ORIGINAL ARTICLE

Ibuprofen Emulgels as Promising Topical Drug Delivery System - A Study of Formulation Design and *In vitro* Evaluation

D. S. Sandeep[1]*, A. Kiran[1], Pankaj Kumar[2]

[1]Nitte (Deemed to be University), NGSM Institute of Pharmaceutical Sciences, Department of Pharmaceutics, Deralakatte, Mangaluru, Karnataka, India, [2]Nitte (Deemed to be University), NGSM Institute of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Deralakatte, Mangaluru, Karnataka, India

Abstract

Aim: Ibuprofen is BCS class-II drug with lower solubility and higher permeability. The present work was undertaken to formulate ibuprofen emulgels with a view to enhance the bioavailability and to make a suitable topical drug delivery system. **Methods:** Xanthan gum was used as gelling agent in different concentrations. Ibuprofen was dissolved in ethanol and propylene glycol. The oily phase was prepared with liquid paraffin. The formulated emulgels were subjected for appearance, pH, spreadability, swelling index, rheological study, drug content, and drug release parameters, and the optimized batch was evaluated for particle size and *in vitro* skin irritation study by HET- CAM test. **Results:** The prepared emulgels showed satisfactory results for the evaluation parameters. The emulgel IG-4 emerged as optimized formulation with higher drug release which had good mean particle size and also found to be non-toxic and non-irritant with the obtained results of HET-CAM test. **Conclusion:** Emulgel can be promising topical drug delivery approach for ibuprofen to enhance the bioavailability with better patient compliance.

Key words: Emulgel, HET-CAM test, Ibuprofen, Xanthan gum

INTRODUCTION

In the recent years, the concept of emulgels has emerged as potential drug delivery approach for topical administration of drugs. The reason being is emulgels provide certain benefits such as controlled and sustained drug release, eliminates the first pass metabolism of orally administered drugs; provide targeted drug delivery approach and enhanced skin permeation by improving drug characteristics.[1]

Emulgels are being used for delivery of wide range of drugs such as analgesics, anti-inflammatory, antifungal, anti-acne drugs, and also for some cosmetic preparations.

Emulgel is formulation combination of emulsions with gel phase. Both o/w and w/o type emulsions can be extensively used for their therapeutic properties and as vehicles to deliver the drugs to the skin. Emulsions usually have certain degree of elegance and can be easily vanished on the skin surface. They also have enhanced skin permeation properties.[2,3]

Ibuprofen is one of most commonly employed NSAID to combat acute and chronic arthritis. Ibuprofen belongs to BCS class II drug, which has poor aqueous solubility and high permeability across the intestinal membrane. The oral dosage form of Ibuprofen has encountered gastric irritation leading to peptic ulcers. In addition to this, Ibuprofen also has low intrinsic skin permeability. There is need to develop a better and stable topical drug delivery approach to reduce the complications of oral and conventional gel formulations of Ibuprofen.[4,5]

The current study was focused on formulating Ibuprofen emulgels with natural polymers such as xanthan gum as better alternative formulation approach to enhance the drug permeation properties and also to provide prolonged duration of action to improve patient compliance.[6]

Address for correspondence:
D. S. Sandeep, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Paneer, Deralakatte, Mangaluru - 575 018, Karnataka, India. E-mail: sandypharama@gmail.com

Received: 12-07-2021
Revised: 18-10-2021
Accepted: 07-11-2021

MATERIALS AND METHODS

Materials

Ibuprofen was procured from Remedix Pharma Private Ltd., Bengaluru. Xathan gum, liquid paraffin, span 20, tween 80, methyl paraben, propyl paraben, ethanol, propylene glycol and triethanolamine were purchased from Hi media Laboratories, Mumbai.

