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# COMPREHENSIVE REVIEW ON EMULGEL: A RECENT APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

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## ABSTRACT

Topical gels are very advantageous both in pharmaceutical preparations and cosmetics preparations. A gel is a colloid which consists of more than 95% of water. They are very friendly to use. But gels have a few limitations, such as, they cannot be used for hydrophobic drug delivery system. Hence, to overcome these limitations, emulgel has come into existence. Emulgel is a dual release drug delivery system, which are typically made of a normal emulsion which is later incorporated with gelling agents. These gelling agents convert water phase of an 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. Studies on emulgel have proven to be a trump card in the novel approach to topical drug delivery system.

**KEYWORDS:** Emulgel, emulsifier, gelling agent, dual release, topical delivery, hydrophobic.

## INTRODUCTION

Topical drug delivery is the simplest and easiest route of delivery of drugs through localized action, by different routes such as rectal, vaginal, opthalamic and skin.[2]

Through topical delivery, drug absorption is enhanced through skin when the drug is in solution form and if it has suitable water partition coefficient. Primary advantage of topical delivery system is the avoidance of first pass metabolism.[2,27] Topical formulations vary in their physicochemical nature- from solid to semisolid to liquid.[23] Semi-solid formulations, in all of their variations, dominate the topical distribution mechanism.[29]

Gels are newer class of dosage forms created by alcoholic liquid in a network of solid particles, consisting of inorganic substances- polymers of natural and synthetic origin and aluminum salts. The major limitation of gels is delivery of hydrophobic drugs and in order to overcome this limitation, novel formulation of emulgel is formulated, which aids in delivery of hydrophobic gels[2,22] but an hydrophobic moiety will enjoy unique properties of the gel.[14] Due to the biocompatibility, network composition, and molecular stability of the integrated bioactive substance, gels have become a preferred material for drug delivery formulations.[39] Topical gel formulations are used for delivery of micro and macromolecules.[25]

In an emulgel, a polymer acts as an emulsifier and thickeners which have gelling capacity and allows formation of a stable emulsion, as it decreases interfacial tension and increases viscosity of aqueous phase. Skin patches are examples of topical delivery system.[5,17] Gels are superior in terms of patient acceptability, higher dissolution of drugs and fast migration.[4,20]

Topical drug delivery systems are the one that aid in direct application of formulation (containing API) on to skin. Emulsions and gels have picking up significance in pharmaceutical topical dosage forms. Emulsions act as control drug delivery system where drug particles are entrapped into internal phase go through external phase to skin and gets absorbed. They are used for they drug solubility property.[16] Gels capture small drug particles and provides its release in controlled manner because of cross linked networks.

Emulgels are either emulsion of water in oil type or oil in water, which is gelled by mixing it with a gelling agent. Incorporation of emulsion into gel makes it a dual control release system[18,32] and also increases its stability.[7,21]

EMULSION+GEL=EMULGEL

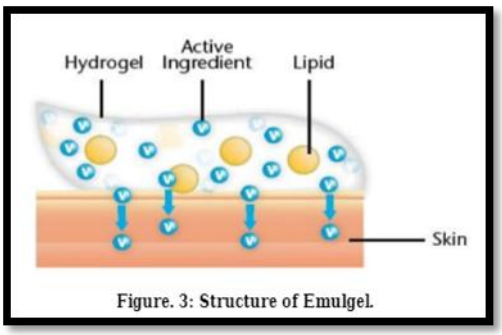

Figure. 3: Structure of Emulgel. [28]

Basically emulgels are thixotropic[24], biofriendly and are easily removable, spreadable, transparent and emollient in nature, non staining, long shelf life, transparent and anti-inflammatory effects.[7,31] Experiments conducted on emulgels containing niacinamide proved to show improvement in lines, wrinkles and blotchiness.[36,37] Nanoparticles are also used in the preparation of pharmaceutical emulgels[30] Nano emulgel has been found to be a successful approach of drug delivery through topical routes.[15,35] Emulgels have advantages on vesicular systems than when compared to conventional systems.[19] These are extensively applied in formulations of dermal health and cosmetic science.[26]

