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EFFECT OF CASTING SOLVENT ON PERMEABILITY OF ANTIHYPERTENSIVE DRUGS THROUGH EUDRAGIT RS 100 FILMS

T. E. GOPALA KRISHNA MURTHY* AND V. SAI KISHORE

Bapatla College of Pharmacy, Bapatla-522101
E-mail: gopalakrishnatalasila@yahoo.com

ABSTRACT

In the present work, Eudragit RS 100 films were prepared and evaluated as rate controlling membrane 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 at a concentration of 15% w/w of the polymer was used as a plasticizer in the preparation films. The casting solvent 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 RS 100 films employed with ethyl acetate:methanol in 8:2 ratio as casting solvent yielded low area of patch with desired release rate for both drugs .

Keywords: Solvents, Folding endurance, Water Vapour Transmission, Drug diffusion and Permeability Coefficient.

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 Eudragit RS 100 films were prepared and evaluated as rate controlling membrane for transdermal drug delivery systems. Diltiazem hydrochloride and Propranolol hydrochloride, which requires controlled release due to their short biological half lives[7], were used as model drugs.

MATERIALS AND METHODS

Diltiazem hydrochloride and Propranolol hydrochloride were obtained as a gift samples from Natco Pharma, Hyderabad. Eudragit RS 100 (S.D. Fine Chem), Acetone, Chloroform, Dichloromethane and Ethyl acetate (Qualigens), Dibutyl phthalate (Ranbaxy Laboratories) and propylene glycol (S. D. Fine Chem) were obtained commercially. All materials were used as received.

Preparation of Drug Free Films

Casting solvent technique was employed in the present work for the preparation of Eudragit RS 100 films. The films were prepared with Eudragit RS 100 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 15% w/w of the polymer was used as a plasticizer in the preparation of films. Eight ml of the casting solution was poured in a glass bangle (6.2 cm diameter) containing mercury placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and stored in a desicator.

Evaluation of Transdermal Films

Thickness Uniformity

The thickness of the films was measured by a 'vernier 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 6, 12, 18 and 24hrs. 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.

$$\text{Water Vapour Transmission Rate (W.V.T)} = \frac{WL}{S}$$

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. 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 0.2 % W/V of drug (diltiazem hydrochloride) solution was poured into the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 + 0.5 ^{0}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 U V spectrophotometer at 237[11]nm for diltiazem hydrochloride and at 290[12]nm for propranolol hydrochloride.

Permeability Coefficient

From the drug diffusion data the Permeability Coefficient for various films was calculated using the equation

$$P_m = K_{app} . \frac{H}{A}$$

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 into13, zero-order equation, $Q=Q_0 - k_0 t$, where Q is the amount of drug released at time t, and k0 is the release rate. First order equation, $\text{Ln } Q=\text{Ln } Q_0 - k_1 t$, 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, M1/M?=Ktn , where Mt/M? 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.

Estimation of Area of Patch required for desired release rate

The mathematical description of drug release that follow zero order kinetics is based on the following equation.[14]

$$K_r^0 = K_e C_d V_d$$

Where, K^0r is zero order rate constant for drug release, Ke is first order rate constant for overall drug elimination, C_d is desired drug level in the body and Vd is volume space in which drug is distributed.

For diltiazem hydrochloride7 t½ = 3.7 h, V_d = 3.1L and C_d = 0.05 µg/ml and therefore the desired drug release rate can be calculated as follows:

$K^0 r = (0.693/3.7) \times 0.05 \times 3.1 \times 70 = 2.032$ mg/h

For propranolol hydrochloride7 t½ = 3.9 h, V_d = 4.3 l and C_d = 0.02 µg/ml and therefore the desired drug release rate can be calculated as follows:

$K^0 r = (0.693/3.9) \times 0.02 \times 4.3 \times 70 = 1.064$ mg/h

Hence, area of patch (A) required for desired release rate is

$A = K^0 r / (Kapp/ S)$

Where, K0r is required drug release rate (mg/h), Kapp is diffusion rate constant (mg/h) ,S is surface area of the film subjected to diffusion(cm^2)

