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Review Article

Emulgels: A Promising Topical Drug Delivery System

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Abstract
Topical drug delivery systems have garnered significant attention in recent years due to their ability to provide localized treatment, minimizing systemic side effects and avoiding first-pass metabolism. Among these, emulgels have emerged as a promising approach, offering a unique combination of the advantages of both emulsions and gels. Emulgels are biphasic systems in which hydrophobic drugs, typically difficult to deliver through the skin, are dispersed in an emulsion and then stabilized within a gel matrix. This system enhances the stability, ease of application, and efficacy of drug delivery, making it an attractive option for a wide range of topical treatments. The composition of emulgels typically includes an oil phase, water phase, emulsifying agents, and gelling agents. These components are selected based on their ability to enhance drug solubility, stabilize the formulation, and facilitate drug release. Common preparation methods involve the formation of an emulsion (oil-in-water or water-in-oil), which is subsequently incorporated into a gel base. Characterization techniques for emulgels include evaluating their rheological properties, particle size, drug release profiles, and stability, which are crucial for ensuring consistent performance and efficacy. One of the major advantages of emulgels over conventional topical formulations is their enhanced ability to permeate the skin. The combination of the emulsion's lipid phase and the gel matrix allows for better absorption of active ingredients, leading to improved therapeutic outcomes. Additionally, emulgels provide a smooth, non-greasy texture that enhances patient compliance, as they are more comfortable and convenient to apply. Despite their many advantages, emulgels also have limitations, such as potential instability over time and the challenge of formulating hydrophobic drugs in water-based gels. However, ongoing research continues to address these challenges, with new formulations and techniques being explored. The growing body of research on emulgels underscores their potential to revolutionize topical drug delivery, providing more effective, patient-friendly treatments across various therapeutic areas, including dermatology, pain management, and wound healing.

Keywords: Emulgels , Topical drug delivery, Semisolid formulations, Dermal absorption, Skin permeation.

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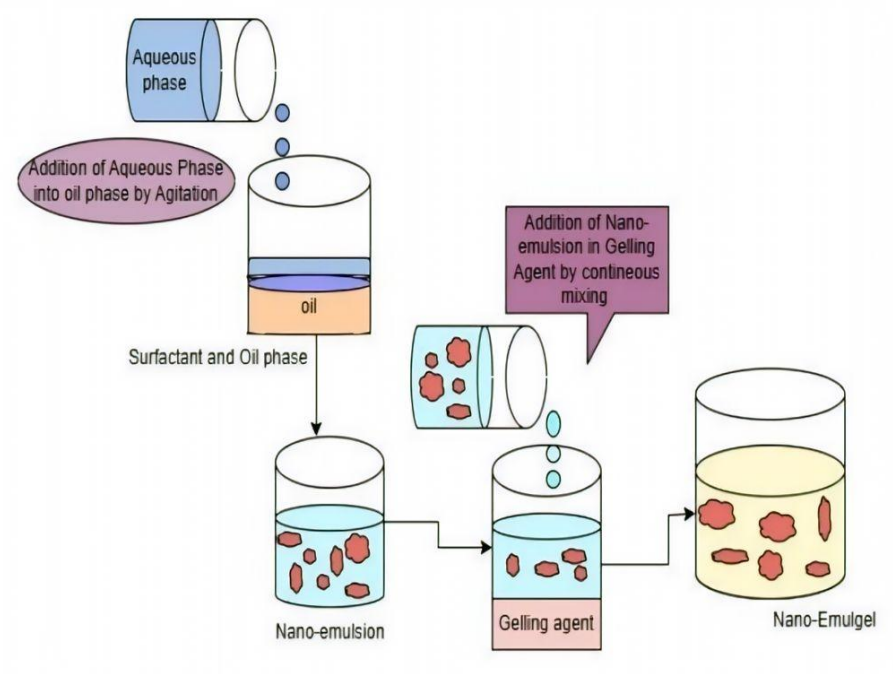
Graphical abstract



1. Introduction

Topical drug delivery has long been recognized as an effective route for treating various dermatological conditions and achieving local therapeutic effects. However, conventional topical formulations often face challenges such as poor drug solubility, limited permeation through the skin, and inadequate retention at the site of action [1]. To overcome these limitations, researchers have developed novel drug delivery systems, among which emulgels have gained significant attention.

