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RESEARCH PAPER

Formulation and In Vitro Evaluation of Polymeric Films of Diltiazem Hydrochloride and Indomethacin for Transdermal Administration

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ABSTRACT

Ethylcellulose-polyvinyl pyrrolidone films containing diltiazem hydrochloride and indomethacin were evaluated for their potential drug delivery at a controlled rate, using rat skin, to select a suitable formulation for the development of transdermal drug delivery systems. The influence of film composition, initial drug concentration, and film thickness on the in vitro drug release rate as well as drug permeation through rat abdominal skin were studied. Drug release studies were carried out employing the paddle over disk method and drug permeation through full thickness of the rat abdominal skin was tested using a modified Franz diffusion cell fastened with O-ring. The drug content of the film decreased at an apparent first-order rate, whereas the quantity of drug released was proportional to the square root of time. The release rates of both drugs increased linearly with increasing drug concentration and polyvinyl pyrrolidone fraction in the film, but was found to be independent of film thickness. The increase in release rate may be due to leaching of hydrophilic fraction of the film former which resulted in the formation of pores. It was also observed that the release of drugs from the films followed a diffusion-controlled model at low drug concentrations. A burst effect was observed initially, however, at high drug loading levels. This may be due to rapid dissolution of the surface drug followed by the diffusion of drug through the polymer network in the film. The in vitro skin permeation profiles showed increased flux values with increase of initial drug concentration in the film and also with the concentration of polyvinyl pyrrolidone. From this study, it is concluded that the films composed of ethylcellulose:polyvinyl pyrrolidone:diltiazem hydrochloride

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(8:2:2) and ethylcellulose:polyvinyl pyrrolidone:indomethacin (8:2:3) should be selected for the development of transdermal drug delivery systems, using a suitable adhesive layer and backing membrane, for potential therapeutic use.

INTRODUCTION

Recently much attention has been focused on developing controlled drug delivery systems using polymers. These developments led to the formulation of transdermal drug delivery systems (TDDS) which release the drug for systemic effects at a controlled rate (1,2). Among the various types of TDDS available for different ailments, one type utilizes the dispersion of a drug in an inert matrix made up of polymer(s) which release the drug at a controlled rate (3). The rate of drug release from these matrices may be altered by variations of the dimensional parameters of the film, the polymer matrix material (4), and the drug concentration in the film (5). The physicochemical properties of the drug molecule and differences in the condition of the skin, region, age, sex, and species will also play an important role in the permeation of the drug through the skin (6–10). The release rate of a drug from an insoluble polymer matrix can be increased by incorporation of hydrophilic polymers such as hydroxypropylmethylcellulose and polyethylene glycol (11–13).

The present study was designed to develop a suitable matrix model TDDS of diltiazem hydrochloride and indomethacin, employing ethylcellulose (EC) and polyvinyl pyrrolidone (PVP) as film formers. Dibutyl phthalate was incorporated into the formulation, at a concentration of 30% w/w of dry polymers, as plasticizer. The dried films were evaluated for various parameters such as thickness uniformity, water absorption capacity, drug content uniformity, drug–carrier interactions prior to the drug release, and skin permeation studies.

MATERIALS

EC (with an ethoxyl content of 47.5–53.5% by weight and a viscosity of 14 cps in a 5% w/w, 80:20 toluene:ethanol solution at 25°C, SD Fine Chem Ltd., India), PVP (molecular weight of 40,000, Loba Chemie, India), dibutyl phthalate (Ranbaxy Laboratories Ltd., India), potassium chloride (Ranbaxy Laboratories Ltd.), and chloroform (Qualigens, India, HPLC grade) were obtained commercially. Diltiazem hydrochloride (a gift sample from M/S Torrent Pharmaceutical Ltd, Ahmedabad, India) and indomethacin (a gift sample from M/S Invinex Laboratories, Hyderabad, India) were used as received.

