Development and Characterization of Topical Medicated Micro emulsions for Enhanced Drug Delivery

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Abstract

Backgrounds: A transparent, thermodynamically stable dispersion of two immiscible liquids with one or more precisely regulated emulsifiers is called a microemulsion. It can carry a wide variety of medications and dosage formats.

Methods: A pseudo ternary phase diagram was created using formulas comprising paraffin oil, cosurfactant (sorbitol or glycerol), surfactant (Brij97), and water in order to create a microemulsion for topical application using inexpensive ingredients. It was shown that microemulsion areas existed. The best formulas for creating gel-based microemulsions were modified to include indomethacin, and their physical characteristics, release rate, chemical and physical stability, and pharmacodynamic properties were assessed.

Results: In gel form, 55 formulas yield stable microemulsions. Only four stable, distinct formulae remain once indomethacin is added. They were employed for additional research. They had a first-order medication release rate. Both under stress and at room temperature, all four formulas remained stable. They have a minimum shelf life of 492 days and a maximum shelf life of 712 days. By varying percentages, indomethacin considerably reduces edoema that is caused in rat paws. The produced microemulsions had an impact that was in between the highest and lowest of commercial injectable and topical forms.

Conclusions: The microemulsion formulations made with water, sorbitol, brij97, paraffin oil, or glycerol demonstrated satisfactory pharmacodynamic effects, stability, and drug release.

Keywords:microemulsion; indomethacin; Paraffin oil; cosurfactantwater; surfactant;

Introduction:

Indomethacin is a well-established drug known for its potent anti-inflammatory, analgesic, and antipyretic properties. It has demonstrated efficacy in managing various inflammatory and painful conditions, including moderate to severe rheumatoid arthritis, osteoarthritis, acute painful shoulder, and acute gouty arthritis. Indomethacin works by inhibiting the synthesis of prostaglandins, thus alleviating inflammation, pain, and fever in affected patients. However, its oral administration is often associated with gastrointestinal side effects, which has led to exploration of alternative delivery systems to enhance its efficacy and safety profile(1-5).

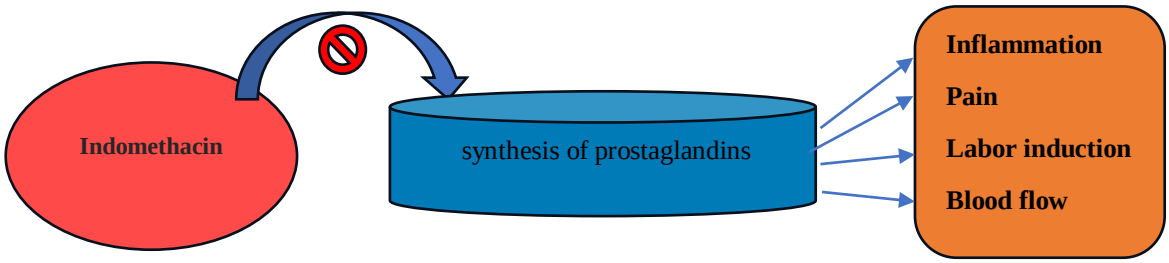


Fig:1Indomethacin block the production of prostaglandin

One promising delivery system is microemulsion, a clear and thermodynamically stable dispersion composed of two immiscible liquids. Microemulsions are unique as they allow for the preparation of homogeneous, isotropic mixtures that exhibit infinite stability. These systems typically consist of four primary components: a surfactant, a cosurfactant, an oil phase, and an aqueous phase(2-8)The optimization and formation of a stable microemulsion depend on these components' interactions, and adjusting their concentrations is essential for achieving a transparent and stable formulation. Importantly, only specific combinations of these components can create a truly stable microemulsion system (8-12).

