

EFFECT OF BLOCK COPOLYMERS ON THE DISSOLUTION OF SOME WATER-INSOLUBLE DRUGS: 1. NIFEDIPINE-PLURONIC F-127 SOLID DISPERSION SYSTEM

Sayed H. Khidr

Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

لقد تمت دراسة تأثير مادتي بلورنيك ف-127 وبولي فينيل بيروليدون (PVP) على زيادة معدل الإتاحة المعلمية لعقار النفيدبين من صياغة الجوامد المنتشرة باستخدام نسبة مختلفة من البوليمر والعقار عند درجة حرارة 37 مئوية في الماء المقطر. وقد قورنت النتائج مع نتائج معدل الإتاحة لنفس العقار من مخاليط طبيعية لها نفس التركيب. وأظهرت النتائج زيادة كبيرة في معدل إتاحة النفيدبين باستخدام مادتي بلورنيك ف-127، (PVP) من صياغة الجوامد المنتشرة وقد استخدمت طريقة الأشعة السينية وكذلك التفاضل السعري الحراري لمعرفة سبب الزيادة في معدل الإتاحة. ودلت النتائج على أن وجود العقار في صورة غير بلورية في صياغة الجوامد المنتشرة هو الذي أدى إلى الزيادة الكبيرة في معدل الإتاحة والتي من المتوقع أن يحسن في الوفرة الحيوية لهذا العقار.

The effect of pluronic F-127, a block copolymer, on enhancing the dissolution rate of water-insoluble drugs was studied. Solid dispersions of nifedipine, a model water-insoluble drug, with pluronic F-127 and PVP at different drug:polymer ratios were prepared using the solvent-evaporation method. The dissolution profiles of solid dispersion samples in distilled water at 37°C were compared to those using physical mixtures of the same composition.

The results showed that solid dispersion technique using both PVP and pluronic F-127 dramatically increased the dissolution rate of nifedipine.

X-ray and differential scanning calorimetric (DSC) studies were performed on different samples in order to elucidate mechanism(s) of the dissolution enhancement effect exerted by both polymers. It was concluded that the increase in dissolution rate of nifedipine from the solid dispersion is due to the lack of the drug crystallinity in these formulations. This improvement in the drug release rate can lead to an improvement in its bioavailability.

INTRODUCTION

A solid dispersion was defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state¹. This technique can be used to enhance the dissolution rate of poorly water soluble drugs using water-soluble carriers^{2,3}. The bioavailability of drugs with a dissolution rate limited absorption can be improved using this approach.

Pluronic F-127 (polaxamer 407) is a member of the nonionic surface active block copolymers (polyoxyethylene polyoxypropylene) with an HLB of 22 and an average molecular

weight of 12,500⁴. It was proved to have low toxicity and was found to be useful in many pharmaceutical applications⁵⁻⁸.

Nifedipine is a poorly water-soluble drug with a low bioavailability when taken orally in crystalline form⁹. It was used in this study as a model water insoluble drug.

The purpose of this research was to study the effect of pluronic F-127 on enhancing the dissolution rate of nifedipine from a solid dispersion system. The enhancement effect produced is compared to that of solid dispersion samples prepared using a well known carrier PVP.

EXPERIMENTAL

Materials:

Pluronic F-127 (BASF, Wyandote Corp., Wyandote, MI), Polyvinylpyrrolidone (PVP K-30) (Fluka Chemika, Buch, Switzerland), Nifedipine (Bayer, Wuppertal, Germany) were used without further purification. Other materials and solvents were of reagent or analytical grades.

Methods:

1. Sample Preparation:

The solvent evaporation method was used in preparing the solid-dispersion of nifedipine in pluronic F-127 and PVP. Calculated amounts of nifedipine and the polymer were dissolved in acetone:isopropanol (4:1 v/v) mixture. The solvent was evaporated at 40°C under reduced pressure using a rotary evaporator. The residue obtained was dried under vacuum at room temperature, then sieved using US standard sieves. The fraction less than 120 μm was stored under vacuum in a dark place for further studies. Samples of 1:3, 1:5 and 1:9 w/w drug:polymer ratio were prepared.

Physical mixtures of nifedipine with pluronic F-127 and PVP with the same composition were prepared using polymers of the same size range ($< 120 \mu\text{m}$).

