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EMULGEL: A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

Snehal Patel*, Chintan Aundhia, Avinash Seth, Nirmal Shah and Kartik Pandya

Department of Pharmacy, Sumandeep Vidyapeeth, Piparia, Vadodara.

***Author for Correspondence: Snehal Patel**
Department of Pharmacy, Sumandeep Vidyapeeth, Piparia, Vadodara.

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ABSTRACT
Topical drug delivery has been used from time for the treatment of local skin disorders. Medications applied to the skin for their local action include antiseptics, antifungal agents, skin emollients, and protectants. When gel and emulsion are used in combined form the dosage form are termed as emulgel. Emulgels have appeared as one of the most advanced topical delivery system as it has dual release control system i.e. gel and emulsion. Despite of many advantages of gels, a major limitation is in the difficulty in delivery of hydrophobic medications. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be effectively incorporated and delivered through gels.

KEYWORDS: Emulgel, Topical Drug Delivery.

INTRODUCTION[1, 2]
Topical drug delivery can be defined as the application of a medication containing formulation to the skin to straightforwardly treat cutaneous disorder. The topical medication conveyance framework is by and large utilized where other routes (like oral, sublingual, rectal, parental) of medication administration fails or in local skin infection like fungal infection. The main advantage of topical delivery system is to bypass first pass metabolism. Shirking 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 additional done 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 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 convey different medications to the skin. They also have a high capacity to infiltrate 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.

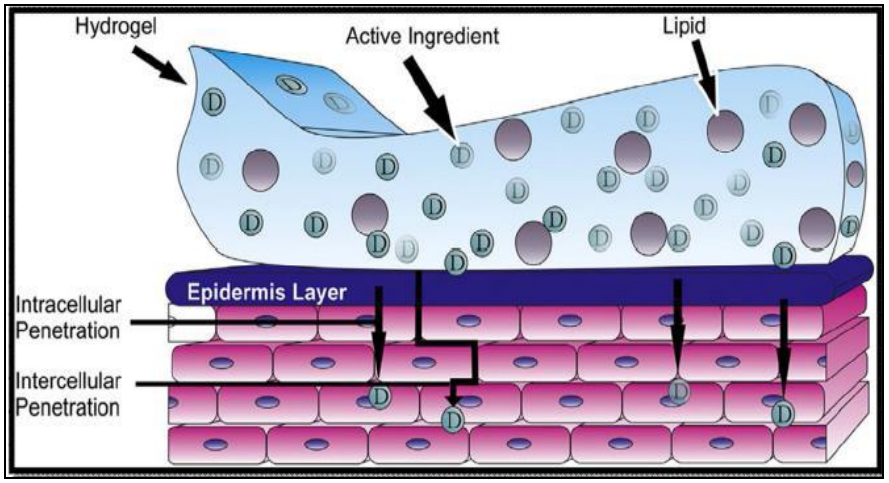

Figure 1: Emulgel.

OBJECTIVES[3, 4]

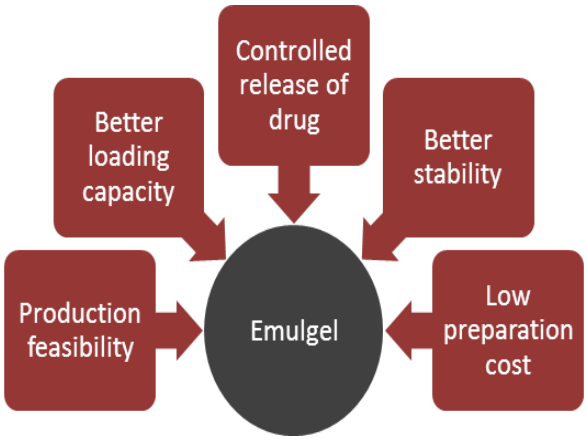

Figure 2: Objectives of Emulgel.

Advantage of Emulgel[3-5]

1) Incorporation of hydrophobic drugs
2) Better loading capacity
3) Better stability
4) No intensive sonication
5) Controlled release
6) Production feasibility and low preparation cost
7) Avoidance of first pass metabolism.
8) Avoidance of gastrointestinal incompatibility.
9) More selective to a specific site.
10) Improve patient compliance and suitability for self-medication.
11) Providing utilization of medication with short biological half-life and narrow therapeutic window.
12) Ability to easily terminate medication when needed.

Disadvantage of Emulgel[3-5]

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

RATIONALE[6, 7]

Numerous broadly utilized topical agents like ointment, cream, lotion have many drawbacks. They have extremely sticky making uneasiness the patient when applied. In addition they likewise 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 utilization of straightforward gels has consumed both in beautifying agents 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. 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 convey through gels.

