EMULGEL: AN ADVANCE TECHNIQUE FOR PENETRATION OF HYDROPHOBIC DRUGS

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ABSTRACT

Gel has many advantages but their main limitation is that delivery of hydrophobic drugs across the membrane to overcome this combination of emulsion and gel and the dosage form is referred as EMULGEL. By this method hydrophobic moiety can enjoy the unique properties of gels. Hydrophobic drugs cannot directly incorporate into gel base because solubility acts as a barrier and causes problem during the release of drug. Emulgel formulation helps the hydrophobic drugs incorporation into the oil phase and then oily globules are dispersed in aqueous phase resulting in O/W emulsion which can mixed into gel base. Emulgel provide better stability and control release of drug with short half life. The use of emulgel is extended in analgesic and antifungal drugs.

KEYWORD: Hydrophobic drugs, Emulgel.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Transdermal drug delivery is an attractive route for local and systemic treatment. Topical preparations pertain to medicaments applied to the surface of a part of a body and are a term used to describe formulations that have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of medicament is minimal. Transdermal drug delivery offers several advantages over
conventional route. Most common examples of topical dosage forms include solution, suspensions, emulsions, semisolids, spray etc.

Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in 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 aluminium 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. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels.

When gels and emulsions are used in combined form the dosage forms are referred as emulgels. As the name suggest they are the combination of emulsion and gel. In recent years, there has been great interest in the use of novel polymers with complex functions 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. Both oil-in-water and water-in-oil emulsions are used 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. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water- soluble, longer shelf life, bio-friendly, transparent & pleasing appearance.

Molecules can basically penetrate into 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% of the total skin surface available for percutaneous drug absorption. Passage through this outer most layer 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).

Preferable characteristics of topical drugs involve molecular mass (600 Da), proper solubility in oil and water, and a high partition coefficient. Except for very small particles, water soluble ions and polar molecules do not penetrate intact stratum corneum. Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and anti-bacterials help a damaged barrier toward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer.

ADVANTAGE\textsuperscript{[6,7]}
- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- More selective to a specific site.
- Improve patient compliance.
- Suitability for self medication.
- Providing utilization of drug with short biological half life and narrow therapeutic window.
- Ability to easily terminate medication when needed
- Convenient and easy to apply.

DISADVANTAGE\textsuperscript{[6,7]}
- Skin irritation on contact dermatitis.
- Possibility of allergenic reactions.
- Poor permeability of some drug through skin.
- Drug of large particle size not easy to absorb through the skin.

RATIONALE OF EMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM
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.

To overcome limitation of various ointments and gels an emulsion based approach is being used so that even a HYDROPHOBIC therapeutic moiety can be successfully incorporated and delivered through gels.

**PHYSIOLOGY OF SKIN**[8,9]

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 dosage form. 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 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.
1. Non-viable epidermis

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes 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 brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

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%.

3. Dermis
Just beneath the viable epidermis is the dermis. It is a 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 amorphose ground substance.

4. 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 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**[^89]

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 fibres. The skin forms a relatively water proof 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 neither absorption nor loss of water and electrolytes. There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the tortuous path around corneocytes 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)

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG\cite{10}

(A) Physiological Factors
1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
5. Skin pH.
8. Inflammation of skin.

(B) 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[13,14]
1. 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 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 e.g. an occlusive vehicle enhanced penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
5. The medication should not affect skin type.

FORMULATION OF EMULGEL[15]

Vehicle
The vehicle has following properties.
o Efficiently deposit the drug on the skin with even distribution.
o Release the drug so it can migrate freely to the site of action.
o Deliver the drug to the target site.
o Sustain a therapeutic drug level in the target tissue for a sufficient duration to provide a pharmacologic effect.
o Appropriately formulated for the anatomic site to be treated.
o Cosmetically acceptable to the patient.
o 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 from 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 or various fixed oils of vegetable origin (e.g., a rachis, 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 e.g. Polyethylene glycol 40stearate, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween80), 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. Carbopol-940, HPMC etc.

