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Emulgel as a Novel Topical Drug Delivery System

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ABSTRACT

Gels are the preferable dosage forms for topical delivery of drugs in present days, but their use is not suitable for drugs with hydrophobic nature. In order to overcome the limitations of gels as a dosage form for hydrophobic drugs, an emulsion based approach is being used. When gels and emulsions are used in combined form; the dosage form is referred as emulgel. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Polymers can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions by decreasing surface as well as interfacial tension and increasing the viscosity of the aqueous phase. Various permeation enhancers can potentiate the effect, so emulgels can be used as better topical drug delivery systems over the conventional systems. Emulgels can be used as formulation system for analgesics, antibacterial and antifungal agents.

Keywords*: Emulgels, Topical drug delivery, Polymers, Emulsifier, Thickener.*

INTRODUCTION

Topical drug delivery system is a way to deliver medication that is applied onto a particular part of the body, typically the skin, to treat various ailments. There are many common forms of topical medication such as lotions, gels, patches, and powders, but they are mainly formulated as creams or ointments. Creams and ointments are usually very sticky causing uneasiness to the patient on application. Moreover they also have less spreading coefficient and need to be applied with rubbing. They also exhibit the problem of stability. In order to overcome these problems, the use of transparent gels has increased both in cosmetics and in pharmaceutical preparations [1,2]. A gel is colloid that is typically 99% by weight liquid, which is immobilized by surface tension between it and a macromolecular network of gelatin fibers. Gels are created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Gel formulations generally provide faster drug release as compared to ointments and creams. Despite many advantages of gels one major limitation is their inability to deliver hydrophobic drugs. To overcome this limitation an emulsion based approach is being used so that a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels.

When gels and emulsions are used in combined form the dosage forms are referred as emulgels as shown in Fig.1. Emulsions possess certain degree of elegance and are easily washed off from skin. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless,

easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, transparent & aesthetic appeal [2,3].

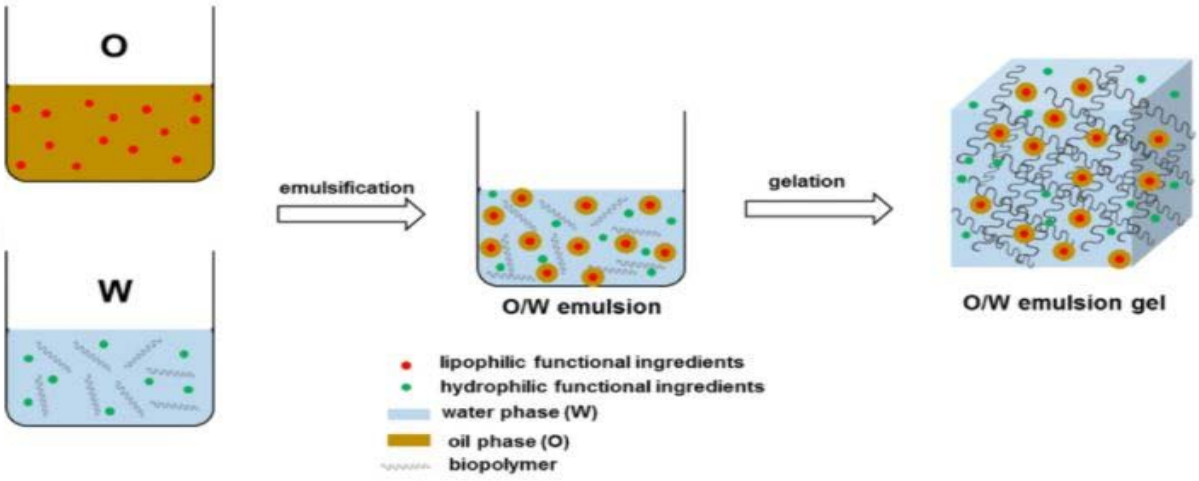

Fig. 1 Emulsion formation and integration of drug

Physiology of skin

Emulgel is meant to be applied on to the skin. The skin of an average adult body covers a surface area approximately 18000cm^{2}and receives about one third of the blood circulating through the body. An average human skin surface has 40-70 hair follicles and 200-300sweat ducts per cm^2 of the skin. The pH of the skin varies from 4 to 5.6.Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin is divided into several layers, as shown in Fig 2. The epidermis is composed mainly of keratinocytes. Beneath the epidermis is the basement membrane (also known as the dermo-epidermal junction); this narrow, multilayered structure anchors the epidermis to the dermis. The layer below the dermis, the hypodermis, consists largely of fat. These structures are described below.