Emulgels are a relatively new class of topical formulations that combine the properties of emulsions and gels [2]. They are formed by incorporating a gelling agent into the aqueous phase of an oil-in-water (o/w) or water-in-oil (w/o) emulsion. This unique combination results in a stable, non-greasy, and easily spreadable formulation with enhanced drug solubility and permeation characteristics [3].

The purpose of this review is to provide a comprehensive overview of emulgels as a topical drug delivery system, discussing their composition, preparation methods, characterization techniques, and applications in various therapeutic areas. Additionally, the advantages and limitations of emulgels compared to conventional topical formulations will be explored, along with future prospects and potential areas for further research.

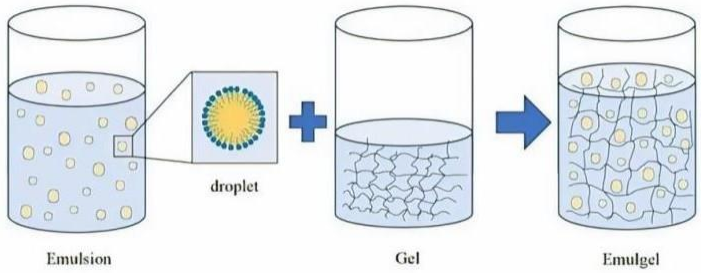


Figure 1.1 Process for making emulgels

1.1 Some marketed emulgels formulations [40-69]

S.No	Brand Name	Active Ingredients	Manufacturing company
1.	Voltaren Emulgels	Diclofenac diethylamine	GlaxoSmithKline
2.	Miconaz-H Emulgels	Miconazole nitrate	Medical union pharmaceutical
3.	Excex Gel	Adapalene	Oreva healthcare
4.	Clobex Emollient cream	Clobetasol propionate	Galderma
5.	Nadifloxacin Emulgels	Nadifloxacin	Cipla Ltd
6.	Topicure Emulgels	Lornoxicam	Natural Healthcare
7.	Zorotene gel	Tazarotene	Glenmark
8.	Deriva CMS gel	Adapalene	Glenmark

9.	Nixgel	Ciclopirox olamine	Swisschem dermacare
10.	Ecobec Emulgels	Econazole nitrate	Padagis
11.	Volini gel	Diclofenac	Ranbaxy laboratories
12.	Diclon Emulgels	Diclofenac	Med Pharma
13.	Isofen Emulgels	Ibuprofen	Beitjala Pharma
14.	Benzolait Emulgels	Benzoyl peroxide	Roydermal
15.	Adwiflam Emulgels	Diclofenac diethylamine	Saja Pharmaceutics
16.	Nucoxia Emulgels	Etoricoxib	Zydus Cadila healthcare

2. Composition of Emulgels

Emulgels are composed of several key components that contribute to their unique properties and efficacy as a topical drug delivery system. The main constituents of emulgels include:

2.1. Active Pharmaceutical Ingredient (API)

The selection of an active pharmaceutical ingredient (API) is influenced by both the desired therapeutic outcome and the specific physicochemical characteristics of the drug. When it comes to formulations like emulgels, these are especially advantageous for drugs that are lipophilic in nature and exhibit poor solubility in water. Emulgels combine the benefits of both emulsions and gels, making them an ideal medium for improving the delivery and effectiveness of such lipophilic drugs, which might otherwise struggle to dissolve or be absorbed effectively in traditional aqueous-based formulations [4].

2.2. Oil Phase

The oil phase typically consists of mineral oils, vegetable oils, or synthetic oils. Common examples include liquid paraffin, isopropyl myristate, and caprylic/capric triglycerides. The oil phase helps solubilize lipophilic drugs and enhances their permeation through the skin [5].

