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Interaction between nicardipine hydrochloride and polymeric microspheres for a controlled release system

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Abstract

The microspheres containing nicardipine hydrochloride (NCH) were prepared by the solvent evaporation method using acrylic polymers, Eudragit RS and L. The results of the release experiments with microspheres proposed that there should exist an interaction between NCH and the acrylic polymers. The mechanism of this interaction was investigated by differential scanning calorimetry (DSC) and powder X-ray diffractometry (XRD). These analysis indicated that NCH and polymers interact at the molecular level, possibly NCH forming a solid solution with polymers. Furthermore, the formulations ended with a solid solution between NCH and acrylic polymers and their blends made possible the preparation of controlled release microspheres to retard and to enhance drug release rate at pH 1.2 and 7.5, respectively.

Keywords: Nicardipine; Eudragit RS; Eudragit L; Drug-polymer interaction; X-ray diffraction; DSC analysis

1. Introduction

Nicardipine hydrochloride (NCH) is a dihydropyridine calcium antagonist that has been shown to be an effective antihypertensive drug. As with many other dihydropyridines, the standard formulation of NCH undergoes rapid absorption and extensive biotransformation in the liver (Higuchi and Sasaki, 1980; Graham et al., 1984). This necessitates a thrice daily dosage regimen which is inconvenient for maintenance therapy in asymptomatic patients. Sustained/controlled release formulations of NCH have been developed in an attempt to reduce the frequency of daily dosing (Webster et al., 1989, 1991).

NCH is a weak basic compound. The in vivo efficacy of oral extended release formulations con-

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taining a basic drug may be limited by the variability in the solubility and dissolution rate of the drug at the different pH values of the gastrointestinal (GI) tract. These parameters can be too high in the gastric (acidic) pH with consequent possible problems in controlling drug release in the stomach and can dramatically decrease when the formulation reaches the neutral/basic pH values of the intestine, with the consequence that drug release can be considerably reduced (Giunchedi et al., 1992).

Controlled release drug delivery systems are dosage forms from which the drug is released by a predetermined rate which is based on a desired therapeutic concentration (in either systemic circulation or a target site) and the drug's pharmacokinetic characteristics (Ritschel, 1989). Polymeric microspheres appear to be an exploitable delivery system for controlled and sustained release of drugs. Microspheres as the multiple-unit dosage forms for oral use offer obvious advantages. They spread out more uniformly in the GI tract, thus avoiding exposure of the mucosa to high concentration of drug and ensuring more reproducible drug absorption. The risk of dose dumping also seems to be considerably lower than with a single-unit dosage form (Bodmeier and Chen, 1989; Follonier and Doelker, 1992).

Eudragit RS is a copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Since Eudragit RS film is only slightly permeable, drug release through the film is relatively retarded. Therefore, Eudragit RS has been widely employed for preparing controlled or slow release formulations. Eudragit L is an anionic copolymer based on methacrylic acid and ethyl acrylate. It is soluble in the region of GI tract where the fluids are neutral to weakly alkaline, and in buffer solutions above pH 6. Eudragit L and RS mixtures have been used successfully for an accelerated release at the neutral/basic pH values (Kim et al., 1994; Pongpaibul et al., 1984).

The purpose of our study is to prepare microspheres which would have a controlled release profile over a period of 12 h by using these acrylic polymers. Zero order release rate ($k_0 = 0.139\%$ min^{-1}) was determined by means of pharmacokinetic data of NCH (Wagner et al., 1987). A target drug release profile (TP) was drawn through this rate and then TP was used to settle the best microsphere formulation for the controlled release rate. To decrease the dissolution of NCH at pH 1.2 in gastric medium, Eudragit RS was used for the controlled drug release and, to increase the solubility and dissolution rate of the drug at pH 7.5 in intestinal medium Eudragit RS and L mixtures were applied for the same purpose. Solvent evaporation technique was used for the preparation of microspheres containing NCH. After testing different formulations, two formulations were found to be suitable to study for TP. In the present study, we investigated the interaction between NCH and the acrylic polymers in microspheres prepared from these two formulations by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD).

