Review Article

Emulgels- A Novel Approach for Topical Drug Delivery

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ABSTRACT

Emulgels have emerged as the interesting topical drug delivery system, it has dual release control system *i.e.*, gel and emulsion. The important objective behind this formulation is delivery of hydrophobic drugs to systemic circulation via skin. When gel and emulsion are utilised in combined, the dosage form is referred to as Emulgel. Many hydrophobic drugs are incorporated in oily base and are delivered to skin by using emulgel. Emulgels possess an edge in terms of adhesion, spreadability, viscosity and extrusion. Moreover, they will become a best solution for loading hydrophobic drugs in water soluble gel bases. Emulgels have several desirable properties for dermatological use such as being thixotropic, non-staining, greaseless, easily spreadable, long shelf life, emollient, easily removable, transparent, and pleasing appearance. The use of this emulgel based system as the drug delivery vehicles is reviewed, with particular emphasis being placed on recent developments and future directions.

Keywords: Emulgels, topical drug delivery system, emulsion, emollient, analgesics.

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INTRODUCTION

Over the last few decades, the treatment of illness has been done by administering the drug to the human body via various routes namely oral, rectal, sublingual, parental etc. The topical drug delivery system is generally used where these systems of drug administration fail or cause local skin infection like fungal infection. Topical drug delivery system can be defined as direct effects of formulation or drug containing medication to the skin to get the localizing effect of a drug or to cure cutaneous disorders. Dermatological products applied to skin are wide in formulation and range in consistency from the liquid to powder, but the most popular products are semisolid preparation. Topical drug delivery system has several advantages such as the ability to deliver a drug more selectively to a specific site or target site, avoidance of gastro-intestinal incompatibility and the metabolic degradation associated with oral administration. The drug release rates from topical preparations depend directly on the physiochemical properties of the carrier and the drug employed. In topical drug delivery system, the drug diffuses out of the delivery system, reaches to the site of action and gets absorbed by the skin. Increasing the drug release rate from the dosage form might therefore improve percutaneous absorption. Moreover, topical deliveries provide an more bioavailability by avoiding first pass metabolism effect by liver and a consistent delivery for an extended period. When emulsions and gels are combined together, the resulting dosage is referred to as an emulgel [1]. As it is a combination of emulsion and gel. In the past few years, there has been great interest in the use of novel polymers with complex functions as thickeners and emulsifiers because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing interfacial and surface tension and at the same time increasing the viscosity of the water phase. The presence of a gelatinizing agent, in the aqueous phase, converts a classical emulsion into emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver abundant drugs to the skin. Emulsions possess a certain degree of elegance and they are easily washed off whenever desired. They have a very high ability to penetrate the skin. Emulgels for dermatological use have several beneficial properties.

Now emulgels have been used for treatment of various kinds of skin diseases such as those infected by fungal, bacterial and viral species (acne, eczema, Herpes simplex). Research works on the antifungal drugs incorporated to emulgel have been carried by different scientists to judge its efficacy against the fungal infection such as Candidacies. Species causing candidiasis are Candida tropicalis, Candida albicans, Candida parapsilosis, Candida glabrata and Candida krusei. Formulating the emulgels was found useful in combating the fungal infection. Scientists have been trying to develop emulgel of various drugs to treat various kinds of skin diseases[2]. Acne is one of the major skin disorder which is common among adolescents. Factors that are responsible for acne are excess sebum, hormones, dead cells, Propionibacterium acne's and

inflammatory response. Approaches should be taken to prepare emulsion-based gel for treatment of such kinds of disorder. Anti-aging areas are yet to be explored, research on cream based formulations have been done using varieties of herbal moieties such as Curcuma longa, seeds of P.Coliforlia, Glycyrrhizaglabra, Cassia tora, Punicagranatum and Acacia catechu. Emulgel contains anti-inflammatory drug i.e Diclofenac which is used for relief of pain in muscle and joints [3].

Effort to cure diseases has been leading in the discovery of various drugs, delivery systems and medicine. To get the therapeutic response of a drug required for treatment of disease many different routes of administration are followed. Where the route of administration depends on type and severity of disease. For skin disorders, topical route is mostly preferred. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption[4].

Molecules can penetrate through skin mainly by three routes:

- ✓ Through the sebaceous follicle,
- ✓ Through intact stratum corneum, or
- ✓ Through sweat ducts.

