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## EMULGEL: AN APPROACH TO CURRENT DRUG DELIVERY- A REVIEW

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### ABSTRACT

Emulgels are used as better topical drug delivery systems over other systems because of many properties. The use of emulgel can be found in analgesics, anti-inflammatory, anti-fungal, anti-acne drugs and various cosmetic formulations. With this approach the use of polymers with enhanced effect in release pattern has been emerged providing sustained and controlled release. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgel show major advantages on novel vesicular system as well as on conventional systems in various aspects. Emulgels have many favourable properties for dermatologic use like being thixotropic, greaseless, simply spreadable, simply removable, emollient, nonstaining, long period, bio-friendly, clear and pleasing look.

### KEYWORDS

Topical drug delivery system, Sustained, Controlled release and Emulgel.

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### INTRODUCTION

Topical drug administration could be a localized drug delivery system anyplace within the body through ophthalmic, rectal, canal and skin as topical routes. These are applying a wide spectrum of preparations for both cosmetic and dermatological, to their healthy or diseased skin<sup>1</sup>. These formulations range in physicochemical nature from solid through semisolid to liquid. Drug substances square measure rarely administered alone, however rather as a part of a formulation, in combination with one or more non medicated agents that serve varied and specialized pharmaceutical function. Drugs square measure administered locally for his or her action at the location of application or for

general effects<sup>2</sup>. Drug absorption through the skin is increased if the drug substance is in resolution, if it's a favourable lipid/water partition constant and if it's a nonelectrolyte. For the foremost half, pharmaceutical preparations applied to the skin square measure meant to serve some native action and in and of itself square measure developed to supply prolonged native contact with negligible systemic drug absorption. Drug applied to the skin for his or her native action embrace antiseptics, fungicide, skin emollients and protectant. The main advantage of topical delivery system is to bypass 1st pass metabolism. Avoidance of the risks and inconveniences of blood vessel medical care and of the numerous conditions of absorption like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations<sup>3,4</sup>. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in fungal infection. Human skin is uniquely engineered organs that perm its terrestrial life by regulating heat and water loss from the body whilst preventing the ingress of noxious chemicals or microorganisms. It is all that the largest organ of the flesh, providing around 100% of the body mass of a mean person, and it covers an average area of 1.7 m<sup>2</sup>. Whilst such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep the insides in and the outside out<sup>5</sup>. Gels square measure a comparatively newer category of dose type created by denial of huge amounts of liquid or hydroalcoholic liquid during a network of mixture solid particles, which may consist of inorganic substances, such as aluminium salts or organic polymers of natural or synthetic origin<sup>6</sup>. They have a higher aqueous component that permits greater dissolution of drugs, and also permit straightforward migration of the drug through a vehicle that's primarily a liquid, compared with the ointment or cream base<sup>7</sup>. These are superior in terms of use and patient acceptability. In spite of the many blessings of gels a significant limitation is

within the delivery of hydrophobic medicine. So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In fact, the presence of a gelling agent within the water section converts a classical emulsion into AN emugel<sup>8</sup>. Each oil-in water and water-in-oil emulsions square measure used as vehicles to deliver various drugs to the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance<sup>1</sup>. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption<sup>9</sup>. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption<sup>10</sup>. Passage through this outer most layer is the rate limiting step for percutaneous absorption. The major steps concerned in body covering absorption embrace the institution of a level gradient, that provides the drive for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical medicine embrace low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for terribly tiny particles, water soluble ions and polar molecules don't penetrate intact horny layer. Topical formulation will be accustomed manipulate the barrier operate of the skin, as an example, topical antibiotics and antibacterial help a damaged barrier toward off infection, sun screening agents and the stratum shield the viable tissues from ultraviolet light and emollient preparations restore pliability to a desiccated stratum<sup>11</sup>. During development of semi-solid preparations for connective tissue application whose formulation contains associate degree antimicrobial preservative, the necessity for and also the effectualness of the chosen preservative shall be

