International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

REVIEW ARTICLE

Microemulsion Based Gel: A Novel Approach in Delivery of Hydrophobic Drugs

Wani RR*, Patil MP, Dhurjad P, Chaudhari CA, Kshirsagar SJ

Department of Pharmaceutics, MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik 422 003 (M.S), India.

Manuscript No: IJPRS/V4/I2/00109, Received On: 26/05/2015, Accepted On: 05/06/2015

ABSTRACT

Microemulsion based gel is an emerging topical delivery system contains both microemulsion as well as gel. Microemulsion based gels are either oil in water or water in oil type of microemulsion, which is gelled by mixing it with suitable gelling agent. Incorporation of microemulsion into gel increases its stability and makes it dual control release system. Presence of gel phase makes it a non-greasy, non-sticky and smooth appearance which favors better patient compliance. These reviews give brief knowledge about microemulsion based gel including its properties, advantages, formulation considerations, and its recent advances in research field. In preparation of microemulsion based gel the factors such as selection of gelling agent, oil phase, surfactants influencing the stability and efficacy of microemulsion based gel are discussed. All justifications are described in accordance with the research work carried out by various research scientists. These brief reviews on formulation method have been included. Current research works that carried out on microemulsion based gel are also discussed and highlighted the wide utility of microemulsion based gel in topical drug delivery system. After the brief study, it can be concluded that the microemulsion based gels appear better and effective drug delivery system as compared to other topical drug delivery system.

KEYWORDS

Microemulsion, Gel, Topical Delivery

INTRODUCTION

Topical drug delivery system has several advantages such as ability to deliver drug more selectively to a specific site, avoidance of gastro-intestinal incompatibility & metabolic degradation associated with oral administration. Moreover topical deliveries provide an increased bioavailability by avoiding first pass metabolism by liver and a consistent delivery for extended period. In topical drug delivery system drug diffuses out of the delivery system, reaches to the site of action and gets absorbed by the skin.[1]

***Address for Correspondence:**
Mr. Wani Rahul Ravindra.
Department of Pharmaceutics
MET's Institute of Pharmacy, Bhujbal Knowledge City,
Adgaon, Nashik 422 003 (M.S), India.
E-Mail Id: rahulwani25690@gmail.com

A remarkably broad range of formulation options are available for topical and transdermal preparations, ranging from simple solutions and lotions, through commonly used creams, ointments, gels and patches. When selecting and designing, account must be taken of physicochemical properties of drug, such as solubility and pKa. Equally, the formulation must be stable, the drug and excipients must be compatible and drug must be released from the dosage form following application. Importantly, the formulation should be cosmetically acceptable with a good skin feel, texture.[2]

Microemulsions have generated considerable interest over the years as potential drug delivery systems. Advantages associated with

microemulsions include their thermodynamic stability, optical clarity and ease of preparation.[3] The existence of microdomains of different polarity within the same single-phase solution enables both water-soluble and oil-soluble materials to be solubilized, and at the same time if this is so desired. Furthermore it is also possible to incorporate amphiphilic drugs into the microemulsion, sometimes even leading to an increase in the extent of existence of the microemulsion region.[4] It should be noted that solubilisate partitions between the microemulsion droplet and continuous phase and that while there may be a preferred site of solubilisation within the microemulsion droplet, solubilisate may be located at one of a number of sites. For example the likely preferred sites of incorporation of a lipophilic, water-insoluble drug into an o/w microemulsion are the disperse oil phase and/or hydrophobic tail region of the surfactant molecule, while a water-soluble material would be most likely to be incorporated into disperse aqueous phase of a water-in-oil droplet. Oil-in-water emulsions are most useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications.

To improve emulsion stability and penetration ability it is incorporated into gel. Further, gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible.[5] The type and concentration of the polymer that form the gel matrix could influence the stability as well as the release rate of the incorporated drug into topical delivery vehicles for enhanced permeation through skin. 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 the microemulsions, their minimal retention in the affected part imposes a resistance in its wide spread use in pharmaceutical industry. It is important to prevent the drug loss due to draining out from the onycholytic cavity or reaching the systemic circulation. In order to circumvent these problems, the colloidal drug delivery carrier should be loaded in a gel base.[6,7] In recent years microemulsions continued to be used as solubilization capacity enhancers and dissolution rate improvers for poorly soluble drugs. The works in this area focus on two aspects: first, the effect of different microemulsion structures on drug solubilization capacity and dissolution efficiency and secondly, on the physicochemical characterization of drug loaded microemulsions compared to drug free systems.[8]

Microemulsion based gels possess the previously mentioned advantages of both emulsions and gels, they have good patient acceptability. Because of its non-greasy nature it can be easily applied to the skin as compared to other topical formulations such as creams, ointments which are very much thick, greasy and require excess rubbing. Scientists nowadays are facing problem during development of new drug since many drugs coming directly from synthesis or from high throughput screening have poor solubility.[9] Based on in vitro solubility and in vivo permeability data biopharmaceutical classification system divides drugs into four classes. Among the four classes class II drugs show poor solubility and high permeability. It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption then their ability to permeate through the membrane.[10] Therefore, when one is concerned with topical delivery of poorly water-soluble drug, microemulsion based gels may serve as better option.

