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EMULGEL- AN OVERVIEW

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ABSTRACT

Emulgel plays a key role in chronic skin infections like fungal infections, acne, poison and inflammatory conditions. The combination of a emulsion and gel combined results into formation osf emulgel resulting in increase in the solubility of a poorly soluble drug. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diaognosis and treatment. Emulgels have several favorable properties of dermatological use such as thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, bio-friendly, transparent and pleasing appearance. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. This review gives basic knowledge of skin & about various affecting factors, formulation, preparation, evaluation and emulgels.

KEYWORDS: Emulgel, Gelling agent, Delivery, Dermatological, Penetration.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat the cutaneous disorder. The topical drug delivery system is generally used where other routes (such as oral, sublingual, rectal, and parental) of drug administration fails or in local skin infection like fungal infection.[1] Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment.[2] The main advantage of the topical delivery system is to bypass first pass metabolism. Avoidance of the

risks and inconveniences of intravenous therapy and the varied conditions of absorption, such as pH changes, the presence of enzymes, and gastric emptying time are another advantage of the topical drug delivery system.[3]

The formulations are available in different forms like from solid through semisolid to liquid. Drugs are administered topically for their action at the site of application or systemic effects. Drug absorption is enhanced through the skin if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a non-electrolyte.[4] Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body while preventing the ingress of noxious chemicals or microorganisms. It is also the largest organ of the human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m^2. While such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep the insides in and the outside out.[5] Dermatological products applied to the skin are diverse in formulation and range in consistency from liquid to powder, but the most popular products are semisolid preparation.

Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and pharmaceutical preparations. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. They have a higher aqueous component that permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream base. These are superior in terms of use and patient acceptability.[2]

In spite, so advantageous gels show a major limitation in the delivery of hydrophobic drugs. Hence, to cover up this lacking, emulgel is prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel.[4] As the name suggest, they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion are used as a vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. Emulgel for dermatological use has several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable,

emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent, and pleasing appearance.[3]

Molecules can basically penetrate into the skin by three routes: Through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). [4]

Rationale of emulgel as a topical drug delivery system

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover, they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and in a pharmaceutical preparation.

A gel is a colloid that is typically 99% wt. liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatin substance present. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and deliver through gels.

Numbers of medicated products are applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents like ointments, creams lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing and they also exhibit the problem of stability. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. [6]

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed areas of the body-the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. There are three primary mechanisms of topical drug absorption: transcellular,

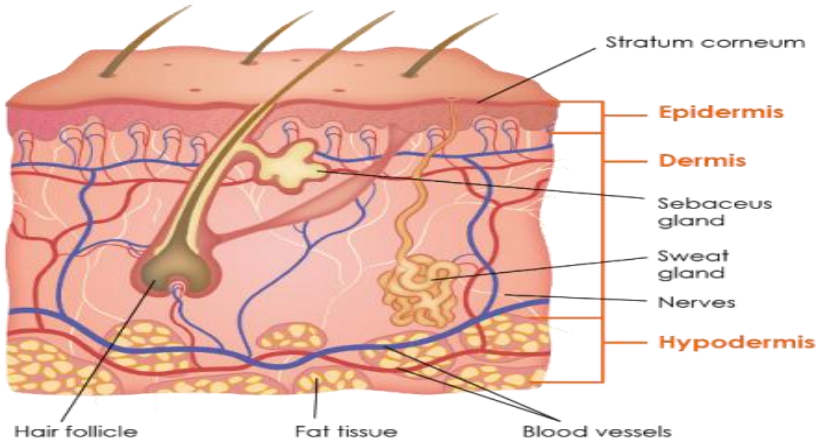

FIGURE-1.

Intercellular, and follicular.Most drugs pass through the torturous path aroundcorneocytes and through the lipid bilayer to viable layers of the skin. The next most common (and potentially under recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (Transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body. (Systemic).[2,3]

Factors Affecting Topical Absorption of Drug[7-8]

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

Factors to be considered when choosing a Topical Preparation[9-10]

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, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

Formulation of Emulgel

Vehicle[11]

The vehicle has following properties.

- Efficiently deposit the drug on the skin with even distribution.
- Release the drug so it can migrate freely to the site of action.
- Deliver the drug to the target site.

- Sustain a therapeutic drug level in the target tissue for a sufficient duration to provide a pharmacologic effect.
- Appropriately formulated for the anatomicsite to be treated.
- Cosmetically acceptable to the patient.
- Due to the efficiency of the epidermal barrier, the amount of topical drug that gets through the stratum corneum is generally low. Rate and extent of absorption vary depending on characteristics of the vehicle but is also influenced by the active agent itself.

Aqueous Material

This forms the aqueous phase of emulsion. The commonly used agents are water, alcohols etc.

Oils

These agents form the oily phase of the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations are nonbiodegradable 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.[12]

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 e.g. Polyethylene glycol 40stearate, Sorbitan mono-oleate (Span 80), Polyoxyethylenesorbitan monooleate (Tween80), Stearic acid and Sodium stearate.[13]

Gelling Agents

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. Carbopol-940 1% HPMC-2910.[14]

Penetration Enhancers

In order to promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupts the skin barrier, fluidize the lipid channels between

coenocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. E.g. Clove oil 8%, Menthol 5%.

Properties of penetration enhancers[15]

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

They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.

1. They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
2. 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.
3. The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
4. They should be cosmetically acceptable with an appropriate skin 'feel'.

Emulgel Preparation

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

Step 2: Formulation of gel base.

Step 3: Incorporation of emulsion into gel base with continuous stirring.

