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Review Article
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Emulgel: A Recent Technique For Topical Drug Delivery- A Review

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ABSTRACT

Emulgels are preferred over other systems for topical medication administration due to a variety of features. They are typically used as skin emollients, protectants, antiseptics, and antifungal agents. The effectiveness of topical preparations depends on a number of variables, including the drug's solubility, lipophilicity, time in contact with the skin, and permeability. Many commonly used topical agents, such as ointments, creams, lotions, and gel, have drawbacks that include stability issues, stickiness and low spreading coefficient, irritability, allergic reactions, poor permeability, poor absorption, and difficulty in absorbing large molecules. To address this, the new concept of Emulgel has been introduced, with the primary goal of delivering hydrophobic drug molecules. In analgesics, anti-inflammatory, anti-fungal, anti-acne, and various cosmetic formulations, emulgel is used. With this method, polymers with improved effects on release patterns have emerged, allowing for regulated and sustained release. The difference between a traditional emulsion and an emulgel is the inclusion of a gelling ingredient in the water phase. These emulgel exhibit significant advantages on both innovative vesicular systems and traditional systems in a number of areas. Emulgels are thixotropic, greaseless, easily spreadable, readily removed, emollient, nonstaining, long shelf life, bio-friendly, clear, and have a beautiful look, all of which are advantageous for dermatological use.

Keywords: *Sustained and controlled release, Topical drug delivery system, Emulgel*

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INTRODUCTION

Localized drug distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. These are treating their healthy or damaged skin using a wide range of aesthetic and dermatological preparations [1]. These formulations are either solid, semisolid, or liquid in terms of physicochemical nature. Drug substances are typically provided in combination with one or more non-medicated compounds that have different and specific pharmacological functions as part of a formulation rather than on their own. Drugs are applied topically for local or systemic effects, depending on the drug's intended use [2]. The skin is more able to absorb a therapeutic ingredient if it is in solution, has a favourable lipid/water partition coefficient, and is not an electrolyte. Pharmaceutical preparations applied to the skin are frequently intended to have a local effect; hence, they are designed to have a sustained local interaction with minimal systemic drug absorption. Drugs that have a local action include antiseptics, antifungal agents, skin emollients, and protectants. The primary advantage of the topical administration technique is that it avoids first pass metabolism. Other benefits of topical preparations include avoiding the hazards and hassles of intravenous therapy as well as the various circumstances of absorption including pH fluctuations, the presence of enzymes, and gastric emptying time [3-4]. The topical medication delivery device is typically employed when other drug administration methods fall short or when a fungal infection is present. The human skin is a specially designed organ that prolongs life on land by controlling heat and water loss from the body and blocking the entry of harmful substances or microbes. It is by far the largest organ in the human body, making up roughly 10% of the average person's body mass and occupying an area of 1.7 m2. Human skin is a highly effective self-repairing barrier meant to keep the insides in and the outsides out, even though it appears to offer optimal and multiple locations to inject therapeutic substances for both local and systemic actions[5]. A more recent class of dosage forms, gels are made by trapping vast amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. These particles may be made of inorganic materials, such aluminium salts,

