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Film-Forming Emulgel: A Novel Approach for Topical Drug Delivery

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ABSTRACT

Advancements in pharmaceutical technologies have spurred exploration into alternative drug delivery routes, beyond oral and parenteral, for efficient and effective targeting of therapeutic agents. Topical drug delivery systems offer a method for localized treatment of superficial areas such as the skin, eyes, nose, and vagina, avoiding issues like first-pass metabolism and plasma level fluctuations associated with oral administration. However, challenges such as restricted permeability and rapid clearance limit their efficacy. Emulgel, a combination of gels and emulsions, offers promising solutions by incorporating hydrophobic drugs into gel bases, improving stability, and enhancing patient compliance. Film-forming systems further enhance drug retention and applicability, offering long-lasting effects. This review explores the rationale, formulation and evaluation of emulgel and film-forming systems as innovative approaches for topical drug delivery.

INTRODUCTION:

Advances in pharmaceutical technologies have encouraged the formulation scientists to explore alternative routes, besides oral/parenteral, for the delivery of drug efficiently and effectively to the target site. Effective drug administration encompasses the optimal delivery of therapeutics at the site of action within the given time frame. The topical delivery system refers to a method wherein the formulation is applied to the superficial areas such as the skin, eyes, nose and vagina for the treatment of local diseases. [1-3]

The drug application to the topical surfaces evades the hepatic first pass metabolism, gastric pH variations and fluctuations in plasma levels, frequently encountered when a drug is administered through the oral route. [4]

The other advantages associated with the topical drug delivery system include the following:

- Patient compliance and acceptance
- Ease and convenience of application
- Painless and non-invasive technique
- Improvement in drug bioavailability
- Better physiological and pharmacological response
- Minimum systemic toxicity and exposure of drug to non-infectious tissue/sites. [5]

The development of a topical delivery system is a challenging task that requires a careful selection of not only the active principle but also the vehicle in which the drug is to be delivered, since the barriers associated with these routes may limit the availability of drug to effective site. The stratum corneum is the major barrier to the access of foreign particles through the skin. [6]

Table 1: Challenges associated with topical drug delivery

ROUTE	CHALLENGES
Skin	Restricted permeability due to stratum corneum Hydration level Acidic pH (4.2 - 5.6)
Vagina	Presence of degradative enzymes Low residence time Continuous vaginal fluid flush Dilution/inadequate spreading of formulation
Nose	Rapid muco-ciliary clearance Enzymatic degradation of drug Permeability barriers due to nasal epithelium
Eye	The high turnover rate of tear fluid Tight junction complexes in epithelial layer Naso-lacrimal drainage Transient residence time in cul-de-sac

95% of topically applied drugs are washed out from the surface of an eye within minutes after drug application. The effectiveness of conventional vaginal formulations is limited because of their short residence time and inadequate spreading over the vaginal tissues. [7]

These limitations reinforce the need for extensive research to develop new/innovative delivery systems by either varying the formulation components or their administration methods.

Various formulations that are currently being researched for topical drug delivery are represented in Figure 1. [8-28]

