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EMULGEL, TOPICAL DRUG DELIVERY SYSTEM

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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 is used in combined form the dosage form is termed as emulgel. Emulgels have appeared as one of the most advanced topical delivery systems 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. Emulsions have a certain degree of elegance and they are easily washed off whenever desired. 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. Emulgels are being used for the delivery of analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations with still wide range to explore

KEYWORDS: Emulgel, Topical Drug Delivery.

INTRODUCTION[1,2]

Topically drug administration is a confined drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. The main advantage of topical delivery system is to evade first pass metabolism.[1] Emulsions possess a definite degree of elegance and are easily washable whenever required. They also have a high ability to cross the skin. Dermatological emulgels have several favourable properties such as thixotropic, easily spreadable, greaseless, easily removable, emollient, staining, longer shelf life, bio-friendly, transparent & pleasing appearance.[2]

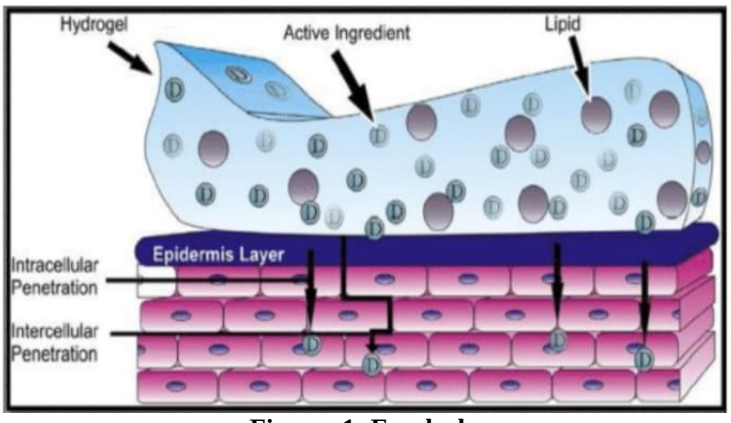


Fig. no. 1: Emulgel.

Topical drug delivery system[3,4]

Topical drug delivery system there are two basic types of topical drug delivery products, externally used topicals and internally used topicals. The externally used topicals are spread ,sprayed or otherwise dispersed on the tissue to shield diseased area, while the internally used topicals are applied to mucous membrane orally, vaginally or on the rectal tissues for local activity. Main benefit of topical drug delivery system is avoiding first pass metabolism, avoiding gastrointestinal incompatibilities, specific site selective, improving patients compliance, possible and easy self-medication, and drugs with short

half-life and narrow therapeutic index is also subjected to be utilized, facility is used to easily terminate medicines whenever required.[3]Disadvantages of topical drug delivery system are skin irritation on contact dermatitis, allergic reactions, poor drug permeability through skin, drugs of large particle size are not absorbed easily through skin. Skin is thick, complex in structure. Molecules moving from the external environs must penetrate the stratum corneum as well as any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph compartment, where upon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex process and challenge in analysis. Factors affecting the topical drug delivery system can be physiological factors e.g., thickness, hydration, inflammation and pH of skin, lipid content, densities of hair follicles and sweat glands, blood flow etc., and physico-chemical factors like partition coefficient, molecular weight, degree of ionization, effect of vehicle etc.[4]

Classification of topical drug delivery system[5]

TCS is a classification system of topical drug products, which when applied will help in approval of topical drug products, without conducting in vivo studies, but assuring product efficacy.

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

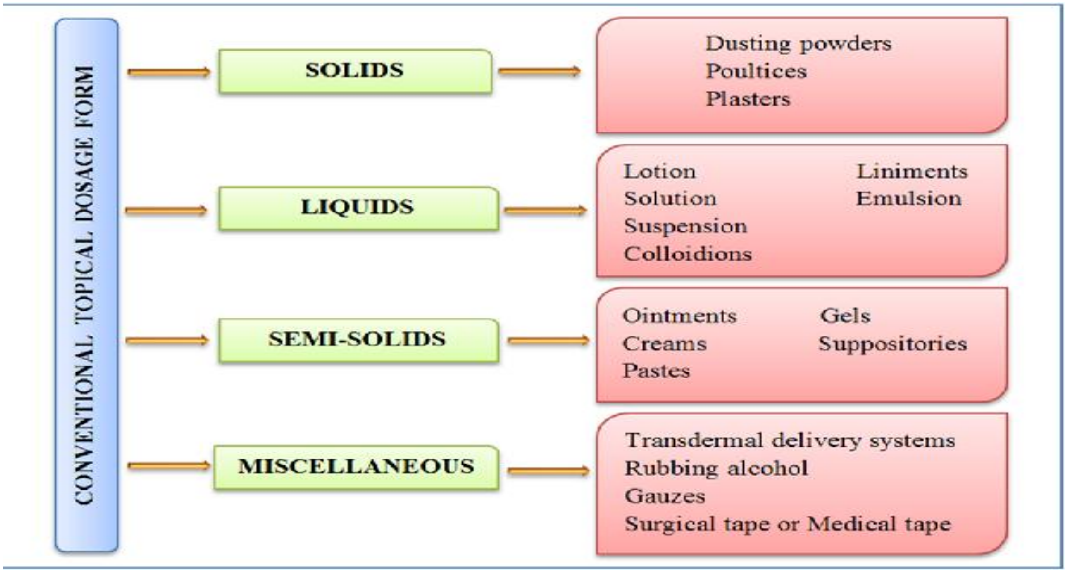


Fig. no. 2: Classification of emulgels.

