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Original Article

INVESTIGATING EFFECTS OF PERMEATION ENHANCERS ON PERCUTANEOUS ABSORPTION OF LOXAPINE SUCCINATE

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ABSTRACT

Objective: The objective of the present work is to explore and screen the potential of selected permeation enhancers in increasing the (Loxapine succinate) LX penetration in the presence of adhesives.

Methods: LX was utilized as a model drug for its possible delivery via the transdermal route. Urea (U)(5,7.5 and 10% w/v), oleic acid (OA) (0.1, 0.5 and 1% w/v), peppermint oil (PO) (0.3,0.5 and 1% w/v), dimethyl sulphoxide (DMSO) (2.5,5 and 7.5 % w/v), propylene glycol (PG) (5,7.5 and 10 % w/v) and ginger oil (GO) (0.3,0.5 and 1% w/v) were explored for their effects on permeation enhancement. Franz-type, six diffusion cell assembly was utilized for the permeation studies across excised pig ear skin section. Flux rate, permeation coefficient of LX and enhancement ratio obtained using different PEs were used as parameters for evaluating the best possible combination of adhesive along with PE for LX permeation.

Results: Results showed that flux of LX improved from 119 µg/cm^2/h to 178.84±4.136µg/cm^2/h with 10 % w/v U. 1% w/v OA, increased the flux up to 442.61 µg/cm^2/h. Incorporation of 1 % w/v PO increased flux up to 505.55±6.195 µg/cm^2/h with ER of 4.22. The use of 7.5 % w/v DMSO raised the flux value to 456.41±6.186 µg/cm^2/h with ER of 3.81. The patches consisting of GO (1% w/v) provided flux 574.10±5.165 µg/cm^2/h and ER up to 4.79. The use of 10 % w/v PG raised the flux value to 414.5±5.189 µg/cm^2/h with ER of 3.45.

Conclusion: It can be concluded by the investigation done in the research that GO provides the maximum possible flux in comparison to other permeation enhancers.

Keywords: Transdermal delivery, Permeation enhancer, Adhesive, Flux rate

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INTRODUCTION

Loxapine succinate belongs to the typical antipsychotics class of drugs. It is a kind of dibenzoxazepine structure. LX is used in the treatment of some mood disorders like schizophrenia. It is believed to be a dopamine antagonist. Also, it is a serotonin blocker. The exact mechanism of action for LX is not established yet [1-3].

LX is available in capsule form [4]. Transdermal delivery of LX can serve as a better alternative to the oral route as it is more patient compliant and also avoids the first-pass effect [5, 6]. Due to the restrictions posed by the skin barrier, it is difficult for drugs to get absorbed. Also, transdermal formulations require adhesives that might interfere with the flux of LX. Hence, permeation enhancers may serve as an aide that would improve the drug flux across the epidermis [7, 8]. Various chemical substances have been reported in the literature as penetration enhancers [9]. Compounds that may be employed in transdermal systems include terpenes, esters, amino acids, fatty acids, organic solvents, peptides, etc. [10]. Essential oils extracted from plants also have been reported to exhibit characteristics of permeation enhancers [11-14]. Selecting an appropriate permeation enhancer is decisive in the successful performance of the transdermal formulation.

In the current study, the objective is to investigate the performance of selected permeation enhancers across pig ear skin for penetration of LX in presence of adhesive. Also, permeation enhancer providing maximum flux of LX would be identified. Selected line containing the name of enhancers. Keshary-Chien cells are utilized for permeation studies using saline phosphate buffer pH 7.4 as the medium [15].

MATERIALS AND METHODS

Materials

Loxapine succinate was gifted kindly by Consern Pharma Pvt. Ltd., Ludhiana, Punjab (India). Urea (UR), oleic acid (OA), peppermint oil (PO), dimethyl sulphoxide (DMSO), sodium lauryl sulfate (SLS), propylene glycol (PG), and ginger oil (GO) were procured from Sigma Aldrich. Dura-Tak 87-6908 was received kindly from Henkel Corporation, USA. Other chemical substances were AR grade and procured from Qualichem chemicals.

