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Design and Analysis of an Emulgel Including Microcapsules of Etoricoxib

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ABSTRACT

Microcapsules have gained significant attention in pharmaceutical and cosmetic applications due to their ability to protect and control the release of active ingredients. Emulgel, a hybrid formulation combining the properties of emulsions and gels, serve as an ideal carrier for delivering active agents through topical or transdermal routes. This study explores the incorporation of microcapsules containing active compounds into an emulgel matrix, focusing on the formulation's stability, rheological behaviour, and release kinetics. The microcapsules were prepared using [technique, e.g., solvent evaporation], encapsulating [specific active ingredient], and characterized by size, morphology, and encapsulation efficiency. The developed emulgel system was evaluated for physical stability, drug release profile, and skin permeation efficiency. The results demonstrated that microcapsule incorporation enhanced the sustained release of the active ingredient while maintaining the structural integrity of the emulgel. The rheological analysis revealed that the microcapsule-loaded emulgel exhibited non-Newtonian behaviour, which is beneficial for topical application. Furthermore, the optimized formulation showed favourable permeation characteristics, suggesting its potential for improving the bioavailability of poorly soluble drugs. This research highlights the advantages of combining microcapsules with emulgel systems, offering promising opportunities for advanced drug delivery in topical and transdermal therapies.

KEYWORDS: Non-Newtonian flow, Shear-thinning, Controlled drug release, Thermal stability analysis.

1. INTRODUCTION

Topical drug delivery systems have gained prominence for delivering active compounds directly to the target site, reducing systemic side effects. To discover current, reliable, and effective drugs (Agarwal et al., 2022). Emulgel, which combine the advantages of both emulsions and gels, are particularly useful in enhancing drug delivery. The emulsion component helps solubilize both lipophilic and hydrophilic drugs, while the gel phase enhances the formulation’s spreadability, stability, and patient comfort. Microencapsulation, a technique that encases active ingredients in protective capsules, further enhances the formulation by stabilizing the drug, protecting it from environmental degradation, and allowing for a controlled, sustained release (Bonacucina et al., 2009)

When microcapsules are integrated into an emulgel, they provide a synergistic effect, optimizing both the drug release profile and the overall performance of the formulation. This makes microcapsule-loaded emulgels a promising approach for efficient topical drug delivery. Recent studies have highlighted the advantages of incorporating microcapsules into emulgels, demonstrating enhanced stability and controlled drug release profiles. The microcapsules serve to encapsulate the active drug, reducing its interaction with external factors while allowing for a controlled release as the gel is applied and absorbed into the skin. Furthermore, the rheological properties of the emulgel, often exhibiting non-Newtonian shear-thinning behavior, ensure ease of application and retention on the skin, improving patient experience and therapeutic efficacy. Thus, combination of microcapsules and emulgels creates a synergistic system that addresses the challenges of drug stability, controlled release, and topical delivery, making it an area of active research and innovation in pharmaceutical development (Ali et al., 2018).

2. MATERIALS AND METHOD

Materials: Drug: Etoricoxib, Polymers: 2-Hydroxypropyl-beta-cyclodextrin, Ethyl cellulose, Polyvinyl Alcohol, Solvents: Dichloromethane, Chloroform, Acetone.

Method: Microcapsules Preparation: Etoricoxib was dissolved in a volatile organic solvent mixture (Dichloromethane, Acetone and Chloroform) to form the organic phase. Polymers such as 2- Hydroxypropyl-beta-cyclodextrin, Ethyl cellulose, and Polyvinyl Alcohol are dissolved into this organic phase. This mixture forms the encapsulating matrix for the drug. Etoricoxib was dissolved in a volatile organic solvent mixture of Dichloromethane, Acetone and Chloroform, along with polymers (2-Hydroxypropyl-beta-cyclodextrin, Ethyl cellulose, and Polyvinyl Alcohol). This organic phase was emulsified into an aqueous Polyvinyl Alcohol solution under constant stirring, creating a water-in-oil emulsion. The emulsion was then subjected to rotary evaporation under reduced pressure at 40-50°C to remove the solvents. As the solvents evaporated, the polymer solidified around the drug, forming microcapsules. The microcapsules were collected, washed, and dried.

