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PHYSICAL CHARACTERIZATION AND DISSOLUTION PROPERTIES OF VERAPAMIL.HCl COPRECIPITATES

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ABSTRACT

Verapamil hydrochloride coprecipitates were prepared using solvent-evaporation technique. Ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose phtalate HP 55 were used as polymers. The solid dispersions obtained were grounded and sieved to prepare solid dispersion granules. The dissolution behavior of solid dispersion granules was studied using buffer solutions with pH 1.5; 6.8 and half-change method during 24 hours. The drug release rate was found to be dependent on the ratio of the polymers in coprecipitates. In order to understand the drug release mechanism better, the release data were tested assuming common kinetic models. The best fit kinetic model was diffusion model and the dissolution rate constants calculated using Higuchi equation, demonstrated that dissolution rate increased with increasing the ratio of HPMCP HP 55 in coprecipitates. Physical characterization was made using X-ray diffractometry, IR spectrophotometry and DTA studies. Prepared coprecipitates were X-ray amorphous. Also, after nine months real time studies they remain amorphous, with no changes in their IR spectra and DTA curves. The dissolution rate of the test dispersions showed no significant changes during the stability studies, reflecting the stability of X-ray amorphous drug phase.

INTRODUCTION

Solid dispesion technique may have numerous pharmaceutical applications which remain to be further explored. The purpose of this study was to prepare solid dispersion granules containing Verapamil hydrochloride, with controlled release of active substance, using different polymers.

Verapamil hydrochloride by its physico-chemical properties a weak base, can experience problems on release from controlled-release dosage forms in the small intestine. 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 (1-3).

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Precipitation of poorly soluble free base occurs within formulation in the intestinal fluids. Precipitated drug is no longer capable of release from formulations(4,5). A possible approach for ensuring pharmaceutical availability of controlled-release dosage forms containing weak bases as active substances, might be preparation of solid dispersion systems incorporating a carrier with possible solubilization effect which may operate in the microenviroiment (diffusion layer), immediately surrounding the drug particle. The carrier used in this study was hydroxypropyl methylcellulose phtalate (HPMCP HP 55), and the polymers also used for controlling the dissolution rate were ethylcellulose 10cp (EC 10cp) and hydroxypropyl cellulose LF (HPC).

MATERIALS

The following chemicals were obtained from commercial supliers and used as received: Verapamil hydrochloride and Norverapamil (Fischer Chemical AG,Germany), Hydroxypropyl Methylcellulose Phtalate (HPMCP HP 55, Shin-Etsu Chemical Co., Ltd., Japan), Ethylcellulose 10cp (EC 10cp, Colorcon, UK), Hydroxypropyl Cellulose LF (HPC, Hercules, USA), Absolute Ethanol (Merck, Germany).

METHODS

Preparation of Solid Dispersions: Solid dispersions containing of Verapamil.HCl, EC 10cp, HPC and various concentrations of HPMCP HP 55 (Table 1) were prepared using solvent-evaporation method. After dissolving or suspending the active substance and the polymers in absolute ethanol, solid dispersions were prepared by vacuum evaporation, with temperature not exceeding 55°C. Solid dispersion granules were prepared by grounding and sieving. Fractions between 25 and 50 mesh were collected and used for further investigations.

HPTLC Studies: HPTLC studies (Camag applicator, Camag scanner II, v 3.14) utilized for detection or possible decomposition and chemical changes that may have occured during preparation of solid dispersion granules or during stability studies. Plate material was Silica gel Merck 60 F_{254}. The plates were developed by a solvent system of cyclohexane:diethylamine 85:15. The detection was carried out at 278 nm.

Dissolution rate studies:Dissolution tests were carried out with samples of solid dispersion granules equivalent to 240 mg Verapamil.HCl, in 1000 ml buffer soutions with pH 1.5, composed of NaCl and HCl and pH 6.8 composed of KH_2PO_4 and NaOH (USP XXII rotating basket mathod, apparatus Erweka DZT, at 100 r.p.m.). Also a half-change dissolution method (by Gaudy) was carried out with the samples during 24 hours, changing pH of the medium from 1.2 (during one hour), 2.5 (for two hours), 5.5 (for two hours) and 7.5 until the end of the test (6).