**Table: The various advantages and disadvantages of Emulgel.**

| **Advantages[6]** | **Disadvantages[6]** |
|---|---|
| It avoids first pass metabolism. | Skin irritation. |
| It avoids gastrointestinal incompatibility. | There are chances of occurring allergic reactions. |
| It shows site specific activity. | The poor permeability of few drugs through the skin. |
| It is suitable for self medication. | Drugs with larger particle size are not absorbed easily through the skin. |
| Convenient and easy to apply. | The formation of bubble during preparation of emulgel. |

## FORMULATION OF EMULGEL[7]

### Vehicle

The vehicles used are aqueous and oily.[7]

Properties of vehicles[34]

- Release of drug so that it can freely migrate to site of action.
- Delivery of the drug to target site.

**Aqueous vehicles**

This forms the aqueous phase of the emulsion. The commonly used agents are water and alcohols (propylene glycol, glycerol).

**Oils**

These agents form the oily phase of the emulsion, for externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are used both as the vehicle for the drug. 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.[7]

E.g.: Arachis oil, wheat germ oil, jojoba oil, castor oil.

**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 months or years.[7]

E.g.: polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), polyoxyethylenesorbitanmonooleate (Tween 80), stearic acid, and sodium stearate.

**Gelling agent**

These are the agents used to increase the consistency of any dosage form can also be used as thickening agents.[7]

Egs: Carbopol-934, Carbopol-940, HPMC.

**Penetration enhancers**

To promote absorption of drugs, vehicles often include penetration enhancers that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures or enhance delivery into the skin.[6] They help improve the diffusibility of the substance across the skin barriers.[38]

E.g. Clove oil, Menthol, Oleic acid.

**Properties of penetration enhancers**

- They should be non-toxic, non-irritating, and non- allergenic.
- They must work rapidly and show reproducible results.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectional.
- The penetration enhancers should be compatible with both excipients and drugs.

- They should be cosmetically acceptable.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.[33]

**Mechanism of penetration enhancers**

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.[6]

**PREPARATION OF EMULSION**

**Phase Inversion Method**

In this method, aqueous phase is added to oil phase, so as to form W/O emulsion. At the point of inversion addition of water causes inversion of emulsion, which gives O/W emulsion.[3]

**Wet Gum Method**

In this method, preparation method is different whereas constituents are same as in dry gum method. Acacia(mucilage of emulsifying agent) is used and oil is added to this mucilage drop wise with continuous titration.[3]

**Continental and Dry Gum Method**

In this method, oil is mixed with emulsifying agent (Acacia) and mixed with aqueous phase. Continental and dry gum method differ in proportion of constituents.[3]

**Membrane Emulsification Method**

It is a method where, drop by drop novel method is used to produce an emulsion. Pressure is applied directly to dispersed phase where it seeps through porous membrane to the continuous phase, where droplets are separated from membrane due to shear motion between membrane and continuous phase.[3]

**EMULGEL PREPARATION**

Step 1: Gel base preparation.

Step 2: Emulsion preparation.

Step 3: Incorporation of emulsion into gel base.