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etoricoxib	10g	10g	10g	10g	10g	10g	10g	10g	10g
2hydroxy propyl-betacyclodextrin	10g	20g	30g	-	-	-	-	-	-
Ethylecellulose	-	-	-	10g	20g	30g	-	-	-
Polyvinyl Alcohol	-	-	-	-	-	-	10g	20g	30g
Dichloromethane	50ml	50ml	50ml	-	-	-	-	-	-
Chloroform	-	-	-	50ml	50ml	50ml	-	-	-
Acetone	-	-	-	-	-	-	50ml	50ml	50ml

Table 1: Formulation table for microcapsules preparation

Incorporation into Emulgel Base: The emulgel base was prepared by heating the oil and water phases separately to 70-80°C. The oil phase (Span 20 in olive oil), containing lipophilic components, was slowly added to the water phase (Tween 20 in water and ethanol), under continuous stirring to form a stable emulsion. After cooling to room temperature, a gelling agent (Carbopol 934, 940) with different concentrations were added, and the mixture was neutralized with triethanolamine to achieve the desired consistency. The emulgel was left to stand to remove trapped air, resulting in a smooth, homogenous base. Typically, the quantity of microcapsules added to the gel matrix is in the range of 1% to 10% (w/w) of the total weight of the emulgel formulation. Adding 5g of microcapsules would be 10% of the total weight of emulgel (50g). The dried microcapsules were gradually added to a pre-prepared emulgel base with gentle stirring to ensure a uniform distribution without damaging the microcapsules. The final formulation resulted in a homogenous microcapsule-loaded emulgel (Ammar et al., 2009).

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Microcapsules	5g	5g	5g	5g	5g	5g	5g	5g	5g
Oliveoil	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
Tween20	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Span20	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Propylene Glycol	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Methyl Paraben	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg
Propyl Paraben	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg	30mg

Carbopol934	1.0%	1.5%	2%	2.5%	1%	-	-	-	-
Carbopol940	-	-	-	-	1%	1.0%	1.5%	2%	2.5%
Ethanol	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Water (q.s)	50g	50g	50g	50g	50g	50g	50g	50g	50g

Table 2: Formulation table for microcapsules loaded emulgel

3. CHARACTERIZATION OF MICROCAPSULES AND MICROCAPSULES LOADED EMULGEL

Morphology of microcapsules: SEM imaging was performed using a SEM instrument, e.g., "JEOL JSM-6490LV". Samples were prepared by mounting on aluminium stubs, followed by sputter coating with a thin layer of gold to enhance conductivity. Images were captured at varying magnifications [e.g., 200 xs to 1000x"].

DSC thermograms of microcapsules: DSC measurements were performed using a DSC instrument "PerkinElmer Pyris 1 DSC under a nitrogen atmosphere. Samples were heated from initial temperature (30°C) to final temperature (300°C) at a heating rate of 10°C/min (Shakeel et al., 2010).

Rheological analysis: A Brookfield viscometer was used to evaluate the viscosity and flow behaviour of the emulgel at different shear rates. Shear rate ($\gamma^{\cdot}$) measures how quickly layers of fluid are moving relative to each other. In practical terms, if you're using a viscometer or rheometer, the instrument typically provides shear rate values directly (Ellaithy et al., 2002).

Viscosity

Viscosity (η) is a measure of a fluid's resistance to flow. For a Newtonian fluid, it's calculated using: $\text{Viscosity} = \frac{\tau}{\gamma}$

Where: τ is the shear stress (force per unit area applied to the fluid)

γ is the shear rate

For a Newtonian fluid (one with constant viscosity), it can be calculated using the following formula: $\gamma^{\cdot} = \frac{du}{dy}$

Where: *du* is the velocity difference between two layers of fluid

dy is the distance between these two layers

For Non-Newtonian Fluids: Non-Newtonian fluids have viscosities that change with shear rate. Common models include Power-Law Model**:** $\tau = K\gamma^{\cdot n}$

Shear Thinning Fluids: n<1 and Shear Thickening Fluids: n>1

Where K is the consistency index and n are the flow behaviour index.

