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ROPINIROLE FILM-FORMING GEL: FORMULATION AND CHARACTERIZATION

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ABSTRACT
The skin is a very attractive organ for the application of pharmaceutically active substances due to its considerable size and easy accessibility. The aim of the drug administration via the skin can be either the local therapy of dermatological diseases or the transdermal delivery of drugs to the underlying tissues or the systemic circulation. Although much work has been done to improve the appearance of the patches some are still criticized by patients for their high visibility and the resulting lack of discreetness. An example for a highly visible finally it has to be pointed out that the production of polymeric patches requires specialized production equipment and generates considerable manufacturing costs.

Keywords: Formulation, Characterization, Ropinirole, Film Forming Gel

INTRODUCTION

Introduction to film forming systems Film forming system (FFS) is a novel approach to the transdermal and dermal drug delivery being an alternative to the current topical preparations. It is described as a non-solid dosage form that produces a film in after application on the skin or other body surface [1].

Ropinirole is a medication that is used to treat restless legs syndrome (RLS) as well as Parkinson's disease (PD). Ropinirole is sold under the brand name Requip, among other names (RLS). When treating PD, the dosage must be modified based on the effect, and patients should avoid abruptly terminating their treatment. It is supposed to be consumed orally. It is authorised for use in the United States and the United Kingdom for the purpose of inducing emesis (vomiting) in dogs that have ingested toxins or foreign material that is not sharp [2].

The formation of the film begins just after the application when the first molecules of solvent start to evaporate. Depending on the solubility of film forming polymer in the used solvent, the FFSs can be either solutions of dispersions. This subsequently influences the process of film formation [3].

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Advantages and disadvantages of current systems

The transdermal administration of a sufficient dose is challenging and only feasible for a small number of drugs. Still the advantages of the transdermal application route in general are numerous with a transdermal application the gastrointestinal tract is avoided altogether. This is especially advantageous for drugs that are sensitive to degradation due to the pH conditions or enzymatic activity in the gastrointestinal tract. There is no impact on the reliability of the medication of the gastrointestinal activity such as gastric emptying or disorders (vomiting, diarrhoea) [4].

METHODOLOGY

Hydrogel preparation

Different proportions of HEC, Sodium Alginate and HPC were mixed by screening through an 80 mesh screen and then sprinkled into purified water to be swollen. The gel was well- swollen after 12 h, and the pH was adjusted to 7.0 with D-Sorbital. Ropinirole was dissolved in ethanol and added dropwise into the gel to be completely mixed. ST-Elastomer 10 was added into the gel as prescribed

and adjusted to a total weight of 100 g with purified water. Experimental conditions for the factorial design are shown [5].

Measurement of film thickness

Film thickness was measured by using a 0.02 mm vernier caliper. A 4 cm 4 cm sample of the film was measured in ten different positions. The determination was performed in triplicate and the average value was used [6].

pH:

The pH of the gel was discovered using automated pH meter. Standardized by using buffer solution (pH 7) before use. The pH measurement of each of the formulation was done in triplicate form and mean values were calculated**.**

Viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer with spindle 04. The formulation which viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min. at the assay temperature (25° ± 1°C) before the measurement was taken. Spindle was lowered perpendicularly in to the center of the gel; taking care that spindle does not touch the bottom of the beaker and rotated at a speed of 30 rpm for 10 min. 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 [7]**.**

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 ethanol [8]**.**

Properties Of Film

For the assessment of properties of the film, films were produced with a solvent evaporation technique by pouring 1 ml of the preparations into a stainless steel mould lined by Teflon (6 cm x 10 cm). 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 [9]**.**

Bioadhesion test

A uniform film was formed on a glass plate and dried for 24 hours at room temperature. The film was divided into equal areas of 1 mm by cutting with scalpel (0.37 mm blade thickness) both in parallel and perpendicular direction. Then pressure-sensitive adhesive cellophane tape was placed on the film and finger was used to smoothen the firm, leaving aside a free piece of tape (unadhered). After few minutes, at 600 C angle, film of gel was pulled manually by grasping the free end of the unadhered tape. 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

Low pressure cotton wool is used to press the dry film in order to determine the stickiness of it. The stickiness is rated depending on how much of the cotton fiber is retained by the film. The stickiness is rated high if there is a thick accumulation of fibers on the film, medium if there is a thin fiber layer on the film and poor if fiber adherence occurs rarely or never. 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 [9].

