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Research Article

FORMULATION AND EVALUATION OF EMULGEL OF FLURBIPROFEN

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ABSTRACT

Topical drug delivery has been used for the treatment of local skin disorders. Emulgel have emerged as one of the most interesting topical delivery systems as it has dual control release system i.e. gel and emulsion form. One side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and secondly delivering the drug for extended period of time at the effected site. The major objective behind this formulation is enhancing the topical delivery of hydrophobic drug (flurbiprofen) by formulating flurbiprofen emulgel using high molecular weight water soluble polymer of hydroxy propyl methyl cellulose (HPMC K100M), carbopol 940, carbopol 941 and xanthan gum. Oleic acid and propylene glycol were used as permeation enhancers. The influence of the type of the gelling agent on the drug release from the prepared emulgel was investigated. The prepared emulgels were evaluated for their physical appearance, pH determination, viscosity, spreadability, extrudability, *in-vitro* drug release, *ex-vivo* drug release and stability. All the prepared emulgels showed acceptable physical properties, homogeneity, consistency, spreadability, viscosity and pH value. The *in-vitro* release rate of emulgel was evaluated using diffusion cell containing dialysis membrane with phosphate buffer pH 7.4 as the receptor medium. FOA4, FOA1, FPG4 and FOA3 have shown more than 75% drug release for 8 h respectively. *Ex-vivo* studies indicated that the FOA4 formulated with xanthan gum in the concentration of 2% have shown superior drug release of 56.63 % compared with the other formulations. The emulgels were found to be stable with respect to physical appearance, pH, rheological properties and drug content at all temperature and conditions for one month.

Keywords: Topical; emulgel; *in-vivo; ex-vivo*, carbopol, rheological properties;

INTRODUCTION

Topical drug administration is a localized application anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery systems[1]. Generally, most common form of delivery of drugs is the oral route which has drawbacks like poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Topical formulations of non steroidal anti-inflammatory drugs have been used and studied as an alternative to oral forms in the treatment of arthritis.

Gel is water soluble, has high skin permeation rate thus, excellent anti-inflammatory and analgesic activities comparable to its oral administration and other topical agents like ointments, creams, lotions. It also shows lowered systemic side effects and gastrointestinal irritation and good physicochemical stability[2].

Flurbiprofen is a propionic acid derivative, which is non steroidal anti-inflammatory agent with antipyretic and analgesic activity. The anti-inflammatory effect of flurbiprofen occurs by reversible inhibition of cyclo oxygenase (COX) enzyme. COX enzyme is responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) from the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandins involved in inflammation, pain, swelling and fever. Flurbiprofen is a non-selective COX inhibitor and inhibits the activity of both COX-1 and 2. It is also one of the most potent NSAIDs in terms of prostaglandin inhibitory activity.

The present work with the aim to develop flurbiprofen emulgel formulation, which would attenuate the gastrointestinal related toxicities associated with oral administration. Because of the better application property in comparison to creams and ointments, gel formulations are superior topical formulation over any other topical formulations[3]. In this research, topical gel formulations of flurbiprofen were prepared using hydroxyl propylmethylcellulose (HPMC K100M), carbopol 940, carbopol 941 and xanthan gum as water soluble polymers. Gel formulations developed contain oleic acid and propylene glycol as permeability enhancers[4]. The prepared emulgels were evaluated for physical appearance, FTIR studies, pH, viscosity, spreadability, extrudability, *in-vitro, ex-vivo* drug release, skin irritation and stability studies.

MATERIALS AND METHODS

Flurbiprofen was obtained as a gift sample from RA Chem Pharma Ltd., Hyderabad; Carbopol 940, HPMC –K100M, Xanthan gum from Yarrow Chem. Products; Span 20, Tween 20, Light liquid paraffin, Propylene glycol, Propyl paraben and Methyl paraben from S.D fine chemicals Ltd. Oleic acid from Thomas bakers (chemicals) Pvt. Ltd. All other chemicals and reagents used were of analytical grade.

Preliminary studies for the selection of gelling agent and concentration of gelling agent

In the preliminary studies, gelling agents like carbopol 940, carbopol 941, xanthan gum, HPMC K4M and HPMC K100M were tried in various concentrations from 1-2%w/w to check at which concentrations the gel was formed. The gel bases were formed by dispersing the gelling agents in distilled water with constant stirring at a moderate speed using mechanical shaker. Optimized gelling agents and its concentrations were selected for further studies.