or organic polymers that can be either natural or synthetic[6]. Compared to the ointment or cream basis, they feature a larger aqueous component that allows for increased drug solubility and facile migration of the drug through a vehicle that is virtually a liquid[7]. These offer greater usability and patient acceptance. Despite the fact that gels have many benefits, hydrophobic medication delivery is a significant drawback. Emulgels are created and used to get over this restriction so that even a hydrophobic medicinal moiety can benefit from the special qualities of gels. In reality, a traditional emulsion becomes an emulgel when a gelling ingredient is present in the water phase[8]. Drugs are delivered to the skin using emulsions made of water and oil, as well as both. Emulgels for dermatological usage offer a number of beneficial characteristics, including being thixotropic, greaseless, readily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, clear, and having a beautiful look[9]. It is important to understand the variables that affect percutaneous absorption while using topical medications[10]. There are three ways that molecules can enter the skin: through the intact stratum corneum, through the sweat ducts, or through the sebaceous follicle. More than 99% of the entire skin surface that can be used for percutaneous medication absorption is on the surface of the stratum corneum [11]. For percutaneous absorption, passage through this outermost layer is the rate-limiting stage. The development of a concentration gradient, which provides the force for the drug to travel across the skin, the release of the drug from the vehicle (partition coefficient), and drug diffusion through the layers of the skin are the main steps in percutaneous absorption (diffusion coefficient). Low molecular mass (600 Da), good solubility in oil and water, and a high partition coefficient are all desirable properties of topical medications. Water soluble ions and polar molecules cannot pass through intact stratum corneum, with the exception of very minute particles. The barrier function of the skin can be altered using topical formulations. For instance, topical antibiotics and antibacterials help a compromised barrier ward off infection, sunscreens and the horny layer shield viable tissues from ultraviolet radiation, and emollient preparations give a desiccated horny layer its pliability back[12]. The requirement for and the effectiveness of the selected preservative must be proven to the satisfaction of the competent authority during the development of semi-solid preparations for cutaneous application whose composition comprises an antimicrobial preservative. In Efficacy of Antimicrobial Preservation, a suitable test procedure and criteria for evaluating the formulation's preservative qualities are given. To assure sterility, prevent the admission of impurities and the growth of microorganisms, and ensure sterility, sterile semi-solid formulations are made for cutaneous application[13]. The active ingredient in the preparation, the formulation in which it is included, the container and closure utilised, or other factors can increase or decrease an antimicrobial preservative's effectiveness. Topical preparations must be microbiological in quality and must pass a sterility test. Total viable aerobic count (aerobic bacteria plus fungus) per gramme shouldn't exceed 102 microorganisms. It should include no more than 101 enterobacteria, a limited number of other gram-negative bacteria per gramme, and be entirely free of Staphylococcus aureus and Pseudomonas aeruginosa[14-15]. This experiment aims to demonstrate that neither the material nor the process employed imparts any microbiological contamination, and that the 0.2% methyl paraben used is adequate to maintain its sterility. micro biology Topical medications including ointments, creams, and lotions are frequently used yet have significant drawbacks. When administered, they are extremely sticky and make the patient uncomfortable. Additionally, they need to be applied with rubbing because they have a lower spreading coefficient. They also display the stability issue. The usage of transparent gels has increased in both pharmaceutical and cosmetic preparations as a result of all these aspects within the main group of semisolid preparations. The surface tension between a colloid, which is normally 99% by weight liquid, and a macromolecular network of fibres constructed from a little quantity of a gelating material present immobilises the colloid. Despite the fact that gels have many benefits, hydrophobic medication delivery is a significant drawback. A method based on emulsions is therefore being employed to get around this restriction, allowing even a hydrophobic medicinal moiety to be successfully integrated and given through gels[16].

Ingredients Used in the Formulation of Emulgel [17-19].

Aqueous material

Make the aqueous phase in emulsion and for the swelling purpose of gelling agent. The most commonly used are water, alcohol etc.

Oil phase

Selection is done by optimizing its effects on the viscosity, permeability, drug release, emulsification and stability for the preparation in oil phase of the emulsion, used for the solubility of hydrophobic drugs. It can also be selected as per the effect of active molecule that gives synergistic effect as various oils had medicinal value. The most commonly used oil phases are as mineral oils liquid paraffin, propylene glycol, isopropyl myristate, isopropyl palmitate, castor oil, olive oil, balsam oil, wool wax, soyabeen oil, cotton seed oil, oleic acid, maize oil, arachis oil etc.

Emulsifiers

They are used for the emulsification and stability purpose of the product by decreasing the interfacial tension. Selection is done by proper hydrophilic and lipophilic balance (HLB) for example the surfactant with HLB value greater than 8 is used in oil in water emulsion where as the surfactant with HLB value less than 8 are used in water in oil emulsion. Tween are applicable for the water phase while the spans are applicable for the oil phase for emulsification.

Mixture of tween and span provide better stability than single. eg Polyethylene glycol , Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, labrasol, Sodium stearate etc.

Gelling agent

Gelling agent may be of natural, synthetic source; selection of these polymers can be based on the multifunction as thickening and acting as emulsifying agents. They are incorporated to make the system thixotropic. Effect of gelling agent on the drug release pattern should be studied. Synthetic polymer is Carbopol. The cellulose derivatives form a colloidal solution. They disperse in water and because of acidic pH the solution have to neutralize by amines, e.g. triethanolamine or bases, e.g. sodium hydroxide. Depending on pH range Carbopol have different grades, e.g. Carbopol 934, 940, etc. Natural materials such as tragacanth, carrageen, pectin, agar, xantham gum, alginic acid and starch; synthetic agents are: cellulose derivatives such as methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxyvinyl polymers, carboxymethylcellulose and magnesium aluminium silicates etc.

