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EMULGEL: A NOVEL APPROACH FOR HYDROPHOBIC DRUGS

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ABSTRACT

The topical drug delivery provides a direct accessibility to the skin as a target organ for diagnosis and treatment without fear of undergoing first pass metabolism. Emulgel is one of the novel technologies widely used for fungal infections, acne, psoriasis and other topical disorders. Emulgel is emulsion, either of o/w or w/o type, which are gelled by mixing with a gelling agent such as Carbapol, HPMC, etc. Major objective behind emulgel is to deliver hydrophobic drugs to systemic circulation via skin. It has the benefit dual release control system i.e., emulsion and gel. Emulgel for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, greater shelf life, bio-friendly, clear & pleasant appearance. Novel polymers are used which can function as emulsifier and thickener because the gelling capacity of these compounds give rise to stable emulsion and creams by decreasing surface and interfacial tension and as well as at same time increasing viscosity of aqueous phase. Multitudinous permeation enhancers can potentiate effect.

KEY WORDS

Emulgel, hydrophobic drugs, Topical drug delivery

Introduction:

Topical drug delivery system has been used for 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 with intent of containing pharmacological or other effect of drug to the surface of the skin or within skin [1]. Basically, there are two types of Topical drug delivery products, External topicals and Internal topicals. The external topicals are spread, sprayed or otherwise dispersed on the tissues to cover diseased area, while the internal topicals are applied to mucous membrane orally, vaginally or on the rectal tissues for local activity [2].

Table 1: Classification of Topical drug delivery system [3]

SOLID PREPARATION	LIQUID PREPARATION	SEMISOLID PREPARATION	MISCELLANEOUS PREPARATION
Topical Powder	Lotion	Ointment	Transdermal drug delivery system
Poultices	Liniment	Cream	
Plaster	Paints	Pastes	Tapes and Gauzes
	Solution	Gel	Rubbing Alcohols Liquid cleaner
	Emulsion	Suppository	
	Suspension		Topical aerosol

In Topical drug delivery system drug diffuses out of the delivery system reaches to the site of action and get absorbed by the skin. The release rates of the drugs from topical preparation depend directly on the physiochemical properties of the carrier and the drug employed [4].

Advantages of topical drug delivery system:

- Avoidance of first pass metabolism.
- 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 and narrow therapeutic window [5,6].

Disadvantages of topical drug delivery:

- Poor permeability of some drug through skin.
- Skin irritation on contact dermatitis.
- Drug of large particle size not easy to absorb through the skin.
- Possibility of allergic reactions [7].

Factors affecting topical absorption of drug:

(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 get absorbed well).
4. Effect of vehicles [8,9,10].

Factors to be considered when choosing a Topical Preparation:

- Effect of the vehicle e.g. an occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
- Match the type of preparation with the site. (e.g., gel or lotion for hairy areas).
- Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.
- Irritation or sensitization potential. Generally, ointments and w/o creams are less irritating, but gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern [11].

EMULGEL

In the mid-1980's, Emulsion-gels have been gaining importance in pharmaceutical topical semisolid dosage forms. Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent [12]. Within the major group of semisolid preparation, the use of transparent gels has expanded widely both in cosmetics and in pharmaceutical preparations [13]. 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 [14]. 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 [15]. 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 [16].

Inspite 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 [17]. 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 [18]. 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 [19]. 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 [20,21].

Advantages of emulgel:

Delivery of hydrophobic drugs: Due to the solubility problem, most of hydrophobic drugs cannot be introduced directly into gel base and thus problem arises during the release of the drug. With the help of Emulgel hydrophobic drugs are incorporated into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be well mixed into gel base. This may be providing better stability and release of drug.

Better loading capacity: Emulgel due to vast network have better loading capacity comparatively to other novel approaches like niosomes and liposomes. As they are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency.

Better stability: Other transdermal preparations are comparatively less stable than emulgel. Like powders are hygroscopic, creams show phase inversion or breaking, and ointment shows rancidity due to oily base. Such problems are not incountered in emulgel.

