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FORMULATION AND EVALUATION OF MULTIPLE EMULSION SYSTEM CONTAINING ECONAZOLE

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Abstract:

The present study aimed to formulate and evaluate a water-in-oil-in-water (W/O/W) multiple emulsion containing Econazole nitrate for sustained topical antifungal drug delivery. Multiple emulsion systems were developed using a two-step emulsification technique with suitable surfactants, polymers, and oil-phase components to enhance drug entrapment, stability, and controlled release. Six formulations (F1–F6) were prepared and evaluated for appearance, pH, viscosity, globule size, drug content, entrapment efficiency, spreadability, extrudability, and in vitro drug release. All formulations exhibited satisfactory physicochemical properties and good emulsion stability. Increasing polymer concentration improved viscosity, entrapment efficiency, and sustained drug release while reducing globule size. Among the formulations, F6 demonstrated the highest drug entrapment (89.1%), drug content (99.2%), excellent stability, and prolonged drug release over 12 hours following Korsmeyer–Peppas kinetics. The optimized multiple emulsion system offers a promising approach for improving topical antifungal therapy by enhancing drug retention, reducing application frequency, and improving patient compliance.

Keywords: *Econazole nitrate, Multiple emulsion, Water-in-oil-in-water (W/O/W), Topical drug delivery, Sustained drug release, Antifungal therapy, Entrapment efficiency, Controlled release, Emulsion stability, Topical formulation.*

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1. INTRODUCTION:

The development of advanced drug delivery systems has significantly improved the effectiveness of pharmaceutical formulations by enhancing drug stability, therapeutic performance, and patient compliance. Among these systems, emulsions have gained considerable attention because they can successfully incorporate both water-soluble and oil-soluble drugs into a single formulation.[1] An emulsion is a dispersion of two immiscible liquids, generally oil and water, stabilized with suitable surfactants to maintain uniformity and prevent phase separation. Owing to their adaptability, emulsions are widely employed in oral, topical, and parenteral drug delivery systems.[2]

Multiple Emulsion Systems

Multiple emulsions represent an advanced form of conventional emulsions and are commonly described as "emulsions within emulsions." The most frequently used system is the water-in-oil-in-water (W/O/W) emulsion, where internal aqueous droplets are enclosed within an oil phase that is further dispersed in an external aqueous medium. This unique structure provides separate compartments capable of carrying both hydrophilic and lipophilic therapeutic agents. In addition to improving drug protection, multiple emulsions offer sustained drug release by controlling the movement of the drug through successive liquid layers.[3]

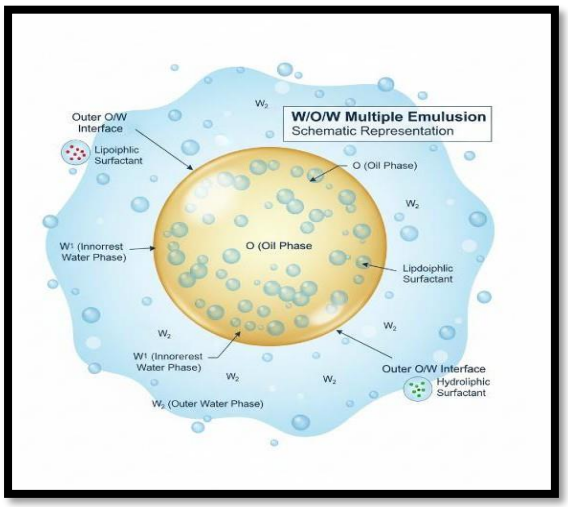

Figure 1: Schematic Representation of a W/O/W Multiple Emulsion

Controlled Drug Release and Topical Delivery

The multilayer structure of multiple emulsions acts as a diffusion barrier, allowing gradual release of the incorporated drug over an extended period. Such controlled release minimizes frequent drug application, maintains therapeutic concentration at the target site, and enhances treatment outcomes. For topical preparations, this approach also improves skin hydration and promotes better penetration of the active ingredient through the stratum corneum.[4]

Role of Econazole in Multiple Emulsions

Econazole is a broad-spectrum imidazole antifungal agent widely used in the treatment of fungal skin infections caused by dermatophytes, yeasts, and related microorganisms. Although conventional creams are clinically effective, their therapeutic action is often limited by poor skin penetration and short residence time, requiring repeated application. Incorporating Econazole into a W/O/W multiple emulsion can overcome these limitations by protecting the drug, prolonging its release, and maintaining effective concentrations at the site of infection.[5] Consequently, multiple emulsion technology offers a promising strategy for developing a stable, sustained-release topical formulation with improved antifungal efficacy and enhanced patient compliance.[6]