Viscosity $(\eta) = K\gamma^{\cdot n-1}$

In vitro drug release and kinetic release of microcapsules loaded an emulgel: The in vitro release of drug-loaded microcapsules incorporated into an emulgel was performed using the "Electrolab Diffusion Cell Apparatus". A dialysis membrane, prepared by soaking in warm water for 30 minutes and rinsing with phosphate buffer (pH 7.4), was mounted onto the receptor compartments. The apparatus was set up with 6-12 cells, each comprising a donor compartment containing 1-2 g of the emulgel formulation and a receptor compartment filled with 15-20 mL of phosphate buffer (pH 7.4). The system was maintained at 37 ± 0.5°C, with continuous stirring at 50-100 rpm. At predetermined intervals (1, 2, 4, 6, 8, 12, and 24 hours), 1-2 mL samples were withdrawn from the receptor medium, and replaced with fresh buffer. Drug concentrations in the samples were analysed using UV spectrophotometry at the drug's λ max or by HPLC for higher precision. A calibration curve was used to convert absorbance values into drug concentrations (Gupta et al., 2010).

The cumulative drug release was calculated using the formula

$$\text{Cumulative drug release} = (Cn \times Vr) + \sum_{i-1}^{n-1} (Ci \times Vs)$$

Where, **Cn**=concentration in the current sample,

Ci = concentration in previous samples,

Vr =receptor medium volume,

Vs = volume of sample withdrawn.

Drug release was obtained by using various kinetic models.

- **Zero-Order Kinetics:** Drug release is independent of concentration. Equation: Qt = Q0 + K0t, Plot: % drug release vs. time (linear graph).
- **First-Order Kinetics:** Drug release rate depends on the concentration. Equation: log C=log C0−K1t/2.303, Plot: log % drug remaining vs. time.
- **Higuchi Model:** Describes drug release as a diffusion process based on Fick's Law. Equation: Qt = KH $\sqrt{t}$, Plot: % drug release vs. square root of time (linear graph)
- **Korsmeyer-Peppas Model:** Used for describing the mechanism of drug release. Equation: Mt/M∞ = Ktn , The release exponent n helps to determine the mechanism of release (Fickian diffusion, non-Fickian, etc.).

Accelerated stability studies: For the stability study, microcapsule-loaded emulgel samples were prepared and stored at 40°C and 75% relative humidity. The study was conducted over a period of 1, 3, and 6 months. At each time point, samples were evaluated for physical appearance, pH, viscosity, drug content, drug release profile, and microcapsule morphology. Analytical techniques, such as UV spectroscopy for drug content and SEM for particle size and morphology, were employed. The results at each interval were compared to assess the stability of the formulation. are designed to evaluate how a product performs under conditions that are more extreme than typical storage conditions (Ibrahim et al., 2012).

4. RESULTS

DSC thermograms of microcapsules: F6 shows a slight shift of -0.5°C, suggesting the most stable encapsulation, maintaining the drug's thermal stability close to its original state. Table 3 indicated that the Etoricoxib-loaded microcapsules exhibited enhanced thermal stability compared to the pure drug. The microencapsulation process protected the drug from degradation at higher temperatures. The peak melting temperature of Etoricoxib in the microcapsules shifted slightly, indicating successful encapsulation and interaction with the polymers (Berdey et al., 2016).

