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Research

Design and In-Vitro Evaluation of Kaempferol-Loaded Emulgel as a Novel Topical Anti-Inflammatory Drug Delivery System

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Abstract
Background: Inflammation is a complex biological response associated with various pathological conditions, necessitating the development of effective and safer therapeutic strategies. Kaempferol, is a naturally occurring flavonoid that exhibits significant anti-inflammatory, antiproliferative, and antioxidant properties but limited due to low bioavailability. Methods: The emulgel was formulated using Carbopol 934 as a gelling agent and a combination of Span 20 and Tween 80 as surfactants to stabilize an oil-in-water emulsion system. Emulgel was assessed for physicochemical properties, drug release, drug content, and stability over 90 days following anti-inflammatory activity. Results: The developed emulgel exhibited desirable characteristics, including smooth texture, homogeneous appearance, non-greasy, and good washability. The pH (6.40 ± 0.01) was within acceptable skin-compatible range, while viscosity and spreadability values indicated suitable rheological behavior. Drug release studies proved controlled release with 91.73% cumulative drug release over 24 hours. The drug content was found to be 98.93 ± 0.29%. The formulation demonstrated notable biological activities. Stability studies indicated minimal changes in physicochemical parameters under both room temperature and accelerated conditions. Conclusion: The developed kaempferol emulgel exhibited potential as a topical anti-inflammatory delivery system for localized inflammatory conditions.

Keywords
Kaempferol, Emulgel, Topical drug delivery, Anti-inflammatory activity

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1. Inflammation

Inflammation is the protective response to harmful stimuli to preserve tissue balance and trigger repair mechanisms (1-3). Although acute inflammation is protective, prolonged or uncontrolled inflammatory responses lead to various pathological conditions, including dermatitis, arthritis, and other chronic inflammatory disorders (4-6). Though effective, long-term use of anti-inflammatory conventional therapies exhibit adverse effects, including gastrointestinal irritation, renal complications, and cardiovascular risks (7-9). These limitations prompted the search for safer and more targeted therapeutic alternatives, chiefly those derived from natural sources. Historically, herbal medicines have been a good source of compounds for modern drug discovery. Still today, underdeveloped countries depend on ethnobotanicals for healthcare (10). These plants are rich in phytochemicals and exhibit

significant pharmacological potential, among which flavonoids have attracted considerable attention for their anti-inflammatory, antioxidant, antimicrobial, and cytoprotective effects (11-13).

Kaempferol is naturally occurring flavone in fruits, vegetables, and medicinal plants and emerged as a promising therapeutic candidate in many studies (14-16). Although, it exhibits broad pharmacological effects (17-19) its use is limited due to compromised bioavailability, restricting effective delivery through conventional formulation (20-22). Thus, topical drug delivery systems offer an effective approach to treat localized inflammatory conditions. Topical formulations reduce systemic exposure, enhance patient compliance, and deliver drug directly to the site of inflammation. Nonetheless, conventional topical vehicles often face challenges in delivering poorly water-soluble drugs due to inadequate release and limited skin penetration (23-25).

Interestingly, emulgel can address above limitation to enhance skin penetration with controlled drug release (26-28). But, choice of components is critical for optimal performance. Carbopol-based gels are widely employed due to biocompatibility, rheological properties, and controlled release. Next, dual surfactant system (Span 20 + Tween 80) improves stability and drug distribution in formulation (29-31). Based on this, we developed and evaluated emulgel by using kaempferol (Figure 1). The objective was to enhance kaempferol solubility, stability, and local bioavailability through emulsion-in-gel system. Study also evaluates physicochemical properties, drug release, and anti-inflammatory related biological activities activity to support the potential of this formulation as an effective topical strategy for localized inflammatory conditions.

2. Materials and Methods

2.1. Preliminary Qualitative Analysis of Flavonoid Functional Groups in Kaempferol

Kaempferol was obtained gift from Chemical Book, China. All ingredients, including Carbopol 934, propylene glycol, ethanol, triethanolamine (TEA), Span 20, and Tween 80, were procured from SD Fine Chemicals (Gujarat, India).

Preliminary qualitative tests were performed to confirm sample as flavonoid. In the Shinoda test (32, 33), 1 mL of sample dissolved in alcohol was treated with several magnesium turnings and few drops of concentrated hydrochloric acid, producing faint pinkish-red color, indicative of flavonoids. Similarly, alkaline reagent test further confirmed their presence, as sample solution turned yellow upon treatment with sodium hydroxide and reverted to colorless with the addition of a few drops of diluted acid (34, 35). These results collectively validate the presence of flavonoid groups in the kaempferol sample.