incontestable to the satisfaction of the competent authority. A suitable check technique at the side of criteria for decision making the preservative properties of the formulation are provided in effectualness of antimicrobial preservation. Sterile semi-solid preparations for connective tissue application are ready mistreatment materials and ways designed to confirm sterility and to avoid the introduction of contaminants and also the growth of microorganisms<sup>12</sup>. The effectualness of associate degree antimicrobial preservative could also be increased or diminished by the active constituent of the preparation or by the formulation during which it's incorporated or by the instrumentation and closure used. Preparation for topical use should have microbiological quality and it is checked with test for sterility. Total viable aerobic count should not be more than 10<sup>2</sup> micro-organisms (aerobic bacteria plus fungi) per gram. It should not have more than 10<sup>1</sup> enterobacteria, certain other gram-negative bacteria per gram and completely devoid of *Pseudomonas aeruginosa* and *Staphylococcus aureus*<sup>13,14</sup>. This project is to reveal the material and method used doesn't imparts any microbial contamination and the methyl paraben 0.2% used is sufficient to maintain its sterility.

### **RATIONALE**

Many wide used topical agents like ointment, cream, lotion have many disadvantages. They have terribly sticky inflicting uneasiness to the patient once applied. Moreover they even have lesser spreading constant and wish to use with rubbing. And they exhibit the problem of stability also. Due to of these factors among the most important cluster of solid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present. In spite of the many benefits of gels a significant limitation is within the delivery of hydrophobic medicine. So to beat this limitation associate degree emulsion based mostly approach is

being employed so even a hydrophobic therapeutic moiety will be with success incorporated and delivered through gels<sup>15</sup>.

### **Drug delivery across the skin**

The stratum is that the most superficial layer of the skin and consists of stratified keratinised squamous epithelial tissue that varies in thickness in several components of the body. It is thickest on with elastic fibres. The skin forms a comparatively waterproof layer that protects the deeper and a lot of delicate structures. Blood vessels are distributed profusely beneath the skin. Especially vital may be a continuous blood vessel anatomical structure that's equipped by flow of blood from the skin capillaries. In the most exposed areas of the body- the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses. A unique side of dermatologic medical specialty is that the direct accessibility of the skin as a organ for designation and treatment. The skin acts as a two-way barrier to forestall absorption or loss of water and electrolytes. There are 3 primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most medicine tolerate the agonizing path around corneocytes and thru the supermolecule bilayer to viable layers of the skin. The next commonest (and doubtless below recognized within the clinical setting) route of delivery is via the oil gland route. The barrier resides within the outer layer of the stratum, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams associated gels that ar rubbed into the skin are used for years to deliver pain medication and infection fighting medicine to an affected website of the body. These embody, among others, gels and creams for canal yeast infections, topical creams for skin infections and creams to appease inflammatory disease pain. New technologies currently enable alternative medicine to be absorbed through the skin (transdermal). These may be wont to treat not simply the affected areas (for example, the skin) however the total body. (Systemic) Topical drug

delivery can be defined as the application of a drug containing formulation to the skin to treat cutaneous disorder directly. The topical drug delivery system is mostly used wherever alternative routes (like oral, sublingual, rectal, parental) of drug administration fails or in native skin infection sort of a zymosis<sup>16</sup>. The main advantage of the topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of blood vessel medical aid and of the various conditions of absorption, like hydrogen ion concentration changes, the presence of enzymes, gastric emptying time are another advantage of The topical drug delivery system is mostly used wherever the others system of drug administration fails. The study is also carried out for the avoidance of the risks and inconvenience of intravenous therapy and of the varied conditions of absorption, like pH changes, the presence of enzymes and gastric emptying time. Topical drug administration is simplest and best route of localised drug delivery anyplace within the body by routes as ophthalmic, rectal, vaginal and skin. These are applied as a wide spectrum of preparations in case of both cosmetic and dermatological, to the healthy or diseased skin<sup>17</sup>. The formulations are available in different forms like from solid through semisolid to liquid. Drugs are administered locally for his or her action at the location of application or for general effects. Drug absorption is enhanced through the skin if the drug substance is in solution, if it has a favourable lipid/water partition coefficient and if it is a non-electrolyte. Skin is one of the most readily accessible parts of human body for topical administration and molecules penetrate in the skin mainly by three routes: through intact stratum corneum, through sweat ducts, and through the sebaceous follicle. Topical drug delivery is employed for localised action on the body through ophthalmic, rectal, canal and skin as topical routes. The topical drug delivery system such as emulgel (gellified emulsion) generally used where the other system<sup>18</sup> as of drug administration fail to directly treat cutaneous disorders such as fungal infections, acne, psoriasis etc Since the mid-1980's, emulsion

gels have been of growing importance in the field of pharmaceutical semisolid dosage forms.

