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PREPARATION AND EVALUATION OF KETOPROFEN FILM FORMING GEL

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ABSTRACT

The objective of the present study was to prepare a topical film-forming gel of Ketoprofen for the treatment of rheumatic diseases, using a patient-friendly drug delivery approach. The localized treatment of diseases of our body tissues requires that the pharmaceutical active to 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 mainly used for treatment of arthritis. This necessitates longer treatment duration. The present work aims at designing a dosage form of Ketoprofen referred to as a 'film-forming gel' which on application forms a thin, transparent film on skin surface Ketoprofen film-forming gels were prepared using hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone polymeric blend in varied concentrations, polyethylene glycol 400 (PEG 400) as plasticizer and ethanol as solvent. Optimization was done by central composite method taking spreadability and drying time as the variables. The prepared film-forming gels and films formed after solvent evaporation were evaluated and the influence of the concentration and ratio of polymeric blends used were investigated. The concentrations of both the polymers were optimized by Central composite design to obtain optimum spreadability and drying time. The formulation F3 with a maximum spreadability and minimum drying time was selected as the optimized formulation.

KEYWORDS: Film-forming gel, Ketoprofen, Hydroxy propyl methyl cellulose and polyvinyl pyrrolidone.

INTRODUCTION

Film-forming gels are the novel drug delivery systems which have recently been used to deliver various drugs to the skin as an alternative to conventional topical and transdermal formulations. These systems consist of drug and film-forming polymers in a vehicle, which on application to the skin surface forms a thin, transparent film on solvent evaporation.[1] Compared to conventional semi-solid topical products like gels and ointments, film-forming gels in addition to their therapeutic effect are esthetically more attractive to the patients. They are non-sticky, get adhered to the affected part for a longer period without getting rubbed off and can be designed to provide sustained drug release such that frequent reapplication is not required. All these provide attractive properties which can improve patient compliance.[2][3] Ketoprofen is a highly potent non steroidal anti-inflammatory drug (NSAID), used for osteoarthritis, rheumatoid arthritis, and various other inflammatory conditions. The oral administration of Ketoprofen like almost other NSAID's has the potential of causing side effects such as peptic ulcers and gastric irritation. Topical delivery of Ketoprofen will not only reduce its systemic side effects but also achieves optimal pain relief by direct targeting to the affected area. In this study, an attempt was made to develop Ketoprofen film-forming gels to deliver it to the site of action in rheumatic diseases, with reduced systemic side effects using a patient-friendly drug delivery approach.[4][5]

METHODOLOGY

MATERIALS

Ketoprofen was purchased from Yarrow Chem, Mumbai, PVP and HPMC were brought from Kemphasol, Mumbai, Tri ethanolamine and PEG 400 were purchased from Medilise, Kannur and Ethanol was purchased from Burogyne Burdidges & Co, Mumbai.

METHOD

The formulation design was done using Design Expert e stat software. The polymeric solutions of polyvinyl pyrrolidone and Hydroxy propyl methyl cellulose were prepared in ethanol using dispersion method. Polyvinyl pyrrolidone was sprinkled over 10 ml of ethanol containing PEG 400 (3 % v/v). Hydroxy propyl methyl cellulose was sprinkled over 10 ml of ethanol separately. The polymeric solutions were mixed properly with continuous stirring. Accurately weighed quantity (0.5 g) of the drug was dissolved in 5 ml ethanol. The drug solution and polymeric dispersion were mixed properly with continuous stirring and the pH was adjusted with tri

ethanolamine solution. Finally the volume was made upto the mark using ethanol.[6,7]

Table 1: Formulation Of Ketoprofen Film Forming Gel.

