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FORMULATION DEVELOPMENT & EVALUATION OF MEFENAMIC ACID EMULGEL FOR TOPICAL DELIVERY

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ABSTRACT

Topical drug delivery is the "process of applying a medication-containing formulation to the skin to treat a cutaneous ailment." The application of topical treatments like ointments, creams, and lotions is uncomfortable for the patient since they are typically very sticky. They must be utilized carefully because they have a reduced spreading coefficient. They struggle with stability as well. To solve this issue, transparent gels have grown in popularity in cosmetic and pharmaceutical formulations. The formation of gels results from the considerable entrapment of an aqueous or hydroalcoholic liquid in a system of colloidal solid particles. Gel compositions offer a quicker therapeutic release than ointments and creams. Gels have one fundamental disadvantage despite all of their benefits: they cannot deliver hydrophobic medications. To get over this restriction, an emulsion-based technique is being created that will efficiently incorporate and deliver a hydrophobic therapeutic component across gels. Emulgels are dosage forms that combine the benefits of gels and emulsions. Emulsions have a refined appearance and can be readily removed from the skin. They also penetrate the skin fairly well. "Emollient, non-staining, water-soluble, easier spreadability, longer shelf life, bio-friendly, translucent, and a pleasing look are just a few of the benefits of emulgels for dermatological treatment.

KEYWORDS: Topical drug delivery, Gels, Emollient, shelf life, bio-friendly.

INTRODUCTION

The skin is the primary mechanical defense against penetration of many pharmacological compounds, and it also serves as an ideal site for local and systemic drug delivery. Over the last few decades, the topical route of medication delivery has been increasingly popular. Despite the limitations of traditional topical medication delivery techniques, such as poor retention and bioavailability. This disadvantage is resolved through intensive research aimed at developing novel topical drug delivery technologies that increase safety, effectiveness, and side effects.[1,2]

Gel

Gel is a "high to low viscosity semisolid formulation made up of a dispersion of either big organic molecules or small inorganic particles, or of both.it can be enclosed and penetrated by liquid phase. The diluted cross link polymer system prevents the gels from flowing in steady state. The gel is a highly liquid rich system when continuous structure is present, solid.[3]

Structure of Gel

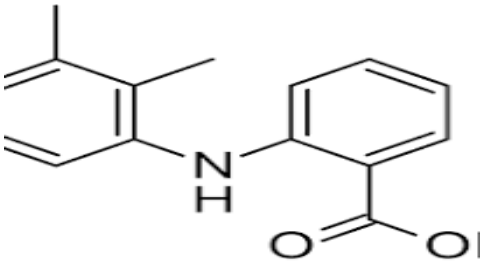
A gel is made up of a natural or synthetic polymer that has been dispersed across a hydrophilic liquid or dispersion media to create a three-gel formulation is applied to the skin, the liquid evaporates, leaving behind a thin film in which the medicine is trapped. Physically, the skin is covered by a thin matrix created by gel composition. The stiffness of gel is provided by a dense network of polymers used in its formation. The nature of the particles and the type of form responsible for links influence the network's structure and the gel's physical characteristics.[4]

Emulge

Emulgel provides significant advantages over both new and conventional vesicular systems in a variety of ways: Having a long shelf life, being emollient, non-staining, water-soluble, thixotropic, greaseless, easily spreadable, rapidly removable, translucent, and visually appealing. Emulgel is a dosage form for steroids, antibiotics, and analgesics and antifungal medications that was recently

expanded. Topical agents like ointment, cream, and lotion have a number of drawbacks. Emulgel must "occasionally be applied, are sticky, and unsettling to patients and they also have a reduced spreading coefficient, they also experience stability issues and all of these aspects within the major group of semisolid preparations have expanded the usage of transparent gel in cosmetics and pharmaceutical preparations". Gels a colloid system has severe disadvantages despite its many benefits, such as the delivery of hydrophobic medicines. An emulsion-based approach is being utilized to address this problem, allowing even hydrophobic medicinal molecules to be effectively incorporated and administered through gel mixtures.[5]

DRUG PROFILE: Mefenamic acid, an anthranilic acid derivative is a prototypical nonsteroidal anti-inflammatory agent (NSAIA).



Molecular Weight: C15H15NO2 =241.3.

Solubility: Mefenamic acid occurs as a white to greyish-white powder and is insoluble in water and slightly soluble in alcohol.

Storage and stability: Store at controlled room temperature, 20 to 25 degrees Celsius.

pKa: 4.2.