Microemulsions have been utilized across various pharmaceutical applications due to their unique properties, particularly as vehicles that can enhance the absorption and bioavailability of active drugs (4). They have been explored as carriers for several drug forms and have even been used as mobile phases in High-performance Liquid Chromatography (HPLC), enhancing the resolution of analytes. Developing a microemulsion for therapeutic purposes involves several crucial steps. After selecting appropriate components (typically oil, surfactant, cosurfactant, and an aqueous medium) and conducting preliminary screenings, researchers create phase diagrams(5-8).These phase diagrams help in identifying different

zones, such as the microemulsion phase and the coarse emulsion phase, which can be identified through physical methods in the absence of the drug. Typically, three-dimensional phase diagrams are constructed, with the fourth component's concentration kept constant or with a fixed ratio between two of the components. Once the microemulsion domain is defined, the next critical step is to evaluate the system in the presence of the drug. The inclusion of a drug in the microemulsion system can alter the proportions and stability of the formulation, impacting the physical and chemical properties. Therefore, it is essential to redefine the composition to ensure a stable, drug loaded microemulsion system (12-15).

The aim of the present investigation was to develop a stable microemulsion formulation using cost-effective components suitable for topical application. This formulation seeks to incorporate Indomethacin with a non-volatile carrier, aiming to enhance its physical and chemical stability (15-19). The objective is not only to improve the pharmacodynamic profile of Indomethacin but also to reduce potential side effects associated with oral administration. Formulating a topical microemulsion for Indomethacin could provide a viable alternative, ensuring effective local delivery, improved stability, and enhanced therapeutic outcomes, ultimately contributing to the development of safer and more effective treatments for inflammatory and pain relatedconditions (19-26)

Materials and methods

Materials

Brij 97, glycerine, sorbitol 70% and liquid paraffin (received from college).

Indomethacin base (received from college).

Screening of Oils and Surfactant for Microemulsion

To identify oils and surfactants with optimal solubilizing capacity for indomethacin, a systematic solubility study was conducted with various oil and surfactant candidates. The solubility assessment involved adding an excess amount of indomethacin to each oil and surfactant solution to ensure saturation. Each solution was then subjected to continuous stirring at 30°C for a period of 72 hours, a duration chosen to allow sufficient time for the indomethacin molecules to dissolve and reach equilibrium within the different media. This temperature and time frame were selected based on preliminary studies, as they provide reliable conditions for assessing solubility without degrading the drug or the formulation components. Following the stirring period, the solutions were centrifuged at 2500 rpm for 30

minutes to separate undissolved particles from the dissolved drug. Centrifugation under these conditions ensures the removal of any residual, undissolved indomethacin, which could otherwise lead to inaccurate solubility measurements. The supernatant from each centrifuged mixture was then filtered through a 0.45 µm membrane filter to remove any particulate matter. The filtration process is critical, as even trace amounts of undissolved particles can interfere with subsequent quantitative analysis. After filtration, the drug concentration in each supernatant was determined by high-performance liquid chromatography (HPLC). HPLC was selected due to its high accuracy and sensitivity in detecting indomethacin concentrations at low levels, as well as its reliability in providing reproducible results across multiple samples. Each sample was appropriately diluted with methanol prior to injection into the HPLC system to ensure the concentration fell within the linear range of detection for indomethacin. Calibration curves for indomethacin were established with standard solutions prepared in methanol to accurately determine drug concentration in each test solution.

This solubility study was performed across all selected oils and surfactants to determine which components provided the highest solubilizing capacity for indomethacin. The findings from this study would guide the choice of oil and surfactant in formulating a stable and efficient microemulsion system, optimizing drug delivery and stability. Such systematic assessment is essential for identifying the most effective combination of components to enhance the solubility and, consequently, the bioavailability of indomethacin in the intended microemulsion formulation.

Formulation

To identify oils and surfactants with high solubilizing capacity for indomethacin, a comprehensive solubility study was conducted across various oils and surfactant candidates. An excess of indomethacin was added to each oil and surfactant solution, followed by continuous stirring at 30°C for 72 hours to allow equilibrium. The temperature and duration were selected to ensure adequate dissolution time without compromising drug or component stability. After the stirring period, each solution underwent centrifugation at 2500 rpm for 30 minutes to separate undissolved drug particles, ensuring accurate solubility measurements. The supernatant was subsequently filtered through a 0.45 µm membrane filter to remove any residual particulate matter. Filtration through a 0.45 µm membrane ensures removal of all undissolved particles, which could otherwise lead to erroneous solubility measurements. Drug concentration in the filtrate was quantified by high-performance liquid chromatography

(HPLC) after appropriate dilution with methanol. HPLC was chosen due to its high sensitivity and specificity in quantifying indomethacin. Calibration curves were prepared with indomethacin standards in methanol to validate quantitative accuracy across a linear concentration range. Each test solution was analyzed in triplicate to ensure reliability and reproducibility of the solubility data.

