REVIEW ARTICLE

Emulsified gel A Novel approach for delivery of hydrophobic drugs: An overview

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ABSTRACT

A unique feature of topical drug delivery is the direct accessibility of the skin as target organ for diagnosis and treatment. Among the various group of semisolid preparation, the use of gel has expanded both in cosmetics and in the pharmaceuticals. Despite of several advantages of the gel there is limitation in delivery of hydrophobic drugs, so to overcome this limitation an emulsion base approach is being most used.
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 better vehicle for hydrophobic or poorly water soluble drugs. In short emulgels are the combination of emulsion and gel.
The major objective behind this formulation is the delivery of hydrophobic drugs to the systemic circulation via the skin .The emulgels for dermatological use has several favourable properties Such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, greater shelf life, bio-friendly, clear and pleasant appearance. Various penetration enhancers can potentiate the effect. So this can be used as superior topical drug delivery systems over present conventional systems available in market.

Keyword: Emulgel, hydrophobic drugs, topical drug delivery, penetration enhancer.

INTRODUCTION

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 favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, greater shelf life, bio-friendly, clear & pleasant appearance.

Emulgel is composed of two parts:

1. Emulsion.
2. Gel.

Emulsion: [6]

Emulsions are biphasic system in which one immiscible liquid is dispersed into other; due to this the system becomes unstable which is stabilized by emulsifying agents. Emulsion can be either o/w or w/o these are used as vehicles to deliver drug. Emulsions are stabilized by use of emulsifying agents. They can be easily washed off from skin and have good penetration capability.

Emulsions are of different types depending on the size of droplets or nature of distribution. [7,8]

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Macroemulsions:

These are most common type of emulsions where the particle size of droplets is more than 400nm. They are visually opaque but the individual droplets can be easily observed under microscope. Macroemulsions are thermodynamically unstable, but can be stabilized using surface active agents.

Types of Macroemulsions:

It is of two type's o/w and w/o. The type of emulsion formed depends primarily on the nature of emulsifier and on the ratio of components involved and method of emulsification.

Microemulsion:

Macroemulsions are thermodynamically stable, optically transparent, isotropic dispersions of aqueous and hydrocarbon liquids stabilized by an interfacial film of surfactant molecules. The monodispersed spherical droplets have diameter of 20nm to 200nm.

Double emulsion:

Small droplets of one phase (e.g. oil) dispersed in larger droplets of second phase(e.g. Water) with the latter further dispersed in the former (i.e. oil) as the continuous medium.

Gel [9]

The term "gel" represents a physical state with properties intermediate between those of solids and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity.

A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material. These are capable of undergoing large deformation in their physical state i.e. from solid to liquid.

Types of emulgels:

Macroemulsions gel:

These are most common type of emulgels where the particle size of droplets of emulsion is more than 400nm. They are visually opaque but the individual droplets can be easily observed under microscope. Macroemulsion are thermodynamically unstable, but can be stabilized using surface active agents. [10]

e.g. Khullar R. et al, mefenamic acid emulgel was prepared using Carbopol 940 as gelling agent. Liquid paraffin was used as oil phase. Mentha oil and clove oil was used as penetration enhancer. Then it was evaluated for rheological studies, spreading coefficient studies, skin irritation test, in-vitro release, etc. [11]

Nanoemulgel:

When nanoemulsion is incorporated into gel it is called as nanoemulgel. Nanoemulsions are thermodynamically stable transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. Nanoemulsion formulations possess improved transdermal and dermal delivery properties in vitro as well as in vivo. Nanoemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels.[12, 13,14]

e.g. Singh B. P et al, prepared Carvedilol nanoemulgel using oleic acid and isopropyl myristate (3:1) as oil phase. Tween 20 and Carbitol were used as surfactant and cosurfactant respectively. Carbopol 934 was used as gelling agent.

Microemulsion:

Microemulsions are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they do not coalesce. Microemulsions are composed of oil, surfactant, co-surfactant and water in specific proportions. The ingredients of microemulsion could facilitate the permeation rate of the drug by reducing the diffusion barrier of the stratum corneum. However, due to low viscosity of microemulsion, their less retention capacity in the skin restrains its application in the pharmaceutical industry To overcome this disadvantage, gelling agents such as Carbopol 940, xanthan gum and carrageenan have been added into the microemulsion for forming microemulsion based gel in order to increase its viscosity which could be

suitable for topical application. Moreover, microemulsion based gel prevents the absorption of drug in the blood stream and provide higher drug accumulation in the skin for efficient action.

E.g. Bachhav Y. G et al, prepared clotrimazole microemulsion based vaginal using Capryol 90 as oil phase and Cremophor EL as surfactant. Carbopol ETD 2020 is used as gelling agent. [15]

Material Use For The Preparation Of Emulgels [16, 17]

1) Aqueous material: This forms the aqueous phase of the emulsion. Commonly used agents e.g. water, alcohols.

2) Oils: These agents form the oily phase. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin's are widely used. In oral preparations non-biodegradable mineral and castor oils that provide a local laxative effect and fish liver oils or various fixed oils of vegetable origin (e.g., arachis, cottonseed, and maize oils) as nutritional supplements.