2. Materials and methods

2.1. Materials

The materials used were NCH (Yamanouchi Pharmaceuticals Co., Ltd., Japan); Eudragit RS and L (Röhm Pharma GmbH, Germany); magnesium stearate (Riedel De Haen AG, Germany); sucrose stearate (Crodesta F160, Croda GmbH Germany).

2.2. Preparation of microspheres

Microspheres were prepared by solvent evaporation method (Kawata et al., 1986; Kawashima et al., 1993). The formulations of microspheres are given in Table 1.

NCH and the polymer were dissolved completely in an acetone–methanol mixture. The dispersing agent, either magnesium stearate or sucrose stearate were added, and the mixture was stirred at 500 rpm in a water bath on a magnetic stirrer at 10°C for 20 min. The above mixture was rapidly poured into the liquid paraffin previously cooled to 10°C while it was stirred at 200 rpm (for F1C formulation) and 600 rpm (for F6I formula-

Table 1
Formulations for the preparation of microspheres

Formulation	F1C	F6I
Nicardipine HCl	1.50 g	0.83 g
Eudragit RS	6.00g	1.20 g
Eudragit L	—	5.50 g
Magnesium stearate	0.85 g	—
Sucrose stearate	—	0.85 g
Acetone (inner phase)	25.0 ml	25.0 ml
Methanol (inner phase)	5.00 ml	5.00 ml
Liquid paraffin (outer phase)	200 ml	200 ml

tion) by a stirrer fitted with a digital revolution counter (Model RZR-2000; Heidolph Elektro). The resulting emulsion was agitated at 35°C for 4 h and at the same time acetone–methanol mixture was completely removed by evaporation. The solidified microspheres were filtered, washed five times with 50 ml *n*-hexane, dried under vacuum at a room temperature for a night and stored in a desiccator.

2.3. Preparation of dispersions

Dispersions were prepared by the solvent method (Shefter and Cheng, 1980). The formulations of dispersions are given in Table 2. Appropriate amounts of the compounds to be dispersed were dissolved in acetone-methanol mixture. The solvent was removed under vacuum at room temperature. Then dispersions were ground by using a microgrinding (Janke and Kunkel KG).

Table 2
Formulations for the preparation of dispersions

Formulation	I	II	III	IV
Nicardipine HCl	—	1.50 g	1.50 g	—
Eudragit RS	6.00 g	—	6.00 g	1.20
Eudragit L	—	—	—	5.50
Magnesium stearate	0.85 g	0.85 g	—	—
Acetone	25.0 ml	25.0 ml	25.0 ml	25.0 ml
Methanol	5.00 ml	5.00 ml	5.00 ml	5.00 ml

2.4. In vitro release studies

Drug release from microspheres was tested using flow through cell (column method) (Desaga). Simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5) (without pepsin) specified in USP XXII were used as the dissolution mediums. Polysorbate 80 (0.02% w/v) was added to the dissolution fluids to overcome the poor wettability of the microspheres (Pongpaibul et al., 1984). During the dissolution test, flow rate of dissolution fluid was adjusted to 9 ml min^{-1} in order to maintain sink conditions. The test was continued for 9 h. The amount of drug released was calculated from spectrophotometric determination of the sample solutions.

2.5. Scanning electron micrography (SEM)

The shape and surface characteristics of microspheres were followed by a scanning electron microscope (Jeol JSM-840A). Microspheres were dusted onto double sided tape on an aluminium stub. The stubs were then coated with gold using a cool sputter coater (Polaron E 5100) to a thickness of 400 Å.

2.6. Powder X-ray diffractometry (XRD)

Powder XRD patterns were obtained with a Philips XRD (Model:1730/10) with CuK_{α} radiation (0.154 nm) at 35 kV and 20 mA over a 2ϑ range of 4–45°. Diffraction patterns for the drug, microspheres of which formulations were given in Table 1, and physical mixtures of these formulations were obtained. The samples were ground before analysis. Physical mixtures were made by grinding drug with the other solid materials.

2.7. Differential scanning calorimetry (DSC)

Thermal analysis was performed on the drug, polymers, magnesium stearate, microspheres (Table 1) and dispersions (Table 2) using a DSC, General V4.1C Dupont 2000. Samples (5 mg) were accurately weighed into aluminium pans and then sealed. The thermograms of the samples were obtained at a scanning rate of 10°C/min conducted over a temperature range of 20–200°C.