RESULTS AND DISCUSSION

The method of casting solvent 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. Thickness measurements of films prepared in various solvents are given in table1. Low standard deviation values in the film thickness measurements ensured uniformity of thickness in each film. The method of casting solvent technique was found to be given reproducible results with regard to film thickness. The folding endurance was measured manually and folding endurance was found to be decreased in the order of films in various solvents is as follows. Acetone-methanol (8:2)> dichloromethane-methanol (8:2)>chloroform-methanol (8:2)> ethyl acetate-methanol (8:2)

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. The results are given in table 1 and shown in figs 1. The rate of water vapour transmission was decreased in the order of films in various solvents is as follows. Ethylacetate-methanol (8:2)> dichloromethane-methanol (8:2)> acetone-methanol (8.2)> chloroform-methanol (8:2).

Drug diffusion through various films was studied with diltiazem hydrochloride and propranolol hydrochloride as a model drugs by using Franz diffusion cell. All the films were found to be permeable to diltiazem hydrochloride and diffusion profiles are shown in figure 2a and 2b.Permeability coefficient values (pm) of the films towards the drugs was calculated from the drug diffusion data and the results were given in table 2. The rate of permeability coefficient was decreased in the order of films in various solvents is as follows ethylacetate-methanol (8:2)>acetone-methanol (8:2)>chloroform-methanol (8:2). Dichloromethane-methanol (8:2)

The correlation coefficient values (r) were reported in table 2. These values revealed that the diffusion profiles follows zero order kinetics (fig.2) and the mechanism of drug release were governed by peppas model. The diffusion exponent of release profiles (slope) has a value of (n>1), which indicates non-analmous transport diffusion15. 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. Area of patches required

TABLE 1: PROPERTIES OF TRANSDERMAL FILMS

FORMULATION	THICKNESS (µm)	FOLDING ENDURANCE	WATER VAPOUR TRANSMISSION (Q X 104 g/ cm2 24 hrs)
F1 (E;A+M)	42.55+0.15	270	4.458
F2 (E;DCM+M)	47.4+0.14	256	3.377
F3 (E;C+M)	42.42+0.13	225	4.422
F4 (E;EA+M)	44.35+0.14	204	5.296

E: Eudragit RS 100; A: Acetone; DCM: Dichloro methane; C: Chloroform; EA: Ethyl acetate; M: Methanol

TABLE 2: DIFFUSION CHARACTERISTICS OF DILTIAZEM HYDROCHLORIDE FROM EUDRAGIT RS 100 FILMS PREPARED WITH VARIOUS ORGANIC SOLVENTS

FORMULATION	CORRELATION COEFFICIENT (R) VALUES		ZERO ORDER RATECONSTANT (K)VALUE (mg/h)	PERMEABILITY COEFFICIENT (Pm X 103 mg /cm.h)	DIFFUSION EXPONENT VALUE (n)	AREA OF PATCH FOR DESIRED RELEASE RATE (cm^2)
	ZERO ORDE	PEPPAS RMODEL				
D1 (E;A+M)	0.9942	0.9996	3.4270	2.271	1.1664	2.9115
D2 (E;DCM+M)	0.9937	0.9995	2.8458	2.74	1.1621	3.50
D3 (E;C+M)	0.9929	0.9988	2.3922	2.066	1.1711	4.170
D4 (E;EA+M)	0.9897	0.9989	4.3873	3.931	1.1782	2.274
P1 (E;A+M)	0.9984	0.9980	2.6544	1.759	1.0719	1.970
P2 (E;DCM+M)	0.9976	0.9996	1.8774	1.328	1.0791	3.80
P3 (E;C+M)	0.9966	0.9979	1.3758	1.621	1.0554	2.785
P4 (E;EA+M)	0.9787	0.9998	3.2256	2.913	1.3355	1.621

D: Diltiazem Hydrochloride; P: Propranolol Hydrochloride; E: Eudragit RS 100; A: Acetone; DCM: Dichloro methane; C: Chloroform; EA: Ethyl acetate; M: Methanol

