

**Review Article****Emulgel: Magnifying the application of topical drug delivery**

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ABSTRACT

Topical drug delivery is mostly culled for the local dermatological action, but recently the new technologies are also enhancing its systemic effect. They are generally applied for the purpose as antiseptics, antifungal agents, skin emollients, and protectants. The activity of topical preparation confide in the various factors as drug solubility, its lipophilicity, contact time to skin, its permeability. Many widely used topical agents like ointments, creams, lotions, gel are associated with disadvantages like stability problems, stickiness and lesser spreading coefficient, irritation, allergic reactions, poor permeability, poor absorption and difficulty in absorption of large molecule, to rectify this the new concept of Emulgel has been introduced with the main objective to deliver hydrophobic drug molecule. Emulgel is oil in water or water in oil emulsion carrying drug to be incorporated in gel base to obtain gellified emulsion. Emulgel shows the controlled and better release effect of drug by virtue of combined effect of gel and emulsion with increased stability. Gel having various advantages as non greasy & favors good patient compliance in field of cosmetology and dermatology but are still limited to the deliver hydrophobic drugs. So the Emulgel comes to favour the hydrophobic drugs to give the advantages of gel. Emulgels have several advantages in the field of dermatology such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance. Factors such as gelling agent, oil agent, emulsifiers influence the stability and efficacy of emulgel. So emulgels can be the better semisolid preparation than other conventional systems. At present the emulgel 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.

Introduction

Topical drug delivery having several years of history, still new technology and methods are investigated; as skin is most accessible organ and are potential to facilitate the delivery of several drugs with better efficacy than rest of any other route of administration. With the recent advancement in technology and knowledge it can deliver drug to the skin and also for systemic purpose. This route is one of the best option for the cutaneous purpose [1]. Topical drug delivery is defined as the localized application of formulation in the body through ophthalmic, rectal, nasal, vaginal and skin with the approach to increase its bioavailability and reduction in side effects [2, 3]. This delivery is preferred when other system fails or has some limitation and generally used for the skin fungal infection. Basically there is two type of topical products one is

external topical that is spread to the tissue to cover the diseased area and other is internal topical that are applied for topical effect to mucous membrane in oral cavity, vagina, or rectal tissues [4]. Advantages for the topical drug delivery are as Patient compliance, Ease of administration, Improvement in drug bioavailability, better physiological and pharmacological response, Minimum systemic toxicity and exposure of drug to non-infectious tissue/sites, easy termination of the treatment, avoid hepatic first pass metabolism, avoid gastric incompatibilities, minimum fluctuation in plasma levels and suitable for the drug with narrow therapeutic window. Topical formulation must allow for optimal penetration of the drug into the skin (pH 5.5), a complex tissue thus the pH of the formulation may change following application to the skin, so

before formulating topical adequate knowledge about the nature and behavior of skin should be reviewed. Challenges associated with the development of topical drug delivery is selection of active principle and also the vehicle in which the drug is being delivered, since the availability of drug to site of action may be limited due to barriers associated with these routes. Stratum corneum the major barrier for the passage of foreign particle through skin. Most of the topical drugs applied to eye are washed out within the minutes. Vaginal formulations efficacy is lowered due to the short residence time and inadequate spreading over the tissues. Due to these limitations researcher are interested to develop the new

approaches [5, 6]. Many widely used topical agents like ointments, creams, lotions, gel are associated with disadvantages like stability problems, stickiness and lesser spreading coefficient, irritation, allergic reactions, poor permeability, poor absorption and difficulty in absorption of large molecule [4,7]. Cream, ointments and gels are the semisolid formulations which are commonly used for local and regional skin disorders. Semisolids can change their shape, because of plastic behaviors, except gels having viscoelastic effect because of showing liquid and solid properties [8-10].

Classification of topical drug delivery systems [11]

