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Preparation And Evaluation of Mefenamic Acid Emulgel

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Abstract

Topical routes include the vagina and skin. These apply to a wide range of situations. The present study was focused on the formulation and estimation of mefenamic acid emulgel. Mefenamic acid (API) was obtained from the Sigma Aldrich Pvt Ltd. The formulated emulgel was evaluated for parameters i.e., physical appearance, droplet size & polydispersity index (PDI), In-vitro drug release, % drug content, viscosity, pH & stability. The drug- mefenamic acid was tested for solubility in different solvents. Mefenamic acid was found poor soluble in solvents i.e., distilled water & peppermint oil. Particles size and particle size index was observed efficient for better drug release and bioavailability of incorporated drug that confirms for its uniqueness in the formulation. In-vitro drug release and viscosity are important factor behind the quality of formulated nano emulsion. In the same context, these two factors showed optimistic behaviour of emulgel. Mefenamic acid (emulgel) can be used as anti-nociceptive & anti-inflammatory for topical delivery. It was successfully formulated and evaluated for authentic and selective parameters. Emulgel better enhances the topical delivery of even poorly soluble drugs like mefenamic acid.

Keywords: Emulgel, Mefenamic Acid, In-Vitro Drug Release, Ph, Particle Size

Introduction

Topical drug delivery methods include topical drug administration to any part of the body via the ophthalmic, rectal [1]. They are an emulsion of gel, as their name would imply. Both the water-in-oil and the oil-in-water types of emulsion are utilized as vehicles to bring numerous medications to the skin [2]. When a medicine is applied to the topical areas, it avoids pre-systemic metabolism, pH of stomach- disturbances and fluctuations in plasma conc. that occur often when a drug is delivered orally [3].

Mefenamic acid is a member of the anthranilic acid derivative class. Mefenamic acid, like other NSAIDs, inhibits the enzyme cyclo-oxygenase (Cox-1&-2) which prevents the creation of intracellular prostaglandins, which are crucial for the pain and inflammatory pathways [4].

Molecular Formula: C15-H15-N-O2 (Figure 1)

Mefenamic acid is quickly absorbed when used orally. Absorption volume averaged 30.5 mcg/h/ml. For a 500mg pill, the apparent volume of distribution was about 1.06 litre/kg. The cytochrome P450 (CYP2C9) enzyme converts mefenamic acid into 3-hydroxylmethylmefenamic acid- as metabolite I. A third oxidation step could lead to a 3-carboxymefenamic acid- as metabolite II. Mefenamic acid is largely eliminated in the urine (52% of a dose) as the glucuronides (6%), 3-hydroxymefenamic acid (25%) and 3-carboxymefenamic acid (21%). Up to 20% of the dosage is eliminated in the faeces. Mefenamic acid has an elimination half-life of around 2 hours [5].

On the basis of above literature survey, I found that emulgel of mefenamic acid can be developed with different gelling agent to facilitate dissolution, bioavailability, and stability of the topical emulgel formulation. This research focuses on the formulation and characterization of topical mefenamic acid emulgel with diverse gelling agents and evaluation of same by following standard parameters.

Materials and Methods

Experimental requirements

The following are the Equipment, Instrument, and Materials that were used for the formulation and evaluation of emulgel- (Table 1)

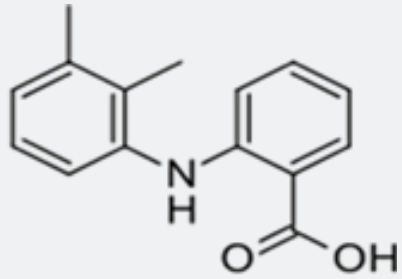

Figure 1: Structure of mefenamic acid.

Table 1: List of products with suppliers.

Chemical	Supplier
Mefenamic acid	Sigma Aldrich Pvt Ltd IN
Span 20	R.K. Enterprises, Meerut
Tween 80	BDL Sciences, Mumbai
Liq. Paraffin	BDL Sciences, Mumbai
Propylene Glycol,	CDH Laboratory, New Delhi
Methyl Paraben,	CDH Laboratory, New Delhi
Menthol,	BDL Sciences, Mumbai
Carbopol 934,	BDL Sciences, Mumbai
HPMC K4M,	BDL Sciences, Mumbai

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:

Drug-Excipients compatibility determinations

During selection of suitable excipients while developing a pharmaceutical formulation it's necessary to check the drug-excipients compatibility. Various organoleptic (macroscopic) properties were observed using this study. Drug excipients compatibility tests give the assurance of the stability of formulation. The API was mixed with KBr, and spectra were plotted on FT-IR. The excipient and KBr mixed in 9:1 ratio and spectra were plotted. The FT-IR band of mefenamic acid was checked with FT-IR spectra of mefenamic acid with other additives used. Shifting of mefenamic acid peak in spectra was examined.