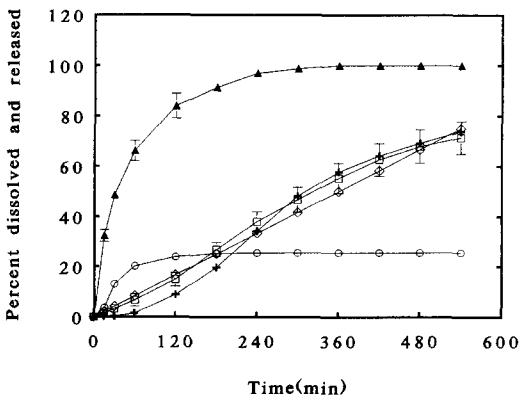

Fig. 1. Dissolution profiles of drug and microspheres in USP dissolution mediums (▲, drug (pH 1.2); ○, drug (pH 7.5); □, F1C (pH 1.2); +, F6I (pH 7.5); ◇, TP)

3. Results and discussion

NCH is a weak basic compound and its solubility, therefore highly depends on the pH of the medium. Although NCH is readily soluble in gastric juice, it is slightly soluble in intestinal fluid (Fig. 1). Controlled drug release profiles of the formulations (F1C and F6I) were shown in Fig. 1. Pure NCH was found to reach a value of 25% dissolved substance at pH 7.5 at the end of 9 h while the microspheres prepared from F6I formulation showed controlled release and dissolved drug increased to 77%. Also, the release of the drug in microspheres of F1C formulation was shown to be retarded at the pH 1.2 compared with pure drug. The results of the release experiments proposed that there should be an interaction between NCH and the acrylic polymers.

The shape and surface characteristics of microspheres were shown in Fig. 2. The surfaces of microspheres prepared from F1C formulation were in porous appearance, whereas those of F6I formulation were quite smooth. This difference between two formulations arose from different dispersing agents existing in these formulations. Magnesium stearate used as a dispersing agent in F1C formulation did not completely dissolve during the microsphere production. While the droplets in emulsion system solidified in the form of microspheres, free magnesium stearate particles formed a porous film on the surfaces of microspheres. This was also confirmed by DSC analysis of microspheres (Fig. 4c). The endotherm at 117.4°C corresponded to the melting of magnesium stearate in crystalline form. Sucrose stearate was used as a dispersing agent in F6I formulation. The absence of the endothermic peaks in DSC analysis of microspheres prepared from F6I formulation indicated that sucrose stearate and other substances in this formulation were in amorphous form (Fig. 7b), in other words, they were in dissolved form during the microsphere production. Therefore, the homogenous droplets in emulsion solidified in microsphere forms possessing uniform, smooth and nonporous surfaces.

The XRD patterns of microspheres prepared from F1C and F6I formulations were examined and compared with those of the pure drug and their physical mixtures. The crystallinity of NCH was clearly demonstrated by its XRD pattern shown in Fig. 3a. It was seen in Fig. 3c–e that the sharp diffraction peaks corresponding to NCH disappeared in the XRD patterns of microspheres and physical mixture of F6I formulation. However, physical mixture of F1C formulation could be expected to contain crystalline drug molecules to a certain extent (Fig. 3b). When the XRD pattern was compared with those of microspheres of that formulation and pure drug (Fig. 3a,d), we observed traces of peaks which arose from crystalline drug.

The absence of the crystalline peaks of NCH in XRD analysis of microspheres prepared from F1C and F6I formulations indicated that NCH and polymers interacted at the molecular level, possibly NCH formed a solid solution with polymers.

DSC was used to examine thermal behaviour of pure drug and formulations. Thermograms of pure drug and Eudragit RS were presented in Fig. 4a,b, respectively. A sharp endothermic peak corresponding to the melting of crystalline drug was found at 170.7°C (Fig. 4a). Given in Fig. 4b for pure polymer, Eudragit RS, the thermal transition at 60.8°C was attributed to the glass transition temperature (T_g) of polymer (Fig. 4b). Thermogram of F1C was taken as heating-cooling-reheating in DSC, Fig. 4c. T_g of the polymer was