2.2. Formulation of kaempferol emulgel

The preparation began with gel base using Carbopol 934, which was dispersed in purified water with continuous gentle stirring and allowed sufficient time to swell completely, ensuring the development of uniform and viscous matrix. Gradual incorporation of triethanolamine neutralized the dispersion and resulted in the formation of a clear, uniformly structured gel suitable for topical application (36-38). An o/w emulsion was prepared by dissolving kaempferol and preservatives in a mixture of propylene glycol and ethanol, providing an appropriate solvent system for poorly water-soluble drug (39-41). Sesame oil and Span 20 were then added to form oil phase, which was thoroughly mixed to achieve uniform distribution (42-44). Purified water was gradually added under vigorous stirring to complete emulsion, and Tween 80 was used as stabilizing surfactant to maintain integrity and prevent phase separation during storage. Finally, prepared emulsion was incorporated into gel base at room temperature under continuous stirring until uniform and consistent emulgel was formed. The final weight of formulation was adjusted using purified water, and gentle stirring was applied to ensure complete homogeneity throughout the product. This stepwise process resulted stable, well-structured kaempferol emulgel suitable for effective topical delivery. The composition of kaempferol-loaded emulgel and specific functions of ingredients are summarized (Table 1).

2.3. Characterization of kaempferol emulgel

The kaempferol emulgel was evaluated for its physicochemical properties, e.g., appearance, pH, viscosity, and spreadability. Appearance was examined by observing colour (visually against a white background), odour (absence of unpleasant smell), texture, homogeneity (rubbing emulgel between fingers-confirm smoothness/uniformity and absence of lumps or phase separation), consistency, and greasiness (oily residue absence on skin after application). The pH and viscosity were measured using calibrated digital pH meter (Systronics-802, India) and Brookfield viscometer (LVDVE, USA), respectively. Spreadability (45, 46) was determined by placing emulgel (measured quantity) between

glass slides, applying weight, and recording time required to move (upper slide) a set distance. Next, washability of developed emulgel was evaluated by applying small amount to skin and rinsing it under running tap water. Formulation was easily removed and left no greasy residue, demonstrating good washability and user-friendly application (47).

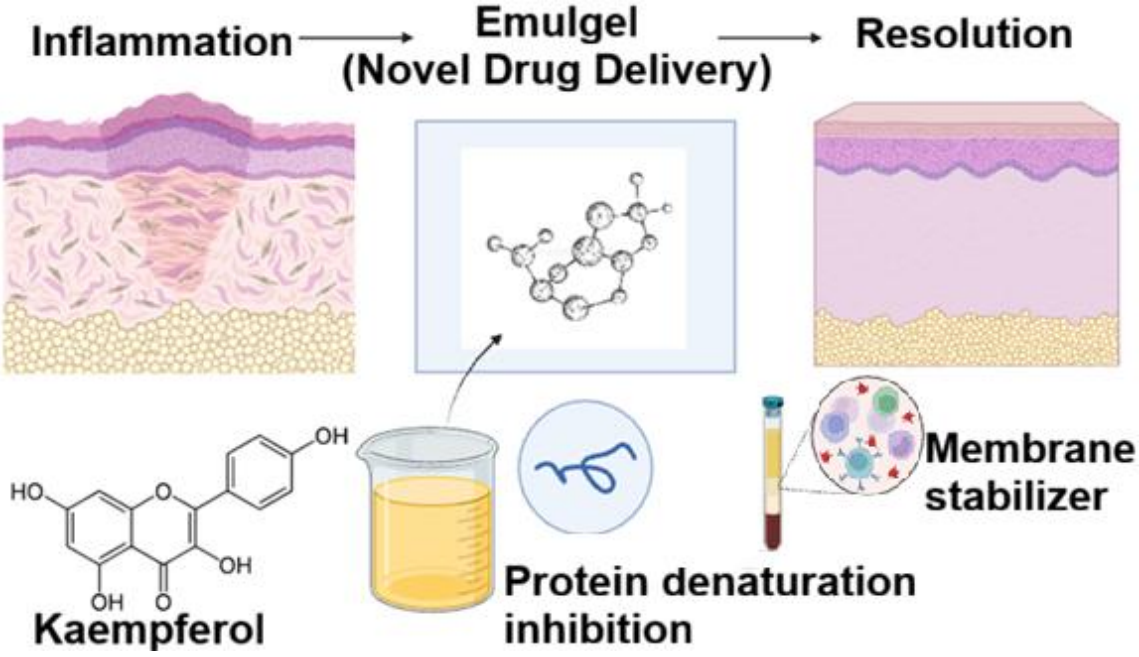

Figure 1: Formulation and evaluation of kaempferol - loaded emulgel.