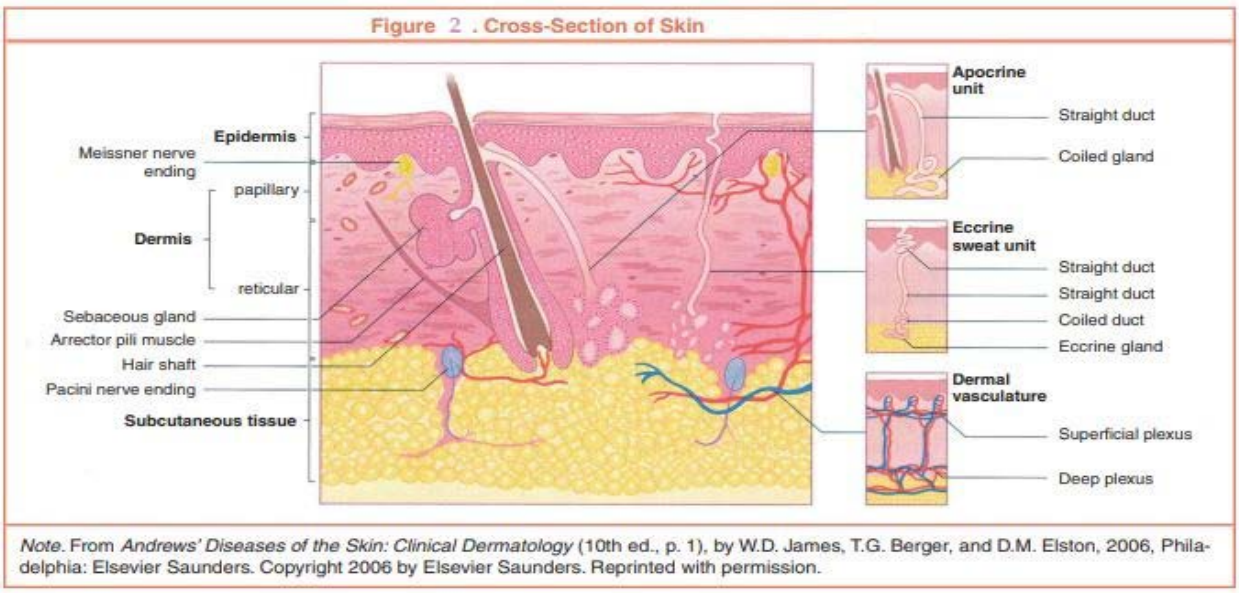

Fig.2 Cross-section of human skin

The epidermis is the outer layer of the skin, defined as a stratified squamous epithelium, primarily comprising keratinocytes in progressive stages of differentiation (Amirlak and Shahabi, 2017).

Keratinocytes produce the protein keratin and are the major building blocks (cells) of the epidermis. As the epidermis is avascular (contains no blood vessels), it is entirely dependent on the underlying dermis for nutrient delivery and waste disposal through the basement membrane. The prime function of the epidermis is to act as a physical and biological barrier to the external environment, preventing penetration by irritants and allergens. At the same time, it prevents the loss of water and maintains internal homeostasis (Gawkrodger, 2007; Cork, 1997). The epidermis is composed of layers; most body parts have four layers, but those with the thickest skin have five. The layers are:

1) Stratum corneum (Horny layer);
2) Stratum lucidum (only found in thick skin – that is, the palms of the hands, the soles of the feet and the digits);
3) Stratum granulosum (Granular layer);
4) Stratum spinosum (Prickle cell layer);
5) Stratum basale (Germinative layer).