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

EMULGEL: Emulgel is emerging field for the topical drug delivery, and till date it has less marketed product, so it is interesting and challenging to focus on emulgel. Before going to emulgel we need to know the advantages of emulsion and gel that is being used for the topical drug delivery. Emulsions are controlled release systems containing two immiscible phase in which one is dispersed (internal or discontinuous phase) into other (external or discontinuous phase), with the use of emulsifying agent to stabilize the system. emulsion are of oil-in-water or water-in-oil type, where the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to provide controlled effect. USP defines gel as a semisolid system consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid. The gel contains the larger amount of aqueous or hydro alcoholic liquid in a cross linked network of colloidal solid particles where it captures small drug particles and maintain the controlled release of drug. The liquid phase builds a three-dimensional polymeric matrix which results a physical or chemical cross-linking. The continuous structure results solid like behavior that are homogenous and clear. The emulsion and gel both are responsible for the controlled drug release from the systems [12-14]. The gels are of two types first the organic solvent based, hydrophobic or organogels and second the water based, hydrophilic or hydrogels. First one consist base liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, aluminium or zinc soaps and the second one with the base of water, glycerol, or propylene glycol[15,16]. gels having various advantages has still limitation in the delivery of hydrophobic drugs so to overcome this limitation and enjoy the delivery in the form of gel for the hydrophobic drug, the concept for emulgel was introduced where the hydrophobic drugs are incorporated in emulsion and then to gel[17]. Emulgel is the approach using the benefits of both emulsion and gels, gaining the dual controlled release effect where the

emulsion either oil in water or water in oil is gelled by incorporation in the gel base [18], simply the Emulgels are emulsion in gel. In emulsion the drug particles are incorporated in the internal phase acting as drug reservoir from where the drug passes through the external phase and to the skin and get absorbed. Emulgel are seen better choice for the class II of drug as per the BCS classification systems that show poor solubility and high permeability [2]. Emulgel possess the properties as thixotropic, grease less, easily spreadable, easily removable, emollient, nonstaining, water soluble, long shelf life, biofriendly and pleasing appearance that improves the patient acceptability [4]. Emulgel are being used for the treatment of various anti-inflammatory activity and other skin related viral, bacterial and fungal infections [19, 20].

Advantages of emulgel [21-23]

1. Increased patient acceptability.
2. Provide targeted drug delivery.
3. Easy termination of the therapy.
4. Improve bioavailability and even the low doses can be effective in comparison with other conventional semi solid preparation.
5. Stable formulation by decreasing surface interfacial tension resulting in increase in viscosity of aqueous phase, more stable than Transdermal preparations that are comparatively less stable, powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
6. Hydrophobic drug can be incorporated in emulgel using emulsion as the drug carrier that is finally dispersed in the gel.
7. Provide the controlled effect of that enhance the prolong effect of the drug with short half life.
8. Easy and cost effective preparation.
9. Drug loading capacity is better than other novel approaches like niosomes and liposomes

10. Penetration to skin is enhanced due to both hydrophilic and hydrophobic nature.

Disadvantages [2, 4]

1. Poor absorption of macromolecules.
2. Entrapment of bubble during formulation.
3. Hydrophobic drugs are the best choice for such delivery systems.

ANATOMY OF SKIN (BARRIER FOR TOPICAL DRUG DELIVERY) [24-27]

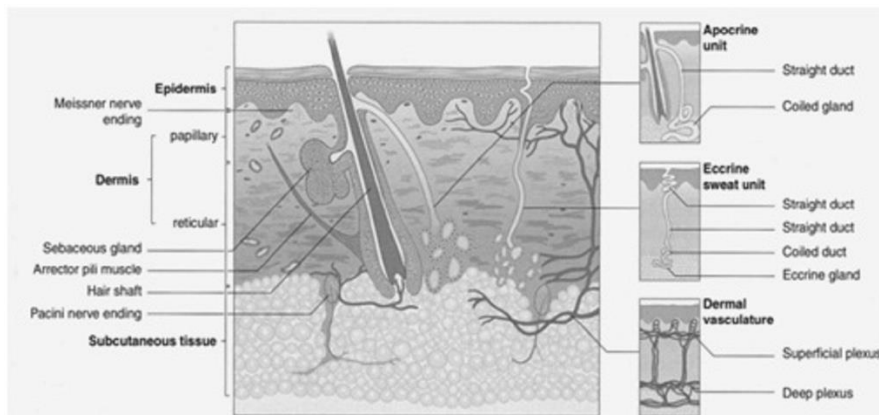


Fig 1: The skin and its appendages [24]

Epidermis the outer layer 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:

1. Stratum basale (basal or germinativum cell layer)

The innermost layer of the epidermis consist mainly 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 touchsensitive sites as the fingertips and lips.

2. Stratum spinosum (spinous or prickle cell layer)

Basal cells moves 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 significant role in immune reactions of the skin, acting as antigen-presenting cells.

3. 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.

