ABSTRACT

Topical drug delivery has been used for centuries for the treatment of local skin disorders. Drugs applied to the skin for their local action include antiseptics, antifungal agents, skin emollients, and protectants. On the other hand, topical delivery system increases the contact time and mean resident time of drug. 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. When gels and emulsions are used in combines form the dosage form is referred as emulgel. Emulgels have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion. When gel and emulsion are used in combined form the dosage form are referred as emulgel. The major objective behind this formulation is enhancing the topical delivery of hydrophobic drugs.

KEYWORDS: Emulgels.

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder. The topical drug delivery system is generally used where other routes (like oral, sublingual, rectal, parental) of drug administration fails or in local skin infection like fungal infection.[1] The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of. The topical drug delivery system is generally used where the others system of drug administration fails. The study is also carried out for the
avoidance of the risks and inconvenience of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes and gastric emptying time.

EMULGEL,\(^{[1,2]}\) As the name suggest they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion used as vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. The presence of gelling agent in water phase converts a classical emulsion into an emulgel. Emulgel 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.

**Formulation consideration\(^{[3]}\)**

The challenges in formulation topical emulgel are:

1. Determining system that is nontoxic, non-irritating, non-comedogenic and non-sanitizing.
2. Formulating cosmetically elegant emulgel.
3. The emulgel formulation must have low allergic potential, good physiological compatibility and high biocompatibility.

**Advantages**

1. **Incorporation of hydrophobic drugs**
   Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2. **Better loading capacity**
   Other novel approaches like noisome and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

3. **Better stability**
   Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
4. **Production feasibility and low preparation cost**

Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

5. **Controlled release**

Emulgels can be used to prolong the effect of drugs having shorter t1/2.

6. **No intensive sonication**

Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

**Disadvantages**

1. Drug of large particle size not easy to absorb through the skin.
2. Poor permeability of some drugs through the skin.
3. Skin irritation or allergic reaction on contact dermatitis.
4. Occurrence of bubble during formation of emulgel.

**Rationale**[8]

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 expended both in cosmetics and in pharmaceutical preparation.

A gel is 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 gelating 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.
Site of drug delivery

Skin
The human skin is the largest organ of the body, with a total area of about 20 square feet. The skin protects us from microbes and the elements, help regulate body temperature, and permit the sensations of touch heat and cold.

Physiology of skin
The skin has various layers. It is composed of three tissue layers mainly:

- The epidermis
- The dermis
- The subcutaneous fat tissues

Epidermis
Outer layer of the skin Composed of stratified squamous epithelial cells. These are held together mainly by highly convoluted interlocking bridges which are responsible for the unique integrity of skin. Microscopic section of epidermis shows two main parts mainly

1. Stratum corneum (horny layer)
2. Stratum germinativum (growing layer)
3. Malpighion layer (pigment layer)
4. Stratum spinousm (prickly cell layer)
5. Stratum lusidum
6. Stratum granulosum (granular layer)

Dermis
It is composed of network of collagen & elastic fibers embedded in a mucopolysaccharide matrix, which contain blood vessels, lymphatic & nerve endings, thereby providing physiological support for epidermis.

Subcutaneous tissue
This is a sheet of fat containing areolar tissue, known as superficial fascia, attaching the dermis to underlying structure.
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 tortuous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most common 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.
Factors Affecting Topical Absorption of Drug\cite{9,10}

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

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

Factors to be Considered When choosing a Topical Preparation\cite{11,12}
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.

Method to Enhance Drug Penetration and Absorption\cite{25}
1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement
Important Constituents of Emulgel Preparation

Ideal properties of additives
1. They must be non-toxic
2. They must be commercially available in acceptable grades.
3. Their cost must be acceptably cheap.
4. They must not be contraindicated.
5. They must be physically and chemically stable by themselves and in combination with drugs and other components.
6. They must be colour compatible.

