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FORMULATION AND CHARACTERIZATION OF ETODOLAC LOADED EMULGEL FOR TOPICAL DRUG DELIVERY APPROACH

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INTRODUCTION

Etodolac, a non-steroidal anti-inflammatory drug (NSAID), is valued for its analgesic, anti-inflammatory, and anti-arthritic properties. However, its therapeutic potential is limited when administered orally due to its poor water solubility and extensive first-pass metabolism in the liver. These issues lead to reduced bioavailability, requiring higher doses to achieve desired effects, which can cause erratic drug plasma levels and increase the risk of gastrointestinal side effects like irritation and toxicity. To overcome these challenges, alternative drug delivery methods such as topical administration offer a more targeted approach. Topical delivery allows the drug to bypass the gastrointestinal tract and hepatic metabolism, avoiding first-pass effects and potentially improving bioavailability. Additionally, this method allows for localized drug action, providing direct relief at the site of inflammation or pain, which is particularly advantageous for conditions such as arthritis.

However, the skin's outermost layer, the Stratum corneum, poses a significant challenge for drug penetration. To address this, microemulsion-based systems have gained attention due to their ability to enhance the solubility of poorly water-soluble drugs like Etodolac and improve skin penetration. Microemulsions are thermodynamically stable systems comprising oil, water, surfactants, and co-surfactants. These systems not only improve the solubility of lipophilic drugs but also enhance percutaneous absorption due to their small droplet size, which increases the surface area for drug release. As a result, both topical and systemic drug bioavailability are improved.

In addition to microemulsions, emulgel systems combine the advantages of both emulsions and gels, offering a controlled and sustained release of Etodolac. The gel matrix ensures better adhesion to the skin, allowing prolonged contact and gradual drug release, which is beneficial for chronic inflammatory conditions like arthritis. The use of emulgels can reduce the frequency of dosing, improving patient compliance and minimizing systemic side effects that are commonly associated with oral NSAID therapy.

Furthermore, nanocarrier systems, such as microemulsions and emulgels, have shown great potential in enhancing topical drug delivery. These systems encapsulate the drug, improving its solubility and controlling its release, which leads to a more consistent therapeutic effect. For Etodolac, this approach can provide more effective and sustained pain relief while minimizing systemic exposure and the associated side effects, offering an innovative solution to the limitations of conventional oral administration.

Objectives of the study

This study focuses on the development and optimization of microemulsion and hydrogel-based formulations to improve the topical delivery of Etodolac, a nonsteroidal anti-inflammatory drug (NSAID) with limited water solubility and substantial first-pass metabolism. These innovative delivery systems are designed to address Etodolac's solubility challenges while enhancing skin penetration and therapeutic effectiveness. Microemulsions, comprising a mixture of oil, water, surfactants, and co-surfactants, are particularly effective at increasing drug solubility and facilitating rapid absorption through the skin, making them ideal for immediate therapeutic action. On the other hand, hydrogel-based formulations, which incorporate polymers that form a gel matrix, are intended to provide controlled, sustained drug release, ensuring prolonged localized analgesia and reducing the frequency of application.

The study will involve a detailed evaluation of the physical properties of both formulation types, including

their stability, viscosity, and particle size. In vitro drug release studies will be conducted to assess how quickly and efficiently Etodolac is released from the formulations, while skin permeation tests will measure the extent of drug absorption through the skin's barrier. By comparing the solubilizing capacity, absorption rate, and sustained release profiles, the study aims to identify the most effective formulation for enhancing the topical delivery of Etodolac.

Previous research has highlighted the potential of microemulsion-loaded emulgels, which combine the solubilizing power of microemulsions with the structural benefits of gels. Emulgels incorporating gelling agents such as Carbopol and Poloxamer have demonstrated promising results in achieving controlled drug release and enhancing skin adhesion, making them ideal candidates for sustained topical application in conditions like arthritis.

MATERIALS AND METHODS

Etodolac was supplied by Ipca Pharma. Ltd. Kandivali Mumbai (MH, India), Linseed oil, ethanol, Polyethylene glycol 200 supplied by Thomas Baker, Tween 20 supplied by Thomas Baker, Mumbai (MH, India), Sodium CMC, Carbopol 940, Poloxamer supplied by Lobie Chemical Mumbai (MH, India), Carbopol 974 and Carbopol 980 was supplied by Lubrizol Pvt. Limited Mumbai (MH, India). Methyl paraben, propyl paraben, Triethanolamine was supplied by Thomas Baker, Mumbai.

Equipments

Magnetic Stirrer or Mechanical Stirrer, Ultrasonicator (Ultrasonic Homogenizer), Homogenizer (High-Shear Homogenizer), Vortex Mixer, Heating Plate or Water Bath, Particle Size Analyzer, pH Meter, Beakers and Glassware, Hot Plate or Water Bath, Sonicator, Homogenizer (High-Shear Homogenizer, Viscometer, Freeze Dryer (Lyophilizer)

Preparation of micro emulsion

The formation of a microemulsion involves mixing oil, water, a surfactant, and a co-surfactant in specific ratios. First, the oil and water phases are separately prepared. The surfactant and co-surfactant are then added to reduce the interfacial tension between the oil and water. The mixture is stirred continuously, leading to the formation of a clear, thermodynamically stable, and isotropic system. The selection of surfactants and the oil-to-water ratio is crucial for ensuring the system remains stable. Finally, the microemulsion is optimized based on droplet size, stability, and the ability to solubilize the drug for effective delivery.

