Spray drying process creates an amorphous solid dispersion where the drug is trapped in the polymer matrix instantaneously, but the dispersion created by this manner may be unstable. XRD measurement which does not utilize heating may not show any crystallinity, whereas DSC which supplies energy in the form of heat to the sample during measurement may indicate the instability of the amorphous nifedipine solid dispersion by showing a melting peak. Explanation for the melting endotherm that appears at a higher nifedipine concentration may be demonstrating instability.

Intrinsic dissolution rates of the samples prepared with this method are given in Table III.

Increasing EPO and HPMCAS LF increase the IDR. However PVPVA 64 at 20 and 40 % drug concentration demonstrates lower rates than the lower drug concentrations. This could be due to the highly water-soluble nature of the PVPVA polymer that the supersaturation that is caused with the release of high concentration of nifedipine may result in a reversion of amorphous nifedipine to crystalline state. Since PVPVA 64 does not have the same inhibition property as HPMCAS LF, the released nifedipine may have crystallized in the dissolution media.

Over all , spray drying process can incorporate 20% of drug in the solid dispersion regardless of the type, molecular weight and structure of the polymers used.

### **Intrinsic Dissolution Rates Comparison**

In Fig. 1- 21, the IDR of all the samples prepared by HME, Rot and SD using three different polymers, EPO, HPMCAS LF and PVPVA 64 at four different drug concentrations are shown. From this plot, it can be seen that NIF-EPO sample that was spray dried with 40 % drug concentration has the highest IDR. To attain a better idea of factors that affected the IDR, we have looked into other properties of the prepared solid dispersion.

Investigation of TableI-II gives us information about the  $\Delta H_{fus}$  which is indicating that the drug was not reverted to the amorphous form. In HME method, the value of  $\Delta H_{fus}$  is 2.4 J/g for NIF-EPO sample at 20 % drug concentration and 20.2 J/g at 40 % drug concentration. For NIF-HPMCAS LF sample, at 40 %, there was a melting endotherm with  $\Delta H_{fus}$  measuring 5.2 J/g.

For Rot, in EPO,  $\Delta H_{fus}$  is 2.8 J/g for the NIF-EPO sample at 20 % drug concentration and 21.1 J/g at 40 % drug concentration. NIF-HPMCAS LF exhibited  $\Delta H_{fus}$  of 12.4 J/g at 40 % drug concentration.

For SD process both NIF-EPO and NIF-HPMCAS LF samples at 40 % drug concentrations were presented with,  $\Delta H_{fus}$  as 20.3 and 8.6 J/g respectively. These findings suggest that Rot process is the least efficient method to convert crystalline drug into amorphous solid dispersions where the crystalline drug is still present at 20 % concentration. On the other hand, SD is the most efficient process where all

polymer converted nifedipine into amorphous solid dispersion up to 20 % drug concentration.

The ANOVA analysis of the IDR of the amorphous solid dispersions in order to determine the factors that may influence the intrinsic dissolution rate showed that interaction of all three factors (i.e. processing, polymer type and drug concentration) which will change the IDR of amorphous nifedipine solid dispersions with changes in any one factor or factors combined.

For example, investigating the interaction plots shown in Fig. 1- 22, we can conclude that if we want to choose the best processing method with the highest drug concentration, we should choose SD method. On the other hand, if we want to choose the optimum process and polymer combination, we should select SD with EPO. EPO at 40 % drug concentration yields the highest IDR. Since all three factors affect the IDR significantly, we cannot conclude that any one of the factor is the dominant one, in terms of yielding a high intrinsic dissolution rate. Since process conditions were not optimized for preparing the amorphous solid dispersions, optimization of each process and using design of experiments may provide the answer to this question.

### **Discussions**

The results from the IDR experiments show that NIF-EPO samples prepared by HME or SD have higher dissolution rate. The slightly acidic nature of nifedipine results in the higher intrinsic dissolution rate in an acidic aqueous medium as shown with amorphous solid dispersions prepared with EPO at all three processing methods.

Overall, the higher drug loading resulted in faster dissolution rates across all three polymers and processing methods.

The MDSC measurements, resulted with a melting endotherm appearing at the drug loading of 20%,w/w, as it is seen in NIF-EPO systems Fig. 1-4, indicated metastability even though its IDR is high. There is high risk in such solid dispersions, because the metastable amorphous NIF, can revert back to the crystalline form either during dissolution or while the samples sit on the shelf. Therefore, NIF-PVPVA 64 samples should be used as more suitable combinations processed by any of the methods tested in this study, even if their IDR are lower. The risk of crystalline conversion of these samples will be much lower as FT-IR analysis demonstrated a secondary interaction between NIF and PVPVA 64 polymer. With such an interaction, the polymer can slow down crystalline conversion and even more, it could possibly stabilize the supersaturated solution for a longer time period during dissolution.

It has been shown that amorphous solid dispersion of nifedipine prepared with EPO with spray drying process yielded the highest intrinsic dissolution rates. This could be due to lack of hydrogen bond interaction of the drug with the polymer which means that the water molecules in the dissolution media won't compete with the polymer to remove the amorphous drug molecule from the bulk. On the other hand, without polymer-drug interaction, the metastable amorphous nifedipine may convert easily to its stable crystalline form. This is evident in the MDSC data presented as the melting

endotherm in 20 and 40% drug loads of NIF-EPO samples. Additionally, the low T<sub>g</sub> of NIF-EPO solid dispersion systems may be unstable according to the well known T<sub>g</sub> -50°C rule, declaring that the glass transition temperature of the solid dispersion should be above 50°C of the storage temperature to keep the system stable [28]. With the high molecular mobility environment, the high intrinsic dissolution rate may not translate to sustained supersaturated nifedipine solution but may result in fast precipitation of the reverted crystal nifedipine.

### **Conclusion**

Amorphous solid dispersions of NIF with three polymers via HME, Rot and SD were made. The highest IDR was achieved when NIF-EPO sample was prepared by spray drying and second highest IDR with HME, with 40% drug loading. The reasons of the differences obtained were explained. However, these samples may not be the best candidates to proceed for formulation due to their unstable amorphous character. In that case, NIF-PVPVA 64 samples may be a better choice which the polymer has a better stabilizing ability compared to EPO polymer

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**Table 1-I.** Physicochemical properties of nifedipine (a), EPO, HPMCAS LF and PVPVA 64 (b) (MW,  $T_g$ ,  $T_m$ ,  $\Delta H_{fus}$  are molecular weight, glass transition and melting point temperature, and heat of fusion, respectively)

(a)	MW (g/mol)	$T_g$ and $T_m$ (°C)	Aqueous solubility	H-bonding	Charge	pKa	$\Delta H_{fus}$
Nifedipine	346.335	$T_m$ 172.1 $T_g$ 47±1	5.6 µg/mL	1 donor 7 acceptors	Neutral	3.93	106.4±3.63

(b) Polymer	Polymer type	Monomer MW (g/mol)	MW (g/mol)	$T_g$ (°C)	Solubility in Methanol	H-bonding	Charge	Aqueous Solubility
Eudragit E 100	Copolymer	399.522	135000	52	1g of polymer dissolves in 7g	7 acceptors	Cationic	≤pH 5.5
HPMCAS LF	Homopolymer	286.28	18000	120	Freely soluble	9 acceptors 6 donors	Anionic	≥pH 5.5
PVP-VA64	Random copolymer	197.23	45000-70000	100	Freely soluble	3 acceptors	Non-ionic	pH 5-7

**Table 1-II.** Melting and glass transition temperature and heat capacity measurement of nifedipine with EPO, HPMCAS LF and PVPVA 64 solid dispersions respectively, processed by HME, Rot and SD with drug loads ranging from 5 to 40% (w/w)

Polymer	Drug Load % (w/w)	HME			Rot			SD		
		T <sub>g</sub> (C)	T <sub>m</sub> (C)	ΔH <sub>fus</sub> (J/g)	T <sub>g</sub> (C)	T <sub>m</sub> (C)	ΔH <sub>fus</sub> (J/g)	T <sub>g</sub> (C)	T <sub>m</sub> (C)	ΔH <sub>fus</sub> (J/g)
EPO	5	47.5 ±2.2			52.6 ±0.5			50.5 ±2.6		
	10	46.9 ±0.3			52.6 ±0.1			54.1 ±3.0		
	20	42.6 ±0.1	147.4 ± 0.4	2.4 ± 0.2	42.0 ±0.4	147.7 ± 0.0	2.8 ± 0.3	43.0 ±0.6		
	40	41.0 ±0.2	160.5 ± 0.0	20.2 ± 3.0	42.6 ±0.0	156.0 ± 0.0	21.1 ± 1.8	41.0 ±0.4	160.2 ± 0.3	20.3 ± 0.7
HPMCAS LF	5	111.4 ±1.2			113.4 ±0.8			104.6 ±1.3		
	10	101.7 ±1.9			105.8 ±1.0			94.9 ±1.7		
	20	90.1 ±0.7			92.2 ±0.1			78.9 ±0.3		
	40	68.3 ±0.3	165.6 ± 0.2	5.2 ± 0.5	68.8 ±1.1	163.6 ± 0.4	12.4 ± 1.3	65.3 ±1.4	164.5 ± 0.1	8.6 ± 0.1
PVPVA 64	5	105.2 ±0.7			106.4 ±0.4			101.2 ±4.5		
	10	104.0 ±0.7			103.9 ±0.8			100.2 ±0.4		
	20	99.4 ±0.4			98.9 ±0.1			97.5 ±0.9		
	40	92.3 ±4.4			88.9 ±0.2			88.9 ±4.8		
	40*				125 .57					

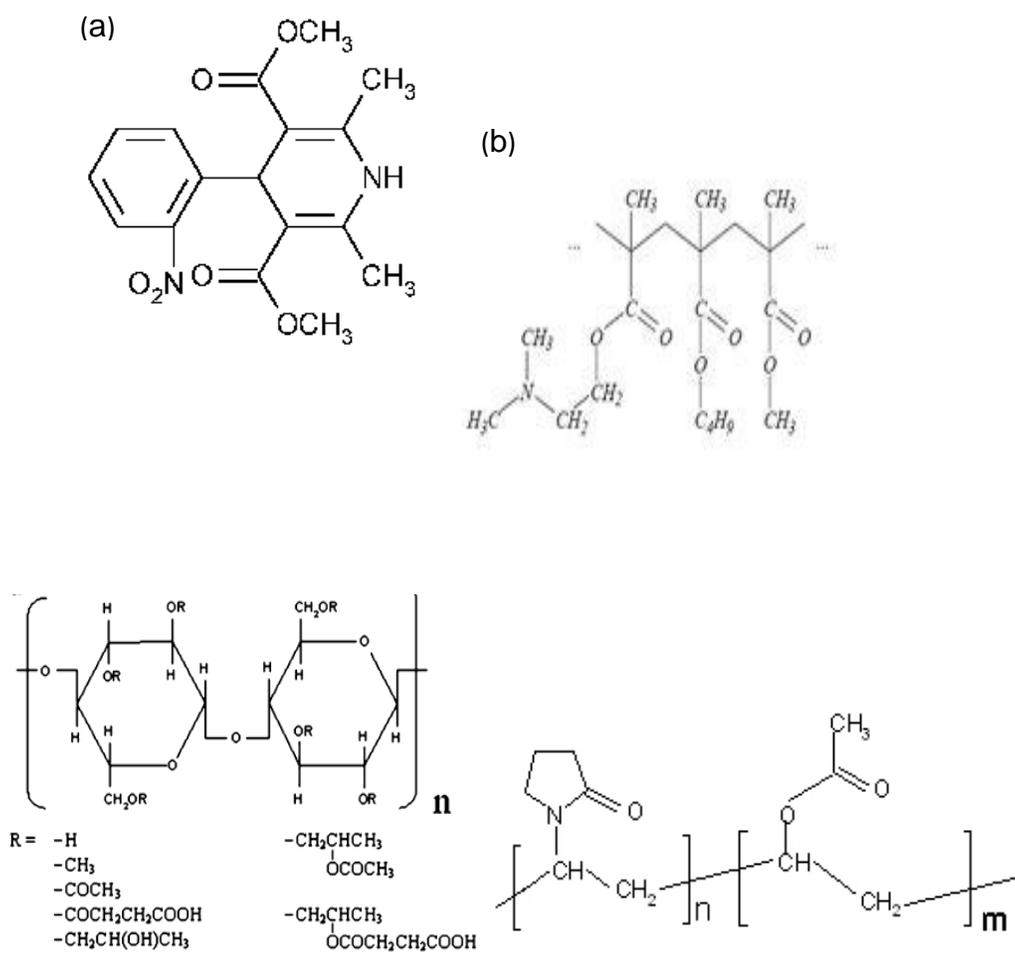
**Table 1-III.** Intrinsic dissolution rates of nifedipine with EPO, HPMCAS LF and PVPVA 64 respectively processed by HME, Rot and SD with drug loads ranging from 5 to 40% (w/w)

Polymer	Drug Load % (w/w)	Intrinsic Dissolution Rate (mg/min/cm <sup>2</sup> )		
		HME	Rot	SD
EPO	5	0.499 ± 0.026	0.147 ± 0.021	0.891 ± 0.095
	10	2.077 ± 0.279	0.191 ± 0.009	1.748 ± 0.14
	20	3.053 ± 0.017	0.223 ± 0.574	4.497 ± 0.574
	40	5.24 ± 0.995	0.0044 ± 0.0004	10.077 ± 0.442
HPMCAS LF	5	0.139 ± 0.096	0.295 ± 0.141	0.065 ± 0.021
	10	0.147 ± 0.034	0.233 ± 0.091	0.109 ± 0.023
	20	0.418 ± 0.059	1.30 ± 0.227	0.221 ± 0.013
	40	0.452 ± 0.124	0.174 ± 0.057	0.478 ± 0.198
PVPVA 64	5	0.383 ± 0.045	0.552 ± 0.129	0.449 ± 0.031
	10	0.71 ± 0.276	0.856 ± 0.269	0.562 ± 0.161
	20	0.769 ± 0.164	0.588 ± 0.236	0.324 ± 0.086
	40	0.153 ± 0.094	0.293 ± 0.064	0.113 ± 0.015

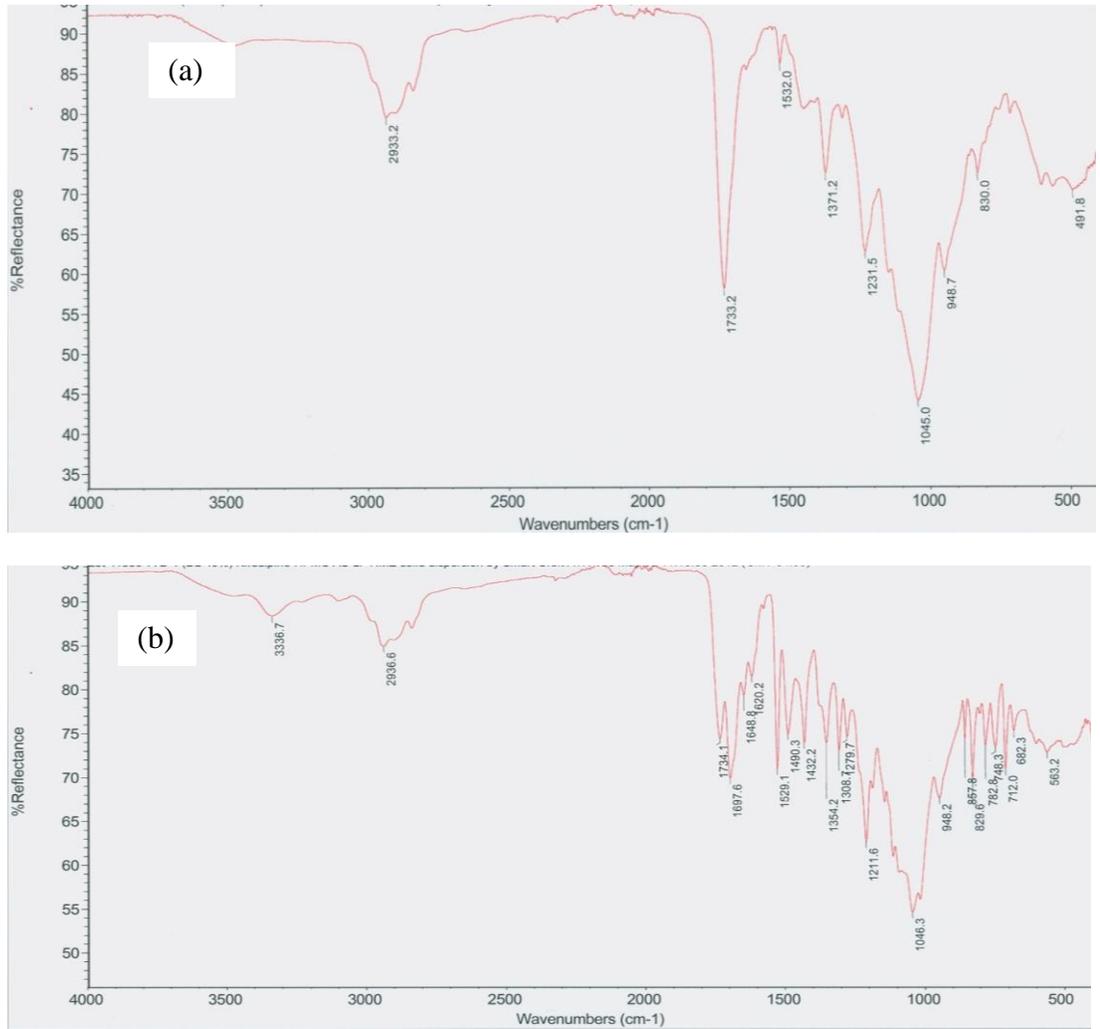
**Table 1-IV** ANOVA analysis of the 3x3x4 factorial design of NIF samples with IDR as response

Analysis of Variance for IDR, using Adjusted SS for Tests

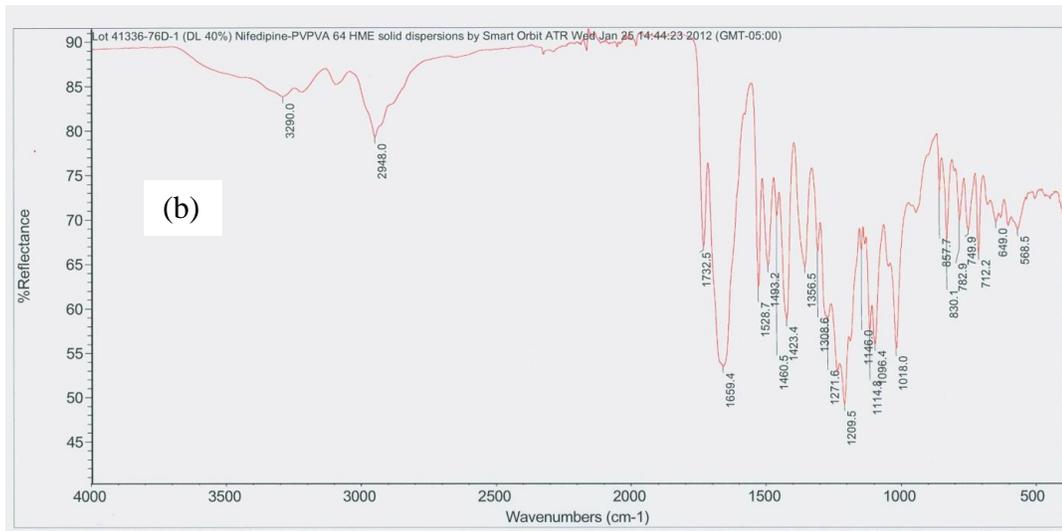
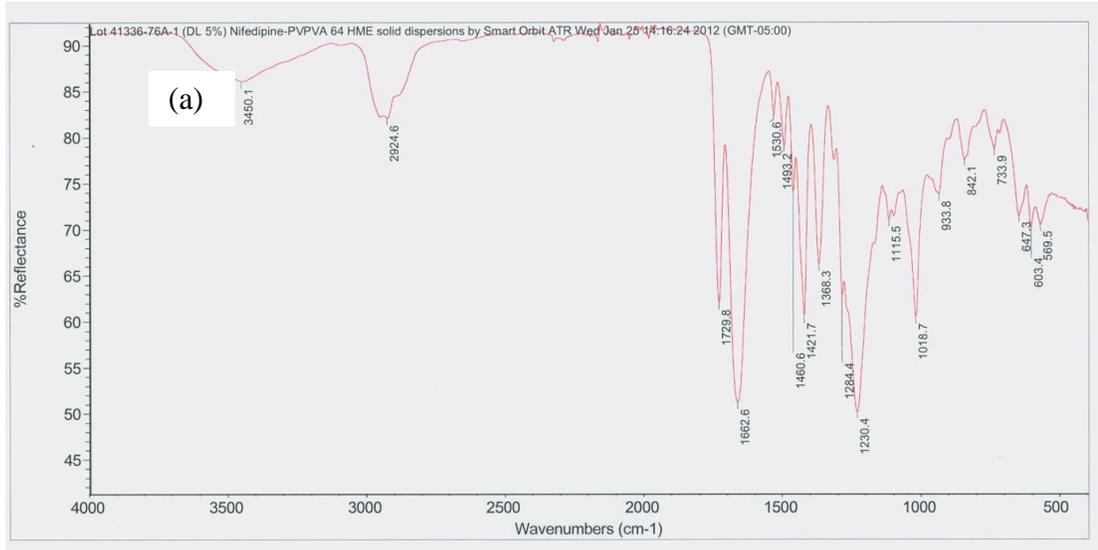
Source	DF	Seq SS	Adj SS	Adj MS	F	P
Process	2	6.8496	6.8496	3.4248	237.66	0.000
Polymer	2	23.6190	23.6190	11.8095	819.50	0.000
DL	3	8.7270	8.7270	2.9090	201.87	0.000
Process*Polymer	4	19.7815	19.7815	4.9454	343.18	0.000
Process*DL	6	7.6740	7.6740	1.2790	88.75	0.000
Polymer*DL	6	19.0706	19.0706	3.1784	220.56	0.000
Process*Polymer*DL	12	13.2428	13.2428	1.1036	76.58	0.000
Error	72	1.0376	1.0376	0.0144		
Total	107	100.0021				