This solubility study was conducted systematically across all selected oils and surfactants to determine the components providing the highest solubilizing capacity for indomethacin. The results from this study were intended to guide the selection of oil and surfactant for the formulation of a stable microemulsion system, optimizing indomethacin's solubility and bioavailability. Such a systematic evaluation is crucial to identify the most effective component combinations to achieve an efficient and stable microemulsion suitable for therapeutic use.

A. Physical Characterization of Gel like Microemulsions (IGMs)

The freshly prepared indomethacin loadedgel like microemulsions (IGMs) were evaluated for the following physical properties:

Phase Separation: Observed for any signs of separation to assess formulation stability.

Clarity: Examined for transparency or turbidity as an indicator of homogeneity and quality.

Gel Formation: Assessed to confirm proper gel structure and consistency suitable for topical application.

B. Determination of Indomethacin Release Rate from IGMs

The release rate of indomethacin from various gel like microemulsion formulations was evaluated using a USP dissolution apparatus. The testing procedure was as follows:

The dissolution medium consisted of 900 mL of a pH 5.5 buffer, maintained at 37 ± 0.5°C, with the paddle rotating at 50 rpm.Approximately 20 g of the selected gel like microemulsion was placed in a cup with a fixed surface area, covered with a cellulose membrane to simulate release conditions.

The cup was then immersed in the dissolution medium and weighted with a 10 g mass to ensure it remained at the bottom of the vessel. Aliquots were withdrawn at 10minute intervals over a period of 2 hours to monitor drug release. Each aliquot was diluted with an equal

volume of methanol and analyzed spectrophotometrically at 318.5 nm to quantify indomethacin concentration.

The release kinetics of indomethacin from the IGMs were evaluated to determine the order of release (zero order, first order, or diffusion controlled). Data were statistically analyzed using the least squares method to characterize the release mechanism of indomethacin from the microemulsion system.

C. Stability Assessment of Selected IGMs

The stability of selected IGMs was assessed under both shelflife and accelerated conditions to evaluate their chemical and physical stability over time.

Shelf-Life Stability:

IGMs were stored at room temperature in glass containers.

Periodic evaluations were conducted to assess chemical stability (drug content) and physical stability, including the following tests

I. Appearance and Clarity: Checked to detect any changes in visual appearance or clarity that might indicate instability.

II. Phase Separation and Centrifugation Test: Samples were centrifuged at 20,000 rpm for 30 minutes at 25°C to evaluate potential phase separation or instability.

III. pH Measurement: Periodic pH testing was conducted to monitor changes that could affect drug stability or formulation integrity.

IV. Viscosity Measurement: Viscosity was measured to confirm that the gel structure and rheological properties remained stable under storage conditions.

Results: Pharmacodynamic Evaluation of Indomethacin-Loaded Microemulsions

The pharmacodynamic effect of indomethacin in different microemulsion formulations was evaluated by assessing their efficacy in reducing carrageenan-induced edema in the rat paw, a standard model for testing anti-inflammatory activity. Carrageenan-induced paw edema in rats was selected for this study based on the established method described. Male albino rats (160–220 g) were utilized, and to minimize variations in the edema response, the animals were fasted overnight and then uniformly hydrated with 3 mL of water via gastric intubation prior to treatment.

The animals were randomly divided into seven groups, with each group consisting of six rats. The control group received a saline solution containing a small amount of Tween 80. Indomethacin was administered parenterally at a dose of 5 mg/kg to one group as a reference for the injection formulation of indomethacin (commercial product), given 1 hour prior to inflammation induction. Inflammation was induced in the right hind paw of each rat by subcutaneous injection of 0.5 mL of 1% carrageenan solution into the plantar tissue, followed by topical application of the test formulations. Topical formulations, including the indomethacin-loaded microemulsions (IGMs), a commercial injection form, and a commercial topical indomethacin form, were applied to the inflamed paw every hour to ensure sustained contact of the formulation with the affected area. The anti-inflammatory effect was measured by calculating the weight difference between the inflamed right hind paw and the non-inflamed left hind paw. The mean weight increase in the carrageenan-treated paw of each animal group was recorded, with (W_t) representing the mean increase for the treated groups and (W_c) for the control group.