Permeation Enhancers

Agents that partition into, and interact with skin constituents to induce a temporary and reversible increase in skin permeability. For example, Oleic acid, Menthol, Clove oil, Lecithine, Isopropyl myristate, Urea, Linoleic acid, Cinnamon etc.

Emulgel

They are an emulsion of gel, as their name would imply. Drugs are delivered to the skin via emulsions of the water-in-oil and oil-in-water types. Additionally, they have a strong capacity for skin penetration. An emulgel is created when a traditional emulsion is present in the water phase. Emulgel for dermatological usage offers a number of advantageous qualities, including being thixotropic, greaseless, readily spreadable, easily removable, emollient, non-staining, water-soluble, prolonged shelf life, bio-friendly, transparent, and having a nice look. Basically, there are three ways for molecules to enter the skin: through the intact stratum corneum, sweat ducts, or sebaceous follicle. More than 99% of the entire skin surface that can be used for percutaneous medication absorption is on the surface of the stratum corneum. For percutaneous absorption, passage through this outermost layer is the rate-limiting stage. [20] The development of a concentration gradient, which provides the force for the drug to travel across the skin, the release of the drug from the vehicle (partition coefficient), and drug diffusion through the layers of the skin are the main steps in percutaneous absorption (diffusion coefficient). Emulgel is a new area for the topical medication delivery and has not yet had many products marketed, making it fascinating and difficult to concentrate on emulgel. Before using emulgel, it is important to understand the benefits of topical emulsion and gel. Emulsions are controlled release systems made up of two immiscible phases, one of which is disseminated (internally or discontinuously) into the other (externally or discontinuously), and which is stabilised by the employment of an emulsifying agent. The drug particle is trapped in the internal phase of the emulsion and passes through the external phase before slowly absorbing into the skin to produce a regulated effect. Emulsions can be of the oil-in-water or water-in-oil variety. According to the USP, a gel is a semisolid structure made up of dispersions formed of either big organic molecules or small inorganic molecules enclosed and interspersed by liquid. The higher quantity of aqueous or hydroalcoholic liquid is present in the gel, which is made up of a cross-linked network of colloidal solid particles. This network traps small drug particles and maintains the drug's regulated release. A three-dimensional polymeric matrix is created by the liquid phase, and this matrix is then physically or chemically cross-linked. Constant structure leads to solid-like behaviour that is uniform and transparent. Both the emulsion and the gel are in charge of the systems' regulated drug release [21–23]. The two types of gels are the water-based, hydrophilic or hydrogels and the organic solvent-based, hydrophobic or organogels. First one consist base liquid paraffin with polyethylene or fatty oils gelled with colloidal silica, aluminium or zinc soaps and the second one with the base of water, glycerol, or propylene glycol[24,25]. gels having various advantages has still limitation in the delivery of hydrophobic drugs so to overcome this limitation and enjoy the delivery in the form of gel for the hydrophobic drug, the concept for emulgel was introduced where the hydrophobic drugs are incorporated in emulsion and then to gel[26]. Emulgel is the approach using the benefits of both emulsion and gels, gaining the dual controlled release effect the emulsion either oil in water or water in oil is gelled by incorporation in the gel base [27], simply the Emulgels are emulsion in gel. In emulsion the drug particles are incorporated in the internal phase acting as drug reservoir from where the drug passes through the external phase and to the skin and get absorbed. Emulgel are seen better choice for the class II of drug as per the BCS classification systems that show poor solubility and high permeability [28]. Emulgel possess the properties as thixotropic, grease less, easily spreadable, easily removable, emollient, nonstaining, water soluble, long shelf life, biofriendly and pleasing appearance that improves the patient acceptability [29]. Emulgel are being used for the treatment of various anti-inflammatory activity and other skin related viral, bacterial and fungal infections [30,31]. Over the past few decades, disease has been treated using traditional methods, such as oral, sublingual, rectal, parental, etc. Localized drug distribution through the skin, vagina, rectal, and ocular cavities is known as topical drug administration. Bypassing first pass metabolism is the topical administration system's key benefit[32–33]. Other benefits of topical preparations include avoiding the hazards and hassles of intravenous therapy as well as the diverse circumstances of absorption including pH fluctuations, the presence of enzymes, and gastric emptying time [34–35]. These are applying a wide spectrum of

