EMULGEL: AN EFFECTIVE APPROACH FOR THE TOPICAL DRUG DELIVERY

Bhavyashree T[1*], Shefali Bhute[1], Shreya H Alva[1], Shubhashree A S[1], Spoorthi C[1], Sushmitha Rai[1], A R Shabaraya[1].

[1]Department of Pharmaceutics, Srinivas College of Pharmacy, Mangaluru, Karnataka, India.

Abstract:

Topical drug delivery systems include administration of drugs through the skin to provide topical therapeutic effects. Gels are the preferable dosage forms for topical delivery of drugs in the modern era as they provide faster drug release compared to other topical drug delivery systems. But their use is limited for the delivery of hydrophobic drugs. An emulsion-based approach (emulgel) is being used to overcome this limitation of gels. Emulgels are the dosage forms containing emulsions incorporated into gel bases. Favourable properties of emulgels when compared with other formulations are being less greasy, being thixotropic, easy to spread, easy to remove, emollient, non-staining and long shelf life. Efficacy and stability of emulgels are influenced by factors such as nature of gelling agent, oil agent and nature of emulsifiers. At present, the emulgels are being used for the delivery of various drugs like analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations.

Key words: Emulgel, emulsifiers, topical drug delivery, hydrophobic drugs.

INTRODUCTION:

Topical drug delivery system is the dosage form which is administered on the skin or mucous membranes as the localized application with the approach to increase its bioavailability and reduction of side effects. Topical drug delivery systems are formulated in different consistency such as solid, semisolid and liquid. Topical drug delivery offers various advantages like patient compliance, ease of administration, improved drug bioavailability, better physiological and pharmacological response, reduced systemic toxicity and least exposure of drugs to non-

infectious tissue/sites, easy termination of the treatment, no gastric incompatibilities, minimum fluctuation in plasma levels and suitable for the drug with narrow therapeutic window. Though topical delivery systems offer various advantages, they are failed in the administration of hydrophobic drug substances. To overcome this limit, approach of emulgel has been designed. [1,2]

Emulgel is a new approach for the topical delivery of drugs, mainly that of hydrophobic drugs. It is combination of emulsion and gel, which is prepared either as oil-in-water or water-in-oil type of emulsion and then mixed with suitable gelling agent. Hydrophobic drugs can be formulated as emulgels because it contains both oil and aqueous phase. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent, pleasing appearance, cosmetically acceptable and also have a good skin penetration. Now a days Emulgels is emerging as a potential drug delivery system in the area of dermatology. [1,3,4]

Advantages of Emulgel: [1,2,5]

- ✓ Can be used for the incorporation of hydrophobic drugs
- ✓ Improved loading capacity
- ✓ Better stability
- ✓ Controlled release
- ✓ No intensive sonication
- ✓ Avoiding first pass metabolism
- ✓ Site specific action
- ✓ Increased patient compliance
- ✓ Convenient and easy to apply
- ✓ Low preparation cost
- ✓ Easy to terminate the therapy
- ✓ No gastrointestinal incompatibility
- ✓ Suitable for self-medication

Disadvantages of Emulgel:[1]

- ✓ Skin irritation on contact dermatitis
- ✓ Possibilities of allergic reactions at the site of application
- ✓ Poor permeation of the skin for some drugs

- ✓ Poor absorption of drugs having large particle size.
- ✓ Bubble formation in the emulgel during the preparation.

The topical preparations are applied on the skin. They are absorbed through the skin and show the action in desired site. So, for the better understanding of topical drug delivery systems, its important to know the physiology of human skin.[1]

PHYSIOLOGY OF SKIN: [6]

A fundamental understanding of skin physiology is essential for designing emulgel. An adult's skin protects the body from foreign particles and it receives around one-third of the blood that circulates throughout the body. pH of the skin is normally around 5.5 and is influenced by the fatty acids and sweat secreted by the individuals. The skin is divided into four layers namely non-viable epidermis, viable epidermis, viable dermis and subcutaneous connective tissue. These layers have their own functions in the absorption of drugs through the skin. The structure of the skin has been described in fig 1.