The percentage inhibition of edema was calculated for each group using the following formula:

$$\textbf{\% Inhibition in Edema Weight}=\left(\mathbf{Wc - Wt}/_{\mathbf{Wc}}\right)\times\mathbf{100}$$

This test was conducted on:

1. Indomethacin-loaded gel-like microemulsions (IGMs),

2. Commercial injection form of indomethacin,

3. Commercial topical form of indomethacin.

Results and Discussion

The development of a microemulsion system for the topical delivery of indomethacin presented unique challenges due to the limited availability of pharmaceutically acceptable components that are both effective and compatible with skin application. Initial solubility studies revealed that indomethacin exhibited the highest solubility in paraffin oil, followed by isopropyl myristate, castor oil, soybean oil, and olive oil. Among the surfactants tested, Brij 97 showed superior solubilizing capacity compared to Tween series surfactants (Tween 20, 40, 60, and 80). Brij 97 was chosen not only for its ability to solubilize indomethacin

effectively but also for its stability across a range of pH and ionic conditions, making it an ideal candidate for consistent formulation properties.

Paraffin oil was selected as the primary oil phase in subsequent experiments, both for its superior solubilizing properties and its economic feasibility. During the preparation of the microemulsions at varying component ratios, it was observed that microemulsions with a surfactant-to-cosurfactant ratio of 9:1 was easier to formulate and displayed better stability, while formulations at a 3:1 ratio were more challenging and less stable.

The formation of stable microemulsions was closely related to the surfactant concentration; higher surfactant concentrations were necessary to stabilize the microemulsion, while an increase in oil content reduced the microemulsion region. Notably, as the paraffin oil content increased, the microemulsion region shifted towards the surfactant apex, indicating a higher requirement for surfactant molecules to stabilize the expanded hydrophobic core created by the oil phase.

The physical state of the microemulsion system also varied with water content. At certain water concentrations, the microemulsions exhibited gel-like consistency; however, as water content increased beyond a threshold, the system reverted to a fluid consistency. This transition varied depending on both the surfactant-to-cosurfactant ratio and the surfactant: cosurfactant: oil ratios, underscoring the importance of careful balance among components.

Preliminary tests confirmed that both the oil content and the surfactant-to-cosurfactant ratio were critical factors in microemulsion formation. The effect of these ratios is likely due to the different roles of surfactants and cosurfactants in stabilizing the interfacial film. Higher surfactant concentrations tend to condense the interfacial film, thereby lowering interfacial tension, while increased cosurfactant levels can increase system polarity, subsequently reducing the system's capacity to incorporate oil.

From the preliminary tests, 55 formulations with varying proportions of surfactant, oil, cosurfactant, and water yielded gel-like microemulsions (IGMs). These formulations were selected for further stability and consistency evaluations. The inclusion of indomethacin in these IGMs, followed by storage, significantly affected their consistency, aligning with observations in previously published research.

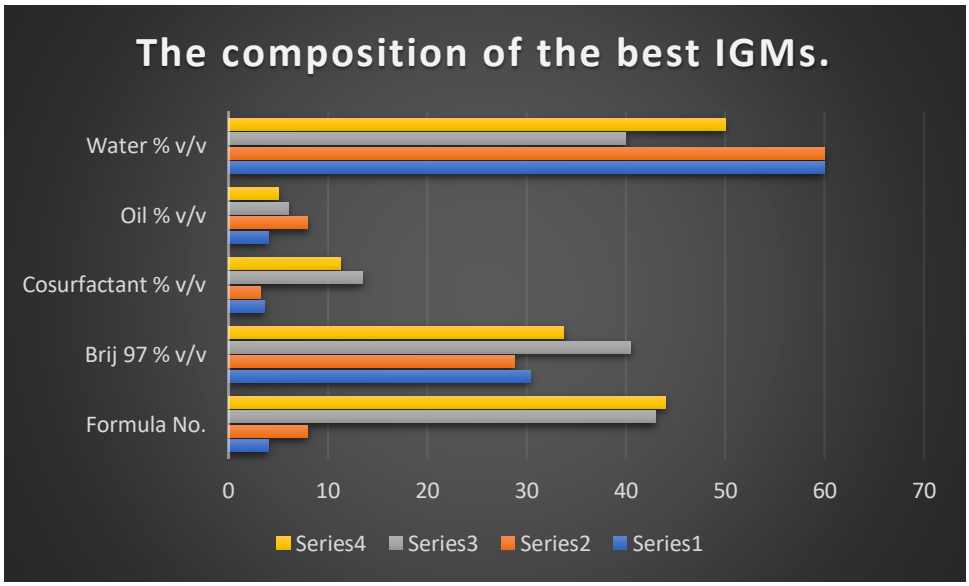
Upon incorporation of indomethacin, phase separation occurred in all but 11 of the IGMs, indicating that the presence of the drug influenced microemulsion stability. Further, after one

