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Pharmaceutical Microemulsion Gel: Functioning as a Drug Delivery System

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ABSTRACT

Pharmaceutical gel is a semisolid system consisting of dispersion of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid. This colloidal preparation is typically 99% liquid by weight. The purpose of the review study was to search the literature and provide most current information regarding pharmaceutical microemulsion gel formulation. Information was obtained from published works in scientific journals, official books and other pharmaceutical relevant books. Academic institution library as well the internet websites assisted in the information gathering. The results of the study gave pharmaceutical gel classification, chemical compounds utilized in the formulation, formulation of microemulsion gel and factors to be considered, characterization of the microemulsion based gel, ideal properties of microemulsion based gel, advantages and disadvantages of microemulsion based gel, as well as applications of microemulsion based gel. The study has revealed that well formulated and characterized microemulsion-based gels are capable of delivering both hydrophobic and hydrophilic drugs transdermally into the systemic circulation.

Keywords: Pharmaceutical gel; Microemulsions; Transdermal drug delivery; Bioavailability enhancement; Solubility enhancement

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INTRODUCTION

Pharmaceutical gel like ointments, creams and lotions is semisolid formulation immobilized by surface tension between it and a macromolecular network of fibers made from a small amount of a gelatinous substance present [1,2]. Microemulsions are isotropic thermodynamically stable transparent pharmaceutical formulations that form spontaneously at certain concentrations of oil, surfactant, cosurfactant and water [3,4]. The cosurfactants (alcohols, amides, sulfoxides) assist the formulation to attain an appropriate fluidilty or viscosity of the interface. Microemulsion droplet size is usually in the range of 20-200 nm. Microemulsion has the potential to incorporate a wide range of hydrophilic and hydrophobic drug molecules because it contains both lipophilic and hydrophilic domains. Microemulsion as a delivery system can improve the solubilization of lipophilic drugs and thus enhance

their bioavailability [5-7]. The delivery of microemulsion-loaded drugs can be achieved through oral and intravenous delivery, transdermal delivery or sustained and targeted delivery. Microemulsion gel formulation is used to overcome the inability of gel to deliver hydrophobic drugs. The present review paper will focus on classifying gels; ideal properties of microemulsion gels; delineates the conditions necessary to produce microemulsion gels; methods commonly used to determine microemulsion gels properties; characterizing microemulsion gel formulations; advantages and disadvantages of microemulsion gel formulations and discuss microemulsion gels as a drug delivery system.

Classes of Pharmaceutical Gels

Pharmaceutical gels are grouped based on [8,9]

Nature of colloid phase, for examples (i) inorganic gels (ii) organic gels.

Nature of solvent, namely (i) aqueous gels (ii) non aqueous gels.

System microstructure, such as (i) covalently bonded polymer network with totally disordered structure. Synthetic hydrophilic polymers are normally used to prepare covalently cross-lined gel networks which are irreversible systems. Infinite gel network emerges from the non-linear copolymerization of at least two monomer species with one being at the minimum trifunctional in the preparation. By the end of the preparation, the final microstructure of this gel is totally disordered because both direction and position by which every polymer chain develops during the reaction is random. (ii) Physically bounded polymer network prevalently found, however containing ordered loci and are reversible systems. Transition between the sol and gel phases can be instigated by factors such as temperature and ion additives. Natural organic polymers (proteins and polysaccharides) and semi synthetic derivatives are mainly used to form these gels. (iii) Well-ordered lamellar, which includes gel mesophases formed by inorganic clays. Certain silica, alumina and clay soils form rigid gels or lyogels at suitable conditions. Gels can be produced when clay, for example bentonite, hectorite and loponite, undergo interlayer swelling spontaneously followed by osmotic swelling as they come into contact with water. The plate like clay particles associates into a "cubic cardhouse" ordered structure that is stabilized by repulsive forces, due to interacting electrical double layer.

Pharmaceutical Gel Forming Substances

Polymers: For the preparation of gels, polymers are imperative and are utilized to give the structural network [8]. Gel forming polymers can be grouped as follows:

Natural polymers: Such as proteins (collagen, gelatin) and polysaccharides (agar, alginate acid, sodium or potassium carageenan, tragacanth, pectin, guar gum, cassiatora, xanthan, gellum gum).