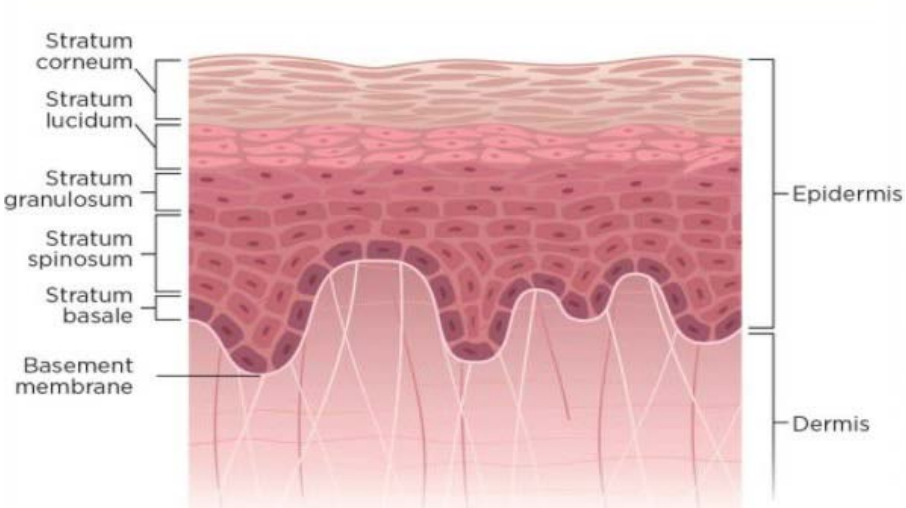

Fig. 3. Layers of skin

Factors Affecting Topical Absorption of Drug

The factors that play for the topical absorption of drugs are as follows [5,6]:

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.

Physicochemical factors

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

Factors to be considered when choosing a topical preparation

Following factors must be taken care of during selection of a topical dosage form [7,8]:

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) Customize the type of preparation with the type of lesions. (e.g., avoid greasy ointments for acute weepy dermatitis).
3) Customize the type of preparation with the site (e.g., gel or lotion for hairy areas).
4) Irritation or sensitization potential.

Components of Emulgel

The formulation components of emulgel include five majors like aqueous phase, oily phase, emulsifiers, gelling agents and permeation enhancers [9,10]:

Aqueous material

This forms the aqueous phase of the emulsion. Commonly water and alcohol are used for this purpose.

Oils

These agents constitute the oily phase of the emulsion. For externally applied emulsions, mineral oils are widely used as the vehicle for the drug as well as occlusive material. Widely used oils in oral preparations are castor oil, fish liver oil, rachis oil, cottonseed oil, and maize oil.

Emulsifiers

Emulsifiers are used to promote emulsification and to control stability during the shelf life. Polyethylene glycol stearate, Sorbitanmonooleate (Span 80), Polyoxyethylenesorbitanmonooleate (Tween 80), Stearic acid and Sodium stearate can be used for this purpose.

Gelling agent

These are the agents that increase the consistency of any dosage form and act as thickening agent. Carbopol 934, Carbopol 940 and HPMC 2910 are gelling agents used in the emulgels.

Permeation/penetration enhancers

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. They temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or enhance delivery into skin. Clove oil and menthol can be used as the permeation enhancers.

The ideal attributes of penetration enhancers are:

1) They should be non-toxic, non-irritating and non-allergenic.

2) They should work rapidly; the activity and duration of effect should be predictable as well as reproducible.
3) They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
4) The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
5) The penetration enhancers should be compatible with both excipients and drugs.
6) They should be cosmetically acceptable with an appropriate skin 'feel'.

Mechanism of permeation enhancers

Permeation enhancers may act by one or more of the following three mechanisms:

1) Disruption of the highly ordered structure of stratum corneum lipid.
2) Interaction with intercellular protein.
3) Improved partition of the drug.

The enhancers act by altering one of three pathways. The key to alter the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increase the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathway by altering the multi laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type ofenhancer employed has a significant impact on the design and development of the product.

Pathway of Transdermal Permeation

1) Permeation can occur by diffusion via:
2) Transdermal permeation, through the stratum corneum.
3) Intercellular permeation, through the stratum corneum.
4) Trans-appendageal permeation, via the hair follicle, sebaceous and sweat glands.