3) Emulsifier: Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life. e.g. Polyethylene glycol 40 stearate, Sorbitan mono-oleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate.

4) Preservatives: e.g. Propyl paraben, methyl paraben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol etc.

5) Antioxidants: e.g. Butylated Hydroxy Toluene(BHT), Ascorbyl palmitate, Butylated hydroxyanisole(BHA), etc.

6) Humectant: e.g. Glycerin, Propylene gylcol, etc

7) Gelling agents: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. e.g. Carbapol 934 , carbapol 940 ,HPMC ,HPMC-2910, sodium CMC .

8) Permeation enhancer: These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. e.g. Oleic acid ,lecithin , isopropyl myristate , urea , eucalyptus oil , chenopodium oil, pyrrolidone, laurocapran, dimethyl sulphoxide ,linoelic acid ,menthol.

Properties of penetration enhancer:

- They should be non-toxic, non-irritating and non-allergenic.
- They would ideally work rapidly and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically suitable with an appropriate skin 'feel'.

Mechanism of penetration enhancer: [18]

Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co enhancer or solvent into the stratum corneum.

Advantages of Emulgels: [19]

Hydrophobic drug can be easily incorporated into gel using o/w emulsion:

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 loading capacity:

Economical:

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.

Control released:

Emulgels can be used to prolong the effect of drugs having shorter T1/2.

Increases the stability of formulation.

Increases contact time and mean residence time of the drug.

Dual release of drug from emulsion and gel.

Emulgels used even for cosmetic purposes.

Topical Route: [20]

A topical dermatological product is designed to deliver drug into the skin in treating dermal disorders, with the skin as target organ.

The skin was not commercially or scientifically exploited as a route of delivery into the systemic circulation until the 1950's. Development of therapeutically effective ointments containing agents such as nitroglycerin and salicylates dispelled the notion that the skin was largely impermeable. Topical salicylates could be absorbed through the skin into the arthritic joints and more recently non-steroidal anti inflammatory agents such as ibuprofen and ketoprofen, estradiol and testosterone have been developed and marketed in semisolid preparations. Topical route is used for local action; it can also be used for systemic drug delivery. It is used to deliver drug at or immediately beneath the point of application. Some investigations with aprotic solvent vehicles such as DMSO also have generated interest in topical administration for systemic effects.

Factors Affecting Topical Absorption of Drug [21]

Physiological Factors

- Skin thickness.
- Lipid content.
- Density of hair follicles.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Inflammation of skin.

Physiochemical Factors:

- Partition coefficient.
- Molecular weight (<400 Dalton).
- Degree of ionization (only unionized drugs gets absorbed well).
- Effect of vehicles.

Topical Delivery Includes Two Basic Types of Products*:* [21]

- External topical that are spread, sprayed or otherwise dispersed on to cutaneous tissues to cover the affected area.
- Internal topical that are applied to the mucous membrane orally, vaginally or on a rectal tissues for local activity.

Advantages Topical Drug Delivery: [21, 22]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- 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 etc.
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intrapatient variations.
- Ability to easily terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.

- Improving physiological and pharmacological response.
- Improve patient compliance.
- Provide suitability for self-medication.

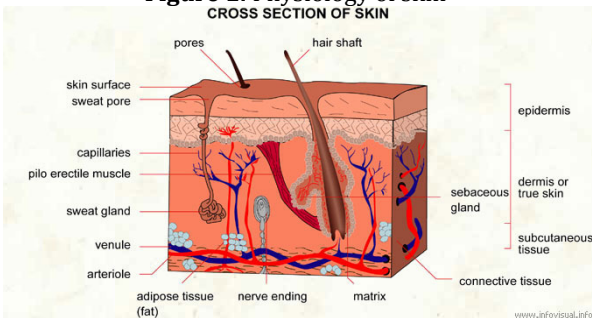
Disadvantages of topical drug delivery: [21, 22]

- Skin irritation of contact dermatitis may occur du e to the drug and excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Can be used only for drugs which require very small plasma concentration for action.
- Enzyme in epidermis may denature the drugss
- Drugs of larger particle size not easy to absorb through the skin.

Physiology Of Skin [23, 24]

Most of the topical preparations are meant to be applied to the skin. So, basic knowledge of the skin and its physiology function are very important for designing topical. The skin of an average adult body covers a surface area approximately $2m^2$ and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, the average 40-70 hair follicles and 200-300 sweat ducts on every square centimetre of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue as shown in figure.

Figure 1: Physiology of skin



1) Non-viable epidermis:

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate like structure 34-44 µm long, 25-36 µm wide, 0.5 to 0.20 µm thick - with surface area of 750 to 1200 µm stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingo lipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2) Viable epidermis:

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. The structures of the cells in the viable epidermis are physiochemically similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

3) Dermis:

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

4) Subcutaneous connective tissue:

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

Drug Delivery Across The Skin: [23]

The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibres. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially

important is a continuous venous plexus that is supplied by inflow 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 aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes.