### **Emulgel**<sup>16-19</sup>

As the name suggest, they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsions are used as a vehicle to deliver various drugs to the skin. They even have a high ability to penetrate the skin. The presence of the gelling agent in water part converts a classical emulsion into associate degree emulgel. Emulgel for medical specialty use has many favourable properties like being thixotropic, greaseless, simply spreadable, simply removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent and pleasing appearance. Molecules will essentially penetrate into the skin by 3 routes: through intact corneum, sweat ducts, or glandulae sebaceae. The surface of the corneum presents over ninety nine of the overall skin surface out there for transdermal drug absorption. Passage through this outermost layer is the rate limiting step for percutaneous absorption. The major steps concerned in transdermal absorption embody the institution of a degree gradient, that provides the drive for drug movement across the skin, unharness of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Emulgel is emerging field for the topical drug delivery, and till date it has less marketed product, thus it's attention-grabbing and difficult to target emulgel. Before getting to emulgel we'd like to grasp the benefits of emulsion and gel that's getting used for the topical drug delivery. Emulsions are controlled release systems containing two immiscible phase in which one is dispersed (internal or discontinuous phase) into other (external or discontinuous phase), with the use of emulsifying agent to stabilize the system. emulsion are of oil-in-water or water-in-oil type, where the drug particle entrapped in internal phase passes through the external phase and then slowly gets absorbed into the skin to provide controlled effect. USP defines gel as a solid system consisting of dispersions created of either tiny inorganic particles or giant organic molecules enclosure and

interpenetrated by liquid. The gel contains the larger amount of aqueous or hydro alcoholic liquid in a cross linked network of colloidal solid particles where it captures small drug particles and maintain the controlled release of drug. The liquid phase builds a three-dimensional polymeric matrix which results a physical or chemical cross-linking. The continuous structure results solid like behavior that are homogenous and clear. The emulsion and gel each area unit chargeable for the controlled drug unharness from the systems<sup>20,2,21</sup>. The gels are of two types first the organic solvent based, hydrophobic or organogels and second the water based, hydrophilic or hydrogels. 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<sup>22,23</sup>. 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 thought for emulgel was introduced wherever the hydrophobic medicine area unit incorporated in emulsion and so to gel<sup>24</sup>. Emulgel is that the approach mistreatment the advantages of each 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<sup>25</sup>, 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 area unit seen better option for the category II of drug as per the BCS classification systems that show poor solubility and high permeableness<sup>26</sup>. Emulgel possess the properties as thixotropic, grease less, easily spreadable, easily removable, emollient, nonstaining, water soluble, long shelf life, bio-friendly and pleasing appearance that improves the patient acceptability<sup>19</sup>. Emulgel are being used for the treatment of various anti-inflammatory activity and other skin related viral, bacterial and fungal infections<sup>27,15</sup>. Over last decades of the treatment of illness has been accomplished by conventional

routes namely oral, sublingual, rectal, parental etc. Topical drug administration may be a localized drug delivery system anyplace within the body through ophthalmic, rectal, vaginal and skin as topical routes. The main advantage of topical delivery system is to bypass initial pass metabolism<sup>28,29</sup>. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations<sup>30,31</sup>. 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 most important cluster of solid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels area unit a comparatively newer category of indefinite quantity type created by defense of huge amounts of liquid or hydro alcoholic liquid in an exceedingly network of mixture solid particles. Gel formulations usually give quicker drug unharness compared with standard ointments and creams. In spite of many advantages of gels a major limitation is in the difficulty in delivery of hydrophobic drugs. So to beat this limitation emulgel area unit ready and with their use even a hydrophobic drug will fancy the distinctive properties of gels. When gels and emulsions are used in combined form the dosage forms are referred as Emulgels. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Direct (oil-in-water) system is used to entrap lipophilic drugs whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) system<sup>32</sup>. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They even have a high ability to penetrate the skin. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble,

longer shelf life, bio-friendly, transparent and pleasing appearance<sup>17</sup>.