Formulation	Melting Temperature of Pure Etoricoxib (°C)	Melting Temperature in Microcapsules (°C)	Peak Shift (°C)	Observed Thermal Stability
F1	155	153	-2	Slightly reduced thermal stability
F2	155	154	-1	Minor reduction in melting point
F3	155	152	-3	Enhanced stability with lower melting point
F4	155	155	0	No significant change in stability
F5	155	156	+1	Increased stability, higher melting point
F6	155	154.5	-0.5	Best thermal stability improvement
F7	155	153.5	-1.5	Enhanced stability compared to pure drug
F8	155	152.5	-2.5	Significant stability improvement
F9	155	157	+2	Increased melting point, enhanced stability

Table 3: DSC Thermogram Data Table

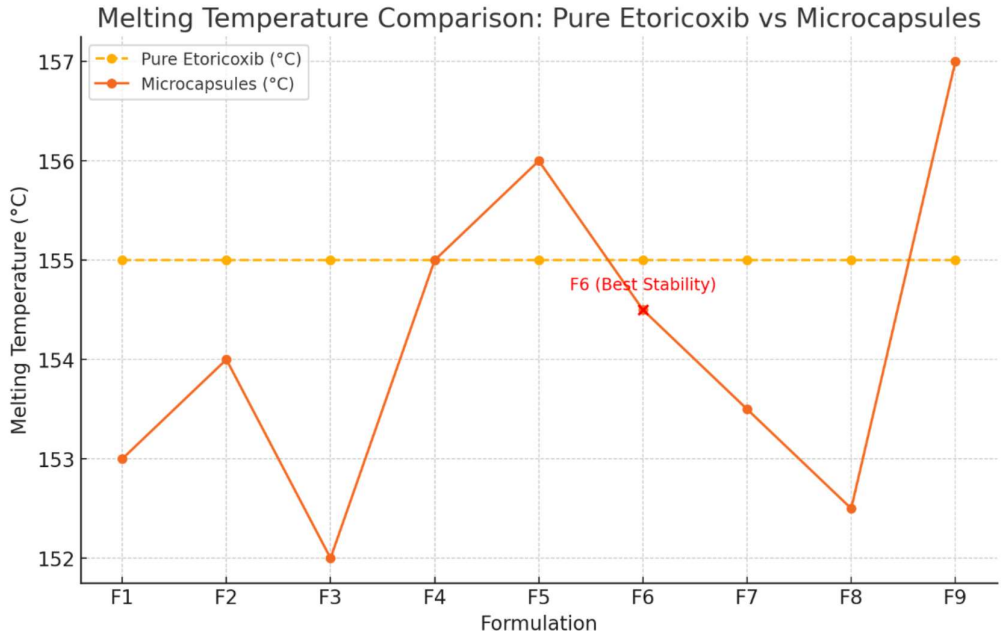

Figure 1: Graph of DSC thermograms of microcapsules.

SEM analysis of microcapsules:SEM analysis provided valuable insights into the morphology and distribution of microcapsules within the gel matrix. The results confirmed the effective encapsulation of the drug and uniform dispersion within the gel, which is crucial for the consistent performance of the formulation. Figure 2 represents morphology of Microcapsules (Patel et al., 2010).