SKIN[6-8]

The skin is an extensive and legitimate focus for drug delivery. Its fundamental capacities constrain its utility for this region. Skin is the largest organ of the body which making up 16% of the body weight, with a surface area of 1.8m^2.

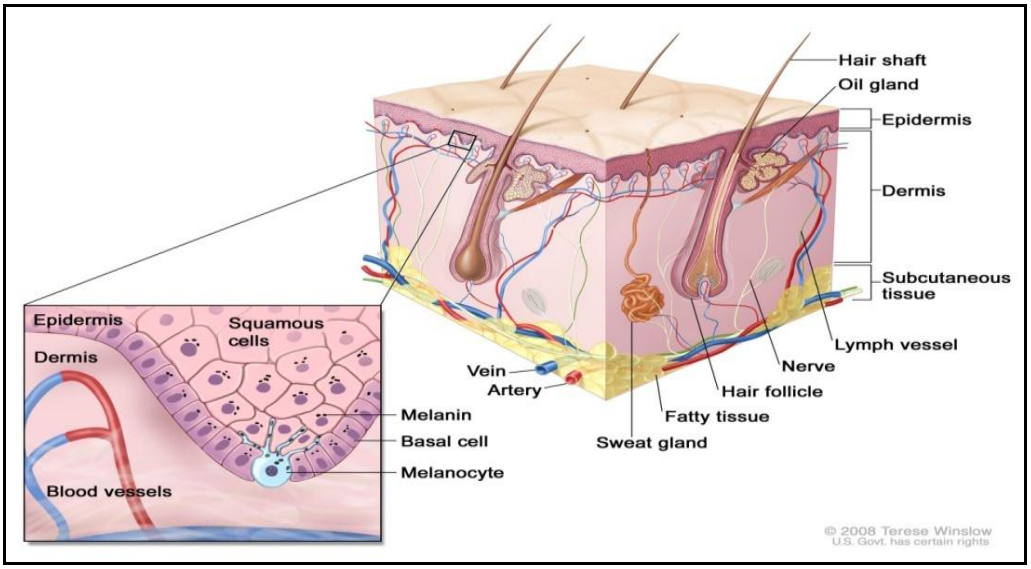

Figure 3: Structure of skin.

Apocrine gland, sweat gland, hair, nails, oil gland are referred as derivatives of skin (shown in figure-1). The elements of the skin are predominantly to shield the body from the unwanted substances and microorganisms and to contain all body liquids.

Skin layers: Skin contains three structural layers – Epidermis, dermis and Hypodermis.

1) Epidermis: The epidermis is a squamous, stratified, keratinized epithelium. The keratinocyte contain the major cell segment greater than 90%. Keratinocytes alter their shape, size and physical properties when relocating to the skin surface. Stratum corneum is approximately 100 – 150 mm thick, has no blood stream. Stratum corneum is the peripheral layer of epidermis. Under the epidermis, the dermis contains the arrangement of vessels that vehicle blood all through the body. On the off chance that the drug has the capacity infiltrate the stratum corneum, then it can enter the circulatory system. A procedure known as passive diffusion, which happens too gradually, is the only means to transfer normal drug across the layer.Epidermis is also containing melanocytes, Langerhans cells and Merkel cells.

2) Basement membrane: Basement membrane is multilayered structure forming the dermoepidermal junction. The limit in the middle of dermis and epidermis layer is called Dermal-Epidermal intersection which gives a physical boundary to the substantial atoms of medication and cells.

3) Dermis: The dermis is the internal layer and bigger (90%) skin layer, involves basically of connective tissue and gives backings to the epidermis layer of the skin. The dermis can be partitioned into two anatomical district, papillary dermis and reticular dermis. Papillary is the more slender peripheral segment of the dermis. Collagen and elastin filaments are basically vertically situated in the papillary locale and associated with the dermal-epidermal intersection. In reticular dermis, strands are on a level plane arranged. As skin is central point for the determination of different medication conveyance angles like permeation and absorption of drug over the dermis.

4) Hypodermis: The hypodermis is the fat tissue layer which is found in the middle of dermis and aponeurosis and fasciae of the muscles. The subcutaneous fat tissue is basically and practically is 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 body.

Factors Affecting Topical Absorption of Drug[6-8]

Physiological Factors

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin

Physiochemical Factors

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

Factors To Be Considered When Choosing A Topical Preparation

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.

ESSENTIAL CONSTITUENTS OF EMULGEL PREPARATION[4]

1. Aqueous Material

This forms the aqueous phase of the emulsion. Normally used agents are water, alcohols.

2. Oils

These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are broadly used both as the vehicle for the drug and for their occlusive and sensory characteristics. Generally 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.

