Review Article

Emulgel Review – A Novel Topical Drug Delivery System

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ABSTRACT

A TDDS is the direct administration of a drug containing an active ingredient to the skin to produce a pharmacological effect or to treat a disease. When gel and emulsion are used in combined form, the dosage form is called emulgel. Emulgels have proven to be one of the most interesting TDDS because they have a dual release control system, namely gel and emulsion. The main goal of the preparation is to transport hydrophobic active ingredients through the skin into the systemic circulation. A unique feature of TDD is the directly contact with the skin as a target organ for diagnosis and treatment. Emulsions have many beneficial properties for dermatological use, such as thixotropy, oil-free, spreadability, easy removability, plasticization, no staining, long shelf life, clarity and pleasing appearance. Therefore, Emulgel can be used as a better TDDS than current systems. This review provides information about Emulgel, including its properties, benefits and formulation instructions, as well as the latest research developments.

Keywords: Emulgel, Hydrophobic drugs, Gel, Emulsion, Topical drug delivery system (TDDS).

INTRODUCTION

Topical formulations are usually used to provide a local effect at the site of application, effectively penetrating the skin or mucous layers of the drug. A topical drug transport machine applies a drug at once to the pores and skin to deal with and heal pores and skin condition. These topical drug delivery systems are often used to treat localized skin infections or in locations where another route of drug delivery is not practical. The topical drug transport machine depended on the exploration of the drug at the frame floor in a method that would be absorbed[1]. The main advantage of topical application is the elimination of first-pass metabolism, thereby avoiding the risks and problems associated with intravenous therapy and various absorption conditions, such as: Other factors, such as pH changes, presence of enzymes, and gastric emptying time, are often benefits of topical application Use Preparation. TDDS is a topical system for delivering a drug to any part of the body via a topical route to the eyes, rectum, vagina, and skin. Most of the body is covered with skin, and the skin is one of the most accessible organs of the human body for topical application and the primary route of administration for the local drug delivery system[2]. Topical drug administration is used for both local and systemic treatment. Most drugs limit their penetration through the skin barrier, which poses a challenge for drug formulation researchers who want to overcome these problems. In nanotechnology, various drug delivery systems such as nanoparticles, nanoemulsions, nanosuspensions, nanosomes, nanofibers and nanosponges have been developed to deliver the drug to the target site in a controlled and predictable manner while reducing side effects[3]. The main limitations of the conventional drug delivery system such as short contact time of the drug with the administration site, lower transdermal permeability and lower bioavailability can be overcome by using a new drug delivery system. The new drug delivery system helps increase the permeability of the drug through the skin by avoiding first-pass metabolism of the drug and increasing the bioavailability of the drug molecule. It is possible to breathe new life into an existing drug molecule in the form of a New DDS[4]. Topical medications can have long-term effects by accumulating and forming a reservoir in one or more layers of skin or subcutaneous fatty tissue[5]. This may be useful to ensure sustained release of the drug into surrounding tissue regardless of concentration gradients. Depending on the type of drug (water/lipid solubility, protein binding capacity, etc.)[6]. Compared to traditional ointments and creams, gel formulations generally provide a faster release of active ingredients. The main limitation of gels is the difficulty in delivering hydrophobic drugs. To overcome this limitation, emulsions are prepared in such a way that even a hydrophobic drug can take advantage of the unique properties of the gels. When gel and emulsion are used in combined form, the dosage form is called emulgel.

In fact, the presence of a gelling agent in the aqueous phase transforms a classic emulsion into an emulsion. The O/W system is used to encapsulate lipophilic drugs while the W/O system is used to encapsulate hydrophilic drugs[7]. As the name suggests, Emulgel is a combination of gel and emulsion. O/W and W/O emulsions that serve as vehicles for delivering various medications to the skin.The presence of a gelling agent in the aqueous phase transforms a conventional emulsion into an Emulgel[8]. Emulgel for dermatological use have several advantageous properties, such as Thixotropy, non-greasy, spreadable, easily removable, softening, non-coloring, water-soluble, longer shelf life, biocompatibility, transparency and pleasant appearance[9].

