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REVIEW ARTICLE

Emulgel: A Novel Approach for Delivery of Hydrophobic Drugs

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ABSTRACT

Most of the drugs are effective by oral, parenteral routes despite of several advantages there are limitation so they are drown back and requires an alternate route of administration like topical, ophthalmic, vaginal. Looking to the better patient compliance topical drug delivery has being growing hastily. Among the various group of semisolid preparation, the use of gel has lengthened both in cosmetics and in the pharmaceuticals. In spite of several advantages of gel there is limitation in delivery of hydrophobic drugs, so to beat this limitation an emulsion base advance is being mostly used. Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Due to presence of oil portion; it leads to more penetration of API in skin. In short Emulgels are the combination of emulsion and gel. The major objective behind this formulation is the delivery of hydrophobic drugs to the systemic circulation via the skin .The emulgels for dermatological use has several favourable properties Such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, greater shelf life, bio-friendly, clear and pleasant appearance.

KEYWORDS

Emulgel, Topical Drug Delivery, Penetration Enhancer, Hydrophobic Drug, Emulsifier

INTRODUCTION

When emulsion and gel both are used in combined form the dosage form prepared is named as Emulgel. As the name suggests it is the combination of emulsion and gel. Therefore, they have been recently used as vehicle to deliver various drugs to the skin for topical as well as systemic actions. In fact, presence of gelling agent in water phase converts an ancient emulsion into emulgel. Direct (oil-in-water) system is used to entrap lipophilic drugs, while hydrophilic drugs are encapsulated in the reverse (water-in-oil) system. Emulsions have certain degree of elegance and are easily washable whenever required. It also has high ability to penetrate the skin.

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Topically used emulgels have several desirable properties like being thixotropic, greaseless, easily spreadable as well as removable, emollient, non-staining, water soluble, longer shelf-life, bio-friendly, transparent, pleasant appearance etc.

Advantages of Emulgels

1. Hydrophobic drugs can be easily incorporated into gels using w/o/w emulsions
2. Avoidance of first pass metabolism.
3. More selective to a specific site.
4. Better stability
5. Better loading capacity
6. Production feasibility and low preparation cost

7. No intensive sonication
8. Avoidance of gastrointestinal incompatibility.
9. Improve patient compliance and suitability for self medication.
10. Providing utilization of drug with short biological half life and narrow therapeutic window.
11. Ability to easily terminate medication when needed.

Disadvantages of Emulgels

1. Skin irritation of contact dermatitis may occur due to the drug and/or excipients
2. Poor permeability of some drugs through the skin.
3. Possibility of allergenic reactions.
4. Drugs of larger particle size not easy to absorb through the skin.

Skin as a Site for Topical Drug Administration[15]

The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately two square meters and receives about one third of the blood circulating through the body. With a thickness of only a few millimeters (2.97 ± 0.28 mm), skin separates the underlying blood circulation network from the outside environment and serves as a barrier against physical and chemical attacks. It acts as a thermostat in maintaining body temperature and shields the body from invasion by microorganisms. Skin is a well known route of drug administration but its applications have earlier been restricted to local effect. Nowadays delivery of drugs or targeting of drugs to specific sites by topical application for systemic effects has been taken as a challenge by number of researchers.

The delivery of drug via transdermal route has been recognized as one of the potential routes for both local and systemic delivery of drugs, due to several advantages. Topical delivery of bioactive substances is indeed a powerful strategy to reduce their systemic toxicity and at the same time restricts the therapeutic effect to specific tissues targeting to a specific site. (Waugh A and Grant A. 2001.) However, the major limitation of transdermal delivery of drugs is that the skin layers provide high resistance to the penetrate molecules. Consequently, many substances are topically and systemically ineffective when applied onto the skin, due to their complete failure to penetrate. Different strategies including the use of skin penetration enhancers iontophoresis and sonophoresis**,** have been developed. (Parker C, Gary A. 1983)

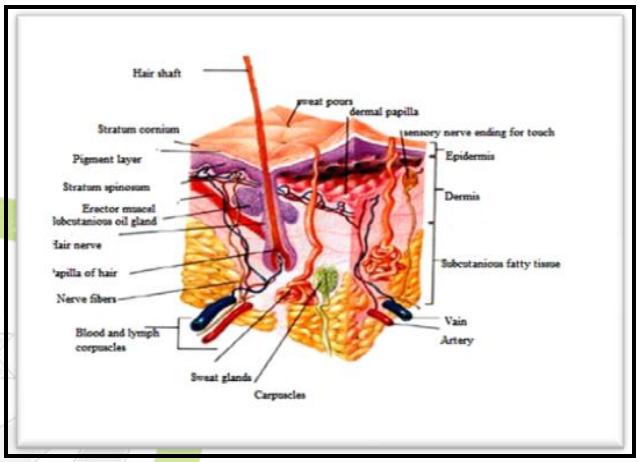

Figure 1: Histology of Skin

Anatomy of Skin

The skin is multilayered organ composed of many histological layers. It is generally described in terms of three tissue layers (Figure 1). Skin is an anatomical barrier between the body and its environment and contributes to 16-18 % of normal body weight. The thickness of the skin varies from 0.5 mm in the eyelid to about 3.6 mm on the palm and sole.

