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EVALUATION OF DRUG-POLYMER INTERACTION IN POLYMERIC MICROSPHERES CONTAINING DILTIAZEM HYDROCHLORIDE

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The aim of this study was to evaluate the drug-polymer interaction in polymeric microsphere formulations containing diltiazem hydrochloride (DH). The microspheres were successfully prepared by solvent evaporation technique using two different polymer types, Eudragit®RS 100 and ethylcellulose. The existence of a possible interaction between DH and the polymers was investigated by using DSC and XRD. The DSC curves and XRD patterns indicated that there was no interaction between DH and the polymers. The peak area calculations in the DSC curves of F1- and F2-coded microsphere formulations showed that DH was dispersed, not dissolved, in the ethylcellulose polymer matrix, while it partly dissolved in the Eudragit ®RS 100 polymer matrix.

Keywords: *diltiazem hydrochloride, DSC, ethylcellulose, Eudragit®RS 100, polymeric microspheres, powder X-ray diffractometry*

Introduction

Diltiazem hydrochloride (DH) is a benzothiazepine calcium channel antagonist that has been widely used in the treatment of angina pectoris, arrhythmias and hypertension. As its biological half-life is about 3 h and its elimination is rapid, repeated daily administrations are needed to maintain effective plasma levels. Modified/controlled release dosage forms of DH have been developed in an attempt to reduce the frequency of daily dosing and to extend its clinical effects [1, 3].

Oral microparticulate dosage forms, such as polymeric microspheres, have attracted much attention from the standpoint of scientific and technical interest as modified/controlled drug delivery systems. The importance of polymeric microspheres in drug dosage form design and development is indisputable. Microspheres have several advantages, e.g. they spread out more uniformly in the gastrointestinal tract, thereby avoiding exposure of the mucosa to a high concentration of the drug, ensuring more reproducible drug absorption and reducing patient-to-patient variability [1–3].

Microspheres represent a polymeric matrix system containing the drug uniformly distributed throughout the polymer matrix. The physical state of the drug in the microspheres is dependent on the solubility of the drug in the polymeric matrix structure. The drug is either completely dissolved in the matrix or a fraction of the drug is dissolved and the rest is dispersed in the matrix. The kinetics of drug release can be influenced by the physical state of the drug in the microspheres. Different qualitative analytical methods, such as differential scanning calorimetry (DSC) and powder X-ray diffractometry (XRD), have been developed to obtain qualitative information about the physical state of the drugs in the microsphere formulations [7–12].

DSC is a well-established method of thermal analysis within the pharmaceutical sciences. It is often used as a qualitative technique to characterize physical and chemical events via changes in either enthalpy or heat capacity of a sample. The measurement of the enthalpy of fusion of the crystalline drug in the matrix formed is the basis of this method. Like DSC, XRD has been used to estimate the solubility of the drug and identify the physical state of the drug in the matrix structure of the polymeric microspheres [7–19].

In our previous studies, DH-loaded polymeric microsphere formulations were successfully prepared by water in oil emulsion solvent evaporation technique. Eudragit®RS 100 and ethylcellulose, which are the most widely used water-insoluble polymers, were employed as the polymeric matrix-forming agents in the microsphere formulations [2, 20].

The aim of this study was to evaluate possible interactions between DH and two different polymer types, and to characterize the physical state of the drug within the microsphere formulations. The solubility of the drug in the polymers and the crystalline or amorphous state of the polymers and drug were estimated by DSC and XRD.

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Experimental

Materials

DH was a gift from Nobel Pharmaceutical Co., Istanbul, Turkey; ethylcellulose was obtained from Sigma, St. Louis, USA; Eudragit®RS 100 was supplied by Röhm Pharma, Weiterstadt, Germany; aluminium tristearate was purchased from Merck, Darmstadt, Germany and triethylcitrate was obtained from Morflex, Greensboro NC, USA. All other chemicals were of analytical or reagent grade used without further purification.

