International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 11; November 2017; Page No. 7167-7173
DOI: http://dx.doi.org/10.24327/ijcar.2017.7173.1093

Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF FILM FORMING EMULGEL OF BETAMETHASONE VALERATE

Saudagar R. B[1] and Khairnar S. B[2]

[1]Department of Pharmaceutical Chemistry, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India
[2]Department of Quality Assurance and Techniques, KCT's R.G. Sapkal College of Pharmacy, Anjaneri, Tal. Trimbakeshwar, Dist. Nashik-422213, Maharashtra, India

A R T I C L E I N F O

Article History:
Received 20th August, 2017
Received in revised form 29th September, 2017
Accepted 30th October, 2017
Published online 28th November, 2017

Key words:
Betamethasone valerate, Film-forming Emulgel, Eudragit RS PO, Hydroxy Propyl Cellulose, Inflammation.

A B S T R A C T

Many agents are applied to the skin deliberately with beneficial outcomes. Conventional formulations intended for topical and dermatological administration of drugs such as creams, foams, gels and lotions are considered to reside for a relatively short period of time at the targeted site. The localized treatment of body tissues, diseases and wounds requires that the particular pharmaceutical component be maintained at the site of treatment for an effective period of time. Sweat, clothing, movements and getting washed away easily on contact with water are some of the problems that have limited the effectiveness and residence time of conventional topical formulations. The present work aims at designing and formulating a 'film- forming emulgel' which on application will form a thin transparent film on the skin. Eudragit RS PO and HPC was used to form a matrix film. The formulations were prepared using 32 full factorial design. They were tested for drying time, drug release, antifungal activity, skin irritation and stability studies. The gel was characterised for pH, viscosity, drug content, effective dosage volume and mechanical properties of the film formed after application; bioadhesion and water vapour permeability were also tested. The optimized formulation showed drug release of 99.64% and antifungal activity in terms of efficacy as 99.56%. Such a formulation can be claimed to decrease duration of therapy, will be more accepted by the patients.

INTRODUCTION

Successful pharmaceutical formulations should deliver active substances to the target organs at therapeutically relevant levels, with negligible discomfort and side effects to the patient. In dermatological treatment, improving clinical efficacy requires high drug levels in specific strata of the skin, while systemic absorption of the drug should be minimized.[1] Therefore, the ideal objective in optimized therapy is to formulate a delivery vehicle that controls the drug release and diffusion rates, reduces the mass of drug reaching systemic circulation, and forms a substantial reservoir in the skin for extended drug delivery. Corticosteroids are the first-line drugs used in the topical treatment of various inflammatory skin disorders, including psoriasis and atopic dermatitis.[2] Unfortunately, topical corticosteroids are associated with many side effects, both local to the site of application and systemic, which limit their use. Local side effects include, but are not limited to, atrophy and striae, whereas systemic adverse effects including Cushing's syndrome, hypothalamic-pituitary adrenal axis suppression, femoral head osteonecrosis, and cataracts have been recorded.[3] Thus, an ideal topical corticosteroid for the treatment of inflammatory skin diseases must diffuse through the stratum corneum (SC) to attain therapeutically relevant concentrations in the skin disease sites without resulting in high serum levels and systemic exposure. This holds true especially for chronic topical therapy. To achieve the goals of drug targeting to the skin, great efforts have been made to design the delivery formulations. [4]

Inflammation is the body's attempt at self-protection; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens and begin the healing process. To know the effect of drugs used in inflammation various animal models are used. Inflammatory changes can be induced in these animals by administration of various agents and anti-inflammatory effect of different drugs can be compared. Inflammation is a complex biological response of vascular tissues to harmful stimuli, pathogens or irritants [5]. Exposure to chemicals, irritants and allergens leads to various inflammatory disorders. The treatment for such disorder includes avoidance of allergens, irritants, adequate cutaneous

Corresponding author:* **Saudagar R. B
Department of Pharmaceutical Chemistry, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India

hydration and judicious use of low to moderate potency corticosteroids. Betamethasone valerate is moderately potent glucocorticoid with anti-inflammatory and immunosuppressive properties. [6]