2.4. FT-IR analysis of kaempferol-loaded emulgel, Drug Content and Franz diffusion study

The sample was prepared using the KBr pellet method, where a small amount of dried emulgel was finely mixed with KBr and compressed into transparent pellet (48, 49). Spectral data were collected over the range of 4000–400 cm^{-1} at room temperature. The resulting spectrum was carefully analyzed to identify characteristic peaks of kaempferol and excipients, providing insight into structural integrity and compatibility of formulation.

For drug content analysis, one gram of gel was dissolved in 50 mL of phosphate buffer (pH 4.5), sonicated and filtered. Appropriate dilutions were prepared, and kaempferol was quantified using using UV spectrophotometer (absorbance 368 nm) in triplicate.

Drug release study was performed using modified Franz diffusion cell equipped with cellophane membrane (50, 51). 1 g of emulgel was evenly spread over membrane surface of donor compartment after positioning it between the compartments. The phosphate buffer (pH 6.8) was filled in receptor compartment with continuous stirring (50 rpm) maintaining system temperature (37±0.5°C). Samples were withdrawn at predetermined intervals maintaining sink conditions. The kaempferol was quantified in sample using a UV spectrophotometer (absorbance 368 nm).

2.5. Protein Denaturation and Membrane stability

The formulated emugel was examined for protein denaturation as explained by Williams et al. (52). Reaction mixtures were prepared by combining 1% aqueous bovine serum albumin with varying test concentrations, incubated (37°C, 10 min) following heat (51°C, 20 min). After cooling, protein denaturation was quantified using a UV spectrophotometer (absorbance 237 nm). Diclofenac sodium was used as reference. Next, emulgel was also evaluated for RBC membrane stabilization (53-55) by preparing mixture containing isotonic saline, Alsever's solution, and human blood (2 mL). Mixture was centrifuged (5 min) to obtain RBC suspension. The suspension was combined with an equal volume of emulgel sample. Mixtures were incubated (37°C, 30 min), mixtures were centrifuged (5 min), and supernatant was collected for analysis. Alsever's solution and blood were used as negative controls, whereas aspirin served as reference. Membrane stabilization was assessed by evaluating supernatant via UV spectroscopy (360 nm).

2.6. Stability study

Stability of kaempferol emulgel was examined under room and accelerated temperature conditions for 3 months. At predetermined intervals, formulation was evaluated in triplicate for key physicochemical parameters, including pH, viscosity, and spreadability, to monitor any changes in its stability and performance over time (45, 56, 57).

Table 1: Ingredients composition in the formulation of emulgel

S. No.	Composition	Quantity (%)	Use
1	Kaempferol	0.25	Active pharmaceutical ingredient
2	Carbopol 934	1	Gelling agent
3	Propylene Glycol	23.83	Humectant
4	Ethanol (95%)	23.83	Solvent
5	Methylparaben	0.14	Preservative
6	Propylparaben	0.048	Preservative
7	Sesame Oil	33.38	Emollient
8	Span 20	4.76	Lipophilic surfactant
9	Tween 80	2.38	Hydrophilic surfactant
10	Triethanolamine	q.s.	Neutralizing agent
11	Purified Water	q.s. to 30 g	Vehicle

3. Results

3.1. Kaempferol Evaluation and Emulgel Formulation

Preliminary qualitative tests confirmed the gifted sample as flavonoid. Shinoda test produced pinkish-red coloration, whereas alkaline reagent test yielded yellow color that disappeared upon acidification, consistent with characteristic flavonoid behavior. Kaempferol emulgel was formulated using emulsion-in-gel method as illustrated (Figure 2). Carbopol 934 formed clear and uniform gel upon neutralization with triethanolamine, providing stable gel base. The oil phase was composed of sesame oil and Span 20 and remained stable without any phase separation throughout the process. Incorporation of emulsion into gel resulted in homogeneous semisolid formulation, exhibiting smooth texture and consistent appearance suitable for topical application.