2. Dissolution Studies:

Dissolution studies were performed using an automated tablet dissolution system (Caliva, BSTM, six units dissolution bath, Philips, PU 8620 Spectrophotometer and W-M 5035/R peristaltic pump). The system is connected to IBM P.C. with TDS software program for data analysis. Samples equivalent to 10 mg drug were used in each experiment. The test was conducted at $37^\circ\text{C} \pm 0.5$ following the USP XXII method 2 (Paddle) at 50 rpm using 750 ml distilled water containing 0.1% w/v sodium dodecyl sulfate (SDS) to improve the wettability of the drug. Nifedipine concentration was continuously monitored spectrophotometrically at 238 nm for 60 minutes. Duplicate runs were performed and

the average reading was calculated at different time intervals. SDS in a concentration of 0.1% was found not to interfere with the assay method.

3. X-Ray Diffraction Studies:

The X-Ray diffraction pattern for different samples ($< 120 \mu\text{m}$) was determined using the Philips automated diffractometer equipped with PW1730/10 generator. The radiation was provided by Cuk (40 KV, 30 mA) and the scanning speed was 0.02, 2θ per second. The wide angle diffraction ($5^\circ < 2\theta < 35^\circ$) was studied.

4. DSC Studies:

All experiments were carried out using Dupont 9900 thermal analyzer (Dupont, CT, U.S.A.) at a scanning speed of $10^\circ\text{C}/\text{min}$. The instrument was initially calibrated with pure indium.

All the previous experiments were strictly carried out in the dark and the flasks were wrapped in aluminum foil to avoid the effect of ultraviolet and day light on nifedipine.

RESULTS AND DISCUSSION

The effect of PVP on the dissolution rate of nifedipine is shown in Fig. 1. The results indicated a substantial increase in the rate and extent of nifedipine release from solid dispersion systems containing different ratios of PVP K-30 compared to the release from the untreated drug or a physical mixture of the same composition. The enhancement effect increased with increasing PVP ratio. There was no significant difference in the release of nifedipine from physical mixture of various ratios. Therefore, only the results of the 1:3 drug:PVP mixture is shown in Fig. 1. This result is in agreement with Simonelli et al¹¹ and can be explained by the possible presence of the drug as a high energy form at the lower ratio.

Similar results were also found using nifedipine sucrose ester coprecipitates. A positive effect on drug dissolution rate by increasing the drug: ester from 1:3 to 1:14

