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FORMULATION AND EVALUATION OF FILM FORMING GEL: CLOBETASOL PROPIONATE

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ABSTRACT

The main challenge facing pharmaceutical research is the creation of new technologies that will give formulations unique properties that overcome the therapeutic constraints of conventional dosage forms, such as adjustable release profiles, flexibility of use, capacity to carry multiple active ingredients, increased patient availability, and compliance. Compared to other forms, these systems offer easier use and application, appropriate consistency and adhesiveness, good flexibility and elasticity and ease of manufacturing.

Keywords: Dermatology, Clobetasol Propionate, Therapeutic effect, Film Forming Gel.

INTRODUCTION

Pharmaceutical formulations that are successful should be able to transport active ingredients to the organs that need them at therapeutically relevant concentrations while causing the patient a minimum amount of discomfort and unwanted effects. In dermatological treatment, improving clinical high drug levels in specific strata of the skin should be the goal of successful pharmaceutical formulations [1].

These formulations should also deliver active substances to the target organs at therapeutically relevant levels, all while causing the patient negligible discomfort and side effects. When treating dermatological conditions, it is necessary to achieve high drug levels in certain layers of the skin in order to improve clinical efficacy, while at the same time minimizing the drug's systemic absorption. In disorders such as eczema, psoriasis, and dermatitis, fast entry of topically administered corticosteroids into the circulation leads in short duration of local impact and unwanted systemic toxicity on chronic usage [2].

The film forming system is an innovative method that can be utilized as an alternative to traditional topical and transdermal formulations. Film-forming gels are designed to be applied to the skin as an emollient or a protective layer, as well as for the local action of medication or the transdermal penetration of medication for systemic action. After being applied to the skin, it results in the creation of film on the surface of the skin due to the loss of the volatile components of the vehicle, which causes the production of residual film [5]. During this stage of the process, the concentration of the drug rises, eventually reaching the point of saturation and with the potential to reach the point of supersaturation on the surface of the skin. As a result of an increase in thermodynamic activity, supersaturation causes an increase in the rate at which drugs pass through the skin. The modified form of Fick's law of diffusion is able to provide an explanation for the concept of supersaturation [3].

Therefore, in order to effectively treat inflammatory skin conditions, the topical corticosteroid that is used must be diffuse. Therefore, a perfect topical corticosteroid for the treatment of inflammatory skin diseases should be able to diffuse through the stratum corneum (SC) in order to achieve therapeutically relevant concentrations at the skin disease sites. This should be accomplished without leading to high serum levels or systemic exposure. This is especially true for treatment that is administered topically on a prolonged basis [8]. In order to accomplish the objectives of medication targeting to the skin, it is necessary to establish clinically relevant concentrations at disease sites on the skin while avoiding high serum levels and systemic exposure [4].

METHODOLOGY

SOLUBILITY STUDY:

Solubilty of the Clobetasol propionate λ max was tested in various solvents according to the standard procedure.

Determination of Λ Max Clobetasol Propionate:

In phosphate buffer pH 7.4 Stock solution was prepared by dissolving 100mg of pure drug in 100ml of

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methanol, this was designated as stock solution A (1mg/ml). 10ml of the stock solution was taken in 100ml volumetric flask and made up to 100 ml with Phosphate buffer pH 7.4. This was designated as stock solution B (100 mcg/ml). This stock solution B is further diluted to get 10mcg/ml. The above solution was scanned between 200-400 nm after suitable dilution.

Standard graph of clobetasol propionate:

From the above stock solution B aliquots of dilutions are made with Phosphate buffer pH 7.4 to get concentration of 2, 4, 6, 8, 10, 12, 14, 16 and 18mcg/ml. The absorbance of these solution was measured at 241 nm and a graph was drawn with concentration on X axis and absorbance on Y axis [5].

Infrared spectroscopy:

The IR studies were performed for Clobetasol propionate and the drug with different polymers used in the formulation. The spectra studied at 4000cm-1 to 400 cm.

