

FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES AND TO STUDY PERMEATION ENHANCEMENT EFFECT USING NATURAL ENHANCER

KALYANI A.L.T*, RAMYA SRAVANI K. M, BABU RAO CH.

Gokaraju Rangaraju College of Pharmacy, Nizampet road, Bachupally, Hyderabad 500092 India. Email: komalsravani@gmail.com

Received: 5 Oct 2011, Revised and Accepted: 3 Dec 2011

ABSTRACT

Various studies have been carried out on ethyl cellulose films with an objective of developing controlled release formulations of some essential antihypertensive agents. The present study shows that the presence of natural penetration enhancer in the formulation greatly influences the permeability of drugs (propranolol hydrochloride and diltiazem hydrochloride) through ethyl cellulose films. All the ethyl cellulose films (0%, 0.25%, 0.5%, 0.75% and 1%) were permeable to water vapor, diltiazem hydrochloride and propranolol hydrochloride. Ethyl cellulose films were treated with four different concentrations of natural permeation enhancer and are prepared by mercury substrate technique. All the prepared films are evaluated for uniformity of thickness, water vapor transmission, drug diffusion and permeability characteristics. The films were found to be thin, flexible, uniformly thick, permeable to water vapor and diffusion of propranolol hydrochloride, diltiazem hydrochloride. Among all the films of ethyl cellulose, the film with 0.75% natural enhancer is more permeable. There exists a good linear relationship between the permeability of ethyl cellulose films.

Keywords: Transdermal patch, Natural enhancer, Ethyl cellulose, Propranolol hydrochloride, Diltiazem hydrochloride.

INTRODUCTION

Diffusion is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and association with a concentration gradient. Percutaneous absorption involves dissolution of a drug into vehicle, diffusion of solubilized drug (solute) from the vehicle to the surface of the skin and then penetration of drug through the layers of the skin (stratum corneum). Many of the diseases can be effectively treated by the drugs that can be absorbed through the skin and thus transdermal drug delivery systems gain a wide importance in dosage form design. Transdermal drug delivery systems are self contained discrete dosage forms which, when applied to intact skin, deliver the drugs through the skin at a controlled rate to the systemic circulation. According to Chien et al¹, Penetration enhancer or promoter agent has no therapeutic effect of their own but they can transport the drug from transdermal system on to the skin and their subsequent transdermal permeation through the skin. The accelerant causes the keratin to swell and leaches out essential structural material from stratum corneum, thus reducing the diffusion resistance and increasing the permeability of drug through skin^{2,3}. The natural permeation enhancer used in present study was prepared from *Sapindus trifoliatus*, soya and quinoa (7:2:1) to enhance the delivery of propranolol hydrochloride and diltiazem hydrochloride.

MATERIALS AND METHODS

Propranolol hydrochloride and Diltiazem hydrochloride were obtained as the gift sample from Natco Pharma Limited, Hyderabad, Andhra Pradesh, India. All other chemicals were used of analytical grade.

Method for the estimation of propranolol hydrochloride

Spectrophotometric method based on the measurement of absorption at 290 nm in distilled water was used in the present study.

Preparation of standard solution

100mg of propranolol hydrochloride was dissolved in distilled water (100ml) in a volumetric flask.

Measurement of absorption

A series of dilutions (2, 4, 6, 8 and 10 µg) were prepared from the standard solution (1mg/ml) of propranolol hydrochloride using distilled water. The absorbance of these diluted solutions was

measured in ELICO U.V-SL 171 model spectrophotometer at 290nm using distilled water as a blank. The concentrations of the propranolol hydrochloride and the obtained absorbance are given in table (1). The absorbance was plotted against concentrations of propranolol hydrochloride as shown in fig (1). The method obeyed Beer's Law in the range of 0 to 10 µg/ml. Reproducibility was tested by analyzing 6 separately weighed samples of propranolol hydrochloride. The relative standard deviation (RSD) in the estimated values was found to be 0.8%. The low RSD value indicated that the method was reproducible. Thus, the method was found to be suitable for the estimation of propranolol hydrochloride in the present study.

