RESEARCH ARTICLE

Effect of casting solvent and polymer on permeability of propranolol hydrochloride through membrane-controlled transdermal drug delivery system

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In the present work, cellulose acetate (CA), ethyl cellulose (EC), and Eudragit RS 100 (ERS100) films were prepared and evaluated as rate-controlling membranes for transdermal drug delivery systems. Acetone-methanol (8:2), chloroform-methanol (8:2), dichloromethane-methanol (8:2), and ethyl acetate-methanol (8:2) were used as solvents in the preparation of films. Dibutyl phthalate or propylene glycol at a concentration of 40% w/w of the polymer was used as a plasticizer in the preparation of CA and EC films. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of ERS100 films. The solvent evaporation technique was employed for the preparation of CA and EC films, and the casting solvent technique was employed for the preparation of ERS100 films. The dry films were evaluated for physical appearance, thickness uniformity, folding endurance, water vapor transmission (WVT), drug diffusion, and permeability coefficient. Both WVT and drug diffusion rate followed zero-order kinetics. The mechanism of drug release was governed by Peppas model. The diffusion exponent of release profiles (slope) has a value of 1.0360-1.3147 ($n > 1$), which indicates super case II transport diffusion. The results obtained in the present study thus indicated that the polymers and solvents used for the preparation of films have shown significant influence on the WVT, drug diffusion, and permeability of the films.

Key words: *Drug diffusion and permeability coefficient, polymer, solvents, water vapor transmission*

INTRODUCTION

The development of transdermal drug delivery systems using polymeric materials has become popular for various reasons. Among the various types of transdermal drug delivery systems developed, membrane-controlled type utilizes a thin polymeric film as rate-controlling membrane, which delivers the drug from the drug reservoir to the systemic circulation for an extended period of time. The permeability of drug through polymeric film is dependent on characteristics of the polymer,[1,2] casting solvent,[3,4] and plasticizer[5,6] used. In the present work, cellulose acetate (CA), ethyl cellulose (EC), and Eudragit RS 100 (ERS100) films were prepared and evaluated as rate-controlling membranes for transdermal drug delivery systems. Propranolol hydrochloride,[7] which requires controlled release due to its short biological half-life (3.9 h), was used as model drug.

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MATERIALS AND METHODS

Propranolol hydrochloride was obtained as a gift sample from Natco Pharma (Hyderabad, Andhra Pradesh, India). Ethyl cellulose (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, Mumbai), CA (viscosity of 6% solution in 95% acetone-water mixture at 20°C having 140 cS viscosity (GS Chemical Testing Lab and Allied Industries, Mumbai), acetone, chloroform, dichloromethane, ethyl acetate (Qualigens, Mumbai), dibutyl phthalate (Ranbaxy Laboratories), and propylene glycol (SD Fine Chem, Mumbai) were obtained commercially. All materials were used as received.

Preparation of drug-free films

The solvent evaporation technique was employed for the preparation of CA and EC films, and the casting solvent technique was employed for the preparation of ERS100 films. The films were prepared with CA (2% w/v), EC (2% w/v), and ERS100 (8% w/v) by employing different casting solvents, namely acetone-methanol (8:2), chloroform-methanol (8:2), dichloromethane-methanol

(8:2), and ethyl acetate-methanol (8:2). Dibutyl phthalate at a concentration of 40% w/w of the polymer was used as a plasticizer in the preparation of CA and EC films. The CA films made from its solution in dichloromethane-methanol (8:2) and EC films made from its solution in acetone-methanol (8:2), incorporating dibutyl phthalate were found to be brittle. In those cases, propylene glycol at 40% w/w of the polymer was used as a plasticizer. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of ERS100 films. CA (2% w/v) and EC (2% w/v) polymer solution (20 ml) were poured in a petri plate (9.4 cm diameter) placed on a horizontal flat surface. ERS100 (8% w/v) casting solution (8 ml) was poured within the glass bangle (6.2 cm diameter) placed on mercury surface in a petri plate placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the petri plate. After 24 h, the dried films were taken out and stored in a desiccator.

Evaluation of transdermal films

All the films prepared were evaluated for physical appearance, uniformity of thickness, folding endurance, water vapor transmission (WVT) and drug diffusion, and permeability characteristics. The thickness of the films was measured by a "Screw Gauge." The mean of the five observations were calculated. The folding endurance was measured manually for the prepared films. A strip of film (2 × 2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.[8]

For the study of WVT rate, vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. Approximately 1 g of calcium chloride was taken in the cell and the polymeric films measuring 3.14 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded, and then kept in a closed desiccator containing saturated solution of potassium chloride (approximately 200 ml). The humidity inside the desiccator was measured by a hygrometer, and it was found to be in between 80% and 90% relative humidity. The cells were taken out and weighed after 18, 36, 54, and 72 h.