Preliminary trials for selection of oil phase, selection of emulsifying agents

Preliminary batches were prepared using liquid paraffin oil. Surfactants like Spans and Tweens were tried in different concentrations. The O/W emulsion was prepared by wet gum method by using oil, water and gum in the ratio of 3:2:1.

Determination of type of emulsion

Dilution test

Based on the solubility of external phase of emulsion; O/W emulsion can be diluted with water. W/O emulsion can be diluted with oil.

Dye-solubility test

Water-soluble dyes will dissolve in the aqueous phase and oil-soluble dyes will dissolve in the oil phase.

Fluorescence test

Oils give fluorescence under UV light, while water doesn't. Therefore, o/w emulsion shows spotty pattern while w/o emulsion fluoresces.

Conductivity test

Water is good conductor of electricity whereas oil is non-conductor. Therefore, continuous phase of water runs electricity more than continuous phase of oil.

Drug-excipient compatibility studies

Fourier Transforms Infrared Spectroscopy (FTIR) analysis of drug and excipients

This study was performed to ensure the compatibility between excipient and drug. FTIR spectra were obtained for pure drug flurbiprofen and liquid FT-IR studies were carried out for the prepared formulations with different excipients and their compatibility was checked. Spectrum of drug was obtained using the potassium bromide disc method. The pellet was prepared with the dry samples by applying 10 tons/inch^2 pressure for 10 min. For liquid samples, the samples were taken in liquid sample holder and measured.[5]

Emulgel preparation

Emulgel was prepared by the method reported by Mohammad *et. al* (2004) with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Triethanolamine (TEA). The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and Propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. And add glutaraldehyde during mixing of gel and emulsion in ratio 1:1 to obtain the emulgel. Formulation batches for emulgel were shown in Table 1.[6,7]

Characterization of emulgel

Emulgels were evaluated for their clarity, pH, spreadability, viscosity, drug content, *in-vitro* diffusion studies, *ex-vivo* permeation studies, skin irritation studies, drug excipient compatibility studies and stability studies.[8-13]

Determination of pH

The pH of emulgel formulations is determined by using digital pH meter. 1 gm of gel is dissolved in 100 ml of distilled water and it is placed for 2 hours. The measurement of pH of each formulation is done in triplicates and average values are calculated.

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregates.

Determination of viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25 ± 1ºC) before the measurement was taken. Spindle was lowered perpendicular into the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.

Spreadability

Spreadability of the formulations was determined by measuring the spreading diameter of 1 g of sample (an excess of emulgel about 2 gm.) between two horizontal glass plates (10 cm × 20 cm) after one minute. The standard weight applied to the upper plate was 25 gm or 80 gm or 1 kg. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Each formulation was tested three times. Spreadability was calculated by using the formula,

$$S = M.L/T \quad \text{-------- Equation 1}$$

Where, S = spreadability, M = Weight tied to upper slide,
L = Length of glass slides,
T = Time taken to separate the slides completely from each other

Extrudability

For a good gel formulation, it should extrude easily from the container. In this test, sample is extruded from the tube by usual procedure. It is a empirical test to measure the force required to extrude the material from the collapsible tube. A closed collapsible tube containing gel was passed firmly at crimpened

end. When the cap was removed, gel extrudes until pressure was dissipates. The weight in grams required to extrude 0.5 cm ribbon of gel in 10 seconds was determined. The results for each formulation were recorded as extrusion pressure in grams.

More quantity extruded better was extrudability. The measurement of extrudability of each formulation was in triplicate and the average values are presented. The extrudability was than calculated by using the following formula

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2) ---- Equation 2

Drug Content Determination

1 gm of emulgel, mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using standard plot.

