ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Design and Evaluation of Flurbiprofen Micro-Emulsion Based Gel

Manish Wani*[1], Akshay Baheti[1], Satish Polshettiwar[1], Tanaji Nandgude[2], Aarti Shastri[1], Yogita Ozarde[1]

[1]Department of Pharmaceutics, School of Pharmacy, Dr. Vishwanath Karad MIT World Peace University, Pune-411038, India
[2]Department of Pharmaceutics, Dr. D Y Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune-411018, Maharashtra, India

Article History:

Received on: 23 Sep 2020
Revised on: 15 Oct 2020
Accepted on: 23 Oct 2020

Keywords:

Flurbiprofen, microemulsion gel, tween 80, propylene glycol, paw oedema, anti-inflammatory

ABSTRACT

Flurbiprofen via oral route has many side effects. Many inflammatory infections occur locally and close to the body's surface, so topical application of flurbiprofen is advantageous. Still, intact skin acts as a barrier and hampers skin penetration of the drug. Present objective of this work was to reduce the adverse effect of flurbiprofen and increase its bioavailability by formulating Flurbiprofen microemulsion based gel, evaluating it for its Physico-chemical properties and then finally conducting its *in-vitro* and animal studies to determine its efficiency. Arachis oil was selected as an oil phase as flurbiprofen showed maximum solubility in it. Microemulsion formulations (A1 to A9) were prepared by varying the qty of tween 80 (as a surfactant) and propylene glycol (as co-surfactant). Microemulsions which were found to give satisfactory results w.r.t microemulsion formation (F1 to F5) were converted to microemulsion gel using Carbopol 934 as gel base. The ability of different microemulsions to penetrate flurbiprofen through the skin was *in-vitro evaluated*. All the formulations were evaluated for their quantity of drug present in the formulation, pH, Viscosity, Spreadability, in vitro diffusion study. Formula F4, which showed good Physico-chemical properties, was subjected to anti-inflammatory study. Results showed that pH, spreadability, viscosity and amount of active ingredient present in formulations were in an acceptable limit. The standard calibration curve for flurbiprofen depicts the linear association between concentration and absorbance. The formulation F4 has the highest % release, 90.54% also showed a higher % inhibition of paw oedema after 4 hrs than marketed formulation.

*Corresponding Author

Name: Manish Wani
Phone: +91- 976235652
Email: manish.wani@mitwpu.edu.in

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3868

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Flurbiprofen belongs to the class of 2-aryl propionic acids group of compounds which have non-steroidal anti-inflammatory drugs activity (Meek *et al.*, 2010). Flurbiprofen is weak acids, with a pKa of 3-5, it undergoes oxidative first past metabolism by enzymes in the hepatic system and excretion of its metabolites is through renal system and bile. On oral administration, flurbiprofen shows side effects like retching, puking, indigestion, ulceration of the intestine, gastric haemorrhage, and loose stool. As the duration of therapy increases, there is a risk

that ulcers present in GIT may also get aggravated and also with an increase in doses there is a risk of increasing side effects (Goldstein and Cryer, 2015). Topical application of flurbiprofen reduces these side effects. Topical routes also have advantages like they prevent the absorption and metabolism issues associated with oral administration; if the oral route is unsuitable, like in case of vomiting and diarrhoea, then the topical route can be a suitable replacement; moreover, topical routes are non-invasive thus minimizing risks and inconveniences associated with injectable; they can increase the bioavailability and drug effectiveness because hepatic first-pass is circumvented; the topical application has shown to have good patient compliance because of its simple application method; the action of the drug can be easily stopped by simple washing of the applied formulation from the surface of the skin, and they deliver the drug directly to the site of action (Kai *et al.*, 2013). The main disadvantage of topical routes is the permeability of drug through barrier properties of intact skin (Paudel *et al.*, 2010). This can be overcome by developing microemulsion gel.

Microemulsions are isotropic solutions which are made stable thermodynamically, by an effective surfactant or surfactant mixture. In this system, significant quantities of two immiscible liquids, often water and oil, are brought into a single-phase (Shehzad and Khaled, 2018).

A mixture of oil, water, and surfactant are converted into clear water-in-oil microemulsion. Water droplets are surfactant-stabilized in a continuous oil process. As per USP Gels are semi-solid structures made up of either small inorganic particles or large organic molecules that are enclosed and interpenetrated by liquid dispersion. A three-dimensional, unique structure of organic particles is an identity of gels.

