



Preparation and evaluation of methyl salicylate counter - Irritant emulgel of mefenamic acid

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ABSTRACT

Topical delivery of hydrophobic drug with good patient acceptance is a big challenge which is successfully handled by Emulgels. The objective of the study was to prepare emulgel of mefenamic acid, a NSAID, using Carbopol 934P as a gelling agent and methyl salicylates as counter irritant agent. The emulsion was prepared and it was incorporated in gel base in the ratio of 1:1. The prepared six formulations were evaluated for rheological studies, spreading coefficient studies, bioadhesion strength, *in vitro* release and *ex vivo* release studies. From the obtained results it can be concluded that topical emulgel of Mefenamic acid possess great suitability for topical delivery.

1. Introduction

Drug delivery systems ensure its rate of release as well as its fate in the body. These systems must take a number of needs into account, ranging from ease of administration, patient compliance to effective drug release^[1]. Topical drug administration is localized drug delivery whether through ophthalmic, rectal, vaginal or skin as topical routes. From them skin is one most readily accessible organs on human body for topical administration and is main route of topical drug delivery system^[2]. In order to formulate an effective and efficient topical preparation consideration must be given to the intended site as well as desired effect^[3].

Gels are network of colloidal solid particles with entrapment of large amounts of aqueous or hydro-alcoholic liquid^[4]. Most topical gels are prepared with organic polymers such as carbomers, alginates, chitosan but one which is prepared with carbomer is easily washed off the skin with water^[4,5].

When gels and emulsions are used in combined form the dosage form are referred as emulgel^[6]. In recent years, there has been

great interest in the use of novel polymers. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The combination of hydrophilic cornified cell both hydrophilic and hydrophobic substances^[7,8]. Emulgel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs as it is engulfed in oil droplets of emulsion. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations.

Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin due to their penetrability. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance^[9]. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption. Molecules can penetrate the skin by three routes: through intact stratum

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corneum, through sweat ducts, or through the sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient^[10]. Except for very small particles, water soluble ions and polar molecules do not penetrate used to manipulate the barrier function of the skin, for restore pliability to a desiccated horny layer^[11].

The aim of the present study was to develop the counterirritant emulgel of mefenamic acid. The drug solubility would be enhanced by the emulgel formulation. Methyl salicylate was incorporated in some formulation which acts as counter irritant.

2. Materials and methods

The following materials were used in the study. Mefenamic acid (ACS chemicals, Mumbai), Carbopol 934 (Coral Pharma Chem.), Tween 80 and Span 20 (Loba Chemicals), Methyl salicylate (Forum Chem.), Light liquid Paraffin, Triethanolamine and propylene glycol (SD fine Chemicals), Propylene glycol (Ases Ltd.), Ethanol (S D Fine Chem.), Cellophane membrane (Chemdyes, Rajkot).

2.1 Preparation of emulgel

The gel in formulations (See Table 1) was prepared by dispersing Carbopol 934 P in purified water with constant stirring at amoderate speed; then the pH was adjusted to 6-6.5 Tri ethanolamine. 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 80 in purified water.

Table 1: Formula of emulgel (Ingredients in % w/w)

INGREDIENTS	F1	F2	F3	F4	F5	F6
Mefenamic acid	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol 934 P	0.5	1	1.5	1	1.5	2
Light liquid paraffin	6	6	6	6	6	6
Tween 80	0.8	0.8	0.8	0.8	0.8	0.8
Span 20	0.4	0.4	0.4	0.4	0.4	0.4
Propylene glycol	5	6	7	6	7	8
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25
Clove oil	3.5	3.5	3.5	-	-	-
Methyl salisylate	-	-	-	8	8	8
Methyl paraben	0.01	0.01	0.01	0.01	0.01	0.01
Propyl paraben	0.05	0.05	0.05	0.05	0.05	0.05
Water (q.s.)	50	50	50	50	50	50

Methyl and propylparabens were dissolved in propylene glycol whereas Mefenamic acid 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. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel^[12-14].

2.2 Evaluation parameters

1. Physical appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity and consistency^[15].

2. pH measurement

The pH of various formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated^[16].