The drug content in the withdrawn aliquots was analyzed spectrophotometricaly at 278 nm (PYE Unicam PU 8610),using aliquots of dissolution test of drug-free sample as blanck to avoid absorption of HPMCP HP 55.

Release Kinetics: The goodness of fit of the release data was tested with following mathematical models :first order kinetics, square-root of time equation and Hixson-Crowell's cube-root equation.

X-ray Diffraction Studies: An X-ray powder diffractometer (Jeol diffractometer, model JDX-7E, goniometer model DX-60-F) was used to determine the physical nature of

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Table 1
Composition of mixtures for preparation of solid dispersions

serie	Verapamil. HCl (parts)	EC 10cp (parts)	HPC (parts)	HPMCP HP 55 (parts)
a	1	1.55	0.45	0.45
b	1	1.55	0.45	0.65
c	1	1.55	0.45	1.05
d	1	1.55	0.45	1.15
e	1	1.55	0.45	1.25

Verapamil hydrochloride in the solid dispersions. Powdered samples of Verapamil HCl and physical mixtures were examined for comparison.

IR Studies: Perkin Elmer infrared spectrofotometer was used to obtain IR spectra of the pure drug , polymers, physical mixtures and solid dispersions (KCl tablets).

Differential Thermal Analysis: The DTA thermograms of Verapamil hydrochloride, physical mixtures and solid dispersions were obtained heating up to 270°C (apparatus NETZSCH Geratebau GmbH Selb, STA 409). Weighed samples were sealed in aluminium pans and sccaned at a rate of 10°C.

Stability Studies: Stability of solid dispersion granules was evaluated during nine months at real time studies. Dissolution tests, HPTLC studies, IR spectroscopy , DTA analysis and X-ray diffraction method were carried out for characterization of the series during real time studies (Kottermann chamber, temperature 26°C, relative humidity 65%).

RESULTS AND DISCUSSION

Verapamil Hydrochloride Content in Solid Dispersion Granules: The results from HPTLC studies are presented in Table 2. No new peaks were detected in HPTLC study of solid dispersion granules. This eliminated the possibility of chemical complexation of the drug molecules with the polymers molecules and also possible decomposition during the preparation of the solid dispersions. Verapamil hydrochloride and Norverapamil were used as standard substances.

Release of Verapamil hydrochloride from Solid Dispersion Granules: The results of dissolution tests for series a-e are shown in Figure 1 (pH 1.5), Figure 2 (pH 6.8) and Figure 3 (half-change method).

Dissolution rate of Verapamil hydrochloride at pH 6.8 depends on the content of HPMCP HP 55 in the series. Increasing the quantity of HPMCP HP 55 the dissolution rate of active substance at pH 6.8 increased. The release of active substance was quantitative from series with higher content of HPMCP HP 55. Dissolution rate of Verapamil hydrochloride from series at pH 1.5 was not significantly influenced by the content of HPMCP HP 55, neither increased nor decreased, during first eight hours. Afterwards, higher content of HPMCP HP 55 resulted with slightly increased dissolution

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Table 2
The determination of Verapamil.HCl content in solid dispersion granules

series	mean weigh±SD,(g),n=20	mean Verapamil.HCl content±SD,(mg),n=5
a	0.8280 ± 0.0020	240.00 ± 5.00
b	0.8760 ± 0.0030	239.00 ± 4.90
c	0.9720 ± 0.0020	241.00 ± 3.80
d	0.9960 ± 0.0030	238.00 ± 4.52
e	1.0200 ± 0.0030	237.00 ± 4.00

