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Original Article

Effect of Permeation Enhancers on Diffusion of Lamotrigine Drug through Cellophane Membrane

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ABSTRACT

The effect of 3 different categories of permeation enhancers on the in vitro permeation of Lamotrigine across cellophane membrane were evaluated using vertical type Franz Diffusion Cell. This work was conducted as a permeation enhancer screening study for development of Lamotrigine Transdermal Drug Delivery System. Dimethyl Sulfoxide (DMSO) at 5% v/v and Tween 80 at 0.1% v/v gave a 6 and 7 folds enhancement in permeation values respectively. SLS and Peppermint Oil did not show any enhancement in the penetration.

Keywords: Lamotrigine, Cellophane membrane, Flux, Penetration enhancers, Transdermal delivery.

INTRODUCTION

Permeation enhancers play an important role in ensuring adequate delivery of drug in to the systemic circulation across the formidable barrier provided by the skin. Permeation enhancers used in transdermal systems belong to different chemical classes and each work by different mechanism of action[1-8]. Selection of the correct penetration enhancer is critical for the successful development of a transdermal drug delivery system. The physico chemical properties of the drug seem to define which penetration enhancer works the best for which drug[9-11].

Lamotrigine is practically water insoluble drug which is widely used for the treatment of epilepsy. It is available as oral immediate release and controlled release tablets. Since it has a long half life of 24 to 34 hours, the transdermal route provides an attractive alternative for controlled diffusion of the drug across the skin over prolonged period in order to maintain blood levels

which are just sufficient to given the therapeutic effect but not the major adverse effects attributed to the drug[12].

Delivering Lamotrigine across the skin is a challenge since it is practically insoluble in water. The present work focuses on evaluating the effect of three different classes of penetration enhancers each at three use levels on the permeation of Lamotrigine from a suspension formulation across an artificial membrane. Cellophane was used as the artificial membrane since it is very well characterized and has a uniform and controlled porosity. The vertical Franz diffusion cell of a fixed surface area of 9 cm^2 was used. Drug diffusion into 200 ml of pH 7.4 phosphate buffer was studied for 24 hours.

MATERIALS AND METHODS

Lamotrigine USP (was obtained as gift sample from RA Chem, Hyderabad, India), HPMC E15 (Dow Chemical's), Dimethyl Sulfoxide (DMSO, AR Grade, Merck, India), Tween 80 USP (Merck, India), Sodium Lauryl Sulphate USP (Merck India) and Peppermint oil (AR Grade, Loba Chemi) All other chemicals and reagents used were of AR grade from Merck. Purified water USP (Millipore) was used wherever specified.

The formulations for *in vitro* diffusion studies were prepared by dissolving the penetration enhancer in 2% dispersion of HPMC E15 in water and then dispersing the drug in this mixture by sonication for 30 minutes. The composition details for all formulations are given in Table 1.

In vitro permeation studies were conducted using the vertical Franz diffusion cell across cellophane membrane. pH 7.4 phosphate buffer was kept in the receptor cell and the diffusion medium was stirred at 100 rpm using magnetic stirrer. 25 ml of sample was withdrawn at predetermined interval and the concentration of the drug diffused was determined using the UV spectrophotometric method. Fresh 25 ml of pH 7.4 phosphate buffer was replaced after each withdrawal.

RESULTS & DISCUSSION

The % of drug diffused at each time interval for all formulations was determined by using UV visible spectrophotometric method. The flux across the membrane was calculated using the formula[13]

$$J = \frac{m}{At}$$

Units: **µg cm^{-2} h^{-1}**
Where,
m= concentration,
A= cross sectional area,
t= time

Flux values for all formulations at different time intervals are given in Table2.
The values of the flux across cellophane membrane at 8 hours, 24 hours were compared in Figure 1.

SLS and Peppermint oil did not show any significant enhancement in permeation at all concentrations.

DMSO at 5% level enhanced the permeation nearly 6 folds. This may be due to the fact that DMSO is reported to increase both the solubility of Lamotrigine[14] as well as its permeability across the membrane.

Tween at 0.1% level enhanced permeation nearly 7 folds, this may be due to thermodynamic activity (driving force of permeant in vehicle) of the enhancer[15]. Tween and SLS at higher concentrations do not show enhancement which may be due to increase drug entrapment in the micelles which are reported to reduce the thermodynamic activity of the permeant[16].

CONCLUSION

DMSO at 5% level and Tween 80 at 0.1% level show excellent enhancement in the permeation of Lamotrigine across artificial

membrane like cellophane. Further work involving permeation across animal skin is under progress.