Emulgel was prepared by the method reported by Mohammad *et al*. (2004) with minor modification. The gel in formulations was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH is adjusted to 6 to 6.5 using triethanolamine. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propylparaben were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70°–80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature and add glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the Emulgel [Figure 3].[16]

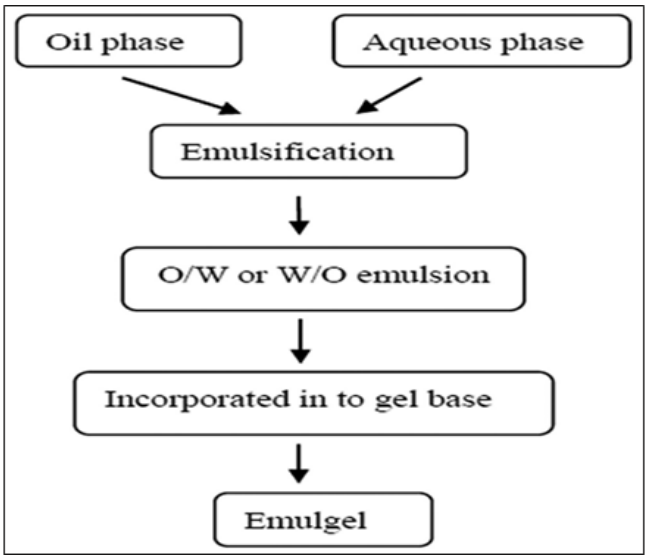

Figure 3: Flowchart Of Emulgel Formulation.

EVALUATION

Physical appearance

The prepared Emulsion formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter DPH 115 pm).[17]

Spreadability

Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for 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 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 of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was 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 completely from each other.

Extrudability study

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 cm2)

Globule size and its distribution in emulgel

Globule size and distribution was determined by Malvern zetasizer. A 1.0 gm sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer. Mean globule diameter and distribution was obtained.[18]

Rheological Study

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

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:

$$\text{Swelling Index (SW) \%} = [(Wt - Wo) / Wo] \times 100.$$

Where, (SW) % = Equilibrium percent swelling,

Wo = Original weight of emulgel at zero time after time t,

Wt = Weight of swollen emulgel

Ex–vivo Bioadheive 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. The bioadhesive strength is calculated by using following:

Bioadhesive Strength = Weight required (in gms) / Area (cm2)

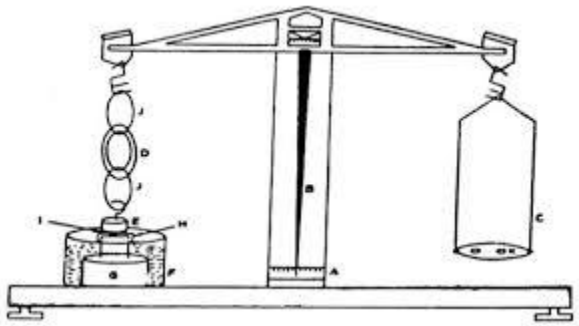

Figure: 3 Setup for bioadhesive test.

Drug Content Determination

Drug concentration in Gellified Emulsion was measured by spectrophotometer. Drug content in Gellified Emulsion was measured by dissolving known quantity of Gellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV-1700 CE, Shimadzu Corporation, Ja pan).[19]

In Vitro Release Study

Franz diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume) was used for the drug release studies. Gellified Emulsion (200 mg) was applied onto the surface of egg membrane evenly. The egg membrane was clam ped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) 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 visiblespectrophotometer 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.[20]

Microbiological assay

Ditch plate technique was used. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates were used. Three grams of the Gellified Emulsion 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 was observed and the percentage inhibition was measured as follows.

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

Where L1 = total length of the streaked culture, and

L2 = length of inhibition.

Skin irritation test

A 0.5 gm sample of the test article was then applied to each site (two sites per rabbit) by introduction under a double gauze layer to an area of skin approximately 1" x 1" (2.54 x 2.54 cm2). The Gellified Emulsion are applied on the skin of rabbit. Animals were returned to their cages. After a 24 hour exposure, the Gellified Emulsion are removed. The test sites were wiped with tap water to remove any remaining test article residue.

Accelerated stability studies of Gellified Emulsion

Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples were analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study was carried out by measuring the change in pH of gel at regular interval of time.[21]

Marketed Emulgels

The preparations of emulgel that are market commercially are listed below

S.no	Brand name	Active ingredient	Manufacturer	Uses
1	Voltarol 1.16% emulgel	Diclofenac diethyl ammonium salt	Novartis	Anti inflammatory
2	Diclomaxemulgel	Diclofenac sodium	Torrent pharma	Anti inflammatory
3	Miconaz-H-emulgel	Miconazole nitrate, hydrocortisone	Medicalunion pharmaceuticals	Topical corticosteroid &anti fungal
4	Dermafeetemulgel	Urea 40%	Herbitas	Intense moisturizing & exfoliation acticity
5	Denacineemulgel	Clindamycin phosphate	Beitjala pharmaceutical company	Anti acne
6	Isofenemulgel	Ibuprofen	Beitjala pharmaceutical company	Anti inflammatory
7	Diclonaemulgel	Diclofenac diethylamine	Kuwait Saudi pharmaceutical industries co.	Anti inflammatory
8	Dosanac emulsion gel	Diclofenac diethyl ammonium	Siam bheasach	Anti inflammatory
9	Diclonemulgel	Diclofenac diethyl ammonium	Medpharma	Anti inflammatoey
10	Cataflamemulgel	Diclofenac potassium	Novartis	Anti inflammatory

CONCLUSION

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel possesses an edge in terms of spreadibilty, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in an water soluble gel bases.

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