Formula code	Ketoprofen (g)	PVP (g)	HPMC (g)	PEG 400 (ml)	Triethanolamine (ml)	Ethanol (ml)
F1	0.5	8	2	5	12	100
F2	0.5	8	4	5	12	100
F3	0.5	8	6	5	12	100
F4	0.5	10	2	5	12	100
F5	0.5	10	4	5	12	100
F6	0.5	10	6	5	12	100
F7	0.5	12	2	5	12	100
F8	0.5	12	4	5	12	100
F9	0.5	12	6	5	12	100

Evaluation of Film-forming Gel

Physical appearance and pH of film-forming gel

The appearance, texture, and transparency of the prepared gels were examined visually. The pH value of film-forming gels formulations were determined using calibrated digital pH meter. 1 gm of gel was dissolved in 100 ml of distilled water and stored for 2 hours. The measurement of pH of each formulation was performed in triplicate and the mean values were calculated.[7]

Drug content

Accurately weighed amount of gel of about 1 g was taken in a 100 ml volumetric flask containing 50 ml of phosphate buffer solution of pH 7.4 and the volume was made up to the mark with phosphate buffer. The volumetric flask containing gel was sonicated for 15 min to ensure complete solubility of the drug. The solution was then filtered through 0.45 µm pore size membrane filter. The absorbance of prepared solution was measured at λmax of 376 nm against phosphate buffer (pH 7.4) as a blank using ultraviolet/visible spectrophotometer.[7]

Spreadability

The spreadability of the formulation was determined by measuring the spreading diameter of 0.5 g of gel formulation in between two horizontal smooth surface glass plates (20 cm × 20 cm). The initial diameter of the spreading of the gel in centimeters formed by placing the gel on the glass plate was noted. Another glass plate with the same dimensions was placed over the gel for 1 min until no more expansion of the gel was observed. The upper plate was gradually removed and diameter of the circle formed after spreading of the gel was measured in centimeters.[7][8]

Drying time

One gram of the gel was placed on a petri dish which was spread uniformly on it and kept on a hot plate at 37˚C and time needed until gel converts into film was measured.[9]

Preparation and characterization of films

Films were produced with solvent evaporation technique by applying and uniformly spreading 1 g of the gel on a Petri dish (approximately 8 cm diameter). The films were left to dry for 48 h at room temperature. The films were peeled off carefully and subjected to further evaluations as follows.[7]

Formulations which formed a transparent, shiny, adhesive, and flexible film on the skin were considered cosmetically preferable.

Film thickness

The films were cut into circular film samples of approximately 2.0 cm diameter and the thickness of the film was measured using a digital Vernier caliper. Each film was measured in triplicate and the mean thickness was calculated.[10]

Folding endurance

Folding endurance of films was measured manually by repeatedly folding a small strip of film (2 cm × 2 cm) at the same place till it broke or was folded up to 200 times without breaking. The number of times the film could be folded at the same place without breaking was the folding endurance value.[10][7]

Weight variation test

For each formulation, three circular film samples (2.0 cm diameter) prepared from dry films were used. Each film sample was weighed individually in triplicate and the average weight was calculated.[11]

Water vapor permeability (WVP) of film

The WVP was performed according to a method modified from the British Pharmacopoeia. Circular films (2.0 cm diameter) were cut from the dry film sheets with the help of a scalpel. Ten milliliter glass vials with an opening of 1.2 cm diameter (A = 1.13 cm2) were filled with approximately 8 g of distilled water, covered with the formed circular film and tied using elastic bands. The vials covered with the circular film samples were weighed and their initial weight was noted and then kept in 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 h and weighed. The decrease in the weight of the vial was determined with an analytical balance.[7]

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 time (t, 24 h) using the following formula:
WVP = W/(A × t) (gcm−2 24 h−1)

In vitro drug release study (Diffusion study)
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 ie, the donor and the receptor compartment between in 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 5.8. 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 hours 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 o C and 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.[8,12,13]

Optimization study
Optimization of the formulations was studied by Central composite design. The amounts of Polivinyl Pyrrolidine (X1) and hydroxypropyl methyl cellulose (X2) were selected as independent variables and the dependent variables were spreadability and drying time. The data obtained were treated using Design expert stat ease software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the effect of PVP and HPMC on the dependent variables.[15,16]