METHODS

Preparation of Films

Films composed of different ratios of EC, PVP, and drug were prepared by mercury substrate method (14). Dibutyl phthalate was incorporated at a concentration of 30% w/w of dry weight of polymers as plasticizer. Briefly, the method involves the pouring a chloroform solution containing drug, polymers, and plastisizers on a mercury surface contained in a Petri dish. The rate of evaporation of the solvent was controlled by placing an inverted funnel over the Petri dish. The dry films were removed from the mercury surface and kept in a desiccator until use.

The thickness of the dried films was measured at five different places using a micrometer (Mitotoyo, Japan) and the mean values were calculated. The uniformity of drug content of the films was determined, based on the dry weight ratios of drug and the polymers used, by a spectrophotometric method. A thin-layer chromatography (TLC) method was followed for the drug carrier interaction studies of diltiazem hydrochloride (15) and indomethacin (16).

Water Absorption Studies

The water absorption capacities of various films were determined at 84% relative humidity (RH) according to the method described elsewhere (17). A rectangular piece of film (2 × 6 cm) was cut using a glass template, weighed, and hung in a glass chamber containing saturated solution of potassium chloride (84% RH) with the help of a glass rod. After equilibrium was attained, the films were taken out from the chamber and weighed. The water absorption capacity of the films was calculated based on the change in the weight with respect to

the initial weight of the film and the values are depicted in Table 1.

In Vitro Drug Release Studies

The paddle over disk method was employed for the drug release determination from the films (18). The dry films of known thickness were cut to circular shape using a glass template and fixed over a glass plate with an adhesive. The plate was immersed in a 500-ml phosphate buffer solution (pH 7.4) maintained at a temperature of 37 ± 1°C. Then the paddle was positioned at a distance of 2.5 cm from the surface of the glass plate and regulated to rotate at a speed of 75 rpm. Aliquots of the samples were taken periodically at predetermined time intervals and analyzed for drug content after suitable dilution with buffer solution by a known spectrophotometric method, at λ_{max} of 236 and 318 nm for diltiazem hydrochloride (19) and indomethacin (20), respectively, using a Shimadzu double-beam UV-visible spectrophotometer. After each sampling, an equal volume of drug-free phosphate buffer solution was added to the dissolution medium to maintain a constant volume. Necessary corrections were made in the calculations for the loss of drug due to each sampling. The experiment was done in triplicate and mean value was calculated. The release rates were calculated from the linear plots of cumulative amount of drug released versus square root of time.

In Vitro Skin Permeation Studies

The in vitro skin permeation of drug from the selected films through the rat abdominal skin was tested by using a modified Franz diffusion cell fastened with an O-ring. The full thickness abdominal skin of male Wistar rats weighing 130–160 g was used. Hair on the abdominal area was clipped by applying depilatory for 10 min and washing with distilled water 1 day before the experiment. Rats were sacrificed by cervical dislocation, abdominal skin was excised, and the fatty material attached to the dermis was peeled off. Then the skin piece was mounted between the two compartments of the diffusion cell with the epidermis facing upward into the donor compartment. The film to be tested was placed on the skin. Isotonic phosphate buffer solution (25 ml) containing 0.02% gentamicin was used as receptor phase and agitated with a magnetic stirrer at a temperature of 37 ± 1°C. The top of the donor compartment was covered with aluminium foil to avoid the problem of drug photosensitivity. Samples (1 ml) were withdrawn at regular periods through the sampling port, and fresh receptor fluid was added to maintain the constant volume of the receptor phase. The samples were

Table 1

Drug Content Uniformity, R_f Values, and Water Absorption Capacity of Various Formulations

Formulation	Amount of Drug per 100 mg of Film	R_f Value	Amount of Water Sorbed (mg/100 mg)
Indomethacin (pure), EC:PVP:drug	-	0.79	-
10:0:2	12.48 ± 0.26	0.78	0.72
9:1:2	12.09 ± 0.42	0.78	2.84
8:2:2	12.65 ± 0.21	0.79	4.98
6:4:2	12.36 ± 0.19	0.77	9.36
5:5:2	12.46 ± 0.12	0.79	11.59
Diltiazem hydrochloride (pure), EC:PVP:drug		0.76	-
10:0:2	12.37 ± 0.25	0.76	0.61
9:1:2	12.52 ± 0.06	0.75	2.42
8:2:2	12.44 ± 0.19	0.76	4.46
6:4:2	12.61 ± 0.16	0.74	6.21
5:5:2	12.42 ± 0.16	0.75	7.98

analyzed as mentioned above and the cumulative amount of drug permeated was plotted against time. The flux values were then calculated from the linear portion of the plots.

