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A REVIEW ON EMULGEL: THE TOPICAL DRUG DELIVERY SYSTEM

C. S. Karthik*[1], D. Shripathy[2] and A. R. Shabaraya[3]

Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India-574143.

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***Corresponding Author**
C. S. Karthik
Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India-574143.

ABSTRACT

Gels offer numerous advantages in topical drug delivery, but a significant limitation is their effectiveness in delivering hydrophobic drugs. To address this challenge, an emulsion-based approach has been adopted to harness the unique properties of gels even for hydrophobic therapeutic agents. The combined use of gels and emulsions results in a dosage form known as an emulgel. In recent years, there has been a notable focus on the utilization of novel polymers in this field. Dermatological pharmacology benefits from the direct accessibility of the skin as a target organ for diagnosis and treatment. However, the skin's structure, with hydrophilic cornified cells and hydrophobic intercellular material, creates a barrier to both hydrophilic and hydrophobic substances. Transparent gels, within the broader category of semisolid preparations, have gained popularity in both cosmetics and pharmaceutical formulations. Polymers play a crucial role in emulgels, functioning as emulsifiers and thickeners. Their gelling capacity enables the formulation of stable emulsions and creams by reducing surface and interfacial tension while increasing the viscosity of the aqueous phase. The introduction of a gelling agent in the water phase transforms a classic emulsion into an emulgel. Emulgels exhibit significant advantages over both novel vesicular systems and conventional systems. The addition of permeation enhancers further enhances their efficacy. Therefore, emulgels emerge as superior topical drug delivery systems compared to existing methods. Their applicability can be extended to anti-inflammatory drugs, showcasing the versatility and potential of emulgels in pharmaceutical and cosmetic formulations.

KEYWORDS: Anti-inflammatory, Emulgel, Pharmaceutical, Hydrophobic, Dermatological.

1. INTRODUCTION

Topical drug delivery system is the dosage form which is administered on the skin and other routes of drug delivery get failed or for skin disorders. The topical drug delivery system has the advantage of negotiating the first pass metabolism. It also helps to avoid the risk and inconvenience of i.v route therapy. Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. In each formulation with the active ingredients many excipients are used. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance.[1] A unique feature of topical drug delivery is the direct accessibility of the skin as a target organ for diagnosis and treatment.[2]

Conventional ointments, creams and gel formulations generally provide faster drug release.[3] Gels generally have faster absorption into skin due to their water-based nature, but their penetration may not be as deep. Disadvantages of gels include residue, stickiness, drying effect, difficulty in application, incompatibility with certain ingredients, sensitivity issues, not ideal for all skin types and limited stability.[4]

Oil-in-water emulsions are most useful as water-washable drug bases and for general cosmetic purposes, water-in-oil emulsions are most useful as water-washable drug bases, for general cosmetic purposes and are employed more widely for the treatment of dry skin and emollient applications.[5]

Emulsions are capable of acting as controlled drug delivery systems where the medicinal agent to be delivered is stored inside the oil phase. This internal oil phase of an emulsion will function as a drug reservoir and the drug will be released to the skin in a controlled manner.[6] Emulgel is more effective in curative aspects than regular gel. It is a thermodynamically stable formulation with low interfacial tension that is made by combining a surfactant and a co-surfactant and has several properties such as increased permeability and good thermodynamic stability. Emulgel has a dual control and a sustained release pattern.[7]

Advantages of emulgel include easy incorporation of hydrophobic drugs, augmented drug loading capacity, production feasibility (simple and short processing steps) and low preparation cost, avoidance of first-pass metabolism and gastrointestinal incompatibility, improved patient compliance, suitability for self-medication, narrow therapeutic window and selective to a specific site.[8]

Emulgel is prepared by different polymers which act as an emulsifying agent and thickening agent because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase.[9] When gels and emulsions are used in combined form the dosage forms are referred as emulgel. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel.[10]

2. ANATOMY OF SKIN

Skin covers almost 15% of an adult body weight. It's a largest organ of the human body. Skin is such an important part of a human body playing super beneficial role that includes protection against many agents such as physical, chemical and biological. There is another important role of skin i.e. thermoregulation. Going on deep there are several layers of skin categorized below:

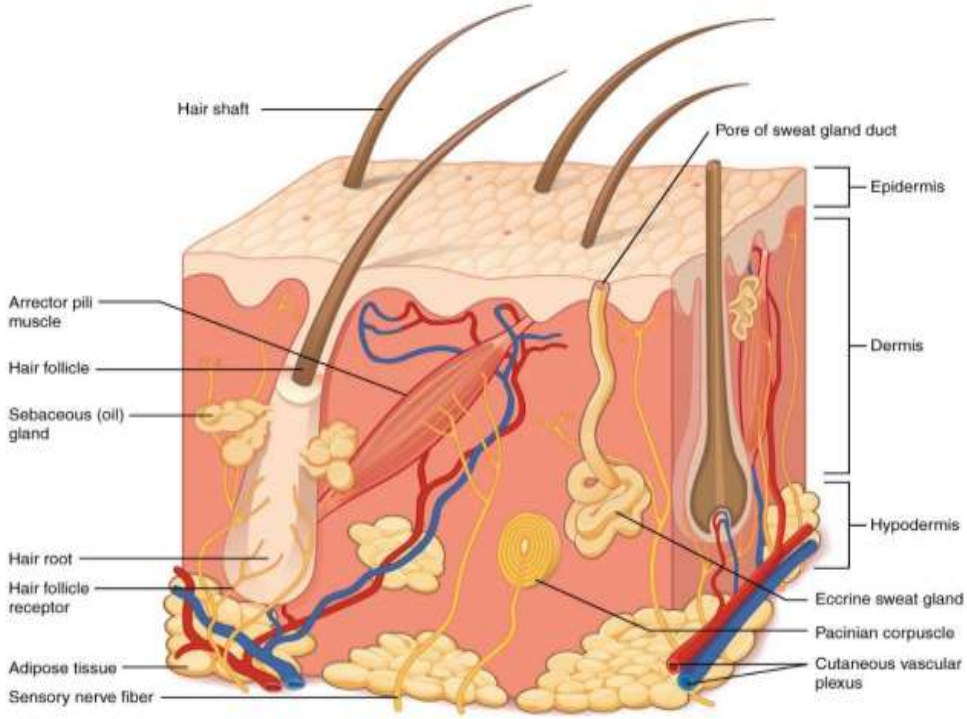

Fig. 1: Anatomy of skin.[11]

- The Epidermis
- The non-viable Epidermis
- A viable Epidermis (Stratum corneum)
- Overlying dermis
- Hypodermis

Epidermis: The epidermis consists of four or five epithelial cells which depends on its location on the body. It is a vascular tissue that does not have any blood vessels.

Non-Viable Epidermis: It is the outermost layer of epidermis, there is a belief in the field of dermatology that this layer consists of dead cells. But now it is believed that it performs various protective functions such as impact resistant, initiation of inflammation through cytokine activity, dendritic cell activity. It has no nuclei and behaves as a selectively permeable membrane for some toxins and allergens.

Viable Epidermis: This layer is situated below the non-viable epidermis and responsible for various barriers of skin. It contains melanocytes and merkel cells also consist of the cells which are at various stages of differentiation.

Dermis: The dermis is the layer between epidermis and subcutaneous tissues and consists of many irregular connective tissues and relieves the body from stress. It is divided into two layers, the superficial area and deep thicker area. The superficial area is known as the papillary region and the deep thicker region is known as the reticular region. Structural components of dermis are collagen, elastic fibers and extrafibiliar matrices. Addition to all this it also contains some receptors like mechano receptor for sense of touch and thermoreceptor for sense of heat. Some hair follicles sweat glands are present in the dermis. These provide nourishment and waste removal for both dermal and epidermal cells.

Hypodermis: It is a layer between dermis and underlying tissue and organs. It consists of adipose tissue that works as a storage site for body fat. It serves to fasten the skin to the underlying surface, providing thermals.

3. Rationale for Topical Preparation

With the purpose to formulate an efficient and effective topical preparation, considerations are mainly concerned with the site of action of the drugs and its effect. Topical preparations may be used produce:

4. Action and Effects of Drugs

The topical preparation includes various effects and action that are as follows:

Effect on Surface

- The cleansing effect of removing germs and dirt.
- Improves cosmetic appearance.
- Protective action against moisture.
- Produce an antimicrobial effect.

Effect on stratum corneum

- Moisturizing effect.
- Keratolytic effects.
- Anesthetic effects, inflammatory effects, antihistamine etc. are the major classes of drugs that penetrate viable epidermis and dermis.

