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TRANSDERMAL DELIVERY OF ACYCLOVIR WITH RESPECT WITH EFFECT OF TERPENE

Sudarshan S. Joshi*¹, Dr. Shashikant D. Barhate¹

¹Department of Pharmaceutics, Smt.Sharadchandrika Suresh Patil College of Pharmacy, Chopda- 425107, Maharashtra, India.

ABSTRACT

Inadequate penetration of acyclovir through stratum corneum of skin may be one of the limiting factors in topical therapy of recurrent cutaneous herpes simplex virus infection in humans. The objective of present study was to investigate the effect of terpene; Nerolidol on skin permeation of acyclovir. The enhancing effect of Nerolidol with different concentration (1.5, 2.5, 3.5, 4.5%w/w) on permeation of acyclovir were evaluated using franz diffusion cell fitted with rat skin and compared with marketed formulation. In present work, w/o emulsion based cream formulation contain suitable combination of oil phase and aqueous phase along with preservative prepared and subjected to various physiochemical parameters like drug content, pH, spreadability, extrudability and viscosity studies. Stability study of selected formulation was done according to ICH guidelines. The in vitro permeation experiments with rat skin revealed that the terpene enhancers were ability to enhance the flux of acyclovir. Nerolidol which possessed the highest lipophilicity ($\log P_{5.3690.38}$) provided the greatest enhancement for acyclovir flux (98.79-fold). Obtained R^2 values for zero-order model suggests that the drug follows zero-order release kinetics. The rheological characterization of formulated systems showed that the systems exhibit non-Newtonian behavior.

Correspondence to Author



Sudarshan S. Joshi

Department of Pharmaceutics,
Smt.Sharadchandrika Suresh
Patil College of Pharmacy,
Chopda- 425107, Maharashtra,
India.

Email

joshisudarshan@gmail.com.

Key Words

acyclovir, Nerolidol, shata-
dhauta-ghrita, thixotrophy.

INTRODUCTION

Acyclovir is antiviral agent. Acyclovir is a synthetic purine nucleoside analog with an acyclic side chain. It is clinically active against herpes simplex virus 1 and 2¹. The oral absorption is dose dependent and highly variable with a bioavailability ranging from 10% to 30%. Nevertheless, the oral route is preferred to parenteral administration because of the risk of local toxicity at the injection site. The mean plasma half life ($t_{1/2}$) of acyclovir is ~2.5 hours. Hence, repeated administration of high doses is required (200 mg 5 times daily for 10 days) for the effective management of HSV infections². This drug showed the low bioavailability and need enhancement in permeability. Looking at these problems, an attempt was made to develop a topical acyclovir cream with shata-dhauta-ghrita using a novel permeation enhancer³.

MATERIALS AND METHODS

Material

Acyclovir was received as gift from Ajanta pharmaceuticals.Ltd, Mumbai, Maharashtra. Nerolidol was received from Sigma Aldrich, Mumbai. Butyl hydroxyl toluene, butyl hydroxy anisole, methyl paraben, propyl paraben, span 60, span 80, tertiary butyl hydroxyl quinone were received from S.D. Fine Chemicals Ltd., Mumbai. All the other solvents and chemicals used were of analytical grade.

Preparation of transdermal acyclovir cream

The acyclovir cream was prepared by melting the oil phase consisting of shata-dhauta-ghrita, penetration enhancer (Nerolidol) sorbitan monostearate and tertiary butyl hydroquinone at 70°C in porcelain dish placed on water bath. Previously sonicated acyclovir in purified distilled water was maintained at same temperature in beaker constituted the aqueous phase. Add aqueous phase through beaker to oil phase in mortar with constant stirring and maintaining temperature 70°C for 10 minutes. Cool down to 50°C with mixing. Add slowly preservative methylparaben and propylparaben to the bulk at 45°C-48°C under constant stirring. Continuous mixing for 15 minute at temperature of 45°C. Cool down to 25°C to 30°C.