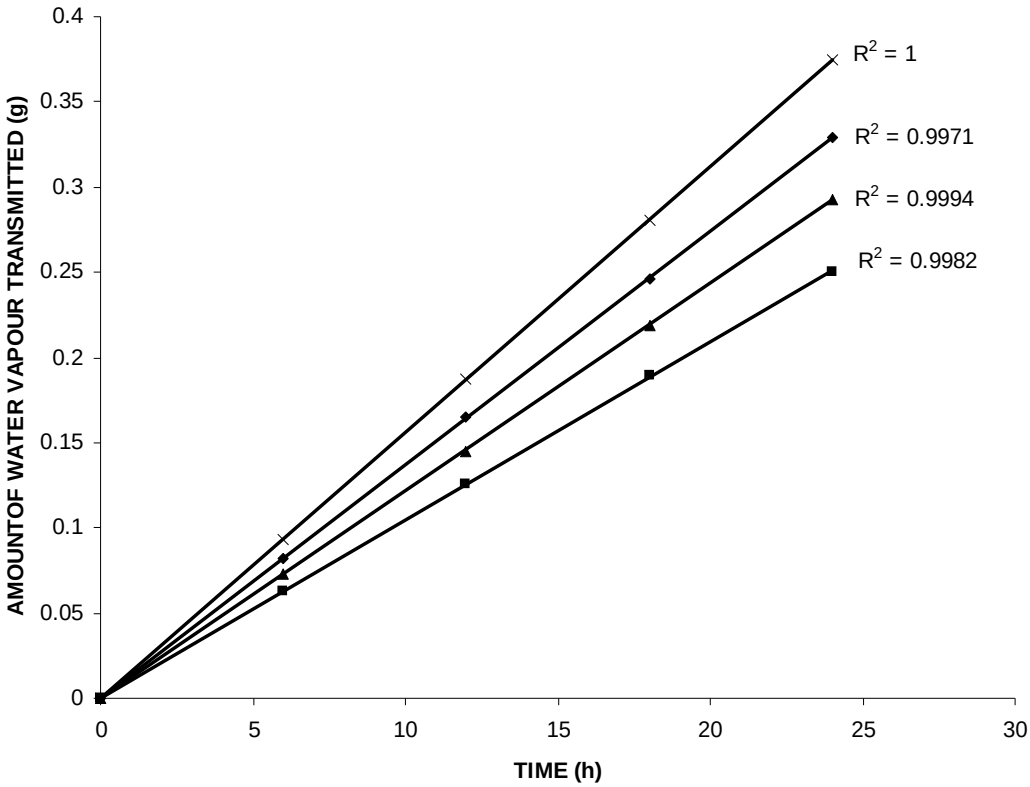

Fig 1: Water Vapour Trasmission Profiles of Eudragit RS 100 Films Casted With Various Solvents

(-●-) F1 (Eudragit RS 100 films prepared with Acetone)

(-■-) F2 (Eudragit RS 100 films prepared with Dichloromethane)

(-▲-) F3 (Eudragit RS 100 films prepared with Chloroform)

(-×-) F4 (Eudragit RS 100 films prepared with Ethyl Acetate)