Methods

Preparation of microsphere formulations

All microspheres were prepared by the water in oil emulsion solvent evaporation technique using liquid paraffin as an external phase. The internal phase consisted of acetone involving DH, polymer, aluminium tristearate and triethylcitrate [2, 20]. Aluminium tristearate was used as an emulsifier to prevent surface electrification and flocculation during the preparation of the microspheres, and triethylcitrate was used as a plasticizer to improve the flexibility of the polymer chains. At first, the polymer, either ethylcellulose or Eudragit®RS 100, was dissolved in acetone by stirring at 500 rpm with a magnetic stirrer. Accurately weighed amounts of DH, aluminium tristearate and triethylcitrate were dispersed in this solution and stirred at the same rate with magnetic stirrer at a temperature of less than 20°C. This mixture was rapidly poured into liquid paraffin. The resultant emulsion was continuously agitated at room temperature using a three-blade propeller stirrer (Stir-pak®, USA) at 1200 rpm for 5 h. During the stirring, acetone was removed completely by evaporation and the droplets gradually solidified and formed microspheres. Then, the system was filtered to separate the microspheres, washed twice with 200 mL *n*-hexane, dried under vacuum at room temperature overnight and stored in a desiccator. The composition of the drug-loaded microsphere formulations is given in Table 1.

Table 1 Compositions of the microsphere formulations coded F1 and F2

Composition	Code and quantity	
	F1	F2
DH/g	3.6	3.6
Ethylcellulose/g	–	3.6
Eudragit®RS 100/g	3.6	–
Triethylcitrate/g	0.36	0.36
Aluminium tristearate/g	1.8	0.54
Acetone/mL	60	18
Liquid paraffin/mL	200	200

Powder X-ray diffractometry (XRD)

The physical state of DH in the various microsphere formulations was investigated by the method of XRD. XRD patterns of the pure drug, polymers and drug-loaded microspheres were obtained from Rigaku D-Max/2200 at 40 kV and 30 mA over a 20 diffraction angle with a range of 0–55°.

Differential scanning calorimetry (DSC)

DSC (Netzsch Geratebau DSC 204) was carried out on pure drug, raw polymers, aluminium tristearate, drug-loaded microspheres and the physical mixtures of microsphere formulations. Samples (5 mg) were accurately weighed into aluminium pans and then sealed. The DSC runs were conducted over a temperature range of 20–300°C at a rate of 5°C min^{-1} under air atmosphere.

Results and discussion

XRD and DSC studies were performed to understand the crystalline or amorphous nature and the solubility of the drug after encapsulation into a polymeric microsphere formulation. For the determination of the existence of a possible interaction between DH and the polymers, ethylcellulose and Eudragit®RS 100, in the microsphere formulations, we first investigated, the XRD patterns of the pure drug and polymers as shown in Fig. 1. The crystallinity of DH was clearly seen by its XRD pattern (Fig. 1a), while Eudragit®RS 100 (Fig. 1b) and ethylcellulose (Fig. 1c) were amorphous state in nature.

The XRD patterns of the drug-loaded Eudragit®RS 100 microsphere formulation (coded F1) and the drug-loaded ethylcellulose microsphere formulation (coded F2) are presented in Figs 2a and b, respectively. Both of the microsphere formulations exhibited sharp peaks indicating crystalline state due to crystalline DH.

The result obtained from thermal analysis of the drug is shown in Fig. 3a. Pure DH showed a sharp endothermic peak at 217.2°C corresponding to its melting point. This result is in agreement with a previous study by Hekmatara *et al*. [3]. The curves of raw polymers, Eudragit®RS 100 and ethylcellulose, are shown in Figs 3b and c, respectively. The thermal transition for Eudragit®RS 100 at 61.9°C was attributed to the glass transition temperature (T_g) of the polymer, as also put forward by other authors [21, 22] and the ethylcellulose curve displayed a large exothermic peak at 205.9°C resulting from oxidative degradation of the polymer. This finding is similar to the DSC