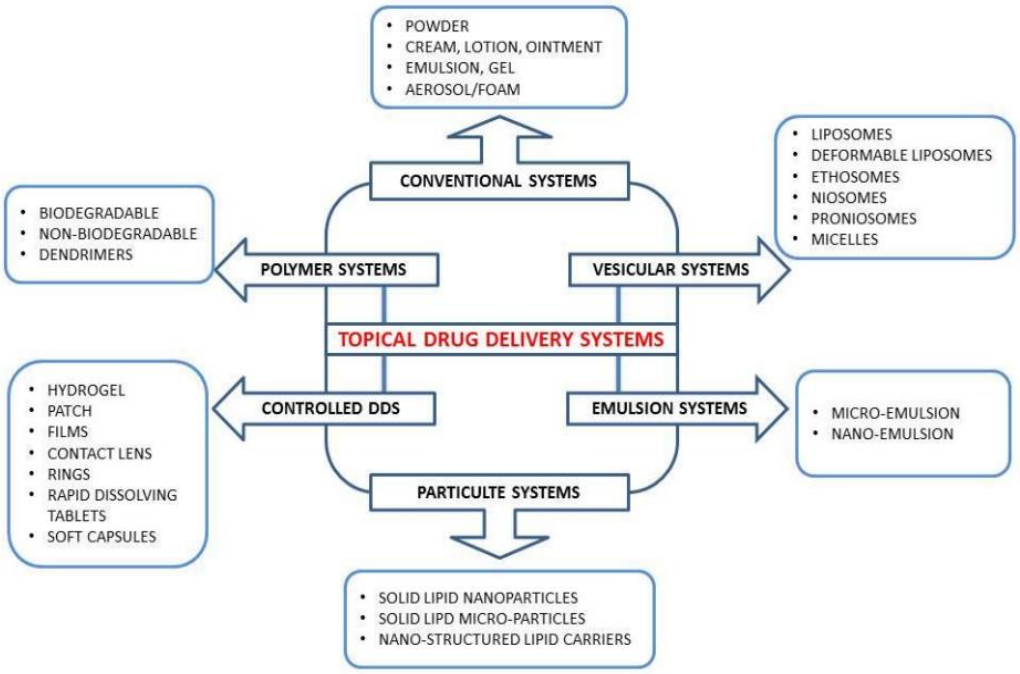

Figure 1: Dosage forms available for topical drug delivery

RATIONALE OF EMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM

INTRODUCTION TO EMULGEL

When gel and emulsion are used in combination form, the dosage form is referred to as "emulgel". Emulgel has major advantages on novel vesicular systems as well as on conventional systems in various aspects: Being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance.

Emulgel dosage form is used for steroids, and some antibiotics and it was extended to analgesics and antifungal drugs. Topical agents such as ointment, cream, lotion have many disadvantages. They are sticky and causing uneasiness to the patients, also have lesser spreading coefficient, and need to be applied sometimes with rubbing. They exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gel has expanded both in cosmetics and in pharmaceutical preparation.

However, despite of offering several benefits, gels a colloid system shows major limitations like delivery of hydrophobic drugs.

In order to overcome this problem an emulsion-based approach is being used so that even hydrophobic therapeutic moiety can be successfully incorporated and delivered through gel mixtures [29-32].

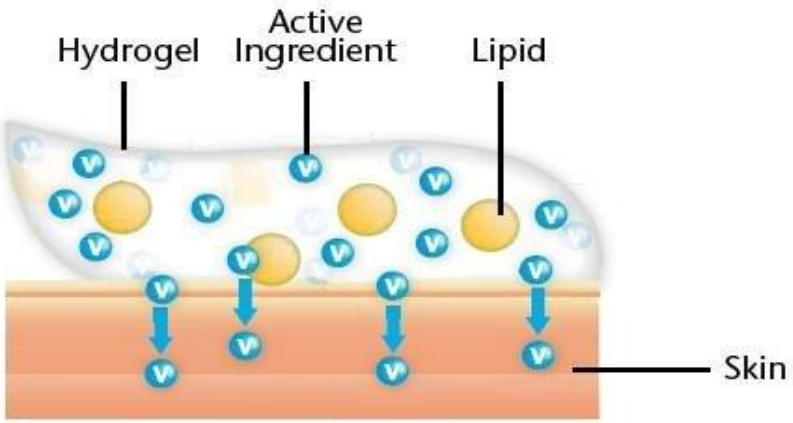

Figure 2: Structure of Emulgel

Advantages of Emulgel:

1. Using water/oil/water emulsions, hydrophobic drugs can be quickly implemented into the gel base.
2. Improved stability and load capacity.
3. Easy for production and a low-cost mechanism.
4. Avoid sonication. The first metabolism is avoided.
5. Avoid gastrointestinal incompatibility.
6. Target drug delivery on the body.
7. Improved patient compliance.
8. Improved patient acceptability and suitability for self-medication.
9. Ability to easily terminate medication. [33]

Disadvantages of Emulgel:

1. The drug and / or excipients can lead to skin irritation in people with contact dermatitis.
2. Some medications have low permeability through the skin.
3. Possibility of allergenic reactions.
4. Larger-particle-size drugs are not easily incorporated into the skin. [33]

FORMULATION OF EMULGEL:

For the preparation of emulgel some constituents are used including drug, which are:

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 40 stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan 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. [34]

Table 2: Examples of components:

COMPONENT	EXAMPLE
Aqueous material	Water, ethanol, isopropyl alcohol
Oil	Mineral oil, coconut oil, olive oil
Emulsifiers	Span 80, Tween 80, Tween 60
Gelling agents	Carbomer, xanthan gum, methylcellulose

STEPS IN FORMULATING AN EMULGEL

STEP 1: Formulation of Emulsion either O/W or W/O.

STEP 2: Formulation of gel base.

STEP 3: Incorporation of emulsion into gel base with continuous stirring.

Step 1: Emulsion Formulation (o/w or w/o type):

For the oil phase of the emulsion, the emulsifier (e.g. span 80) is dissolved in an oil vehicle such as liquid paraffin. Simultaneously, the water phase is prepared by dissolving a hydrophilic emulsifier-like a tween in purified water. Methyl paraben and propyl paraben are dissolved in a humectant like propylene glycol, and the drug is dissolved in ethanol. Both solutions are mixed with the watery phase through continuous blending. The oily and aqueous phases are separately heated to 70°C to 80°C, after which the oily phase is added to the aqueous phase with constant blending. This mixture is allowed to cool to room temperature to form an emulsion. [34]

Step 2: Gel Base Formulation:

The gel phase is established by dissolving the polymer in purified water with continuous stirring at a moderate speed using a mechanical shaker. The pH is then adjusted to 6 - 6.5 using triethanolamine or sodium hydroxide. [34]

Step 3: Emulsion Incorporation into Gel Base with Continuous Blending:

The gel phase is blended into the emulsion phase in a 1:1 ratio to obtain an emulgel. [34]

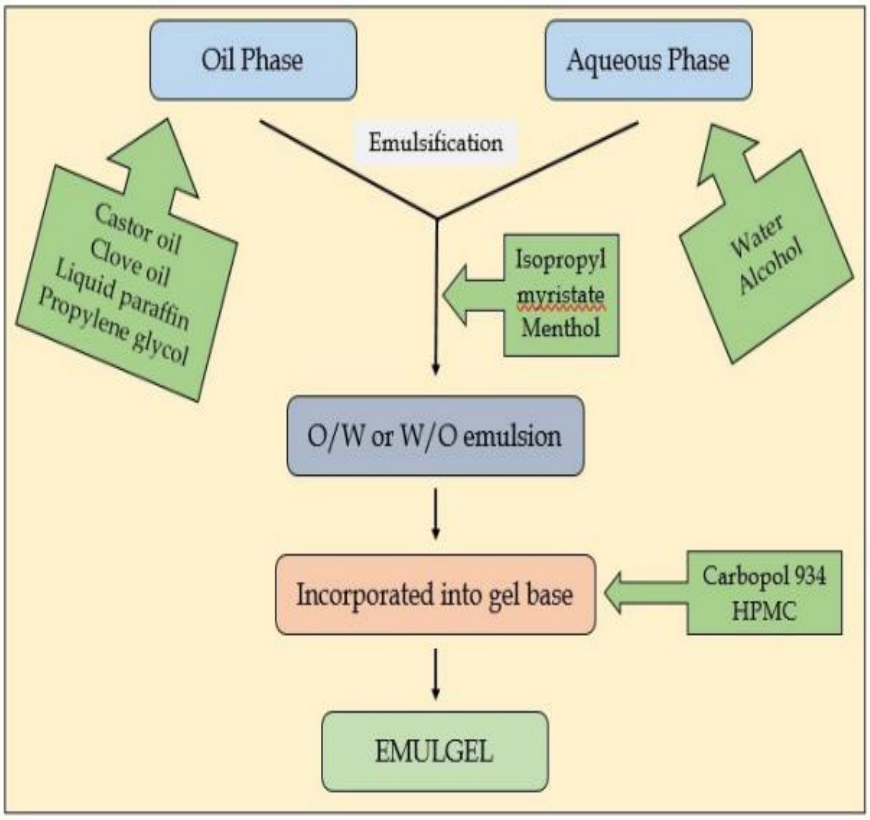

Figure 3: Method of formulation of Emulgel.