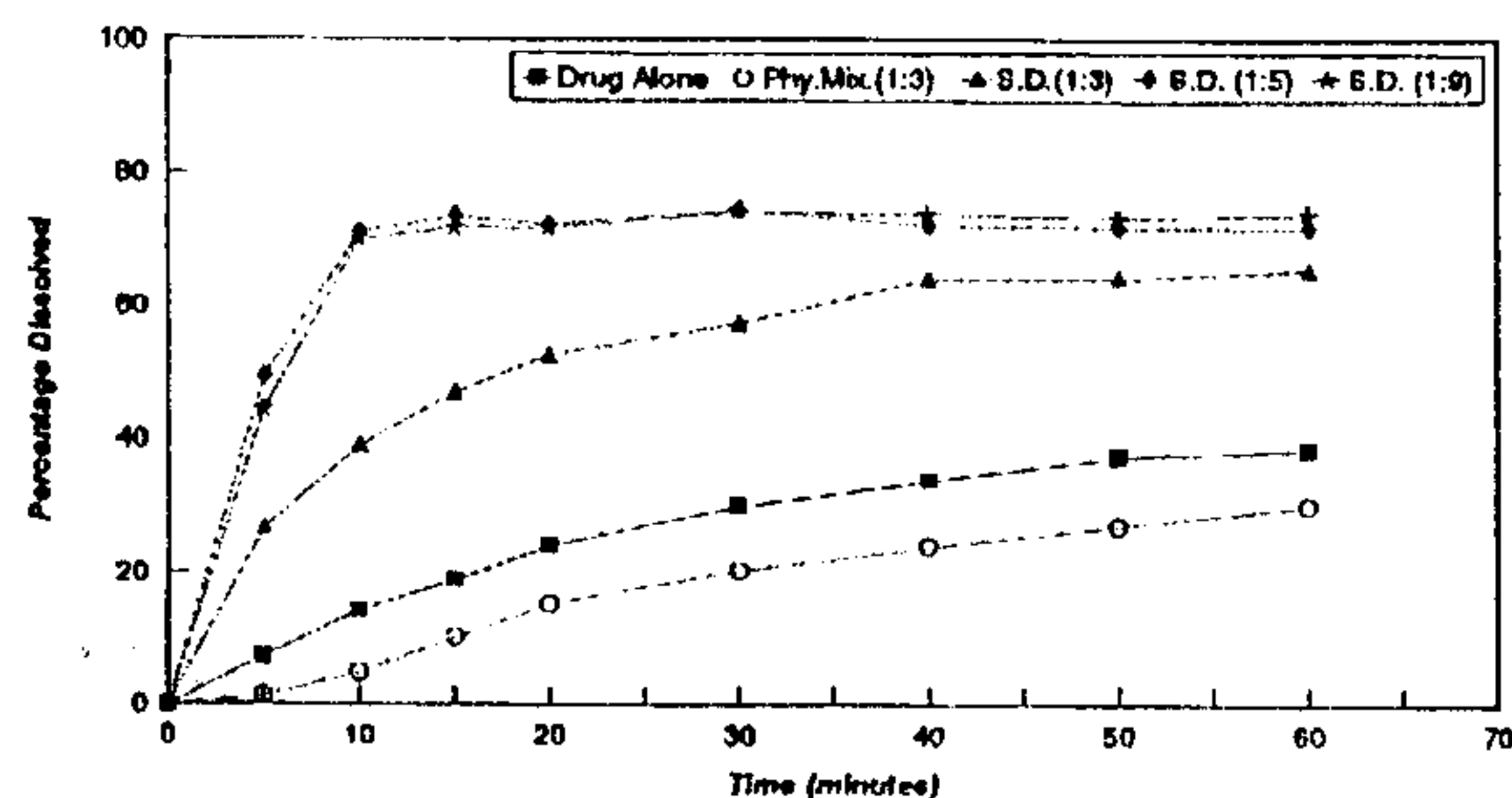


Fig. 1: Effect of PVP-K30 on the Dissolution Rate of Nifedipine.

(w/w) was found and was attributed to the increased amorphousness of the product.

Figure 2 shows that the influence of pluronic F-127 on the dissolution rate of nifedipine is greater than that of PVP, specially at lower polymer concentrations. With both polymers the concentration of nifedipine released from the solid dispersion systems reached a plateau after about ten minutes. This plateau is thought to be due to the supersaturation of the dissolution medium with the drug which has a low water solubility of approximately 11 mg/L¹³. This phenomena of supersaturation was also observed when griseofulvin was allowed to release from coprecipitated dispersion in neutral medium¹⁴ and in case of piroxicam solid dispersion with PEG 4000¹⁵.