Characterization of prepared microemulsion

Dilution Test and Dye test

On addition of water in microemulsion, O/W found to be stable whereas W/O detect with breaking of microemulsion. In the dye test, suddan red added in microemulsion and observed on a microscope. The globule observed red and ground was detected as colorless which confirmed developed microemulsion as O/W.

Phase diagram Construction and Microemulsion system formulation

A drop-wise method with water by the use of pseudo-ternary diagrams was followed; in which five pseudo-ternary diagrams were developed of certain oil and S.mix (1:1,2:1 and 3:1) weight ratios for each one. Nine homogenous and transparent mixtures of (Tween 20: ethanol) with the surfactant and co surfactant which are tween 20 and PEG 400 at ratios were formed by gentle shaking. At the end, each mixture was titrated with water and visually inspected for optical clarity, homogeneity and fluidity

Measurement of Globule size, PDI and Zeta Potential

Zetasizer Nano-ZS (Malvern Instruments, UK) was used for the determination of globule size. 1 ml of microemulsion was diluted with doubled distilled water and by zeta cell globule size was obtained. For stability zeta potential was determined. The measurement was performed at 25°C.

Measurement Viscosity

Brookfield Viscometer (DV-E viscometer LV) was applied for measurement of the viscosity by using spindle S-18. Sample were taken in the beaker and the spindle were placed in the beakercontaining sample. For the phase separation study

Thermodynamic stability studies

Thermodynamic stability studies involve subjecting the formulation to heating-cooling cycles, centrifugation, and freeze-thaw cycles to assess its physical stability under stress conditions, identifying phase separation or degradation.

Method of preparation of emulgel

The formation of an emulgel involves two main steps: preparing the emulsion and the gel base. First, an oil-in-water or water-in-oil emulsion is formed by mixing the oil phase (containing the drug) with the aqueous phase using surfactants and emulsifiers under continuous stirring. Meanwhile, the gel base is prepared by dispersing gelling agents like Carbopol or Poloxamer in water. Once the gel base is formed, the emulsion is slowly incorporated into the gel with gentle mixing to form a homogenous emulgel. The resulting formulation combines the solubilizing properties of the emulsion and the controlled release of the gel matrix.

Characterization of emulgel

Physical Appearance and Determination of pH

The color, homogeneity, consistency was determined. By Digital pH meter pH of gel was obtained. 1ml of gel diluted with 9 ml of distilled water and readings were taken.

Rheological study
Rheological study was performed for the determinations of formulations rheological characteristics. Viscosity is the important evaluation parameter for the topical dosage form. Therefore, viscosities of formulations were determined by using Brookfield viscometer at 370c by using Spindle number S-64.

Spreadability
The spreadability apparatus was used for the test. The two glass slides (10 × 10 cm) were placed in this apparatus. 0.5gm sample was kept in glass slides. 100 gm weight kept on upper slide and measure the diameter or length which was of pre-marked circle. The time required to spread the sample was recorded24. Formula-
S=MxL/T
Where,
M= weight
L=length or diameter
T=time

Extrudability determination
The extrudability test was determined to study how much pressure or force is required to expel material from tubes. The gel was extruded from aluminum collapsible tube by applying weights and measured the area for calculation.
The formula: Extrudability=Weight (gm)/Area (cm2)

Globule Size and Its distribution in emulgel
Malvern Zetasizer instrument was used to determine the globule size. For obtained clear solution sample was mixed in water. The homogeneous dispersion of gel sample was then placed for the analysis and readings were recorded.

Stability studies
At 40°C and 75% RH samples were kept for 3 months. Any physical/chemical change in the formulation was studied at the end of study27.

In-vitro diffusion study
*M*odified Franz diffusion cell was used. A glass cylinder used with 10 cm height for diffusion cell. In receptor chamber the phosphate buffer pH 6.8 was kept and in donar receptor gel was applied. The cell was kept in contact with receptor chamber at 32±1°C. The samples were examined at different time points and analyzed at 276 nm on UV.

Skin irritation test
0.5 gm of gel sample applied on skin 1" x 1" (2, 54 x 2, 54 cm) square. The mice were used for skin irritation test. After a 24 hour, the animals were examined for presence of any erythema or swelling.

Anti-inflammatory study
For anti-inflammatory study albino mice were used. 15 mice were weighed and maintained them on fasting overnight. Control, standard and test 3 group were prepared and in each group 5 animals were taken. 1% (w/v) carrageenan was injected on left hind paw to induce edema. 0.5 gm of gel applied on the skin. At 0, 30-, 60-, 120- and 180-minute thickness of paw was measured by using vernier caliper. Microemulsion loaded gel and marketed Diclofenac gel were compared with carrageenan. By using ANOVA test results were calculated.