2.3. Aqueous Phase

Water constitutes the majority of the aqueous phase in a formulation, serving as its main component. In addition to water, the aqueous phase may include various water-soluble ingredients that play important roles in the stability and effectiveness of the formulation. These ingredients can include preservatives, which help prevent microbial growth and extend the product's shelf life; humectants, which are used to retain moisture and keep the formulation hydrated; and solubilizers, which assist in dissolving ingredients that might otherwise have difficulty dispersing in water. Together, these components ensure the formulation remains effective, stable, and safe for use [6].

2.4. Emulsifiers

Emulsifiers play a vital role in the stabilization of emulsions, whether they are oil-in-water or water-in-oil types. Their primary function is to ensure that the oil and water phases, which would naturally separate, remain well-mixed and stable over time. In emulgel formulations, emulsifiers are particularly important because they help maintain the integrity and homogeneity of the mixture. Some of the most commonly used emulsifiers in these formulations include Tween 80, Span 20, and lecithin. Tween 80 is often selected for its ability to stabilize oil-in-water emulsions, while Span 20 is useful for creating water-in-oil emulsions. Lecithin, a natural phospholipid, is valued for its versatile emulsifying properties, making it a popular choice in a wide range of pharmaceutical and cosmetic applications. These emulsifiers work together to ensure that the formulation remains stable, effective, and suitable for the intended therapeutic or cosmetic use [7].

2.5. Gelling Agents

Gelling agents are essential for providing the gel-like consistency in emulgels, which enhances the formulation's stability and ease of application. These agents work by thickening the mixture and forming a semi-solid structure. Common gelling agents used in emulgels include carbomers, which are synthetic polymers that create a smooth gel texture. Cellulose derivatives, such as hydroxypropyl methylcellulose, are also widely used for their thickening properties and biocompatibility. Additionally, natural gums like xanthan gum are popular due to their natural origin and ability to form stable gels. Together, these agents ensure the emulgel has the desired consistency and stability [8].

2.6. Penetration Enhancers

Permeation enhancers are used in formulations to improve the ability of drugs to penetrate through the skin, ensuring better absorption and therapeutic effect. These agents work by altering the skin's barrier function, allowing the drug to reach deeper layers. Common examples include propylene glycol, which increases solubility and enhances skin penetration, and dimethyl sulfoxide (DMSO), a potent solvent that helps transport drugs across the skin. Essential oils, known for their natural permeation-enhancing properties, are also widely used in topical formulations. By incorporating these agents, drug delivery through the skin becomes more effective and efficient for therapeutic applications [9].

2.7. Preservatives

Preservatives are crucial in formulations to inhibit microbial growth, ensuring the product remains safe and stable over time. They help extend the shelf life by preventing contamination from bacteria, fungi, or molds, which can compromise the formulation's quality and effectiveness. Commonly used preservatives include parabens, known for their broad-spectrum antimicrobial activity, benzyl alcohol, which acts as

both a preservative and a solvent, and phenoxyethanol, a versatile preservative with low toxicity. By incorporating these preservatives, the formulation remains protected against microbial degradation, ensuring it remains effective and safe for use throughout its intended shelf life [10].

3. Preparation Methods

The preparation of emulgels typically involves a two-step process:

3.1. Emulsion Formation

The oil phase and aqueous phase are prepared separately. The oil phase contains the lipophilic drug, oil, and lipophilic emulsifier, while the aqueous phase contains water, hydrophilic emulsifier, and other water-soluble components. The two phases are then mixed using high-speed homogenization or ultrasonication to form a stable emulsion [11].

3.2. Gel Formation

The gelling agent is dispersed in a separate portion of the aqueous phase and allowed to hydrate. Once fully hydrated, it is added to the emulsion under gentle stirring to form the final emulgel [12].

Alternative methods, such as the one-step process where all components are mixed simultaneously, have also been reported in the literature [13].