Film forming emulgels have emerged as one of the most interesting topical drug delivery systems as I has dual release control i.e. emulsion and gel. Film forming emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. Hey have a high patient acceptability since they posses the previously mentioned advantages of both emulsion and gels. Therefore, have been recently used as vehicles to deliver various drugs to the skin. Film Forming Emulgel is stable one and better vehicle for hydrophobic or water insoluble drugs. [7] Dermatological product applied to the skin are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparations. Within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are relatively newer class of dosage form created by entrapment of large amount of aqueous or hydro alcoholic liquid in network of colloidal solid particles. Gel formulations generally provide faster drug release compared with ointment and creams. In spite of many advantages of gel a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation emulgels are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gels. Emulsion posses a certain degree of elegance and are easily washed off whenever desired. They also have a ability to penetrate the skin. Emulgels are dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water soluble, longer shelf life, bio-friendly transparent and pleasing appearance.[8] by acting as a controlled formulation emulgel provide a defence against skin irritation.[9]

It is more efficient to use a multi-factorial design than one-factor-at-a-time experimentation since it can give a combination of variables that give better results for the optimization study.[10] Using the response surface analysis technique, we evaluated the effects of two factors: the amount of Eudragit and the amount of HPC on the drug release rate and antifungal activity by utilizing 32 full factorial design. The optimized formulation was also evaluated for skin irritation in rats.

MATERIALS AND METHODS

Betamethasone valerate was received as gift sample from Cipla Ltd., Mumbai, India. . Eudragit RS PO and HPC HF and were purchased from Modern science, Nashik. TEC was received as gift sample from Evonik Degussa India Pvt. Ltd., Mumbai. Liquid paraffin, Propylene glycol, Tween 20, Span 20 and all other chemicals were of analytical grade and were obtained commercially.

Method of Preparation

Step-1: Formulation of Emulsion either O/W or W/O
Step-2: Formulation of gel base
Step-3: Incorporation of emulsion into gel base with continuous stirring
Step-4: After formulation of emulgel addition of film forming solution.[7]

3^2 factorial design was followed for the development of the formulations. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in table I.

Table I Composition of formulations as per 32 factorial design

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient					%				
Betamethasone valerate (w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Eudragit RS PO (w/v)	10	10	10	12.5	12.5	12.5	15	15	15
Hydroxy Propyl Cellulose (w/v)	4	6	8	4	6	8	4	6	8
Liquid Paraffin(w/w)	4	6	8	4	6	8	4	6	8
Propylene Glycol(w/w)	5	5	5	5	5	5	5	5	5
Tween 20(w/w)	0.343	0.343	0.343	0.343	0.343	0.343	0.343	0.343	0.343
Span 20(w/w)	1.653	1.653	1.653	1.653	1.653	1.653	1.653	1.653	1.653
Ethanol (v/v)	50	50	50	50	50	50	50	50	50
Distilled water (v/v) q.s.	100	100	100	100	100	100	100	100	100

Evaluation of formulations

The formulations were tested clarity, pH, and viscosity. Clarity was checked visually and pH of the formulations was checked using digital pH meter 335. [11,12] The rheological properties of gels were determined by the Brookfield viscometer; type DV-II + PRO using spindle SC4-18.Viscosity values of the formulations were recorded at varying shear rates. [12]

Drug content

To determine drug content 1 g of gel was taken in a 100 mL volumetric flask containing 10 mL phosphate buffer solution pH 5.8 and volume was made up to the mark with phosphate buffer solution pH 6.8 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 phosphate buffer solution pH 6.8. The absorbance of prepared solution was measured at λ max of 241 nm by using UV visible spectrophotometer.[12]

Drying time

For the assessment of the drying time the formulation was applied to the inner sides of the forearm of a volunteer, who participated in the study on informed consent basis. After 2 minutes a 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. [13]

Integrity of formulation on skin

The formulation was applied to the forearm of a volunteer as described for the assessment of the drying time. The dry film was then worn overnight by the test subject. After 24 hours the test area was examined visually for completeness of the film, appearance of cracks or flaking. [13]

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.

The stickiness of the outer surface was tested by pressing cotton wool on the dry film under low pressure. Depending on the quantity of cotton fibres that were retained by the film the stickiness was rated high (dense accumulation of fibres on the film), medium (thin fibre layer on the film) or low (occasional or no adherence of fibres).

The cosmetic attractiveness of the film was assessed by visual examination of the dry films. Transparent films with a low skin fixation had a high attractiveness as they were almost invisible. Opaque films and films with a medium skin fixation were considered less attractive as they exhibited an increased visibility and a slight wrinkling of the skin. Whitish films and films causing heavy wrinkling of the skin due to strong skin fixation displayed only a low attractiveness.

