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The Use of Emulgel as an Innovative Method of Topical Drug Delivery

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Abstract

Gels are the preferred dosage forms for topical medication administration in the modern era, although they are not appropriate for hydrophobic medicines. An emulsion-based method is being developed to address the constraints of gels as a dosage form for hydrophobic medicines. When gels and emulsions are mixed, the dosage form is known as "emulgel." A barrier to both hydrophilic and hydrophobic substances is formed by the mixture of hydrophilic cornified cells in hydrophobic intercellular material. Polymers can act as emulsifiers and thickeners because their gelling capacity allows for the formation of stable emulsions by lowering surface and interfacial tension and increasing aqueous phase viscosity. Because different permeability enhancers can increase the impact, emulgels can be employed as superior topical drug delivery methods compared to traditional systems. Emulgels can be used in the formulation of analgesics, antibiotics, and antifungal medicines.

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

INTRODUCTION

A topical drug delivery system is a method of delivering medication to a specific portion of the body, often the skin, to treat various disorders. Lotions, gels, patches, and powders are all frequent types of topical treatment, although they are mostly prepared as creams or ointments. Creams and ointments are typically quite sticky, giving the patient discomfort when

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applied. They also have a lower spreading coefficient and must be applied by rubbing. They also have difficulty with stability. To address these issues, the usage of translucent gels in cosmetics and medicinal preparations has expanded [1, 2]. A gel is a colloidal substance that is normally 99% liquid by weight and is held in place by surface tension between it and a macromolecular network of gelatin fibres. Gels are formed when substantial volumes of aqueous or hydroalcoholic liquid are entrapped in a network of colloidal solid particles. In general, gel formulations give quicker medication release than ointments and creams. Despite the many benefits of gels, one significant restriction is their inability to deliver hydrophobic medicines. To circumvent this constraint, an emulsion-based technique is being employed to successfully integrate and distribute a hydrophobic medicinal component via gels.

When gels and emulsions are mixed, the dosage forms are referred to as "emulgels," as seen in Fig. 1. Emulsions have a certain level of elegance and are readily removed from the skin. They can also enter the skin quite well. Emulgels for dermatological application are thixotropic, greaseless, readily spreadable, easily removable, emollient, non-staining, water-soluble, have a longer shelf life, are clear, and have an aesthetic appeal [2, 3].

Physiology of skin

Emulgel is intended to be applied to the skin. An average adult's skin has a surface area of around 18000 cm2 and receives approximately one-third of the blood moving through the body. Per cm2 of skin, an average human skin surface has 40–70 hair follicles and 200–300 sweat ducts. The skin's pH ranges from 4 to 5.6. Sweat and fatty acids released by sebum have an effect on the pH of the skin's surface. As seen in Figure 2, the skin is separated into various layers. Keratinocytes make up the majority of the epidermis. The basement membrane (also known as the dermo-epidermal junction) is located underneath the epidermis and connects the epidermis to the dermis. The hypodermis, the layer beneath the dermis, is mostly made up of fat. These structures are discussed in detail below.

The epidermis is the skin's outer layer, characterised as a stratified squamous epithelium composed mostly of keratinocytes in various stages of development (Amirlak and Shahabi, 2017). Keratinocytes are the primary building blocks (cells) of the epidermis

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and manufacture the protein keratin. Because the epidermis lacks blood vessels, it is solely reliant on the underlying dermis for nourishment supply and waste removal via the basement membrane. The epidermis' primary role is to act as a physical and biological barrier to the external environment, keeping irritants and allergens from penetrating. Simultaneously, it inhibits water loss and preserves internal balance (Gawkrodger, 2007; Cork, 1997). The epidermis is made up of layers; the majority of body parts have four layers, while those with the thickest skin have five. The layers are as follows:

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).