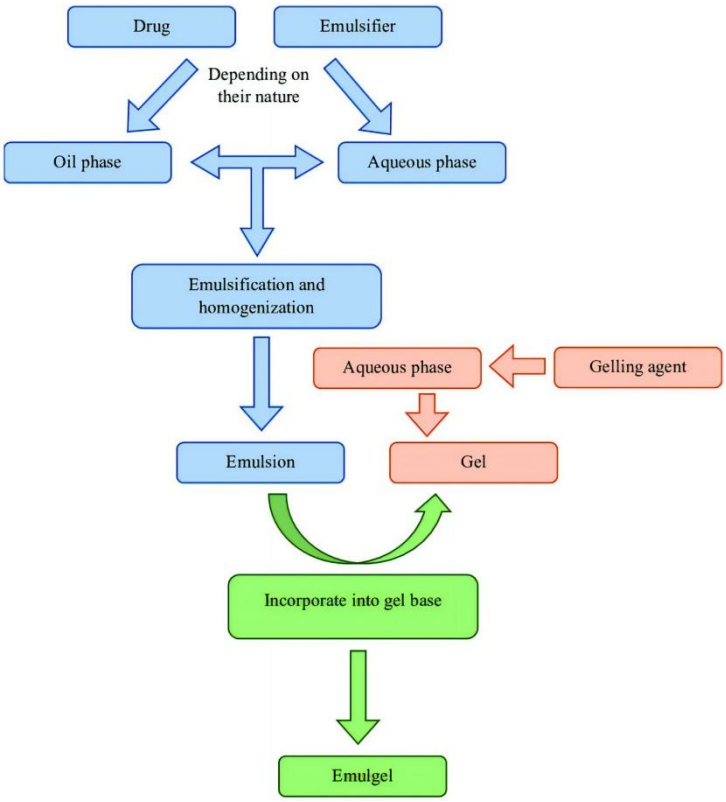


Figure 3.1: Flow chart of preparing emulgels

4. Characterization Techniques

Several techniques are employed to characterize emulgels and evaluate their physicochemical properties:

4.1. Physical Appearance and Homogeneity

Visual inspection and microscopic examination are employed to evaluate the emulgel's color, texture, and homogeneity. Visual inspection provides an overall assessment of appearance, while microscopic examination offers detailed insights into the uniformity of the dispersed phases, ensuring the formulation is well-mixed and free from inconsistencies or particles. [14].

4.2. pH Measurement

The pH of emulgels is commonly measured using a pH meter to ensure it aligns with the natural pH of the skin, which is crucial for maintaining skin health and preventing irritation. Proper pH levels also ensure the stability and efficacy of the formulation during use [15].

4.3. Viscosity and Rheological Properties

Viscosity measurements and rheological studies are conducted using instruments such as rheometers or viscometers to assess the flow properties and stability of emulgels. These tests help determine how the emulgel responds to stress, such as spreading or application to the skin. Viscosity is crucial for ensuring that the emulgel has an appropriate consistency for easy application, while rheological studies provide insights into the product's long-term stability, ensuring that it maintains its texture and performance over time. [16].

4.4. Spreadability

The spreadability of emulgels is evaluated using methods such as the parallel plate method or a texture analyzer. These techniques measure how easily the emulgel can be applied to the skin, assessing its ability to spread evenly and smoothly, which is crucial for user comfort and effectiveness. [17].

4.5. Drug Content and Uniformity
The drug content in emulgels is quantified using analytical techniques like UV spectrophotometry or high-performance liquid chromatography (HPLC). These methods ensure that the drug is uniformly distributed throughout the formulation, which is essential for consistent therapeutic efficacy and product quality [18].

4.6. In Vitro Drug Release Studies
Franz diffusion cells or similar apparatus are employed to assess the drug release profile from emulgels. This method involves placing the emulgel in a cell and measuring the amount of drug that diffuses through a membrane into a receptor fluid over time. By analyzing the release rate and pattern, researchers can evaluate how effectively the drug is delivered from the emulgel, providing critical insights into its performance and efficacy in therapeutic applications [19].