4. Stratum corneum (horny layer)

Result of keratinocyte maturation is found in the stratum corneum, made up of layers of hexagonal-shaped, non-viable

skin the dynamic and largest organ of the body with 16 % of body weight and surface area of 1.8m². The pH of the skin varies from 4 to 5.6, Sweat and fatty acid secreted from sebum influence the pH of the skin surface. It is constantly changing by inner cells that replace the outer layer and are consistent throughout the body but varies in thickness according to site and age of the individual. Hair, nails, sebaceous, sweat and apocrine glands are regarded as derivatives of skin (Fig. 1).

cornified cells known as corneocytes. 10±30 layers of stacked corneocytes are found in most area of skin with maximum layer in palms and soles. Protein covers the corneocyte and is filled with water-retaining keratin proteins. Strength is gained due to 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%.

Dermis

Structural support and bulk of the skin is provided by the dermis the deeper layer and is 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.

Subcutis

The subcutis or hypodermis is an important depot of fat and are made up of loose connective tissue and fat, which can be up to 3 cm thick on the abdomen.

Skin Functions [24-27]

Provide barrier to the environment that allows and limits the inward and outward passage of water, electrolytes and various substances while providing protection against micro-organisms, ultraviolet radiation and toxic agents. Water loss from the skin is prevented by the cornified cell envelope and the stratum corneum while keratinocyte provide an innate immune defence against bacteria, viruses and fungi. Langerhans' cells functions to survey the epidermal environment and to initiate an immune response against microbial threats, although they may also contribute to immune tolerance in the skin. Melanin provides protection against DNA damage from UV radiation. An important function of skin is thermoregulation. Vasodilatation or vasoconstriction of the blood vessels in the deep or superficial plexuses helps regulate heat loss. Eccrine sweat glands present in densities of 100–600/cm²; they play a role in heat control and produce approximately 1 litre of sweat per hour during moderate exercise. Secretions from apocrine sweat glands contribute to body odour (pheromones). Skin lubrication and waterproofing is provided by sebum secreted from sebaceous glands. Subcutaneous fat helps in cushioning trauma as well as providing insulation and a calorie reserve. Fat also has an endocrine function, releasing the hormone leptin, which acts on the hypothalamus to regulate hunger and energy metabolism. Other functions of fat cells include tissue remodelling and phagocytosis. Skin also has a key function in synthesizing various metabolic products, such as vitamin D of hemidesmosomal-anchoring filament complexes (more in the leg than the arm).

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUGS [28, 29]**Physicochemical factors****Drug substances**

1. Molecular weight (<400 dalton)
2. Diffusion coefficient
3. Water/lipid partition coefficient
4. Permeability coefficient
5. Ionization- unionized drug are well absorbed
6. Protein binding capacity.

Vehicle

7. Solubility/polarity
8. Volatility
9. Concentration
10. Distribution in a stratum corneum
11. Excipients
12. Penetration enhancer
13. PH

Physiological Factors

14. Skin thickness
15. Lipid content

16. Density of hair follicles
17. Density of sweat glands
18. Skin pH
19. Blood flow
20. Hydration of skin
21. Inflammation of skin

Site of application

22. Skin area dose (film thickness, concentration)
23. Total skin area in contact with vehicle
24. Duration of exposure

CONSIDERATION TAKEN IN ACCOUNT FOR THE TOPICAL DRUG DELIVERY SYSTEMS [30]

Efficacy and penetration of active drug is enhanced by the proper selection of vehicle which may itself possess the cooling, drying, emollient or protective activity. Preparation should be matched with the type of lesions; For example, avoid greasy ointments for acute weepy dermatitis. Type of preparation should be matched with the site of application. Irritation or sensitization potential should also be taken in consideration before selecting the type of topical preparation.

DRUG ENTRY THROUGH SKIN [31-34]

Drug mostly penetrate the stratum corneum by passive diffusion whereas limited active transport follows these steps: drug dissolution in its vehicle than drug diffusion from the vehicle to surface of the skin and finally the actual penetration of the drug through the different layers of the skin. Active pass through the stratum corneum (lipophilic) into the viable epidermis and continue passively through to the dermis (hydrophilic) to the dermal-epidermal junction where the blood vessels carry it to the systemic circulation. Topical drugs are generally applied for three different functions. First, active for the surface of the skin e.g. for disinfection, insect repellents and cosmetics, so called epidermal formulations. Second functions when formulations are designed to penetrate into the deeper regions of the skin such as the viable epidermis and the dermis, so called endodermal or diadermal formulations. Thirdly, for the systemic action of drugs by transdermal application can be the aim of the topical therapy. Drug penetrates the stratum corneum by two options: the transepidermal route and the route via pores. The transepidermal route can be divided into the transcellular and the intercellular route. Transcellular route is the direct and the shortest route where the drug directly passes through both the lipid structures of the stratum corneum and the cytoplasm of the dead keratinocytes, but encounter significant resistance to permeation because they have to cross both lipophilic and hydrophilic structures. Intercellular is the common route where the drug passes between the corneocytes. Since the skin appendages (glands and hair follicles) occupy only 0.1% of the total human skin surface, the contribution to the pore route was primarily considered to be small. However, for very lipophilic and large molecules (and some electrolytes) the appendages and other diffusion shunts may also play an important role. The follicular apparatus of hair follicles, the sweat glands and microlesions in the

