REVIEW ARTICLE

Emulgel: A Comprehensive Review for Topical Delivery of Hydrophobic Drugs

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Abstract

In comparison with the other semisolid preparations, the use of gels has been emerged both in cosmetics and pharmaceutical preparations. When gel and emulsion used in the combined form, they are referred as Emulgel. Emulgel is the promising drug delivery system for the delivery of hydrophobic drugs. Emulgel is an emulsion which is gelled by mixing it with gelling agents. Many advantages of gels have the major limitation of delivery of hydrophobic drugs. Hence, to overcome this limitation, the emulsion based approach is being used. Emulgel is an interesting topical drug delivery system as it has dual release control system, i.e., gel and emulsion. Emulgels have several favorable properties for dermatological use such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, transparent, and pleasing appearance. Hence, emulgels can be used as better topical drug delivery system over present systems. This review gives knowledge about emulgel including its properties, advantages, and formulation considerations and its recent advances in the research field.

Key words: Emulgel, emulsifiers, emulsion-based gel, hydrophobic drugs

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat the cutaneous disorder. The topical drug delivery system is generally used where other routes (such as oral, sublingual, rectal, and parental) of drug administration fails or in local skin infection like fungal infection.[1] Topical drug delivery is an attractive route for local and systemic treatment. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment.[2] The main advantage of the topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and the varied conditions of absorption, such as pH changes, the presence of enzymes, and gastric emptying time are another advantage of the topical drug delivery system.[3]

The formulations are available in different forms like from solid through semisolid to liquid. Drugs are administered topically for their action at the site of application or systemic effects. Drug absorption is enhanced through the skin if the drug substance is in solution, if it has a favorable lipid/water partition coefficient and if it is a non-electrolyte.[4] Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body while preventing the ingress of noxious chemicals or microorganisms. It is also the largest organ of the human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m^2. While such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep the insides in and the outside out.[5] Dermatological products applied to the 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 pharmaceutical preparations. Gels are a relatively newer

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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 aluminum salts or organic polymers of natural or synthetic origin. 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. These are superior in terms of use and patient acceptability.[2]

In spite, so advantageous gels show a major limitation in the delivery of hydrophobic drugs. Hence, to cover up this lacking, emulgel is prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel.[4] As the name suggest, they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion are used as a vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. Emulgel for dermatological use has several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent, and pleasing appearance.[3]

Molecules can basically penetrate into the skin by three routes: Through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Passage through this outer most layer is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient).[4]

RATIONALE

Many widely used topical agents such as ointment, cream, and lotion 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. Moreover, they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in cosmetics and a pharmaceutical preparation.[3]

A gel is a colloid that is typically 99% wt. liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelatin substance present. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs. Hence, to overcome this limitation, an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and deliver through gels.[1]

Numbers of medicated products are applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents such as ointments, creams, and lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing, and they also exhibit the problem of stability. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and pharmaceutical preparations. In spite of many advantages of gels, a major limitation is in the delivery of hydrophobic drugs.[3]

PHYSIOLOGICAL FACTORS

1. Skin thickness: Varies from epidermis to subcutaneous layer. Epidermis has high thickness about 100–150 µm. Skin on the sole and palm has a high rate of diffusion.
2. Lipid content: It is an effective water barrier, percutaneous penetration increases when lipid weight in stratum corneum is low.
3. The density of hair follicles: Hair follicle infundibulum has a large storage capacity about 10 times more than the stratum corneum.
4. The density of sweat glands.
5. Skin pH: Sweat and fatty acid secreted from sebum influence the pH of the skin surface.
6. Blood flow.
7. Hydration of skin: Can enhance permeation of drug.
8. Inflammation of skin: That disrupts the continuity of stratum corneum increases permeability.
9. Skin temperature: Increase in temperature gives rise to increase in the rate of skin permeation.

PHYSICOCHEMICAL FACTORS

1. Partition coefficient: More the value of log p more easily will be the percutaneous absorption of the drug.
2. The molecular weight (<400 Dalton).
3. The degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles:
   - Hydroalcoholic gel provides the most efficient absorption through the skin.

PHYSIOLOGY OF SKIN[2,3,6]

Most of the topical preparations are meant to be applied to the skin. Hence, a basic knowledge of the skin and its physiology function are very important for designing topical dosage form. The skin of an average adult body covers a surface area approximately 2 m^2 and receives about one-third of the blood

circulating through the body. An average human skin surface is known to contain, on the average 40–70 hair follicles, and 200–300 sweat ducts on every square centimeter 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. The skin can be considered to have four distinct layers of tissue [Figures 1 and 2].