Procedure

Mefenamic acid was mixed with excipients in the ratio as given in below table. It filled in glass vials with polyethylene closures with holes in stopper & subjected to different environmental conditions i.e., room temperature, 60 ˚C & 2-8 ˚C for 4 weeks. After given time-period, mixtures were tested for their physical modifications i.e., moisture content.

API- Excipient compatibility test

The API of mefenamic acid was made tested with different excipients. In this way, all the ingredients were tested in the ration of 1:1 i.e., Span 20, Tween 20, Carbopol etc (Table 2).

Table 2: API- Excipient compatibility test.

Ingredients	API: Excipient Ratio
Span 20	1:01
Tween 20	1:01
Liquid Paraffin	1:01
Propylene Glycol	1:01
Methyl Paraben	1:01
Carbopol	1:01
Menthol	1:01
HPMC K4 M	1:01
Purified Water	1:01

All the excipients were evaluated with the drug for compatibility studies. The Preformulation studies were performed according to the formula and results were recorded based on the data was obtained accordingly (Table 3) (Figure 2).

Preparation of mefenamic acid stock solution (100µg/ML.) In 0.1N NAOH

The drug (mefenamic acid) 100 mg was completely dissolved in 0.1N NaOH in a volumetric flask of 100 mL capacity.

Determination λmax

Max. Absorbance (λmax.) of mefenamic acid was determined by UV visible spectrophotometer by scanning drug samples between 203-280 nm and spectra were found.

Formulation development

The material and method required for the formulation of the Emulgel, and the associated evaluation parameter of the latter are explained in the following section.

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Table 3: Result analysis of mefenamic acid.

Test	Specification	Observation	Conclusion
Description	White color powder	White color powder	Complied
Odor	Odorless	Odorless	Complied
Solubility	Poor soluble in water	Poor soluble in water	Complied
	Partially soluble in methanol	Practically partially soluble in methanol	Complied

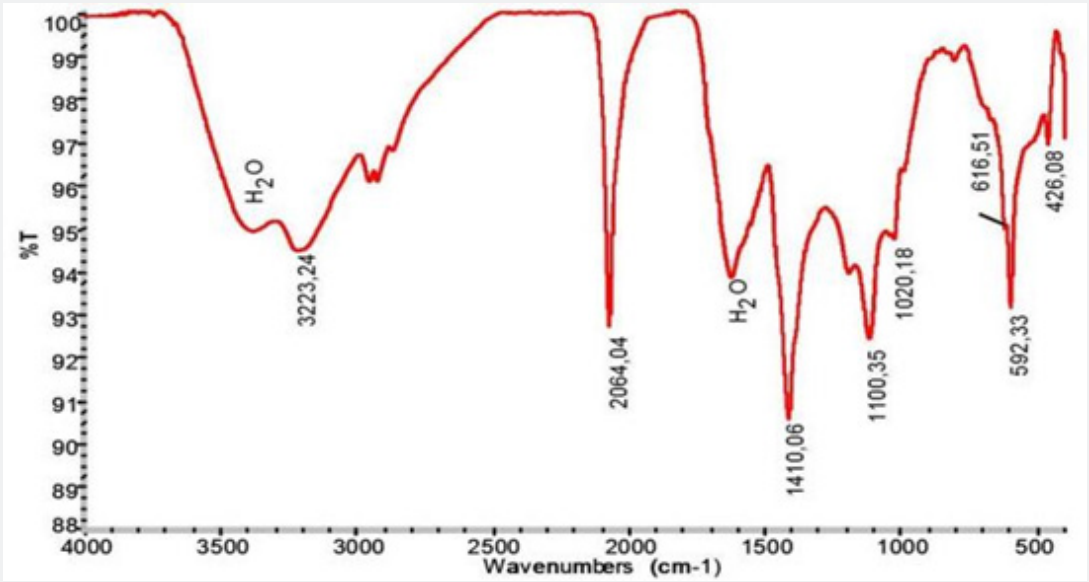

Figure 2: FT-IR Spectroscopy.

Method for the preparation of the mefenamic acid Emulgel

Preparation of Emulsion

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 [6].

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 Emulgel.

Material Sifting

Mefenamic acid, Span 20, Tween 80, Carbopol 934, Liq. Paraffin, Propylene Glycol, HPMC K4M, Methyl Paraben shall be sifted through #20, #40 and filter through a suitable filter separately.