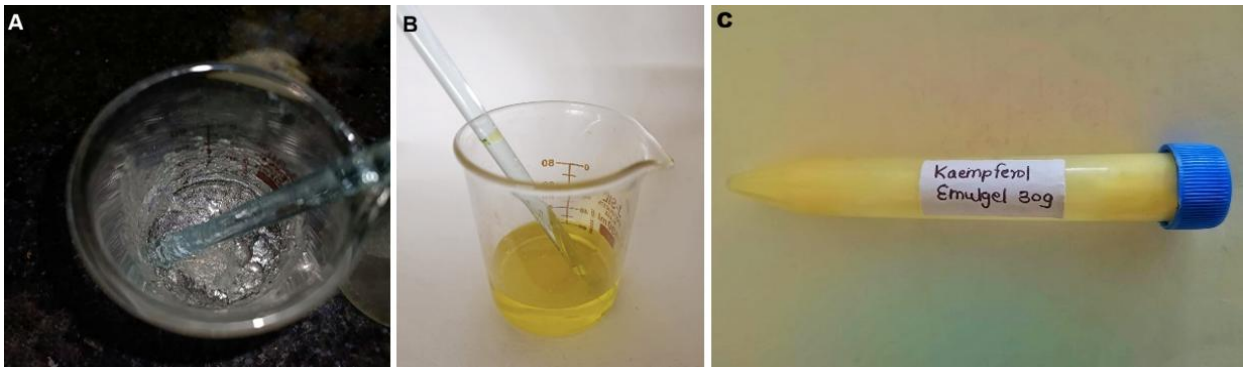

Figure 2: Preparation of kaempferol-loaded emulgel. (A) Gel base formation, (B) Oil phase preparation, and (C) Final optimized emulgel with uniform consistency.

3.2. Characterization of emulgel

Kaempferol emulgel was thoroughly characterized to assess its suitability for topical application. Formulation appeared as pale-yellow, homogeneous semisolid with smooth texture, showing no signs of aggregation or phase separation. It was non-greasy and spread evenly upon application, indicating good patient acceptability. The pH was recorded as 6.40 ± 0.01, which was within physiological skin range, suggesting minimal potential for irritation. Furthermore, rheological evaluation showed viscosity of 2441.6 ± 3.5 cP, reflecting a stable gel network capable of maintaining structural integrity

and ensuring prolonged retention on skin. Spreadability testing yielded a value of 5.22 ± 0.01 g·cm/s, demonstrating that emulgel can be applied easily and uniformly without requiring excessive force. Moreover, formulation was readily washable with water and left no oily residue, highlighting its convenience and favorable user experience. These characteristics indicate that emulgel is physically stable, easy to apply, and appropriate for topical delivery of kaempferol.

3.3. FT-IR analysis of kaempferol-loaded emulgel

FT-IR spectrum of kaempferol-loaded emulgel showed characteristic absorption peaks relating to both kaempferol and Carbopol 934, confirming successful incorporation of kaempferol into gel matrix (Figure 3). A broad band observed between 3400 and 3200 cm^{-1} indicates O–H stretching vibrations, attributable to phenolic hydroxyl groups of kaempferol and hydrogen-bonded hydroxyl groups of Carbopol 934. The peaks at 2926.01 cm^{-1} and 2858.51 cm^{-1} reflect C–H stretching vibrations. A peak at 1741.72 cm^{-1} is ester C=O stretch or carboxylic groups of Carbopol, whereas at 1641.42 cm^{-1} band corresponds aromatic C=C stretching. Peak (near 1458.18 cm^{-1}) is associated with C–H bending vibrations, and strong absorption near 1095.57 cm^{-1} indicates C–O–C stretching vibrations. Additionally, peaks observed in lower region (400–500 cm^{-1}) correspond to skeletal vibrations. Importantly, no significant shifts or disappearance of major characteristic peaks of kaempferol were detected. These observations confirm that kaempferol is physically entrapped in gel matrix and remains compatible with polymeric base.