Production practibility and low preparation cost: Preparation of emulgel comprises of simpler and shorter steps which increases the possibility of the production. No specialized instruments are required for the production of emulgel. Moreover, additional materials used are easily available and inexpensive resulting in lower production cost.

Controlled Release: Emulgel can be used to prolong the effect of drugs having shorter half-life. It can be used for both hydrophobic drugs (o/w emulgel) and hydrophilic drugs (w/o emulgel).

No intensive sonication: Production of vesicular molecules requires intensive sonication which may result in drug degradation and leakage. But this problem can be avoiding during production of emulgel as no sonication is needed.

Improve Patient Compliance: 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 [22,23,24].

Disadvantages of emulgel:

1. Poor permeability of some drugs through skin.
2. Occurrence of bubble during formation of emulgel.
3. Drug of large particle size not easy to absorb through the skin.
4. Skin irritation or allergic reaction on contact dermatitis [25].

IMPORTANT CONSTITUENTS OF EMULGEL PREPARATION:

Ideal properties of additives

- ✓ 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 play an important role in successful development of a topical drug delivery products. 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 nor 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 [26].

Vehicle

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., solubilizing the drug in vehicle and maximizing partitioning of drug from vehicle to stratum corneum[27].

Properties of a Vehicle

- 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 patent [28].

Aqueous phase

For the preparation of aqueous phase of the emulgelaqueous materials are required. Commonly used aqueous phase agents are normal water, distilled water, alcohol [29].

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 paraffins. It works both as vehicle for the drug and for their occlusive and sensory characteristics. Non-biodegradable mineral and castor oils are widely used oils for oral preparations that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g., Arachis, cottonseed, and maize oils) are used as nutritional supplements [30]. 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[31].A number of natural oils from plant sources processed to remove impurities or to separate various fractions of the original product are available and suitable for use in topical formulation. 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 TDDS. Modified or hydrolyzed 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 [32,33].

Table 2: Examples of oils used in Emulgel formulation

Name of oils	Properties	Reference No.
Castor oil	Topical NASIDS, antioxidants	34
Olive oil	Antioxidant, antimicrobial	35, 36, 37
Wheat germ oil	Topical steroids, topical NSAIDs, drugs for psoriasis	38, 39,40
Wool wax	Antimicrobials, antifungal	41
Thyme oil	Topical antibiotics, topical NSAIDs	42, 43, 44, 45
Birch oil	Topical NSAIDs, corticosteroids, anti-microbials	46
Rose hip oil	Topical steroids, topical NSAIDs, drugs	47,48
Myrrh oil	Antifungal, antiviral	49
Geranium oil	insecticidal and anti-bacterial	50, 51
Isopropyl myristate	Drugs for acne, topical steroids	52, 53, 54
Balsam oil	Antifungals, topical antibiotics	55
Light liquid paraffin	--	56

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 [57].

The selection of a suitable emulsifying agent & its appropriate concentration are mattered of experience and of trial & error [58]. Emulgel was developed using tween 20 as emulsifier in its aqueous phase & span 20 in its oily phase [59]. Both surfactants are sorbitanlauric acid esters with the same cyclic structure. However, Tween 20 contains additional polyoxyethylene units. Tween surfactants are polysorbate molecules each attached to a hydrophilic head group of oligo (ethylene glycol) (OEG) chains and a hydrophobic tail of fatty acid ester moiety [60,61]. Emulgel for mucoadhesive buccal formulation was prepared using Polymeric emulsifier pemulen. Pemulens are hydrophobically-modified copolymers of acrylic acid (Acrylates/C10–C30 alkyl acrylates) that could act both, as primary emulsifiers for o/w emulsions and viscosity enhancing agents. They are able to stabilize o/w emulsions because their short lipophilic part integrates into the oil droplets while their long hydrophilic part forms a micro-gel around the droplet [62].

