FORMULATION OPTIMIZATION AND EVALUATION OF FLURBIPROFEN EMULGEL

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ABSTRACT

Objective: The objective of the present study was to formulate flurbiprofen (FLB) emulgel, evaluation of the formulations and the selection of an optimized formulation through in vitro drug release and drug content studies. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) requiring frequent administration and its chronic intake can lead to systemic side effects like gastric irritation and GI bleeding. The development of a dermal drug delivery system can overcome these side effects.

Methods: The emulgel formulations were produced using different combinations of oil and emulsifying agents. Carbopol 940 was used as a gelling agent. The prepared emulgels were evaluated for general appearance, pH, spreadability, extrudability, drug content, average globule size and viscosity.

Results: Optimized formulation F7 showed a better in vitro drug release compared to the marketed gel preparation. The stability study for the optimized formulation was carried out at 25 °C/60 % RH for 3 mo and the emulgel was found to be stable concerning the physical appearance, pH and drug content.

Conclusion: The study revolved around the formulation of emulgel containing Flurbiprofen for dermal delivery of the drug. Emulgel was formulated with the purpose to enhance the permeation of poorly water-soluble drug FLB. The study concluded that the optimized emulgel containing FLB exhibited better in vitro drug release profile compared to the marketed formulation.

Keywords: Flurbiprofen, Emulgel, Carbopol 940, Optimization, Evaluation

INTRODUCTION

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are the category of drugs used for the long term treatment of Rheumatoid arthritis (RA) and osteoarthritis. When administered by oral route, these drugs cause systemic side effects like gastric ulceration and irritation but when administered as a dermal drug delivery system, the systemic side effects as well as the first-pass metabolism of the drug is bypassed thereby delivering the drug at a predetermined rate and improving patient compliance. Flurbiprofen, [2-(2-fluoro-4-biphenyl) propionic acid] is a potent, chiral non-steroidal anti-inflammatory agent with antipyretic and analgesic action and is approved by USFDA for the treatment of rheumatoid arthritis, osteoarthritis, and alkylosing spondylitis. It has a half-life of 4.7 h and needs frequent administration and its chronic intake could result in systemic side effects like gastric irritation and gastric bleeding [1-5].

Owing to the various disadvantages associated with semisolids like ointments, creams and lotions like stickiness, less spreading abilities and the need for the application of semisolids with rubbing and stability issues, transparent gels are more preferred in cosmetics as nature.

The effect of varying concentration of emulsifying agents and oil phase on the drug release was investigated.

MATERIALS AND METHODS

Flurbiprofen was obtained as a gift sample from FDC-Ltd (Roha Maharashtra), carbopol 940 was obtained from lubrizol, tween 80, span 80 and triethanolamine were obtained from molychem, liquid paraffin was obtained from SB-chemicals and fines ltd. All the solvents were of analytical grade.

Preparation of an emulgel

The composition of an emulgel is as shown in table I.

Preparation of Carbopol 940 gel base

Carbopol 940 was soaked in a sufficient quantity of distilled water for 3 h and then pH was adjusted to 6.5 using triethanolamine to yield the gel.

Preparation of an emulsion

Preparation of oil phase: Oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin followed by dispersing the drug in it since Flurbiprofen is hydrophobic by nature.

Preparation of an aqueous phase: The aqueous phase was prepared by dissolving Tween 80 in purified water. Methylparaben was then dissolved in a sufficient quantity of ethanol and propylene glycol and added to the aqueous phase. Both the oil and aqueous phases were separately heated to 70-80°C, then the oily phase was added to the aqueous phase with continuous stirring followed by cooling to room temperature to yield an o/w emulsion.

Preparation of an emulgel

The final emulgel was formed by the addition of the emulsion to Carbopol gel in the ratio of 1:1 with constant stirring [8].
Drug-polymer compatibility study

The drug-polymer compatibility study was carried out using FTIR spectrophotometer (Shimadzu). The IR spectra of the drug as well as the physical mixture of the drug and polymer in the ratio of 1:1 were recorded. All the spectra were recorded in the range of 400-4000 cm⁻¹ [8].