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 [10]**.**

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 [11]**.**

Water Vapour Permeability

They were kept at a determined temperature (37°C) for 72 hours and weighed. From the weight loss of the vials W (g) the WVP was calculated as the amount of water that had permeated through the film in relation to the surface area (A cm2) and the time (t, 24 hours) using the following formula:

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

***In Vitro* 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 [12]**.**

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.

Zero order release kinetics:

To study the zero order release kinetics the release data was fitted into the following equation;

dQ / dt = Ko

Where 'Q' is the amount of drug release, 'Ko' is the zero order release rate constant and't' is the release time. The graph is plotted percentage cumulative drug release (%CDR) verses time.

First order release kinetics:

To study the first order release kinetics the release rate data are fitted into the following equation;

dQ / dt = K1 Q

Where, 'Q' is the fraction of drug release, 'K1' is the first order release rate constant and 't' is the release time. The graph is plotted log %CDR remaining verses time.

Higuchi Release Model:

To study the Higuchi release model the release rate data are fitted into the following equation.

Q = KH t ½

Where, 'Q' is the fraction of drug release, 'KH' is the release rate constant and 't' is the release time. The graph plotted % CDR verses square root of time.

Kosmeyers and Peppas Kinetics:

To study Kosmeyers and Peppas release kinetics the release rate data are fitted into following equation:

Mt / M∞ = KKP tn

Where, Mt/M∞ is the 'fraction of drug release, 'KKP' is the release rate constant and't' is the release time and 'n' is the diffusion exponent related to mechanism of drug release. The graph is plotted log %CDR verses time [13].

Results and Discussion

Formulation of Triamcinolone Film Forming gel:

The film forming gel formulation was prepared by using HEC as gelling agent and Sodium Alginate and HPC as film forming polymer. The gels were prepared in ethanol by dispersion method. Six different batches of gels were prepared by varying the concentration of film forming polymer. All the prepared formulations were subjected to characterization of gel and film and invitro drug diffusion studies to find out the best formulation.

Evaluation Of Film Forming Gel

pH, Spreadability, Viscosity

The pH value of Film Forming gel formulation is shown in table. They were found to be in the range of 5.5 to 7. The diameter of the gels spreading following the spreadability test are found to be between 4 to 5.4 cm. 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. Ideally film forming gel should dry to form thin film on skin application within 4 to 7 mins, so as to minimize discomfort to the patient. All the formulations showed satisfactory results within the acceptable range.

Evaluation Film Properties

Weight variation test

The films were tested for weight variation. The results have been tabulated in table no. Weight of the films was found to be in the range of 0.0503g to 0.0605g.

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 in table.

Drug content of film:

The content uniformity was performed for all the formulations and results are shown in table. 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 between15 to 20.

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. The results for the bioadhesion test have been given below in table.

Water vapour permeablity:

The results of water vapour permeability test are represented in table. 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:

The formulations F4 to F6 consist of HEC increases the percentage of drug release while increasing the concentration of the polymer. The formulation F6 containing HEC, Sodium Alginate, HPC was selected as best formulation, for sustain the release of drug.