Tensile strength and Elongation

Films were evaluated for tensile strength and % elongation using an apparatus assembled in the laboratory. Films of dimension 10 x 40 mm were attached to a support that was inextensible but flexible and this support was in turn held between two clamps separated by a distance of 3 cm. Clamps were designed to secure the patch without crushing it during the test. These were supported on a metal base. One of the clamps was fixed; the other one was movable and weights could be added to the movable clamp. During measurement, the films were pulled by the movable clamp with the addition of weights. The strength and elongation were measured when the films broke and tensile strength and % elongation were calculated using the following formulae. [14-17]

Tensile strength = Tensile load at break
Cross sectional area

% Elongation = Maximum length recorded at break-Original length x 100

Original length

Water vapour permeability: [13]

The water vapour permeability (WVP) was investigated according to a method modified from the British Pharmacopoeia. Films were produced with a solvent evaporation technique as described earlier. Circular samples with a diameter of 2.0 cm were cut from the dry film sheets with the help of a scalpel. For the sample preparation 10 ml glass vials with an opening of 1.2 cm diameter (A = 1.13 cm^2) were filled with approximately 8 g of distilled water, covered with the circular film samples and the vial was sealed tightly with an aluminium foil. To start the experiment, the top of the vial cap was opened and the weight of the vial was determined with an analytical scale. The vials (three replicates per formulation) were then placed into a desiccator containing a desiccant to create a climate of low relative humidity (approximately 0%). 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 cm^2) and the time (t, 24 hours) using the following formula:
WVP = W/ (A*t) (g cm-2 24 hrs-1)

In-vitro Drug Release Study (Diffusion study): [11,18-19]

Laboratory-assembled apparatus resembling a Franz diffusion cell was used to determine the release profile of drug from film forming gel. The cell consisted of two chambers, the donor and the receptor compartment between which a diffusion membrane (egg membrane) was mounted. The donor compartment, with inner diameter 24 mm, was open i.e. exposed to the atmosphere at one end and the receptor compartment was such that it permitted sampling. The diffusion medium used was phosphate buffer solution pH 6.8 (PBS). 1 mL of the drug containing film forming gel was placed in the donor compartment over the drug release membrane and was separated from the receptor compartment by the egg membrane. The egg membrane was previously soaked for 24 hr. in PBS. The donor and receptor compartments were held together using a clamp. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. The whole assembly was fixed on a magnetic stirrer. The receptor compartment with 100 mL of PBS was placed on a thermostatically controlled magnetic stirrer. It was maintained at 37 ± 0.5 ^{0}C and stirred constantly at 50 rpm. Samples of 1 mL were collected at predetermined time intervals and analysed 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.

Optimization study [13]

Optimization of the formulations was studied by 32 full factorial design. The amounts of eudragit RS PO (X1) and hydroxypropyl cellulose (X2) were selected as independent variables and the dependent variables were % drug release and antifungal activity. The data obtained were treated using Design expert version 8.0.4.1 software and analysed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the effect of eudragit RS PO and hydroxypropyl cellulose on the dependent variables.

Evaluation of Optimized formulation

The batch which was selected from the solutions obtained by optimization study was further evaluated for skin irritation, best fit kinetic model and stability study.

Best fit kinetic model: [13]

To examine the drug release kinetics, the release data of optimized formulation was fitted to models representing zero order, first order, Higuchi's square root of time kinetics and Korsemeyer Peppas kinetics. The coefficient of determination (r^2) values were calculated from the plots of %CDR vs. t for zero order, log % CDR remaining vs. t for first order and %CDR vs. t1/2 for Higuchi model, where %CDR is the amount of drug released at time t, log %CDR is the amount of drug remaining after time t. The best fit kinetic model was determined from r^2 values.

Stability study: [20]

The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 1 month up to 3 months and after 6 months. Physical appearance/clarity, pH, viscosity, drug content were evaluated.

RESULTS AND DISCUSSION

All formulations were found to be clear on visual inspection. The pH of the formulations was found to be between 5.65 and 5.88. Ideally, the dermal gel should possess pH in the range of

5-6, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH. [21] Hence, the formulations displayed pH values within acceptable range. The viscosity profile of formulations F1 to F9 has been shown in figure I.

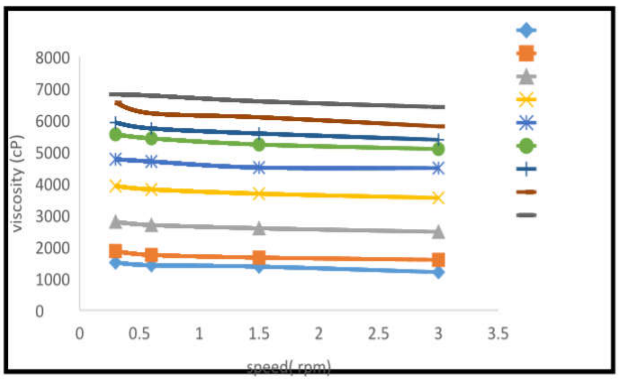

Figure I: Viscosity profile of formulations

Viscosity v/s rpm plots for all formulations shows decrease in viscosity as shear rate (rpm) was increased. Concentration of hydroxypropyl cellulose and Eudragit RS PO was a major factor affecting viscosity of formulations. Formulations exhibited considerable increase in viscosity when concentration of hydroxypropyl cellulose increased over the range of 2% w/v to 10% w/v.