Materials

All chemicals and reagents used in the present investigation were of pharmaceutical or analytical grade to ensure formulation quality, reproducibility, and experimental reliability. Econazole nitrate served as the active pharmaceutical ingredient (API), while a combination of hydrophilic and lipophilic surfactants was employed to develop a stable water-in-oil-in-water (W/O/W) multiple emulsion system. The excipients were selected based on their compatibility with the drug, emulsifying ability, viscosity-modifying properties, and suitability for sustained topical drug delivery. Pharmaceutical-grade oils, polymers, co-solvents, and humectants were incorporated to obtain an emulsion with desirable physicochemical characteristics and prolonged drug release.[7] Distilled water was used for both internal and external aqueous phases, whereas phosphate buffer (pH 7.4) was utilized during in vitro drug release studies. Standard microbiological media were employed for antifungal evaluation.[8] The materials used in the formulation are summarized in Table 1.

Table 1. Materials Used in the Development of Econazole Nitrate Multiple Emulsion[9]

Material	Category	Functional Role
Econazole Nitrate	Active pharmaceutical ingredient	Broad-spectrum antifungal drug
Span 80	Lipophilic surfactant	Stabilization of primary W/O emulsion
Tween 80	Hydrophilic surfactant	Stabilization of secondary O/W emulsion
Liquid Paraffin	Oil phase	Formation of lipid barrier for sustained drug release
Medium Chain Triglycerides	Oil phase modifier	Improves drug solubility and emulsion stability

Glycerin	Humectant	Maintains hydration and droplet stability
Distilled Water	Aqueous phase	Internal and external aqueous medium
Carbopol 934P	Polymeric stabilizer	Increases viscosity and emulsion stability
HPMC K4M	Hydrophilic polymer	Enhances viscosity and sustained release
Propylene Glycol	Co-solvent	Improves drug solubility
Ethanol	Solvent	Drug dissolution and analytical studies
Sabouraud Dextrose Agar	Microbiological medium	Antifungal activity evaluation
Phosphate Buffer (pH 7.4)	Dissolution medium	In vitro drug release studies

Preformulation Studies

Preformulation evaluation plays an important role in the successful development of any pharmaceutical dosage form. These studies provide essential information regarding the physicochemical characteristics of the drug and its compatibility with formulation excipients before product development. In the present investigation, Econazole nitrate was subjected to a series of preformulation studies to evaluate its identity, purity, solubility profile, lipophilicity, analytical characteristics, stability, and compatibility with selected formulation components.[10] The information obtained from these investigations served as the scientific basis for selecting suitable excipients and optimizing the multiple emulsion system.

Organoleptic Characteristics

The physical appearance of Econazole nitrate was examined to verify its identity and quality before formulation. The drug powder was inspected under normal laboratory illumination for colour, texture, and crystalline nature. The sample exhibited a uniform white crystalline appearance with a fine, free-flowing texture and was practically odourless. No visible contamination or foreign particles were detected during visual examination. These observations confirmed the acceptable physical quality of the drug for further pharmaceutical processing.[11]

Melting Point Determination

Melting point analysis was performed as a preliminary indicator of drug purity and identity. Finely powdered Econazole nitrate was filled into a capillary tube and analysed using a digital melting point apparatus. The temperature at which melting initiated and the point of complete liquefaction were recorded. The observed melting range corresponded closely with the reported pharmacopoeial value, indicating that the drug possessed satisfactory purity and had not undergone thermal degradation during storage.[12]

Solubility Studies

Determination of drug solubility is a critical step in designing an emulsion-based drug delivery system because the distribution of the drug between aqueous and oily phases governs encapsulation efficiency and release behaviour. The solubility of Econazole nitrate was evaluated in distilled water, ethanol, methanol, propylene glycol, liquid paraffin, medium-chain triglycerides, Span 80, and Tween 80 using equilibrium solubility techniques.[13]

The investigation demonstrated that Econazole nitrate exhibited negligible solubility in water but showed significantly higher solubility in organic solvents and lipid-based vehicles. Good solubility in ethanol and propylene glycol facilitated drug dissolution during formulation, whereas appreciable affinity toward liquid paraffin and MCT oil supported their selection as the oil phase for the multiple emulsion system. These findings confirmed the lipophilic nature of Econazole nitrate and justified the development of a W/O/W multiple emulsion for sustained topical delivery.[14]