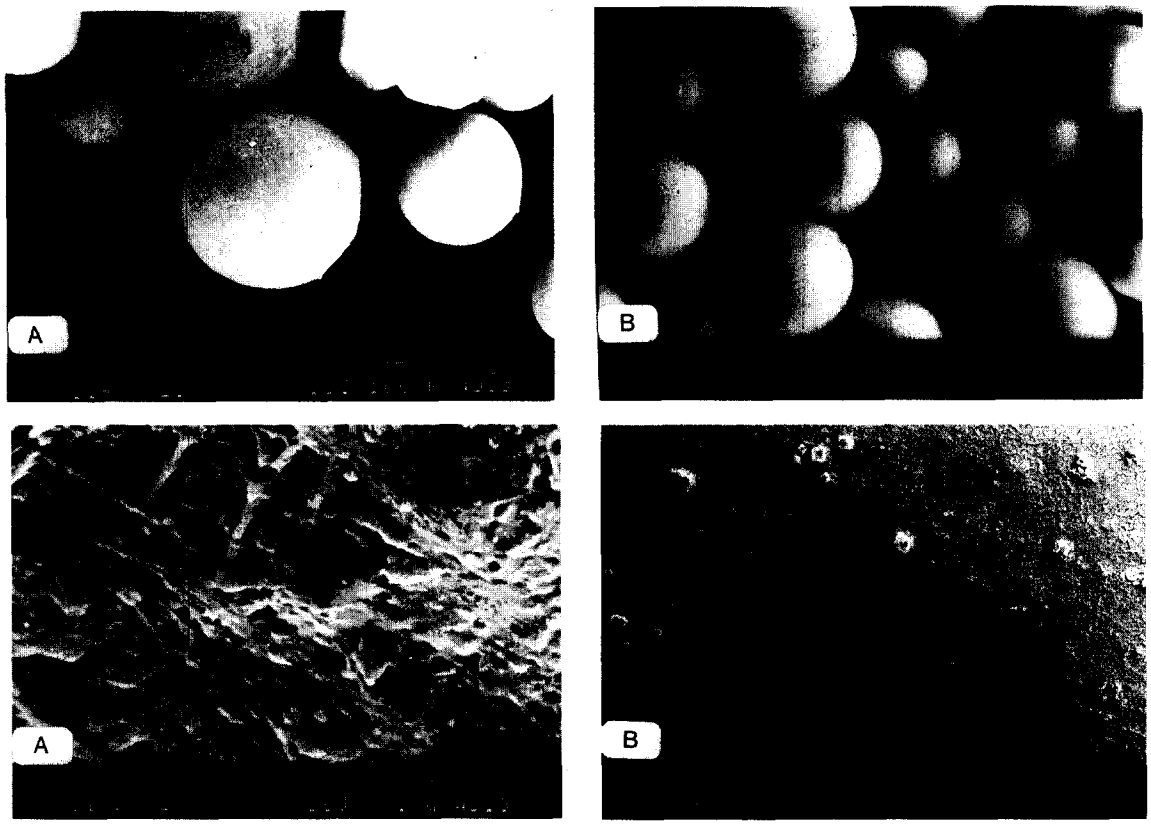

Fig. 2. Scanning electron micrographs of microspheres (A, F1C formulation; B, F6I formulation).

observed at 62.4°C while the endotherm 117.4°C was determined as the melting point of magnesium stearate, dispersing agent in microspheres of F1C formulation (see following discussions) (Fig. 4c, run*1). No endothermic peak confirming crystalline drug was present. Hence, it can be concluded that the drug is found in amorphous state rather than a phase separated crystalline phase.

Pure magnesium stearate and the dispersion formulations given in Table 2 were also examined by DSC (Fig. 5a–c) in order to determine whether the peak at 117.4°C could be attributed to magnesium stearate. As seen in Fig. 5a, two melting peaks, 87.7°C and 111.2°C were raised from the melting of magnesium stearate. The shoulder appeared next to 87.7°C peak, which was the possible presence of humidity in magnesium stearate. This thermogram agreed well with Miller and York (Miller and York, 1985). The thermogram in Fig. 5b, the mixture of NCH and magnesium stearate also showed almost the same melting peak with some depression in melting of magnesium stearate, however the crystalline melting of NCH was absent. In the third DSC in this series (Fig. 5c), Eudragit RS and magnesium stearate mixture (see Table 2, Formulation I), three melting peaks, 81.2, 102.5 and 112.2°C were observed. They were also arisen from magnesium stearate, where the two former ones were due to the presence of H_2O in which the second peak was shifted to a higher temperature compared with the pure magnesium stearate possibly because of the strong interaction between H_2O molecules and amine groups in polymer. In thermogram of NCH-Eudragit RS dispersion shown in Fig. 5d, the transition at 66°C corresponding T_g of polymer was observed and no peak referring to NCH was seen.