Emulsified gel has proven a stable one and better vehicle for hydrophobic or poorly water-soluble drugs. Albumin coupled gel of diclofenac also used for targeted delivery at site of inflammation.[11] Low-surfactant microemulsion gels were formulated and characterized to enhance topical delivery of poorly soluble drugs. It was found that the choice of viscosity imparting agent (Xanthan gum or Carbopol 934) played an important role in governing drug release from microemulsion gel. Microemulsion based gels now have been used for treatment of

various kinds of skin disorder such as those infected by viral, bacterial, and fungal species (eczema, Herpes simplex, acne). Research works on antifungal drugs incorporated to microemulsion based gel have been carried by different scientist to judge its efficacy against fungal infection such as candidiasis. Species causing candidiasis are *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis and Candida krusei*.[12,13] Preparing microemulsion based gels was found useful in combating fungal infection. Scientist has been trying to develop microemulsion based gel of various drugs to treat various kinds of skin disorder. Acne is one of the major skin disorder common among adolescents. Factors that are responsible for acne are hormones, excess sebum, dead cells, propionibacterium acne's and inflammatory response. Approaches should be taken to develop microemulsion based gel for treatment of such kinds of disorder. Anti-aging area are yet to be explored researches on its cream based formulations have been done using varieties of herbal moieties such as *Glycyrrhizaglabra, Curcuma longa*, seeds of *P. coliforlia, Cassia tora, Acacia catechu & Punicagranatum*. Microemulsion based gel containing anti-inflammatory drug (Diclofenac), aspirin is used for relief of pain in muscle and joints.[14,15]

Wade and co-workers (1990) investigated the potential of microemulsion gels as a matrix for transdermal delivery of scopolamine. They found that skin barrier for scopolamine was significantly lowered with a lecithin isopropyl myristate gel when compared with aqueous control. The amount of drug passing through the skin during a period of 75 hours increased significantly, implying that lecithin of the fatty acid ester may acts as penetration enhancer. Gasco et al. (1990) studied gel- like system obtained by adding the polymer carbopol 934 to a microemulsion of dodecanol, decanol, Tween 20 and propylene glycol containing solubilized azelaic acid. The diffusion studies on hairless mouse skin implied that the microemulsion gels are more efficient than gel alone or cream. The gel microemulsions comprising oil –in- water microemulsion and polymeric hydrogels were designed to solubilize lipophilic antiviral/ antimicrobial agents and these exhibited rapid spermicidal activity in human semen. Gel microemulsions had potent contraceptive activity. Repeated intravaginal applications of gel microemulsions in the rabbit vaginal irritation test were not associated with local inflammation or damage of vaginal mucosa or epithelium.[16]

Formulation Considerations

Selection of Oil Phase

The oil shows excess solubility of drug which is selected as an oil phase in preparation of microemulsion based gel. 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 oils used for formulation differ in application, properties & utility. The oil also acts as a penetration enhancer therefore no need of penetration enhancer in microemulsion based drug delivery system.

The oils used in preparation of microemulsions by various researchers are from natural, synthetic and semisynthetic origin. Bachhav YG et al (2009) carried out research using capryol 90 as a oil phase in preparation of microemulsion based vaginal gel of clotrimazole and capryol 90 is found to be compatible with other excipients as well as enhances the penetration of clotrimazole through skin.[17] Silva AE. et al (2013) prepared oral microemulsion of amphotericin B using lipids as oil phase such as Capryol 90 (C90), Capryol PGMC (CPGMC), Lauroglycol 90 (L90), Labrafac lipophile WL 1349 (LWL), Labrafac PG (LPG) and Peceol because lipid-based formulations have been extensively investigated as a suitable approach to improve the solubility and bioavailability. Capmul 908P used as an oil phase by Kumar N. et al (2014) in preparation of Itraconazole microemulsion[18] Desai KG (2004) carried out researched work using isopropyl myristate as an oil phase in preparation of rofecoxib microemulsion gel, IPM is acts as a penetration enhancer, improving skin penetration. Pisseri F. et al (2009) used tea tree

oil as oil phase showing antifungal activity against *Trichophyton equinum*.[19] Okur NU et al (2011) prepared nanoemusion of naproxen using labrafil as an oil phase.[20] Transcutol as the penetration enhancer showed 1.7-fold enhancement in flux and permeation coefficient as compared to marketed cream and ointment formulation. Oleic acid is a kind of fatty acid, which may be employed as an oil phase of emulsion. Oleic acid is a monounsaturated omega-9 fatty acid found in various animal and vegetable fats.

It is odorless, colorless oil, although commercial samples may be yellowish. Triglyceride esters of oleic acid compose most of olive oil. It also makes up 59–75% of pecan oil, 36–67% of peanut oil, 15–20% of grape seed oil, sea buckthorn oil, and sesame oil, and 14% of poppy seed oil.[21] Dasgupta S. et al. (2013) used triacetin as oil phase in preparation of nanoemulsion of aceclofenac. Khullar R. et al. (2012) used liquid paraffin as oil phase in mefenamic acid emulgel. Chen H. et al. (2006) used ethyl oleate as oil phase in preparation of microemulsion based hydrogel of ibuprofen, due to a good solubilizing capacity of the microemulsion systems and excellent skin permeation rate of ibuprofen.[22] The various oils used by above researchers showing better compatibility with drug and other excipients, improving drug solubility as well as permeability across the skin.

Selection of Surfactants

The surfactants used to stabilize such systems may be: (i) non-ionic, (ii) zwitterionic, (iii) cationic, or (iv) Anionic surfactants. Combinations of these, particularly ionic and non-ionic, can be very effective at increasing the extent of the microemulsion region. Examples of non-ionics include polyoxyethylene surfactants such as Brij 35, tween20/80 or a sugar esters such as sorbitan monooleate (Span 80).[23,24] Phospholipids are a notable example of Zwitterion exhibit excellent biocompatibility. Microemulsion based gels are simply oiled in water or water in oil emulsions that are gelled by mixing with a gelling agent as emulsions are thermodynamically unstable systems however by using appropriate emulsifying agents, to decrease the interfacial tension, the stability of this system can be significantly increased. A satisfactory emulsifier should have a reasonable balance among its hydrophilic & lipophilic groups & should be capable of producing stable emulsions.