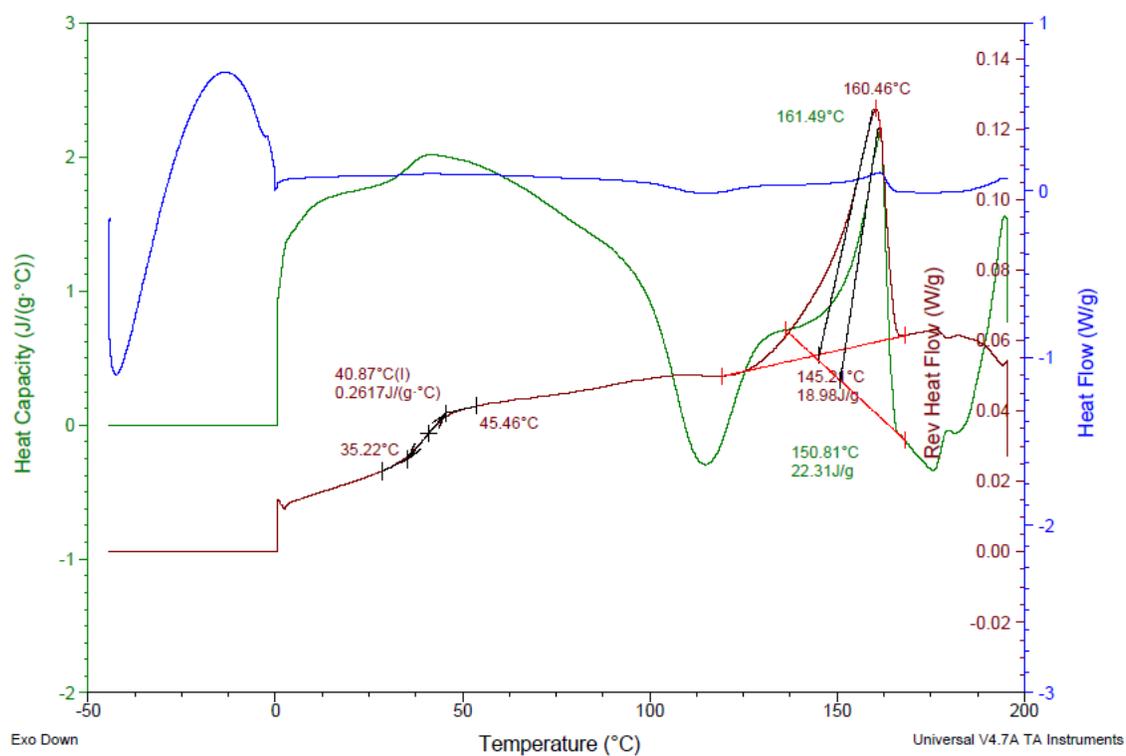
**Fig. 1-1.** Chemical structures of nifedipine and the polymers used in the study (a) nifedipine, (b) EPO, (c) HPMCAS LF and (d) PVPVA 64.



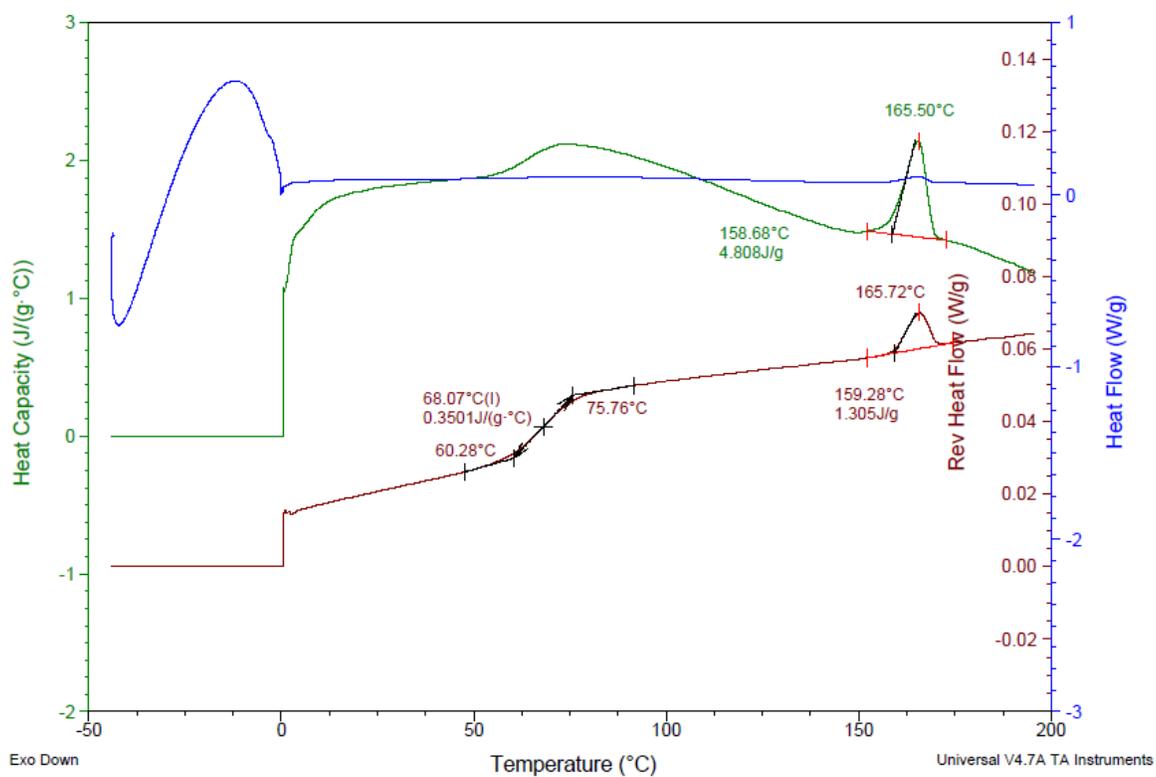
**Fig. 1-2 a and b** FT-IR spectra of HME processed NIF-HPMCAS LF with 5% (a) and 40% (b) drug loading



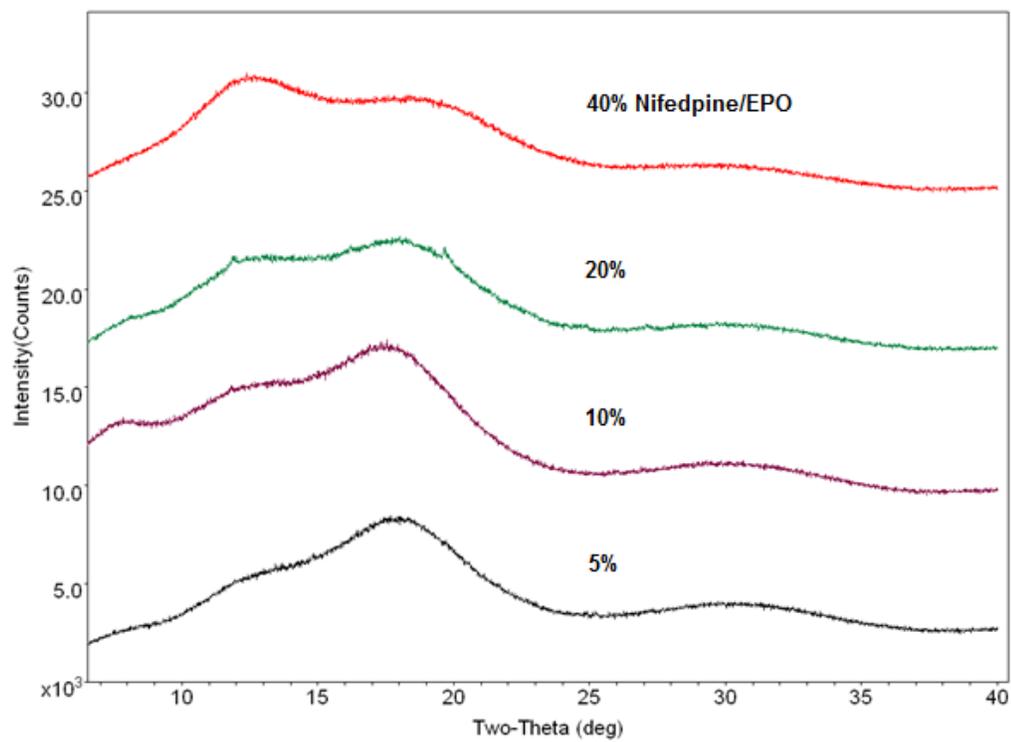
**Fig. 1-3 a and b** FT-IR spectra of HME processed NIF-PVPVA 64 with 5% (a) and 40% (b) drug loading



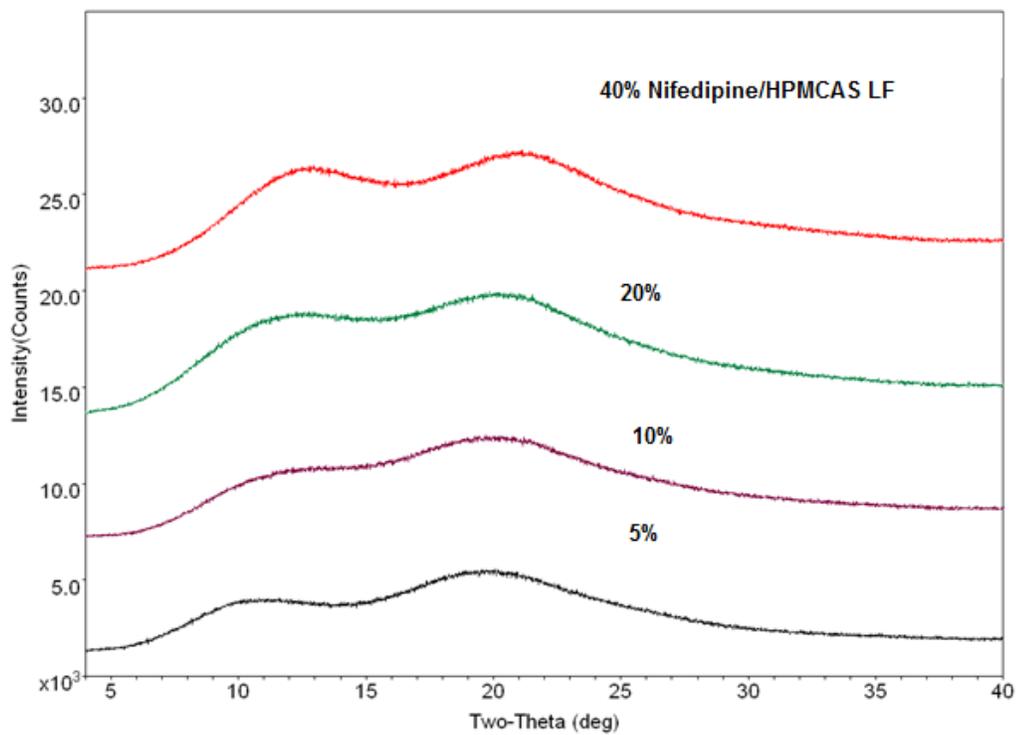
**Fig. 1-4.** DSC thermogram of HME processed 40% DL of nifedipine-EPO



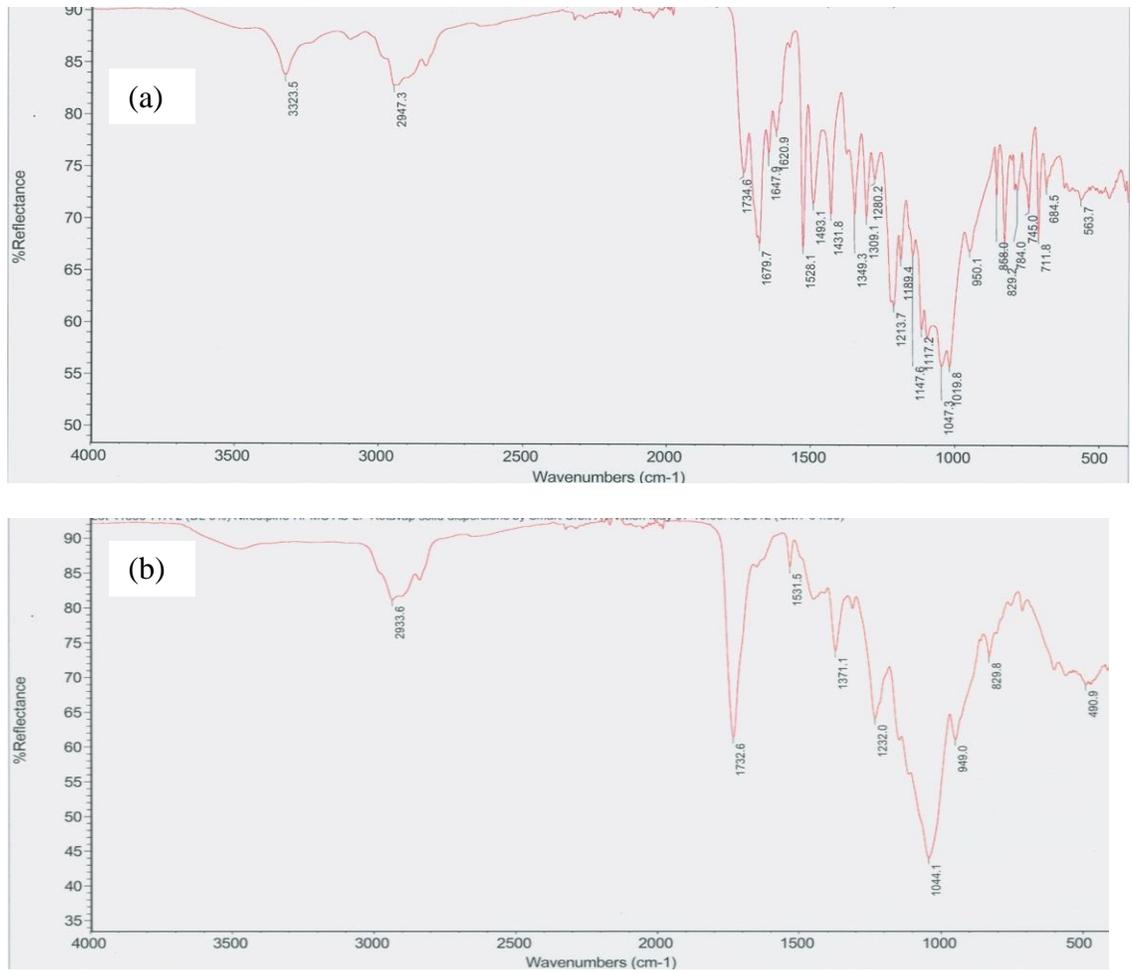
**Fig.1-5.** DSC thermogram of HME processed 40% NIF-HPMCAS LF



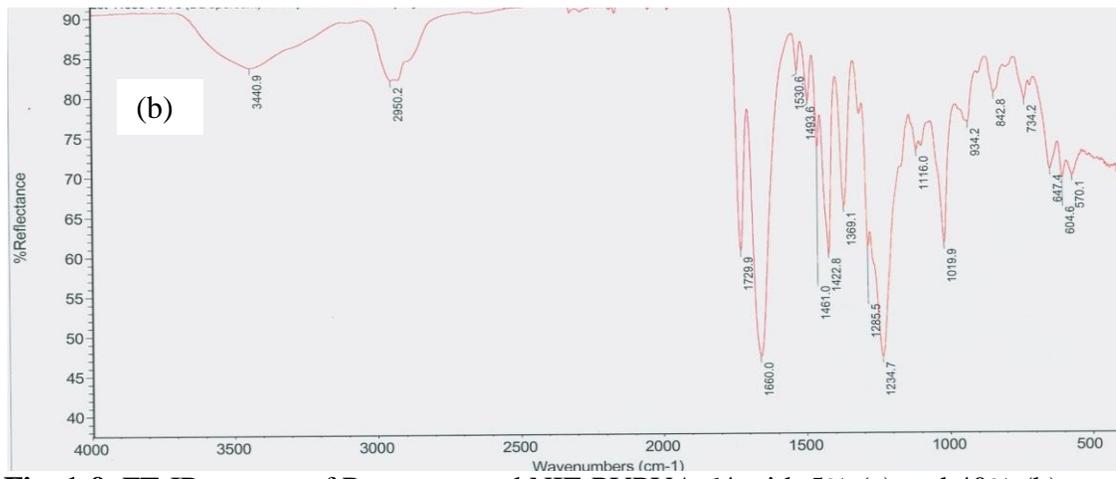
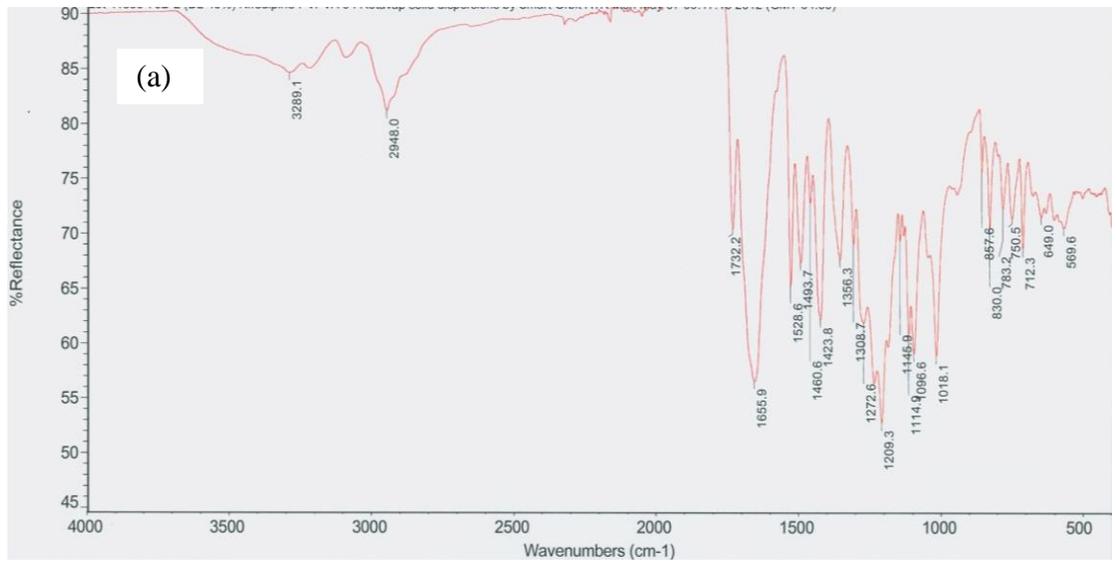
**Fig.1-6.** XRD diffractogram of HME processed NIF-EPO samples at 5, 10, 20 and 40 % nifedipine concentrations



