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Review on topical gellified emulsion: Superior vehicle for hydrophobic drugs

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ABSTRACT
When gels and emulsions are used in combined form the dosage form are referred as emulgel. In recent years, there has been great interest in the use of novel polymers. Emulgel is an emulsion, either of the oil-in-water or water-in-oil type, which is gelled by mixing with a gelling agent. Emulgel shows dual release control system of the gel and emulsion. Many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. The emulgel for dermatological use has several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. The bioavailability of an emulgel can be enhanced by using permeation enhancers. The use of emulgel can be extended to analgesic, antifungal drugs & various cosmetic formulations.

KEY WORDS: Emulgel, Hydrophobic drugs, Permeation enhancers, Analgesic, Antifungal, Cosmetic.

INTRODUCTION
Topical drug delivery systems have been used for centuries for the treatment of local skin disorders. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. On the other hand, topical delivery system increases the contact time and mean time of drug at the applied site leading to an increase in local drug concentration while the pharmacological activity of emulgel formulation may not change as rapidly as the solution form. Topical drug delivery offers several advantages these avoids the first-pass metabolism and the gastric tract. Topical delivery has the potential for sustained controlled drug release. It is a non-invasive mode of drug delivery with no trauma or risk of infection.[1] Dermatological products which are applied to skin are diverse in formulation and range in consistency from liquid to powder but the most popular products are semisolid preparation.[2] (2. 231-335-1) The major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Relatively gels are a newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal solid particle. In spite of many advantages offered by gels a major limitation in the delivery of hydrophobic drug. So this limitation overcome by using an emulsion based approach where gels and emulsion are combined to form emulgel.[1] Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and

superior vehicle for hydrophobic or poorly water soluble drugs. In short emulgels are the combination of emulsion and gel. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used, so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In recent years, there has been great interest in the use of novel polymers which can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, greater shelf life, bio-friendly, clean and pleasant appearance.[3]

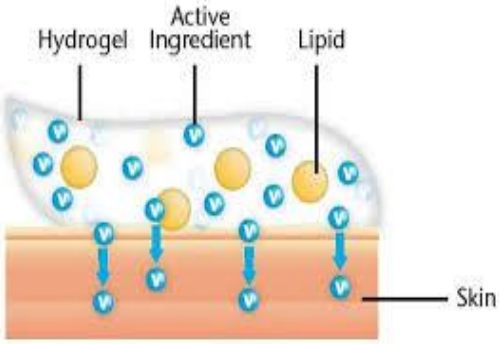


Fig.1. Emulgel structure

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG

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

PHYSIOCHEMICAL FACTORS

1. Partition coefficient.
2. Molecular weight (<400 Dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.[4]

ADVANTAGES OF USING EMULGELS AS A DRUG DELIVERY SYSTEM

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.

BETTER STABILITY

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

BETTER LOADING CAPACITY

Other novel approaches like niosomes and liposomes are of nano size 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.[1]

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 emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

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.

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).[4]

PATIENT COMPLIANCE

They are less greasy and easy to apply.[5]

Avoidance of first pass metabolism.

Convenient and easy to apply.

Avoidance of the risks and inconveniences of intravenous therapy and of varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time.

Avoidance of gastrointestinal incompatibility.

Providing utilization of drugs with short biological half-life, narrow therapeutic window.[6]

Self-applied medication

Improve patient complains.

Suitable for potent drug and drugs having shorter half life

Site specific drug delivery.

DISADVANTAGES OF EMULGEL

1. Large particle sized drugs are not easy to absorb through the skin
2. Some drugs have poor permeability through skin
3. On contact, skin irritation or allergic reaction may occur.[2]

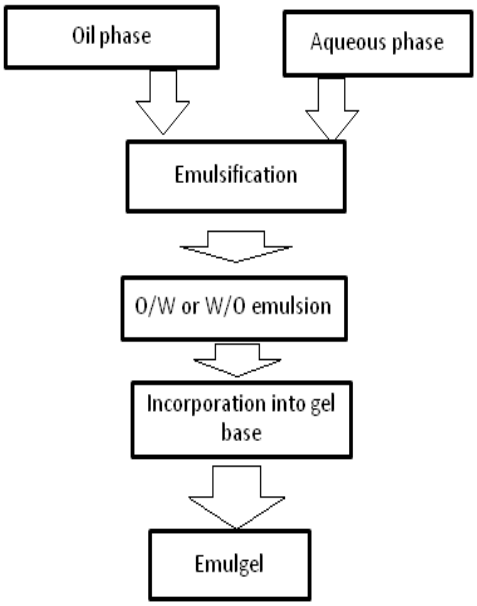
METHOD OF PREPARATION

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

The flow chart of emulgel preparation is shown in figure.[7]