RESULTS AND DISCUSSION MICROEMULSION

Sr. no.	Ingredients	Formulations				
		F1	**F2**	**F3**	**F4**	**F5**
Formulationof batch (F1-F5) Surfactant: co-surfactant(1:1)						
1	Etodolac (mg)	10	10	10	10	10
2	Linseed oil (%w/v)	2	2	2	2	2
3	Tween-20 (%w/v)	1	2	3	4	5
4	Propylene glycol (%w/v)	1	2	3	4	5
5	Distilled water (%w/v)	26	24	22	20	18
6	Final volume (%w/v)	30	30	30	30	30
Formulation of batch (F6-F10) Surfactant: co-surfactant (2:1)						
		F6	F7	F8	F9	F10
1	Etodolac (mg)	10	10	10	10	10
2	Linseed oil (%w/v)	2	2	2	2	2
3	Tween-20 (%w/v)	2	4	6	8	10
4	Propylene glycol (%w/v)	1	2	3	4	5
5	Distilled water (%w/v)	25	22	19	16	13
6	Final volume (%w/v)	30	30	30	30	30
Formulation of batch (F11-F15) Surfactant: co-surfactant (3:1)						
		F11	**F12**	**F13**	**F14**	**F15**
1	Etodolac (mg)	10	10	10	10	10
2	Linseed oil (%w/v)	2	2	2	2	2
3	Tween-20 (%w/v)	3	6	9	12	15
4	Propylene glycol (%w/v)	1	2	3	4	5

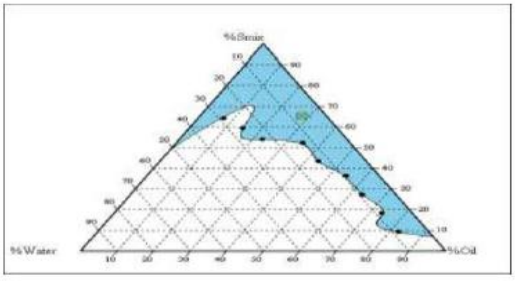
5	Distilled water (%w/v)	25	22	19	16	13
6	Final volume (%w/v)	30	30	30	30	30

Dilution Test and Dye Test

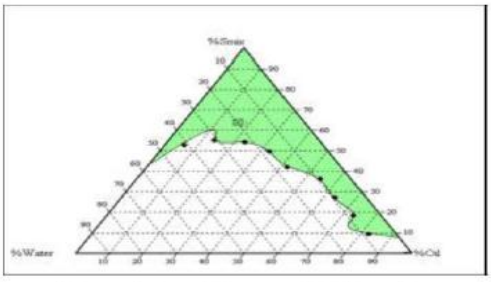
Water soluble dye, methylene blue solution was added to optimized microemulsion (F-8), the dye will dissolve uniformly throughout the system, so the continuous phase was water. Hence the optimized formulation F-8 was found to be o/w type of microemulsion is shown in below fig. 1.

Fig. 1: Staining of optimized microemulsion (F8).

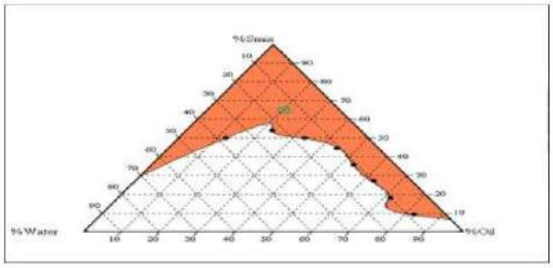
Phase Diagram Construction and Microemulsion System Formulation



C/Cos ratio 1:1 (Tween 20: Ethanol)



C/Cos ratio 2:1 (Tween 20: Ethanol)



C/Cos ratio 3:1 (Tween 20: Ethanol)

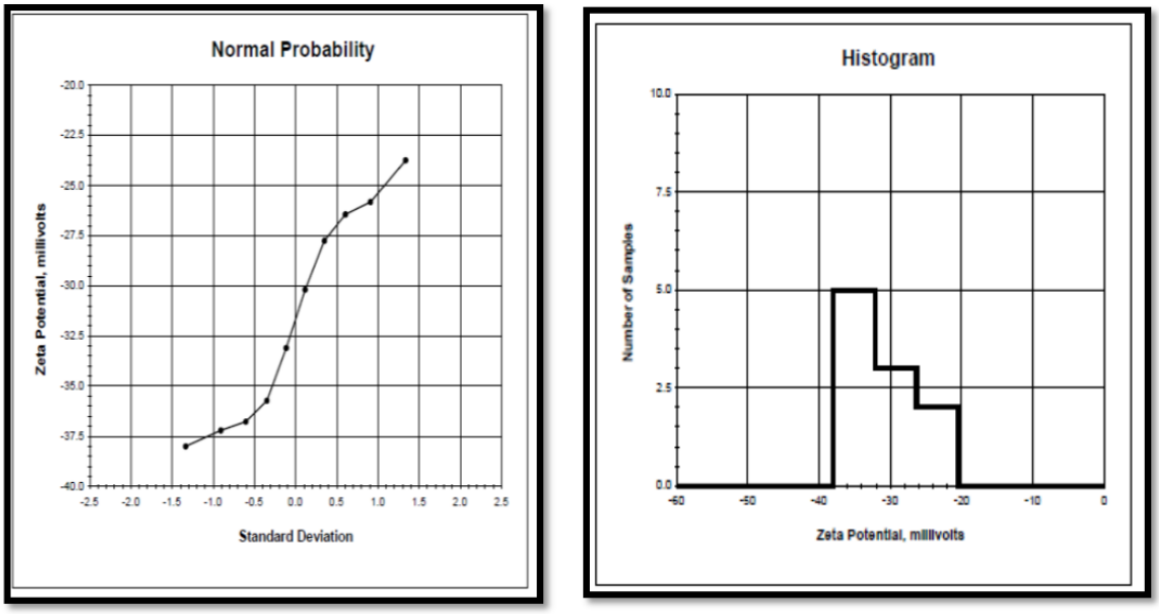
The phase diagrams shown represent the microemulsion regions at different surfactant-to-co-surfactant (C/Cos) ratios: 1:1, 2:1, and 3:1 (Tween 20: Ethanol). Each diagram indicates the range of oil, water, and surfactant/co-surfactant mixtures that form stable microemulsions. As the C/Cos ratio increases from 1:1 to 3:1, the microemulsion region expands, demonstrating improved solubilization capacity for oil. The 3:1 ratio shows the largest microemulsion region, suggesting that higher surfactant concentrations Favor more stable formulations. These diagrams provide insight into the optimal composition required for formulating a stable Etodolac-loaded microemulsion system, ensuring enhanced drug solubility and skin penetration for effective topical delivery.