Most molecules penetrate through skin via intercellular micro route and therefore many enhancing techniques disrupt or bypass its elegant molecular architecture.

Emulgel Preparation

Broadly speaking, the preparation of emulgel includes three steps [11]:

Step1: Formulation of emulsion either O/W or W/O
Step2: Formulation of gel base
Step3: Incorporation of emulsion into gel base with continuous stirring

The gel in formulations is prepared by dispersing Carbopol 934 and Carbopol 940 in purified water with constant stirring at a moderate speed. pH is adjusted to 5.0 - 6.0 using triethanolamine (TEA). The oil phase of the emulsion is prepared by dissolving Tween 80 in light liquid paraffin while the aqueous phase is prepared by dissolving Tween 80 in purified water. The drug is dissolved in ethanol followed by mixing of both solutions in the aqueous phase.

Both the oily and aqueous phases are separately heated at 70^0C to80^0C; then the oily phase is added to the aqueous phase with continuous stirring and cooled to room temperature. Mixing of gel and emulsion is done in ratio 1:1 to obtain the emulgel [12].

Characterization of Emulgel

Emulgels can be evaluated using several parameters like physical appearance, spreadability, extrudability study, globule size distribution, rheological study, swelling index, ex–vivo bio-adhesive strength measurement, drug content determination, in-vitro release study, microbiological assay, skin irritation test, accelerated stability studies and drug release kinetic study [13-16].

Physical Appearance

Theemulgel is inspected visually for colour, homogeneity, consistency and pH. The pH value of aqueous solution of emulgel is measured by a pH meter.

Spreadability

Spreadability is determined by texture analyzers.
Spreadability is calculated by using the formula,

$$S = M.L/T$$

Where,
S = spreadability,
M = Weight tied to upper slide,
L = Length of glass slides,
T = Time taken to separate the slides apart.

Extrudability Study

It is a test to determine the force required to extrude the material from a lacquered aluminum collapsible tube. The test is based upon the quantity of emulgel extruded from the tube on application of weight in grams required to extrude at least 0.5cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability.

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

Globule size distribution

A 1.0 g sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is injected to photocell of zeta sizer to obtain mean globule diameter.

Rheological study

The viscosity of different emulgel formulations is determined at 25^0C using Brookefield viscometer.

Swelling index

To determine the swelling index of 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 are removed from beaker at different time intervals and reweighed. Swelling index is calculated as follows:

$$Swelling\ Index\ (SW)\ \% = [(Wt - W0) / W0] \times 100$$

Where,
(SW) % = Equilibrium percent swelling,
W0 = Original weight of emulgel,
Wt = Weight of emulgel after time‘t’

***Ex–vivo* bio Adhesive Strength Measurement**

The fresh skin of shaven mice is cut into pieces and washed with 0.1N NaOH. Two pieces of skin are tied to the two glass slide separately. One of the glass slides is fixed on the wooden piece and other piece is tied with the balance on right hand side.1 g of topical emulgel is placed between the two slides containing 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 5minutes. Weight is added slowly at 200 mg/ min to the left-hand pan until the patch gets detached from the skin surface. The weight required to detach the emulgel from the skin surface indicates the bioadhesive strength. The bioadhesive strength is calculated by using formula:

$$\textit{Bioadhesive Strength} = \textit{Weight required (g)} / \textit{Area (cm}^2\textit{)}$$

Drug content determination

Drug concentration in emulgel is measured by spectrophotometer. A known quantity of emulgel is dissolved in solvent (methanol); sonication is done if required. Absorbance is measured after suitable dilution in UV spectrophotometer.

***In-vitro* release study**

Diffusion cell is used for the drug release studies. A fixed quantity of emulgel is applied onto the surface of egg membrane evenly. The egg membrane is clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared phosphate buffer (pH 5.5) solution. The receptor chamber is stirred by a magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time interval and analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. The cumulative amount of drug released across the egg membrane is determined as a function of time.