#### **ADVANTAGES**<sup>33,34</sup>

1. Hydrophobic drugs can be easily incorporated into gels using o/w emulsions. Most of the hydrophobic medication can't be incorporated directly into gel base as a result of solubility act as a barrier and drawback arises throughout the discharge of the drug. Emulgel helps within the incorporation of hydrophobic medication into the oil section so oily globules area unit distributed in liquid section leading to o/w emulsion. And this emulsion is mixed into gel base. This may be proving higher stability and unharness of drug than merely incorporating medication into gel base.
2. Higher stability: alternative transdermic preparations area unit relatively less stable than emulgel. Like powders area unit absorbent, 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 thanks to large network have relatively higher loading capability.
4. Production feasibility and low preparation cost: Preparation of emulgels contains of easier and short steps that will increase the feasibility of the assembly. There are not any specialised instruments required for the assembly of emulgel. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgel.
5. No intensive sonication: Production of sac molecules wants intensive sonication which can lead to drug degradation and escape. 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 t<sub>1/2</sub>. It is used for each hydrophobic (o/w emulgel) and hydrophilic medication (w/o emulsion).

#### **Advantages of Emulgel**<sup>35,36</sup>

1. Increased patient acceptability.
2. Provide targeted drug delivery.
3. Easy termination of the therapy.
4. Improve bioavailability and even the low doses can be effective in comparison with other conventional semi solid preparation.
5. 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.
6. Hydrophobic drug can be incorporated in emulgel using emulsion as the drug carrier that is finally dispersed in the gel.
7. Provide the controlled effect of that enhance the prolong effect of the drug with short half life.
8. Easy and cost effective preparation.
9. Drug loading capacity is better than other novel approaches like niosomes and liposomes
10. Penetration to skin is enhanced due to both hydrophilic and hydrophobic nature.

#### **Disadvantages**<sup>37,38</sup>

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 FOR EMULGEL**<sup>39,40</sup>

It has very simple and cost effective method of preparation basically including three steps; first the preparation of oil in water or water in oil emulsion where the drug is incorporated as per our

formulation requirement then second step is to formulate the gel base and finally the addition of emulsion to gel in continuous stirring to form emulgel in detail for the formulation of emulsion the aqueous phase is prepared by taking the purified water to which the soluble ingredient are added and heated up to 70°C including emulsifying agent as tweens and then the oil phase are prepared by dissolving the surfactant such as spans also heated to same temperature with the addition of hydrophobic drug. 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 2 glass slides and cargo of five hundred g was applied for five min to expel air and to produce a standardized film of the emulgel between the two slides. Second glass slide is provided with the hook. Measured amount of weight was placed within the pan connected to the simple machine with the assistance of hook. The time required to slip off the slides was measured. Lesser the time taken for separation of 2 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 intercalary to the gel base in magnitude relation 1:1 to get the emulgel.

#### **METHOD OF PREPARATION**<sup>41,42</sup>

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

#### **CHARACTERIZATION OF EMULGEL**

##### **Physical examination**

The prepared emulgel formulations are analysed visually for their appearance, colour, consistency, grittiness, homogeneity and phase separation<sup>43</sup>.

##### **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 micrometers are calibrated with a stage micrometer and calibration factor are obtained. Subsequently, mean globule size is calculated<sup>44</sup>.

##### **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<sup>45</sup>.

##### **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<sup>46</sup>.

##### **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 Mutimer *et al.* (1956)<sup>47</sup> which consists of a wooden block and is attached by a pulley at one end. Spreadability is measured on the idea of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is mounted 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 disposed 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:

$$S = M \cdot L / T$$

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<sup>48,3</sup>.

#### **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 shear rate 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 at least 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:

$$\text{Extrudability} = \frac{\text{Applied weight to extrude emulgel from tube (ingm)}}{\text{Area (incmsq)}}$$

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<sup>4</sup>.