X-ray Diffraction Studies

X-ray diffraction patterns of the pure drugs and formulations were measured with a Philips x-ray diffractometer (PW 1140) with graphite monochromator, CuKα radiation (X = 1.5418 Å), voltage 30 Kv, current 12 MHz, chart speed 2°/min, divergence slit 1°.

Scanning Electron Microscopic Studies

The surface morphologies of the drug-dispersed films before and after drug release studies were examined by scanning electron microscopy (SEM). The dried films were mounted on aluminum stubs using a double-sticky cellophane tape, gold-coated in a vacuum evaporator, and observed under a Hitachi S-520 scanning electron microscope.

RESULTS

Table 1 indicates that the drug was distributed uniformly throughout the film. The TLC method for drug carrier interaction studies exhibited the same R_f values which revealed that there is no chemical interaction between the drug and carriers used. The x-ray diffraction studies of drug in combination with polymers showed absence of the peaks which revealed that the crystalline nature of the active ingredient was converted into an amorphous state. The water absorption capacity of the films was also increased as the PVP fraction in the film increased.

Figure 1 shows the influence of initial drug concentration of diltiazem hydrochloride on the release rate constant from the films composed of EC:PVP (10:0). The increase in release rate constant was linear up to 20% w/w of drug concentration. Initial burst effect, however, was observed when the initial concentration exceeded 20%. Figure 2 shows the effect of film composition on the release rate of indomethacin from films containing a 10% w/w initial drug concentration. It was clear from this figure that as the PVP content of the film increased, the release rate of the drug also increased. A linear relationship between the ratio of PVP in the film and release rate constant was observed up to a 0.4 fraction of PVP in the films. Further increase of PVP content in the film showed an initial rapid release.

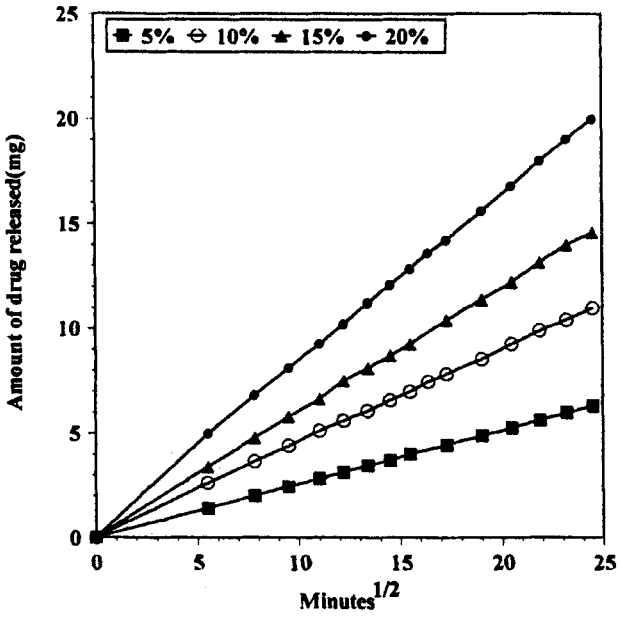

Figure 1. Drug release from films containing EC and PVP (10:0) loaded with different concentrations (% w/w) of diltiazem hydrochloride.

