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Formulation and Evaluation of Flurbiprofen Emulgel by Using Natural Permeation Enhancers

Priyanka D. Manmode[1], Navnath A. Gaikawad[2], Ankita A. Giramkar[3], Bharati R. Hole[4], Dr. Deepak G. Umalkar[5]

Assistant Professor Department of Pharmaceutics
SDF's Shri Saikrupa Institute of Pharmacy, Ghargaon, Ahmednagar, India

Abstract: ***Flurbiprofen is more active antiinflammtory agent than other NSAIDs product and is usually well tolerated. Emulgel have more absorption power than any other topical formulation like cream, ointment etc. Enhance permeation of flurbiprofen by using natural permeation enhancers and also study physibility of emulgel by using natural permeation enhancers like, Terpenes- Menthol, Camphor, Essential oil- Basil oil, Neem oil, Eucalyptus oil. Emulgel were evaluated for drug content, viscosity, and In-vitro release through the Franz diffusion cell apparatus. The physical stability were check by using stability chamber. Analytical parameters were determined by I.R, SEM, DSC, and Dissolution. Flurbiprofen is highly permeable with Basil oil as permeation enhance.***

Keywords: Flurbiprofen, Basil oil, Permeation Enhancer, Topical drug delivery, Franz diffusion

1. Introduction

Most of the non-steroidal anti-inflammatory drugs (NSAID) is extensively used for the treatment of arthritis diseases (rheumatoid and osteoarthritis). Inconvenience to oral administration leading to side effect like gastric irritation, ulcer and other systemic side effect. The main advantage of topical drug delivery system is drug reach to the site of action. Cream, gel, ointment, and paste are some of the topical semisolids in use for many years. Emulgel is recently use semisolid dosage form out of various semisolids dosage form and becoming more popular due to ease of application and better percutaneous absorption than other semisolid dosage form. When mixture of gel and emulsion are used the dosage form are referred as emulgel.

To avoid drawback of various ointments and gels an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels. The effectiveness of topical preparations are depend upon the rate and extent of drug release from base. So study on formulation of flurbiprofen emulgel with different natural permeation enhancers was selected as a principle objective for anti-inflammatory activity.

2. Material and Method

A. Selection and Procurement of Drugs and Excipients

Table 1: Procurement

Sr. No	Ingredient	Suppliers
1	Flurbiprofen	FDC Pharma Pvt. Ltd.
2	Linseed oil	SD Fine- CHEM limited Mumbai.
3	Menthol	SD Fine- CHEM limited Mumbai.
4	Camphor	SD Fine- CHEM limited Mumbai.
5	Eucalyptus oil	Lobachemie limited Mumbai.
6	Turpentine oil	Lobachemie limited Mumbai.
7	Neem oil	Narmada valley fertilizers & chemicals limited Gujarat.
8	Tulsi oil	Aramacs pure essential oil Delhi.
9	Methyl salicylate	SD Fine- CHEM limited Mumbai.
10	Tween 80	SD Fine- CHEM limited Mumbai
11	Propylene glycol	SD Fine- CHEM limited Mumbai.
12	Polyethylene glycol	Thermo fisher scientific Mumbai.
13	Carbopol 934	Lobachemie limited Mumbai.

B. Method Experimental Work

a) Preparation of drug loaded nanoemulsion:

The clear oil phase was obtained by mixing menthol, camphor and methyl salicylate with union of linseed oil. Exactly 0.6gm of flurbiprofen was kept constant in all selected formulation and which dissolved in the oil phase of nanoemulsion formulation. The aqueous phase was prepared by dissolving tween 80, propylene glycol, PEG 400 into distilled water under magnetic stirring. Then aqueous phase was blended with oil phase using magnetic stirrer at 1000 rpm for 30 minutes and then nanosize range of flurbiprofen loaded nanoemulsion were obtained.

