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EMULGEL: A NEW DOSAGE FORM FOR TOPICAL DRUG DELIVERY

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ABSTRACT

When gels and emulsions are used in combined form the dosage form are referred as emulgel. In recent years, there has been great interest in the use of novel polymers. 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 enjoy the unique properties of gels. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Polymer can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. Various permeation enhancers can potentiate the effect, so emulgels can be used as better topical drug delivery systems over present systems.

INTRODUCTION^{1,10}

Emulgel are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and better vehicle for hydrophobic or poorly water soluble drugs. They have a high patient acceptability since they possess the advantages of both emulsions and gels. Direct (oil-in-water) systems are used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) systems. Therefore, they have been recently used as vehicles to deliver various hydrophobic drugs to the skin. In the local market, Emulgel are available: Voltaren emulgel (Novartis Pharma, Switzerland), containing diclofenac diethylamine and Miconaz-H emulgel (Medical Union Pharmaceuticals, Egypt), containing miconazole nitrate and hydrocortisone. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The emulsion gels are hydrogels containing randomly distributed oil microdroplets. Topical drug delivery systems have been used for centuries for the treatment of local skin disorders, one side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering the drug for extended period of time at the effected site that mainly acts at the related regions. On the other hand, topical delivery system increases the contact time and mean resident time of drug at the applied site leading to an increase in local drug concentration while the pharmacological activity of Emulgel formulations may not change as rapidly as the solution form. Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. In addition, the formulator can control the viscosity, appearance, and degree of greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications. Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible.

RATIONALE

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 preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations.

PHYSIOLOGY OF SKIN^{3,8}

Most of the topical preparations are meant to be applied to the skin. So, basic knowledge of the skin and its physiology function are very important for designing topical. The skin of an average adult body covers a surface area approximately 2m² and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, the average 40-70 hair follicles and 200-300 sweat ducts on every square centimeter 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 as shown in figure.

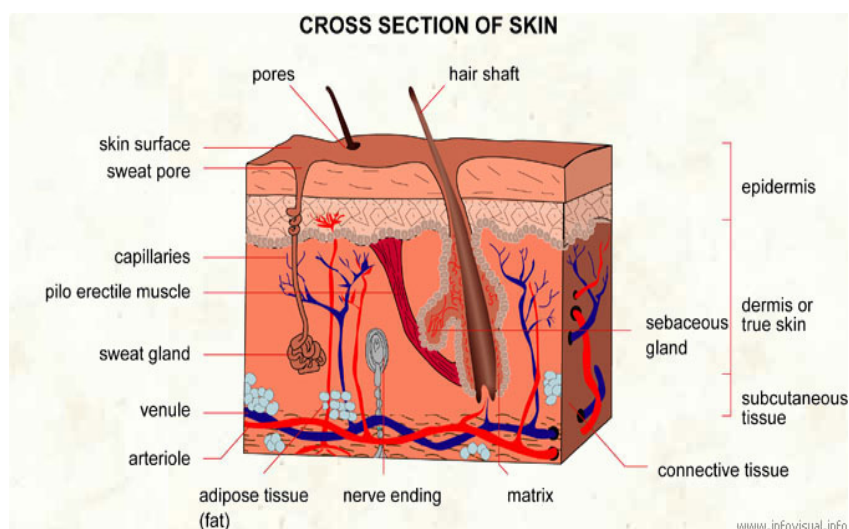


Fig:1. Physiology of skin

1. Non-viable epidermis
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG^{6,9}

A) 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.

