Indo Global Journal of Pharmaceutical Sciences, 2022; 12: 92-103

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Emulgel – Emerging as a Smarter Value-Added Product Line Extension for Topical Preparation

Neelam Patel [1,2], Sunita Chaudhary [2,3], Ankit Chaudhary [4]

[1] *SAL Institute of Pharmacy, Department of Pharmaceutics, Ahmedabad, Gujarat – 380060, India*

[2] *Gujarat Technological University, Ahmedabad, Gujarat- 382424, India*

[3] *Arihant School of Pharmacy and Bio- Research Institute, Department of Pharmaceutics, Ahmedabad, Gujarat -382421, India*

[4] *Saraswati Institute of Pharmaceutical Science, Department of Pharmaceutical Analysis, Gandhinagar, Gujarat-382355, India*

Address for Correspondence: Neelam Patel, patel.neelam86@gmail.com

Received: 12.03.2020
Accepted: 06.10.2020
Published: 31.01.2022
Keywords
Emulgel, Hydrophobic drug, Topical product, Semisolid.

ABSTRACT: Topical products applied to skin in consistency from liquids to powder in formulation but the most popular product is semisolid preparation. In semisolid preparation comparison with others, the use of gels has been emerged for both in dermatology and cosmetology. Despite of many advantages of gels one limitation for in delivery of hydrophobic drug moiety. Emulgel technique contains both oil and aqueous gel base so it can be used for hydrophobic drugs. Emulgel technique also useful for product line extension for drug available in ointment and cream formulation. Emulgel can also provide local concentration of drug in affected area so it is more effective than regular gel in curative aspects and more depth permeation of drug. Emulgel are thermodynamically stable systems having several features like enhanced permeability; prolong drug release, stability of emulsion and good thermodynamic stability. From this review, we get the knowledge about emulgel formulation, advantages, characterization and recent advances in the research field.

Cite this article as: Patel, N.; Chaudhary, S.; Chaudhary, A. Emulgel – Emerging as a Smarter Value-Added Product Line Extension for Topical Preparation. Indo Global J. Pharm. Sci., 2022; 12: 92-103. **DOI**: http://doi.org/10.35652/IGJPS.2022.12008 .

INTRODUCTION

Topical drug delivery system has been used from centuries for the treatment of local skin disorders and is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as a topical route. Topical drug delivery system is defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders like acne or the cutaneous manifestations of a general disease like psoriasis or in local skin infection like fungal infection with intent of containing pharmacological or other effect of drug to the surface of the skin or within skin.[1] These are applying a wide spectrum of preparations for both cosmetic and dermatological, to their healthy or diseased skin.[2] A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. [3] Human skin is a uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body whilst 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.[4] Skin being the most readily accessible part of human body, the molecules on surface application easily penetrate the skin via three routes: through intact stratum corneum, through sweat ducts, and through sebaceous follicles.[5] Drug applied to the skin for their local action include antiseptics, antifungal agent and skin emollients. 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. [6, 7]

Table 1: Classification of Topical drug delivery system [8]

Solid Preparation	Liquid Preparation	Semisolid Preparation	Miscellaneous Preparation
Topical Powder Poultices Plaster	Lotion Liniment Paints Solution Emulsion Suspension	Ointment Cream Pastes Gel Suppository	Transdermal drug delivery system Tapes and Gauzes Rubbing Alcohols Liquid cleaner Topical aerosol

ADVANTAGES OF TOPICAL DRUG DELIVERY SYSTEM [9]

1. Avoidance of first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Improve patient compliance
5. Avoidance of the risks and inconveniences of intravenous therapy and of varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time
6. Suitability for self-medication.
7. Drug with short biological half-life and narrow therapeutic window can use this method.
8. Ability to stop medication when needed
9. Convenient and easy to apply**.**

DISADVANTAGES OF TOPICAL DRUG DELIVERY SYSTEM [9]

1. Skin irritation on contact dermatitis.
2. Possibility of allergenic reactions.
3. Poor permeability of some drug through skin.
4. Larger particle size drugs are not easy to absorb through the skin.