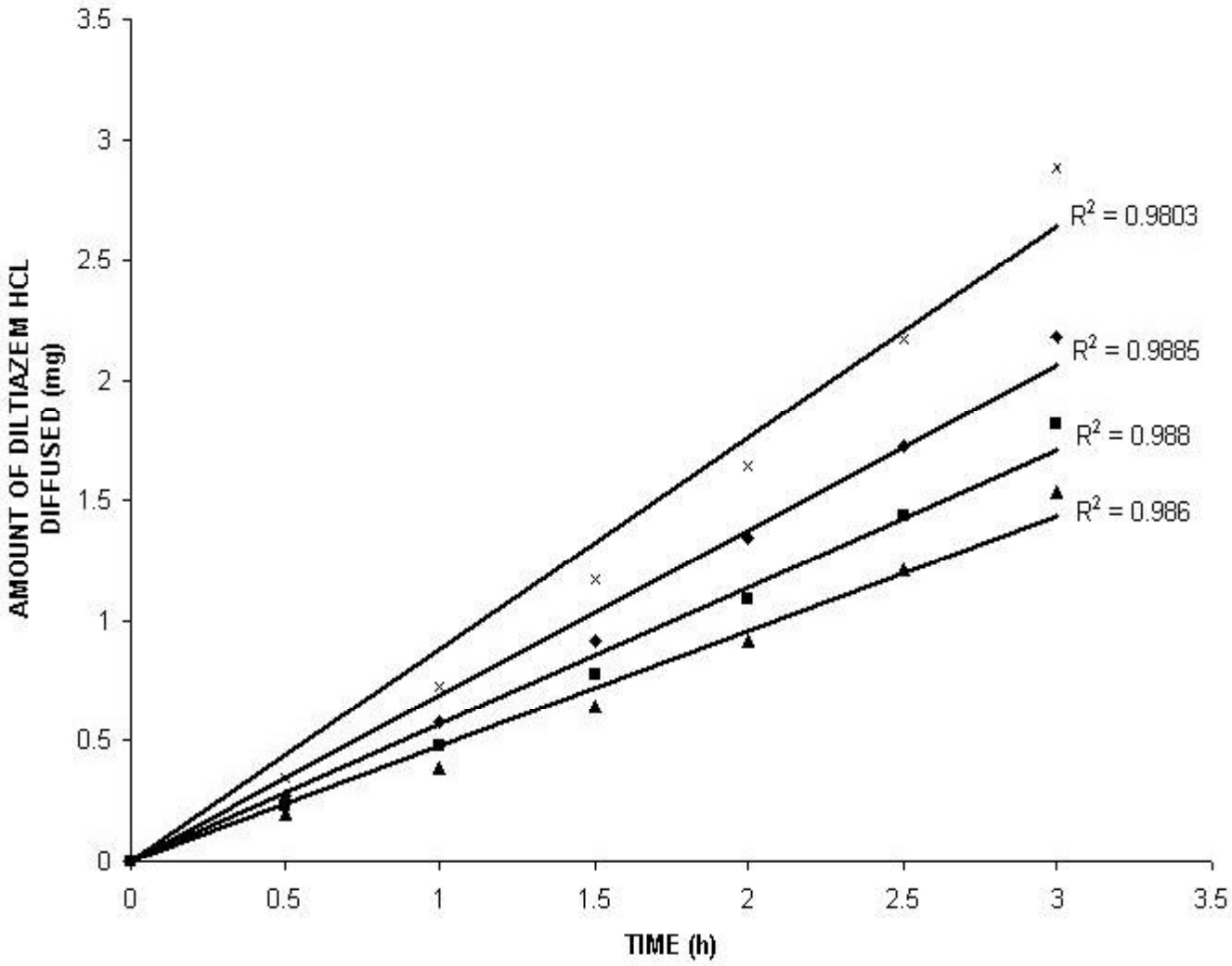

Fig 2 A: Diffusion Profiles of Diltiazem Hydrochloride Through Eudragit RS 100 Films Prepared With Various Solvents

(-◆-) D1 (Eudragit RS 100 films prepared with Acetone)

(-■-) D2 (Eudragit RS 100 films prepared with Dichloromethane)

(-▲-) D3 (Eudragit RS 100 films prepared with Chloroform)

(-×-) D4 (Eudragit RS 100 films prepared with Ethyl Acetate)

