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EMULGEL: A COMPREHENSIVE REVIEW ON THE RECENT ADVANCES IN TOPICAL DRUG DELIVERY

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ABSTRACT
Emulgel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs. When gel and emulsion are used in combined form they are referred as Emulgel. Emulsion in gel have emerged as one of the most interesting topical drug delivery system as it have dual release control system i.e. emulsion and gel. Gels are relatively newer class of dosage form created by entrapment of large amount of aqueous or hydro alcoholic liquid in a network of colloidal solid particles which may consist of inorganic substances or organic polymers of natural or synthetic origin. In recent years there has been great interest in the use of novel polymers with complex function such as emulsifiers and thickeners. The gelling capacity of these compounds allows the formulation of stable emulsion and creams by decreasing surface and interfacial tension at the same time increasing the viscosity of aqueous phase. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drug. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic moiety can enjoy the unique property of gel.
Key words: Emulgel, hydrophobic drug, inorganic substances, emulsifiers, thickeners, hydro alcoholic.

INTRODUCTION

Topical preparation was used for the localised effect at the site of their application by virtue of drug penetration into the underlying layer of skin or mucous membrane [1] . Over the last decades the treatment of illness has been accomplished by administrating drug to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous disorders (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment [2]. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier to both hydrophilic and hydrophobic substances. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. When gels and emulsions are used in combined form the dosage forms are referred as **Emulgel** [3, 4]. As the name suggest they are the combination of emulsion and gel. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel [5].

Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. 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. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption [6]. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through the sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption [7]. Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, water soluble ions and polar molecules do not penetrate intact stratum corneum. Topical formulation can be used to manipulate -the barrier function of the skin, for example, topical antibiotics and antibacterial help a damaged barrier to ward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer [8].

Advantages of Emulgel

1. Avoidance of first pass metabolism.
2. Medication can be self applied.
3. Improve patient compliance.
4. Medication can be terminated when needed.
5. Suitable for drug with short half life and potent drug.
6. Site specific drug delivery.

Disadvantages of Emulgel

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

Rationale of Emulgel as a Topical Drug Delivery System

So many formulations is applied to the skin or mucous membrane that either improves or repairs a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products [9]. Many widely used topical agents like ointments, creams lotions have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing [10]. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibres built from a small amount of a gelating substance present. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion

based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels.

Physiology of the skin

The skin has several layers shown in figure 1. The overlaying outer layer is called epidermis. The layer below epidermis is called dermis. The dermis contains a network of blood vessels, hair follicle, sweat gland. Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair project into these fatty tissues, bulbs of hair project in to these fatty tissues. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every square centimetre of the skin. 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. Most of the topical preparations are meant to be applied to the skin so basic knowledge of the skin and its physiology function is very important for designing topical formulation. The skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body[11-14].

The layers of epidermis are

- Stratum germinativum (growing layer).
- Malpighion layer (pigment layer).
- Stratum spinousm (prickly cell layer).
- Stratum granulosum (granular layer).
- Stratum lucidum.
- Stratum corneum (horny layer).

Drug Delivery across the Skin

The skin barrier properties reside in outermost layer, the stratum corneum. The stratum corneum is effectively a 10-15µm thick matrix of dehydrated, dead keratinocytes (coenocytes) embedded in a lipid matrix. There are two important layers in the skin: the dermis and epidermis. The outer most layer, the epidermis, is approximately 100 to150µm thick, has no blood flow and includes a layer within it known as the stratum corneum. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, then it can enter the blood stream and the process is known as passive diffusion. There are two concepts in the design of transdermal delivery, namely, the reservoir type and the matrix type. Others are actually extensions of these two concepts and both involve diffusion of drug molecule through the skin barrier [15]. Modulation of formulation excipients and addition of chemical enhancers, such as fatty acids, surfactants, esters and alcohols that exert their action via a temporary alteration of barrier properties of the stratum corneum by various mechanisms, including enhancing solubility, partitioning the stratum corneum, fluidizing the crystalline structure of the stratum corneum and causing dissolution of stratum corneum lipids can enhance drug flux. However, due to low permeability coefficients of macromolecules, the enhancement effects required to ensure delivery of pharmacologically effective concentrations are likely to be beyond the capability of chemical enhancers tolerated by the skin. Therefore, several new active transport technologies have been developed for the transdermal delivery of 'troublesome' drugs. There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipid bilayer to viable layers of the skin. The next most common (and potentially under-recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (the skin) but the whole body (systemic) [2,8].

Factors Affecting Topical Absorption of Drug

Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<500 Dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.

Physiological Factors

1. Skin thickness.
2. Density of hair follicles.
3. Density of sweat glands.
4. Blood flow.
5. Hydration of skin.
6. Inflammation of skin.
7. Type of skin (i.e. dry or oily skin).
8. Skin pH.
9. Lipid content. [16, 17]

Factors to be considered when choosing a Topical Preparation

1. 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.
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. 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.
5. The medication should not affect the skin type. [17, 18]

Method to Enhance Drug Penetration and Absorption

1. Chemical enhancement.
2. Physical enhancement.
3. Biochemical enhancement.
4. Supersaturation enhancement. [19]

Advantages of Using Emulgel as a Drug Delivery System

1. Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions: Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2. Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.

3. Better loading capacity: Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

4. Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

5. No intensive sonication: Production of vesicular molecules need intensive sonication which may result in drug degradation and

leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

6. Controlled release: Emulgels can be used to prolong the effect of drugs having shorter T1/2.

7. Patient compliance: They are less greasy and easy to apply.[20,21,5]

Important Constituents of Emulgel Preparation

1. **Aqueous Material-** This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohol.