Methods

Loxapine succinate-eudragit L100 compatibility study by FTIR

LX was examined for any possible interaction with excipients viz. Eudragit L100 by FTIR analysis (Perkin Elmer). Analysis of results was done by Origin 2019, which revealed possible interaction among LX and polymer as shown in fig. 1.

Preparation of LX transdermal patches

Transdermal patches containing Using composition mentioned in table 1, control transdermal patches were fabricated utilizing solvent cast evaporation technique. A ratio of 7:3 concentration of polymers was mixed in a 15 ml methanol: dichloromethane mixture (2:1). The mixture was stirred employing a magnetic stirrer for thirty minutes. LX was separately dispersed in 5 ml of solvent. Polyethylene glycol 400 was added to the mixture for plasticity. Varying ratios of different permeation enhancers were added to the liquid dispersion to formulate different patches as per table 2. This mixture was then poured onto petridishes with a fabricated ring so that patch of 1.32 cm^2 is obtained. Petri dishes were then covered with an inverted glass funnel to dry film for forty-eight hours. Formulated patches were stored in a desiccator [16].

Table 1: Formulation of control LX transdermal patches

Component	Quantity
LX	12 mg
Duratak 87-6908	1.5% w/v
Polymer (Eudragit L100: HPMC 5cPs)	7:3 (1000 mg)
PEG 400	30 % w/v
Solvent (Methanol: Dichloromethane)	2:1 (q. s. 20 ml)

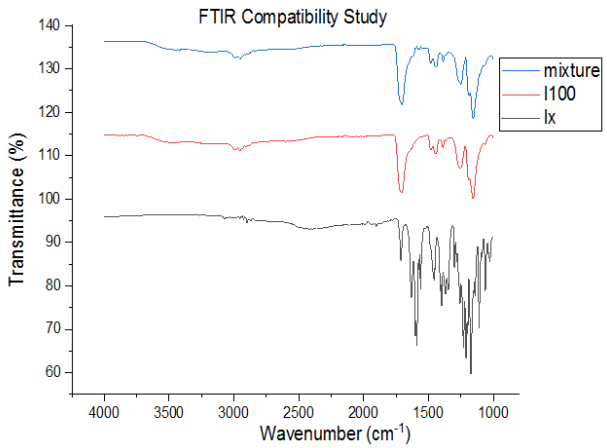

Fig. 1: FTIR spectra showing the absence of any incompatibility between LX and Eudragit L100

Table 2: Formulation table of permeation enhancers with control formulation

Component	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
UR	5	7.5	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OA	-	-	-	0.1	0.5	1	-	-	-	-	-	-	-	-	-	-	-	-
PO	-	-	-	-	-	-	0.3	0.5	1	-	-	-	-	-	-	-	-	-
DMSO	-	-	-	-	-	-	-	-	-	2.5	5	7.5	-	-	-	-	-	-
GO	-	-	-	-	-	-	-	-	-	-	-	-	0.3	0.5	1	-	-	-
PG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	7.5	10

LX formulations with penetration enhancers

UR, OA, PO, DMSO, PG, and GO were used as permeation enhancers. Formulation codes of LX patches with the concentration of permeation enhancers have been mentioned in table 1.