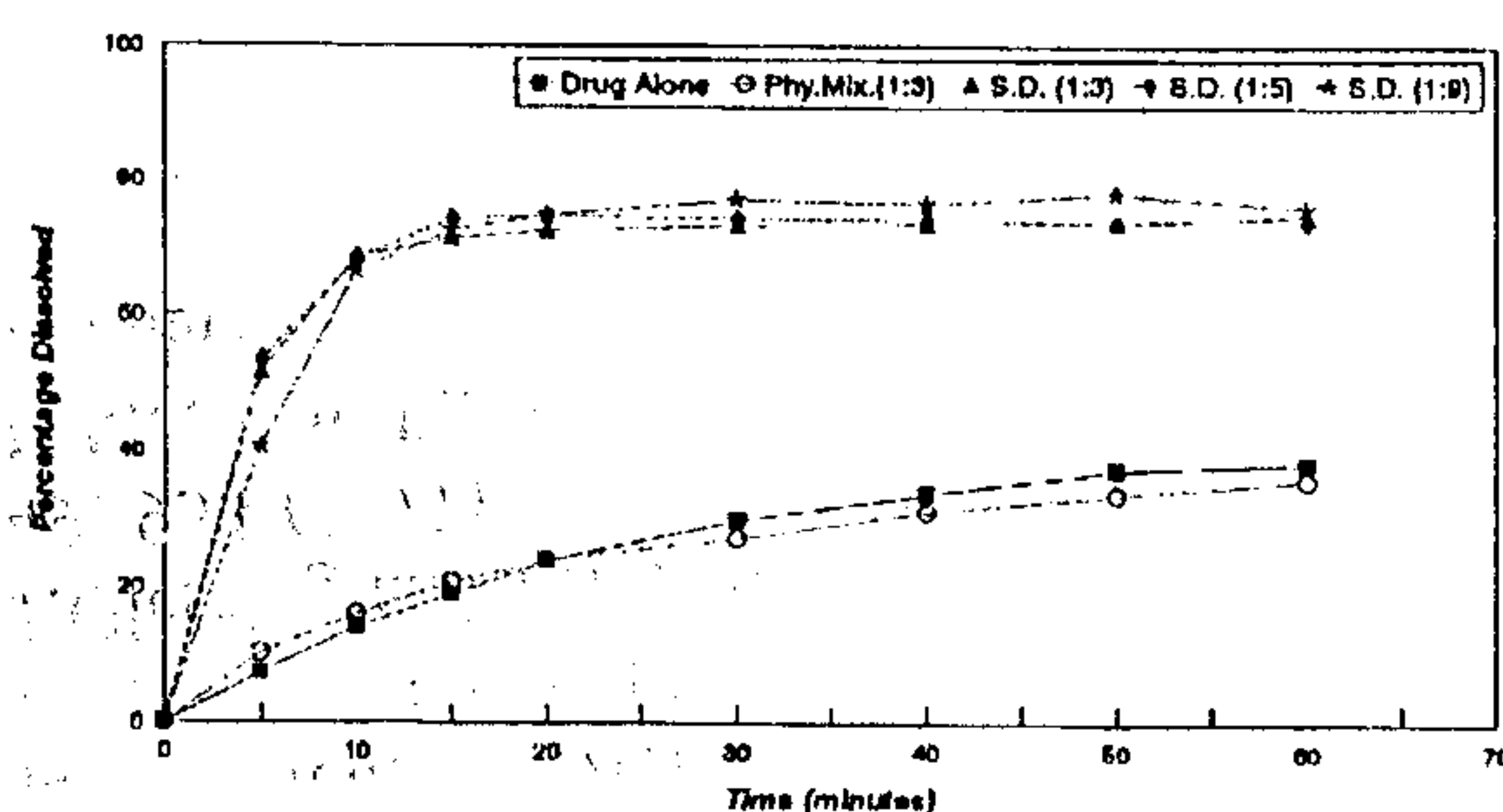


Fig. 2: Effect of Pluronic F-127 on the Dissolution Rate of Nifedipine.

In order to elucidate the mechanism of dissolution enhancing of nifedipine from the coprecipitate systems, an X-ray diffraction and a thermal analysis using the differential scanning calorimeter technique were used. Figure 3 shows the X-ray diffraction patterns of different