Drug content

The Drug content of formulations is shown in table IV. The percentage drug content of all prepared dermal formulations was found to be in the range of 98-102 %. Therefore uniformity of content was maintained in all formulations.

Table II Percent Drug content of Emulgel

Sr. no.	Formulation code	Drug content (%) (±S.D.)
1.	F1	99.5 ±0.17
2.	F2	99.89 ±0.41
3.	F3	100.9 ±0.17
4.	F4	101.7 ±0.3
5.	F5	99.60 ±0.34
6.	F6	98.12 ±0.14
7.	F7	99.20 ±0.18
8.	F8	99.86 ±0.41
9.	F9	98.75 ±0.16

Drying time

The drying time or film formation time for formulations F1 to F9 has been tabulated in table III.

Table no. III Drying time of emulgel

Sr. no.	Formulation code	Drying time
1.	F1	3 min 07 sec ±5 sec
2.	F2	3 min 30 sec ± 5 sec
3.	F3	4 min 37 sec ± 5 sec
4.	F4	4 min 36 sec ± 5 sec
5.	F5	5 min 29 sec ± 5 sec
6.	F6	5 min 41 sec ± 5 sec
7.	F7	6 min 12 sec ± 5 sec
8.	F8	6 min 38 sec ± 5 sec
9.	F9	7 min 2 sec ± 5 sec

Ideally, the dermal gel should dry to form a thin invisible film on the surface of skin at the application site within few minutes, so as to minimize discomfort to patient. [13]

Integrity of formulation on skin

Table no. IV Results for Integrity of film after 24 hours

Sr. no.	Formulation code	Integrity of film after 24 hours
1.	F1	Flaky and partly missing
2.	F2	Flaky and partly missing
3.	F3	Flaky
4.	F4	Good
5.	F5	Good
6.	F6	Good
7.	F7	Flaky
8.	F8	Flaky and partly missing
9.	F9	Flaky and partly missing

The integrity of the formulations on the skin in the form of a thin, almost invisible film was evaluated for formulations F1 to F9. The results of the test have been tabulated below.

Films formed from formulations F1 and F2 were flaky due to brittleness of the film and parts of the film were missing. F3 and F8 formed flaky film. Formulations F4, F5 and F6 formed films that were flexible, soft to touch and completely present after 24 hours. F8, F9 formulations formed films that were flaky and ruptured in some parts.

Properties of film

Outward stickiness

The results for outward stickiness of the formulations have been tabulated in table V

Table no V Results for Outward stickiness

Sr. no.	Formulation code	Observation
1.	F1	Low
2.	F2	Low
3.	F3	Medium
4.	F4	Low
5.	F5	Low
6.	F6	Medium
7.	F7	Low
8.	F8	Low
9.	F9	Medium

Cosmetic attractiveness

Results for cosmetic attractiveness of the film formed after drying have been given in table no. VI.

Table no. VI Results for Cosmetic attractiveness

Sr. no.	Formulation code	Observation
1.	F1	Medium
2.	F2	Medium
3.	F3	Medium
4.	F4	High
5.	F5	High
6.	F6	High
7.	F7	Low
8.	F8	Low
9.	F9	Low

Tensile strength and % Elongation

Mechanical properties such as tensile strength and % elongation at break are determined to characterise polymeric films for their abrasion resistance and flexibility respectively. Tensile strength results have been tabulated in table no. VII. Table no. 41 shows the results for % elongation measurements.