Method for estimation of diltiazem hydrochloride

Spectrophotometric method based on the measurement of absorption at 240 nm in distilled water was used in the present study.

Preparation of standard solution

100mg of Diltiazem hydrochloride was dissolved in 30ml of 0.1N Hydrochloride solution in a volumetric flask and the volume was made up to 100ml using distilled water.

Measurement of absorption

A series of dilutions containing 2,4,6,8 and 10µg of Diltiazem hydrochloride was prepared from the stock solution (0.3mg/ml) using distilled water. The absorbance of these solutions was measured in ELICO U.V SL 171 model spectrophotometer at 240nm using distilled water as a blank. The obtained absorbance's for the prepared concentrations of Diltiazem hydrochloride are shown in Table (2). The absorbance was plotted against concentrations of Diltiazem hydrochloride as shown in fig (2).The method obeyed Beer's Law in the range of 0 to 10 µg/ml. Reproducibility was tested using 6 separately weighed samples of Diltiazem hydrochloride. The relative standard deviation (RSD) in the estimated values was found to be 1.2%. The low RSD value indicates that the method was reproducible. Thus, the method was found to be suitable for the estimation of diltiazem hydrochloride in the present study.

Preparation of Films⁴

Preparation of ethyl cellulose films (with out natural enhancer)

The films were prepared by the method of casting on mercury surface. Films were prepared by dissolving the polymer ethyl

cellulose (2%w/w) in toluene: ethanol (8:2). Dibutylphthalate in a concentration of 40% w/w of the polymer was used as a plasticizer. 6 ml of the polymer solution was poured within the glass bangles (5.3 cm diameter) placed on mercury surface in a petri dish. The rate of evaporation was controlled by inverting a funnel over the petri dish. The films were evaluated for their uniformity of thickness, water vapor transmission, drug diffusion and permeability characteristics. After 24 hrs the dried films were taken out and stored in a desiccator.

Preparation of ethyl cellulose films with natural enhancer

The films were prepared by the method of casting on mercury surface. Films were prepared by dissolving the polymer ethyl cellulose (2%w/w) in toluene:ethanol (8:2). Dibutylphthalate in a concentration of 40% w/w of the polymer was used as a plasticizer. Natural enhancer (prepared from *Sapindus trifoliatus*, soya and quiloa (7:2:1)) and 6 ml of the polymer solution were poured within the glass bangles (5.3 cm diameter) placed on mercury surface in a petri dish. The films are prepared using different concentrations of natural enhancer (0.25, 0.5, 0.75 and 1.0%w/v). The rate of evaporation was controlled by inverting a funnel over the petri dish. The films were evaluated for their uniformity of thickness, water vapor transmission, drug diffusion and permeability characteristics. After 24 hrs the dried films were taken out and stored in a desiccator.

Evaluation of Films

Film thickness

Film thickness was measured by a compator at five different points on the film, and the average of the 5 readings was calculated. Results are tabulated in Table-3.

Water vapor transmission studies

For water vapor transmission studies, glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1.0 gm of fused calcium chloride powder was taken in the cells and the polymer film was fixed over the brim with the help of an adhesive. Then, the cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride. The humidity inside the desiccator was measured by a Hygrometer and was found to be 84% RH. The cells were taken out and weighed after 6, 12, 24, 33, 36, 42 & 48 h of storage. The increase in the weight i.e., the amount of water vapor transmission (Q) is usually expressed as the number of grams of moisture gain per 24h per Sq.Cm. From the data so obtained, water vapor transmission (Q) was calculated. The results are given in table 4, 5 and in Fig 3.