1. Aqueous Material
This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.[14]

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 paraffins, 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.[15,16]

3. 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 stearate,[17] Sorbitan mono-oleate (Span 80)[18] Polyoxyethylene sorbitan monooleate (Tween 80),[19] Stearic acid,[20] Sodium stearate.[21]

4. Gelling Agent
These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.[22,23]

5. Permeation Enhancers[24]
These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.
Properties of penetration enhancer
- They should have no pharmacological activity within the body i.e. should not bind the receptor sites.
- They should be nontoxic, non-allergic, and non-irritating. The penetration enhancer should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- The penetration enhancer should work unidirectional i.e. should allow therapeutic agent into the body whilst preventing the loss of endogenous material from the body when removed from the skin, barrier properties should return both rapidly and fully.
- They should be cosmetically acceptable with skin and should cause irritation.

Method of preparation of emulgel
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 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 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.\[25\]

CHARACTERIZATION OF GELLIFIED EMULSION
1. 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).\[26\]
2. 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.

3. 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 gm. 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,

\[ S = \frac{M \times T}{L} \]

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.

4. 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)
5. 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 is 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.

6. 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, Japan).[28]

7. 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.

8. 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 0.1N 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: Swelling Index (SW) % = \([(Wt. – Wo) / Wo]\) × 100.
Where, (SW) % = Equilibrium percent swelling,
Wo = Original weight of emulgel at zero time
After time t, Wt. = Weight of swollen emulgel

9. 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.

\[
\text{% inhibition} = \frac{L2}{L1} \times 100
\]
Where \(L1\) = total length of the streaked culture, and \(L2\) = length of inhibition.

10. **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 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.\(^{[29]}\)

**Equation used to determine drug release**

1. **Higuchi’s equation**

\[
Q = k2\sqrt{t}
\]
Where-
\(Q\) = Percent of drug release at time \(t\).
\(k2\) = Diffusion rate constant.

2. **Zero-order equation**

\[
Q = k0t
\]
Where-
\(Q\) = Amount of drug release at time \(t\).
\(k0\) = Zero order release rate.

3. **First-order equation**

\[
\ln = (100-Q) = \ln 100 - k1t
\]
Where-
Q = Percent of drug release at time t.

k1 = the first order release rate constant.

11. Ex–vivo Bio adhesive strength measurement of topical emulgel

(MICE SHAVEN SKIN): The modified method is used for the measurement of bio adhesive 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 bio adhesive strength. The bio adhesive strength is calculated by using following:

Bio adhesive Strength = Weight required (in gm.) / A

Figure 2. Setup for bioadhesive test
Table 1. Use of different gelling agent

<table>
<thead>
<tr>
<th>Gelling agent</th>
<th>Quantity</th>
<th>Dosage form</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapol 934</td>
<td>1%</td>
<td>Emulgel</td>
<td>Mohamed, M.I.AAPS</td>
</tr>
<tr>
<td>Carbapol 940</td>
<td>1%</td>
<td>Emulgel</td>
<td>Jain, ankur. IJPRD</td>
</tr>
<tr>
<td>HPMC2910</td>
<td>2.5%</td>
<td>Emulgel</td>
<td>Mohamed, M.I.AAPS</td>
</tr>
<tr>
<td>HPMC</td>
<td>3.5%</td>
<td>Gel</td>
<td>Gupta, A. drug invention today</td>
</tr>
<tr>
<td>Poloxamer407</td>
<td>1%</td>
<td>Gel</td>
<td>Singh, S., Pak J. Pharm.Sci.</td>
</tr>
</tbody>
</table>