Drug Content= (Concentration × Dilution Factor × Volume taken) × Conversion Factor ---- Equation 3

***In-vitro* diffusion studies**

Diffusion study of emulgel formulations were performed using modified Keshary-Chien or frandz diffusion cell. The pretreated dialysis sac (Cellophane membrane) was used in franz diffusion cell. The cell was locally fabricated and volume of receptor compartment was 20 ml. Phosphate buffer of pH 7.4 was used for *in-vitro* release as receptor medium. The emulgel sample was applied on the membrane and then fixed in between donor and receptor compartment of quality diffusion cell. The receptor compartment contained phosphate buffer pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37º ± 0.5ºC by surrounding water in jacket and the medium was continuously stirred by magnetic stirrer at speed of 600 rpm. At pre-determined time intervals, 5 ml of sample were withdrawn, and an equal volume of buffer was replaced and replaced by equal volume of freshly prepared media. The withdrawn samples were analyzed spectrophotometrically for drug content.

Release rate studies

Plot amount of drug permeated per square centimeter versus square root of time and calculate slope. Slope is release rate. Units - $mg/cm^2/hr^{1/2}$.

***Ex-vivo* skin permeation studies**

Preparation of rat abdominal skin

The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) (ID number: PCE/ACE-6). Male Wister rats (150-200 g) were used for permeation study. The animal was sacrificed by cervical dislocation and hair was removed on abdomen using an animal hair clipper. Abdominal skin section was excised and observed for existence of cuts and wounds. The fat adhering on dermis was removed using scalpel and finally it was washed under tap water. The skin was stored at -20 ^{0}C and used within a week.

Permeation study

For the permeation studies locally fabricated modified Keshary - Chien diffusion cells with an area of 4.9 cm^2 and 20 ml receptor volume were used. The thawed rat skin was mounted onto diffusion cell such that the dermis side was in constant contact with receptor solution. 500 mg of gel was applied to the stratum corneum facing the donor compartment and the hydrodynamics in the receptor compartment were maintained by stirring on magnetic stirrer at 600 rpm. 1 ml sample was withdrawn at predetermined time intervals for 24 hours and drug content was analyzed by UV-VIS double beam spectrophotometer at 248 nm.

Calculation of permeability parameters

Parameters were calculated in this part of the study to compare the drug transfer and permeation properties among the tested formulae. Descriptions of these parameters include steady state flux, permeability coefficient and enhancement ratio and lag time.

Steady state flux (@$g/cm^2/h$)

Flux is defined as the rate of diffusion or transport of a substance through a permeable membrane. After reaching the steady state of drug permeation, flux was calculated.

Permeability coefficient (cm/hr)

The permeability coefficient (Kp) was calculated with the following equation:

Kp = JSS/ CV ---- Equation 4

Where, 'CV' is the total donor concentration of the formulation
'JSS' is steady state flux

Enhancement ratio

Used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules and is calculated by

ER = Flux of drug with enhancer/ Flux of drug alone ---- Equation 5

Skin Content

The amount of flurbiprofen retained in the skin was determined by skin deposition studies. At the end of the permeation studies (24 hrs), the skin was washed 10 times with a cloth immersed in methanol. A sample of skin was weighed and homogenized with methanol for 5 min using an electric stirrer. The resulting solution was centrifuged at 7000 rpm for 10 mins and supernatant was analyzed by UV-VIS double beam spectrophotometer (Chemito Spectrascan UV 2600, India) at 248 nm.

Regression coefficients (r^2) were calculated for all the formulations. Release component "n" was calculated from Korsmeyer-peppas equation. The release kinetic calculations were carried out using MS-office excels. Applied mathematical models to the diffusion data of gel or emulgel formulations shown in Table 2 and Interpretation of diffusion release mechanisms from "n" values in Table 3.

Skin irritation studies

Skin irritation study was performed by using control, standard skin irritant, placebo and test which were applied on the left and dorsal surface of rabbit skin and rabbits were examined for 8 hrs. Erythema and edema was evaluated and the score was given according to the Primary Dermal Irritation Index classification (PDII) in Table 4.