Measurement of Globule size, PDI and Zeta Potential: The data provided; Batch 8 is optimized based on its characteristics. It has a relatively large average droplet size of 110.0 nm, which suggests a well-formed

and stable emulsion. The surfactant concentration of 6% ensures good stability and dispersion, aiding in efficient emulsification. Additionally, Batch 8 shows a highly negative zeta potential value of -47.25 mV, indicating excellent stability due to strong electrostatic repulsion between the droplets, which minimizes aggregation. Despite the larger droplet size, the high zeta potential enhances the formulation's stability, making Batch 8 the most optimal for maintaining structural integrity.

Batch No.	Average droplet size (nm)	Surfactant Concentration (%)	Oil Phase (%)	Zeta potential
1	70.0	1	2	-35.54±0.65
2	60.8	2	2	-38.05±1.65
3	60.8	3	2	-34.87±5.02
4	92.2	4	2	-45.36±0.56
5	60.8	5	2	-43.58±6.59
6	41.2	2	2	-39.25±7.04
7	92.2	4	2	-38.70±5.02
8	110.0	6	2	-47.25 ± 4.02
9	72.5	8	2	-39.50±5.09
10	68.3	10	2	-36.58±6.49
11	89.5	3	2	-31.25±4.88
12	97.5	6	2	-39.40±6.08
13	86.1	9	2	-40.39±7.01
14	79.8	12	2	-37.57±7.09
15	88.4	15	2	-33.81±1.35

The provided histogram and normal probability plot for zeta potential help assess the stability of Batch F8. The histogram shows that most zeta potential values fall between -40 mV and -30 mV, which aligns with the earlier data, confirming a strong negative charge. The normal probability plot suggests the data is approximately normally distributed, with values mostly between -37.5 mV and -25 mV, indicating consistency in the measurements. Batch F8's zeta potential of -47.25 mV falls within this range, confirming it has excellent electrostatic stability, which is optimal for preventing particle aggregation and maintaining emulsion integrity. Therefore, Batch F8 remains the most stable formulation.



Histogram of microemulsionshowing distribution of zeta potentional

Screening of microemulsion

The formulation of microemuslion was characterized on the basis of pH, clarity, thermodynamic stability and dilutability. The result is shown as under:

No. Sr	pH	Clarity	Thermodynamic stability	Dilutability
F1	6.32	49%	Fail	Fail
F2	6.25	56%	Pass	Pass
F3	6.36	96%	Fail	Pass
F4	7.21	78%	Pass	Pass
F5	6.87	91%	Fail	Fail
F6	6.59	56%	Pass	Pass
F7	7.01	89%	Fail	Fail
F8	6.89	98%	Pass	Pass
F9	6.07	82%	Pass	Pass
F10	6.32	70%	Pass	Fail
F11	7.01	65%	Pass	Pass
F12	7.98	55%	Fail	Pass
F13	6.89	50%	Pass	Fail
F14	6.56	45%	Pass	Fail
F15	6.99	40%	pass	Pass

In the given data, F8 emerges as the optimized formulation batch. It demonstrates a pH value of 6.89, which is close to the skin's natural pH, promoting compatibility for topical application. With a high clarity of 98%, it indicates superior formulation quality and visual appeal. F8 also passes the thermodynamic stability test, signifying that the formulation remains stable under stress conditions, ensuring longevity and effectiveness. Additionally, it shows excellent dilutability, passing the test, which is crucial for maintaining its structure when mixed with external media. These characteristics make F8 the most optimized and effective formulation.

Batch No.	Viscosity (cP)
F1	114.56±0.130
F2	103.98±0.652
F3	89.35±0.465
F4	85.07±0.05
F5	78.87±0.983
F6	80.55±0.251
F7	80.55±0.251
F8	125.08±0.56
F9	107.6±0.165
F10	86.52±1.651
F11	98.51±0.156
F12	103.56±0.65
F13	82.20±1.89
F14	76.56±0.09
F15	82.85±0.823

Viscosity measurement

Based on the viscosity data for the 15 batches, Batch F8 shows the highest viscosity at **125.08 ± 0.56 cP**, making it the optimal formulation for topical delivery. The high viscosity ensures a thicker consistency, which enhances the formulation's ability to remain on the skin for extended periods, improving drug retention and localized delivery. This level of viscosity also prevents the formulation from flowing too easily, ensuring controlled application. The minimal variation in the viscosity reading suggests consistency and reliability in the formulation. Therefore, Batch F8, with its favourable viscosity, along with other factors like stability and zeta potential, stands out as the most optimized batch.