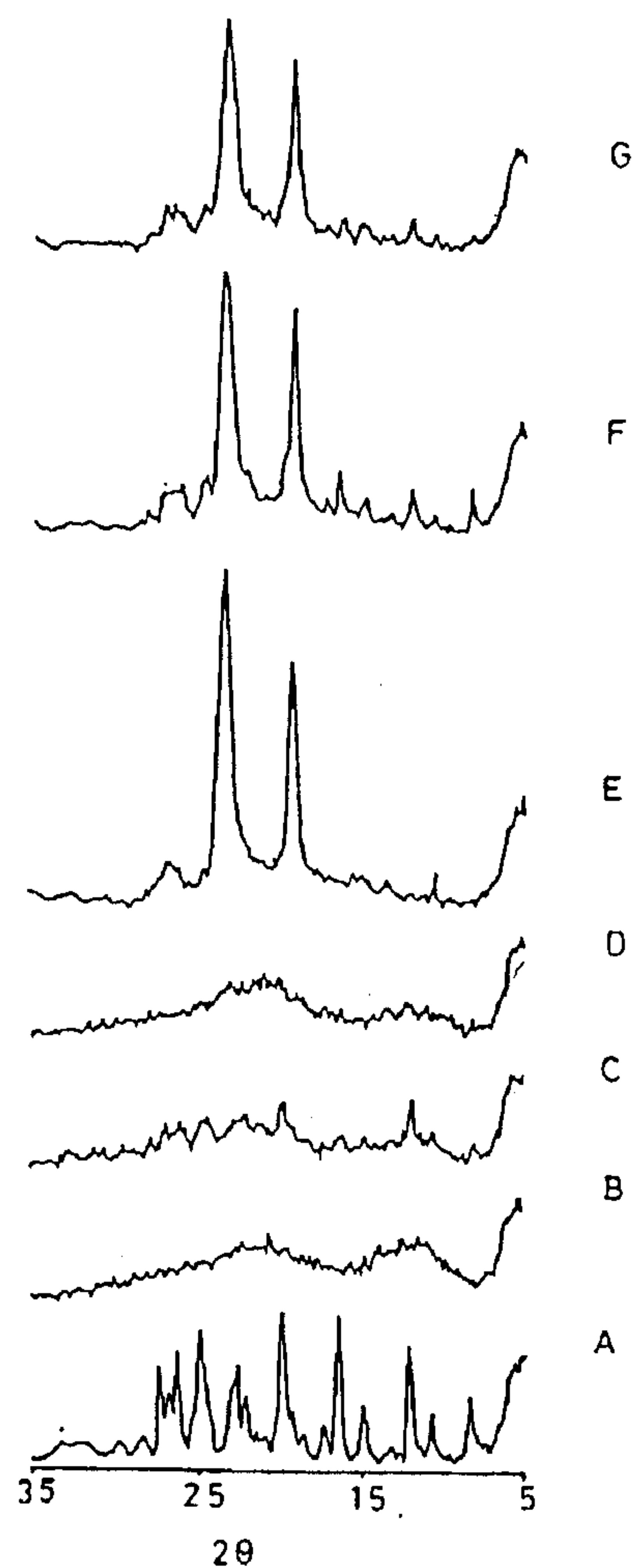


Fig. 3: X-Ray Diffraction Patterns of (A) Nifedipine, (B) PVP alone, (C) 1:3 w/w Nifedipine-PVP Physical Mixture, (D) 1:3 w/w Nifedipine-PVP Solid Dispersion, (E) Pluronic F-127 alone, (F) 1:3 Nifedipine-Pluronic F-127 Physical Mixture, (G) 1:3 Nifedipine-Pluronic F-127 Solid Dispersion.

samples. No sharp peaks were indicated in the diffraction pattern of PVP alone, while untreated nifedipine showed a crystalline structure with many sharp characteristic peaks. These peaks disappeared completely when nifedipine was dispersed with PVP, yielding an amorphous pattern. In case of the physical mixture of the same composition (1:3), some of nifedipine characteristic peaks were seen. These peaks, though smaller than those of the untreated drug due to the dilution effect with the carrier, indicate that nifedipine is present in the crystalline form in the physical mixture. This

may explain the similarity of dissolution profiles of nifedipine alone and in the physical mixture, Fig. 1. The increase in dissolution of nifedipine from the solid dispersion may be attributed to either the formation of an amorphous structure^{10,13} or to the molecularly dispersed form of the drug in the polymer, possibly by H-bonding of the drug with the pyrrolidone moiety of the mixture¹⁶.

Similar X-ray patterns were found for pluronic F-127 with the exception that in this case the polymer exhibits characteristic diffraction peaks. These peaks overshadow some of the drug peaks in the physical mixture. An amorphous structure was seen in case of the solid dispersion, Fig. 3.

