



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


November 2021 Vol.:22, Issue:4

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A Comprehensive Review on Emulgel - Novel Drug Delivery System



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

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Submitted: 24 October 2021
Accepted: 30 October 2021
Published: 30 November 2021

Keywords: Emulgel, Gelling agent, Emulsion, Topical agents, Skin Diseases, NDDS

ABSTRACT

Emulgel is one of the recent technology in NDDS Used topically characteristics of dual control release i.e. Emulsion as well as a gel when gel and emulsion are used in combined form the dosage form are referred to as emulgel. Therefore, the presence of a gelling agent in the water phase and this phase converts a classical emulsion into an emulgel. This emulgel are both oils in water and water in oil emulsion are used as vehicles phase deliver various drugs to the skin they are generally emulgel are used and purpose as antiseptics, antifungal agents skin emollients and protestants to the skin and they are emulgel are is more effective than regular gel in curative aspects and permeation depth of the drug in emulgel and is more pharmaceutical preparation the activity of topical preparation reveals the various factors as the drug solubility, contact time to the skin, its lipophilicity and its permeability Topical application of therapeutic agents offers various advantages over the other route of administration. It is an attractive route for local and systemic application of a drug to treat various complications. The patient adherence to topical formulations is significant in chronic skin diseases, like fungal infections, acne, and psoriasis. Emulgels have numerous advantages in the area of dermatology such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance. The use of emulgel-based systems as drug delivery vehicles is reviewed, with particular emphasis being placed on recent developments and future directions.



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INTRODUCTION

Topical therapy has been used for centuries for the treatment of dermatological disorders. The spectrum of drugs/agents applied directly to the skin ranges from anti-inflammatory, antiseptic, antibacterial, antifungal, antiviral, anti-acne, antipigmentary, anesthetic compounds to skin emollients and protectants. The topical route has the main advantage of the direct delivery of drug to the target tissue i.e. skin and mucous membranes, bypassing the first-pass effect. However, skin permeation of a drug moiety from the topical formulation is a multi-step process. ⁽¹⁾ Dermatological products are diverse in the formulation and varied in consistency from liquid to powder but the most popular products are semisolid preparations. Within the major group of semisolid preparations, the use of clear, translucent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are a somewhat newer class of dosage form formed by entrapment of large amounts of aqueous or hydroalcoholic liquid in a complex of colloidal solid particles. Gel formulations usually provide faster drug release as compared with traditional ointments and creams. Rather than the many advantages of gels, a major limitation is a difficulty in the delivery of hydrophobic drugs. To minimize this limitation emulgels are prepared so that even a hydrophobic drug can enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage forms are known as Emulgels. The presence of a gelling agent in the water phase converts a traditional emulsion into an emulgel. The oil-in-water system is used to entrap lipophilic drugs while hydrophilic drugs are captured in the water-in-oil system. ⁽²⁾ Now emulgels have been used for the treatment of various kinds of skin diseases such as those infected by fungal, bacterial, and viral species (acne, eczema, Herpes simplex).

Research works on the antifungal drugs incorporated into emulgel have been carried by different scientists to judge their efficacy against fungal infections such as candidiasis. Species causing candidiasis are *Candida tropicalis*, *Candida albicans*, *Candida parapsilosis*, *Candida glabrata* and *Candida krusei*. Formulating the emulgels was found useful in combating fungal infection. Scientists have been trying to develop emulgel of various drugs to treat various kinds of skin diseases. ⁽³⁾

EMULGEL ⁽⁴⁾

As the name suggests, they are a combination of gel and emulsion. Both oil-in-water and water-in-oil types of emulsion are used as a vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. The presence of the gelling agent in the water

phase converts a classical emulsion into an emulgel. Emulgel for dermatological use has 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. Molecules can penetrate the skin by three routes: through intact stratum corneum, sweat ducts, or 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 outermost 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).