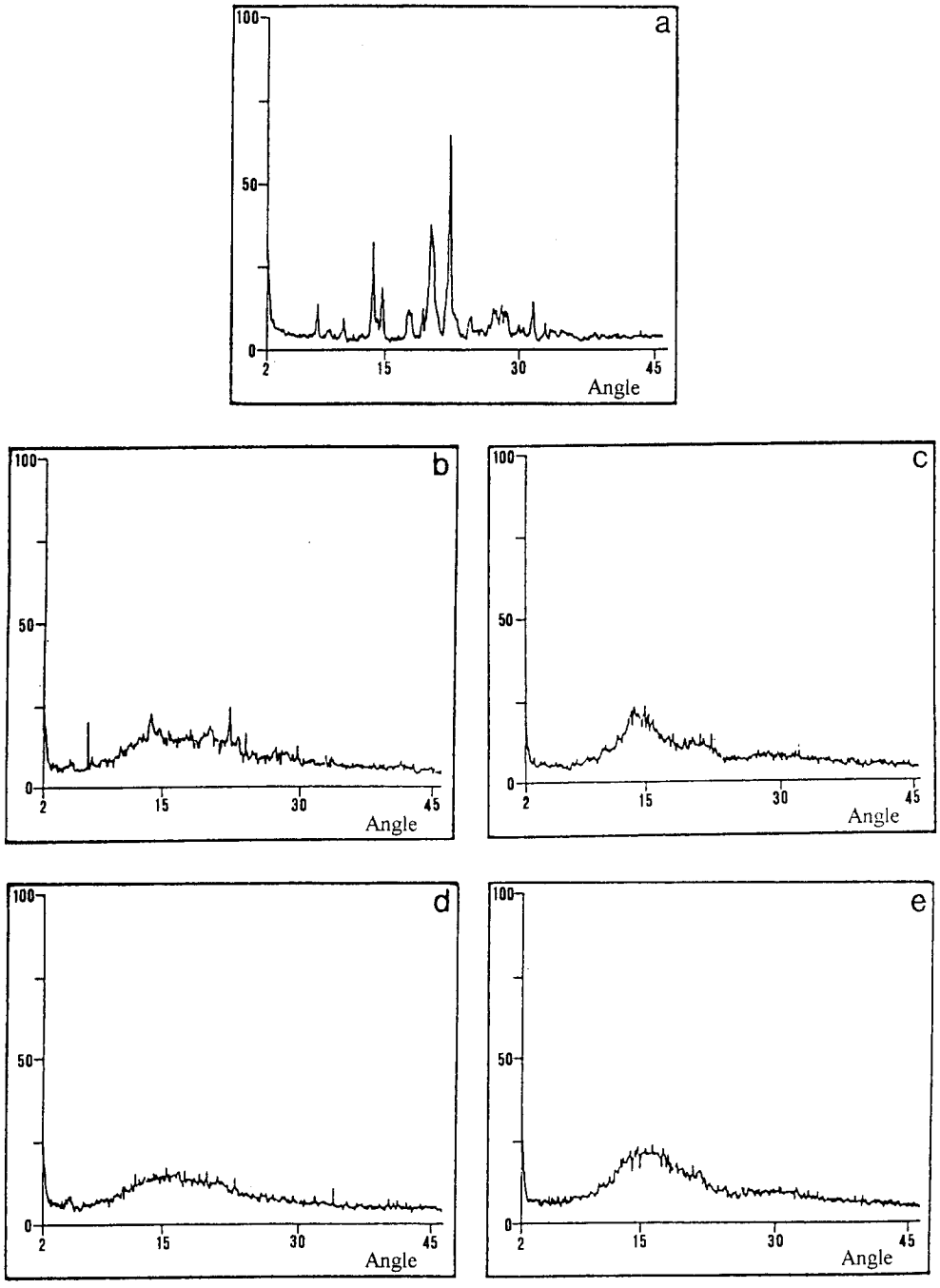

Fig. 3. Powder XRD patterns of: (a) pure NCH; (b) physical mixture of F1C formulation; (c) physical mixture of F6I formulation; (d) microspheres of F1C formulation; and (e) microspheres of F6I formulation.