**Step1: Gel base preparation**

Sufficient quantity of gelling agent is weighed and sprinkled onto warm distilled water with continuous stirring. The dispersion was allowed to hydrate for 1-2 hours. Other ingredients like propylene glycol and glycerol are added subsequently to the aqueous dispersion with continuous stirring. A required quantity of drug is added and properly dispersed. The dispersion is neutralized to pH 6 using triethanolamine and the final weight was adjusted with distilled water. The gel was sonicated for 15 minutes and kept overnight to remove air bubbles.[7]

**Step 2: Emulsion preparation**

It is prepared by mixing either oil in water or water in oil in an homogenizer depending upon the stability of the drugs. The prepared emulsions are usually not stable, they separate out, hence, to stabilize the emulsion, emulsifying agents are added. Thus the emulsion is prepared.[7]

**Step 3: Incorporation of the emulsion into gel base**

Finally emulsion is incorporated into gel base to form emulgel.[7]

## 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.[8]

**Material for laminates tubes[8]**

1. Foil laminates - It provides light, air and moisture barrier which are used for sensitive preparations.
2. All plastic laminates - It has a chemical resistant barrier which are used for reactive preparations.

## EVALUATION OF EMULGEL

**Physical Examination**

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and phase separation.[7]

**Determination of pH**

pH of the formulation was determined using digital pH meter. The pH meter was calibrated with standard buffer solution having pH 4 and 7 before use.[40] pH meter electrode was washed by distilled water and then dipped into the formulation to measure pH, and this process was repeated 3 times.[7]

**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.[7]

**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 a dry place for some time after it reweighed.[7] Swelling index is calculated as follows.

$$Swelling Index(SW)\% = \frac{(Wt - Wo)}{Wo} * 100$$

Where, (SW) % = Equilibrium percent swelling,

Wt = Weight of swollen Emulgel after time t,

Wo = Original weight of Emulgel at zero time.

**Reducing power assay**

Different concentrations of standard ascorbic acid and sample, namely, 20, 40, 60, 80, and 100 mcg/ml in 1ml of methanol were mixed with 2.5ml of phosphate buffer (200 mM, pH 6.6) and 2.5 ml of 1% potassium ferricyanide separately. The mixtures were placed in a water bath for 20 min at 50°C, cooled rapidly, mixed with 2.5 ml of 10% tri chloroacetic acid, and 0.5 ml of 0.1% ferric chloride. The intensity of iron (II)–ferricyanide complex was determined by measuring the formation of Perl's Prussian blue color at 700 nm after 10 min. The higher absorbance of the reaction mixture indicates increased reducing power.[10] The scavenging activity of the sample was calculated using the following equation.

**Scavenging activity (%)=(A−B/A) 100**

Where,

A is absorbance of control

B is absorbance of sample.

**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 shaven skin of a rabbit.[13] 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.[6]

**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.[6]

**Hydrogen peroxide assay**

A solution of hydrogen peroxide (20 mM) was prepared in PBS (pH 7.4). Various concentrations of 1 ml of the samplesor standards in methanol were added to 2 ml of hydrogen peroxide solutions in PBS. The absorbance was measured at 230 nm, after 10 min against blank solution that contained extracts in PBS without hydrogen peroxide. IC50 value is the concentration of the sample required to scavenge 50% free radical.[10] The above experiments were performed (in triplicate) and the percentage inhibition was calculated using the following formula.

**% Scavenged [H2O2] = [(A0−A1)/A0]×100**

Where,

A0 was the absorbance of the standard (ascorbic acid)

A1 was the absorbance of samples.

**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 (1 g) was applied onto the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples (1 ml aliquots) were collected at suitable time interval sample and were analyzed for drug content by ultraviolet (UV)-visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug released at each time interval. The

cumulative amount of drug release across the egg membrane was determined as a function of time. The cumulative percentage drug release was calculated using standard calibration curve.[6]

**In vitro antioxidant studies**

2,2-diphenylpicrylhydrazyl (DPPH) free radical scavenging assay: Different concentrations of standard ascorbic acid and sample, namely, 20, 40, 60, 80, and 100 mcg/ml were prepared in methanol. 0.002% DPPH in methanol was used as free radical. Equal volume of different concentrations of standards and DPPH was mixed in a clean and labeled test tubes separately, and the tubes were incubated at room temperature in the dark for 30 min. The absorbance was measured at 517 nm using UV-Vis spectrophotometer. The degree of stable DPPH* decolorization to DPPHH (reduced form of DPPH) yellow indicated the scavenging efficiency of the sample.[10] The scavenging activity of the sample against the stable DPPH* was calculated using the following equation.