Nonionic surfactants such as spans, tweens have HLB values greater than 8 and are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB values less than 8 & therefore are employed in the formulation of water in oil emulsions. Surfactants generally employed, are toxic in nature and may raise problems regarding to health and environment.[25,26]

In such case biosurfactants may serve as alternative. Biosurfactants are produced by microbes and they are genera sometimes species specific. Because of their short fatty acid tail and polar head groups, biosurfactants are highly sticky and both hydrophilic and hydrophobic. Co surfactants are used along with surfactants to increase solubility of drug in particular microemulsion system.

The cosurfactants generally medium chain fatty alcohols, acid or amine taken along with the surfactant to lower the interfacial tension to a very small or even transient negative value. At this value fine droplets form due to the interface expansion and more of surfactant/cosurfactant get adsorbed on the surface until the bulk condition is depleted enough to make the interfacial tension positive again. Cosurfactant of short medium chain length alcohols also ensures that the interfacial film is flexible enough to deform readily around droplets, as the interaction between primary surfactant molecules decreases both the polar head group interaction and hydrocarbon chain interaction. Polyethyene glycol derivatives of distearoyl phosphatidyl ehanolamine, ethanol, fatty acid esters of propylene glycol, oleic esters of polyglycerol, ethyldiglycol and propylene glycol were also evaluated as cosurfactant in microemulsion drug delivery system.[27,28] The surfactants used in preparation of microemulsion are in optimum concentrations and generally regarded as safe.

Selection of Gelling Agent

Addition of gelling agent to these formulations gives a gelled structure. Gelling agents are of two types natural and synthetic. Incorporation of gelling agent to a system makes it thixotropic. According to the Swedish National Encyclopedia (1989–1996)[29] thixotropy is "property of viscous (viscid) or gel-like product turning more liquid as the longer time and the more vigorous, which is deformed (e.g. by stirring)." However, stability of system can be affected by many factors like pH, temperature, polymer concentrations, polymer modification or combinations, addition of cations or anions. Carbomers, cellulose derivatives, such as carboxy methyl cellulose or hydroxylpropyl methyl cellulose and natural gums such as tragacanth are generally preferred as a gelling agent.

Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 to 6.0 μm average diameter. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking. Carbomers readily absorb water, get hydrated and swell. Besides its hydrophilic nature, its cross-linked structure and it's insolubility in water makes carbopol a potential candidate for use in controlled release drug delivery system. Their viscosity depends on their polymeric composition. The NF contains monographs for six such polymers, carbomers 910, 934, 934P, 940, 941, and 1342 used as gelling agents at concentrations of 0.5% to 2.0% in water. Carbomer 940 yields the highest viscosity between 40,000 and 60,000 centipoise as a 0.5% aqueous dispersion.[30] A kind of insect repellent cream was developed using carbopol in base composition. Quality and quantity of carbopol and other base contents were found to have profound effect on consistency of compositions. Effect of gelling agent has been studied on release rate of drug from micromulsion based gel. It has been found that there is an inverse correlation between the concentration of gelling agent and the extent of drug released. The microemulsion based gel showed Non-Newtonian shear thinning behavior with little or no thixotropy and variable viscosity dependent on both the concentration and type of gelling agent. Stability testing under several conditions (centrifugation, temperature cycle test or storage for 1 year) showed that formulation containing low level of Carbopol or combination of two gelling agents has better stability compared to other formulations.[31]

Other types including synthetic, semisynthetic, natural gelling agent can also be employed. The major drawback of natural gelling agents is that they are prone to microbial degradation. Various kinds of synthetic and semisynthetic gelling agents are replacing natural gelling agent now these days. Cellulose derivatives are now been commonly using as gelling agent. One of the popular cellulose derivatives is sodium carboxymethyl cellulose. Sodium carboxymethyl cellulose is a suitable vehicle for sterile jellies because it can withstand autoclaving without serious deterioration. Hydroxypropyl methylcellulose is an odorless and tasteless, white to slightly off-white, fibrous or granular, free-flowing powder that is a synthetic modification of the natural polymer cellulose. It can be used as thickening agent, tablet binding, modified release and film coating. HPMC based emulgel was found to be better than Carbopol based emulgel since it showed better drug release rate.

Hussain A. et al (2014) prepared nanoemulsion based gel of amophotericin B using carbopol 980 as a gelling agent and could be considered as an efficient, stable and safe carrier for enhanced and sustained topical delivery for AmB in local skin fungal infection. Carbopol ETD 2020 used as a gelling agent by Bacchav YG. et al (2008) in preparation of fluconazole microemulsion based gel and carbopol ETD 2020 was found to be compatible with microemulsion structure, feel and ease of spreadability. Desai KG et al (2004) used carbopol 940 as a gelling agent in preparation topical microemulsion gel of rofecoxib and carbopol 940 was found to be effective carrier for microemulsion in topical delivery. Sharma PK.et al. (2012) used carbopol 934 as a gelling agent in preparation of celecoxib gel showing better stability with microemulsion

structure. Carbopol 940 used as a gelling agent by Khullar R. et al. (2012) in mefenamic acid emulgel showing better consistency, ease of spreadability and stability.[32]