Methodology

Preparation of Ibuprofen Emulgels

For preparing the Ibuprofen emulgels, firstly gel phase was prepared using varying concentrations of xanthan gum by dispersing in purified water followed by mechanical stirring. In liquid paraffin, span 20 was added in the required quantity to prepare the oily phase of emulsion. The aqueous phase was prepared by the dispersion of small amount of tween 80 in distilled water followed by magnetic stirring. Ibuprofen in the required amount (1%) was dissolved in ethanol followed with magnetic stirring and the methyl and propyl parbens in the required amounts were added and dissolved in propylene glycol. The aqueous and oily phases were separately heated to 70°C for 20 min. Later, the emulsion phase was mixed with the gel phase by equal amounts followed by gentle mixing to get clear emulgel. At the end, triethanolamine was added drop wise to the emulgel to adjust the pH.[7]

The formulation composition of Ibuprofen emulgels is shown in Table 1.

Evaluation of emulgels

Drug-polymer compatibility by FTIR Study

ATR-Bruker FTIR method is followed for assessing the compatibility of pure drug of ibuprofen with xanthan gum.

Table 1: Formulation composition of Ibuprofen emulgels

Ingredients	Formulation code				
	IG-1	IG-2	IG-3	IG-4	IG-5
Ibuprofen (% w/w)	1	1	1	1	1
Xanthan gum (%)	0.5	1	1.5	2	2.5
Liquid paraffin (%)	5	5	5	5	5
Span 20 (%)	0.2	0.2	0.2	0.2	0.2
Tween 80 (%)	0.4	0.4	0.4	0.4	0.4
Methyl paraben (%)	0.03	0.03	0.03	0.03	0.03
Propyl paraben (%)	0.03	0.03	0.03	0.03	0.03
Ethanol (%)	3	3	3	3	3
Propylene glycol (%)	7	7	7	7	7
Distilled water	q.s	q.s	q.s	q.s	q.s
Triethanolamine	q.s	q.s	q.s	q.s	q.s

The IR spectrum of pure drug of ibuprofen and xanthan gum was interpreted with their physical mixture to confirm whether both the drug and polymer were in compliance with one another or not.[8]

Appearance

The prepared Ibuprofen emulgels were visually inspected for appearance by checking the color, clarity and homogeneity parameters.[9]

pH

The pH of all the prepared emulgels was measured with digital pH meter.[9]

Rheological study

The viscosity predicts the flow properties of the formulations. Viscosity of all the formulated emulgels was determined by Brookfield viscometer using spindle no. 94 with shear rate of 5 rpm at 25°C. The viscosity measurement was taken in cps.[10]

Spreadability

This was evaluated by placing about 1 g of formulation on a glass slide. Another glass slide of the same length was placed above that and a weight of 100 g was put on both the glass slides so that the gel gets sandwiched between the two glass slides and spreads at certain distance. The time taken for the gel to travel the distance from the original place of its position was noted.[11] Spreadability was calculated by the formula as shown below.

$$S = \frac{M \times L}{T} \quad (1)$$

Where,
S - Spreadability, g.cm/s
M - Weight put on the upper glass
L - Length of glass slide
T - Time for spreading gel in sec.

Swelling index

To determine swelling index, 1 g of the emulgel was wrapped in an aluminium foil and the wrapped foil was kept in a beaker containing 10 ml of 0.1 N sodium hydroxide as solvent. At different time intervals, the samples were withdrawn from the beaker and weights were recorded, the process was continued till a constant weight was obtained. Swelling index was calculated from the following formula.[12]

$$\text{Swelling index } (SW)\ \% = \frac{([W_t - W_o])}{Wo} \times 100 \quad (2)$$

Where,
(SW) % = Equilibrium percent swelling
W_t = Weight of swollen emulgel after time t,
W_o = Weight of emulgel before swelling at zero time, t.