Non-viable epidermis

Stratum corneum is the outermost layer of skin, which is the actual physical barrier to the most substance that comes in contact with the skin. The stratum corneum is 10–20 cell layer thick over most of the body. Each cell is a flat, plate-like structure - 34–44 µm long, 25–36 µm wide, and 0.5–0.20 µm thick with a surface area of 750–1200 µm stocked up to each other in brick-like fashion. Stratum corneum consists of lipid (5–15%) including phospholipids, glycosphingolipid, cholesterol sulfate, and a neutral lipid, protein (75–85%) which is mainly keratin.

Viable epidermis

This layer of the skin resides between the stratum corneum and dermis and has a thickness ranging from 50 to 100 µm. The structures of the cells in the viable epidermis are physicochemically similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

Dermis

Just beneath the viable epidermis is the dermis. It is structural fibrin, and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland, and cutaneous nerves. Most investigators consider drug is permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

DRUG DELIVERY ACROSS THE SKIN[2,3]

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium

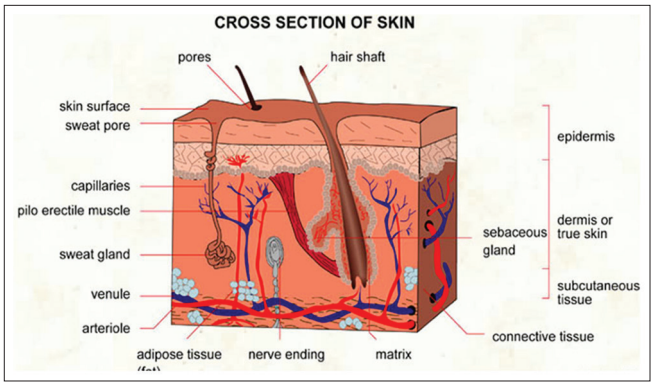

Figure 1: Structure and physiology of the skin[4]

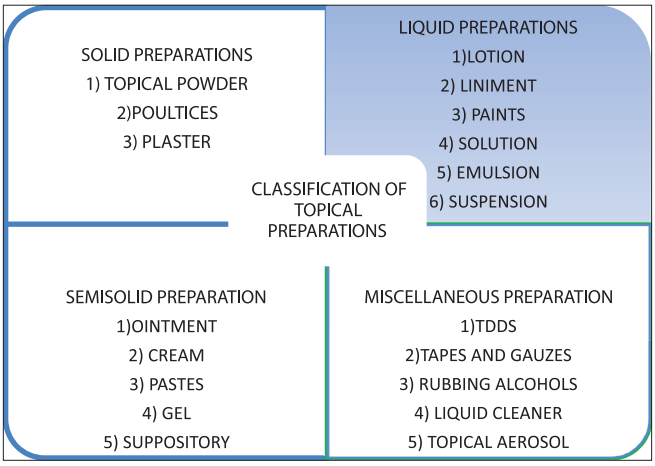

Figure 2: Classification of topical preparation[5]

which varies in thickness in different parts of the body. It is thickest on with elastic fibers. 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 are 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 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 through 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).

FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION[1,3]

1. Irritation or sensitization potential. In general, 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, for example, an occlusive vehicle enhanced penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action.

METHODS TO ENHANCED DRUGS PENETRATION AND ABSORPTION

Advantages[3,6]

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Improve patient compliance.
5. Suitability for self-medication.
6. Providing utilization of drug with short biological half-life and narrow therapeutic window.
7. Ability to easily terminate medication when needed.
8. Convenient and easy to apply.
9. Incorporation of hydrophobic drugs:[8]
   The hydrophobic moieties cannot be added directly to the gel bases because of the improper release shown by the drug as of lack of solubility. The emulgel allows the addition of such hydrophobic drugs in the oil phase which leads to the dispersion of oil globules in an aqueous phase resulting in the formation of o/w emulsion. Further, this emulsion can be simply added to the gel base, thereby providing good stability, and better release of drugs, as given in Table 1 and Table 2.
10. Better loading capacity:[2]
    Other novel approaches such as niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. However, gels due to the vast network have comparatively better loading capacity.
11. Better stability:[9,10]
    Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams show phase inversion, or breaking and ointment show rancidity due to the oily base.
12. Production feasibility and low preparation cost:[8]
    Preparation of emulgels comprises simpler and short steps which increase 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.
13. Controlled release:[9,10]
    Emulgels can be used to prolong the effect of drugs having shorterT1/2.
14. No intensive sonication:[9,10]
    Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. However, this problem is not seen during the production of emulgels as no sonication is needed.