RATIONALE

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 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. [10]

A gel is a colloid that is typically 99% weight of 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. [11]

PHYSIOLOGY OF THE SKIN [5, 9]

The skin of average adult body covers surface area Approximately 2 m^2 and receive about one third of blood circulating through body. An average human skin surface is mainly contains forty to seventy hair follicles and two to three hundreds of sweat ducts per square meter of skin. The skin consists of several layers. The outer layer is called epidermis; the layer below the epidermis is called dermis. The dermis contains 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. Human skin surface is known to contain, on 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.

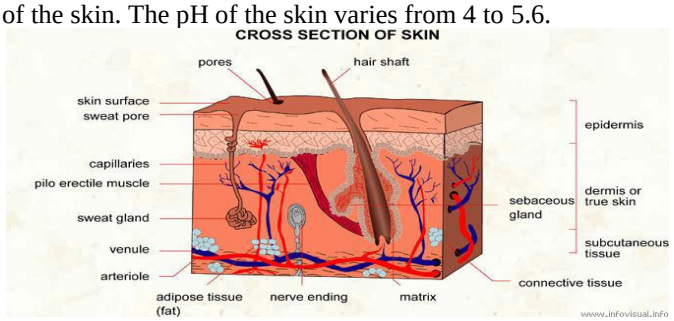

Figure 1: Cross section of skin

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG [8, 12]

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.

EMULGEL

In the mid-1980's, Emulsion-gels have been gaining importance in pharmaceutical topical semisolid dosage forms. Emulgel are emulsion, either of the oil-in-water or water-in-oil type, which is gelled by mixing with a gelling agent. [13, 14] Within the major group of semisolid preparation, the use of transparent gels has expanded widely both in cosmetics and in pharmaceutical preparations. [15] The USP defines gels as semisolid systems containing either suspensions made up of either small inorganic particles, or large organic molecules interpenetrated by a liquid. [16] Gel forms cross linked network where it captures small drug particles and provides its release in a controlled manner. Due to its mucoadhesive property it prolongs the contact period of medication over the skin. [17] Within biphasic liquid doses forms Emulsion is a controlled release system where entrapped, drug particles in internal phase pass through the external phase to the skin and slowly get absorbed. Internal phases act as reservoir of drug and slowly release drug in a controlled way through the external phase to the skin. [18] Inspire of many advantages of gels and emulsions a major limitation is their inability to delivery of hydrophobic drugs and instability during storage respectively. So to overcome these limitations an emulsion based approach i.e., Emulgel is being used so that a hydrophobic therapeutic moiety is successfully incorporated and enjoy the unique property of gels. [19] Since Emulgel possesses the property of both emulsion and gel it acts as dual control release system. Emulgel are a class of biphasic semisolid formulation. Nowadays, they are being used for controlled delivery applications. Emulgel offer the capability of delivering both hydrophilic and lipophilic drug moieties due to presence of both aqueous and non-aqueous phases. It is suitably applied to the skin due to its non-greasy nature in comparison to other topical formulations such as ointments, creams etc. which are very much thick and require excess rubbing. [20] It is accepted that utility of any topical preparation lies on its penetration ability and refers to the disappearance of product or oiliness from skin. The processes of penetration into skin are simplified, if emulsion is thixotropic, i.e. if it becomes less viscous during shearing. Thus, to improve emulsion stability and penetration ability it is incorporated into gel. [21] Further, Emulgel for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, greater shelf life, bio-friendly, clear & pleasant appearance. [22, 23]

ADVANTAGES OF EMULGEL

1. Incorporation of hydrophobic drugs:[15]

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.

2. Better loading capacity:[3]

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.

3. Better stability:[12, 24]

Other transdermal preparations are comparatively less stable than emulgel. Like powders are hygroscopic, creams show phase inversion, or breaking and ointment show rancidity due to the oily base.

4. Production feasibility and low preparation cost:[17]

Preparation of emulgel comprises simpler and short steps which increase the feasibility of the production. There are no specialized instruments needed for the production of emulgel. Moreover, materials used are easily available and cheaper. Hence, decreases the production cost of emulgel.

5. Controlled release: [12, 24]

Emulgel can be used to prolong the effect of drugs having shorterT1/2. It can be used for both hydrophobic drugs (o/w emulgel) and hydrophilic drugs (w/o emulgel).

6. No intensive sonication: [12, 24]

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 emulgel as no sonication is needed.

7. Improve Patient Compliance: [25, 26, 27]

They are less greasy and easy to apply. More selective to a specific site. It increases the contact time and mean residence time of the drug. It is a non-invasive mode of drug delivery with no trauma, or risk of infection. Emulgel are used even for the cosmetic purposes.