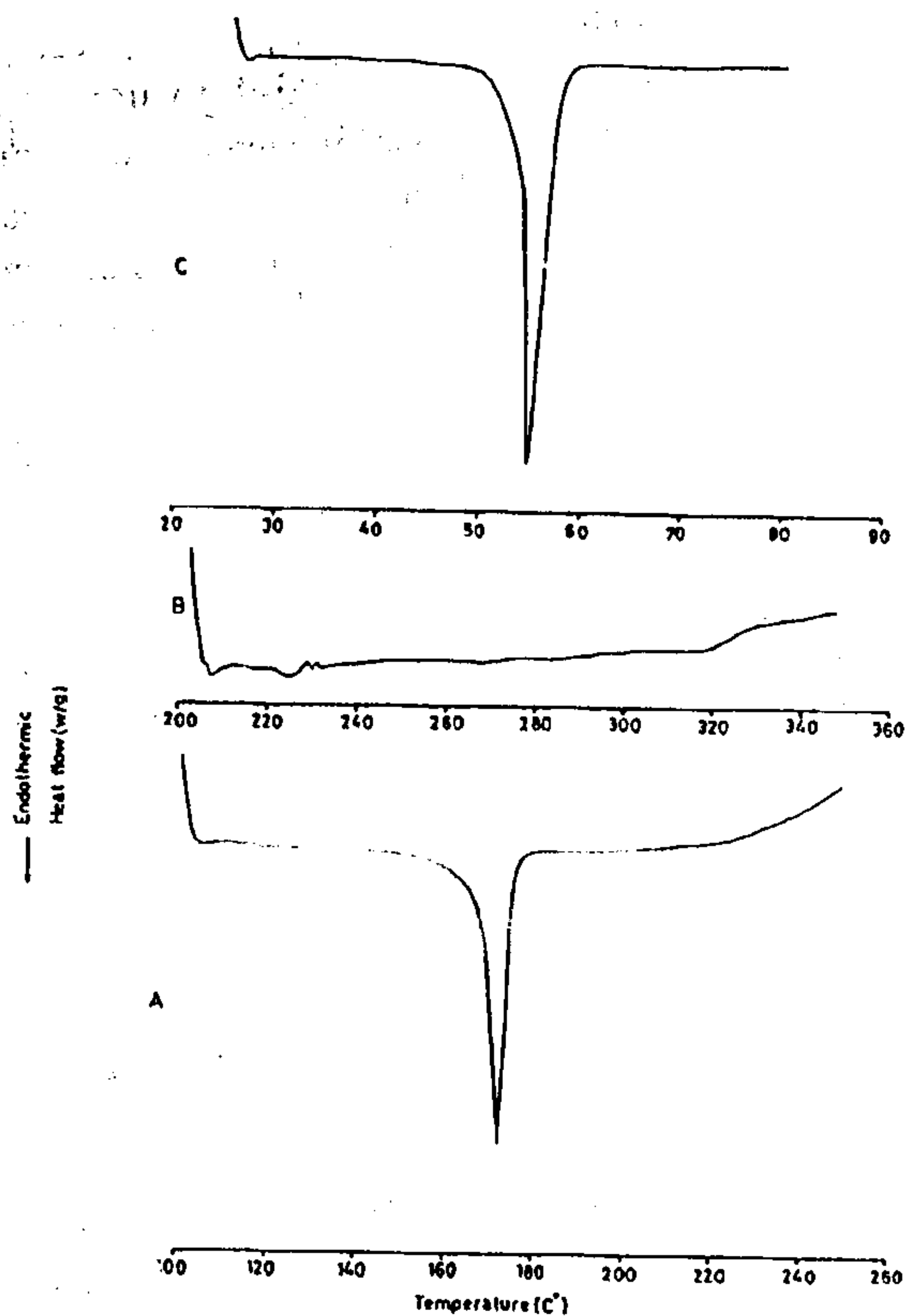


Fig. 4: DSC Thermograms of (A) Nifedipine, (B) PVP, (C) Pluronic F-127.