Disadvantages[3,7]

1. Skin irritation on contact dermatitis.
2. The possibility of allergenic reactions.
3. The poor permeability of some drug through the skin.
4. Drug of large particle size not easy to absorb through the skin.
5. The occurrence of the bubble during formation of emulgel.

CLASSIFICATION OF TOPICAL DRUG DELIVERY

The delivery of drugs into and through the skin has been an important area of research for many years. Historically, topical pharmaceuticals were developed by incorporating new drug compound into the vehicles such as hydrophilic petrolatum. In last two decades there is radical change in the manner in which dermatologicals are formulated, developed and tested.

Topical drug delivery means drug administration via the skin for local therapeutic effect on diseased skin. Topical preparations are applied to skin for surface, local, or systemic effects. They may be used for prophylaxis (e.g. sunscreens, astringents, etc.) or for treatment (e.g. inflammation, bacterial infection, viral infection, etc.). The primary goal of topical products is to increase the retention of drugs in the skin rather than penetration through the skin. It differs from the transdermal drug delivery as transdermal products are designed to deliver the drugs through the skin to achieve systemic effects, hence here skin is not the target site. The topical drug products are designed to deliver the drugs into the skin for treating various dermal disorders, and here skin is the target organ. But penetration of drugs through the stratum corneum is essential for both types of deliveries, as given in Table 3, and hence the rate limiting step in percutaneous absorption i.e. permeation through stratum corneum is common for both topical as well as transdermal drug products. Although some medication from topical

products may unintentionally reach the systemic circulation, it is usually in sub-therapeutic concentrations, and hence does not produce side effects of any major concern. (4, 5) Classification of Topical preparations are shown in Figure 2

FORMULATION OF EMULGEL

Vehicle[2]

The vehicle has following properties:

- Efficiently deposit the drug on the skin with even distribution.
- Release the drug so it can migrate freely to the site of action.
- Deliver the drug to the target site.
- Sustain a therapeutic drug level in the target tissue for a sufficient duration to provide a pharmacologic effect.
- Appropriately formulated for the anatomic site to be treated.
- Cosmetically acceptable to the patient.
- Due to the efficiency of the epidermal barrier, the amount of topical drug that gets through the stratum corneum is generally low. Rate and extent of absorption vary depending on characteristics of the vehicle but is also influenced by the active agent itself.

Aqueous material[10]

This forms the aqueous phase of the emulsion. The commonly used agents are water and alcohols.

Oils[1]

These agents form the oily phase of the emulsion, as given in Table 4. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used both as the vehicle for the drug and 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.

Emulsifiers[7]

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, for example, polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid, and sodium stearate.

Gelling agents[11,12]

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent, as given in Table 5.

Penetration enhancers[1]

To promote absorption of drugs, vehicles often include penetration enhancing ingredients that temporarily disrupt the skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into the skin, as given in Table 6.

Properties of penetration enhancers

- They should be non-toxic, non-irritating, and non- allergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body, i.e., should not bind to receptor sites.
- The penetration enhancers should work unidirectional, i.e., should allow therapeutic agents into the body while preventing the loss of endogenous material from the body.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin "feel."

Mechanism of penetration enhancers[3,14]

Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer, or solvent into the stratum corneum.

The enhancers act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid-protein portion of the stratum corneum. Some enhancers act on both polar and non-polar pathway by altering the multi-laminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product.

EMULGEL PREPARATION[7,15]

Step 1: Formulation of emulsion either O/W or W/O.
Step 2: Formulation of gel base.

Step 3: Incorporation of emulsion into gel base with continuous stirring.

Emulgel was prepared by the method reported by Mohammad *et al*. (2004) with minor modification. The gel in formulations was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH is adjusted to 6 to 6.5 using triethanolamine. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propylparaben were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase.

Both the oily and aqueous phases were separately heated to 70°–80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature and add glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the Emulgel [Figure 3].