interfollicular horny layer were introduced as theoretical vertical pathways for percutaneous penetration (Fig. 2). The lipophilic drug that easily crosses the stratum corneum, show slow diffusion when it reaches the hydrophilic epidermis that causes the temporary deposition, so called reservoir effect. Small molecular size substances having both lipid and aqueous solubility are capable of best permeation effect. Electrolytes are difficult

to absorb when they are applied in aqueous solutions because they create a field of stable hydration that increases the size of the diffusing component. The permeability coefficient of the drugs depends on the solute size, lipophilicity and the diffusion path length. Although Fick's law describes that penetration depends on the thickness of the skin, later works show its dependency more on the lipid composition of the skin.

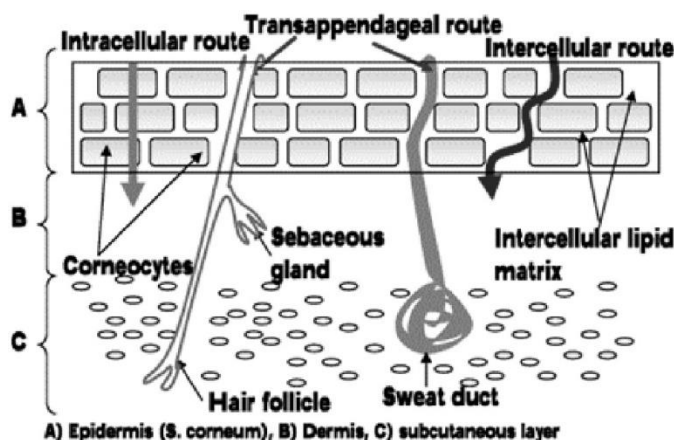


Fig 2: pathways for drug entry

CONSIDERATION ACCOUNTED AND INGREDIENTS USED IN THE FORMULATION OF EMULGEL. [2, 4, 11]

Aqueous material

Make the aqueous phase in emulsion and for the swelling purpose of gelling agent. The most commonly used are water, alcohol etc

Oil phase

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

Emulsifiers

They are used for the emulsification and stability purpose of the product by decreasing the interfacial tension. Selection is done by proper hydrophilic and lipophilic balance (HLB) for example the surfactant with HLB value greater than 8 is used in oil in water emulsion where as the surfactant with HLB value less than 8 are used in water in oil emulsion. Tween are applicable for the water phase while the spans are applicable for the oil phase for emulsification. Mixture of tween and span provide better stability than single. eg Polyethylene glycol, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, labrasol, Sodium stearate etc

Gelling agent

Gelling agent may be of natural, synthetic source; selection of these polymers can be based on the multifunction as thickening and acting as emulsifying agents. They are incorporated to make the system thixotropic. Effect of gelling agent on the drug release pattern should be studied. Synthetic polymer is Carbopol. The cellulose derivatives form a colloidal solution. They disperse in water and because of acidic pH the solution have to neutralize by amines, e.g. triethanolamine or bases, e.g. sodium hydroxide. Depending on pH range Carbopol have different grades, e.g. Carbopol 934, 940, etc. Natural materials such as tragacanth, carrageen, pectin, agar, xanthan gum, alginic acid and starch; synthetic agents are: cellulose derivatives such as methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxyvinyl polymers, carboxymethylcellulose and magnesium aluminium silicates etc

Permeation Enhancers

Agents that partition into, and interact with skin constituents to induce a temporary and reversible increase in skin permeability. For example, Oleic acid, Menthol, Clove oil, Lecithine, Isopropyl myristate, Urea, Linoleic acid, Cinnamon etc

METHOD OF PREPARATION FOR EMULGEL [21, 30]

It has 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 second step is to formulate the gel base and finally the addition of emulsion to gel in continuous stirring to form emulgel. In detail for the formulation of emulsion the aqueous phase is prepared by taking the purified water to which the soluble ingredient are added and heated up to 70°C including emulsifying agent as

tweens and then the oil phase are prepared by dissolving the surfactant such as spans also heated to 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 are adjusted to 6 to 6.5 as per the requirement of the polymer. For example pH of gel with carbopol is adjusted by Tri ethanol amine (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 were 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.