Drug content

The drug content of emulgels was estimated by UV spectroscopy. Emulgel of 1 g was diluted with 10 ml of phosphate buffer pH 7.4 followed by sonication for 3 min and then the solution was filtered and absorbance was measured at 268 nm and the drug content was noted in percentage.[13]

In vitro drug release study

Modified 6 diffusion cell apparatus was used to perform the drug release study for the prepared emulgels. The diffusion cell was filled with 25 ml of phosphate buffer pH 7.4 in the receptor chamber. The dialysis membrane that was soaked in the buffer for about 24 h was tied to the upper end of diffusion cell and it was kept in contact with receptor compartment filled with buffer. The diffusion cell assembly was kept on magnetic stirrer and was operated at 50 rpm. The diffusion cell was maintained at 37 ± 0.5°C. Formulation of 0.5 g was placed on the dialysis membrane. Samples (1 ml) were withdrawn at different time periods of 30, 60, 120, 180, 240, 300, and 360 min. The samples were diluted with 10 ml of phosphate buffer pH 7.4 and then analyzed at 268 nm using UV spectrophotometer and the percentage cumulative drug release was calculated.[13]

Particle size analysis

The optimized emulgel formulation was evaluated for particle size measurement. Emulgel of 1g was diluted with ultra-pure water suitably and the sample was observed under high resolution particle size analyzer. The mean particle size range for the formulation was recorded.[14]

In vitro skin irritation study by HET-CAM test

HET-CAM was used as *in vitro* skin irritation approach to evaluate the irritancy of the optimized emulgel. The study involved treatment of samples on the chick embryo developed in the embroyonated eggs which were incubated for about 8 days in incubator at temperature of 37 ± 0.5°C and relative humidity of 58 ± 2°C. Three groups were made each containing 3 eggs. For negative control group, the chick embroyo was treated with 0.9% NaCl, positive control and test groups were treated with 1% SDS as strong irritant and optimized emulgel. The chick embryo of all the study groups was observed for time period of 5 min (300 s) for the signs of blood vessel lysis, haemorrhage and coagulation.[15,16] The irritation scores for the samples were determined using the following formula and the level of irritancy was evaluated by comparing with standard score levels as given in the Table 2.

$$IS = \frac{(301-H)\times 5}{300} + \frac{(301-L)\times 7}{300} + \frac{(301-C)\times 9}{300} \quad (3)$$

Where,
H - Haemorrhage
L - Lysis of blood vessels
C - Coagulation

Table 2: Irritation score value with inference for HET-CAM Test

Irritation score	Inference
0–0.9	No irritation
1–4.9	Weak irritation
5–8.9	Moderate irritation
9–21	Severe irritation

HET-CAM: Hen's egg test with chorioallantonic membrane

RESULTS AND DISCUSSION

FTIR spectroscopy

From the obtained IR peaks of pure ibuprofen and its physical mixture with xanthan gum, it was observed that there were no additional peaks and the interpretation analysis confirmed that both the drug and polymer were compatible with each other and there were no signs of chemical interaction. The IR spectrum of ibuprofen pure drug and the physical mixture were depicted in the Figures 1 and 2.

Appearance and pH

All the formulated Ibuprofen emulgels were found to appear as white translucent gels with good homogeneity. The pH of the emulgels was ranging from 6.6 to 7.2 and was found to be satisfactory. The results of appearance and pH of the Ibuprofen emulgel were discussed in the Table 3.

Table 3: Evaluation parameters of the Ibuprofen emulgels

Parameter	Formulation code				
	IG-1	IG-2	IG-3	IG-4	IG-5
Appearance	White translucent gel	White translucent gel	White translucent gel	White translucent gel	White translucent gel
pH	6.8	6.6	7.1	7.0	6.9
Spreadability (g.cm/s)	14.36	24.08	28.17	36.42	30.63
Viscosity (Cps)	354.2	412.7	486.6	518.5	578.6
Swelling index (%)	26.22	19.59	25.14	28.66	34.51
Drug content (%)	90.06	92.45	93.18	95.88	93.37