DISADVANTAGES OF EMULGEL [9, 28, 29]

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.

IDEAL PROPERTIES OF DRUG CANDIDATE TO FORMULATE AS EMULGEL [30]

1. Drug dose should be low i.e. less than 10 mg.
2. Molecular weight of drug should be 400 Dalton or less
3. Half-life of drug 10 hr or less
4. Partition coefficient i.e. Log p (Octanol-water) between 0.4-0.8
5. Having a skin –permeability coefficient more than
6. Oral bioavailability and therapeutic index should be low.
7. Drug should be non-irritating and non-sensitizer having a less polarity

IMPORTANT CONSTITUENTS OF EMULGEL PREPARATION

Ideal properties of additives [31]

- They must be non-toxic.
- They must be commercially available in acceptable grades.
- Their cost must be acceptably cheap.
- They must not be contraindicated.
- They must be physically and chemically stable by themselves and in combination with drugs and other components.
- They must be colour compatible.

Drug substances

Mainly NSAID's agent, antibacterial agent, antifungal agent etc. can be used for delivery of drug across the skin. The reasonable choice of the drug plays an important role in successful development of a topical drug delivery product. Some of desirable properties of drug that effect its diffusion through the device as well as through skin are as follow:

Physicochemical properties

- Molecular weight of drug should be less than 500 Daltons.
- Drug should have better affinity for both hydrophilic and hydrophobic phases.
- Drug should have a low melting point.
- Drug should not be highly acidic or alkaline in solution.
- pH of saturated aqueous solution of drug should be in range of 5 - 9.

Biological properties

- The drug should be potent enough.
- Half-life of drug should be short.
- Drug should not induce any allergic reactions or trauma.
- The drug should not be immunogenic.
- Drugs, which degrade in gastrointestinal tract or are inactivated by hepatic first pass effect, are suitable for topical delivery.
- Tolerance to the drug must not develop under the near zero order release profile of topical delivery.
- Drugs, which have to be administered for a long time or which cause adverse effects to non-targeted tissue can also be formulated for topical delivery. [32]

FORMULATION OF EMULGEL

1. Vehicle [3]

Drug potency and therapeutic effectiveness of a dosage form depend on the vehicle and its composition that influences the rate and extent of absorption (bioavailability). Two factors are of critical importance in the rational design of dermatologic vehicles that maximize bioavailability i.e., solubilising the drug in vehicle and maximizing partitioning of drug from vehicle to stratum corneum. [33]

Ideal Properties of Vehicles: [2, 34]

- 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 phase

For the preparation of aqueous phase of the emulgel, aqueous materials are required. Commonly used aqueous phase agents are normal water, distilled water, alcohol. [9]

Oil Phase

For the preparation of oily phase of emulgel oily materials are required. Most widely used oils for externally applied emulsions are mineral oils either alone or in combination with soft or hard paraffin. It works both as vehicle for the drug and for their occlusive and sensory characteristics. [35] The oil phase may include a wide variety of lipid of natural or synthetic origin. The consistency of these lipids may range from mobile liquids to high solids. Depending on their application, properties, and utility different oils are used for formulation. [36] Naturally occurring oils and fats are mixture of triglycerides, which contains fatty acids of varying chain lengths and degrees of unsaturation. The melting point of particular oil is directly proportional to degree of unsaturation, which also increases the relative susceptibility to oxidation. To decrease the degree of unsaturation and conferring resistance to oxidative degradation these might be hydrogenated synthetically. Both long chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used for the formulation of Transdermal Drug Delivery System (TDDS). Modified or hydrolysed vegetable or edible oils have contributed widely to the success of TDDS owing to

their formulation and physiological advantages. Several semi synthetic liquids and thermo softening (semisolid) excipients, usually prepared by chemically combining medium chain saturated fatty acids or glycerides from natural oils are also used in topical formulations. [37, 38]

