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Review Article **Novel drug delivery system**

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EMULGEL : A NOVEL APPROACH TO TOPICAL DRUG DELIVERY

DADWAL MEENAKSHI*

School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Baddi (173205), Distt. Solan (H.P.) India

ABSTRACT

Emulgel is emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. Emulsion in gel have emerged as one of the most interesting topical drug delivery system as it has dual release control system i.e. emulsion and gel. Also the stability of emulsion is increased when it is incorporated in gel. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Gel formulations generally provide faster drug release compared with ointments and creams. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation emulgels are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gels.

KEYWORDS : Emulgel, Topical drug delivery, Hydrophobic drugs, Important constituents.

DADWAL MEENAKSHI
School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and Technology, Baddi (173205), Distt. Solan (H.P.) India

Corresponding author

INTRODUCTION

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system[1]. Drugs are administered topically for their action at the site of application or for systemic effect[2]. Dermatological products applied to skin are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminium salts or organic polymers of natural or synthetic origin[3]. They have a higher aqueous component that permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream base[4]. These are superior in terms of use and patient acceptability. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels.Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and 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[5]. In addition; the formulator can control the viscosity, appearance and degree of greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications[6]. Gels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients and water-soluble or miscible[7]. Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. They have a high patient acceptability since they possess the previously mentioned advantages of both emulsions and gels[8-9]. Therefore, they have been recently used as vehicles to deliver various drugs to the skin.

Advantages of topical drug delivery systems [10-11]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time.
- Ability to easily terminate the medications, when needed.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow the rapeutic window.
- Improve patient compliance.
- Provide suitability for self-medication.

Disadvantages of topical drug delivery systems[12-14]

- Skin irritation of contact dermatitis may occur due to the drug and/or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Drugs of larger particle size not easy to absorb through the skin

RATIONALE OF EMULGEL AS A TOPICAL DRUG DELIVERY

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They

are very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficients 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 preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% w/v 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. Inspite 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[15].

PHYSIOLOGY OF THE SKIN [16-19]

The skin has several layers. The overlaying outer layer is called epidermis, the layer below the epidermis is called dermis. They dermis contain a network of blood vessels, hair follicle, sweat gland & sebaceous gland. Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair project into these fatty tissues.

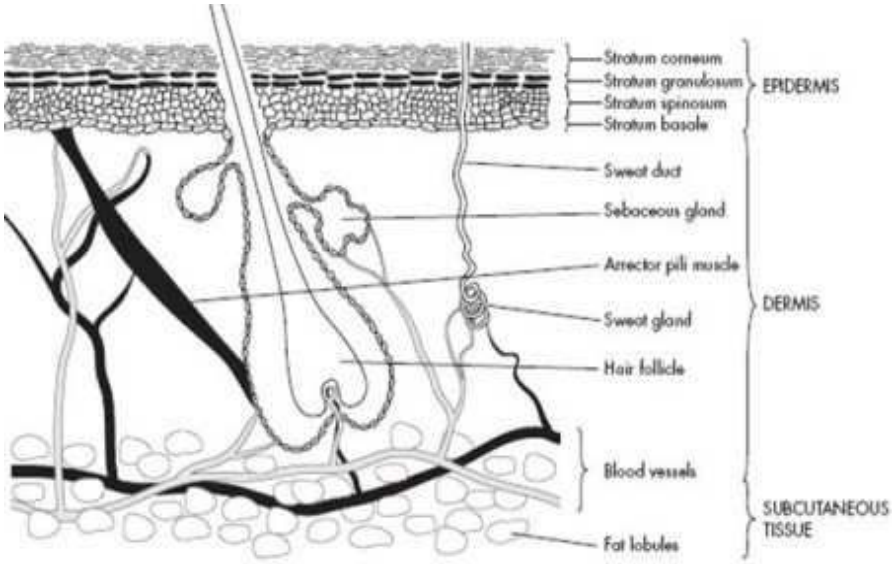

Figure 1
Cross section of human skin

***The layers of epidermis are*:**

- Stratum Germinativum (Growing Layer)
- Malpighion Layer (pigment Layer)
- Stratum Spinosum (Prickly cell Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Lucidum
- Stratum Corneum (Horny Layer)

Epidermis

It is the outermost layer of the skin, which is approximately 150 micrometers thick. Cell from lower layers of the skin travel upward during their life cycle and become flat dead cell of the corneum. The source of energy for lower portions of epidermis is also glucose, and the end product of metabolism, lactic acid accumulates in skin.

Stratum Germinativum

Basal cells are nucleated, columnar. Cells of this layer have high mitotic index and constantly renew the epidermis and this

proliferation in healthy skin balances the loss of dead horny cells from the skin surface.

Malpighion Layer
The basal cell also include melanocytes which produce the distribute melanin granules to the keratinocytes required for pigmentation a protective measure against radiation.

Stratum Spinosum
The cell of this layer is produced by morphological and histochemical alteration of the cells basal layers as they moved upward. The cells flatten and their nuclei shrink. They are interconnected by fine prickles and form intercellular bridge the desmosomes. These links maintain the integrity of the epidermis.