Note**:** In order to prepare Flurbiprofen loaded nanoemulsion camphor is used as natural permeation enhancer in formula F1 and which is replace in formula F0, F2-F5, by other natural permeation enhancer such as Eucalyptus oil, Turpentine oil, Neem oil, Tulsi oil.

Method of Preparation of emulgel:

STEP 1: Preparation of Emulsion either O/W or W/O STEP 2: Formulation of gel base

STEP 3: Mixing of emulsion into gel base with continuous stirring

Formulation of Flurbiprofen nanoemulsion based Emulgel

1gm of Carbopol 934 which was selected as a gelling agent in a enough quantity of distilled water. After complete dispersion, the carbopol 934 was kept in the dark for 24 hrs to swell completely. Triethanolamine was added into swollen carbopol 934 to adjust the pH value of gel matrix (7.4). Flurbiprofen loaded nanoemulsion formulation were taken and incorporated with gel matrix and nanoemulsion based emulgel were prepared after stirring by remi stirrer for 15 minutes at 250 rpm.

Table 2: Formulation Design

Sr.No	Ingredients	F0	F1	F2	F3	F4	F5
1	Flurbiprofen(%w/v)	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**	**2.5**
2	Linseed oil (%v/v)	**9**	**9**	**9**	**9**	**9**	**9**
3	Menthol (%w/v)	**2**	**2**	**2**	**2**	**2**	**2**
4	Camphor (%w/v)		**2**				
5	Eucalyptus oil(%v/v)			**2**			
6	Turpentine oil(%v/v)				**2**		
7	Neem oil(%v/v)					**2**	
8	Tulsi oil(%v/v)						**2**
9	Methyl salicylate(%v/v)	**2**	**2**	**2**	**2**	**2**	**2**
10	Tween 80(%v/v)	**18**	**18**	**18**	**18**	**18**	**18**
12	Propylene glycol(%v/v)	**9**	**9**	**9**	**9**	**9**	**9**
13	Polyethylene glycol(%v/v)	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
14	Carbopol 934(%w/v)	**1**	**1**	**1**	**1**	**1**	**1**
15	Distilled Water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**

3. Result and Discussion

1. Analytical Profile: Sample of Flurbiprofen procured for study was identified by Infrared spectrum, Differential Scanning Calorimetry.

2. Determination of Analytical wavelength. a) Determination of λmax of Flurbiprofen using Ethanol

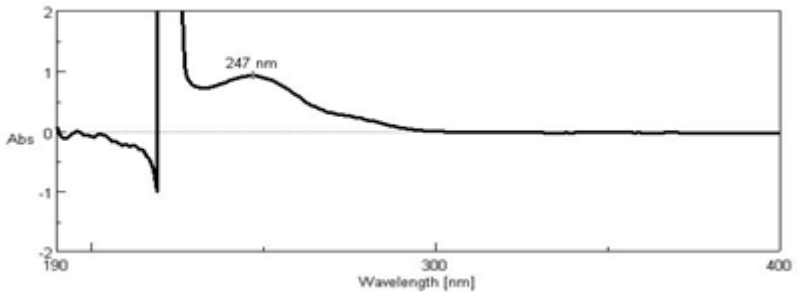


Figure 1: U.V Spectrum of Flurbiprofen in Ethanol

b) Standard calibration curve of Flurbiprofen in Ethanol

UV absorption spectrum of Flurbiprofen in Ethanol showed λ max at 247nm (Figure No.7.1). Absorbance's obtained for various concentrations of Flurbiprofen in Ethanol are given in Table No.7.1 the graph of absorbance vs. concentration for Flurbiprofen was found to be linear in the concentration range of 20 – 100 mcg/ml (Figure No. 7.2). The drug obeys Beer Lambert's law in the range of 20 – 100 mcg/ml.