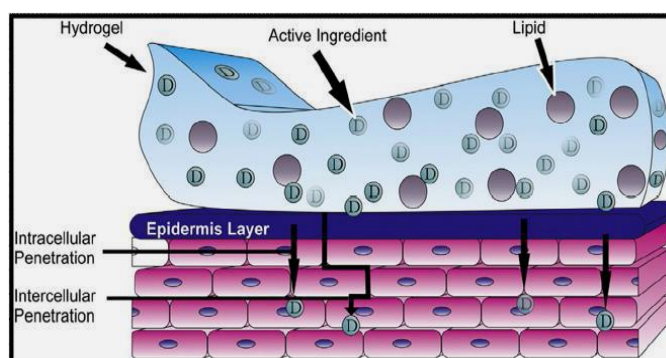


Figure No. 1: Emulgel. ⁽⁵⁾

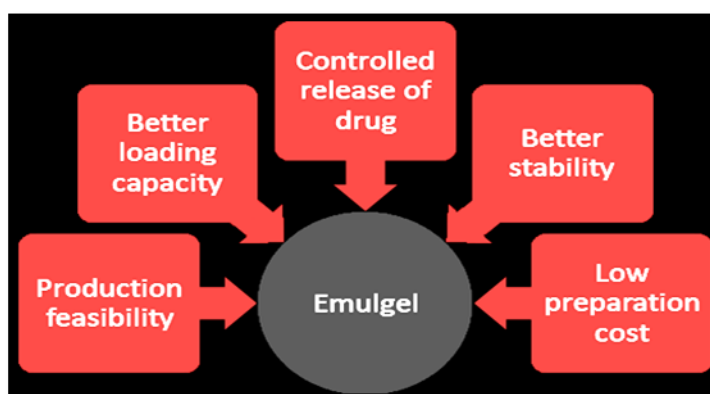


Figure No. 2: Objectives of Emulgel. ⁽⁶⁾

TOPICAL DRUG DELIVERY SYSTEM

Three primary mechanisms of topical drug absorption are transcellular, intercellular, and follicular. 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. ⁽⁶⁾

The surface of the stratum corneum presents more than 99 % of the total skin surface available for percutaneous drug absorption. Passage through this outermost layer is the rate-limiting step for percutaneous absorption. ⁽⁷⁾

❖ Anatomy & Physiology of Skin:

Skin covers almost 15 % of an adult body weight. It's the largest organ of the human body. Skin is such an important part of the human body playing a super beneficial role that includes protection against many agents such as physical, chemical, and biological. There is another important role of skin i.e. thermoregulation. ⁽⁸⁾

Going on deep there are several layers of skin categorized below:

- The Epidermis.
- The non-viable Epidermis.
- A viable Epidermis. (Stratum corneum)
- Overlying dermis.
- Hypodermis.

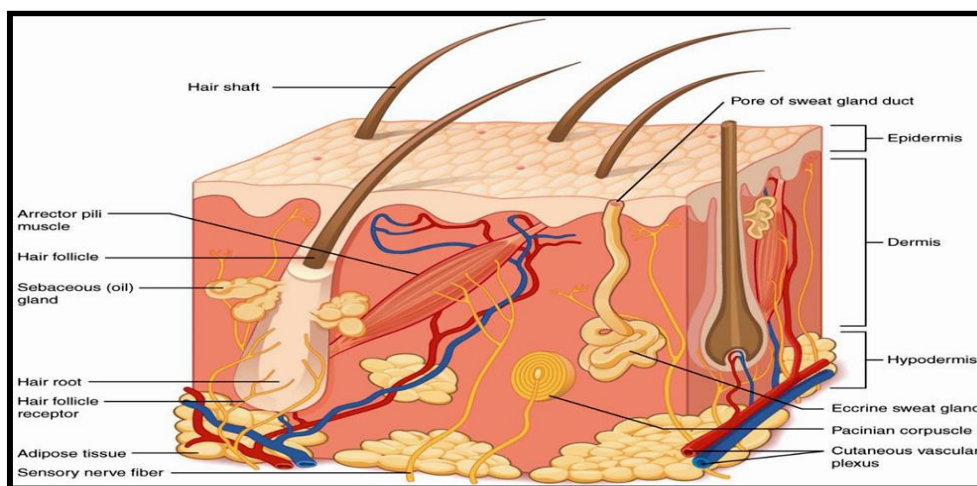


Figure No. 3: Anatomy of the skin

❖ **Epidermis:**⁽⁹⁾

Epidermis: The outer layer is mainly composed of keratinocytes and is typically 0.05 – 0.1 mm in thickness, serving as the physical and chemical barrier between the interior body and exterior environment. Other cells in the epidermis are the Melanocytes, Langerhans' cells, and Merkel cells. The four layers of the epidermis are:

➤ **Stratum basale (basal or germinativum cell layer):**

The innermost layer of the epidermis consists mainly of dividing and non-dividing keratinocytes, which are attached to the basement membrane by hemidesmosomes. It also consists of melanocytes producing melanin pigment. Merkel cells are also found in the basal layer with large numbers in touch-sensitive sites as the fingertips and lips.

➤ **Stratum spinosum (spinous or prickle cell layer):**

Basal cells move towards the outer layer as they reproduce and mature forming the stratum spinosum. Intercellular bridges, the desmosomes, which appear as 'prickles' at a microscopic level, connect the cells. Langerhans cells are dendritic, immunologically active cells derived from the bone marrow, and are found on all epidermal surfaces but are mainly located in the middle of this layer having a significant role in immune reactions of the skin, acting as antigen-presenting cells.

➤ **Stratum granulosum (granular cell layer):**

Continuing their transition to the surface the cells continue to flatten, lose their nuclei and their cytoplasm appears granular at this level.

➤ **Stratum corneum (horny layer):**

The result of keratinocyte maturation is found in the stratum corneum, made up of layers of hexagonal-shaped, non-viable cornified cells known as corneocytes. 10 ± 30 layers of stacked corneocytes are found in most areas of skin with the maximum layer in palms and soles. Protein covers the corneocyte and is filled with water-retaining keratin proteins. Strength is gained due to the cellular shape and orientation of the keratin proteins. Surrounding the cells in the extracellular space are lipid bilayers. The resulting structure provides the natural physical and water-retaining barrier of the skin. The corneocyte layer is capable to absorb

water of about three times its weight but it cracks and no longer remains pliable if water content drops below 10 %.