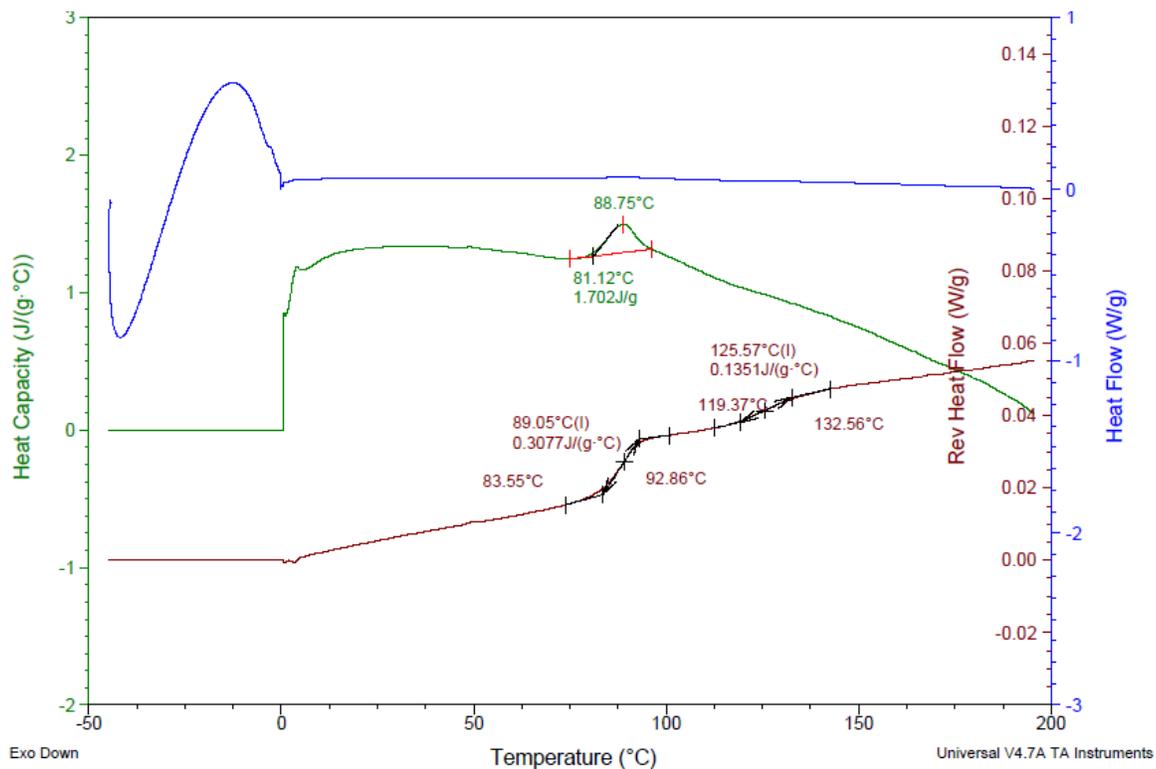
**Fig. 1-7** XRD diffractions of HME processed NIF-HPMCAS LF samples with 5, 10, 20 and 40 % drug concentrations



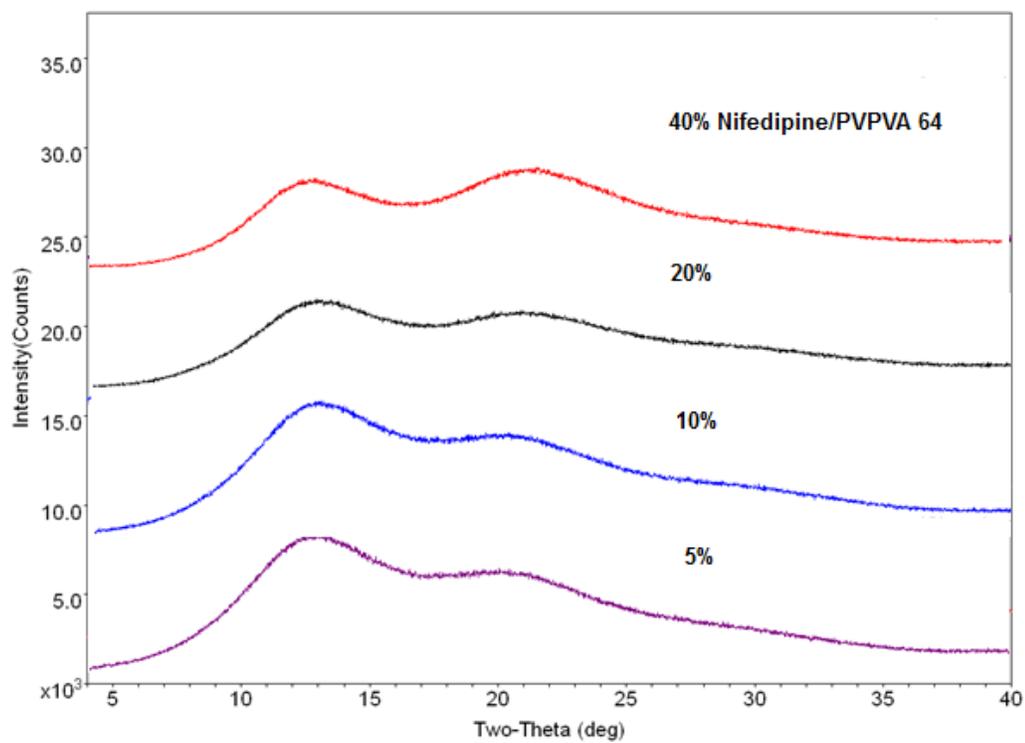
**Fig. 1-8.** FT-IR spectra of Rot processed NIF-HPMCAS LF with 5% (a) and 40% (b) drug loadings



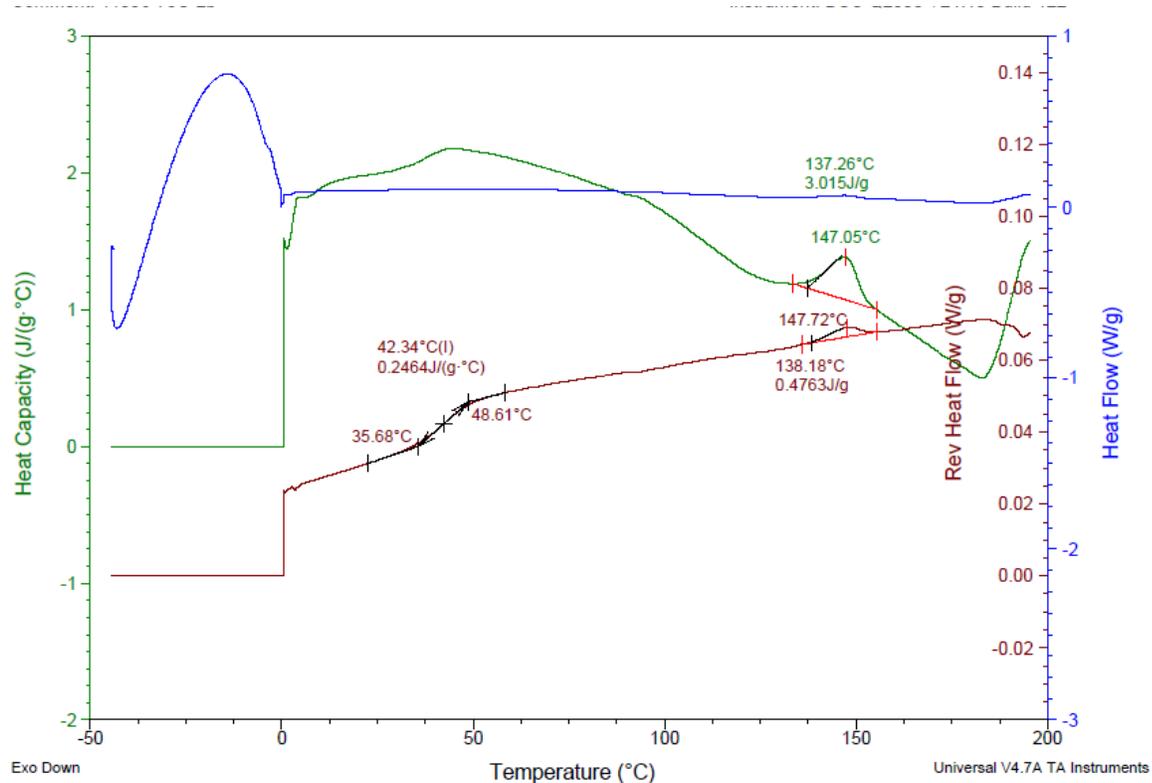
**Fig. 1-9** FT-IR spectra of Rot processed NIF-PVPVA 64 with 5% (a) and 40% (b) drug loadings



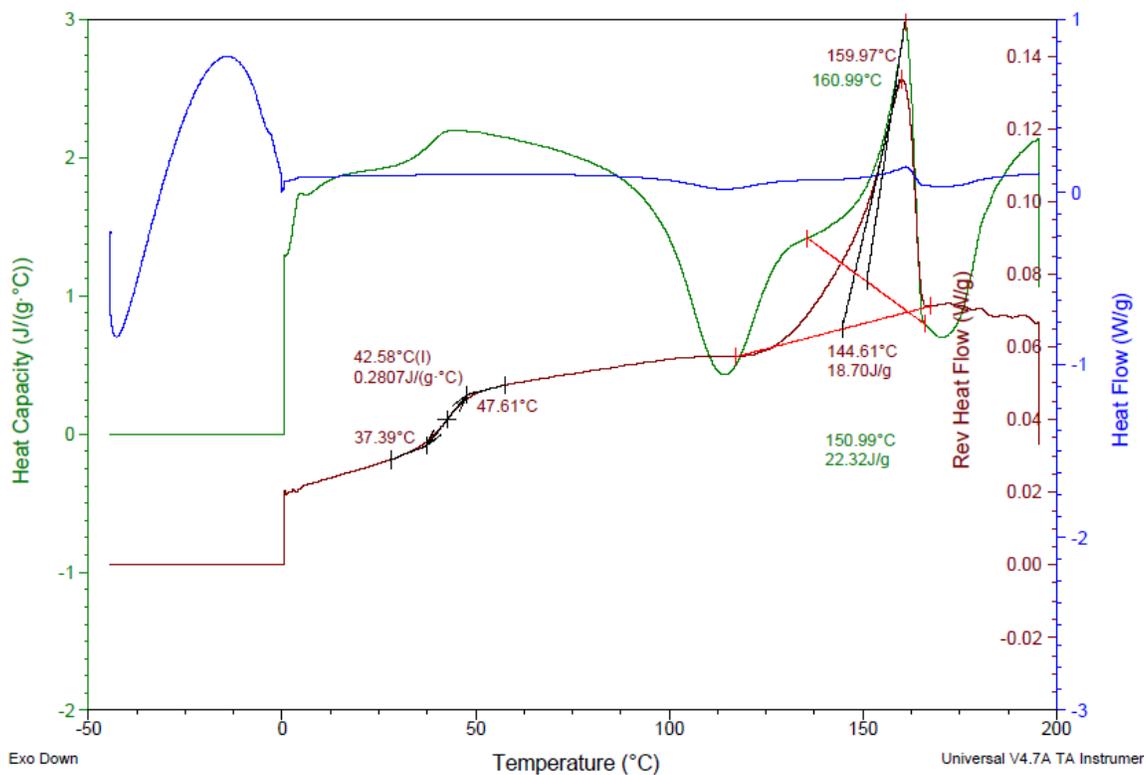
**Fig. 1-10.** DSC thermogram of Rot processed 40% NIF-PVPVA 64 with a presence of two  $T_g$ s



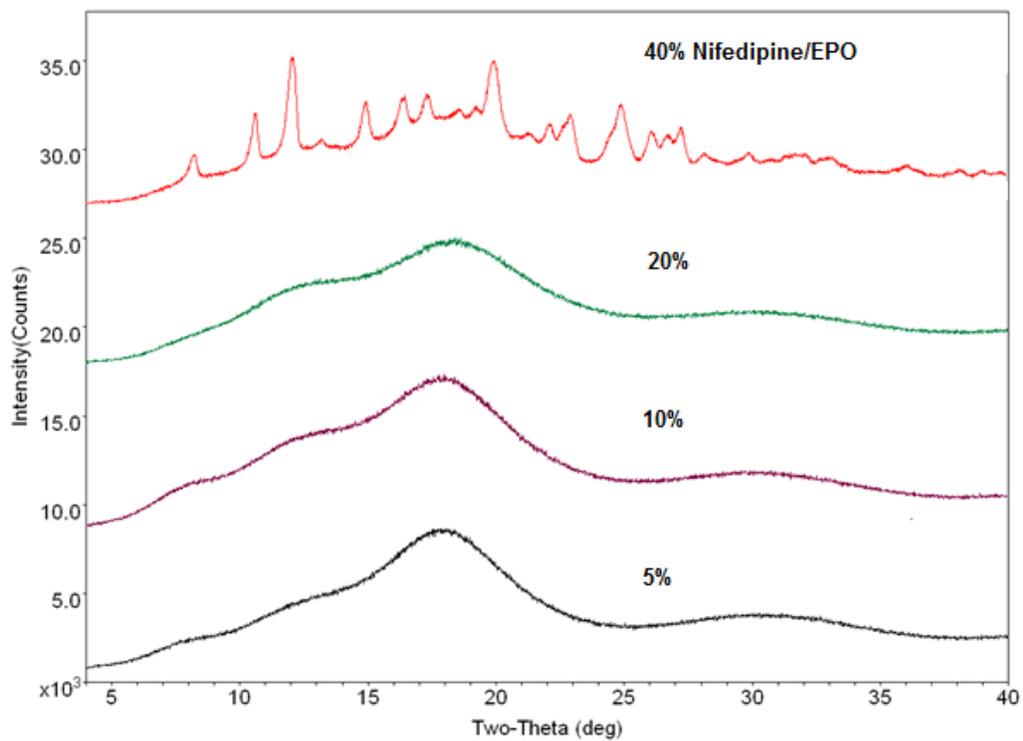
**Fig. 1- 11.** XRD spectrograms of Rot processed NIF-PVPVA 64 at 5, 10, 20 and 40 % nifedipine concentrations



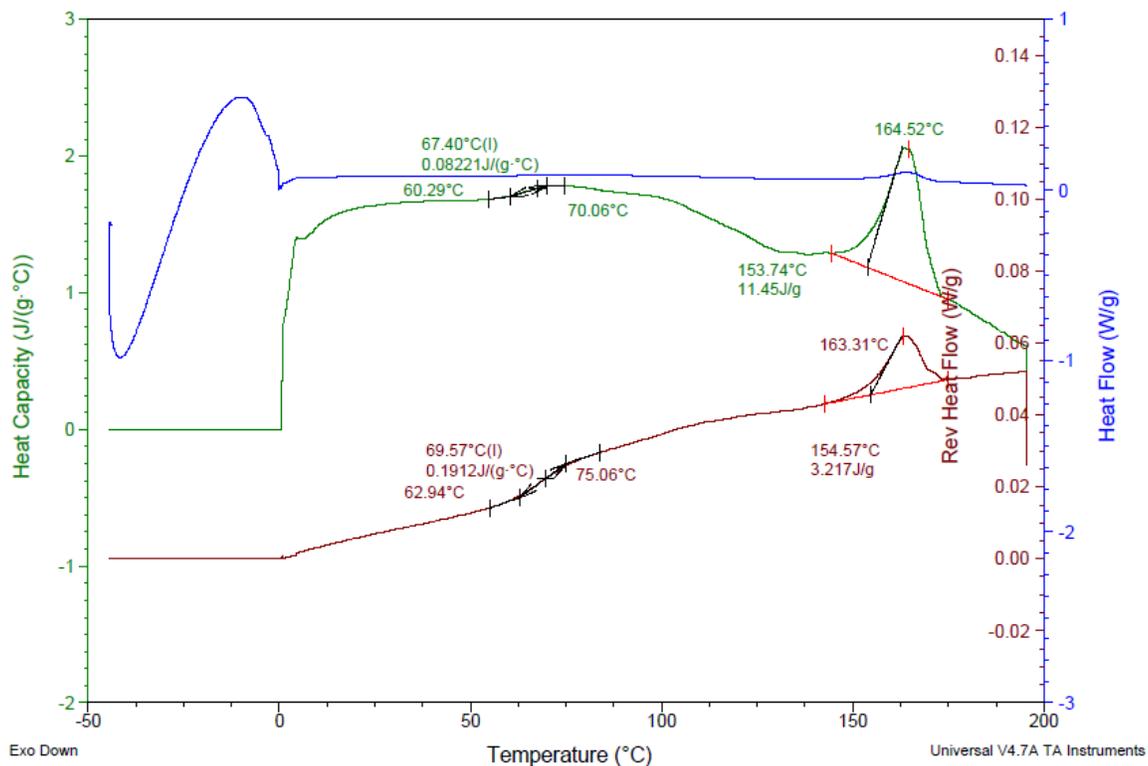
**Fig. 1- 12.** DSC thermogram of Rot processed 20% NIF-EPO with a presence of melting endotherm



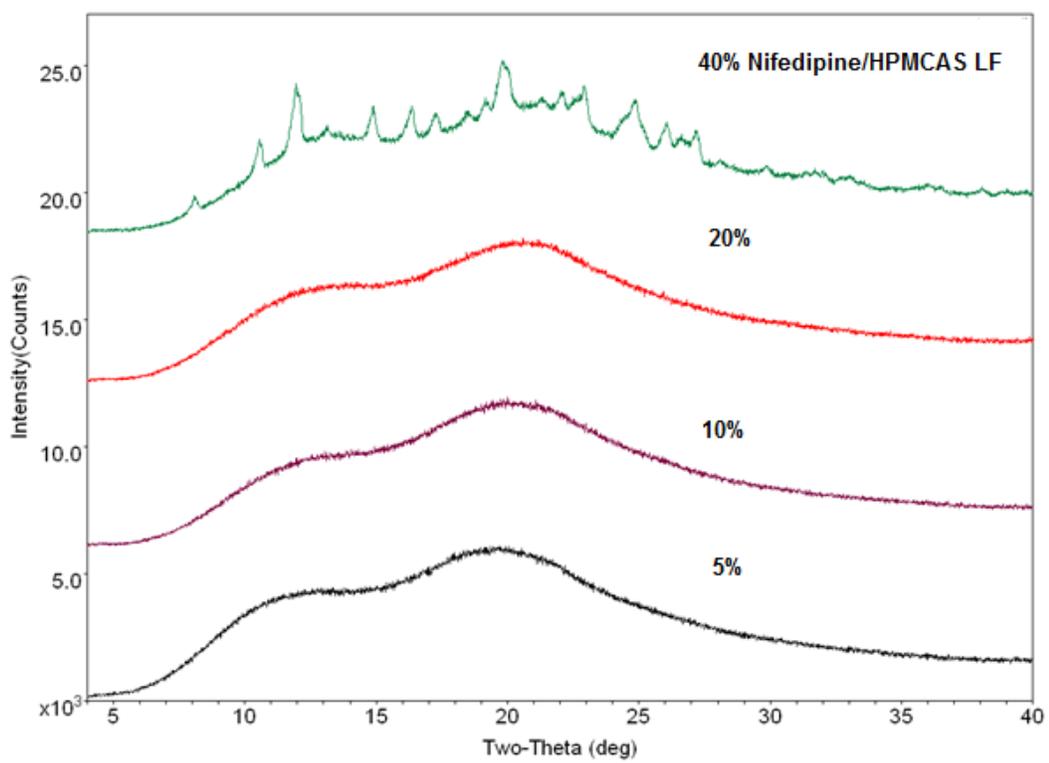
**Fig. 1- 13.** DSC thermogram of Rot processed 40% NIF-EPO with a presence of melting endotherm