Table 2. Purpose of Major Preformulation Studies

Study	Objective	Significance
Organoleptic evaluation	Verify physical identity	Confirms appearance and purity
Melting point	Assess purity	Detects degradation or impurities
Solubility study	Select suitable vehicle	Optimizes formulation components
λmax determination	Develop analytical method	Drug estimation by UV spectroscopy
Partition coefficient	Determine lipophilicity	Predicts drug distribution
pH stability	Evaluate chemical stability	Selects suitable formulation pH
FTIR compatibility	Detect drug–excipient interaction	Confirms formulation compatibility

Determination of λmax and Calibration Curve

Quantitative estimation of Econazole nitrate was carried out using UV-visible spectrophotometry. A stock solution was prepared and serially diluted to obtain different concentrations. The solutions were scanned over the ultraviolet region to identify the wavelength corresponding to maximum absorbance (λmax). The absorbance values obtained at the selected wavelength were used to construct a calibration curve by plotting absorbance against concentration.[15]

The calibration plot exhibited excellent linearity within the selected concentration range, confirming compliance with Beer–Lambert's law. The

developed analytical method was subsequently employed for drug content estimation, entrapment efficiency determination, and in vitro drug release analysis throughout the study.[16]

Partition Coefficient

The partition coefficient was determined to evaluate the affinity of Econazole nitrate toward lipophilic and aqueous environments. The drug was equilibrated between mutually saturated n-octanol and water phases, followed by spectrophotometric analysis of the aqueous layer. The calculated partition coefficient indicated a high preference of the drug for the organic phase, demonstrating its pronounced lipophilic character.[17]

This behaviour is advantageous for multiple emulsion systems because the oil layer functions as a diffusion barrier that regulates drug migration from the internal aqueous compartment to the external phase, thereby contributing to sustained drug release.

pH Stability Studies

The stability of Econazole nitrate under different pH conditions was investigated using buffer solutions representing acidic, mildly acidic, and neutral environments. Drug samples were stored under controlled conditions and analysed periodically for changes in concentration.

The results indicated that the drug remained comparatively stable under mildly acidic and neutral conditions, suggesting that topical formulations prepared within this physiological pH range would preserve drug stability during storage and application. The findings also supported the suitability of the selected formulation components for topical administration.[18]

Drug–Excipient Compatibility Study

Compatibility between Econazole nitrate and formulation excipients was investigated using Fourier Transform Infrared (FTIR) spectroscopy. The pure drug and its physical mixtures with Span 80, Tween 80, Carbopol 934P, and HPMC K4M were analysed using the potassium bromide pellet technique over the infrared region.[19]

The characteristic absorption bands of Econazole nitrate corresponding to the imidazole ring, aromatic functional groups, and carbon–chlorine stretching vibrations remained unchanged in the spectra of the physical mixtures. No additional peaks, disappearance of characteristic peaks, or significant spectral shifts were observed. These findings indicated the absence of chemical interactions between the drug and selected excipients, confirming their compatibility and suitability for developing a stable multiple emulsion formulation.[20]

