Comparison Effect of Penetration Enhancer on Drug Delivery System

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Abstract **- Propranolol hydrochloride is used for the treatment of hypertension the purpose of this research article to study the comparison effect of penetration enhancer on drug delivery system using the natural permeation enhancer by using two polymer HPMC & EC and glycerin as plasticizer. Transdermal patches were prepared by solvent evaporation techniques. Controlled releases polymer was used for the formulation of patches. For in vitro drug release study pretreated with cellophane membrane using Franz diffusion cell. From the acquired results, propranolol hydrochloride with permeation enhancer (glycerin) was also successfully synthesized. DMSO remained to be an effective enhancer with hydrophilic polymer, the drug release kinetics of all transdermal patches follows the zero order kinetics, although the mechanism of drug release for all formulations was non-fickian diffusion.**

Index Terms **- Propranolol Hydrochloride, Transdermal Patches, DMSO, Permeation Enhancer, Diffusion Cell.**

INTRODUCTION

The most complex organ of human body the skin serves as an effective obstacle for chemical transmission. It stops the body from losing vital physiological chemicals. The difficulty of transdermal administration of medicinal substances is due to the barrier provided by the skin. By rupturing the skin barrier qualities and modifying these characteristics of the skin, the absorption over the skin was increased. These are the agents that help promote medication absorption through the skin by temporarily increasing skin permeability.

Absorption of the drug can be enhanced by the incorporation of the permeation enhancers which are inert and non-toxic as well. If the adopt the chemical change approach by using different chemicals like terpenes, surface active agents etc. we can enhance the permeation through skin1.

Basically there are three different approaches- Chemical approach, Physical Approach and Biochemical Approach2. Polar head groups present on the lipids interact with the enhancers and ultimately enhances the penetration. The mechanism followed by the penetration enhancers is generally by partitioning promotion, lipid disruption and protein modification.3 By bringing the change in the stratum corneum lipid disruption enhancers generally work and drugs like terpenes, Dimethyl sulfoxide gets absorbed. Drugs gets more partitioned by the help of the partitioning promoters which bring changes in the superficial solution layer.4Lastly, compound like Dimethyl Sulfoxide enhances the permeation of the drugs by opening up the dense protein structure.

Pathway of Transdermal Permeation5-

1. Transdermal permeation=through stratum corneum
2. Intercellular permeation=through the skinbarriers, SC
3. Transappendaged permeation=via cavities associated with hair roots, sebaceous and sweat glands.

Ideal characteristics of permeation enhancers-6,7

1. They should not cause toxin, irritation and any allergic response
2. They should have no adverse pharmacological activity inside the body.
3. They should be compatible with the drug
4. When removed from the skin, barrier properties it should return both rapidly and fully to normal.
5. It should be cosmetically accepted with an appropriate skin

6. They should not be expensive and possess good solvent properties
7. They should not have colour, taste, odor
8. They should be stable chemically or physically
9. They have course of action should be reproducible, sustainable and rapid.

In the present study we examine the effect of penetration enhancers from different classes was selected for study. Reversible disruption of the various barriers of the skin is the main function of chemical enhancers. The flux is enhanced and is called absorption promoters. The selected enhancers were natural (limonene, cineol), surfactant (dimethyl oxide), span (oleic acid) and complex forming (β-cyclodextrin).8

The object of this was to compare the release effect of with permeation enhancer or without permeation enhancer from transdermal patches using the diverse polymer with variable concentration and plasticizer. The release of the drug from the patches was used as criteria for selecting the best permeation enhancer.

MATERIALS AND METHODS

All chemical and Excipients used were of laboratory grade. Propranolol hydrochloride was received from Simplex Manufacturing Company Kotdwar India. Polymers, Other chemicals and excipients obtained from CDH, New Delhi were used in the study (Methanol, Di chloro methane), DMSO, Glycerin, sodium hydroxide, Potassium di-hydrogen phosphate, etc.) Were of analytical grade and Dialysis Membrane obtained from Sigma Aldrich, Mumbai. Distilled water was prepared in laboratory using all glass distillation apparatus.

Formulation of Transdermal Patches

A. Preparation of drug incorporated Transdermal Patches:

In requisite ratio 2 polymers were weighed and 20 ml of solvent mixture of Methanol & Di chloromethane (1:1) was added and shacked with the help of vortex shaker. Glycerin as 5 % w/w was used as plasticizer.120 mg of drug was added (in 2ml solvent mixture) of the total weight of polymer, with a magnetic stirrer with magnetic bead for slow stirring and a consistent mixture. On Petri dish dried at room temperature uniform dispersion was placed. For the study of in vitro permeation patches dried were wrapped with aluminum foil and kept in desiccator.