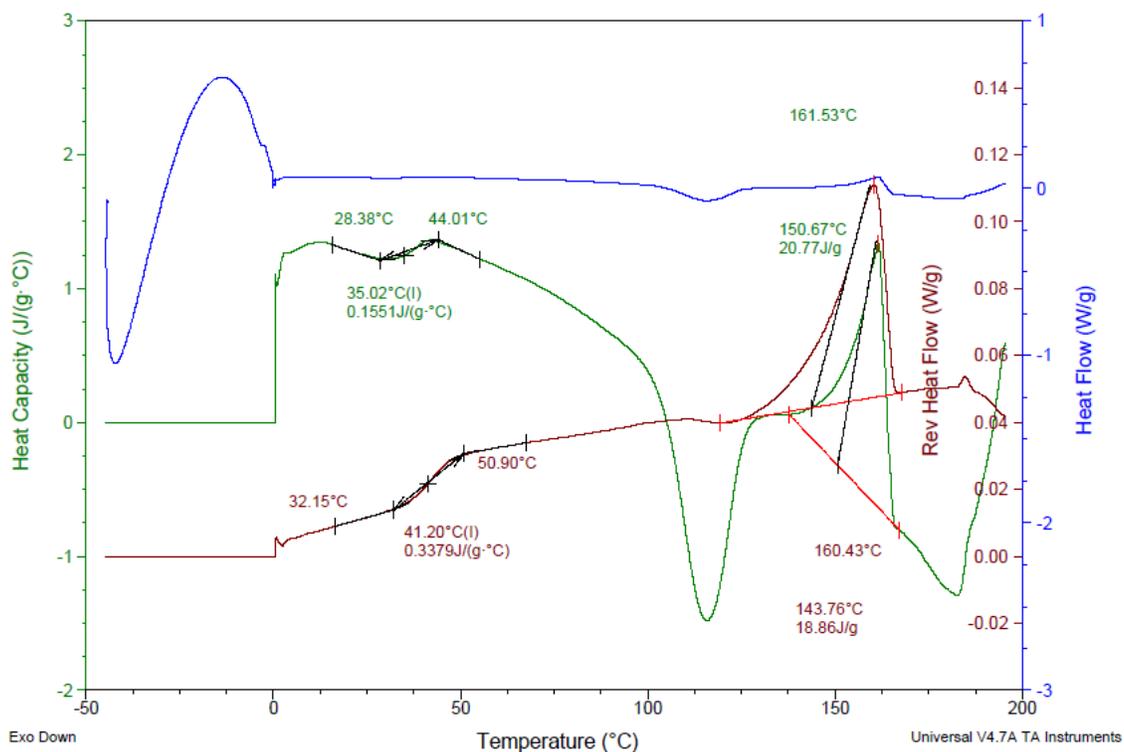
**Fig. 1- 14.** XRD spectrograms of Rot processed NIF-EPO with 5, 10, 20 and 40 % drug concentrations



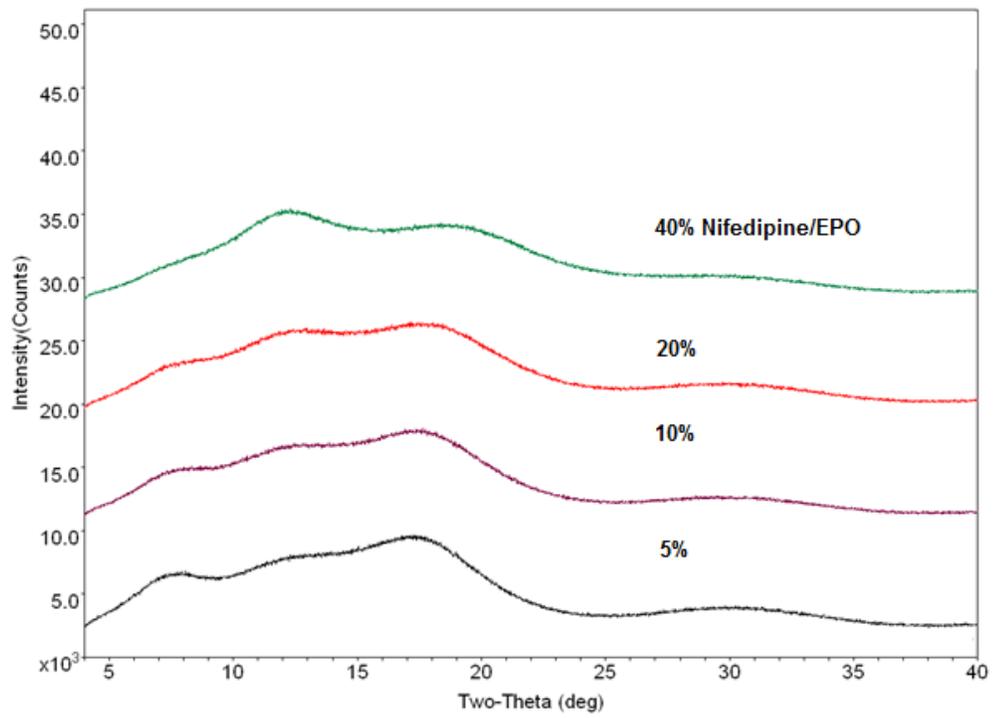
**Fig. 1- 15.** DSC thermogram of Rot processed 40% NIF-HPMCAS LF with a presence of melting endotherm



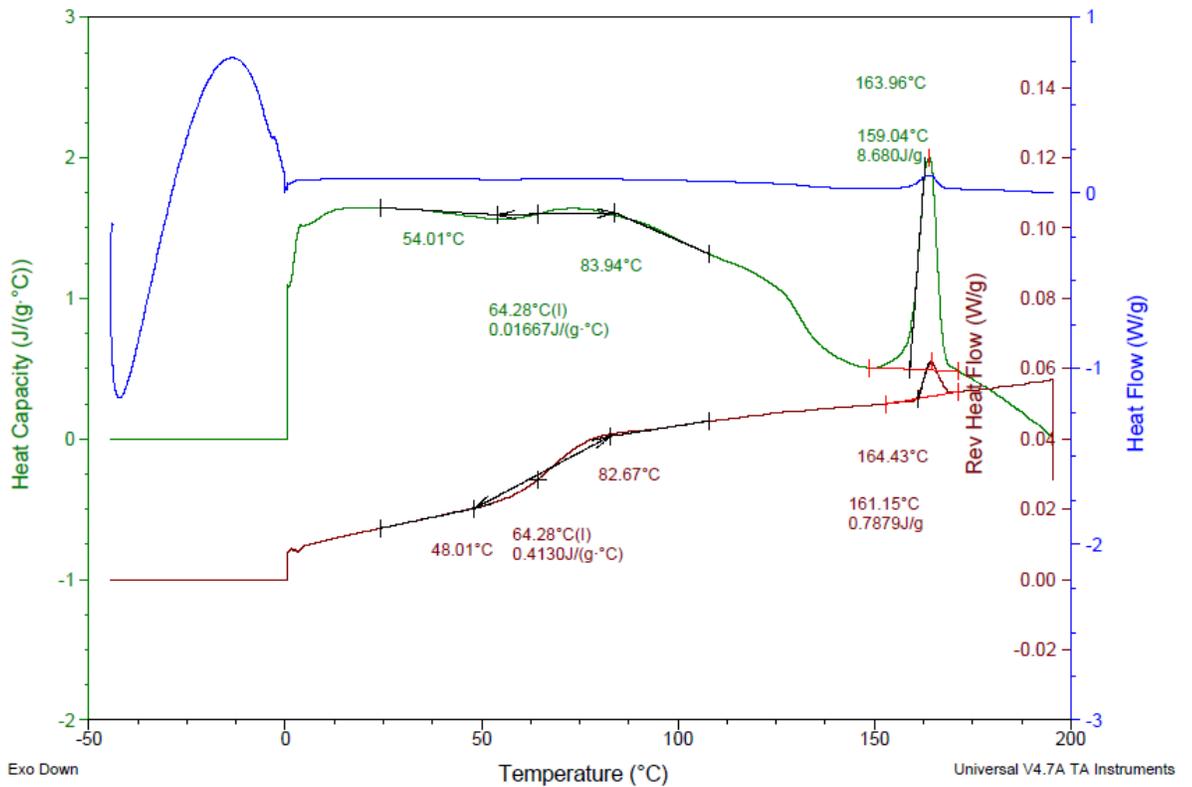
**Fig. 1- 16.** XRD spectrograms of Rot processed NIF-HPMCAS LF with 5, 10, 20 and 40 % drug concentrations



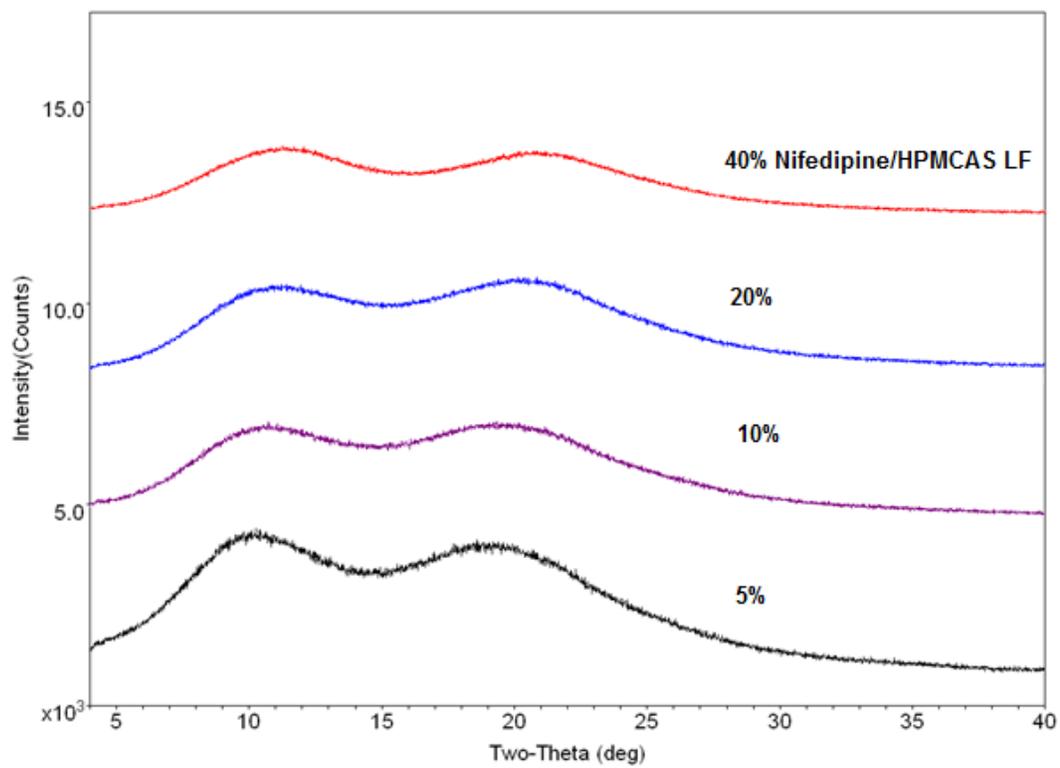
**Fig. 1- 17.** DSC thermogram of SD processed 40% NIF-EPO with a presence of melting endotherm



**Fig. 1- 18.** XRD of SD processed NIF-EPO with drug concentrations of 5, 10, 20 and 40%

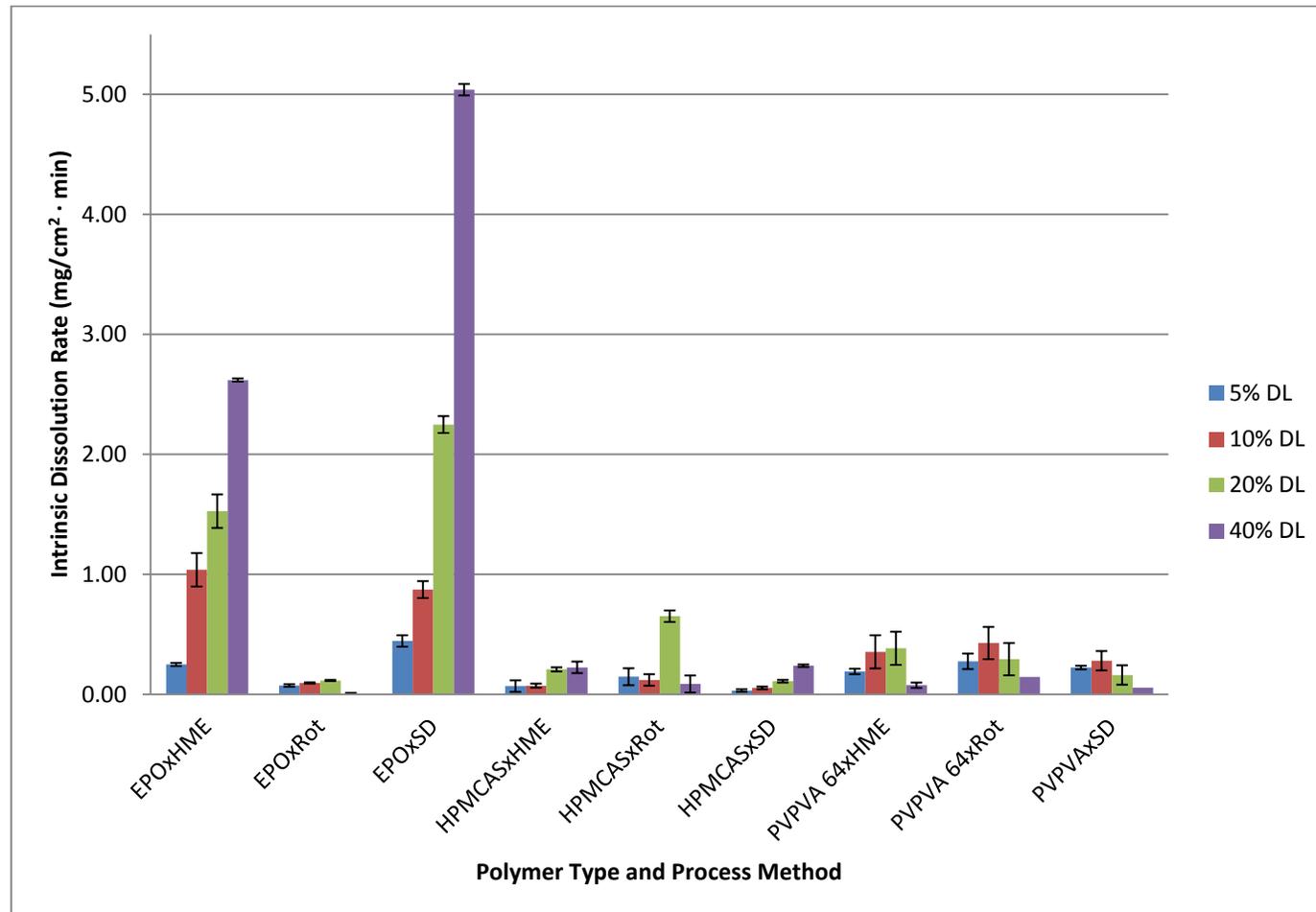


**Fig. 1- 19.** DSC thermogram of SD processed 40% NIF-HPMCAS LF with a presence of melting endotherm

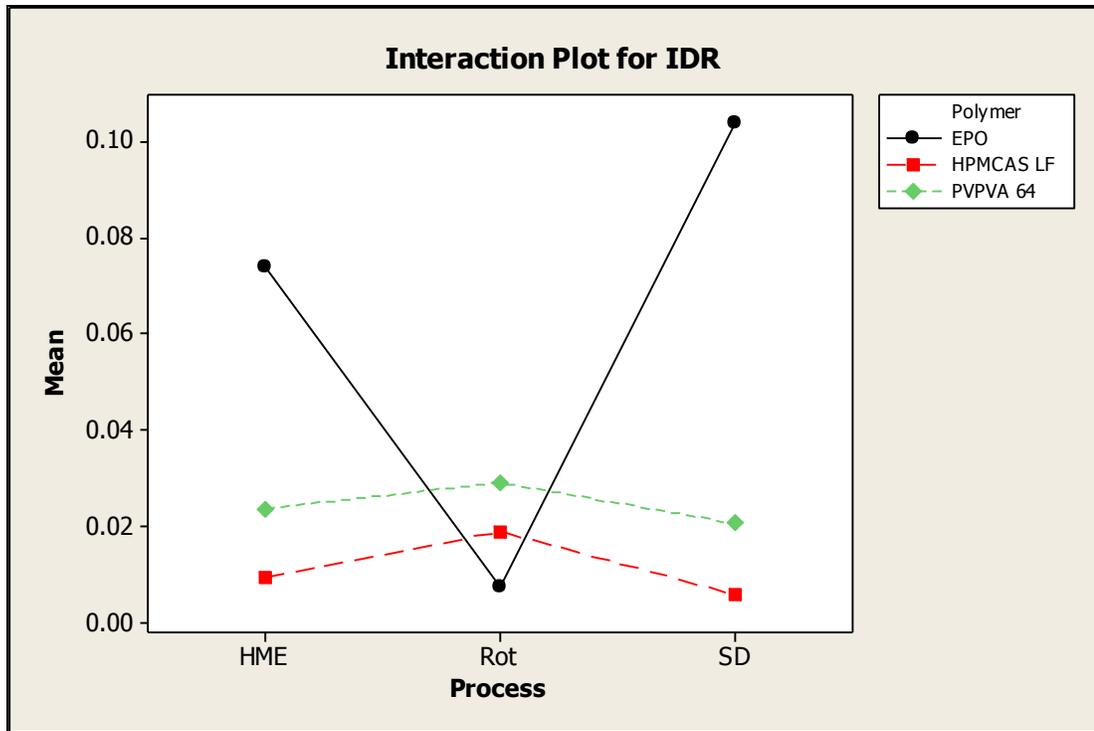


**Fig. 1- 20.** XRD of SD processed NIF-EPO with drug concentrations of 5, 10, 20 and

40



**Fig. 1- 21.** Intrinsic dissolution rates of nifedipine comparing polymer and processing methods with drug concentrations 5, 10, 20 and 40 %



**Fig. 1-22.** Interaction plots of process methods, polymer types and nifedipine concentration in the samples. 1, 2 and 3 are EPO, HPMCAS LF and PVPVA 64 respectively and for process 1, 2 and 3 are HME, Rot and SD respectively

## Manuscript 2

Testing the use of “heat of fusion” in calculations of interaction parameter ( $\chi$ ) in Flory-Huggins and its comparison with the use of melting point depression and solubility parameters

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## **Abstract**

Flory-Huggins (F-H) interaction parameter is used to predict the miscibility of drug-polymer amorphous solid dispersions. Most commonly used method to determining the interaction parameter is by using the solubility parameters or by measuring the melting point depression of the two mixed components. Although these are very popular methods, they are not without limitations. For the solubility parameters, there is a problem with accurate calculations and with melting point depression, the temperature and composition of the system keeps changing even though the interaction parameter is dependent on these values. By annealing the drug-polymer mixture at a set temperature and by determining the equilibrium solubility of nifedipine in polymers, we have been able to improve on the determination of the F-H interaction parameters.

**Keywords:** Flory-Huggins interaction parameter, melting point depression, solubility parameter, DSC, nifedipine, miscibility, polymer

## **1. Introduction**

Most of the poorly water soluble drugs have crystalline structures. Therefore they are challenging to prepare as pharmaceutical formulations due to the low solubility which leads to low bioavailability. In many cases for such a drug, this property can be the limiting factor minimizing the success of the product.

There have been numerous techniques used to formulate such drugs by improving their solubility by manipulating the morphological and other physical-chemical properties. One such technique is to prepare an amorphous solid dispersion of a drug in a water soluble polymer. Compared to the crystalline state, a drug in an amorphous state has higher solubility in a solution due to the higher energy state which is the result of greater entropy and free energy [1]. However in the amorphous form, the drug is thermodynamically unstable for the same reason. Suitable polymers can modify crystallinity of the drug and degree of crystallization thus, improve the thermodynamic stability.

The purpose of producing an amorphous solid dispersion of a drug in an amorphous polymer is to improve the bioavailability of the drug. In this way, high therapeutic concentrations can be incorporated into the formulation. In many cases, if therapeutic concentration is high, the supersaturation state is created. However in the supersaturated state, faster crystallization of the drug may occur during storage as the result of higher kinetic driving force (the molecular mobility of drug in the polymer matrix) and the thermodynamic instability of the amorphous drug.

In order to extend shelf-life, besides limiting drug concentration, polymers with high glass transition temperatures (T<sub>g</sub>s) should be kept at much lower storage temperature (when temperature of storage is deducted from the glass transition temperature of the solid dispersion, the value obtained should be higher than 50 °C) in order to minimize molecular mobility of the drug [1-5]. The drug which is transformed to an amorphous state by the interaction with the polymer must stay so during the shelf life of the product. Therefore knowing the degree of the miscibility of the polymer with the drug is very important.

Flory-Huggins define this interaction parameter,  $\chi$ , eq. (1)

$$\Delta G_{mix} = RT (n_d \ln \phi_d + n_p \ln \phi_p + \chi_{dp} n_d \phi_p) \dots \dots \dots (1)$$

where  $\Delta G_{mix}$  is the change in Gibbs free energy,  $R$  is the gas constant and  $T$  is temperature,  $n_{d,p}$  is the number of moles of drug and polymer respectively,  $\phi_{d,p}$  is the volume fractions of the drug and the polymer respectively and  $\chi$  is the interaction parameter. The first two terms of the equation is the entropy contribution of the system and the last term is the contribution from the change in enthalpy as the result of mixing in eq. (1).