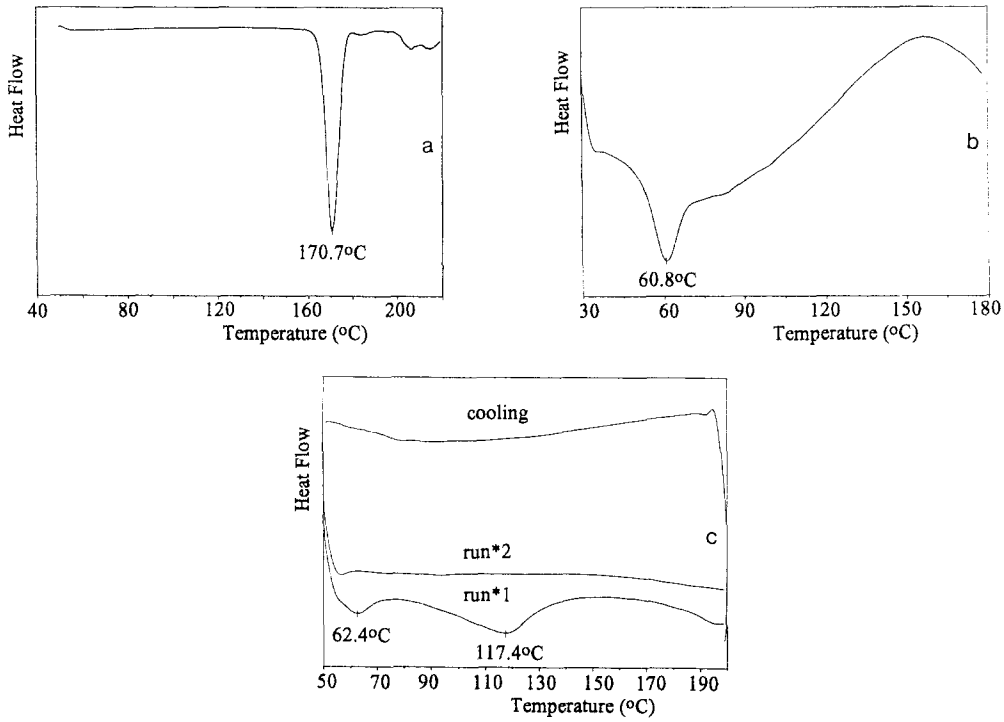

Fig. 4. DSC thermograms of: (a) NCH; (b) Eudragit RS; and (c) microspheres of F1C formulation.

Therefore the peak at 117.4°C in thermogram of microspheres prepared from F1C formulation determined as the melting peak of magnesium stearate. The absence of NCH crystalline peak, which should have been expected at approximately 170.7°C, proved that NCH was in amorphous state in this formulation, F1C. Furthermore, an annealing experiment was carried out in order to find the state of NCH in the dispersions, whether a solid-state solution or a molecular dispersion. The annealing was performed at 80°C for 48 h. The characteristic peak of the melting point of NCH at 170.7°C was still absent after annealing (Fig. 6). It was expected from the annealing experiment that by increasing the temperature during the process, and thereby causing increased mobility of the polymeric chain (by going above T_g), the drug could be able to diffuse in the polymer and crystallize (Beten and Moës, 1994; Benoit et al., 1983). If this condition could be satisfied it could have been said that they produced structure molecular dispersion. However, there was no peak referring the existence of crystalline NCH and hence NCH formed a solid solution with Eudragit RS and the NCH molecules were accordingly embedded between the macromolecular chains.

In addition, cooling and then reheating (run*2) procedures were applied to microspheres of F1C formulation (Fig. 4c). It was aimed to follow possible recrystallization of NCH. No peak corresponding to NCH crystallization was observed in this trial. This also confirms the annealing experiment which is long term compared with heating–cooling–reheating cycle in DSC.