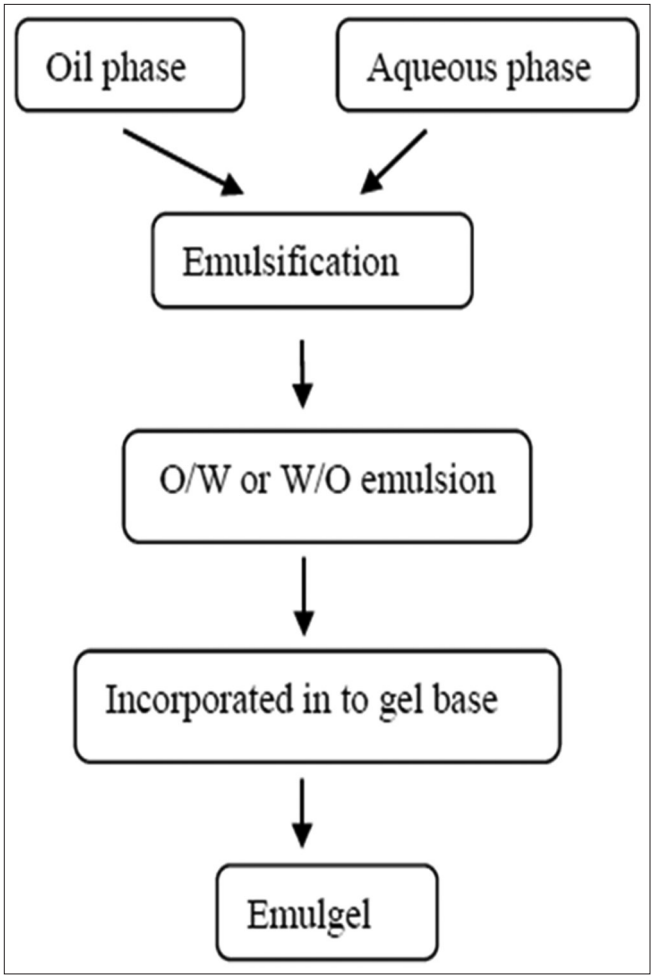

Figure 3: Flowchart of emulgel formulation[7]

CHARACTERIZATION OF EMULGEL

Physical examination[3,16]

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

Determination of pH[3,16]

pH of the formulation was determined using digital pH meter. pH meter electrode was washed by distilled water and then dipped into the formulation to measure pH, and this process was repeated 3 times.

Spreadability[1,17,18]

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 g) under study is placed on this ground slide.

The emulgel is then sandwiched between this slide and another glass slide having the dimension of the fixed ground slide and provided with the hook. A 1 kg weight is placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability.

Globule size and its distribution in Emulgel[3,17]

Globule size and distribution are determined by Malvern Zeta size. A 1.0 g sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample was injected to photocell of Zeta size. Mean globule diameter and distribution are obtained.

Swelling index[2,18]

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 a 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.

In vitro drug release study[5,18]

The *in vitro* drug release studies of the emulgel were carried out on diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1 g) was applied onto the surface of egg membrane dialysis membrane.

The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer. The samples (1 ml aliquots) were collected at suitable time interval sample and were analyzed for drug content by ultraviolet (UV)-visible spectrophotometer after appropriate dilutions.

Cumulative corrections were made to obtain the total amount of drug released at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time. The cumulative percentage drug release was calculated using standard calibration curve.

Microbiological assay[4]

Ditch plate technique is used. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates are 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 18–24 h at 25°C, the fungal growth is observed, and the percentage of inhibition is measured as follows.

% inhibition = L2/L1 × 100, Where, L1 = Total length of the streaked culture, and L2 = Length of inhibition.

Skin irritation test[5,19]

A 0.5 g 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" × 1" (2.54 × 2.54 cm^2). The gellified emulsion was applied to the skin of a rabbit. Animals were returned to their cages. After a 24 h exposure, the gellified emulsion is removed. The test sites were wiped with tap water to remove any remaining test article residue.

Stability studies[13,20]

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 mo. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles.

Extrudability study[2]

It is a usual empirical test to measure the force required to extrude the material from the tube. The method applied for the 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 on the quantity in the percentage of emulgel and emulgel extruded from the lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 s. More quantity extruded better is extrude ability. The measurement of extrudability of each formulation is in triplicate, and the average values are presented. The extrude ability is then calculated using the following formula:

Extrudability = Applied weight to extrude Emulgel from the tube (in g)/Area (in cm^2)

Drug content determination[7,17,20]

Take 1 g of emulgel, mix it in a suitable solvent. Filter it to obtain a clear solution. Determine its absorbance using ultraviolet UV spectrophotometer. Standard plot of the drug is prepared in the same solvent. Concentration and drug content can be determined using the same standard plot by putting the value of absorbance.