From increase in weights, the amount of water vapor transmitted and the rate at which water vapor transmitted were calculated by using the following formula:[9]

WVT rate = WL/S, where W is water vapor transmitted (in g), L the thickness of the film (in cm), and S the exposed surface area (in cm^2).

Drug diffusion study[10]

Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. A aliquot of 10 ml of the 0.25% W/V solution of drug (propranolol hydrochloride) was poured into the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 ± 0.5°C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 h. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content, using a UV spectrophotometer at 290 nm.[11]

Permeability coefficient

From the drug diffusion data, the permeability coefficient for various films was calculated using the equation: $P_m = (K_{app} \cdot H)/A$, where K_{app} is the diffusion rate constant (mg/h) calculated from the slope of linear drug diffusion profiles (d/p), H the thickness of the film (cm), and A the surface area of the film (cm^2).

The rate and the mechanism of release of propranolol hydrochloride through the prepared films were analyzed by fitting the diffusion data into,[12] zero-order equation, $Q = Q_0 - k_0 t$, where Q is the amount of drug released at time t, and k_0 is the release rate. First-order equation, $L_n Q = L_n Q_0 - k_1 t$, where k_1 is the release rate constant and Higuchi's equation, $Q = k_2 t^{1/2}$, where Q is the amount of the drug released at time t and k_2 is the diffusion rate constant. The diffusion data was further analyzed to define the mechanism of release by applying the diffusion data following the empirical equation, $Mt/M_\alpha = Kt^n$, where Mt/M_α is the fraction of drug released at time t, K is a constant and n characterizes the mechanism of drug release from the formulations during the diffusion process.

RESULTS AND DISCUSSION

In the present work, CA, EC, and ERS100 films were prepared and evaluated as rate-controlling membrane for transdermal drug delivery systems. The solvent evaporation technique and the casting solvent technique were found to be giving thin uniform films. The films prepared with polymer alone were found to be brittle. To prevent embrittlement, a plasticizer, dibutyl phthalate, was tried at various concentrations ranging from 10% to 50% w/w of the polymer. Preliminary experiments indicated that lower concentrations of dibutyl phthalate were found to give rigid and brittle films, whereas higher concentrations gave soft films. Dibutyl phthalate at a concentration of 40% w/w of the polymer was found to give good flexible films. Hence, dibutyl phthalate was included as a plasticizer in the preparation of CA and EC films at a concentration of 40% w/w of the polymer (or 2% w/v of the polymer solution).

The CA films made from its solution in dichloromethane-methanol (8:2) and EC films made from its solution in acetone-methanol (8:2), incorporating dibutyl phthalate were found to be brittle. In those cases, propylene glycol at 40% w/w of

the polymer was found to give good flexible films. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of ERS100 films and are found to give good flexible films.

Thickness measurements of films prepared in various solvents are given in Table 1. Low standard-deviation values in the film thickness measurements ensured uniformity of thickness in each film. The folding endurance was measured manually and folding endurance was found to be high in EC films compared with CA and ERS100 films. Water vapor transmission studies indicated that all the films were permeable to water vapor. Water vapor transmission through the films followed zero-order kinetics. The results are given in Table 1 and shown in [Figure 1A-C].

Table 1: Properties of transdermal films

Formulation	Thickness (μm)	Folding endurance	Water vapor transmission ($Q \times 10^4$ g/cm^2 24 h)	Permeability coefficient ($Pm \times 10^3$ mg/cm.h)
F1 (EC; A + M)	45.95 ± 0.15	198	4.01	2.28
F2 (EC; DCM + M)	45.30 ± 0.17	223	3.77	1.27
F3 (EC; C + M)	44.28 ± 0.26	286	2.84	1.03
F4 (EC; EA + M)	46.70 ± 0.26	164	4.16	2.37
F5 (CA; A + M)	49.88 ± 0.65	129	6.11	3.36
F6 (CA; DCM + M)	54.25 ± 0.37	196	5.61	2.64
F7 (CA; C + M)	56.75 ± 0.15	234	5.38	1.86
F8 (CA; EA + M)	51.40 ± 0.28	132	6.49	4.27
F9 (E100; A + M)	42.55 ± 0.15	270	4.45	2.30
F10 (E100; DCM + M)	47.4 ± 0.14	256	3.37	1.81
F11 (E100; C + M)	42.42 ± 0.13	225	4.42	1.18
F12 (E100; EA + M)	44.35 ± 0.14	204	5.29	2.91