Drug permeation studies across pig ear skin

Ex vivo permeation studies for different formulations were carried out in Franz diffusion assembly utilizing freshly excised skin of pig ears. The study was carried out for 24 h with a temperature maintained at 37±0.5 ℃ utilizing an external water jacket outside the receptor cell with continuous stirring utilizing a magnetic bead (500 rpm). Pig ear skin was equilibrated utilizing PBS pH 7.4. The quantity of LX penetrated across pig ear skin in diffusion assembly using different formulations was calculated by measurement of absorbance at 297 nm in Shimadzu 1700 UV spectrophotometer by withdrawing samples every three hours intervals. Cumulative LX penetrated across skin per unit surface area was plotted versus time. The slope of the linear portion was reported as flux.

$$Kp = (Slope \times Vd) \div SA$$

where, Vd — Volume of donor solution, SA — tissue surface area

Permeability coefficient, Kp = Jss ÷ Cvhere Jss is the steady-state flux and Cv is the initial concentration of LX in the donor compartment,

Enhancement ratio,
ER = Kp of drug with enhancer ÷ Kp of drug alone

Various pharmacokinetic parameters, namely enhancement ratio, the flux of LX, and permeability coefficient, have been reported to establish the best possible combination utilizing LX, permeation enhancer, and adhesive for optimum results [17].

RESULTS AND DISCUSSION

Penetration of drug from topical preparations is crucial as well as difficult stage. In the present study, various permeation enhancers have been explored for permeation enhancement in control patches by zanalyzing the effect of varying concentrations of penetration enhancers.

With the ex vivo permeation study of the control patch, it was found that the flux of LX was 119.93±3.412 µg/cm²/h. The flux of other formulations was calculated and compared to obtain an enhancement ratio that gives the efficiency of different penetration enhancers.

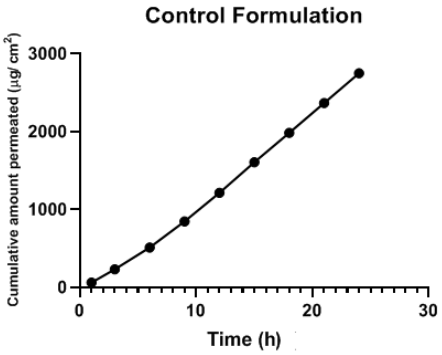

Fig. 2: Ex-vivo permeation profile of control formulation (Values are expressed as mean, n=3)

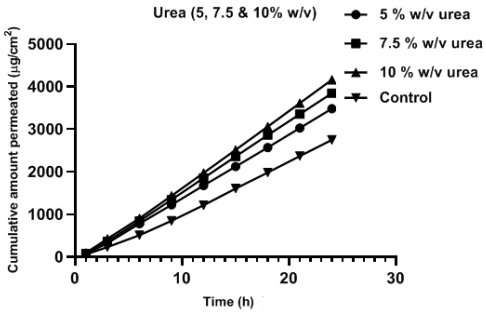

Fig. 3: Ex-vivo permeation profile of Urea as penetration enhancer in control formulation (Values are expressed as mean, n=3)

Fig. 3 represents the results of Urea as permeation enhancer when used in 5 %, 7.5 % and 10 % w/v. Urea is an amide compound that may serve as a permeation enhancer when utilized in the 4-10 % range [18]. Urea being a hygroscopic compound, hydrates skin, thereby improving the permeation of drugs across the stratum corneum. Due to increased water proportion in the stratum corneum, it swells and the pathway for drugs becomes longer but simultaneously, due to cell decompression, the flux of the drug increases leading to increased drug penetration [19]. Upon increasing the concentration of urea in control patches from 5 to 7.5 % to 10 % w/v, ER was found to increase to 1.49 (F3) as compared to 1.24 (F1). It proved that urea could improve Loxapine permeation in control patches. As confirmed from results in table 2, the permeation extent by urea use is quite less as compared to DMSO, peppermint oil, and ginger oil which may be cited due to the property of urea to promote permeation of hydrophilic molecules to a greater extent [20].

Penetration parameters obtained from ex vivo penetration studies for different penetration enhancers have been reported in table 3.