The drawback of surfactants are their toxicity which may raise problems regarding to health and environment. It can be replaced by using biosurfactant. Biosurfactant are produced by microbes and have short fatty acid tail and polar head groups. They are sticky to both hydrophilic and hydrophobic molecules. They have lower toxicity, high biodegradability and are environment friendly. It has better foaming properties and stability at extreme pH and temperature. They possess the characteristic property of reducing surface and interfacial tension using same mechanism as chemical surfactants. So these may serve as better option as emulsifier for disperse system (emulsions) and one could effectively take the advantage of its property. Various biosurfactant used in medical field are rhamnolipid obtained from *Pseudomonas aeruginosa*, surfactin (very powerful surfactant commonly used as an antibiotic) obtained from microbial strains of *Bacillus subtilis*. Some of the example of emulsifier is Polyethylene Glycol Stearate, Sorbitan Monooleate (Span 80), Polyoxyethylene Sorbitan Monooleate (Tween 80), Stearic Acid, and Sodium Stearate [63].

Gelling agent

These are those agents which imparts the consistency of any dosage form and provide a gelled structure. Administration of gelling agent to a system makes it thixotropic. According to the Swedish National Encyclopedia (1989–1996), thixotropy is “property of viscous (viscid) or gel-like product turning more liquid

as the longer time and the more vigorous, which is deformed (e.g. by stirring)." It is generally accepted that thixotropy is the phenomenon of the fluid which shows a reversible structural transition (i.e., gel–sol–gel conversion) due to the time-dependent changes in the viscosity induced by temperature, pH or other components without any changes in the volume of the system.Gel–sols–gel behavior 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 [64,65].

Gelling agents are of three types natural (Gelatin, Xanthin), semisynthetic (Carboxy methyl cellulose, HPMC) and synthetic (Carbopol, Polyacrylamide) [66].

HPMC is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer cellulose. It can be used as thickening agent, tablet binding, modified release and film coating agent [67]. Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol.They are produced from primary polymer particles of about 0.2 to 6.0 µm average diameter. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking. Carbomers readily absorb water, get hydrated and swell. Besides its hydrophilic nature, its cross-linked structure and it's insolubility in water makes carbopol a potential candidate for use in controlled release drug delivery system [68].

Table 3: Examples of Gelling agents used in Emulgel formulation

Gelling agents	Advantages	Concentration	Reference No.
HPMC	Produce neutral gels of very stable viscosity, microbial resistance & good film strength	2.5%	69, 70
Pluronic® F127	Have better solubility in cold water with good clarity	1–3%	71
Carbopol 934	Form gels at very low concentrations & provide control release of incorporated drug	1%	72, 73
Carbopol 940	Form highly viscous gels and provide controlled release of incorporated drug	1%	74, 75
Combination of HPMC &Carbopol	Combination produces more stable emulsion in comparison with individual gelling agents	1.2%	76, 77
NaCMC	Suitable for sterile gels as	3–4%	78
Pemulen	Has excellent stability, low irritancy & provide rapid release of oil phase	0.1–0.4%	79

Penetration Enhancers

The agents which increases 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 [80].

Mechanism of Penetration Enhancer

The penetration enhancers act by altering one of the 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[81,82].

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.

- ✓ They should work unidirectional i.e. should allow therapeuticagents into the body whilst 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'[83].

Table 4: Examples of Penetration Enhancers used for Emulgel

Penetration Enhancer	Quantity	Dosage form	Reference no.
Oleic acid	1%	Gel	84
Lecithine	5%	Gel	84
Urea	10%	Gel	84
Isopropyl myristate	5%	Gel	84
Linoleic acid	5%	Gel	85
Clove oil	8%	Emulgel	85
Mentha oil	5%	Emulgel	85
Eucalyptus oil	NA	None	86
Chinopodium oil	NA	None	86
Laurocapran	NA	None	86
Dimethyl sulphoxides	NA	None	86

Preservatives

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

Antioxidants

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

Humectant

These are used to minimize water loss from formulation, they prevent drying out and improve their rubbing qualities and consistency. Eg. Glycerin, Propylene glycol, etc[87].

PREPARATION OF EMULGEL

The methodology for preparation of emulgel include 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 humectant 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 cooled 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[88,89].

CHARACTERIZATION OF EMULGEL

Physical examination

The prepared emulgel formulations areanalysed visually for their appearance, colour, consistency, grittiness, homogeneity and phase separation [90].