Figure 1. Possible permeation routes through the skin according to Barry

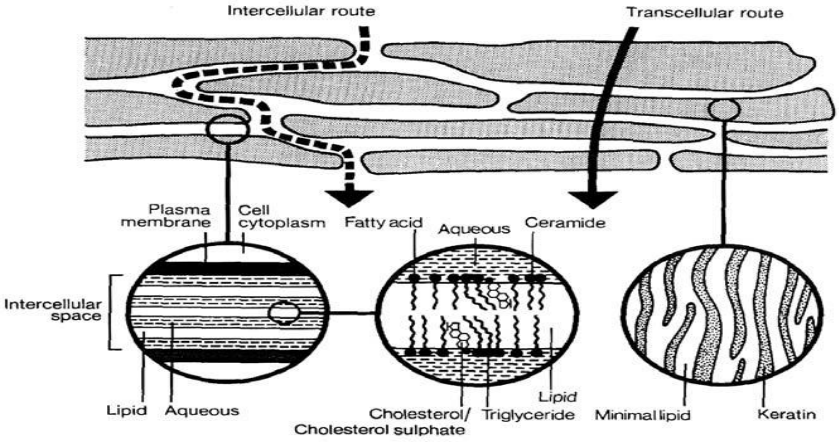

Table 1: Formulation of Ropinirole Film Forming Gel

FORMULATION CODE						
INGREDIENTS	F1	F2	F3	F4	F5	F6
Ropinirole	`0.1	0.1	0.1	0.1	0.1	0.1
HEC	-	-	-	1	1	1
Sodium Alginate	-	-	-	1	1	1
HPC	-	-	-	1	1	1
D-Sorbital	0.5	0.5	0.5	0.5	0.5	0.5
Glycerol	0.5	0.5	0.5	0.5	0.5	0.5
PEG 400	0.5	0.5	0.5	0.5	0.5	0.5
PEG 400	0.5	0.5	0.5	0.5	0.5	0.5
PEG 400	0.5	0.5	0.5	0.5	0.5	0.5
PEG 400	0.5	0.5	0.5	0.5	0.5	0.5

Ethanol	q.s	q.s	q.s	q.s	q.s	q.s
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s

HEC – hydroxyethyl cellulose, HPC – hydroxypropyl cellulose, PEG 400 – polyethylene glycol

Table 2: pH, Spreadability, Viscosity developed Film Forming gel

FORMULATION CODE	pH	SPREADABILITY DIAMETER (cm)	VISCOSITY
F1	5.6±0.030	4.9±0.15	12400
F2	5.7±0.032	4.8±0.17	12750
F3	5.9±0.025	4.8±0.05	12850
F4	6.1±0.025	4.25±0.20	12980
F5	6.3±0.02	5.13±0.20	13150
F6	6.5±0.035	5.45±0.15	13540

Table 3: Drying Time of Film Forming gel

S. No	FORMULATION CODE	DRYING TIME
1.	F1	4mins 27secs±13 secs
2.	F2	5mins 15secs±29 secs
3.	F3	5mins 21secs±28 secs
4.	F4	4mins 34secs±15 secs
5.	F5	6mins 40secs±13 secs
6.	F6	6mins 28secs±17 secs

Table 4: Weight variation test for the dried films

S. No	FORMULATION CODE	WEIGHT VARIATION(g)
1.	F1	0.0529± 0.03
2.	F2	0.0543± 0.02
3.	F3	0.0548± 0.04
4.	F4	0.0592± 0.03
5.	F5	0.0623± 0.01
6.	F6	0.0582±0.03

Table 5: Thickness and Stickness of the Film

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
		Good

Table 6: Content uniformity of the film

FORMULATION CODE	DRUG CONTENT
F1	91.85%
F2	94.86%
F3	97.03%
F4	93.65%
F5	97.76%
F6	95.84%

Table 7: Folding endurance of the formulation

FORMULATION CODE	FOLDING ENDURANCE (no. of. folds)
F1	15
F2	12

F3	16
F4	18
F5	21
F6	20

Table 8: Percentage peel off developed film

FORMULATION CODE	% PEEL OFF
F1	5
F2	5
F3	8
F4	10
F5	10
F6	5

Table 9: Water vapour permeability of developed film

FORMULATION CODE	WATER VAPOUR PERMEABILITY (g cm-1h-1)
F1	0.041
F2	0.046
F3	0.035
F4	0.029
F5	0.026
F6	0.045

Table 10: Percentage cumulative drug release of developed Film Forming gel (F1-F6)

% CUMULATIVE DRUG RELEASE						
TIME (Hrs)	F1	F2	F3	F4	F5	F6
0.5	1.42	2.71	2.28	3.21	4.81	4.16
1	3.15	4.86	4.20	5.69	8.55	8.20
2	5.37	7.40	6.87	8.96	13.34	12.37
3	8.47	11.04	10.41	12.83	18.54	17.21
4	12.06	14.63	14.49	17.19	24.61	22.54
5	16.63	18.88	19.50	19.07	31.05	29.05
6	21.97	23.71	25.49	25.01	38.30	36.02
8	28.30	29.02	32.70	32.36	46.12	44.03
10	34.85	34.20	41.80	40.94	53.97	52.14
12	45.68	47.41	52.36	56.00	66.43	66.84

CONCLUSION

Ropinirole film forming gel by dispersion method by using various film forming polymer with different concentration along with addition of permeation enhancer. The developed film forming gel were subjected to the following evaluation parameters pH, Viscosity, drying time, Drug content. All the parameters were within the limits. The formed film were also evaluated to the following parameters, thickness, stickness, weight variation, folding endurance, bioadhesion, drug content, water vapour permeability and in-vitro diffusion studies. Based on all these results, drying time, drug content, bioadhesion, water vapour permeability and diffusion data, F6 was selected as the best formulation.

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