Formulation development:

The gel was prepared using high speed homogenizer rotated at 1500 rpm. HPMC K100M dispersed in water taken in a beaker. The dispersion was kept undisturbed for one hour. Clobetasol propionate was dissolved in about 3 ml of ethanol and mixed the gel was prepared using high speed homogenizer rotated at 1500 rpm. HPMC K100M was dispersed in water taken in a beaker. The dispersion was kept undisturbed for one hour. Clobetasol propionate was dissolved in about 3 ml of ethanol and mixed thoroughly with the HPMC dispersion until a uniform dispersion is formed. Then film forming polymer was dissolved in sufficient quantity of ethanol previously mixed with Polyethylene glycol and the solution was mixed with the dispersion of HPMC and Clobetasol propionate until a uniform dispersion was obtained. Mixture of Menthol and Camphor (1:1) was dissolved in propylene glycol and added to the dispersion and it was thoroughly mixed for about two hours to obtain a smooth uniform dispersion. The formulated gel was packed in a collapsible tube [6]**.**

EVALUATION OF FILM FORMING GEL:

Properties of gel Ph:

The pH measurement of each of the formulation was done in triplicate form and mean values were calculated**.**

Viscosity:

The viscosity reading was noted down. The average of three readings was taken in 10 minutes was noted as the viscosity of gel**.**

Spreadability:

100 mg of the sample was kept at the center of a glass slide. The slide was covered with another slide and the slides were pressed between fingers until no more expansion of the circle formed by the gel between the slides is observed. The diameter of the circle formed by the gel is measured in centimeters**.**

Drying time:

For the assessment of the drying time the formulation was applied to the glass slide. After 2 minutes another glass slide was placed on the film without pressure. If no remains of liquid were visible on the glass slide after removal, the film was considered dry. If remains of liquid were visible on the glass slide the experiment was repeated until the film was found to be completely dry**.**

Drug content:

10 mg equivalent of gel was taken in a 100 ml volumetric flask containing 10 ml methanol and volume was made up to the mark with methanol to get a concentration of 100µg/ml. An aliquot of 0.5 ml was transferred to a 10 ml volumetric flask and volume was made up with methanol. The absorbance of prepared solution was measured at λ max by using UV visible spectrophotometer [7]**.**

Properties of film:

The films were left to dry for 72 hours at room temperature (three hours ventilated in the open air to allow the evaporation of ethanol**.**

Bioadhesion test:

Total number of squares of the film that adhered on the tape was determined and percentage peel off was determined by the formula.

Percentage peel off =Initial squares of film/Final squares of filmInitial squares of film ×100

Film thickness:

The films were cut into size of 10 x 40 mm and the thickness of the film using a digital vernier caliper. Each film was measured at five positions (central and the four corners) and the mean thickness was calculated**.**

Film stickness:

This parameter of assessment is important, as the developed formulation is supposed to be non sticky to prevent sticking to the clothing of the patients**.**

Folding endurance:

Folding endurance was measured manually for the prepared films. A strip of film (10 x 40 mm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Weight variation test:

For each formulation, three film samples (10 x 40 mm) were used. Each film sample was weighed individually and the average weight was calculated**.**

Drug content of film:

Prepared film was put into 100 ml phosphate buffer solution pH 5.8 and stirred vigorously for 2 hours. Then the whole solution was sonicated for 15 minutes. The above solution was filtered and drug was estimated spectrophotometrically at λ max [8]**.**

Water vapour permeability:

The water vapour permeability (WVP) was investigated according to a method modified from the British Pharmacopoeia, the time (t, 24 hours) using the following formula:

WVP = W/ (A*t) (g cm-2 24 hrs)

Invitro drug diffusion study:

The whole assembly was fixed on a magnetic stirrer. The receptor compartment with 100 ml PBS was placed on a thermostatically controlled magnetic stirrer. It was maintained at 37 ± 0.5 0 C stirred constantly at 50 rpm. Samples of 1 ml were collected at predetermined time intervals and analyzed for drug content by UV Spectrophotometer at λ max against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal**.**

Kinetic modeling and mechanism of drug release:

Determination of the release pattern of the prepared film forming gel formulation, the data of ex-vivo release was considered & it is treated by several mathematical models which are zero order, first order, higuchi & korsmeyerpeppas model. In which the R (correlation coefficient), n (diffusion exponent) and K (release constant) values getting from curve fitting of release data were determined a model which is suitable for the film forming formulation [9].

RESULTS AND DISCUSSION

Preformulation study:

Solubility studies:

The solubility of Triamcinolone was determined in various solvents and it was observed that the solubility of drug is better in Methanol when compared to other solvents.

Determination of wavelength:

The λ max of Triamcinolone was determined by scanning the diluted concentration of drug solution (10µg/ml) in phosphate buffer pH 7.4 by UV Spectrophotometer in the UV range of 200-400 and at 239nm maximum absorbance was obtained and thus the λ max of drug was identified.

PREPARATION OF CALIBRATION CURVE:

The calibration curve of Triamcinolone drug was done by accurately weighing 100mg of pure drug and made up to 100ml with methanol which is Stock-A 10ml was taken from stock-A and made up to 100ml using Phosphate buffer 7.4 which is Stock B

From this dilution like 2,4,6,8,10,12,14,16 and 18 were made accordingly using phosphate buffer 7.4 and the regression value was found to be 0.9998.