The three layers of skin are.

1. Epidermis
2. Dermis
3. Hypodermis or subcutaneous fat layer
4. Skin appendages

Routes of Skin Permeation

The structure of skin shows number of diffusional pores like hair follicles, sweat glands,

and intracellular spaces etc which help in the absorption. The routes are as follows: (figure 2).

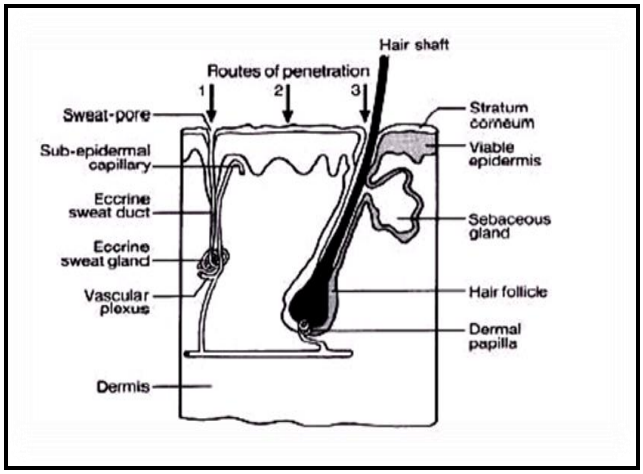

Figure 2: Routes of Skin Permeation

Table 1: Possible Routes of Penetration of Drugs through Skin

Route	Relative Surface Area	Diffusional Path Length (µm)
Transcellular	99	25
Intercellular	0.7	350
Transappendageal	0.1	200

Method to Enhance Drug Penetration and Absorption

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Super saturation enhancement

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, but gels are irritating.

Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

Factors Affecting Topical Absorption of Drug[15]

Physiological Factors

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin

Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<400 Dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles

Advantages of Topical Drug Delivery System

1. Avoids hepatic first pass effect (metabolism) and also gastrointestinal incompatibility of drugs, thus reducing the total drug administered.
2. Avoids gastrointestinal irritation caused by various types of agents like NSAIDs. It also avoids the degradation of drug due to pH, enzymatic activity, and drug-food interaction etc.
3. Minimizes inter- and intra- patient variation.
4. Reduces the dosing interval of drug and thus improves patient compliance.
5. Enhances therapeutic efficacy.

6. Can be substituted for oral drug administration in cases where patient is unable to swallow the drug or in cases of vomiting and diarrhoea.
7. Avoids risks and inconvenience of parenteral therapy and hence, suitable for self administration.
8. Extends the activity of drug with short biological half life, thus reducing the frequency of dosing.
9. The drug effect can be rapidly terminated by washing out the application or removing the system. This is not possible or is difficult either parenteral or oral therapy.

Disadvantages of Topical Drug Delivery System

1. Drugs with high blood concentration levels cannot be administered.
2. It can be difficult for drugs to permeate through skin. (This is so because the skin, in addition to being a physical barrier, also acts as a chemical barrier)
3. Drugs incorporated in transdermal formulation should be checked for skin irritation. (As the formulation also contains various adjuvants which may produce irritation or contact dermatitis.)
4. In transdermal gel preparation, it may stain clothes.
5. Drugs with low molecular size are only suitable for formulation.
6. Drugs have limited permeability through skin.
7. Drugs cannot be delivered in pulsatile fashion transdermally.

Emulgel is Composed of Two Parts

1. Emulsion
2. Gel

A. Emulsion

Emulsions are biphasic system in which one immiscible liquid is dispersed into other; due to this the system becomes unstable which is stabilized by emulsifying agents. Emulsion can be either o/w or w/o these are used as vehicles to deliver drug. Emulsions are stabilized by use of emulsifying agents. They can be easily washed off from skin and have good penetration capability.

Different Types of Emulsions Depending on the Size of Droplets or Nature of Distribution

Macroemulsions

These are most common type of emulsions where the particle size of droplets is more than 400nm. They are visually opaque but the individual droplets can be easily observed under microscope. Macroemulsions are thermodynamically unstable, but can be stabilized using surface active agents.

Microemulsion

Microemulsions are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they do not coalesce. Microemulsions are composed of oil, surfactant, cosurfactant and water in specific proportions.

Multiple Emulsion

Small droplets of one phase (e.g. oil) dispersed in larger droplets of second phase (e.g. Water) with the latter further dispersed in the former (i.e. oil) as the continuous medium.

B. Gel

The term “gel” represents a physical state with properties intermediate between those of solids and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material. These are capable of undergoing large deformation in their physical state i.e. from solid to liquid.

Important Constituents of Emulgel Preparation[3,23]

1. Aqueous Material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols[14].

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 non-biodegradable 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.

Table 2: List of oil

Chemical	Quantity	Dosage form
Light Liquid Paraffin	7.5%	Emulsion & Emulgel
Isopropyl stearate	7-7.5%	Emulsion
Isopropylmyristate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion
Propylene glycol	3-5%	Gel

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[17], Sorbitan monooleate (Span 80)[18], Polyoxyethylene sorbitan monooleate (Tween 80)[19], Stearic acid[20], Sodium stearate[21].