Semi-synthetic polymers: (cellulose derivatives) to be specific carboxymethyl cellulose, methylcellulose, hydroxypropyl cellulose, hydroxy propyl methyl cellulose and hydroxyethyl cellulose.

Synthetic polymers: For example carbomers (carbopol 940, carbopol 934), poloxamer, polyacrylamide, polyvinyl alcohol, polyethylene and its co-polymers.

Non-polymers: Non-polymers substances utilized in pharmaceutical gels include:

Inorganic substances: Aluminium hydroxide and bentonite and so on.

Surfactants: Cebrostearyl alcohol and Brij-96 and so on.

Classification of Microemulsion

There are various types of microemulsion based on the ratios between the components. Oil in water microemulsions (o/w microemulsion) are formulated when oil droplets are dispersed in water phase whereas water in oil microemulsions (w/o microeemulsion) is formed when very tiny water droplets are dispersed in oil phase. There are mixture changes continuously from one to another extreme, for instance, from a cylindrical to tubular, spherical in the microstructure of bicontinuous microemulsion and in the middle, a very thin layer of surfactant molecule divides the interconnected continuous oil and water phases [10]. Each type of microemulsions are transparent solutions and thermodynamically stable.

Microemulsion-based Gel

The major limitation of gels is the inability to convey hydrophobic drugs. Microemulsion approach is used to overcome this constraint. The lipophilic drug is successfully incorporated directly into the microemulsion and the microemulsion containing the lipophilic drug is then added into appropriate gel. Microemulsion-based gels are the term given to the combined dosage form of microemulsion and gel. Both hydrophilic and hydrophobic drugs are able to be delivered by microemulsion-based gels since hydrophobic drugs can be entrapped by the oil in water system while the reverse water in oil systems are used to encapsulate hydrophilic drugs. Micoemulsion-based gels could be water-in-oil (organogels) delivery systems or oil-in-water (hydrogels).

Optimal Characteristics of Microemulsion Based Gel

Microemulsion-based gel has the following characteristics: Microemulsion-based gel should be;

Non-toxic, Economical and efficient, Inactive, compatible with other additives, free from microbial contamination maintained all rheological properties of the gel, stable at storage condition, washed with water and free from staining nature, convenient in handling and its application [11].

Advantages of Microemulsion Based Gel

Better stability: The microemulsion based gel has better stability when compared with other transdermal preparations. It does not show phase inversion or breaking as found creams, creaming effect as in normal topical emulsion, rancidity (due to oily base) as in ointment and hygroscopic properties as in powders [1,12].

Greater loading capacity: When compared with other novel approaches like liposomes and niosomes, gels have comparatively greater loading capacity of the drug due to vast network.

Production feasibility: Production of microemulsion-based gel is carried out in short and simple steps, this increases the feasibility of the preparation also in the preparation of microemulsion-based gels, no specialized instruments needed for the production.

Low production cost: The production cost of microemulsion- based gels are low because the materials used are cheap and easily accessible.

Incorporation of hydrophobic drugs: The major problem of incorporating most of the hydrophobic drugs (mainly Biopharmaceutical class 11 drugs) directly into the gel base is solubility. Microemulsion-based gel helps to avoid this constraint. Microemulsion-based gel incorporates these lipophilic drugs into the oil phase and then oily globules are dispersed in an aqueous phase bringing about o/w emulsion. Instances of such drugs are ketoconazole, fluconazole, and so on.

No intensive sonication: Intensive sonication is needed in the preparation of vesicular molecules which may result in leakage and drug degradation. But this problem is not encountered during the preparation of microemulsion-based gel as sonication is not required.

Avoids first pass effect: Concentration of drugs are reduced as the drug substance move through the portal circulation following gastrointestinal absorption. The deactivation of the drug by digestive and liver enzymes can be avoided by the use of microemulsion-based gels.

Controlled release: The effect of drugs having shorter half-lives can be prolonged by the use of microemulsion based gel.

Gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity also drug interaction with foods and drinks can be avoided.

Oxidation and hydrolysis of drugs does not occur since microemulsion based gel provides protection as it is not exposed to attack by air and water. The efficacy of a drug can improve by the use of microemulsion based gels as a delivery system, this reduces side effects by allowing the total dose to be decreased.