Table 3: Standard calibration curve of Flurbiprofen in Ethanol

Sr.No.	Concentration	Absorbance
1	0	0.0956
2	2	0.2059
3	4	0.4062
4	6	0.5660
5	8	0.7077
6	10	0.8999

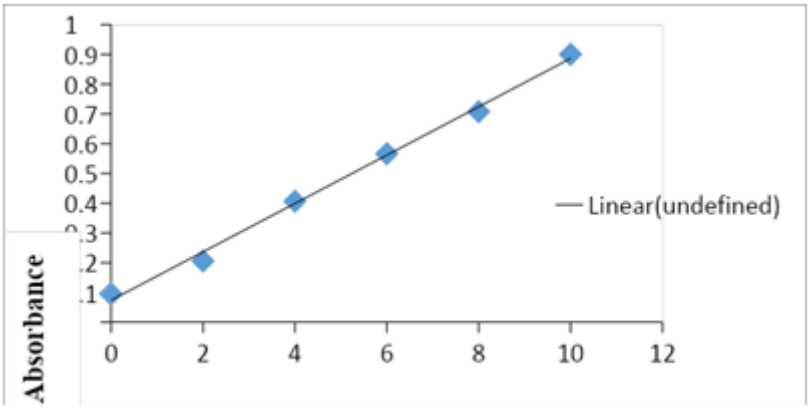


Figure 2: Calibration Curve of Flurbiprofen in Ethanol

3. Melting point determination:

Melting point of Flurbiprofen was found to be 116˚C as reported in literature, thus indicating purity of sample.

4. Evaluation of gel

The formulation of emulgel were evaluated for pH, viscosity, drug content, Spreadability, Swelling index, Melting point and in vitro release study and compare with marketed gel for anti-inflammatory activity.

Table 4: Drug Content, Viscosity, Spreadability and Swelling index of prepared Formulation

Formulation	Drug content (%w/w)	Viscosity of Emulgel Formulation(Cp)	Spreadability	Swelling index
F0	71.25%	1432	68%	15%
F1	87.5%	4662	70%	18%
F2	97.16%	3234	71%	17%
F3	69.18%	1956	80%	20%
F4	91.70%	4488	79%	19%
F5	97.83%	6000	85%	21%

Table 5: pH Determination

Sr.No	Formulation code	pH
1	F0	5.4
2	F1	5.8
3	F2	6.0
4	F3	6.1
5	F4	6.0
6	F5	6.1

The in-vitro diffusion profile of the optimized emulgel and marketed available gel (Brugel 5% of Flurbiprofen Abbott Company) were compared. The optimized nanoemulgel showed a maximum cumulative release of 99.5 % over a period of 7 hr, while marketed gel showed a maximum cumulative release of 86.66 %. It may be due to the high drug loading capacity and powerful permeation ability. The maximum release in the optimized formulation may be due to having the lowest droplet size and lowest viscosity of all the formulations. The comparative release study of optimized nanoemulgel and marketed gel was showed in the (fig.no.4)

Table 6: In vitro release profile of drug prepared formulation

Sr.No.	Time (min)	F0	F1	F2	F3	F4	F5
1	0	0	0	0	0	0	0
2	15	14.21	12.5	11.12	9.78	15.41	20
3	30	16.05	15.24	17.34	16.23	18.91	21.66
4	45	23.26	20.33	22.3	19.02	26.5	31.6
5	60	28.5	24.83	30	21	38.3	35
6	120	41	42.16	50	37.66	53.01	43.33
7	180	49	54.16	76.66	48.16	67	50
8	240	50.5	60.33	84.16	52.33	72.5	66
9	300	51.16	68.66	89.5	65.5	81.66	71.5
10	360	53.16	71.16	96.66	73..83	90.33	89.5
11	420	55	82.5	96.66	92	97.33	99.5

Cumulative Percentage Drug release:

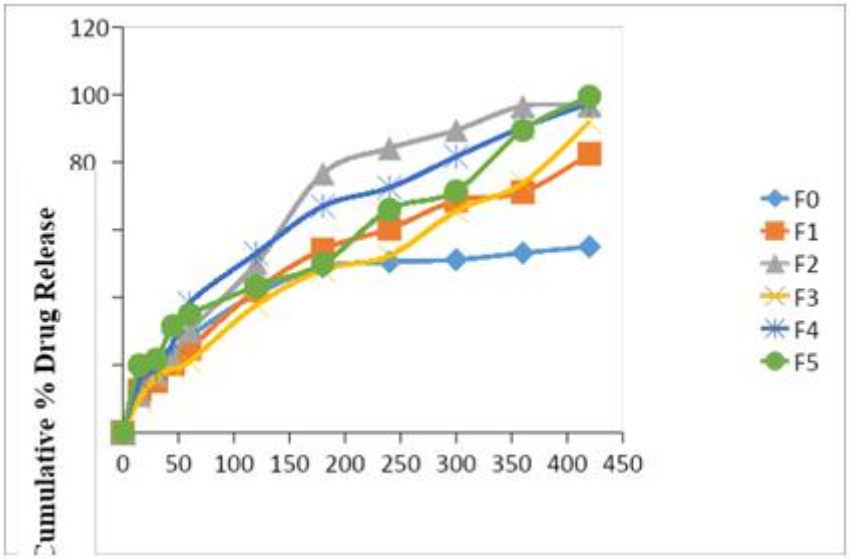


Fig No: 3 % Cumulative Drug Release

Table 7: Comparative in-vitro release study of the optimized Nanoemulgel and Marketed gel (Brugel).

Cumulative Percentage Drug release

Sr.No	Time (min)	Nanoemulgel(F5)	Marketed Gel
1	0	0	0
2	15	20	5
3	30	21.66	11.66
4	45	31.6	20
5	60	35	28.33
6	120	43.33	33.62
7	180	50	41.66
8	240	66	48.33
9	300	71.5	56.66
10	360	89.5	73.33
11	420	99.5	86.66

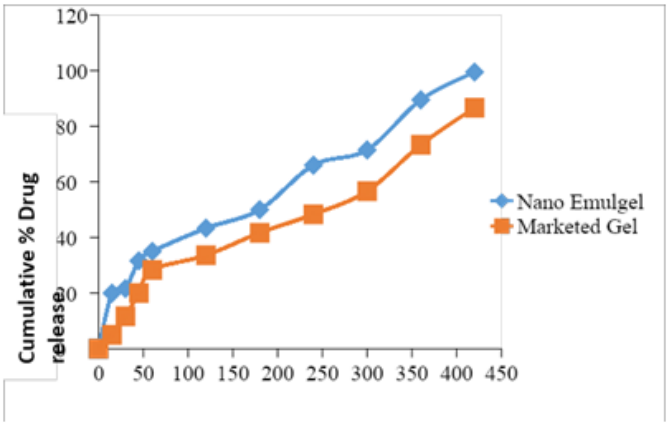


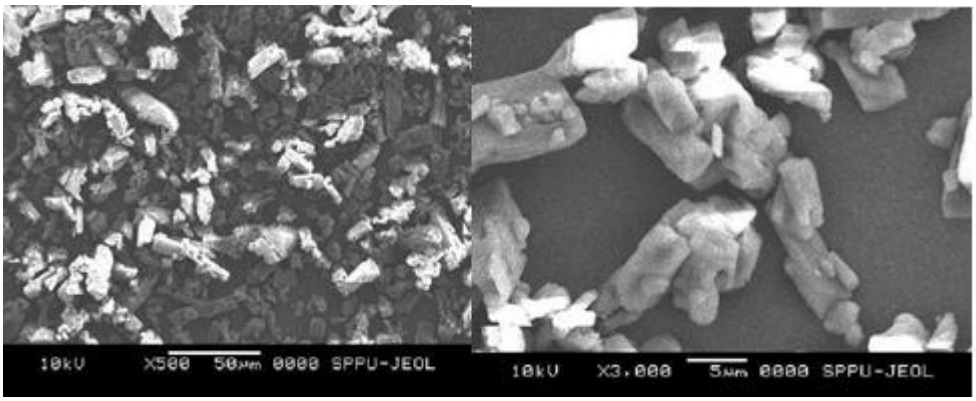
Figure 4: Comparative In-vitro release study of optimized nanoemulgel formulation and marketed gel