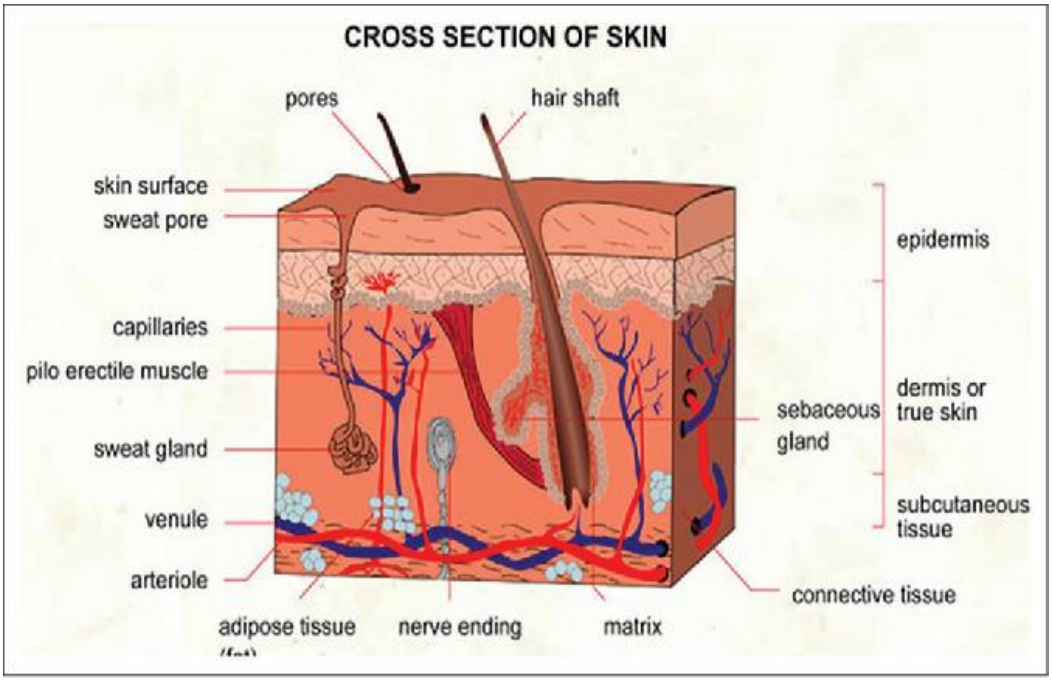

Fig.1: Structure of skin [7]

Non-viable epidermis:

The stratum corneum is the skin's outermost layer, and it serves as a physical barrier to the majority of substances that come into contact with it. Over majority of the body, the stratum corneum is 10 to 20 cell layers thick. The stratum corneum is made up of lipids (5-15%), which include phospholipids, glycosphingolipids, cholesterol sulphate, and neutral lipids, and protein (75-85%), which is mainly keratin.

Viable epidermis:

Viable epidermis lies between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. The cellular structure of the viable epidermis is physicochemically similar to other living tissues. Tonofibrils are the connective tissue that holds cells together. The density of this region is similar to that of water. The water content is approximately 90%.

Dermis:

The dermis is the layer of skin that lies beneath the epidermis and subcutaneous layer. It's a structural fibrin made up of a matrix of loose connective tissue composed of fibrous protein and embedded in an amphorphose ground material. Dermis thickness varies between 2000 to 3000 µm.

Subcutaneous connective tissues:

Hypodermis or subcutaneous tissue, is made up of loosely structured, white fibrous connective tissue that contains blood and lymph arteries, secretary pores of the sweat gland and cutaneous nerves. Most investigator consider that a drug passes through the epidermis enters the circulatory system before reaching the hypodermis and fatty tissues could act as a drug storage.

