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Review article

Micro emulsion based gel: recent expansions for topical drug delivery system

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ABSTRACT

Micro emulsion based Gel formulation provides better application property and stability & makes it dual control release system in comparison to cream and ointment. Topical Micro emulsion based gel drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation Micro emulsion based approach is being used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. When gels and Micro emulsions are used in combined form the dosage form are referred as Micro emulsion based gel. It is prepared by mixing an oil-in-water type or water- in-oil type emulsion with a gelling agent. The use of Micro emulsion based gels can be extended in analgesics and antifungal drugs.

Keywords: Antifungal activity, Gelling agent, Hydrophobic drugs, Micro emulsion gel, Topical drug delivery.

INTRODUCTION

Topical dosage forms have been used since very ancient times. The application of medicinal substance to skin or to various body orifices is a concept as old as humanity. Various ointments, creams, gels, lotions, pastes, powders and plasters have been used for many years. The primary topical drug delivery system (TDDS) is that could provide controlled constant administration of a medicament by simple application to the skin surface. Topical delivery administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Efforts to cure diseases have been leading in the discovery of various drugs, medicine and delivery systems. Route of administration depends on type and severity of disease. For skin disorders topical route is most preferred. Topical drug delivery system can be defined as direct application of formulation containing medication to the skin to get localized effect of drug [1].

Topical drug delivery system has several advantageous such as ability to deliver drug more selectivity to specific site. Most and favorable reason for using topical delivery is avoidance of gastro-intestinal incompatibility and metabolic degradation associate with oral administration. Moreover, topical delivery provides an increased bio-availability by avoiding first pass metabolism by liver and a consistent delivery for extended period. The release rates of drugs from topical preparation depend directly on the physiochemical properties of the carrier and the drug employed.

Gel is semisolid system of at least two interpenetrating phases: a gelling agent and a liquid. When gel and Micro emulsion are used in combined form and the dosage forms are referred as Micro emulsion based gel. Micro emulsion based gels have emerged as one of the most interesting topical drug delivery system as it has dual control release system i.e. gel and Micro emulsion. The Micro emulsion based gel 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, transport, and pleasing appearance, transparent, etc Micro emulsions have gained a great attention for delivery of hydrophobic agents for systemic and local treatment. Also, gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydro alcoholic liquid in a network of colloidal

solid particles. Which may be consist of inorganic substances such as aluminium salts, organic polymers of natural and synthetic origin.

For topical delivery semisolid preparation are widely accepted over solid and liquid dosage forms. Micro emulsions, which are optically isotropic and thermodynamically stable systems of water, oil, surfactant, and co-surfactant, can be used as drug delivery system because of their capacity to solubilise poorly water-soluble drugs as well as their enhancement of topical. For topical delivery Micro emulsion is incorporated in to gel base to prolong the local contact to the skin.

Advantages of topical drug delivery system

Avoidance of gastrointestinal incompatibility

Avoidance of first pass metabolism more selective to a specific site (local action)

Ketoconazole Microemulsion based gel directly penetrate in to specific site where is it suffering from fungal disease and start to results in inhibition of Ergosterol synthesis.

Disadvantages of topical drug delivery system

Skin irritation of dermatitis may occur due to the drug or excipients.

Possibility of allergic reactions

Main limitations of Micro emulsion based gel that remains are poor absorption of microparticle via skin and entrapment of bubble during formulation

Some drugs of larger particle size not easy to absorb through the skin.

The Skin

The skin is the most extensive and readily accessible organs of the human body. The skin of an average adult body covers a surface area of approximately 2 cm2 (or 3000 inch2) and receives about one-third of the blood circulating through the body. It is elastic, rugged and under normal physiological conditions. Self-regenerating, with a thickness of only a few mm (2.97 ± 0.28mm).

Anatomy of Skin

The skin is one of the largest organs of the body in surface area and weight. In adults, the skin covers an area of about 2 square meters and weight 4.5 to 5 kg. Structurally, the skin consists of two principle parts. The outer, thinner portion, which is composed of epithelium is called epidermis. The epidermis is attached to the inner, thicker, connective tissue part called dermis.

