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A COMPREHENSIVE REVIEW: CHARACTERIZATION AND EVALUATION OF GELLIFIED EMULSION

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ABSTRACT: Emulgel represents an innovative topical drug delivery system that merges the advantages of emulsions and gels. It enhances drug absorption, particularly for hydrophobic drugs, by improving solubility, stability, and penetration through the skin. The increasing demand for patient-friendly and effective drug delivery has led to the evolution of emulgels, which offer better spreadability, prolonged retention, and controlled drug release. These formulations incorporate emulsifiers, gelling agents, penetration enhancers, and oils to optimize drug delivery. Compared to conventional topical formulations such as ointments and creams, emulgels provide a non-greasy, easy-to-apply alternative with improved bioavailability. This review explores various aspects of emulgel formulation, including essential components, preparation techniques, drug release mechanisms, and evaluation parameters. The role of penetration enhancers in boosting therapeutic effectiveness is also discussed. Recent advancements in nanotechnology, bioadhesive polymers, and smart drug delivery systems have further enhanced emulgel formulations, making them suitable for various therapeutic applications, including anti-inflammatory, antifungal, and cosmetic treatments. While emulgels present numerous advantages, challenges such as formulation stability and drug release optimization require further research. With ongoing advancements, emulgels hold significant potential for improving topical drug delivery.

KEY WORDS: Emulgel, Topical Drug Delivery, Hydrophobic Drugs, Skin Penetration, Nanoemulgel, Controlled Release, Skin Barriers, Physiological Barriers, etc.

INTRODUCTION

Topical drug delivery is an efficient method for treating skin-related disorders by providing localized therapeutic effects while bypassing first-pass metabolism. Conventional topical formulations, including creams, ointments, and gels, often encounter challenges such as limited drug penetration, instability, and poor permeability. To overcome these issues, emulgels have been developed as an advanced system that incorporates emulsions within a gel matrix. This formulation enhances drug solubility, stability, and permeation, making it particularly useful for managing conditions like fungal infections, acne, and psoriasis. Emulgels also offer improved drug retention and controlled release, ensuring better therapeutic outcomes.

In addition to dermatological treatments, topical drug delivery is applied through ophthalmic, rectal, vaginal, and dermal routes, serving both cosmetic and medicinal purposes. These formulations are available in solid, semisolid, and liquid forms, with drug absorption influenced by factors such as solubility, lipid-water partitioning, and molecular characteristics. The primary pathways for skin penetration include the stratum corneum, sweat ducts, and sebaceous follicles. Since their emergence in the mid-1980s, emulgels have gained prominence for enhancing drug delivery by improving permeation and bioavailability. Their ability to overcome the limitations of traditional topical formulations makes them a valuable approach for effective and sustained drug administration.

Skin Structure and Its role in drug delivery

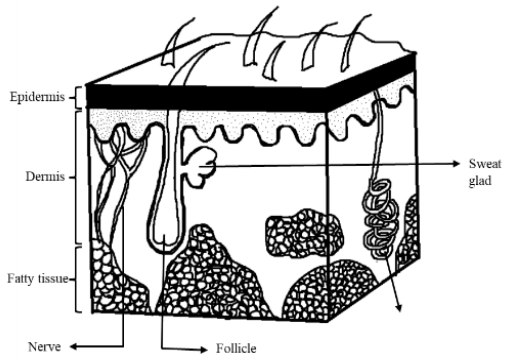

Figure no. 1: Structure of skin.

The skin is the body's largest organ, serving as a protective barrier and a medium for drug absorption. It consists of three primary layers:

- Epidermis: The outermost layer, primarily composed of keratinocytes, with the stratum corneum acting as the primary barrier to drug permeation.
  Epidermis is divided into 5 layers i.e.

1. Stratum Corneum
2. Stratum Lucidum
3. Stratum Granulosam
4. Stratum Spinosum
5. Stratum Basale.

- Dermis: Contains connective tissue, blood vessels, and nerves, supporting and nourishing the epidermis. Dermis consist of two layers i.e. papillary layer and the reticular layer and both the layer consist of substances such as elastin, fibrillin and collagen.
- Hypodermis (Subcutaneous Tissue): Composed of fat cells that provide insulation and cushioning.

Drug absorption through the skin occurs via transcellular, intercellular, and follicular pathways. Since the stratum corneum restricts drug penetration, formulation strategies like emulsions and gels, along with penetration enhancers, are used to improve drug delivery.

Skin penetration mechanisms

To achieve local therapeutic effects or systemic absorption, a topically applied drug must pass through different layers of the skin. The three primary pathways for skin penetration include intercellular, transcellular, and follicular routes:

1. Intercellular penetration allows the drug to diffuse between epithelial cells.
2. Transcellular penetration involves the movement of the drug directly through epithelial cells.
3. Follicular penetration utilizes hair follicles as entry points to bypass skin barriers.