Drug content = (Concentration × Dilution factor × Volume taken) × (Conversion factor)

Ex vivo bioadhesive strength measurement of topical emulgel (mice shaven skin)[5]

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 another piece is tied with the balance on the 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 min. Weight is added slowly at 200 mg/min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The

Table 1: Primary requirements of chemical moiety[7]

Properties	Criteria
Effective concentration	<10 mg
t1/2	≤10 h
Molecular mass	800 Dalton or less; desirably 500 Dalton or less; limit could indeed more than this by a change in permeability of skin
Log *P* value	0.8–5
Skin permeability coefficient	≥0.5×10–3 cm/h
Irritation of skin	Nonirritating
Polarity	Less
Molecular size	Small
pKa	Higher

Table 2: Ideal properties of excipients candidate[7]

Properties	Criteria
Skin reaction	No-irritant and non-allergic
Effects on final preparation	Little or no deleterious effect on activity and stability
Regulatory status	IIG listed, GRAS listed, or biologically safe
Concentration	Under regulatory limit
Compatibility	Compatible with API and the other excipients, etc.

API: Active pharmaceutical ingredient

Table 3: Types of methods to enhance drug penetration through the skin[3]

Chemical	Biochemical	Physical
Water	Peptides	Stripping
Solvents	Metabolic inhibitors	Iontophoresis
Surfactant		Electroporation
		Ultrasound (thermal)
		Ultrasound (cavitational)
		Thermal ablation
		Mechanical abrasion
		Microneedles

bioadhesive strength is calculated using the following:

Bioadhesive strength = Weight required (in g)/Area (cm^2).

Drug release kinetic study[5,20]

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

Table 4: Use of oil

Chemical	Quantity (%)	Dosage form
Light liquid paraffin	7.5	Emulsion and Emulgel
Isopropyl myristate	7–7.5	Emulsion
Isopropyl stearate	7–7.5	Emulsion
Isopropyl palmitate	7–7.5	Emulsion
Propylene glycol	3–5	Gel

Table 5: Use of gelling agents[3]

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
Poloxamer 407	1	Gel

CMC: Carboxymethyl cellulose, HPMC: Hydroxypropyl methylcellulose

Table 6: Use of penetration enhancers[13]

Penetration enhancer	Quantity (%)	Dosage form
Oleic acid	1	Gel
Lecithin	5	Gel
Urea	10	Gel
Isopropyl myristate	5	Gel
Linoleic acid	5	Gel
Clove oil	8	Emulgel
Menthol	5	Emulgel
Eucalyptus oil	NA	None
Chenopodium oil	NA	None

Zero-order equation: $Q = k0\ t$

Where, Q is the amount of drug released at time t, and k0 is zero-order release rate.

First-order equation: $\ln (100 - Q) = \ln 100 - k1\ t$

Where, Q is the percent of drug release at time t, and k1 is the first-order release rate constant.

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

Where, Q is the percent of drug release at time t, and K2 is the diffusion rate constant.

Table 7: Marketed preparations

Product name	Drug	Manufacturer
Voltaren emulgel	Diclofenac-diethyl-ammonium	Novartis pharma
Miconaz-H-Emulgel	Miconazole nitrate, hydrocortisone	Medical union pharmaceuticals
Excex gel	Clindamycin, adapalene	Zee laboratories
Pernox gel	Benzoyl peroxide	Cosme remedies Ltd.
Lupigyl gel	Metronidazole, clindamycin	Lupin pharma
Clinagel	Clindamycin phosphate, allantoin	Stiefel pharma
Topinate gel	Clobetasol propionate	Systopic pharma
Kojivit gel	Kojic acid, dipalmitate arbuti	Micro gratia pharma
Accent gel	Aceclofenac	Intra Labs India Pvt. Ltd.
Avindo gel	Azithromycin	Cosme pharma lab
Cloben gel	Clotrimazole, betamethasone	Indoco remedies
Nadicin cream	Nadifloxacin	Psycho remedies
Zorotene gel	Tazarotene	Elder pharmaceuticals