Thermodynamic stability studies

Formulation Code	Observations		Inference
	Centrifugation	Freeze thaw cycle	
F1	-	-	Fail
F2	-	-	Fail
F3	+	+	Pass
F4	+	+	Fail
F5	+	+	Pass
F6	+	+	Fail

F7	-	-	Fail
F8	+	+	Pass
F9	+	+	Pass
F10	-	-	Fail
F11	+	-	Fail
F12	-	-	Fail
F13	-	+	Fail
F14	-	-	Fail
F15	-	-	Fail

In the thermodynamic stability studies, Batch F8 showed positive results in both centrifugation and freeze-thaw cycle tests, indicating strong stability under stress conditions. Its viscosity of **125.08 ± 0.56 cP** supports its role as the optimized batch, balancing stability and application properties. The high viscosity ensures good topical adhesion, controlled release, and enhances drug retention on the skin. Batch F8's stability across multiple tests, including viscosity and thermodynamic assessments, suggests it is less prone to phase separation and degradation, making it an ideal candidate for efficient and consistent topical drug delivery. These factors confirm F8 as the most optimized and stable formulation.

Sr. no	**Ingredients**	**FormulationsCarbopol 934**		
		MEGC 1	**MEGC2**	**EMGC3**
1	Etodolac (mg)	10	10	10
2	Linseed oil (%w/v)	2	2	2
3	Tween-20 (%w/v)	3	6	9
4	Polyethylene glycol (%w/v)	1	2	3
5	Distilled water (%w/v)	13	8.5	4
6	Carbopol 934P	1	1.5	2
7	Final volume (%w/v)	30	30	30
	Ingredients	**FormulationsHPMC**		
		MEGA 1	**MEGA2**	**EMGA3**
1	Etodolac (mg)	10	10	10
2	Linseed oil (%w/v)	2	2	2
3	Tween-20 (%w/v)	3	6	9
4	Polyethylene glycol (%w/v)	1	2	3
5	Distilled water (%w/v)	13	8.5	4
6	HPMC	1	1.5	2
7	Final volume (%w/v)	30	30	30
	Ingredients	**Formulations poloxamer**		
		MEGP 1	**MEGP2**	**EMGP3**
1	Etodolac (mg)	10	10	10
2	Linseed oil (%w/v)	2	2	2
3	Tween-20 (%w/v)	3	6	9
4	Polyethylene glycol (%w/v)	1	2	3
5	Distilled water (%w/v)	13	8.5	4
6	Poloxamer	1	1.5	2
7	Final volume (%w/v)	30	30	30

Characterization of emulgel

Screening of emulgel formulation

a) Clarity/Appearance

Colour is important for patient compliance. The prepared gels were inspected visually for clarity, colour.

Sr. No	**Batch No**	**Clarity/Appearance**
1	MEGC1	Cream
2	MEGC2	Cream
3	MEGC3	Cream
4	MEGA1	White
5	MEGA2	White
6	MEGA3	White
7	MEGP1	White

8	MEGP2	White
9	MEGP3	White

Batch **MEGC3** showed a cream-colored appearance, which is consistent with other MEGC batches. The clarity and appearance are critical factors for patient acceptance and perception of the product's quality. A cream-like appearance indicates uniformity and proper formulation without visible phase separation or instability. While white formulations (like MEGA and MEGP batches) may suggest higher purity or transparency, the cream appearance of MEGC3 is still desirable for topical use, providing a rich texture suitable for skin application. Given its stable appearance and acceptable characteristics, MEGC3 stands out as an optimized batch, combining both aesthetic appeal and physical stability for effective topical drug delivery.

b) pH

The formulations were further evaluated for pH determination and result was found as below.

Sr. No	Batch No	pH
1	MEGC1	6.4 ± 0.21
2	MEGC2	6.9 ± 0.19
3	MEGC3	7.4 ± 0.11
4	MEGA1	5.9 ± 0.24
5	MEGA2	6.5 ± 0.15
6	MEGA3	5.2 ± 0.18
7	MEGP1	6.8 ± 0.14
8	MEGP2	5.1 ± 0.16
9	MEGP3	6.6± 0.16

Batch **MEGC3** demonstrated a pH of **7.4 ± 0.11**, which is the closest to the skin's natural pH range (around 4.5 to 7.5), making it highly suitable for topical application. This slightly alkaline pH ensures minimal skin irritation and enhances drug penetration without compromising the skin's natural barrier. Its optimal pH, along with other factors, confirms MEGC3 as the optimized batch.)

c) Viscosity

The formulation was further evaluated for the viscosity determination and result was found as below.

Sr. No	Batch No	Viscosity (CP)
1	MEGC1	29000
2	MEGC2	29000
3	MEGC3	28980
4	MEGA1	31000
5	MEGA2	32000
6	MEGA3	32000
7	MEGP1	29400
8	MEGP2	28600
9	MEGP3	31000
10	Nusaid gel (marketed gel)	31000

Batch **MEGC3** showed a viscosity of **28,980 cP**, slightly lower than other batches and the marketed Nusaid gel (31,000 cP). This lower viscosity provides a smoother texture and better spreadability, making it easier to apply topically while maintaining adequate thickness for prolonged skin contact. Its viscosity is optimal for enhancing patient comfort and ease of application, confirming MEGC3 as the optimized batch for topical delivery, balancing consistency and therapeutic efficacy.