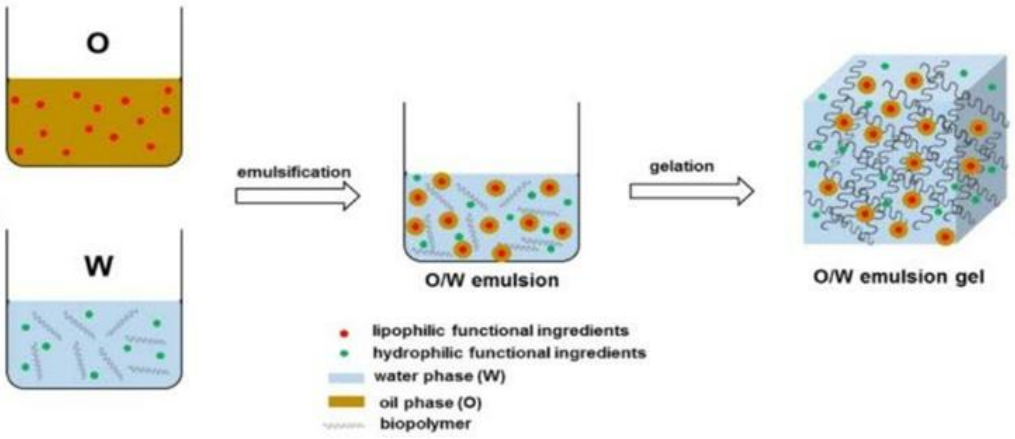

Fig. 1 Emulsion formation and integration of drug

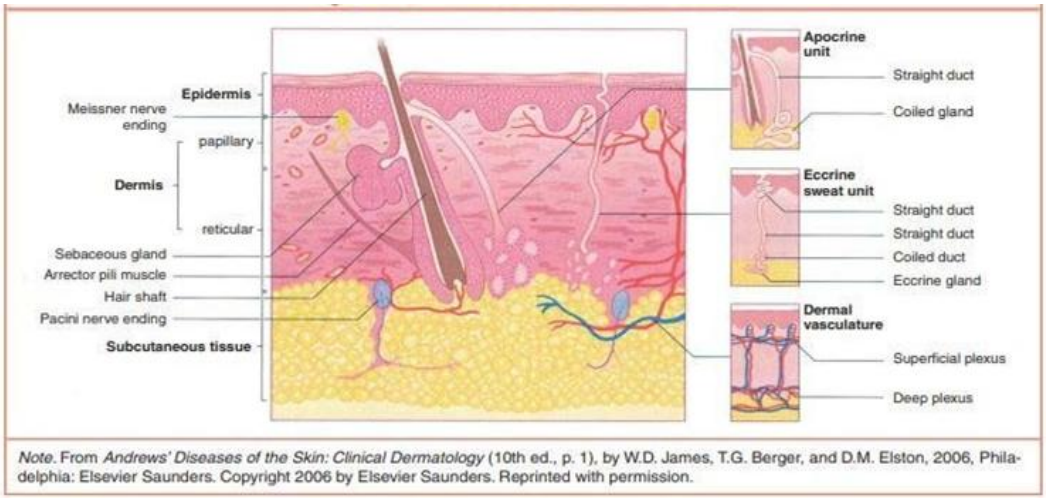

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Fig.2 Cross-section of human skin

