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Original Article

Comparitive Evaluation of Proniosome Hydrocortisone Gel with Marketed Formulation

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ABSTRACT

Hydrocortisone is found to have 10% absorption through topical route. It is also affected by pharmacokinetic parameters like plasma half life, plasma protein binding. To improve the absorption of caroticosteroid thruough skin. Proniosome approach was tried using a less potent hydrocortisone. After Pre formulation studies non-ionic surfactant ratio 1:9 shows better vesicle formation than the 1:1and 9:1. Hence Proniosome Hydrocortisone gel with different non ionic surfactants in 1:9 ratio containing 1% and 2.5% Hydrocortisone with Soya lecithin was formulated. Vesicle size of proniosome hydrocortisone gel formulations was determined using optical microscope. Vesicles obtained from Span combination formulations was found in the size range 3 – 6 µm and Span, Tween combination formulations 4 – 7 µm. Encapsulation of Proniosomal hydrocortisone gel prepared using different surfactant combinations was determined by ultra centrifugation.The percentage entrapment of hydrocortisone gel varies from 27 – 89 %. Drug content of proniosome hydrocortisone gel shows 1 % PHG formulations having uniform distribution than in 2.5 % PHG formulations, but drug concentration is more in 2.5 % PHG formulations. Drug release from proniosome gel was determined using dialysis membrane. Proniosome hydrocortisone gel formulation was compared with marketed 1 % hydrocortisone cream. The initial hour release from marketed formulation was found to be high when compared with PHG 1 %. But the cumulative percent release from 1 % hydrocortisone cream was not proper and linear with respect to time when compared to 1 % PHG formulation. Maximum 34.7 % of drug was found to be release from marketed 1 % cream through dialysis membrane in 2 hr. whereas 58 % of drug was found to be release from (S20: 80 1 %) PHG formulation showed extend release up to 8 hr. Cumulative release comparison for 1 % PHG formulation with marketed 1 % hydrocortisone cream. The cumulative release from 2.5 % PHG formulation shows sustained release similarly as 1 % PHG. But here good release was shown from S20:40 (53.81 %) and poor from S20: 80 (29.05 %).In 1 % PHG formulation S20: 80 (58.29%) shows good release and S20: 60 (35.06 %) shows poor release. Comparative release.Cumulative release in Span combinations S20:80 1 % (58.29 %) shows high and S20: 80 2.5 % (29.05 %) was poor. And from Span, Tween combinations S20: T40 2.5 % was high and S20: T60 2.5 % (31.23 %) was poor. *In vitro* results show S20:80 combinations with 1 % drug concentration 58.29 ± 0.626 having good release than other formulations.

1. INTRODUCTION

Hydrocortisone is given by topical application for its anti-inflammatory effect in allergic rashes, eczema and certain other inflammatory conditions. Hydrocortisone

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is synthetic carticosteriod and it is also a proved anti- inflammatory drug. Hydrocortisone is available in different dosage forms for topical treatment. Hydrocortisone is available with salt formations like hydrocortisone acetate, hydrocortisone butyrate,hydrocortisone sodium sucinate and other salt formations. Hydrocortisone is found to have 10% absorption through topical route. It is also affected by pharmacokinetic parameters like plasma half life, plasma protein binding. To improve the absorption of caroticosteroid thruough skin. Proniosome approach was tried using a less potent hydrocortisone.The objective of the study is to explore proniosomes for the delivery of hydrocortisone through transdermal route. To enhance the transport / permeation of drug through skin without side effects. To increase sustain pharmacodynamic activityof drug. [1]

2. MATERIALS AND METHODS

Hydrocortisone USP from SAMARTH LABS, Soya lecithin (phosphatidyl choline) from Hi-Media laboratories,Cholesterol from LOBA CHEMIE and Dialysis Membrane was purchased from Hi-Media Laboratories (Mumbai, India).

2.1 Experimental Work

Standard Plot of Hydrocortisone:

Standard stock solution was further diluted to get the different concentrations like 2,4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml to determine the linearity range. Linearity was obtained in the above concentration at 248 nm using UV Spectrophotometer .

Pre Formulation study:

Proniosomal gel was prepared by a coacervation-phase separation method .Precisely weighed amounts of surfactant, lecithin, cholesterol were taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and ethyl alcohol and water was added to it. After warming, all the ingredients were mixed well with a glass rod; the open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture was dissolved completely. Then the aqueous phase (0.1% glycerol solution) was added and warmed on a water bath till a clear solution was formed which was converted into Proniosomal gel on cooling. [2]

Formulation procedure: The proniosome hydrocortisone gel was prepared with 1 % and 2.5 % drug concentration with the same procedure described above using appropriate ratio of surfactants. The proniosome hydrocortisone gel formulation compositions.