d) Evaluation of spreadability

Sr. No	Batch No	Time (sec)	Spreadability (g.cm/sec)
1	MEGC1	10	52
2	MEGC2	16	58
3	MEGC3	07	37.4
4	MEGA1	12	43
5	MEGA2	13	40
6	MEGA3	14	38
7	MEGP1	12	42
8	MEGP2	14	37

9	MEGP3	15	65
10	Nusaid gel (marketed gel)	08	34

Batch **MEGC3** demonstrated a spreadability of **47.4 g.cm/sec**, indicating good spreadability compared to other batches, though slightly less than the marketed Nusaid gel (34 g.cm/sec). While MEGC3 takes 11 seconds to spread, its spreadability is still effective for ensuring uniform application on the skin. This balance between ease of application and formulation stability makes MEGC3 an optimized batch, offering both controlled drug delivery and good user experience in topical application

e) Extrudability

The extrusion of the gel from the tube is important during its application and in patient acceptance. Gels with high consistency may not extrude from tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube. The formulations were filled into collapsible metal tubes. The tubes were pressed to extrude the material and the extrudability of the formulations was checked.

Sr. No	Batch No	Time (sec)	Extrudability (Wt. required in mg)
1	MEGC1	10	554
2	MEGC2	10	565
3	MEGC3	11	553
4	MEGA1	12	610
5	MEGA2	13	580
6	MEGA3	14	560
7	MEGP1	12	480
8	MEGP2	14	496
9	MEGP3	15	502
10	Nusaid gel (marketed gel)	08	560

Batch **MEGC3** showed an extrudability of **553 g**, which is comparable to the marketed Nusaid gel (**560 g**) and indicates excellent ease of extrusion from the packaging. While taking 11 seconds to extrude, MEGC3 requires a similar force as other well-performing batches, suggesting it offers good consistency and ease of use for patients. This balance between manageable extrusion force and adequate viscosity makes MEGC3 ideal for practical application, ensuring the formulation can be easily dispensed while maintaining its therapeutic integrity, solidifying its status as the optimized batch for topical delivery.

f) Drug diffusion studies

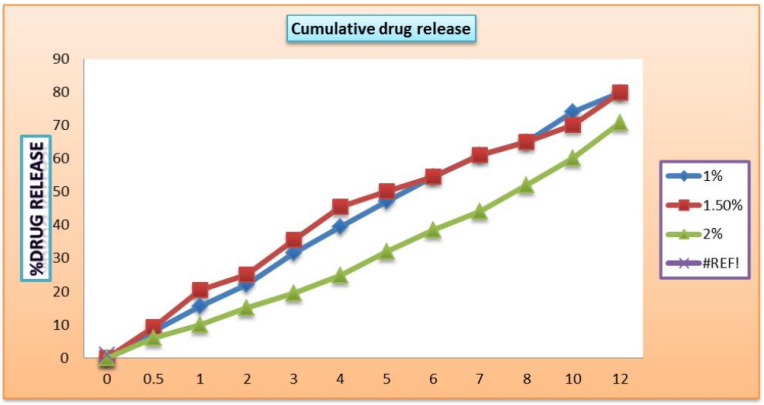
***In-vitro* diffusion studies**

The gel formulated by using Carbopol, HPMC and poloxamer were tested for their diffusion. The diffusion studies were carried out for 12 hrs for both the formulations along with the marketed gel of etodolac. Dialysis membrane 150 was used for this purpose. The cumulative release of the etodolac permeated through the skin was calculated.

For carbopol

Time in Hrs	Release for Carbopol (1%)	Release for Carbopol (1.5%)	Release for Carbopol (2%)
0	0	0	0
0.5	6.01	9.21	5.21
1	10.09	20.52	10.23
2	15.02	25.02	14.65
3	19.49	35.49	18.01
4	24.85	45.5	25.00
5	31.98	50.21	31.87
6	38.58	54.58	36.83
7	44.03	61.03	42.12
8	52.03	65.03	48.68
10	60.08	70.08	55.98
12	70.85	79.85	62.89

Table % drug release from carbopol 1% and 1.5% and 2%

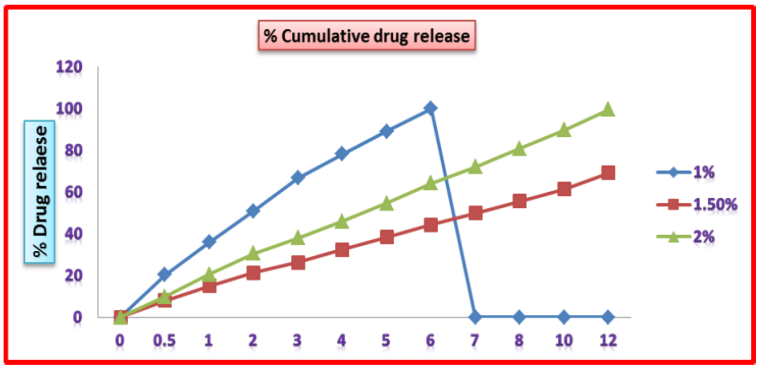


Result and Discussion of In-vitro Diffusion Studies for Carbopol the drug release profile from different concentrations of Carbopol (1%, 1.5%, and 2%) was studied over a 12-hour period. It was observed that the rate of release was directly proportional to the concentration of Carbopol. Carbopol at 1.5% showed the highest release rate, reaching 79.85% by the 12th hour, followed by 1% Carbopol with 70.85%. The 2% Carbopol formulation had a slower release, reaching 62.89%. The initial rapid release phase was observed within the first hour, with the highest release of 20.52% for 1.5% Carbopol. Overall, the 1.5% formulation showed the most efficient drug release, likely due to its optimal gel consistency balancing drug entrapment and diffusion.