Infrared spectroscopic analysis:

Infrared spectroscopic studies were carried out to confirm the compatibility between drug and the excipients used for the preparation of Film Forming gel and to identify the possible interactions. The IR studies were performed for Triamcinolone, HPMC K100M, Eudragit RL100, Eudragit RS100 and physical mixture of drug and excipients. The spectra studied at 4000cm-1 to 400 cm^{-1}. The principle peaks and physical mixture peaks of the drug appear in the spectrum indicates that there was no interaction between drug and the excipients in the formulation.

Formulation of triamcinolone film forming gel:

The film forming gel formulation was prepared by using HPMC 100M as gelling agent and Eudragit RS100 and Eudragit RL100 as film forming polymer. The gels were prepared in ethanol by dispersion method. Ten different batches of gels were prepared by varying the concentration of film forming polymer.

EVALUATION OF FILM FORMING GEL:

pH:

The pH value of Film Forming gel formulation is shown in table.8. They were found to be in the range of 4.5 to 6.8. This is considered to be close to the pH of skin and is considered as satisfactory for application with minimal risk of tissue irritation or discomfort due to acidic pH.

Spreadability:

The diameter of the gels spreading following the spreadability test are found to be between 4.13 to 5.53 cm.

Viscosity:

The viscosity of developed formulations was evaluated by using Brookfield viscometer.

Drying time:

The drying time or film formation time has been tabulated in table no.10. Ideally film forming gel should dry to form thin film on skin application within 5 to 7 mins, so as to minimize discomfort to the patient. All the formulations showed satisfactory results within the acceptable range.

Weight variation test:

The films were tested for weight variation. Weight of the films was found to be in the range of 0.0412g to 0.063g. As the concentration of polymer increased, the weight of the film also increased.

Film thickness:

Formulations were capable of giving films with a thickness ranging from 0.0335mm to 0.071mm. As the concentration of polymer increased, there was increase in the thickness of films due to higher amount of polymer used.

Film stickness:

The results for outward stickness of the all formulations have been tabulated.

Drug content of film:

The content uniformity was performed for all the formulations and results are shown in tabulated. The drug content of each formulations were analyzed spectrophotometrically. The drug content of the film was found between 89.88% to 97.93% of Clobetasol propionate.

Folding endurance:

Folding endurance measures the ability of the film to withstand rupture. Higher the folding endurance lower will be the chances of film rupture. The folding endurance values were found between 12 to 21.

Bioadhesion test:

Bioadhesion of the film formed on drying must be sufficient to ensure that it remains adherent to the skin for the duration of 24hrs.

Water vapour permeablity:

Water vapour permeability test are represented and show that film had water vapour permeability ranging from 0.017 to 0.046 g cm-1h-1. As the water vapour permeability of films exceed the limit of 0.05 g cm-1h-1, the films are considered permeable to water vapour and can therefore be non-occlusive.

In–vitro Drug Diffusion Study:

From these data we have found that the prepared Film Forming gel releases drug over a period of 12 hrs. The data for the in-vitro drug diffusion study of prepared topical gel. The graphical representation of in-vitro drug diffusion study of topical gel.

The formulations F1 to F5 consist of Eudragit RL100 increases the percentage of drug release while increasing the concentration of the polymer. But the formulations Consist of Eudragit RS 100 decreases the percentage of drug release while increasing the concentration of the polymer and sustain the release of drug for prolonged period of time. The formulation F10 containing 12.5% of Eudragit RS100 was selected as best formulation, for sustain the release of drug.

Table 1: pH, Spreadability, Viscosity.

FORMULATION CODE	pH	SPREADABILITY DIAMETER (cm)	VISCOSITY
F1	5.9±0.030	5.03±0.15	12500
F2	5.7±0.032	4.8±0.17	12650
F3	5.01±0.025	4.8±0.05	12800
F4	5.8±0.025	4.13±0.20	12960
F5	5.4±0.02	5.56±0.20	13200
F6	5.5±0.035	5.53±0.15	12700
F7	4.9±0.020	5.23±0.15	12940
F8	5.3±0.026	4.8±0.15	13300
F9	5.2±0.020	4.8±0.20	13600
F10	5.8±0.020	5.73±0.32	13900