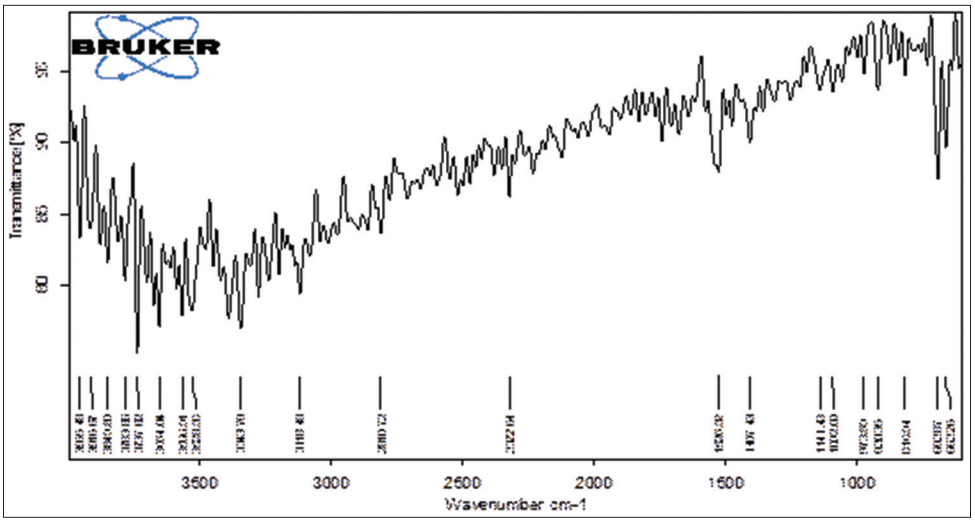

Figure 1: IR spectra of Ibuprofen pure drug

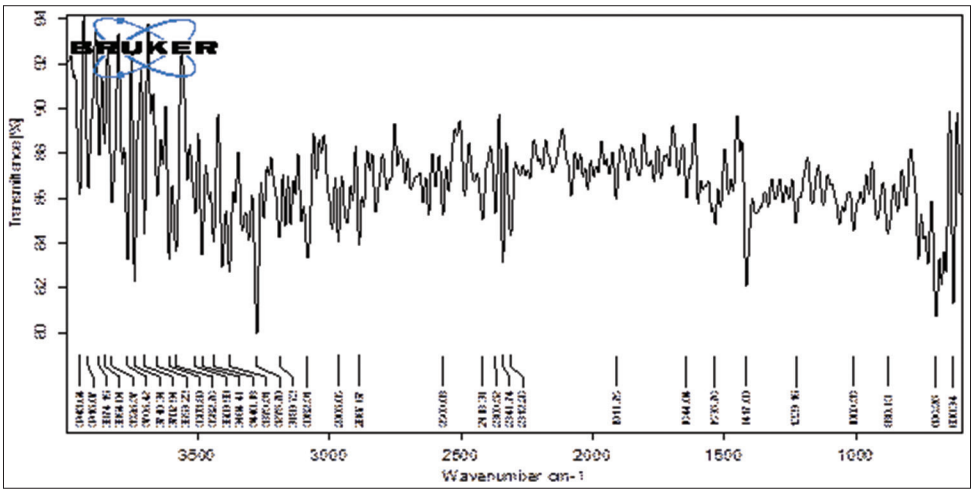

Figure 2: IR spectra of Ibuprofen and xanthan gum physical mixture

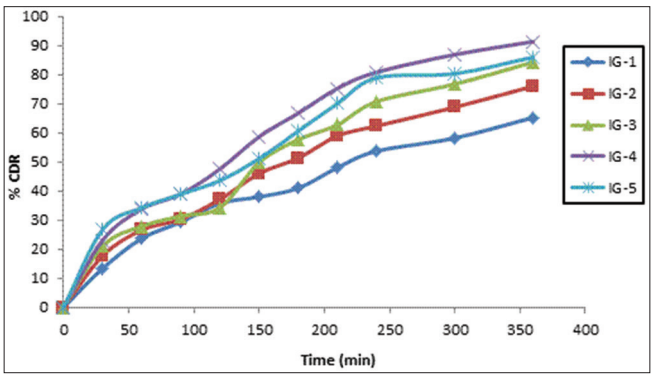

Figure 3: Drug release profile of Ibuprofen emulgels

Rheological study

The viscosity of the Ibuprofen emulgels was found to be in the range of 354.2–578.6 cps. The viscosity of the emulgels was directly influenced by xanthan gum. The viscosity was gradually increased as there was increase in the concentration of xanthan gum in the emulgel formulations. The results of viscosity for all the Ibuprofen emulgels was shown in Table 3.

Spreadability

The spreadability of the prepared emulgels was in the range of 14.36–36.42 g.cm/s. The formulations IG-4 and IG-5 showed higher spreadability which may be due to increased amount of xanthan gum. The results of spreadability were represented in the Table 3.

Swelling index

Ibuprofen emulgels showed swelling index ranging from 19.59 to 34.51 % which was found to be satisfactory. The results of the swelling index were reported in the Table 3.

Drug content