Table 1: Formulation batches for emulgel

Ingredients (% w/w)	FPG1	FPG2	FPG3	FPG4	FOA1	FOA2	FOA3	FOA4
Flurbiprofen	1	1	1	1	1	1	1	1
Carbopol 940	1	-	-	-	1	-	-	-
Carbopol 941	-	1	-	-	-	1	-	-
HPMC K 100M	-	-	2	-	-	-	2	-
Xanthan gum	-	-	-	2	-	-	-	2
Liquid paraffin (ml)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Span 20	1	1	1	1	1	1	1	1
Tween 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol (ml)	5	5	5	5	-	-	-	-
Oleic acid	-	-	-	-	2	2	2	
Propyl paraben (%)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Methyl paraben (%)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water (ml)	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

Table 2: Applied mathematical models to the diffusion data of gel or emulgel formulations

Model	Equation	Plot of graph	Parameters
Zero order	$Qt = Q_0 + K_0t$	% drug release versus Time	K0- release rate Constant
First order	$In\ Qt = \ln Q_0 + K1t$	Log % drug release versus time	K1- release rate constant
Higuchi Release	$Qt = KHt^{1/2}$	% drug release versus square root of time	KH- Higuchi constant
Korsmeyer- Peppas	Qt/Q8 = Kktn	Log % drug release versus log time	n- release exponent

Table 3: Interpretation of diffusion release mechanisms from "n" values

Release Exponent (n)	Drug Transport Mechanism	Rate as a function of Time
>0.5	Fickian diffusion	$_t$-0.5
0.5<n>1.0	Anomalous transport	$_t$n-1
1.0	Case-II transport	Zero order release
Higher than 1.0	Super case-II transport	$_t$n-1

Table 4: Categories of PDII classification

Irritancy level	Grading
0.0	Non irritant
>0.0 - 0.5	Negligible irritant
>0.5 - 2.0	Mild irritant
>2.0 - 5.0	Moderate irritant
>5.0 - 8.0	Severe irritant

Table 5: Interpretation of pure drug

Region in cm^{-1}	Function group
2880	-C-H
1700	-C=0
1579.59	N-H Bending
1323.08	C-N

Table 6: Interpretation of pure drug and xanthan gum

Region in cm^{-1}	Function group
2880	-C-H
1700	-C=0
1579.59	N-H Bending
1323.08	C-N

Table 7: Preliminary studies for the preparation of gels

Formulation Code	Type of gelling agent	Concentration of gelling agent (%)	Result
G1	Carbopol 940	0.75 and 1	Gel formed
G2	Carbopol 941	0.75 and 1	Gel formed
G3	HPMC K4M	1 and 2	Gel formed
G4	HPMCK100M	1 and 2	Gel formed
G5	Xanthan gum	1 and 2	Gel formed

Table 8: Preliminary studies for the selection of oil phase and emulsifying agents

Oil phase	Emulsifying agent	Concentration of emulsifying agent	Result
Liquid paraffin	Span 80 Tween 80	1% 0.5%	No phase separation
Liquid paraffin	Span 60 Tween 60	1% 0.5%	Phase separation
Liquid paraffin	Span 20 Tween 20	1% 0.5%	No phase separation
Liquid paraffin	Span 80 Tween 20	1% 0.5%	Phase separation
Liquid Paraffin	Span 20 Tween 80	1% 0.5%	Phase separation

Liquid paraffin	Span 60 Tween 20	1% 0.5%	Phase separation
Liquid paraffin	Span 20 Tween 60	1% 0.5%	Phase separation
Liquid paraffin	Span 80 Tween 60	1% 0.5%	Phase separation
Liquid paraffin	Span 60 Tween 80	1% 0.5%	Phase separation

Table 9: Evaluation of prepared emulgels for physicochemical properties – I

Formulation code	Colour	pH	Homogeneity	Spreadability (g.cm/sec)
FPG1	White	6.98	+++	19.7±0.1
FPG2	White	6.82	+++	18.3±0.3
FPG3	White	6.68	++	28.1±0.01
FPG4	White	6.3	++	25.3±0.2
FOA1	White	6.15	+++	17.3±0.3
FOA2	White	6	+++	15.8±0.3
FOA3	White	5.96	++	28±0.99
FOA4	White	6.23	++	22.9±0.4

Note: Values are expressed as Mean ± SD, n = 3. Homogeneity: +++ Excellent, ++ clear, + turbid

Table 10: Evaluation of prepared emulgels for physicochemical properties – II

Formulation code	Extrudability	Drug content		Viscosity (Cps)
FPG1	+++	98.29	± 0.5	33,371±165
FPG2	+++	99.41	± 0.28	31,100±120
FPG3	+++	97.21 ± 0.9		43,000±120
FPG4	+++	100.13 ± 0.99		24,400±100
FOA1	+++	97.98	± 2.29	32,900±130
FOA2	+++	98.01	± 0.28	34,200±165
FOA3	+++	97.36	± 0.13	42,600±110
FOA4	+++	99.24	± 1.43	21,100±180