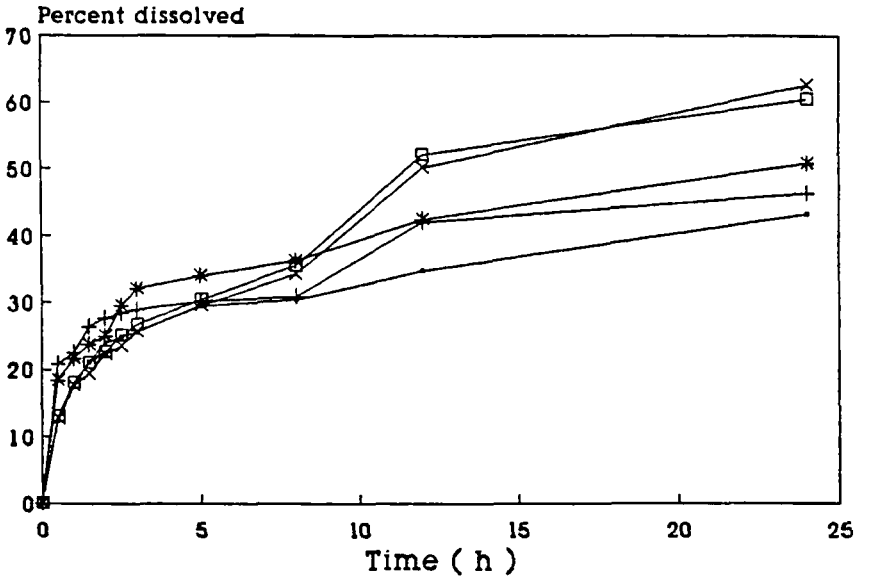

FIGURE 1
Cumulative amounts of Verapamil .HCl released from series a, b, c, d and e(pH 1.5) Each point represents the mean (n=5-10):a, b, c, d, e

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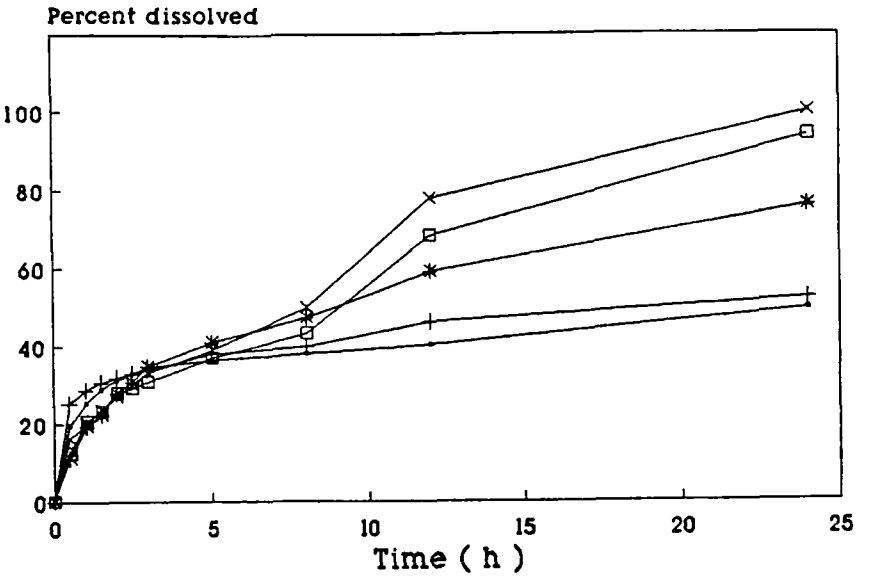

FIGURE 2
Cumulative amounts of Verapamil.HCl released from series a, b, c, d and e(pH 6.8). Each point represents the mean(n=5-10).Symbols:a, b, c, d, e

