EMULGELS: A REVIEW FOR TOPICAL DRUG DELIVERY OF HYDROPHOBIC DRUGS

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Abstract
For the treatment of local as well as systemic skin disorders, topical drug delivery systems have been used for centuries offering the advantage of delivering the drug directly to the site of action and also delivering the drug for extended period of time at the affected area that mainly acts at the related regions. Also these systems increase the contact time and mean resident time of the drug. When gel and emulsion are used in combination, they are referred to as Emulgel, hence containing dual control release systems: a gel and an emulsion. Despite of several advantages of gels, there is a limitation in delivery of hydrophobic drug moiety. This limitation can be overcome by the use of novel topical drug delivery i.e. emulgel. The major objective behind emulgel is delivery of hydrophobic drugs via skin. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgels are having major advantages on novel vesicular system as well as on conventional systems in various aspects. They are referred for topical use due to their favourable properties for dermatological use such as being greaseless, non-staining, thixotropic, emollient, easily removable, water soluble, bio-friendly, long shelf-life, transparent and pleasant appearance. The use of emulgels can be expanded in different classification namely analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations.

Keywords: - Emulgel, topical drug delivery systems, hydrophobic drugs, gelling agent.

Introduction
Drugs have been applied to human body via various routes namely oral, sublingual, rectal, parenteral, etc. for the treatment of illness over the last decades. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection [1,2]. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne, psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within. For diagnosis and treatment, skin provides direct accessibility as a target organ which becomes a unique aspect of dermatological pharmacology [3]. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Topical drug administration through various routes applies a wide spectrum of preparations for both cosmetic and dermatological, to their healthy and diseased skin [4].Topical preparations are applied to the surface of a part of the body and have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal [5].Advantages of topical drug delivery over conventional routes are that it avoids the first pass metabolism and the gastrointestinal tract. Also, topical delivery has the potential for sustained and controlled drug release [6,7]. Moreover, it is a non-invasive mode of drug delivery with no trauma or risk of infection [8]. The most common examples of topical dosage forms are solutions, suspensions, emulsions, semisolids (e.g. foams, ointments, pastes, creams and gels), sprays and solids (e.g. powders and aerosols)[9]. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and
in pharmaceutical preparations. Gels are created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. In spite of many of its advantages, the delivery of hydrophobic drugs is the major limitation of gels. This can be overcome by using a combination of gel and emulsion known as Emulgel [10].

**Emulgels**

Emulgels are dosage forms in which gels and emulsions are used in combined form [11]. In recent years, there has been wide use of new polymers with complex functions as emulsifiers and thickeners because the gelling property 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. The gelling agent in the water phase converts a classical emulsion into an emulgel [12]. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver the drugs to the skin. Emulsions have a certain degree of elegance and can be easily washed off whenever required. These can penetrate the skin with high efficiency. 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 and pleasing appearance. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption.

**Molecules can penetrate the skin by three routes:**

i. Intact stratum corneum
ii. Sweat ducts
iii. Sebaceous follicles

Passage through stratum corneum 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 movement of drug 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 include low molecular mass (600 Dalton), adequate solubility in oil and water and a high partition coefficient. Topical formulation can be used to manipulate the barrier function of the skin, for e.g., topical antibiotics and antibacterials help a damaged barrier to ward off infection, sun-screening agents and the horny layer protect the viable tissues from ultra-violet radiation and emollient preparations restore pliability to a desiccated horny layer [13].

**Rationale of emulgel**

Many of the topical agents like creams, lotions, ointments, etc. have disadvantages of being sticky thus causing uneasiness to the patient when applied. Also, these need to be applied with rubbing and have lesser spreading coefficient [14]. They also exhibit the problem of stability. Due to all these problems, the use of transparent gels among semisolid preparations has expanded both in cosmetics and in pharmaceutical preparations. But also the problem with gels is that they fail to deliver hydrophobic drugs. So to overcome this limitation, an emulsion based approach is being used so that the hydrophobic drugs can be easily incorporated and delivered through gels.

**Advantages of emulgel**

There are following advantages of emulgel.

I. Avoidance of first pass metabolism.
II. Avoidance of gastrointestinal incompatibility.
III. Self-medication is possible.
IV. Improve patient compliance.
V. Site specific drug delivery.
VI. Suitable for drugs with short half-life and potent drug.
VII. Medication can be terminated when needed.
VIII. Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions.
IX. Better stability.
X. Better loading capacity.
XI. Production feasibility and low preparation cost.
XII. No intensive sonication.
XIII. Controlled release [15,16].

**Disadvantages of emulgel**

There are following advantages of emulgel.

I. Drug of large particle size not easy to absorb through the skin.
II. Skin irritation or allergic reaction on contact dermatitis.
III. Poor permeability of some drugs through skin [17].
Formulation considerations
The challenges in formulating topical emulgels are:
I. Determining systems that are non-toxic, non-irritating, non-comedogenic and non-sensitizing.
II. The emulgel formulation must have low allergic potential, good physiological compatibility and high biocompatibility.
III. Formulating cosmetically elegant emulgel [18].