Table 8: Physical Examination

Sr. No.	Formulation code	Colour	Odour	Consistency	Phase separation
1	F0	White	Pleasant	Good	None
2	F1	Yellow	Pleasant	Good	None
3	F2	Yellow	Pleasant	Good	None
4	F3	Yellow	Pleasant	Good	None
5	F4	Creamy white	Irritating	Good	None
6	F5	White	Pleasant	Good	None

5. Globule size and its distribution in emulgel: The SEM images are show in fig.no 5 (A) and (B).The morphology and structure of the nanoemulsion were studied using (SEM). The particle size of flurbiprofen nanoemulsion were smaller in size and shape as compare to flurbiprofen (API), hence increases the permeation through the skin. The droplet size was in agreement with the results obtained from particle size analysis. A positive image was seen using SEM (fig.no:5)

(A)



(B)

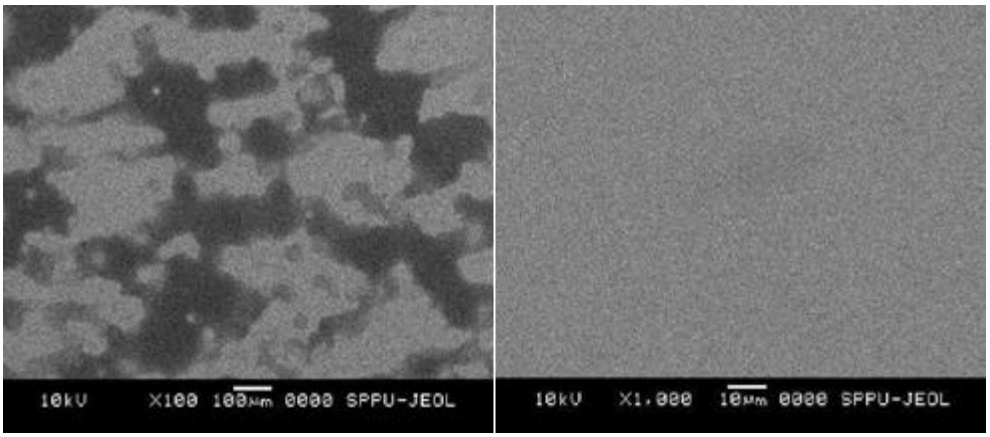


Figure 5: SEM images for (A) Flurbiprofen (API) (B) Flurbiprofen Nanoemulsion.

6. Accelerated stability studies of the optimized formulation:

The samples (in triplicate) of best formulation kept sealed and exposed to controlled temperature (40±2 °C) and relative humidity (75±5 %) for a period of 45 days in stability chambers (Thermolab Scientific Equipment Pvt. Ltd.). After 30 and 45 days, samples were taken out and analyzed for the following tests.

Table 9: Stability Parameters of 3 month

Formulation	Study conditions specification	Month	Viscosity (Cp)	Drug Content (%w/w)
F5	400c + Initial 20c/75% + 5% RH	Month 1	33.08	92.21%
		Month 2	34.14	92.11%
		Month 3	35.09	92.7%

4. Conclusion

1) The emulgel of Flurbiprofen was prepared using various natural permeation enhancers. e.g. Camphor, Tulsi oil, Neem oil, Eucalyptus oil, Turpentine oil and was found to be stable.

2) Natural permeation enhancers were increase permeation of drug.
3) The dermal Emulgel prepared in this study fulfills all necessary parameters required for topical use. This novel dosage form will improve both the accuracy and the positioning of a delivered dose.
4) The optimized batch (F5) of Emulgel showed the highest drug release, appropriate spreadability, good consistency and higher percentage inhibition.
5) Hence, the results of the present study clearly indicated promising potentials of Flurbiprofen Emulgel as topically in the treatment of pain and could be viewed as a potential alternative to conventional dosage forms.

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