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Formulation and Evaluation of Flurbiprofen Topical Emulgels

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Abstract

Topical drug delivery has been used for centuries for the treatment of local skin disorders. Emulgel have emerged as one of the most interesting topical delivery system as it has dual control release system i.e. gel and emulsion. One side the topical applications of the drug offers 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. Topical non-steroidal anti-inflammatory drug (NSIAD) formulations are designed to deliver therapeutic levels of the active ingredients to the inflamed tissue without elevating serum levels after application on the skin. This route is an attractive alternative to the oral administration of NSAIDS which is associated with high incidence of gastrointestinal tract (GIT) complications and other systemic toxic effects. Flurbiprofen is a potent non-steroidal anti-inflammatory agent usually well tolerated as compared to other NSAIDS product. It has analgesic and antipyretic properties. It is used in the treatment of rheumatic disorders such as ankylosing spondilities, oesteoarthritis and intraoperative miosis. It suffers from major GIT disturbances. The aim of the present study was to develop an emulgel formulation of flurbiprofen using 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 emulgels were found to be stable with respect to physical appearance, pH, and rheological properties and drug content at all temperature and conditions for one month.

Keywords: Emulgel, Topical drug delivery, Flurbiprofen, Carbopol, Hydroxy propyl methyl cellulose

Introduction

Topical drug delivery system (TDDS) is a type of dosage form which distributes an adequate amount of drug across the skin[1]. TDDS gives a greater chance of success of drug delivery over traditional methods like use of injectables and oral formulations. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin[2]. They have a higher aqueous component that permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream base[3, 4]. These are superior in terms of use and patient acceptability. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels[5]. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS[6]. Emulgels are also called as creamed gel, quassi emulsion, gelled emulsion[7]. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase[8]. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, no staining, long shelf life, bio-friendly, transparent and pleasing appearance[9]. Flurbiprofen is a propionic acid type NSAID, highly effective for the treatment of many types of inflammatory and arthritic diseases such as rheumatoid arthritis, arthralgia, ankylosing spondilytis and other related conditions[10]. It is readily absorbed after oral administration (>95%) and has an apparent half life of 2-6 h. As is the case for the many NSAIDs, oral administration of flurbiprofen often produces gastric irritation and sometimes patients can develop ulceration and severe gastrointestinal bleeding[10, 11]. In order to minimize these adverse effects associated with oral administration, topical delivery of flurbiprofen has been studied[12, 13]. 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[14]. In this research, topical gel formulations of flurbiprofen were prepared using hydroxyl propyl methyl cellulose (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[15]. The prepared emulgels were evaluated for physical appearance, FTIR studies, pH, viscosity, spreadability, extrudability, and stability studies.

Materials and methods

Materials

Flurbiprofen was obtained as a gift sample from Sun Pharmaceutical Ltd. Ahmedabad. 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 used were of analytical grade and were used without any further chemical modification.

Preformulation studies[16, 17]

Physical characteristics

By visual examination, the drug was identified for physical characters like colour, texture, odour etc.

Solubility

Solubility of the drug was determined by taking some quantity of drug (about 10 mg) in the 10 ml volumetric flasks separately and added the 10 ml of the solvent (water, ethanol, methanol, 0.1N HCL, 0.1N NaOH, chloroform and 7.4 pH buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature).

Melting point

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (Chemline) containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

FTIR spectroscopy

The concentration of the sample in KBr should be in the range of 0.2% to 1 %. The pellet is a lot thicker than a liquid film, consequently a decrease concentration in the sample is required (Beer's Law). For the die set that you'll be the usage of, about 80 mg of the mixture is wanted. Too excessive of an attention causes typically difficulties to obtain clean pellets. FTIR spectra of the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Determination of λ_{max} of flurbiprofen

Flurbiprofen, 100 mg, was accurately weighted into a 100 ml volumetric flask, dissolved in methanol and the volume was made up with methanol. Pipette 1 ml of this solution into a 10 ml volumetric flask with methanol as the volume and marks it as stock. Prepare an appropriate dilution to bring the concentration down to 2-12µg/ml. The resulting solution is scanned with a UV spectrophotometer (UV-1700 Shimadzu corporation, Japan) in the range of (200-400 nm) to determine the absorption maximum (λ max). Concentration vs. absorbance was shown on a graph.

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 941 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[18, 19]. Formulation batches for emulgel were shown in Table 1.

Table 1: Composition of different formulation of emulgel

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

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[20-23].