B. Preparation of drug burdened transdermal patches with permeation enhancer:

In requisite ratio 2 polymers were weighed and 20 ml of solvent mixture of Methanol & Di chloromethane (1:1) was added and shacked with the help of vortex shaker. Glycerin as 5 % w/w was used as plasticizer 120 mg of drug was added (in 2ml solvent mixture) of the total weight of polymer, with a magnetic stirrer with magnetic bead for slow stirring and a consistent mixture. Permeation enhancers (DMSO) 10 % (w/v) was separately added of total composition of polymer. On Petri dish uniform dispersion was casted and dried at room temperature. For the study of in vitro permeation patches dried were wrapped with aluminum foil and kept in desiccator.

Table 1.1 Composition of Transdermal film

S.No.	Formulation Code	Polymer (HPMC:EC) 600 mg	Plasticizer (%w/w) (Glycerin)	(SolventSystem) (Methanol:Di Chloro methane) 10 ml	Drug (mg)	Penetration Enhancer (DMSO) (%w/v)
1.	F1	10:0	5%	1:1	120	--
2.	F2	9.5:0.5	5%	1:1	120	--
3.	F3	9:1	5%	1:1	120	--
4.	F4	8.5:1.2	5%	1:1	120	--
5.	F5	8:2	5%	1:1	120	--
6.	P6	10:0	5%	1:1	120	10%
7.	P7	9.5:0.5	5%	1:1	120	10%
8.	P8	9:1	5%	1:1	120	10%
9.	P9	8.5:1.2	5%	1:1	120	10%
10.	P10	8:2	5%	1:1	120	10%

In vitro membrane permeation studies:

Table-1.2 In-vitro permeation study of formulation F1 to F5 on dialysis membrane

As a barrier Dialysis membrane was used for the In-vitro permeation studies for all the formulations.

Using dialysis membrane Franz diffusion cell:

In the phosphate buffer of pH7.4 the dialysis membrane was soaked overnight and was fixed carefully on the receptor compartment of the diffusion cell so that receptor fluid surface is in contact. Above the dialysis membrane fixed to the donor compartment the transdermal system of 1 cm2 area was positioned. As diffusion medium phosphate buffer pH7.4 was used and up to 45ml receptor compartment was filled. For consistent drug distribution, the receptor media was magnetically agitated with a magnetic bead and kept at 370.5°C. To assess the amount of medication released, 1 ml samples were taken every hour and for 8 hours diluted 10 ml with pH 7.4 phosphate buffer was used before being estimated spectrophotometrically (UV) at 290 nm. With pre warmed and fresh phosphate buffer solution pH 7.4, volumes withdrawn at each interval were placed. A graph was plotted for cumulative amount of drug permeated. The data of release pattern was fitted into the graphs.

In-vitro permeation studies (without permeation enhancer)

For. Code	Time (min.)	√T	Log T	Cumulative amount of drug permeated (µg/cm^2/hr)	Log cumulative % permeated	Log Cumulative % Drug Remaining
F1	30	5.47	1.47	0.01	0.16	1.99
	60	7.74	1.77	0.03	0.32	1.99
	120	10.95	2.07	0.06	0.64	1.98
	180	13.41	2.25	0.11	0.88	1.96
	240	15.49	2.38	0.17	1.06	1.94
	300	17.32	2.47	0.25	1.22	1.92
	360	18.97	2.55	0.33	1.34	1.89
	420	20.49	2.62	0.43	1.45	1.85
	480	21.90	2.68	0.53	1.55	1.80
F2	30	5.47	1.47	0.03	0.39	1.98
	60	7.74	1.77	0.08	0.73	1.97
	120	10.95	2.07	0.126	0.92	1.96
	180	13.41	2.25	0.176	1.06	1.94
	240	15.49	2.38	0.225	1.17	1.92
	300	17.32	2.47	0.278	1.26	1.91
	360	18.97	2.55	0.338	1.35	1.88
	420	20.49	2.62	0.401	1.42	1.86
	480	21.90	2.68	0.469	1.49	1.83
F3	30	5.47	1.47	0.03	0.31	1.99
	60	7.74	1.77	0.06	0.64	1.98
	120	10.95	2.07	0.10	0.85	1.96
	180	13.41	2.25	0.15	1.00	1.95
	240	15.49	2.38	0.19	1.12	1.93
	300	17.32	2.47	0.25	1.23	1.91
	360	18.97	2.55	0.31	1.32	1.89
	420	20.49	2.62	0.38	1.41	1.86
	480	21.90	2.68	0.46	1.49	1.83
F4	30	5.47	1.47	0.01	0.08	1.99
	60	7.74	1.77	0.05	0.56	1.98
	120	10.95	2.07	0.09	0.80	1.97
	180	13.41	2.25	0.14	0.97	1.95
	240	15.49	2.38	0.18	1.10	1.94
	300	17.32	2.47	0.24	1.20	1.92
	360	18.97	2.55	0.29	1.29	1.90