PREPARATION OF EMULGEL

First, the gel was prepared by dispersing Carbopol 934 in heated purified water (80 °C), and the dispersion was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving Span 80 in liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl and Propyl parabens were dissolved in propylene glycol whereas drug was

dissolved in ethanol, and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70 to 80 °C then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel. Finally pH of emulgel was adjusted by using triethanolamine (TEA).[8]

CHARACTERIZATION OF EMULGEL

PHYSICAL APPEARANCE

The Emulsion formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter.

SPREADABILITY

Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used or the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) under 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 1Kg 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.

$$S = M * \frac{L}{T}$$

Where, S = spreadability,

M = Weight tied to upper slide,

L = Length of glass slides

T = Time taken to separate the slides completely from each other.

EXTRUDABILITY STUDY

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm2)

RHEOLOGICAL STUDIES

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.[7]

FTIR SPECTRA

The IR absorption spectrum of the pure drug is taken in the range of 4000-400 cm-1 using KBr pellet method. The major peaks are reported for evaluation of purity.[6]

SWELLING INDEX

To determine the swelling index of topical emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaoH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

$$\text{Swelling Index (\%)} = \left[\frac{Wt-Wo}{Wo}\right] * 100$$

Where, (SW) % = Equilibrium percent swelling,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of emulgel at zero time.

DRUG CONTENT DETERMINATION

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

Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

SKIN IRRITATION TEST (PATCH TEST)

The emulgel is applied on the properly shaven skin of rat and its adverse effect like change in color, change in skin morphology should be checked up to 24 hours. The total set of 8 rats can be used of the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated.

EX–VIVO BIOADHESIVE STRENGTH MEASUREMENT OF TOPICAL EMULGEL

(MICE SHAVEN SKIN)

The modified method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1 N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The right and left pans were balanced by adding extra weight on the left-hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg/ min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The bioadhesive strength is calculated by using following:

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

IN VITRO RELEASE STUDY

Franz diffusion cell (with effective diffusion area3.14 cm2 and 15.5 ml cell volume) was used for the drug release studies. Emulgel was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The sample (1.0 ml aliquots) were collected at suitable time interval. Sample were analyzed for drug content by UV visible spectrophotometer after appropriate 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.

ACCELERATED STABILITY STUDIES OF EMULGEL

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 analyzed 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.[7]

BIO ADHESIVE STRENGTH

The Bioadhesive strength of the emulgel is determined by means of modified analytical two pan balance. The burn human skin is washed with saline solution to 370 C before use. At the time of testing a section of skin was attached to upper glass vial using a rubber band. One vial with a part of tissue was connected to the balance and the other vial was fixed on a height adjustable pan. To the lower vial, emulgel applied. The height of the vial is adjusted so that the gel could adhere to the burn skin of upper vial, which is connected to the pan balance. Weights are added at a certain rate to the pan on the other side of the modified balance of the used device until the gel gets detached from skin. The bioadhesive strength, expressed as the detachment stress in dyne/cm2, was determined from the minimal weights required for the detachment using the following equation Bioadhesive Strength = Weight required (gm) / Area (cm2).[2] (232-335-1)

CONCLUSION

The main advantage of topical delivery system is to bypass first pass metabolism. 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. As the emulgel is the recent technique for the topical drug delivery it is better suitable for hydrophobic drugs and obviously it is a very good technique for drug delivery of combination of both hydrophilic and hydrophobic drugs. Mainly the hydrophobic drug formulation can be developed using emulgel technique because it contain both oil and aqueous phase while hydrogels are not suitable for hydrophobic drugs. Since emulgel is helpful in enhancing spreadibility, adhesion, viscosity and extrusion, this novel drug delivery become a popular formulation in future.

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