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EFFECT OF CASTING SOLVENT ON PERMEABILITY OF FLURBIPROFEN THROUGH EUDRAGIT RLPO FILMS

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Abstract:

In the present work, Eudragit RLPO films were prepared and evaluated as rate controlling membrane for transdermal drug delivery systems. Acetone, chloroform, dichloromethane and ethyl acetate were used as solvents in the preparation of films. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation films. The solvent evaporation technique was found to be giving thin uniform films. The dry films were evaluated for Physical appearance, Thickness uniformity, Folding endurance, Water Vapour Transmission, Drug diffusion and Permeability Coefficient. Both Water vapour transmission 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 n>1, which indicates non analmous transport diffusion. The results obtained in the present study thus indicated that the solvents used in the preparation of films have been shown significant influence on the water vapour transmission, drug diffusion and permeability of the films. Eudragit RLPO films employed with ethyl acetate as casting solvent shown high Permeability when compared to other films for both drugs .

Key Words: *Solvents, Water Vapour Transmission, Drug diffusion and Permeability Coefficient.*

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INTRODUCTION:

The development of transdermal drug delivery systems using polymeric materials have 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 Eudragit RLPO films were prepared and evaluated as rate controlling membrane for transdermal drug delivery systems. Flurbiprofen which requires controlled release due to their short biological half life[7], was used as model drug.

MATERIALS AND METHODS:

Flurbiprofen was obtained as a gift sample from Natco Pharma, Hyderabad. Eudragit RLPO (S.D. Fine Chem), Acetone, Chloroform, Dichloromethane and Ethyl acetate (Qualigens), Dibutyl phthalate (Ranbaxy Laboratories) (S. D. Fine Chem) were obtained commercially. All materials were used as received.

Preparation of drug free films:

The solvent evaporation technique was employed in the present work for the preparation of Eudragit RLPO films. The films were prepared with Eudragit RLPO by employing different casting solvents namely Acetone, chloroform, dichloromethane and ethyl acetate. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation of films. 20 ml of the polymer solution was poured in a Petri plate (9.4 cm diameter) 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:

Thickness Uniformity:

The thickness of the films were measured by a 'venire calipers'. The mean of the five observations were calculated.

Folding Endurance[8]:

The folding endurance was measured manually for the prepared films. A strip of film (2x2 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.

Water Vapour Transmission (W.V.T) Rate[9]:

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0 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 (about 200 ml). The humidity inside the desiccator was measured by a hygrometer, and it was found to be in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36, 54 and 72 hrs. From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula.

WVT rate = WL/S, Where, W is Water vapour transmitted in gms, L is thickness of the film in cm, S is exposed surface area in cm^2

Drug Diffusion Study[10]:

Drug diffusion study was conducted using Franz diffusion cell[4].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. 10 ml of the drug solution (0.05% W/V of flurbiprofen) was poured into the donor compartment. Dialysis membrane was kept between the receptor compartment and the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5 $^{\circ}$C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a UV spectrophotometer at 247 nm for flurbiprofen.[11]

Permeability Coefficient:

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

The rate and the mechanism of drug release through the prepared films were analyzed by fitting the diffusion data into[12], zero-order equation, $Q=Q_0 - k_0t$,where Q is the amount of drug released at time t,

and k_0 is the release rate. First order equation, Ln Q=Ln Q_0 – k_1t, where k_1 is the release rate constant and Higuchi's equation, Q= $k_2t^{1/2}$, 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 , $M_t/M_\alpha=Kt^n$, where M_t/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 diffusion process.

RESULTS AND DISCUSSION:

The solvent evaporation technique was 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. Preliminary experiments indicated that lower concentrations of dibutyl phthalate were found to give rigid and brittle films where as higher concentrations gave soft films. Dibutyl phthalate at a concentration of 15% w/w of the polymer was found to give good flexible films.