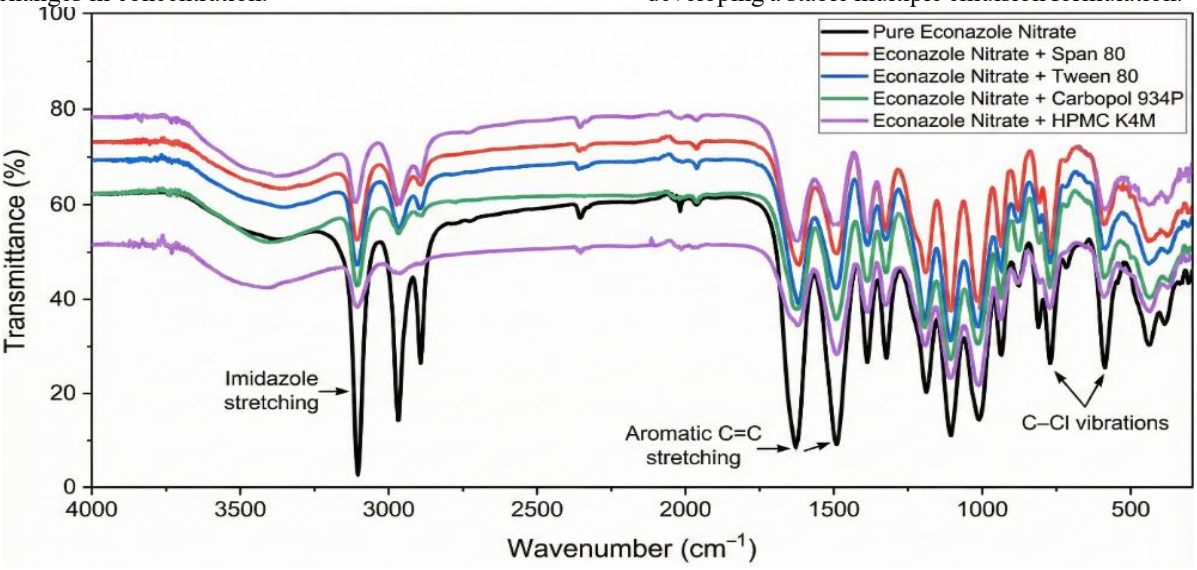

Fig 2. FTIR Spectrum of Econazole Nitrate and Drug–Excipient Mixtures

The successful completion of these preformulation investigations provided a strong scientific foundation for formulation development. The physicochemical characteristics, favourable compatibility profile, and analytical behaviour of Econazole nitrate supported its incorporation into the W/O/W multiple emulsion system intended for sustained topical antifungal therapy.[21]

Formulation of Multiple Emulsion

The multiple emulsion containing Econazole nitrate was developed using a **two-step emulsification technique**, a well-established approach for preparing water-in-oil-in-water (W/O/W) systems. This method was selected because it enables efficient encapsulation of hydrophilic and lipophilic components while providing a diffusion-controlled pathway for sustained drug release. During formulation development, several trial batches were prepared by varying the concentrations of surfactants, oil phase, and polymeric stabilizers to identify the optimum composition that produced satisfactory emulsion stability, drug entrapment, and controlled release characteristics.[22]

The formulation process was carefully standardized to ensure reproducibility. Parameters such as homogenization speed, stirring rate, emulsification

time, and temperature were optimized to minimize droplet coalescence and maintain the integrity of the internal aqueous phase. Six formulation batches (F1–F6) were prepared to investigate the influence of formulation variables on the physicochemical properties and performance of the developed multiple emulsion.[23]

Formulation Composition

The composition of all experimental batches was designed by maintaining a constant drug concentration while systematically modifying the proportions of surfactants, oil phase, and polymer concentration. These variations enabled evaluation of their influence on viscosity, droplet stability, drug entrapment, and sustained drug release.[24]

Table 3. Composition of Experimental Formulation Batches

Ingredients	F1	F2	F3	F4	F5	F6
Econazole Nitrate (%)	1.0	1.0	1.0	1.0	1.0	1.0
Liquid Paraffin (%)	20	22	25	20	22	25
Span 80 (%)	4	5	6	4	5	6
Tween 80 (%)	6	7	8	6	7	8
Glycerin (%)	5	5	5	5	5	5
HPMC K4M/Carbopol 934P (%)	0.50	0.75	1.00	0.50	0.75	1.00
MCT Oil (%)	3	3	3	3	3	3
Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation of Primary Water-in-Oil (W/O) Emulsion

The primary emulsion was prepared by dispersing the internal aqueous phase into the oil phase under controlled homogenization conditions. Initially, liquid paraffin was gently heated to approximately **40°C**, after which Span 80 was dissolved completely to obtain a homogeneous lipophilic phase. The internal aqueous phase containing Econazole nitrate, glycerin, ethanol, and distilled water was prepared separately with continuous stirring until a uniform dispersion was achieved.[25]

The aqueous phase was then added slowly to the oil phase under high-speed homogenization. Continuous mixing generated fine aqueous droplets uniformly distributed throughout the oil phase, resulting in the formation of a stable primary W/O emulsion. Careful control of homogenization speed prevented excessive shear that could destabilize the internal droplets while ensuring adequate droplet size reduction.

The prepared primary emulsion exhibited a smooth, glossy appearance with excellent dispersion characteristics and no visible phase separation, indicating successful formation of the W/O system.[26]

Preparation of Secondary Water-in-Oil-in-Water (W/O/W) Emulsion

The external aqueous phase was prepared by dissolving Tween 80 in distilled water. Polymeric stabilizers (HPMC K4M or Carbopol 934P) were allowed to hydrate completely before incorporation into the external phase to obtain the desired viscosity and improve long-term emulsion stability.