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
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. time for zero order, log % CDR remaining vs. time for first order, % CDR vs. t1/2 for Higuchi model and log % CDR vs. log time for kosmeyer-peppas 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. The mechanism of drug release was determined by the release exponent value '*n*' obtained from the kosmeyer-Peppas plot.[7,17]

Stability study
The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 3 months, 6 months and after 9 months. Physical appearance/clarity, pH and drug content were evaluated at two different temperatures.[8,14]

Skin Irritation study
As per OECD Guidelines 404, animals are divided into groups each containing 6 rats. Approximately 24 hours before test, fur on back of the rats are removed and 2 fields with dimensions 2 cm^2 was marked. The formulation should be applied to small area of skin and covered with gauze patch, which is held in place with a non- irritating tape and rats were treated as follows:
1. Group 1 : Blank formulation
2. Group 2: Marketed formulation containing Ketoprofen
3. Group 3: Optimized film forming gel Formulation[18]

RESULTS AND DISCUSSION

Physical Appearance and pH of Film-forming Gel
The physical appearance of lornoxicam film-forming gel was shown in figure. 1

The pH value of film-forming gel formulations is shown in Table 2. They were found to be in the range of 6.8–7.1; this is considered to be close to the p^H of the skin and is considered satisfactory for application with minimal risk of tissue irritation.

Table 2: Determination of p^H

Formula code	p^H
F1	6.8 ± 0.5
F2	6.8 ± 0.2
F3	6.8 ± 0.1
F4	7.1 ± 0.3
F5	07 ± 0.2
F6	07 ± 0.5
F7	07 ± 0.5
F8	07 ± 0.3
F9	6.8 ± 0.5

All values are expressed as mean, SD ± n=3

Drug Content

The drug content of film-forming gel formulations as shown in Table 3 was found in the range of 96.56 ± 0.997–99.32 ± 0.328% indicating uniform distribution of drug in formulation.

Table 3: Determination of Drug Content.

Formula code	Drug content
F1	98.77 ± 0.488
F2	97.34 ± 0.154
F3	99.32 ± 0.328
F4	96.56 ± 0.997
F5	97.89 ± 0.197
F6	98.74 ± 0.156
F7	96.88 ±0.634
F8	98.01 ± 0.998
F9	98.69 ± 0.287

All values are expressed as mean, SD ± n=3

Spreadability

The diameters of gels spreading following the spreadability test are found to be between 2.10 ± 0.08 and 5.5 ± 0.13 cm. This indicates that the spreadability increased with decrease in polymer concentration.

Table 4: Determination of Spreadability.

Formula code	Spreadability
F1	5.0 ± 0.10
F2	5.2 ± 0.15
F3	5.5 ± 0.13
F4	3.5 ± 0.18
F5	4.0 ± 0.22
F6	4.7 ± 0.26
F7	2.1 ± 0.08
F8	3.5 ± 0.10
F9	3.8 ± 0.06

All values are expressed as mean, SD ± n=3

Determination of drying Time

The drying time of all the formulations were found to be in between 180 sec to 310 sec indicating a decreased drying time on increasing the polymer concentration.

Table 5: Determination of Drying Time.

Formula code	Drying time
F1	200 sec
F2	195sec
F3	180 sec
F4	290 sec
F5	270 sec
F6	255 sec
F7	315 sec
F8	310 sec
F9	300 sec

All values are expressed as mean, SD ± n=3

Film Thickness

Formulations were capable of giving films with a thickness ranging from 0.03 ± 0.01 to 0.06 ± 0.02 mm. As the concentration of polymers increased, there was an increase in the thickness of the film due to higher amount of polymer used.

Table 6: Determination of film thickness.