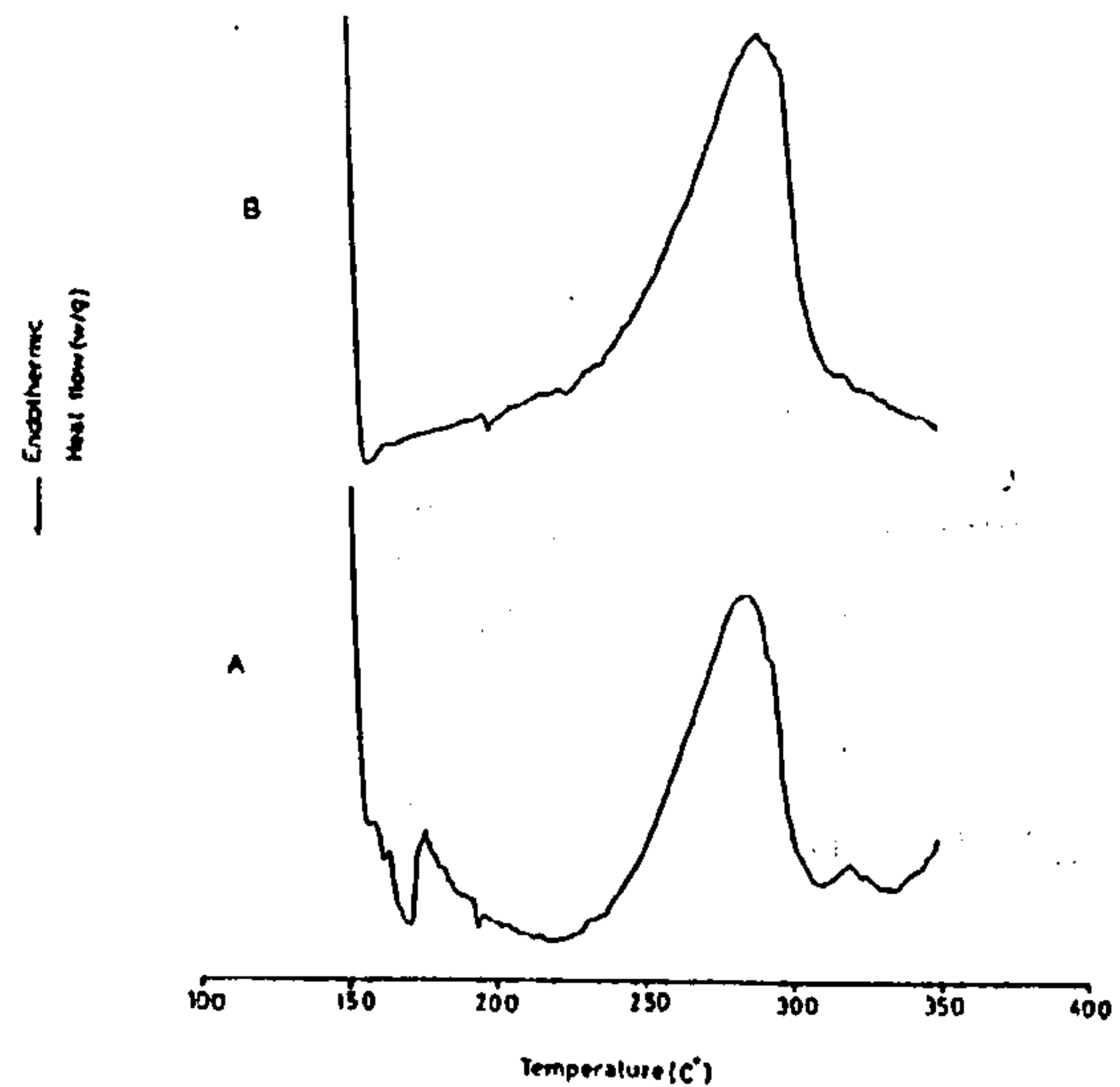


Fig. 5: DSC Thermograms of (A) 1:5 w/w Nifedipine-PVP Physical Mixture, (B) 1:5 w/w Nifedipine-PVP Solid Dispersion.