Table no VII Results for Tensile strength

Sr. no.	Formulation code	Observed value (±S.D.) (Kg/cm^2)

1.	F1	0.0940 ±0.0002
2.	F2	0.0991 ±0.0004
3.	F3	0.1015 ±0.002
4.	F4	0.180 ±0.001
5.	F5	0.1224 ±0.0001
6.	F6	0.1334 ± 0.0005
7.	F7	0.1410 ±0.0001
8.	F8	0.1514 ± 0
9.	F9	0.1611 ±0.001

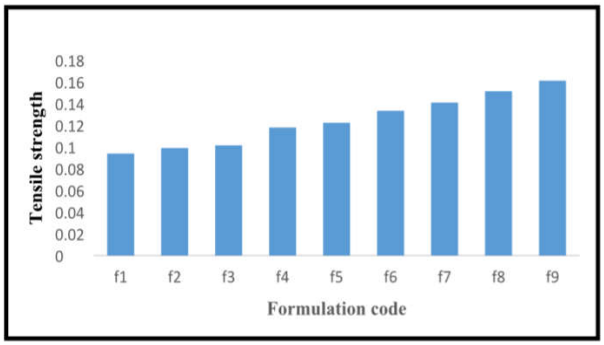

Figure no II Comparative evaluation for Tensile strength of film

Table no VIII Results for % Elongation

Sr. no.	Formulation code	Observed value (±S.D.) (%)
1.	F1	3.16 ±0.14
2.	F2	4.6 ±0.12
3.	F3	5.1 ±0.12
4.	F4	4.08 ±0. 14
5.	F5	4.41 ±0. 14
6.	F6	5.58 ±0. 38
7.	F7	4.25 ±0. 4
8.	F8	4.8 ± 0.17
9.	F9	5.75 ±0.25

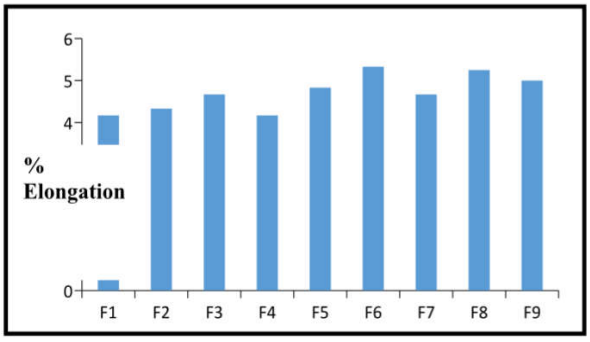

Figure no: III Comparative evaluation for % Elongation of film

Water vapour permeability

Results for WVP have been tabulated in table no. IX.

Table no IX Results for WVP determination

Sr. no.	Formulation code	Observed value (±S.D.) (gm cm^{-2} $24h^{-1}$)
1.	F1	0.0504 ± 0.00007
2.	F2	0.0512 ± 0.0001
3.	F3	0.0540 ±0.00007
4.	F4	0.0571 ± 0.0001
5.	F5	0.0533 ± 0.00007
6.	F6	0.0524 ± 0.00007
7.	F7	0.0487 ± 0.0007
8.	F8	0.0480 ± 0.00005
9.	F9	0.0469 ± 0.00015

According to the British Pharmacopoeia a material can be considered permeable to water vapour when the WVP exceeds 0.05 g cm^{-2} $24h^{-1}$. [13] The films displayed such WVP values that show permeability above the limit set in the Pharmacopoeia and can therefore be considered non-occlusive.

In-vitro drug release study

The *In-vitro* drug release study of formulations is shown in table X.

It can be deduced from *in vitro* diffusion study that formulations F1 to F3 did not sustain the drug release over 24 hours. This may be attributed to low levels of drug release modulating polymers and low viscosity of the formulations. [22] Formulations F4 and F5 sustained drug release over 24 hours. On the other hand, formulations F6 to F9 did not completely release the drug. Drug release was found to be sustained at intermediate levels of hydrophobic polymer, Eudragit and hydrophilic polymer, HPC.

Of the nine formulations, maximum release was found to be for formulation F5 after 24 hours. 99.56% of the drug in the formulation was available for antifungal activity. The composite film had hydrophobic and hydrophilic portions which provide competition for drug release as both the polymers have different release properties. Therefore, as the polymer ratio varies, competition to release drug also varies. Formulation F5 showed steady state release up to 24 hours which also indicates that this formulation would show better contact with biological membrane. *In-vitro* drug release profile of formulations has been shown in figure VI.

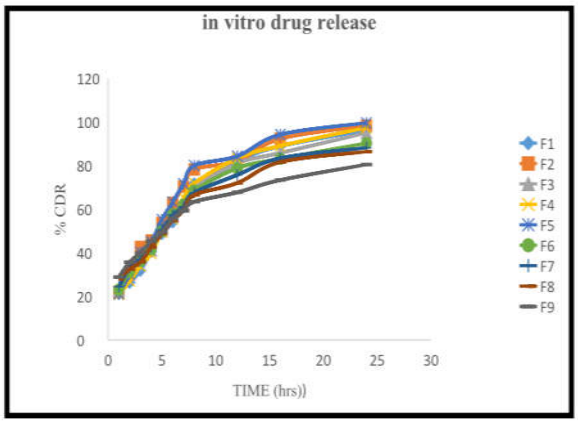

Figure no: IV *In-vitro* drug release profile of formulations F1 to F9

Optimization [23]

From design expert version 8.0.4.1 thirty nine solutions were found. The batch with Eudragit 12.5 % w/v and HPC 6 % w/v with desirability 1 was found to be optimum.