❖ **Non-Viable Epidermis:-⁽⁸⁾**

It is the outermost layer of the epidermis, there is a belief in the field of dermatology that this layer consists of dead cells. But now it is believed that it performs various protective functions such as impact-resistant, initiation of inflammation through cytokine activity, dendritic cell activity. It has no nuclei and behaves as a selectively permeable membrane for some toxins and allergens.

❖ **Viable epidermis:-⁽¹⁰⁾**

The viable epidermis layer of the skin resides between the dermis and the stratum corneum. This layer has a thickness ranging from 50 - 100 μ m. The structures of the cells in the viable epidermis are mostly physicochemically similar to the other living tissues. Cells are held together by ton fibrils and whereas, the density of this region is not much different than that of water. The water content is about 90 %.

❖ **Dermis:-⁽⁹⁾**

Structural support and bulk of the skin are provided by the dermis the deeper layer and are responsible for pliability, elasticity, and tensile strength. It is an integrated system of fibrous, filamentous, and amorphous connective tissue that accommodates stimulus-induced entry by nerve and vascular networks, epidermally derived appendages, fibroblasts, macrophages, and mast cells. Blood-borne cells as lymphocytes, plasma cells, and other leukocytes, enter the dermis in response to various stimuli. It protects the body from mechanical injury, binds water, aids in thermal regulation, and includes receptors of sensory stimuli. The dermis interacts with the epidermis in maintaining the properties of both tissues.

The two regions collaborate during development in the morphogenesis of the dermal-epidermal junction and epidermal appendages and interact in repairing and remodeling the skin as wounds are healed. Collagen a fibrous protein representing 70 % of the skin's dry weight is the main component of the dermis.

❖ **Hypodermis:-**⁽⁵⁾

The hypodermis is the fat tissue layer that is found in the middle of the dermis and aponeurosis and fasciae of the muscles. The subcutaneous fat tissue is basically and practically very much coordinated with the dermis through the nerve and vascular systems. The hypodermis layer is made out of free connective tissues and its thickness differs as indicated by the surface of the body.

CLASSIFICATION OF TOPICAL DRUG DELIVERY SYSTEM

Classification of topical drug delivery systems: ⁽¹¹⁾

- ❖ **Solid:** Powders, Plasters Ointments,
- ❖ **Semi-solid:** Creams, Poultices, Gels, Pastes
- ❖ **Liquid:** Liniment, Lotions, solution, tinctures, Emulsions, Suspensions, Paints
- ❖ **Miscellaneous:** Transdermal drug delivery systems, Tapes, and Gauzes Rubbing alcohols, Liquid cleanser, and Topical aerosol.

RATIONALE OF EMULGELS AS NEW FORMULATION:⁽¹²⁻¹³⁾

Numerous broadly utilized topical agents like ointment, cream, lotion have many drawbacks. They have extremely sticky making uneasiness to the patient when applied. In addition, they likewise have a 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 utilization of straightforward gels has consumed both in beautifying agents and in pharmaceutical preparation. A gel is a 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. Despite numerous points of interest of gels, a noteworthy constraint is in the conveyance of hydrophobic Medications.

So to defeat this restriction an emulsion-based methodology is being utilized so that even a hydrophobic remedial moiety can be effectively fused and conveyed through gels.

✚ **Emulsion:**

Emulsions are phases of two or more immiscible liquids. The one phase is dispersed into a dispersed medium. Several types as oil-in-water (O/W), water-in-oil (W/O), oil-in-oil (O/O),

micro-emulsions, double and multiple emulsions, mixed emulsions, etc. for preparation and stability of emulsion the emulsifier is necessary. ⁽¹⁴⁾ Various factors could affect the process of emulsification, such as the nature of oil, emulsifier, the emulsifier concentration used, rpm, as well as, temperature. ⁽¹⁵⁾

✚ *Gels:*

Gels are constituted by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may be inorganic or organic polymers of natural or synthetic origin. The higher aqueous component permits the greater dissolution of drugs and permits easy migration of the drug as compared to the ointment or cream base. However, this makes gels a poor vehicle for hydrophobic drugs. This limitation of gels can be overcome by making emulgel. ⁽¹⁶⁾

✚ *Emulgel:*

Emulsion and gel could be mixed in a preparation called emulgel,⁽¹⁷⁾ O/W emulsion for lipophilic materials while W/O for hydrophilic materials. ⁽¹⁸⁾ Emulgels are thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, biofriendly, transparent, and cosmetically acceptable. ⁽¹⁶⁾ They also have good cutaneous penetration and a long shelf-life. ⁽¹⁹⁾ This all makes emulgels an advantageous topical drug delivery system.