preparations for both cosmetic and dermatological, to their healthy or diseased skin. Dermatological products are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particles. Gel formulations generally provide faster drug release compared with conventional ointments and creams. In spite of many advantages of gels a major limitation is in the difficulty in delivery of hydrophobic drugs. So to overcome this limitation emulgel are prepared and with their use even a hydrophobic drug can enjoy the unique properties of gels. Emulgels are the dosage forms that are employed when gels and emulsions are mixed. In reality, a traditional emulsion becomes an emulgel when a gelling ingredient is present in the water phase. Hydrophilic medications are encapsulated in the reverse (water-in-oil) system, whereas lipophilic pharmaceuticals are encapsulated in the direct (oil-in-water) system [36]. Emulsions are easily removed whenever wanted and have a certain level of elegance. Additionally, they have a strong capacity for skin penetration. Emulgels for dermatological usage are thixotropic, greaseless, readily spreadable, easily removed, emollient, non-staining, water-soluble, prolonged shelf life, bio-friendly, clear, and have a beautiful look [37].

Advantages

1. Hydrophobic drugs can be easily incorporated into gels using o/w emulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.
2. Better stability: Other transdermal preparations are comparatively less stable than emulgel. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
3. Better loading capacity: Other novel approaches like niosomes and liposomes are of nanosize and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.
4. Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgel. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgel.
5. No intensive sonication: Production of vesicular molecules needs intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed. 6. Controlled release: Emulgels can be used to prolong the effect of drugs having shorter t1/2. It can be used for both hydrophobic (o/w emulgel) and hydrophilic drugs (w/o emulsion). [38-39]
6. Increased patient acceptability.
7. Provide targeted drug delivery.
8. Easy termination of the therapy.
9. Improve bioavailability and even the low doses can be effective in comparison with other conventional semi solid preparation.
10. Stable formulation by decreasing surface interfacial tension resulting in increase in viscosity of aqueous phase, more stable than Transdermal preparations that are comparatively less stable, powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
11. Hydrophobic drug can be incorporated in emulgel using emulsion as the drug carrier that is finally dispersed in the gel.
12. Provide the controlled effect of that enhance the prolong effect of the drug with short half life.
13. Easy and cost effective preparation.
14. Drug loading capacity is better than other novel approaches like niosomes and liposomes
15. Penetration to skin is enhanced due to both hydrophilic and hydrophobic nature. [40-41]

Disadvantages [42-43]

1. Poor absorption of macromolecules.
2. Entrapment of bubble during formulation.
3. Hydrophobic drugs are the best choice for such delivery systems.

Method of Preparation of Emulgel [44-45]

Its preparation process is very straightforward and economical, generally consisting of three steps: first, creating an oil in water or water in oil emulsion in which the drug is incorporated in accordance with our formulation requirements; second, creating the gel base; and third, adding the emulsion to the gel while continuously stirring to create the emulgel. In order to create an emulsion, the aqueous phase must first be created by dissolving a surfactant such as spans in purified water, which is then heated to the same temperature as the aqueous phase while adding a hydrophobic substance. The

aqueous phase is then combined with the oil phase to create an emulsion. The gel phase is prepared by dispersing the polymer in purified water with constant stirring at a moderate speed and then the pH are adjusted to 6 to 6.5 as per the requirement of the polymer. For example pH of gel with carbopol is adjusted by Tri ethanol amine (TEA). Preservatives were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the a Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. One gram of emulgel was placed between the two glass slides and load of 500 g was applied for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Second glass slide is provided with the hook. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time required to slip off the slides was measured. Lesser the time taken for separation of two slides, better the spreadability. Spreadability was calculated using formula

S = M. L / T

Where M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides. Queous phase with continuous stirring until cooled to room temperature. Now the emulsion is added to the gel base in ratio 1:1 to obtain the emulgel.

Method of Preparation [46-47]

Step1: Formulation of Emulsion either O/W or W/O

Step2: Formulation of gel base

Step3: Incorporation of emulsion into gel base with continuous stirring

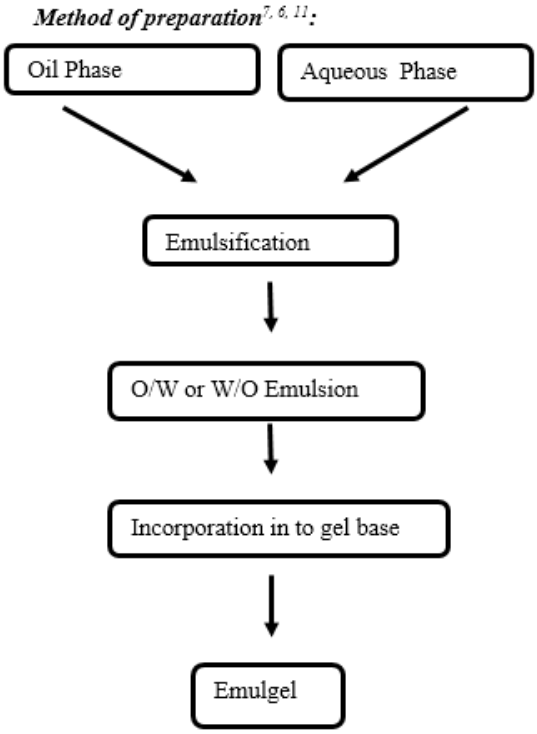

Figure 3: Flowchart of emulgel prepration.