5. Advantages of Topical Drug Delivery System

- Avoidance of primary pass metabolism.
- Easily to terminate the medication.
- Easy to use and apply.
- Drugs delivered to specific sites.
- The gastro intestinal incompatibility will be avoided.
- Self-medication.
- Better patient compliance.
- Avoids fluctuation in drug levels and risks.

6. Disadvantage of Topical Drug Delivery System

- Possibility of skin irritation at the site of application.
- Some drugs with poor permeability do not penetrate via skin.
- Contact dermatitis due to some drug may occur.
- Possibility of allergic reactions.
- Drugs with larger particle sizes are difficult to penetrate.

7. Factors Affecting Topical Drug Adsorption

Physiological factors

1. Thickness of skin: From epidermis to subcutaneous layer skin thickness varies and high rate of diffusion present on the palm and soles. The thickness of epidermis layer is about 100-150µm.
2. Lipid content: It is an effective water barrier. When lipid weight in stratum corneum is low, percutaneous penetration increases.
3. Hair follicles Density: Hair follicle infundibulum has a large storage capacity about 10 times more than the stratum corneum.
4. The density of sweat glands.
5. Skin pH: Sweat and fatty acid secreted from sebum influence the pH of the skin surface.
6. Blood flow.
7. Permeation of drug can enhance by skin hydration.
8. Continuity of stratum corneum disrupt by the inflammation of skin which increases permeability.
9. When skin temperature increases the rate of skin permeation also increases.

Physiochemical factors

- Partition coefficient: Percutaneous absorption of the drug will be more easily when more the value of log p.
- The molecular weight (<400 Dalton).
- The degree of ionization (only unionized drugs gets absorbed well).
- Vehicles effect: the most efficient absorption through the skin provided by the hydro alcoholic gel.

8. Factors to be considered when choosing a Topical Preparation

1. Effect of the vehicle E.g. An occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.
3. Match the type of preparation with the site. (e.g., gel or lotion for hairy areas)
4. Irritation or sensitization potential. Generally, ointments and w/o creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.[11]

Method to Enhance Drug Penetration and Absorption

1) **Chemical enhancement:** Chemical enhancers, also known as penetration enhancers, are compounds that alter the physicochemical properties of the stratum corneum to facilitate drug penetration. These enhancers can disrupt the lipid bilayers of the stratum corneum, increasing the permeability of the skin barrier to allow drugs to penetrate more effectively. Examples of chemical enhancers include surfactants, fatty acids, alcohols, and various chemical agents like dimethyl sulfoxide and ethanol.
2) **Physical enhancement:** Physical enhancement techniques involve the use of physical methods to enhance drug penetration through the skin or mucosal membranes. Examples of physical enhancement methods include:

a. **Microneddles:** These are small, minimally invasive needles that create microchannels in the skin, allowing drugs to penetrate through the barrier.

b. Sonophoresis: This technique uses ultrasound waves to transiently disrupt the stratum corneum, enhancing drug penetration.
c. Electroporation: Applying electric pulses to the skin creates temporary pores in the cell membrane, facilitating drug absorption.
d. Iontophoresis: This method utilizes a low-level electric current to drive charged drug molecules across the skin barrier.

3) Biochemical enhancement: Biochemical enhancement involves using biological agents or substances to enhance drug absorption through specific pathways or mechanisms. Examples of biochemical enhancement methods include the use of enzyme inhibitors to prolong the presence of drugs at the absorption site, or the use of prodrugs that are converted into active drugs in the body to enhance absorption.

4) Supersaturation enhancement: Supersaturation enhancement involves increasing the concentration of a drug in solution beyond its equilibrium solubility, leading to enhanced absorption. Techniques to achieve supersaturation include the use of cosolvents, pH adjustment, complexation with cyclodextrins, or formulation of amorphous solid dispersions. Supersaturation can improve drug absorption by increasing the concentration gradient across the absorption membrane, enhancing the driving force for drug transport.

Advantages

1. Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.
2. Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
3. Better loading capacity: Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.
4. Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.
5. No intensive sonication: Production of vesicular molecules need intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.
6. Controlled release: Emulgels can be used to prolong the effect of drugs having shorter t1/2.