Tables 2 and 3 show the relationship between the release rate constants of the diltiazem hydrochloride and indomethacin and film thickness, initial drug concentration, and film composition, respectively. The release rate constants were dependent on the initial drug load-

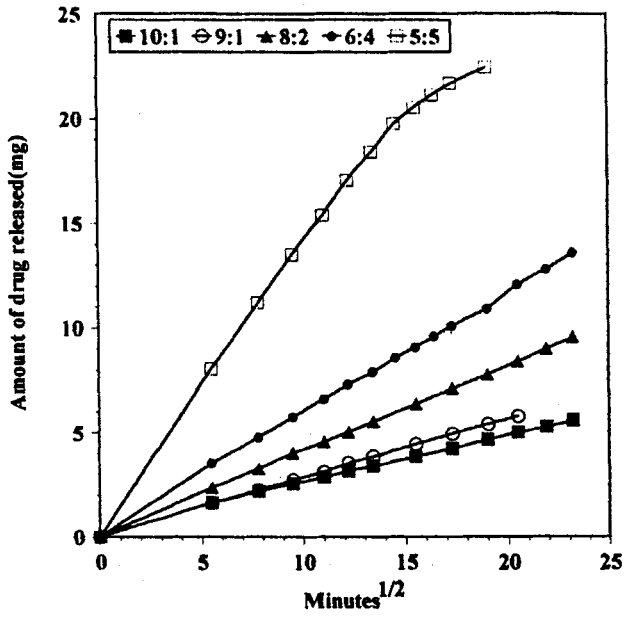

Figure 2. Drug release from films containing various ratios of EC:PVP loaded with 10% w/w indomethacin.

Table 2

Influence of Film Composition, Initial Drug Concentration, and Film Thickness on the Release Rate Constant of Diltiazem Hydrochloride

Film Composition (EC:PVP)	Initial Drug Concentration (% w/w)	Film Thickness (μm)	Release Rate Constant ($mg/cm^2 \cdot min^{1/2}$)
10:0	5	93.9 ± 4.1	0.0065
		79.5 ± 4.0	0.0065
		125.4 ± 6.2	0.0067
	10	91.3 ± 3.6	0.0138
		73.1 ± 2.8	0.0137
9:1	5	107.1 ± 3.8	0.0103
		82.31 ± 2.5	0.0098
	10	69.1 ± 2.9	0.0183
		103.2 ± 5.0	0.0176
	15	120.9 ± 4.9	0.0256
		83.8 ± 3.2	0.0239
	20	110.4 ± 2.7	0.0321
		79.8 ± 4.1	0.0317
8:2	10	95.6 ± 3.4	0.0244
	20	124.7 ± 4.8	0.0459
6:4	10	77.1 ± 1.9	0.0467
	20	106.4 ± 4.4	0.0852
5:5	10	82.1 ± 2.9	0.0811

Table 3

Influence of Film Composition, Initial Drug Concentration, and Film Thickness on the Release Rate Constant of Indomethacin

Film Composition (EC:PVP)	Initial Drug Concentration (% w/w)	Film Thickness (μm)	Release Rate Constant ($mg/cm^2 \cdot min^{1/2}$)
10:0	5	86.5 ± 5.4	0.0049
		104.6 ± 4.1	0.0051
		130.5 ± 6.2	0.0048
	10	85.6 ± 5.2	0.0093
		109.1 ± 4.6	0.0096
9:1	5	101.1 ± 2.8	0.0065
		87.7 ± 3.9	0.0063
	10	131.2 ± 7.6	0.0118
		114.6 ± 4.8	0.0116
	15	96.4 ± 5.8	0.0182
		120.2 ± 6.1	0.0185
	20	88.9 ± 4.3	0.0228
		115.6 ± 5.6	0.0219
	30	94.5 ± 3.6	0.0348
		122.5 ± 6.3	0.0343
8:2	10	75.1 ± 3.5	0.0166
	20	104.6 ± 6.2	0.0318
6:4	10	82.6 ± 2.5	0.0228
	20	112.9 ± 4.1	0.0442
5:5	10	73.5 ± 2.1	0.0551
	20	96.9 ± 3.8	0.0926

ing into the film and the film composition were independent of film thickness. However, the linearity between the release rate constant and initial drug concentration varies with individual drugs, which may be due to differences in the drug's physical properties. The increase in release rate constant with initial drug concentration was limited up to 20% w/w for films containing diltiazem hydrochloride, and in the case of indomethacin it was extended up to 30% w/w from the films composed of EC:PVP 10:0 and 9:1. It was also observed that as the PVP content of the film increased the crystallinity of the drug decreased, which resulted in an increase of drug release. Irrespective of the initial drug concentration of either drug, a burst effect was observed when the PVP content of the film exceeded 0.5 fraction.