EMULGEL REVIEW

Rationale of Emulgel as a topical drug delivery

There are many medications that are applied to the skin or mucous membranes and improve or restore basic skin functions or pharmacologically alter their effects on stressed tissue. These products are called topical products or dermatological products[10]. Many commonly used topical products such as ointments, creams, and lotions have numerous disadvantages. They are very sticky, which causes anxiety in patients after use. In addition, they also have a lower melt index and suffer from crushing and stability problems. All these factors led to the development of the use of transparent gels in cosmetic and pharmaceutical preparations of the main group of semi-solid preparations. The gel is a colloid that typically contains 99% by weight. A liquid held in place by surface tension between itself and a macromolecular fiber network composed of a small amount of a gelling agent present. Despite the many advantages of gels, there are major limitations in the administration of hydrophobic drugs. Therefore, to overcome this limitation, an emulsion-based approach is used, which can successfully incorporate and release even a hydrophobic therapeutic molecule through the gel[11].

Advantages of using emulgels as a drug delivery system

Hydrophobic drugs without difficulty integrated into gels using emulsions

Most hydrophobic active ingredients cannot be integrated directly into the base gel because the solubility acts as a barrier and drug release is problematic. Emulgel helps to incorporate the hydrophobic active ingredients into the oil phase. The oil beads are then dispersed in the aqueous phase to form O/W emulsion. And this emulsion can be mixed with a gel base. This may indicate improved drug stability and delivery compared to simply incorporating the drugs into a gel base. The production of emulgel requires simpler and shorter steps, which increases the feasibility of production. No special equipment is required to make the emulgel. Furthermore, the materials used are readily available and inexpensive. Therefore, the production cost of the emulgel is reduced[12].

Controlled release

Emulgels can be used to prolong the effect of the drug with a shorter T1/2.

Patient compliance

They are less greasy and are easy to apply.

No intensive sonication

The production of vesicular particles requires intensive ultrasound treatment, which can lead to drug degradation and leakage. However, this problem does not arise when producing the emulsion because ultrasound treatment is not required[13].

Better loading capability

Other innovative approaches such as niosomes and liposomes have nanometric dimensions and vascular structures can cause leakage and reduce capture efficiency. But gels have relatively better ability to recharge a large network.

Better durability

Other transdermal preparations are much weaker than emulgels. Just as powders are hygroscopic, creams show phase reversal or cracking & ointments go rancid due to the oil base.

Disadvantages[14]

- Skin irritation with contact dermatitis
- Possible allergic reactions
- Poor skin permeability to various medications
- Medicines contain large molecules that are not easily absorbed through the skin
- Bubble formation during emulsion formulation

Physiology of skin [15,16,17]

Most topical preparations are intended for use on the skin. Therefore, a fundamental understanding of the skin and its physiological functions is very important when developing topical therapies. The skin of an average adult human covers an area of about 2 m2 and contains about a third of the blood circulating in the body. We know that on average there are 40 to 70 hair follicles and 200 to 300 sweat ducts per square centimeter of skin. The pH value of the skin is between 4 and 5.6. Sweat and fatty acids secreted by sebum influence the pH value of the skin surface. We can assume that the skin is made up of four different tissue layers, as shown in the figure.

1. Non-viable epidermis
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue

Non-viable epidermis

The stratum corneum is the outermost layer of skin and serves as a physical barrier against the greatest possible amount of materials coming into contact with the skin. The stratum corneum has a cell thickness of 10 to 20 cells over the maximum body surface. Each cell is a flat, plate-like structure—34 to 44 µm long, 25 to 36 µm wide, and 0.5 to 0.20 µm thick—with an area of 750 to 1,200 µm, arranged like a brick. The stratum corneum is composed of lipids (5 to 15%), including phospholipids, glycosphic lipids, cholesterol sulfate, and neutral lipids, and proteins (75 to 85%), primarily keratin.

Viable epidermis

This layer of skin lies between the stratum corneum and

the dermis and is between 50 to100 µm thick. The cellular structures of the living epidermis are physically and chemically similar to those of other living tissues. The cells are held together by tonofibrils. The density of this zone is not significantly different from the density of water. The water content is approx. 90%.