EVALUATION OF EMULGEL

Physical appearance [35]

The prepared formulations were inspected visually for their colour, homogeneity, consistency.

pH [35]

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

Spreadability [8,35]

Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. One gram of emulgel was placed between the two glass slides and load of 500 g was applied for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Second glass slide is provided with the hook. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time required to slip off the slides was measured.

Lesser the time taken for separation of two slides, better the spreadability. Spreadability was calculated using formula

$$S = M \cdot L / T$$

Where M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides.

Extrudability[35]

Here the weight required to extrude 0.5 cm ribbon of emulgel in 10 sec from lacquered collapsible aluminum tube is determined. Test was repeated and the average values were used for the calculation.

Formula for extrudability calculation

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

Viscosity [12]

Viscosity Determined by using a cone and plate type of Brookfield viscometer (Brookfield viscometer RVT) with spindle No.7. The maximum shear rate was 100 RPM while minimum shear rate was 10 RPM.

Swelling Index [36]

Formulation with maximum swelling index indicates its tendency to absorb extrudates from wound. the swelling index is calculated by placing 1gm of emulgel on porous aluminum foil and then it was placed in petridish containing 10 ml 0.1 N

Sodium Hydroxide. Then samples were removed from dish at different time intervals and put it on dry place for some time after it reweighed. Swelling index was calculated using formula.

$$\text{Swelling Index (SW) \%} = \frac{(W_t - W_o)}{W_o} \times 100$$

Where (SW) % = Equilibrium percent swelling,

W_t = Weight of swollen emulgel after time t,

W_o = Original weight of emulgel at zero time

Photomicroscopy[37]

Emulgel was viewed under light microscope to study the globular structure in gel base. The emulgel was suitably diluted, mounted on glass slide and viewed by light microscope under magnification of 40x

Dilution test [4]

50 to 100 times aqueous dilution of emulgel was done by adding Continuous phase and visually checked for phase separation and clarity.

Drug content

One gram of emulgel is mixed with the suitable solvent, sonicated and filtered with whatman filter paper no. 41 to obtain the clear solution. Absorbance of the solution after proper dilution is determined using UV spectrophotometer. Standard plot of drug is prepared in the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance in the standard equation [38].

$$\text{Drug Content} = (\text{Concentration} \times \text{Dilution Factor} \times \text{Volume taken}) \times \text{Conversion Factor.}$$

Globule size and its distribution in emulgels

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. Or it is determined by motic microscope where the same sample is added on slide and observes under microscope [39].

Zeta potential

Zeta Potential of emulsions is determined by Zetatrac, measuring the response of charged particles to an electric field. In a constant electric field particles drift at a constant velocity. Through the velocity, the charge and Zeta Potential are determined. Zetatrac utilizes a high frequency AC electric field to oscillate the charged particles. The Brownian motion power spectrum is analyzed with the Nanotrac controlled reference technique of particle sizing to determine the Modulated Power Spectrum, a component of the power spectrum resulting from the oscillating particles. Zeta Potential is calculated from the MPS signal [37].

In vitro drug release study

Franz diffusion cell (with effective diffusion area 3 cm² and 30 ml cell volume) was used for the drug release studies. Emulgel (500 mg) was applied onto the surface of cellophane membrane evenly. The membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared buffer pH 5.8 solutions to solublize the drug. The receptor chamber was stirred by magnetic stirrer at 50 rpm and maintained at

$37 \pm 0.2^\circ\text{C}$. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 260 nm after appropriate

dilutions. Cumulative amount of drug released across the membrane was determined as the function of time [39].

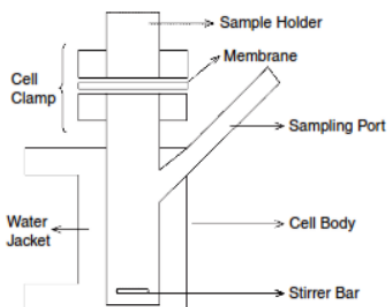


Fig 3: Franz vertical diffusion cell

Skin irritation test

Few portion of rat 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 [38].