**Scavenging activity (%)=(A−B/A) 100**

Where,

A is absorbance of control

B is absorbance of sample[12]

**Rheological Study**

The viscosity of the formulated batches is determined by a cone and plate viscometer with spindle 7 and it is connected to a thermostatically controlled circulating water bath maintained at 25$^{o}$. The spindle was allowed to move freely into the emulgel in a beaker covered with thermostatic jacket and reading was noted.

**Centrifugation study**

This method is used to determine the stability of emulgel. It is done only after one week of preparation. This study can be done by using minicentrifuge at 3000 rpm for 30 minutes.[8]

**Drug Content Determination**

Take 1 g of emulgel, mix it in a suitable solvent. Filter it to obtain a clear solution. Determine its absorbance using ultraviolet UV spectrophotometer. Standard plot of the drug is prepared in the same solvent. Concentration and drug content can be determined using the same standard plot by putting the value of absorbance.[6]

**Drug content = (Concentration × Dilution factor × Volume taken) × (Conversion factor)**

**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.[6] After incubation for 18–24 h at 25°C, the fungal growth is observed, and the percentage of inhibition is measured as follows.

**% inhibition = L2/L1 × 100**

Where,

L1 = Total length of the streaked culture

L2 = Length of inhibition.

**Accelerated Stability Studies**

Stability studies were performed according to ICH guidelines. The formulations were stored in a hot air oven at 37 ± 2°, 45 ± 2°, and 60 ± 2° for 3 months. The samples were analyzed for drug content every 2 weeks by UV-visible spectrophotometer. Stability study was carried out by measuring the change in pH of the gel at regular interval of time.[7]

**Extrudability**

It is an empirical test to measure the force required for the cream to extrude out from the tube. The prepared cream was filled into a collapsible tube and it was sealed and the weight of the tube was recorded. Placed a 500 g weight on the tube and the amount of cream that extruded out was collected and weighed. Then, the percentage of cream extruded was calculated.[10]

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

**MARKETED PRODUCTS[6]**

| Drug | Brand Name | Manufacturer |
|---|---|---|
| Diclofenac-Diethyl-Ammonium | Voltaren Emulgel | Novartis Pharma |
| Clobetasol Propionate | Topinate Gel | Systopic Pharma |
| Metronidazole, Clindamycin | Lupigyl Gel | Lupin Pharma |
| Clindamycin Phosphate, Allatoin | Clinagel | Stiefel Pharma |
| Benzoyl Peroxide | Pernox Gel | Cosme Remedies Ltd. |
| Clindamycin, Adapalene | Excex Gel | Zee Laboratories |
| Miconazole Nitrate, Hydrocortisone | Miconaz-H-Emulgel | Medical Union Pharmaceuticals |

## CONCLUSION

In the coming years, topical drug delivery will be used to promote better patient compliance. Emulgel being a recent novel technique for delivery of hydrophobic drugs, as it has a potential to enhance viscosity, globule size and its distribution, swelling index, etc, It is a novel technique of incorporating hydrophobic drugs in a water soluble gel base while providing the necessary stability to the preparation. Emulgel is likely to emerge as a more convenient and accepted drug delivery system future.

Now a days, a large number of formulations in topical drug delivery are used, which have their disadvantages. They are overcome by using emulgel, which acts as a dual control release system and solves problems of stability, phase separation, creaming caused by emulsion. emulgel has thixotropic properties, bio-friendly, spreadable and easily removable. Evaluation of an emulgel is necessary and the tests include swelling index, drug content determination, invitro drug release studies, skin irritation test, etc,. Emulgels are commonly used in preparations of anti-aging, anti-inflammatory, anti-fungal formulations.

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