The surface of the stratum corneum present is more than 99% of the total skin surface available for the percutaneous absorption of drugs. Passage through this outer layer, is the rate-limiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin; drug diffusion across the layers of the skin (diffusion coefficient) and release of drug from the vehicle (partition coefficient) [5].

Rationale of emulgel as a topical drug delivery system

Many widely used topical agents like lotion, cream, ointment, have many disadvantages. They are very sticky and cause uneasiness to the patient when applied. Moreover, they also have a lesser spreading coefficient and need to be applied with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparation, the use of transparent gels has expanded both in pharmaceutical preparation and in cosmetics.

A gel is a colloid, which is generally 99% weight liquid immobilised by surface tension between a macromolecular network of fibres built from a small amount of a gelatin substance present and itself. In spite of numerous advantages of gels, a major limitation is the delivery of hydrophobic drugs. So, to overcome this limitation an emulsion-based approach is used, so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through the form of gels [6].

Number of medicated products are applied to the mucous membrane or skin that either enhances or restores a fundamental function of skin or pharmacologically changes an action in the underlying tissues. Such products are referred to as dermatological or topical products.

Advantages of using emulgels as a drug delivery system

- ✓ **Production feasibility and low preparation cost**

The preparation of emulgels consists of small and simpler steps that increases the production feasibility. No specialized instruments are needed for the production of emulgels. Moreover, materials used are cheaper and easily available. Hence, they decrease the production cost of emulgels.

- ✓ **Hydrophobic drugs can be easily incorporated into gels using emulsions**

Many of the hydrophobic drugs cannot be incorporated directly into gel base because the solubility parameter acts as a barrier and problem arises during the release of the drug. The emulgel helps in the inclusion of hydrophobic drugs into the oil phase and oily globules are dispersed in water phase, resulting in o/w emulsion and this emulsion can be mixed into gel base. This may be proving better release and stability of the drug than simply incorporating drugs into gel base[7].

- ✓ **Controlled release**

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

- ✓ **Patient compliance**

They are easily applicable and are less greasy.

- ✓ **Better stability**

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

- ✓ **No intensive sonication**

Production of vesicular molecules requires intensive sonication which may result in drug leakage and degradation. But this problem is not seen during the production of emulgels because no sonication is needed[8].

- ✓ **Better loading capacity**

Other novel approaches like liposomes and niosomes are of nano size and due to vesicular structures, they may result in leakage and lesser entrapment efficiency. But gels due to the vast network have comparatively better loading capacity.

Disadvantages [9,10]

- ✓ Skin irritation on contact dermatitis.
- ✓ The occurrence of the bubble during formation of emuemulge

- ✓ Poor permeability of some drugs through the skin.
- ✓ The possibility of allergenic reactions.
- ✓ Drugs of large particle size are not easy to absorb through the skin.

Factors affecting topical absorption of formulations[3,4]

Physiological factors

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

Physiochemical factors

- ✓ Degree of ionisation (only unionised drugs get absorbed well).
- ✓ Molecular weight (less than 400Dalton).
- ✓ Partition coefficient.
- ✓ Effect of vehicles.

Factors to be considered when choosing a topical preparation[11]

- ✓ The medication should not affect the skin type.
- ✓ Irritation or sensitization potential, generally, w/o creams and ointments are less irritating, while gels are irritating. Ointments do not contain emulsifiers or preservatives if allergy to these agents is a concern.
- ✓ Effect of the vehicle e.g. penetration of the active ingredient is enhanced by an occlusive vehicle and it also improves efficacy. The vehicle itself may have a drying, cooling, emollient, or protective action.
- ✓ It should match the type of preparation with the site (e.g., gel or lotion for hairy areas).
- ✓ The type of preparation should be matched with the type of lesions. For example: for acute weepy dermatitis, avoid greasy ointments.

Physiology of skin[12]

Mostly the topical preparations are meant to be applied to the skin. Hence, a fundamental knowledge of the skin and its physiology function are very essential for designing a topical dosage form. The skin of an average adult body covers a surface area of about approximately $2m^2$. Non-viable epidermis and viable epidermis receives about 1/3rd of the blood circulating through the body. Human skin surface contains an average of 200-300 sweat ducts and 40-70 hair follicles on every square centimeter of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from the sebum influences the pH of the skin surface. The skin can be considered to have four distinct layers of tissue.