Table 8: Current study and development on emulgel formulation

Study	Drug	Polymer	Enhancer	Purpose	References
Formulation, development and *in vitro* evaluation.	Terbinafine hydrochloride	Carbopol 934	Propylene glycol	Fungal infection	[21,22]
Preparation, characterization and pharmacodynamic evaluation	Ketoprofen	HPMC	Propylene glycol	Anti-inflammatory	[23]
Formulation and evaluation	Mefenamic acid	Carbopol 934	Propylene glycol	Anti-inflammatory	[24]
Formulation and optimization	Chlorphenesin	Carbopol 934	Propylene glycol	Antifungal	[25]
Formulation design and development	Piroxicam	Carbopol 934	Propylene glycol	Anti-inflammatory	[26]
Development and optimization	Diclofenac	HPMC	Propylene glycol	Anti-inflammatory	[21,27]
Formulation and evaluation	Commiphora mukul+Psoralea corylifolia	Carbopol 934	Propylene glycol	Antipsoriatic	[28]
Preparation and evaluation	Clotrimazole	Carbopol 934	Propylene glycol	Antifungal	[21,29]
Development and characterization	Clarithromycin	Carbopol 934	Propylene glycol	Broad spectrum antibiotic	[30]
Development and characterization	Ketoconazole	HPMC	Propylene glycol	Antifungal	[21,30]
Formulation and *in vitro* evaluation	Ciprofloxacin	Carbopol 934	Propylene glycol	Antimicrobial	[21,31]
Optimization	Chlorphenism	Carbopol 934, HPMC	Propylene glycol	Effect of gelling agent on release	[32]
Development and characterization	Ketoconazole	Carbopol 934, 940	Propylene glycol	Comparative study of polymer and drug release	[33]
Percutaneous absorption study	Diclofenac	Carbopol 934, 940, HPMC	Transcutol, myrj 52 cineol	Effect of penetration enhancer	[2,33]

(Contd...)

Table 8: *(Continued)*

Study	Drug	Polymer	Enhancer	Purpose	References
Development study	Miconazole	Carbopol 934, 940	Propylene glycol	Controlled delivery, antifungal	[34]
Formulation	Itraconazole	Carbopol 934, 940	Propylene glycol	More selective, antifungal	[35]
Formulation, design, development, evaluation	Meloxicam	Carbopol 934	DMSO, menthol, clove oil, oleic acid	Treatment of rheumatoid arthritis	[36]
Formulation, evaluation	Capsicum frutescens L	Carbomer	Menthol, propylene glycol	Analgesic	[37]
Formulation, evaluation	Guggulsterone	Xantham gum	Propylene glycol	Anti-arthritic	[38]
Formulation, evaluation	Lantana Camara	Carbopol 934, HPMC K 15 M, HPMC	Propylene glycol	Wound healing activity	[39]
Formulation, development, evaluation	Indomethacin	Carbopol 934, HPMC K4M, xantham gum, pregelatinized starch from ipomoea batata tubers	Propylene glycol	Using four types of gelling agents.	[40]
Formulation, evaluation of nanoemulgel	Adapalene	Carbopol 934	Soybean oil	Decrease systemic side effect and make more selective effect of adapalene	[41]
Formulation, evaluation	Loratadine	Carbopol 934	Propylene glycol	Treatment of localized skin allergy	[42]
Formulation, evaluation	Itraconazole	Carbopol 934, 940	Propylene glycol	Antifungal	[43]
Formulation, characterization	Ketoprofen	Carbopol 934, HPMC K4M, K15M	Propylene glycol	Anti-inflammatory	[44]
Formulation, evaluation	Indomethacin	Carbopol 934, xantham gum	Propylene glycol	Using two types of polymers	[45]

HPMC: Hydroxypropyl methylcellulose

Accelerated stability studies[5]

Stability studies were performed according to ICH guidelines. The formulations were stored in a hot air oven at 37 ± 2°, 45 ± 2°, and 60 ± 2° for 3 months.

The samples were analyzed for drug content every 2 weeks by UV-visible spectrophotometer. Stability study was carried out by measuring the change in pH of the gel at regular interval of time.

Syneresis measurement test[7]

On rest gel shrinks and little liquid are pressed out called syneresis. This could be measured by means of centrifuge tubes in specific apparatus.

Syneresis (%) = Liquid separated from Emulgel/Total weight of Emulgel before centrifugation × 100

MARKETED PREPARATIONS[5]

The various preparations of Emulgels available in market are shown in Table 7

FUTURE PROSPECTIVE

Hydrophobic behavior of drugs is one of the most common problems faced during formulation, as given in Table 8 and development of any new formulation. This behavior is

responsible for poor water solubility and bioavailability of drugs. Many numbers of drugs are hydrophobic in nature. Their delivery to the biological system has been challenging. For topical delivery of drugs different delivery systems such as ointments, lotion, creams, and pastes are applied. These topical formulations generally include large number of oleaginous bases such as petrolatum, beeswax, or vegetable oils those themselves are hydrophobic in nature that does not allow the inclusion of water or aqueous phase. It makes them an excellent emollient but retards the release of drugs and makes the product thick and greasy.

Whereas gel provides an aqueous environment to the drug, favors its dissolution and provides quicker release of drug as compared to other topical delivery systems. Emulsion-based gel provides a suitable medium for delivery of such hydrophobic drugs where such drugs can be incorporated into its oily phase and delivered to the skin. All such advantages of emulgel over other topical delivery systems make them more efficient and productive. In future, these properties will be used to deliver more number of topical drugs in the form of emulgel.

