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Preparation, Physical Characterization, Mechanisms of Drug/Polymer Interactions, and Stability Studies of Controlled-Release Solid Dispersion Granules Containing Weak Base as Active Substance

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ABSTRACT

Verapamil hydrochloride solid dispersion granules were prepared using solvent evaporation technique. Ethyl cellulose, hydroxypropyl cellulose, Eudragit L or Eudragit S were used as polymers for controlling the dissolution rate of the drug substance, and to avoid the continuous decrease of drug dissolution rate at higher pH values. By incorporating Eudragit L in ethyl cellulose network it is possible to prepare controlled-release formulation with increased release rate of active substance (weak base) at higher pH values without causing abrupt drug release at lower pH values. The release rate at low pH values was not highly influenced by Eudragit L content. The behavior of Eudragit L and Eudragit S in coprecipitates was different relating to the solubilization effect and the release of active substance. In order to understand the drug release mechanism better, the release data were tested assuming Higuchi model and first-order kinetic model. Since the calculated correlation coefficients were very close for both kinetics, to distinguish between the mechanisms the differential forms of first-order and square root of time equation were used. The differential test showed that diffusion-controlled release was operative in solid dispersions, except for series with higher content of Eudragit S. X-ray powder diffraction method, IR spectroscopy studies, and differential ther-

mal analysis were used for physical characterization of coprecipitates and drug-polymer interaction evaluation. After 24 months of real time stability studies, the prepared coprecipitates were still x-ray amorphous, with no changes in their IR spectra and DTA studies. The dissolution rates of the tested formulations showed no significant changes during the stability studies, reflecting the stability of x-ray amorphous drug phase.

INTRODUCTION

Drug substances that are weak bases by their physicochemical properties can experience release rate problems from sustained-release dosage forms. Since the solubility of the weak bases is highly pH dependent, being very soluble in acidic media with a drop of solubility at higher pH values, in conventional sustained-release dosage forms a slow and continuous decrease of drug dissolution rate at higher pH values can be expected. Also, precipitation of poorly soluble free base may occur within formulation in the intestinal fluids. Precipitated drug is no longer capable of release from the formulations (1,2).

The objective of this study was to obtain controlled-release solid dispersion granules with ensured pharmaceutical availability especially at higher pH values, containing weak base verapamil HCl as a model drug substance, using different polymers. The solubility of verapamil HCl drops from 0.165 g/cm^3 to 0.025 g/cm^3 and 0.010 g/cm^3 at pH 5.0, 6.0, and 7.0, respectively, at 37°C (3,4). To achieve the goal to prepare controlled-release dosage form containing weak base as active substance, with even increased release rate at higher pH values, solid dispersion granules containing verapamil HCl, hydroxypropyl cellulose (HPC), ethyl cellulose 10 cp (EC 10 cp), and enteric soluble polymers such as Eudragit L or Eudragit S were prepared. Our previous investigations (series **a–e**) showed that it is possible to increase verapamil HCl release rate at higher pH values incorporating HPMCP HP 55 in coprecipitates (5,6).

MATERIALS

The following chemicals were used in this study: verapamil hydrochloride and norverapamil (Fischer Chemicals AG, Germany), Eudragit L and Eudragit S (Rohm Pharma, Germany), ethyl cellulose 10 cp (EC 10 cp, Colorcon, UK), hydroxypropyl cellulose LF (HPC, Hercules, U.S.), and absolute ethanol (Merck, Germany).

METHODS

Preparation of Solid Dispersion Granules

Solid dispersions containing verapamil HCl, EC 10 cp, HPC, and various concentrations of Eudragit L or Eudragit S (Table 1) were prepared by solvent evaporation technique, at 55°C, after dissolving or suspending the drug substance and polymers in absolute etha-

Table 1

Composition of Mixtures for Preparation of Solid Dispersions

Series	Verapamil HCl (parts)	EC 10 cps (parts)	HPC (parts)	Eudragit L (parts)	Eudragit S (parts)
f	1	1.55	0.45	0.90	—
g	1	1.55	0.45	1.00	—
h	1	1.55	0.45	1.15	—
i	1	1.55	0.45	1.25	—
j	1	1.55	0.45	—	0.40
k	1	1.55	0.45	—	0.50
l	1	1.55	0.45	—	0.75
m	1	1.55	0.45	—	0.90
n	1	1.55	0.45	—	1.05

nol. Solid dispersion granules were prepared by grounding and sieving. Fractions between 25 and 40 mesh were collected and used for further investigations.