#### **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:

$$SW\% = \frac{[W_t - W_o] * 100}{W_o}$$

Where,

SW% = Equilibrium percent swelling

W<sub>o</sub> = Initial weight of emulgel at time zero

W<sub>t</sub> = Weight of swollen emulgel after time t<sup>49</sup>.

#### **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<sup>50</sup>.

#### **Phase Separation**

The emulgel formulation are subjected to centrifugation at 10,000 rpm for 10 min and examined for any change in phase separation<sup>51</sup>.

#### **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<sup>52</sup>.

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 area 3.14 cm<sup>2</sup> 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°C 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<sup>53</sup>.

#### **Ex-vivo Bio-adhesive strength mensuration of topical emulgel (MICE beardless SKIN)**

The method is used for the measurement of bio-adhesive strength. The contemporary skin is delved items and washed with 0.1N NaOH. Two pieces of skin were tied to the two glass slides 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 g of topical emulgel is placed between these 2 slides containing bald-pated skin items, and extra weight from the left pan is removed to sandwich the two pieces of skin and a few pressure is applied to get rid of the presence of air. The balance is unbroken during this position for five minutes. Weight is intercalary slowly at two

hundred mg/ min to the left-hand pan till the patch detached from the skin surface. The weight (gram force) needed to detach the emulgel from the skin surface gave the live of bio-adhesive strength. The bio-adhesive strength is calculated by using following<sup>27</sup>: Bio-adhesive Strength = Weight required (in gms) / Area (cm<sup>2</sup>)

#### **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.

$$\% \text{ Inhibition} = L2 / L1 \times 100$$

Where

L1 = total length of the streaked culture,

L2 = length of inhibition<sup>54,51</sup>.

#### **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<sup>2</sup> to make a hairless area. The rats are randomly divided into three equal groups.

#### **Group I**

Receives 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<sup>55,4</sup>.

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

*In vivo* anti-inflammatory study is performed by using Wistar rats as animal model weighing approximately 200-250gms 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:

$$\% \text{ Inhibition of the drug} = \frac{V_c - V_t}{V_c} * 100$$

Where,

$V_c$  = inflammatory increase in paw volume of control group

$V_t$  = inflammatory increase in paw volume in (drug+ Carragenan) treated animals<sup>56</sup>

#### **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:

$Q = K_0t$  Where  $Q$  is the amount of drug released at time  $t$ , and  $K_0$  is the zero – order release rate.

First – order equation:  $\ln(100 - Q) = \ln 100 - K_1t$

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:

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

$$Q_0^{1/3} - Q_t^{1/3} = KHC t$$

Where,  $Q_t$  is the amount of drug released in time  $t$ ,  $Q_0$  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)<sup>57</sup> 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  $M_t / M_\infty$  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.

## **CHARACTERIZATION OF GELLIFIED EMULSION**

### **Physical appearance**

The prepared Emulsion formulations were inspected visually for their colour, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter DPH 115 pm)<sup>58</sup>

### **Spreadability**

Spreadability is determined by apparatus suggested by Mutimer *et al* (1956)<sup>47</sup> which is suitably modified in the laboratory and used for the study. It consists of a picket block, that is provided by a block at one finish. By this technique, spreadability is measured on the idea of 'Slip' and 'Drag'

characteristics of emulgels. A ground glass slide is fastened on this block. An more than emulgel (about a pair of gm) below study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80 grams. With the assistance of string hooked up to the hook and also the time (in seconds) needed by the highest slide to hide a distance of seven. 5cm be noted. A shorter interval indicates better Spreadability. Spreadability was calculated by using the formula,

$$S = M.L/T$$

Where,

S = spreadability,

M = Weight tied to upper slide,

L = Length of glass parate the slides completely from each other.

Extrudability s slides

T = Time study:

It is a usual empirical take a look at to live the force needed to produce the fabric from tube. The method applied for determination of applied shear within the region of the rheogram cherish a shear rate extraordinary the yield price and exhibiting resulting plug flow. In the gift study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminium collapsible tube on application of weight in grams needed to produce a minimum of zero.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The activity of extrudability of every formulation is in triplicate and also the average values area unit bestowed. The extrudability is than calculated by victimisation the subsequent formula: Extrudability = Applied weight to produce emulgel from tube (in gramme.) / space (in cm<sup>2</sup>)<sup>59,60</sup>.

