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AN OVERVIEW ON EMULGEL

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Abstract:

Topical drug delivery system can be defined as direct effects of formulation or drug containing medication to the skin to get localizing effect of drug or directly cure cutaneous disorders. Emulgels has to be used as a topical drug delivery system for hydrophobic drugs. When gels and emulsions are used in combined form the dosage forms are referred as emulgels. Emulgels have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion. The major objective behind this formulation is delivery of hydrophobic drugs to systemic circulation via skin. In recent years, there has been great interest in the use of novel polymers which 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. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, and emollient, no staining, water-soluble, longer shelf life, and bio-friendly, transparent & pleasing appearance. These emulgels 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 emulgel formulations can be used as better topical drug delivery systems over present conventional systems available in market.

Keywords: Topical drug delivery system, Emulgels, Hydrophobic drugs, Gelling agents, enetration enhancers.

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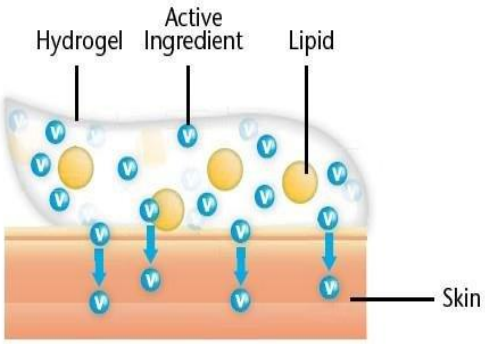
INTRODUCTION:

Topical drug delivery system is the dosage form which is administered on the skin and other routes of drug delivery get failed or for skin disorders. The topical drug delivery system has the advantage of negotiating the first pass metabolism. It also helps to avoid the risk and inconvenience of i.v route therapy. Topical formulations are prepared in different consistency such as solid, semisolid, and liquid. The topical delivery system is failed in the administration of hydrophobic drug. In each formulation with the active ingredients many excipients are used. Sometimes more than one formulation can be combined to enhance the drug delivery; emulgel is such type of combination. It is the combination of emulsion and gel]. Emulgel is prepared both in oil-in- water and water- inoil type emulsion mixed with gel. Oil- in- water type is used for lipophilic drugs and water- in- oil type is used for hydrophobic drugs' delivery].

The emulgel have many advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf- life.

The emulsion and gel preparations have their own properties. But the gels show some limitations as hydrophobic drug delivery. This limitation is overcoming by emulgel. By the use of gelling agent classical emulsion can be converted in to emulgel.



EMULGEL STRUCTURE

Two types of topical delivery products are available. They are external and internal products. As their name indicates, the external products are applied by spreading or spraying, and the internal products are applied orally, vaginally or rectally. The topical preparation can be classified by their consistencies, which are solid preparation, liquid preparation, semi-solid preparation and miscellaneous preparation.

Some factors will affect the absorption of drug through every route. Some factors like skin thickness, skin pH, hydration, inflammation, partition coefficient, molecular weight and other factors affect topical route. The topical delivery system has many advantages and also disadvantages. The main advantage is avoidance of first pass metabolism and gastrointestinal incompatibility. Nearly all topical preparations are applied on the skin. They penetrate through the skin and give the action in right site.

PHYSIOLOGY OF SKIN

Most of the topical preparations are meant to be applied to the skin. Hence, a basic knowledge of the skin and its physiology function are very important for designing topical dosage form. The skin of an average adult body covers a surface area approximately 2 m2 and receives about one-third of the blood circulating through the body. An average human skin surface is known to contain, on 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.

Non-viable epidermis

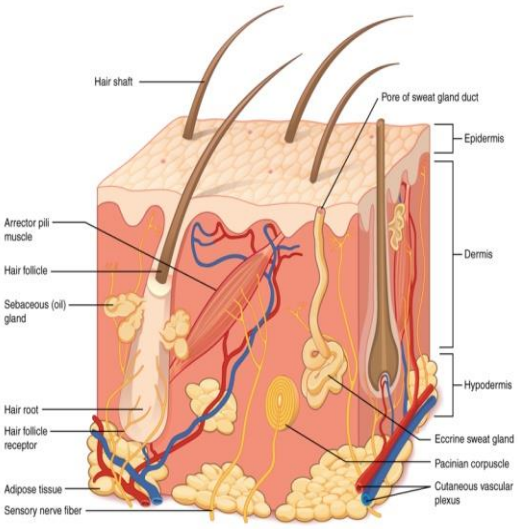
Stratum corneum is the outermost layer of skin, which is the actual physical barrier to the most substance that comes in contact with the skin. The stratum corneum is 10–20 cell layer thick over most of the body. Each cell is a flat, platelike structure - 34–44 μm long, 25–36 μm wide, and 0.5–0.20 μm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

Viable epidermis

This layer of the skin resides between the stratum corneum and dermis and has a thickness ranging from 50 to 100 μm. The structures of the cells in the viable epidermis are physicochemically 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%.

Dermis

Just beneath the viable epidermis is the dermis. It is structural fibrin, and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 μm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground



STRUCTURE OF SKIN

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which 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 drug is permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibres. 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, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipidbilayer to viable layers of the skin. The next most common (and potentially underrecognized 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 arerubbed 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.

Factors Affecting Topical Absorption of Drug

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
4. Effect of vehicles

FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION

1. Irritation or sensitization potential. In general, 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.
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. Effect of the vehicle, for example, an occlusive vehicle enhanced penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action.

Method to Enhance Drug Penetration and Absorption

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

ADVANTAGES AND DISADVANTAGES OF EMULGEL

ADVANTAGES

- Incorporation of hydrophobic drugs
- Better loading capacity
- Better stability
- Controlled release
- No intensive sonication
- Avoiding first pass metabolis
- Avoiding gastrointestinal incompatibility
- More selective for a specific site
- Improved patient compliance
- Convenient and easy to apply.