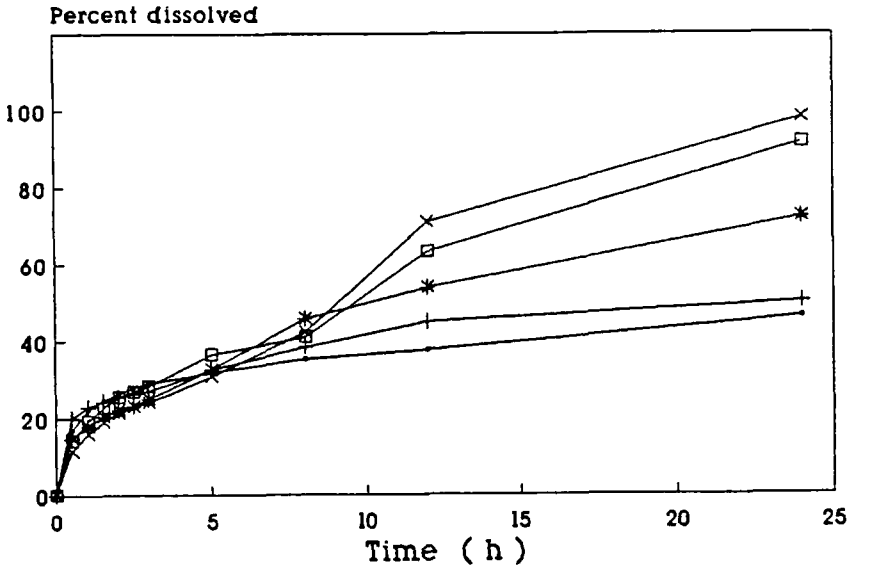

FIGURE 3
Cumulative amounts of Verapamil.HCl released from series a, b, c, d and e(half-change method).Each point represents the mean (n=5-10). Symbols:a, b, c, d, e

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Table 3
Kinetic parameters for series a, b, c, d, e

series	Diffusion model		Cube-root eqn.		First-order kinetic	
	r	k (%$h^{-1/2}$)	r	k (%$h^{-1/3}$)	r	k (h^{-1})
a	0.9899	5.8742	0.8707	0.0349	0.8347	0.0331
b	0.9901	7.7031	0.9177	0.0406	0.9037	0.0376
c	0.9951	14.3550	0.9378	0.0712	0.9149	0.0644
d	0.9924	18.0910	0.9567	0.0826	0.9259	0.0707
e	0.9920	21.1010	0.9556	0.0972	0.9271	0.0846

Legend: r-correlation coefficient
k-dissolution rate constant

rate of Verapamil hydrochloride, probably becouse of higher permeability of those series. Even though, the dissolution rate was increased with higher content of HPMCP HP 55 in the series, no quantitative release of active substance at pH 1.5 was noticed from non at all. From half-change disssolution test one can see that significant differences in the release rate from the samples can be noticed after the fifth hour, esspecialy at the 12-th and 24-th hour of the test, due to the different content of HPMCP HP 55 in the series.

Kinetic of Verapamil hydrochloride Release from Solid Dispersion Granules: When the abcissa was converted in the square-root of time, the dissolution curves for all formulations showed the highest linearity in comparison with other kinetic models. The dissolution profiles for all the series were more approximate for that of the leaching type for the matrix, presented by T.Higuchi. Channels were formed in the solid dispersion granules after the dissolution of the soluble polymers; Verapamil hydrochloride in ethylcellulose was diffused and dissolved into the dissolution medium in the channels. HPMCP HP 55 may show its solubilization effect in the microenviroiment (diffusion layer), immediately surrounding the drug particle, which size is reduced to minimum in the solid dispersions, what makes the process of solubilisation and dissolution easier. Also there is a good correlation between the dissolution rate constants calculated using Higuchi equation and composition ratio of HPMCP HP 55 in the formulations (0.9810). The kinetic parameters for the series are presented in Table 3.

X-ray Diffraction studies: The X-ray diffraction patterns of Verapamil hydrochloride, physical mixtures and solid dispersions are illustrated in Figure 4. The diffraction spectra of pure Verapamil hydrochloride showed that the drug was highly crystallin in nature as indicated by numerous distinctive peaks in the X-ray diffractogram. The spectra of physical mixtures possessed all the characteristic diffraction lines of crystalline Verapamil hydrochloride. This reveals that inspite of its small proportion in the mixture, crystalline Verapamil hydrochloride is detectable and appears in crystalline state in the physical mixtures. Also diffraction spectra of solid dispersions point out to X-ray amorphous drug phase.