Drug diffusion study and evaluation of permeability

For drug diffusion studies a permeation apparatus was designed as described by Fites et al. Glass vials of 15ml capacity were used as permeation cells. Base of the vials were opened and the polymer film was fixed over the brim with the aid of an adhesive to result in a permeation cell. 10 ml of drug solution in distilled water (Propranolol hydrochloride / Diltiazem hydrochloride) was taken in the cell (donor compartment) and the cell was immersed in a beaker containing drug free distilled water, 60 ml (the receptor compartment). The cell was immersed to a depth of 1 cm below the surface of drug free distilled water in a receptor compartment. The medium in the receptor compartment was agitated using a magnetic stirrer and a temperature of 37°C was maintained throughout. Samples from the receptor compartment were taken at various intervals of time over a period of 3h and assayed for the drug content (Propranolol hydrochloride/Diltiazem hydrochloride). Diffusion of propranolol hydrochloride and Diltiazem hydrochloride through various films were studied using the above described permeation cells. Known U.V methods were used for the estimation of Propranolol hydrochloride and Diltiazem hydrochloride. And the values are tabulated in Tables (6,8). Amount of drug (Propranolol hydrochloride/Diltiazem hydrochloride) diffused at various time intervals was calculated and plotted against time figures (4, 5).

From the drug diffusion data (Propranolol Hydrochloride/Diltiazem hydrochloride), the permeability coefficient (P_m) for various films was calculated using the following equation:

$$P_m = K_{app} \cdot H/A$$

Where, K_{app} = Diffusion rate constant (mg/h) calculated from the slope of the linear drug (d/p) diffusion profiles, H = Thickness of the film (cm), A = Surface area of the film (Cm²).

And the results obtained are tabulated in tables (7, 9).

RESULTS AND DISCUSSION

A comparative evaluation of the permeability of ethyl cellulose films and the influence of natural penetration enhancer on the film permeability in case was studied. Polymeric films can be prepared by various methods such as melt extrusion, bubbling, air spray, thermosetting and casting methods. Among the various methods, casting on mercury surface (mercury substrate technique) produces films with controlled, uniform and reproducible films. This method is also convenient and the film can be readily removed from the liquid surface and hence more suitable for laboratory purposes.

Ethyl cellulose show good film forming property. The method of casting on mercury surface was found to give thin uniform films. The films prepared with ethylcellulose alone were found to be brittle. To prevent embrittlement, a plasticizer i.e. dibutylphthalate was tried at various concentrations ranging from 10-50% w/w of the polymer. Preliminary experiments indicated that lower concentrations of dibutylphthalate were found to give rigid and brittle films, where as higher concentrations give soft films. Dibutylphthalate at a concentration of 40% w/w of the polymer was found to give good flexible films.

Absorbance at different concentrations of propranolol hydrochloride and diltiazem hydrochloride were taken. Graphs were plotted with absorbance against concentration, and the said results are depicted in tables (1 & 2) and in figs (1 & 2). In each case films were prepared using different concentrations of natural enhancer (0%, 0.25%, 0.5%, 0.75% and 1%) to evaluate the influence of the enhancer on the permeability properties of the film. All the films prepared were evaluated for uniformity of thickness, water vapor transmission studies and drug diffusion profiles by employing propranolol hydrochloride and diltiazem hydrochloride. Thickness measurement of percent elongation, tensile strength of various films is detailed in table (3). Water vapor transmission values are detailed in table (4) and are also depicted in fig (3). Water vapor transmission studies indicated that all the films prepared were permeable to water vapor. The rate of water vapor transmission values were calculated and the results are detailed in table (5).

Influence of the natural penetration enhancer on the permeability of the film

Among the films water vapor transmission value (Q) was more in the case of ethyl cellulose with 0.75% natural enhancer when compared to other ethyl cellulose films. It indicates that the ethyl cellulose film with natural penetration enhancer were more permeable to water vapor when compared with normal ethyl cellulose films. The order of increasing permeability to water vapor (Q) by ethyl cellulose films with various concentrations of natural penetration enhancer is, 1% > 0.75% > 0.5% > 0.25% > 0%.

Drug diffusion through various films was studied by employing model antihypertensive drugs namely propranolol hydrochloride and diltiazem hydrochloride. Drug diffusion through the films was studied employing permeation apparatus designed as described by Fites et al. All the films were found to be permeable to these drugs and the results are given in table (6), (8) and shown in figures (4), (5). Permeability coefficient values (P_m) of the films towards these 2 drugs were calculated from the drug diffusion data and the results are detailed in table (7), (9).