Characterization of the formulated emulgel

General appearance

The prepared emulgel formulations were visually inspected for color and appearance since no quantitative estimation could be done on this parameter due to the non-availability of the required facility.

pH

The pH of the skin is normally between 6 to 7, and it is therefore desirable that the preparation used for topical application does not fall beyond this value or else it will cause severe irritation to the skin. The pH of all the formulations was evaluated using a pH meter and the pH was measured at room temperature [8].

Spreadability

To study the spreadability of formulations, a special apparatus was designed. Spreadability was expressed in terms of time in seconds taken by two slides to slip off from formulations placed between, under the application of a certain load. Lesser the time taken to separate the two slides, better is the spreadability. Two glass slides of 6×2 cm each were selected. The formulation was placed over one of the slides. This slide was placed on another slide in such a way that the formulation was sandwiched between the two slides. The formulation between the two slides was squeezed consistently to frame a slight layer; for this reason, weight 100 g was placed on the upper slide. The excess of the formulation adhering to the slide was scrapped off after the weight was removed. The lower slide was fixed on the surface of the apparatus and the upper slide was tied to the string. To this string, 20 g load was applied with the help of a simple pulley. Under the direction of weight applied, the time taken for the upper slide to move the distance i.e. of 6 cm and separate away from the other slide (lower) was noted. The experiment was repeated three times and the average of such determination was calculated for each formulation by using the formula [9, 10]:

\[ S = \frac{M \times L}{T} \]

Where, \( S \) = spreadability,
\( M \) = weight tied to the upper slide,
\( L \) = length of glass slides
\( T \) = time taken to separate the slides completely from each other

Extrudability

Test to measure the force required to expel the material from the tube. The formulation whose extrudability was to be checked was filled in a clean, lacquered aluminum collapsible metal tube. Extrudability of the emulgel was the weight required to extrude from a lacquered aluminum collapsible tube at least 0.5 cm ribbon of emulgel in 10 s on the application of weight in grams. More the quantity extruded better is the extrudability. The measurement of the extrudability of each formulation was determined in triplicate and the average values are presented. The extrudability is than calculated by using the following formula [11]:

\[ \text{Extrudability} = \frac{\text{Applied weight to extrude emulgel from tube (in g)}}{\text{Area (in cm²)}} \]

Drug content

Gel formulation (1 gram) was dissolved in methanol. The solution was filtered to obtain a clear solution. The absorbance of the resulting solution was measured using a UV Visible spectrophotometer after suitable dilution to determine the drug content [12].

In vitro drug release

In vitro release studies were done using diffusion studies. In vitro drug release behavior of the drug from the emulgel formulations was investigated using the dialysis membrane. Dialysis membrane previously soaked in the phosphate buffer pH 7.4 was used as the permeation membrane. 50 ml of Phosphate buffer pH 7.4 was placed in a beaker (receptor compartment). An accurately weighed quantity (1 g) of the formulated emulgel was then uniformly spread on the dialysis membrane (donor compartment) and this membrane was tied to the diffusion tube (a hollow tube open on both sides). One

Table 1: Composition of different formulation batches (% w/w)

| Formula       | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---------------|----|----|----|----|----|----|----|----|----|
| Flurbiprofen  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| Carbopol 940  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| Liquid paraffin | 5  | 5  | 5  | 7.5 | 0.9 | 0.9 | 0.9 | 0.9 | 0.9 |
| Span 80       | 2.1 | 3.2 | 1.1 | 0.2 | 1.9 | 2.8 | 1.9 | 2.8 | 1.9 |
| Tween 80      | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| Propylene glycol | 5 | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Ethanol       | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| Purified water | qs to 100 ml | qs to adjust pH to 6 to 7 |
side of the dialysis membrane was kept in contact with the medium phosphate buffer pH 7.4. The medium was constantly agitated using a magnetic stirrer and the temperature was maintained at a constant of 37 ± 1 °C throughout the operation. Samples of 5 ml volume were then withdrawn from the receptor compartment at intervals of 1 hour for 8 h and the amount withdrawn was replaced with a fresh volume of the medium. The samples withdrawn were then analyzed for the amount of Flurbiprofen released by UV spectrophotometric method by measuring the absorbance of the samples at 247 nm against Phosphate Buffer pH 7.4 taken as blank [8].