Gels are a two-phase system where big organic particles are dissolved in the continuous phase, while inorganic particles are dispersed in the continuous phase (Sharadha *et al.*, 2020). Microemulsion gel is an amalgamation of microemulsion and gel.

The aim and objectives of the present study were to formulate microemulsion gel of flurbiprofen which would be stable and have good permeation of flurbiprofen and would not cause irritation to skin.

MATERIALS AND METHODS

Flurbiprofen was obtained from FDA India, Arachis Oil from McW Health Care Indore, Carbopol (934) from S. D. Fine Chemicals Mumbai and Tween 80, Propylene glycol from Lobachemie, Mumbai.

Drug Identification Studies

The drug under consideration, i.e. flurbiprofen, was checked for its purity by checking its melting point, FTIR and λ max. The melting point was determined by capillary method (Kshirasagar *et al.*, 2019). The FTIR spectrum was compared with standard FTIR spectra of Flurbiprofen (Kshirasagar *et al.*, 2019). The UV spectrum was recorded over suitable wavelength, and λ max was determined by dissolving 10mg of the drug in 100ml of phosphate buffer (PB) pH 6.4, to obtain a concentration of 100μg/ml (Kshirasagar *et al.*, 2019).

Preformulation Studies

Checking solubility of the drug in oils

To determine oil that can be used to solubilize active ingredient flurbiprofen so that the same can be dispersed phase in the microemulsion, flurbiprofen was mixed in various oils, and its solubility was measured (Sabale and Vora, 2012). Oils used in this study were cottonseed oil, Arachis oil, corn oil, sesame oil, olive oil, mineral oil, IPM. For 5 ml of each oil, an excess amount of flurbiprofen was added and shaken for 72 h at 30°C. A cellophane membrane filter was used to filter the suspension, and the drug concentration in the filtrate was measured using the UV process. The flurbiprofen oil mixture was filtered through a cellophane membrane filter, and the drug concentration in the filtrate was determined using the UV method (Sabale and Vora, 2012).

Compatibility studies

FT-IR spectrum of the drug mixed with excipients was compared with Individual IR spectra of the Flurbiprofen (Damor, 2017) taken using KBr pellet, between 4000cm^{-1} to 500cm^{-1} range.

Calibration Curve

Standard curve of the Flurbiprofen in PB pH 6.4 (Abd-Alhammid and Saleeh, 2014) was plotted by recording the absorbance of solutions at different concentrations (4-20μg/ml).

Formulation and Development of Flurbiprofen Microemulsion Gel

Formulation of Flurbiprofen Microemulsion

Surfactant, Co-surfactant mixture with different ratios were prepared (Table 1). Flurbiprofen was dissolved in Arachis oil. In the next step, the surfactant/ co-surfactant mixture was added to Flurbiprofen in Arachis oil. Oily mixtures were subjected to gentle agitation with the help of magnetic stirrer and drop by drop water was added to each of them. Beginning of phase inversion area is noted when the clear mixture became turbid at a certain point. O/W

Table 1: Formulation of Flurbiprofen Microemulsion

Sr No	Material	Trail Batches								
		A1	A2	A3	A4	A5	A6	A7	A8	A9
1	Flurbiprofen	3g	3g	3g	3g	3g	3g	3g	3g	3g
2	Arachis oil	8g	8g	8g	8g	8g	8g	8g	8g	8g
3	Tween 80	10	10	10	12	12	12	14g	14g	14g
4	Propylene Glycol	6g	7g	8g	6g	7g	8g	6g	7g	8g
5	Distilled Water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Table 2: Formulation of Flurbiprofen Microemulsion gel

Sr No	Material	Final Batches				
		F1	F2	F3	F4	F5
1	Flurbiprofen	3g	3g	3g	3g	3g
2	Arachis oil	8g	8g	8g	8g	8g
3	Tween 80	10g	12g	14g	14g	14g
4	Propylene Glycol	8g	8g	6g	7g	8g
5	Distilled Water	qs	qs	qs	qs	qs
6	Carbopol 934	2g	2.5g	3g	3.5g	4g
7.	Triethanolamine	1.5 ml	1.5 ml	1.5 ml	1.5 ml	1.5 ml