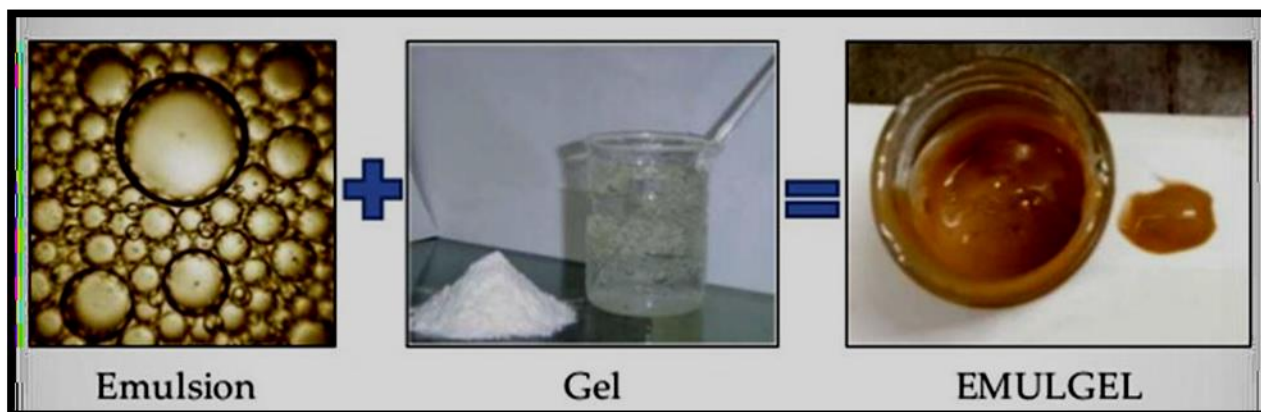


Figure No. 4: Diagrammatical Emulsion + Gel = Emulgel⁽²⁰⁾

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUGS ^(21, 22)

Physiochemical factors:

🌈 Drug substances:

- ❖ Molecular weight. (<400 Dalton)
- ❖ Diffusion coefficient.
- ❖ Water/lipid partition coefficient.
- ❖ Permeability coefficient.
- ❖ Ionization - unionized drugs are well absorbed.
- ❖ Protein binding capacity.

🌈 Vehicle:

- ❖ Solubility/polarity.
- ❖ Volatility.
- ❖ Concentration.
- ❖ Distribution in a stratum corneum.
- ❖ Excipients.
- ❖ Penetration enhancer.
- ❖ pH.



FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION

(23)

- The medication should not affect the skin type.
- Irritation or sensitization potential: Generally, w/o creams and ointments are less irritating, while gels are irritating. Ointments do not contain emulsifiers or preservatives if allergy to these agents is a concern.

- Effect of the vehicle: e.g. penetration of the active ingredient is enhanced by an occlusive vehicle and it also improves efficacy. The vehicle itself may have a drying, cooling, emollient, or protective action.
- It should match the type of preparation with the site (e.g., gel or lotion for hairy areas).
- The type of preparation should be matched with the type of lesions. For example: for acute weepy dermatitis, avoid greasy ointments.

THE IDEAL PROPERTIES OF EMULGEL ⁽²⁴⁻²⁵⁾

- Being greaseless.
- Easily spreadable.
- Easily removable
- Emollient.
- Non-staining.
- Longer shelf life, bio-friendly.
- Pleasing appearance.



ADVANTAGES OF EMULGEL ⁽²⁶⁻²⁷⁾

- Improved patient acceptability.
- Offer targeted drug delivery.
- Termination of the therapy at any time.
- Enhance bioavailability, as well as the low doses, can be effective in comparison with another conventional semi-solid preparation.
- Became a stable formulation by decreasing surface interfacial tension which leads to an increase in the viscosity of aqueous phase, more stable as compared to transdermal preparations which are comparatively less stable.
- The hydrophobic drug can be easily incorporated in emulgel form by using emulsion as the drug barrier which is finally dispersed into a gel.

- Providing the controlled effect that helps to prolong the effect of the drug with a short half-life.
- Easy to formulate and cost-effective preparation.
- Drug loading capacity is better than other novel dosage forms like niosomes and liposomes.
- Skin penetration is enhanced due to both hydrophilic and hydrophobic nature.

DISADVANTAGES OF EMULGEL :⁽²⁸⁻²⁹⁾

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

FORMULATION CONSIDERATIONS :⁽³⁰⁾

The challenges in formulating topical emulgel are:

1. Determining systems that are non-toxic, non-irritating, non-comedogenic, and non-sensitizing.
2. Formulating cosmetically elegant emulgel.
3. The emulgel formulation must have low allergenic potential, good physiological compatibility, and high biocompatibility.

CONSIDERATION ACCOUNTED AND INGREDIENTS USED IN THE FORMULATION OF EMULGEL:

❖ Aqueous material:⁽³¹⁾

In this, it forms an aqueous phase of the emulsion. And water is generally used.