Viable epidermis

Dermis Directly beneath the living epidermis is the dermis. This is structural fibrin and only very few cells histologically resemble those of normal tissue. The thickness of the dermis varies between 2,000 and 3,000 µm and consists of a loose connective tissue matrix composed of fibrous proteins embedded in a ground, amphora-like substance.

Subcutaneous connective tissue

Subcutaneous tissue or subcutaneous tissue is not actually considered a true part of structured connective tissue, which consists of loosely woven white fibrous connective tissue containing blood and lymphatic vessels, sweat gland secretor pores and cutaneous nerves. Most researchers believe that a drug that penetrates the skin enters the circulation before reaching the subcutaneous tissue, although fatty tissue can act as a pharmacy.

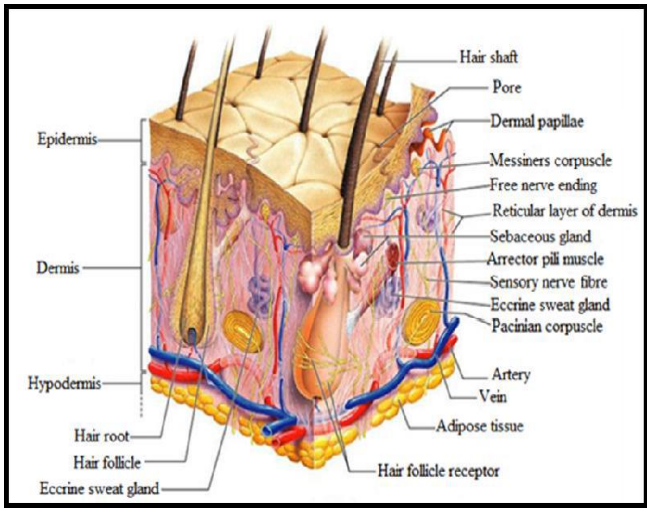

Figure 1: Structure & physiology of the Skin

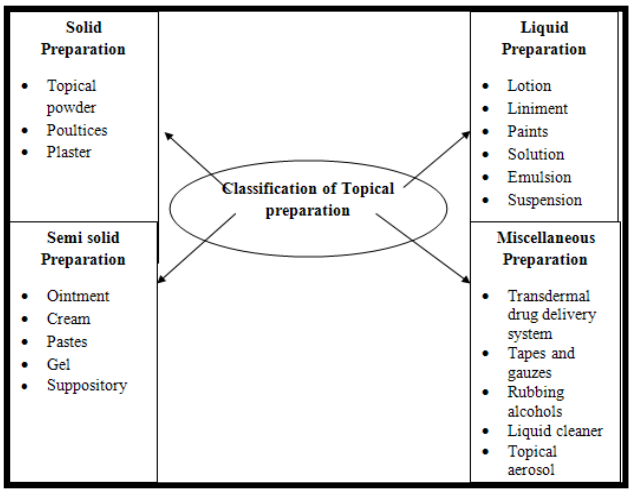

Figure 2: Classification of the topical preparation[18]

Formulation of emulgel

Vehicle[15]

The vehicle has the following characteristics:

- Distributes the medicine effectively and evenly on t he skin.
- Release the medication so that it can reach the site of action unhindered.
- Bring the medication to its destination.
- Deliver the medicines to their destination.
- Maintain a therapeutic concentration of the drug in the target tissue for a sufficient period of time to produce a pharmacological effect.
- Formula adapted to the anatomical site to be treated.
- Aesthetically acceptable to the patient.
- Due to the effectiveness of the epidermal barrier, the amount of topical drug that penetrates the stratum corneum is generally small. The rate and degree of absorption vary depending on the properties of the vehicle, but are also influenced by the active ingredient itself.

Water[19]

Creates the aqueous phase of the emulsion. Water and alcohols are commonly used as agents.

Oils[20]

These active ingredients form the oil phase of the emulsion. For topical emulsions, mineral oils are commonly used alone or in combination with soft or hard paraffin, both as a therapeutic vehicle and for their occlusive and sensory functions. Oils commonly used in oral preparations include non-biodegradable mineral oils and castor oils, which have a local laxative effect, as well as fish liver oils or various fatty oils of plant origin.