3. Spreadability

Spreadability was determined by apparatus suggested by Mutimer. It consists of a wooden block, attached to a pulley at one end. Spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. An excess of emulgel (about 2 g) under study was placed on the ground slide which was fixed on the wooden block. The emulgel was then sandwiched between this slide and second glass slide, provided with the hook, having same dimension as that of the fixed ground slide. Weight of 500 mg was placed on the top of the two slides for 5 min to expel air and to provide a uniform film between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in second) required by the top slide to cover a distance of 5 cm was noted. The shorter the time interval, better the spreading coefficient^[17].

4. Extrudability

The various emulgel formulations were filled into collapsible tubes after formulating them. The extrudability of the formulations has been checked^[16].

5. Rheological study

The viscosity of various formulated batches was determined using a Brookfield viscometer with spindle 7. The assembly was connected to a thermostatically controlled circulating water bath which was maintained at 25 °C. The formulation was added to a beaker which was covered with thermostatic jacket. Spindle was allowed to move freely into the emulgel formulation and the reading was noted^[15].

6. *In-vitro* release studies

The *in vitro* drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. The temperature of the cell was maintained at 37 °C by circulating water jacket. Phosphate buffer pH 7.4 was used as a dissolution media. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously

using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 285 nm and the cumulative % drug release was calculated. The difference between the readings of drug release and control was used as the actual reading in each case^[16].

7. *Ex-vivo* release study

The *ex-vivo* drug release study of selected formulations was carried out in a modified Franz diffusion cell, using Goat skin. A section of skin was cut and placed in the space between the donor and receptor compartment of the FD cell, keeping the dorsal side upward. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained constant at 32°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously. The samples (5 ml) were withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 285 nm.

8. Bioadhesive strength

The modified method was used for the measurement of bioadhesive strength. The apparatus consist of two arm balance. Both the ends are tied to glass plates using strings. One side contains two glass plates. Other side contains single glass plate for keeping weight. The right and left pans were balanced by adding extra weight on the left hand pan. The balance was kept in this position for 5 min. Accurately weighed 1 g of emulgel was placed between these two slides containing hairless fresh rat skin pieces, and extra weight from the left pan was removed to sandwich the two pieces of glass and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 min. Weight was added slowly at 200 mg/min to the left hand pan until the two glass slides got detached from each other. The weight (gram force) required to detach the emulgel from the glass surface gave the measure of bioadhesive strength^[18].

The bioadhesive strength is calculated by using following:

$$\text{Bioadhesive strength} = \text{Weight required (in gm)} / \text{Area (cm}^2\text{)}$$

9. Stability studies

The prepared emulgels were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties and drug content^[19].

3. Results and discussions

1. Physical appearance

Total 6 batches of Emulgel were prepared, First three Emulgel formulations were yellowish white while rest were white; viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table 2.

2. Rheological studies

A Brookfield programmable viscometer (LV) along with helipath assembly was used to determine viscosity (cps). The spindle used was 7. The tests were performed at 100 rpm for 10 min. Results are given in Fig. 1.

3. Bio adhesive strength measurement

The bio adhesive strength of various emulgel formulations have been shown below in Fig. 2.

4. In vitro release study

The study showed the release of the drugs from its emulsified gel formulations. The drug release of the selected batches is shown in the Fig. 3

5. Ex-vivo release studies

This study was carried out only on two best optimized formulations. The study showed the release of the drugs from its emulsified gel formulation F4 and F5 were 53.47% and 51.60%, respectively in 4.5 hr. The results are show in Fig. 4.

Table 2: Physical parameters of formulation batches

Batches	Color	Consistency	pH	Spreadability	Extrudability	Viscosity (cps)
1	Yellow	+	5.5	-	-	1000
2	Yellow	+	5.6	++	+	1100
3	Yellow	++	5.5	++	+	960
4	White	++	5.6	+++	+++	1249
5	White	++	5.5	+++	+++	1300
6	White	++	5.8	+	++	800