The thermograms of microspheres prepared from F6I formulation containing Eudragit RS-L mixture and Eudragit L were given in Fig. 7a and b. Eudragit L showed T_g at 90.5°C (Fig. 7a). In formulation F6I, polymer composition of 18% Eudragit RS and 82% Eudragit L by weight, no NCH peak appeared, but a transition around 55°C. The heating–cooling–reheating cycle in DSC was also carried out for F6I and no NCH crystallization was observed (Fig. 7b).

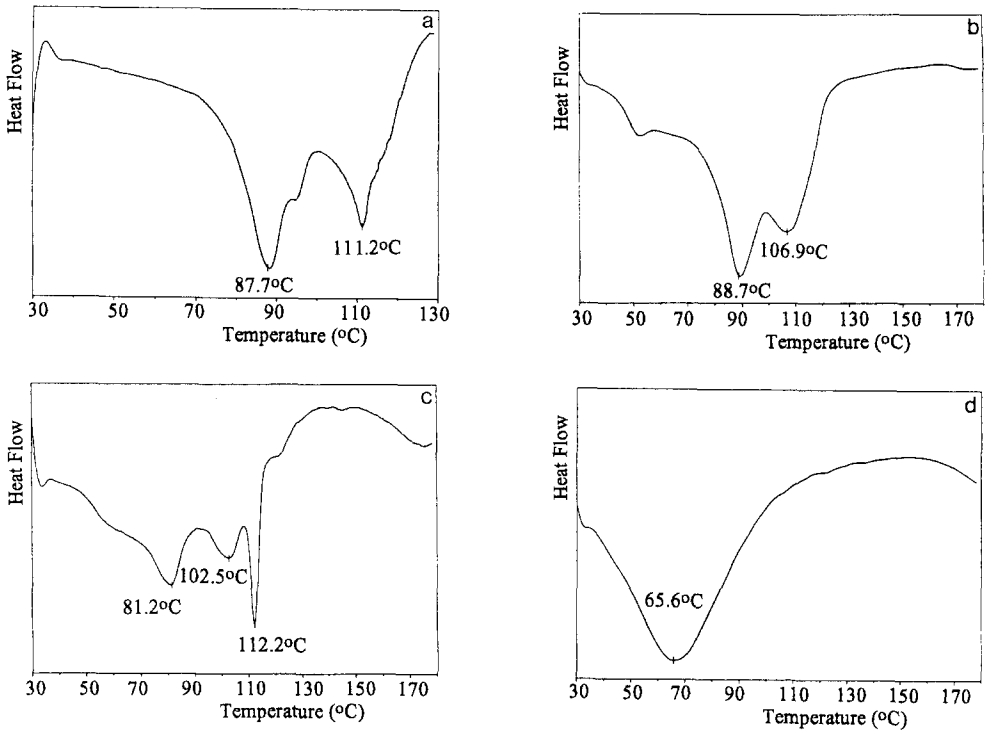

Fig. 5. DSC thermograms of: (a) magnesium stearate; (b) NCH-magnesium stearate dispersion; (c) Eudragit RS-magnesium stearate dispersion; and (d) NCH-Eudragit RS dispersion.

The transition, 55°C, was attributed to T_g of that polymer mixture in the microspheres. Whereas the pure mixture of polymers at the same compositions (Table 2) showed two Tg transitions, 70.7 and 145°C (Fig. 7c). The lower transition, 70.7°C, is most likely to correspond the polymer blend T_g.

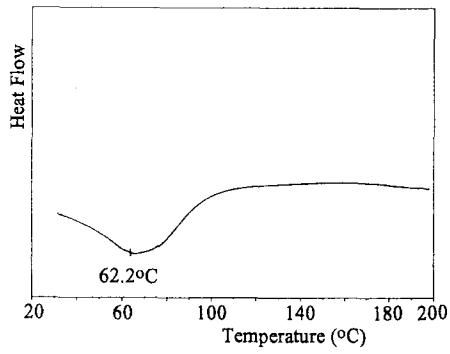

Fig. 6. DSC thermograms of NCH-Eudragit RS dispersion after annealing.