3.4 Kaempferol content and release

Kaempferol content in emulgel was 98.93 ± 0.29%, demonstrating a high degree of uniformity and confirming consistent distribution of compound throughout the formulation. This indicates that preparation method effectively incorporated kaempferol into gel matrix without significant loss or degradation. In vitro diffusion of kaempferol emulgel had sustained drug release, reaching 91.73% over 24 hours. This release pattern was described by Higuchi model (R^2 = 0.992) indicating drug release primarily occurred through diffusion from gel matrix. Further analysis using Korsmeyer–Peppas model yielded an n value of 0.62, suggesting anomalous (non-Fickian) transport indicating diffusion and polymer matrix contributed to release mechanism. This highlights emulgel maintaining therapeutic concentration at application site over an extended period to improve efficacy and reduce application frequency. Complete in vitro drug release profile is summarized (Table 2), providing a clear representation of formulation controlled-release characteristics.

3.5. Protein Denaturation and Membrane stability

Kaempferol emulgel had concentration-dependent effect progressively increasing from 56.94% to 86.25% against protein denaturation. This suggests that higher concentrations of formulation are more effective at stabilizing proteins against denaturation, which is a key mechanism underlying anti-inflammatory activity. The results indicate that emulgel can protect cellular proteins from stress-induced structural changes, thereby reducing inflammatory responses. Complete data obtained from protein denaturation assay are summarized (Figure 4), illustrating formulation potential as a topical anti-inflammatory agent. Next, kaempferol emulgel exhibited significant membrane-stabilizing activity in RBC, with highest stabilization at 125 µg/mL. Interestingly, slight decrease in membrane stabilization was noted at higher concentrations, suggesting optimal protective effect occurs. These findings indicate that formulation can effectively protect erythrocyte membranes against lysis, reflecting its potential anti-inflammatory activity. Detailed results of membrane stabilization study are presented (Figure 5).

3.6. Stability Studies

Kaempferol-loaded emulgel formulation showed good physical stability (Table 3) under both room temperature and accelerated storage conditions throughout 90-day study period. During this period, slight variations in measured physicochemical parameters were observed; indicating formulation maintained its integrity over time. The pH of emulgel showed minor decrease from 6.40 ± 0.01 to 6.30 ± 0.01, but it remained in an acceptable range for topical application. Similarly, viscosity exhibited small reduction from 2441.6 ± 3.5 cP to 2304 ± 6 cP, suggesting slight decrease in internal resistance to flow while maintaining semisolid consistency of formulation. In contrast, spreadability of emulgel showed a marginal increase from 5.22 ± 0.01 to 5.40 ± 0.01 g·cm/s, indicating slight improvement in its ability to spread easily over skin surface. These minor changes in pH, viscosity, and spreadability may be attributed to normal physicochemical adjustments that occur during storage and do not necessarily indicate instability. Importantly, no phase separation, creaming, or other signs of physical instability were observed throughout storage period.

These results suggest kaempferol-loaded emulgel formulation maintained satisfactory stability and suitable physicochemical characteristics during 90-day stability study.

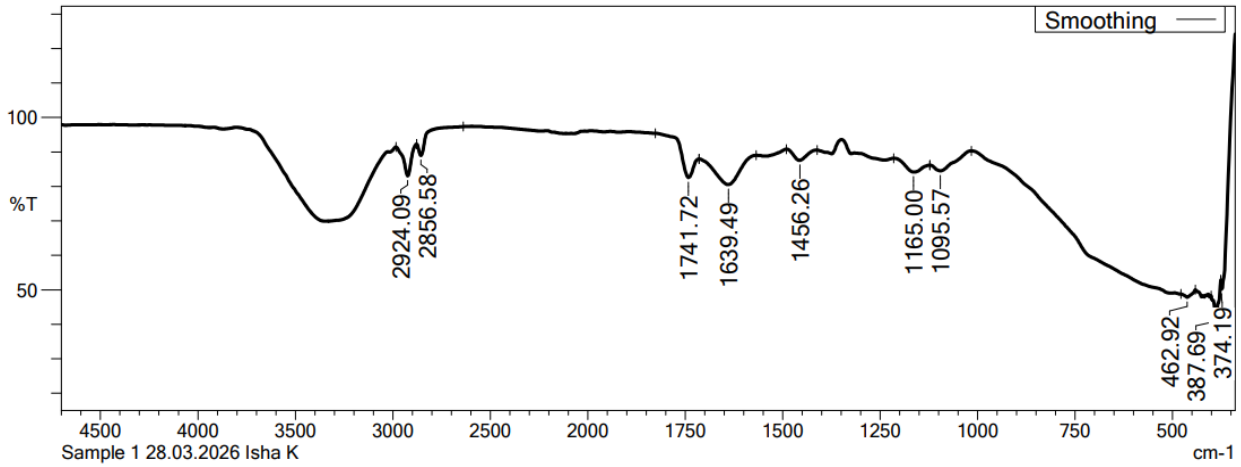

Figure 3: FT-IR spectrum of kaempferol-loaded emulgel.