Flory-Huggins interaction parameter,  $\chi$ , is defined as “ the thermodynamic interaction energy of a solvent and a solute” [6] and has been used as a predictive tool to determine the interaction between a drug and a polymer in the molten state. The calculated  $\chi$  can tell whether the drug will be miscible with the polymer used where ( $\chi < 0$ ). Very little or no interaction will produce a ( $\chi > 0$ ) value. In a strong

interaction state between the drug and polymer, the amorphous mixture of the drug will remain stable much longer than if there was no interaction with the polymer.

### 1.1 Solubility parameter for calculating $\chi$

The Flory-Huggins interaction parameter can be calculated using the solubility parameters of Hildebrand [6], by measuring melting point depression or with computational analysis of the drug and a polymer [6-13].

Solubility parameters,  $\delta$ , show similar values for similarly structured solvents and solutes which can be used to select a better solvent for a solute to make a solution.

Solubility parameter can be used to predict the solubility of the solid drug in the polymer in the solid form.

Solubility parameter,  $\delta$ , is defined as the square root of cohesive energy density which is related to the change in the internal energy per volume of a substance eq.

(2).

$$\delta = \left( \frac{E_{coh}}{V} \right)^{1/2} \dots\dots\dots (2)$$

The cohesive energy has been predicted by using structural group contributions of the compounds. The three groups that contribute to the cohesive energy are the dispersion forces, polar interaction and hydrogen bonding interaction which is represented in eq. 3.

$$E_{coh} = E_d + E_p + E_h \dots\dots\dots (3)$$

Since the solubility parameter is the square root of the cohesive energy density, individual solubility parameter component can be represented in eq. (4) suggested by Hansen [15].

$$\delta_{coh}^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \dots\dots\dots(4)$$

By using the solubility parameters of a solvent and a solute, Hildebrand and Scott [16] developed an equation to calculate the Flory-Huggins interaction parameter shown in eq. (5).

$$\chi = \frac{v(\delta_{drug} - \delta_{polymer})^2}{RT} + 0.34 \dots\dots\dots(5)$$

where  $\chi$  is the interaction parameter,  $v$  is the volume of each lattice site,  $R$  is the gas constant and  $T$  is the absolute temperature. The first term is the enthalpy contribution and 0.34 is the value for entropy.

Flory-Huggins theory is based on the Gibbs free energy and it is used to determine the thermodynamic miscibility of a solute in a solvent system shown in eq. (6)

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \dots\dots\dots(6)$$

where entropy of mixing will usually be positive due to mixing of two components but depending on the sign of  $\Delta H_{mix}$ . The miscibility can be favored when  $\Delta G_{mix}$  is negative, where, the solute will readily solubilize in the solvent. They will not mix if  $\Delta G_{mix}$  is positive.

Eq. (5) can be rewritten to determine the interaction parameter shown in eq. (1).

In eq. (1), since the number of moles and volume fraction will always remain as positive values, the sign of the enthalpy term will be determined by the value of

the interaction parameter,  $\chi$ . Therefore, calculating the Flory-Huggins interaction parameter can be useful to predicting the solubility of a component in a system.

### *1.2. Calculations based on melting point depression*

Marsac *et al.* [7] have argued that sometimes specific hydrogen bonding between a drug and a polymer contributes to the miscibility which cannot be distinguished by the solubility parameter calculations. The changes occurred in the melting point of an insoluble drug and a polymer is specific for each polymer which can be measured by the melting point depressions. Starting from that finding the interaction parameter,  $\chi$ , can be calculated.

Melting point depression of a drug and polymer systems have been measured and studied by number of groups in hope to determine the Flory-Huggins interaction parameter [6,8,12]. Nishi and Wang [17] determined the melting point depression of a crystalline polymer (poly (vinylidene fluoride), PVF<sub>2</sub>) by melting it with an amorphous one (poly (methyl methacrylate), PMMA) at 10-80% (w/w) PVF<sub>2</sub> to PMMA ratio. They explained that the depression of melting temperature of the crystalline polymer as the result of mixing of the crystalline polymer with the amorphous one which led to an energy reduction in the overall mixture. This was not the result of morphological effects such as particle size reduction etc. as speculated earlier. They have successfully calculated the interaction parameter for the crystalline and amorphous polymers.

Therefore the melting point depression method was more specifically used to calculate the interaction parameter instead of using solubility parameter [7]. The idea is based on the two compounds' melting point temperature to be specific to its

structure and thus mixing of the two should be predicted. The interaction parameter  $\chi$  can be calculated by using the eq. (7):

$$\left( \frac{1}{T_M^{mix}} - \frac{1}{T_M^{pure}} \right) \frac{\Delta H_{fus}}{-R} - \ln \Phi_{drug} - \left( 1 - \frac{1}{m} \right) \Phi_{polymer} = \chi \Phi_{polymer}^2 \quad \dots(7)$$

where  $T_M$  is the melting point temperature of the drug in the mixture or in its pure state indicated by “mix” and “pure” respectively,  $\Delta H_{fus}$  is the heat of fusion of a drug,  $m$  is the degree of polymerization and  $\Phi$  is the volume fraction.

This approach has been used quite frequently since it is a convenient and practicable because melting points can be easily determined by the differential scanning calorimeters. However, it must be mentioned that the interaction parameter,  $\chi$ , is both temperature and concentration dependent which means that the value of  $\chi$  can change with change in either temperature or concentration of the drug present in the polymer [6]. However, these are not taken into consideration with the melting point depression method where  $\chi$  is calculated using a set of drug-polymer mixtures with decreasing drug concentrations which alters the melting point temperature in return. To obtain the interaction parameter,  $\chi$ , with one set of temperature and concentration, another approach has to be taken.

### *1.3 Calculations based on heat of fusion*

In this study, heat of fusion of the undissolved drug in the polymer will be used to determine the equilibrium solubility. Using this value we can calculate the solubility of the drug in the polymer which will be used to calculate the actual volume fraction of the dissolved drug in the drug-polymer mixture. The Flory-

Huggins interaction parameter,  $\chi$ , have been calculated for a drug-polymer system of nifedipine with three polymers: (Eudragit E 100, hydroxypropyl methylcellulose acetate succinate and poly (vinyl pyrrolidone vinyl acetate) by using the melting point depression approach with the actual volume fraction of drug in the mixture and one annealing temperature that is specific for one measurement at a time.

The Flory-Huggins theory eq. (6) takes into account of the size differences between a small molecule (i.e. drug) and a larger molecule (i.e. polymer) by accepting that the segments of the polymer chain are in equal size as the smaller molecule (drug). Since then, research groups have taken this work and applied to crystalline drug and amorphous polymer systems to calculate the interaction parameters [6-12]. The idea is that when a crystalline drug is mixed in an amorphous polymer and they are miscible, the chemical potential of the drug will be smaller than the pure drug which will be shown through a depression in the melting point of the drug in the mixture. However, it must be noted again that the interaction parameter,  $\chi$ , is dependent on drug concentration (melting of the drug at a specific volume fraction) and the melting temperature of each combination. With the melting point depression approaches these two are not constant throughout which can lead to overestimated value of  $\chi$  than the actual one.

In this paper, an amorphous solid dispersion of a drug and a polymer that are “miscible” means that the amorphous drug and amorphous polymer exist as a one-phase by a liquid-liquid mixing of the two components in the molten state [5].

## **2. Materials and Methods**

## 2.1. Materials

Eudragit E-100, EPO (Methacrylate copolymer) was kindly provided by Evonik (Parsippany, NJ). Nifedipine was purchased from RIA International (East Hanover, NJ), HPMCAS LF (hydroxypropyl methylcellulose acetate succinate) by Shin-Etsu Chemical Co., Ltd (Biddle Sawyer Corp, New York, NY) and PVPVA 64 (polyvinyl pyrrolidone co-vinyl acetate 64) by BASF (Florham Park, NJ) were purchased. Chemical structures and physical-chemical properties of the drug and polymers used are given in Figure 1-1 and in table 1.

## 2.2. Methods

### 2.2.1. Solubility parameter calculations

Solubility parameters of nifedipine and polymers were calculated using Eqs. (18) - (20).

#### 2.2.1.1. Sample preparation, annealing; characterization of the annealed samples; the measurement of heat of fusion and melting point temperature determination

Physical mixtures of nifedipine and a selected polymer; EPO, HPMCAS LF and VA 64, respectively, in loads of 30 to 90% (w/w) were prepared in a mortar by mildly stirring the weighed amount of the drug and the polymers. The samples were packed into aluminum pans individually (5-7 mg each) and annealed at a set temperature (130, 155 and 165 °C) in a muffle furnace for 18 hours. The annealing temperatures were chosen based on the drugs melting point (172-173 °C). We selected two temperatures (10 and 20 °C) below the melting point of the drug and another temperature based on the polymer with the highest glass transition

temperature was also selected and our third temperature was 10 °C above the glass transition temperature (130°C). At this temperature, there is no chemical decomposition and the polymer will be flexible.

Following thermal annealing, each sample pan was quench-cooled and reheated at 10 °C/ minute in a Differential Scanning Calorimeter (DSC) Q2000 (TA Instruments, New Castle, DE) to measure the change in heat capacity and the melting point of the sample. Heat of fusion ( $\Delta H_{fus}$ ) of nifedipine obtained from the DSC measurement was used to calculate the weight fraction of the undissolved nifedipine in a gram of polymer. The weight fraction was used to estimate the volume fraction ( $\phi$ ) of dissolved nifedipine. By applying this value, the volume fractions used in the Flory-Huggins equation were corrected accordingly for  $\chi$  calculation. The value of  $\chi$  was also calculated from the observed melting point depression ( $\Delta T_m$ ) data and estimated  $\phi$  (from the total weight fraction in the formulation). The solubility parameters were determined based on eq. (3) and Hildebrand and Scott's method eq. (4) was used to calculate the interaction parameter.

#### *2.2.1.2. Determination of $\chi$ by the use of melting point depression*

In an amorphous solid dispersion, mixing of a crystalline drug which has a high melting temperature with an amorphous polymer having some miscibility with the drug, will lower the melting temperature of the drug in a mixture containing increasing amounts of polymer furthermore. Their melting point temperature should be determined individually and placed in eq. (7).

2.2.1.3. *Development of formula to determine nifedipine solubility with heat of fusion measurements*

In the annealing experiments of the physical mixtures of nifedipine and polymer, heats of fusion of undissolved nifedipine were measured as described in 2.2.1.1 the values measured were plotted against the drug weight fraction in each mixture to obtain standard curves for each set of nifedipine -polymer mixture. These were used to determine the solubility of nifedipine in each polymer and in estimation of the amount of nifedipine in a mixture with an unknown drug load.

From the heat of fusion measurement we can determine the amount (weight) of undissolved nifedipine by the following mass balance eq. (8)

$$[\text{Wt. of undissolved drug}] = [\text{Total wt. of drug}] - [\text{Wt. of drug dissolved in polymer}] \dots (8)$$

If we divide eq.(8) with the total weight of the formulation, we can obtain the equation expressed in weight fraction eq.(9)

$$f_{d,u} = f_d - Xf_p \dots (9)$$

where  $f_d$  is the total weight fraction of nifedipine,  $f_p$  is the weight fraction of the polymer and X is the solubility which is the amount of nifedipine in grams dissolved in one gram of polymer.

Since the mixture consists of two components, by adding  $f_d$  and  $f_p$  will equal unity (=1) in which case, eq. (9) will become eq. (10)

$$f_{d,u} = f_d(1 + X) - X \dots (10)$$

It also represents  $\Delta\bar{H}_m$ , the heat required to melt the undissolved nifedipine in a gram of formulation, which is determined by the DSC. Since eq. (3) involves

calculation of  $\Delta h_m$ , which is the molar heat of fusion of nifedipine per gram of the drug, we can replace  $f_{d,\mu}$  with  $\Delta\bar{H}_m$  leading to eq. (11)

$$\Delta\bar{H}_m = f_{d,u} \Delta\bar{h}_m \dots\dots\dots(11)$$

and rearranging eq. (11) and substituting it into eq. (10) it will yield eq. (12)

$$\Delta\bar{H}_m = f_d(1 + X)\Delta\bar{h}_m - X\Delta\bar{h}_m \dots\dots\dots(12)$$

Once heat of fusions ( $\Delta\bar{H}_m$ ) are obtained they can be plotted against weight fraction of nifedipine, having the slope  $(1 + X)\Delta\bar{h}_m$  and the intercept of  $-X\Delta\bar{h}_m$  as shown in Figure 3 a, b and c.

Once the solubility of nifedipine in a given polymer is determined, the interaction parameter,  $\chi$ , can be further obtained by using eq. (15).

$$\Delta h \left( 1 - \frac{T}{T_{melt}} \right) RT \ln \phi_1 - RT\phi_2 = \chi\phi_2^2 RT \dots\dots\dots(15)$$

The solubility parameters of the polymers and nifedipine were calculated using the Hoftzyer and Van Krevalen method and are reported in Table 2. Each solubility parameter component can be calculated using the equations shown below:

$$\delta_d = \frac{\sum F_{di}}{V} \dots\dots\dots(16)$$

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \dots\dots\dots(17)$$

$$\delta_h = \frac{\sqrt{\sum E_{hi}}}{V} \dots\dots\dots(18)$$

In the aforementioned equation,  $F_{di}$  is molar attraction constant due to dispersion component,  $F_{pi}$  is molar attraction constant due to dispersion component and  $V$  is the molar volume of substance.

### 3. Results

Once the solubility parameters were calculated, Flory-Huggins interaction parameters were calculated using eq. (4) and are reported in Table 2.

The heat of fusion of undissolved nifedipine in each polymer mixture will change depending on the concentration of polymer in the mixture as well as the polymer used shown in Fig 2a-c. Plotting the change in heat of fusion of nifedipine ( $\Delta H_m$ ) annealed at different temperatures at different weight fraction of nifedipine and polymer physical mixtures will yield slopes shown in Figure 2-2 a-c. From the estimated solubility, the interaction parameters were calculated and are reported in Table 3. The only problem with determining the solubility of nifedipine came when the solubility value of nifedipine in EPO annealed at 130°C which was negative because the nifedipine was not soluble in EPO after a certain increase in the polymer concentration at that temperature. Since the solubility value was negative, we could not calculate the interaction parameter. The standard curves obtained for nifedipine dispersed in EPO, HPMCAS LF and PVPVA 64 respectively, seem to be all linear ( $R^2 = 0.9972, 0.9992$  and  $0.974$  respectively in the given order); indicating that the solubility (X) of nifedipine can be determined from these graphs. The related equations are shown by eqs. (8)-(12). Accordingly, we obtained 6.7% solubility with nifedipine in EPO, 13.9% in PVPVA 64 and 13.2% in HPMCAS LF with no further calculations. This rough estimates could be used in formulation developments since it is fast method for comparisons and evaluations. Nifedipine-EPO EPO, which has the lower Tg (52°C) than the other

two polymers (100 and 120 °C) seems to dissolve more drug. Therefore, at the annealing temperatures, EPO chains are much more flexible compared to the other two polymers which may lead to more mixing. The more miscible the drug is with the polymer, the slope tends to be smaller.

If the hydrogen bonding was the dominant cause of the drug-polymer miscibility, as seen from Table 1, HPMCAS LF should have been the best candidate for solubilizing the drug having 1 donor and 7 acceptor sites whereas EPO has only 7 acceptors and PVPVA 64 has 3 acceptors. However, the T<sub>g</sub> of values in Table 1 show that HPMCAS LF has the highest T<sub>g</sub> and this polymer property is dominating the miscibility of the drug-polymer mixture.

As the annealing temperature increases, the interaction parameter,  $\chi$ , obtained in the heat of fusion as well as melting point depression show a decreasing trend except for nifedipine-HPMCAS LF combination around 155 and 165 °C, which could be explained by the insignificant differences created by small increase of temperature from 155 to 165 °C. When these two are grouped and compared with the interaction parameter value calculated at 130 °C, the same decreasing trend can be seen.

The decreasing trend in the interaction parameter values can be explained by the increase in polymer mobility and flexibility at elevated temperatures.

Following the annealing processes of drug polymer mixtures, melting points were measured and used to calculate the interaction parameter as well shown in Table 3 under melting point depression.

#### 4. Discussions

The  $\chi$  values calculated by each method, heat of fusion and melting point depression as well as from solubility parameters are shown in Table 2.3. As the annealing temperature increases, the interaction parameter calculated by the heat of fusion and melting point depression methods show a trend to decrease which should be the case with the polymer being more mobile and flexible ready to incorporate more drug molecules within themselves. The interaction parameters calculated from solubility parameters a different trend compared to those calculated from the other two methods. It has been suggested that solubility parameter calculation by itself maybe too limited to be used as a guide for predicting the miscibility of a drug in polymer [17, 20]. For example, the solubility parameter calculations may not be as accurate or specific to the state (crystalline vs. amorphous) of the compound as it should be and it could change with changes in the temperature of the system. Since the solubility parameter values used for the calculation were taken at a lower temperature than the annealing temperature, this discrepancy may be explained. Also it has been suggested that solubility parameter may change with the change in system's temperature [17] and suggested earlier, it does not differentiate specific bonding interaction that could contribute to a stable mixture [21]. With this in mind, the results obtained using the solubility parameter calculations show a deviation from the interaction parameters calculated using the other two methods. In general,  $\chi$  values calculated by melting point depression were lower than the  $\chi$  calculated by heat of fusion method. This could be so, because the heat of fusion method takes into consideration only the dissolved

portion of the drug and only that particular amount is used to calculate the actual weight fraction. Melting point depression does not take into account the actual weight fraction of the dissolved drug which leads to a gross over estimation of solubilized drug in each drug-polymer system.

The second problem with the use of melting point depression approach is that the temperatures used to calculate  $\chi$  keep changing with the change in drug fraction in each system. Since  $\chi$  is temperature dependent, it would be a better choice to use one temperature setting (i.e. the heat of fusion approach) than to use a range of temperatures.

Since the melting point depression method calculates the interaction parameter from a slope where the change in temperature is plotted against the change in the fraction of the polymer, the  $\chi$  obtained from the slope is neither from one temperature nor a single concentration. Therefore, the melting point depression method does not follow the assumption of the Flory-Huggins theory for interaction parameter calculations where it is temperature and concentration dependent.

However, the heat of fusion method determined the solubility of nifedipine in the polymer and then determined the equilibrium solubility of the drug. The calculated amount of the dissolved nifedipine volume fraction was used to determine volume fraction of the polymer. Also, by annealing the mixtures of nifedipine and the polymer at a set temperature, the miscibility of the two were determined at one temperature setting which meant that the temperature and the concentration were kept constant for calculating the interaction parameter.

There are several assumptions that are made in this solubility estimation that need to be addressed. Firstly, during the annealing process, not all of the drug will melt because the melting point of the drug was not exceeded while annealing. The changes in the heat of fusion are the result of the change in the polymer concentration only. If the total mass of the drug were melted, we will not observe a heat of fusion. Secondly, the heat of fusion of nifedipine, per gram, remains the same without taking into account of the formation of other polymorphs. Thirdly, there is no surface effect added to the equation since the assumption is that the particles in the physical mixture are not small enough to cause melting point depression by giving off excess energy. Since the amount of drug in the physical mixture is at the higher end, it can be assumed that the residual undissolved drug left in the mixture, the particles are large enough to not contribute to providing excess energy. Lastly, the period of time which the physical mixture is being annealed is long enough for the drug to thoroughly mix with the polymer at the selected annealing temperature and thus the dissolved drug is homogeneously spread within the polymer.

There was a trend that could be observed with using the heat of fusion method especially with the PVPVA 64 polymer where the increase in the annealing temperature resulted in a smaller interaction parameter,  $\chi$ , value whereas the melting point depression method does not show that trend but does the opposite with increasing values. This shows that the melting point depression method is not sensitive to temperature change of the system.

## **5. Conclusions**

We have been able to show that by annealing a drug in a polymer before obtaining the melting point depression temperature of nifedipine in polymer systems and calculate the solubility of the drug in polymer, we can correct the overestimated volume fraction of the actual dissolved drug in the polymer. Also by using an annealing method, there is only one temperature value that was used throughout the experiment. These have been done in order to stay true to the obtaining the Flory-Huggins interaction parameter where the composition and temperature must stay constant. This is something research groups have not considered doing previously which we believe adds value to estimating a more accurate interaction parameter values. The solubility determination of nifedipine in polymer mixtures using the heat of fusion method have shown to give a crude estimation for selecting a polymer which can dissolve the highest amount of nifedipine. This can be used as a quick method of detection while selecting different polymers for amorphous drug-polymer mixtures.