	420	20.49	2.62	0.36	1.38	1.88
	480	21.90	2.68	0.42	1.45	1.85
F5	30	5.47	1.47	0.01	0.06	1.99
	60	7.74	1.77	0.02	0.29	1.99
	120	10.95	2.07	0.06	0.62	1.98
	180	13.41	2.25	0.10	0.82	1.96
	240	15.49	2.38	0.14	0.97	1.95
	300	17.32	2.47	0.18	1.08	1.94
	360	18.97	2.55	0.22	1.18	1.92
	420	20.49	2.62	0.27	1.26	1.91
	480	21.90	2.68	0.33	1.34	1.89

In the present study hydrophilic (HPMC) and hydrophobic (EC) polymer are used to prepared patch. With the addition of hydrophobic polymer, the cumulative amount of drug released from formulation F1 containing hydrophilic polymer releases drug faster. The combination of HPMC and ethyl cellulose has shown maximum moisture pickup values. It was determined that the release pattern was not affected by hydrophilic polymer in another formulation that demonstrated a slower release rate in 8 hours than the other formulation. So it was necessary to use hydrophobic polymer (EC).

The data acquired from the in vitro permeation study of final selected formulation F5 was fitted to the kinetic models (Higuchi and Korsmeyer-peppas model) to conclude the pattern of drug release from the drug-polymer in the patches resulted in higher amount of drug release within lesser time period discussed in Table 1.2. The release of drug through the patch is raised in the initial hours of the formulation which is the predominant requirement for the success of transdermal formulations.

Drug release kinetics-

Table-:1.3 Kinetic models for in vitro drug permeation studies through dialysis membrane

Formulation Code	R^2				n-value
	Zero order	First order	Higuchi	Korsemeyerpeppa's	
F1	0.987	0.983	0.896	0.992	0.635
F2	0.990	0.985	0.951	0.998	0.646
F3	0.984	0.973	0.984	0.993	0.656
F4	0.992	0.988	0.991	0.995	0.660
F5	0.971	0.939	0.892	0.987	0.648

The values of drug release kinetics were shown in table 1.3.Release kinetic of drug of different formulations follow zero order (R2=0.987 to 0.971),First order(R2=0.983 to 0.938),Higuchi model(R2=0.895 to 0.893) & korsemeyer equation different formulations & their release kinetic models with regression-coefficient & the n value were obtained for all formulations was above 0.5 .intermediate n value indicate an anamolus behavior that is nonfickian kinetics corresponding to couple diffusion/polymer relaxation. in diffusion controlled system, fickian diffusion dominates the drug release process, where as in swelling controlled drug delivery system, the rate of drug release depends on the swelling rate of polymer. The n value of transdermal patch formulation ranged from 0.635 -0.648. Non-fickian or anamolus diffusion is characterized by these values. In this situation, the idea that the drug release from the patches remained dominated by diffusion, the results of fitting the data in korsemeyer peppas& zero order kinetics confirmed it.

In-vitro membrane permeation studies (with permeation enhancer)

Table-:1.4 In-vitro permeation study of formulation P1 to P5 on dialysis membrane.