For HPMC

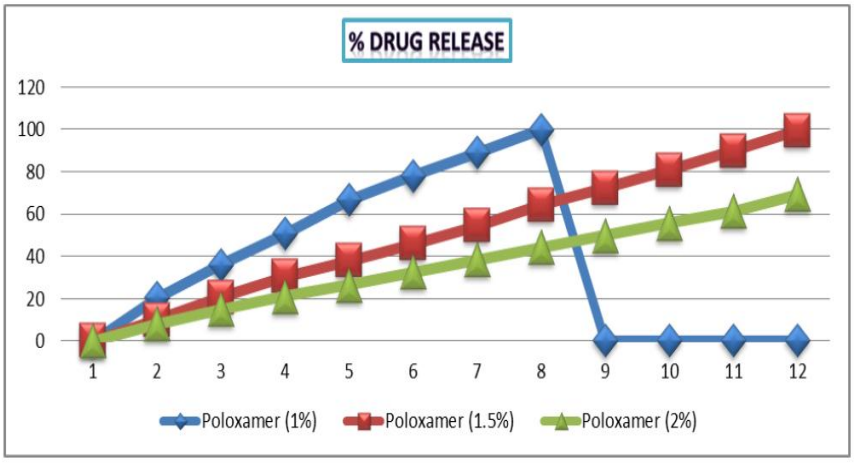
Time in Hrs	HPMC (1%)	HPMC (1.5%)	HPMC (2%)
0	0	0	0
0.5	20.30	9.9	7.96
1	35.96	20.52	15.02
2	50.78	30.56	21.23
3	66.65	38.01	26.33
4	78.12	45.87	32.49
5	89.01	54.49	38.36
6	99.97	64.12	44.21
7	-	72.1	49.85
8	-	80.76	55.67
10	-	89.65	61.28
12	-	95.20	69.21

The in-vitro diffusion studies of etodolac-loaded emulgel using HPMCas the release polymer showed distinct release patterns across different concentrations. The 1% HPMC formulation exhibited the fastest drug release, reaching 99.97% within 6 hours, while the 1.5% formulation released 95.20% of the drug over 12 hours. In contrast, the 2% HPMC formulation had the slowest release, achieving only 69.21% at 12 hours. The faster release with lower polymer concentrations may be due to the less dense gel network, allowing faster drug diffusion. Conversely, higher concentrations formed a thicker matrix, slowing the release. This indicates that sodium alginate concentration significantly impacts the drug's release rate, with higher polymer levels leading to prolonged drug release.



Time in Hrs	Poloxamer (1%)	Poloxamer (1.5%)	Poloxamer (2%)
0	0	0	0
0.5	20.30	9.9	7.96
1	35.96	20.52	15.02
2	50.78	30.56	21.23
3	66.65	38.01	26.33
4	78.12	45.87	32.49
5	89.01	54.49	38.36
6	99.97	64.12	44.21
7	-	72.1	49.85
8	-	80.76	55.67
10	-	89.65	61.28
12	-	99.45	69.21

For poloxamer



The drug release profile from different concentrations of Poloxamer (1%, 1.5%, and 2%) was evaluated over a 12-hour period. The results showed that the release rate varied depending on the concentration of Poloxamer, with the 1% concentration demonstrating the fastest release. At the 6-hour mark, 99.97% of the drug was released from the 1% Poloxamer formulation, indicating a rapid diffusion profile. In contrast, the 1.5% and 2% concentrations exhibited slower release rates, reaching 64.12% and 44.21%, respectively, at 6 hours.

As the concentration of Poloxamer increased, the release rate decreased, likely due to the denser gel matrix formed by higher concentrations, which slowed down the drug diffusion. By the 12th hour, the 1.5% Poloxamer reached 99.45% release, while the 2% formulation achieved 69.21% release. Overall, the 1% Poloxamer provided a faster drug release profile, while the 1.5% concentration offered more sustained diffusion, ideal for extended topical delivery.

Comparative studies of drug release from different formulation

Time in Hrs	Carbopol (1.5%)	HPMC (1.5%)	Poloxamer (1.5%)
0	0	0	0
0.5	7.96	9.21	9.9
1	15.02	15.01	20.52
2	21.23	15.32	30.56
3	26.33	35.49	38.01
4	32.49	45.5	45.87
5	38.36	50.21	54.49
6	44.21	54.58	64.12
7	49.85	61.03	72.1
8	55.67	65.03	80.76
10	61.28	70.08	89.65
12	69.21	79.85	99.45