Table 3: Permeation parameters of different formulations

Formulation	Flux (µg/cm²/h)*	Enhancement ratio
F1	149.16±3.143	1.24
F2	165.78±3.165	1.38
F3	178.84±4.136	1.49
F4	328.47±2.155	2.74
F5	428.43±4.178	3.57
F6	442.71±4.136	3.69
F7	284.19±6.188	2.37
F8	407.01±5.163	3.39
F9	505.55±6.195	4.22
F10	209.49±7.176	1.75
F11	310.01±7.164	2.58
F12	456.41±6.186	3.81
F13	302.76±4.196	2.52
F14	493.18±4.157	4.11
F15	574.10±5.165	4.79
F16	285.62±.4.174	2.38
F17	342.75±5.168	2.86
F18	414.15±5.189	3.45

*(Values of flux are expressed as mean±SD, n=3); Effects of OA in 0.1, 0.5 and 1 % w/v with control patches on penetration across pig ear skin are presented in fig. 4.

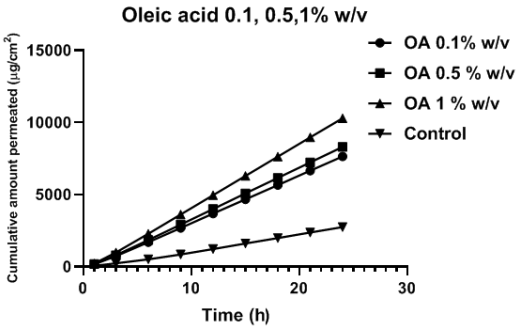

Fig. 4: Ex-vivo permeation profile of OA as penetration enhancer in control formulation (Values are expressed as mean., n=3)

OA penetrates across the stratum corneum causing decompression, thereby reducing resistance to drug permeation [21]. Results indicate that 0.5 % w/v OA incorporation increased ER to 3.57. Higher levels of OA in control patch incorporation may hinder the penetration of LX owing to the slowing down of the partition phenomenon [22]. 0.5 % w/v OA incorporation increased ER to 3.69 along with flux of 442.61±4.136 µg/cm²/h.

Peppermint oil was used in 0.3, 0.5 and 1% w/v. Results given in fig. 5 indicate a significant increase up to 5 in the case of F9. But its capability of penetration enhancement was considerably lesser than ginger oil. PO increases permeation by inducing conformational modifications and skin lipids disintegration. Flux of 442.61±4.136 µg/cm²/h was achieved using 1 % w/v PO and the maximum ER with this was 4.22. Also, a further increase in the concentration of peppermint oil could cause an irritant effect on the skin [23].

DMSO was also explored as a possible permeation enhancer for F10, F11, and F12. Results are depicted in fig. 6. DMSO in 2.5, 5 and 7.5 % w/v was used in LT5 formulations. DMSO is believed to improve the penetration of drugs across the skin. The maximum flux was 456.41±6.186 µg/cm²/h and ER achieved was 3.81 (F12). Lipid extraction is the mechanism proposed [24]. A higher concentration of DMSO causes erythema [25].

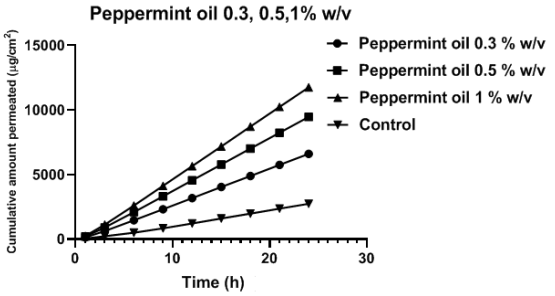

Fig. 5: Ex-vivo permeation profile of PO as a penetration enhancer (Values are expressed as mean, n=3)

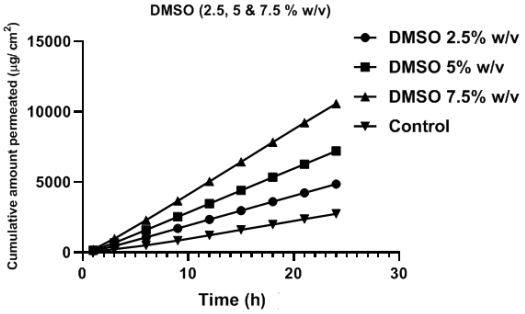

Fig. 6: Ex-vivo permeation profile of DMSO as a penetration enhancer (Values are expressed as mean, n=3)