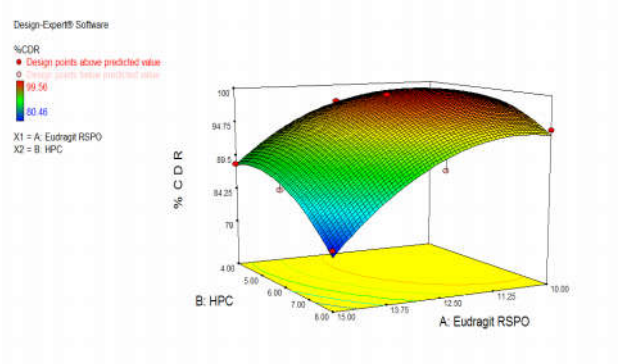

Figure VI Surface response plot showing effect of Eudragit RS PO and Hydroxypropyl cellulose on Drug release

Table X Cumulative Drug release of formulations

Time (hr.)	Cumulative Drug Release (%) (±S.D.)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.19±0.21	22.08±0.2	22.52±0.41	20.89±0.20	21.19±0.21	23.12± 0	24.45±0.21	28 ± 0.21	28.89± 0.21
2	26.37±0.84	30.22±0.4	30.67±0.21	27.11±0.20	30.22±0	31.40±0.61	33.33±0.20	32.54±0.49	35.7±0.21
3	31.85±0.16	42.66±4.1	37.04±0	33.93±0.21	40.14±0.20	36.29 ±0.62	37.04±0	35.85±0	40 ± 0
4	40.59±0	45.63±0	41.18±0.41	39.70±0.41	45.03±0.41	41.63±0.21	42.81±0.20	42.66±0.59	45.33±0.41
5	48.74±0.21	53.63±0.4	50.07±0.96	49.48±0	55.25±0.2	49.92±0.20	50.51±0.21	48.89 ±0	49.48±0.41
6	54.07±0.21	62.81±0	57.33±0.21	55.55±0.20	63.25±0.20	57.63±0.21	57.33±0.21	54.81±0.61	55.70±0.41
7	61.63±0	70.36±0.20	62.37±0.21	65.18±0	71.69±0.65	62.07±0.20	61.03±0.61	59.41±0.21	59.26±0
8	71.7±0.4	78.22±1.4	69.78±0.21	71.85±0.21	79.99±0.61	68.59±0.20	66.55±0.61	66.52 ±0.21	63.41±0.41
12	82.07±0	82.02±0.68	81.03 ±0.21	83.40±0.20	84.29±0.20	78.81±0.61	75.70±0.61	72.00±0.41	67.71±0.20
18	88.89±0	92.3±0.21	85.78±0.21	89.04±0.21	94.22±0.61	83.12±0.61	83.41±0.20	78.63±0.20	73.35±0.21
24	96.15±0.2	98.23±0.21	94.97±0.21	97.34±0.21	99.56±0.61	90.23±0.21	88.15±0.21	86.38±0.21	80.46±0.21

From this data formulation F5 was selected as the optimum formulation. The figures below show the effect of concentration of Eudragit RS PO and Hydroxypropyl cellulose on drug release and antifungal activity. It is shown that both the independent variables have a significant effect on the dependent variables and drug release and antifungal activity decrease as N concentration of polymers increases.

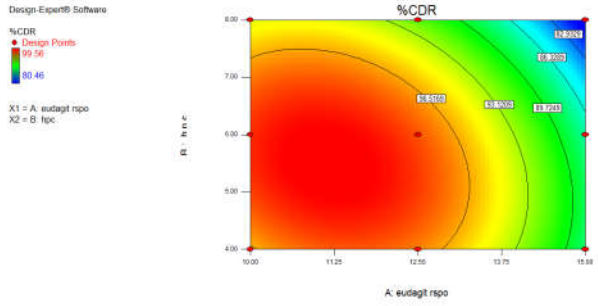

Figure no V Contour plot showing effect of Eudragit RS PO and Hydroxypropyl cellulose on Drug release

The figures above show the effect of concentration of eudragit and HPC on drug release. It is shown that both the independent variables have a significant effect on the dependent variables and, drug release.