2**. Oils-** Various oils are used for oil phase formation Widely used oils in oral preparations are non-biodegradable 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 [25] are Isopropyl, Myristate, Capmul, Isopropyl myristate e.t.c are used as oil phase. The use of oil is given below in the table1 [26,4].

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. E.g. polyethylene, glycol 40 stearate , span-80, tween 80, stearic acid, sodium stearate [25].

4**. Gelling Agent-** These are the substances which are used to increase the consistency of any formulation and can also be used as thickening agent. Different gelling agents are given below in table2 [4, 7, 27, 28].

5. Permeation enhancer- These are agents that cross into and interact with skin constituents to induce a temporary disrupts the skin barrier fluidize the lipid barrier and reversible increase in skin permeability for e.g. - oleic acid (1%), lecithin (5%). Use of penetration enhancers are given in table [20,29]**.**

Properties of Penetration enhancers

- They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
- They should be non-toxic, non-irritating and non- allergic. The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body When removed from the skin, barrier properties should return both rapidly and fully.
- They should be cosmetically acceptable with skin and should not cause irritation.

The mechanism of action of Permeation enhancers

The mechanism of penetration enhancers are by[30]-

(i) Disruption of the highly ordered structure of SC lipids,

(ii) Interactions with intracellular proteins.

(iii) Improvement in partitioning of the drug, co enhancers or co solvent in to the stratum corneum. It is reported that terpenes enhance diffusion of drugs by extracting lipids from stratum cornea[31, 32, 33]**,** which results in re-organization of lipid domain and barrier disruption [34, 35].

Method of preparation

Step 1: Preparation of gel using gelling agent and water by constant stirring and Optimization of their pH.

Step 2: Preparation of emulsion.

Step 3: Incorporation of emulsion into gel.Flow diagram showing Emulgel preparation

1) Physical appearance - The prepared emulgel formulations are inspected visually for their colour, homogeneity, consistency and phase separation.

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 spreadibility.

4) Skin irritation study - The preparation is applied on the properly shaven skin of rat and its adverse like change in colour, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

5) Drug Content Determination - Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drug is prepared in same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor

***6) In Vitro* Permeation Study -** In vitro release studies were carried out using Franz diffusion cell.

a) Equation used to determine drug release –

i) Higuchi's equation: $Q = k2\sqrt{t}$

Where -

Q - Percent of drug release at time t.

k2 - Diffusion rate constant.

ii) Zero – order equation: $Q = k0t$

Where -

Q - Amount of drug released at time t.

k0 - zero order release rate.

iii) First – order equation: $\ln (100 - Q) = \ln 100 - k1t$

Where -

Q - Percent of drug release at time t.

k1 - The first order release rate constant.

***7) Ex-Vivo* bioadhesive strength measurement of topical emulgel -** The modified method is used for the measurement of bioadhesive 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 The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following formula. Bioadhesive Strength = Weight required (in gms) / Area (cm^2).

8) Extrudability Study of Topical Emulgel (Tube Test): 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 cm2)

9) 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 0.1 N 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, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time .

10) 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 profile.

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 with Emulgel technique because it contain both oil and aqueous(i.e gel phase) on the other hand hydrogel are not suitable for hydrophobic drugs. In the coming years, topical drug delivery will be used extensively to impart better patient compliance Since emulgel is helpful in enhancing spreadibilty, adhesion, viscosity and extrusion, this novel drug delivery become a popular formulation in future.

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Table 1 Use of oils

CHEMICALS	QUANTITY	DOSAGE FORM
Isopropyl Myristate	7-7.5%	Emulsion
Isopropyl Palmitate	7-7.5%	Emulsion
Isopropyl Stearate	7-7.5%	Emulsion
Light liquid paraffin	7.5%	Emulgel

Table 2. Use of different gelling agent

GELLING AGENT	QUANTITY	DOSAGE FORM
HPMC 2910	2-2.5%	Emulgel
HPMC	3.5%	Gel
Sodium C.M.C	1%	Gel
Carbopol-934	1%	Emulgel
Carbopol-940	1%	Emulgel

Table 3. Use of different penetration enhancers

PERMEATION ENHANCERS	QUANTITY	DOSAGE FORM
Oleic acid	1%	Gel
Lecithine	5%	Gel
Urea	10%	Gel
Eucalyptus oil	NA	None
Isopropyl myristate	5%	Gel
Menthol	4-6%	Emulgel

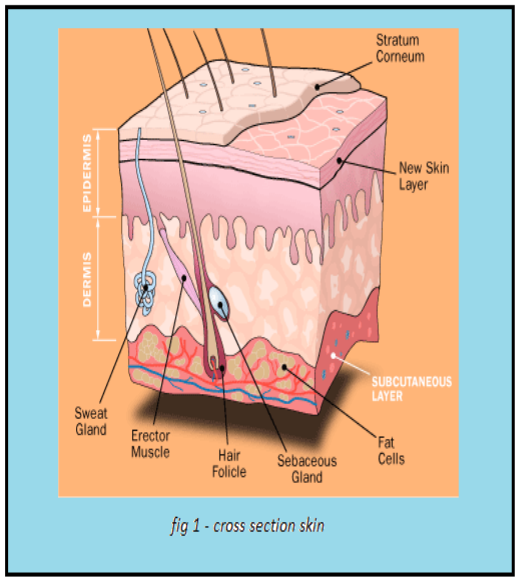

fig 1 - cross section skin