❖ **Oil phase:**⁽⁹⁾

Selection is done by optimizing its effects on the viscosity, permeability, drug release, emulsification, and stability for the preparation in the oil phase of the emulsion, used for the solubility of hydrophobic drugs. It can also be selected as per the effect of the active molecule that gives the synergistic effect as various oils had medicinal value. The most commonly used oil phases are mineral oils, liquid paraffin, propylene glycol, isopropyl myristate, isopropyl palmitate, castor oil, olive oil, balsam oil, wool wax, soybean oil, cottonseed oil, oleic acid, maize oil, Arachis oil, etc.

Table No. 1: Use of oils. ⁽³⁶⁻³⁷⁾

| Chemical | Quantity | Dosage form |
|-----------------------|----------|----------------------|
| Light Liquid Paraffin | 7.5 % | Emulsion and Emulgel |
| Isopropylmyristate | 7-7.5 % | Emulsion |
| Isopropyl stearate | 7-7.5 % | Emulsion |
| Isopropyl palmitate | 7-7.5 % | Emulsion |
| Propylene glycol | 3-5 % | Gel |

❖ **Emulsifiers:** ⁽³²⁾

Emulsifiers are used to control the emulsification process and stability. By incorporating appropriate emulsifying agents stability of the emulsion can be increased because these are thermodynamically unstable. Surfactants having HLB values greater than 8 such as the nonionic surfactant (spans, tweens) are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB values less than 8 and therefore are used in the formulation of water-in-oil emulsions. In comparison to the individual system of span or tween, mixtures of span 20 and tween 20 result in greater stability of the emulsion.

❖ **Penetration Enhancers:** ⁽³³⁾

To promote absorption of drugs, vehicles often include penetration-enhancing ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between coenocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into the skin. e.g. Clove oil 8 %, Menthol 5 %.

Table No. 2: Use of penetration enhancer ⁽⁴⁰⁾

| Penetration enhancer | Quantity | Dosage form |
|----------------------|----------|-------------|
| Oleic acid | 1 % | Gel |
| Lecithine | 5 % | Gel |
| Urea | 10 % | Gel |
| Isopropyl myristate | 5 % | Gel |
| Linoleic acid | 5 % | Gel |
| Clove oil | 8 % | Emulgel |
| Menthol | 5 % | Emulgel |
| Cinnamon | 8 % | Emulgel |

➤ **Properties of penetration enhancers:**⁽⁴⁾

1. They should be non-toxic, non-irritating, and non-allergenic.
2. They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
3. They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
4. 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.
5. The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
6. They should be cosmetically acceptable with an appropriate skin 'feel'.

➤ **Mechanism of penetration enhancers:** ⁽⁴⁾

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, co-enhancer, or solvent into the stratum corneum.

The enhancers act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change of solvent swelling. The fatty acid enhancers increase the fluidity of the lipid-protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathways by altering the multi-laminate pathway for penetration. Enhancers can increase drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product.

❖ **Gelling Agents:**⁽³⁴⁻³⁵⁾

Gelling agents are used to form a gel base by incorporating emulsion to form an emulgel. These are also known as thickening agents which expand the consistency of any dosage form by swelling in the aqueous phase and forming a jelly-like structure. The incorporation of a gelling agent into a system makes it thixotropic. HPMC-based Emulgel was found to be superior to Carbopol based Emulgel since it showed a better drug release rate. NaCMC based Emulgels for the vaginal application showed higher mucoadhesive which increased drug residence time and also best *in-vitro* and *in-vivo* performance.

HEC based Emulgel showed low mucoadhesion but good drug release profiles and rheological characteristics. Pemulen based Emulgel was meant for buccal administration.

Table No. 3: Use of gelling agents ⁽³⁸⁻³⁹⁾

| Gelling agent | Quantity | Dosage form |
|---------------|-------------|-------------|
| Carbopol-934 | 0.5 % - 2 % | Emulgel |
| Carbopol-940 | 0.5 % - 2 % | Emulgel |
| HPMC-2910 | 2.5 % | Emulgel |
| HPMC | 3.5 % | Gel |
| Sodium CMC | 1 % | Gel |

METHOD OF PREPARATION FOR EMULGEL:⁽⁴¹⁻⁴²⁾

It has a very simple and cost-effective method of preparation basically including three steps; first the preparation of oil-in-water or water-in-oil emulsion where the drug is incorporated as per our formulation requirement then.

The second step is to formulate the gel base and finally the addition of emulsion to gel in continuous stirring to form an emulgel. in detail for the formulation of emulsion the aqueous

phase is prepared by taking the purified water to which the soluble ingredients are added and heated up to 70°C including emulsifying agent as tweens and then the oil phase is prepared by dissolving the surfactant such as spans also heated to the same temperature with the addition of hydrophobic drug.

The gel phase is prepared by dispersing the polymer in purified water with constant stirring at a moderate speed and then the pH is adjusted to 6 to 6.5 as per the requirement of the polymer. For example pH of gel with carbopol is adjusted by Triethanolamine (TEA). Preservatives were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. Now the emulsion is added to the gel base in ratio 1:1 to obtain the emulgel.