In the figures above, it can be seen that as the concentration of polymers increases the drug release go on decreasing. Hence it can be concluded that the two factors: X1 and X2 have a combined effect on drug release.

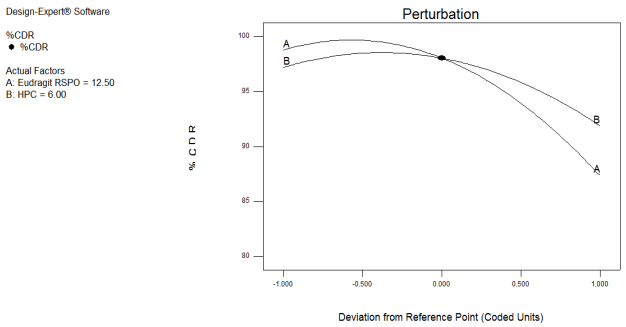

Figure no VI Perturbation plot showing effect of Eudragit RS PO and Hydroxypropyl cellulose on Drug release

It can be seen from the figures above, that the effect of concentration of HPC on drug release is more pronounced than that of eudragit.

Evaluation of Optimized batch

Best fit kinetic model for optimized formulation

The diffusion kinetics of optimized formulation was studied. The best fit model with highest R2 value and least slope value was the first order model.

Table XI R2 and slope values for optimized formulation F5

Sr. no.	Model	R^2	Slope
1.	Zero order	0.688	0.039
2.	First order	0.948	-0.089
3.	Higuchi	0.798	3.270
4.	Korsemeyer-Peppas	0.652	0.024

Stability study

The optimized formulation was evaluated after storage at room temperature and after accelerated stability study at elevated temperature (40oC/75% RH) in stability chamber.[24] Results have been given in table XII and table XIII.

Table no XII Stability studies data for F5 formulation at room temperature

Sr. no.	Observation		Before study	During study
				3rd month
1.	Clarity		Opaque	Opaque
2.	pH		5.82 ±0.01	5.83 ±0.01
3.	Viscosity (rpm)	0.3	4783.65	4786.19
		0.6	4693.43	4696.45
		1.5	4501.89	4512.24
		3	4487.06	4489.32
4.	Drug content		99.60 ±0.34	99.60 ±0.24

Table no XIII Accelerated Stability studies data for F5 formulation

Sr. no.	Observation		Before study	During study
				3rd month
1.	Clarity		Opaque	Opaque
2.	pH		5.83 ±0.01	5.87±0.01
3.	Viscosity (rpm)	0.3	4783.65	4783.65
		0.6	4693.43	4693.43
		1.5	4501.89	4501.89
		3	4487.06	4487.06
4.	Drug content		99.60 ±0.34	99.55 ±0.68

CONCLUSION

Film forming Emulgel of Betamethasone valerate was prepared using Eudragit RS PO, hydroxypropyl cellulose, Liquid paraffin, Propylene glycol, Tween 20 and Span 20. The concentrations of both the polymers were optimized by 32 full factorial design to obtain optimum drug release. Thus, desirable goals could be achieved by systematic formulation approach. The film forming Emulgel prepared in this study fulfils all necessary parameters required for topical use. This novel dosage form will improve both the accuracy and the positioning of a delivered dose. The optimized formulation

with better Drug release may improve the bioavaibility of topical administration of Betamethasone in novel form and can be alternative to the conventionally administered topical formulations.

Acknowledgements

The authors duly acknowledge Cipla Ltd., Mumbai, India, for providing Betamethasone valerate as a gift sample, Evonik Degussa India Pvt. Ltd., Mumbai for the gift sample of Eudragit RS PO and Triethyl citrate.

References

Schafer-Korting M, Mehnert W, Korting HC. 2007. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv Drug Deliv Rev* 59(6):427–443.

DiPiro JT. 2008. Pharmacotherapy: A pathophysiologic approach. 7th ed. New York: McGraw-Hill Medical. pp xxxii, 2559.

Del Rosso J, Friedlander SF. 2005. Corticosteroids: Options in the era of steroid-sparing therapy. *J Am Acad Dermatol* 53(1, Suppl. 1):S50–S58.

Muller RH, Radtke M, Wissing SA. 2002. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev* 54(Suppl. 1): S131 S155.

Meena MK, Jain AK, Jain CP, Gaur K, Kori ML, KakdeAetal. Screening of anti-inflammatory and analgesic activity of Cassia grandis Linn. *Academic Journal of Plant Sciences* 2009; 2:51-5.