CONCLUSION

After thorough literature survey, we reached into a conclusion that emulgels have proven as most convenient, better, and effective delivery system. Due to its non-greasy, gel-like property, it provides and lacks of oily bases, and it provides better release of drugs as compared to other topical drug delivery system. Incorporation of emulsion into gel makes it a dual control release system further problem such as phase separation, creaming associated with emulsion gets resolved, and its stability improves. Emulgel loaded with specific drugs has been found effective in some topical disorders, and it is emerging as potential drug delivery system in the area of dermatology. In future, emulgel will provide a solution for topical delivery of hydrophobic drugs.

Many of drugs that have utility in the treatment of skin disorders are hydrophobic in nature. Such drugs can be delivered in the form of emulgel where they can be incorporated in the oil phase of the emulsion and combined with gel. Drugs which are still unexplored in this area are Retinoic acid, Adapalene, Tolnaftate, Betamethasone, Dexamethasone, etc.

REFERENCES

1. Pant S, Badola A, Baluni S, Pant W. A review on emulgel novel approach for topical drug delivery system. World J Pharm Pharm Sci 2015;4:1728-43.
2. Sonaje S, Gondkar S, Saudagar R. Gellified emulsion: A new born formulation for topical delivery of hydrophobic drugs. World J Pharm Pharm Sci 2013:3:233-51.
3. Yadav S, Mishra M, Tiwari A, Shukla A. Emulgel: A novel approach for enhanced topical drug delivery. Int J Curr Pharm Res 2017;9:15-9.
4. Hardenia A, Jayronia S, Jain S. Emulgel: An emergent tool in topical drug delivery. Int J Pharm Sci Res 2014;5:1653-60.
5. Vats S, Saxena C, Easwari T, Shukla V. Emulsion based gel technique: Novel approach for enhancing topical drug delivery of hydrophobic drugs. Int J Pharm Sci Res 2014;3:2277-7873.
6. More S, Nandgude T, Poddar S. Vesicles as a tool for enhanced topical drug delivery. Asian J Pharm 2016;10:S196-209.
7. Ashara K, Shah K. Emulgel: A novel drug delivery system. J Prev Alzheimer' Dis 2016;26:243-9.
8. Kuller R, Saini S, Seth N, Rana AC. Emulgel: A surrogate approach for topical used hydrophobic drugs. Int J Pharm Sci 2011;1:117-28.
9. Sharma S. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Pharm Rev 2008;6:278-87.
10. Dadwal M. Emulgel: A novel approach to topical drug delivery. Int J Pharm Sci 2013;4:847-56.
11. Aher SD, Banerjee SK, Gadhave MV, Gaikawad DD. Emulgel: A new dosage form for topical drug delivery. Int J Inst Pharm Life Sci 2013;3:1-10.
12. Ajazuddin A, Alexander A, Khichariya A, Gupta S, Patel RJ. Recent expansion in an emergent novel drug delivery technology: Emulgel. J Controlled Release 2013;171:122-32.
13. Singla V, Saini S, Joshi B, Rana AC. Emulgel: A new platform for topical drug delivery. Int J Pharm Sci 2012;3:485-98.
14. Mortazavi SA, Aboofazeli R. An investigation into the effect of various penetration enhancers on percutaneous absorption of piroxicam. Int J Pharm Res 2003;135-40.
15. Rieger MM, Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia, PA: Lea and Febiger; 1986. p. 502-33.
16. Sathe S, Bagade M, Nandgude T, Kore K, Shete R. Formulation and evaluation of thermo reversible *in-situ* nasal gel of terbutaline sulphate. Indo Am J Pharm Res 2015;5:3680-7.
17. Nandgude T, Thube R, Jaiswal N, Deshmukh P, Chatap V, Hire N. Formulation and evaluation of pH induced *in-situ* nasal gel of salbutamol sulphate. Int J Pharm Sci Nanotechnol 2008;1:177-82.
18. Taufik BN, Adhav AJ, Payghan SA. Composition of terbinafine HCL polymeric gel for mucosal drug delivery. Int J Biol Pharm Allied Sci 2016;5:2146-68.
19. Payghan SA, Mane YV, Kate VK, Tamboli ZJ. Anhydrous emulsion: Vehicles for topical delivery of ketoconazole. Inventi Impact NDDS 2015;1:43-53.
20. Jadhav CM, Kate V, Payghan SA. Formulation and evaluation of antifungal non-aqueous microemulsion for topical drug delivery of griseofulvin. Inventi Impact Pharm Tech 2015;1:38-50.