IR Studies: The IR spectra of the drug and physical mixtures of the drug substance and the polymers showed all characteristic bands of Verapamil hydrochloride. For coprecipitates changes in the range of ν C-O-C skeletal vibrations (1200-1000 cm^{-1}) of glucose units

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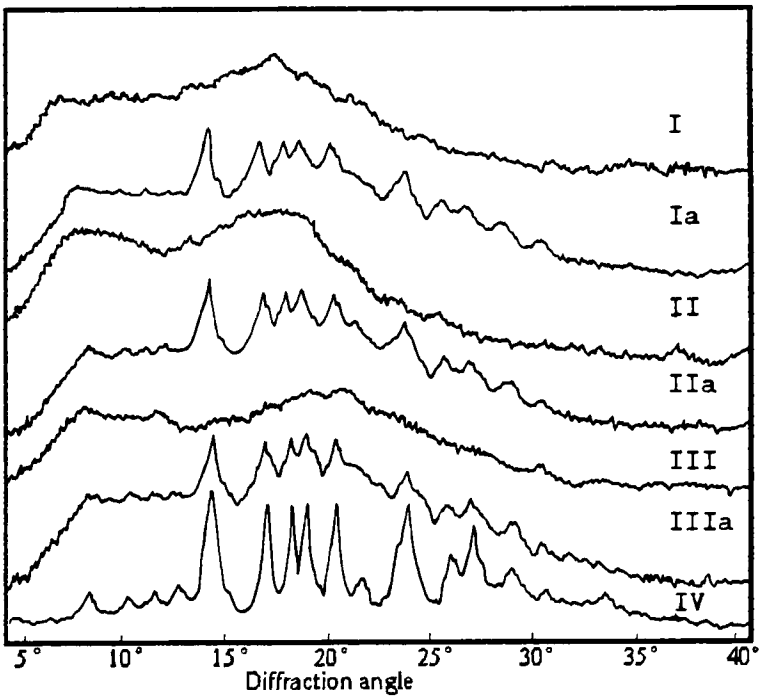

FIGURE 4

X-ray diffractograms of: I - serie b (solid dispersion), Ia - serie b (physical mixture),II - serie d (solid dispersion), IIa - serie d- (physical mixture), III - serie e (solid dispersion),IIIa - serie e (physical mixture) and IV - Verapamil hydrochloride.

in cellulose polymers appared, showing differences in glucose bonds orientation in solid dispersions. Basicaly, no changes in the frequency and shape of Verapamil hydrochloride bands in coprecipitates were noticed, which leads to conclusion that no significant redistribution of the electronic density in the structure of the drug molecules appared, indicating that there is no strong interaction between the drug and the polymers, so interactions of van der Waal's type or dipol-dipol interactions exist between the drug and the polymers in solid dispersions.IR spectra of the drug substance, physical mixture, coprecipitate and ethylcellulose are presented in Figure 5(range from 2000-400 cm^{-1}).

DTA Studies: Endothermic DTA effects that results from melting are observed in the thermograms of Verapamil hydrochloride, physical mixtures and coprecipitates. Figure 6 showes the DTA curves for Verapamil hydrochloride, physical mixture of serie d and coprecipitate d. A melting peak for Verapamil hydrochloride was present at the DTA curve of the physical mixture. No melting peak was observed for Verapamil hydrochloride in coprecipitate what can be due to precipitation of drug substance in amorphous form in