Table 3: Group specifications for In vivo Anti-inflammatory study

Sr. No.	Formulation	Group
1. 1.	Control 1	I
1. 2.	Formulation F4- A	II
1. 3.	Control 2	III
1. 4.	Formulation F4-B	IV
1. 5.	Marketed gel	V

Table 4: Flurbiprofen solubility in various oils

Oil	Solubility mg/ml
Arachis oil	20.63
Corn oil	3.25
Sesame oil	3.42
Olive oil	4.31
Mineral oil	0.57
IPM	5.73

Table 5: % of the active ingredient in Microemulsion Gel

Sr. No.	Formulations	% of the active ingredient				pH*	Viscosity* (centipoise)	Spreadability* (Mean ± SD)
		1	2	3	Mean ± S. D.			
1	F1	95.54	96.74	96.74	96.34	7.64	92400	15.882 ± 0.291
2	F2	97.51	98.54	96.24	97.43	7.35	107100	17.928 ± 0.300
3	F3	100.23	97.45	91.58	96.42	7.47	107600	18.382 ± 0.191
4	F4	99.47	99.85	98.49	99.27	7.37	108100	21.962 ± 0.187
5	F5	94.87	94.58	96.57	95.34	7.85	108300	27.252 ± 0.214

*Mean of three determinations (n=3)

Table 6: In Vitro Diffusion Study of Microemulsion Gel

Sr. No.	Time	Avg. %R F1	Avg. %R F2	Avg. %R F3	Avg. %R F4	Avg. %R F5
1	0	0	0	0	0	0
2	15	1.007	1.742	1.742	1.007	2.476
3	30	9.122	6.209	4.005	4.715	6.234
4	60	21.188	16.704	10.018	13.69	9.384
5	120	35.128	31.227	28.72	32.519	23.654
6	180	54.666	46.231	39.975	47.574	32.528
7	240	68.226	60.247	53.789	55.764	52.699
8	300	80.722	73.225	66.564	65.652	61.042
9	360	81.042	75.255	81.188	79.491	71.082
10	420	–	–	–	83.051	–
11	480	–	–	–	90.544	–
t50		164min	199min	215min	223min	228min

Table 7: Percent oedema inhibition shown by formulation F4

Sr. No.	Formulation	Mean paw oedema volume after (± S. E. M.)			
		1hr.	2hr.	3hr.	4hr.
1.	Control	0.258 ± 0.019	0.329 ± 0.0025	0.296 ± 0.020	0.301 ± 0.052
2.	F4	0.163 ± 0.0046**	0.114 ± 0.0028**	0.097 ± 0.0054**	0.142 ± 0.0039**
3.	Marketed	0.179 ± 0.0038**	0.184 ± 0.0026**	0.097 ± 0.0014**	0.946 ± 0.0021**

** $P \leq 0.01$

microemulsion formation takes place when the turbid mixture turns clear.

Finally, we can say O/W microemulsion has terminated when the system becomes turbid once again with the continuous addition of water (Yadav *et al.*, 2018).

The experiment was repeated at different quantities of S/CoS keeping constant ratio (Yadav *et al.*, 2018). Suitable oil, surfactant and co-surfactant quantities were selected (Formulation F1 to F5) for further studies, based on the results obtained from the above experiment.

Converting of Flurbiprofen Microemulsion to Flurbiprofen Microemulsion Gel

To the formulated microemulsions, carbopol 934 (Naeem, 2019) was added in incremental quantity (Table 2) and dispersed. To this mixture, slowly, triethanolamine was added (Naeem, 2019). This gel was used for further studies

Evaluation of Microemulsion Gel

Psycho rheological analysis

The prepared gels were examined with naked eye against a white and black background for trans-