HPTLC Studies

HPTLC technique (Camag applicator, Camag scanner II) was utilized for detection of possible decomposition that may have occurred during preparation of solid dispersion granules or during stability studies. Plate material was silica gel, Merck $60F_{254}$. The plates were developed by solvent system composed of cyclohexane:diethylamine 85:15. The detection was carried out at 278 nm. Verapamil HCl and norverapamil were used as standard substances.

Dissolution Rate Studies

Samples of solid dispersion granules equivalent to 240 mg verapamil HCl were tested for dissolution rate studies in 1000 ml buffer solutions, with pH 1.5 composed of NaCl and HCl, and pH 6.8 composed of KH_2PO_4 and NaOH (USP XXII rotation basket method, apparatus Erweka DZT, at 100 rpm). Also a half-change dissolution method (by Gaudy) was carried out during 24 hours by changing the pH of the medium from 1.2 (during 1 hour), to 2.5 (for 2 hours), to 5.5 (for an additional 2 hours), to 7.5 (until the end of the dissolution test). The drug content in the withdrawn aliquots was analyzed spectrophotometrically at 278 nm (Hewlett Packard hp 8452).

Analysis of Drug Release Data

The goodness of fit of the release data was tested with first-order kinetics and Higuchi model. Also, as both above plots were acceptably linear and gave high and close values of correlation coefficients, a more stringent test was needed to distinguish between the mechanisms. For diffusion-controlled mechanisms, the rate will be inversely proportional to the total amount of drug released (Q') in accordance with

$$dQ'/dt = K^2S^2/2Q' \quad (1)$$

where $Q' = Q \times S$ (S is the surface area). The rate predicted by first-order kinetics is given by

$$dQ'/dt = kC_o - kQ' \quad (2)$$

where $C = C_o - Q'$ (7–11). This indicated that rate will be proportional to Q'.

The rates of release were determined by measuring the slopes at different points on the percent of verapamil release versus time curves.

X-ray Diffraction Studies

The physical nature of verapamil hydrochloride in solid dispersion granules was determined using x-ray diffraction method (Jeol diffractometer, model JDX-7E, goniometer model DX-60-F). Powder samples of verapamil HCl and physical mixtures were examined for comparison.

IR Studies

IR spectra of the drug substance, polymers, physical mixtures, and solid dispersions (KBr tablets) were obtained using Perkin Elmer infrared spectrophotometer.

Differential Thermal Analysis

The DTA thermograms of verapamil HCl, physical mixtures, and solid dispersions were obtained heating up to 270°C (apparatus NETZSCH Geratebau GmbH Selb, STA 409). Weighted samples were sealed in aluminum pans and scanned at a rate of 10°C/min.

Stability Studies

Stability of solid dispersion granules was evaluated during 24 months at real time studies. Dissolution tests, HPTLC studies, IR spectroscopy, DTA, and x-ray diffraction method were carried out for characterization of the series during real time studies (Kotterman chamber, temp. 26°C, relative humidity 65%).

RESULTS AND DISCUSSION

Determination of Verapamil Hydrochloride Content

The content of verapamil hydrochloride in solid dispersion granules obtained by HPTLC is presented in Table 2. The possibilities of complexation of drug molecules with the polymer molecules and decomposition during preparation of solid dispersions were eliminated since no new peaks were detected in HPTLC study of solid dispersions.