- : Poor; +: Good; ++: Better; +++: Excellent

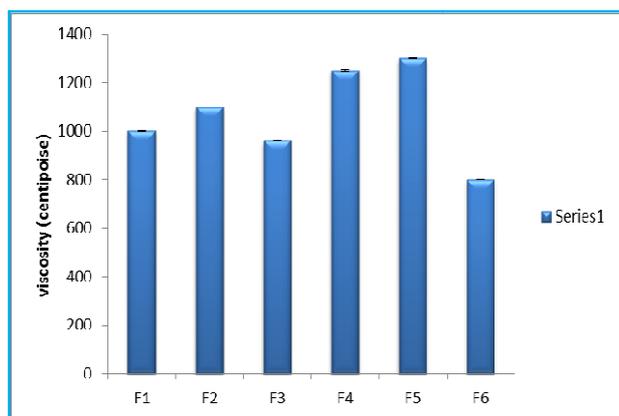


Figure 1: Viscosity of the prepared batches (n = 3, ± SD)

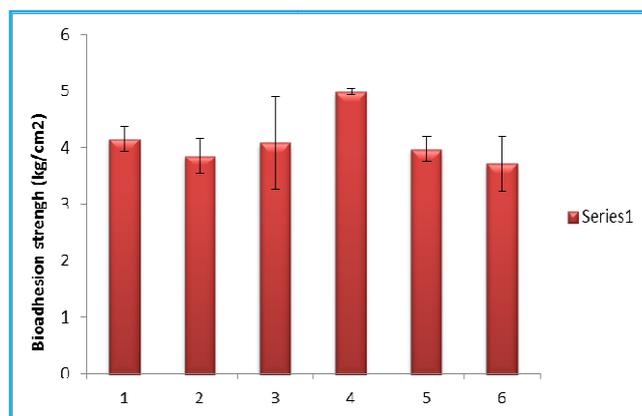


Figure 2: Bio adhesive strength of prepared batches (n = 3, ± SD)

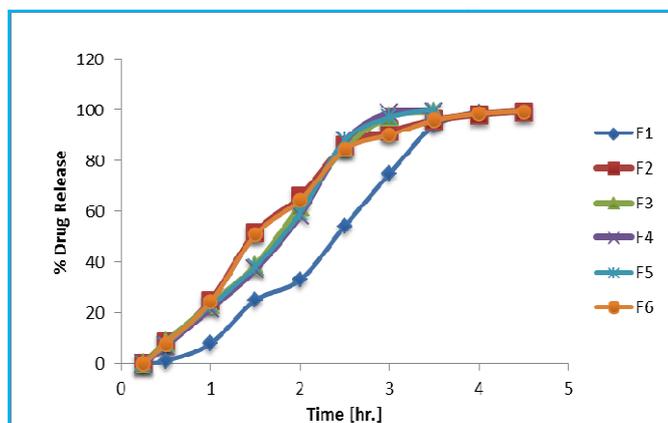


Figure 1: Comparative dissolution profile of prepared batches

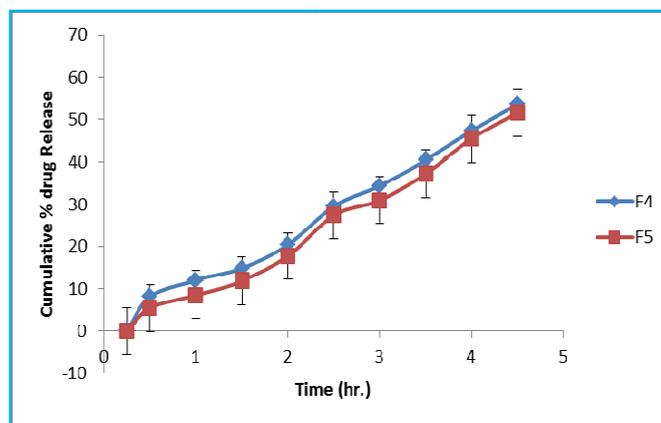


Figure 2: Ex-vivo release of selected batches (n = 3, ± SD)

6. Stability study

All the prepared emulgel formulations were found to be stable upon storage for 1 months, no change was observed in their physical appearance, pH, rheological properties and drug content, But the batches containing clove oil as permeation enhancer were found to become fluid on 3 month storage which may be due to the purity aspect of the oil.

4. Conclusion

Since emulgel is helpful in enhancing spreadability, adhesion, viscosity and extrusion, this novel drug delivery become popular, it is worth to go for the topical application of the hydrophobic agents for local as well as systematic actions. From the above results we can conclude that

Mefenamic acid emulgel formulations prepared with Carbopol 934P showed acceptable physical properties and drug release which remained unchanged upon storage for 3 months. However, the clove oil based emulgel showed fluidity on 3 months of storage.

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