Evaluation of transdermal acyclovir cream

Measurement of pH

2.5g gel was accurately weighted and dispersed in 25ml of purified distilled water. The pH of dispersion was measured using cyber pH 14L pH meter which was calibrated before use with buffered solution at 4.0, 7.0 and 9.0 at 25°C. The measurement of pH of each formulation was done in triplicate and average values are calculated⁴.

Determination of Extrudability

Extrudability test is the measure of the force required to extrude the material from a collapsible tube when certain amount of force has been applied on it in the form of weight. The cream formulation was filled in standard capped collapsible aluminum tube and sealed by crimping the ends. The weight of the tube was recorded. The tube was placed between the two glass slides and was clamped. A 500gm of weight was placed over the glass slides and then the cap was removed. The amount of cream extruded was collected and weighed⁴.

Determination of Spreadability

Spreadability is a term expressed to denote the extent of area to which the cream readily spreads on application to skin or affected part. Two glass slides of standard dimensions were selected for this study. The cream formulation whose spreadability was to be determined was placed over one slide and the other slide was placed over the top of the cream such that the cream sandwiched between the two slides was pressed uniformly to form a thin layer. The pressure was removed and the excess of the cream adhering to the slides was scrapped off. The two slides were fixed to a stand without disturbance in such a way that only the lower slide was held firmly by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of the weight tied to it. 20gm weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 6 cm and separate away from the lower slide under the direction of weight was noted. The experiment was repeated and the mean time taken for five such determinations was calculated. The results were recorded and tabulated.

Spreadability is calculated by using the formula -

$$S = ML / T$$

Where, W is the weight tied to upper slide, L is the length of glass slides and T is the time taken to separate the slides⁵.

Drug content

1 g of the each prepared Acyclovir transdermal cream were taken in 100ml volumetric flask containing 20ml of phosphate buffer pH 7.4 and stirrer for 30mins. The volume was made up to 100ml. The solution was filtered through 0.45 μm membrane filter and analyzed at 252 nm spectrophotometrically and the drug content was calculated⁴.

Rheological studies

Rheological studies were carried out on Brookfield LVDV-III ultra viscometer using small sample adapter and SCW-7 spindle. The choice of accessories was based upon the requirement of small sample of acyclovir cream. The data at 10, 20, 30, 40, 50 and 70 RPM was accumulated with respect to % torque, viscosity, shear stress and shear rate at 25 °C for characterization of the prepared systems.

In-vitro skin permeation and release kinetics

The in vitro release of ACV from the cream formulation was studied through freshly excised hairless rat abdominal skin using modified Franz diffusion apparatus. The donor cell was filled with 1 g of Acyclovir cream. The receptor compartment was filled with phosphate buffer pH 7.4. The temperature of the receptor compartment was maintained at 37 ± 0.5 °C by circulating hot water through the jacket of Franz-diffusion cell. The samples were removed at predetermined intervals and replaced immediately with an equal volume of receptor solution to maintain a sink condition. The removed samples were analyzed at 252 nm on UV/VIS spectrophotometer

The data obtained from in-vitro diffusion study of formulations of transdermal Acyclovir cream was fitted to various kinetic models to determine the kinetics of drug release^{6,7,8}.

RESULT AND DISCUSSION

(Refer Table No. 01- 04 & Figure No. 01-02)

The Trial batches formulation of Acyclovir cream showed pH between 5.10 and 7.63 (average 6.4pH), spreadability between 15.11 and 15.49 (average

spreadability 15.3 gmcm/sec) and drug content between 97.89 and 99.62 % (average drug content 98.92 %). Thus all the parameters of formulations of Acyclovir cream were found to be practically within limits. The in-vitro permeation studies of formulations of Acyclovir cream were performed on freshly excised rat abdominal skin. The result showed that Nerolidol having different concentration plays an important role in the enhancement rate(ER). The flux J , permeability coefficient K_p and enhancement rate of enhancer are listed in Table 4. The table shows that, generally all the concentration of Nerolidol used in the study can promote the transport of Acyclovir. Fig. 1 indicates that, as general rule, the highest permeation rate is achieved with the solution containing the highest concentration (4.5%w/w) of Nerolidol. The most outstanding concentration of penetration enhancer was (4.5%w/w), providing an almost 98.86 fold increase in permeability coefficient of acyclovir. In addition to providing the highest (ER), Nerolidol also provided the highest Q_{12} (15613.81 $\mu\text{g}/\text{cm}^2$).