Characterization of Emulgel

Physical examination

The prepared emulgel formulations are analysed visually for their appearance, colour, consistency, grittiness, homogeneity and phase separation [48].

Globule size and its distribution in emulgel

Globule size and distribution was determined by Optical Miscroscope. A compound microscope is used for examination and the globules are observed under 40 X magnification. Prior to observation, the eye-piece micrometers are calibrated with a stage micrometer and calibration factor are obtained. Subsequently, mean globule size is calculated [49].

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

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 [50] .

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 [51] .

Spreading coefficient

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 Mutimeret. 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:

$$S = M.L/T$$

where,

S = spreadability,

M = Weight bound 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 [52-53].

Extrudability study

It is general confirmable test to estimate the force required to extrude the emulgel from tube. The method practiced for verification of applied shear in the 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 from lacquered Aluminium collapsible tube on application of weight in grams mandatory to extrude atleast 0.5cm ribbon of emulgel in 10 seconds. Major quantity extruded more excellent is extrudability. The measurement of extrudability of prepared emulgel formulation can be done triplicate and the average values are represented. The extrudability is calculated by applying the following formula:

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

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 [54] .

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:

$$SW\% = [Wt - Wo] * 100 / Wo$$

Where,

SW% = Equilibrium percent swelling

Wo = Initial weight of emulgel at time zero

Wt = Weight of swollen emulgel after time t[55] .

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 [56] .

Phase Separation

The emulgel formulation are subjected to centrifugation at 10,000 rpm for 10 min and examined for any change in phase separation [57].

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 [58] .

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 cm2 and 15.5 ml cell volume). Prepared emulgel formulation is applied onto the surface of dialysis membrane 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℃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 [59]

***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 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 [60]:

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

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 [61-62] .

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 cm2 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 [63-64] .

In vivo anti-inflammatory study

In vivo anti-inflammatory study is performed by using Wistar rats as animal model weighing approximately 200-250 gms each. 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 = $\boldsymbol{Vc - Vt * 100 / Vc}$

Where,

Vc = inflammatory increase in paw volume of control group

Vt= inflammatory increase in paw volume in (drug+Carragenan) treated animals[65]

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 = K0t Where Q is the amount of drug released at time t, and K0is the zero – order release rate.

First – order equation: In (100 – Q) = In 100 – K1t

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

Hixson-Crowell:

Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles of formulation.

$Q0^{1/3} - Qt^{1/3} = KHC\ t$

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:

Korsmeyeret. 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:

$Mt/M\infty = Ktn$

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.

CONCLUSION

Topical medicine delivery will be widely employed in the upcoming years to improve patient compliance. Emulgel is a relatively new method for topical drug delivery that works well with hydrophobic medications. Considering that it can also improve spreadability, adhesion, viscosity, and extrusion. They'll become a well-liked medicine delivery method. Additionally, they will serve as a means of encapsulating hydrophobic medications in a gel foundation that is water soluble. A careful review of the literature has led us to the conclusion that emulgels are one of the most efficient, superior, and practical drug delivery systems since they can distribute both hydrophobic and hydrophilic medicines. Emulgels produce greater drug release than other transdermal drug delivery systems because they are non-greasy and have a gel-like quality where the gel acts as an aqueous environment for the drug, aiding in breakdown. Emulgels are a more recent category of dosage form that are produced by trapping significant volumes of aqueous or hydroalcoholic liquid within a web of colloidal solid particles. Emulgels contain a higher aqueous component than other medications, allowing for easier drug migration through a vehicle that is virtually a liquid as well as greater drug solubility. Thus, the water phase contains the gelling ingredient that changes a conventional emulsion into an emulgel. Emulgels have gained popularity in recent years as a result of increased patient compliance. Emulgels will be a reasonable option as a topical drug administration system and a way to load hydrophobic pharmaceuticals in water soluble gel bases since they have an advantage in terms of spreadability, adhesion, viscosity, and extrusion.

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