Table 8: Stability Study of Formulation F4

Formulation		Storage condition 25° C ± 2° C at 75 ± 5 % RH Months				40° C ± 2° C at 75 ± 5 % RH Months			
Sr. No.	Parameter	0	1	2	3	0	1	2	3
1.	Drug content (%)	99.7 ± 0.232	98.98 ± 0.548	98.66 ± 0.654	98.25 ± 0.145	99.59 ± 0.148	98.23 ± 0.784	97.82 ± 0.481	97.99± 0.412
2.	Viscosity (Poise)	102458	124578	102457	104578	103568	110458	102478	104578
3.	pH	9.21	9.24	9.45	9.24	9.54	8.94	9.14	8.91
4.	Spreadability (gcm/sec)	27.45± 0.145	27.56± 0.247	26.97± 0.548	27.12± 0.462	28.01± 0.476	27.94± 0.157	28.07± 0.459	27.66± 0.457
5.	Diffusion study	90.14± 0.478	90.47± 0.014	89.76± 0.125	89.47± 0.478	90.48± 0.125	90.01± 0.784	90.00± 0.412	89.75± 0.047

parency, the appearance of any lumps (Sharma *et al.*, 2013) and any unexpected changes in viscosity. The preparations were applied on the skin to measure the sensation, and the sensations were documented clinically.

Drug Content

0.5g of the formulation was drawn in a volumetric flask of 50 ml capacity, and it was diluted with PB and drug was dissolve in phosphate buffer by continuous shaking (Sharma *et al.*, 2013). This solution was passed through Whatman filter paper no. 42. From the filtrate obtained 1 ml of was withdrawn and diluted to 10 ml with PB. The standard curve was used to spectrophotometric calculation of the quantity of the drug present (Sharma *et al.*, 2013) infiltrate.

pH determination

The pH of prepared microemulsion gels was decided using pH meter (Raja *et al.*, 2012).

Viscosity

Brookfield viscometer was used to find out viscosity of prepared gels. For this, in the cylindrical tube, 10g of microemulsion gel was loaded, and the dial reading was recorded at 60 rpm (Raja *et al.*, 2012). Dial readings were multiplied with factor given in the catalogue. The results obtained indicated the viscosity in cps.

Spreadability

For determining spreadability of preparations, the apparatus was fabricated in the laboratory as suggested by Multimer et al. 2.5 g of microemulsion gel sample was placed between movable and fixed glass. Weight of 1000g (Raja *et al.*, 2012) was kept on movable slides for 5 min so that the uniform distribution of gel takes place between both glass sides. 60g weight was kept on the pan which was attached to a movable glass slide with thread. The time required for the movable glass slide to separate and to travel distance l in seconds was observed. Spreadability was calculated using the formula (Raja *et al.*, 2012).

S = m.l / t. Where, S - Spreadability in g.cm / sec, t - Time measured in sec, l – distance traveled by, m - Weight inside pan.

***In Vitro* Diffusion Study**

In vitro diffusion experiment was done to evaluate the process of release of drugs from formulations. Prepared gels were subjected to in vitro diffusion analysis using Franz diffusion cell and cellophane membrane (Sharma *et al.*, 2013). PB (pH 7.4) was filled in the receiving compartment (Sharma *et al.*, 2013). Sink conditions were maintained with the help of PB throughout the analysis. The entire assembly was held at 37 ± 1^0C, and the receptor solution was mixed at 600 rpm during the procedure with a magnetic stirrer. Care was taken to keep air bubbles from being caught under the membrane. Aliquots (1 ml) were extracted at fixed one h intervals for a period of 8h, and an equal volume of fresh medium was replaced (Sharma *et al.*, 2013). Samples were correctly diluted with PB medium and spectrophotometrically analyzed for flurbiprofen content at 247 nm. At each time, the total qty of flurbiprofen diffused per unit area of the membrane was analyzed.

***In vivo* Anti-inflammatory study**

Using 30 albino rats of both sex, and *in-vivo* anti-inflammatory analysis was carried out (Murthuza and Manjunatha, 2018) (approved by the Institutional Animal Ethical Committee, MAEERS MIP

Pune). The weight of theses rats was in the range of 100-150g. They were divided into five groups. Acute inflammation was produced in all groups, by injecting 0.1 ml (sub-planter) in left hind paw of the rats freshly prepared carrageenan 1 % suspension in normal saline (Murthuza and Manjunatha, 2018). 0.25g of medicated gel or base was topically dabbed on the paw of each rat of respective group one hour before and after the carrageenan challenge. 1, 2, 3 and 4 hours after injection of carrageenan paw oedema volume was measured using plethysmometer (Murthuza and Manjunatha, 2018). The average volume of the groups was determined and compared with control. The per cent inhibition of oedema was calculated by using the following formula (Murthuza and Manjunatha, 2018).