4.7. Stability Studies
Stability studies are carried out under different storage conditions to evaluate the long-term stability of emulgel formulations. These studies involve exposing the emulgel to various environmental factors, such as temperature, humidity, and light, to determine how these conditions affect its physical and chemical properties over time. By monitoring changes in appearance, consistency, drug content, and efficacy, researchers can ensure that the emulgel maintains its quality and performance throughout its intended shelf life [20].

5. Applications in Therapeutic Areas
Emulgels have shown promise in various therapeutic areas, including:

5.1. Dermatology
Emulgels have been extensively studied for the treatment of various skin conditions such as acne, psoriasis, and fungal infections. For example, a clotrimazole emulgel showed enhanced antifungal activity compared to conventional formulations in the treatment of cutaneous candidiasis [21].

5.2. Pain Management
Topical emulgels containing nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated improved efficacy in managing musculoskeletal pain and inflammation. A diclofenac emulgel formulation exhibited enhanced skin permeation and anti-inflammatory effects compared to a commercial gel [22].

5.3. Cosmeceuticals
Emulgels have found applications in cosmeceutical products, including anti-aging formulations and skin lightening agents. A vitamin C emulgel showed improved stability and enhanced skin penetration compared to conventional formulations [23].

5.4. Wound Healing
Emulgels containing growth factors or antimicrobial agents have shown potential in promoting wound healing. A silver sulfadiazine emulgel demonstrated improved wound healing properties in burn wound models compared to conventional creams [24].

5.5. Hormone Delivery
Emulgels have been investigated for the topical delivery of hormones, such as testosterone and estradiol, for hormone replacement therapy. An estradiol emulgel formulation showed improved skin permeation and pharmacokinetic profile compared to a commercial gel [25].

6. Advantages of Emulgels
Emulgels offer several advantages over conventional topical formulations:

6.1. Enhanced Drug Solubility
The unique structure of emulgels, which combines both oil and aqueous phases, enables the incorporation of hydrophilic and lipophilic drugs within a single formulation. This dual-phase system enhances the solubility of drugs that may otherwise be challenging to dissolve, offering improved bioavailability. Emulgels provide a versatile platform for drug delivery, as they can accommodate a wide range of active ingredients with different solubility profiles. This makes them an effective solution for formulating complex drug combinations, ensuring better therapeutic outcomes and increased patient compliance [26].

6.2. Improved Skin Permeation
The combination of aqueous and oil phases in emulgels, along with penetration enhancers, improves drug permeation through the skin. This system allows for more effective delivery of both hydrophilic and lipophilic drugs, enhancing their absorption and therapeutic effects, making emulgels a promising option for transdermal drug administration [27].

6.3. Increased Stability
The gel network in emulgels enhances the stability of the emulsion system by preventing phase separation, which is a common issue in traditional emulsions. This structural support ensures that the oil and aqueous phases remain well-dispersed, contributing to a more uniform and consistent formulation. As a result, emulgels exhibit improved shelf life and maintain their therapeutic efficacy over extended periods. The stability provided by the gel network also reduces the need for additional stabilizers, making emulgels a more efficient and reliable drug delivery system. [28].

6.4. Controlled Drug Release
Emulgels offer controlled and sustained drug release, ensuring prolonged therapeutic effects and reducing the need for frequent dosing. This gradual release enhances patient compliance while maintaining consistent drug levels in the system over time. Emulgels are thus effective for delivering medications that require long-lasting action with fewer applications [29].

6.5. Better Patient Compliance

The non-greasy nature of emulgels, along with their easy spreadability, makes them more appealing to patients compared to conventional ointments or creams. This enhanced sensory experience improves patient acceptability, as emulgels are lightweight and comfortable on the skin without leaving a sticky residue. As a result, patients are more likely to adhere to their treatment regimen. Emulgels also allow for better skin penetration, leading to more efficient drug delivery, further increasing their effectiveness in topical therapy compared to traditional formulations. [30].

7. Limitations and Challenges

Despite their numerous advantages, emulgels also face some limitations:

7.1. Limited Drug Loading

The drug loading capacity of emulgels can be limited, particularly for highly lipophilic or high-dose drugs. This restriction arises from the emulgel's dual-phase nature, which may not fully accommodate large amounts of lipophilic substances. As a result, achieving the desired therapeutic concentration may require careful formulation adjustments [31].