Table 2

Verapamil Hydrochloride Content in Solid Dispersion Granules

Series	Mean Weight ±SD (g), n = 20	Mean Verapamil HCl Content ± SD (mg), n = 5
f	0.9360 ± 0.0020	239.00 ± 4.30
g	0.9600 ± 0.0030	240.00 ± 3.15
h	0.9960 ± 0.0020	238.00 ± 4.00
i	1.0200 ± 0.0050	239.00 ± 4.00
j	0.8160 ± 0.0040	238.00 ± 5.00
k	0.8400 ± 0.0046	241.00 ± 3.80
l	0.9000 ± 0.0072	240.00 ± 2.30
m	0.9360 ± 0.0068	239.00 ± 5.00
n	0.9720 ± 0.0073	240.00 ± 2.50

Dissolution Rate Studies: The Role of Eudragit L and Eudragit S

The results from dissolution tests of series **f–n** are shown in Figure 1 (pH 1.5), Figure 2 (pH 6.8), and Figure 3 (half-change method).

Series Containing Eudragit L

Dissolution rate of verapamil HCl at pH 1.5 and pH 6.8 from solid dispersion granules containing Eudragit L depends on the content of the methacrylic acid copolymer in the formulations. Increasing the percentage of copolymer in the series, the dissolution rate at pH 1.5 (Figure 1) decreased. At pH 6.8 (Figure 2) increased percentage of Eudragit L in the formulations resulted with faster release rate of drug substance. The drug substance has low solubility at neutral pH values and its solubility decreases from 0.156 g/cm^3 at pH 5.0 to 0.025 and 0.010 g/cm^3 at pH 6.0 and 7.0, respectively. Quantitative release at pH 1.5 was not noticed from either series. The formulation containing the lowest percentage of methacrylic acid copolymer releases only 70% of the drug substance during 24 hours. At pH 6.8 quantitative release was noticed from both series (**h** and **i** series), containing 1.15 and 1.25 parts of Eudragit L in formulation, respectively. From half-change dissolution method one can see that the release rate differences within series magnify with increasing the pH of the dissolution medium. No significant differences in the release rate from all series was noticed during the first 3 hours of the dissolution test. Quantitative dissolution rate was noticed from series **h** and **i**, containing 1.15 and 1.25 parts of copolymer Eudragit L in formulation, respectively (Figure 3).

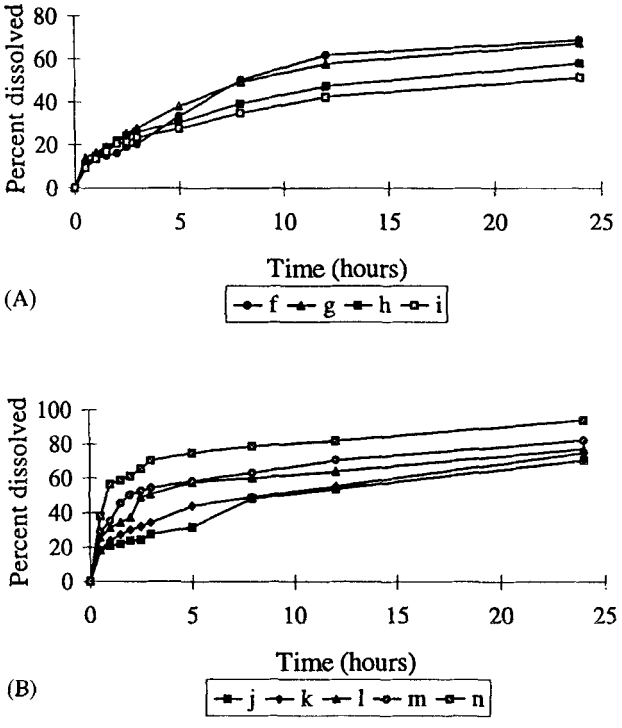

Figure 1. Cumulative amounts (%) of verapamil HCl released from solid dispersion granules (pH = 1.5). A-series with Eudragit L; B-series with Eudragit S. Each point represents the mean (n = 5–10).

In spite of the low solubility of the drug substance at higher pH values from prepared formulations containing Eudragit L copolymer, increased release rate was noticed as the pH of the medium increases. The enhancement of the dissolution rate at higher pH values was primarily due to the presence of Eudragit L, and its solubilization effect in the microenvironment immediately surrounding the drug substance particle. The drug particle size in solid dispersions is reduced to a minimum, making the process of solubilization and dissolution easier.