Table 2: Drying Time, Weight Variation

FORMULATION CODE	DRYING TIME	WEIGHT VARIATION(g)
F1	5mins 38secs±12 secs	0.0529± 0.03
F2	6mins 10secs±20 secs	0.0543± 0.02
F3	5mins 16secs±25 secs	0.0548± 0.04
F4	4mins 11secs±17 secs	0.0592± 0.03
F5	4mins 58secs±10 secs	0.0623± 0.01
F6	5mins 35secs±18 secs	0.0582±0.03
F7	5mins 43secs±25 secs	0.0456± 0.03
F8	6mins 46secs±20 secs	0.0505± 0.02
F9	4mins 43secs±25 secs	0.0546± 0.03
F10	4mins 13secs±25 secs	0.0412± 0.01

Table 3: Thickness of the Films and Outward stickness of the films

FORMULATION CODE	FILM THICKNESS (mm)	FILM STICKNESS
F1	0.032± 0.02	Fair
F2	0.048± 0.02	Good
F3	0.052± 0.03	Fair
F4	0.063± 0.01	Good
F5	0.075± 0.01	Good
F6	0.038± 0.02	Good
F7	0.047± 0.01	Good
F8	0.056± 0.02	Fair
F9	0.069± 0.02	Good
F10	0.071± 0.01	Good

Table 4: Content uniformity of the film, Folding endurance of the formulations and Percentage peel off developed films

FORMULATION CODE	DRUG CONTENT	FOLDING ENDURANCE (no.of.folds)	% PEEL OFF	WATER VAPOUR PERMEABILITY (g cm-1h-1)
F1	91.85%	15	5	0.041
F2	94.86%	12	5	0.046
F3	97.03%	16	8	0.035
F4	93.65%	18	10	0.029
F5	97.76%	21	10	0.026
F6	95.84%	20	5	0.045
F7	90.78%	18	5	0.017
F8	97.24%	20	10	0.043
F9	89.88%	16	0	0.038
F10	97.93%	22	0	0.019

Table 5: Percentage cumulative drug release of developed Film Forming gel (F1-F5)

% CUMULATIVE DRUG RELEASE					
TIME (Hrs)	F1	F2	F3	F4	F5
0.5	1.42	2.71	2.28	3.21	4.81
1	3.15	4.86	4.20	5.69	8.55
2	5.37	7.40	6.87	8.96	13.34
3	8.47	11.04	10.41	12.83	18.54
4	12.06	14.63	14.49	17.19	24.61
5	16.63	18.88	19.50	19.07	31.05
6	21.97	23.71	25.49	25.01	38.30
8	28.30	29.02	32.70	32.36	46.12
10	34.85	34.20	41.80	40.94	53.97
12	45.68	47.41	52.36	56.00	66.43

Table 6: Percentage cumulative drug release of developed Film Forming gel (F6-F10).

% CUMULATIVE DRUG RELEASE					
TIME (Hrs)	**F6**	**F7**	**F8**	**F9**	**F10**
0.5	4.16	1.62	2.60	3.48	1.01
1	8.20	4.31	4.71	6.39	3.57
2	12.37	8.23	7.67	9.87	6.38
3	17.21	12.74	11.19	13.24	9.66
4	22.54	17.65	15.15	17.33	13.22
5	29.05	23.57	20.28	22.13	17.86
6	36.02	30.25	26.11	27.19	22.65
8	44.03	37.65	32.41	32.82	28.02
10	52.14	45.37	39.61	38.53	33.55
12	66.84	59.89	53.21	45.75	43.59

Table 7: Kinetic modelling and drug release mechanism of F10

Formulation	Kinetic models					
	Zero order	Higuchi	Peppas		First order	Hixon crowel
	R^2	R^2	R^2	n	R^2	R^2
F10	0.9955	0.9293	0.9913	0.830	0.9706	0.9851