Formula code	Film thickness
F1	0.03 ± 0.01
F2	0.03 ± 0.01
F3	0.04 ± 0.02
F4	0.04 ± 0.02
F5	0.04 ± 0.03
F6	0.04 ± 0.01
F7	0.05 ± 0.01
F8	0.06 ± 0.01
F9	0.06 ± 0.02

All values are expressed as mean, SD ± n=3

Weight Variation Test

Weight of the films was found to be in the range of 0.0440 ± 0.02 mg – 0.0700 ± 0.05 mg. As the concentrations of the polymers increased, the weight of film also increased.

Table 7: Determination of film weight.

Formula code	Film weight
F1	0.0440 ± 0.05
F2	0.0476 ± 0.02
F3	0.0499 ± 0.01
F4	0.0517 ± 0.02
F5	0.0555 ± 0.01
F6	0.0590 ± 0.01
F7	0.0692 ± 0.04
F8	0.0655 ± 0.02
F9	0.0700 ± 0.05

All values are expressed as mean, SD ± n=3

WVP of Film

The results of WVP test shows that films had water vapor permeability ranging from 0.194 ± 0.01 to 0.299 ± 0.04 g cm−2 24 h−1. As the WVP of films exceeds the limit set in British Pharmacopoeia of 0.05 g cm−2 24 h−1, the films are considered permeable to water vapor

and can, therefore, be considered non-occlusive. The values of WVP test indicate that as the concentration of PVP increased, the amount of water absorption also increased.

Table 8: Determination of WVP.

Formula code	Water vapour permeability
F1	0.231 ± 0.03
F2	0.299 ± 0.04
F3	0.220 ± 0.02
F4	0.231 ± 0.03
F5	0.194 ± 0.01
F6	0.274 ±0.02
F7	0.199 ± 0.04
F8	0.240 ± 0.01
F9	0.257 ± 0.02

All values are expressed as mean, SD ± n=3

In vitro drug release study

The release of the drug from the film forming gels varies from 90.06 to 97.00 % that indicates that maximum drug release was found to be in formulation F3 with 97 % drug release.

Table 9: Cumulative % drug release.

TIME (hrs)	CUMULATIVE % DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.1	21.04	28.02	28.62	22.39	29.79	26.00	25	26.17
2	32.5	32.00	38.01	35.67	35.55	37.09	33.45	38.38	40.05
3	50.6	51.94	55.99	53.33	53.70	54.09	51.53	55.90	56.22
4	67.4	67.11	69.66	68.00	68.07	69.01	68.03	69.47	70.05
5	80.00	80.77	86.84	82.11	85.56	85.95	82.06	86.99	87.92
6	90.06	91.73	97.00	93.60	95.07	95.89	91.65	95.92	94.64

All values are expressed as mean, SD ± n=3

Optimization

From design expert software 6 solutions were found. The batch with PVP 8 g and HPMC 6 g with desirability 0.956 was found to be optimum. From this data formulation F3 was selected as the optimum formulation. The figures below show the effect of concentration of PVP and HPMC on spreadability and drying time. It is shown that both the independent variables have a significant effect on the dependent variables and spreadability and drying time decreases as concentration of polymers increases.

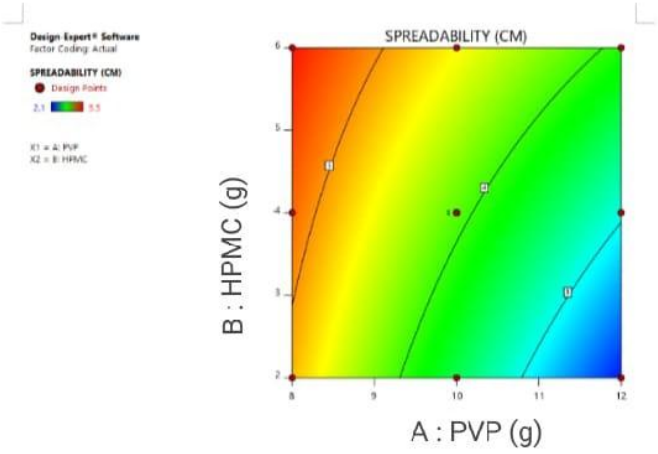

Figure 2: Contour plot showing effect of Polyvinyl Pyrrolidine andHydroxypropyl methyl cellulose on spreadability.