month of storage at room temperature, only 4 of these 11 formulations remained stable, clear, and gel-like. These stable formulations are detailed in Table 1 and represent promising candidates for further development as topical indomethacin delivery systems.

Table 1. The composition of the best IGMs.

Cosurfactant in formulae 4 and 8 was sorbitol 70% and in Formulae 43 and 44 was glycerol

Formula No.	Brij 97 % v/v	Cosurfactant % v/v	Oil % v/v	Water % v/v
4	30.3	3.5	4	60
8	29.2	3.1	8	60
43	40.7	13.8	6	40
44	34.15	11.28	5	50



Results and Discussion

The four selected indomethacin-loaded gel-like microemulsion (IGM) formulations were further evaluated for release rate, stability, and pharmacodynamic activity. The release rates of indomethacin from these IGMs, as presented in Figure 1, demonstrate that all four formulations exhibited first-order release kinetics. Among the tested formulations, formula 8 exhibited the highest release rate, followed by formula 4, formula 43, and finally formula 44.

This difference in release rates may be attributed to the presence of glycerol in formulas 43 and 44, which potentially slowed release more effectively than sorbitol in formulas 8 and 4.

Stability testing indicated that all IGMs maintained physical stability after one year of storage at room temperature, as well as under accelerated conditions of 40°C, 50°C, and 60°C for three months. A minor pH increase was noted, particularly in samples stored at 60°C, though these changes remained within acceptable limits. Viscosity measurements revealed that the IGMs exhibited plastic flow with thixotropic properties both when freshly prepared and after stability testing. Formula 8 displayed the highest viscosity, while formula 4 had the lowest, with the viscosity ranking as follows:

Formula 8 > Formula 44 > Formula 43 > Formula 4

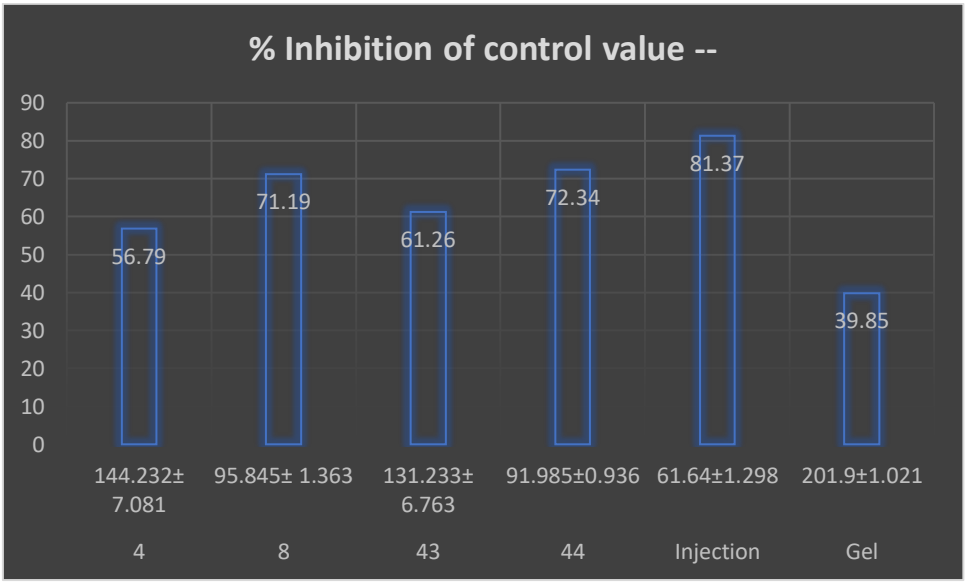
The degradation kinetics of indomethacin in the IGMs followed first-order kinetics, with degradation rate constants (K values) calculated at various temperatures to estimate the K20 value for accelerated stability assessment. Comparison of the K20 values obtained from both accelerated and shelf-life stability tests revealed no significant differences. Estimated shelf lives ranged from 492 days (1.349 years, formula 4) to 712 days (1.952 years, formula 8), with formulas 43 and 44 having shelf lives of 642 days (1.759 years) and 568 days (1.556 years), respectively, indicating satisfactory stability across all formulations, with formula 8 showing the best stability profile.The rheological properties of the IGMs after stability testing showed only minor increases in viscosity and shear stress, likely due to slight evaporation of the aqueous phase, which remained within acceptable ranges. In pharmacodynamic studies, indomethacin in the tested IGMs significantly inhibited carrageenan-induced paw edema, with varying levels of inhibition across formulations, as summarized in Table 2.