Construction of Pseudo Ternary Phase Diagram

Pseudoternary phase diagrams are constructed to obtain the concentration range of oil, surfactant, cosurfactant, and water for microemulsion to enhance its permeability through the skin. Phase behaviour studies are essential for the study of surfactant systems and are performed by constructing phase diagrams that provide information on the boundaries of the different phases as a function of composition variables and temperatures, and, more important structural organization can also be inferred. One approach to characterize these multicomponent systems is by means of pseudoternary diagrams that combine more than one component in the vertices of the ternary diagram. Surfactant and cosurfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in free energy required for the microemulsion formation consequently improves the thermodynamic stability of the microemulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to surfactant/ cosurfactant play an important role in the formation of microemulsions.[33]

Pseudo-ternary phase diagrams were constructed by employing aqueous titration method in order to get concentration range of components of microemulsion. The ratio of surfactant to co-surfactant (Smix) is altered at 3:1, 2:1, 1:1, 1:2, 1:3, 3:2. For the construction of pseudo-ternary phase diagram at each Smix ratio, the oily mixtures containing oil, surfactant and co-surfactant are prepared with volume ratio of oil to Smix at 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 respectively. Double distilled water is added drop by drop to the oil and Smix mixture under magnetic stirring at ambient temperature. Transparent and clear microemulsion is taken as the end point of aqueous titration method. The concentrations of components are then calculated in order to plot the pseudo-ternary phase diagram.[34,35,36]

Formulation Methods

There are various methods of formulation of Emulgel, employing different kinds of ingredient, one method reported by Mohamed (2004) in his research work (optimization of chlorphenesin in Emulgel) includes formation of emulsion (o/w or w/o), followed by addition of gelling agent to form Emulgel. Here first step involves formation of aqueous phase of emulsion. Aqueous phase of emulsion is prepared by first dissolving tween 20 in purified water, then solution of propylene glycol is prepared by dissolving methyl paraben and propyl paraben in propylene glycol and then both the solutions are mixed and set aside. Oily phase of emulsion is prepared by dissolving span 20 in light liquid paraffin. Formation of emulsion involves separate heating of oily and aqueous phase to 70–80 °C then both the phases are mixed with constant stirring until cooled to room temperature. Gel phase of Emulgel is prepared by dispersing HPMC or Carbopol in water. HPMC is required to soak overnight in water, while Carbopol gel is prepared by simply dispersing it in purified water. When both the components both emulsions & gel get ready then the microemulsion based gel is prepared by mixing emulsion with gel in 1:1 ratio with gentle stirring.[37]

Another method was reported by Perioli et al. (2008) in their research work based on design & characterization of Emulgel for buccal administration. Here formulation of Emulgel involves three step (i) polymer dispersion in water, (ii) neutralization of the polymeric aqueous dispersion and (iii) emulsification of the oil phase. With respect to the first step, three different TR-1 percentages, namely 0.3, 0.4 and 0.5%, w/v, are required. First step involves suspension of polymer in deionized water with continuous stirring at 900 rpm for 20 min at room temperature using a mechanical stirrer equipped with a three blade helical impellers & then slurry is neutralized with NaOH solution (18%w/v) to final pH value of 5.5, 6.0 and 6.5. The

neutralization process causes the distension of polymer chains resulting in clear stable gels. Now for the complete hydration of polymer gels are required to be stored at 4 °C for 24 h before the addition of oil phase. After completing the hydration of gel different quantities of oil phase at three o/w ratio (w/w) 0.5, 1.0 and 1.5 respectively are added with stirring at 800 rpm (80 °C) there after it is left for cooling and its pH is measured.[38]

Shahin et al. (2011) followed a different method to develop Emulgel for clotrimazole delivery. This method involves the preparation of oily phase of emulsion by dissolving drug and span 60 in oily phase (jojoba oil) with the aid of magnetic stirrer at 75°C with subsequent cooling followed by addition of Carbopol to the oily phase. Secondly aqueous phase is prepared by dissolving Brij-35 in propylene glycol. Third step involves addition of oily phase to the aqueous phase following their emulsification using the over head mixer for 10 min at 1400 rpm, and then introducing emulsion into the homogenizer for 5 min at 10,000 rpm. Gellification of emulsion involves addition of gelling agent triethanolamine (formulae containing Carbopol either alone or in combination) and/or HPMC to the emulsion using over head mixer at 200 rpm for 45 min thereby adjusting the pH of formulation containing Carbopol to 5.5–6.5 using TEA.

Evaluation Parameters

Microemulsion

- **pH:** The pH of topical preparation should be compatible with skin pH. A change in pH may cause disruption or irritation of skin. The pH is measured by digital pH meter and calibrated using pH 4 and 7 buffers before use.
- **Viscosity:** Rheology is a fundamental approach to investigate the structural properties and acquire helpful information not only on stability of such systems, but also on handling, storage and transportations of MEs. The microemulsion systems showed a linear relationship between the shear stress and shear rate, which is a feature of Newtonian flow materials. The viscosity is measured by Brookfield viscometer using different spindle and rotations.
- **Refractive Index:** Refractive index is a sign of a uniform microemulsion structure. It is measured by Abbe's refractometer.
- **Conductivity:** The conductivity measurements divides microemulsions into o/w and w/o type. Conductivity measurements rely on the poor conductivity of oil compared with water and give low values for water in oil ME where oil is the continuous phase. The reverse happens for oil in water ME. The electrical conductivity of microemulsion is measured by digital conductometer at ambient temperature.
- **Percent Transmittance:** The percent transmittance value closer to 100 indicated that microemulsion formulations are clear and transparent. Micro-emulsion will be diluted to 50-100 times with continuous phase. The percent transmittance of formulation was measured using UV Visible spectrophotometer at specific wavelength using UV-Visible spectrophotometer against continuous phase as blank.
- **Droplet Size and Polydispersity Index:** The droplet size is particularly important for understanding the behaviour of microemulsion. The droplet size increased with increasing ratio of oil and water. The microemulsion had the less globule size as compared to the coarse emulsion due to presence of co-surfactant, which reduces the interfacial tension to ultra-low value. The polydispersity value described the homogeneity of the droplet size. The polydispersity values of the formulations are low which indicates uniformity of droplet size with in the formulation. It is measured by Malvern zeta sizer.
- **Zeta Potential:** The significance of the zeta potential is that it can be related to the stability of colloidal dispersions. Zeta potential indicates degree of repulsion