% Edema inhibition = (1- Vt / Vc) 100

Where, Vt - Mean oedema volume of test and Vc - Mean oedema volume of control

Statistical significance was calculated by using the student's unpaired 't' test. Group specifications are shown in (Table 3) .

Stability Study

Freeze-thaw and thermal cycling test

In a cyclic pattern, the chosen microemulsion gel were subjected to varying temperature conditions that mimic the condition that is likely to occur during its use or in the delivery process. One cycle was completed when the chosen formulations were exposed to cooling temperatures (2-8°C) for two days, followed by 40°C for next two days (Dantas *et al.*, 2016). Such three freeze-thaw cycles were accomplished in twelve days. During this period, any significant changes in microemulsion gel were observed.

Once no significant change was observed, these microemulsion gel were then subjected to the following condition of temperature and relative humidity during stability studies.

25°C ± 2°C at 75 ± 5% RH and 40°C ± 2°C at 75 ± 5% RH

Formulations were evaluated for various parameters after every month for three months. The parameters (Dantas *et al.*, 2016) of the microemulsion gel studied were the amount of active ingredient, rheology, pH change and In vitro diffusion study.

RESULTS AND DISCUSSION

Drug Identification Studies

The melting point of the drug sample was found in the range of 161-163°C, as reported in the literature for flurbiprofen. FTIR of drug sample (Figure 1) was found to match with standard FTIR of Flurbiprofen. Standard functional group frequencies matched with observed frequencies of flurbiprofen. The recorded UV spectra of drug sample showed the absorbance maxima (λmax) at 247nm confirming the purity of Flurbiprofen (Figure 2).

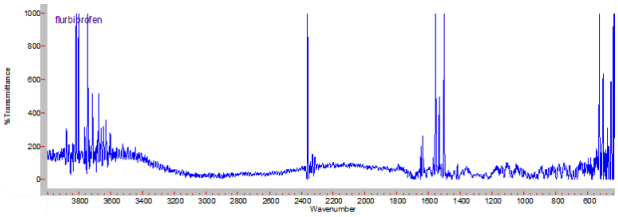

Figure 1: FT-IR Spectra of Flurbiprofen

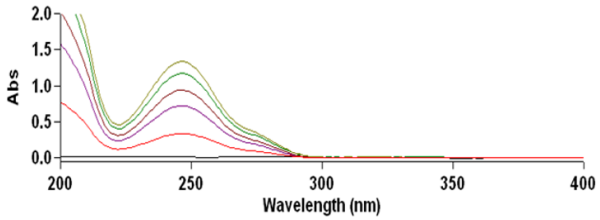

Figure 2: UV Spectra of Flurbiprofen

Formulation and Development of Flurbiprofen Microemulsion Gel

The solubility of flurbiprofen in various oils at 35°C observed were tabulated in (Table 4). Flurbiprofen was found to have maximum solubility in Arachis oil, and hence that was selected as an excipient for formulating microemulsion. Combination IR spectra of Flurbiprofen with Arachis oil (Figure 3) and Flurbiprofen with Carbopol (Figure 4) were obtained. When compared with individual IR spectra of flurbiprofen, no peak distortions were found. Thus it can be concluded that flurbiprofen is compatible with Arachis oil Carbopol. Absorbance recorded at different concentrations (1-5μg/ml) showed that Beer and Lambert's law was followed, the coefficient of correlation was 0.995 and equation of regressed obtained was Y = 0.0731X. Microemulsions containing flurbiprofen was successfully formulated, taking the optimum quantity of Arachis oil, Tween 80 - Propylene Glycol as a surfactant - co-surfactant combination. This formulated flurbiprofen microemulsion was then successfully converted to gel using carbopol as a gelling agent.

