RESEARCH PAPER

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Drug Diffusion from Cellulose Acetate-Polyvinyl Pyrrolidone free Films for Transdermal Administration

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Plasticized free films of cellulose acetate (CA) alone and in combination with different concentrations of polyvinyl pyrrolidone (PVP) were prepared and evaluated for transdermal use. Adaptation of mercury substrate method and incorporation of dibutyl phthalate [40% w/w of polymer(s)] yielded thin, uniform and flexible films. Tensile strength of films decreased with increase of PVP fraction in the film. Both water vapour transmission and drug diffusion through the free films followed zero order kinetics and decreased with increase in film thickness. Permeability of films increased with increasing PVP concentration and this may be due to leaching out of PVP fraction, which leads to improved porosity and permeability. Free films composed of CA:PVP (2:1) can be used as rate of controlling membranes for the development of Transdermal Drug Delivery systems (TDDS) systems using a suitable drug reservoir.

THE development of technology for the release of drugs at controlled rate to systemic circulation, using skin as a port of entry, has become popular for various reasons[1]. The transdermal entry of a drug to systemic circulation at a desired rate can be achieved by using a suitable rate controlling membrane and a drug reservoir.[2]

The present investigation was carried out to study the influence of polyvinyl pyrrolidone (PVP) on the permeability of cellulose acetate (CA) films, used as rate controlling membranes for transdermal drug delivery.[3] The free films were evaluated for various parameters such as uniformity of thickness, tensile strength, percentage elongation and water vapour transmission (WVT). Diltiazem hydrochloride and indomethacin were used as model drugs for permeability studies.

MATERIALS AND METHODS

Cellulose acetate (with acetic acid content of 53.5 to 56%, Loba Chemie); Polyvinyl pyrrolidone (Mol. wt. 40,000, Loba Chemie); Dibutyl phthalate (Ranbaxy Laboratories Ltd.); Chloroform (HPLC grade, Qualigens); Diltiazem hydrochloride (gift sample from M/s Torrent Pharmaceuticals Ltd.); Indomethacin I.P. (gift sample from M/s Invinex Laboratories); Potassium chloride (Ranbaxy Laboratories Ltd.) and Sodium Hydrogen sulfate monohydrate (Loba Chemie).

Preparation of free films

Free films of cellulose acetate alone and with different proportions of CA : PVP were prepared by mercury surface method[4]. Dibutyl phthalate at a concentration of 40% w/w of dry polymer(s) was used as plasticizer. Chloroform solutions containing either CA or CA and PVP were poured on mercury surface contained in a petri dish. The solvent was allowed to evaporate at a controlled rate by placing an inverted funnel over the petri dish. The dry films were removed from the mercury surface and stored in a desiccator until use.

The thickness of free films was measured at five different places using a micrometer (MITOTOYO,

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Table 1 : Mechanical Properties of Pure CA and CA-PVP Free Films

Film	Tensile Strength (Kg/cm^2)	Percentage of Elongation	Water Vapour Transmission Rate	
			At 84% R.H.	At 52% R.H.
CA	290.1	23.34	2.06×10^{-4}	1.84×10^{-4}
CA:PVP (8:1)	260.46	20.42	3.15×10^{-4}	2.56×10^{-4}
CA:PVP (4:1)	220.54	22.15	4.32×10^{-4}	3.70×10^{-4}
CA:PVP (2:1)	180.29	21.67	5.34×10^{-4}	4.41×10^{-4}

* All values are average of three determinations

Table 2: Influence of film thickness and concentration of polyvinylpyrrolidone on diffusion rate and permeability coefficient of diltiazem hydrochloride

Film	Film Thickness (μm) Mean ± S.D.	Diffusion Rate (mg/hr)	Average Permeability Coefficient (mg/hr.cm)
CA	28.3 ± 0.62	0.182	9.81×10^{-5}
	41.9 ± 0.47	0.125	
	65.2 ± 0.55	0.080	
CA : PVP (8:1)	50.1 ± 0.42	0.313	2.88×10^{-4}
	64.2 ± 0.81	0.238	
	79.0 ± 0.46	0.188	
CA : PVP (4:1)	45.9 ± 0.52	0.775	6.76×10^{-4}
	57.8 ± 0.62	0.625	
	70.2 ± 0.51	0.510	
CA : PVP (2:1)	50.4 ± 0.68	1.250	1.22×10^{-3}
	60.1 ± 0.56	1.075	
	80.2 ± 0.74	0.825	

Japan) and the mean value was calculated (Table 2). The tensile strength and percentage elongation of the free films was calculated according to the A.S.T.M. standards (INSTRON 1026 TYPE 2512-19, Model MA. 30-1014, Made in England) (Table 1).