Table 1: Measured absorbance for the estimation of propranolol hydrochloride

S. No.	Concentration ($\mu\text{g/ml}$)	Absorbance ($\bar{X}\pm\text{Sd}$)
1	0	0
2	2	0.045 \pm 0.003
3	4	0.091 \pm 0.002
4	6	0.136 \pm 0.002
5	8	0.182 \pm 0.004
6	10	0.224 \pm 0.003

Table 2: Measured absorbance for the estimation of diltiazem hydrochloride

S. No.	Concentration ($\mu\text{g/ml}$)	Absorbance ($\bar{X}\pm\text{Sd}$)
1	0	0
2	2	0.126 \pm 0.002
3	4	0.251 \pm 0.004
4	6	0.378 \pm 0.002
5	8	0.505 \pm 0.003
6	10	0.629 \pm 0.003

Table 3: Mechanical properties of ethyl cellulose free films in the presence of natural enhancer

Concentration of natural enhancer (%w/v)	Thickness (μm)	Tensile Strength (Kg.Cm ²)	Percentage Elongation
0	30.4 \pm 1.2	38.2 \pm 1.6	51.2 \pm 3.8
0.25	32.8 \pm 1.4	37.1 \pm 1.4	51.8 \pm 2.6
0.5	34.5 \pm 0.8	36.2 \pm 1.2	52.4 \pm 2.4
0.75	36.3 \pm 1.6	35.4 \pm 1.8	53.1 \pm 1.9
1.0	38.9 \pm 1.3	34.7 \pm 1.4	53.7 \pm 2.4

Table 4: Water vapour transmission profiles of ethyl cellulose films in presence of various concentrations of natural enhancer

Sl. No.	Time (Hrs)	Amount of Water Vapour Transmitted (mg)				
		0% Natural Enhancer	0.25% Natural Enhancer	0.5% Natural Enhancer	0.75% Natural Enhancer	1.0% Natural Enhancer
1	0	0	0	0	0	0
2	6	23.54 \pm 1.8	26.28 \pm 2.8	29.42 \pm 1.6	32.12 \pm 2.2	34.56 \pm 1.9
3	12	48.12 \pm 2.2	53.22 \pm 1.4	57.38 \pm 1.2	59.26 \pm 1.8	61.98 \pm 1.2
4	18	71.34 \pm 1.4	77.48 \pm 1.7	81.52 \pm 1.9	85.18 \pm 1.6	87.72 \pm 2.4
5	24	95.09 \pm 1.6	102.24 \pm 1.4	106.94 \pm 1.2	109.46 \pm 2.6	112.14 \pm 1.4
6	30	118.28 \pm 1.8	126.54 \pm 2.6	131.26 \pm 2.4	134.84 \pm 2.4	136.36 \pm 1.8

Table 5: Water vapour transmission (q) values of ethyl cellulose films in the presence of natural enhancer

Concentration of Natural Enhancer (%W/v)	Q \times 10 ⁴ gm/cm ² 24hrs
0	1.135
0.25	1.317
0.5	1.449
0.75	1.561
1	1.714

Table 6: Diffusion profiles of propranolol hydrochloride through ethyl cellulose films prepared with various concentrations of natural enhancer

Sl. No.	Time (Hrs)	Amount of Propranolol Hydrochloride Diffused (μg) ($\bar{X}\pm\text{Sd}$)				
		0% Natural Enhancer	0.25% Natural Enhancer	0.5% Natural Enhancer	0.75% Natural Enhancer	1.0% Natural Enhancer
1	0	0	0	0	0	0
2	0.5	261.53 \pm 14.94	291.24 \pm 14.48	303.61 \pm 24.44	321.18 \pm 20.12	314.12 \pm 9.12
3	1	513.72 \pm 18.97	577.86 \pm 17.74	594.13 \pm 18.86	632.24 \pm 17.81	623.26 \pm 12.84
4	1.5	759.51 \pm 20.32	822.36 \pm 21.38	901.46 \pm 15.59	959.54 \pm 12.43	939.84 \pm 16.76
5	2	1006.82 \pm 13.38	1141.63 \pm 19.82	1189.98 \pm 18.32	1254.77 \pm 18.36	1234.38 \pm 21.12