Epidermis

The epidermis is composed of stratified squamous epithelium and contains 4 proncipal types of cells. Epidermal cells are keratinocytes cell, malenocytes cell, langerhans cells, Merkel cell. The names of the five layers (strata) from the deepest to the most superficial are.

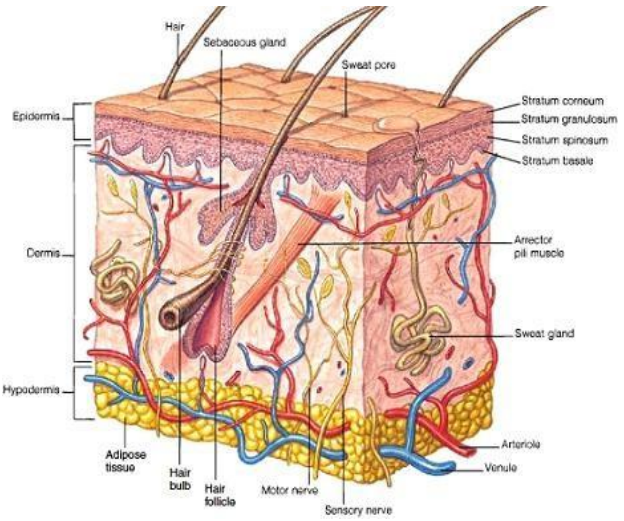
Stratum basale: this single layer of cuboidal cells contains stem cells which are capable of continued cell division and melanocytes. The Stem cells producing keratinocytes, which push up toward the surface and become part of the more superficial layer.

Stratum spinosum: this layer of the epidermis contains 8 to 10 rows (sheets) of polyhedral cells that fit closely together. Many cells have delicate “spines” producing from their surface, hence also called as “prickle cells”. Some new cells are formed and are pushed to surface to replace conified cells of stratum corneum.

Stratum granulosum: The third layer of the epidermis consists of three to five rows of flattened cells that develop darkly staining granule of a substance called keratohyaline.

This layer initiates the process of keratinisation, associated with dying process of cells.

Figure 1: Cross section structure of skin



Stratum Lucidum: Normally only the thick skin of the palms and soles has this layer. It consists of three to five rows of clean, flat, dead cells that contain droplets of an intermediate substance that is formed from keratohyalin and is eventually transformed to keratin.

Stratum Corneum: this layer consists of 25 to 30 rows of flat, dead cells completely filled with keratin. These cells are continuosly shed and replaced by cells from deeper strata.

Dermis

The second principal of the skin, the dermis is composed of connective tissue containing collagen and elastic fibers. The outer portion of dermis, about one-fifth of the thickness of the total layer is named the papillary region. It consists of alveolar connective tissue containing five elastic fibers. The deeper portion of the dermis is called the reticular region.

Epidermal derivatives

Hair: hairs or Pilli are growths of the epidermis variously distributed over the body. Their primary function is protection. Although the protection is limited, hair on the head guards the scalp from injury and the sun rays. It also decreases heat loss. Glands: several kinds of glands are associated with the skin viz. Sebaceous glands, sundoriferous glands, and ceremonious glands.

Sebaceous glands: sebaceous glands or oil glands with few exceptions are connected to hair follicle. Sebaceous glands secrete an oily substance called sebum.

Sundoriferous (sweat) glands: three to four million Sundoriferous or sweat glands empty their secretions onto the skin surface. They are divided into principal types, eccrine and apocrine, based on their structure, location and type of secretion.

Sweat: is the fluid produced by fluid glands, mainly eccrine sweat glands because they are so much numerous.

Nails: are plates of tightly packed, hard keratinized cells of epidermis. The cells form a clear, solid covering over the dorsal surfaces of the terminal positions of the figures and toes. Each nail consists of a nail body, a free edge and a nail root.

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinized squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibers. Skin forms a relatively waterproof layer that protects the deeper and more delicate structures. The outer most epidermis layer is approximately 100-150-µm thick. And has no blood flow and induces a layer within it known as the stratum corneum. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, then it can enter the blood stream and the process is known as passive diffusion. 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 arteriolar venous anatomizes. Such as fatty acid, surfactants, co-surfactants include enhancing solubility partitioning the stratum corneum, fludizing the crystalline structure of the stratum corneum and dissolution of the stratum corneum lipids can enhance drug flux. Due to low permeability co-efficients of micromolecules. The enhancement effects required to ensure delivery of pharmacologically effective concentrations are likely to be beyond the capability of chemical enhancers tolerated by the skin. Therefore, several new active transport technologies have been developed for the transdermal delivery of troublesome drugs [2].