The previously prepared W/O emulsion was gradually introduced into the external aqueous phase under moderate stirring. A lower mixing speed was maintained during this stage to preserve the integrity of the internal aqueous droplets and avoid rupture of the primary emulsion. Continuous stirring for approximately 15 minutes resulted in the formation of a uniform milky-white W/O/W multiple emulsion.[27]

Following emulsification, the formulation was allowed to stand undisturbed to facilitate structural stabilization before subsequent evaluation. The final product exhibited a homogeneous appearance with no evidence of creaming, oil separation, or droplet aggregation, confirming successful preparation of the multiple emulsion system.

Influence of Formulation Variables

The prepared batches were broadly categorized into two groups according to polymer concentration and expected viscosity.

The **F1–F3 series** contained comparatively lower polymer concentrations and was primarily designed to investigate the influence of surfactant concentration on droplet formation and primary emulsion stability. These formulations exhibited relatively lower viscosity, facilitating easier mixing and improved spreadability.[28]

The **F4–F6 series** incorporated higher concentrations of polymeric stabilizers to improve viscosity, structural integrity, and sustained drug release. These batches were expected to demonstrate enhanced resistance against phase separation and improved physical stability during storage and stress conditions.

The systematic variation in formulation composition enabled optimization of the surfactant-to-polymer ratio required for producing a physically stable multiple emulsion with prolonged drug release characteristics.[29]

Table 4. Functional Role of Formulation Components

Component	Functional Contribution
Econazole Nitrate	Active antifungal agent
Span 80	Stabilizes primary W/O emulsion
Tween 80	Stabilizes secondary O/W emulsion
Liquid Paraffin	Forms diffusion barrier for sustained release
MCT Oil	Enhances drug solubilization
Glycerin	Maintains hydration and improves stability
HPMC K4M / Carbopol 934P	Increases viscosity and prevents droplet coalescence
Distilled Water	Forms internal and external aqueous phases

Confirmation of Multiple Emulsion Structure

Successful formation of the W/O/W multiple emulsion was confirmed through several qualitative tests. The dilution test demonstrated uniform dispersion upon dilution with water, indicating an external aqueous phase. Microscopic examination revealed numerous small aqueous droplets enclosed within larger oil globules, which is characteristic of a multiple emulsion system. In addition, dye incorporation studies showed localization of the water-soluble dye within the internal aqueous droplets, further confirming successful encapsulation and preservation of the W/O/W architecture.[30]

These observations collectively verified that the developed formulation possessed the intended multiple emulsion structure suitable for sustained topical drug delivery.

Preliminary Characteristics of Formulated Batches

Immediately after preparation, all formulation batches were examined visually to assess their appearance, consistency, flow characteristics, and emulsion stability. Differences in viscosity and texture were primarily attributed to variations in polymer concentration. Formulations containing higher polymer levels exhibited greater consistency and superior resistance to phase separation.[31]

Table 5. Preliminary Characteristics of Formulated Multiple Emulsions

Batch	Appearance	Consistency	Emulsion Integrity	Preliminary Stability
F1	Milky white	Thin	Moderate	Fair
F2	Milky white	Moderate	Good	Good
F3	Creamy white	Thick	Excellent	Excellent
F4	Smooth white	Medium	Good	Good
F5	Thick and smooth	High	Excellent	Excellent
F6	Very thick	Very High	Excellent	Excellent

Overall, all six formulations were successfully prepared using the optimized double-emulsification technique. Among the trial batches, formulations containing balanced surfactant concentrations together with higher polymer content demonstrated superior physical stability and were expected to provide enhanced drug entrapment and sustained release during subsequent evaluation studies.

Evaluation of Multiple Emulsion

The developed multiple emulsion formulations were systematically evaluated to determine their physicochemical characteristics, structural integrity, drug-loading efficiency, and suitability for topical administration. Each formulation was subjected to standardized analytical procedures under identical laboratory conditions to ensure reproducibility and reliable comparison among batches. The evaluation parameters were selected to assess the stability of the multiple emulsion system, compatibility with skin physiology, and its capability to provide sustained delivery of Econazole nitrate. The findings obtained from these investigations facilitated the identification of the optimized formulation possessing desirable pharmaceutical characteristics.[32]

Visual Appearance and Homogeneity

Visual examination was performed immediately after preparation to assess the physical quality of the developed formulations. Each batch was observed under normal laboratory illumination for colour, opacity, consistency, and evidence of phase separation. Homogeneity was evaluated by gently

spreading a small quantity of the formulation over a clean glass slide and observing the presence of any coarse particles, clumps, or oil droplets.