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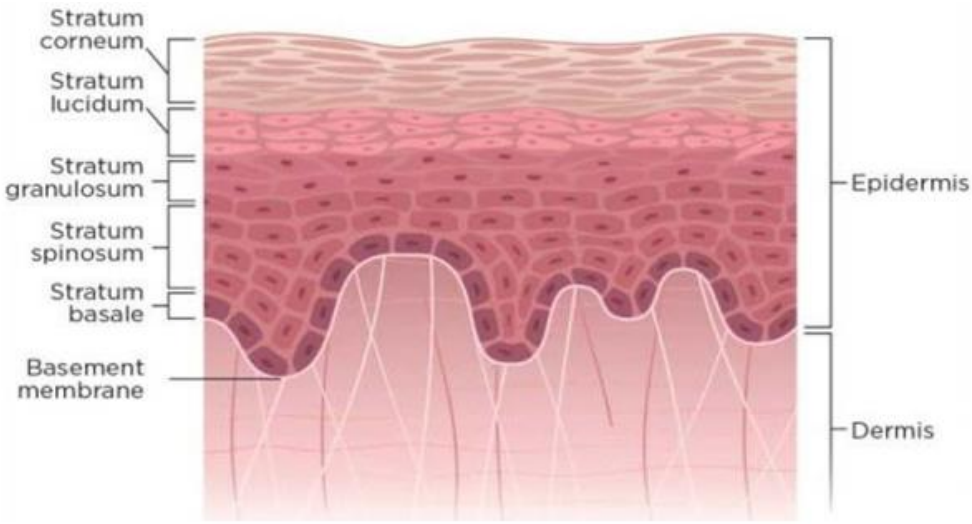

Figure:- 3 Layers of skin

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.

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Components of Emulgel

The five key emulgel formulation components are: aqueous phase, oily phase, emulsifiers, gelling agents, and permeation enhancers [9, 10].

Aqueous material

This is the emulsion's aqueous phase. Water and alcohol are commonly used for this purpose.

Oils

These components make up the emulsion's oily phase. Mineral oils are commonly employed as both a medication carrier and an occlusive substance in topically administered emulsions. Castor oil, fish liver oil, rachis oil, cottonseed oil, and maize oil are all commonly used oils in oral treatments.

Emulsifiers

Emulsifiers are used to enhance emulsification and to maintain stability over time. For this purpose, polyethylene glycol stearate, sorbitan monooleate (Span 80), polyoxyethylenesorbitan monooleate (Tween 80), stearic acid, and sodium stearate can be utilised.

Gelling agent

These are the chemicals that thicken and enhance the consistency of any dosage form. Gelling agents used in the emulgels include carbopol 934, carbopol 940, and HPMC 2910. Enhancers of permeation and penetration Agents that partition into and interact with skin components to cause a transient and reversible increase in skin permeability They either briefly break the skin barrier, fluidize the lipid channels between corneocytes, change the drug's partitioning into skin structures, or improve transport into skin. Clove oil and menthol can be used to improve permeability.

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.

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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.

Enhancers work by changing one of three routes. The key to changing the polar route is to create a change in protein structure or solvent swelling. The fatty acid enhancers improve the fluidity of the stratum corneum's lipid-protein component. Some enhancers function on both polar and non-polar pathways for penetration by modifying the multilayer pathway. Enhancers can boost medication diffusion through skin proteins. The type of enhancer used has a considerable influence on the product's design and development.

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

In formulations, the gel is made by dispersing carbopol 934 and carbopol 940 in purified water while constantly swirling at a moderate pace. Triethanolamine is used to alter the pH from 5.0 to 6.0 (TEA). Tween 80 is dissolved in light liquid paraffin to make the oil phase of the emulsion, and Tween 80 is dissolved in purified water to make the aqueous phase. The medication is dissolved in ethanol, and the two solutions are mixed in the aqueous phase. Both the oily and aqueous phases are heated separately at 700°C to 800°C; then, with continuous stirring, the oily phase is added to the aqueous phase

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and cooled to room temperature. To make emulgel, combine gel with emulsion in a 1:1 ratio [12].

Characterization of Emulgel

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 are all parameters that can be used to evaluate emulgels [13–16].

Physical Appearance

The emulgel is visually evaluated for colour, homogeneity, consistency, and pH. A pH metre is used to determine the pH of an emulgel aqueous solution.

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's a test to see how much power is needed to extrude material from a lacquered aluminium collapsible tube. The test is based on the amount of emulgel extruded from the tube when the weight in grammes necessary to extrude at least a 0.5-cm ribbon of emulgel in 10 seconds is applied. The greater the quantity extruded, the greater the extrudability.