In order to investigate the effect of Nerolidol in formulation, these were compared with a commercial acyclovir cream. The fig. 2 shows that the presence of Nerolidol resulted in profound increase in permeation of acyclovir cream formulation. Moreover, cream formulation containing 4.5%w/w Nerolidol has a higher flux value than the commercial cream. The flux value for the commercial cream and cream formulation containing Nerolidol were 236.53 and 414.37 $\mu\text{g}/\text{cm}^2/\text{h}$, respectively. The obtained R^2 values of zero-order model are nearer to one than the first order and Higuchi model, which suggest that the drug follows zero-order release kinetic. The results of rheological studies indicated that the formulations were non-Newtonian systems because as shear rate changes the formulations showed change in the viscosity. On the basis all the evaluation parameters of formulation including viscosity, spreadability, and extrudability initially and after exposure to accelerated stability conditions and finally on the basis of invitro permeation studies, R5 was selected as optimized formula for topical delivery of acyclovir

Table 1: Manufacturing batches

Ingredient (%w/w)	Batches				
	R1	R2	R3	R4	R5
Acyclovir	5	5	5	5	5
SDG	85	83.5	82.5	81.5	80.5
Nerolidol	--	1.5	2.5	3.5	4.5
TBHQ	0.01	0.01	0.01	0.01	0.01
Methyl paraben	0.2	0.2	0.2	0.2	0.2
Propyl paraben	0.02	0.02	0.02	0.02	0.02
Span 60	2	2	2	2	2
Purified water	7.77	7.77	7.77	7.77	7.77

Table 2: Evaluation of formulation batches

Batch NO.	pH *	Viscosity (Centi-Poise)	Spreadability* (gcm/sec)	Extrudability* (%)	% Drug content*
R1	7.15 ± 0.01	9770	11.54 ±0.26	81 ±0.44	98.52 ± 0.96
R2	6.46 ±0.03	9548	15.34 ±0.24	85 ±0.67	98.47 ± 0.28
R3	6.43 ±0.04	9523	15.49 ±0.14	90 ±0.79	99.67±0.56
R4	6.81±0.12	9223	13.33±0.34	80 ±0.45	99.87±0.30
R5	6.63 ±0.15	9156	15.55±0.35	80 ±0.16	98.98 ±0.17