Rational[6]

Topical dosage forms like cream, lotion, ointment have many disadvantages. Some of which are greasiness and stickiness, causing problems to patients in application and having low spreading coefficient and requirement of rubbing are also considered as disadvantages. Also may causes stability problem of hydrophilic drug formulation. Due to these shortcomings with the semisolid group of preparations, the use of gellified formulation has been expanded both in pharmaceutical preparations and in cosmetics. Gel is colloidal preparation containing 99 % part of liquid where macromolecular network of fibers built from a gelling agent and liquids are immobilized by surface tension between them. In spite of advantages a major problem is to delivery of hydrophobic natured drugs. Emulsion based strategies can be used to incorporate lipophilic therapeutic moiety in gel built system to overcome this problem.

Skin[7,8]

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 1.8m2.Apocrine gland, sweat gland, hair, nails, oil gland are referred as derivatives of skin. The elements of the skin are predominantly to shield the body from the unwanted substances and microorganisms and to contain all body liquids.

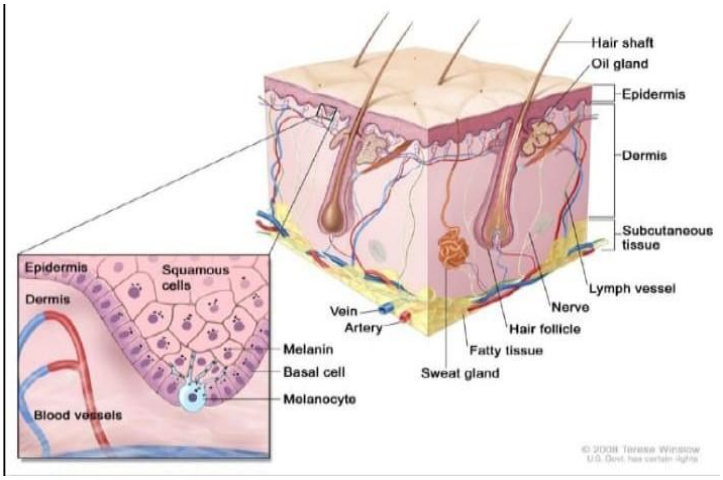


Fig. no. 3: Skin.

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 dermo epidermal 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 slenderer 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 dermibody.

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.[7,8]

Factors affecting topical absorption of drug[7,8]

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

Emulgel[9,10]

Emulgel is evolving field for the topical drug delivery, and up to the date it has less marketed product, so it is thought-provoking and challenging to focus on emulgel formulation. Before starting the concept of emulgel we need to know the concept of emulsion and gel that is being used for the topical drug delivery.

Emulsions are well-ordered drug release system containing two immiscible phase in which one is dispersed (internal phase) into other (external phase), with the use of emulsifying agent to make system stable. Emulsions are of oil-in-water or water-in-oil type, in which the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to deliver controlled effect. USP defines gel is a semisolid system comprises dispersions of either small inorganic particles or large organic molecules enfolding and interpenetrated by liquid. The gel contains the larger amount of aqueous or hydro alcoholic liquid entrapped in a network of colloidal solid particles where it entangled small drug particles and maintain the controlled release of drug. The liquid phase

form a three-dimensional polymeric matrix like structure which results a physical or chemical cross-linking network. The continuous structure which behaves like solid that are homogenous and clear. The emulsion and gel both are liable for the controlled drug release from the systems.

Objectives of emulgel[11]

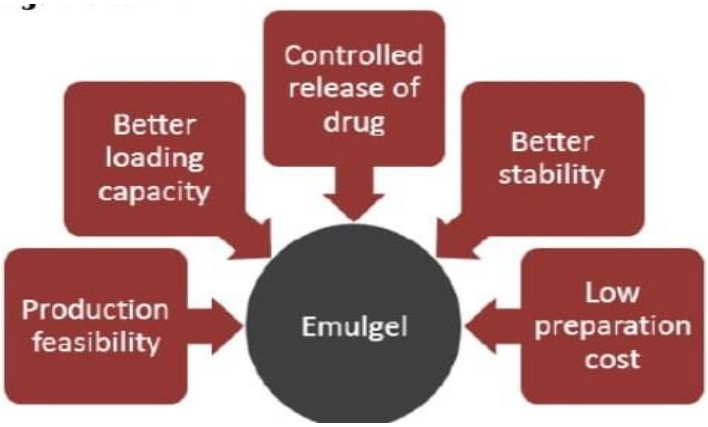


Fig. no. 4: Objectives of emulgel.