The drug content of all the formulated emulgels was found to be in the range of 90.06–95.88%. The results of the drug content were shown in Table 3.

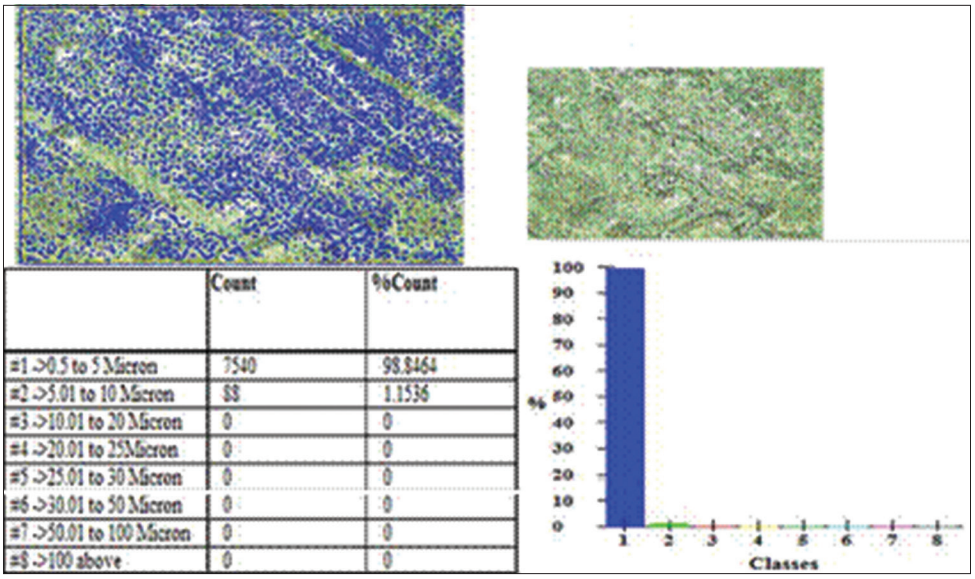

Figure 4: Particle size analysis of optimized emulgel IG-4

Figure 5: HET-CAM test for 0.9% NaCl (a), IG-4 emulgel (b) and 1% SDS (c)

In vitro drug release study

The drug release profile of all the formulated emulgels is depicted in Figure 3. The drug release study was conducted for 6 h (360 min). The drug release of the prepared emulgels was ranging from 65.33 to 91.43%. The formulation IG-4 predicted highest drug release among all the prepared emulgels and emerged as optimized formulation. This may be due to the optimum concentration of xanthan gum for the easy diffusion of the drug through dialysis membrane for the drug release in the buffer. The optimized emulgel (IG-4) was further evaluated for particle size analysis and *in vitro* skin irritation studies.

Particle size analysis

The average particle size of the optimized emulgel (IG-4) was found to be in the range of 0.5–10 microns and was found to be favorable for enhancing the drug permeation through skin. The particle size analysis report was depicted in Figure 4.