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**Table 2-1.** Physicochemical properties of (a) nifedipine, (b)the polymers used; Eudragit E 100, HPMCAS LF and PVPVA 64 where Tg and Tm are the glass transition and melting point temperatures and  $\Delta H_{fus}$  is the heat of fusion of pure nifedipine

(a)	Molecular Weight (g/mol)	Tg Tm (°C)	H-bonding	Charge	$\Delta H_{fus}$
Nifedipine	346.34	Tm 172.1 Tg 47±1	1 donor 7 acceptors	Neutral	106.4±3.63

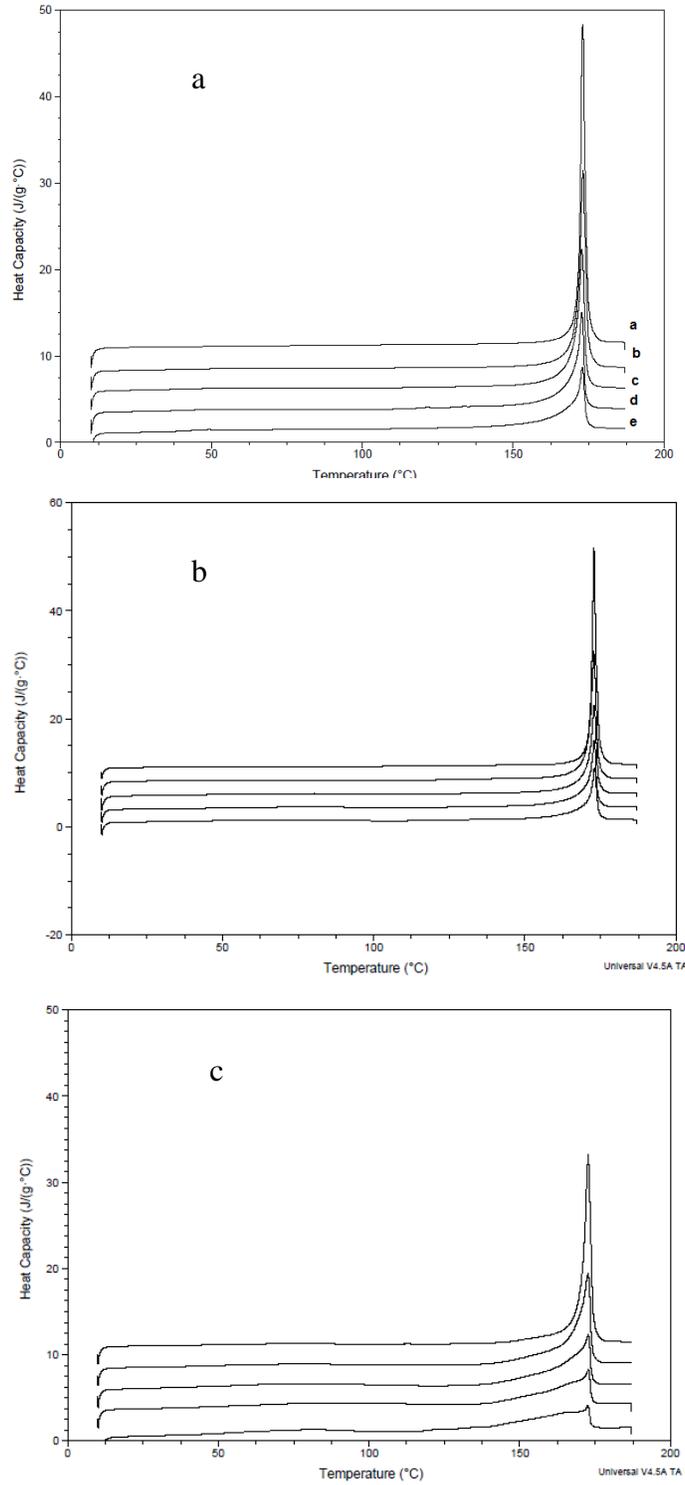
(b) Polymer	Polymer type	Monomer Molecular Weight (g/mol)	Mol. Weight (g/mol)	Tg (°C)	H-bonding	Charge
Eudragit E 100	Copolymer	399.52	135000	52	7 acceptors	Cationic
HPMCAS LF	Homopolymer	286.28	18000	120	9 acceptors 6 donors	Anionic
PVPVA64	Random copolymer	197.23	45000-70000	100	3 acceptors	Non-ionic

**Table 2-2.** Calculated solubility parameters of nifedipine and polymers

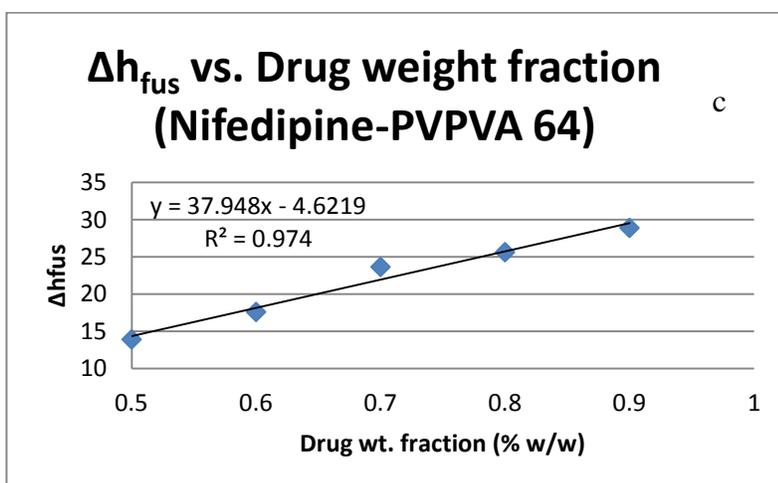
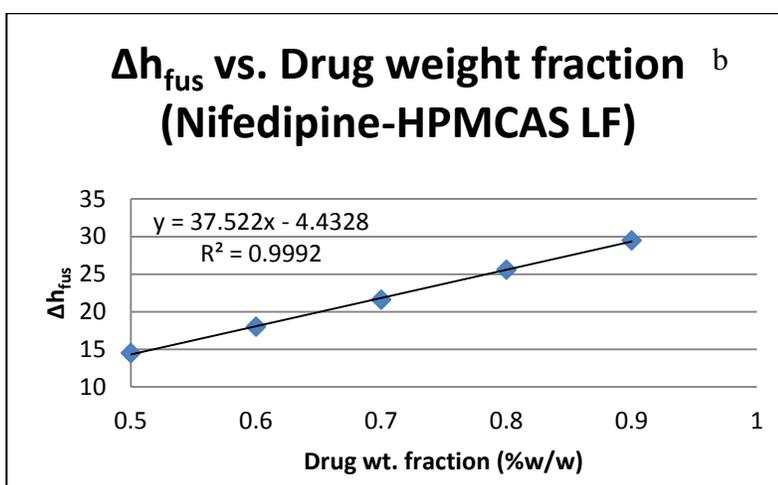
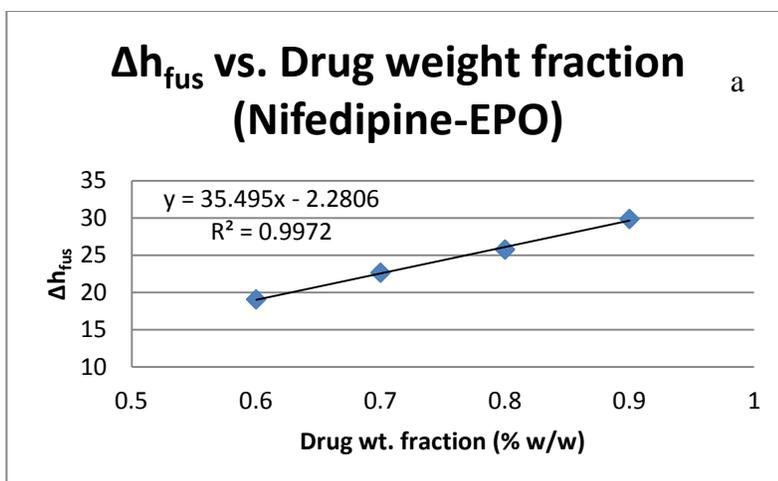
<b>R group</b>	mono MW (g/mol)	$\bar{\delta}_i$ (J/cm <sup>3</sup> ) <sup>1/2</sup>	V <sub>i</sub> (cm <sup>3</sup> /mol)	$\bar{\delta}$ (van Krevelen)
<b>Eudragit EPO (Methyl:Butyl=1:1)</b>				
R=CH <sub>3</sub>	257.33	20.76	221.58	
R=C <sub>4</sub> H <sub>9</sub>	299.41	19.96	270.69	20.4
<b>HPMCAS</b>				
R=H (C 12 H 20 O 10)	324.3	38.40	147.94	
R=CH <sub>3</sub> (C 18 H 32 O 10)	408.4	20.95	293.74	
R=COCH <sub>3</sub> (C 24 H 32 O 16)	576.5	23.20	378.94	
R=COCH <sub>2</sub> CH <sub>2</sub> COOH (C 36 H 44 O 28)	924.7	28.14	499.18	
R=CH <sub>2</sub> CH(OH)CH <sub>3</sub> (C 30 H 56 O 16)	672.8	26.02	463.96	
R=CH <sub>2</sub> CH(OCOCH <sub>3</sub> )CH <sub>3</sub> (C 42 H 68 O 22)	925	20.96	694.96	
R=CH <sub>2</sub> CH(OCOCH <sub>2</sub> CH <sub>2</sub> COOH)CH <sub>3</sub> (C 54 H 80 O 34)	1273.2	24.49	815.2	26.0
<b>PVP VA64</b>				
1-vinyl-2-pyrrolidone	111.1	25.96	82.28	
vinyl acetate	86.1	22.28	66.87	24.3
<b>Nifedipine</b>	346.34			24.8

**Table 2-3.** Calculated  $\chi$  interaction parameter by three different methods

Physical Mixture	Annealing Temp (K)	Flory-Huggins $\chi$ Parameter		Solubility Parameter Calculated $\chi$
		Heat of Fusion	Melting point depression	
Nifedipine-EPO	403.15 (130°C)	N/A	0.623	2.165
	428.15 (155°C)	1.46	-0.0055	
	438.15 (165°C)	1.34	-0.259	
Nifedipine-HPMCAS LF	403.15 (130°C)	3.41	0.420	0.166
	428.15 (155°C)	1.26	0.315	
	438.15 (165°C)	2.12	0.386	
Nifedipine-PVPVA 64	403.15 (130°C)	2.41	-1.391	3.48
	428.15 (155°C)	1.45	-1.313	
	438.15 (165°C)	1.39	-0.554	



**Figure 2-1 a-c** Overlay plot of heat capacity measurements from DSC of nifedipine-polymer mixtures (EPO, HPMCAS LF and PVPVA respectively) annealed at 155°C for 18 hours of various concentrations (a) 90 % (w/w) (b) 80 % (w/w) (c) 70% (w/w) (d) 60 % (w/w) and (e) 50 % (w/w).



**Figure. 2-2 a-c.** Plot of change in heat of fusion against drug weight fraction for each nifedipine -polymer , EPO, HPMCAS LF and PVPVA 64, respectively

### Manuscript 3

A Study of Stability Prediction of the Nifedipine Solid Dispersions Prepared with Hot Melt Extrusion, Spray Drying and Rotary Evaporation

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## **Abstract**

Miscibility and solubility prediction studies of poorly water soluble drugs with amorphous water soluble polymer have been reported. However, these studies have some drawbacks to be used universally for any drug-polymer combinations. Specific drug-polymer interaction and temperature used in the experimental setting and temperature used in the prediction of the drug solubility are two of the most important factors that need to be considered.

The solubility of nifedipine with amorphous polymers, Eudragit E 100 (EPO), HPMCAS LF and PVPVA 64, in amorphous solid dispersions prepared by hot melt extrusion (HME), rotary evaporation (Rot) and spray drying (SD) processes, were predicted at room temperature (25 °C). The prediction was carried out by using a thermodynamic model utilizing heat capacity measurements made with differential scanning calorimeter (DSC) and Flory-Huggins interaction parameter,  $\chi$ . The model calculated the change in Gibbs free energy of the amorphous solid dispersions prepared at the range of nifedipine drug concentrations. By calculating the  $\chi$  interaction parameter using the solubility parameters of nifedipine and polymers and measuring the changes in the amorphous solid dispersion of nifedipine from room temperature to its melting point temperature, we were able to estimate the solubility of nifedipine in the polymers at room temperature.

**Keywords:** amorphous; solid dispersion; Flory-Huggins interaction parameter; Gibbs free energy; solubility parameter; DSC; HME; rotary evaporation; spray drying

## **Introduction**

With the use of modern high throughput screening (HTS) techniques and combinatorial chemistry in drug discovery, more compounds that are poorly soluble in water are entering the drug pipelines of pharmaceutical companies. To enhance the solubility of these poorly soluble drugs, solid dispersions, or amorphous molecular level dispersions in polymeric systems have been used as pharmaceutical dosage forms. By dispersing the drug molecularly in a polymer matrix, given that the interaction between the drug and the polymer is not too strong, the dissolution and/or apparent solubility of the drug which will lead to greater absorption and bioavailability of the drug can be increased [1-8].

There are two important criteria when preparing a solid dispersion of a drug in an amorphous polymer. Firstly; the drug must be molecularly miscible with the polymer. Secondly, the drug incorporated in the system should be accommodated by the polymer molecules to have an acceptable shelf life. In other words, it should stay as an amorphous solid dispersion and not crystallize out during the shelf life. The miscibility of a drug in a polymer is important because it affects the stabilization of the drug when it is dispersed in the polymer matrix. It also lowers the chemical potential ( $\Delta\mu$ ) of the drug as the result of mixing with the polymer [8].

Drug concentration can also affect the stability of the drug in the system i.e. with high drug concentration, the solid dispersion becomes unstable. The equilibrium solubility of the crystalline drug will be much less than the solubility of amorphous drug. The amorphous drug will have an experimentally determined “apparent” solubility and not an equilibrium solubility since the amorphous drug will be metastable.

There have been various approaches to understand the miscibility of a drug and a polymer in an amorphous solid dispersion [9-14]. These include measurement of the changes in the glass transition temperatures [9-11], determination of Flory-Huggins interaction parameter by using melting point depression method or solubility parameters [12-14], measuring the miscibility of a drug in a monomer or oligomer of the same polymer [14] or using a hot stage microscope to visibly determine miscibility of the melt [9]. However, there are limitations to the methods mentioned above such as:

- (1) Polymers used in these experiments tend to have high glass transition temperatures which reduce the molecular mobility in the solid dispersion. They will be highly viscous and may not be suitable to determine miscibility on a hot stage microscope.
- (2) Determining miscibility with the use of a liquid monomer or an oligomer will limit the types of polymers that can be used to determine miscibility. Also there are assumptions that can interfere with the accuracy of such monomers, i.e. the interaction of a drug with a monomer will be the same as the drug with the polymer which could be different from drug-oligomer
- (3) Melting point depression can only be measured where the drug and the polymer are in their liquid state.

An amorphous solid dispersion may contain high drug concentrations if the drug is miscible with the polymer in that case the concentration of the drug incorporated to the amorphous polymer is much higher than the solubility of its crystalline state. If the drug concentration exceeds the miscibility of the drug in the polymer, there is danger

of recrystallization. Therefore, it is important to determine the solubility and the miscibility of the drug in the polymer of interest to estimate the drug concentration that can be incorporated into the polymer without jeopardizing high amounts of amorphous drug reverting to the crystalline state.

In this paper, the term “solubility” is referred to the solubility of a crystalline drug in a polymer as an amorphous molecular dispersion (solid form), where the chemical potential of the solid state of the drug is equal to its liquid state. “Miscibility” is referred to that amount of liquefied drug that can mix with a liquid polymer. Since the temperature at which this mixing occurs is much higher than the glass transition temperature at this condition, reaching equilibrium state is very difficult.

The solubility of a drug in a solid dispersion can be expressed with the change in the chemical potential ( $\Delta\mu$ ) of its pure form. If  $\Delta\mu$  of the drug in the solid dispersion is lower than the  $\Delta\mu$  of the pure drug, the drug present in the solid dispersion will dissolve fully and the final concentration of the drug will be its apparent solubility.

The term “apparent solubility” refers to a metastable or supersaturated solution which may initially contain high concentration of the drug and over time reduced concentrations that are thermodynamically stable. If  $\Delta\mu$  of the solid dispersion is higher than that of the pure drug, then some of the drug dissolved as solid dispersion will revert back to the pure crystals in the polymer matrix and precipitate. The maximum amount of drug that can be loaded in a solid dispersion is, when  $\mu$  of the

drug in the solid solution is equal to  $\mu$  of the drug at a solid state [10]. This is the highest stable concentration of drug in a drug-polymer matrix that can be achieved.

In addition to the methods determining miscibility of a crystalline drug with a polymer discussed, there are other methods that have been developed to estimate the drug-polymer miscibility by using Flory-Huggins solution Theory [15], which were carried out by measuring melting point depression or solubility parameter [12-14]. The calculation of  $\chi$  according to solubility parameter and melting point depression were already explained in the previous paper [16]. However, these authors have explained the solid-solid solubility by using data obtained when both components were in the liquid state.

For predicting amorphous solubility of a drug in a solid polymer, a temperature that is close to the room temperature (25 °C) should be used to mimic the real-life conditions. Not all methods used utilize this temperature. In such cases, solubility parameter ( $\delta$ ) can be used. The only problem in its use is that; it does not take into account the specific secondary bondings in the calculations. To incorporate information of these bondings is important since they increase miscibility of a drug with a polymer.

Another predictive method published recently, proposed a thermodynamic model to calculate the miscibility of a drug at room temperature [8]. These authors analyzed changes involved in the Gibbs free energy of solid dispersions ( $\Delta G_{SS}$ ) as the result of formation of the amorphous solid dispersion by calculating the contributions of three

components ( $\Delta G_1$ ,  $\Delta G_2$  and  $\Delta G_3$ ). The heat capacities of pure drug, pure polymer and the solid dispersions prepared are measured with differential scanning calorimeter (DSC) and the values were used to calculate  $\Delta G_1$ :

$$\Delta G_1 = \int_T^{T_{M1}} [f_1 C_{P1} + f_2 C_{P2} - C_{P12}] dT - T \int_T^{T_1} \left[ \frac{f_1 C_{P1} + f_2 C_{P2} - C_{P12}}{T} \right] dT \dots \dots (1)$$

where  $\Delta G_1$  is one of the component of the total change in the Gibbs free energy,  $C_P$  is heat capacity,  $T$  is initial temperature and  $T_M$  is the drug melting temperature,  $f$  denotes the weight fraction, 1, 2 and 12 denote the drug, polymer and the mixture, respectively in Eq. 1.

$\Delta G_2$  is calculated by measuring  $\Delta h_M$ , which is the molar enthalpy of melting of the pure drug, via DSC and replacing the value obtained in Eq. 2.

$$\Delta G_2 = n_1 \Delta h_{M1} \left( 1 - \frac{T}{T_{M1}} \right) \dots \dots \dots (2)$$

where  $\Delta G_2$  is the second component of  $\Delta G_{SS}$  and  $n$  is the number of moles per gram of formulation in Eq. 2.  $\Delta G_3$  is obtained purely by calculation using Flory-Huggins solution theory in Eq. 3.

$$\Delta G_3 = RT n_1 \phi_2 \chi(T) + RT (n_1 \ln \phi_1 + n_2 \ln \phi_2) \dots \dots \dots (3)$$

where  $R$  is gas constant,  $\phi$  is volume fraction and  $\chi(T)$  is Flory-Huggins interaction parameter at temperature T.  $\Delta G_{SS}$  is calculated by using Eq. 4.

$$\Delta G_{SS} = \Delta G_1 + \Delta G_2 + \Delta G_3 \dots \dots \dots (4)$$

$\Delta G_{SS}$  is the combination of the total components of  $\Delta G$  1-3 where  $\Delta G_{SS}$  is the total change of Gibbs free energy of the solid dispersion and by using  $\Delta G_{SS}$  value obtained, we can determine  $\Delta \mu$ .

$$\Delta \mu_{1,SS} = \left( \frac{\partial \Delta G_{SS}}{\partial n_1} \right)_{T,P,n_2} \dots \dots \dots (5)$$

where  $P$  is pressure.