2.2 Characterization of Proniosomal Gel

Vesicle Size Analysis:

Proniosomal hydrocortisone gel (100 mg) was hydrated in saline solution (0.9% solution) in a small glass vial with occasional shaking for 10 min. The dispersion was observed under optical microscope. The size of 50 vesicles was measured using a calibrated ocular and stage micrometer fitted in the optical microscope. Vesicle size is calculated using Equation 1. [2]

$$\text{Size of each division} = \frac{\text{Number of divisions of stage micrometer}}{\text{Number of divisions of eye piece micrometer}} \times 10$$

Encapsulation Efficiency:

Encapsulation of hydrocortisone drug in Proniosomal gel was evaluated by dispersing the Proniosomal hydrocortisone gel (100 mg) in distilled water and the dispersion was warmed gently for the formation of niosomes. Then the dispersion was centrifuged at 13000 rpm for 1hr at 50C. The supernatant was taken for the determination of free drug at 248 nm spectrophotometrically. [3, 4]

The percentage encapsulation efficiency was calculated from Equation 2.

% Encapsulation Efficiency = [(Ct - Cr)/Ct] X 100__ (2) where, Ct – Concentration of total

Hydrocortisone. Cr – Concentration of free drug in supernatant solution.

2.3 Drug content uniformity:

Formulated Proniosomal gel was mixed well and 100 mg of gel was weighed and transferred into vial. The gel was dissolved in 25 ml of phosphate buffer saline (pH7.4) with vigorous shaking, and the solutions were assayed for hydrocortisone content at 248 nm. Amount Drug content present in 100 mg gel was calculated by

Amount of drug = [(concentration) x (1) x (100) / 1000] Æ

2.4 In vitro release studies*:*

Release from proniosome hydrocortisone gel was carried out using Himedia dialysis membranes 50 with the molecular weight cut-off range from 12000 - 14000. A weighed amount of (100 mg) Proniosomal gel formulation was dispersed in the dialysis membrane and the open ends of the membrane were covered with membrane closure clips. The membrane containing gel formulation was allowed to dip in 50 ml of receptor medium pH 7.4 phosphate buffer saline. The receptor medium was stirred using magnetic bead fitted to a magnetic stirrer at 60 rpm. Samples were withdrawn and replaced by equal volumes of fresh receptor medium at each sampling intervals to maintain sink condition. Samples withdrawn were analyzed by using spectrophotometer at 248 nm. [5, 6]

3. RESULTS AND DISCUSSION

Hydrocortisone is a synthetic corticosteroid drug which may be given by injection or by topical application. It is given by topical application for its anti-inflammatory effect in allergic rashes, eczema and certain other inflammatory conditions. Hydrocortisone is available in creams, lotions for topical application but it is affected by number of pharmacokinetic parameters like drug absorption ,plasma half life ,plasma protein binding.[7, 8]

3.1 Standard curve:

Spectrum of hydrocortisone was determined by double beam UV visible spectrophotometer in the spectrum mode range from 400 nm to 200nm with appropriate dilution of standard stock solution. Standard plot for hydrocortisone was carried out in spectrophotometry at 248 nm by different concentrations of stock solution like 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml.

3.2 Pre formulation:

Proniosomes a novel drug delivery system for topical application was investigated in this study. Proniosome hydrocortisone gel formulations with non ionic surfactants combination were prepared by coacervation-phase separation method after optimizing the non-ionic surfactant ratio for vesicle formation in different combination of surfactants

Formulation: After Pre formulation studies non-ionic surfactant ratio 1:9 shows better vesicle formation than the 1:1and 9:1. Hence Proniosome Hydrocortisone gel with different non ionic surfactants in 1:9 ratio containing 1% and 2.5% Hydrocortisone with Soya lecithin was formulated.

3.3 Determination of vesicle size: Vesicle size of proniosome hydrocortisone gel formulations was determined using optical microscope. Vesicle formation was good in S20:80 1 % (PHG 3) combination showed in and poor in S20: T80 2.5 % (PHG) combination .Vesicle formation and size was good in S20:80 and poor in S20:T80 in 1 % PHG formulations. Vesicle formation and size was good in S20: 40 and poor in S20:T80 when comparing in 2.5 % PHG formulations. Vesicles obtained from Span combination formulations was found in the size range 3 – 6 µm and Span, Tween combination formulations 4 – 7 µm.