For. Code	Time (min.)	√T	Log T	Cumulative amount of drug permeated (µg/cm^2/hr)	Log cumulative % permeated	Log Cumulative % Drug Remaining

P1	30	5.47	1.47	0.03	0.42	1.98
	60	7.74	1.77	0.09	0.79	1.97
	120	10.95	2.07	0.16	1.03	1.94
	180	13.41	2.25	0.25	1.23	1.91
	240	15.49	2.38	0.36	1.38	1.87
	300	17.32	2.47	0.48	1.51	1.82
	360	18.97	2.55	0.62	1.61	1.76
	420	20.49	2.62	0.77	1.71	1.68
	480	21.90	2.68	0.95	1.80	1.55
P2	30	5.47	1.47	0.03	0.37	1.98
	60	7.74	1.77	0.08	0.77	1.97
	120	10.95	2.07	0.16	1.03	1.95
	180	13.41	2.25	0.24	1.21	1.92
	240	15.49	2.38	0.34	1.35	1.88
	300	17.32	2.47	0.45	1.47	1.84
	360	18.97	2.55	0.57	1.58	1.78
	420	20.49	2.62	0.73	1.68	1.70
	480	21.90	2.68	0.90	1.78	1.59
P3	30	5.47	1.47	0.02	0.26	1.99
	60	7.74	1.77	0.07	0.69	1.97
	120	10.95	2.07	0.13	0.96	1.95
	180	13.41	2.25	0.22	1.16	1.93
	240	15.49	2.38	0.31	1.32	1.89
	300	17.32	2.47	0.44	1.46	1.84
	360	18.97	2.55	0.57	1.58	1.78
	420	20.49	2.62	0.72	1.68	1.71
	480	21.90	2.68	0.90	1.77	1.60

P4	30	5.47	1.47	0.02	0.16	1.99
	60	7.74	1.77	0.05	0.59	1.98
	120	10.95	2.07	0.10	0.85	1.96
	180	13.41	2.25	0.16	1.03	1.94
	240	15.49	2.38	0.23	1.19	1.92
	300	17.32	2.47	0.33	1.35	1.88
	360	18.97	2.55	0.47	1.50	1.83
	420	20.49	2.62	0.63	1.62	1.76
	480	21.90	2.68	0.81	1.73	1.66
P5	30	5.47	1.47	0.01	0.08	1.99
	60	7.74	1.77	0.04	0.50	1.98
	120	10.95	2.07	0.09	0.80	1.97
	180	13.41	2.25	0.15	1.02	1.95
	240	15.49	2.38	0.23	1.19	1.92
	300	17.32	2.47	0.33	1.34	1.89
	360	18.97	2.55	0.45	1.48	1.84
	420	20.49	2.62	0.60	1.60	1.77
	480	21.90	2.68	0.75	1.70	1.69

The data obtained from in-vitro permeation study is shown graphically according to various modes of treatment. The permeation test was carried out in a diffusion cell using a dialysis membrane and 25 mL of

phosphate buffer (pH 7.4) as diffusion media. Chemical permeation enhancers DMSO, at a concentration of 10% w/v of the total polymer, were incorporated into each of the following formulations individually to conduct a permeation enhancement research. It was discovered that adding DMSO in patch formulations improved medication penetration through the membrane considerably. The maximum percentage cumulative drug release at the end of 8 hours for formulation P1 was 69.74 percent in the case of DMSO.

sThe activity of various chemical permeation enhancers on lipophilic matrix and/or hydrophilic protein gel in the stratum corneum may be attributed to their contact with intercellular lipids, which leads to disruption of their organisation and increased fluidity. The results of in vitro permeation tests were used to fit several kinetic models. Each model's regression values were within the range of these models and satisfactory, indicating that they all followed zero order and Higuchi model kinetics.

Drug release kinetics- (with permeation enhancer)

Table-:1.5 Kinetic models for in vitro drug permeation studies through dialysis membrane

Formulation Code	R^2				n-value
	Zero order	First order	Higuchi	Korsemeyer peppa's	
P1	0.982	0.930	0.859	0.993	0.657
P2	0.979	0.928	0.857	0.998	0.658
P3	0.977	0.932	0.907	0.994	0.656
P4	0.948	0.905	0.859	0.984	0.660
P5	0.960	0.912	0.876	0.992	0.648

The values of cumulative release invitro release study are shown in Table 1.5. release kinetic of drug of different formulations follow zero order (R2=0.982-0.960), First order (R2=0.930-0.912), Higuchi model (R2=0.859-0.876) & korsemeyer equation diverse preparations & their release kinetic models with regression-coefficient & n value were obtained between 0.657-0.648 for all formulations. These values are characteristic of non-fickian or anamolus diffusion. The findings of fitting the data in korsemeyer peppas& zero order kinetics further backed up the assumption that the drug was released from the patches via diffusion. Comparison study of permeation enhancer and without permeation enhancer-