Globule size and its distribution in emulgel

Globule size and distribution was determined byOptical Miscroscope. A compound microscope are used for examination and the globules are observed under 40 X magnification. Prior to observation, the eye-piece micrometer are calibrated with a stage micrometer and calibration factor are obtained. Subsequently, mean globule size are calculated [91].

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°C. The prepared emulgel is transfered 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 [92].

pH Measurement

The pH value of a prepared emulgel is measured by using a Digital pH Meter. Before use the pH meter is calibrate with standard buffer solution. 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 [93].

Spreading coefficient

One of the ideal property 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 Mutimer*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 emulgels. 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 off 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 spreadibility. It is estimated by using formula as follows:

$$S = \frac{\mathbf{M.L}}{\mathbf{T}}$$

where, S = spreadability,

M = Weight bouned 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[94,95].

Extrudability study

It is general confirmable test to estimate the forcerequired to extrude the emulgel from tube. Themethod practiced for verification of applied shear inthe region of the rheogram equivalent to a shearrate exceeding the yield value and exhibiting successive plug flow. The method can be based upon the percentage quantity of emulgel and emulgel extruded fromlacquered Aluminium collapsible tube on applicationof weight in grams mandatory to extrude atleast 0.5cm ribbon of emulgel in 10 seconds. Major quantityextruded more excellent is extrudability. The measurement ofextrudability of prepared emulgel formulation can be done triplicate andthe average values are represented. The extrudabilityis calculated by applying the following formula:

$$\boldsymbol{Extrudability} = \frac{\textbf{Applied weight to extrude emulgel from tube (in gm)}}{\textbf{Area (in cm sq)}}$$

The alternative method to determine the Extrudability of prepared emulgel can be done using hardness tester. Aluminium tube can be filled with 15 gm of emulgel. The plunger is adjusted to hold the tube suitably. 1kg/cm weight is applied for 30 second. The quantity of emulgel extruded can be weighed. The process can be repeated thrice at equidistance of the tubes [96].

Swelling Index

The Swelling Index of prepared topical emulgel is performed by taking weighed 1 gm of emulgel on porous aluminium foil and then kept aside undisturbed in a 50-ml beaker containing 10 ml 0.1 N NaOH. Then at different time intervals the sample is removed from beaker and put it on dry place for some time and reweighed it. Swelling index is calculated by using following formula:

$$SW\% = \frac{[\mathbf{Wt} - \mathbf{Wo}] * \mathbf{100}}{\mathbf{Wo}}$$

Where, SW% = Equilibrium percent swelling

Wo = Initial weight of emulgel at time zero

Wt = Weight of swollen emulgel after time t[97].

Syneresis measurement

Upon standing sometimes emulgel shrinks a bit and little liquid is pressed out. This phenomenon is known as syneresis. In this test, emulgel are put in cylindrical plastic tube with a perforated bottom which can be covered with filter paper (Whatmann No. 4). These tubes are then placed in centrifuge tubes and centrifuged for 15 min. The cylindrical plastic tube and liquid which had separated from emulgel can be weighed. The percentage of syneresis can be calculated as the ratio of weight of liquid separated from the emulgel to the total weight of emulgel before centrifugation and multiplied by 100. The data can be calculated [98].

Phase Separation

The emulgel formulation are subjected to centrifugation at 10,000 rpm for 10 min and examined for any change in phase separation [99].

Drug Content Determination

A known quantity of 1 gm of prepared emulgel formulation is dissolved in 100 ml methanol by mean of sonication. It is kept for 2 hours in a volumetric flask and shaken well with the help of shaker to mix it properly. Then solution is filtered through Millipore filter paper. UV/VIS spectrophotometer is used to measure the absorbance after suitable dilutions [100].

Drug content = (conc * dilution factor * volume taken * conversion factor)

***In-Vitro* Drug Release Study**

The in- vitro drug release studies are performed using a modified Franz diffusion cell (with effective diffusion area3.14 cm^2 and 15.5 ml cell volume). Prepared emulgel formulation is applied onto the surface of dialysismembrane which is fixed between donor and receptor compartment of FD cell. To solubilize 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 FD cell is maintained at 37°Cby 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 [101].