Table 2: Examples of oils used in Emulgel formulation

Name of oils	Properties	Reference No.
Olive oil	Antioxidant, antimicrobial	39
Castor oil	Topical NSAIDS, antioxidants	40
Thyme oil	Topical antibiotics, topical NSAIDs	41
Myrrh oil	Antifungal, antiviral	42
Wheat germ oil	Topical steroids, topical NSAIDs, drugs for psoriasis	43
Balsam oil	Antifungals, topical antibiotics	44
Wool wax	Antimicrobials, antifungal	45
Rose hip oil	Topical steroids, topical NSAIDs, drugs	46
Birch oil	Topical NSAIDs, corticosteroids, anti-microbial	47
Isopropyl myristate	Drugs for acne, topical steroids	48
Geranium oil	insecticidal and anti-bacterial	49
Light liquid paraffin	--	44

2. Emulsifying agents

The choice of emulsifying agents to be used are depend not only on its emulsifying ability, but also on its route of administration and, consequently, on its toxicity. Each surfactant is allocated an HLB number representing the relative proportions of the lipophilic and hydrophilic parts of the molecule. High numbers indicate a surfactant exhibiting mainly hydrophilic or polar properties, whereas low numbers represent lipophilic or non-polar characteristics. The inclusion of an emulsifying agents is necessary to facilitate actual emulsification during manufacture, and also to ensure emulsion stability during the shelf-life of the product. [50] The selection of a suitable emulsifying agent & its appropriate concentration are mattered of experience and of trial & error. [51] Emulgel was developed using tween 20 as emulsifier in its aqueous phase & span 20 in its oily phase. [52] Some of the example of emulsifier is Polyethylene Glycol Stearate, Sorbitan Monooleate (Span 80), Polyoxyethylene Sorbitan Monooleate (Tween 80), Stearic Acid, and Sodium Stearate. [53]

3. Gelling agent

These are those agents who impart the consistency of any dosage form and provide a gelled structure. Gel–sols–gel behaviour imparts stability as well as improves bioavailability of system. However, stability of system can be affected by many factors like pH, temperature, polymer concentrations, polymer modification or combinations, addition of cations or anions. [54] Gelling agents are of three types natural (Gelatin, Xanthan gum), semi synthetic (Carboxy methyl cellulose, HPMC) and synthetic (Carbopol, Polyacrylamide). [55]

Table 3: Examples of Gelling agents used in Emulgel formulation [56, 57, 58]

Gelling agents	Advantages	Concentration
HPMC	Produce neutral gels of very stable viscosity, microbial resistance & good film strength	2.5%
Pluronic® F127	Have better solubility in cold water with good clarity	1–3%
Carbopol 934	Form gels at very low concentrations & provide control release of incorporated drug	1%
Carbopol 940	Form highly viscous gels and provide controlled release of incorporated drug	1%
Combination of HPMC &Carbopol	Combination produces more stable emulsion in comparison with individual gelling agents	1.2%
NaCMC	Suitable for sterile gels as	3–4%
Pemulen	Has excellent stability, low irritancy & provide rapid release of oil phase	0.1–0.4%

4. Penetration Enhancers [59, 60]

The agents which increase the penetration power of the drug through skin are known as Penetration enhancers. In order to promote absorption of drugs through skin barrier, vehicles often include penetration enhancing agents which temporarily disrupts the highly ordered structure of stratum corneum skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin · Examples of Penetration Enhancers are Oleic acid, Lecithine, Urea, Isopropyl myristate, Linoleic acid, Clove oil, Mentha oil, and Eucalyptus oil.

5. Preservatives

These are **t**hose agents which prevent or retard microbial growth and thus protect formulation from spoilage. The commonly used preservatives are Propyl paraben, methyl paraben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol etc.

6. Antioxidants

Butylated Hydroxy Toluene (BHT), Ascorbyl palmitate, Butylated hydroxyl anisole (BHA), etc.

7. Humectants

These are used to minimize water loss from formulation; they prevent drying out and improve their rubbing qualities and consistency. Ex. Glycerin, Propylene glycol, etc. [61].

PREPARATION OF EMULGEL

The methodology for preparation of emulgel includes three steps:

Step 1: Formulation of gel base: The gel phase is set up by dissolving the polymer in the purified water with enduring mixing at moderate speed using mechanical shaker and the pH was adjusted to 6-6.5 using triethanolamine or NaOH.