Series Containing Eudragit S

The fast release of drug substance at pH 1.5 (Figure 1) was noticed from series containing a higher percent of copolymer, Eudragit S. Almost 70% of drug substance was released from series **n** containing 1.05 parts of Eudragit S, during the first 3 hours at pH 1.5. No

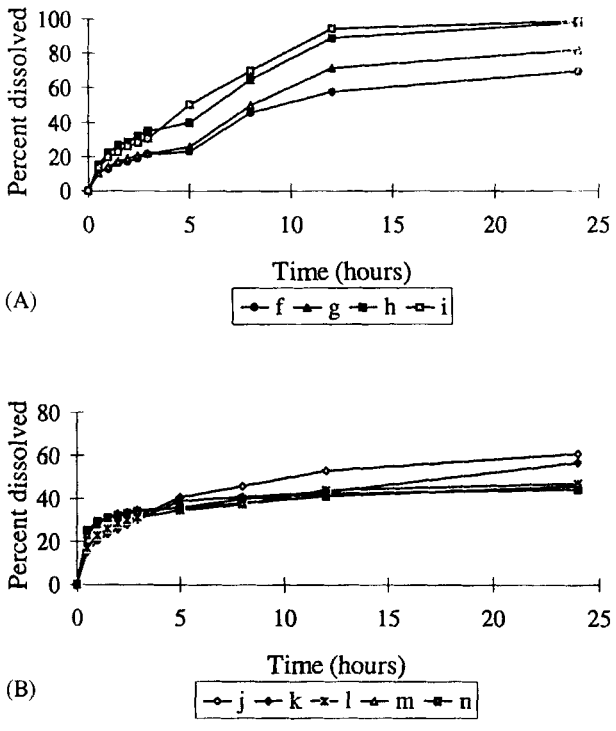

Figure 2. Cumulative amounts (%) of verapamil HCl released from solid dispersion granules (pH = 6.8). A-series with Eudragit L; B-series with Eudragit S. Each point represents the mean (n = 5–10).

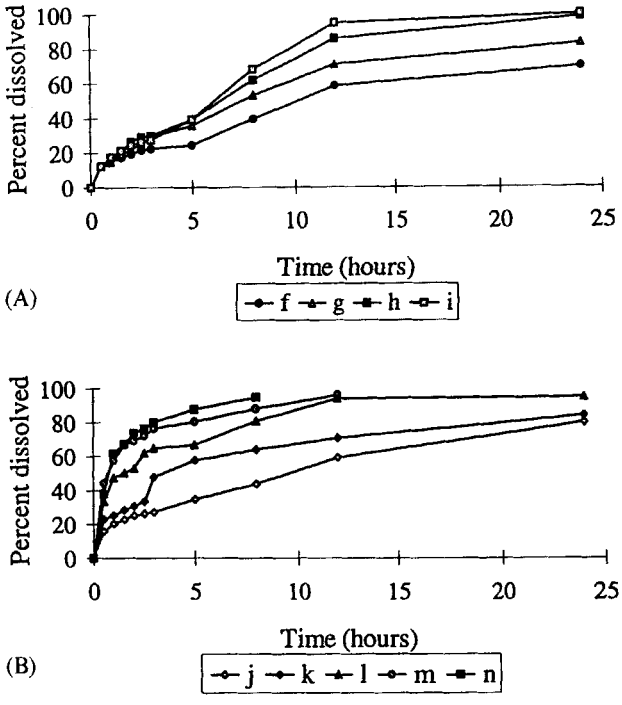

Figure 3. Cumulative amounts (%) of verapamil HCl released from solid dispersion granules (half-change method). A-series with Eudragit L; B-series with Eudragit S. Each point represents the mean (n = 5–10).

quantitative release from series with Eudragit S copolymer was noticed during 24 hours at pH 6.8 (Figure 2). The release rate at pH 6.8 was faster from series containing a lower percent of Eudragit S (0.4 and 0.5 parts of Eudragit S, or series **j** and **k**). Dissolution rates from series containing 0.75, 0.9, and 1.05 parts (series **l**, **m**, and **n**) were almost the same, considering pH 6.8.

Half-change dissolution results (Figure 3) point that significant differences in the release rate from the samples appeared during the first hours of the test, which is different from samples containing Eudragit L copolymer.