Figures 3 and 4 show the representative cumulative amounts of diltiazem hydrochloride and indomethacin permeated through the rat abdominal skin, into an isotonic buffer solution, as a function of time on the films composed of various ratios of EC and PVP loaded with 10% w/w of initial drug concentration, respectively. It is evident from these figures that the flux values of both drugs increased as the PVP content of the film increased. In addition, the lag time (the time required to attain steady rate permeation of indomethacin) decreased with an increase of PVP content in the film. Table 4 shows the influence of initial drug concentration of flux values of diltiazem hydrochloride and indomethacin, as well as its effect on the lag time. The permeation rate of both drugs increased as the initial concentration of the drug in the film increased.

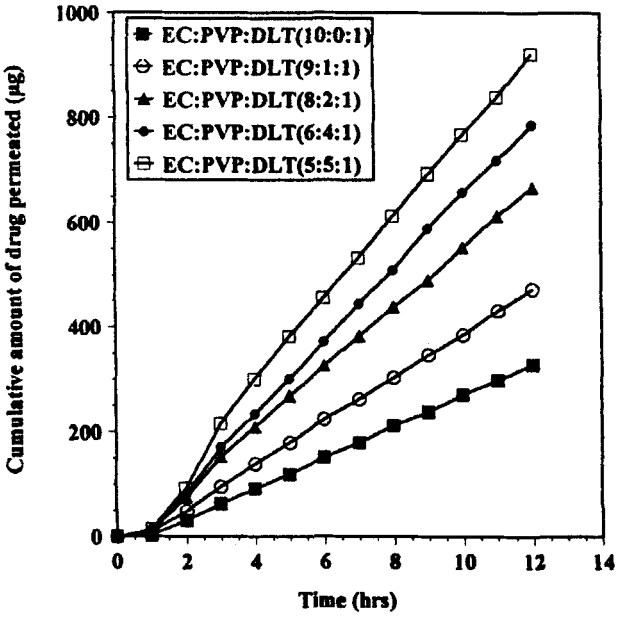

Figure 3. Effect of film composition on the permeation of diltiazem hydrochloride through rat abdominal skin.

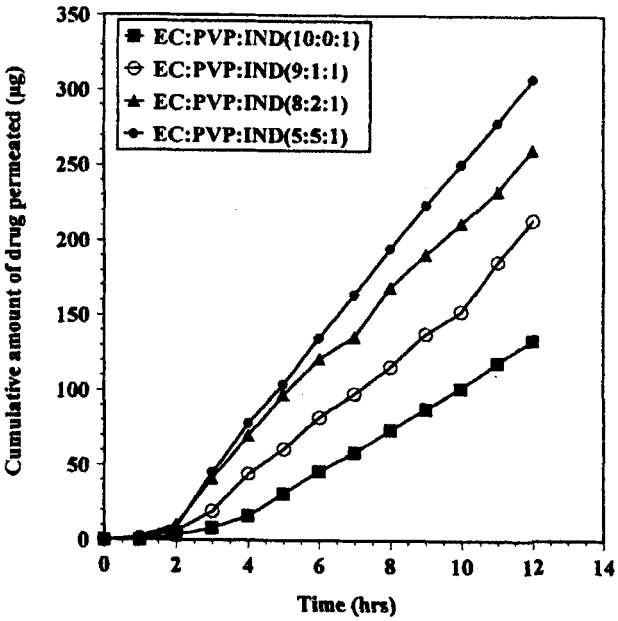

Figure 4. Effect of film composition on the permeation of indomethacin through rat abdominal skin.