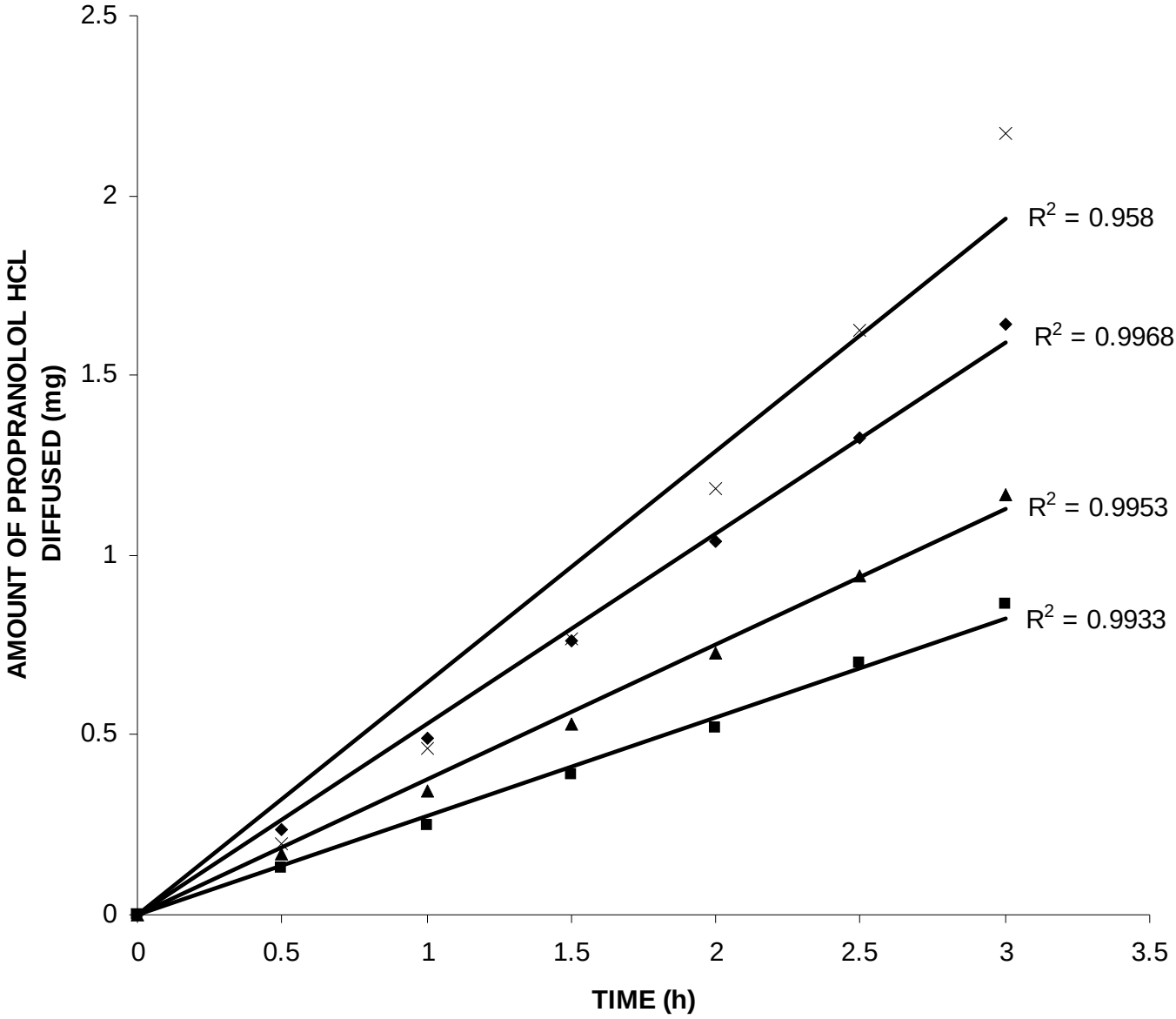

Fig 2 B: Diffusion Profiles of Propranolol Hydrochloride Through Eudragit RS 100 Films Prepared With Various Solvents

(-◆-) D1 (Eudragit RS 100 films prepared with Acetone)

(-■-) D2 (Eudragit RS 100 films prepared with Dichloromethane)

(-▲-) D3 (Eudragit RS 100 films prepared with Chloroform)

(-×-) D4 (Eudragit RS 100 films prepared with Ethyl Acetate)

for desired release rate were calculated and are reported in table 2. Area of patches ranging from 2.274 – 4.17 cm^2 was found to yielding the desired release rate of diltiazem hydrochloride. Eudragit rs 100 films employed with ethyl acetate: methanol in 8:2 ratio as casting solvent yielded low area (2.274 cm^2) of patch with desired release rate. Area of patches ranging from 1.621 – 3.80 cm^2 was found to yielding the desired release rate of propranolol hydrochloride. Eudragit rs 100 films employed with ethyl acetate: methanol in 8:2 ratio as casting solvent yielded low area (1.621 cm^2) of patch with desired release rate.

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