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG: [8,9]

The factors that affect the topical absorption of drug are as follows:

1) Physiological factors

- **Skin condition**: Outermost layer of human skin, the stratum corneum normally serves as a physical barrier to the drug substances. The permeability increases as the skin gets inflamed, with the loss of stratum corneum and altered keratinization. The permeability decreases as the organ thickened with corns and warts.
- **Lipid content**: It is an effective water barrier of the skin through which percutaneous penetration increases when lipid weight in stratum corneum is low.
- **Skin age**: Skin of fetus, young ones and elders is more permeable than adult tissue.
- **Blood flow**: An increased blood flow could increase the penetration as there will be raise in the concentration gradient across the skin.
- **Hydration of skin**: The penetration rate of most of the drugs is increased by hydration of the stratum cornuem.
- **Skin temperature**: Increase in temperature gives rise to increase in the rate of skin permeation.

2) Physiochemical factors

- **Partition coefficient**: The optimum partition coefficient (K) of the drug is required for good action. Drugs with high K value will not leave the lipid portion of skin readily and also drugs with low K value will not be permeated.
- **Molecular weight**: Drugs with high molecular weight have low permeation rate.
- **Drug concentration**: The amount of drug percutaneously absorbed per unit of surface area per time interval increases with an increase in the concentration of drug in the drug delivery system.
- **Effect of vehicles:** If the vehicles used are occlusive in nature, they enhance the penetration of active ingredient and also it improves efficacy of the drug. The vehicle used will also have a cooling, drying, emollient and protective action.

FORMULATION OF EMULGEL:

Following ingredients are being used in the preparation of emulgels;

1. Vehicle:[7]

The vehicle used in the preparation should have following properties:

- Should deliver the drug to target site.
- Deposit the drug on skin with even distribution.
- Easily release the drug so it can migrate freely to the site of action.
- Sustain the therapeutic drug level in target tissue for a sufficient duration to provide a pharmacological effect.
- Cosmetically acceptable to the patient.

Examples: Aqueous and oil phases are separately used as vehicles.

Aqueous Material:[4]

This forms the aqueous phase of the emulsion. Water and alcohols are commonly used as aqueous materials.

Oils: [4,10]

These form the oily phase of the emulsion. In the emulsions meant for external application, the mineral oils, either alone or combined with soft or hard paraffins are widely used. Oils are generally used as the vehicle for the drug and also for their occlusive and sensory characteristics. Oils those are extracted from various types of plants having different medicinal values can be used in preparation of emulgels.

Examples: various mineral and vegetable oils

2. Emulsifiers:[10]

The emulsifying agents are used to promote emulsification of oil and aqueous phases as well as to maintain the stability during the storage.

Eg. Sorbitan mono-oleate (Span 80), polyethylene glycol 40 stearate, sodium stearate, stearic acid, etc.

3. Gelling agents:[10]

These are the agents through which the consistency and the gelling property of emulgels can be increased. Various gelling agents are being used in preparing emulgels like Carbopol, HPMC etc

4. Penetration enhancers:[1]

These are the agents which help in the absorption of drugs by increasing skin permeability and decreasing the barrier resistance.

Examples: Oleic acid, lecithin, linoleic acid, menthol, urea, eucalyptus oil etc

5. pH adjusting agent:[1]

A pH adjuster is a chemical used to alter the pH or potential hydrogen ion level.

Examples: NaOH, triethanolamine

6. Humectant:[10]

These are used to prevent loss of moisture from the formulation. These agents help in minimizing the drying of emulgels and thereby enhance qualities such as ease of application, consistency, etc.

Examples: Glycerine, propylene glycol

METHOD OF PREPARATION OF EMULGELS:[11]

Method of preparation of emulgel includes development of emulsion first (o/w or w/o), followed by incorporating it into gelling agent to form Emulgel.

Aqueous phase of emulsion is prepared by first dissolving surfactants in purified water.

The solution of preservatives is prepared by dissolving them in propylene glycol and the solution containing active ingredient is prepared using suitable solvent, then both the solutions are mixed and then added to the aqueous phase.

Oily phase of emulsion is prepared by dissolving surfactants in light liquid paraffin.