Table 2: Details of in vitro release studies

| Diffusion medium                  | pH 7.4 Phosphate buffer |
|----------------------------------|-------------------------|
| Volume of diffusion medium used  | 50 ml                   |
| Temperature                      | 37 °C ± 1 °C            |
| Time interval for sampling       | 1 h                     |
| Speed                            | 50 rpm                  |
| Volume of sample withdrawn       | 5 ml                    |
| Detection wavelength             | 247 nm                  |

**Average globule size**

The average globule size was measured by a light microscope at 40X magnification [8].

**Viscosity**

The viscosity of the optimized emulgel formulations is determined by Brookfield Viscometer using spindle no. 64 at 10 rpm [5].

**Stability study**

Stability study was performed on the optimized formulation F7. The preparation was packed in an aluminum collapsible tube (5g) and was subjected to stability studies as 25 °C/60 % RH for 3 mo. Thereafter the samples were withdrawn and evaluated for physical appearance, rheological properties, and drug content. All the test results were found to be in limits. Hence the formulations were stable under stated storage conditions [6, 13, 16].

**RESULTS**

**Drug-polymer compatibility study**

The FTIR spectra of the pure Flurbiprofen and 1:1 mixture of Flurbiprofen and carbopol 940P is shown in fig. 2 and fig. 4, respectively. There was no change in the position or disappearance of any characteristic peak of Flurbiprofen, indicating the compatibility between the drug Flurbiprofen and polymer carbopol 940.

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**Fig. 2: FTIR spectra of flurbiprofen**

**Fig. 3: FTIR spectra of 1:1 mixture of flurbiprofen and carbopol 940**
General appearance
All formulation batches were found to be homogenous yellowish milky emulsions while emulgels were found to be yellowish-white viscous, creamy preparations.

pH
The pH of all the formulations was found to be as in table 3 follows

Spreadability
The spreadability of all the formulations ranged as follows, as in table 4. Formulation F7 was found to possess the highest spreadability.

Drug content
%. Drug content of all the formulations is as follows in table 5.

Table 3: pH of formulations F1-F9

| Formulation code | pH       |
|------------------|----------|
| F1               | 6.2±0.76 |
| F2               | 6.4±0.88 |
| F3               | 6.7±0.79 |
| F4               | 6.1±0.66 |
| F5               | 6.2±0.50 |
| F6               | 6.8±0.77 |
| F7               | 6.7±0.87 |
| F8               | 6.3±0.99 |
| F9               | 6.8±0.95 |

*Data are represented as mean±standard deviation (SD), n=3

Table 4: Spreadability of formulations F1-F9

| Formulation code | Spreadability value (cms) |
|------------------|---------------------------|
| F1               | 6.66                      |
| F2               | 5.83                      |
| F3               | 6.66                      |
| F4               | 7.66                      |
| F5               | 7.00                      |
| F6               | 6.83                      |
| F7               | 7.97                      |
| F8               | 7.33                      |
| F9               | 7.33                      |

Table 5: Drug content of formulations F1-F9

| Formulation code | Drug content (%) (mean±SD, n=3) |
|------------------|---------------------------------|
| F1               | 98.90±0.73                      |
| F2               | 99.50±1.54                      |
| F3               | 99.80±2.59                      |
| F4               | 99.40±0.78                      |
| F5               | 98.42±0.98                      |
| F6               | 97.93±0.89                      |
| F7               | 100.0±0.99                      |
| F8               | 98.32±1.65                      |
| F9               | 99.42±0.84                      |