Factors affecting topical absorption of drug

Physiological Factors

Skin thickness.

Lipid content.

Density of their follicles.

Density of sweat glands.

Skin pH.

Blood flow.

Physiochemical Factors

Partition coefficient.

Molecular weight (<600Dalton).

Degree of ionization (only unionized drugs gets absorbed well).

Method to enhance drug penetration and absorption.

Chemical enhancement

Physical enhancement

Biochemical enhancement

Super saturation enhancement

Fungal Diseases

Fungi

Fungi are eukaryotic protista that differ from bacteria and other prokaryotes. They possess rigid cell walls containing chitin, mannan and other polysaccharides. The cytoplasmic membrane contains sterols. They possess true nuclei with nuclear membrane and paired chromosomes. They divide asexually, sexually or by both processes. They may be unicellular or multicellular.

Fungi had been recogniazed as causative agents of human disease earliar than bacteria. Fungi causing farms and thrush (candidia albicans) had been described as early as in 1839.

Fungus infections are extremely common and some of them are serious and even fatal. With the control of most bacterial infections in the developed countries, fungus infections have assumed greater importance.

Classification

Depending on cell morphology fungi can be divided into four classes:

Yeasts

Yeast like fungi Moulds

Dimorphic fungi Yeasts

The yeasts are unicellular fungi which occur mainly as single spherical or ellipsoidal cells and reproduce by budding on artificial media, they from compact colonies with a creamy, mucoid or pasty consistence (e.g., like those of Staphylococcus). Cryptococcus neoformens is the only important pathogen.

Yeast like fungi

The yeast like fungi grow partly as yeast and partly as long filamentous cells joined end to end, forming a “pseudo-mycelium” e.g., candida Albicans.

Moulds

The moulds (filamentous, mycelia fungi) grow as long filaments or hyphae which branch and interlace to form a meshwork or mycelium, and reproduce by the formation of various kinds of spores. When grown to a large size on artificial medium, the mycelium is seen as a filamentous mould colony, this may become powdery on its surface due to the abundant formation of spores (e.g., ring worm fungi) [3].

Dimorphic fungi

Dimorphic fungi can occur as filamentous or as yeasts, depending on the conditions of growth. In those tissues or cultures at 370C they occur as yeasts, while in the soil and in cultures at 220C, they appears as moulds. Most fungi causing systemic infections are dimorphic fungi.

Fungal infections

Fungal infections are termed mycoses and in general can be divided into superficial infections (affecting skin, nails, hairs, or mucous membrane) and systemic infections (affecting deeper tissues and organs).

In the last 20-30 years, there has been a steady increase in systemic fungal infections, not only by known pathogenic fungi but also by fungi previously thought to be innocuous. There last are termed opportunistic infections. In the UK, the commonset systemic fungal infections is systemic candidiasis. In the rest of the world the commenset systemic fungal infections are blastomycosis, histoplasmosis, coccidimycosis and paracoccidiomycosis.

Superficial fungal infections

Superficial fungal infections can be classified into the dermatomycoses and candidiasis.

Dermatomycoses

Dermatomycoses are infections of the skin, hair and nails, caused by dermatophytes. The common set is due to tinea organisms, which cause various types of ringworm.

Tinea capitis affects the scalp, tinea cruris, the groin, tinea pedis, the feet and tinea corporis, the body. In superficial candidiasis, yeast – like organism infects the mucous membrane of the mouth (thrush) or vagina, or skin. Some of the surface fungal infections and cutaneous fungal infections which fall into superficial mycoses groups are:

Tinea nigra

Tinea nigra is a localized infection of the stratum corneum, particularly of the palms, producing black or brownish macular lesions. It is found mainly in the tropics and is caused by cladosporium wernickii (now designated as Hortea Wernickii). Skin scrapings show brownish, branched, septate hyphae and budding cells [4].