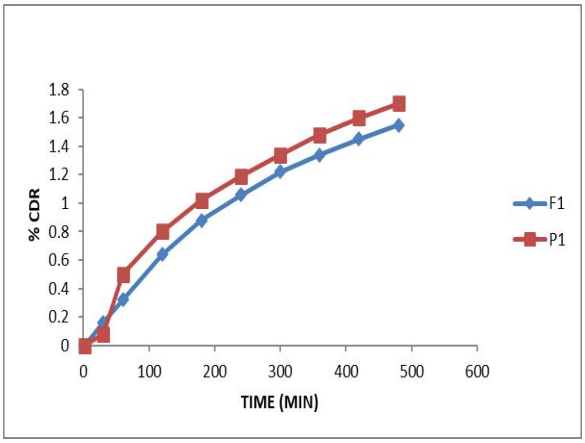

Fig.2.1 Plot of Log cumulative percent drug remaining versus time across dialysis membrane. (First order)

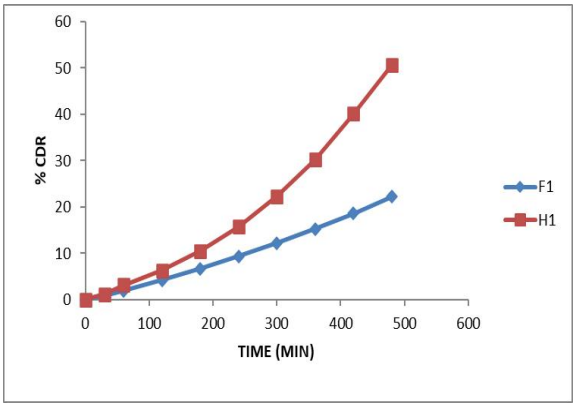

Fig.2.2 Plot of cumulative percent permeated versus time across dialysis membrane. (Zero order)

In order to study the effect of DMSO as penetration enhancer on drug permeation through membrane. It was observed from the fig. 2.1 and 2.2. That the permeation of drug across membrane without enhancer was less but the permeation was significantly increased the formulation F1 & maximum 63.61 drug was penetrating.

CONCLUSION

In conclusion, the extent of propranolol hydrochloride release from transdermal patches revealed that patches with a higher proportion of ethyl cellulose F5 8:2 (ratio) were suitable for once-daily drug delivery, while films with a higher proportion of EC were expected to be suitable for a prolonged regimen of sustained drug delivery via transdermal route for more than 48 hours.

Propranolol hydrochloride with a permeation enhancer was also synthesized and analyzed satisfactorily, with a high in vitro penetration rate. For the in-vitro study, DMSO was discovered to be an effective enhancer

with increasing hydrophilic polymer range. The use of a 10% concentration of DMSO was also found to be more efficient in terms of drug penetration into the stratum corneum. During the research time period, the property of film did not change.

The drug release rate kinetics of all transdermal patches follows zero order kinetics, whereas the mechanism of drug release for all formulations was non-fickian diffusion. After observing the release studies, the Formulation F5 was designated as the optimized preparation because it showed the sustained release which we need for the transdermal drug delivery system.

Studies have shown promising result, hence, there is scope for further pharmacodynamics and pharmacokinetics evaluation.

REFERENCES

[1] Hadgraft J. Passive Enhancement Strategies in topical and transdermal drug delivery. Int J Pharm 1999; 184:1-6.

[2] Victor MM, Clive SR Inter-and intra-individual variability in human skin barrier function: a large scale retrospective study. Toxi in Vitro2008; 22:1062–9

[3] Singh PB, Choudhury PK, Penetration enhancers for transdermal drug delivery of systemic agents. JPharmRes 2007; 6: 44-50

[4] Baby B, Abraham A, Jayaprakas S. Design and evaluation of transdermal patches of propranolol hydrochloride. Research J. Pharm. and Tech. 2009; 2(1):195-200.

[5] Hiremath S.P et al"Formulation, characterisation and evaluation of transdermal patches of Diltiazem Hydrochloride"Ind Drugs 2010;47(10):47.

[6] Saxena M. Et al."Formulation and evaluation of transdermal patches of metoclopramide hydrochloride"Ind.drugs2006;43(9):740-745.

[7] Benson HA. Transdermal drug delivery: Penetration enhancement techniques. Curr Drug Deliv.2005; 2: 23-33.

[8] Tanwar et al."Development and evaluation of carvedilol transdermal patches"Acta Pharm.2007;57:151-159.