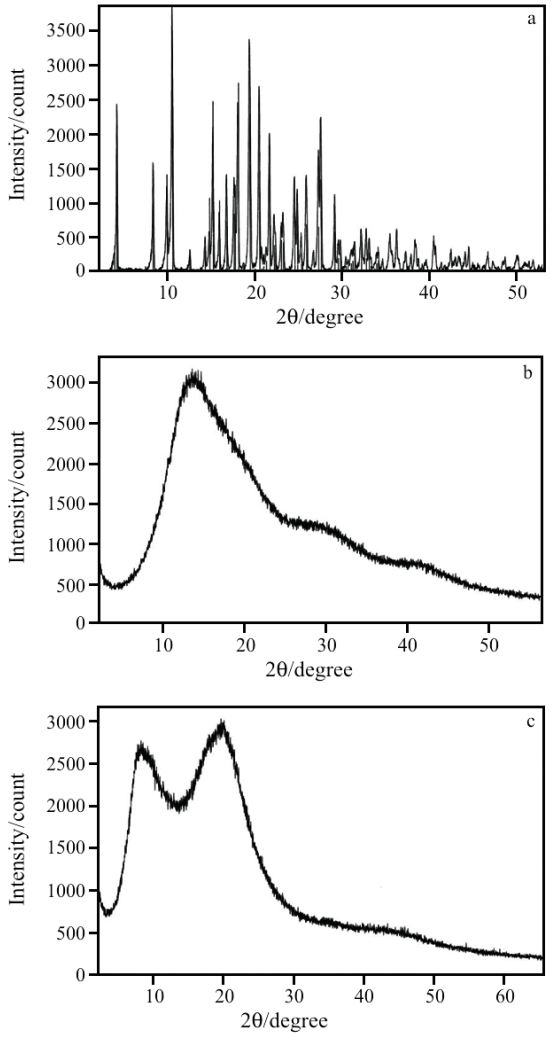

Fig. 1 XRD patterns of a – DH, b – Eudragit®RS 100 and c – ethylcellulose

curve of ethylcellulose reported previously by Guyot and Fawaz [23].

When the DSC curves of DH and the polymers were examined, it was shown that DH was crystalline, while Eudragit®RS 100 and ethylcellulose were both amorphous state. These results correlate with those of the XRD analysis.

The DSC curve of aluminium tristearate, which was used as an emulsifier in the microsphere formulations, is shown in Fig. 4a. In the curve, two melting endothermic peaks at 66.7 and 106.2°C were observed. The first peak was the possible presence of surface humidity in aluminium tristearate and the second was the melting point of aluminium tristearate. A similar finding about the melting point of aluminium tristearate has been reported previously [24, 25]. As seen in the curve, aluminium tristearate was amorphous state in nature.

The curve of the physical mixture of the F1-coded Eudragit®RS 100 microsphere formulation is presented