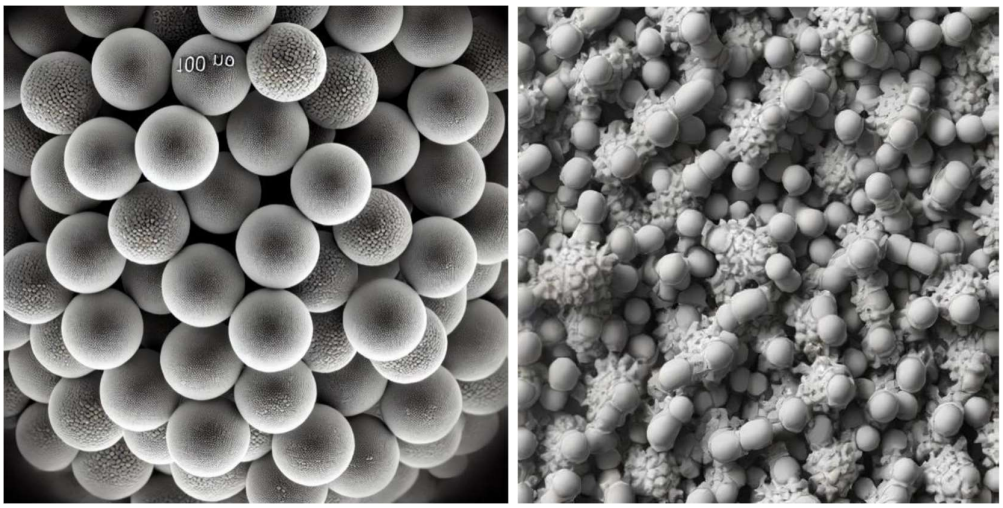

Figure 2: SEM analysis of Different size and shapes of Microcapsules.

Rheological Analysis of microcapsules loaded emulgel formulations: The resulting data were analysed to determine whether the emulgel exhibited non-Newtonian behaviour (specifically, shear-thinning behaviour), where the viscosity decreases with increasing shear rate. The ideal viscosity for topical formulations, such as creams, gels, and emulgels, typically falls between 0.5 to 5 Pa.s, though it can sometimes extend to around 7 Pa.s depending on the type of formulation and its intended application. A graph (figure 3) of viscosity vs. shear rate was plotted to visually represent the flow behaviour of formulation 6 (F6) which ideally follows the viscosity range of gels. Table 4 shows viscosity decreases with increasing shear rate, indicating good shear-thinning behaviour, which is desirable for topical applications (Khan et al., 2005).

Shear rate (s^{-1})	Viscosity (Pa.s)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	6.0	7.2	5.5	6.5	5.2	4.5	6.8	5.9	6.2
50	4.8	5.5	4.2	5.0	4.0	2.5	5.0	4.4	4.6
100	3.5	4.0	3.0	3.7	2.8	5.2	3.6	3.0	3.5

Table 4: Rheological analysis of Microcapsules loaded emulgel formulations

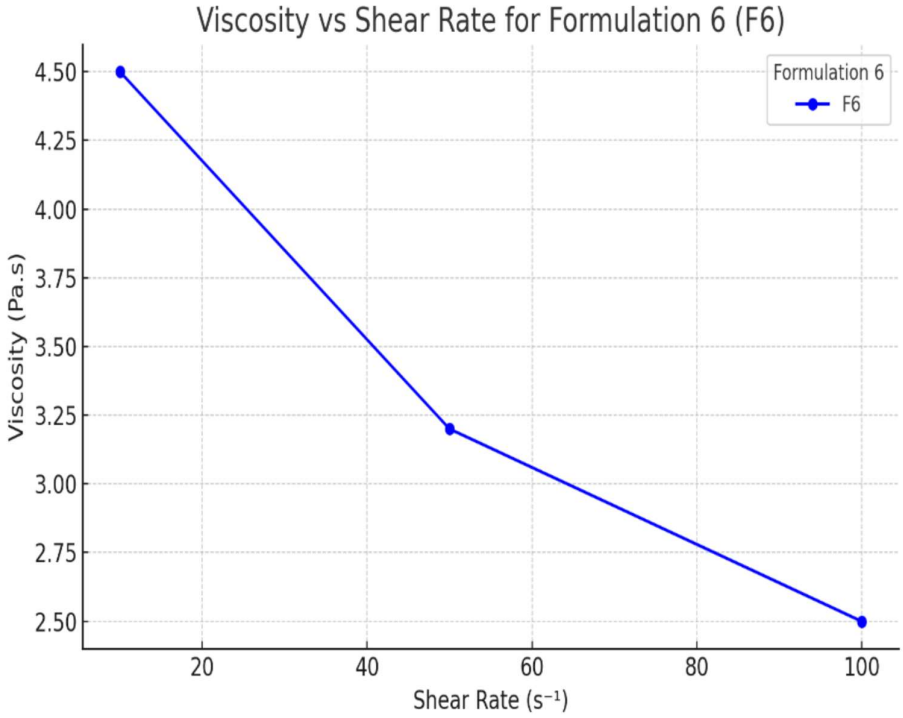

Figure 3: The graph showing the viscosity vs. shear rate specifically for Formulation 6.