Evaluation of Microemulsion Gel

Flurbiprofen gel formulations were found to be transparent and possessed smooth texture; this was because carbopol quantity was kept below 4.5g. The pH of all gel formulation was found in between 7.35 to 7.85, the high values of pH are attributed to the addition of tri ethanol amine which is used as pH

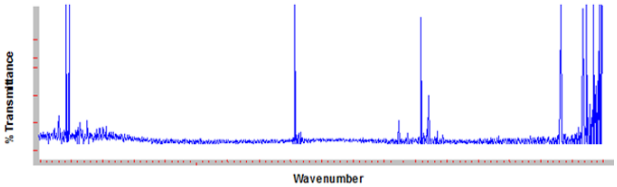

Figure 3: Combination Flurbiprofen- Arachis oil FTIR Spectra

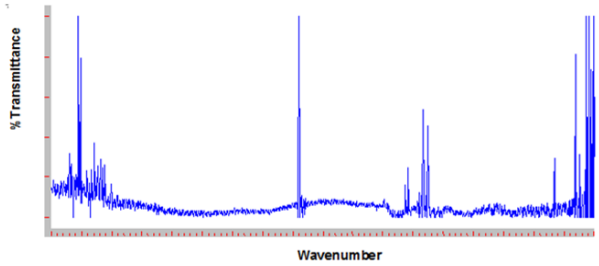

Figure 4: Combination Flurbiprofen- Carbopol FTIR Spectra

modulator to bring about sol to gel conversion of gelling agent carbopol. Viscosity is an essential parameter in semi-solid preparations low viscosity would cause draining of the preparation from the skin. In contrast, high viscosity would result in poor spreadability, poor extrudability and would affect drug release too.

The viscosity of the formulated gel was found to be optimum in the range of 92400cps to 108300. Drug content study indicated that the Flurbiprofen microemulsion was uniform during gel formation and the drug content within permissible limits. Spreadability is vital from the view of patient compliance as easily spreadable gel gives a good feel to the patient. It also helps in the uniform application of gel on the skin.

The spreadability of the formulated gel decreased as the concentration of gelling agent increased. Amount of active ingredient present in the gel was 95.34% (F5) to 99.27% (F4) showing that the drug is evenly distributed in the formulation. The results of pH, Viscosity and Spreadability are tabulated in Table 5.

In Vitro Diffusion Study

The drug release data obtained are tabulated in Table 6. It was observed that % release of drug was 81.04%, 75.25%, 81.18%, 90.54% and 71.08% in formulations from F1 to F5 respectively.

F4 formulation show 90.54% release of the active ingredient after twelve hours.

In vitro release, results showed that sustained release was shown by the F4 formulation and could keep the release medicament for an extended amount of time (12 hours). It was therefore further used for animal research and trials of stability.

In vivo Anti-inflammatory study

The results of the effect of formulation F4 of Flurbiprofen microemulsion gel on carrageenan-induced oedema are shown in Table 7. Formulation F4 of Flurbiprofen microemulsion gel demonstrated noteworthy anti-inflammatory activity when compared with control and marketed.

Stability Study

No significant change was found in formulation F4 with regards to % of the amount of active ingredient, Viscosity, pH, Spreadability & Diffusion study after one month, two months and three months of stability studies (Table 8).

CONCLUSIONS

The received sample of flurbiprofen was checked for its characterization and was found to be of good quality. The purity of excipients was verified, and they were found to be compatible with the drug. Different topical formulations were developed successfully and were evaluated for various quality control test, which will determine its safety efficacy and stability. It was observed that all formulations had a good texture which was evident from the fact that no lump was present in a smooth microemulsion gel. It was found that the pH, spreadability, viscosity and qty of active ingredient were in the correct range. Standard calibration curves for flurbiprofen were prepared. The line equation was $y = 0.0731x$ ($R^2 = 0.995$). Correlation coefficient (R^2) values indicate the linear association between absorbance and concentration. % release of Formulation F4 was highest at 90.54%, and hence the same was used for further studies. The formulation F4 showed a higher % inhibition of paw oedema after 4 hrs than the marketed formulation. Finally, formulation F4 was found to be stable and doesn't show precipitation, aggregation, separation of phases and significant rheological changes in freeze-thaw and thermal cycling test. From the studies, we can conclude that developed Flurbiprofen microemulsion gel is having enhanced anti-inflammatory activity than marketed formulations.

Acknowledgement

We are very much thankful to BCUD (now BOD), SPPU, Pune for funding this work and we also thank the management of Dr Vishwanath Karad, MIT World Peace University, School of Pharmacy, MIT Campus, Kothrud, Pune, 411038 for providing necessary help in carrying out the study in their laboratories.