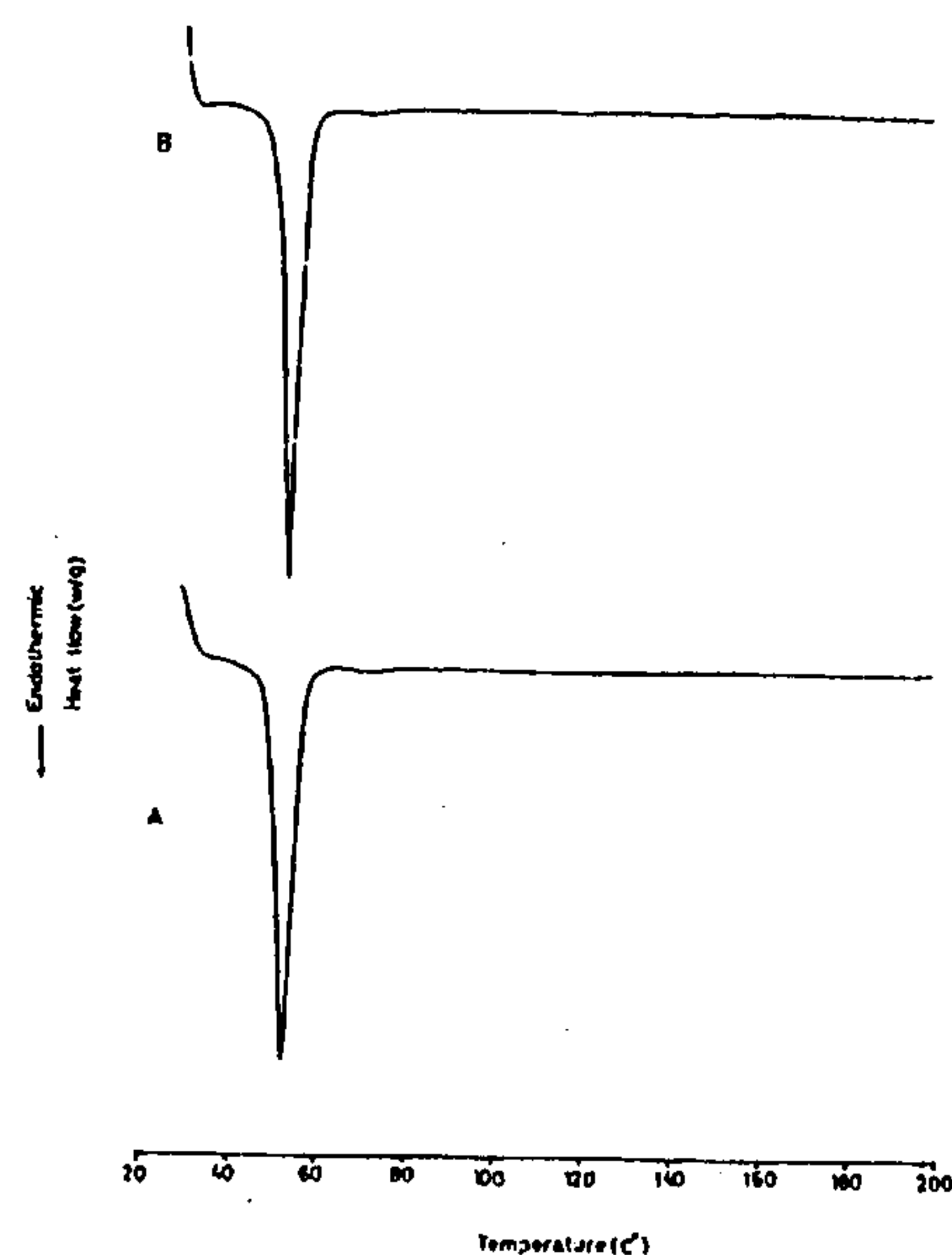


Fig. 6: DSC Thermograms of (A) 1:5 Nifedipine-Pluronic F-127 Physical Mixture, (B) 1:5 Nifedipine-Pluronic F-127 Solid Dispersion.

The DSC is a useful tool widely used in the analysis of solid dispersion^{17,18} and it was found to be suitable in detecting solid state changes in PEG¹⁹. In this study the DSC was used to confirm the previous findings. Figure 4 shows the DSC thermograms of pure nifedipine, PVP, and pluronic F-127. A sharp endothermic peak at about 172°C, represents the melting point of nifedipine, was found at a scanning rate of 10°C/min for the untreated drug. This characteristic peak appeared again on scanning the physical mixture of the drug within PVP, while it disappeared in case of the solid dispersion of the same composition, Fig. 5. This lack of crystallinity proved the formation of a solid dispersion of nifedipine with PVP¹⁶. The exothermic peak at higher temperature shown in Fig. 5, may be attributed to matrix transformation from the amorphous to the crystalline state during the heating cycle in the DSC²⁰. On the other hand, pluronic F-127 showed a single endothermic transition peak at 54.9°C indicating the melting point of this polymer (Fig. 4). When nifedipine was either physically mixed or dispersed with pluronic F-127, a slight decrease in the melting point of this polymer was observed, while the drug's melting point peak disappeared (Fig. 6). This may be explained by the solubility to the drug crystals in the molten polymer during the heating process. This was confirmed when nifedipine was added to a molten pluronic F-127 at a temperature just above the polymer melting point at a drug: polymer ratio of 1:5. The drug dissolved immediately in the polymer melts and a DSC scan on the solidified mass shows the same behavior as mentioned earlier (Fig. 6). Similar observations were found with phenobarbital-citric acid solid dispersion system where a single sharp endotherm by DSC at compositions below 70% w/w phenobarbital were observed and attributed to the solubility of phenobarbital in the molten citric acid²¹.

In conclusion, pluronic F-127 was found to enhance the dissolution rate of nifedipine, a water insoluble model drug, from a solid dispersion formulation to a level, at least equal to the enhancing effect exerted by PVP, a well established solid dispersion carrier. The effect of storage on the properties of the solid dispersion

formulations containing this polymer will be studied.

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