Note: Values are expressed as Mean ± SD, n = 3; +++ Excellent, ++ clear, + turbid

Table 11: Permeability parameters of optimized emulgels

Permeability parameters	FOA1	FOA3	FPG4	FOA4
Q8 (g/cm^2)	289.45 ± 0.05	234.02 ± 0.03	259.68 ± 0.15	308.44 ± 0.02
Flux ($g/cm_2/hr$)	34.29 ± 0.004	27.08 ± 0.05	29.95 ± 0.02	37.66 ± 0.15
Permeability coefficient (cm/hr×10-3)	3.29 ± 0.025	2.78 ± 0.004	2.99 ± 0.015	3.76 ± 0.005
Lag time (hr)	1.3 ± 0.57	2 ± 0.025	1.8 ± 0.03	2.4 ± 0.06
Skin content (mg/g)	2.86 ± 0.6	3.66 ± 0.6	4.01 ± 0.24	2.71 ± 0.52

Note: Values are expressed as Mean ± SD, n = 3

Table 12: Model dependent kinetic analysis of the *ex-vivo* permeation studies

Formulation Code	Zero order release	First order release	Higuchi release	Korsmeyer- Peppas release		Release mechanism
	r^2	r^2	r^2	r^2	N	
FOA1	0.988	0.891	0.981	0.996	0.872	Anomalous transport
FOA3	0.984	0.9303	0.982	0.989	0.739	Anomalous transport
FPG4	0.992	0.935	0.98	0.994	0.747	Anomalous transport
FOA4	0.991	0.948	0.976	0.986	0.814	Anomalous transport

Table 13: Stability study of optimized formulation FOA4

Time in weeks for FOA4				
Parameters	**O (Initial)**	**1st week**	**2nd week**	**4th week**
Appearance	+++	+++	+++	+++
Drug content (%)	99.24 ± 1.43	96.98 ± 1.22	98.28 ± 1.23	98.28 ± 1.74
Viscosity (cps)	2100 ± 180	2100 ± 120	2100 ± 150	2100 ± 140
pH	6.23 ± 0.24	6.08 ± 1.23	6.06 ± 1.24	5.94 ± 1.23

Note: Values are expressed as Mean ± SD, n = 3; **Homogeneity:** +++ Excellent, ++ clear, + turbid