Extrudability = Applied weight to extrude emulgel from tube (in g) / Area (in cm2)

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 250C 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

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reweighed. Swelling index is calculated as follows:

Swelling Index (SW) % = [(Wt – W0) / W0] × 100

Where,

(SW) % = Equilibrium percent swelling,

W0 = Original weight of emulgel,

Wt = Weight of emulgel after time‘t’

Ex–vivo bio Adhesive Strength Measurement

Shaved mice's fresh skin is chopped into pieces and rinsed with 0.1N NaOH. Separately, two pieces of skin are connected to the two glass slides. One of the glass slides is attached to the wooden piece, while the other is linked to the balance on the right side. 1 g of topical emulgel is inserted between the two slides holding skin pieces, and excess weight from the left pan is removed to sandwich the two pieces of skin and apply pressure to remove the presence of air. For 5 minutes, the balance is held in this posture. Weight is steadily added to the left-hand pan at a rate of 200 mg/min until the patch separates from the skin surface. The force required to separate the emulgel from the skin surface reflects bioadhesive strength. The bioadhesive strength is computed using the following formula:

Bioadhesive Strength = Weight required (g) /Area (cm2)

Drug content determination

A spectrophotometer is used to determine the drug concentration in emulgel. A known amount of emulgel is dissolved in a solvent (methanol); sonication is performed if necessary. In a UV spectrophotometer, absorbance is measured after appropriate dilution.

In-vitro release study

For drug release experiments, a diffusion cell is employed. A set amount of emulgel is equally placed on the surface of the egg membrane. The egg membrane is pinched between the donor and the diffusion cell's receptor chamber. A newly prepared phosphate buffer (pH 5.5) solution is placed in the receptor chamber. A magnetic stirrer is used to agitate the receptor chamber.

After proper dilutions, the samples (1.0 ml aliquots) are collected at appropriate time intervals and tested for drug content using a UV visible spectrophotometer. The total amount of medication released across the egg membrane over time is calculated.

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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.

% inhibition = L2 / L1 × 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 cm2). 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 ± 20C, 45 ± 20C and 60 ± 20C 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: $Q = k2\sqrt{t}$

Where,

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

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Marketed preparations available as Emulgel

S.N.	ProductName	Medicament	Manufacturer
1	Voltaren Emulgel	Diclofenac Diethyl Ammonium	Novartis
2	Miconaz-Hemulgel	Miconazolenitrate,Hydrocortisone	MUP
3	Excex Gel	Clindamycin,Adapalene	ZeeLaboratories
4	AvindoGel	Azithromycin	Cosme Pharma Lab.
5	Topinate	ClobetasolPropionate	Systopic Pharma

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].

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 hydrophobic medicines cannot be integrated directly into gel because solubility acts as a barrier, causing difficulty during drug release. Emulgel aids in the integration of hydrophobic medicines into the oil phase, after which the oily globules are disseminated in the aqueous phase, yielding an o/w emulsion. This o/w emulsion can be combined with gel.

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

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materials used are easily available and cheaper. This reduces the overall production cost of emulgels.

6) No intensive Sonication

Sonication is essential for the creation of vesicular preparations (niosomes and liposomes), which can lead to drug breakdown and leakage. However, because emulgels do not require extensive sonication, drug degradation problems can be avoided.

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 recent type of dosage form that is made by entrapping significant volumes of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. Emulgels contain a larger aqueous component, which allows for increased drug solubility and easier drug migration through a medium that is virtually a liquid. As a result, the gelling ingredient is in the water phase, converting a traditional emulsion into an emulgel. Emulgels have gained popularity in recent years because to improved patient compliance. Emulgels will be a good alternative as a topical drug administration method and a solution for loading hydrophobic pharmaceuticals in water soluble gel bases since they have an advantage in terms of spreadability, adhesion, viscosity, and extrusion.

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