In vitro skin irritation by HET-CAM test

The results of the HET-CAM test showed that there were no signs of irritation in the chick embryo when tested with both 0.9% NaCl and optimized emulgel. Severe irritation was observed with 1% SDS only. Hence, the study confirmed that the optimized emulgel was found to be non-toxic and non-irritant in nature. The HET-CAM images were shown in Figure 5.

CONCLUSION

Ibuprofen emulgels were successfully formulated with xanthan gum as gelling agent. The evaluation parameters of the formulated emulgels were found to be satisfactory. The optimized emulgel IG-4 showed highest drug release for about 6 h with better particle size range. The optimized emulgel was found to be non-irritant and non-toxic as confirmed by the *in vitro* skin irritation studies. Overall, from the present investigation, it was concluded that Ibuprofen emulgel is better novel topical drug delivery approach to enhance the drug bioavailability.

REFERENCES

1. Mayuresh RR, Patil SV, Tushar GR. Emulgel: A modern tool for topical drug delivery. World J Pharm Res 2019;8:586-97.

2. Yadav SK, Mishra MK, Tiwari A, Shukla A. Emulgel: A new approach for enhanced topical drug delivery. Int J Curr Pharm Res 2017;9:15-9.
3. Anil RP, Nandgude TD, Ganapathy RS. Emulgel: A comprehensive review for topical delivery of hydrophobic drugs. Asian J Pharm 2018;12:S382-93.
4. Maru S, Okaru AO, Kamau FN, Kuria KA, Ng'ang'a BN, Gathu L, *et al*. Formulation and evaluation of ibuprofen gel using a natural polymer. East Cent Afr J Pharm Sci 2015;18:18-22.
5. Kashyap A, Das A, Ahmed AB. Formulation and evaluation of transdermal topical gel of ibuprofen. J Drug Deliv Ther 2020;10:20-5.
6. Kumar S, Ashutosh B, Kumar NB. Emulgel: Magnifying the application of topical drug delivery. Ind J Pharm Biol Res 2017;5:25-33.
7. Marwaha K, Bhise K. Formulation design and evaluation of anti-psoriatic emulgel. J Pharm Sci Innov 2013;2:30-42.
8. Rajesh A, Nitin N, Deepak S. Development and evaluation of novel fluticasone propionate emulgels for topical drug delivery. J Chem Pharm Res 2015;7:772-80.
9. Tanwar Y, Jain A. Formulation and evaluation of topical diclofenac sodium gel using different gelling agent. Asian J Pharm Res Health Care 2012;4:1-6.
10. Khalil YI, Khasraghi AH, Mohammed EJ. Preparation and evaluation of physical and rheological properties of clotrimazole emulgel. Iraqi J Pharm Sci 2011;20:19-27.
11. Pakhare AV, Deshmane SV, Deshmane SS, Biyani KR. Design and development of emulgels preparation containing diclofenac potassium. Asian J Pharm 2017;11:712-6.
12. Ramakanth A, Sateesh kumar V. Formulation and characterization of ketoprofen emulgels. J Appl Pharm Sci 2015;5:112-9.
13. Prajakta KK, Ritu MG, Manoj MN, Vrunal VM. Formulation and evaluation of itraconazole emulgel for various fungal infections. Asian J Pharm 2019;19:19-22.
14. Nitin PA, Dandagi PM, Gadad AP, Mandora P. Formulation and characterization of tapentadol loaded emulgels for topical application. Ind J Pharm Educ Res 2017;5:525-35.
15. Vinardell MP, Mitjans M. Alternative methods for eye and skin irritation tests: An overview. J Pharm Sci 2008;97:46-59.
16. HET-CAM Test, Methods in Molecular Biology. ECVAM DB-ALM: INVITOXX Protocol; 1995.

Source of Support: Nil. **Conflicts of Interest:** None declared.