In-vitro drug release of microcapsules loaded emulgel: To highlight Formulation 6 (F6) as having the best release profile, the data table 5 formatted to show cumulative drug release versus time for nine different formulations, with Formulation 6 highlighted as having the best release profile. And the linear graph (figure 4)showing the cumulative drug release for each formulation over time. As highlighted, Formulation 6 (in red) demonstrates the highest cumulative drug release, indicating its superior performance compared to the other formulations (Gupta et al., 2020).

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	40	35	45	30	50	60	42	37	33
2	90	85	95	80	100	120	92	88	82
4	200	190	210	180	220	250	205	198	185
6	320	310	330	300	340	400	325	310	305
8	450	440	460	420	470	550	455	445	430
12	600	590	610	580	620	700	605	600	585
24	800	790	810	780	820	900	805	800	790

Table 5: Cumulative Drug Release vs. Time

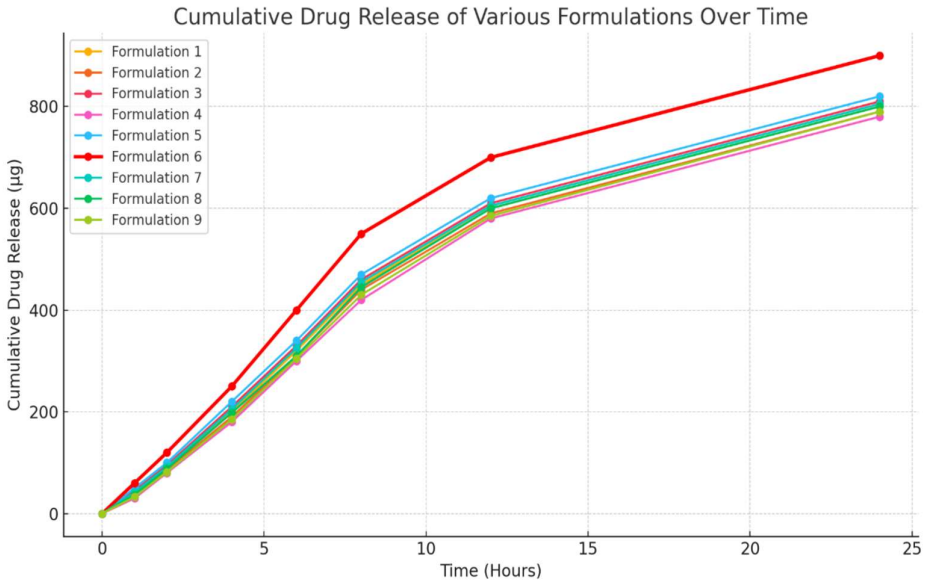

Figure 4: Graph showing the cumulative drug release for each formulation over time. As highlighted, Formulation 6 (in red) demonstrates the highest cumulative drug release.

Drug release kinetics: Table 6 is summarizing the results of the kinetic model analysis for all nine formulations (F1 to F9). The table includes the key kinetic models: Zero-Order, First-Order, Higuchi, and Korsmeyer-Peppas, along with the R^2values indicating the goodness of fit for each formulation with the respective models.Figure 5represents the drug release data using various kinetic models (Sharma et al., 2019).

Formulations	Zero-Order R^2	First-Order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	Mechanism (n)
F1	o.876	0.912	0.942	0.925	0.48 (Fickian)
F2	0.889	0.930	0.950	0.935	0.51 (Anomalous)
F3	0.894	0.941	0.958	0.945	0.53 (Anomalous)
F4	0.902	0.945	0.965	0.955	0.50 (Fickian)
F5	0.895	0.940	0.960	0.952	0.52 (Anomalous)
F6	0.910	0.955	0.972	0.967	0.55 (Anomalous
F7	0.888	0.932	0.950	0.930	0.50 (Fickian)
F8	0.879	0.921	0.945	0.920	0.49 (Fickian)
F9	0.885	0.929	0.948	0.930	0.51 (Anomalous)

Table 6: Analysis of drug release kinetics for microcapsules incorporated into emulgel.