Advantage of Emulgels[12,14]

1. Improved patient acceptability.
2. Offer targeted drug delivery.
3. Termination of the therapy at any time.
4. Enhance bioavailability as well as the low doses can be effective in comparison with other conventional semi solid preparation.
5. Easy to formulate and cost effective preparation.

Disadvantages[15]

1. Create problem in absorption of macromolecules.
2. Entrapment of air bubble during formulation.
3. Only hydrophobic drugs are the best choice for such delivery systems.

Essential constituents of emulgel preparation[13]

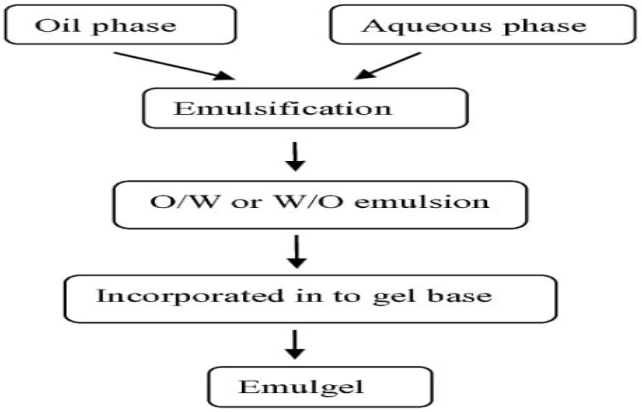
1. Aqueous Material This forms the aqueous phase of the emulsion. Normally used agents are water, alcohols.
2. Oils These agents form the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are broadly used both as the vehicle 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[13]

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.



Evulation parameters of emulgel[11,14]

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. Spread ability Spread ability is determined by apparatus suggested by Multimer 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, spread ability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgel. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm.) Spread ability 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.
   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 Seaboard'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.

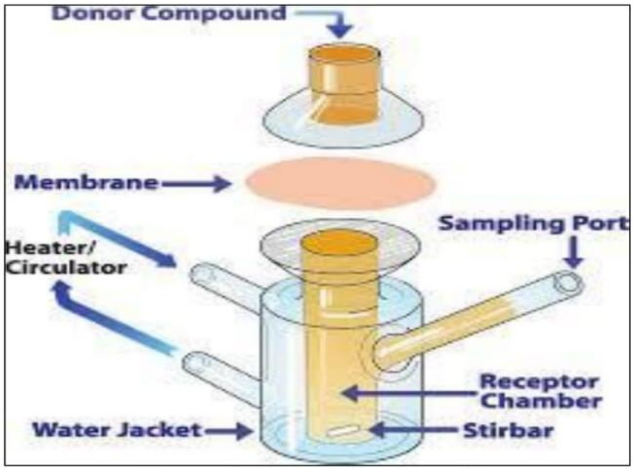


Fig. no. 5: Franz diffusion cell.

Drug Release Kinetic Study To analysis the mechanism of drug release from the topical gel, the release data were fitted to following equations. Zero – order equation Q = K 0t Where Q is the amount of drug released at time t, K0 is the zero – order release rate. First – order equation in (100 – Q) = In 100 – K1t Where Q is the percentage of drug release at time t, K1 is the first – order release rate constant. Higuchi's equation Q = K2t1/2 Where Q is the percentage of drug release at time t, K2 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.
12. 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 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

Marketing products of emulgel[16]

Sr. No.	Brand name	Active ingredient	Manufacturer	Use
1	Voltarol 1.16% Emulgel	Diclofenac diethylammoinium salt	Novartis	Anti-inflammatory
2	Diclon emulgel	Diclofenac Diethylamine	Mepharma	Anti-inflammatory
3	Diclomax emulgel	Diclofenac sodium	Torrent pharma	Anti-inflammatory
4	Miconaz-h-emulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals	Topical corticosteroid and Antifungal
5	Dermafeet emulgel	Urea 40%	Herbitas intense	Moisturizing and exfoliation activity
6	Denacine emulgel	Clindamycin Phosphate	Belt jala pharmaceutical	Antiacne

			Company	
7	Isofen emulgel	Ibuprofen	Belt jala pharmaceutical Company	Anti-inflammatory
8	Diclona emulgel	Diclofenac Diethylamine	Kuwait saudi pharmaceutical industries co.	Anti-inflammatory
9	Dosanac emulsion gel	Diclofenac diethylammoinium	Siam bheasach	Anti-inflammatory
10	Cataflam	Diclofenac potassium	Novartis	Anti-inflammatory

Methods of formulation[17]

Selection of components

Drug Solubility was checked in various oils by excess addition of drug followed by
continuously stirred for 72 hours to achieve equilibrium. After that samples centrifuged and supernatant was taken and solubility was determined by suitable analytical methods. Then, excipients in each category with the highest solubility of drug are selected for further studies.

CONCLUSION

Emulgel is a modern tool for topical delivery of hydrophobic drugs with advantages of emulsion and gel to improve patient acceptability. Emulgel helps in enhancing spread ability,
adhesion, viscosity, and extrusion. It is used both pharmaceutical and cosmetical applications
as well as it allows to incorporate herbal formulations.

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