DISCUSSION

The uniformity of the EC and PVP films was evidenced by the low SD values in thickness measure-

Table 4

Influence of Initial Drug Concentration on Lag Time and Skin Flux of Diltiazem Hydrochloride and Indomethacin

Drug Concentration (% w/w)	T_{lag} (hr)	Flux (µg/cm² · hr)
Diltiazem hydrochloride		
5	1.4	6.94
10	0.9	10.42
15	1.2	13.86
20	0.8	16.51
Indomethacin		
5	2.45	3.43
10	1.80	4.38
15	2.15	5.76
20	1.75	7.14
30	1.60	7.98

ments. The incorporation of dibutyl phthalate at a concentration of 30% w/w dry polymer weights yielded smooth and flexible films. The estimation of the drug content at different sites on the film indicated the uniform distribution of the drug throughout the film. The x-ray diffraction studies revealed that the crystallinity of the drug decreased as the proportion of the PVP in the film increased (Figs. 5 and 6). In addition, the in vitro release studies employing a paddle over disk method clearly indicated that the release of the drug from the films followed the diffusion-controlled matrix model, in which the amount of drug released per unit area is proportional to the square root of time. This relationship was obeyed in the case of film composed of EC:PVP (10:0, 9:1, and 8:2) and with initial drug loadings of up to 20% w/w diltiazem hydrochloride and 30% w/w indomethacin films. As the initial concentration of diltiazem hydrochloride increased, the 20% w/w diltiazem and 30% w/w indomethacin concentrations led to rapid dissolution of the drug present on the surface followed by diffusion of the drug from the matrix. The same pattern was observed when indomethacin concentration exceeded 30% w/w dry polymers. The addition of hydrophilic component to an insoluble film former tends to enhance its release rate constants, as reported by Donbrow et al. (21) and Bodmeich et al (22). This may be due to the dissolution of the aqueous soluble fraction of film, which leads to the formation of pores and to higher dissolution rates. The release rate constants of both drugs increased with an increase in the PVP fraction in the film. This may be attributed to the leaching of the PVP component which resulted in the formation of pores, and thus led to the decrease of mean diffusion path length of the drug molecules to release into dissolution medium and hence, to higher release rates. In addition, the PVP acts as an antinucleating agent (23) which retards the crystallization of the drug and thus plays a significant role in improving the solubility of the drug in the matrix. The drug is in an amorphous form with high energy and undergoes rapid solu-

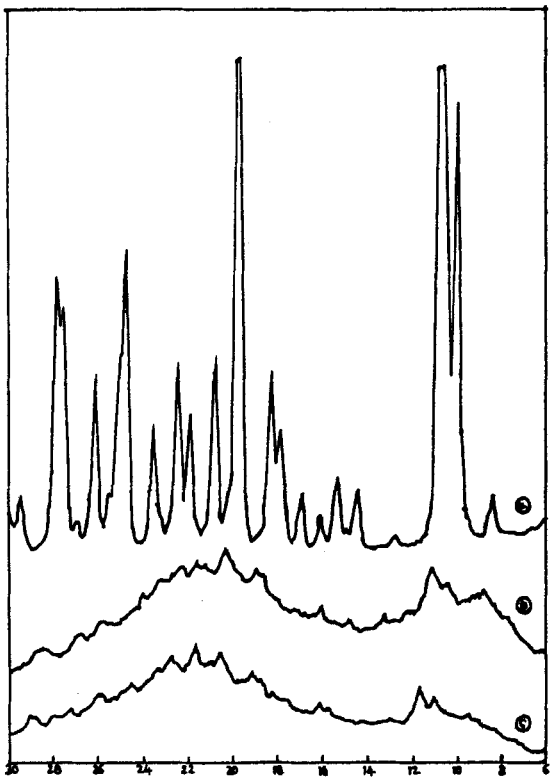

Figure 5. X-ray diffraction profiles of pure diltiazem hydrochloride and its formulations. (a) Pure drug, (b) EC:PVP:drug (9:1:1.5), (c) EC:PVP:drug (8:2:2).