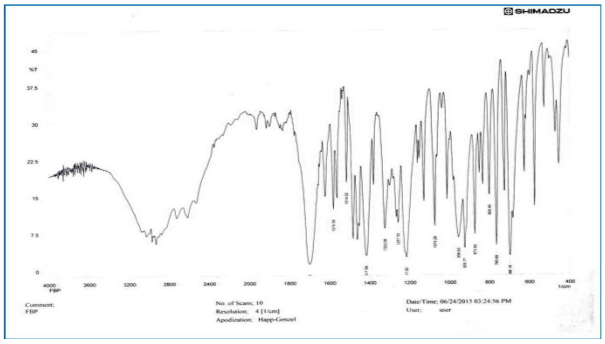

Figure 1: FTIR graph of pure drug

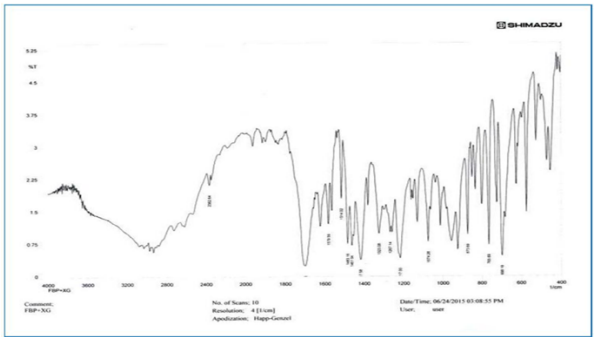

Figure 2: FTIR graph of pure drug and xanthan gum

Figure 3: Addition of 2 ml, 3 ml and 5 ml water to the emulsion

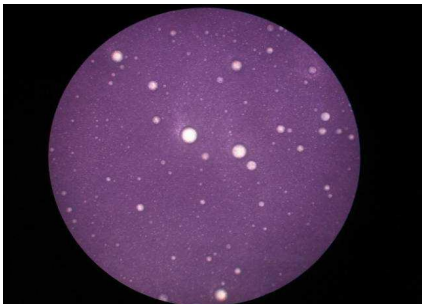

Figure 4: Photomicrograph of dye test

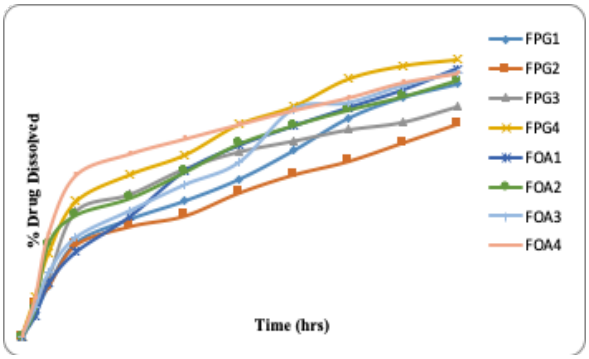

Figure 5: *In-vitro* release data of emulgel formulations

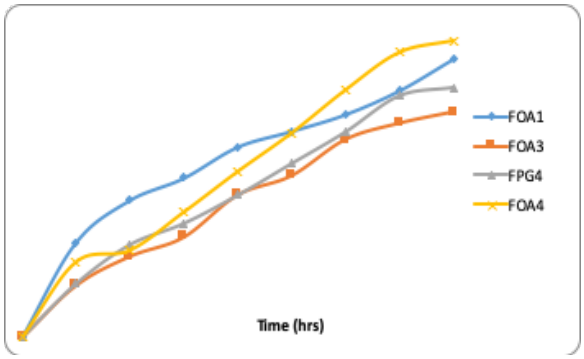

Figure 6: *Ex-vivo* release data of optimized emulgel formulation

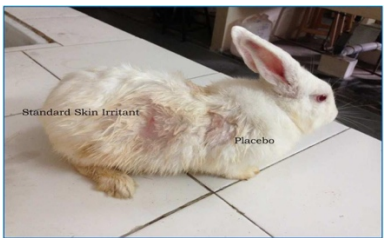

Figure 7: Skin irritation study on rabbit before application of the formulations

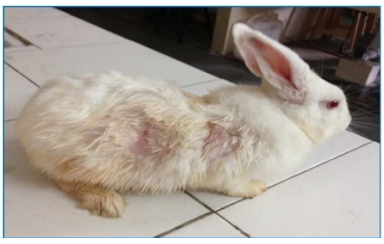

Figure 8: Skin irritation study on rabbit after application of standard skin irritant and placebo

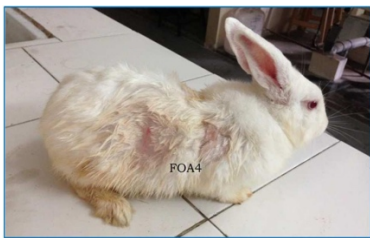

Figure 9: Skin irritation study on rabbit after application of FOA4 formulation

Stability studies

The optimized formulation was evaluated for physical stability testing carried out by keeping optimized formulations in glass containers with polypropylene closure for one month at room temperature. Fixed quantity of gel was taken out at different time intervals like 0, 1st, 2nd, 3rd week and was analyzed for appearance, pH, drug content, spreadability and viscosity.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy analysis of pure drug and formulation

Flurbiprofen is compatible with excipient/s, which was studied by FTIR. The FTIR spectra of formulations with excipients reveal no interaction between drug and excipient. Both the drug and excipient peaks were identified and interpreted in the spectra. The FTIR studies from the spectra confirmed the absence of any chemical inter action between the drug and excipients. The FT-

IR spectra of drug and formulation are shown in Figure 1 and 2 and interpretation data shown in Table 5 and 6.

Preliminary studies for the preparation of emulgels

In preliminary studies as shown Table 7, gelling agents in low concentrations gave gels with less consistency whereas high concentrations gave good consistency. Hence gelling agents Carbopol 940, Carbopol 941, HPMC K100M, Xanthan gum in concentration range of 1-2% were selected for further studies. Preliminary studies for the selection of oil phase and emulsifying agents is shown in Table 8.