21. Upadhyaya S, Chauhan S, Kothiyal P. Emulgel: A boon for dermatological diseases. Int J Pharm Res Sci 2014;3:1-9.
22. Kaushal R, Basarkar G. Formulation development and *in vitro* evaluation of terbinafine hydrochloride emulgel for topical fungal infection. Int J Pharm Sci 2013;21:168-73.
23. Khaled M, Satha M Subhi S, Fahmy U. Ketoprofen emulgel: Preparation, characterization and pharmacodynamic evaluation. Int J Pharm Sci 2013;20:306-10.
24. Khullar R, Kumar D, Seth N, Saini S. Formulation and evaluation of mefenamic acid emulgel for topical delivery. Sci Pharm J 2012;20:63-7.
25. Magdy M. Optimization of chlorfenrs in emulgel formulation. Am Assoc Pharm Sci J 2004;6:1-7.
26. Khunt D, Mishra A, Shah D. Formulation design and development of piroxicam emulgel Int J Pharm Res 2012;4:1332-44.
27. Bhanu P, Shanmugum V. Development and optimization of diclofenacemulgel for topical drug delivery. Int J Clin Pract 2011;9:1-4.
28. Marwaha T, Bhise K. Formulation design and evaluation of anti psoriatic emulgel. J Pharm Sci Innov 2013;2:30-42.
29. Yehia K, Abeer K. Preparation and evaluation of physical and rheological properties of clotrimazoleemulgel. Int J Pharm Sci 2011;20:19-27.
30. Joshi B, Singh G, Rana A, Saini S. Development and characterization of clarithromycin emulgel for topical delivery. Int J Drug Dev Res 2012;4:310-23.
31. Ranga P, Sellakumar V, Natranjan R, Mohan K. Formulation and *in vitro* evaluation of ciprofloxacin loaded topical Emulgel. Int J Pharmacol Clin Sci 2012;1:232-7.
32. Mohamad M. Optimization of chlorphen is in emulgel formulation. Am Assoc Pharm Sci J 2014;6:1-5.
33. Wang M, Fang L. Percutaneous absorption of diclofenac acid and its salts from emulgel. Asian J Pharm Sci 2008;3:131-8.
34. Jain A, Jain S, Vyas N, Deveda P. Development of antifungal emulsion based gel for topical fungal infection. Int J Periodont Restorat Dent 2011;2:18-23.
35. Deveda P, Jain A, Vyas N, Jain S, Khambete H. Gellified emulsion for sustain delivery of itraconazole for topical fungal diseases. Int J Pharm Sci 2010;2:104-12.
36. Wesley Z, Gude R. Formulation, design, development and evaluation of emulgel for topical delivery of meloxicam in the treatment of rheumatoid arthritis. Indo Am J Pharm Res 2015;5:1271-6.
37. Effionora A, Delly R, Harmita E. Formulation and Evaluation Gel and Emulgel of Chilli Extract (Capsicum Frutescens) As Topical Dosage Form. International Journal of Pharmacy and Pharmaceutical Science 2014; 6(3): 13-16.
38. Sundari P, Mullapudi D, Srinivas P. Formulation and Evaluation of Anti-Arthritic Poly Herbal Emulgel. International Journal of Pharmaceutical Technology 2014; 6(2): 6608-6621.
39. Shaheda S, Devi S, Nirmala J. Formulation and evaluation of herbal emulgel of *Lantana camara* leaves extract for wound healing activity in diabetic rats. Indo Am J Pharm Res 2016;6:6404-17.
40. Kusuma R, Rao S. Formulation, development and evaluation of indomethacin emulgel using pregelatinized starch from *Ipomoea batata* Tubers. Asian J Pharm 2015;9:43-50.
41. Bhura R, Bhagat K. Formulation and evaluation of topical nano emulgel of adapalene. World J Pharm Pharm Sci 2015;3:1013-24.
42. Kumar V, Mahant S, Rao R, Nanda S. Emulgel based topical delivery system for loratadine. ADMET DMPK 2014;2:254-71.
43. Sawant A, Mohite S. Formulation and evaluation of itraconazole emulgel for topical drug delivery. Asian J Pharmacol Toxicol 2015;5:91-6.
44. Ambala R, Vemula S. Formulation and characterization of ketoprofen emulgels. J Appl Pharm Sci 2015;5:112-7.
45. Mulye S, Wadkar K, Kondawar M. Formulation development and evaluation of indomethacin emulgel. Pelagia Res Der Pharm Sin 2013;4:31-45.

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