FILM-FORMING SYSTEMS

Film forming systems can be defined as liquid or semi-solid formulations that form films after application on the skin on evaporation of the solvent.

Films formed on the skin are occlusive, and prevent adhesion and reduce risks of re-infection. Film-forming systems can thereby be explored to circumvent the issues of low residence time and poor applicability feel on the skin associated with the conventional topical.

Combining a gelling agent and a film former in the aqueous phase of a classical emulsion forms a film-forming emulgel, which provides the pros of a gel by increasing patient compliance due to low incidences of wiping off of the formulation. [35]

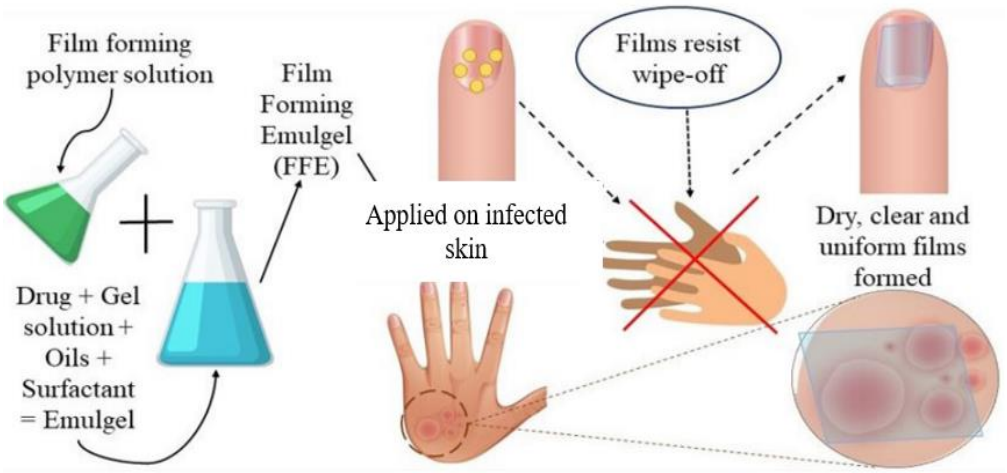

Figure 4: Film forming Emulgel

The term "film-forming" refers to the ability of a substance to create a thin, continuous layer or film upon application and drying. The film-forming aspect can be particularly advantageous in dermatological formulations or products designed for long-lasting effects on the skin.

The film forming preparation can be applied to the site regardless of shape and area, and can be retained for a long time as compared to conventional semi-solid preparations. [35]

Fig A) shows that FFS forms an almost completely transparent fast drying film on application.

Fig B) shows that after drying, a non-tacky, flexible and easily peel able film is formed.

There is an excellent adhesion of the formed film to the skin, hence wipe off resistance. Therefore the risk of transfer of active other people or clothes is reduced. [35]