B Physiochemical Factors

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

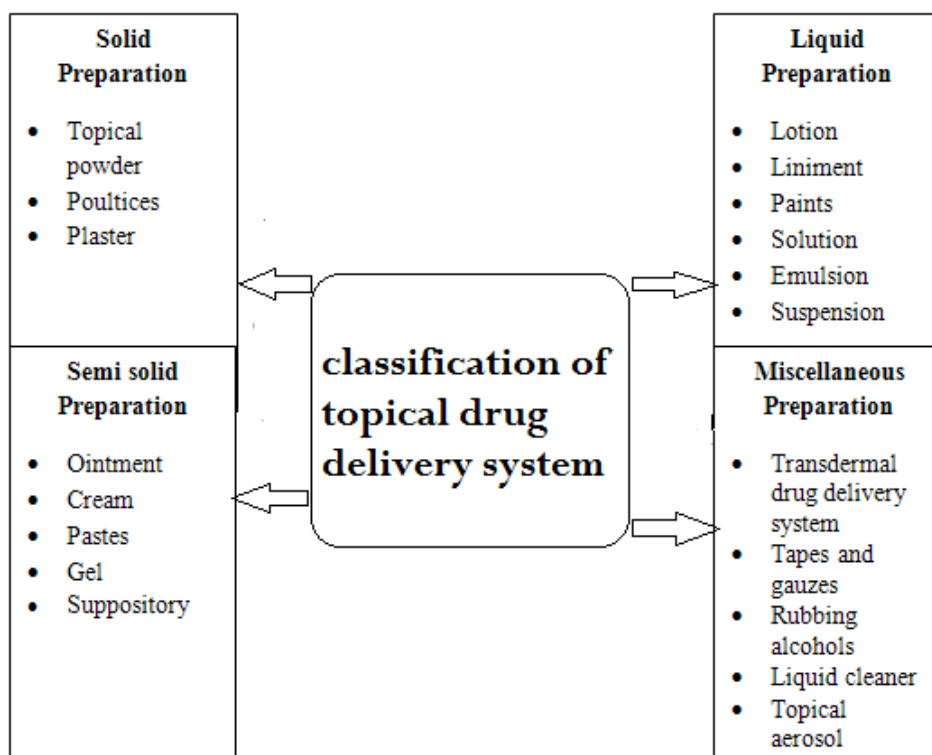


Fig no.2: Classification of topical drug delivery

FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION²

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.

METHOD TO ENHANCE DRUGPENETRATION:

1. Chemical enhancement
2. Biochemical enhancement
3. Physical enhancement

Important Constituents of Emulgel Preparation^{3,6}

1. Aqueous Material:

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

2. 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 non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils.

2. 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 40 stearate, Sorbitan mono-oleate (Span 80),

3. 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

4. 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 corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin. So called penetration enhancers.

E.g. Clove oil 8% , Menthol 5%

EMULGEL PREPARATION⁴

Emulgel was prepared by the method reported by Mohammad et al (2004) with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA).The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween20 in purified water.

METHOD OF PREPARATION

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 flow chart of emulgel preparation is shown in figure 3.

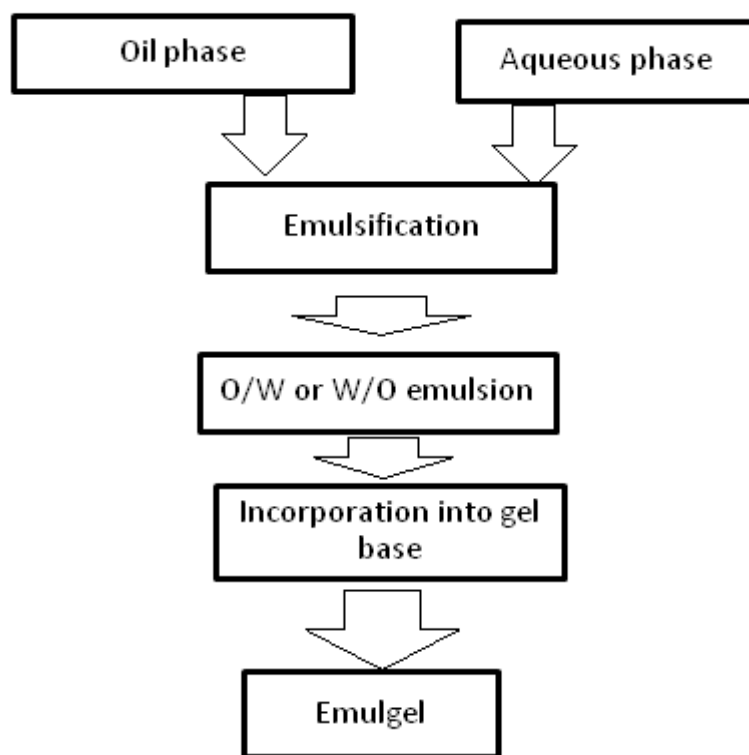


Fig no: 3. Method of emulgel preparation

CHARACTERIZATION OF EMULGEL^{6,7}**Physical appearance:**

The 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.

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 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.

$$S = M * \frac{L}{T}$$

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 0.5cm 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 then calculated by using the following formula:

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

Rheological Studies:

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 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:

$$\text{SwellingIndex(\%)} = \left[\frac{W_t - W_o}{W_o} \right] * 100$$

Where, (SW) % = Equilibrium percent swelling,

W_t = Weight of swollen emulgel after time t,

W_o = Original weight of emulgel at zero time.

Drug Content Determination:

Take 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 the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance in the standard equation.

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

Skin Irritation Test (Patch Test):

The emulgel is applied on the properly shaven skin of rat and its adverse effect like change in color, change in skin morphology should be checked up to 24 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. The bioadhesive strength is calculated by using following:

$$\text{Bioadhesive Strength} = \text{Weight required (in gms)} / \text{Area (cm}^2\text{)}$$

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. Emulgel 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 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 visible spectrophotometer 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.

Accelerated stability studies of Emulgel:

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.

Marketed preparations

Product name	Drug	Manufacturer
Voltarenemulgel	Diclofenac diethyl ammonium	Novartis Pharma
Miconaz-H-emulgel	Miconazole nitrate, Hydrocortison	MedicalunionPharmaceuticals

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 spreadibility, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in a water soluble gel bases.

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