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,

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

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 crimpier 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 cm2) ---- 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

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 Discussions

The melting point of flurbiprofen (pure drug) was found to be 118-120°C. Flurbiprofen was soluble in methanol and ethanol, sparingly soluble in chloroform and insoluble in water. Identification of flurbiprofen was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Figure 1. The calibration curve of flurbiprofen was found to be linear in the concentration range of 2-12 µg/ml at 247 nm Figure. 2. 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. The pH was found to be in the range from 5.96 to 6.23 as shown in Table 2, 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. The formulations having oleic acid as permeation enhancer was shown further decrease in pH due to its acidic nature. It was evaluated by visual observation and the results were given in Table 2. All formulated emulgels showed good homogeneity without lumps. The physical appearances of emulgels are opaque in nature were found to be white in color. From the Table 2, the value of spreadability varies from 15.8±0.3to 28±0.99g.cm/s indicating that the emulgels are easily spreadable by small amount of shear. All emulgel preparations indicated good spreadability. FOA2 (15.8 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. 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 3. The content of drug per 500 mg of emulgel ranged from 97.36% to 99.24 % as given in Table 3, which indicates that efficient drug loading and uniform distribution of drug in the formulations. FOA4 formulated using gelling agent xanthan gum in the

concentration of 2% has shown more drug content compared with other formulated using HPMC K100M gelling agent and penetration enhancer propylene glycol in the concentration of 2% and 5% respectively. 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 42,600cps as shown in the Table 3. Among all the formulations FOA4 formulated using xanthan gum as gelling agent in the concentration 1% of has shown very less viscosity. 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 4.

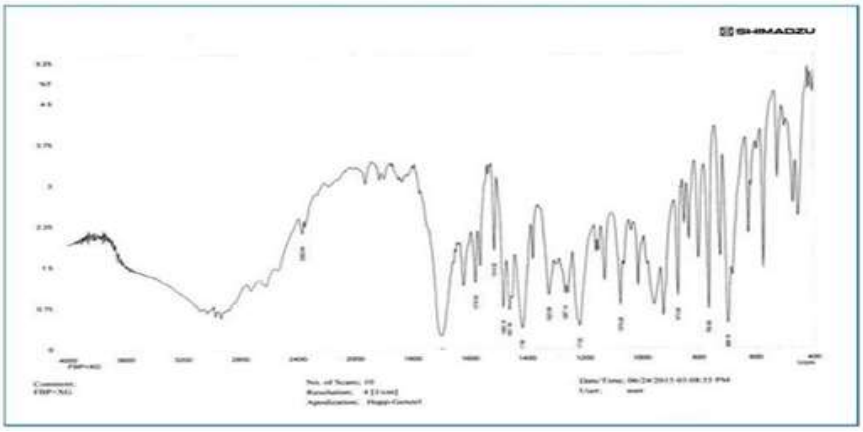

Figure 1: FT-IR spectrum of pure drug (Flurbiprofen)

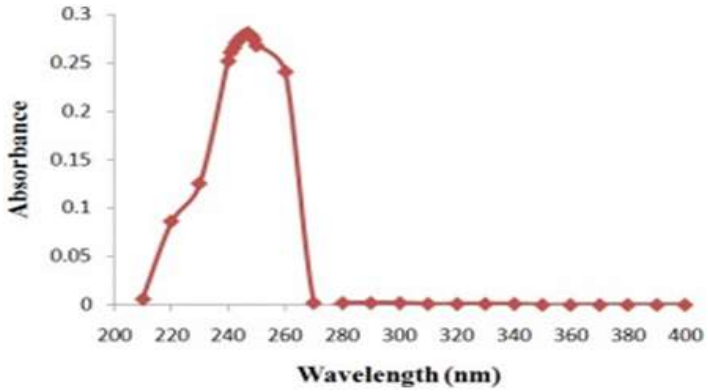

Figure 2: Wavelength maxima of flurbiprofen in methanol

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

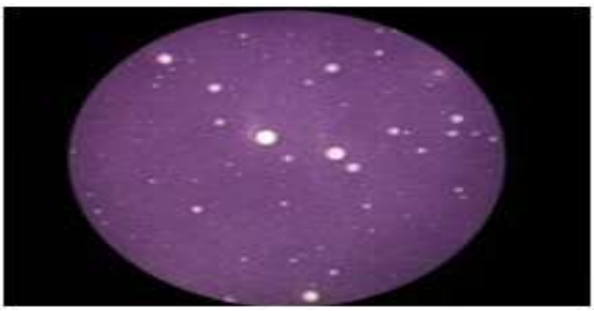

Figure 4: Photomicrograph of dye test

Table 2: Evaluation of prepared emulgels for physicochemical properties

Formulation	Colour	pH	Homogeneity	Spreadability
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 3: Evaluation of prepared emulgels for physicochemical properties

Formulation code	Extrudability	Drug content	Viscosity (Cps)
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 4: Stability study of optimized formulation FOA4

Time in weeks for FOA4				
Parameters	**0 (Initial)**	**1st week**	**2nd week**	**4th week**
Appearance	+++	+++	+++	+++
Drug	99.24 ± 1.43	96.98 ± 1.22	98.28 ± 1.23	98.28 ± 1.74
Viscosity	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

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 and the formulation was found to be stable for one month at room temperature.

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