Emulsifiers[21]

Emulsifiers are used both to facilitate emulsification during production and to control stability during shelf life, which can vary from a few days for improvised emulsions to months or years for commercial preparations, e.g. B. Polyethylene glycol 40 stearate, monooleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid and sodium stearate.

Gelling agent[22, 23]

These are active ingredients that increase the consistency of any dosage form and can also be used as thickeners.

Penetration Enhancer[20]

To facilitate drug absorption, excipients often contain penetration-promoting ingredients that temporarily disrupt the skin barrier, liquefy lipid channels between

corneocytes, redistribute the drug into skin structures, or improve drug delivery to the skin.

Properties of Penetration Enhancers

- They must be non-toxic, non-irritating and hypoallergenic.
- Ideally they should act quickly and the activity and duration of the action should be predictable and repeatable.
- They cannot have a pharmacological effect on the organism, so cannot bind to receptor sites.
- Penetration amplifiers must be unidirectional; so it should allow therapeutic agents to penetrate the body while preventing the loss of endogenous material from the body.
- Penetration enhancers must be able to be used in various topical formulations and therefore be compatible with excipients and drugs.
- Must be cosmetically acceptable and feel good on the skin.

Penetration enhancement mechanism[16, 24]

Penetration enhancers can work through one or more of 3 mechanisms:

1. Destruction of the highly ordered lipid structure of the stratum corneum.

2. Interaction with extracellular proteins.

3. Better penetration of the drug, activator or solvent into the stratum corneum.

Amplifiers work by switching one of three paths. The key to modifying the polar pathway is to induce a protein conformational change or solvent swelling. Fatty acid activators increased the fluidity of the lipid-protein portion of the stratum corneum. Some activators work in both polar and non-polar ways, changing the way they penetrate multiple layers. Activators can increase the permeability of drugs through proteins of skin. The type of amplifier used has a significant impact on product plan and formulation.

Preparation of the Emulgel[25, 26]

Step 1: Formulation of an O/W or W/O emulsion.

Step 2: Preparing the gel base.

Step 3: Work the emulsion into the base gel while stirring constantly.

Emulgel was prepared according to the method described by Mohammad et al.Method described. (2004) with minor modification. Gel formulations were prepared by dispersing Carbopol 934 in purified water with continuous stirring at moderate speed and Carbopol 940 in purified water with continuous stirring at moderate speed. The pH was then adjusted from 6 to 6.5 with triethanolamine. The oil phase of the emulsion was obtained by dissolving Span 20 in slightly liquid paraffin, while the aqueous phase was obtained by dissolving Tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol, the drug was dissolved in ethanol, and both solutions were mixed with the aqueous phase. The oil and aqueous phases were heated separately to 70–80 °C; Then, the oil phase was added to the aqueous phase with constant stirring until it cooled to room temperature, and glutaraldehyde was added while mixing gel and emulsion at a ratio of 1:1 to obtain an emulgel.

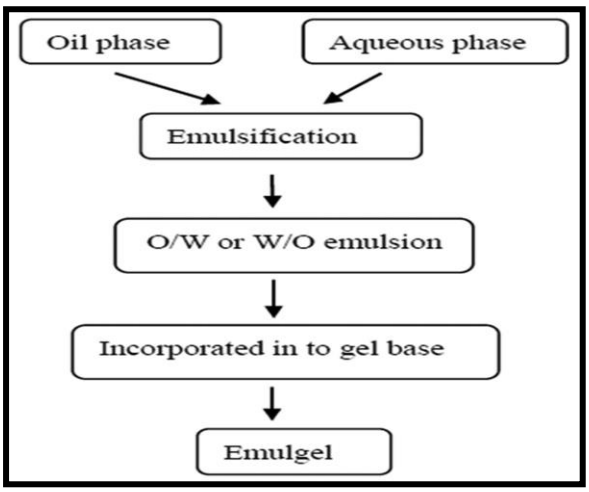

Figure 3: Methods for Preparation of the Emulgel

Characterization of the Emulgel

Physical examination[16, 27]

The prepared emulgel formulations were visually assessed for color, uniformity, texture and phase separation.

Determination of pH value[16, 17]

In, the pH value of the preparation led to the decision to use a virtual pH meter. The electrode of the pH meter is washed with distilled water, then the preparation is immersed to measure the pH and this process is repeated three times.