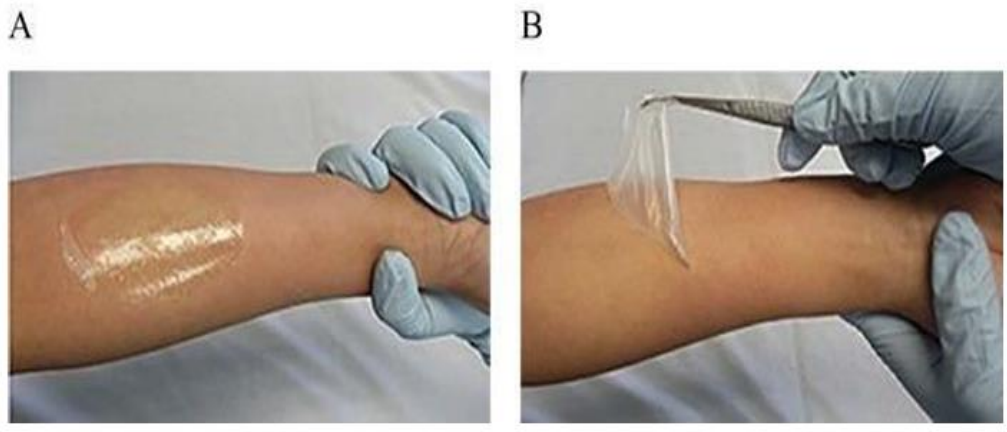

Figure 5: A) BEFORE DRYING B) AFTER DRYING

Film forming application:

1. They can provide a unit dose and reduced dose frequency.
2. Improved drug delivery.
3. Easily applied to large application areas and the rapidly drying/absorbing nature can help to minimize losses of product onto cloths or other people.
4. Fast dissolving and also, we can make from it sustained drug delivery.
5. Good patient compliance, and reduced dose frequency.
6. Used in wound care, as a tissue glues for closing of operative wounds. [35]

Table 3: Film Forming Polymers

POLYMERS	PROPERTIES
Hydroxypropyl Methylcellulose (HPMC) HPMC (E4M, E15, E50M K4M,)	Produce a light, non-greasy uniform film with good texture. Do not interact significantly with other ingredients.
Ethyl cellulose (EC)	Good film-forming properties that form tougher films.
Polyvinyl Pyrrolidine (PVP) (PVP K30, PVP VA64)	Solubility in water and other solvents Adhesive and binding property. Acts as a bioavailability enhancer

EVALUATION OF EMULGEL [36]

1. PHYSICAL APPEARANCE:

For the evaluation of the prepared formulation, visual observations were made to determine its appearance, categorizing it as clear, opaque, or white.

2. pH:

To assess the pH of the emulgel, a digital pH meter was utilized. This involved dissolving 1 g of emulgel in 100 ml of distilled water to create a clear solution, and the pH was measured using pH digital meter.

3. VISCOSITY:

Viscosity measurements were conducted using a Viscometer (Brookfield, DV-E model) with the use of spindle S94 (T-shaped spindle). Around 1g of emulgel was placed on the plate of the Brookfield viscometer and allowed to settle for 5-10 minutes. Subsequently, the spindle was positioned on the gel-covered plate, and rotation was initiated at a speed of 5 rpm. The temperature was maintained at 25°C, and the corresponding dial reading was recorded. This recorded reading serves as an indicator of the viscosity of the formulations, measured in centipoises (cps).

4. SPREADABILITY:

The spread ability assessment involved employing two glass slides of length 7.5 cm lined with butter paper. A measured quantity (0.5 g) of the emulgel was positioned between the two slides, and the initial diameter was recorded. Subsequently, a consistent weight of 5gm was applied to the assembly for a duration of 1 minutes, and the increase in diameter was observed and noted.

5. EXTRUDABILITY:

The tubes were sealed at the extremity, and the extruded strand of the emulgel was examined for its continuity. If a continuous strand was extruded, it received a grade of 1. Additional strands were designated as grade 2 if they exhibited intermittent breaks, and a rating of 3 was assigned if the strands were completely discontinuous.

The extrudability was then calculated by using the following formula.

$$\text{EXTRUDABILITY} = \frac{\text{Weight applied to extrude emulgels from tube (in g)}}{\text{Extrudability Area (in cm)}}$$

6. *DRUG CONTENT:*

A measured amount of 0.5 g of the emulgel was dissolved in 50 mL of phosphate buffer with a pH of 6. Subsequently, the solution underwent sonication for approximately 10 minutes and was then filtered through a Whatman filter paper. The drug concentration was determined spectrophotometrically at specific nm, employing the same buffer as the blank. The calculation of drug content was performed using the linear regression equation derived from a standard curve in phosphate buffer with a pH of 6.