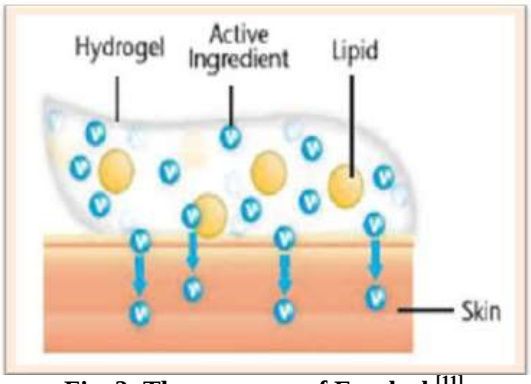

Fig. 2: The structure of Emulgel.[11]

Important Constituents of Emulgel Preparation

1. Aqueous Material: This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.
2. Oils: These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are nonbiodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.
3. Emulsifiers: Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. Eg Polyethylene glycol 4031 stearate, Sorbitan monooleate (Span 80), Polyoxyethylenesorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.
4. Gelling Agent: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.
5. Permeation Enhancers: These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.[12]

PREPARATION OF EMULGEL

Emulgel are prepared by incorporating gel and emulsion. The emulsion and gel are prepared separately and mixed together. For preparing emulsion, aqueous phase and oil phase are taken separately and mixed together. Then the gel is prepared by using gelling agent. After preparing

gel and emulsion, they are mixed with gentle stirring. The chemicals are used as oil phase are castor oil, clove oil liquid paraffin, etc. Water and alcohol are used as aqueous phase.

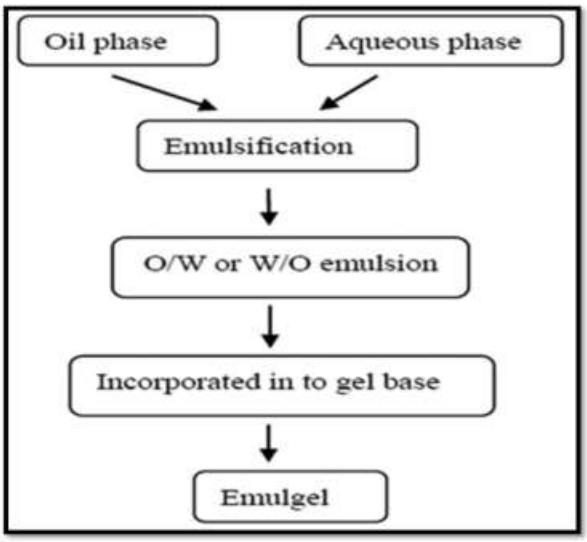

Fig. 3: Flow chart of emulgel preparation.[13]

The aqueous phase is prepared by mixing tween 80 and water and also the oil phase prepared by mixing paraben and propylene glycol. The drug is dissolved in ethanol and the two phases are mixed with continuous stirring. Then the polymers are dissolved in water with the pH of 6.0-6.5. After preparing emulsion and gel separately, they are mixed together to get emulgel.[13]

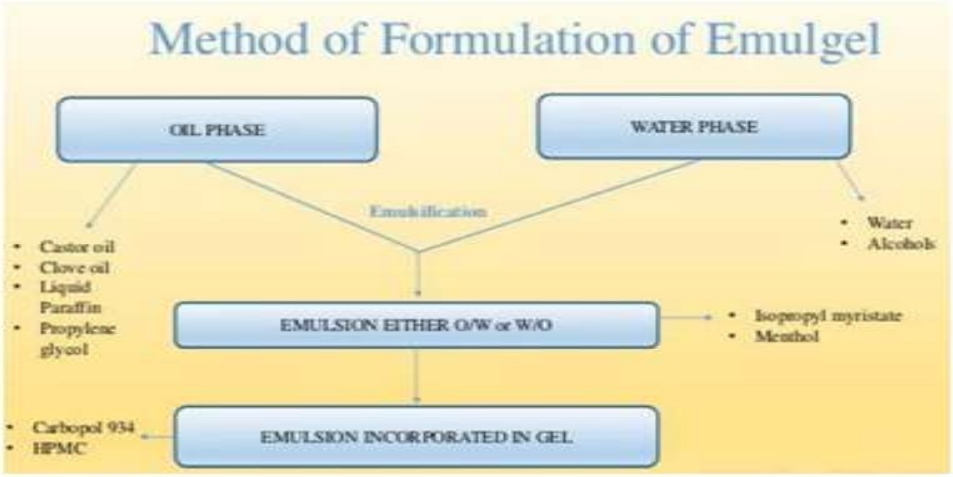

Fig. 4: Method of formulation of emulgel.[13]

Evaluation Parameter Of Emulgel

Fourier transforms infrared spectroscopy (FTIR): The primary aim of analysis of FTIR was to find a stable storage condition for the drug in solid state and excipient compatibility for Emulgel formulation.[14]

Physical appearance: The prepared emulgel formulations were examined visually for their colour, consistency and phase separation.

pH: Digital pH meter was used for measuring the pH of prepared emulgels. 1gm of emulgel was dissolved in 100 ml of distilled water and was placed for 2 hrs. Glass electrode was dipped in the above solution and pH values were noted.[15]

Determination of viscosity: The viscosity of the formulated batches was determined using a Brookfield Viscometer. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25 ± 1ºC) before the measurement was taken. Spindle was lowered perpendicular into the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.