Spreadability[20, 28, 29]

The spreadability is carried out using the method described by Mutimer et al. developed method measured device. (1956), which is modified in the laboratory and used for research purposes. It contains a block of wood with a pulley at one end. In this method, Spreadability is measured using the “sliding” and “pulling” properties of the emulgel. A piece of ground glass is inserted into this block. An additional amount of the tested emulgel (approximately 2 g) is applied to the slide. The emulgel is then placed between this slide and another sturdy ground glass slide and clamped. A 1kg weight is placed on the slides for five minutes to remove air and ensure an even layer of emulgel between the slides. Excess emulgel is scraped off the edges. The upper plate is then subjected to a tensile stress of 80 g. Using the string attached to the hook, record the time (in seconds) it takes for the top slider

to move 3 inches. A shorter gap means better spreadability.

***Globule size and its distribution in Emulgel*[16, 28]**

The size and arrangement of the globules depends on the size of Malvern Zeta. A 1.0 g sample is dissolved in purified water and combined to obtain a homogeneous dispersion. The sample was injected directly into the zeta-length photocell. The diameter and distribution of the globules are determined.

***Swelling index*[15, 29]**

To determine the swelling index of the prepared topical emulgel, 1 g of gel is applied to a porous aluminum foil and placed individually in a 50 mL beaker containing 10 mL of 0.1NNaoH.

The samples are then removed from the beaker at different intervals and, after being weighed again, stored several times in a dry place. It is calculated as follows:

Swelling index (SW) % = [(Wt - Wo)/Wo] × 100,

Where, (SW) % = Equilibrium percent swelling, Wt = Weight of swollen Emulgel after time t, Wo = Original weight of Emulgel at zero time.

***In vitro drug release study*[29, 30]**

In vitro drug release studies from emulsions were performed in a diffusion chamber using an egg membrane. This leads to a careful connection with the exit of the opening of the glass tube of the dialysis chamber. The emulgel (1 g) was replaced with another one that was applied to the surface of the egg membrane dialysis membrane. The receptor chamber was modified and filled with freshly prepared PBS solution (pH 7.4) to dissolve the drug. The receptor chamber was stirred with a magnetic stirrer. Samples (1 ml aliquots) were collected at appropriate intervals and, after appropriate dilutions, analyzed for drug content using an ultraviolet (UV) spectrophotometer. Cumulative adjustments were made to obtain the total amount of drug released in each time interval. The cumulative amount of drug released from the egg membrane varied over time. The cumulative drug release rate was calculated using the preferred calibration curve.

***Microbiological assay*[31]**

The Ditch plate technique is used. This is a technique for evaluating the bacteriostatic or fungistatic activity of a compound. It is mainly used for semi-solid preparations. Ready-to-use plates containing dried Sabouraud agar are used. Three grams of gelled emulsion are placed in a groove dug in the plate. Freshly prepared culture loops are spread on the agar at a right angle from the well to the edge of the plate. After 18-24 hours of incubation fungal growth was observed at 25°C and the percentage of inhibition was measured as follows.

% inhibition = L2/L1 × 100, Where, L1 = Total length of the streaked culture, and L2 = Length of inhibition.

***Skin irritation test*[30, 32]**

A 0.5 gram sample of the test article was then applied to each site (two sites per rabbit) by placing a double layer of gauze over an area measuring approximately 2.54 x 2.54 cm2 (1 inch x 1 inch). The gelled emulsion was applied to the rabbit's skin. The animals returned to their cages. After 24 hours of exposure, the gelled emulsion is removed. The test sites were cleaned with tap water to remove all traces of the test item.

***Stability studies*[33, 34]**

The prepared emulgels were packed in aluminum tubes (5 g) and subjected to stability tests at 5 °C, 25 °C/60% RH, 30 °C/65% RH and 40 °C/75% RH, with the samples were taken at intervals of 15 days and evaluated for appearance, pH value, rheology, active ingredient content and active ingredient release profiles.