Table 2: Kaempferol release profile from emulgel

Time (hr)	Absorbance	Conc. (µg/mL)	Conc./10 (mg)	DR (mg)	CLA (mg)	CDR (mg)	% CDR
0	0	0	0	0	0	0	0
1	0.17	8.53	0.085	0.085	0	0.085	8.53
2	0.298	14.96	0.15	0.15	0.009	0.159	15.9
4	0.488	24.52	0.245	0.245	0.024	0.269	26.9
6	0.655	32.95	0.329	0.329	0.051	0.38	38
8	0.823	41.38	0.414	0.414	0.089	0.503	50.3
12	1.11	55.85	0.559	0.559	0.139	0.698	69.8
16	1.327	66.68	0.667	0.667	0.209	0.876	87.6
20	1.495	75.08	0.751	0.751	0.297	1.048	88
24	1.64	82.35	0.824	0.824	0.402	1.226	91.73

DR: Drug release at each sampling interval, CLA: Correction for loss of drug due to sampling, CDR: Cumulative drug release, % CDR: Percentage cumulative drug released

4. Discussion

Present study successfully demonstrates the development of kaempferol-loaded emulgel with desirable physicochemical and functional characteristics, making it a promising system for topical drug delivery. Formulation incorporated kaempferol into stable semisolid dosage form combining emulsion and gel properties, improving dispersion, and skin application. Emulgels are widely recognized to improve poor water-soluble drugs delivery (27, 58, 59), and successful preparation of kaempferol-loaded emulgel in this study highlights its potential as an effective topical formulation. Confirmations of flavonoid presence through phytochemical tests validate identity and integrity of kaempferol used in the formulation. This confirmation is important because pharmacological activities of kaempferol, including its antioxidant, anti-inflammatory, and therapeutic effects, are closely associated with its flavonoid structure (17, 60, 61). Ensuring the presence of these characteristic compounds supports the reliability of formulation and indicates that active ingredient retained its essential chemical properties during preparation process. Furthermore, successful formation of stable emulgel system suggests good compatibility between selected formulation components. The use of Carbopol 934 as gelling agent provided an appropriate gel structure and viscosity, contributing to overall stability and consistency of formulation (62-64). In addition, surfactant system consisting of Span 20 and Tween 80 played a crucial role in stabilizing emulsion phase by reducing interfacial tension and promoting uniform dispersion of oil and aqueous phases (65-67). Combined effect of these

excipients facilitated the formation of homogeneous and stable emulgel with suitable characteristics for topical application, indicating that selected formulation strategy was effective for kaempferol delivery.

Physicochemical parameters of formulation were within acceptable limits. The 6.4 pH of formulation falls in the physiological range of skin, which helps minimize irritation risk and supports better patient compliance during use (68, 69). Maintaining a pH close to that of the skin is an important factor in topical formulations, as it contributes to both safety and comfort upon application (68, 70). The emulgel viscosity indicates well-structured gel network to maintain formulation stability. An appropriate viscosity also ensures that the product remains on skin surface for a longer duration, thereby promoting prolonged contact with application site and potentially enhancing therapeutic effectiveness (71, 72). Additionally, observed spreadability demonstrates balanced rheological property, allowing formulation to be easily applied and uniformly distributed over skin without compromising its structural integrity. Furthermore, non-greasy nature of emulgel contributes to more pleasant sensory experience during application, which is highly desirable for topical products (28, 58, 73). The formulation also exhibited good washability, indicating that it can be easily removed from skin when required. These characteristics improve user acceptability and convenience, which are important considerations in the development of effective and patient-friendly topical drug delivery systems.