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.eg Polyethylene glycol stearate, Sorbitan mono- oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

4. Gelling Agent

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

5. Permeation Enhancers

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

Method to Enhance Drug Penetration and Absorption

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement

METHOD OF PREPARATION[4]

STEP1: Formulation of Emulsion either O/W or W/O
STEP2: Formulation of gel base
STEP3: Incorporation of emulsion into gel base with continuous stirring.

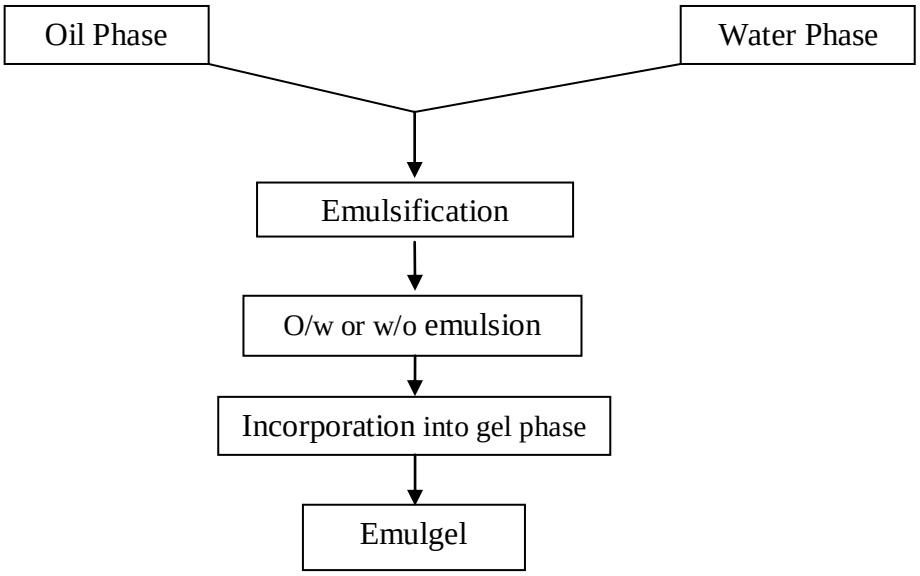

Figure 4: Method of Preparation of Emulgel

CHARACTERIZATION OF EMULGEL[3-5]

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).

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= M.L/T

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 cm 2)

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 cm 2). 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).

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
Wt. = Weight of swollen emulgel after time t.

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.

% Inhibition = L2 / L1 × 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 cm 2 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.

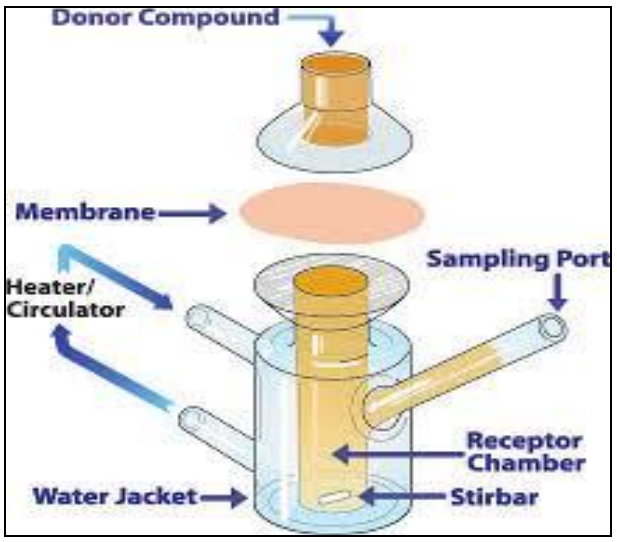

Figure 5: Franz diffusion cell.

Drug Release Kinetic Study

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

Zero – order equation

$$Q = K_0 t$$

Where Q is the amount of drug released at time t,
K_0 is the zero – order release rate.

First – order equation

$$\text{In } (100 - Q) = \text{In } 100 - K_1 t$$

Where Q is the percentage of drug release at time t,
K_1 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,
K_2 is the diffusion 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.

Bioadhesive Strength = Weight required (in gm) / Area (cm^2)

12. Stability Studies

The prepared emulgels were packed in aluminium 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 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

CONCLUSION

As the emulgel is the recent technique for the topical drug delivery it is better suitable for hydrophobic drugs and obviously it is a very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Mainly the hydrophobic drug formulation can be developed using emulgel technique because it contain both oil and aqueous phase while hydrogels are not suitable for hydrophobic drugs. In future, topical drug delivery will be used extensively to impart better patient compliance. Since Emulgel is helpful in enhancing Spreadability, adhesion, viscosity and extrusion, this novel drug delivery will become a popular formulation in future.

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