Step 2: Formulation of o/w or w/o kind of emulsion: Oil phase of the emulsion is set up by dissolving emulsifier e.g. span in oil vehicle like liquid paraffin while the water phase is set up by dissolving hydrophilic emulsifier like tween in purified water. Methyl paraben and propyl paraben are dissolved in humectants like propylene glycol and drug is dissolved in ethanol and both the prepared solutions are mixed with watery phase with consistent blending. Both the oily and aqueous phase are freely warmed to 70°C to 80°C, then the oily phase is added to aqueous phase with constant blending. This mix is allowed to cool to room temperature to shape an emulsion.

Step 3: Incorporation of emulsion into gel base with steady blending: the gel stage is mixed into the emulsion stage in the extent of 1:1 to procure emulgel. [62, 63]

CHARACTERIZATION OF EMULGEL

Physical examination [64, 65]

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

pH Measurement

The pH value of a prepared emulgel is measured by using a Digital pH Meter. 1 gm of emulgel is dissolved in 100 ml distilled water to make 1% aqueous solution of emulgel and stirred well until it forms uniform suspension. Undisturbed the system for 2 hours. After 2 hours, the pH is measured by dipping the glass electrode in the suspension and is done in triplicate and average values are calculated. [11]

Globule size and its distribution in emulgel

Globule size and distribution was determined by Optical Microscope. A compound microscope is used for examination and the globules are observed under 40 X magnification. Prior to observation, the eye-piece micrometer is calibrated with a stage micrometer and calibration factor are obtained. Subsequently, mean globule sizes are calculated. [10]

Rheological studies

The rheological properties of prepared emulgel are observed using Cone and Plate Brookfield Viscometer. The assembly is connected to thermostatically controlled circulating water bath maintained at 25℃. The prepared emulgel is transferred into a sample holder that is covered with thermostatic jacket. The particular spindle is immersed into the sample and can be allowed to rotate freely at particular speed and viscosity of formulation can be measured at 2 min. and is done in triplicate and average values are calculated. [66]

Spreading coefficient [23]

One of the ideal properties of an emulgel is that it should possess better Spreadability. It is term used to denote the extend of area to which emulgel readily spreads on application to the skin or affected area. Spreadability is determined by apparatus suggested by Multimer *et. al.* (1956) which is consists of a wooden block and is attached by a pulley at one end. Spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgel. A ground glass slide is fixed on this block. About 2 gm of prepared emulgel is placed on this ground slide. The emulgel is then squeezed between this slide and another glass slide having the same dimension of subjected fixed ground slide and equipped with the hook. Weight of 1 Kg is placed on the top of the two slides for about 5 minutes to expel air and to offer a homogenous film of the emulgel between the two slides. Excess of the emulgel is dispose of from the edges. With the help of a hook, measured quantity of weight is fixed on the top plate and the time in second taken by two slides to slip off from emulgel is noted. Minimum time taken for detached of two slides, better the Spreadability.

It is estimated by using formula as follows: $S = M.L/T$

Where, S = Spreadability,
M = Weight bounded to upper slide,
L = Length of glass slides
T = Time taken to detach the slides

The therapeutic efficacy of a formulation also depends upon Spreadability.

Swelling index [3]

To determine the swelling index of prepared topical emulgel, 1 g of gel is taken on porous aluminium 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

Extrudability study [5]

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 extrudability. 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 cm2)

Syneresis measurement test [67]

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

Phase Separation

The emulgel formulation are subjected to centrifugation at 10,000 rpm for 10 min and examined for any change in phase separation. [68]

Drug content determination [69]

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)

***In-Vitro* Drug Release Study [68]**

The *in- vitro* drug release studies are performed using a Franz diffusion cell. Prepared emulgel formulation is applied onto the surface of dialysis membrane which is fixed between donor and receptor compartment of Franze Diffusion cell. To solubilise the drug, freshly prepared phosphate buffer solution having pH 7.4 is used as dissolution medium and filled inside the receptor compartment. The temperature of Franze Diffusion cell is maintained at 37℃ by circulating water jacket. The assembly is kept on a magnetic stirrer for continuous stirring. 5 ml sample is withdrawn at suitable time intervals and replaced with equal amount of fresh dissolution medium to maintain the sink condition. The aliquots are collected and analysed by UV-Vis Spectrophotometer at particular wavelength and cumulative percentage drug release is calculated as a function of time.