Stratum Granulosum
This layer is above the keratinocytes. They manufacturing basic staining particle, the keratinohylline granules. This keratogenous or transitional zone is a region of intense biochemical activity and morphological change.

Stratum Lucidum
In the palm of the hand and sole of the foot, and zone forms a thin, translucent layer immediately above the granule layer. The cells are non-nuclear.

Stratum corneum
At the final stage of differentiation, epidermal cell construct the most superficial layer of epidermis, stratum corneum. At friction surface of the body like palms and soles adapt for weight bearing and membranous stratum corneum over the remainder of the body is flexible but impermeable. The horny pads (sole and palm) are at least 40 times thicker than the membranous horny layer.

Dermis
Non-descriptive region lying in between the epidermis and the subcutaneous fatty region. It consist mainly of the dense network of structural protein fibre i.e. collagen, reticulum and elastin, embedded in the semigel matrix of mucopolysaccaridic 'ground substance'. The elasticity of skin is due to the network or gel structure of the cells. Beneath the dermis the fibrous tissue open outs and merges with the fat containing subcutaneous tissue. Protein synthesis is a key factor in dermal metabolism.

Subcutaneous tissue
This layer consist of sheet of fat rich areolar tissue, know as superficial fascia, attaching the dermis to the underlying structure. Large arteries and vein are present only in the superficial region.

DRUG DELIVERY ACROSS THE SKIN
The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibres. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed areas of the body-the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. 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 (for example, the skin) but the wholebody. (systemic)

ADVANTAGES OF USING EMULGELS AS A DRUG DELIVERY SYSTEM[20,21,22]

1. ***Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions:***
   Most of the hydrophobic drugs cannot be incorporated directly into the 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.

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG[23,24]

(A) 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
.

(B) Physiochemical Factors

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

IMPORTANT CONSTITUENTS OF EMULGEL PREPARATION

1. Aqueous Material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols[20].

2. Oils

These agents form the oily phase of the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. 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[21,25].

Table 1
Use of oils

Chemicals	Quantity	Dosage form
Light liquid paraffin	7.5%	Emulsion and Emulgel
Propylene glycol	3-5%	Gel
Isopropyl myristate	7-7.5%	Emulsion
Isopropyl stearate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion

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, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate[26].

4. Gelling Agents

These are the agents used to increase the consistency of any dosage form and can also be used as thickening agent[27]. The examples are given in table 2.

Table 2
Use of different gelling agents

Gelling agent	Quantity	Dosage form
Carbopol-934	1%	Emulgel
Carbopol- 940	1%	Emulgel
HPMC- 2910	2.5%	Emulgel
HPMC	3.5%	Gel
Sodium CMC	1%	Gel

5. Permeation Enhancers:

These are agents that partition into, and interact with skin constituents to induce a temporary and reversible increase in skin permeability[28]. Some of these materials included in Table 3.

Table 3
Use of penetration enhancers

Permeation enhancer	Quantity	Dosage form
Oleic acid	1%	Gel
Lecithine	5%	Gel
Isopropyl myristate	5%	Gel
Urea	10%	Gel
Linoleic acid	5%	Gel
Clove oil	8%	Emulgel
Menthol	5%	Emulgel

METHOD OF PREPARATION[29,30]

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
The flow chart of Emulgel preparation is shown in figure 2.

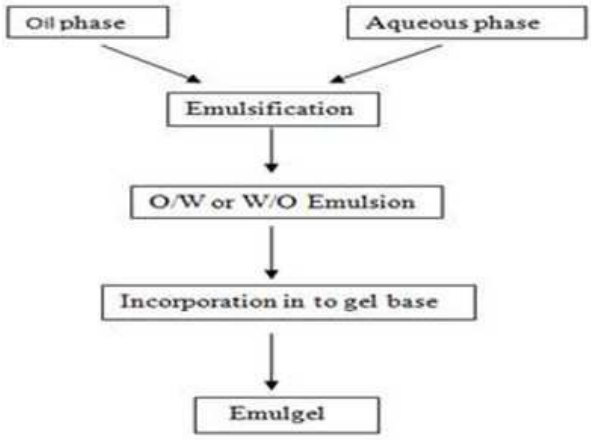

Figure 2
Flow chart of emulgel preparation

CHARACTERIZATION OF EMULGEL[15,31-35]

1. Physical Examination

The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation.

2. Rhelogical Studies

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. Spreading Cofficient

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 80g. 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[36].

4. 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 g) / Area (in cm2).

5. Swelling Index

To determine the swelling index of prepared topical emulgel, 1 g 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[37].

6. Drug Content Determination

Take 1g 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 the same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance[38].

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

7. Skin Irritation Test (Patch Test)

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 upto 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.

8. *Ex–Vivo Bioadhesive strength measurement of topical emulgel*

(MICE SHAVEN SKIN): 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 slides 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 g 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 200mg/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 bioadhesive strength. The bioadhesive strength is calculated by using following formula[38].

Bioadhesive Strength = Weight required (in gm) / Area (cm2)

9. *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 mlaliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible 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[39].

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[40].

CONCLUSION

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel possesses an edge in terms of spreadibilty, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in an water soluble gel bases.

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