Formation of emulsion involves separate heating of oil and aqueous phase to 70–80°C then mixing of both the phases with constant stirring and cooled to room temperature.

Gel phases of Emulgels are prepared by dispersing gelling agents in water.

When the emulsions & gels get ready then the Emulgel is prepared by mixing emulsions with gels in 1:1 ratio with gentle stirring

Below mentioned are the common steps to prepare the emulgel:

Step 1: Preparation of emulsion either O/W or W/O type.

Step 2: Formulation of gel base.

Step 3: Addition of emulsion into gel base with continuous stirring.

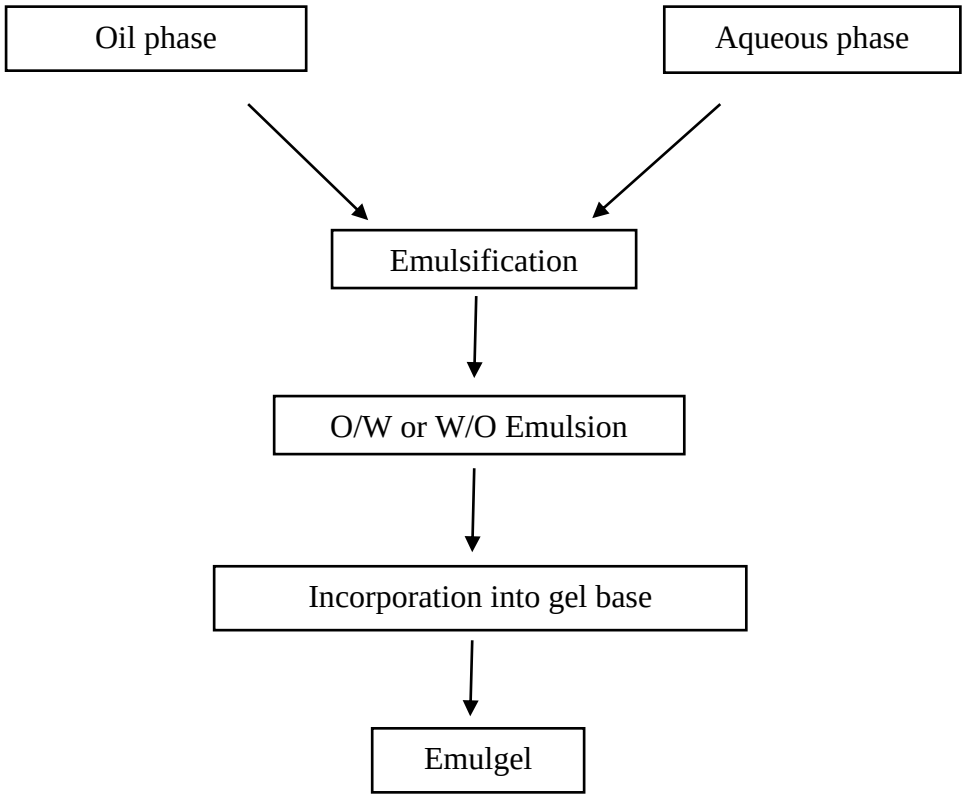

Fig.2: Flow chart of emulgel formulation

EVALUATION OF EMULGEL:

- **Physical examination:[7]**

  The prepared emulgel formulations are inspected visually for their colour, appearance, homogeneity, consistency, phase separation etc.

- **pH: [2,7,12]**

  pH evaluation is the important criteria especially for the topical formulations. pH of the emulgel can be determined using digital pH meter. pH meter electrode is washed by distilled water and then dipped into the formulation to measure pH, and this process is repeated 3 times and average values are calculated.

  pH values should be in the range of 5 to 6 which is similar to the skin pH to prevent any skin irritations.

- **Viscosity:[13]**

  Viscosity of the emulgel formulations is determined by using Brookfield viscometer. For the determination of viscosity, prepared emulgel formulation is added to the beaker and allow it to settle for 30 minutes at 25-30^{0}C. Adjust the spindle in the way that it does not touch the bottom of the jar and rotate at a moderate speed of 100 RPM for 10 minute and viscosity values are noted.