EC: ethyl cellulose; CA: cellulose acetate; E100: Eudragit RS100, A: acetone; DCM: dichloromethane; C: chloroform; EA: ethyl acetate; M: methanol

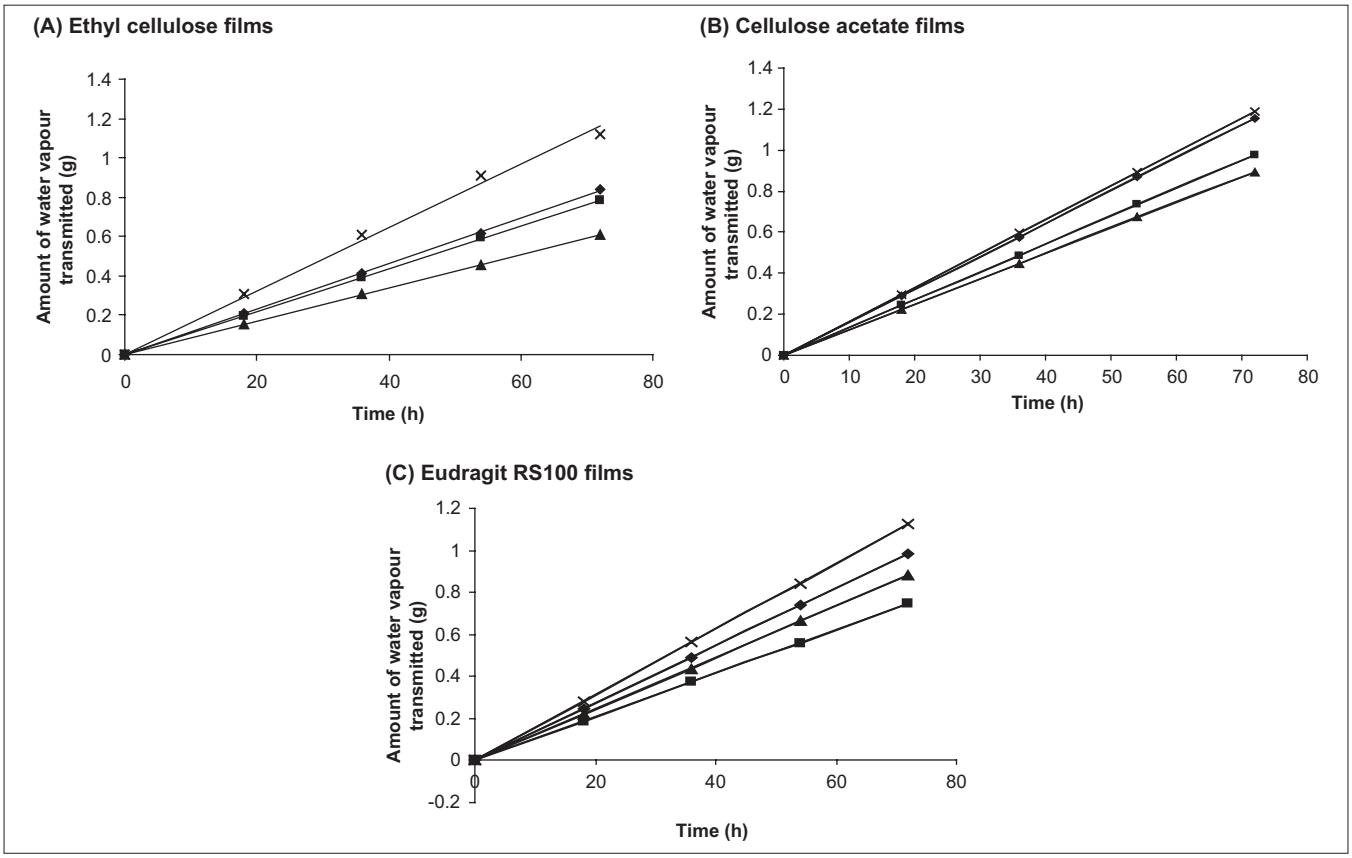

Figure 1: Water vapor transmission profiles of (A) ethyl cellulose films, (B) cellulose acetate films, and (C) Eudragit RS100 Films casted with various solvents. (A) (-♦-) F1 (ethyl cellulose films prepared with acetone); (-■-) F2 (ethyl cellulose films prepared with dichloromethane); (-▲-) F3 (ethyl cellulose films prepared with chloroform); (- × -) F4 (ethyl cellulose films prepared with ethyl acetate); (B) (-♦-) F5 (cellulose acetate films prepared with acetone); (-■-) F6 (cellulose acetate films prepared with dichloromethane); (-▲-) F7 (cellulose acetate films prepared with chloroform); (- × -) F8 (cellulose acetate films prepared with ethyl acetate) (C) (-♦-) F9 (Eudragit RS100 films prepared with acetone); (-■-) F10 (Eudragit RS100 films prepared with dichloromethane); (-▲-) F11 (Eudragit RS100 films prepared with chloroform); (- × -) F12 (Eudragit RS100 films prepared with ethyl acetate)

The water vapor transmission (Q) was more in the case of CA films when compared with EC. Water vapor transmission values indicated that the CA films were more permeable to water vapor. The rate of WVT was decreased in the order of films in various solvents is as follows in three to four cases: ethylacetate-methanol (8:2) > acetone-methanol (8.2) > dichloromethane-methanol (8:2) > chloroform-methanol (8:2).

Drug diffusion through the various films was studied with propranolol hydrochloride as a model drug by using Franz diffusion cell. All the films were found to be permeable to propranolol hydrochloride and diffusion profiles are shown in [Figure 2A-C]. Permeability coefficient values (Pm) of the films toward the propranolol hydrochloride was calculated from the drug diffusion data and the results were given in Table 1. The rate of permeability coefficient was decreased in the order of films in various solvents is as follows in three to four cases. Ethylacetate-methanol (8:2) > acetone-methanol (8:2) > dichloromethane-methanol (8:2) > chloroform-methanol (8:2).

The correlation coefficient values (r) were reported in Table 2. These values revealed that the diffusion profiles follow zero-order kinetics and the mechanism of drug release was governed by Peppas model. The diffusion exponent of release profiles (slope) has a value of 1.0360-1.3355 ($n > 1$), which indicates super case II transport diffusion.[13] The results obtained in the present study thus indicated that the polymers and solvents used in the preparation of films have been shown significant influence on the WVT, drug diffusion, and permeability of the films.