These findings collectively suggest that the selected IGMs offer a stable and effective delivery system for indomethacin, with formula 8 emerging as the most promising candidate for further development based on its optimal release profile, stability, and pharmacodynamic efficacy.

Table 2. Anti-inflammatory activity of different formulation of Indomethacin using carrageenan-induced paw oedema in rats.

Formulation	Mean oedema weight in mg (M ± SD)	% Inhibition of control value

Control	334.133 ± 7.178	--
4	144.232± 7.081	56.79
8	95.845± 1.363	71.19
43	131.233± 6.763	61.26
44	91.985±0.936	72.34
Injection	61.64±1.298	81.37
Gel	201.9±1.021	39.85



The pharmacodynamic effects observed for formulae 4 and 43 were less pronounced than those of formulae 8 and 44, potentially due to the influence of higher viscosity in formulas 8 and 44, which may have enhanced the drug's retention and release at the application site. Notably, the efficacy of the indomethacin-loaded IGMs was positioned between that of the commercial injection form (which showed the highest anti-inflammatory effect) and the commercial topical gel form (which demonstrated the lowest effect).

These findings indicate that the microemulsion formulation of indomethacin significantly improved drug absorption compared to conventional topical gel forms, aligning with previous studies that advocate for microemulsions as effective drug delivery systems. The enhanced absorption achieved through the microemulsion system supports its potential as a promising vehicle for indomethacin, potentially offering sustained therapeutic effects and improved bioavailability in topical applications.

Conclusion

Based on the comprehensive evaluation of the gel-like microemulsion formulations, we can confidently conclude that the formulations prepared with paraffin oil, Brij 97, sorbitol or glycerol, and water exhibited satisfactory physical properties, consistent drug release, stability, and favorable pharmacodynamic effects. These characteristics indicate that the microemulsion system is suitable for the effective topical delivery of indomethacin. Among the tested formulations, formula 8 emerged as the most promising candidate. This formula consisted of 29.2% v/v Brij 97, 3.1% v/v sorbitol 70%, 8% v/v paraffin oil, and 60% v/v water. The combination of these components resulted in the formulation with the highest stability, optimal drug release rate, and viscosity, which is crucial for ensuring prolonged contact of the drug with the inflamed area. The viscosity measurements were particularly significant, as they indicated the ideal consistency for a gel-like system, which is essential for maintaining the formulation's effectiveness during topical application.

Additionally, formula 8 demonstrated superior anti-inflammatory activity compared to the other formulations tested. Its ability to significantly inhibit carrageenan-induced paw edema supports its potential as an effective therapeutic option for managing inflammation. The enhanced anti-inflammatory effect can be attributed to the microemulsion's ability to improve drug solubility and facilitate better absorption of indomethacin, which is consistent with findings from previous studies on microemulsion systems used for topical drug delivery.In summary, formula 8 not only exhibited excellent physicochemical properties and stability but also demonstrated the best pharmacodynamic performance among the tested formulations. This makes it the most suitable candidate for the formulation of an indomethacin gel-like microemulsion, with the potential for improved therapeutic efficacy and enhanced patient compliance in the management of inflammatory conditions.

Conflict of Interest: None

Financial support: None

Ethical statement: None

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