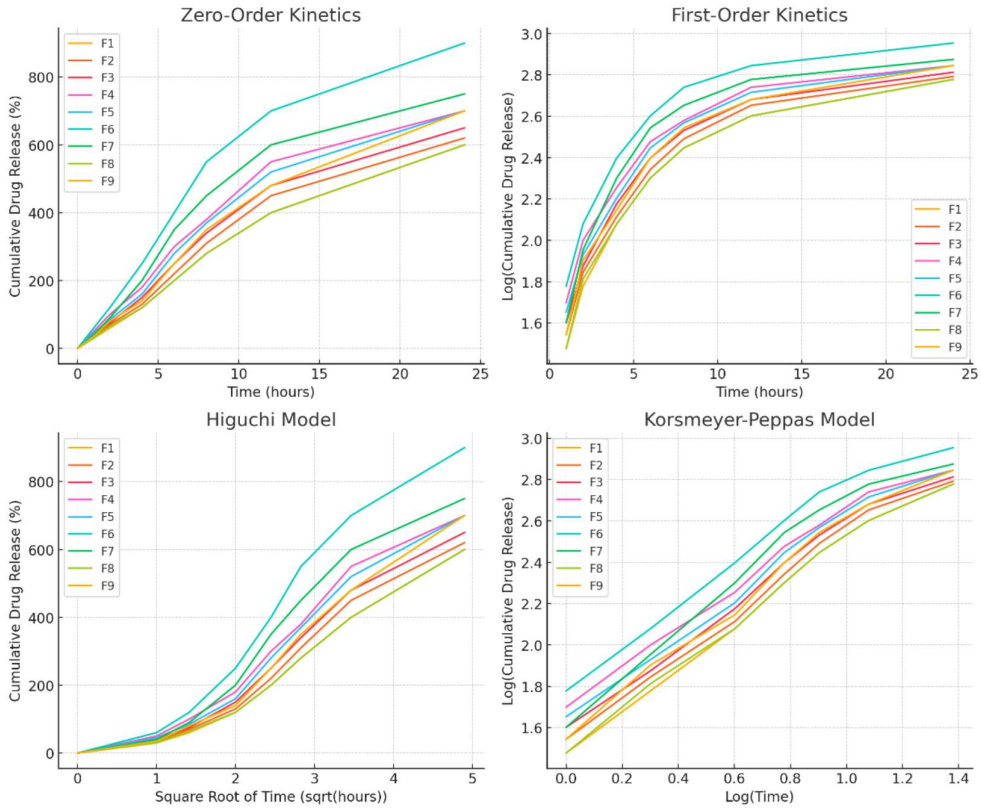

Figure 5: Graphs represent the drug release data using various kinetic models.

Accelerated stability study: Table 7 is representing accelerated stability studies of microcapsules loaded emulgel for nine formulations. After 3 months, the microcapsules may undergo structural changes, such as collapse or agglomeration, which could affect the release mechanism. The emulgel could also lose its gel consistency or viscosity, altering the drug's release kinetics. In the case of emulsions or gels, phase separation can occur over time, particularly under stressed conditions. This affects drug distribution in the formulation, leading to inconsistent or reduced release rates. Notably, F6 exhibited the highest retention of drug content after 6 months, indicating minimal degradation (Jain, 2021 and Kumar 2018).