A successful formulation was characterized by a smooth, creamy appearance with uniform consistency and complete absence of creaming or cracking. Homogeneous distribution of dispersed droplets indicated efficient emulsification and uniform incorporation of the active ingredient throughout the formulation. All optimized formulations exhibited a milky-white appearance with satisfactory smoothness, demonstrating successful formation of the multiple emulsion system.[33]

Determination of pH

The pH of topical formulations is an important quality parameter because it influences drug stability, skin compatibility, and patient acceptability. Approximately 1 g of each formulation was dispersed in distilled water and allowed to equilibrate before analysis using a calibrated digital pH meter.

The formulations exhibited pH values within the physiological range of human skin, indicating that the prepared emulsions were unlikely to produce irritation or discomfort during topical application. Maintenance of an appropriate pH also suggested good chemical stability of both the drug and excipients throughout the formulation process.[34]

Viscosity Measurement

Viscosity was determined using a Brookfield digital viscometer under controlled temperature conditions. Measurements were performed at different spindle speeds to evaluate the rheological behaviour of each formulation.

The viscosity of the emulsions increased progressively with increasing polymer concentration. Formulations containing higher concentrations of Carbopol 934P or HPMC K4M demonstrated greater consistency due to enhanced three-dimensional polymeric network formation. All formulations exhibited pseudoplastic flow behaviour, which is considered desirable for topical preparations because it facilitates easy spreading during application while maintaining adequate residence time on the skin surface.[35]

Microscopic Examination and Globule Size Analysis

Microscopic evaluation was performed to confirm successful formation of the W/O/W multiple emulsion system and to observe droplet morphology. A small amount of formulation was placed on a clean glass slide, covered with a coverslip, and examined under an optical microscope equipped with a calibrated ocular micrometer.

The microscopic images revealed numerous small aqueous droplets enclosed within larger oil globules, confirming the characteristic multiple emulsion architecture. The droplets appeared uniformly distributed without significant aggregation or coalescence, indicating efficient emulsification and good physical stability. Uniform globule size distribution is advantageous because it contributes to improved formulation stability and reproducible drug release behaviour.[36]

Entrapment Efficiency

Entrapment efficiency was determined to estimate the proportion of Econazole nitrate successfully encapsulated within the internal phase of the multiple emulsion. A measured quantity of formulation was centrifuged to separate the free drug present in the external aqueous phase. The concentration of unentrapped drug was quantified using UV-visible spectrophotometry, and the percentage entrapment efficiency was subsequently calculated.

Higher entrapment efficiency reflects improved drug retention within the emulsion and contributes to sustained drug release. Formulations containing balanced surfactant concentrations and higher polymer content demonstrated superior encapsulation because the stabilized interfacial membrane effectively minimized drug leakage during emulsification.[37]

Drug Content Uniformity

Uniform distribution of the active pharmaceutical ingredient throughout the formulation is essential to ensure consistent therapeutic performance. Drug content analysis was performed by dissolving accurately weighed samples of each formulation in a suitable solvent followed by spectrophotometric estimation.

The obtained drug content values demonstrated uniform distribution of Econazole nitrate among different batches, indicating efficient mixing during formulation and the absence of drug sedimentation or localized concentration differences. Good content uniformity also confirmed the reproducibility of the formulation process.[38]

Spreadability

Spreadability is an important characteristic of topical formulations because it influences ease of application and patient compliance. The test was carried out by placing a fixed amount of formulation between two glass plates under standardized weight, after which the spread diameter was measured.

Formulations possessing moderate viscosity showed superior spreadability while maintaining adequate consistency on the skin surface. Although higher polymer concentrations slightly reduced spreading characteristics, they significantly improved formulation retention after application, thereby supporting prolonged therapeutic action.

Extrudability

Extrudability was evaluated to determine the suitability of the developed formulation for packaging in collapsible tubes. The force required to expel the formulation from the tube was measured under standardized pressure.

The optimized formulations extruded smoothly without excessive resistance or leakage, demonstrating appropriate consistency for convenient patient use. Proper extrudability also indicates desirable rheological properties and formulation stability during storage.[39]

In Vitro Drug Release Study

The release behaviour of Econazole nitrate from the developed multiple emulsion was investigated using a Franz diffusion cell. The receptor compartment contained phosphate buffer (pH 7.4) maintained at physiological temperature with continuous stirring to simulate topical drug diffusion conditions.

Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically to determine cumulative drug release. The multiple emulsion system exhibited a gradual and controlled release profile throughout the study period. The oil membrane surrounding the internal aqueous droplets acted as a diffusion barrier, thereby regulating drug migration into the external phase before release across the membrane.