Piedra

Piedra is a fungus infection of the hair, characterized by the appearance of firm, irregular nodules along the hair shaft. The nodules are composed of fungus elements cemented together or the hair. Two varieaties are recobniazed black piedra caused by piedraia hortae and white piedra caused by Trichosporon beigelli.

Chromoblastomycosis

The most common form of chromo mycosis is known as chromoblastomycosis or verrucous dermatitis. The lesion consists of warty cutaneous nodules which resemble the florest of cauliflower. The disease is usually confined to the subcutaneous tissue of the feet and lower legs.

Blastomycosis

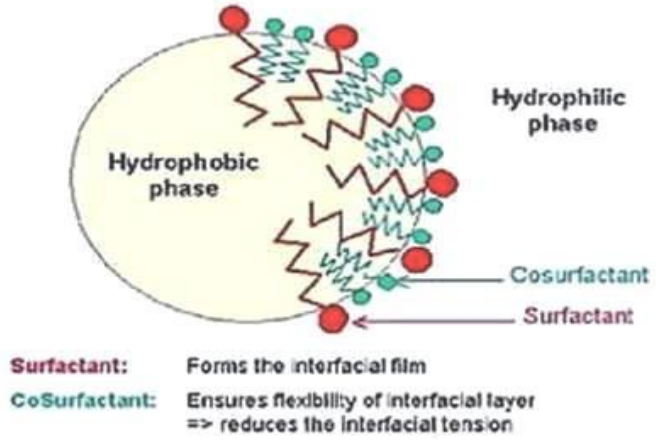
This is a chronic infection caused by the dimorphic fungus blastomyces dermatitis.

USP gives the following definition of gels Gels are semisolid systems consisting of either suspension made up of small inorganic particle or large organic molecules interpenetrated by liquid where the gel mass consists of a network of small discreate particles. The gel is classified as two phase system (e.g. aluminium hydroxide gel). In a two phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as magma. (e.g. bentonite magma). Both the gel & magmas may be thixotropic forming semisolids on standing & become liquid on agitation. They should be shaken before use to ensure homogeneity & should be labelled to the effect.

Microemulsion Based Gel

Micro emulsions are thermodynamically stable, transparent, low viscosity and isotropic dispersions of oil and water stabilized by an interfacial film of surfactant molecules, typically in conjunction with co surfactants which is a short chain length amphiphile, possessing limited water solubility. Micro emulsions contain huge oil/water interfacial areas and very low interfacial tension. Micro emulsions are thermodynamically stable which means that they form spontaneously when the components are brought together and stay stable as long as the ingredients are intact. Its oil and water domains are much smaller, which means light can pass through without much scattering and so micro emulsions are clear or translucent. Micro emulsions are dynamic systems with structures, which may or may not be droplets that form, disintegrate and reform in milliseconds. Microemulsion was first introduced by hoar and schulman in 1943. Microemulsion based gel has been increased interest during recent years in the use of topical vehicle systems that could modify drug permeation through the skin. One of the most promising techniques for enhancement of transdermal permeation of drugs is Micro emulsion. Micro emulsions are thermodynamically stable, transparent (translucent) dispersions of oil and water stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 100nm.

Figure 2: Micro emulsion having very large oil-water interface which is stabilized by a monolayer of surfactant



Micro emulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels. Delivery of drug using these Micro emulsions

through skin increases the local/systemic delivery of the drug by different mechanisms that make them suitable vehicles for the delivery of Antifungal [5].

Formulation aspects

Formulation of TDDS mainly depends on the nature of Gelling agent, Surfactant, co- surfactant, Penetration enhancers and their concentration and temperature. In addition; factors affecting Topical absorption of the drug compound from TDDS include gelling agent concentration, co-surfactant, and oil/surfactant ratio.

Aqueous material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols. Etc.

Oils

Oils are the essential excipients for the TDDS. Micro emulsion Based gels are micro emulsion. Which are gelled by mixing with a gelling agent and micro emulsion may be o/w or w/o type depending on the purpose of use. For pharmaceutical & cosmetic products, the oil phase until it is an active ingredient may include a wide variety of lipid of natural or synthetic origin. The consistency of these lipids may range from mobile liquids to high solids. Different oil used for formulation differs in application, properties, and utility. Like as, a number of natural oils, resulting primarily from plant sources, processed to remove impurities or to separate various fractions of the original product, are available and suitable for use in encapsulated oral formulation [6].