- **Spreadability:[3]**

  Spreadability of emulgel is usually measured 48 hours after preparation of the emulgel. It is determined from the diameter of circle produced when emulgel was deposited between two glass plates of definite weight. A weighed quantity of emulgel is taken on one glass plate and drop another glass plate from a distance of 5cm on the first plate. The diameter of the circle of spread area is measured.

- **Extrudability:[13]**

  It is a usual empirical test for the measurement of force required to extrude the material from tube. Extrudability is based upon the quantity of emulgel extruded from collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of emulgel in 10 seconds. More the quantity extruded better is the extrudability.

  The extrudability is determined by using the formula,

  Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)

- **Drug content: [2,14]**

  The drug content is determined by UV spectroscopic analysis method. 1g of emulgel is mixed with the suitable solvent, sonicated and filtered with whatman filter paper to obtain a clear solution. Absorbance of the solution after proper dilution is determined using UV-Visible spectrophotometer. Drug content was determined from calibration curve for study.

- **Stability studies:[2]**

  Stability studies are carried out for the optimized emulgel formulation according to ICH guidelines. The formulations are packed in aluminium collapsible tubes and studies are carried out for 3 months by keeping at 25 + 2^0C / 60 + 5% RH and 40 + 2^0C / 75 + 5%RH and the samples are withdrawn at a regular interval of 1, 2 & 3 months.

- ***In vitro* drug release study: [2,3]**

  The *in vitro* drug release study of the formulated emulgel is carried out by using Franz diffusion cell with dialysis membrane. Emulgel is evenly applied onto the surface of cellophane membrane. The membrane is clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared buffer pH 5.8 solutions to solubilize the drug. The receptor chamber is stirred by magnetic stirrer at 50 rpm and maintained at 37±0.2^{0}C. The samples are collected at specific time interval and are analysed by UV spectrophotometer to measure the amount of drug release.

- **Skin irritation test:[10]**

  The skin irritation of emulgels can be tested using rat or rabbit skin that has been shaved. Apply a weighed sample of emulgel to the selected area of skin and keep them in the cage for the next 24 hrs. Examine the rat or rabbit skin area after 24 hrs to see whether there has been any color change or any adverse effects. If no negative effects are discovered, the formulation passes the test.

  Swelling index:[14]

  The swelling index is defined as the volume in ml taken up by the swelling of 1g of formulation under specified conditions. To determine the swelling index of prepared topical emulgel, 1g of emulgel is taken on porous aluminium foil and then place separately in a 50ml beaker containing 10ml of 0.1N NaOH. Then samples are removed from beakers at different time intervals and then set it aside to dry for a while and reweigh it. The following formula is used to determine the swelling index:

  Swelling index (SW) % = $[(Wt - W_O)/ W_O] \times 100$

  Where,

  (SW) % = Equilibrium percent swelling

  Wt = Weight of the swollen emulgel after time t

  W_o= Original weight of emulgel at zero time.

CONCLUSION:

The present review focuses on the approaches used for the topical delivery of drugs. It has highlighted the technique of developing Emulgel formulations for the delivery of drugs onto the skin which is mainly suitable for hydrophobic drugs. Review reveals that topical drug delivery system plays an important role to impart better patient compliance. In comparison with various other topical formulations, emulgels are widely used due to enhanced spreadability, being less greasy, longer shelf-life, low viscosity, emollient and glossy appearance.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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First Author: Bhavyashree T, Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India.

Second Author: Shefali Bhute, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India

Third Author: Shreya H Alva, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India

Fourth Author: Shubhashree A S, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India

Fifth Author: Spoorthi C, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India

Sixth Author: Sushmitha Rai, Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India.

Seventh Author: A R Shabaraya, Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangaluru, Karnataka, India.

***Corresponding Author:**

Bhavyashree T

Department of Pharmaceutics

Srinivas College of Pharmacy

Valachil, Mangaluru- 574143

Karnataka, India

Email: bhavyashreebhat91@gmail.com