Determination of water vapour transmission (WVT)

The method of Utzumi et al[5] was adopted for the determination of water vapour transmission. The

Fig. 1. The Sacanning Electron Micrograph depicting the film with only CA which is smooth, uniform and nonporous.

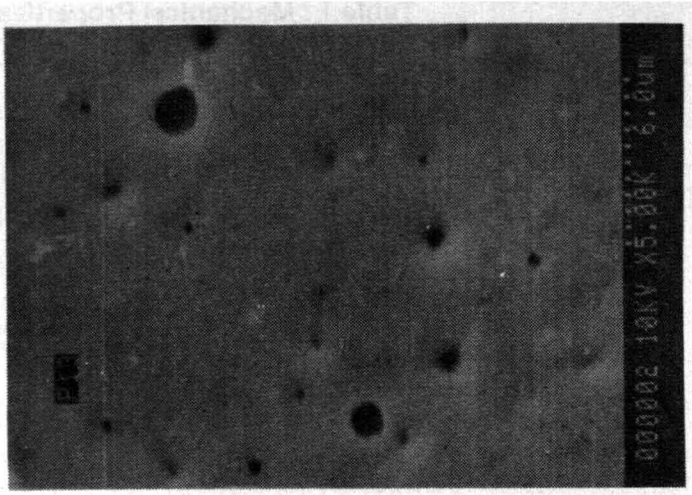

Fig. 2. The Scanning Electron Micrograph depicting the film with CA : PVP (4:1) which has smooth surface, irregular and non- uniform pores.

WVT of various films was studied at different relative humidities. For WVT, the film of known thickness was fixed over the brim of a glass vial containing 3 gms of fused calcium chloride as a desiccant, using an adhesive. The charged vial was weighed and kept in a desiccator, maintained at 52% or 84% RH. The vial was taken out periodically and weighed, for a period of 72 h. The experiment was triplicated and the average values were calculated. The WVT was determined from the plots of moisture gained vs time.

Drug diffusion studies

The diffusion of drugs such as diltiazem hydrochloride and indomethacin, through the free films was studied using Keshary- Chien diffusion cells.[6] Polymer film was sandwiched between two compartments, namely donor and receptor. 25 ml phosphate buffer (pH 7.4) was used as a receptor fluid. 10 ml of drug solution (2% w/v) was poured into the donor compartment. The receptor fluid was agitated using magnetic stirrer and temperature was maintained at 37 ± 1°. Samples (1 ml) were withdrawn periodically from the receptor compartment over a period of 8 hrs and the amount of drug diffused at various time intervals was determined, after suitable dilution at 236 nm and 318 nm, for diltiazem HCl[7] and indomethacin[8] respectively, using double beam UV spectrophotometer (Schimadzu, Japan). After each sampling, equal volume of drug free buffer solution was added to the receptor compartment to ensure constant volume of receptor fluid. The diffusion rate and permeability coefficient of various films were calculated from the plots of amount of drug diffused vs time.

Scanning Electron Microscopy (SEM)

For SEM study, the film was mounted on aluminium stabs using double sticky cellophane tape and gold coated in a vacuum evaporator and observed under HITACHI S-520 Scanning Electron Microscope (Fig. 1, 2 and 3).