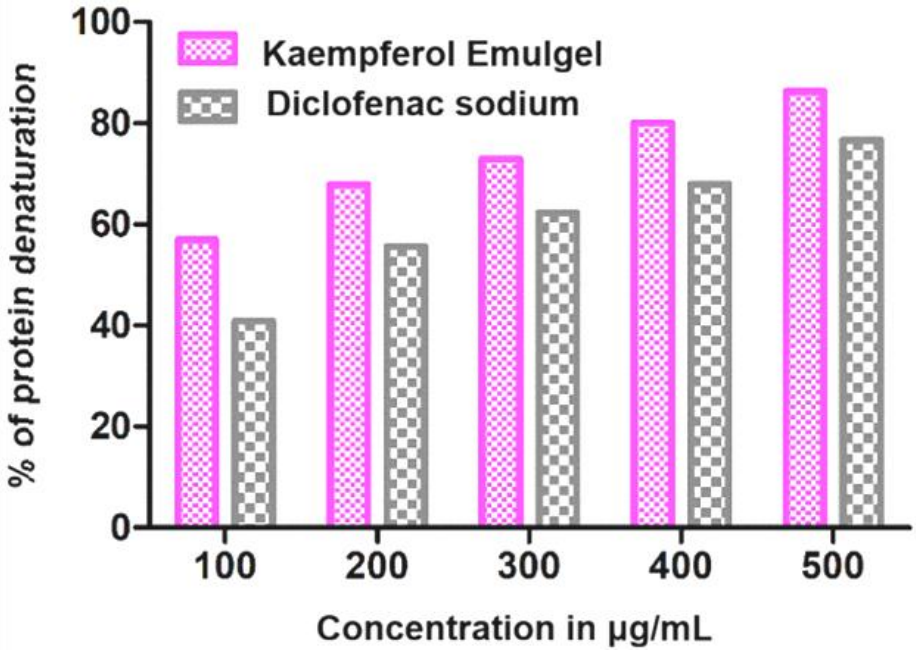

Figure 4: Kaempferol-loaded emulgel effect in protein denaturation assay.

FT-IR spectrum of kaempferol-loaded emulgel retained all the characteristic peaks corresponding to both kaempferol and Carbopol 934, with no significant peak shifts or formation of new peaks observed. This indicates excellent kaempferol and excipients physicochemical compatibility. Preservation of characteristic absorption bands suggests that fundamental chemical structures of both kaempferol and Carbopol 934 remained unchanged during formulation process. A slight broadening of O–H stretch absorption band can be explained for hydrogen bond interactions in formulation. Such interactions are common in gel-based systems and may contribute to strengthening gel network structure, improving the overall stability of emulgel (74, 75). Importantly, absence of major spectral changes indicates that no chemical interaction between kaempferol and polymer matrix. This confirms kaempferol physically entrapment in carbopol-based gel network. This physical entrapment maintains structural integrity of active compound with uniform distribution in formulation. The FT-IR results also support compatibility of the formulation components and indicate that the developed emulgel system is stable and suitable for topical drug delivery.

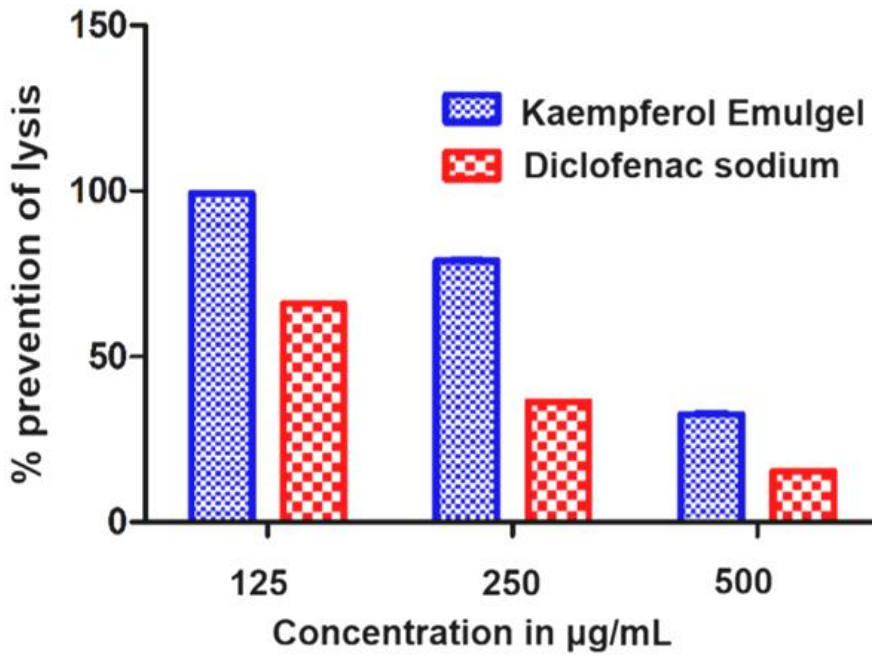

Figure 5: Assessment of kaempferol emulgel in RBC membrane stabilization.