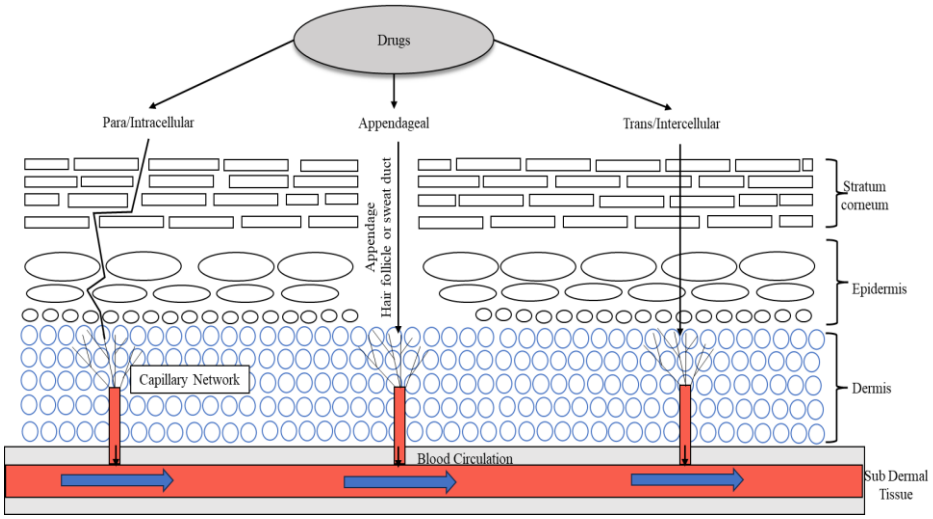

Figure no. 2: Skin penetration mechanisms.

Skin Barriers and Physiological Barriers

1. Skin barriers

- Stratum corneum: The primary barrier to drug penetration.
- Sebaceous Glands & Sweat Ducts: Influence drug diffusion and retention.

2. Physiological barriers

- pH Variability: The skin's pH (4.5–5.5) affects drug solubility and absorption.
- Enzymatic Metabolism: Skin enzymes can degrade drugs before they reach systemic circulation.

Key Factors Affecting Skin Penetration and Absorption of Topical Drugs

Several factors influence the absorption and penetration of topically applied drugs, impacting their effectiveness. These include:

1. Skin Hydration & Lipid Content – Higher moisture levels and lipid composition enhance permeability.
2. Blood Flow (Vascularity) – Increased circulation can improve drug uptake into the systemic circulation.
3. Skin pH – The natural acidity of the skin affects drug solubility and stability.
4. Hair Follicle & Sweat Gland Density – These structures provide additional routes for drug entry.
5. Skin Inflammation – Conditions affecting skin integrity can alter permeability.
6. Molecular Properties – Factors like molecular weight, partition coefficient, and ionization state determine how easily a drug crosses the skin barrier.
7. Formulation & Vehicle Type – The composition of the drug carrier plays a crucial role in absorption efficiency.

Methods to Enhance Skin Penetration and Absorption

Improving the absorption of topically applied drugs involves various techniques that enhance their ability to pass through the skin barrier:

1. Chemical Methods – Utilize specific agents to temporarily alter the skin's structure, increasing permeability.
2. Physical Techniques – Include approaches like microneedles, ultrasound, and iontophoresis to facilitate deeper drug entry.
3. Biochemical Strategies – Employ biological carriers such as liposomes or enzyme-based systems to improve drug transport.
4. Supersaturation Techniques – Increase drug concentration beyond its normal solubility limit to promote greater absorption.

Emulgel: A hybrid drug delivery system

Emulgel combines the properties of emulsions and gels, making it a suitable vehicle for hydrophobic drugs. It consists of an emulsion (either oil-in-water or water-in-oil) incorporated into a gel base, which enhances stability and improves drug penetration.

Types of emulgel

1. Oil-in-Water (O/W) Emulgel: Ideal for hydrophobic drugs, offering enhanced absorption and a non-greasy texture.
2. Water-in-Oil (W/O) Emulgel: Suitable for hydrophilic drugs, providing better occlusive properties and extended drug retention.

Advantages of emulgel

Figure no. 3: Advantages of emulgel.

Disadvantages of emulgel

1. Drugs with larger molecular weight and particle size face challenges in penetrating the skin, leading to reduced absorption.
2. The presence of small bubbles in the emulgel formulation can hinder drug penetration, affecting its effectiveness.
3. Skin irritation is a frequently observed side effect associated with emulgel applications.

Key components of emulgel

An emulgel comprises various essential components that contribute to stability, drug release, and penetration enhancement.