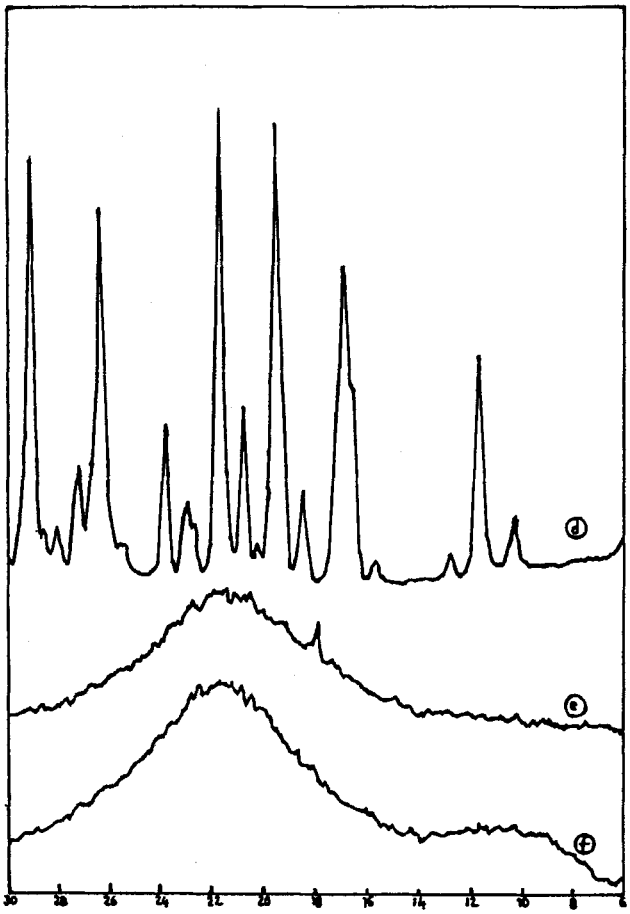

Figure 6. X-ray diffraction profiles of pure indomethacin and its formulations. (d) Pure drug, (e) EC:PVP:drug (8:2:2), (f) EC:PVP:drug (10:0:0.5).

bilization by the penetration of the solvent medium. This is further confirmed by the SEM study of the films after drug release studies (Figs. 7 and 8).

The stratum corneum is the main barrier for penetration of drugs through the skin. It is composed of keratinocytes embedded in lipid domains consisting of hydrophillic and lipophilic layers. In general, the lipophilic compounds may be penetrated through the intercellular domain of stratum corneum and hydrophilic compound through the transcellular route. The permeation rate of drug can be altered by changing the drug concentration in the vehicle. The increase of drug concentration up to certain levels may enhance the permeation of drugs and it also yields a plateau curve because of saturation of the drug thermodynamic activity. The permeation rate of both drugs increased with increase of drug loading in the film and resulted in a plateau curve because of attainment of drug saturation on the skin surface where the permeation of drug molecules was controlled by stratum corneum. The lag time values of the indomethacin decreased as the initial concentration of drug increased from 5 to 20%, but further increase may not have any influence on T_{lag} values. The PVP fraction in the film showed significant effect on permeation of both drugs. This may be a result of the initial rapid dissolution of the PVP when the patch is in contact with the hydrated skin that results in accumulation of high amounts of drug on the skin surface and thus leads to the saturation of the skin with drug molecules at all times. Figures 3 and 4 indicate a relationship of drug release from the films to skin flux values at various initial drug concentrations from films composed of EC:PVP (9:1). As the release rate constant increased the permeation rate of drug also increased up to the initial drug loading of 20% w/w. Further increase did not result in any enhancement of skin permeation of the drug. This may be because attainment of saturation of drug thermodynamic activity at the loadings was specified in the EC:PVP (9:1) films.

CONCLUSIONS

EC alone and in combination with PVP has a good film-forming property. The incorporation of 30% w/w dibutyl phthalate resulted in smooth, uniform, and flexible films. The preliminary studies, revealed that the drug was distributed uniformly throughout the film and no drug carrier interactions were observed. The release rate of drug from films followed Higuchi equation in which the amount of drug released is linear to the square root of time. The release rate constant was found to be