*Data are represented as mean±standard deviation (SD), n=3

Table 6: Average droplet size range for formulations F1-F9

| Formulation code | Average globule size (μm) (mean±SD, n=3) |
|------------------|------------------------------------------|
| F1               | 14.5±0.25                                |
| F2               | 13.5±0.75                                |
| F3               | 11.5±1.00                                |
| F4               | 17.5±0.25                                |
| F5               | 17.0±0.95                                |
| F6               | 13.1±0.25                                |
| F7               | 14.0±1.25                                |
| F8               | 12.4±1.25                                |
| F9               | 16.7±0.95                                |

*Data are represented as mean±standard deviation (SD), n=3

Average droplet size
The average droplet size measurements are as shown in the table 6.

In vitro drug release
The In vitro drug release of all the formulations F1-F9 and marketed gel formulation ranged as follows.
The pH of all the formulations was found to be neutral.

The appearance of the formulations was found to be white, creamy, viscous. The IR scans of pure drug flurbiprofen and 1:1 physical mixtures of flurbiprofen and carbopol 940 were taken. From the IR spectra shown in fig. 2 and fig. 3, it was observed that there was no interaction of the drug with any of the excipients. The appearance of the formulations was found to be satisfactory. The pH of all the formulations was found to be neutral and was close to the pH of the skin and hence it should not cause any irritation to the skin [14].

The extrudability of all the formulations was satisfactory. The highest spreadability was shown by the optimized formulation F7.

**Table 7:** In vitro drug release of formulations F1-F9 and marketed gel formulation

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | Marketed gel formulation |
|---------|----|----|----|----|----|----|----|----|----|--------------------------|
| 0       | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0                       |
| 1       | 19.77 | 15.39 | 13.53 | 17.32 | 22.16 | 13.51 | 26.59 | 22.00 | 20.59 | 6.73                   |
| 2       | 30.14 | 29.68 | 21.74 | 29.30 | 32.16 | 23.83 | 42.71 | 40.42 | 38.71 | 10.73                  |
| 3       | 41.41 | 37.44 | 35.25 | 45.44 | 43.14 | 30.99 | 57.40 | 55.98 | 50.40 | 15.20                  |
| 4       | 44.52 | 42.08 | 39.76 | 53.90 | 51.57 | 34.84 | 68.72 | 65.47 | 62.88 | 23.54                  |
| 5       | 51.30 | 48.48 | 42.90 | 60.44 | 56.57 | 40.31 | 79.59 | 78.28 | 70.90 | 26.22                  |
| 6       | 58.98 | 55.25 | 52.88 | 63.54 | 60.11 | 50.31 | 80.42 | 83.09 | 81.44 | 30.32                  |
| 7       | 64.74 | 63.67 | 58.96 | 69.88 | 66.39 | 57.06 | 97.97 | 93.80 | 90.54 | 34.17                  |
| 8       | 69.23 | 66.91 | 63.26 | 74.10 | 71.59 | 62.90 | 99.00 | 95.18 | 92.67 | 38.90                  |

**Table 8:** Values of the regression coefficient (R²) and release kinetics of formulation in phosphate buffer pH 7.4

| Code | Zero-order | First-order | Peppas | Higuchi |
|------|------------|-------------|--------|---------|
|      | R²         | K           | R²     | K       | R²     | K     | R²     |
| F1   | 0.9485     | 7.99        | 0.9672 | 0.287   | 0.994  | 0.59  | 0.994  |
| F2   | 0.9599     | 7.91        | 0.9416 | 0.323   | 0.985  | 0.68  | 0.991  |
| F3   | 0.9712     | 7.65        | 0.9540 | 0.357   | 0.987  | 0.75  | 0.987  |
| F4   | 0.9341     | 8.96        | 0.9160 | 0.331   | 0.977  | 0.70  | 0.983  |
| F5   | 0.9278     | 8.13        | 0.890  | 0.0668  | 0.994  | 0.56  | 0.994  |
| F6   | 0.9815     | 7.40        | 0.974  | 0.346   | 0.991  | 0.71  | 0.977  |
| F7   | 0.967      | 10.56       | 0.956  | 0.310   | 0.995  | 0.65  | 0.994  |
| F8   | 0.955      | 10.39       | 0.930  | 0.335   | 0.985  | 0.70  | 0.991  |
| F9   | 0.970      | 10.23       | 0.943  | 0.343   | 0.991  | 0.72  | 0.996  |