***Ex–vivo* Bioadhesive strength measurement of topical emulgel: [25]**

(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 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 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 bioadhesive strength is calculated by using following:

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

Skin irritation test

For testing skin irritation studies, the approval is needed by Institutional Animal Ethics Committee. The test is performed on male Wistar Albino rats weighing 200-250 gm. Standard laboratory conditions are provided to animals with temperature of 25 ± 1℃ and relative humidity of 55 ± 5%. The hairs on the dorsal side are removed by hair removal cream (Anne French or by using electric hair clipper) from an area 2 cm^2 to make a hairless area. The rats are randomly divided into three equal groups.

Group I receive 0.8% v/v aqueous solution of formalin as a standard irritant.
Group II receives an optimized formulation 100 mg.
Group III serves as control, no application.

The formulation is washed after 24 hours and skin is examined for any sign of symptoms *i.e.*, change in colour, change in skin morphology, any sign of erythema and oedema. The animals are applied with fresh emulgel or fresh formalin solution, each day up to 6 days. The resulting reactions are compared against control group. [70]

***In vivo* anti-inflammatory study**

In vivo anti-inflammatory study is performed by using Wistar rats as animal model weighing approximately 200-250 gm each. For the study animals are divided into three groups i.e. the Control, Standard and test. Each group containing 6 animals,

GROUP I (Control Group): Carragenan (1%) is administered in the plantar surface of rat.
GROUP II (Standard group): Topical marketed emulgel gel +Carragenan.
GROUP III (Test Group): Optimized formulation +Carragenan.

Edema is induced on the left hind paw of the rats by sub plantar injection of 1% Carragenan. The test formulation and Standard are applied 30 min before carrageenan administration. The paw volume is measured at intervals of 30, 60, 90, 120, 150 and 180 min by mercury displacement method using Plethysmos meter.
The percentage inhibition of paw edema in drug treated group is compared with Carragenan control group and calculated according to the formula:

$$\% \text{ Inhibition of the drug} = \frac{Vc - Vt}{Vc} \times 100$$

Where, Vc = inflammatory increase in paw volume of control group

Vt= inflammatory increase in paw volume in (drug + Carragenan) treated animals. [71]

Microbiological assay

Ditch plate technique is used for evaluation of bacteriostatic or fungi static activity of a compound. It is mainly applied for semisolid preparations. Previously prepared Sabouraud's agar dried plates were used. Three grams of emulgel are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth was observed, and the percentage inhibition was measured as follows.

% Inhibition = L2 / L1 x 100

Where L1 = total length of the streaked, L2 = length of inhibition. [70]