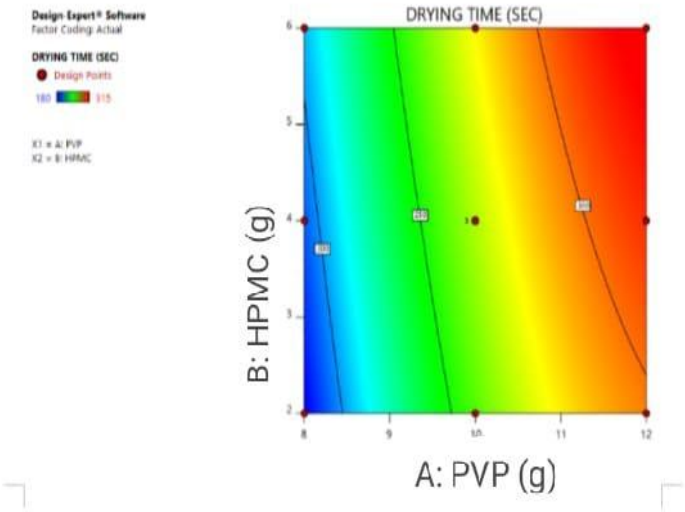

Figure 3: Contour plot showing effect of Polyvinyl Pyrrolidine and Hydroxypropyl methyl cellulose on drying time.

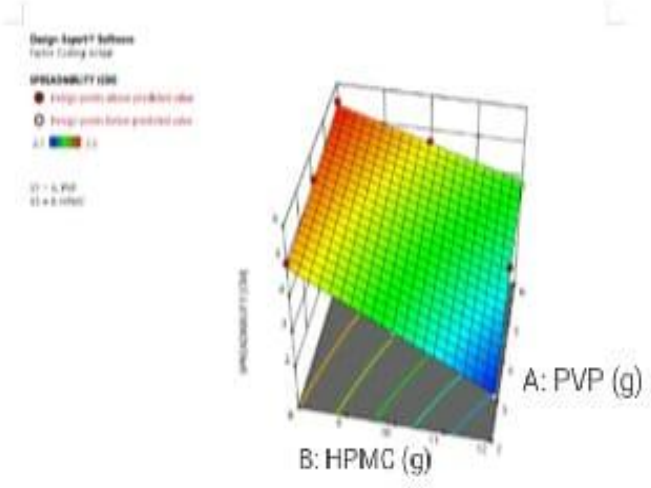

Figure: 3-D plot showing effect of Polyvinyl Pyrrolidine and Hydroxypropyl methyl cellulose on spreadability.

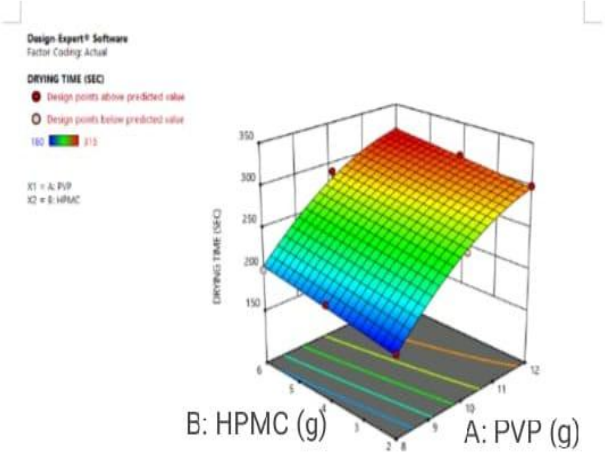

Figure 4: 3-D plot showing effect of Polyvinyl Pyrrolidine and Hydroxypropyl methyl cellulose on drying time.