Dissolution Studies Concerning Eudragit L and Eudragit S Free Formulations

In Eudragit L and Eudragit S free formulations, drug release rate depends on the percentage of hydroxypropyl cellulose and it decreases as the pH of the medium increases, which is not acceptable for controlled-release dosage forms. Also no quantitative release was noticed from those series (very slow release was noticed as the pH of the medium increases followed by an interruption of release at pH 6.8). Increased percentage of hydroxypropyl cellulose in formulations resulted with abrupt release of verapamil HCl at pH 1.5.

Analysis of the Drug Release Data

Since estimation of dissolution test results showed very close values of the correlation coefficients and linear plots for the diffusion model and first-order kinetics, it was necessary to distinguish between the mechanisms. The treatment based on the use of the differential forms of the first order and square root of time equations showed that the plots of rates of release versus $1/Q$ were linear and those of rates versus Q were curved or nonlinear (Figure 4). This indicated that diffusion controlled release of the active substance from coprecipitates was operative (except for series that contain 0.9 and 1.05 parts of Eudragit S). Also good linearization, high values of correlation coefficients of log-log curves (log Q/versus log t), and calculated slope of the curves (0.5) is another confirmation that the diffu-

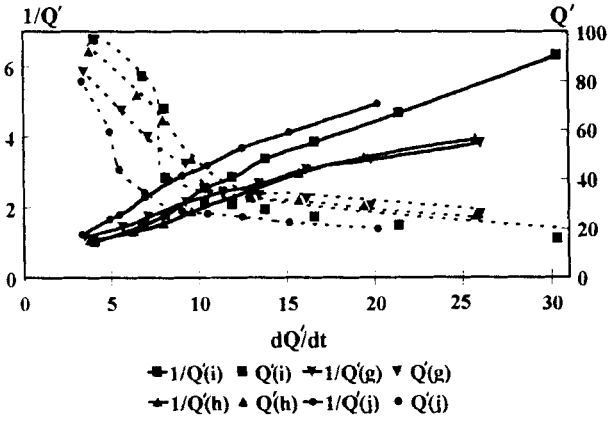

Figure 4. Plots of release rate (dQ'/dt) of verapamil against amount (Q') and reciprocal of the amount ($1/Q'$) of drug released for series **g, h, i, j.**

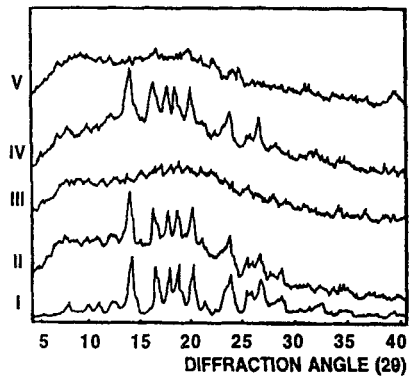

Figure 5. X-ray diffractograms of verapamil HCl (I), physical mixture of series **h** (II), solid dispersion (III), series **h**; physical mixture of series **m** (IV), and solid dispersion (V), series **m**.

sion is the rate-determining step in coprecipitates. The kinetic parameters for the diffusion model, first-order kinetics, and results from the differential test are presented in Table 3.

X-ray Diffraction Studies

X-ray diffractograms point out the amorphous appearance of verapamil HCl in prepared coprecipitates as presented in Figure 5. The diffraction spectra of pure verapamil HCl showed that the drug is highly crystalline in nature, which is indicated by numerous distinctive peaks in the x-ray diffractogram. In spite of the small proportion of drug in the physical mixtures, the x-ray diffractograms possessed all characteristic verapamil HCl diffraction lines.