Surfactants (Emulsifiers)

Surfactant molecules consist of two part, polar head group region and non-polar head group region. They are classified into four categories according to the nature of hydrophilic group within the molecule: Anionic surfactant, Cationic surfactant, Non-ionic surfactant, Ampholytic surfactant. Surfactant reduces the interfacial tension between two immiscible liquids and makes them miscible. When surfactants are incorporated in oil and water mixture then their polar heads is self-associated towards water phase and non-polar tails towards oil phase or they can easily locate at the interface, which is thermodynamically very stable. Non- ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) were used for the design of topical drug delivery systems, where the various liquid or solid polyoxyethylene 20oleate (Tween 80) are the most frequently used excipients. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for TDDS (topical drug delivery system) use despite their limited ability to emulsification. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents.

Co-surfactants (Co-emulsifiers)

Relatively high concentration (usually, more than 30%w/w) are needed in order to produce an effective Micro emulsion for topically drug delivery system. Organic solvents: which is Suitable for topical administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play important role of the co-surfactant in the Microemulsion systems. Polymeric liquid and semi-solid excipients can be used alone or in mixture with other lipid excipients to improve solubilizing power of formulation. Among the polymeric glycol based excipients, PEGs are versatile, well characterized and widely applied class of solubilizers which are available as both liquid and thermo softening semisolid.

Gelling agents

Addition of gelling agent to these formulations gives a gelled structure. Gelling agent are of two types: natural and synthetic. Incorporation of gelling to a system makes it thixotropic. According to the Swedish national encyclopedia: thixotropy is “property of viscous (viscid) or gel-like product turning more liquid as the longer time and the more vigorous, which is deformed (i.e. stirring).” It is generally accepted thixotropy the phenomenon of the fluid which shows a reversible structural. Carbapol polymers are polymers of acrylic acid cross-linked with polyalkanyl ethers or divinyl glycol [7].

Penetration Enhancers

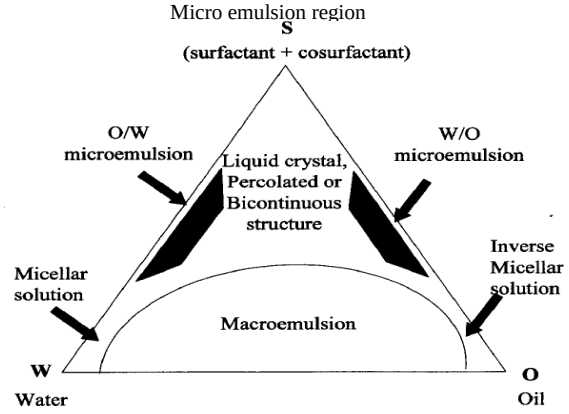
Penetration enhancers are the agents which increases the penetration power of the drug through skin. In order to promote absorption of drugs through skin barrier, vehicles often include penetration enhancing ingredients which temporarily disrupts the highly ordered structure of stratum corneum skin barrier, fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or otherwise enhance delivery into skin.

Method of Preparation

(Micro Emulsion) Phase Titration Method

Micro emulsions are prepared by the spontaneous emulsification method (phase titration method) and can be drawn with the need of phase diagrams. Construction of phase diagram is a useful method to study the complex series of interactions that can occur when different components are mixed. Micro emulsions are formed along with various association diagram (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersions) depending on the chemical composition and concentration of each component. The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time consuming and difficult to intercept. Pseudo structure is often constructed to find the different zones including micro emulsion zone. In which each corner of the diagram represents 100% of the particular component Fig. (2). the region can be separated into w/o or o/w micoemulsion by simply considering the composition whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included [8].

Figure 3: Pseudo-ternary phase diagram of oil, water and surfactant showing Micro emulsion region



CONCLUSION

In the recent years, topical drug delivery system will be used extensively due to better patient compliance. Since Micro emulsion based gel possesses an edge in terms of spredability, adhesion, also transparent Micro emulsion, viscosity, antifungal activity. They will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in a water soluble gel bases.

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