Mechanism of action: Mefenamic acid has pharmacologic actions similar to those of other prototypical NSAIAs. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. The exact mechanisms have not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Mefenamic acid inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase; at least 2 isoenzymes, cyclooxygenase-1 {COX-1) and -2 (COX-2), respectively), have been identified that catalyze the formation of prostaglandins in the arachidonic acid pathway. Mefenamic acid, like other prototypical NSAIAs, inhibits both COX-1 and COX-2.

Absorption: Mefenamic acid appears to be rapidly absorbed from the Gl tract. Following oral administration of a single 1-g dose of mefenamic acid to healthy adults, peak plasma drug concentrations of approximately 10-20 mcg/mL are reached in 2-4 hours.

Distribution: Mefenamic acid is extensively bound to plasma proteins. It is not known if the drug or its metabolites cross the placenta. The drug is distributed into milk in very small amounts.

Elimination: The plasma half-life of mefenamic acid has been reported to be 2 hours.

Therapeutic Uses: Mefenamic acid is used for the management of mild to moderate pain and primary dysmenorrhea. The potential benefits and risks of mefenamic acid therapy as well as alternative therapies should be considered prior to initiating mefenamic acid therapy. The lowest possible effective dosage and shortest duration of therapy consistent with treatment goals of the patient should be employed.

Administration: The potential benefits and risks of mefenamic acid therapy as well as alternative therapies should be considered prior to initiating mefenamic acid therapy. Mefenamic acid is administered orally.

Dosage: The lowest possible effective dosage and shortest duration of therapy consistent with treatment goals of the patient should be employed. Dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

Adverse effects

- ✓ Cardiovascular Effects
- ✓ Gl Effects
- ✓ Hematologic Effects
- ✓ Nervous System Effects
- ✓ Ocular and Otic Effects
- ✓ Renal Effects
- ✓ Hepatic Effects.[6]

MATERIALS AND METHODS

Preformulation studies

Preformulation studies are performed for the improvement of Emulgel before the initiation of plan advancement. The significant objective of the investigation is to create or foster steady, safe, and restoratively powerful and effectual dose frames that are essentially identified with the portrayal of the physicochemical properties of medication. The major aim of the pre-formulation studies before product development are.

Formulation Development

Preparation of aqueous phase

The aqueous phase of the emulsion was prepared by dissolving Tween80 in contaminated free water.

Preparation of oil Phase: Methyl Paraben and Propyl Paraben were dissolved in propylene glycol whereas the mefenamic acid was previously dissolved in ethanol. These both the solutions are added into aqueous solution. Both the oily and aqueous phases were separately heated

to 75°c. Then the oil phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

Preparation of Gel

The gel bases are prepared by adding different concentrations of polymers in distilled water separately with constant stirring using mechanical shaker. The pH of all formulations was adjusted to 6-6.5 using triethanolamine.

Formulation of Emulgel

The prepared emulsion is mixed with the gel with gentle stirring to obtain the respective emulgel [38]. A sum of 3 preparations were developed using various steps. The different formulation prepared for mefenamic acid emulgel is given in the below table.

The steps used in the preparation of Emulgel were as follows

Molecular dispersion technique with micronized active drug mefenamic acid by using excipients, the process will be the same for every trial batch from Batch No. F1 – Batch No. F3 for the manufacturing of Emulgels.

Process Analysis

Emulgels Formulations are analysed as per the official guidelines for all parameters and a comparative study shall be done with the existing market brand (Table 1).

Table 01: Composition of Different Formulation Batches.

		Unit Formula (g)		
Sr. No.	**Ingredients**	**F-1**	**F-2**	**F-3**
1	Mefenamic Acid	1.5	1.5	1.5
2	Span 20	1	1	1
3	Tween 20	0.5	0.5	0.5
4	Liquid Paraffin	7.5	7.5	7.5
5	PG	5	5	5
6	Methyl Paraben	0.03	0.03	0.03
7	Menthol	3	3	3
8	Carbopol	1	0	0.5
9	HPMC K4 M	0	1	0.5
10	Purified Water	1.5	1.5	1.5
Net Wt. / Tab. in mg		**21.03**	**21.03**	**21.03**

Evaluation of Emulgel[8,9]

Physical Tests: The prepared Emulgel was found optimum in terms of their color, grittiness, and appearance.

Viscosity Determination: At room temperature (23 °C-2 °C), the viscosity of emulgel was determined using a Brookfield viscometer. Three separate tests were carried out using two spindle speeds to measure viscosity.