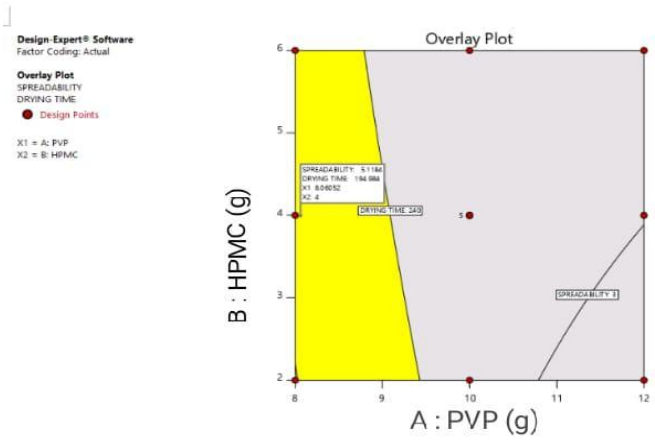

Figure 5: Overlay plot.

Best fit kinetic model for optimized formulation

The diffusion kinetics of optimized formulation was studied. The best fit model with highest R^2 value and least slope value was the zero order model.

Table 10: Best fit kinetic model.

Seriel No.	Model	R^2
1	Zero order	0.970
2	First order	0.239
3	Higuchi	0.946
4	Kosemeyer-Peppas	0.020 (n = 2.995)

Stability study

The optimized formulation was evaluated after storage at room temperature and after accelerated stability study at elevated temperature (40°C/75% RH) in stability chamber.

Table 11: Stability Studies
All values are expressed as mean, SD ± n=3.

FORMULATION CODE	STORAGE CONDITION	SAMPLING INTERVAL	APPEARANCE	pH	DRUG CONTENT (%)
F3	40°C ± 2°C at 75% ± 5%RH	30 days	Clear, Transparent	6.8 ± 0.1	99.32 ± 0.328
		60 days	Clear, Transparent	6.5 ± 0.1	98.29 ± 0.96
		90 days	Clear, Transparent	6.4 ± 0.1	96.8 ± 0.854
	25°C ± 2°C at 60% ± 5% RH	30 days	Clear, Transparent	6.8 ± 0.1	99.32 ± 0.846
		60 days	Clear, Transparent	6.7 ± 0.1	99.00 ± 0.74
		90 days	Clear, Transparent	6.7 ± 0.1	98.21 ± 0.98

Skin irritaton study

The animals were tested for skin irritation study according to the draize scoring method with IAEC Approval No. CCPS/IAEC/2021/02.

Table 12: Skin irritation studies.

Erytheme/oedema	Score
None	0
Slight	1
Well defined	2
Moderate	3
Scar formation	4

No presence of erythema or oedema were seen on the animals after 14 days of animal study and were scored as 0.

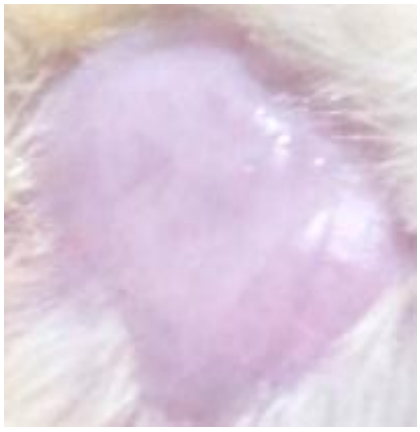

Figure 6: The skin irritation test on application of film forming gel of ketoprofen on 1st day.

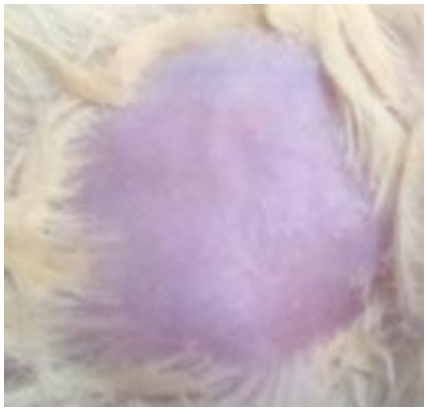

Figure 7: The skin irritation test on application of film forming gel of ketoprofen after 14 days.