RESULTS AND DISCUSSION

Cellulose acetate alone and in combination with PVP has a good film forming property. Uniformity of the thickness of films was good as evident from Table 2 and 3. The tensile strength of the films was decreased slightly as the proportion of PVP in the film is increased, but the percentage elongation changes are negligible over the proportion of PVP used (Table 1). The WVT through the films followed

Table 3: Influence of film thickness and concentration of polyvinylpyrrolidone on diffusion rate and permeability coefficient of Indomethacin

Film	Film Thickness (μm) Mean ± S.D.	Diffusion Rate (mg/hr)	Average Permeability Coefficient (mg/hr.cm)
CA	30.4 ± 0.35	0.128	7.35×10^{-5}
	42.2 ± 0.61	0.092	
	52.1 ± 0.44	0.075	
CA : PVP (8:1)	55.2 ± 0.51	0.200	2.10×10^{-4}
	59.3 ± 0.43	0.183	
	80.4 ± 0.66	0.144	
CA : PVP (4:1)	54.2 ± 0.50	0.450	4.52×10^{-4}
	60.1 ± 0.46	0.400	
	68.9 ± 0.71	0.340	
CA : PVP (2:1)	58.0 ± 0.48	0.650	7.12×10^{-4}
	62.5 ± 0.39	0.600	
	89.5 ± 0.59	0.425	

zero order kinetics. The WVT increased with increase in the proportion of PVP at each relative humidity and decreased with increasing the film thickness (Table 1).

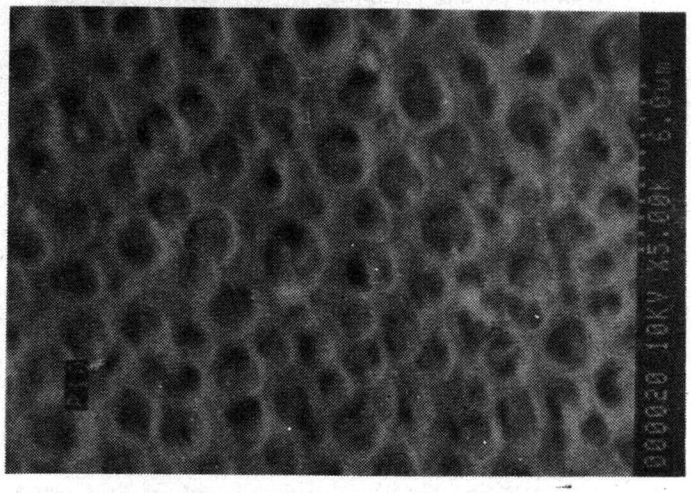

Fig. 3. The Scanning Electron Micrograph depicting the film with CA : PVP (2:1) shows regular and uniform pores throughout the film.

Both the drugs diffused through the films at zero order rate. An inverse relationship was observed between the diffusion rate and film thickness (Table 2 and 3). It was earlier reported that the permeability of an insoluble cellulose polymer such as ethyl cellulose can be greatly increased by the incorporation of hydrophilic polymer such as polyethylene glycol 4000[9]. In agreement with this, the incorporation of PVP into CA free films markedly increased the permeability without losing its integrity at the ratios used for the preparation of free films. However, it was experimentally observed that when the PVP concentration was increased further (i.e., CA:PVP is 1:1), the film lost its integrity and the drug was released within 5 min. Hence it was concluded that the ratio of CA:PVP (2:1) was optimum for the preparation of free films for transdermal use to deliver the drug at controlled rate. The improvement in film permeability may be due to leaching out of PVP from the film because of its soluble nature in the aqueous fluids, thus increasing the porosity of the film and hence the permeability. The SEM photo-

graphs of the films after diffusion studies were shown in Fig. 1, 2 and 3. From this study, it was clear that the surface of the films made up of pure CA was smooth and nonporous (Fig. 1). The films composed of CA and PVP (4:1) also have a smooth surface but irregular, nonuniform pores (Fig. 2) whereas the films containing CA and PVP (2:1) were found to have regular and uniform pores throughout the film (Fig. 3). These SEM studies clearly support the above proposed mechanisms for increase of film permeability with increase of PVP content in the films. The films composed of CA : PVP (2:1) will be further evaluated as rate controlling membranes, using a suitable drug reservoir to develop a transdermal system.

From the above observation it was concluded that the free films composed of CA and PVP can be conveniently used as rate controlling membranes for transdermal delivery of drugs for systemic medication employing a suitable drug reservoir system.

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