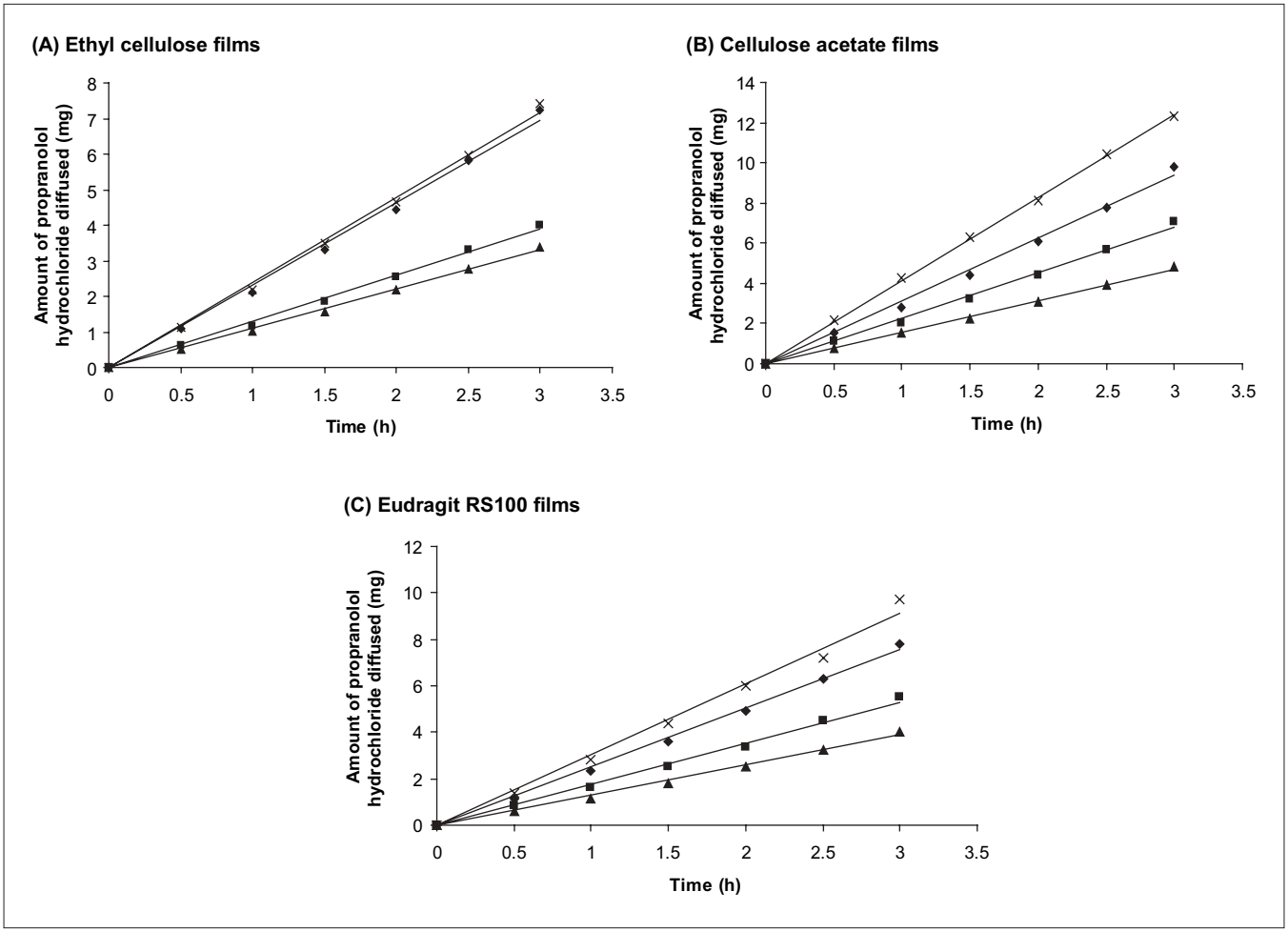

Figure 2: Diffusion profiles of propranolol hydrochloride through (A) ethyl cellulose films, (B) cellulose acetate films, and (C) Eudragit RS100 films casted with various solvents. (A) (-♦-) F1 (ethyl cellulose films prepared with acetone); (-■-) F2 (ethyl cellulose films prepared with dichloromethane); (-▲-) F3 (ethyl cellulose films prepared with chloroform); (- × -) F4 (ethyl cellulose films prepared with ethyl acetate); (B) (-♦-) F5 (cellulose acetate films prepared with acetone); (-■-) F6 (cellulose acetate films prepared with dichloromethane); (-▲-) F7 (cellulose acetate films prepared with chloroform); (- × -) F8 (cellulose acetate films prepared with ethyl acetate) (C) (-♦-) F9 (Eudragit RS100 films prepared with acetone); (-■-) F10 (Eudragit RS100 films prepared with dichloromethane); (-▲-) F11 (Eudragit RS100 films prepared with chloroform); (- × -) F12 (Eudragit RS100 films prepared with ethyl acetate)

Table 2: Diffusion characteristics of propranolol hydrochloride from various films prepared with various organic solvents

Formulation	Correlation coefficient (r) values		Zero order rate constant	Diffusion exponent
	Zero order	Peppas model	(K) value (mg/h)	value (n)
F1 (EC; A + M)	0.9977	0.9994	2.4476	1.0644
F2 (EC; DCM + M)	0.9982	0.9983	1.3771	1.0524
F3 (EC; C + M)	0.9985	0.9986	1.1570	1.0416
F4 (EC; EA + M)	0.9800	0.9987	2.5218	1.3116
F5 (CA; A + M)	0.9978	0.9996	3.3127	1.0772
F6 (CA; DCM + M)	0.9978	0.9990	2.3945	1.0574
F7 (CA; C + M)	0.9989	0.9996	1.6164	1.0360
F8 (CA; EA + M)	0.9761	0.9971	4.0809	1.3147
F9 (E100; A + M)	0.9990	0.9980	2.590	1.0719
F10 (E100; DCM + M)	0.9977	0.9996	1.825	1.0791
F11 (E100; C + M)	0.9984	0.9979	1.336	1.0554
F12 (E100; EA + M)	0.9962	0.9998	3.141	1.3355

EC: ethyl cellulose; CA: cellulose acetate; E100: Eudragit RS100, A: acetone; DCM: dichloromethane; C: chloroform; EA: ethyl acetate; M: methanol

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