between adjacent, similarly charged particles in dispersion. For molecules that are small enough a high zeta potential will confer stability, i.e., the solution or dispersion will resist aggregation. Zeta potential controls charge interactions. It is measured by Malvern zeta sizer.

- ***Ex-vivo* Release Study:** It is done by using Franz diffusion cell with an effective diffusion area of 7.1 cm^2 is used for the experiment. The animal skin is placed between the donar and receptor compartment of Franz diffusion cell with the stratum corneum facing donar compartments. The receptor chamber is filled with buffer solution and maintained at 37 ± 1^0 C and stirred magnetically at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed using UV spectrophotometer. Fresh buffer solution is immediately replaced in the receptor chamber after each sampling.[33,39,40]

Microemulsion Based Gel

- **Physical Examination:** Microemulsion based gel inspected for their color, consistency, homogeneity, texture etc.
- **pH:** The change in pH may cause irritation or disruption of skin therefore pH of formulation is acceptable at the site of application. The 10% dispersion of gel in aqueous medium is prepared and measured by digital pH meter.
- **Viscosity:** Rheology is a significant parameter for the evaluation of the gel when applied topically. The relationship between the shear stress and shear rate on the samples are measured to study the flow behavior and to determine the viscosity. It is measured by Brookfield viscometer using different spindle.[40]
- **Spreadability Measurement:** Spreading and adherence behavior of topical formulations to the skin surface need to be evaluated. Good spreadability is an essential criteria for topical preparations. To determine the spreadability of microemulsion based gel, 0.5 gm of microemulgel will be placed within circle of 1cm diameter pre-marked on a glass plate, over which second plate will be placed. A weight of 5gm will be allowed to rest on the upper glass plate for 5 min. The increase in diameter due to microemulsion based gel, the spreading will be noted, which was gm-cm/sec.
- **Drug Content Determination:** Drug content in microemulsion based gel will be measured by dissolving 1gm of microemulgel in solvent by sonication. Absorbance will be measured after suitable dilution at λmax using UV spectrophotometer.
- **Tube Test (Extrudability Test):** It depends on viscosity of gel. The gel having less viscosity lesser be the extrudability. It is usually empirical test to measure the force required to extrude the material from tube. The method adopted for microemulsion based gel formulation for extrudability is based upon the quantity in percentage of gel and gel extruded from aluminium collapsible tube on application of weights in grams required to extrude at least 0.5 cm ribbon of microemulsion based gel in 10 sec.
- ***In-vitro*-Release Study**: The skin sample was rinsed with phosphate buffer saline. The skin is clamped between the donar and receptor chamber of vertical diffusion cell with an effective diffusion area of 2.8 cm^2. The receptor chamber is filled with freshly PBS. The diffusion cell was maintained at 37^0 C using a re-circulating water bath and the solution in the receptor chamber was stirred continuously at 300 rpm. The formulation (1g) gently placed in the donar compartment. At 1, 2, 3, 4, 5, 6, 7 and 8 hr, 5 ml of the solution is removed from receptor compartment and replaced immediately with an equal proportions of fresh PBS. The samples are analyzed in UV – Visible spectrophotometer after suitable dilution.[41,42]
- **Skin Irritation Study:** The skin irritation study is performed to check whether the formulations may produce skin irritation or not after topical application. The

microemulsion based gel formulations are applied on properly shaven skin of rat. Undesirable skin changes i.e., change in color, change in skin morphology are checked for a period of 24 hr.[32]

- **Accelerated Stability Study of Optimized Microemulgel:** To evaluate physical and chemical stability of prepared formulations the stability test is performed. Sample of API loaded microemulgel will be sealed in ampoule and then placed in accelerated stability chamber at 40℃ ± 5℃ temperature and 70% ± 5% RH. Duplicate sample will be withdrawn at 1, 2 and 3 month to evaluate their physicochemical parameters. The physical stability will be evaluated by visual inspection for physical changes such as phase separation and drug precipitation. Chemical stability will be expressed as the content of drug determined by UV visible spectroscopic method at λmax in nm.

Routes of Administration

Topical drug delivery generally means direct application of drug onto the skin to the site of action to get the desired pharmacological response but it has some of its own limitations such that the applied drug has to cross the different barriers of skin to reach systemic circulation so to overcome this problem different routes of administration such as rectal, nasal, vaginal have been investigated.[43,44,45] Lipid nanocarriers of lutein prepared by Mitria K. et al (2011) for dermal delivery.[46] Direct application of drug to mucus membrane led to increase in rate and extent of absorption of drug from delivery system thus increasing its efficacy.[47,48] Emulgels have been investigated for various routes of administration such as buccal, vaginal, and topical.[49,50] The topical delivery of drug through microemulsion based gel is maximum and many numbers of antifungals and NSAID's delivered by topical route.[51,52,53] The work done by various researchers on microemulsion and microemulsion based gels with their route of administration mention in below table.