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Table 1. Formulation Composition

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Drug	+	+	+	+	+	+	+	+	+	+	+	+	+
2% HPMC	+	+	+	+	+	+	+	+	+	+	+	+	+
1% DMSO	-	+	-	-	-	-	-	-	-	-	-	-	-
5% DMSO	-	-	+	-	-	-	-	-	-	-	-	-	-
10% DMSO	-	-	-	+	-	-	-	-	-	-	-	-	-
0.1% SLS	-	-	-	-	+	-	-	-	-	-	-	-	-
1% SLS	-	-	-	-	-	+	-	-	-	-	-	-	-
2% SLS	-	-	-	-	-	-	+	-	-	-	-	-	-
0.1% Tween	-	-	-	-	-	-	-	+	-	-	-	-	-
0.5% Tween	-	-	-	-	-	-	-	-	+	-	-	-	-
2% Tween	-	-	-	-	-	-	-	-	-	+	-	-	-
Peppermint oil (1%)	-	-	-	-	-	-	-	-	-	-	+	-	-
Peppermint oil (5%)	-	-	-	-	-	-	-	-	-	-	-	+	-
Peppermint oil (8%)	-	-	-	-	-	-	-	-	-	-	-	-	+

Table 2. Flux (µg cm^{-2} h^{-1}) Values for all formulations at different time intervals (hours)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
1hour	0.11	0.26	0.16	0.31	0.27	0.44	0.52	0.3	0	0.25	0.06	0.11	0.12
4hours	1.02	1.75	5.61	3.87	1.46	2.76	3.56	6.91	0.5	3.02	0.85	0.7	0.65
8hours	2.55	3.57	20.7	8.11	3.51	5.85	7.48	23.7	4.38	7.03	2.06	5.32	2.04
12hours	5.16	5.5	38.1	13.5	5.71	9.66	12.56	45.65	11.73	16.05	3.4	11.7	3.76
24hours	14.9	11.1	89.2	31.03	12.3	21.3	27.1	110.86	35.0	43.66	9.46	30.1	11.73

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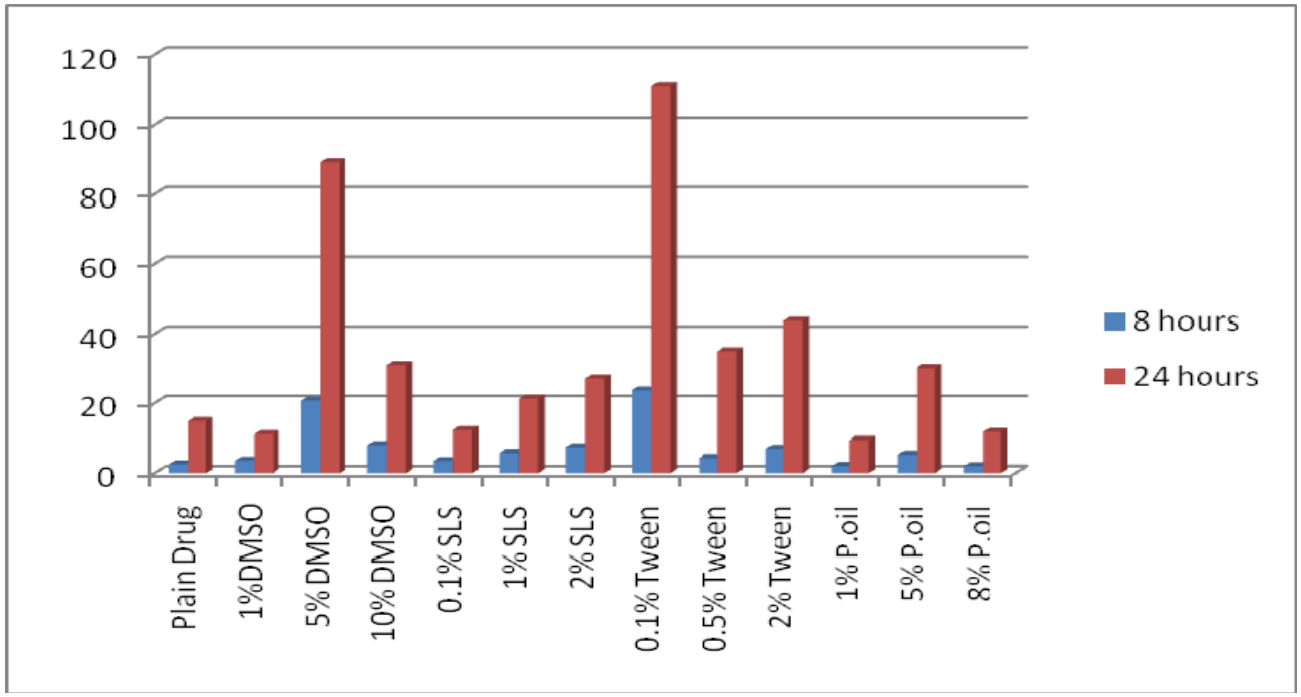

Figure 1. Flux comparison for all formulations at 8hours and 24hours