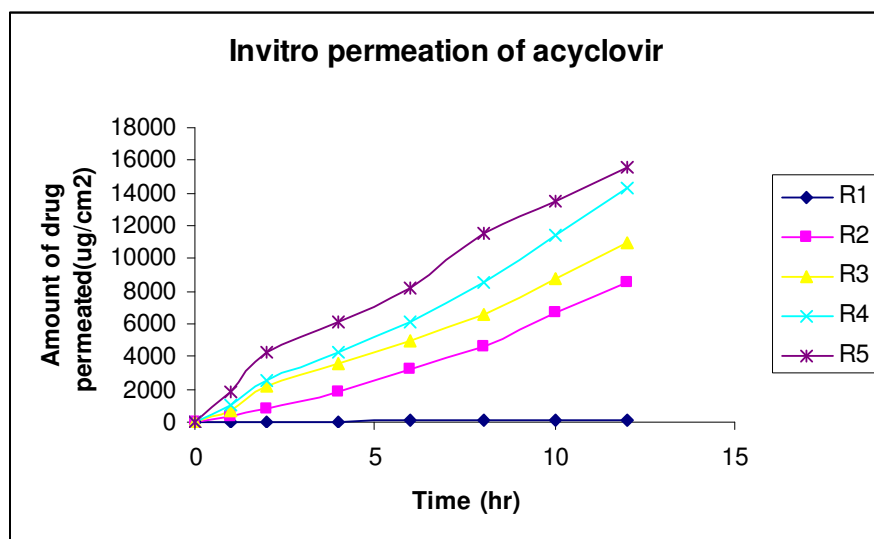
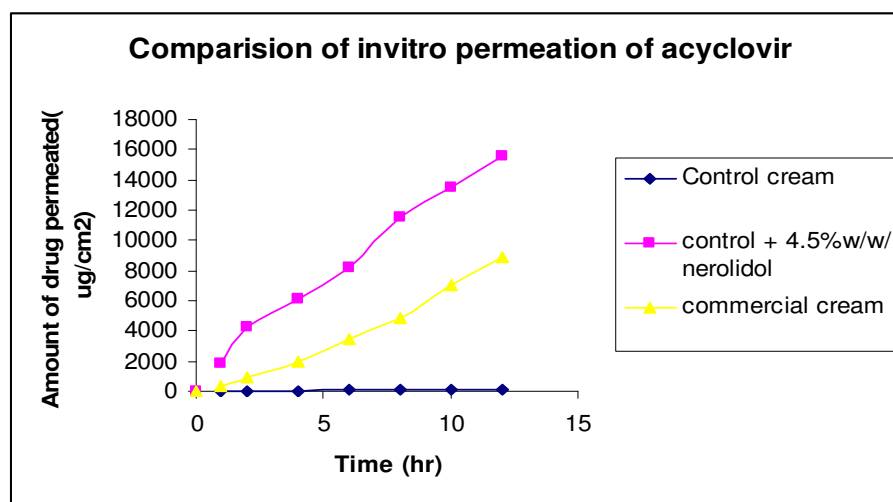
Note: * = Mean ± S.D

Table 3: Results of *In-vitro* skin permeation study of formulation R1-R6

Time (h)	Amount of drug permeated (µg/cm ²)					
	R1	R2	R3	R4	R5	R6(Acyclovir commercial cream)
0	00	00	00	00	00	00
1	7.18	294.52	725.54	1048.8	1788.707	301.81
2	27.53	805.75	2134.71	2533.404	4284.996	904.33
4	53.87	1889.27	3581.007	4241.895	6085.676	1964.37
6	80.21	3239.78	4960.251	6139.553	8245.534	3512.45
8	106.55	4607.05	6605.287	8482.592	11582.3	4823.12
10	132.89	6708.25	8789.091	11463.77	13532.06	7012.23
12	159.23	8514.91	10939.37	14306.07	15613.81	8912.78

Table 4: Results of skin permeation parameters of formulation R1-R6

Batch	Parameters		
	Steady state flux($\mu\text{g}/\text{cm}^2/\text{h}$)	Permeability coefficient ($* 10^3 \text{cm}/\text{hr}$)	Enhancement rate
R1	4.225	0.117	1.00
R2	225.97	6.30	53.84
R3	290.32	8.10	69.23
R4	379.67	10.59	90.51
R5	414.37	11.55	98.79
R6	236.53	6.57	56.15

**Figure 1:** In-vitro permeation-time profile of formulation R1-R5**Figure 2:** In-vitro permeation-time profile of Acyclovir commercial cream, control cream and 4.5% Nerolidol.

CONCLUSION

Present study showed that the nature of Nerolidol exert an important influence on cutaneous barrier impairment. Significantly high flux value was obtained when using Nerolidol as a penetration enhancer. The enhanced permeability flux of acyclovir with *shata-dhauta-ghrita* using 4.5% Nerolidol through skin, was observed in this study may useful in the selection of relatively safe penetration enhancer to aid transdermal drug delivery for the treatment of HSV-1. After the stability period, evaluation of the batches in relation to all the parameters showed that R5 exhibited good results as compared to other batches. The optimized batch shows faster and better drug released than commercial acyclovir cream.

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