All the films prepared were evaluated for uniformity of thickness, folding endurance, water vapour transmission and drug diffusion and permeability characteristics. The film thickness measurements ensured uniformity of thickness in each film. The solvent evaporation technique was found to be given reproducible results with regard to film thickness. The folding endurance was measured manually and offered good mechanical strength and flexibility. Water vapour transmission studies indicated that all the films prepared were permeable to water vapour. Water vapour transmission through the films followed zero order kinetics and was shown in the figure 1 . The rate of water vapour transmission was decreased in the order of films in various solvents is as follows. Ethyl acetate > acetone > dichloromethane > chloroform

TABLE 1: CHARACTERIZATION OF EUDRAGIT RLPO FILMS

POLYMER	EUDRAGIT RLPO FILMS			
	Acetone	Dichloromethane	Chloroform	Ethyl acetate
THICKNESS (µm)	48.6±0.01	53.2±0.02	55.4±0.01	50.2±0.03
FOLDING ENDURANCE	168	172	184	159

TABLE 2: Diffusion Characteristics of Eudragit RLPO Films Prepared With Various Casting Solvents

POLYMER	Eudragit RLPO Films			
	SOLVENT EMPLOYED			
	Acetone	Dichloromethane	Chloroform	Ethyl acetate
WATER VAPOUR TRANSMISSION RATE Q × 10^4g/cm 24 hrs	4.394	3.748	3.376	4.744
DIFFUSION RATE VALUES (mg/hr)	3.231	2.334	1.594	4.104
PERMEABILITY COEFFICIENT (P_m×10^4 mg/cm.h)	3.28	2.57	1.84	4.29
T_{50}(h)	3.28	2.57	1.84	4.29

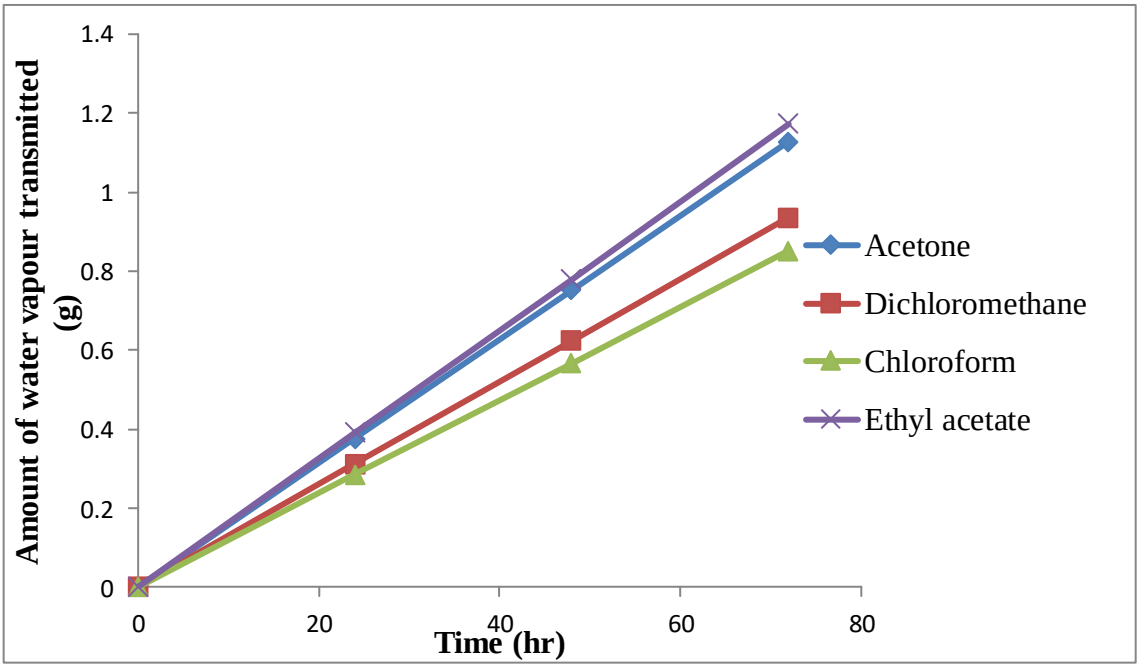

Fig 1: Water-Vapour Transmission Profiles of Eudragit RLPO Films Casted with Various Solvents