Spreadability: Spreadability of the formulations was determined by measuring the spreading diameter of 1 g of sample (an excess of emulgel about 2 gm.) between two horizontal glass plates (10 cm × 20 cm) after one

minute. The standard weight applied to the upper plate was 25 gm or 80 gm or 1 kg. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Each formulation was tested three times. Spreadability was calculated by using the formula,

$$S = M.L/T \text{ -------- Equation 1}$$

Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides, T = Time taken to separate the slides completely from each other.[16]

Globule size and its distribution in emulgel: Globule size and distribution is determined by Malvern zeta sizer. A 1.0 g sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample was injected to photocell of zeta sizer. Mean globule diameter and distribution is obtained.

Swelling index: To determine the swelling index of prepared topical emulgel, 1 g of gel is taken on porous aluminium foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaoH. Then samples were removed from beakers at different time intervals and put it on a dry place for some time after it reweighed.[2]

***In-vitro* diffusion studies:** Diffusion study of emulgel formulations were performed using modified Keshary-Chien or frandz diffusion cell. The pretreated dialysis sac (Cellophane membrane) was used in franz diffusion cell. The cell was locally fabricated and volume of receptor compartment was 20 ml. Phosphate buffer of pH 7.4 was used for *in-vitro* release as receptor medium. The emulgel sample was applied on the membrane and then fixed in between donor and receptor compartment of quality diffusion cell. The receptor compartment contained phosphate buffer pH 7.4. The temperature of diffusion medium was thermostatically controlled at 37º ± 0.5ºC by surrounding water in jacket and the medium was continuously stirred by magnetic stirrer at speed of 600 rpm. At pre-determined time intervals, 5 ml of sample were withdrawn, and an equal volume of buffer was replaced and replaced by equal volume of freshly prepared media. The withdrawn samples were analyzed spectrophotometrically for drug content.

Release rate studies: Plot amount of drug permeated per square centimeter versus square root of time and calculate slope. Slope is release rate. Units - mg/cm2/hr1/2.[16]

Drug content: 1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 246 nm. Drug content was calculated by linear regression analysis of the calibration curve.[17]

Phase separation testing by centrifugation: 6g of emulgel formulation was taken in centrifuge tubes and centrifuged at 4000 RPM for 10 min. After 10 minutes all formulations were observed for any phase separation occurrence.[18]

Skin Irritation Test: A set of 4 rats was used in the study. A 0.5 gm of emulgel formulation was applied on the properly shaven area of skin approximately 1" x 1" (2.54 x 2.54 cm) square^2. When the undesirable changes like skin color; change in skin morphology was checked for a period of 24 hr.[3.19]

Stability studies: For more satisfactory formulation, the stability study was performed. The formulation was packed in collapse tubes and stored for three months at room temperature. The formulations were analyzed after every one month for physical properties, spreadability, pH, and drug content.[20]

Drug release kinetic study: Drug release of topical formulation were calculated by the following equation.

(1) Zero order equation; Q=ko t

Q=amount of drug release
T=time
Ko=zero-order release constant

(2) 1ST order equation; In (100-Q)=In 100-k1t

Q= % of drug release
T= time
K1= 1st order release constant

(3) Higuchi equation; Q= k2√t

Q= % of drug release
T= time
K2= rate constant of diffusion.[14]

CONCLUSION

After an extensive literature review, it is concluded that emulgels serve as highly convenient, superior, and effective delivery systems. By virtue of their non-greasy, gel-like consistency, emulgels offer advantages over traditional oily bases, facilitating enhanced drug release compared to other topical delivery systems. This is particularly beneficial for hydrophobic drugs commonly utilized in the treatment of various skin disorders, as they can be seamlessly incorporated into the oil phase of the emulsion and combined with the gel component.

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