The final permeation enhancer to be explored was ginger oil in 0.3, 0.5, and 1% w/v. As per the results mentioned in fig. 7, there was a considerable enhancement of drug permeation across pig ear skin, leading to a maximum ER of 4.79 times and flux of 574.10±5.165 µg/cm²/h with F15. It is expected penetration of drugs by essential oils is enhanced due to disrupting lipids of the topmost skin layer. Further increase in the concentration of ginger oil could cause an irritant effect on the skin [23].

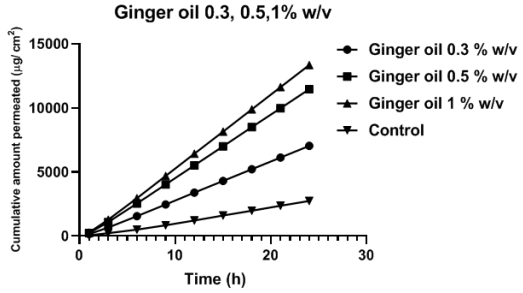

Fig. 7: Ex-vivo permeation profile of GO as a penetration enhancer (Values are expressed as mean, n=3)

The effect of PG as a penetration enhancer has been depicted in fig. 8 where it has been used in 5 %, 7.5 % and 10 % w/v. PG is reported to improve drug flux by occupying its Hydrogen bonding sites and preservation of keratin in the stratum corneum layer [26]. It may also be attributed to lipid extraction out of the stratum corneum [27]. As expected, enhancement ratio LX patches increased as the concentration of PG increased from 5 % to 7.5 %, whereas reduction might be attributed to higher solvation of LX in a higher concentration of PG [28]. The maximum possible ER value of 3.45 was achieved with 10 % w/v PG with a flux value of 414.5±5.189 µg/cm²/h.

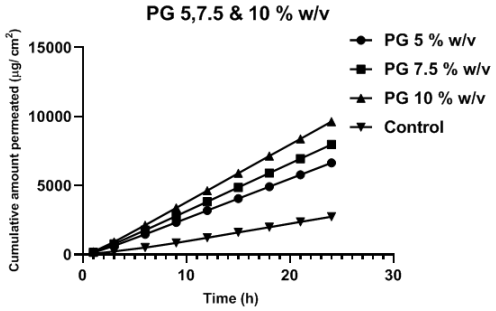

Fig. 8: Ex-vivo permeation profile of PG as a penetration enhancer (Values are expressed as mean, n=3)

As per the results, ER of formulation with 7.5 % was 4 approx. Which was better than the formulation in which DMSO was present in 2.5 and 5 % w/v.

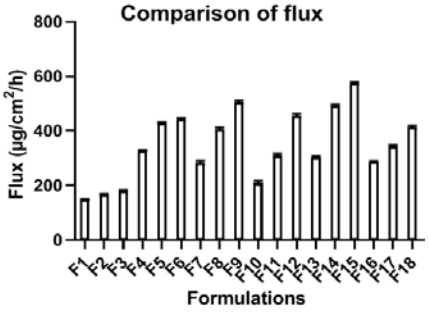

Fig. 9: Comparison of flux obtained using different formulations (Values of flux are expressed as mean, n=3)

Results cited in fig. 9 show the comparison of flux obtained by different penetration enhancers which can be utilized for transdermal drug penetration facilitation.

CONCLUSION

For formulating a good transdermal patch for LX, permeation of LX is a primary requirement. Through this present investigation efficacy of different penetration enhancers was explored. It was found from flux calculation and enhancement ratio calculation, a transdermal patch containing GO (1% w/v). F15 provided a maximum flux of 574.1±5.165 µg/cm²/h with an enhancement ratio of 4.79.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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