The use of microemulsion based gels as a delivery system ultimately leads to increase in the rate of absorption and bioavailability of drug because microemulsion based gel increases the rate at which drug substances penetrate the skin barrier.

Microemulsion based gel can easily be removed from the skin since it is less greasy in nature. It is non-invasive and patient compliance is increased.

Disadvantages of Microemulsion Based Gel

The disadvantages of microemulsion-based gel are as follows [1,2];

Poor absorption because of poor permeability of some drugs through the skin. Microemulsion-based gel can only be used for drugs which need very small plasma concentration for action. Allergenic reactions may occur.

Formulation Consideration for Microemulsion-Based Gel (MEG)

Factors to be considered during the process of formulating microemulsion-based gels are stated below [1,2]:

Drug substance: For a successful development of MEG judicious choice of drug substance plays a significant role. There should be thorough examination of both the physicochemical properties (molecular weight, pH, etc.) and the biological properties (tolerance, irritation).

Vehicle (micromeulsion): The vehicle selected should be able to deliver and release drug at the required site, sustain a therapeutic drug level for a sufficient period to provide a pharmacological effect and maintain even distribution of the drug substance on the skin. Depending majorly on the properties of the vehicle, the rate and extent of absorption vary.

Penetration enhancers: Penetration enhancers alter the structure of the skin thereby promoting skin permeability. These are considered as fundamental part of most topical formulations. Water, oils, surfactants and co-surfactants can be used as penetration enhancer in most cases.

Gelling agent: It is used to improve the consistency of any dosage form and can also be utilized as thickening agent.

Preservatives: To resist microbial attack, a preservative is used. Examples include methyl paraben, propyl paraben.

Chelating agent: Chelating agents are incorporated in the formulation to avoid any further reaction because bases and medications in gels are sensitive to heavy metal. Examples of chelating agents include ethylenediamine tetra acetic acid (EDTA) and methylated cyclodextrin.

METHODS

Methods of preparation of microemulsion-based gel includes

Dispersion method: The polymer is dispersed over water for 2 hours and allowed to soaked with water in this method. A homogenous mass is achieved after the addition of chemical ingredients with adequate mixing and stirring [9,13].

Cold method: Under low temperature (at about 50°C), all the constituents are mixed together to form a homogenous mass. In this method, a solution containing the drug is formed by the addition of the drug to the appropriate solvent. Another solution is formed by the adding permeation enhancer into the polymer. The microemulsion-based gel is achieved by pouring the drug solution into polymer solution containing the enhancer gradually with complete stirring.

Chemical reaction: In this method, microemulsion-based gel is prepared by precipitation from solution. For example, aluminum hydroxide is precipitated by reacting sodium carbonate and aqueous solution of an aluminum salt. A gel structure is produced when the concentration of reactants is increased. Another example is silica gel, it is prepared by the reaction of sodium silicate and acids in aqueous solution.

Temperature effect: The solubility of most lyophilic colloids, for example agar, gelatin, sodium-oleate, are decreased at lower temperature. The hydrogen bonding of these sols break at increased temperature and the decreased solubility will produce gel.

Flocculation with salts and non-solvents: Gelatin is a well-known collagen derivative mainly utilized in food, pharmaceutical, photographic and technical products. Gelatin has the capacity to melt in-the-mouth in foods and achieves a thermo-reversible gel property. Gelatin is prepared by adding sufficient amount of precipitant which will bring about complete precipitation to produce the gel structure state. Rapid mixing is necessary to avoid high concentration of precipitants. Rapid mixing of appropriate amount of a non-solvent such as petroleum ether can be used in gelling solutions of ethyl cellulose, polystyrene, etc, in benzene. Moderate sols such as aluminum hydroxide, ferric hydroxide and bentonite produce gels by the addition of salts to the sols.

Characterization of Microemulsion Gel (MEG)

Microemulsion-based Gel (MEG) can be characterized by determining the following factors [14-17]: pH, drug content, viscosity, spreadability, extrudability study, skin irritation studies, *in vitro* release, *in vivo* study, stability and consistency.

Measurement of pH

Digital pH meter is used to determine pH of various gel preparations. About one gram of gel is dissolved in 100 ml distilled water and allowed to stay for two hours. The measurement of pH of each preparation is normally done in triplicate and average value calculated.