There are three primary mechanisms of topical drug absorption:

Transcellular.

Intercellular.

Follicular.

Most drugs pass through the torturous path around corneocytes and through the lipidbilayer to viable layers of the skin. The next most common (and potentially under-recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body (systemic).

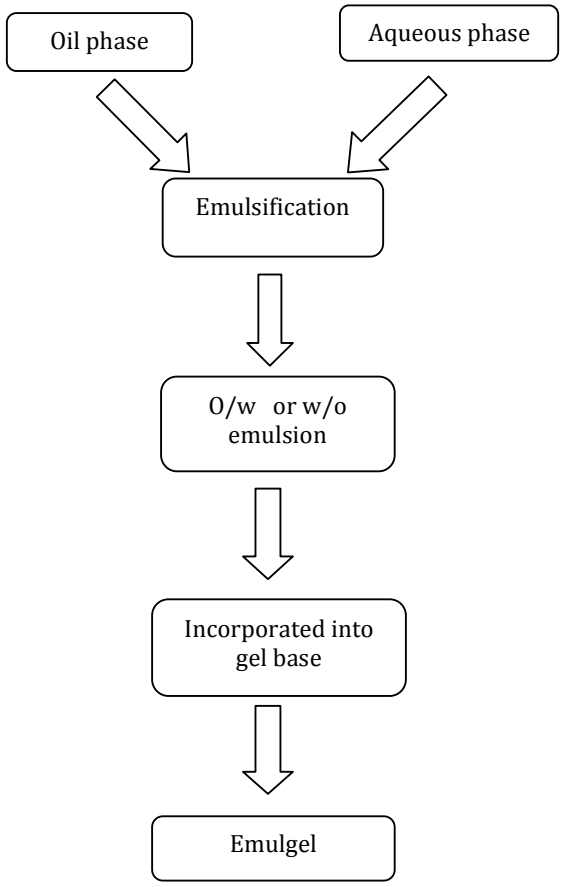
Rationale:

Various topical formulation are available used to apply on skin or mucous membrane restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. On the same time the topical agent such as ointment, cream, lotion have many disadvantages. They are sticky and causing uneasiness to the patients and also have lesser spreading coefficient and need to apply with rubbing. They exhibit the problem of stability also .due to all these factors within the major group of semisolid preparation, the use of transparent gel has expanded both in cosmetics and in pharmaceutical preparation.

Method of preparation of emulgels: [25]

Step-1

Oil/water emulsion



Drug is incorporated into either oil or aqueous phase depending upon its solubility.

Step 2

Formation of gel base.

Step 3

Incorporation of emulsion in gel base.

Preparation of gel phase:

The gel phase in the formulations is prepare by dispersing polymer in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5 using tri ethanol amine (TEA).

Preparation of oil phase of emulsion:

Oil phase of the emulsion is prepare by dissolving emulsifier e.g. span 20 in oil phase like light liquid paraffin.

Preparation of aqueous phase:

The aqueous phase is prepared by dissolving emulsifier e.g. tween 20 in purified water.

Preparation of drug solution:

The drug is dissolved in ethanol.

Characterization : [26, 27]

Physical examination:

The prepared emulgel formulation are inspected visually for there colour, homogeneity, consistency, and phase separation.

Rheological studies:

The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 and connected to a thermostatically controlled circulating water bath.

Spreadability: [28]

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.

$S=M\times L/T$

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 of Topical Emulgel (Tube Test):

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 0.5 cm 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 cm^2)

Swelling Index:

To determine the swelling index of prepared 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:

Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100.

Where,

(SW) % = Equilibrium percent swelling.

Wt = Weight of swollen emulgel after time t.

Wo = Original weight of emulgel at zero time.

Drug Content Determination:

Take 1gm of 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 same solvent. Concentration and drug content can be determined by using the same standard plot by putting the value of absorbance.

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

Skin Irritation Test (Patch Test):

The preparation is applied on the properly shaven skin of rat and its adverse like change in colour, 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.

In Vitro Release/Permeation Studies:

In vitro release studies were carried out using Franz diffusion cell.

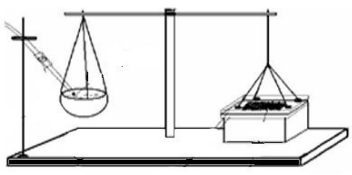
Ex–Vivo Bioadhesive Strength Measurement of Topical Emulgel:

(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 (cm^2)

Figure 1: Bioadhesive strength measurement apparatus



Stability Studies:

The prepared emulgels were packed in aluminum 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.

Marketed products of emulgel:

Sr. No	Brand name	Content	manufacturer
1	Voltaren emulgel	Diclofenac Diethyl Amine	Novartis Pharma Switzerland
2	Miconaz–H emulgel	Miconazole Nitrateand Hydrocortisone.	Medical Union , Pharmaceuticals , Egypt

CONCLUSION

Emulgels is one of the best approach for topical drug delivery of hydrophobic drugs, as emulgels has several favourable properties Such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Various penetration enhancers can potentiate the effect. So this can be used as better topical drug delivery systems over present conventional systems available in market.

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