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Process– 2: Manufacturing Process

Here, two formulations were prepared by same method, but they differed only in their type of gelling polymer used to formulate gel. The preparation method of emulsion was same. Gel was prepared by dissolving 1gm of Carbopol 934 and HPMC K4M separately in purified water (50 ml) with constant stirring at optimum speed by mechanical stirrer. The pH was adjusted by TEA (triethanolamine) to 6-6.5. The emulsion was prepared by following method, the Oil phase was prepared by dissolving span 20 in liquid paraffin. Then the drug was added to the above mixture. The aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben was dissolved in propylene glycol separately and this mixture was added to above mixture with constant stirring. Both oil and aqueous phases are heated to 70-80°C. Then oil phase is added to aqueous phase with constant stirring until to get cooled to temperature to form emulsion with constant stirring [6] (Table 4).

Table 4: List of Ingredients and their quantities required during different Experimental Formulations of Emulgel of mefenamic acid.

Sr. No.	Ingredients	Approx. Quantity Required (g)
1	Span 20	0.262
2	Tween 20	0.021
3	Liquid Paraffin	0.021
4	PG	0.045
5	Methyl Paraben	0.045
6	Carbopol	1.151
7	Menthol	0.027
8	HPMC K4 M	0.006
9	Purified Water	0.006
	Total Weight	1.626

Process Analysis

Emulgel Formulations are analyzed as per the official guidelines for all parameters and a comparative study shall be done with the existing market brand (Table 5).

Table 5: F1-F3 Formulation for Emulgel.

		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

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Evaluation of Emulgel [7,8]

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 (Makhmalzadeh et al. 2012).

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.

In-Vitro drug release study

In vitro diffusion estimated was performed by Franz diffusion cell in phosphate buffer at 7.2 pH. A 20ml of medium was filled in receptor compartment up to the mark of collection limb. Then membrane was placed on the receptor compartment. Cellophane membrane is used as semi-permeable membrane for diffusion. Receptors compartment up is filled with 20 ml medium up to the mark of collection limb. Then membrane is kept on the receptor compartment.

The *in-vitro* drug release study was recorded from 0.5-8 hrs. Formulation no. 1, 2 and 3 demonstrated a time dependent drug release. The optimum drug release was found at 8 hours.

Accurately weigh 1gm of emulgel and place on the membrane in between donor and receptor compartment and fit them firmly. The rotation per minute (rpm) of magnetic stirrer in the donor compartment and external stirrer are adjusted in such a way to make laminar flow in the medium. 5 ml of sample is collected on different time intervals from the collection limb and replace the same volume with buffer medium. Then the samples are estimated by UV spectrophotometer at 276 nm wavelength and thus concentrations are determined.

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 (Samadhan et al. 2019).

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.

Results and Discussion

Drug-Excipient compatibility determination

The drug was evaluated along with all the excipients for compatibility studies and the results were recorded as per the data obtained after completion of the studies in following table- (Table 6)

Table 6: Drug-excipient compatibility data.

	Condition		
API+ Excipient	**Room temp**	**Hot air oven temp**	**Freezing temp**
Mefenamic acid (API)	Unaltered	Unaltered	Unaltered
API + Span 20	Unaltered	Unaltered	Unaltered
API + Tween 20	Unaltered	Unaltered	Unaltered
API + Carbopol 934	Unaltered	Unaltered	Unaltered
API + HPMC K4 M	Unaltered	Unaltered	Unaltered
API + Liq. Paraffin	Unaltered	Unaltered	Unaltered
API + Propylene glycol	Unaltered	Unaltered	Unaltered
API + Menthol	Unaltered	Unaltered	Unaltered
API + Methyl Paraben	Unaltered	Unaltered	Unaltered

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Evaluation of Emulgel

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 7).

Table 7: Physical observations.

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 8).

Table 8: Viscosity determination.

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

Rheological properties

Table 9: Rheological Properties of Emulgel.

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

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 9).

In 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.

Table 10: *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

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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 10).

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. 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 11).

Table 11: 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 12).

Table 12: 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 13).

Table 13: Swelling Index.

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

Conclusion

Two formulations (out of three) were excellent in their elegance and absorption. *In-vitro* drug release test demonstrated that Carbopol-934 was the best polymer to formulate Emulgel with 64.04% w/w of drug release than HPMC-K4M as 57.30% w/w.

Mefenamic acid (emulgel) can be used as anti-nociceptive & anti-inflammatory for topical delivery. It was successfully formulated and evaluated for authentic and selective parameters. Emulgel better enhances the topical delivery of even poorly soluble drugs like mefenamic acid.

Doubtless, the emulgels of mefenamic will the top procuring dosage form having the better therapeutic potential and less patient complication.

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