Infrared Spectroscopy Studies

The IR spectra of the drug substance and physical mixtures of the drug substance and polymers showed all characteristic bands of verapamil HCl. In the case of coprecipitates (series **f–n**), changes in the area of ν C—O—C skeletal vibrations (1200–1000 cm^{-1}, Figure 6) of glucose units in cellulose polymers appeared, showing differences in glucose bond orientation in solid dispersions. Basically, no changes in the frequency and shape of verapamil HCl bands were noticed, which

Table 3

Kinetic Parameters for Series f-n

	Diffusion Model		First Order Kinetics		Differential Test dQ'/dt Versus $1/Q'$ Diffusion (r)	Differential Test dQ'/dt Versus Q' First Order (r)	Log-Log
Series	r	k% $min^{-½}$	r	k, min^{-1}			r
f	0.9999	14.8899	0.9788	0.0207	0.9931	0.4012	0.9909
g	0.9932	18.6194	0.9933	0.0319	0.9883	0.7502	0.9910
h	0.9931	22.9249	0.9931	0.0709	0.9823	0.7880	0.9903
i	0.9923	24.2797	0.9723	0.0818	0.9607	0.8900	0.9898
j	0.9945	15.5379	0.9985	0.0263	0.9888	0.7193	0.9927
k	0.9901	15.9700	0.9652	0.0297	0.9864	0.7533	0.9658
l	0.9898	16.6883	0.9336	0.0504	0.9649	0.9037	0.9586
m	0.9509	16.9200	0.9896	0.0882	0.9415	0.9703	0.8955
n	0.9223	23.6601	0.9982	0.1326	0.9065	0.9777	0.8937

r = correlation coefficient; k = dissolution rate constant.

leads to the conclusion that no significant redistribution of the electronic density in the structure of the organic molecules appeared. This indicates that there is no strong interaction between the drug and the polymers, so interactions of van der Waal's type and/or dipole-dipole interactions exist in coprecipitates.

In order to study interactions between drug substance and each polymer, simple binary coprecipitates consisting of drug and Eudragit L, drug and Eudragit S, as well as drug and ethyl cellulose were prepared. The prepared simple binary coprecipitates were x-ray amorphous.

Comparing IR spectra of verapamil HCl, Eudragit L, and simple binary coprecipitates consisting of drug and Eudragit L copolymer, new small-intensity bands appeared in the range of 1200–800 cm^{-1}. This points out that changes in the skeletal vibrations of the ester part of the polymer molecule appeared as a result of the dispersion of drug molecules in the polymer network and dipole-dipole interactions between drug and polymer molecules (Figure 6). Some changes were noticed in Eudragit S/drug substance simple binary coprecipitates. In the IR spectra of ethyl cellulose/drug (simple binary coprecipitates), changes of ν C—O—C skeletal vibration bands of molecules were also noticed (1200–1000 cm^{-1}).

In spite of the dissimilarities in the dissolution rate studies, no differences were noticed in the IR spectra of coprecipitates containing Eudragit L or Eudragit S (series **f–n**) , as well as in the simple binary coprecipitates of copolymers (Eudragit L and Eudragit S) with drug substance.

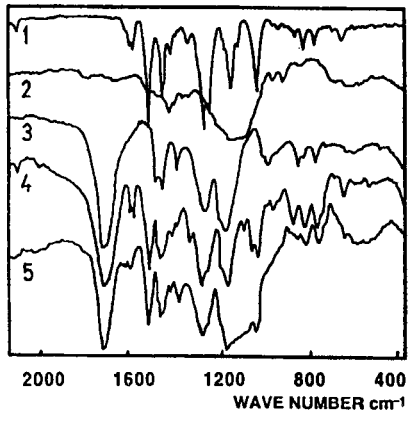

Figure 6. IR spectra of verapamil HCl (1), ethyl cellulose (2), Eudragit L (3) binary coprecipitate with Eudragit L, and verapamil HCl (4), coprecipitate, series **h** (5).

Differences were noticed between IR spectra of simple binary solid dispersions consisting of polymers only. The range from 1500–1000 cm^{-1} in the IR spectra of solid dispersion containing Eudragit L and ethyl cellulose was completely different by number and shape of the bands compared with the IR spectra of solid dispersions containing Eudragit S and ethyl cellulose (Figure 7). These differences in skeletal vibration shape and intensity point to different orientation and splicing between polymer chains, resulting with different networks of ethyl cellulose and copolymers (Eudragit L or S). Also, these differences in the drug-containing coprecipitates were not noticed because of substantial overlap between bands of drug molecules and polymers in that region. It is well known that incorporated drug will also influence the polymer chain orientation and splicing and we cannot take this as the only factor responsible for release differences between coprecipitates containing Eudragit L or Eudragit S copolymers. Another factor responsible for release differences might be polymer swelling and solubility differences at higher pH values.