Determination of type of emulsion

The type of emulsion (Figure 3) i.e., o/w or w/o can be determined by four methods.

Dilution test

In this method the 5-10 ml of emulsion is taken and is further diluted by adding water or oil phase, based on the solubility of external phase of emulsion we can determine the emulsion type. The emulsions are o/w type as by addition of water as external phase the emulsion was stable as it completely dispersed into emulsion without phase separation.

Conductivity test

As water is a good conductor of electricity, when the cathode and anode wire are dipped in emulsion the passage of certain voltage is determined, this indicates an o/w type emulsion as water is a continuous phase

Dye test

In this method water soluble or oil soluble dye is used for determining the type of emulsion. In this case a water soluble dye is used and is completely dispersed in external phase, and observed using microscope were the continuous phase is colored leaving oil droplets. Thus it indicates water as a continuous phase (Figure 4).

Particle size

The Particle size of the emulsions was determined using optical microscopy. Formulations showed size range of 40 µm. It may be due to the interfacial tension between the two phases.

Evaluation of flurbiprofen emulgels

pH

The pH was found to be in the range from 5.96 to 6.98 as shown in Table 9, thus indicating suitability for application on skin along with good extrudability and spread ability. Among all the formulations pH was less in case of FOA3 (5.96) formulated using xanthan gum as gelling agent and pH was more in case of FPG_1 (6.98) formulated using Carbopol 940 as gelling agent. The formulations having oleic acid as permeation enhancer was shown further decrease in pH due to its acidic nature.

Homogeneity

It was evaluated by visual observation and the results were given in Table 9. All formulated emulgels showed good homogeneity without lumps. The physical appearances of emulgels are opaque in nature were found to be white in color.

Spreadability

From the Table 9, the value of spreadability varies from 15.8 to 28.1g.cm/s indicating that the emulgels are easily spreadable by small amount of shear. All emulgel preparations indicated good spreadability. FPG3 (28.1 g/cm/sec) formulated using HPMC K100M in the concentration of 2% has shown more spreadability compared with remaining formulations. FOA2 (15.1 g/cm/sec) formulated using Carbopol 941 in the concentration of 1% and FOA1 (17.3 g/cm/sec) formulated using Carbopol 940 in the concentration of 1% has shown very less spreadability.

Extrudability

The extrusion of the emulgel from the tube is important during its application and in patient acceptance. The extrudability of all formulations was found to be good and compatible as shown in Table 10.

Drug content

The content of drug per 500 mg of emulgel ranged from 97.21% to 100.13% as given in Table 10, which indicates that efficient drug loading and uniform distribution of drug in the formulations. FPG4 (100.13%) formulated using gelling agent xanthan gum and penetration enhancer propylene glycol in the concentration of 2% and 5% respectively has shown more drug content compared with FPG3 formulated using HPMC K100M gelling agent and penetration enhancer propylene glycol in the concentration of 2% and 5% respectively.

Viscosity

Viscosity is an important parameter for characterizing the gels as it affects the extrudability and release of drug. Viscosity of prepared emulgels was determined by Brookfield programmable viscometer LVDV-II+PRO. The spindle was rotated at 50 rpm. Samples of the emulgels were allowed to settle over 30 minutes at the temperature (25 ± 1ºC). The viscosity of the formulations ranged between 21,100 to 43,000 cps as shown in the Table 10. Among all the formulations FPG3 prepared using HPMC K100M as gelling agent in the concentration of 2 % has shown more viscosity of 43,000 cps and FOA4 formulated using xanthan gum as gelling agent in the concentration 1% of has shown very less viscosity.

***In-vitro* diffusion studies of the prepared flurbiprofen emulgels**

In-vitro diffusion studies were performed with dialysis membrane using Frandz diffusion cells. Samples were withdrawn periodically and analyzed using UV-VIS double beam spectrophotometer at 248 nm. The *in vitro* drug release profiles showed in Figure 5.

From the *in-vitro* diffusion studies, the formulations FPG4, FOA1, FOA3 and FOA4 has shown more than 75% of drug release for 8 hrs. As the *in-vitro* diffusion studies were performed on dialysis membrane wherein only water filled pores do not mimic the surface of skin, which is also lipophilic made up of phospholipids. Hence the above same formulations when performed for *ex-vivo* permeation studies on rat abdominal skin, the results were not similar because the emulgel formulations contain permeation enhancers which show effect on the surface of lipophilic skin by interacting with skin or by rupturing skin integrity which does not show on dialysis membrane. So, for getting better results and to study the effect of permeation

enhancers on the skin, all the optimized emulgel formulations were subjected to *ex-vivo* permeation studies.