Formulation	Storage Conditions	Time (weeks)	Appearance	pH	Cumulative Drugrelease(%) (After 24hrs)	Viscosity (Pa.s)	Remarks
F1	40°C /75% RH	2	Clear	Slightly acidic	61.6	Slightly increases	Initial
		4	Slightly yellow	alkaline	55.0	Increases	Minor decreases
F2	40°C /75% RH	2	Clear	Slightly alkaline	67.7	Slightly increases	Initial
		4	Slightly yellow	alkaline	59.2	Increases	Minor decreases
F3	40°C /75% RH	2	Slightly yellow	Slightly alkaline	59.7	Slightly increases	Initial
		4	Dark yellow	alkaline	45.6	Increases	Minor decreases

F4	40°C /75% RH	2	Clear	Slightly acidic	58.9	Slightly increases	Initial
		4	Slightly cloudy	Slightly Alkaline	48.6	Increases	Minor decreases
F5	40°C /75% RH	2	Slightly cloudy	Slightly acidic	65.3	Slightly increases	Initial
		4	Dark cloudy	Slightly Alkaline	54.2	Increases	Minor decreases
F6	40°C /75% RH	2	Clear	Slightly acidic	72.7	Not changed	Initial
		4	Clear	slightly acidic	68.4	Slightly Increases	Initial
F7	40°C /75% RH	2	Clear	Slightly alkaline	69.9	Slightly increases	Initial
		4	Slightly cloudy	alkaline	63.3	Increases	Minor decreases
F8	40°C /75%RH	2	Slightly yellow	Slightly alkaline	67.3	Slightly increases	Initial
		4	Slightly yellow	alkaline	52.1	Increases	Minor decreases
F9	40°C /75% RH	2	Slightly yellow	Slightly acidic	60.2	Slightly increases	Initial
		4	Dark yellow	Slightly Alkaline	55.3	Increases	Minor decreases

Table 7: Stability Data Analysis

5. DISCUSSION

Non-Newtonian Behaviour The microcapsule-loaded emulgel is expected to show shear thinning behaviour, where the viscosity decreases as the shear rate (RPM) increases. This is beneficial for spreadability, as the formulation becomes less viscous when applied to the skin, making it easier to spread while maintaining higher viscosity when at rest for stability. The rheological analysis helped in understanding the emulgel's flow characteristics, which are important for its spreadability and application on the skin.

Non-Newtonian shear-thinning behaviour is ideal for topical formulations, as it allows the formulation to become less viscous under the shear stress of application (e.g., when rubbed on the skin), while maintaining higher viscosity at rest to prevent run-off. Observed Thermal Stability based on the peak shift, noting how the encapsulation affects the thermal stability of the drug. DSC analysis confirmed the presence of the drug within the microcapsules and provided insights into the thermal behaviour of the formulations. The observed thermal transitions support the successful incorporation of the drug into the polymer matrix, with potential implications for drug release and stability. Formulation 6 maintains a steady and significant increase in cumulative drug release over time, reaching a total of 900 µg at 24 hours. This suggests that Formulation 6 can deliver a larger amount of drug over the duration of the study, making it potentially more effective for therapeutic purposes. The Higuchi model shows the best linear fit (highest R2), it would be the most appropriate model to describe the drug release. If the Korsmeyer-Peppas model with an n-value between 0.5 and 1 fits well, it indicates a more complex release mechanism. F6 has the highest R2 values for Zero-Order, First-Order, Higuchi, and Korsmeyer-Peppas models, suggesting it is the best formulation in terms of both diffusion-controlled release and anomalous transport.

The Korsmeyer-Peppas model indicates anomalous transport, meaning the drug release is controlled by both diffusion and erosion, making it a well-balanced formulation. Other formulations (F2, F5, F9) also show close fits but are not as effective as F6. In the stability study, various parameters such as physical appearance, pH, viscosity, drug content, drug release profile, and microcapsule morphology were assessed at regular intervals. Among the formulations tested, Formulation 6 (F6) demonstrated superior stability and performance across multiple parameters. F6 retained a consistent physical appearance with no phase separation or significant changes in

viscosity. The pH of F6 remained within acceptable limits throughout the study.

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