Table 2. Different grades of carbapol

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Viscosity</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapol 910</td>
<td>3000-7000</td>
<td>Effective in low concentration and will provide a low viscosity formulation.</td>
</tr>
<tr>
<td>Carbapol 934</td>
<td>30,500-39,400</td>
<td>Effective in thick formulation such as emulsion, suspension, sustain release formulation, transdermal, and topical forms clear gels with water.</td>
</tr>
<tr>
<td>Carbopol 934 P</td>
<td>29,400-39,400</td>
<td>Same properties as carbopol 934 but intended of pharmaceutical formulation purified product.</td>
</tr>
<tr>
<td>Carbapol 940</td>
<td>40,000-60,000</td>
<td>Effective in thick formulation, very good clarity in water or hydroalcoholic topical gels. From clear gel with hydroalcoholic system.</td>
</tr>
<tr>
<td>Carbapol 940</td>
<td>4,000-11,000</td>
<td>Produces low viscosity gels, very good clarity.</td>
</tr>
</tbody>
</table>

Table 3. Use of permeation enhancer

<table>
<thead>
<tr>
<th>Permeation enhancer</th>
<th>Quantity</th>
<th>Dosage form</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oleic acid</td>
<td>1%</td>
<td>Gel</td>
<td>Mortazavi, S.A,Iranian journal, of pharmaceutical science</td>
</tr>
<tr>
<td>Lecithin</td>
<td>5%</td>
<td>Gel</td>
<td>Mortazavi, S.A,Iranian journal, of pharmaceutical science</td>
</tr>
<tr>
<td>Eucalyptus oil</td>
<td>NA</td>
<td>None</td>
<td>Pathan, I.B.,Trop J. Pharm Res.</td>
</tr>
<tr>
<td>Chenopodium oil</td>
<td>NA</td>
<td>None</td>
<td>Pathan, I.B.,Trop J. Pharm Res.</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>5%</td>
<td>Gel</td>
<td>Mortazavi, S.A,Iranian journal, of pharmaceutical science</td>
</tr>
<tr>
<td>Urea</td>
<td>10%</td>
<td>Gel</td>
<td>Mortazavi, S.A,Iranian journal, of pharmaceutical science</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>5%</td>
<td>Gel</td>
<td>Kasliwal, N.,AJPS</td>
</tr>
</tbody>
</table>

Table 4. Marketed preparation: Some marketed preparations are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miconazole nitrate, Hydrocortisone</td>
<td>Miconaz-H-emulgel</td>
<td>Medical union Pharmaceuticals</td>
</tr>
<tr>
<td>Diclofenac diethyl ammonium</td>
<td>Voltaren emulgel</td>
<td>Novartis Pharma</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Lupigyl gel</td>
<td>Lupin Pharma</td>
</tr>
<tr>
<td>Clindamycin, Adapalene</td>
<td>Exccex gel</td>
<td>Zee laboratories</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>Pernox gel</td>
<td>Cosme Remedies Ltd</td>
</tr>
<tr>
<td>Aceclofenac, Methyl salisylate,Capsaicin</td>
<td>Acent gel</td>
<td>Intra labs India Pvt. Ltd</td>
</tr>
<tr>
<td>Kojic acid, Dipalmitate Arbutin, Octinoxate</td>
<td>Kojivit gel</td>
<td>Micro Gratia Pharma</td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>Topinate gel</td>
<td>Systopic Pharma</td>
</tr>
<tr>
<td>Clindamycin phosphate Allantoin</td>
<td>Clinagel</td>
<td>Stiefel Pharma</td>
</tr>
<tr>
<td>Tezarotene</td>
<td>Zorotene gel</td>
<td>Elder Pharmaceuticals</td>
</tr>
<tr>
<td>Clotrimazole, Beclomethasone Dipropionate,</td>
<td>Cloben gel</td>
<td>Indoco Remedies</td>
</tr>
<tr>
<td>Neomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadifloxacin</td>
<td>Nadicin cream</td>
<td>Psychoremedies</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Avindo gel</td>
<td>Cosme Pharma laboratories</td>
</tr>
</tbody>
</table>
CONCLUSION
In the coming years, topical drug delivery will be used extensively to impart better patient compliance. As the emulgel is the recent technique for the topical drug delivery it is better suitable for hydrophobic drugs and obviously it is very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Since emulgel had appear as a new and novel technique for topical drug delivery so it can be a very effective technique 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 drug in a water soluble gel base.

REFERENCE