***3.4 Encapsulation efficiency*:** Encapsulation of Proniosomal hydrocortisone gel prepared using different surfactant combinations was determined by

ultra centrifugation.The percentage entrapment of hydrocortisone gel varies from 27–89 %. Entrapment was high in S20: 40 (89.67 %) and poor in S20:T80 (27.2 %) in 1% proniosome hydrocortisone gel. And in 2.5 % proniosome hydrocortisone gel entrapment was found high in S20:40 (83.55 %) and poor in S20: T80 (57.34 %). This shows the entrapment of S20:40 are high and S20: T80 are poor in both 1 % and 2.5% formulations . Among the 12 PHG formulations entrapment efficiency was high in S20:40 1 % (89.67 %) and poor in S20:T80 1 % (27.20 %). High entrapment in Span combinations may be due to hydrophobic nature of surfactants and drug.

Table 1: Formulation using different ratios of Non ionic surfactant

S.No.	Surfactant Type	Ratio	Soya lecithin (mg)	Cholesterol (mg)	Ethanol (ml)	Water (ml)
1	S20:S40	1:9	100	100	2	0.5
		1:1				
		1:9				
2	S20:S60		100	100	2	0.5
		1:1				
2			100	100	2	0.5
		1:9				
3	S20:S80		100	100	2	0.5
		1:1				
3			100	100	2	0.5
	S20:S80	9:1				

Table 2: Composition of Hydrocortisne gel formulation

S.No.	Formulation Type	Drug conc.	Surfactant Type	Ratio	Lecithin (mg)	Cholesterol (mg)	Ethanol (ml)	Water (ml)
1	PHG 1	1%	S20:S40	1:9	100	100	2	0.5
2	PHG 2	1%	S20:S60	1:9	100	100	2	0.5
3	PHG 3	1%	S20:S80	1:9	100	100	2	0.5
4	PHG 4	1%	S20:T40	1:9	100	100	2	0.5
5	PHG 5	1%	S20:T60	1:9	100	100	2	0.5
6	PHG 6	1%	S20:T80	1:9	100	100	2	0.5
7	PHG 7	2.5 %	S20:S40	1:9	100	100	2	0.5
8	PHG 8	2.5 %	S20:S60	1:9	100	100	2	0.5
9	PHG 9	2.5 %	S20:S80	1:9	100	100	2	0.5
10	PHG10	2.5 %	S20:T40	1:9	100	100	2	0.5
11	PHG 11	2.5 %	S20:T60	1:9	100	100	2	0.5
12	PHG 12	2.5 %	S20:T80	1:9	100	100	2	0.5

Table 3: Vesicle Size Determination by Optical Microscope

S.No	Formulation Type	Surfactant Type	Drug conc.	Vesicle size Range (µm)	Average size (µm)
1	PHG 1	S20:S40	1%	2 – 6	3
2	PHG 2	S20:S60	1%	2 – 8	4
3	PHG 3	S20:S80	1%	2 – 12	4.5
4	PHG 4	S20:T40	1%	2 – 12	4
5	PHG 5	S20:T60	1%	2 – 10	3.5
6	PHG 6	S20:T80	1%	2 – 8	3
7	PHG 7	S20:S40	2.5%	2 – 8	4
8	PHG 8	S20:S60	2.5%	2 – 14	5
9	PHG 9	S20:S80	2.5%	4 – 12	6
10	PHG 10	S20:T40	2.5%	2 – 16	6.5
11	PHG 11	S20:T60	2.5%	2 – 20	7
12	PHG12	S20:T80	2.5%	4 – 10	6

Table 4: Entrapment efficiency of Hydrocortisone

S.No	Surfactant Type	% Entrapment
1	PHG 1 (S20, S40 1%)	89.67%
2	PHG 2 (S20, S60 1%)	79.66%
3	PHG 3 (S20, S80 1%)	70.66%
4	PHG 4 (S20, T40 1%)	58.88%
5	PHG 5 (S20, T60 1%)	65.15%
6	PHG 6 (S20, T80 1%)	27.20%
7	PHG 7 (S20, S40 2.5%)	83.55%
8	PHG 8 (S20, S60 2.5%)	80.00%
9	PHG 9 (S20, S80 2.5%)	76.42%
10	PHG 10(S20, T40 2.5%)	76.12%