Ex-vivo absorption studies

Ex-vivo studies performed using rat intestine after obtaining the approval of the Institutional Animal Ethical Committee (IAEC) and in accordance with disciplinary principles and guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA). (320/CPCSEA; Dated 03-01-2001 and Student ID number GPRCP/IAEC/10/18/ 02/PCE/AE-I-Rats-M-21; G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, India).

Ex-vivo Release data of optimized formulations

Ex-vivo diffusion studies performed with rat abdominal skin using frandz diffusion cells after obtaining the approval of the Institutional Animal Ethical Committee (IAEC) and in accordance with disciplinary principles and guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA). (320/CPCSEA; Dated 03-02-2015 and Student ID number GPRCP/IAEC/10/15/ 02/PCE/AE-I-Rats-M-21; G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, India).

Ex-vivo diffusion studies were performed with rat abdominal skin using frandz diffusion cells. Samples were withdrawn periodically and analyzed using UV-VIS double beam spectrophotometer at 248 nm. The *ex-vivo* drug release profiles were showed in Figure 6.

The optimized formulation showed maximum drug release rate of 145.62 (g/cm^2/hr for 8 hrs with flux 37.66 (g/cm^2/hr and Q8 of 308.44 (g/cm^2).

Permeability parameters of optimized emulgels

Upon comparing the ratio of permeability of drug as shown in Table 11, the FOA4 formulation with xanthan gum (1%) and oleic acid (2%) was optimized as it shown high permeation and high skin deposition.

Drug release kinetics

The results obtained from *ex-vivo* release studies of the optimized batch was attempted to fit into various mathematical models. The regression coefficient (r^2) values of zero order, first order, Higuchi matrixes, Peppas are tabulated in Table 12 for all the formulations. When the regression coefficient 'r' value of zero order and first order plots of optimized formulation (FOA4) were compared, it was observed that 'r' value of zero order was 0.991 whereas the 'r' value of first order plots was found to be 0.948 indicating that the drug release from the optimized formulation was found to follow zero order release kinetics. The 'r' value of Higuchi kinetics was found to be 0.976.

The *ex-vivo* dissolution data as log cumulative percent drug release versus log time were fitted to Korsmeyer-Peppas equation, value of the exponent 'n' was found to be 0.814 indicating the drug release by anomalous transport.

Skin irritation study

Skin irritation study was performed by using control, standard skin irritant, drug solution and test which were applied on the left and right dorsal surface of rabbit skin and rabbits were examined for 8 h. Erythema and edema was evaluated and the score was given according to the Primary Dermal Irritation Index classification (PDII) (Figure 7-9).

Stability studies

The stability of this optimized formulation was known by performing stability studies for one month at room temperature. The formulation was found to be stable, with insignificant change in the appearance, drug content, viscosity and pH and the results are tabulated in Table 13.

CONCLUSION

Emulgels are relatively newer and better topical drug delivery systems since they enjoy the advantages of both emulsion and gels. They enable the poorly aqueous-soluble drugs to be loaded into a hydrophilic gel base. Emulgels of flurbiprofen were prepared and optimized. All the physicochemical properties of the emulgels were checked and were found to be good.

Among all the gelling agents used, xanthan gum based formulation FOA4 using oleic acid as penetration enhancer gave superior drug release compared to the other formulations.

In-vitro releases of the test formulations were performed to determine drug release rate from emulgel. It was concluded that FOA4, FOA1, FPG4 and FOA3 have shown more than 75% drug release for 8 h respectively. *Ex-Vivo* studies indicated that the FOA4 formulated with xanthan gum in the concentration of 2% and oleic acid as penetration enhancer has shown better release of flurbiprofen for 8 h with the flux of 37.66 ± 0.15 5 g/cm^2/hr and Q8 of 308.44 5 g/cm^2. The optimized formulation FOA4 has shown no drug interaction. Skin irritation studies proved that the formulation was non-toxic and non-irritant and the formulation was found to be stable for one month at room temperature.

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