Table 1: Routes of administration of different active ingredient

Sr. No	Active Ingredient	Route of Administration	Reference
1	Diclofenac diethylamine	Topical	54
2	Quercetin	Topical	55
3	Voriconazole	Topical	56
4	Caffeine	Transdermal (Percutaneous)	58
5	Buspirone	Intranasal	59
6	Chloramphenicol	Eye	60
7	Lidocaine	Transdermal (Percutaneous)	61
8	Tripterygium Wilfordii	Transdermal	63
9	Ketoprofen	Topical	64

Marketed Formulations

Voltaren Emulgel is a topical analgesic gel that provides relief in back, neck and shoulder pain and reduces swelling. Voltaren Emulgel is available in a 100 g tube and is a white pleasant-smelling, non-greasy gel. Diclofenac sodium 1% w/w (as diclofenac diethyl amine) a non-steroidal anti-inflammatory drug is the active ingredient. It is useful for inflamed tendons, ligaments, muscles and joints suffering from trauma, soft tissue rheumatism and localized rheumatic conditions. Voveron Emulgel is available in 21 g tube and is non sticky, non-greasy and having whitish smooth appearance contain diclofenac diethyl amine 1.16% which is equivalent to 1% diclofenac sodium. Voveron Emulgel is manufactured by Novartis Pharma. It is used in the treatment of localized forms of soft-tissue rheumatism, e.g. shoulder-hand syndrome, bursitis, rheumatic diseases, osteoarthritis of the spine and peripheral joints,

periarthropathy, inflammation of the ligaments, tendons, muscles, and joints.

Future Prospective

Hydrophobic nature of drug is one of the most common problem arise during formulation and development of any new formulation. The hydrophobic nature is responsible for poor water solubility and bioavailability. The numbers of drugs are hydrophobic in nature and their delivery to the biological system is a challenging work. For the topical delivery of drug different delivery systems are available such as creams, ointments, pastes and lotions are applied. These topical formulations generally include large number of oleaginous bases such as petrolatum wax, bees wax or vegetable oils that are hydrophobic in nature that do not allow the inclusion of water or aqueous phase. It makes them an excellent emollient but retards the release of drugs and makes the product thick, sticky and greasy. Whereas gel provides aqueous environment to drug, favors its dissolution and provides quicker release of drug as compared to other topical delivery systems. Microemulsion based gel provides a suitable medium for delivery of such hydrophobic drugs where such drugs can be incorporated into its oily phase and delivered to skin. All such advantages of microemulsion based gel over other topical delivery systems make them more efficient and productive and because of non-greasy, non-sticky and smooth appearance increases patient compliance.

CONCLUSION

After a thorough literature review we reached into a conclusion that microemulsion based gels are convenient, safe and effective drug delivery system. Due to its non-greasy, non-sticky and smooth gel like property favors patient compliance. It provides better release of drugs as compared to other topical drug delivery systems. Incorporation of microemulsion into gel makes it a dual control release system further problem such as phase separation, creaming associated with emulsion gets resolved and its stability increases. Microemulsion based gel loaded with specific drugs has been found effective in some topical disorders & it is emerging as potential drug delivery system in area of dermatology. In future microemulsion based gel will provide an alternative for topical delivery of hydrophobic drugs. Many of drugs that have utility in treatment of skin disorders and most of the non-steroidal and anti-inflammatory drugs are hydrophobic in nature. Such drugs can be delivered in the form of microemulsion based gel where they can be incorporated in oil phase of emulsion and combined with gel & therefore microemulsion based gel serve as a better option for delivery of hydrophobic drugs.

REFERENCES

1. Alexander, A., Khichariya, A., Gupta, S., Patel, R. J., Giri, T. K., & Tripathi, D. K. (2013). Recent expansions in an emergent novel drug delivery technology: Emulgel. *Journal of Controlled Release*, *171*(2), 122-132.
2. Aulton, M. E., & Taylor, K. M. (2013). *Aulton's pharmaceutics: the design and manufacture of medicines*. Elsevier Health Sciences, Churchill Livingstone., 436-464.
3. Lawrence, M. J., & Rees, G. D. (2000). Microemulsion-based media as novel drug delivery systems. *Advanced Drug Delivery Reviews*, *45*(1), 89-121.
4. Panwar, A. S., Upadhyay, N., Bairagi, M., Gujar, S., Darwhekar, G. N., Jain, D. K., & Bhadoriya, U. (2011). Emulgel: a review. *Asian Journal of Pharmacy and Life Science ISSN*, *2231*, 4423.
5. Sarisozen, C., Vural, I., Levchenko, T., Hincal, A. A., & Torchilin, V. P. (2012). PEG-PE-based micelles co-loaded with paclitaxel and cyclosporine A or loaded with paclitaxel and targeted by anticancer antibody overcome drug resistance in cancer cells. *Drug Delivery*, *19*(4), 169-176.
6. Desai, K. G. H. (2004). Enhanced skin permeation of rofecoxib using topical microemulsion gel. *Drug Development Research*, *63*(1), 33-40.