STEP 1: Formulation of Emulsion either O/W or W/O

STEP 2: Formulation of gel base

STEP 3: Incorporation of an emulsion into gel base with continuous stirring

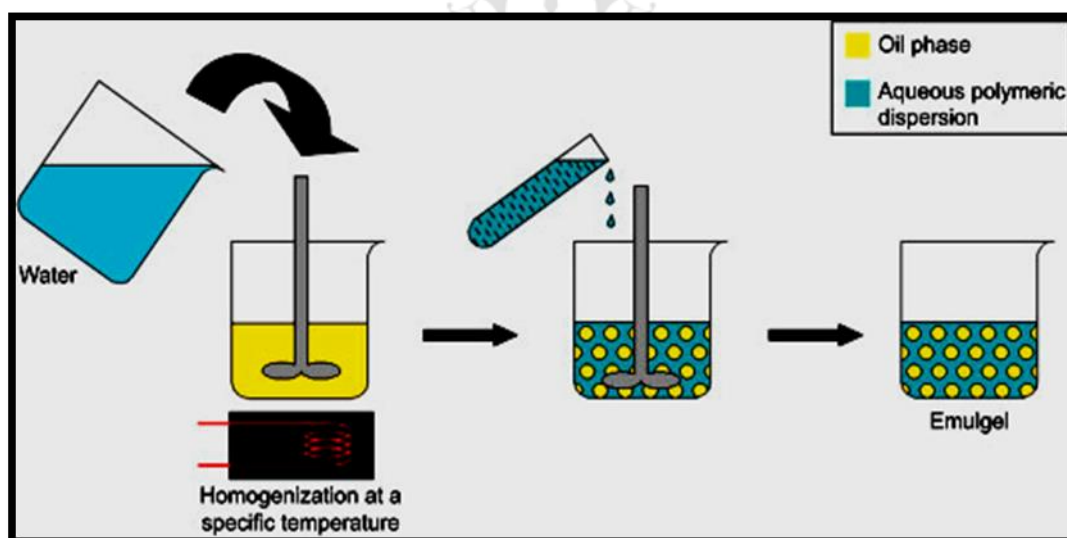


Figure No. 5: Method of Preparation of Emulgel.

EVALUATION OF EMULSION:⁽⁴³⁻⁴⁵⁾

- **Viscosity:** Cone and plate rotational viscometer with spindle can be used to measure viscosity.
- **pH:** pH could be measured by a digital pH meter.

- **Drug content:** Drug-loaded emulsion could be subjected to extract the drug from the emulsion in an appropriate solvent. Suitable dilution could be made with solvent and concentration could be measured by UV visible spectroscopic method at λ_{\max} nm by keeping solvent as the reagent blank.
- **Centrifugation:** This parameter could be measured to evaluate physical stability. Emulsion could be centrifuged at ambient temperature and 5000 RPM for 10 minutes to evaluate the system for creaming or phase separation. The system could be observed visually for appearance.
- **Conductivity:** Electric conductivity of emulsion could be measured at ambient temperature with digital conduct meter.
- **Dilution test:** If the continuous phase is added into an emulsion, it could not be separated into phases. 50 - 100 times continuous phase dilution of emulsion could be carried out and visually checked for phase separation and clarity.
- **Zeta potential and micelle size analysis:** Micelle size, size distribution, and zeta potential of emulsion could be determined using a particle size analyzer.
- **Diffusion study:** By D-cell at 37°C using rat skin as a membrane.
- **Microbial assay of emulsion:** Ditch plate technique could be used for evaluation of the bacteriostatic or fungistatic activity of an antimicrobial agent.

$$\% \text{ inhibition} = \text{length of inhibition} / \text{whole length} \times 100$$

optimization of emulsion using the suitable design of experiments, screening of gelling agent and its concentration, screening of penetration enhancer and its concentration if any, formulation of antimicrobial agent loaded emulgel.

EVALUATION OF EMULGEL:

- **Physical appearance:**⁽⁴⁶⁾

The prepared emulsion formulations were checked visually for homogeneity, color, pH, and consistency. The pH values of 1 % aqueous solutions of the prepared gellified emulsion were measured by a pH meter i.e. digital pH meter.

➤ **pH:**⁽⁴⁷⁾

One gram of gel is dissolved in 100 ml distilled water and stored for two hours and pH is measured with a digital pH meter. pH values should be in the range of 5 to 6 similar to the skin pH 5.5 that avoid the risk of irritation.

➤ **Spreadability:**⁽⁴⁸⁾

To study the spreadability of formulations, special apparatus was designed. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from formulations, placed between, under the application of a certain load. Lesser the less time is taken for the separation of the two slides, the better is the spreadability. Two glass slides of size 6 x 2 cm each were selected. The formulation was placed over one of the slides whose spreadability had to be determined (500 mg). This slide was placed over the other slide in such a way that the formulation was sandwiched between the two slides. The formulation between the two slides was squeezed consistently to form a slight layer, for this reason, weight (100 gm) was set upon the upper slide. The excess of the formulation adhering to the slides was scrapped off after the weight was removed. The lower slide was fixed on the surface of the apparatus and the upper slide was tied to a string.