1. Vehicle

Characteristics of an Ideal Vehicle: A well-designed emulgel vehicle should-

- Ensure even drug distribution on the skin.
- Release the drug efficiently for better absorption.
- Maintain stability during storage.
- Be compatible with skin and excipients.
- Have an aesthetically pleasing texture and feel.

2. Aqueous phase

The aqueous phase consists of ingredients that dissolve hydrophilic components and contribute to drug diffusion.

Examples

- Purified Water – Primary solvent.
- Alcohols (Ethanol, Isopropanol) – Act as co-solvents and absorption enhancers.

3. Oily phase

This phase solubilizes lipophilic drugs and helps in the formulation's occlusive effect, reducing moisture loss.

Commonly Used Oils:

- Light Liquid Paraffin – Provides occlusion and smooth application.
- Mineral Oils – Enhance drug stability and spreadability.
- Isopropyl Myristate & Isopropyl Palmitate – Improve skin penetration.
- Castor Oil – Known for its medicinal benefits.

Other oils with functional benefits

- Jojoba Oil – Enhances hydration and skin conditioning.

- Arachis Oil – Acts as an emollient.
- Cottonseed & Maize Oil – Often used for their soothing properties.
- Fish Liver Oil – Provides essential fatty acids.

4. Emulsifying agents

Emulsifiers maintain the stability of the emulsion by preventing phase separation and ensuring uniform dispersion.

Types of Emulsifiers:

For Oil-in-Water (O/W) Emulsions – Surfactants with HLB > 8.

For Water-in-Oil (W/O) Emulsions – Surfactants with HLB < 8 (e.g., Liquid Paraffin).

Commonly Used Emulsifiers:

- Polyethylene Glycol (PEG) 40 Stearate – Ensures emulsion stability.
- Span 80 (Sorbitan Monooleate) – Used in W/O emulsions.
- Tween 80 (Polyoxyethylene Sorbitan Monooleate) – Used in O/W emulsions.
- Stearic Acid & Sodium Stearate – Serve as emulsifiers and thickening agents.

5. Gelling agents

These agents increase viscosity and provide the formulation with structural integrity.

Examples

- Carbopol 934 & Carbopol 940 – Acrylic polymers commonly used for gelling.
- Hydroxypropyl Methylcellulose (HPMC 2910, HPMC K4M) – Improve consistency.
- Sodium Carboxymethyl Cellulose (NaCMC) – Enhances viscosity and stability.

6. Penetration enhancers

Penetration enhancers help increase drug absorption through the skin by modifying its barrier properties.

Modes of Action

- Breaking down the lipid structure of the skin barrier.
- Altering skin proteins to facilitate drug passage.
- Enhancing drug solubility within the skin layers.

Commonly used penetration enhancers

- Oleic acid – Modifies lipid structure for improved permeability.
- Clove oil – Provides mild anesthetic and penetration-enhancing effects.
- Lecithin – A phospholipid that increases solubility.
- Eucalyptus Oil & Menthol – Help open up skin pores.
- Urea – Acts as a hydrator and penetration enhancer.

Method of preparation of emulgel

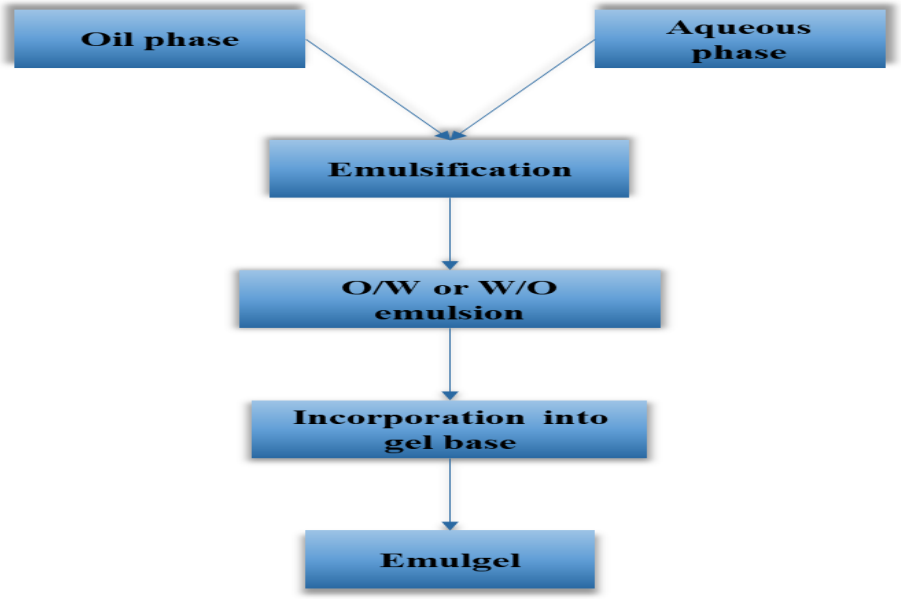

Figure no. 4: Preparation method of emulgel.