Ex vivo drug release study

The ex vivo drug release study is carried out in a modified Franz diffusion cell. A section of skin was cut from the male rat and placed in the space between the donor and receptor compartment of the Franz diffusion cell, keeping the dorsal side upward. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained constant at $37 \pm 0.2^\circ\text{C}$ by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. The samples were withdrawn at proper time intervals and replaced with same amounts of fresh dissolution media. Samples were analyzed by proper dilution under UV spectrophotometre [40].

Microbiological assay

29.5gm of sabouraud dextrose agar was transferred in a 500 ml of conical flask and 500 ml of purified water and heat is applied to dissolve completely. Sterilization was done for 15 min at 121°C at 15 lb pressure in autoclave. Then the bacterial strain or fungus was dispersed in the medium as per the requirement of the test after cooling it to room temperature.

And then the medium was poured it into the three petridish and cooled for sometime at room temperature until it forms solidifies at room temperature and then the three cups are bored in each petridish with the help of sterile steel bore of 6 mm and calculated concentration of the standard drug, emulgel formulation and emulgel without drug were placed in the bores with help of 18 gauges needles and incubated the petri plates for 18 h at 37°C in incubators. Then the radius zone of inhibition was observed and calculated [39].

Kinetic analysis of the drug release

Kinetic analysis of the data was carried out to determine the release model which describes the proper order of drug release as follow: Zero order (cumulative% drug release vs. time), first order (log cumulative % drug retained vs. time), and Higuchi model (cumulative % drug retained vs. square root of time) [41].

Stability studies

Stability test were performed for the optimized formulation; the formulations were packed in aluminum collapsible tubes and studies were carried out for 3 months as per ICH guidelines by keeping at $25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{RH}$ and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$ and Samples were withdrawn on a regular interval of 1, 2 & 3 months for evaluation of physical appearance, pH, rheological properties, drug content and drug release [42].

Marketed Emulgels

The preparations of emulgel that are market commercially are listed below in table 1.

Table 1: Marketed emulgels

| Sr.No. | Brand name | Active ingredient | Manufacturer | Uses |
|--------|------------------------|------------------------------------|----------------------------------|---|
| 1. | Voltarol 1.16% emulgel | Diclofenac Diethylammonium salt | Novartis | Antiinflammatory |
| 2. | DiclomaxEmulgel | Diclofenac sodium | Torrent pharma | Antiinflammatory |
| 3. | Miconaz-H-emulgel | Miconazole nitrate, Hydrocortisone | Medical union Pharmaceuticals | Topical corticosteroid and antifungal |
| 4. | Dermafeet Emulgel | Urea 40% | Herbitas | Intense moisturizing and exfoliation activity |
| 5. | Denacine emulgel | Clindamycin phosphat | Beit jala pharmaceutical company | Antiacne |

| | | | | |
|-----|----------------------|----------------------------|--|-------------------|
| 6. | Isofen emulgel | Ibuprofen | Beit jala pharmaceutical company | Anti-inflammatory |
| 7. | Diclona emulgel | Diclofenac diethylamine | Kuwait Saudi pharmaceutical industries co. | Anti-inflammatory |
| 8. | Dosanac emulsion gel | Diclofenac diethylammonium | Siam bheasach | Anti-inflammatory |
| 9. | Diclona emulgel | Diclofenac diethylamine | medpharma | Anti-inflammatory |
| 10. | Cataflam emulgel | Diclofenac potassium | Novartis | Anti-inflammatory |

Conclusion

Recently most of the new drug molecules are hydrophobic in nature, and difficulty has been raised to researcher for the delivery of such drug in any form of dosage, because of their limited solubility. There has been always a challenging task for the formulation of such drugs; here the focus is given for the hydrophobic drug that needs to deliver topically. When we consider delivering these drugs in conventional dosage form as cream, ointment, lotions, emulsion the problem of stability and bioavailability rises due to their hydrophobic nature. In gel also it is almost negative result to deliver hydrophobic drugs. So the new concept of formulation emulsion in gel has shown better delivery as here the drug are incorporated in oil phase of emulsion and emulsion is better stabilize in the gel and the combination of both of the phase provide the controlled release effect, that improves the bioavailability of that drugs. Such advantages of emulgel provide the big scope in future for the delivery of hydrophobic drug topically with more efficacy and less production cost. Oils with medicinal value provide the Synergistic effect to emulgel.

Conflict of interest: We declare that we have no conflict of interest.

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