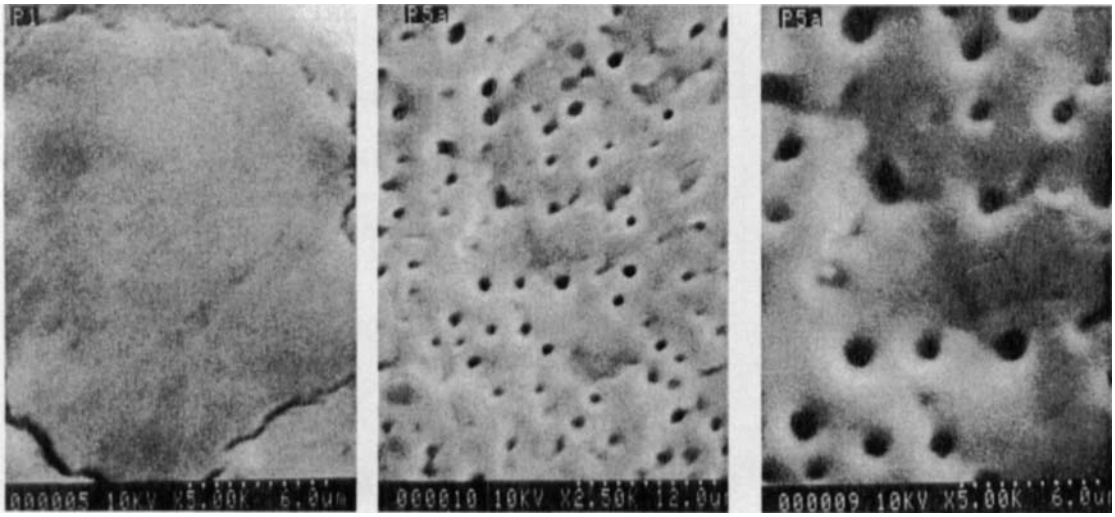

Figure 7. Scanning electron micrographs of films (EC:PVP, 9:1) containing 15% w/w diltiazem hydrochloride. (a) Before release of the drug, (b) and (c) after release of the drug.

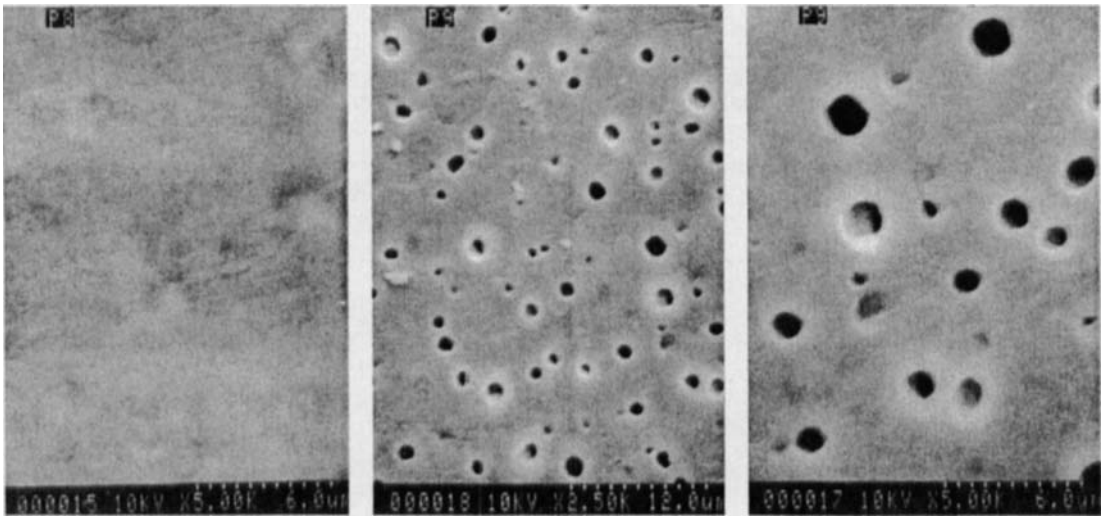

Figure 8. Scanning electron micrographs of films (EC:PVP, 9:1) containing 10% w/w indomethacin. (a) Before release of the drug, (b) and (c) after release of the drug.

dependent on initial drug loading as well as the film composition, but was independent of the film thickness. The release rates of the drug can be altered by the change of surface area of the film in contact with the skin.

From this study it is concluded that the films composed of EC:PVP (8:2) loaded with 20% w/w diltiazem hydrochloride or 30% w/w indomethacin can be evaluated for their pharmacodynamic and pharmacokinetic characteristics in a suitable animal model.

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