Table 7: Permeability co-efficient (p_m) values of propranolol hydrochloride through ethyl cellulose films in the present of natural enhancer

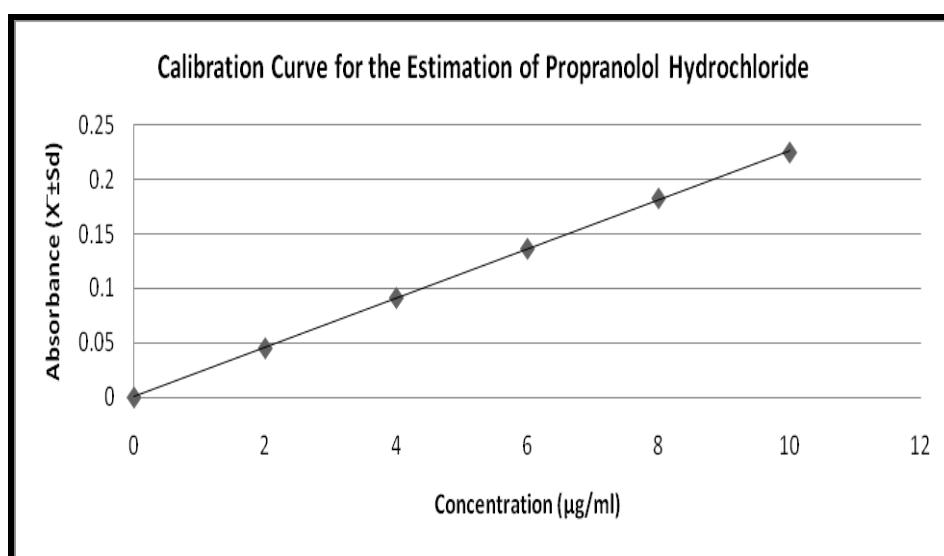
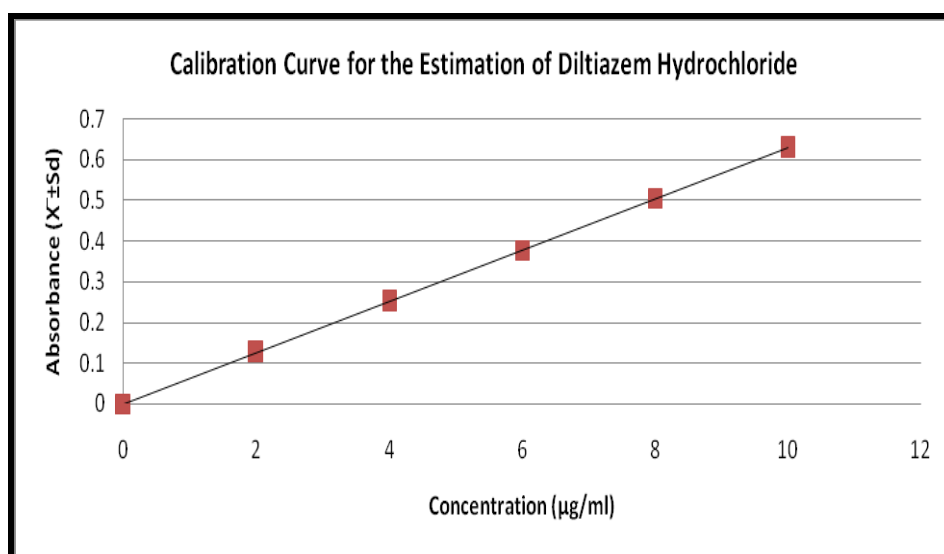
Concentration of Natural Enhancer (%W/v)	P _m \times 10 ⁴ (mg/cm/h)
0	6.08
0.25	7.34
0.5	8.02
0.75	8.96
1	9.49