To this string load (20 gm) could be applied with the help of a simple pulley. Under the direction of weight applied the time taken for the upper slide to move the distance i.e. of 6 cm and separate away from the other slide (lower) was noted. The experiment was repeated (n = 3) and the average of such determinations was calculated for each formulation.....

$$S = M.L/T$$

Where M = Weight which is tied to the upper slide (20 gm)

L = Length taken of glass slide (6 cm)

T = Time taken (seconds)

The delivery of the correct dose of the drug depends highly on the spreadability of the formulation.

➤ **Swelling Index:**⁽⁴⁹⁾

For determination of the swelling index of formulated emulgel following procedure was adopted, 1 gm of the gel is taken on porous aluminum foil and then placed separately in a beaker of 50 ml containing 10 ml 0.1 N NaOH. Then samples were taken from beakers at different time points and put in a dry place for some time after it reweighed. The swelling index is calculated as follows:

$$\text{Swelling Index (SW) \%} = [(Wt. - W_o) / W_o] \times 100.$$

Where, (SW) % = Equilibrium percent swelling,

W_o = Original weight of emulgel at zero time

W_{t.} = Weight of swollen emulgel after time t.

➤ **Extrudability study of topical emulgel (Tube Test):**⁽⁵⁰⁾

It is a typical experimental test to measure the force required to expel the material from the tube. The formulation, whose extrudability is to be checked is filled in clean, lacquered aluminum collapsible metal tubes. The tubes were pressed with the help of a finger to extrude the material. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in the percentage of emulgel. Emulgel extruded from a lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. The experiment was repeated (n = 3) and the average of such determinations was calculated for each formulation:

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

➤ **Bio-adhesive strength measurement:**⁽⁵¹⁾

A modified balance method was used for adhesion measurement. The two pans were removed from the physical balance. On the left side, a glass slide was hanged and a 100 ml beaker was used in place of the right-side pan. A weight of 20 g was hung on the left side, for balancing the assembly. Another glass slide was placed below the hanged slide. On both sides, portions of hairless fresh rat skin were attached. One gram of gel was placed between two rat skin faces. To form a bioadhesive bond, a little pressure was applied, and then slowly

water was added to the right side beaker, till the gel was separated from one face of rat skin attached. The volume of water added was converted to mass. This gave the bioadhesive strength of gel in grams.

➤ **Drug Content Determination:**⁽⁵⁾

Drug concentration in Gellified Emulsion was measured by spectrophotometer. The drug content in Gellified Emulsion was measured by dissolving a known quantity of Gellified Emulsion insolvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV -1700 CE, Shimadzu Corporation, Japan).

➤ ***In-vitro* drug release studies:**⁽⁵²⁾

In-vitro release behavior of the drug from emulgel formulations was investigated using an eggshell membrane. An interesting investigation used egg membrane which, like the human stratum corneum, consists mainly of keratin.⁶² By using 0.5M hydrochloric acid outer shell of the whole egg was dissolved which resulted in a membrane. Thereafter, the contents of the egg may be detached and the membrane was washed and refrigerated or soaked in isopropyl myristate under vacuum to impregnate the keratin matrix. The replacement of water in the membrane with this lipid is assumed to increase its likeness to stratum corneum biochemistry. The Keshary-Chien cell was used for release and permeation study. One gram of gel was applied on the 9.8 cm² area of the surface of the egg membrane tied to the lower end of the donor compartment. The volume of the receptor fluid was reserved at 37.5 ml. The temperature condition of the receptor fluid was maintained at 37 °C and stirred continuously at 100 rpm on a magnetic stirrer.

Aliquots of 3.0 ml were withdrawn and analyzed for the drug content after suitable dilutions by spectrophotometric method. The volume of fluid that was withdrawn for analysis is replaced with the same volume of the fresh buffer after each sampling. The cumulative amount released across the egg membrane was calculated and plotted against time. The best batches showing high percent release were selected further for *ex-vivo* studies using rat skin.

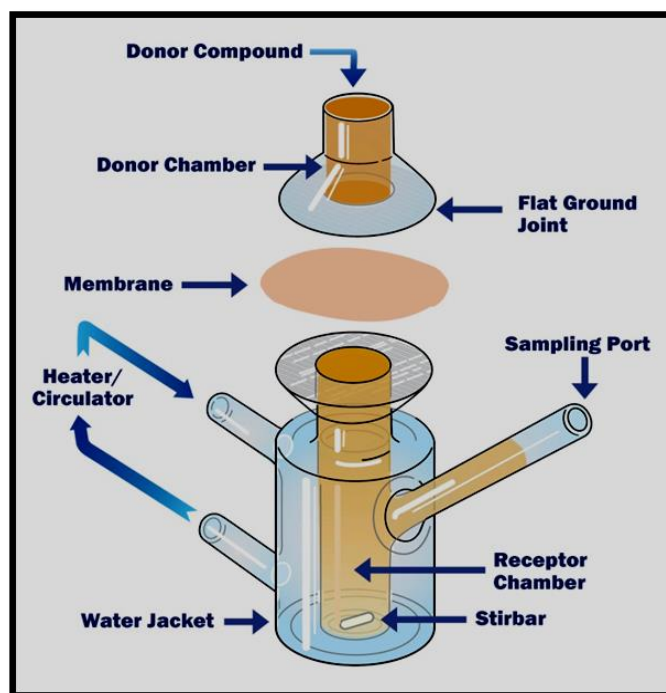


Figure No. 6: Franz vertical diffusion cell.