4. Gelling Agent

These are the agents used to increase the consistency of any dosage form which can also be used as thickening agent.

Table 3: List of gelling agents

Gelling agent	Quantity	Dosage Form
Carbopol-934	0.5%- 2%	Emulgel
Carbopol-940	0.5%-2%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

5. Permeation Enhancers

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

Table 5: List of various penetration enhancers used in Emulgels

Penetration Enhancer	Quantity	Dosage Form
Oleic acid	1%	Gel
Lecithin	5%	Gel
Urea	10%	Gel
Isopropyl myristate	5%	Gel
Linoleic acid	5%	Gel
Clove oil	8%	Emulgel
Menthol	5%	Emulgel
Cinnamon	8%	Emulgel

6. Preservatives

e.g. Propyl paraben, methyl paraben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol etc.

7. Antioxidants

e.g. Butylated Hydroxy Toluene(BHT), Ascorbyl palmitate, Butylated hydroxyanisole (BHA), etc.

8. Humectant

e.g. Glycerin, Propylene gylcol, etc.

Method of Preparation[21]

STEP 1: Formulation of gel base

STEP 2: Formulation of Emulsion either O/W or W/O

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

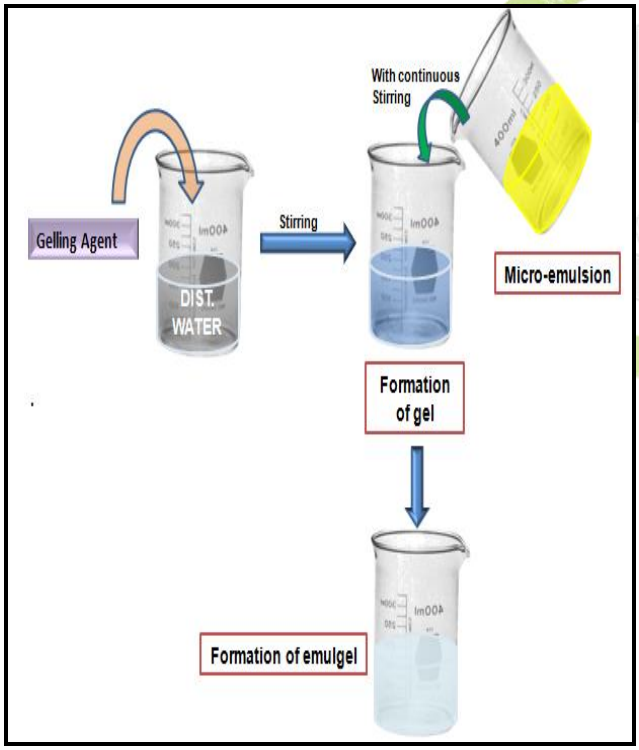

Figure 2: Formation of emulgel

Evaluation Parameters[2,21,23]

Physical Examination

The prepared emulgel formulation are inspected visually for their colour, homogeneity, consistency, and phase separation.

Rheological Studies

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 64 and connected to a thermostatically controlled circulating water bath.

Spreadability

Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used or the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, Spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges.

$$S=M\times L/T$$

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.

Extrudability Study of Topical Emulgel (Tube Test)

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in

grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

Swelling Index

To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum 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 dry place for some time after it reweighed. Swelling index 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.

Drug Content Determination:

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

Skin Irritation Test (Patch Test)

The preparation is applied on the properly shaven skin of rat and its adverse like change in colour, change in skin morphology should be checked up to24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

Ex–Vivo Bioadhesive Strength Measurement of Topical Emulgel (Mice Shaven Skin)

The modified method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left – hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg/ min to the left – hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength (Kasliwal et al., 2008, Jain et al., 2007). The bioadhesive strength is calculated by using following:

Bioadhesive Strength = Weight required (gm) / Area (cm^2)[4]

In Vitro Release/Permeation Studies

In vitro release studies were carried out using Franz diffusion cell. Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5 ml cell volume) can be used for the drug release studies. Gellified Emulsion was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval .The cumulative amount of drug released across the egg membrane was determined as a function of time.

Stability Studies

The prepared emulgels were packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

Marketed Products of Emulgel

Brand Name	Content	Manufacturer
Voltaren Emulgel	Diclofenac Diethyl Amine	Novartis Pharma Switzerland
Miconaz–H Emulgel	Miconazole Nitrate and Hydrocortisone .	Medical Union, Pharmaceuticals, Egypt

CONCLUSION

Most of the drugs are very much effective by oral and / parenteral route but have drown back because of some unwanted side effects, so requires alternate route of administration like topical, ophthalmic, vaginal etc. Most drugs are poorly water soluble, so have problem to penetrate through skin. So, to overcome this problem and looking to better patient compliance and advances in topical drug delivery emulgels are better suited for hydrophobic drugs. As it improves and possesses an edge in terms of spreadability, adhesion, viscosity and extrusion and will become a popular drug delivery system.

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