Table 8: Diffusion profiles of diltiazem hydrochloride through ethyl-cellulose films prepared with various concentrations of natural enhancer

Sl. No.	Time (Hrs)	Amount of Diltiazem Hydrochloride Diffused (μg) ($\bar{X} \pm \text{Sd}$)				
		0% Natural Enhancer	0.25% Natural Enhancer	0.5% Natural Enhancer	0.75% Natural Enhancer	1.0% Natural Enhancer
1	0	0	0	0	0	0
2	0.5	220.16 \pm 10.34	248.72 \pm 10.32	277.14 \pm 18.41	295.24 \pm 16.28	281.84 \pm 17.72
3	1	432.68 \pm 18.96	487.64 \pm 14.48	540.12 \pm 19.48	589.98 \pm 18.37	560.16 \pm 18.84
4	1.5	664.32 \pm 16.12	724.28 \pm 12.86	817.18 \pm 15.32	864.56 \pm 14.43	830.28 \pm 20.24
5	2	862.44 \pm 12.58	965.18 \pm 15.46	1070.34 \pm 16.84	1153.84 \pm 18.62	1115.64 \pm 12.58

Table 9: Permeability co-efficient (p_m) values of diltiazem hydrochloride through ethyl cellulose films in the present of natural enhancer

Concentration of Natural Enhancer (%W/v)	$P_m \times 10^4$ (mg/cm/h)
0	5.17
0.25	6.03
0.5	7.27
0.75	8.34
1	8.53

**Fig. 1: Calibration curve for the estimation of propranolol hydrochloride****Fig. 2: Calibration curve for the estimation of diltiazem hydrochloride**

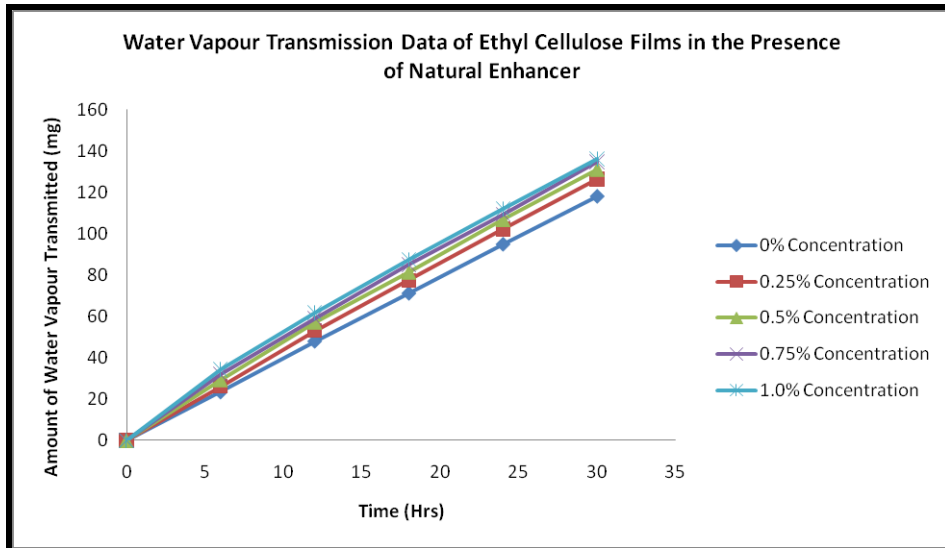


Fig. 3: Water vapor transmission data of ethyl cellulose films in the presence of natural enhancer