Formulations containing optimized surfactant ratios together with higher polymer concentrations exhibited slower and more sustained drug release compared with low-viscosity formulations. This behaviour demonstrates the effectiveness of the multiple emulsion system in maintaining prolonged drug availability at the site of application.

The comprehensive evaluation demonstrated that all prepared formulations possessed acceptable physicochemical characteristics for topical administration. The optimized batches showed excellent homogeneity, appropriate pH, satisfactory viscosity, high drug entrapment efficiency, and controlled release behaviour. Microscopic examination confirmed successful formation of the characteristic W/O/W multiple emulsion structure, while the sustained release profile indicated the suitability of the developed delivery system for prolonged topical antifungal therapy. Collectively, these findings confirmed that the optimized multiple emulsion formulation has the potential to improve therapeutic efficacy, reduce application frequency, and enhance patient compliance compared with conventional Econazole topical formulations.[40]

Results and Discussion

The developed W/O/W multiple emulsion formulations (F1–F6) were successfully prepared and evaluated for their physicochemical characteristics, topical applicability, drug release behaviour, and stability. The results demonstrated that variations in surfactant concentration and polymer content significantly influenced the performance of the formulations. Overall, all batches exhibited acceptable pharmaceutical properties, confirming the successful development of a stable multiple emulsion system for topical delivery of Econazole nitrate.

Physicochemical Evaluation

Visual examination revealed that all formulations possessed a smooth, milky-white appearance without evidence of creaming, cracking, or phase separation, indicating successful formation of stable W/O/W multiple emulsions. The pH values ranged from **5.42 to 5.84**, which is compatible with normal skin physiology and suitable for topical administration.

Viscosity increased progressively with increasing polymer concentration, with formulation F6 exhibiting the highest viscosity (13,450 cP). Higher viscosity contributed to improved droplet stabilization and prolonged retention on the skin surface. Microscopic analysis confirmed the characteristic W/O/W structure, where fine internal aqueous droplets were enclosed within larger oil globules. Increasing surfactant concentration reduced globule size from **5.2 µm (F1)** to **3.4 µm (F6)**, thereby improving physical stability and drug encapsulation.

Entrapment efficiency and drug content also increased with polymer concentration and optimized surfactant ratio. Formulation F6 demonstrated the highest entrapment efficiency (89.1%) and drug content (99.2%), indicating efficient incorporation of Econazole nitrate into the multiple emulsion system.

Topical performance evaluation showed that lower viscosity formulations exhibited greater spreadability and easier extrusion, whereas highly viscous formulations provided better retention on the application site. Although F6 exhibited comparatively lower spreadability and moderate extrudability, these characteristics are advantageous for sustained topical drug delivery.

The in vitro drug release study demonstrated a controlled release pattern over 12 hours. Formulations containing lower polymer concentrations released the drug more rapidly, whereas F6 exhibited the slowest release (72.8% at 12 h) due to higher viscosity, smaller droplet size, and greater drug entrapment. Drug release kinetic analysis indicated that the optimized formulation followed the **Korsmeyer–Peppas model (R^2 = 0.991)**, suggesting a non-Fickian diffusion mechanism.

Stability studies performed under refrigerated, room temperature, and accelerated conditions showed only minor changes in pH and viscosity over 60 days without evidence of phase separation or structural instability, confirming excellent formulation stability.

Table 2. Evaluation Results for Multiple Emulsion Formulations

Parameter	F1	F2	F3	F4	F5	F6

Appearance	Smooth	Smooth	Creamy	Smooth	Creamy	Excellent
pH	5.42	5.56	5.63	5.48	5.71	5.84
Viscosity (cP)	7200	8350	10240	7600	11120	13450
Mean Globule Size (µm)	5.2	4.8	3.9	4.9	3.7	3.4
Entrapment Efficiency (%)	64.2	69.8	78.4	71.2	82.6	89.1
Drug Content (%)	94.2	95.8	98.1	95.3	97.4	99.2
Spreadability (g·cm/sec)	16.3	15.1	13.8	15.6	13.2	12.4
Extrudability	Excellent	Very Good	Good	Very Good	Good	Moderate
Drug Release at 12 h (%)	93.4	89.7	82.1	90.2	78.5	72.8
Release Kinetics	First-order	First-order	Higuchi	First-order	Higuchi	Korsmeyer–Peppas
Overall Stability	Good	Good	Excellent	Good	Excellent	Excellent