Skin: The site of drug delivery
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. Blood vessels are distributed profusely beneath the skin. The skin acts as a two way barrier to prevent absorption, loss of water and electrolytes.

There are three primary mechanisms of topical drug absorption:
I. Transcellular,
II. Intercellular
III. Follicular.

Most drugs pass through the tortuous path around corneocytes and through the lipid bilayer to viable layers of the skin. The barrier resides in the outermost layer of the epidermis, the stratum corneum. To overcome this problem various penetration enhances are used to improve the drug absorption through stratum corneum [19].

Factors to be considered when choosing a topical preparation
I. Effect of the vehicle. For 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.
II. Match the type of preparation with the type of lesions. For e.g., avoid greasy ointments for acute weepy dermatitis.
III. Match the type of preparation with the site. For e.g., gel or lotion for hairy areas.
IV. Irritation and sensitization potential [22,23].

Methods to enhance drug penetration
I. Chemical enhancement.
II. Biochemical enhancement.
III. Physical enhancement.
IV. Super-saturation enhancement [24].

Excipients used in emulgel formulation

• Ideal Properties Of Excipients
I. They must be non-toxic.
II. They must be commercially available in acceptable grade.
III. Their cost must be acceptably cheap.
IV. They must not be contraindicated.
V. They must be physically and chemically stable by themselves and in combination with drugs and other components.
VI. They must be color compatible [25].

• Emulgel formulation: There are following excipients used in emulgel formulation

I. Vehicles
The vehicle should have the 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.
• Cosmetically acceptable to the patient.
• Appropriately formulated for the anatomic site to be treated.

Rate and extent of absorption vary depending on the characteristics of the vehicle but is also influenced by the active ingredient itself.
Aqueous materials and oils
This forms the aqueous phase of the emulsion. Commonly used agents are water and alcohols. Oil forms are the oily phase of the emulsion. Mostly used oils in oral preparations are non-biodegradable mineral and castor oils and various fixed oils of vegetable origin (e.g. arachis, cottonseed, and maize oils).

II. Emulsifiers
Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life for commercial preparations. e.g. polyethylene glycol 40 stearate, sorbitan mono-oleate, polyoxymethylenesorbitan mono-oleate, stearic acid and sodium stearate.

III. Gelling Agents
These are used to increase the consistency of any dosage form. These can also be used as thickening agent [26,27]. The examples are given in table no 1.

<table>
<thead>
<tr>
<th>Gelling agent</th>
<th>Quantity (Percentage on anhydrous basis)</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbopol 934</td>
<td>1%</td>
<td>Emulgel</td>
</tr>
<tr>
<td>Carbopol 940</td>
<td>1%</td>
<td>Emulgel</td>
</tr>
<tr>
<td>HPMC 2910</td>
<td>2.5%</td>
<td>Emulgel</td>
</tr>
<tr>
<td>HPMC</td>
<td>3.5%</td>
<td>Gel</td>
</tr>
<tr>
<td>Sodium CMC</td>
<td>1%</td>
<td>Gel</td>
</tr>
</tbody>
</table>

IV. Permeation Enhancers
These are the agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. Some of these materials are given in table no 2.

<table>
<thead>
<tr>
<th>Penetration enhancer</th>
<th>Quantity (Percentage on anhydrous basis)</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clove oil</td>
<td>5%</td>
<td>Emulgel</td>
</tr>
<tr>
<td>Menthol</td>
<td>5%</td>
<td>Emulgel</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>1%</td>
<td>Gel</td>
</tr>
<tr>
<td>Lecithin</td>
<td>5%</td>
<td>Gel</td>
</tr>
<tr>
<td>Urea</td>
<td>10%</td>
<td>Gel</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>5%</td>
<td>Gel</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>5%</td>
<td>Gel</td>
</tr>
</tbody>
</table>

Properties of Penetration Enhancers
a. They should be non-toxic, non-irritating and non-allergic.
b. They should work rapidly and the activity and duration of effect should be both predictable and reproducible.
c. They should have no pharmacological activity within the body.
d. They should work unidirectional, i.e., should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
e. They should be appropriate for the formulation thus should be compatible with both excipients and drugs.
f. They should be cosmetically acceptable with an appropriate skin ‘feel’.

Mechanism of Permeation Enhancers
The following are the mechanisms by penetration enhancers act:
a. Disruption of the highly ordered structure of stratum corneum lipid.
b. Interaction with intercellular protein.
c. Improved partition of the drug, co-enhancer or solvent into the stratum corneum.

Protein conformational changes or solvent swelling is the key to altering the polar pathway. The fatty acid enhancers act by increasing the fluidity of the lipid protein 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 [28].

Pathway of transdermal permeation
Diffusion is the mechanism for permeation and it occurs through the following ways:
a. Transdermal permeation, through the stratum corneum.
b. Intercellular( permeation, through the stratum corneum.
c. Trans-appendaged permeation, through the hair follicles, sebaceous glands and sweat glands.

Most of the permeation occurs through skin intercellularly so most of the techniques aim of disrupting or bypassing the elegant molecular structure of the skin.
Method of 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 [29].