7. IN VITRO DIFFUSION STUDIES:

In vitro diffusion studies using a Franz Diffusion cell and cellophane membrane were conducted to assess drug release characteristics. A quantity of 0.5 g emulgel was applied to the cellophane membrane, positioned between the donor and receptor compartments, containing 13 ml of phosphate buffer at pH 6. The temperature of the diffusion medium was maintained at 37 ± 0.5°C, and continuous stirring at 100 rpm was maintained using a magnetic stirrer. Aliquots of 2 ml were withdrawn at specific time intervals and replaced with an equal volume of fresh buffer. These withdrawn samples were then analysed spectrophotometrically at specific nm, and the cumulative percentage of drug release was calculated.

8. SKIN IRRITATION TEST:

Conducting the skin irritation test followed OECD guidelines for in vitro skin irritation test No. 439, Wistar rats (12) of either sex were employed. The rats were divided into two groups: control and test, each consisting of 6 animals. A 5 cm^2 area on the back skin of the rats was shaved one day prior to the study. After 24 hours, the control group received an application of gel base (without the drug), while the test group was treated with the optimized emulgel. Subsequently, the rats were observed for any signs of irritation, and scores were assigned based on the observed signs of irritation.

9. STABILITY STUDIES:

The emulgels formulated were enclosed in collapsible aluminium tubes and underwent stability studies at two different conditions: 25±5°C /60% RH and 40±5°C /75% RH, spanning a duration of 1 month. Throughout this period, the emulgels were scrutinized for changes in their physical properties as well as their in vitro and ex vivo release characteristics. [36]

EVALUATION OF FILM FORMING EMULGEL (FFE) [36]

1. *FILM FORMING TIME:*

The film-forming time of formulation was determined by applying 0.5g of the product as a 2x2 cm^2 patch on five volunteers' forearms. The time taken for the emulgel to completely dry and form a film on the volunteers' hands was documented. Complete drying was verified by

placing a glass slide on the film without applying pressure, and the film was considered dry when no residues were visible after removing the slide.

2. *PEEL ABILITY*:

Peel ability was assessed by gently peeling the films from the skin and inspecting their uniformity. The peeled films were expected to be continuous and non-flaky.

3. *FOLDING ENDURANCE:*

Folding endurance was gauged by repetitively folding the peeled film at the same spot until it broke. The folding endurance of the film was determined by the number of times it could be folded at the same location without breaking.

4. *TACKINESS:*

Tackiness of the outer surface was evaluated by pressing cotton wool onto the dry film at low pressure. The stickiness level was determined based on the amount of cotton fibers retained by the film, categorizing it as high, medium, or low tackiness.

5. *COSMETIC ATTRACTIVENESS:*

Cosmetic attractiveness was determined through visual examination of the dried films, with a rating scale from 1 to 3. Transparent films, almost invisible and highly attractive, were rated as 1. Opaque films forming translucent films with slight skin wrinkling were rated as 2. Whitish films causing heavy wrinkling of the skin and displaying low attractiveness were rated as 3.

6. *SWAB STUDIES*:

Swab studies involved applying the optimized FFE on a glass plate marked with six squares of 3x3 cm^2. Formulations were removed using cotton swabs at 0 min, 30 min, 60 min, 120 min, 180 min, and 240 min the swabs were placed in vials containing 10 ml methanol and sonicated for 10 min to extract the drug completely. [36]

CONCLUSION:

The exploration of emulgel and film-forming systems marks a significant leap forward in pharmaceutical technology for topical drug delivery. Emulgels, through their unique

combination of gel and emulsion properties, offer a versatile platform for efficiently delivering hydrophobic drugs while ensuring stability and patient adherence.

Similarly, film-forming systems offer distinct advantages by forming occlusive films upon application, thereby enhancing drug retention and improving applicability. The integration of gelling agents and film formers in film-forming emulgels further amplifies patient compliance and minimizes the risk of formulation removal, ensuring prolonged therapeutic effects.

Overall, the development and research into these innovative delivery systems highlight their potential to revolutionize topical drug administration, overcoming the limitations of traditional dosage forms. By providing localized treatment for superficial conditions and addressing patient needs for convenience and efficacy, emulgels and film-forming systems pave the way for the development of novel formulations with enhanced therapeutic outcomes.

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