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Recent Advancement in Emulgel: A Novel Approach for Topical Drug Delivery

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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 limitation 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 are referred as emulgel. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Polymer 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. The use of emulgels can be used as formulation system for analgesics and antifungal drugs.

Keywords: Emulgels, Topical drug delivery, Gellified emulsion, Polymers, Emulsifier, Thickener.

1. Introduction

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder. The topical drug delivery includes the use of topical agents like ointments, creams and lotions, but they 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. In spite of many advantages of gels a 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. Emulsions possess acertain 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, bio-friendly, transparent &pleasing appearance [2,3]. The structure of emulgel has been shown in Fig. 1.

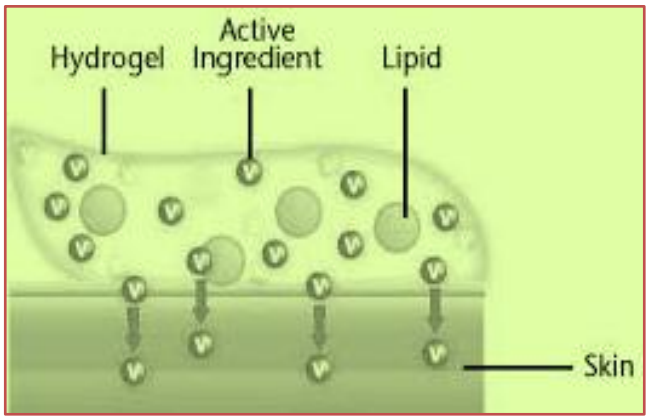

Fig. 1: Emulgel structure

2. Physiology of skin

The emulgel preparation is meant to be applied to the skin, so basic knowledge of the skin physiology is very important for designing emulgel. The skin of an average adult body covers a surface area approximately $2m^2$ 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 can be considered to have four distinct layers of tissue namely non-viable epidermis, viable epidermis, viable dermis and subcutaneous connective tissue [2,4]. The cross section of skin has been depicted in Fig. 2.

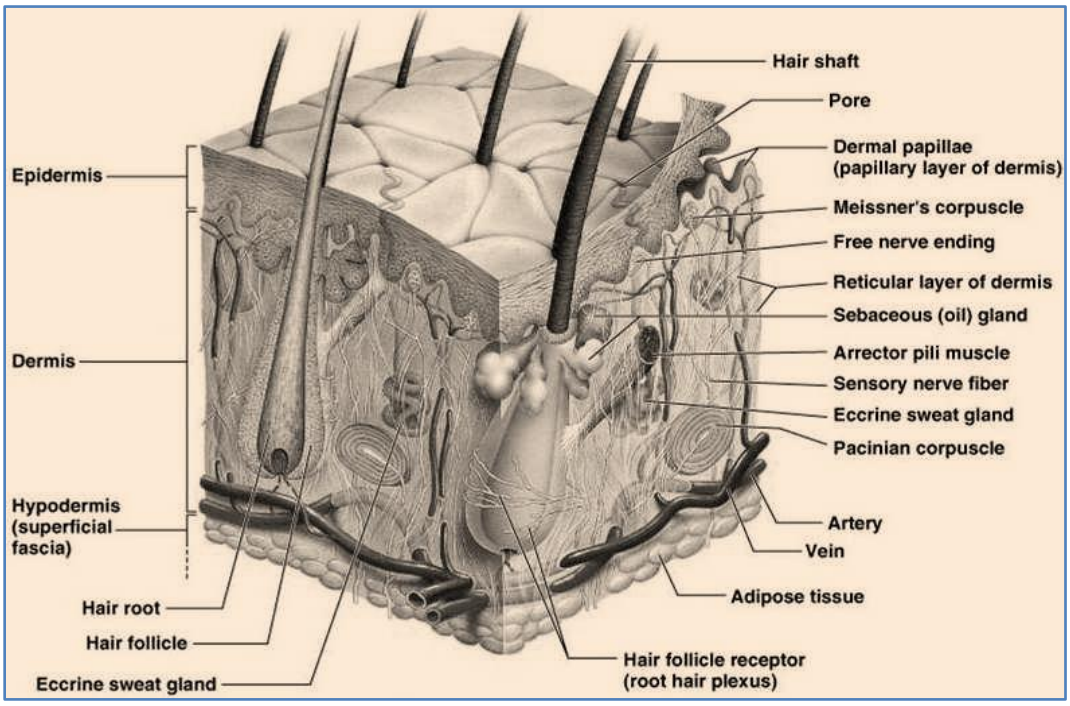

Fig. 2: Skin cross section

2.1 Non-viable epidermis

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to the most substances that come in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate like structure; 34-44 µm long, 25-36 µm wide,0.5 to 0.20 µm thick with surface area of 750 to 1200 µm stocked up to each other in form of bricks. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulphate and neutral lipid, protein (75-85%) which is mainly keratin.