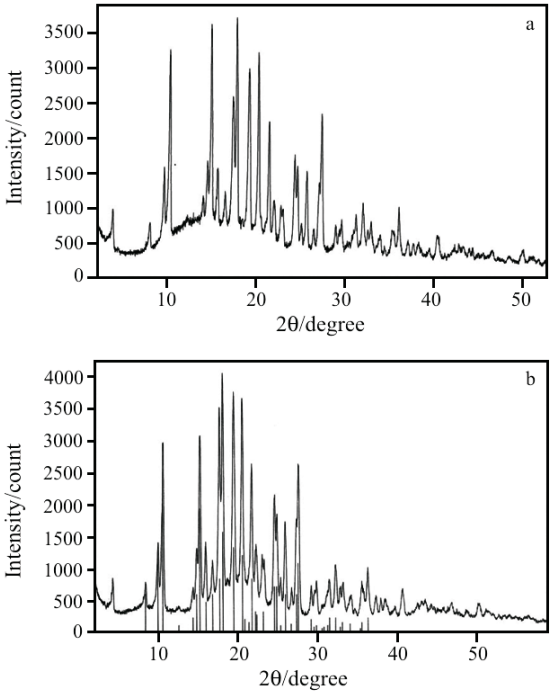

Fig. 2 XRD patterns of a – F1 and b – F2 microsphere formulations

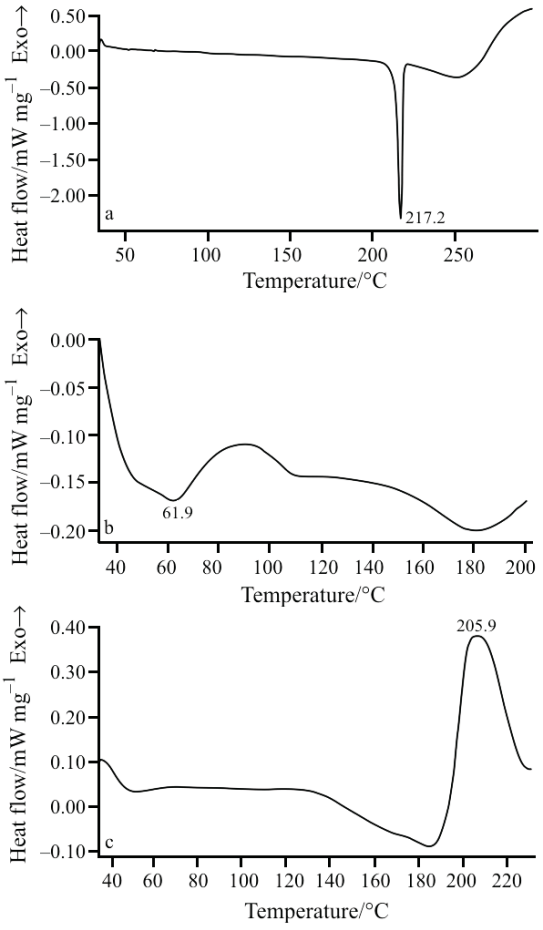

Fig. 3 DSC curves of a – DH, b – Eudragit®RS 100 and c – ethylcellulose

in Fig. 4b. A sharp endothermic peak corresponding to the melting point of crystalline DH was found at 212.7°C. The T_g of the polymer was observed at 65.0°C, while the endotherm at 99.5°C was thought to be the melting point of aluminium tristearate.

When the DSC curves of the physical mixture of the F2-coded ethylcellulose microsphere formulation (Fig. 4c) were examined, three melting endothermic peaks at 66.9, 104.9 and 213.4°C, corresponding to the surface humidity in aluminium tristearate, melting points of aluminium tristearate and DH, respectively, and one exothermic peak at 174.2°C, indicating the oxidative degradation of ethylcellulose, were observed. This finding is similar to the oxidative degradation of ethylcellulose reported in a previous study by Guyot and Fawaz [23] and in agreement with their results.

The DSC curve of the drug-loaded Eudragit®RS 100 microsphere formulation (coded F1) is given in Fig. 5a. The T_g of the polymer was observed at 72.6°C, and an endothermic peak at 217.2°C was observed as the melting point for DH. The increase in the T_g value of Eudragit®RS 100 is presumably caused by DH being partly soluble in the polymer. This should also result in the broadening of the melting point peak for DH. This result is similar to that mentioned previously [22]. It can be postulated that the drug is semi-crystalline in the microsphere formulation.

The DSC curve of the F2-coded ethylcellulose microsphere formulation is seen in Fig. 5b. In the curve, one exothermic peak at 161.2°C, corresponding to the oxidative degradation of ethylcellulose, and two melting endothermic peaks at 112.1 and 213.0°C, indicating aluminium tristearate and DH, respectively, were observed. During the solvent evaporation process and dissolution of the polymer, the slower evaporation of the solvent and the longer mixing of dispersion probably caused the decrease in the oxidative degradation peak of ethylcellulose from 205.9 to 161.2°C. No peak change was observed in the curve to denote a crystal change of the drug indicating that DH is still in crystalline form in the microsphere formulation.

The area under a signal peak is directly proportional to the heat evolved or absorbed during the event from which it arises. The peak area, which is calculated automatically by computer using a software program, is related to the enthalpy (energy) change and used to compare the peaks [10, 16]. The increases in the enthalpy of fusion are attributed to the loss of amorphous structure of the drug, thus relatively decreasing