Nayak V, Satyam SM, Lakshinarayana K, Chandrashekhar BR, Pawan Kumar AV, et al. Effect of Betamethasone dipropionate, Betamethasone valerate and combination of Betamethasone valerate and Neomycin sulphate with Biopolymer on skin inflammatory model in Wistar rats, *International Journal of Advanced Research* (2014), Volume 2, Issue 10, 740-743.

Chemate SZ and Anbhule RM "Formulation and evaluation of terbinafine hydrochloride film forming emulgel", *International Journal of Drug Research and Technology*, Vol. 6 (3):2016; 164-174.

Singla V, Saini S, Joshi B, Rana AC, "Emulgel: A New Platform for topical drug delivery" *International Journal of Pharma and Bio Sciences*, Vol 3(1): 2012;485-498.

Upadhyaya S, Chauhan BS, Kothiyal P, "Emulgel: A Boon For Dermatological Diseases" *International Journal of Pharmaceutical Research and Allied Sciences*, Vol 3(4):2014;1-9.

Li X, R. Zhang, R. Liang, W. Liua, C. Wanga, Z. Su, F. Sun, Y. Li, Preparation and characterization of sustained-release rotigotine film-forming gel, International Journal of Pharmaceutics, 2014, 460(1):273-79.

H. Vaghasiya, A. Kumar, K. Sawant, Development of solid lipid nanoparticles based controlled release system for topical delivery of terbinafine hydrochloride, *European Journal of Pharmaceutics and Biopharmaceutics*, 2013, 49:311-22.

K. Saroha, S. Singh, A. Aggarwal, S. Nanda, Transdermal Gels- An alternative vehicle for drug delivery, *International Journal of Pharmaceutical, Chemical and Biological Sciences* 2013, 3(3):495-03.

I.Z. Schroeder, P. Franke, U.F. Schaefer, C.M. Lehr, Development and characterization of film forming polymeric solutions for skin drug delivery, *European Journal of Pharmaceutics and Biopharmaceutics*, 2007, 65:111-21.

B.K. Dey, P.K. Kar, L.K. Nath, Formulation, design, preparation and in vitro-in vivo evaluation of propranolol hydrochloride transdermal patches using hydrophilic and hydrophobic polymer complex, *Research Journal of Pharmacy and Technology*, 2009, 2(1):155-60.

Y.B. Ubarchande, T. Regupathy, C. Vijaya, S.V. Deshmane, Formulation and evaluation of mucoadhesive buccal films of losartan potassium, *Research Journal of Pharmacy and Technology*, 2009, 2(4):833-36.

C. Suja, C. Ramasamy, R. Narayanacharyula, Development and evaluation of lisinopril transdermal patches, *Research Journal of Pharmacy and Technology*. 2011, 4(8):1260-64.

S.V. Kulkarni, R.P. Kumar, N. Patel, R.B. Someshwara, A.P. Kumar, Development and evaluation of diltiazem HCl transdermal patches by using glycerol and castor oil as plasticizers, *Research Journal of Pharmacy and Technology*, 2010, 3(3):905-09.

J.R. Kumar, S. Muralidharan, S.A. Dhanaraj, Formulation and in-vitro evaluation of terbinafine hydrochloride transdermal patches, *Journal of Pharmaceutical Sciences & Research*, 2012, 4(6):1840-43.

D.S. Kumar, R. Sairam, S. Anandbabu, L. Karpagavalli, A. Maheswaran, N. Narayanan, Formulation and evaluation of transdermal patches of salbutamol, *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 2012, 3(3):1132-38.

International Conference on Harmonization Steering Committee, ICH Harmonized Tripartite Guideline-Stability Testing of New Drug Substances and Products, ICH Q1A (R2), February 6, 2003.

Vij NN, Saudagar RB, "Formulation, Development & Evaluation of film forming gel for prolonged dermal delivery of Terbinafine Hydrochloride", *International Journal of Pharma Sciences and Research*, Vol 5(9)2014, 537-554.

P.D. Sawant, D. Luu, R. Ye, R. Buchta, Drug release from hydroethanolic gels, Effect of drug's lipophilicity (log P), polymer–drug interactionns and solvent lipophilicity, *International Journal of Pharmaceutics*, 2010, 396:45-52.

Vaghasiya H, Kumar A, Sawant K. Development of solid lipid nanoparticles based controlled release system for topical delivery of terbina ne hydrochloride. *European Journal of Pharmaceutics and Biopharmaceutics.* 2013; 49:311-22.

I. Weuts, D. Kempen, A. Decorte, G. Verreck, J. Peeters, M. Brewster, G.V. Mooter, Physical stability of the amorphous state of loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64, *European Journal of Pharmaceutical Sciences,* 2005, 25:313-20.

****