*Data are represented as mean±standard deviation (SD), n=3

Extrudability

The extrudability values of formulations F1-F9 were found to be as per table 9.

Viscosity

Viscosity measurement was performed on the optimized formulation (F7) and was found to be 36300 cPs.

Stability studies

The results of the stability studies are as follows in table 10.

**DISCUSSION**

FTIR was performed to detect any sign of interaction, which would be reflected by a change in the position or disappearance of any characteristic peak of Flurbiprofen. IR scans of pure drug flurbiprofen and 1:1 physical mixtures of flurbiprofen and carbopol 940 were taken. From the IR spectra shown in fig. 2 and fig. 3, it was observed that there was no interaction of the drug with any of the excipients. The appearance of the formulations was found to be satisfactory. The pH of all the formulations was found to be neutral and was close to the pH of the skin and hence it should not cause any irritation to the skin [14].

The spreadability of all the formulations was satisfactory. The highest spreadability was shown by optimized formulation F7 in 7.97 cm. Drug content was almost uniform in all the formulations and was found to be between 97.9 to 100.8 %.

The release of the drug from the emulgel had better release compared to the marketed Brufen gel. Optimized formulation F7 showed a release of 99%, whereas the marketed formulation showed a release of 38.90% indicating that the formulated emulgel had better release compared to the marketed product. The release of the drug from the emulgel formulations could be ranked in the descending order as follow: F7>F8>F9>F4>F5>F6=F1>F2>F3.

The release was found to vary according to the concentration of liquid paraffin, span 80 and tween 80. When the concentration of emulsifiers i.e. span 80 and tween 80 was less; the release exhibited was more.

The in vitro release data was fitted to the curve kinetic models to know the mechanism of drug release. Regression coefficient (R²)
values for zero-order ranged from 0.927-0.981 and for first-order plots ranged from 0.890-0.974. R² values were found to be higher for zero-order than for first-order. According to the regression coefficients tabulated in Table 8 for all the formulations, it is evident that all the formulations follow zero-order drug release kinetics. Since regression coefficients of Higuchi plot were found to be close to 1 according to the above-tabulated data, it also reveals that all the formulations exhibit diffusion drug release mechanism. In the case of Korsmeyer peppas plot ‘n’ values were more than 0.5, which indicates non-fickian drug release kinetics. Hence, from the data obtained from all the models, it was concluded that the drug release through the flurbiprofen emulgel formulations is diffusion-controlled following zero-order kinetics with non-fickian diffusion pattern [11, 18].

The viscosity of the optimized formulation was found to be satisfactory.

The results of the stability studies indicated that the optimized emulgel was found to be stable concerning to physical appearance, pH and drug content at 25 °C/60 % RH for a period of 3 mo.

CONCLUSION

The present study deals with the formulation development and optimization of flurbiprofen emulgel. The optimization was done based upon the drug content and in vitro drug release. The kinetic modeling revealed that Flurbiprofen was a good fit to the zero-order and Higuchi model. The emulgel was found to exhibit diffusion controlled drug release according to Higuchi model. Overall the release from the emulgel was zero-order, non-fickian drug release. Formulation batch F7 showed better drug release compared to the marketed gel (Brufen) formulation thus revealing the better results of the formulated emulgel. Thus the successful attempt of emulgel formulation was made.

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AUTHORS CONTRIBUTIONS

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CONFLICT OF INTERESTS

Declared none

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