CONCLUSION

Film forming gel of Ketoprofen was prepared using Polyvinyl Pyrrolidine and hydroxypropyl Methyl cellulose. The concentrations of both the polymers were optimized by Central composite design to obtain optimum spreadability and drying time. The formulation F3 with a maximum spreadability and minimum drying time was selected as the optimized formulation. The same formulation also showed a highest percentage of drug. Ski irritation study on rats for 14 days showed for no presence of oedema and erythema that proved the medication to be safe for use on human beings. The film forming dermal gel 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. Thus, the formulation can be a better alternative for treating osteoarthritis as well as rheumatoid arthritis and other inflammatory conditions by increasing patient compliance and reducing the gastro-intestinal related toxicities associated with the oral administration of NSAID's like Ketoprofen.

REFERENCES

1. Larissa Carine Piinnel, Dominique Jasmin Lunter. Film forming systems for drug delivery. Pharmaceutics, 2021; 13: 1-19.
2. International Journal of Drug Delivery, 2010; 2: 314-321.
3. Singh V, Singh M, Kukreti G, Agarwal A, Bajaj H. Rheumatoid arthritis: Treatment by film forming gels. J Analgesics, 2015; 3: 9-14.
4. Abrar B, Anis S, Tanu B, Singh S. Formulation and *in-vitro* evaluation of NSAID's gel. International Journal of Current Pharmaceutical Research, 2012; 4: 56-8.
5. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. Asian Journal of Pharmaceutical Sciences, 2017; 12: 487-97.
6. Mundada M, Wankhede S, Patwardhan S, Avachat A. Formulation and evaluation of topical gel of lornoxicam using a range of penetration enhancers. Indian Journal of Pharmaceutical Education and Research, 2013; 47: 168-71.
7. Abeer H. Khasragi, Lena Murad Thomas. Preparation and evaluation of Lornoxicam film forming gel. Drug Invention Today, 2019; 11(8): 1906-1913.
8. Saudagar RB. Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of terbinafine hydrochloride. International Journal of Pharmaceutical Science and Research, 2014; 5: 537-54.
9. R. B Saudagar, P. A Gangurde. Film forming gels: A review, 2017; 8(3): 244-248.
10. R. B Saudagar, P. A Gangurde. Formulation, development and Evaluation of Film forming gel for prolonged delivery of Miconazole Nitrate. International Journal of Chemtech Research, 2017; 10(15): 282-299.
11. S. Z Chemate, Shubhangi N. Albhar, Formulation and Development of Flurbiprofen containing Film Forming Gel. World Journal of Pharmaceutical Research, 2017; 6(11): 652-662.
12. Li X, R. Zhang, R. Liang, W. Liua, C. Wanga, Z. Su, F. Sun, Y. Li, Preparation and characterization ofsustained-release rotigotine film-forming gel, International Journal of Pharmaceutics, 2014; 460(1): 273-79.
13. Design of Experiments (DoE) and Process Optimization. A Review of Recent Publications. Steven A. Weissman and Neal G. Anderson. June 27, 2014. https://doi.org/10.1021/op500169,2014 American Chemical Society.
14. Utkarsh Verma, Nidhi Bhatt, Rohit Kumar, Shefali Srivastava. Preparation and Evaluation of Econazole containing film forming gel. European Journal of Molecular and Clinical Medicine, 2021; 8(3): 2881-2895.
15. Sangshetti J. N, Chitlange S. S, Zaheer. Z. Quality by design in pharmaceuticals, 2015; 1.
16. Quality by Design (QbD) Approach used in Development of Pharmaceutical Formulations [Internet]. [cited 2020 July 16]. Available from: https://www.researchgate.net/publication/328265374_Quality_by_Design_QbD_Approach_used_in_Development_of_Pharmaceutical_Formulations.
17. ICH Q8(R2) Pharmaceutical Development, 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf. [Accessed on May 21,2015].
18. https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecdtg404.pdf