Differential Thermal Analysis

Endothermic DTA effects that result from melting are observed in the thermograms of verapamil HCl, physical mixtures, and coprecipitates (Figure 8). A melting peak of verapamil HCl was present at the DTA curve of the physical mixture. No melting peak was observed for verapamil HCl in coprecipitate, which could be ex-

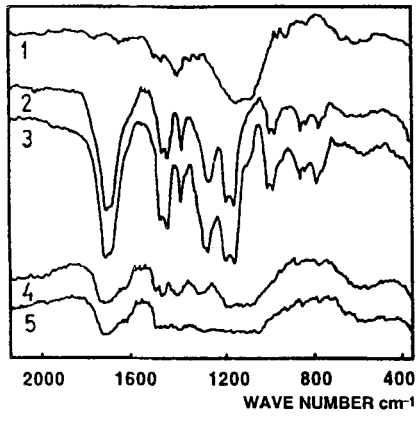

Figure 7. IR spectra of ethyl cellulose (1), Eudragit L (2), Eudragit S (3), binary coprecipitate with ethyl cellulose and Eudragit L (4), and binary coprecipitate of ethyl cellulose and Eudragit S (5).

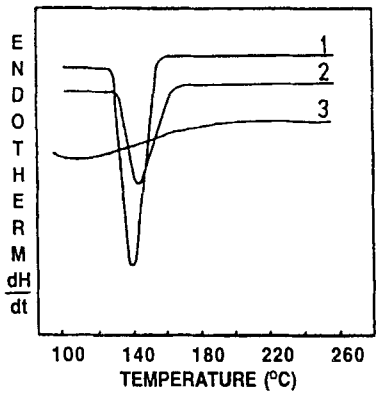

Figure 8. DTA curves of verapamil HCl (1), physical mixture (2), and coprecipitate **h**.

plained by precipitation of the drug substance in amorphous form on the polymer particles.

The x-ray diffraction patterns depicted in Figure 5 confirm the amorphous appearance of the drug in coprecipitates. Differences in the DTA studies among coprecipitates containing Eudragit L or Eudragit S copolymer were not noticed.

Stability Studies

After 24 months of real time studies, no changes in HPTLC studies, x-ray diffraction studies, IR studies, and DTA curves were noticed in tested coprecipitates containing Eudragit L or Eudragit S. Also, no significant changes in the drug dissolution rate were noticed during the study, reflecting the stability of the x-ray amorphous drug phase.

CONCLUSIONS

Incorporating Eudragit L in ethyl cellulose network, it is possible to inhibit to a great extent the dissolution of a weak base (verapamil HCl) in acidic medium and to increase the release rate of the active substance (weak base) at higer pH values, in spite of the decreasing solubility of the drug substance as the pH of the medium increases. This gives an opportunity of increasing drug release rate at higher pH values to the necessary rate by changing the copolymer content in the formulations, not causing abrupt drug release at a lower pH value (the release rate at low pH values was not highly influenced by copolymer content).

The alteration of physical properties of the active substance (particle size, crystal structure), as well as drug/polymer interactions, participate in the mechanism of controlled drug release. Physical characterization of solid dispersions points out that drug molecules are enslaved in the polymer's network and only van der Waal's or dipole-dipole interactions exist between polymers and drug molecules. Significant differences were noticed between the series containing different copolymers, Eudragit L or Eudragit S, considering dissolution rate studies. The differences might be due to the different orientation and splicing between ethyl cellulose and copolymer chains, resulting with a different network of ethyl cellulose and Eudragit L, compared to the polymer network of ethyl cellulose and Eudragit S. Also differences in swelling and solubility properties of the copolymers may contribute to the variations in dissolution rate studies considering series containing Eudragit L and Eudragit S. The coprecipitates showed no significant changes after 24 months of real time studies, which confirms the stability of the x-ray amorphous drug phase.

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