### **Globule size and its distribution in emulgel**

Globule size and distribution made up our minds by Malvern zetasizer. A 1gm sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer. Mean globule diameter and distribution was obtained<sup>31</sup>.

### **Rheological Study**

The consistence of the various emulgel formulations is decided at 25°C employing a cone and plate measuring instrument with spindle fifty two (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath<sup>61</sup>.

### **Swelling Index**

To determine the swelling index of ready topical emulgel, 1 gm 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 dry place for some time after it reweighed. Swelling index is calculated as follows: Swelling Index (SW) nada = [(Wt – Wo) / Wo] × a hundred.

Where, (SW) % = Equilibrium percentage swelling, Wo = Original weight of emulgel at zero time when time t,

Wt = Weight of swollen emulgel<sup>62</sup>

### **Drug Content Determination:**

Drug concentration in Gellified Emulsion was measured by spectrophotometer. Drug content in Gellified Emulsion was measured by dissolving known quantity of Gellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV-1700 CE, Shimadzu Corporation, Japan)<sup>61</sup>.

### **In Vitro Release Study**

Franz diffusion cell (with effective diffusion area 3.14 cm<sup>2</sup> and 15.5 ml cell volume) was used for the drug release studies. Gellified Emulsion (200 mg) was applied onto the surface of egg membrane equally. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was full of freshly ready

PBS (pH five. 5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analysed for drug content by ultraviolet radiation visible photometer when acceptable dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the egg membrane was determined as a function of time<sup>63</sup>.

#### 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 formulations. Previously prepared Sabouraud's agar dried plates were used. Three grams of the Gellified emulsion square measure placed during a ditch cut within the plate. Freshly ready culture loops square measure patterned across the agar at a right angle from the ditch to the sting 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.

$$\% \text{ inhibition} = L2 / L1 \times 100$$

Where L1 = total length of the streaked culture

L2 = length of inhibition<sup>64</sup>.

#### Skin irritation test

A 0.5 gm sample of the test article was then applied to each site (two sites per rabbit) by introduction under a double gauze layer to an area of skin approximately 1" x 1" (2.54 x 2.54 cm<sup>2</sup>). The Gellified Emulsion was applied on the skin of rabbit. Animals were returned to their cages. After a twenty four hour exposure, the Gellified Emulsion is removed. The test sites were wiped with tap water to remove any remaining test article residue<sup>61</sup>.

#### Accelerated stability studies of Gellified Emulsion

Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples were analysed for drug content every two weeks by UV-Visible spectrophotometer. Stability study was carried out

by measuring the change in pH of gel at regular interval of time<sup>64</sup>.

Drug unlash Kinetic Study. To analyse the mechanism of drug unlash from the topical gel, the discharge information 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<sub>0</sub> 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<sub>1</sub> 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<sub>2</sub> is the diffusion rate constant<sup>38</sup>.

#### STABILITY STUDIES

The prepared emulgels were packed in aluminium collapsible tubes (5 g) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles<sup>38</sup>.

#### Factors Affecting Topical Absorption of Drugs<sup>65,66</sup>

Physiochemical factors Drug substances

1. Molecular weight (<400 dalton)
2. Diffusion coefficient
3. Water/lipid partition coefficient
4. Permeability coefficient
5. Ionization- unionized drug are well absorbed
6. Protein binding capacity.

#### Vehicle

1. Solubility/polarity
2. Volatility
3. Concentration
4. Distribution in a stratum corneum
5. Excipients
6. Penetration enhancer
7. PH

**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

**Site of application**

1. Skin area dose (film thickness, concentration)
2. Total skin area in contact with vehicle
3. Duration of exposure

**Merits of using emulgel**

Following are the benefits of using emulgel over conventional topical dosage forms<sup>53</sup>:

**Better stability**

Emulgel show higher stability than different stratum preparations, e.g.: powders are absorptive, creams show part inversion on breaking and ointment shows rancidity because of oily part.