***Extrudability test*[15]**

This is a simple empirical test to measure the force required to extrude material from a pipe. A method for determining the applied shear in the rheogram region, which corresponds to the shear rate above the yield point and thus indicates plug flow. In this work, a method was used to evaluate the extrusion of an emulgel preparation based on the percentage of emulgel and emulgel extruded from an aluminum tube after applying at least the mass in grams necessary to extrude 0.5 cm of emulgel in 10 seconds is required. The best amount extruded is the extrusion efficiency. The extrusion measurement of each formulation is carried out three times and the average values are reported.

It is calculated by using the following formula:

Extrudability = Weight with which the emulgel is extruded from the tube (in g)/area (in cm2)

***Determination of active ingredient content*[21, 28, 34]**

Take 1 g of Emulgel and mix it with a suitable solvent. Filter to get a clear solution. Determine absorbance using an ultraviolet-UV spectrophotometer. Many standard medications are made in the same solvent. The concentration and content of the drug can be determined using the same standard graph that provides the absorbance value.

Active ingredient content = (concentration × dilution factor × volume withdrawn) × (conversion factor)

***Ex vivo measurement of the bioadhesive strength of a topical emulgel (shaved mouse skin)*[30]**

A modified method was used to measure bioadhesive strength. Cut the fresh skin into pieces and wash with 0.1 N NaOH. Two pieces of skin were separately attached to two slides, one to a piece of wood and the other to the scales on the right. The left and right pans were balanced by adding weight to the left pans. 1g of topical emulgel is placed between these two hairless preparations of skin pieces, then additional weight is removed from the left cup

to position the two pieces of skin and some pressure is applied to remove any air present. The scale is held in this position for 5 minutes. The mass is slowly added to the left pan at a rate of 200 mg/min until the patch separates from the skin surface. The mass (force in grams) required to separate the emulgel from the skin surface was a measure of bioadhesive strength.

Bioadhesive strength = Required weight (g)/ Surface area (cm2).

***Accelerated stability tests*[30]**

Stability studies were performed according to ICH guidelines. The preparations were stored in a hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for 3 months. The samples were analyzed for active ingredient content every two weeks using a UV-VIS spectrophotometer. Stability tests were performed by periodically measuring changes in the pH of the gel.

***Syneresis measurement test*[21]**

When at rest, the gel contracts and expels a small amount of fluid, called syneresis. This can be measured using centrifuge tubes in a special device.

Syneresis (%) = liquid separated from emulgel/total mass of emulgel before centrifugation × 100

Preparations available on the market

The different formulations of emulgels available on the market are listed in the table below.

Product name	Drug	Manufacturer
Voltaren emulgel	Diclofenac-diethyl-ammonium	Novartis pharma
Miconaz-H-Emulgel	Miconazole nitrate, hydrocortisone	Medical union pharmaceuticals
Excex gel	Clindamycin, adapalene	Zee laboratories
Pernox gel	Benzoyl peroxide	Cosme remedies Ltd.
Lupigyl gel	Metronidazole, clindamycin	Lupin pharma
Clinagel	Clindamycin phosphate, allantoin	Stiefel pharma
Topinate gel	Clobetasol propionate	Systopic pharma
Kojivit gel	Kojic acid, dipalmitate arbuti	Micro gratia pharma
Accent gel	Aceclofenac	Intra Labs India Pvt. Ltd.
Avindo gel	Azithromycin	Cosme pharma lab
Cloben gel	Clotrimazole, betamethasone	Indoco remedies
Nadicin cream	Nadifloxacin	Psycho remedies
Zorotene gel	Tazarotene	Elder pharmaceuticals

CONCLUSION

A review of the literature suggests that topical drug administration will be widely used in the coming years to improve patient compliance. Emulgel is a recently developed topical drug delivery technique that is more suitable for hydrophobic drugs and is obviously a better drug delivery technique when combined with hydrophilic and lipophilic drugs. It is mainly used for hydrophobic and hydrophilic drug delivery. The emulgel technique uses both oil and water (e.g. a gel base), allowing its use in hydrophobic drugs. Like Emulgel, it is suitable for increasing diffusion, adhesion, viscosity and extrusion; This new treatment regimen has gone viral. In addition, they provide a solution for loading hydrophobic active ingredients into water-soluble gel bases to ensure long-term stability.

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