Conflict of Interest

The researchers mention no conflicts of interest. The composition and writing of the document are the sole responsibility of the writer.

Funding Support

We have received funds from BCUD (now BOD), Savitribai Phule Pune University, Pune (Reference No. BCUD/OSD/84) for this work.

REFERENCES

Abd-Alhammid, S. N., Saleeh, H. H. 2014. Formulation and evaluation of flurbiprofen oral film. *Iraqi Journal of Pharmaceutical Sciences*, 23(1):53–59.

Damor, H. 2017. Formulation and Evaluation of Flurbiprofen Aqueous Injection. *Open Access Journal of Science*, 1(2):37–42.

Dantas, M. G. B., Reis, S. A. G. B., Damasceno, C. M. D., Rolim, L. A., Rolim-Neto, P. J., Carvalho, F. O. 2016. Development and Evaluation of Stability of a Gel Formulation Containing the Monoterpene Borneol. *The Scientific World Journal*, 2016:1–4.

Goldstein, J., Cryer, B. 2015. Gastrointestinal injury associated with NSAID use: a case study and review of risk factors and preventative strategies. *Drug, Healthcare and Patient Safety*, 7:31–41.

Kai, S., Kondo, E., Kawaguchi, Y., Kitamura, N., Yasuda, K. 2013. Flurbiprofen concentration in soft tissues is higher after topical application than after oral administration. *British Journal of Clinical Pharmacology*, 75(3):799–804.

Kshirasagar, N., Puchchakayala, G., Balamurgan, K. 2019. Formulation and characterization of flurbiprofen loaded microsponge based gel for sustained drug delivery. *International Journal of Research in Pharmaceutical Sciences*, 10(4):2765–2776.

Meek, I. L., de Laar, M. A. V., Vonkeman, H. E. 2010. Non-Steroidal Anti-Inflammatory Drugs: An Overview of Cardiovascular Risks. *Pharmaceuticals*, 3(7):2146–2162.

Murthuza, S., Manjunatha, B. K. 2018. In vitro and in vivo evaluation of anti-inflammatory potency of Mesua ferrea, Saraca asoca, Viscum album & Anthocephalus cadamba in murine macrophages raw 264.7 cell lines and Wistar albino rats. *Beni-Suef University Journal of Basic and Applied Sciences*, 7(4):719–723.

Naeem, M. 2019. Microemulsion and microemulsion based gel of Zaleplon for transdermal delivery: Preparation, optimization, and evaluation. *Acta Poloniae Pharmaceutica - Drug Research*, 76(3):543–561.

Paudel, K. S., Milewski, M., Swadley, C. L., Brogden, N. K., Ghosh, P., Stinchcomb, A. L. 2010. Challenges and opportunities in dermal/transdermal delivery. *Therapeutic Delivery*, 1(1):109–131.

Raja, J., Kumar, D. E., Chuah, C., Jaya, R., Selvadurai, M., Dhanaraj, S. 2012. Development and evaluation of microemulsion based gel (MBGs) containing econazole nitrate for nail fungal infection. *Journal of Pharmacy Research*, 5(4):2385–2390.

Sabale, V., Vora, S. 2012. Formulation and evaluation of microemulsion-based hydrogel for topical delivery. *International Journal of Pharmaceutical Investigation*, 2(3):140–140.

Sharadha, M., Gowda, D. V., Gupta, V., Akhila, N., R, A. 2020. An overview of the topical drug delivery system - An updated review. *International Journal of Research in Pharmaceutical Sciences*, 11(1):368–385.

Sharma, M., Bhowmick, M., Pandey, G. K., Joshi, A., Dubey, B. 2013. Formulation and Evaluation of Hair Gel for the Treatment of Chronic Inflammatory Disorder Seborrheic Dermatitis. *International Journal for Pharmaceutical Research Scholars (IJPRS)*, 2(4):33–41.

Shehzad, A., Khaled, E. 2018. Microemulsion in Enhanced Oil Recovery, Science and Technology Behind Nanoemulsions. Selcan Karakuş, IntechOpen.

Yadav, V., Jadhav, P., Kanase, K., Bodhe, A., Dombe, S. 2018. Preparation And Evaluation Of Microemulsion Containing Antihypertensive Drug. *International Journal of Applied Pharmaceutics*, 10(5):138.