This transition was depressed to a lower temperature, 55°C, because of the presence of other chemicals, NCH and sucrose stearate. It was reported that this could be an indication of solid solution formation, i.e. the drug molecules are accordingly embedded between the macromolecular chains in a solid solution. By separating them, they would tend to reduce the secondary polymer–polymer bonds. The free volume available for each chain and hence its degree of freedom, would accordingly increase. Therefore, the drug would act as a sort of plasticizer for the polymer and apart from the absence of crystalline regions in the polymer mass, T_g of the latter would be lowered (Benoit and Puisieux, 1986). Therefore, NCH in microspheres prepared from F6I formulation formed a solid solution.

The additional transition of 145°C, not observed in any formulations, may arise from a direct interaction of these two polymers. Indeed, there was no clear indication for this transition in F6I as seen in Fig. 7b, possibly the interaction

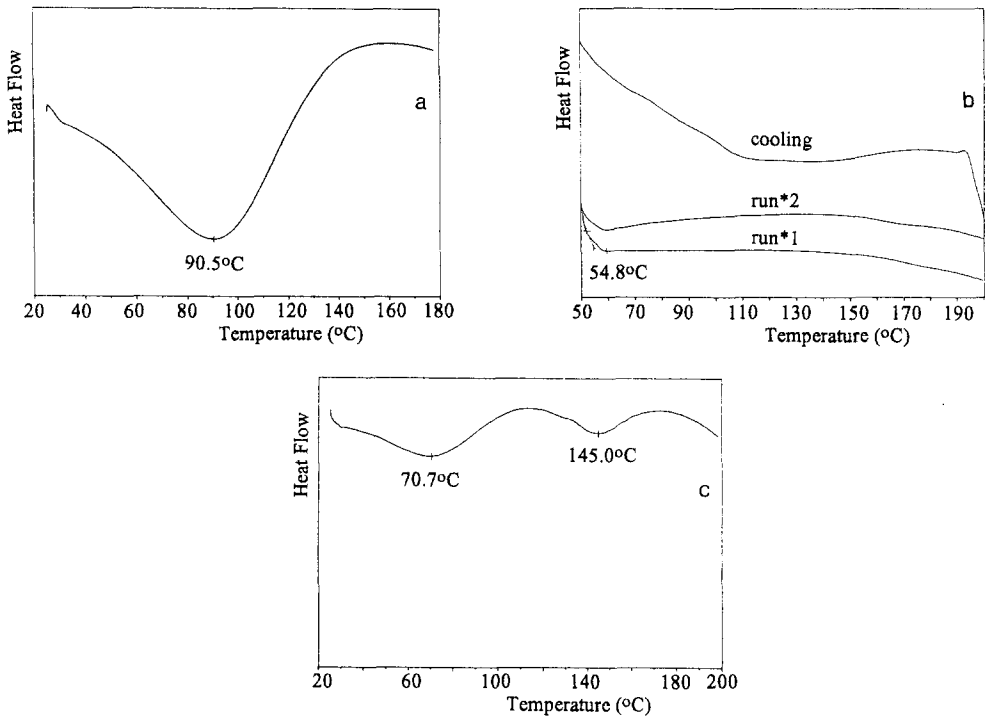

Fig. 7. DSC thermograms of: (a) Eudragit L; (b) microspheres of F6I formulation; and (c) Eudragit RS-L dispersion.

between anionic Eudragit L and nonionic Eudragit RS, yet containing quaternary ammonium salt, might be broken by the addition of sucrose stearate and NCH.

4. Conclusion

In this study, two formulations possessing controlled release characteristics at pH 1.2 and 7.5, were developed. Eudragit RS in the formulation F1C retarded the dissolution rate of NCH at pH 1.2, while Eudragit RS and L mixture in the formulation F6I showed an initial retardation in dissolution rate of the drug and reached to the aimed TP for longer times. The drug release rates from both formulations ($k_0 = 0.144\%$ min^{-1} for F1C, $k_0 = 0.155\%$ min^{-1} for F6I) were close to that of TP ($k_0 = 0.139\%$ min^{-1}).

According to the results of DSC and XRD analysis, NCH was found to be in solid state solution in the polymeric microspheres and not recrystallize upon cooling and annealing experiments. Finally, the formulations ended with solid solution between NCH and acrylic polymers and their blends made possible the preparation of controlled release microspheres to retard and to enhance drug release rate at pH 1.2 and 7.5, respectively.

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