Drug Content

100 ml of suitable solvent is mixed with about 1gm of the prepared gel. Suitable dilutions are made to prepare aliquots of different concentrations. After filtering the stock solution, absorbance is measured. The equation, obtained by linear regression analysis of calibration curve is used to calculate drug content.

Viscosity Study

Brookfield Viscometer is used to measure the viscosity of the prepared gel. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. The corresponding dial reading is noted at each speed. Multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues is carried out in order to obtain the viscosity of the gel.

Spreadability

Good spreadability is one of the criteria; a gel must possess in order to be effective. The extent of area to which a gel readily spreads when applied to skin or affected part is known as spreadability. The spreading value of a formulation greatly affects its therapeutic efficacy. It is expressed in terms of time in seconds taken by two slides to slip off from gel placed in between the slides under the direction of certain load. Spreadability will be better if the time taken to separate the two slides is small. It is determined by using the formula:

S=M.L/T

Where M: Weight tied to upper slide, L: Length of glass slides, T: Time taken to separate the slides.

Extrudability Study

In extrudabilty study the formulations are allowed to set in a container after which they are filled in the collapsible tubes. The extrudability of the gel is determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 seconds.

Skin Irritation Study

Skin irritation study is carried out using guinea pigs (400-500 gms) of either sex. The animals are held under standard conditions and are maintained on standard animal feed and had free access to water. The guinea pig's hair is shaved from back and area of 4 cm^2 is marked on both the sides, one side served as test and the other side as the control. Gel is applied (500 mg/guinea pig) twice a day for 7 days and the site is observed for any sensitivity. The reaction if any is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

***In vitro* Diffusion Studies**

The *in vitro* diffusion studies of the gel formulations can be carried out using Franz diffusion cell. Franz diffusion cell is used for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5 gms) is placed in cellophane membrane and the diffusion studies are carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample is withdrawn intermittently at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample is replaced with the same volume of fresh dissolution medium. The samples are then analyzed for the drug content by using phosphate buffer as blank.

Stability

The stability studies for all gel formulations are carried out by freeze-thaw cycling. This involves subjecting the formulation to a temperature of 4°C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. Gel is exposed to ambient room temperature at the end and liquid exudates' separating is recorded.

Consistency

The consistency of the gel formulation is measured by dropping a cone affixed to a holding rod from a fixed distance of 10 cm in such manner that it should fall on the centre of the glass cup filled with the formulation. The penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is recorded after 10 seconds.

Application of Microemulsion Based Gel

Microemulsion based gel has been utilized in the following areas: When compared to conventional formulations such as solutions, gels or creams, microemulsion based gel enhance the transdermal permeation of drugs significantly [18-20].

They are able to incorporate both hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine, hydrochloride, tetracaine hydrochloride, methotrexate etc.) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide, etc.).

High solubilizing capacity of the formulation makes it possible for the incorporation of large amount of drug.

The affinity of a drug to the internal phase in micro emulsion may be easily altered to favor partitioning into the stratum corneum, thereby increasing the rate of permeation of the drug from the micro emulsion as a result of increase in thermodynamic activity towards the skin.

The diffusional barrier of the stratum corneum may reduce by using different internal phases that act as penetration enhancers. If the water content in the gel preparation is sufficiently high, the percutaneous absorption of drug will increase because of the hydration effect of micro emulsion based gel on the stratum corneum.

It is a dual controlled release system because of the incorporation of micro emulsion into gel. Problems associated with micro emulsion for example phase separation, creaming is avoided. Micro emulsion based gel loaded with specific drugs has been found effective in some topical disorders for instance fungal and rheumatic disorders [21-25].

CONCLUSION

Microemulsion gels have the ability to protect labile drug, increase drug solubility, increase bioavailability, control drug release and reduce patient variability. Furthermore, percutaneous absorption of drug will increase due to the hydration effect as well as increase in thermodynamic activity towards the skin. The delivery system can also provide protection against oxidation, enzymatic hydrolysis of drugs. They could be amenable for sustained and targeted delivery through ophthalmic, dental, pulmonary, vaginal and topical routes. The organogels are preferred over hydrogels because hydrogels are susceptible to microbial contamination. Finally, the use of micro emulsion-based gels offers many potential benefits as drug delivery systems despite some challenges that might be associated with such formulations.

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