***Ex–vivo* Bioadhesive strength measurement of topical emulgel (MICE SHAVEN SKIN)**

The method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1N NaOH. Two pieces of skin were tied to the two glasses 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. To balance both the pans i.e., right and left pans the extra weight are added 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 ofair. 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 themeasure of bioadhesive strength. The bioadhesive strength is calculated by using following [102]:

Bioadhesive Strength = Weight required (in gms) / Area (cm^2)

Microbiological assay

Ditch plate technique was used. It is a technique used for evaluation of bacteriostatic or fungistatic 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 × 100

Where L1 = total length of the streaked culture,

L2 = length of inhibition [103,104].

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°C 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 upto 6 days. The resulting reactions are compared against control group [105-106].

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

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

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 subplantar 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 Plethysmometer.

The percentage inhibition of paw edema in drug treated group is compared with Carragenan control group and calculated according to the formula:

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

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

Vt= inflammatory increase in paw volume in (drug+Carragenan) treated animals [107].

Drug Release Kinetic Study

To analyse the mechanism of drug release from the topical gel, the release data were fitted to following equations

Zero – order equation:

$Q = K_0 t$

Where Q is the amount of drug released at time t, and $K_0$is the zero – order release rate.

First – order equation:

$\ln (100 - Q) = \ln 100 - K_1 t$

Where Q is the percentage of drug release at time t, and K_1 is the first – order release rate constant.

Higuchi's equation:

$Q = K_2 \sqrt{t}$

Where Q is the percentage of drug release at time t, and K_2 is the diffusion rate constant.

Hixson-Crowell:

The Hixson-Crowell cube root law describes the release from systems where there is a

change in surface area and diameter of particles of formulation.

$Q_0^{1/3} - Qt^{1/3} = K_{HC}\, t$

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in emulgel and KHC is the rate constant for Hixson-Crowell rate equation.

When this model is used, it is assumed that the release is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

Korsmeyer-Peppas Model:

Korsmeyer*et. al.* (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was

fitted in Korsmeyer–Peppas model:

$M_t / M_\infty = Kt^n$

Where Mt / M∞ are fraction of drug released at time t, k is the rate constant and n is the release exponent.

The n value is used to characterize different release mechanisms as given in table for cylindrical shaped matrices.

Table 5: Diffusion exponent and release mechanism [108]

Diffusion exponent (n)	Diffusion mechanism
<0.5	Fickian diffusion (Higuchi matrix)
0.5 < n < 1	Anamolous (non fickian diffusion)
1	Case-II transport (zero order release)
N > 1	Super case-II transport

Stability studies

Stability studies are performed according to ICH guidelines. The formulations are stored at different temperatures, 4 ± 2°C, 25 ± 2°C and 40 ± 2°C for a period of three months. The prepared emulgel are analyzed for the appearance, pH, drug content and in vitro diffusion studies at one-month intervals [109,110].

TABLE 6: Current investigations in emulgel using different drugs

Drug	Aim	Use	References
Amlodipine besylate	Preparation of amlodipine besylateemulgels for transdermal administration and its percutaneous permeability *in vitro*	Transdermal delivery	111
Acyclovir and ketoconazole	Topical delivery of acyclovir and ketoconazole	Viral and fungal cutaneous manifestations	112
Allopurinol	Design and development of allopurinol emulgel		113
Amphotericin B	Evaluation of the *in vivo* leishmanicidal activity of amphotericin B emulgel: An alternative for the treatment of skin leishmaniasis	Leishmaniasis therapy	114
Betamethasone dipropionate	Development of a topical ointment of betamethasone dipropionate loaded nanostructured lipid carrier	For the treatment of atopic dermatitis	115
Calcipotriol	Calcipotriol delivery into the skin as emulgel for effective permeation	In treatment of Psoriasis.	116
Cyclosporin A	Formulation and evaluation of Cyclosporin A emulgel for ocular delivery	Topical ocular delivery	117
Ciprofloxacin	Genipin-CrosslinkedGelatin-Based Emulgels: an Insight into the		118