The plot of change in Gibbs free energy versus drug concentration while normalizing each by the weight of polymer in the formulation, we will be able to obtain the slope shown in Eq. 5. Since we have different drug and polymer weight fractions for each formulation,  $\Delta G_{SS}$  should be calculated per gram of formulation. By plotting the right hand side of Eq. 6 against the drug weight fraction, the slope can be determined.

$$\frac{\Delta G_{SS}}{w_2} = \frac{\Delta G_{SS}^*}{f_2} \dots \dots \dots (6)$$

$\Delta G_{SS}^*$  is the change in Gibbs free energy per gram of formulation and  $f$  denotes the weight fraction.

The change in the Gibbs free energy of the solid dispersion can be related to the chemical potential of the drug in the solid dispersion. The drug concentration where supersaturation of the drug may occur ( $\Delta\mu_{1,SS} > 0$ ) can be determined from the slope of  $\Delta G_{SS}$  that is plotted against drug fraction in the solid dispersion. The drug concentration where separation occurs will have a positive slope.

Flory-Huggins interaction parameter,  $\chi$ , can be determined using solubility parameter,  $\delta$ , of a drug and a polymer as shown in Eq.7 which is based on Hansen's idea to correlate solubility to cohesive energy [17]. The solubility parameter can be calculated by using the method developed by van Krevelen and Hoftyzer as shown in Eq. 7 [18].

$$\chi = \frac{V(\delta_1 - \delta_2)^2}{RT} + 0.34 \dots \dots \dots (7)$$

where  $V$  is molar volume per structure unit

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \dots \dots \dots (8)$$

where  $\delta$  is the solubility parameter and  $d$ ,  $p$  and  $h$  represents dispersion, polar and hydrogen bonding, respectively. Solubility parameter components  $\delta_d$ ,  $\delta_p$  and  $\delta_h$  can be calculated as shown in Eqs. 9-11.

$$\delta_d = \frac{\sum F_{di}}{V} \dots \dots \dots (9)$$

where  $F$  is the group contribution from dispersion

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \dots \dots \dots (10)$$

$$\delta_h = \frac{\sqrt{\sum E_{hi}}}{V} \dots \dots \dots (11)$$

where  $E$  is the molar cohesive energy.

In this paper Bellantone et al.'s solubility estimations will be used for the solid dispersions obtained with three different methods, hot melt extrusion (HME), rotary evaporation (Rot) and spray drying (SD) and polymers used for the preparations were, EPO, HPMCAS LF and PVPVA 64. Heat capacities of the prepared samples were measured for further calculations. We have also used three different methods of calculating Flory-Huggins interaction parameter,  $\chi$ , as previously reported to compare the resulting  $\Delta G_3$  values.

**Materials**

The API (Active pharmaceutical ingredient) used in this study was nifedipine (NIF) which was purchased from RIA International (East Hanover, NJ). Eudragit E-100 (EPO) was kindly provided by Evonik (Parsippany, NJ), HPMCAS LF by Shin-Etsu

Chemical Co., Ltd (Biddle Sawyer Corp, New York, NY) and PVPVA 64 was purchased from BASF (Florham Park, NJ)

Methylene chloride was used as the solvent in both spray drying process and rotary evaporation process except for processing NIF (with HPMCAS LF in which case methanol was used). Both solvents were purchased from Sigma-Aldrich Co. (St. Louis, MO).

## **Methods**

### **1. Hot melt extrusion (HME)**

Physical mixtures of NIF and EPO were prepared using a mortar and pestle with drug loadings of 5, 10, 20 and 40 % w/w. The mixture was then extruded using Haake Minilab micro compounder (Thermo Scientific, Waltham, MA). The extruded material was ground and sized through a # 40 sieve. The physical mixture went into the extruder through the funnel on the left hand side and softened with the temperature applied and extrudes out from the flush hole. The extrusion screw speed was set to 50 RPM throughout the experiments and no shear force was additionally applied to the mixture.

### **2. Rotary evaporation (Rot)**

The same physical mixtures prepared for HME were used for rotary evaporation. 5-10 grams of the physical mixture was dissolved in 50-100 mL of methylene chloride, with HPMCAS LF methanol had to be used as solvent, and the solvent was removed

by using a rotary evaporator apparatus Büchi Rotavapor from Büchi (New Castle, DE). The samples were collected by removing the foamy film created on inside of the flask with a metal spatula and ground by using a mortar and pestle. The particles were sized through a # 40 sieve.

### **3. Spray drying (SD)**

Mini Spray Dryer B-290 (Büchi, New Castle, DE) attached to Inert Loop B-295 cooling block was used in the spray drying experiment to manufacture amorphous solid dispersion of nifedipine with three different polymers. A solution of NIF and polymer was made using either methylene chloride or methanol (in the case when HPMCAS LF was chosen as the polymer matrix) with drug loads ranging from 5-40% w/w and the solid content of 3-5% w/w.

All the collected materials were transferred into amber colored vials and were kept in a desiccator until further analysis was required

### **Modulated Differential Scanning Calorimetry MDSC**

NIF-polymer samples were thermally analyzed with a MDSC instrument Q2000 (TA Instruments, New Castle, DE). Samples were weighed (6- 8 mg) and placed in to aluminum pans with lids. Heating was controlled throughout the measurement and the samples were heated from room temperature up to 20- 30°C above the melting point of the pure drug at a rate of 5°C/ minute unless noted otherwise.

### **True Density Measurements of Polymers**

EPO, HPMCAS-LF and PVPVA 64 polymers were dried in a vacuum oven for 72 hours at 40 °C. The true density was measured using AccuPyc 1340 (Micrometrics, Norcross, GA) and Helium gas used as the analyzer gas with 10 repeated cycles. The true density measurements were used to determine the theoretical change in glass transition temperatures using Gordon-Taylor equation of solid dispersions and compare them to experimentally determined glass transition temperatures.

### **PXRD**

PXRD was performed using X-Ray Diffraction Bruker D8 PXRD (Bruker AXS, WI). The samples were analyzed using Cu K  $\alpha$  radiation to determine the crystalline or amorphous phases of the drugs. The X-Ray pattern was collected in the angular range of  $1 < 2\theta < 40^\circ$  in the step scan mode (step width  $0.02^\circ$ , scan rate  $1^\circ$  per minute)

### **Estimation of the stable drug load in a polymer mixture**

The estimation for the most stable drug loads were calculated using Bellantone's method described in [8]. The Flory-Huggins interaction parameter were determined using heat of fusion method which was previously reported, melting point depression method and with the use of solubility parameters.

### **Results and Discussions**

The Flory-Huggins interaction parameter,  $\chi$ , obtained for each polymer was calculated using Eq. 6 and the results are shown in Table I. From the interaction parameter obtained with PVPVA 64, it is observed that the product has the lowest  $\chi$  therefore it

will show the highest miscibility. PVPVA 64 will be the most likely candidate to form a stable amorphous solid dispersion with nifedipine.

The changes in total Gibbs free energy against nifedipine weight fractions were calculated and plotted in Figs. 3- 1 a-c. There are three components that make up the total change in the free energy which includes  $\Delta G_1$  and  $\Delta G_2$  that are calculated from the DSC data using Eqs. 1 and 2 and  $\Delta G_3$  which is calculated by using Flory-Huggins theory and can be determined by Eq. 3. In Figs. 3-1 a-c, the  $\Delta G_1$ ,  $\Delta G_2$  and  $\Delta G_3$  components of  $\Delta G_{SS}$  were calculated according to solubility parameter, melting point depression and heat of fusion methods [16].  $\Delta G_1$  and  $\Delta G_2$  were found the same in but  $\Delta G_3$  differs in each application. However, the slopes the changes appear to be very small meaning that they are not sensitive enough to detect the stable concentration. In the total change in Gibbs free energy of nifedipine-EPO solid dispersions processed by HME, shown in Fig. 3- 2, no clear deflection point is observed. On the other hand, both Rot and SD processed nifedipine-EPO have minima at 10-15 % nifedipine concentration as seen in Figs. 3- 3 and 4. This may suggest that the use of HME for the nifedipine-EPO mixtures may not provide sufficient mixing to form a stable solid dispersion. Both Rot and SD were efficient for more effective mixing.

Using HME method, nifedipine-HPMCAS LF solid dispersions showed similar results to EPO, having no minimum concentration seen in the  $\Delta G_{SS}$  vs. weight fraction of nifedipine curve in Fig. 3- 5.

For Rot and SD processed solid dispersions the predicted concentrations were 10 and 15 % as seen in Figs. 3- 6 and 7. This could be due to the high viscosity of the

polymer during the HME processing which may interfere with mixing of the drug with the polymer well. The use of solvent could improve this drawback.

Using this prediction model, Nifedipine-PVPVA 64 solid dispersions appear to be the best candidates for forming stable amorphous solid dispersions. The solid dispersions prepared with this polymer show clearly identified minima in the plots drawn, Figs. 3-8-10. For plots obtained as in Fig. 3- 10 the lowest concentration (15 % in this case) is taken to be on the safe side.

In Fig. 3- 11, the processing effects on the  $\Delta G_{SS}$  for each method used to prepare nifedipine-PVPVA 64 amorphous solid dispersions are presented. With the HME method, the predicted drug concentration is 5 % which is much lower than that of the Rot or SD methods. This may indicate that HME method used is not effective in incorporating higher concentration of the drug compared to the other two methods. SD provided drug concentration of 15 %, shown in Fig. 3- 11 that can be accepted as the concentration that can be used to maintain amorphous character of the solid dispersion. Although some  $\Delta G_{SS}$  observed in SD which pointed out 10-30 % drug concentration could be incorporated, for safe incorporation in such cases it is advisable to use the lower concentration that provides the same  $\Delta G$  reduction [8].

As it was indicated earlier,  $\Delta G_{3s}$  calculated with each polymer used were different with the use of Flory-Huggins interaction parameter,  $\chi$ , calculated using three different methods. They are presented on Table 3-II a-c for each method. For all of the methods used,  $\Delta G_3$  change with increasing drug concentration is similar and the overall trend does not change. This finding indicates that mixing of nifedipine with polymers,  $\Delta G_3$ ,

is not the most important factor to determine the solubility of nifedipine in the polymers used as it has been suggested by Pajula *et al.* [12] and Marsac *et al.* [14].

Changes in the enthalpy and entropy of a crystalline drug to an amorphous solid dispersion may be the result of different bond modes or another translational change for the stabilization of the amorphous solid dispersions.

There are some evidence of phase separation occurring in the higher drug concentration with some of the nifedipine-polymer combinations. In Figs 3-3, 3-4, 3-8 and 3-9 which show the prediction models of solid dispersions prepared by Rot and SD for NIF-EPO and HME and Rot for NIF-PVPVA 64, there were sudden change in the slopes of  $\Delta G/w_2$  vs. drug weight fraction plots which could be the indication of existence of two separate phases [18]. At the concentration region above 20 %, amorphous nifedipine may be coexisting with crystalline nifedipine. This was confirmed with XRD analysis for 40% drug concentration of Rot processed NIF-EPO sample but not for the other samples. With the use of DSC, melting endotherms were present for 20 and 40 % Rot and SD processed NIF-EPO samples but none was present in the NIF-PVPVA 64 samples. Therefore, it is possible that phase separation of nifedipine and EPO can occur. However, NIF-PVPVA 64 solid dispersions may require further testing to confirm the existence of the two phases. Since these predictions are made for determining suitable drug concentration that will remain stable over the period of pharmaceutical products' shelf life, we need to select the drug concentration where there is only one, amorphous, phase present.

## Conclusions

By applying Bellantone *et al.* prediction equations, SD samples of nifedipine-PVPVA 64 polymer at 15-30 % nifedipine concentrations were predicted to be the most stable solid dispersions which agreed with the Flory-Huggins interaction parameter calculation to be the most miscible drug-polymer combinations between the three polymers tested.

Data obtained can be treated in an hour time when all the equations are fed into a spreadsheet for plotting the change in the Gibbs free energy.

$\Delta G_3$  component which was accepted as the main variable in the former to be a small contributor compared to  $\Delta G_1$  solubility estimations, was found that its contribution was small compared to  $\Delta G_1$ .

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**Table 3-I.** Flory-Huggins interaction parameter,  $\chi$ , for nifedipine and each polymer combination were calculated using Eq.6 and the solubility parameter,  $\delta$ , calculated with van Krevelen's method Eqs. 7-10 at 25 °C.

Calculated values of $\chi$ interaction parameters at 25 °C			
	EPO	HPMCAS LF	PVPVA 64
Nifedipine	2.165	0.166	0.027

**Table 3-II a.** Change in Gibbs free energy,  $\Delta G_3$ , contributed from mixing of nifedipine with EPO polymer

Drug load % (w/w)	$\Delta G_3$ J/g (Heat of Fusion)	$\Delta G_3$ J/g (Melting Pt. Depression)	$\Delta G_3$ J/g (Sol. Parameter)
40	-2.67	-8.66	0.21
20	-2.33	-4.86	-1.08
10	-1.62	-2.80	-1.06
5	-1.05	-1.61	-1.02

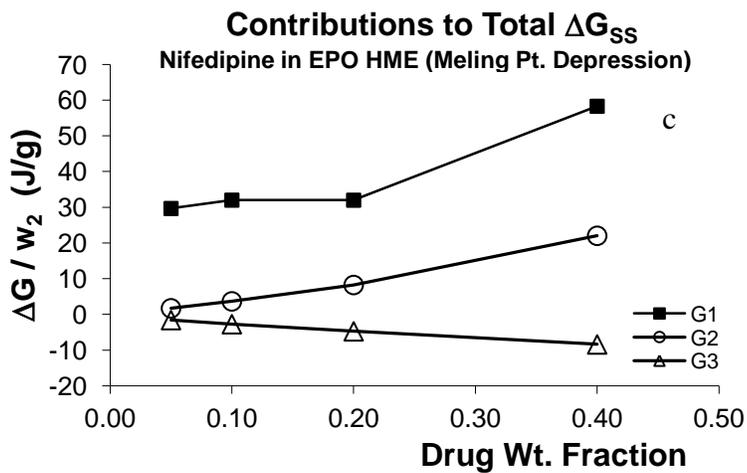
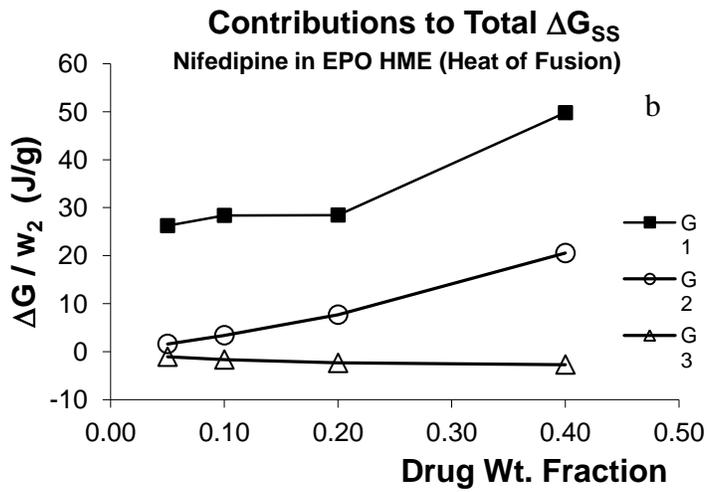
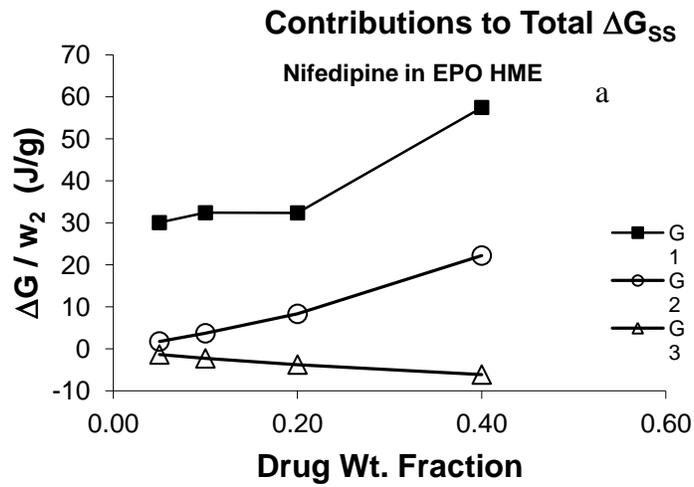
**Table 3-II b.** Change in Gibbs free energy,  $\Delta G_3$ , contributed from mixing of nifedipine with HPMCAS LF polymer

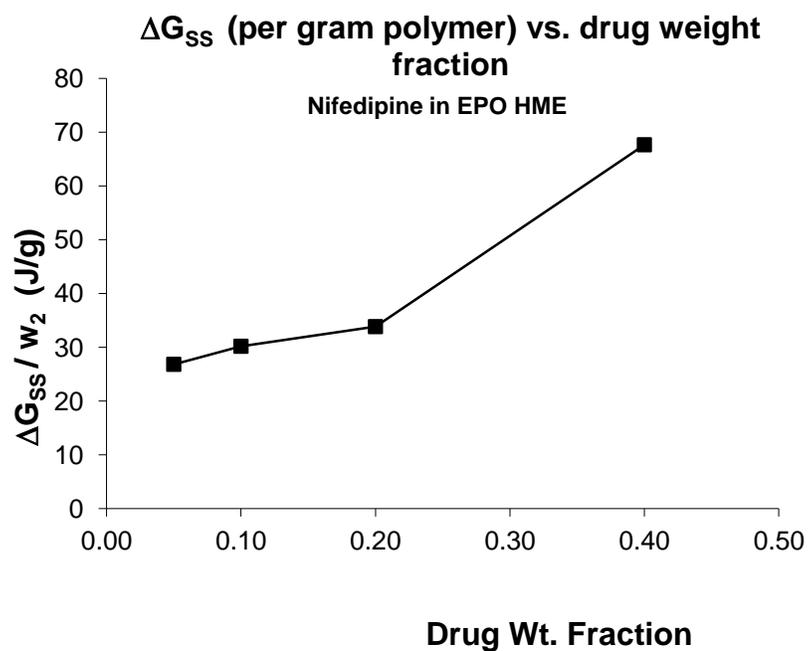
Drug load % (w/w)	$\Delta G_3$ J/g (Heat of Fusion)	$\Delta G_3$ J/g (Melting Pt. Depression)	$\Delta G_3$ J/g (Sol. Parameter)
40	-1.17	-4.19	-4.67
20	-1.37	-2.83	-3.06
10	-1.11	-1.82	-1.93
5	-0.78	-1.13	-1.19

**Table 3-II c.** Change in Gibbs free energy,  $\Delta G_3$ , contributed from mixing of nifedipine with PVPVA 64 polymer

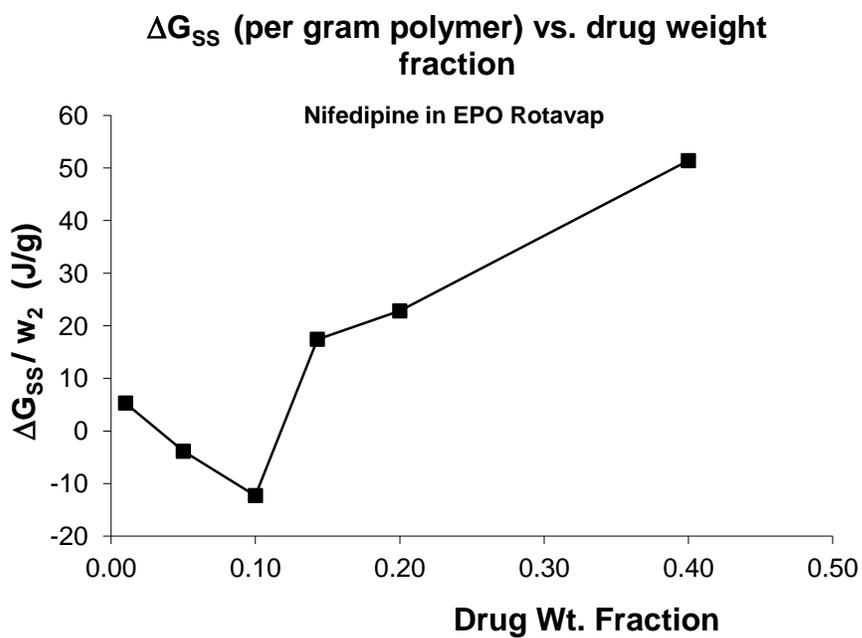
Drug load % (w/w)	$\Delta G_3$ J/g (Heat of Fusion)	$\Delta G_3$ J/g (Melting Pt. Depression)	$\Delta G_3$ J/g (Sol. Parameter)
40	-1.21	-11.15	6.10
30	-1.39	-8.01	3.47
20	-1.52	-6.02	1.79
15	-1.34	-4.46	0.95
10	-1.21	-3.36	0.37
5	-0.84	-1.89	-0.06
1	-0.28	-0.49	-0.13