7. Barot, B. S., Parejiya, P. B., Patel, H. K., Mehta, D. M., & Shelat, P. K. (2012). Microemulsion-based antifungal gel delivery to nail for the treatment of onychomycosis: formulation, optimization, and efficacy studies. *Drug Delivery and Translational Research*, *2*(6), 463-476.
8. Fanun, M. (2012). Microemulsions as delivery systems. *Current Opinion in Colloid & Interface Science*, *17*(5), 306-313.
9. Weissig, V., Lizano, C., & Torchilin, V. P. (2000). Selective DNA release from DQAsome/DNA complexes at mitochondria-like membranes. *Drug Delivery*, *7*(1), 1-5.
10. Dasgupta, S., Dey, S., Choudhury, S., & Mazumder, B. (2013). Topical delivery of aceclofenac as nanoemulsion comprising excipients having optimum emulsification capabilities: preparation, characterization and in vivo evaluation. *Expert Opinion on Drug Delivery*, *10*(4), 411-420.
11. Kandadi, P., Syed, M. A., Goparaboina, S., & Veerabrahma, K. (2012). Albumin coupled lipid nanoemulsions of diclofenac for targeted delivery to inflammation. *Nanomedicine: Nanotechnology, Biology and Medicine*, *8*(7), 1162-1171.
12. Silva, A. E., Barratt, G., Chéron, M., & Egito, E. S. T. (2013). Development of oil-in-water microemulsions for the oral delivery of amphotericin B. *International Journal of Pharmaceutics*, *454*(2), 641-648.
13. Hussain, A., Samad, A., Singh, S. K., Ahsan, M. N., Haque, M. W., Faruk, A., & Ahmed, F. J. (2014). Nanoemulsion gel-based topical delivery of an antifungal drug: *in vitro* activity and *in vivo* evaluation. *Drug Delivery*, (0), 1-16.
14. Tang, S. Y., Sivakumar, M., Ng, A. M. H., & Shridharan, P. (2012). Anti-inflammatory and analgesic activity of novel oral aspirin-loaded nanoemulsion and nano multiple emulsion formulations generated using ultrasound cavitation. *International Journal of Pharmaceutics*, *430*(1), 299-306.
15. Fouad, S. A., Basalious, E. B., El-Nabarawi, M. A., & Tayel, S. A. (2013). Microemulsion and poloxamer microemulsion-based gel for sustained transdermal delivery of diclofenac epolamine using in-skin drug depot: in vitro/in vivo evaluation. *International Journal of Pharmaceutics*, *453*(2), 569-578.
16. Jain N. K., (2004). *Progress in Control and Novel drug delivery*, CBS Publishers and distributors, First edition, 328.
17. Bachhav, Y. G., & Patravale, V. B. (2009). Microemulsion-based vaginal gel of clotrimazole: formulation, in vitro evaluation, and stability studies. *AAPS PharmSciTech*, *10*(2), 476-481.
18. Kumar, N. (2015). D-optimal experimental approach for designing topical microemulsion of itraconazole: Characterization and evaluation of antifungal efficacy against a standardized Tinea pedis infection model in Wistar rats. *European Journal of Pharmaceutical Sciences*, *67*, 97-112.
19. Pisseri, F., Bertoli, A., Nardoni, S., Pinto, L., Pistelli, L., Guidi, G., & Mancianti, F. (2009). Antifungal activity of tea tree oil from Melaleuca alternifolia against Trichophyton equinum: An *in vivo* assay. *Phytomedicine*, *16*(11), 1056-1058.
20. Okur, N. Ü., Apaydın, Ş., Yavaşoğlu, N. Ü. K., Yavaşoğlu, A., & Karasulu, H. Y. (2011). Evaluation of skin permeation and anti-inflammatory and analgesic effects of new naproxen microemulsion formulations. *International Journal of Pharmaceutics*, *416*(1), 136-144.
21. Subramanian, B., Kuo, F., Ada, E., Kotyla, T., Wilson, T., Yoganathan, S., & Nicolosi, R. (2008). Enhancement of anti-inflammatory property of aspirin in mice by a nano-emulsion preparation. *International Immunopharmacology*, *8*(11), 1533-1539.
22. Chen, H., Chang, X., Du, D., Li, J., Xu, H., & Yang, X. (2006). Microemulsion-based hydrogel formulation of ibuprofen for topical

delivery. *International Journal of Pharmaceutics*, *315*(1), 52-58.