➤ **Skin irritation test:**⁽⁵³⁾

A portion of the rat skin was shaved for the application of emulgel and an area of 4 cm² was marked, emulgel was applied (500 mg) two times a day for 7 days and the site was observed for any sensitivity and reaction. The sensitivity was graded as 0, 1, 2, and 3, for no reaction, slight patchy erythema, patchy erythema, and severe erythema with or without edema, respectively. If the skin irritation symptom arises then the test was repeated in more than 2 rats.

➤ **Stability Studies:**⁽⁵⁴⁾

The optimized emulgel formulation was selected for the stability study. Sufficient quantity of emulgel formulation was sealed in 10 gm collapsible tube in triplicate, and subjected to stability studies at 5°C, 25°C, /60%RH, 30°C 65%RH and 40°C/ 75%RH for 3 months. The samples were analyzed at predetermined time intervals for pH, physical appearance, rheological properties, and drug content.

➤ **Drug Release Kinetics Study:**⁽⁵⁾

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

Zero-order equation

$$Q = K_0 t$$

Where Q is the amount of drug released at time t, K₀ is the zero-order release rate.

First-order equation

$$\ln(100 - Q) = \ln 100 - K_1 t$$

Where Q is the percentage of drug release at time t, K₁ is the first-order release rate constant.

Higuchi's equation

$$Q = K_2 t^{1/2}$$

Where Q is the percentage of drug release at time t, K₂ is the diffusion rate constant.

VARIOUS MARKETED EMULGEL FORMULATIONS:

Emulgel is commercially available in markets; some preparations of which are listed as follows in Table No.4.

Table No. 4:

| Sr. No. | Product name | Drug | Manufacturer |
|---------|------------------------|------------------------------------|--|
| 1 | Avenida gel | Azithromycin | Cosme Pharma laboratories |
| 2 | Excec gel | Adapalene, Clindamycin | Zee laboratories |
| 3 | Clinagel | Allantoin, Clindamycin Phosphate | Stiefel Pharma |
| 4 | Voltarol 1.16% emulgel | Diclofenac sodium | Novartis |
| 5 | DiclomaxEmulgel | Diclofenac sodium | Torentpharma |
| 6 | Miconaz-H-emulgel | Miconazole nitrate, Hydrocortisone | Medical union Pharmaceuticals |
| 7 | Voltarol 1.16% emulgel | Diclofenac Diethyl ammonium salt | Novartis |
| 8 | Derma feetEmulgel | Urea 40% | Herbitas Intense |
| 9 | Diclonaemulgel | Diclofenac diethyl amine | Kuwait Saudi pharmaceutical industries co. |
| 10 | Denacineemulgel | Clindamycin phosphate | Beit jala pharmaceutical company |
| 11 | Cataflamemulgel | Diclofenac potassium | Novartis |
| 12 | Isofenemulgel | Ibuprofen | Beit jala pharmaceutical company |

FUTURE PROSPECTIVE:

Emulgel is one of the recent technologies in Novel Drug Delivery System topically having characteristics of dual control release i.e. emulsion as well as a gel when gel and emulsion are used in combined form, the dosage form is referred to as emulgel. When gel and emulsion are used in the combined form, they are referred to as emulgel. Emulgel is a promising drug delivery system for the delivery of a hydrophobic drug. Emulgel it with gelling agent. Many advantages of gels have the major limitation of delivery of a hydrophobic drug. Because of the hydrophobic nature of many drugs delivery of these to the biological system has been challenging. Creams, ointments, and lotion are of different types of drug delivery system which has been applied topically have excellent emollient properties but retards the release of drugs due to the presence of oleaginous bases. As compared to other topical systems gel provides quicker release of a drug because gel provides an aqueous environment to drugs.

The hydrophobic drug can be incorporated into an oily base and delivered to the skin by using an emulgel. All such points of interest of Emulgel over other topical drug delivery systems make them more effective and profitable. In the future, these properties will be utilized to convey more topical preparations, and as well as various drug delivery systems it can be used as Emulgel. and this emulgel is a better therapeutic effect and as well as therapeutic efficacy.

CONCLUSION:

Emulgel plays an important role in pharmaceutical and cosmetical applications as well as allows pharmacotherapy. The topical drug delivery system will be used extensively due to better patient compliance. After a thorough literature survey, we concluded that emulgel has proof that a very convenient, better, and effective drug delivery system. Many hydrophobic drugs are incorporated in oily bases and are delivered to the skin by using emulgel. Emulgels possess an edge in terms of adhesion, spreadability, viscosity, and extrusion. Moreover, they will become the best solution for loading hydrophobic drugs in water-soluble gel bases.

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