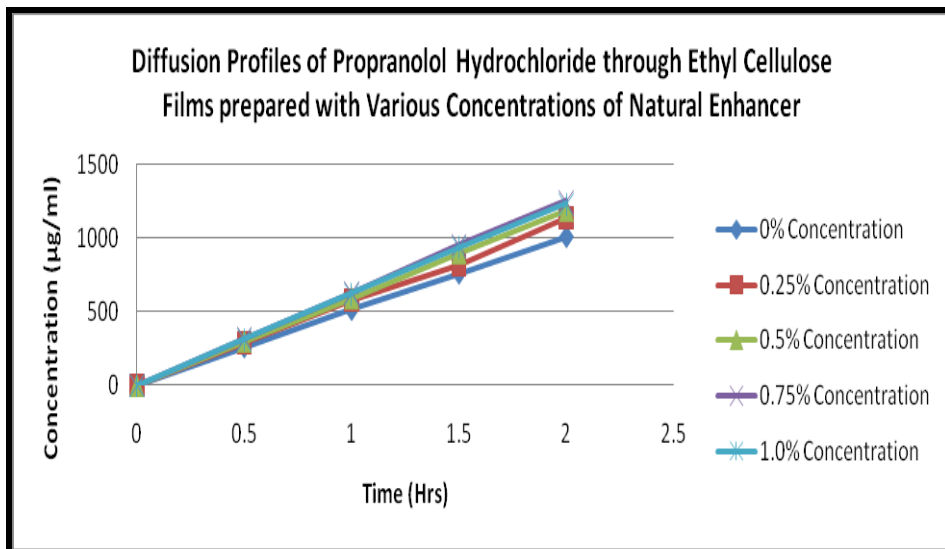


Fig. 4: Diffusion profiles of propranolol hydrochloride through ethyl cellulose films prepared with various concentrations of natural enhancer

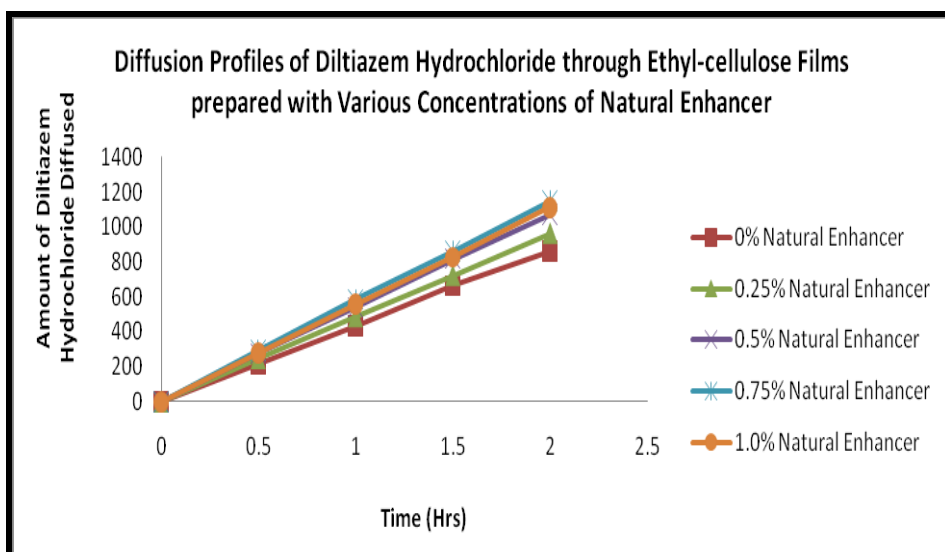


Fig. 5: Diffusion profiles of diltiazem hydrochloride through ethyl-cellulose films prepared with various concentrations of natural enhancer

CONCLUSIONS

Studies have been carried out on ethyl cellulose films with an objective of developing controlled release of some essential antihypertensive agents. Ethyl cellulose films treated with four different concentrations of natural permeation enhancer are prepared by mercury substrate technique. The films are evaluated for uniformity of thickness, water vapor transmission, drug diffusion and permeability characteristics. The following conclusions were drawn from the results obtained:

1. Ethyl cellulose films with various percentage of natural permeability enhancer could be prepared by the method of casting on mercury surface. The films were found to be thin, flexible and uniformly thick.
2. Normal Ethyl cellulose films and ethyl cellulose with various percentages of natural permeability enhancers were permeable to water vapor and diffusion of propranolol hydrochloride and diltiazem hydrochloride. Among all the films, ethyl cellulose film with 0.75% natural enhancer is found to be more permeable when compared to other films.
3. Good linear relationship was observed between the permeability of ethyl cellulose films.

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