DISADVANTAGES

- Skin irritation on contact dermatitis
- The possibility of allergenic reactions
- The poor permeability of some drugs through the skin
- Drugs of large particle size are not easy to absorb through the skin
- The occurrence of the bubble during formulation of emulgel.

FORMULATION OF EMULGEL

Vehicle

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 anatomic site 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 the emulsion. The commonly used agents are water and alcohols.

Oils

These agents form the oily phase of the emulsion, as given in Table 4. 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 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 or various fixed oils of vegetable origin (e.g., Arachis, cottonseed, and maize oils) as nutritional supplements.

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, for example, polyethylene glycol 40stearate, Sorbitan mono-oleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid, and sodium stearate.

Gelling agents

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.

Penetration enhancers

To promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into the skin.

Properties of penetration enhancers

- 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.
- 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 while preventing the loss of endogenous material from the body.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs. • They should be cosmetically acceptable with an appropriate skin “feel.”

Mechanism of penetration enhancer

Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer, or solvent into the stratum corneum.

The enhancers act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased 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.

IDEAL PROPERTIES OF ADDITIVES

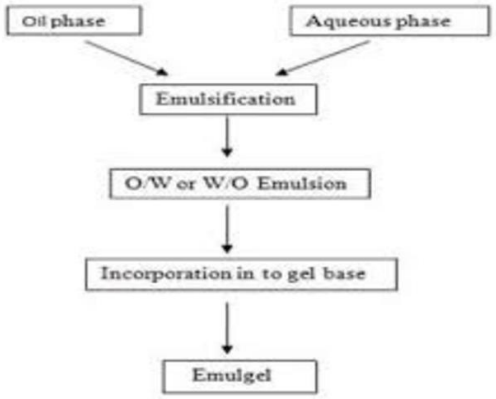
- ♣ They should be easily available.
- ♣ They should be cheap.
- ♣ They do not be contraindicated.
- ♣ They should chemically and physically be stable
- ♣ They should be nontoxic.

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.



FLOW CHART OE EMULGEL FORMULATION

CHARACTERIZATION OF EMULGEL

Physical examination

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, and phase separation.

Determination of pH

pH of the formulation was determined using digital pH meter. pH meter electrode was washed by distilled water and then dipped into the formulation to measure pH, and this process was repeated 3 times.

Spreadability

Spreadability is used to express the extent of area to which gel readily spread on application to skin or affected part and the therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time were noted for upper slide (movable) to separate completely from the fixed slides.

Spreadability was then calculated by using the formula:

$$S = M \times L / T$$

Where, S = Spreadability; M = Weight tide to upper slide; L = Length of glass slide; T = Time taken to separate the slide completely from each other.

Swelling index:

One gram of emulgel is taken in a porous aluminum foil and placed separately in a 50 ml beaker containing 10 ml of 0.1 N NaOH. Then, the samples are removed at different time intervals, and reweighed.

Swelling index is determined by the equation;

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

Where, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time.

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Globule size and its distribution in Emulgel

Globule size and distribution are determined by Malvern Zeta size. A 1.0 g sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample was injected to photocell of Zeta size. Mean globule diameter and distribution are obtained.

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Skin irritation test

A 0.5 g 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" × 1" (2.54 × 2.54 cm2). The gellified emulsion was applied to the skin of a rabbit. Animals were returned to their cages. After a 24 h exposure, the gellified emulsion is removed. The test sites were wiped with tap water to remove any remaining test article residue.

Extrudability study

It is a usual empirical test to measure the force required to extrude the material from the tube. The method applied for the 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 on the quantity in the percentage of emulgel and emulgel extruded from the lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 s. More quantity extruded better is extrude ability. The measurement of extrudability of each formulation is in triplicate, and the average values are presented.

The extrude ability is then calculated using the following formula:

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

Drug content determination

The prepared emulgels were tested for the drug content uniformity. Accurately weighed quantity of formulation was transferred to a 100 ml volumetric flask containing 50 ml of methanol and allowed to stand for 5 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with methanol. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at 260nm.

In vitro drug release studies

Franz diffusion cell (with effective diffusion area 3.14 cm 2 and 15 ml cell volume) was used for the drug release studies. Emulgel (200 mg) was applied onto the surface of cellophane membrane evenly. The membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared buffer pH 5.5 solutions to solublize 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 at 260 nm after appropriate dilutions.

In vitro drug release kinetics

To elucidate the drug release pattern and mechanism from the prepared formulations, the data obtained from the in vitro dissolution studies was integrated to zero order, first order and Higuchi models (Valluru et al., 2008). Then the dissolution data was also used to calculate the T10% and T80% (time in hours to take 10% and 80% drug release, respectively) to elucidate the drug release from emulgels.

Microbiological assay:

For this method Ditch plate technique is used. Through this method the bacteriostastic or fungiststic activity is evaluated.

Stability studies

The prepared emulgels were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 mo. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

PACKAGING OF EMULGELS

Packaging of emulgels are usually done in membrane sealed lacquered aluminum tube with inner coating of a phenoxy-epoxy based lacquer closed with propylene screw cap or an aluminum laminated tubes closed by a moulded seal, with a propylene screw cap.

Material for laminates tubes

1. Foil laminates It provides light, air and moisture barrier.
2. All plastic laminates

It has a chemical resistant barrier.

CONCLUSION:

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Emulgel is a recent technique for topical drug delivery and it is suitable for hydrophobic drugs. Since it is also capable in enhancing 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 base.

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