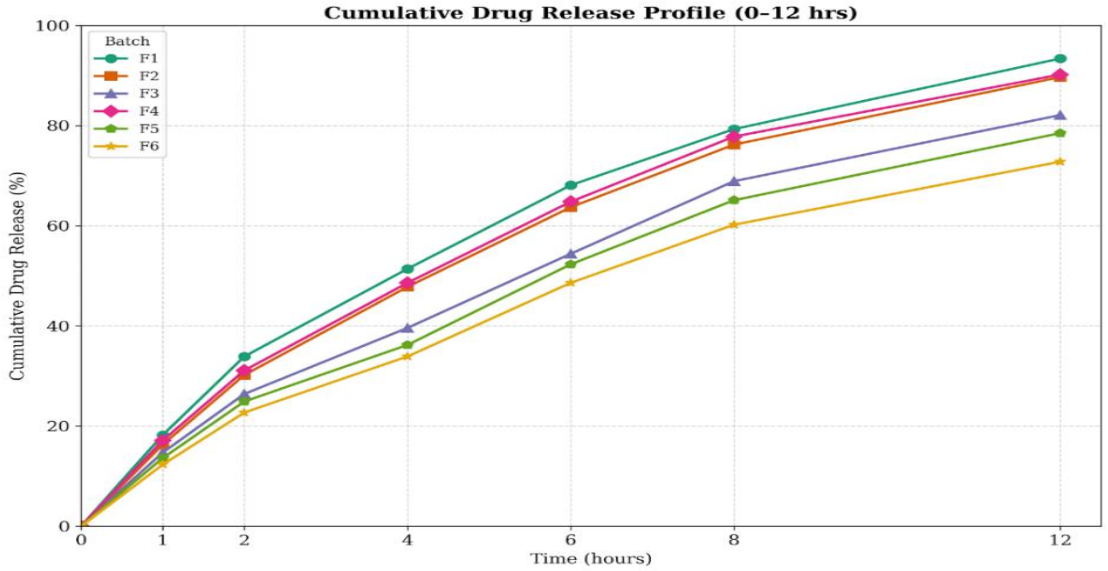

Fig. 3: Cumulative Drug Release Profile (0–12 hrs)

The results clearly demonstrate that the concentration of surfactants and polymers significantly influenced the quality and performance of the developed multiple emulsion formulations. Increasing polymer concentration improved viscosity, reduced globule size, enhanced drug entrapment, and prolonged drug release. Although higher viscosity slightly reduced spreadability and extrudability, it improved topical retention and sustained release characteristics. Among all formulations, **F6** exhibited the most desirable pharmaceutical properties, including the highest drug content, maximum entrapment efficiency, controlled drug release, and excellent stability. Therefore, formulation **F6** was identified as the optimized multiple emulsion suitable for sustained topical delivery of Econazole nitrate.

Future Prospectus

The development of Econazole nitrate multiple emulsion offers significant opportunities for future pharmaceutical research. Further studies should focus on improving formulation stability by exploring novel natural surfactants, bio-based emulsifiers, and advanced polymeric stabilizers that provide enhanced biocompatibility and reduced skin irritation. The incorporation of bioadhesive and penetration-enhancing polymers may further improve drug retention and permeation through the stratum corneum, resulting in better therapeutic efficacy. Smart or stimuli-responsive multiple emulsion systems capable of releasing the drug in response to pH, temperature, or infection-specific conditions represent another promising area of investigation. Additionally, large-scale manufacturing techniques, including membrane emulsification and high-pressure homogenization, should be optimized to ensure reproducibility and commercial feasibility. Future in vivo pharmacokinetic, pharmacodynamic, and clinical studies are essential to validate the long-term safety, efficacy, and patient acceptability of the developed formulation and facilitate its successful translation into clinical and industrial applications.

SUMMARY AND CONCLUSION:

The present study successfully developed and evaluated a water-in-oil-in-water (W/O/W) multiple emulsion containing Econazole nitrate for sustained topical antifungal therapy. The optimized formulations demonstrated satisfactory physicochemical characteristics, including appropriate pH, desirable viscosity, uniform globule distribution, high drug entrapment efficiency, and excellent drug content. In vitro drug release studies confirmed prolonged and controlled release of Econazole nitrate, indicating the suitability of the multiple emulsion system for reducing application frequency while maintaining therapeutic drug levels. Stability studies further established that the optimized formulation remained physically and chemically stable without significant phase separation or degradation during storage. Overall, the findings demonstrate that the developed multiple emulsion is a promising carrier for topical antifungal delivery, offering improved drug retention, enhanced stability, and sustained therapeutic action compared with conventional formulations. Further in vivo investigations and scale-up studies are recommended to establish its clinical effectiveness and commercial potential.

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