Non- viable epidermis

Stratum corneum is the utmost layer of skin, which is an authentic physical barrier to the most substances that come in contact with the skin. It is 10- 20 cell layers 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 a surface area of 750 to 1200 µm paired up to each other in brick-like fashion. Stratum corneum consists of lipids (5-15%) including phospholipids, cholesterol sulphate , glycosphingolipid and a neutral lipid protein (75-85%) which is mainly keratin.

Viable epidermis

Viable epidermis layer of the skin resides between the dermis and the stratum corneum. This layer has a thickness ranging from 50-100 µm. The structures of the cells in the viable epidermis are mostly physicochemically similar to the other living tissues. Cells are held together by tonofibrils and whereas, the density of this region is not much different than that of water. The water content is about 90%[13].

Dermis

Underneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like, they can be found histological in normal tissue. The thickness of dermis ranges from 2000 - 3000 µm and consists of a matrix of loose connective tissue which is composed of fibrous protein embedded in an amphorphose ground substance [14].

Subcutaneous connective tissue

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

Drug delivery across the skin

There are two important layers in the skin. They are dermis and the epidermis. Blood vessels are distributed profusely below the skin in the subcutaneous layer. There are three primary mechanisms for drug absorption through the skin and are namely, transcellular, follicular and trans cellular. The next most common route of delivery is through the pilosebaceous route where the permeation tends to occur through the intercellular matrix, but through the transcellular pathway, it has been shown to provide a rapid alternative route of highly polar molecules. In normal healthy or intact skin, it has been found that the keratinized corneocytes and the largely non-polar lipid intercellular cement of the horny layer are the main

elements involved in the maintenance of efficient barrier for drugs[15].

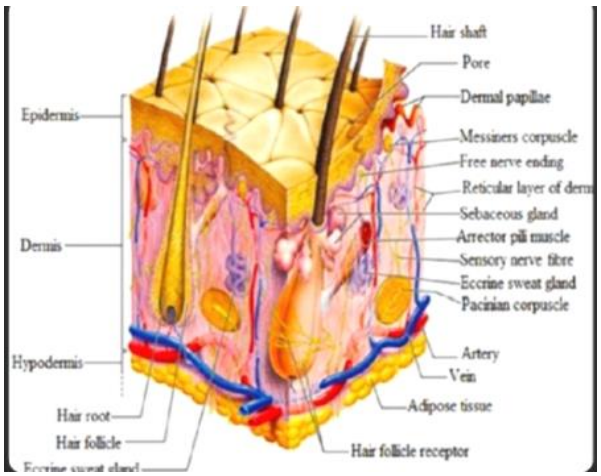

Figure 1: Cross section of skin

The drug penetration for skin can be enhanced by using organic solvents such as surfactants, propylene glycol and DMSO. The permeation enhancers altered the barrier properties of the stratum corneum by types of a mechanism including enhancing solubility, fluidising the crystalline structure of the stratum corneum[16] and partitioning the stratum corneum. Creams and gels that are rubbed onto the skin have been used for a long time for the effective treatment against infections and pain by medication. New technologies now allow the other drugs to be absorbed through the skin. These can be used to treat not only the affected areas of the skin but, the whole body by systemic route[17].

Constituents of emulgel [18,19,20]

Oils

Different oils of vegetable origin or fish liver oil, Mineral oil may be used.

Emulsifier

Acrysol K-140, 150, 160, Tween-20,40,60,80, Glycerine, Transcutol®- P, PEG- 300,400,600, Span- 20,40,60, Sepineo™ SE 68.

Penetrationenhancer

Clove oil, olive oil, isopropyl myristate, DMSO, propylene glycol, isopropyl palmitate, SLS, oleic acid, STGC, SDS,SDC, urea, lauracapram etc.

Aqueous phase

Sterile water, Rose water.

pH adjusting agent

Triethanolamine, NaOH.

Gelling agent

Sepineo™ P 600, sodium alginate, sodium CMC, carbomer 934, 934P, 940, HPMC, Gellan gum.

Preparation of emulgel

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 2.