CURRENT STUDY AND DEVELOPMENT ON EMULGEL FORMULATION

1. Salem HF, et. al., (2019) work done on Nano sized nasal emulgel of resveratrol: preparation, optimization, in vitro evaluation and in vivo pharmacokinetic study. Nano emulgel prepared Using Carbopol 934 and Poloxamer 407 as the gelling agents and Tween 20, Capryol 90, and Transcutol as a surfactant and co-surfactant in different ratio. The optimized nasal nano-emulgel established intranasal safety and bioavailability enhancement so it is considered as a well-designed system to target the brain.[72]
2. Pal RR, et. al., (2019) work done on Tamanu oil potentiated novel sericin emulgel of Levocetirizine: repurposing for topical delivery against DNCB-induced atopic dermatitis, QbD based development and in vivo evaluation. In this study use Tamanu oil based microemulsion and it was optimised utilising Box-Behnken design. The optimised formulation was further incorporated into sericin gel to form emulgel. From *In vivo* pharmacodynamic studies revealed enhanced therapeutic potential of emulgel in terms of reduced scratching frequency and erythema score when compared with conventional gel.[73]
3. Mohamed MI, et. al., (2019) work done on Preparation and evaluation of optimized Zolmitriptan niosomal emulgel. In this study design twelve formulations using Box-Behnken. Ztolmitriptan loaded niosomes were prepared by the thin film hydration method using Span 60, Span 80 along with cholesterol at three different levels. Optimized formulation give transdermal drug delivery system to treat both topical and systemic diseases.[74]
4. EI- salamouni NS, et. al., (2019) work done on Evaluation of chamomile oil and nanoemulgels as a promising treatment option for atopic dermatitis induced in rats. Formulations were developed comprising chamomile oil: olive oil (1:1), Tween 20/80 or Gelucire 44/14 as surfactant-co surfactant mixtures, propylene glycol (10%w/w), water and hydroxypropyl methylcellulose (3%w/w). Treatment with nanoemulgels showed a two-fold decrease in duration of skin healing and no spongiosis compared to chamomile oil.[75]
5. Mahajan VR, et. al., (2019) work done on Formulation design, development and characterization of dexibuprofen emulgel for topical delivery: In-vitro and In-vivo evaluation. The objective of the study was to prepare emulgel of Dexibuprofen, a NSAID, using Carbapol 940 as a gelling agent. Clove oil and Mentha oil were used as penetration enhancers. When compare with marketed preparation diclofenac sodium gel the topical emulgel of Dexibuprofen possess an effective anti-inflammatory and analgesic activity.[76]
6. Sekar M, et. al., (2019) work done on Formulation and evaluation of embelin emulgel for topical delivery. Emulsion prepared by dissolving Span 20, embelin and butylated hydroxy toluene in olive oil and Tween 60 in distilled water. For gel formulation use carbomer as gelling agent. The formulations were evaluated for physicochemical properties and tested for in vitro antioxidant activity and in vitro anti-inflammatory activity by inhibition of albumin denaturation and lipoxygenase inhibition.[77]
7. Khule PK, et. al., (2019) work done on Formulation and Evaluation of Itraconazole Emulgel for Various Fungus. To enhancing the topical delivery of Itraconazole by preparing emulgel using natural gelling agents' xanthan gum and guar gum. In 0.75% and 1% concentration. The prepared formulations were evaluated for their physical appearance, viscosity, drug release, globule size, skin irritation test, antifungal activity, and stability. Xanthan gum 0.75 % show optimum result. [78]
8. Kumar R, et. al., (2019) work done on Development and evaluation of polyherbal emulgel formulation. In this formulation carbopol 934 is used as gelling agent. Oil phase is prepared by dissolving span 80 in liquid paraffin and aqueous phase with extract in aqueous solvent.[79]
9. Shelke O, et. al., (2019) work done on Formulation, Development and Evaluation of Nifedipine Emulgel for Treatment of Anal Fissures using Polymeric Emulsifiers. Emulgel formulations are prepared with the lowest concentration of emulsifiers 1.5-4.0%. Light liquid paraffin as oil and Sorbitan monooleate and Polysorbate 20 used as surfactants.[80]

Table -4: Marketed formulations of emulgel [81]

Product name	Drug name	Manufacturer
Voltaren emulgel	Diclofenac-diethyl-ammonium	Novartis pharma
Miconaz-H-Emulgel	Miconazole nitrate, hydrocortisone	Medical union pharmaceutic

		als
Diclobaremulgel	Diclofenac diethyl amine	Barakatpharma
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

FUTURE PROSPECTIVE

During formulation and development of any new dosage form the most common dilemma faced from hydrophobic behaviour of drugs which ultimately leads to poor water solubility and bioavailability problems. Because of hydrophobic nature of many drugs delivery of these to the biological system have be challenging. Creams, ointments and lotion are of different types of drug delivery system which has been applied topically have excellent emollient properties but retards the release of drugs due to presence of oleaginous bases such as petrolatum, bees wax or vegetable oils that themselves are hydrophobic in nature that do not allow the inclusion of water or aqueous phase. As compared to other topical systems gel provides quicker release of drug because gel provides aqueous environment to drugs. Hydrophobic drug can be incorporated in oily base and delivered to skin by using emulgel. All such points of interest of Emulgel over other topical drug delivery systems make them more effective and profitable. In future these properties will be utilized to convey more number of topical medications as Emulgel.

CONCLUSION

After thorough literature survey, we reached into a conclusion that emulgel 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.

ACKNOWLEDGEMENT

The authors would like to gratefully acknowledge all cooperation from their respective institutions.

CONFLICT OF INTEREST

The authors confirm no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not declared.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

AUTHOR CONTRIBUTIONS

The entire study was conceptualized, designed and conducted the study with the help of other authors, wrote the first draft of the manuscript, and other authors contributed significantly to the revision of the manuscript. All Authors read and approved the final manuscript.

SOURCE OF FUNDING

Declared none.

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Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in CrossRef (DOI Enabling), CNKI, EMBASE (Elsevier), National Library of Medicine (NLM) Catalog (NCBI), ResearchGate, Publons (Clarivate Analytics), CAS (ACS), Index Copernicus, Google Scholar and many more. For further details, visit http://iglobaljournal.com