Microbiological Assay

Ditch plate technique is used, which is meant for evaluation of bacteriostatic or fungistatic activity of a compound. Previously prepared Sabouraud's agar dried plates are used. Three grams of the emulgel is placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth is observed and the percentage inhibition is measured as follows.

$$\textit{\% inhibition} = L2 / L1 \times 100$$

Where,
L1 = total length of the streaked culture
L2 =length of inhibition

Skin Irritation Test

0.5 g sample of the emulgel is applied to each site (two sites per rabbit) by introduction under a double gauze layer to an area of skin approximately 1"x1" (2.54 x 2.54 cm^2). Animals are returned to their cages and remained as such for 24 hours. After a 24 hour exposure, the emulgel is removed. The test sites are wiped with tap water to remove any remaining residue and the animals are observed for any sign of irritation or rashes.

Accelerated Stability Studies

Stability studies are performed according to ICH guidelines. The emulgel formulations are stored in hot air oven at 37 ± 2^0C, 45 ± 2^0C and 60 ± 2^0C for a period of 3 months. The samples are analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study is carried out by measuring the change in drug concentration and pH of emulgel at regular intervals of time.

Drug release Kinetic Study

To analyze the mechanism of drug release from the emulgel, the release data are fitted to following equations:

Zero order Equation: Q = k0 t

Where,

Q is the amount of drug released at time t, and k0 is the zero order release rate.

First order Equation: In (100 – Q) = In 100 – k1 t

Where,

Q is the percent of drug release at time t, and k1 is the first order release rate constant.

Higuchi's Equation: Q = k2√t

Where,

Q is the percent of drug release at time t, and K2 is the diffusion rate constant.

Marketed preparations available as Emulgel

Marketed products which are commercially available in emulgel type of dosage form are listed in Table 1 with their marketed name and manufacturer company name [2-20].

S.N.	Product Name	Medicament	Manufacturer
1	Voltaren Emulgel	Diclofenac Diethylammonium	Novartis
2	Miconaz-Hemulgel	Miconazole nitrate, Hydrocortisone	MUP
3	Excex Gel	Clindamycin, Adapalene	Zee Laboratories
4	Avindo Gel	Azithromycin	Cosme Pharma Lab.
5	Topinate	Clobetasol Propionate	Systopic Pharma

Merits of using Emulgel

Following are the benefits of using emulgel over conventional topical dosage forms [21]:

1) **Better stability**

Emulgel show better stability than other transdermal preparations, e.g.: powders are hygroscopic, creams show phase inversion on breaking and ointment shows rancidity due to oily phase.

2) More loading capacity

Emulgels have better loading capacity due to their vast network, while other novel approaches like niosomes and liposomes are of nanosize and have vesicular structures. So niosomes and liposomes cause leakage and have lesser entrapment efficiency.

3) Ease of incorporating hydrophobic drugs

Most of the hydrophobic drugs cannot be incorporated directly into gel because solubility acts as a barrier and problem arises during release of drug. Emulgel helps in incorporation of

hydrophobic drugs into oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. This o/w emulsion can be mixed into a gel base.

4) Production feasibility

The emulgel preparation method comprises of simple and short steps, which increase the feasibility of production.

5) Low Preparation Cost

No specialized instruments are needed for preparation of emulgel. Moreover materials used are easily available and cheaper. This reduces the overall production cost of emulgels.

6) No intensive Sonication

Production of vesicular preparations (niosomes and liposomes) needs intensive sonication, which may result in drug degradation and leakage. But emulgels don't require intensive sonication, so drug degradation problems can be overcome.

7) Controlled Drug Release

Emulgels can be used to prolong the effect of drugs with shorter half-life.

8) Patient Compliance

They are less greasy and easy to apply and thus patient compliance is enhanced.

CONCLUSION

Emulgels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Emulgels have a higher aqueous component which permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid. So the gelling agent is in the water phase which converts a classical emulsion into an emulgel. In the recent years, emulgels are popular due to better patient compliance. Since emulgels possess an edge in terms of spreadability, adhesion, viscosity and extrusion, they will become a fair choice as topical drug delivery system and a solution for loading hydrophobic drugs in water soluble gel bases.

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