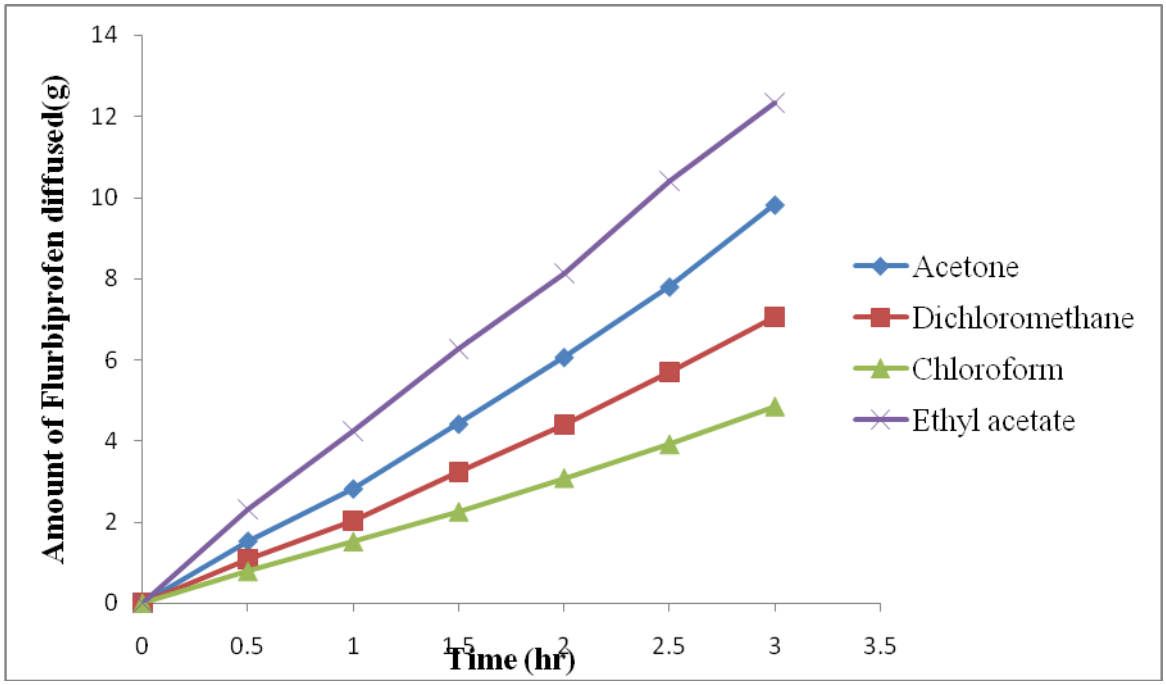

FIG 2: DIFFUSION PROFILES OF FLURBIPROFEN THROUGH EUDRAGIT RLPO FILMS PREPARED WITH VARIOUS SOLVENTS

Drug diffusion through various films were studied with diltiazem hydrochloride and propranolol hydrochloride as a model drug by using Franz diffusion cell. All the films were found to be permeable to diltiazem hydrochloride and propranolol hydrochloride. The correlation coefficient values (r) 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 (n>1), which indicates Super Case II transport diffusion. Permeability coefficient values (Pm) of the films towards the drugs 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 Ethyl acetate > acetone > dichloromethane > chloroform

The results obtained in the present study thus indicated that the casting solvents used in the preparation of films have been shown significant influence on the water vapour transmission, drug diffusion and permeability of the films. Eudragit RLPO films employed with ethyl acetate as casting solvent shown high Permeability when compared to other films.

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