The preparation of emulgel consists of three primary steps

1. **Preparation of the emulsion:** The oil phase is prepared by dissolving emulsifiers in the chosen oils, while the aqueous phase is prepared separately. Both phases are heated to 70–80°C, and the oil phase is incorporated into the aqueous phase with continuous stirring.
2. **Preparation of the gel base:** Gelling agents are dispersed in purified water under continuous stirring, and the pH is adjusted to the required range.
3. **Incorporation of the emulsion into the gel base:** The prepared emulsion is gradually added to the gel base with continuous stirring until a uniform emulgel is formed.

Characterization of gellified emulsion

1. **Physical appearance:** The prepared emulsion formulations were visually evaluated for color, homogeneity, consistency, and pH. The pH of a 1% aqueous solution of the gellified emulsion was determined using a digital pH meter.

2. **Spreadability:** The spreadability of the emulgel was assessed using a method adapted from Mutimer et al. (1956). The test involved placing a fixed amount of emulgel between two glass slides, applying a 1 kg weight for 5 minutes, and then determining the time required for the top slide to move a fixed distance under an 80 g force. Spreadability was calculated using the equation:

$S=M\times L/T$

where S= spreadability,
M= weight tied to the upper slide,
L= slide length,
T= time taken for the slide separation.

3. **Extrudability study:** The extrudability of the emulgel was measured as the quantity of formulation extruded from a collapsible aluminum tube when a specific weight was applied. The extrudability was calculated using:
Extrudability=Applied weight to extrude emulgel from tube (gm) / Area (cm2)

4. **Globule Size and Distribution:** The average globule size and its distribution in the emulgel were determined using a Malvern Zetasizer. A sample of 1 g was dispersed in purified water, stirred, and then injected into the instrument's photocell to measure the mean globule diameter and size distribution.

5. **Rheological study:** The viscosity of the emulgel formulations was assessed at 25°C using a cone and plate viscometer (Brookfield Engineering Laboratories) with spindle 52. The viscometer was connected to a thermostatically controlled circulating water bath.

6. **Swelling Index:** The swelling index was determined by placing 1 g of emulgel on a porous aluminum foil and immersing it in a beaker containing 10 ml of 0.1N NaOH. The sample was weighed at different time intervals after removal and drying. The swelling index was calculated as:

$SW\%=[(Wt-Wo)/Wo]\times 100$

Where, SW%= equilibrium swelling percentage,
Wo= initial weight,
Wt= weight after swelling.

7. **Ex-Vivo bioadhesive strength measurement:** The bioadhesive strength was determined using a modified balance method. Freshly excised mouse skin was tied to two glass slides—one fixed and the other attached to a balance. A 1 g sample of emulgel was placed between the slides, and a force of 200 mg/min was applied until the skin pieces detached. Bioadhesive strength was calculated as:
Bioadhesive Strength=Weight required (gms) / Area (cm2)

8. **Drug content determination:** The drug concentration in the gellified emulsion was determined using a UV-visible spectrophotometer. A known quantity of emulgel was dissolved in methanol, sonicated, and analyzed spectrophotometrically after appropriate dilution.

9. **In vitro release study:** A Franz diffusion cell with an effective diffusion area of 3.14 cm^2 and a 15.5 ml receptor chamber volume was used to evaluate drug release. A 200 mg sample of emulgel was applied to an egg membrane, which was clamped between the donor and receptor chambers. The receptor chamber contained phosphate-buffered saline (PBS, pH 5.5) and was stirred continuously. At specified intervals, 1 ml samples were withdrawn and analyzed using a UV-visible spectrophotometer.

10. **Microbiological assay:** The antibacterial and antifungal activity of the gellified emulsion was assessed using the ditch plate method. Sabouraud's agar plates were prepared, and 3 g of the emulgel was placed in a ditch cut into the plate. Freshly prepared culture loops were streaked across the agar perpendicularly from the ditch. After incubation at 25°C for 18–24 hours, the inhibition zone was measured. The percentage inhibition was calculated as:

$\%\ inhibition=L2L1\times 100$

where L1= total streak length
L2= inhibition zone length.

11. **Skin irritation study:** The potential for skin irritation was evaluated using a rabbit model. A 0.5 g sample of emulgel was applied to a defined skin area (2.54 × 2.54 cm^2) under a double gauze layer. After 24 hours, the site was wiped with tap water and assessed for irritation.

12. **Accelerated stability studies:** Stability testing was conducted per ICH guidelines. The emulgel formulations were stored at 37 ± 2°C, 45 ± 2°C, and 60 ± 2°C for three months. Drug content and pH were measured every two weeks using a UV-visible spectrophotometer to assess formulation stability.

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