Rheological study: The consistency was dictated by utilizing Brooke field viscometer DV II+ Pro, a cone and plate kind of viscometer with axle no 52. The instrument was collected, and room temperature was kept up with at 25°C all through try. The emulgel whose consistency was to be estimated was weighed about 0.5 gm and set in plate and shut. Then the spindle is allowed to run, and the viscosity was measured at 0.2 rpm.

Measurement of Ph: The pH was recorded using the digital pH meter under ambient & standard conditions. The pH of the emulgel preparations was determined by using digital pH meter. Solution of emulgel was made by dissolving 1 gm of emulgel in 100 ml of distilled water and it was kept a side for 2 hours. The measurement of pH of each formulation was done in triplicate and average values were noted.

Drug content: In a 10ml volumetric flask, a specific amount of the formulations was taken and diluted with ethanol. The absorbance of the resulting solution was sonicated for three minutes at room temperature, and its absorbance was measured at a maximum of 240 nm against a blank.

Swelling Index: In this methodology, 1 gm of emulgel is taken on aluminum foil (permeable) and afterward positioned in a container containing 10 ml 0.1N Sodium hydroxide (NaOH). Then, at that point tests were taken out from the containers (at various time breaks) and put it on dry spot.

Bio adhesive strength measurement: The modified method was used for the measurement of bio adhesive strength. The apparatus consists 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 bio adhesive strength.

Extrudability study: The extrudability of gel formulations were determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel.

Homogeneity and Grittiness: All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. Also, the homogeneity can be detected when a small quantity of the gel is rubbed on the skin of the back of the hand. The grittiness of prepared gel is also observed in the same manner.

Spreadability: squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected. Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations.

RESULT AND DISCUSSION

Physical Tests: Firstly, all the formulations i.e., F1, F2 and F3 were evaluated for their colour, grittiness, and appearances. F1, F2 and F3 were shown white in colour, absence of grittiness and glossy (Table 02).

Table 02: Physical Observation.

Formulation	Colour	Grittiness	Appearance
F1	White,	Absent	Glossy
F2	White	Absent	Glossy
F3	White	Absent	Glossy

Viscosity Determination: Under ambient conditions, the viscosity was observed as 517.40±0.18, 511.23±0.30 and 539.17±0.37 in the F1, F2 and F3, respectively. While maximum viscosity was seen in F3 formulation. A viscous emulgel is a sign of better formulation due to enhanced adherence at the site (Table 03).

Table 03: Viscosity determination.

Formulation	Viscosity± S.D.
F1	517.40±0.18
F2	511.23±0.30
F3	539.17±0.37

Rheological Properties: The different formulations of Emulgels were evaluated for their rheological properties. All the formulations were evaluated at RPM 0.2. At shear stress of 165.8 for F1 demonstrated the% transmittance as 87. For F2 at shear stress 168.6 the % transmittance as 85. At last, for F3 at shear stress of 172.4 the % transmittance as 82. By exhibiting such viscosity strengths, all the formulation were found as suitable emulgel having the optimum level of rheological properties (Table 04).

Table 04: Rheological Determination.

Formulation	Spindle No.	RPM	Shear Stress	% T
F 1	31	0.2	165.5	87
F2	31	0.2	168.6	85
F3	31	0.2	172.4	82

I**n Vitro Drug Release**: After formulation development, the formulations F1, F2 & F3 were determined for in vitro drug release profile from 0.5 hour to 8 hours. At 0.5 hour, F1, F2 and F3 showed in vitro drug release as 12.2±0.56, 10.32±0.41 and 9.92±0.48, respectively. While at 4 hours, the results were more prominent in terms of their drug release. It was observed as 34.8±0.56, 33.02±0.48 and 36.12±0.38 in F1, F2 and F3, respectively at 4 hours. It was found ascending as the time increase. At 8 hours, in vitro drug release was demonstrated as 71.2±0.29, 67.52±0.38, 69.22±0.33 in F1, F2 and F3, respectively that was highest in each time interval frame (Table 05)

Table 05: In vitro drug release.