**Fig. 3-1 a-c.** Calculated changes in the total Gibbs free energy of amorphous solid dispersions of nifedipine-EPO solid dispersions were prepared by hot melt extrusion with drug concentrations 5, 10, 20 and 40% w/w. (c)  $\Delta G_3$  was calculated with Flory-Huggins interaction parameter,  $\chi$ , by using the (a) solubility parameter, (b) heat of fusion calculation and (c) melting point depression method

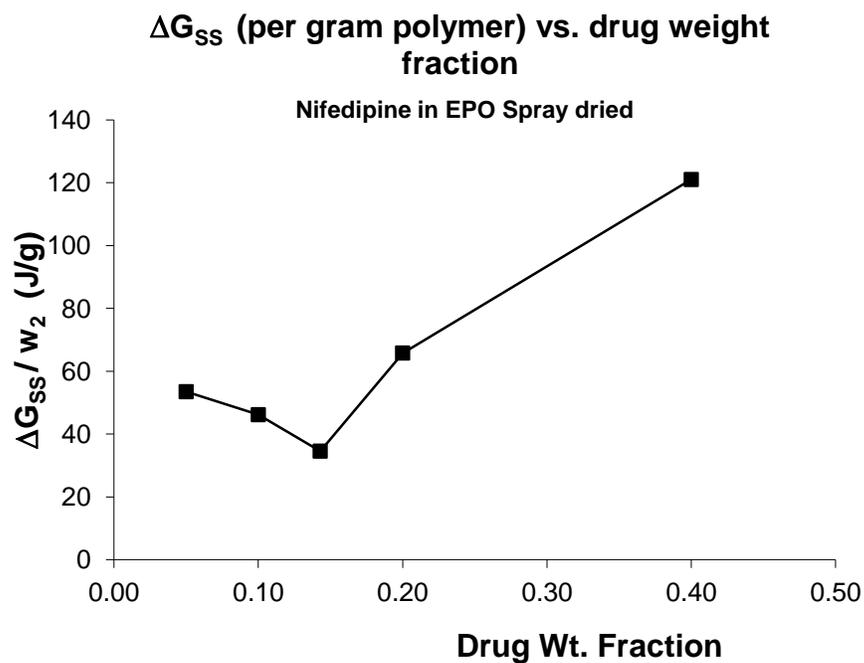




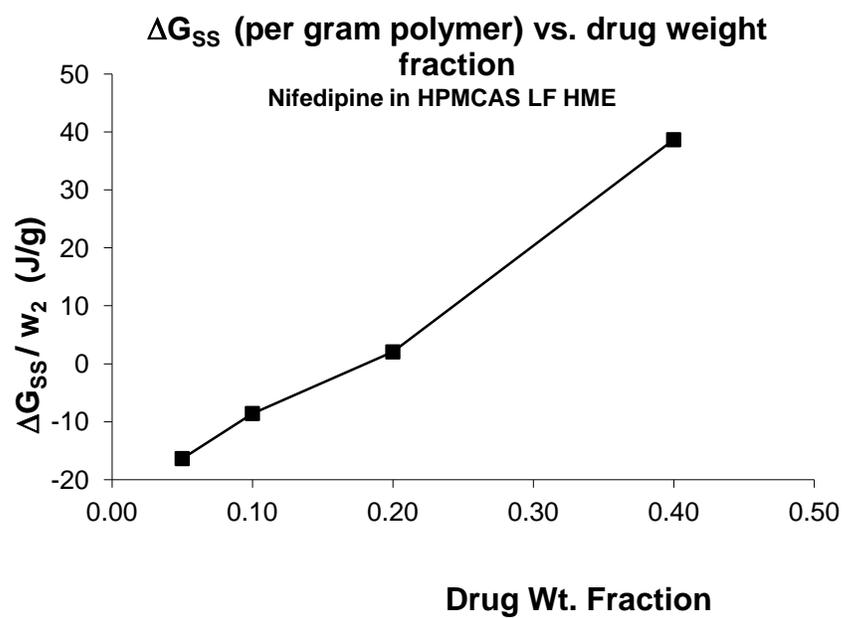
**Fig. 3-2.** Overall change in Gibbs free energy of amorphous solid dispersions of nifedipine with EPO prepared by hot melt extrusion with drug concentrations 5, 10, 20 and 40% w/w.



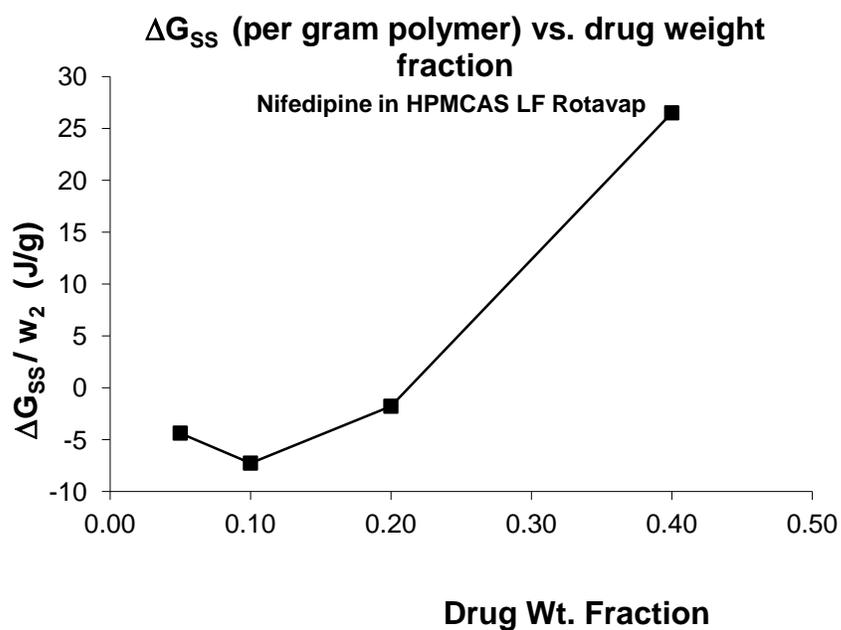
**Fig. 3-3.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with EPO prepared by rotary evaporation with drug concentrations 5, 10, 20 and 40% w/w



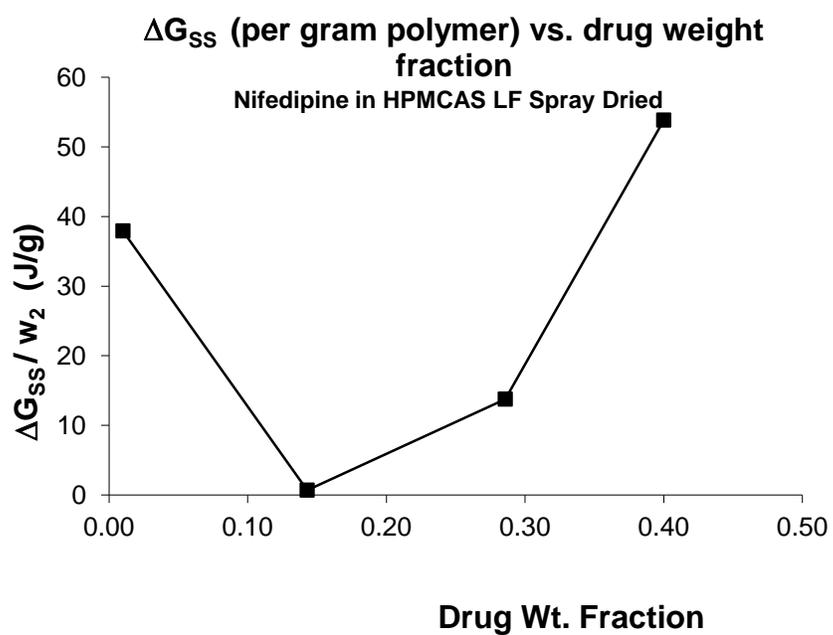
**Fig. 3-4.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with EPO prepared by Spray drying with drug concentrations 5, 10, 20 and 40% w/w



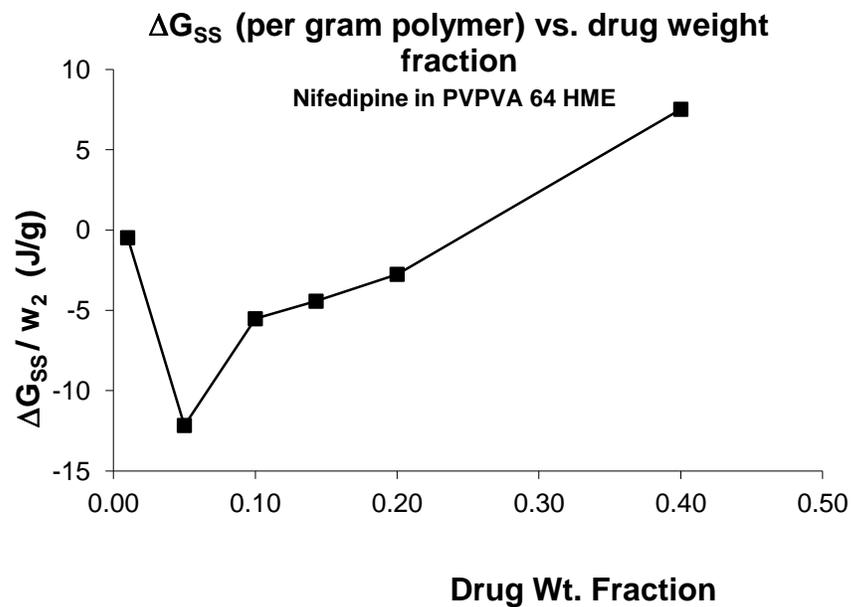
**Fig. 3-5.** Calculated changes in total Gibbs free energy amorphous solid dispersions of nifedipine with HPMCAS LF prepared by hot melt extrusion with drug concentrations 5, 10, 20 and 40% w/w



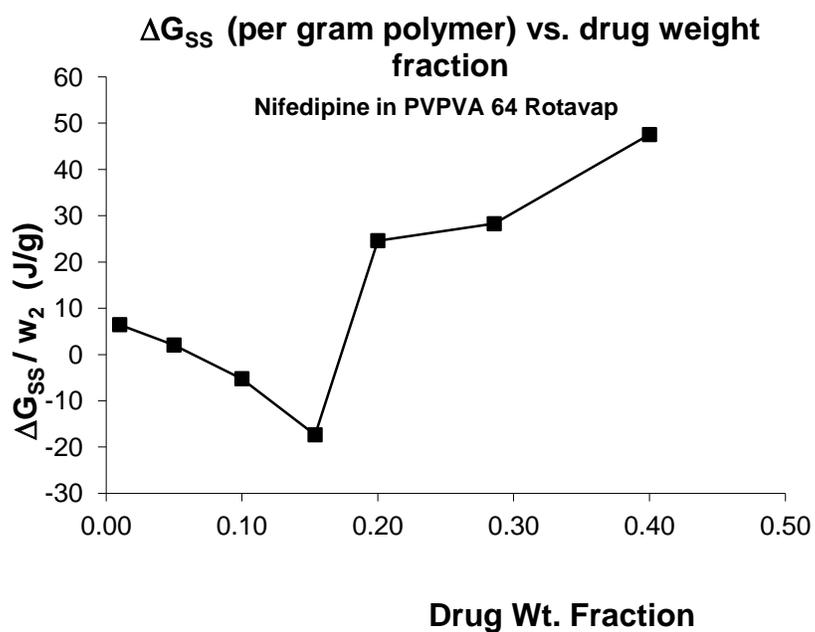
**Fig. 3-6.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with HPMCAS LF prepared by rotary evaporation with drug concentrations 5, 10, 20 and 40% w/w



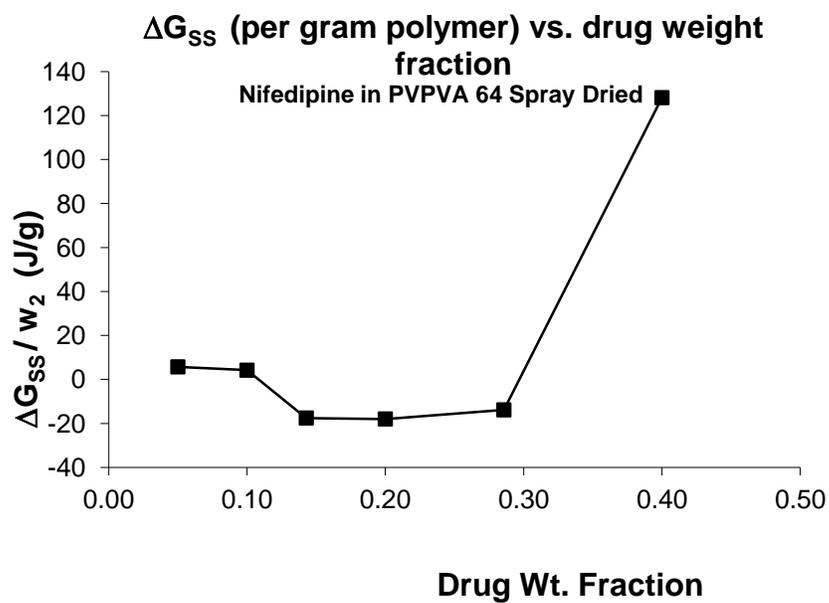
**Fig. 3-7.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with HPMCAS LF prepared by spray drying with drug concentrations 5, 10, 20 and 40% w/w



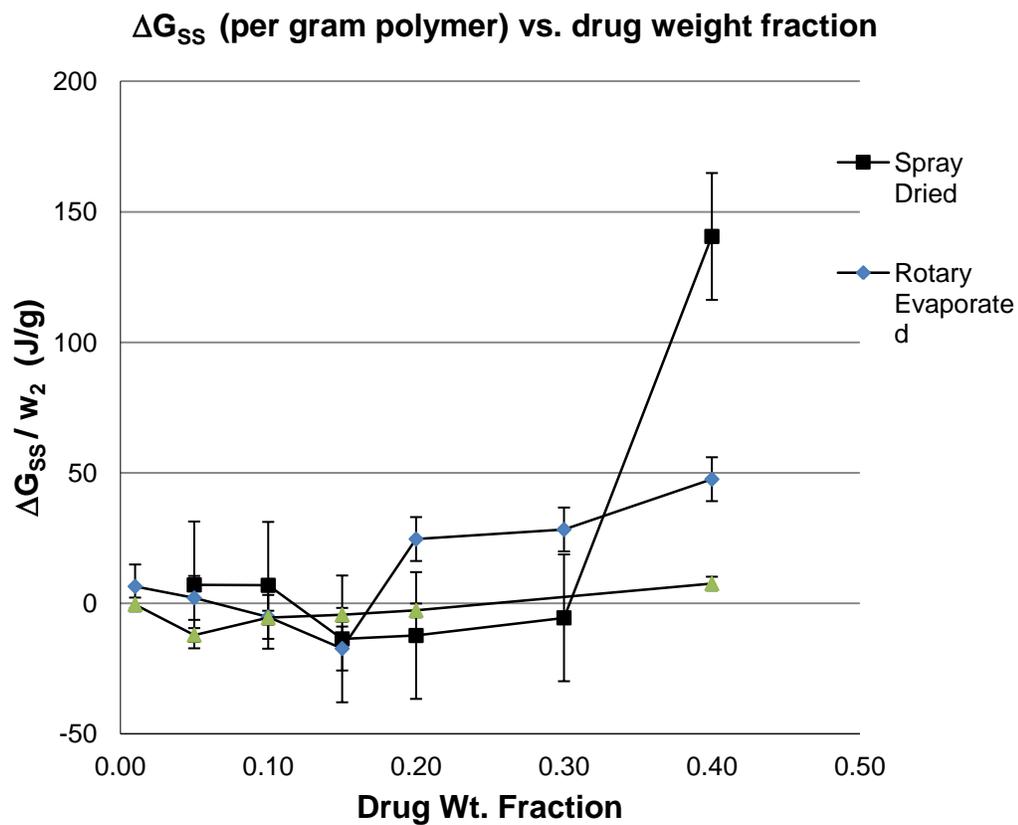
**Fig 3-8.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with PVPVA 64 prepared by hot melt extrusion with drug concentrations 5, 10, 20 and 40% w/w



**Fig 3-9.** Calculated changes in total Gibbs free energy of amorphous solid dispersions of nifedipine with PVPVA 64 prepared by rotary evaporation with drug concentrations 5, 10, 20 and 40% w/w

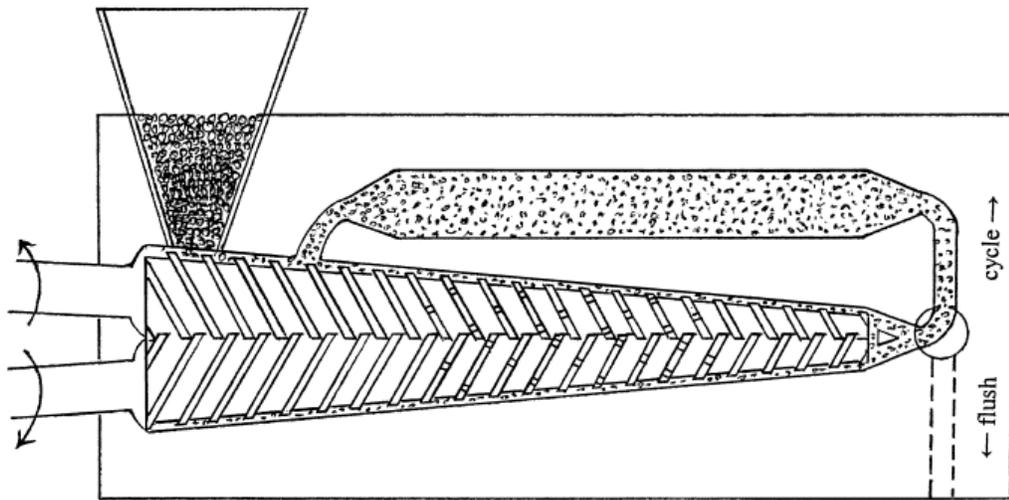


**Fig 3-10.** Calculated changes in total Gibbs free energy of nifedipine-polymer amorphous solid dispersions of nifedipine with PVPVA 64 prepared by spray drying with drug concentrations 5, 10, 20 and 40% w/w

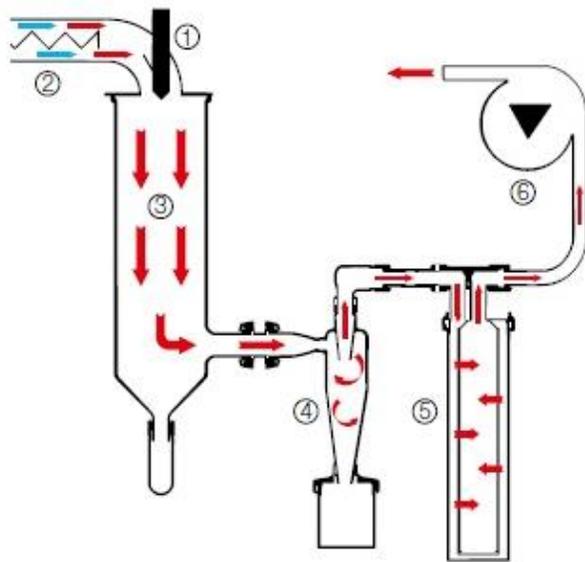


**Fig 3-11.** Comparison of processing methods (HME, Rot and SD) and the resulting change in Gibbs free energy of nifedipine-PVPVA 64 solid dispersions

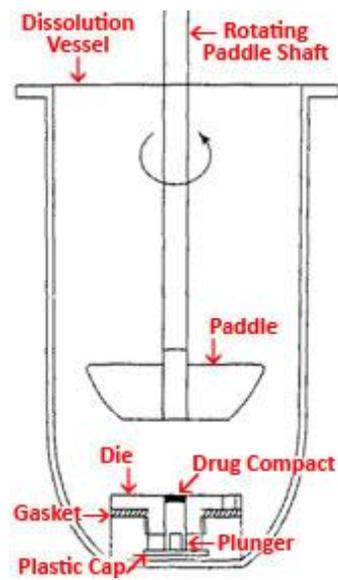
APPENDIX I



**Fig. IA-1.** A schematic diagram of a bench top conical twin-screw extruder.



**Fig. IA-2.** Diagram of spray dryer



**Fig. IA-3** A schematic drawing of an intrinsic dissolution apparatus setup