**More loading capacity**

Emulgels have better loading capacity due to their vast network, while other novel approaches like niosomes and liposomes are of nanosize and have vesicular structures. So niosomes and liposomes cause leakage and have lesser entrapment efficiency.

**Ease of incorporating hydrophobic drugs**

Most of the hydrophobic medicine cannot be incorporated directly into gel as a result of solubility acts as a barrier and downside arises throughout unharness of drug.

Emulgel helps in incorporation of hydrophobic medicine into oil part then oily globules are distributed in liquid part leading to o/w emulsion. This o/w emulsion can be mixed into a gel base.

**Production feasibility**

The emulgel preparation method comprises of simple and short steps, which increase the feasibility of production.

**Low preparation cost**

No specialized instruments are needed for preparation of emulgel. Moreover materials used are easily available and cheaper. This reduces the overall production cost of emulgels.

**No intensive sonication**

Production of vesicular preparations (niosomes and liposomes) needs intensive sonication, which may result in drug degradation and leakage. But emulgels don't require intensive sonication, so drug degradation problems can be overcome.

**Controlled drug release**

Emulgels can be used to prolong the effect of drugs with shorter half-life.

**Patient compliance**

They are less greasy and easy to apply.

**Table No.1: Various marketed emulgel formulations**

S.No	Marketed formulation	API	Manufacturer	Use
1	Voltarol 1.16% emulgel	Diclofenac sodium	Novartis	Anti-inflammatory
2	Diclomax Emulgel	Diclofenac sodium	Torentpharma	Anti-inflammatory
3	Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals	Topical corticosteroid and antifungal

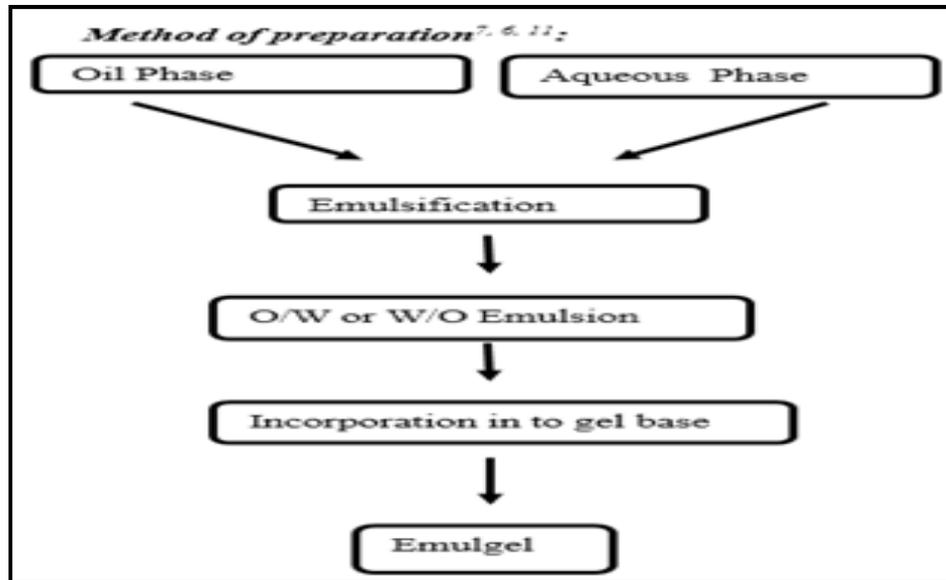


Figure No.1: Flowchat of emulgel Preparation

## CONCLUSION

Emulgels are a comparatively newer category of dose type created by demurrer of enormous amounts of binary compound or hydro alcoholic liquid in a very network of mixture solid particles. Emulgels have a higher aqueous component which permits greater dissolution of drugs, and also permit easy migration of 2the drug through a vehicle that is essentially a liquid. So the gelling agent is in the water phase which converts a classical emulsion into an emulgel. In the recent years, emulgels are popular due to better patient compliance. Since emulgels possess an edge in terms of spreadability, adhesion, viscosity and extrusion, they will become a fair choice as topical drug delivery system and a solution for loading hydrophobic drugs in water soluble gel bases.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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