Time (hr)	In vitro drug release		
	F1	F2	F3
0.5	12.2±0.56	10.32±0.41	9.92±0.48
1	16.2±0.46	14.02±0.33	15.3±0.22
1.5	18.4±0.85	19.10±0.74	18.7±0.20
2	22.2±0.82	26.01±0.91	24.12±0.62
2.5	31.1±0.44	30.12±0.12	31.12±0.38
3	33.2±0.76	32.42±0.48	31.12±0.18
3.5	32.5±0.26	36.44±0.23	34.32±0.80
4	34.8±0.56	33.02±0.48	36.12±0.38
5	35.3±0.11	40.32±0.25	41.52±0.32
6	41.6±0.72	43.05±0.28	43.12±0.78
7	44.2±0.50	43.12±0.28	46.32±0.68
8	71.2±0.29	67.52±0.38	69.22±0.33

pH Estimation: The pH was estimated as 6.3±0.4, 6.2±0.1 and 6.2±0.3 in the F1, F2 and F3, respectively y. It exhibited that all the preparations are suitable for human use as they resemble to human body's pH level. The pH was estimated for different preparations as below mentioned- (Table 06).

Table 06: Estimation of pH.

Formulation	pH
F1	6.3±0.4
F2	6.2±0.1
F3	6.2±0.3

Drug content Estimation: The drug content was found to be 1.43mg, 1.35mg and 1.32mg in 1 gm of Emulgel formulations i.e., F1, F2 and F3. It demonstrated that drug content was found almost similar, but most was in case of F1 (Table 07).

Table 07: Drug Content Estimation.

Formulation (1gm)	Drug Content (mg)
F1	1.43
F2	1.35
F3	1.32

Swelling Index: Swelling index also encounters a better quality of emulgel. Swelling index was estimated as 109.32%, 117.20% and 126.37% in formulation of F1, F2 and F3, respectively at the time break of 0.5, 1.0 and 1.5 hours (Table 08).

Table 08: Swelling Index.

Formulation	Time (hr)	Swelling index (%)
F1	0.5	109.32
F2	1	117.2
F3	1.5	126.37

Spreadability study: Spreadability is a term expressed to denote "the extent of the area to which the topical application spreads on application to the skin on the affected parts and the efficacy of a topical therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose, hence, the determination of spreadability is very important in evaluating topical application characteristics". The spreadability of the f1, f2, f3 shown in table 09.

Table 09: Spreadability study.

Formulation	Diameter (cm)
F1	4.2
F2	4.1
F3	4.3

Homogeneity and Grittiness of various formulations.

Table 10: Homogeneity and Grittiness of various Formulations.

Formulation	Homogeneity	Grittiness
F1	Yes	No
F2	Yes	No
F3	Yes	No

Extrudability of various Formulations: It is a "usual empirical test to measure the force required to extrude from a material tube, and the emulgels were filled into crimped, collapsible tubes and the extrudability of all formulation from the packed material was tested".

Table 11: Extrudability of various Formulations.

Formulation	Extrudability
F1	+ (Easily Extrudable)
F2	+ (Easily Extrudable)
F3	+ (Easily Extrudable)

CONCLUSION

Topical medicine administration will be widely employed in the upcoming years to improve patient compliance. Since "emulgel benefits in enhancing spreadability, adhesion viscosity, and extrusion this novel drug delivery becomes popular moreover they will become a solution for loading hydrophobic drugs in water-soluble gel bases for long-term stability.

The goal of this study was to make formulation and assess Mefenamic Acid Emgels. Mefenamic Acid identity and purity were verified as part of our preliminary investigation.

The "texture, pH, drug content, rheological characteristics, in vitro release, stability studies, of each gel (F1, F2, F3). It was discovered that the pH range of Carbapol gels was adequate for topical use. The range of the drug content of the gel formulations was NLT 90 to NMT 120%.

At room temperature, a Brookfield viscometer was utilized to test the viscosity of a few different gels, it ranged from 2000 to 5000 cps. All evaluation parameter was satisfactory and result shows in different tables. The "post-formulation parameters and in vitro drug release indicate no obvious alterations according to the stability investigation and this shows that under storage conditions, the gels are quite stable".

Physical Tests like Colour, appearance Grittiness of F1. F2, F3, was satisfactory. Viscosity Determination of F1. F2, F3 was 517.40±0.18, 511.23±0.30 and 539.17±0.37. Rheological properties F1. F2, F3 was satisfactory. The pH was estimated as 6.3±0.4, 6.2±0.1 and 6.2±0.3 in the F1, F2 and F3, respectively.

The drug content was found to be 1.43mg, 1.35mg and 1.32mg in 1 gm of Emulgel formulations i.e., F1, F2 and F3. It demonstrated that drug content was found almost similar, but most was in case of F1. Swelling index also encounters a better quality of emulgel. Swelling index was estimated as 109.32%, 117.20% and 126.37% in formulation of F1, F2 and F3, respectively at the time break of 0.5, 1.0 and 1.5 hours.

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