7.2. Potential for Skin Irritation

Certain components of emulgels, like penetration enhancers or preservatives, can potentially cause skin irritation in sensitive individuals. These additives, while essential for enhancing drug absorption or prolonging shelf life, may trigger allergic reactions or discomfort, requiring careful selection and formulation to minimize adverse effects for sensitive users [32].

7.3. Stability Concerns

Emulgels can be prone to physical and chemical instability when exposed to certain storage conditions, such as extreme temperatures, humidity, or light. These factors may lead to phase separation, degradation of active ingredients, or changes in texture and viscosity, compromising the formulation's effectiveness. To ensure stability, careful formulation strategies, such as the use of stabilizers, are needed. Additionally, appropriate packaging, including opaque or airtight containers, can help protect the emulgel from environmental factors and extend its shelf life and therapeutic efficacy [33].

7.4. Regulatory Challenges

As a relatively new dosage form, emulgels may encounter regulatory challenges in certain regions. Regulatory bodies may require additional safety and efficacy data to ensure their approval, as there may be limited long-term studies. This can lead to extended timelines for market entry and increased development costs [34].

8. Future Prospects

The field of emulgel-based drug delivery systems continues to evolve, with several promising areas for future research:

8.1. Nanotechnology Integration

Incorporating nanocarriers, such as nanoparticles or nanofibers, into emulgels can significantly enhance drug delivery efficiency and targeting. These nanocarriers improve the dispersion and penetration of the drug through the skin, potentially increasing therapeutic efficacy and allowing for more precise targeting of specific tissues or conditions [35].

8.2. Smart Emulgels

The development of stimuli-responsive emulgels that release drugs in response to external triggers, such as changes in pH or temperature, offers the potential for more precise and controlled drug delivery. These advanced formulations can be designed to respond to specific physiological conditions or environmental factors, allowing for targeted and on-demand release of the drug. This approach enhances therapeutic efficacy by ensuring that the drug is delivered at the optimal time and location, improving treatment outcomes and minimizing side effects [36].

8.3. Combination Therapy

Exploring emulgel formulations with multiple active ingredients can offer synergistic therapeutic effects for complex dermatological conditions. By combining various drugs or compounds, these formulations can address multiple aspects of a condition simultaneously, potentially improving treatment efficacy. This approach allows for a more comprehensive management of skin disorders, where different ingredients can work together to enhance overall therapeutic outcomes, target diverse symptoms, and offer a more effective solution than single-ingredient treatments [37].

8.4. Bioadhesive Emulgels

The development of bioadhesive emulgels aims to improve the retention time of the formulation on the skin and enhance drug absorption. By incorporating bioadhesive agents, these emulgels adhere more effectively to the skin's surface, reducing the likelihood of the formulation being rubbed off or washed away. This increased adhesion extends the contact time between the drug and the skin, facilitating better absorption and ensuring a more sustained and effective therapeutic effect [38].

8.5. Large-Scale Manufacturing

Optimizing large-scale manufacturing processes is crucial to ensure the consistent quality and commercial viability of emulgel products. This involves refining production techniques, standardizing raw material inputs, and implementing rigorous quality control measures. By addressing these factors, manufacturers can achieve uniformity in product characteristics, such as texture and drug content, while minimizing production costs. Effective optimization also enhances the scalability of the manufacturing process, ensuring that high-quality emulgels are produced efficiently and cost-effectively for market distribution [39].

9. Conclusion

Emulgels have emerged as a promising topical drug

delivery system, offering numerous advantages over conventional formulations. Their unique combination of emulsion and gel properties allows for improved drug solubility, enhanced skin permeation, and better patient compliance. As research in this field continues to grow, emulgels are likely to play an increasingly important role in the treatment of various dermatological conditions and in the development of novel topical therapies. Future advancements in emulgel technology, including the integration of nanotechnology and smart delivery systems, hold the potential to further revolutionize topical drug delivery and improve patient outcomes.

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