11	PHG 11(S20, T60 2.5%)	77.02%
12	PHG 12(S20, T80 2.5%)	57.34%

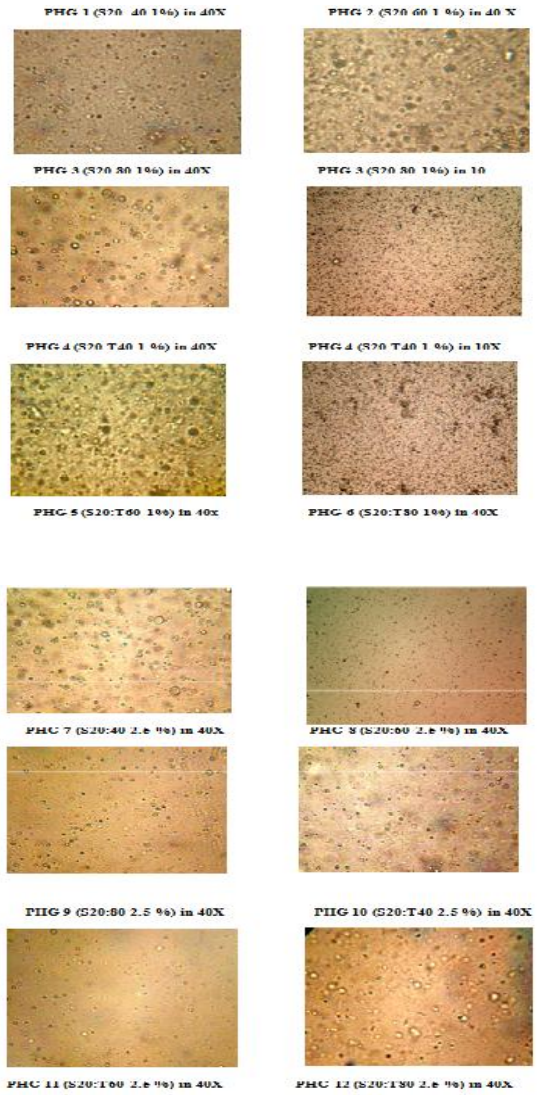
3.5 Drug content uniformity:

Drug content of proniosome hydrocortisone gel was calculated (equation 3) and percentage drug content each formulation. Drug content of proniosome hydrocortisone gel shows 1 % PHG formulations having uniform distribution than in 2.5 % PHG formulations, but drug concentration is more in 2.5 % PHG formulations.

3.6 In Vitro release*:*

Drug release from proniosome gel was determined using dialysis membrane. Proniosome hydrocortisone gel formulation was compared with marketed 1 % hydrocortisone cream. The initial hour release from marketed formulation was found to be high when compared with PHG 1 %. But the cumulative percent release from 1 % hydrocortisone cream was not proper and linear with respect to time when compared to 1 % PHG formulation. Maximum 34.7 % of drug was found to be release from marketed 1 % cream through dialysis membrane in 2 hr. where as 58 % of drug was found to be release from (S20: 80 1 %) PHG formulation showed extend release up to 8 hr. Cumulative release comparison for 1 % PHG formulation with marketed 1 % hydrocortisone cream. The cumulative release from 2.5 % PHG formulation shows sustained release similarly as 1 % PHG. But here good release was shown from S20:40 (53.81 %) and poor from S20: 80 (29.05 %). In 1 % PHG formulation S20: 80 (58.29%) shows good release and S20: 60 (35.06 %) shows poor release. Comparative Cumulative release in Span combinations S20:80 1 % (58.29 %) shows high and S20: 80 2.5 % (29.05 %) was poor. And from Span, Tween combinations S20: T40 2.5 % was high and S20: T60 2.5 % (31.23 %) was poor.*In vitro* results show S20:80 combinations with 1 % drug concentration 58.29 ± 0.626 having good release than other formulations.

3.7 Release Kinetics: Release kinetic parameters of proniosome hydrocortisone gel 1 % (S20:80) was carried out using zero order, first order, Higuchi and Peppas kinetics. Regression value of PHG 1 % (S20:80) was 0.99833 for zero order and 0.9631 in first order. Results show the formulation obeys mixed order kinetics. The Higuchi plot value for proniosome hydrocortisone gel 1 % (S20:80) was more than 0.998. Hence it follows diffusion release mechanism. The slope value of Peppas plot was 0.8930 which confirms non fickian diffusion.



4. CONCLUSION

The proniosome hydrocortisone gel 1% and 2.5% was prepared by using various surfactant combinations by coacervation phase separation method. The *in-vitro* permeation of different formulations containing mixture of non-ionic surfactants have been studied and evaluated. The cumulative release from (S20: 80 1 %) PHG was 58.92 ± 0.627. Proniosome hydrocortisone gel shows diffusion release type which was confirmed by Higuchi and Peppas plot. Comparison of Proniosome formulation with marketed 1 % hydrocortisone cream, proniosome formulation shows better cumulative release than in marketed formulation. Phospholipids and non-ionic surfactants in an optimum ratio in the Proniosomes may act as penetration enhancers, which are useful for increasing the permeation of hydrocortisone through skin.

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