The flow chart of emulgel preparation is shown in figure no 1.

<table>
<thead>
<tr>
<th>Process</th>
<th>Unit Operation</th>
<th>Formulation/Process Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil phase (contains drug + permeation enhancer + emulsifier such as span)</td>
<td>Mixing</td>
<td>Concentration and type of: a. Oil phase b. Aqueous phase Stirling time, stirring speed</td>
</tr>
<tr>
<td>Aqueous phase (contains emulsifier tween)</td>
<td>Homogenization</td>
<td>Concentration of emulgent Stirling speed, stirring time, temperature</td>
</tr>
<tr>
<td>Emulsification</td>
<td>Mixing</td>
<td>Concentration and type of: a. Oil phase b. Aqueous phase Concentration of emulgent, concentration and type of gelling agent, volume ratio of emulsion and gel Stirling speed, stirring time, temperature</td>
</tr>
<tr>
<td>g/w or w/o emulsion</td>
<td>Incorporation into gel base (contains gelling agent)</td>
<td>pH adjusted using triethanolamine</td>
</tr>
</tbody>
</table>

![Flowchart of emulgel formulation](image)

**Figure no 1: Flowchart of emulgel formulation**

Evaluation of emulgels

I. Physical appearance

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

II. Measurement of pH

It is determined with the help of digital pH meter. 1gm of gel is dissolved in 100 ml of distilled water and placed for two hours. The measurement of pH of each formulation is done in triplicate and average value is calculated.

III. Spreadability

Spreadability is determined by apparatus consists of a wooden block, which is provided by a pulley at one end. By this method, the spreadability is measured on the basis of Slip and Drag characteristic of emulgel. A ground slide is on this block. An excess of emulgel (2g) under study is placed on this ground slide. The emulgel is 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. The top plate is then subjected to pull off a definite weight. 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.

IV. Rheological study

The viscosity of the different emulgel formulations is determined at 25oC using a cone and plate viscometer with spindle 52 and connected to a thermostatically controlled circulating water bath.

V. Extrudability study of topical emulgel (Tube Test)

It is a usual empirical test to measure the force
required to extrude the material from tube. It is based upon the determination of weight required to extrude 0.5 cm ribbon of emulgel in 10 seconds from lacquered collapsible aluminium tube. More quantity extruded better is extrudability. The test is performed in triplicate and the average value is calculated [30]. The formula used to calculate extrudability is as follows:

\[
\text{Extrudability} = \frac{\text{Weight applied to extrude emulgel from tube (in gm)}}{\text{Area (in cm}^2\text{)}}
\]

VI. Drug content determination

Take 1gm of 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 same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance in the standard plot equation:

\[
\text{Drug content} = (\text{Concentration} \times \text{Dilution factor} \times \text{Volume taken}) \times \text{Conversion Factor}
\]

VII. Swelling Index

To determine swelling index of prepared emulgel, 1 gm of gel is taken on porous aluminium foil and then placed separately in a 50 ml beaker containing 10 ml 0.1N NaOH. Then samples are removed from beaker at different time intervals and put it on dry place for some time and then it is reweighed [31]. Swelling index is calculated as follows:

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

Where, SW\% = Equilibrium percent swelling
Wt= Weight of swollen emulgel after time t
Wo = Weight of original emulgel at zero time.

VIII. In vitro permeation study

In vitro release study is carried out using Franz diffusion cell.

Equations used to determine drug release:

i. Higuchi’s equation

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

Where, Q-Percent of drug release at time t
k2-Diffusion rate constant

ii. Zero-order equation

\[
Q = k_0 t
\]

Where, Q-Amount of drug released at time t
k0- Zero order drug release.

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iii. First-order equation

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

Where, Q-Percent of drug release at time t
k1- First order release rate constant.

IX. 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 0.1N NaOH. Two pieces of skin were tied to the two glass slides 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. 1gm 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 200mg per minute to the left hand pan until the patch detached from the skin surface. The weight required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using the following formula:

\[
\text{Bioadhesive strength} = \frac{\text{Weight required (in gm)}}{\text{Area (in cm}^2\text{)}}
\]

X. Skin irritation study (Patch test)

The preparation is applied on the properly shaven skin of rat and its adverse 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 is occurred then test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

XI. Stability studies

The prepared emulgels are packed in aluminium collapsible tubes (5gm) and subjected to stability study at 5oC, 25oC/60% RH, 30oC/65% RH, and 40oC/75% RH for a period of 3 months. Samples are withdrawn at 15 day time intervals and evaluated at physical appearance, pH, rheological properties, drug content and drug release profile [32]. Some of the drugs incorporated in emulgel are given in table no 3.
Conclusion
In the coming years, topical drug delivery especially emulgel will be used extensively to deliver both hydrophilic and hydrophobic drugs as well as their combination in water soluble gel bases. Emulgel assures better patient compliance. It also has the capability to enhance spreadability, adhesion, viscosity and extrusion. Due to all these factors, emulgel possesses the chance to become a popular drug delivery system in future.

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