Table 3: Physicochemical Stability of kaempferol emulgel

Parameters	Day	pH	Viscosity (cP)	Spreadability (g·cm/s)
Room temperature	Initial	6.40 ± 0.01	2441.6 ± 3.5	5.22 ± 0.01
(25 °C ± 2 °C /RH 60 ± 5%)	30th	6.40 ± 0.01	2441.6 ± 3.5	5.22 ± 0.01
	60th	6.39 ± 0.01	2429 ± 3.6	5.25 ± 0.01
	90th	6.37 ± 0.01	2409 ± 3.6	5.28 ± 0.01
Accelerated temperature	Initial	6.36 ± 0.01	2385 ± 5	5.31 ± 0.01
(40°C ± 2°C /RH 75 ± 5%)	30th	6.36 ± 0.01	2385 ± 5	5.31 ± 0.01
	60th	6.33 ± 0.01	2346.6 ± 4	5.36 ± 0.01
	90th	6.30 ± 0.01	2304 ± 6	5.40 ± 0.01

There was sustained kaempferol release (24 h) through carbopol matrix. Strong correlation with Higuchi model indicates diffusion-controlled release (76-78). Furthermore, Korsmeyer–Peppas model indicated non-Fickian transport, suggesting that drug release is governed by a combination of diffusion and polymer relaxation mechanisms (79-81). Similar release behavior has been reported in other flavonoid-based emulgel systems, supporting suitability of this delivery approach for poorly water-soluble compounds (82-84). The high drug content (98.93%) confirms efficient incorporation and uniform distribution of kaempferol in formulation, with minimal drug loss during preparation, reflecting the effectiveness of formulation strategy in achieving homogeneity.

Anti-inflammatory activity observed in both protein denaturation and RBC membrane stabilization assays highlights the therapeutic potential of developed emulgel (85). Concentration-dependent inhibition of protein denaturation suggests that kaempferol can prevent structural alterations in proteins during inflammatory conditions. Similarly, membrane stabilization indicates protection of lysosomal membranes, which may reduce release of inflammatory mediators. Stability study indicated that formulation maintained its physicochemical integrity under both room temperature and accelerated storage conditions over a period of 90 days. Throughout the study period, only minor variations in key parameters such as pH, viscosity, and spreadability were observed without affecting quality. Importantly, no phase separation, creaming, or other signs of physical instability were detected during evaluation period. Formulation also retained its homogeneous appearance and consistency, indicating the emulgel structure remained stable under tested conditions. These results suggest that the developed formulation possesses adequate physical stability and can maintain its essential characteristics during storage (86-88). These support

formulation suitability in topical application indicating its potential to maintain stability over an extended period.

This study demonstrates that developed emulgel system enhances topical delivery of kaempferol, addressing its inherent limitations of poor solubility and low bioavailability. The formulation combines sustained drug release, notable anti-inflammatory activity, and robust physicochemical stability, highlighting its potential as an efficient platform in the management of localized inflammatory conditions.

5. Conclusion

Here, we developed kaempferol emulgel with desirable physicochemical properties e.g., skin-compatible pH, optimal viscosity, good spreadability, non-greasy texture, and excellent washability. FT-IR analysis confirmed the preservation of characteristic functional groups of kaempferol and Carbopol 934, indicating good compatibility and physical incorporation without chemical interaction. The formulation exhibited sustained and controlled drug release over 24 hours, with kinetics suggesting diffusion-controlled anomalous transport, while uniform drug content reflected efficient incorporation. Membrane stabilizing and stability studies confirmed formulation robustness. Thus, kaempferol-loaded emulgel represents stable topical system to manage localized inflammatory conditions, and further studies are warranted.

Author contribution

SAV; Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project Administration, VGK; Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation, ASK; Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation, SSK; Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation, IVK; Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation, PPK; Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation.

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Declaration of interest

None.

Ethical statement for human or animal-derived data

Not applicable

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