2.2 Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. The structures of the cells in the viable epidermis are physiochemically similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

2.3 Dermis

Dermis lies just beneath the viable epidermis. It is a structural fibrin that consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance. The thickness of dermis ranges from 2000 to 3000 µm.

2.4 Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators

consider that the drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

3. Factors affecting topical absorption of drug

The factors that affect the topical absorption of drug are as follows [5,6]:

3.1 Physiological factors

- Skin thickness.
- Lipid content.
- Density of hair follicles.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Inflammation of skin.

3.2 Physiochemical factors

- Partition coefficient.
- Molecular weight (<400 dalton).
- Degree of ionization (only unionized drugs gets absorbed well).
- Effect of vehicles.

4. 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]:

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

5. Composition of emulgel preparation

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

5.1 Aqueous material

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

5.2 Oils

These agents constitute the oily phase of the emulsion. For externally applied emulsions, mineral oils (with or without soft or hard paraffin), 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.

5.3 Emulsifiers

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

5.4 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.

5.5 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:

• They should be non-toxic, non-irritating and non-allergenic.

• They should work rapidly; the activity and duration of effect should be predictable as well as reproducible.

• They should have no pharmacological activity within the body i.e. should not bind to receptor sites.

• 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.

• The penetration enhancers should be compatible with both excipients and drugs.

• They should be cosmetically acceptable with an appropriate skin ‘feel’.

5.5.1 Mechanism of permeation enhancers

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

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, co enhancer or solvent into the stratum corneum.

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 of

enhancer employed has a significant impact on the design and development of the product.

5.5.2 Pathway of transdermal permeation

Permeation can occur by diffusion via:

- Transdermal permeation, through the stratum corneum.
- Intercellular permeation, through the stratum corneum.
- Transappendaged 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.

6. 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

Mohammad suggested a method for preparing emulgel. 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 6-6.5 using triethanolamine (TEA). The oil phase of the emulsion is prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase is prepared by dissolving Tween 20 in purified water. Methyl and propyl paraben are dissolved in propylene glycol whereas 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 70^0 to80^0C; then the oily phase is added to the aqueous phase with continuous stirring and cooled to room temperature. Glutaraldehyde is added during mixing of gel and emulsion in ratio 1:1 to obtain the emulgel[12].

7. Characterization of emulgel

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

7.1 Physical appearance

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

7.2 Spreadability

Spreadability is determined by an apparatus that consists of a wooden block, provided by a pulley at one end. A ground glass slide is fixed on this block. An excess of emulgel is sandwiched between this slide and another glass slide provided with the hook. A 1 Kg 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. The top plate is then subjected to pull off 80 gm. With the help of string attached to the hook, the time (in seconds) required by the top slide to cover a distance of 7.5 cm is noted. A shorter interval indicates better spreadability.

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

7.3 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 gm) / Area (in cm^2)

7.4 Globule size distribution

A 1.0 gm sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample is injected to photocell of zeta sizer. Mean globule diameter and distribution is obtained.

7.5 Rheological study

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

7.6 Swelling index

To determine the swelling index of emulgel, 1 gm 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 beakers at different time intervals and reweighed.

Swelling index is calculated as follows:

Swelling Index (SW) % = [(Wt – W_0) / W_0] × 100

Where, (SW) % = Equilibrium percent swelling,

W_0 = Original weight of emulgel,

Wt = Weight of emulgel after time t

7.7 Ex–vivo bioadhesive 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 gm 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:

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

7.8 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.

7.9 In-vitro release study

Franz 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.

7.10 Microbiological assay

Ditch plate technique is used, which is meant for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates are used. Three grams of the emulgel are 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

7.11 Skin irritation test

0.5 gm 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.

7.12 Accelerated stability studies

Stability studies are performed according to ICH guidelines. The emulgel formulations are stored in hot air oven at 37 ± 2^0, 45 ± 2^0 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.

7.13 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.

8. Marketed preparation 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].

Table 1: Some marketed preparations of emulgel

S. No.	Product Name	Drug	Manufacturer
1	Miconaz-Hemulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals
2	Excex gel	Clindamycin, Adapalene	Zee laboratories
3	Lupigyl gel	Metronidazole	Lupin Pharma
4	Avindo gel	Azithromycin	Cosme Pharma laboratories
5	Zorotene gel	Tezarotene	Elder Pharmaceuticals
6	Topinate gel	Clobetasol propionate	Systopic Pharma
7	Clinagel	Clindamycinphosphate Allantoin	Stiefel Pharma
8	Pernox gel	Benzoyl peroxide	Cosme Remedies Ltd
9	Voltarenemulgel	Diclofenac diethyl ammonium	Novartis Pharma

9. Merits of using emulgel

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

9.1 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.

9.2 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.

9.3 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.

9.4 Production feasibility

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

9.5 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.

9.6 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.

9.7 Controlled drug release

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

9.8 Patient compliance

They are less greasy and easy to apply.

10. 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 ahigher 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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