**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**

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 whilst 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’.
EMULGEL PREPARATION[16]

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 were 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 are adjusted to 6 to 6.5 using Triethanolamine (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 Tween 20 in purified water. Methyl and propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were 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.
EVALUATION OF EMULGEL \cite{17,18,19,20,21}

Fourier transforms infra red spectroscopy (FTIR)

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for formulation.

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

Measurement of viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1°C) before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.

Spreadability

To determine spreadability of the gel formulations, two glass slides of standard dimensions were selected. Formulation whose spreadability was to be determined was placed over one slide and the other slide was placed over its top such that the gel is sandwiched between the two slides. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of weight tied to it. 20 gm weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted. The spreadability was calculated by using the following formula.

\[
S = M \cdot \frac{L}{T}
\]
Where, $M =$ weight tied to upper slide  
$L =$ length of glass slides  
$T =$ time taken to separate the slides  

**Globule size and its distribution in emulgel**  
Globule size and distribution is determined by Malvern zeta sizer. A 1.0 gm sample is dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zeta sizer. Mean globule diameter and distribution is obtained.

**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:

\[
\text{Swelling index (SW) %} = \left[ \frac{(Wt - Wo)}{Wo} \right] \times 100.
\]

Where,

(SW) % = Equilibrium percent swelling,

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

**Extrudability**  
The prepared emulgel formulations were filled in clean, lacquered aluminium collapsible tubes with a 5 mm opening nasal tip. Extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 kg. was placed over the pan. The Extrudability of prepared Emulgel formulations was calculated by using following formula.

\[
\text{Extrudability} = \frac{\text{Amount of gel extruded from the tube}}{\text{Total amount of gel filled in the tube}} \times 100
\]

**Drug content study**  
Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The
solution was passed through the filter paper and filtered the mixer then measured absorbance by using spectrophotometer.

Drug Content = (Conc. × Dilution Factor × Vol. taken) × Conversion Factor

**In-vitro Drug release study**

The in vitro drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilise the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval sample 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 release across the egg membrane was determined as a function of time. The cumulative % drug release was calculated using standard calibration curve.

**Microbiological assay**

Ditch plate technique is 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 are 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 is observed and the percentage inhibition is measured as follows.

\[
\% \text{ inhibition} = \frac{L2}{L1} \times 100
\]

Where \( L1 \) = total length of the streaked culture, and
\( L2 \) = length of inhibition.

**Accelerated stability studies of Gellified Emulsion**

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

To analyze the mechanism of drug release from the topical gel, the release data should be fitted to following equations

**Zero – order equation**

\[ Q = k_0 t \]

Where \( Q \) is the amount of drug released at time \( t \), and \( k_0 \) is the zero – order release rate.

**First – order equation**

\[ \ln(100 - Q) = \ln 100 - k_1 t \]

Where \( Q \) is the percent of drug release at time \( t \), and \( k_1 \) is the first – order release rate constant.

**Higuchi’s equation**

\[ Q = k_2 \sqrt{t} \]

Where \( Q \) is the percent of drug release at time \( t \), and \( k_2 \) is the diffusion rate constant.

**MARKETED PREPARATIONS**

<table>
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<tr>
<th>Drug</th>
<th>Product name</th>
<th>Manufacturer</th>
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<td>Miconazole nitrate, Hydrocortisone</td>
<td>Miconaz-H-emulgel</td>
<td>Medical union Pharmaceuticals</td>
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<tr>
<td>Diclofenac diethyl ammonium</td>
<td>Voltaren emulgel</td>
<td>Novartis Pharma</td>
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<td>Lupigyl gel</td>
<td>Lupin Pharma</td>
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<td>Excez gel</td>
<td>Zee laboratories</td>
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<td>Benzoyl peroxide</td>
<td>Pernox gel</td>
<td>Cosme Remedies Ltd</td>
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<td>Acent gel</td>
<td>Intra labs India Pvt Ltd</td>
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**CONCLUSION**

In the recent years, topical drug delivery will be used extensively due to 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.

REFERENCES