Figure 1: Wavelength

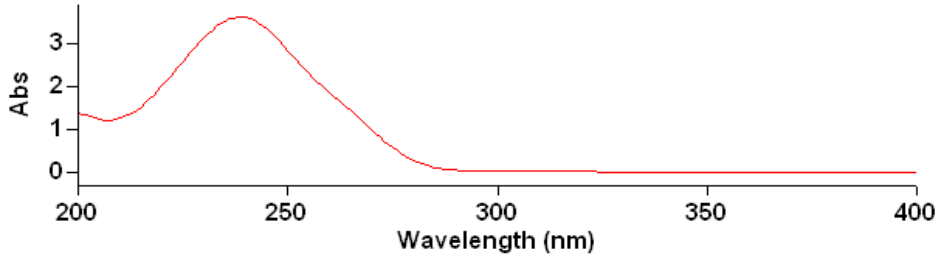


Figure 2: Calibration curve of Clobetasol propionate

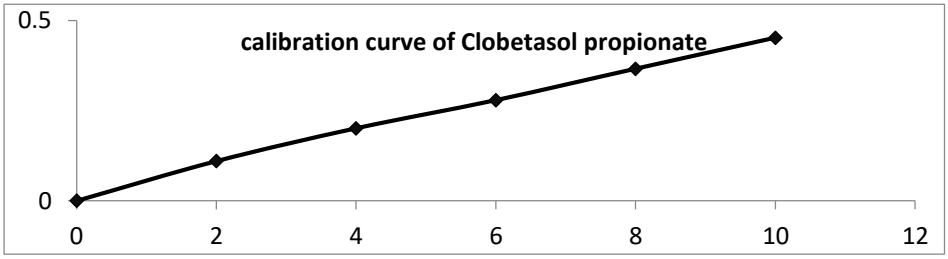


Figure 3: IR spectrum of Triamcinolone.

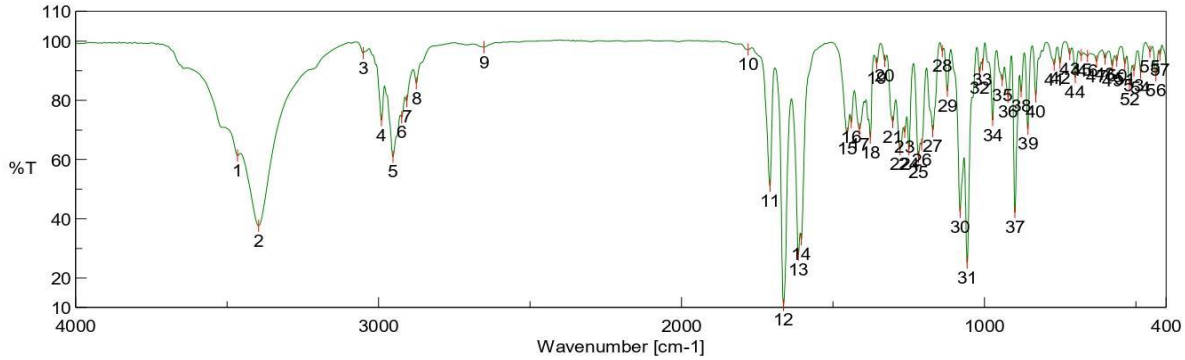
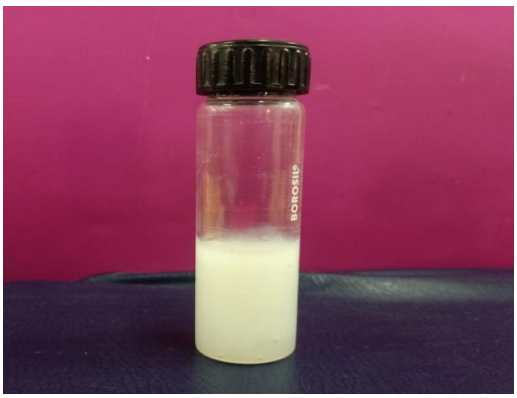
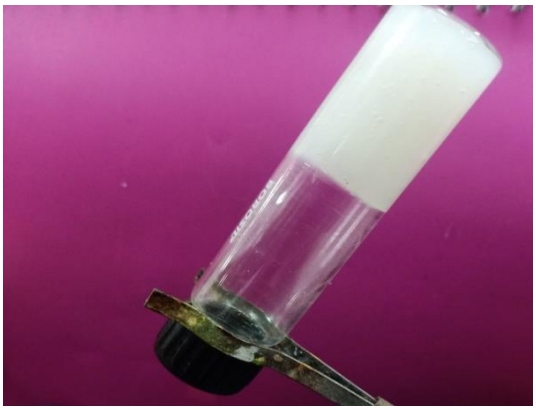


Figure 4: Triamcinolone Film Forming gel





KINETIC ANALYSIS

Kinetic analyses of in vitro drug release data for formulation (F10) was studied shown in the examination of the regression coefficient values (R^2) indicated that the drug release followed diffusion-controlled mechanism. The results of the release kinetics elucidated from the Korsmeyer–Peppas equation show that the release exponent values (n) for the formulation was within the range of $0.5 < n < 1.0$; this indicates non-Fickian (anomalous) release mechanism in these formulations.

CONCLUSION

From the above studies, it is revealed that the present work was a satisfactory preliminary study of improving patient compliance by development of transdermal delivery of Clobetasol propionate. Optimized formulation shows a sustained drug release profile suggests that Clobetasol propionate release was predominantly controlled by the diffusion process. It could be applied on the skin easily and can be an innovative and promising approach for the administration of Clobetasol propionate for the treatment of psoriasis.

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