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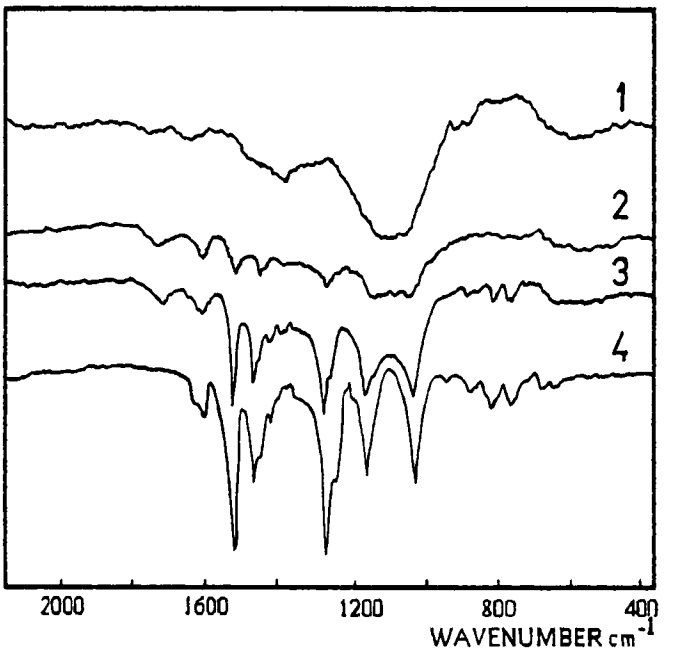

FIGURE 5

IR spectra of ethylcellulose (1), solid dispersion of serie e (2), physical mixture of serie e (3) and Verapamil hydrochloride (4).

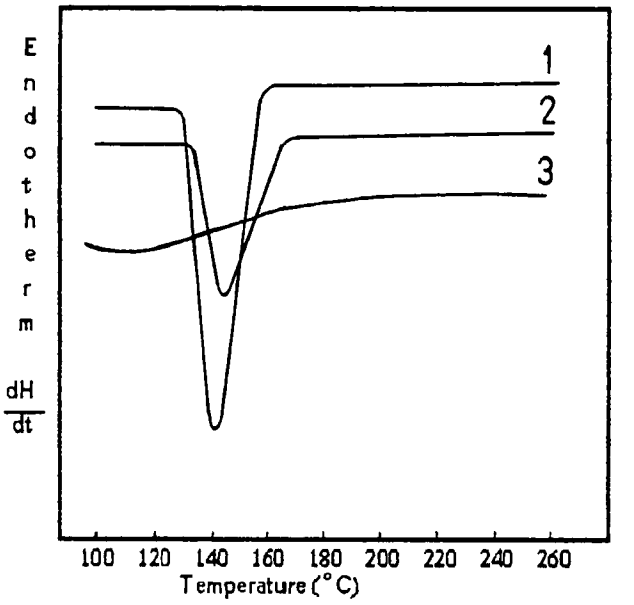

FIGURE 6

DTA curves of Verapamil hydrochloride (1), physical mixture of serie e (2) and solid dispersion of serie e (3).

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the polymer network, where it is completely enslaved.X-ray diffraction patterns present in Figure4 show that coprecipitates were indeed amorphous.

Stability Studies: No changes were noticed with X-ray diffraction spectra, IR analysis, DTA curves after nine months at real time studies. Also no significant changes in the dissolution rate of the tested dispersions were noticed during the study, reflecting the stability of X-ray amorphous drug phase.

CONCLUSIONS

It is possible to prepare Verapamil hydrochloride solid dispersion granules with controlled-release of drug substance using solvent-evaporation technique.Inspite of the low solubility of the drug substance at pH 6.8 with prepared formulations increased release rate with time was noticed as the pH of the medium increased (half-change method). The enhancement of dissolution rate at higher pH values was primarly due to the presence of HPMCP HP 55, with its solubilization effect in the microenviroiment immediately surrounding the drug particle, which size in the solid dispersions is reduced to minimum, what makes the process of solubilization and dissolution easier. The dissolution rate from HPMCP HP 55 free formulations was dependent on the percentage of HPC in formulations, showing no quantitative release at lower percentages of HPC and very fast release at pH 1.5 with icreasing the quantity of HPC in formulations. Physical characterization of solid dispersions point out that drug molecules are enslaved in the polymer network and only interactions of van der Waal's type or dipol-dipol interactions exist between polymers and drug molecules. The coprecipitates showed no significant changes after nine months real time studies, which confirm stability of X-ray amorphous drug phase.

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