	Thermal, Mechanical, and Electrical Studies		
Diclofenac sodium	Nanoemulsion-based gel formulation of diclofenac diethylamine: design, optimization, rheological behavior and in vitro diffusion studies	Management of pain	119
Diclofenac sodium	Evaluation of skin penetration of diclofenac from a novel topical non aqueous solution: A comparative bioavailability study	Pain relief	120
Ketoprofen	Formulation development, *in vitro* and *in vivo* evaluation of microemulsion-based gel loaded with ketoprofen	Anti-inflammatory	121
Lacidipine	Novel non-ionic surfactant proniosomes for transdermal delivery of lacidipine: optimization using 23 factorial design and in vivo evaluation in rabbits	Antihypertensive	122
LEVORAG® Emulgel : Hibiscus esculentus extract, Carboxymethyl beta-glucanDimethicone, glycerine, prunusamygdalusdulcis oil, boragoofficinalis seed oil Malvasylvestris extract, calendula officinalis extract, glycyrrhizaglabra extract	Prospective multicenter observational trial on the safety and efficacy of LEVORAG® Emulgel in the treatment of acute and chronic anal fissure	For treatment of acute and chronic anal fissure	123
Metronidazole and ciprofloxacin	Groundnut oil based emulsion gels for passive and iontophoretic delivery of therapeutics	Passive and iontophoretic delivery of therapeutics	124
Meloxicam	Formulation and characterisation of Meloxicam loaded emulgel for topical application	Anti-inflammatory	125
Nimorazole	Preparation and evaluation of Radiosensitizing agent Nimorazole in topical emulgel	hypoxic cell radiosensitizing agent	126
Pravastatin	Optimised transdermal delivery of pravastatin		127
Pinhão starch	Pinhão starch and coat extract as new natural cosmetic ingredients: Topical formulation stability and sensory analysis	Antioxidant activity	128
Terpinen-4-ol	The effect of rheological behavior and microstructure of the emulgels on the release and	Antimicrobial properties	129

	permeation profiles of Terpinen-4-ol		
Terbinafine hydrochloride	Formulation, development and *in-vitro* evaluation of Terbinafine hydrochloride emulgel for topical	In treatment of fungal infection	130

Table 7: Marketed formulations of emulgels

Drug	Marketed product	Manufacturer
Azithromycin	Avindo gel	CosmePharma Lab.
Aceclofenac, Methyl salisylate, Capsaicin	Acent gel	Intra Labs India Pvt. Ltd.
Benzoyl peroxide	Pernox gel	Cosme Remedies Ltd.
Clobetasol propionate	Topinate gel	SystopicPharma
Clotrimazole, BeclomethasoneDipropionate, Neomycin	Cloben gel	Indoco Remedies
Clindamycin phosphate, Allantion	Clinagel	StiefelPharma
Clindamycin, Adapalene	Excex gel	Zee Laboratories
Diclofenac diethyl ammonium	Voltarenemulgel	Novartis Pharma
Diclofenac diethyl amine	Diclobaremulgel	Barakatpharma
Diclofenac sodium	Pennsaid	Nuvopharma
Hibiscus, liqourice and natural extracts	Levorag® emulgel	THD Ltd.
Kojic acid, DipalmitateArbuti, Octinoxate	Kojivit gel	Micro Gratia Pharma
Miconazole nitrate, Hydrocortisone	Miconaz-H-emulgel	Medical union pharmaceuticals
Metronidazole, Clindamycin	Lupigyl gel	LupinPharma
Nadifloxacin	Nadicin cream	Psycho remedies
Tezarotene	Zorotene gel	Elder Pharmaceuticals

FUTURE PROSPECTIVE

During formulation and development of any new dosage form the most common dilemma faced from hydrophobic behavior 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 basessuch 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

Emulgels have proven as most convenient, better and effective delivery system. It provides gel like property due to its non-greasy nature and lacks oily bases therefore 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 and solves the 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 area of dermatology. In future Emulgel will provide a solution for topical delivery of hydrophobic drugs. Many of drugs that have utility in treatment of skin disorders are hydrophobic in nature. Such drugs can be delivered in the form of Emulgel where they can be incorporated in oil phase of emulsion and combined with gel. Drugs, which are still unexplored in this area, are Retinoic Acid, Adapalene, Tolnaftate, Betamethasone, Dexamethasone etc.

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