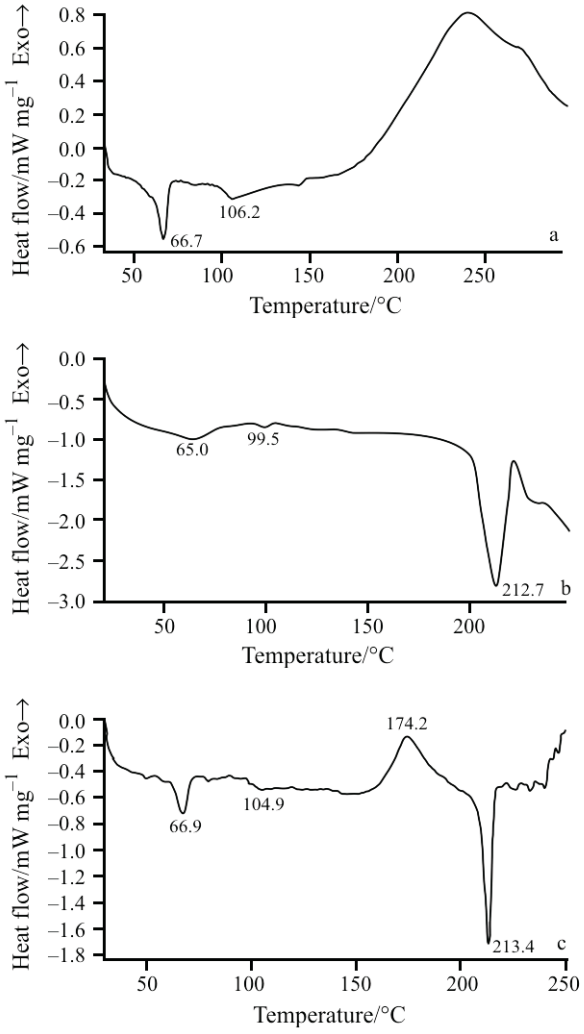

Fig. 4 DSC curves of a – aluminium tristearate, b – physical mixture of F1 microsphere formulation and c – physical mixture of F2 microsphere formulation

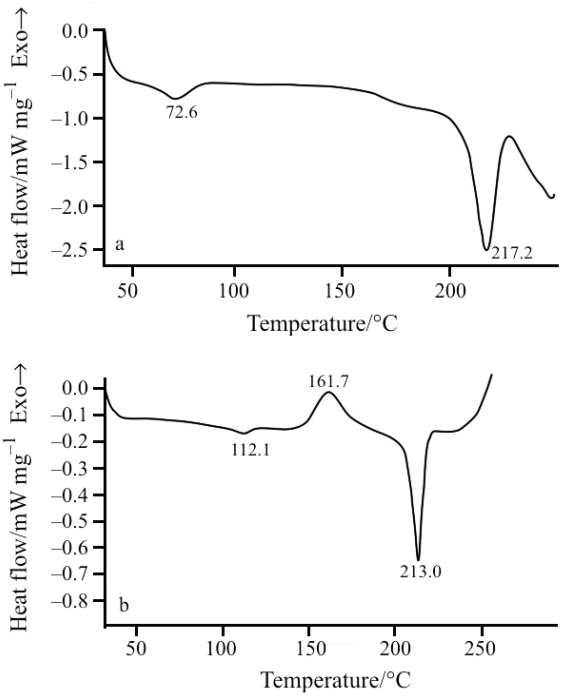

Fig. 5 DSC curves of a – F1 and b – F2 microsphere formulations

the amorphous fraction and increasing the crystalline fraction of the sample [9, 17–19]. According to the DSC curves of DH, the enthalpy of reaction in the peak area of DH is –90.59 J g^{-1} (Fig. 3a). When the DH peaks in the DSC curves of F1- and F2-coded microsphere formulations were compared, it was seen that the enthalpy of reaction for the F1-coded microsphere formulation is –32.42 J g^{-1} and for the F2-coded microsphere formulation –62.20 J g^{-1} (Fig. 5a and b). When the DSC curves of F1 and F2 microsphere formulations were examined, it was shown that DH was dispersed, not dissolved, in the ethylcellulose polymer matrix, while it was partly soluble in the Eudragit®RS 100 polymer matrix. The peak area calculations and the XRD patterns of microsphere formulations confirmed that result.

Conclusions

In the present research, DSC and XRD methods were successfully applied to DH-loaded microsphere formulations containing two different polymers, Eudragit®RS 100 and ethylcellulose. All of the DSC and XRD analyses showed that there was no drug-polymer interaction between DH and the polymers in the microspheres. DH was still in crystalline state in both of the microsphere formulations. The peak area calculations in the DSC curves of F1- and F2-coded microsphere formulations indicated that DH was dispersed, not dissolved, in the ethylcellulose polymer matrix, while it was partly soluble in the Eudragit®RS 100 polymer matrix.

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