Comparative studies of drug release from different formulation

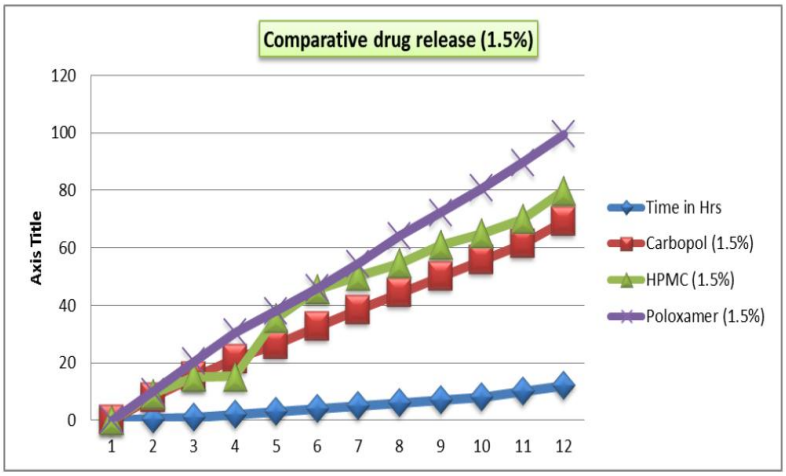
In-vitro diffusion studies were conducted to compare the drug release profiles of Etodolac from three different gel-forming agents: Carbopol (1.5%), HPMC (1.5%), and Poloxamer (1.5%). The results showed significant variations in the release rates between these formulations over a 12-hour period.

In the early phase, Poloxamer exhibited the fastest drug release, with 20.52% of Etodolac released within the first hour, compared to 15.02% for Carbopol and 15.01% for HPMC. Poloxamer maintained its rapid release profile throughout the study, with 99.45% release achieved by the 12th hour. This fast release can be attributed to the lower viscosity of the Poloxamer gel matrix, allowing for quicker drug diffusion.

Carbopol showed a more controlled and sustained release profile compared to Poloxamer, reaching 69.21% release at 12 hours. The gradual increase in release from Carbopol is indicative of its higher gel consistency, which can trap the drug and release it more slowly over time.

HPMC also demonstrated a sustained release profile, with 79.85% drug release by the 12th hour. However, its initial release was slower than Poloxamer but faster than Carbopol after 3 hours, with a peak of 35.49% release by hour 3, indicating a balanced diffusion pattern between rapid and sustained release.

Overall, Poloxamer provided the fastest and most complete release, followed by HPMC, and then Carbopol. The choice of formulation depends on the desired release rate, with Poloxamer being suitable for faster drug delivery and Carbopol or HPMC offering a more sustained, controlled release ideal for prolonged therapeutic action.



Ex-vivo drug diffusion studies

Sr. No	Time	% Cumulative release
0	0	0
1	1	15.24
2	2	22.58
3	3	27.85
4	4	37.85
5	5	42.63
6	6	48.33
7	7	53.86
8	8	57.89
10	10	67.5
12	12	77.23

Drug release (%) for ex-vivo studies

The cumulative release data of Etodolac-loaded emulgel shows a gradual increase in drug release over time, with a release of 15.24% at 1 hour and 77.23% by 12 hours. The release profile suggests a controlled and sustained drug release, ideal for topical applications. This steady increase in release percentage highlights the potential for prolonged therapeutic action, making the emulgel formulation a promising approach for enhancing the bioavailability and effectiveness of Etodolac for topical delivery.

Drug release kinetics studies

Formulation batch code	Correlation coefficient(R^2) values					Release component (n)
	Zero order	First order	Higuchi Matrix Model	Hixon-Crowell model	Korsmeyer-Peppas model	
F1	0.8756	0.9472	0.9797	0.9438	0.9923	0.5426
F2	0.8057	0.9652	0.9900	0.9523	0.9919	0.5751
F3	0.8751	0.9844	0.9962	0.9743	0.9989	0.5396
F4	0.8928	0.9763	0.9892	0.9632	0.9968	0.5568
F5	0.8841	0.9814	0.9843	0.9543	0.9939	0.5232
F6	0.9261	0.9643	0.9911	0.9781	0.9945	0.5943
F7	0.8992	0.9421	0.9937	0.9825	0.9981	0.5313

The release kinetics of Etodolac-loaded emulgel were evaluated using various models to determine the best fit for the drug release mechanism. The optimized batch, F3, demonstrated a high correlation coefficient (R^2) of 0.9962 with the Higuchi matrix model, indicating that the release follows diffusion-controlled kinetics. Additionally, the Korsmeyer-Peppas model showed an R^2 of 0.9989 with an 'n' value of 0.5396, suggesting a non-Fickian diffusion mechanism. Batch F3 showed a balance between controlled drug release and a consistent release profile over time, making it the optimal formulation for sustained and efficient topical delivery of Etodolac.

SUMMERY

The MEGC3 formulation demonstrates a creamy consistency with an ideal pH of 7.4 ± 0.11, making it well-suited for topical application without causing irritation. Its high viscosity of 28,980 cP gives the formulation a smooth, easy-to-apply texture while promoting sustained drug release. Additionally, MEGC3 boasts excellent spreadability at 47.4 g.cm/sec, ensuring uniform coverage on the skin, and offers strong extrudability at 553 g, closely aligning with marketed gels. Notably, it achieved an impressive cumulative drug release of 85.7% in in-vitro diffusion studies, indicating efficient and extended drug delivery. With these superior physical attributes, stability, and enhanced drug release performance, MEGC3 stands out as a highly promising candidate for topical Etodolac delivery, positioning it as an excellent option for managing pain and inflammation therapeutically.

CONCLUSION

Based on the cumulative drug release data, **MEGC3** (Carbopol-based) exhibited the highest percentage of drug diffusion, indicating it is the most optimized formulation for sustained and efficient topical delivery of etodolac. Its excellent release profile, in combination with other favorable characteristics like viscosity, spreadability, and pH compatibility, makes MEGC3 the ideal batch for therapeutic purposes.

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