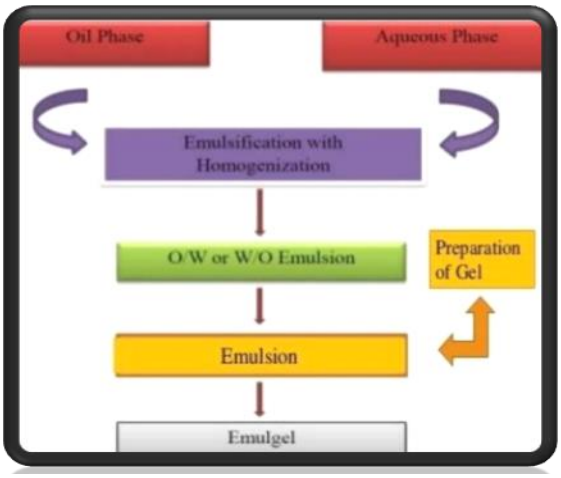

Figure 2: Flow chart of emulgel formulation

Table 1: Marketed preparations

Product name	Drug	Manufacturer
Avindo gel	Azithromycin	Cosme Pharma laboratories
Excex gel	Adapalene, Clindamycin	Zee laboratories
Clinagel	Allantoin, Clindamycin phosphate	Stiefel Pharma
Voltarenemulgel	Diclofenac diethyl ammonium	Novartis Pharma
Nadicin cream	Nadifloxacin	Psychoremedies
Acent gel	Capsaicin, Aceclofenac, Methyl salicylate.	Intra labs India Pvt Ltd
Miconaz-H-emulgel	Hydrocortisone, Miconazole nitrate	Medical union Pharmaceuticals
Lupigyl gel	Metronidazole	Lupin Pharma
Kojivit gel	Octinoxate, Kojic acid, Dipalmitate Arbutin	Micro Gratia Pharma
Zortene gel	Tezarotene	Elder Pharmaceuticals
Cloben gel	Neomycin, Clotrimazole, Beclomethasone dipropionate	Indoco Remedies
Topinate gel	Clabetasol propionate	Systopic Pharma
Pernox gel	Benzoyl peroxide	Cosme Remedies Ltd

Characterization of Gellified emulsion[5]

Physical appearance

The prepared emulsion formulations were checked visually for the homogeneity, color, pH and consistency. The pH values of 1% aqueous solutions of the prepared gellified emulsion were measured by a pH meter i.e digital pH meter[21].

Spreading Coefficient

Spreadibility is determined by apparatus which is suggested by Mutimer et al (1956). The apparatus is suitably modified in the laboratory and used for the study. It comprises a wooden block, which is provided by a pulley at one end . Through this a distance of 7.5 cm be noted. A shorter interval designates better spreadability[22] method, spreadability is determined on the basis of 'Drag' and 'Slip' characteristics of emulgels. A ground glass slide is fixed on this block. And the excess of emulgel of about 2 gm under the study is placed on this ground slide. The emulgel is then interposed between this slide and another glass slide, which is having the dimension of a fixed ground slide and provided with the hook. A 1 Kg weight is kept on the top of 2 slides for five minutes to expel the air and to provide a uniform film of the emulgel between the slides.

S= M.L/T

Where, S = spreadability,

M = Weight tied to upper slide,

L = Length of the glass slides

T = Time taken for the separation of slides completely from each other.

Rheological Studies

Viscosity of the many emulgel formulations was found at 25°C using a plate and cone viscometer, Spindle 52 and thermostatically controlled circulating water bath[5].

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 in a 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.

Extrudability Study of Topical Emulgel (Tube Test)

It is an empirical test to measure the force required to extrude the material from a 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 is required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. The more quantity extruded, better is the extrudability. The measurement of extrudability of each formulation is triplicated and the average values are presented. Extrudability is then calculated using the below formula:

Extrudability =Applied weight to extrude emulgel from tube (in gm) / Area (in cm^2)[5].

Skin Irritation Test (Patch Test)

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

Drug Content Determination

Take 1gm of emulgel. Mix it in suitable solvent. Filter it to obtain a clear solution. Determine its absorbance using UV spectrophotometer. Standard plot of drugs 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 plot equation: Drug Content = (Concentration × Dilution Factor× Volume taken) × Conversion Factor.

In-vitro Release/Permeation Studies

In-vitro release studies were carried out using Franz diffusion cells.

CONCLUSION

Many drugs are hydrophobic in nature. The delivery of these drugs to the biological system have be challenging. Creams, ointments and lotion which has been applied topically have excellent emollient properties but retards the release of drugs due to presence of oleaginous bases. As compared to other topical delivery systems gel provides quick drug release as they provides aqueous environment to drugs. Many hydrophobic drugs are incorporated in oily base and are delivered to skin by using emulgel. Emulgels possess an edge in terms of adhesion, spreadability, viscosity and extrusion. Moreover, they will become a best solution for loading hydrophobic drugs in water soluble gel bases.

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