23. Patel, R. B., Patel, M. R., Bhatt, K. K., & Patel, B. G. (2013). Formulation consideration and characterization of microemulsion drug delivery system for transnasal administration of carbamazepine. *Bulletin of Faculty of Pharmacy, Cairo University*, *51*(2), 243-253.
24. Katzer, T., Chaves, P., Bernardi, A., Pohlmann, A. R., Guterres, S. S., & Beck, R. C. (2014). Castor oil and mineral oil nanoemulsion: development and compatibility with a soft contact lens. *Pharmaceutical Development and Technology*, *19*(2), 232-237.
25. Shakeel, F., Baboota, S., Ahuja, A., Ali, J., & Shafiq, S. (2008). Celecoxib nanoemulsion: Skin permeation mechanism and bioavailability assessment. *Journal of Drug Targeting*, *16*(10), 733-740.
26. Sharma, P. K., & Kumar, A. (2012). Development, Characterization, and Evaluation of Celecoxib Microemulsion for Topical Delivery. *Journal of Dispersion Science and Technology*, *33*(10), 1411-1418.
27. Vyas, S. P., Murthy, R. S. R., Narang, R. K. (2011). *Nanocolloidal Carriers: Site Specific and Controlled Drug Delivery*, CBS Publishers & Distributors, First edition, 530-531.
28. Fontana, M. C., Rezer, J. F. P., Coradini, K., Leal, D. B. R., & Beck, R. C. R. (2011). Improved efficacy in the treatment of contact dermatitis in rats by a dermatological nanomedicine containing clobetasol propionate. *European Journal of Pharmaceutics and Biopharmaceutics*, *79*(2), 241-249.
29. Lee, C. H., Moturi, V., & Lee, Y. (2009). Thixotropic property in pharmaceutical formulations. *Journal of Controlled Release*, *136*(2), 88-98.
30. Ansel, H. C., Allen Jr, L. V., Popovich, N. G. (1999). *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th ed. Lippincott Williams and Wilkins, New York**.**, 278-279.
31. Shahin, M., Hady, S. A., Hammad, M., & Mortada, N. (2011). Novel jojoba oil-based emulsion gel formulations for clotrimazole delivery. *AAPS PharmSciTech*, *12*(1), 239-247.
32. Khullar, R., Kumar, D., Seth, N., & Saini, S. (2012). Formulation and evaluation of mefenamic acid emulgel for topical delivery. *Saudi Pharmaceutical Journal*, *20*(1), 63-67.
33. Bali, V., Ali, M., & Ali, J. (2010). Study of surfactant combinations and development of a novel nanoemulsion for minimising variations in bioavailability of ezetimibe. *Colloids and Surfaces B: Biointerfaces*, *76*(2), 410-420.
34. Patel, H. K., Barot, B. S., Parejiya, P. B., Shelat, P. K., & Shukla, A. (2013). Topical delivery of clobetasol propionate loaded microemulsion based gel for effective treatment of vitiligo: ex vivo permeation and skin irritation studies. *Colloids and Surfaces B: Biointerfaces*, *102*, 86-94.
35. Bachhav, Y. G., & Patravale, V. B. (2009). Microemulsion based vaginal gel of fluconazole: Formulation, in vitro and in vivo evaluation. *International Journal of Pharmaceutics*, *365*(1), 175-179.
36. Doh, H. J., Jung, Y., Balakrishnan, P., Cho, H. J., & Kim, D. D. (2013). A novel lipid nanoemulsion system for improved permeation of granisetron. *Colloids and Surfaces B: Biointerfaces*, *101*, 475-480.
37. Mohamed, M. I. (2004). Optimization of chlorphenesin emulgel formulation. *The AAPS Journal*, *6*(3), 81-87.
38. Perioli, L., Pagano, C., Mazzitelli, S., Rossi, C., & Nastruzzi, C. (2008). Rheological and functional characterization of new antiinflammatory delivery systems designed for buccal administration. *International Journal of Pharmaceutics*, *356*(1), 19-28.

39. Aggarwal, N., Goindi, S., & Khurana, R. (2013). Formulation, characterization and evaluation of an optimized microemulsion formulation of griseofulvin for topical application. *Colloids and Surfaces B: Biointerfaces*, *105*, 158-166.

40. Mou, D., Chen, H., Du, D., Mao, C., Wan, J., Xu, H., & Yang, X. (2008). Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. *International Journal of Pharmaceutics*, *353*(1), 270-276.

41. Zhao, L., Wang, Y., Zhai, Y., Wang, Z., Liu, J., & Zhai, G. (2014). Ropivacaine loaded microemulsion and microemulsion-based gel for transdermal delivery: Preparation, optimization, and evaluation. *International Journal of Pharmaceutics*, *477*(1), 47-56.

42. Sahoo, S., Pani, N. R., & Sahoo, S. K. (2014). Effect of microemulsion in topical sertaconazole hydrogel: *in vitro* and *in vivo* study. *Drug Delivery*, (0), 1-8.

43. Narang, A. S., Delmarre, D., & Gao, D. (2007). Stable drug encapsulation in micelles and microemulsions. *International Journal of Pharmaceutics*, *345*(1), 9-25.

44. Chen, L., Zhao, X., Cai, J., Guan, Y., Wang, S., Liu, H., & Li, J. (2013). Triptolide-loaded microemulsion-based hydrogels: physical properties and percutaneous permeability. *Acta Pharmaceutica Sinica B*, *3*(3), 185-192.

45. Rao, J., & McClements, D. J. (2012). Lemon oil solubilization in mixed surfactant solutions: Rationalizing microemulsion & nanoemulsion formation. *Food Hydrocolloids*, *26*(1), 268-276.

46. Mitri, K., Shegokar, R., Gohla, S., Anselmi, C., & Müller, R. H. (2011). Lipid nanocarriers for dermal delivery of lutein: preparation, characterization, stability and performance. *International Journal of Pharmaceutics*, *414*(1), 267-275.

47. Khurana, S., Jain, N. K., & Bedi, P. M. S. (2013). Development and characterization of a novel controlled release drug delivery system based on nanostructured lipid carriers gel for meloxicam. *Life Sciences*, *93*(21), 763-772.

48. Khurana, S., Jain, N. K., & Bedi, P. M. S. (2013). Nanoemulsion based gel for transdermal delivery of meloxicam: physico-chemical, mechanistic investigation. *Life Sciences*, *92*(6), 383-392.

49. Kuo, F., Subramanian, B., Kotyla, T., Wilson, T. A., Yoganathan, S., & Nicolosi, R. J. (2008). Nanoemulsions of an anti-oxidant synergy formulation containing gamma tocopherol have enhanced bioavailability and anti-inflammatory properties. *International Journal of Pharmaceutics*, *363*(1), 206-213.

50. Rahn-Chique, K., Puertas, A. M., Romero-Cano, M. S., Rojas, C., & Urbina-Villalba, G. (2012). Nanoemulsion stability: experimental evaluation of the flocculation rate from turbidity measurements. *Advances in Colloid and Interface Science*, *178*, 1-20.

51. Kong, M., Chen, X. G., Kweon, D. K., & Park, H. J. (2011). Investigations on skin permeation of hyaluronic acid based nanoemulsion as transdermal carrier. *Carbohydrate Polymers*, *86*(2), 837-843.

52. Bouchemal, K., Briançon, S., Perrier, E., & Fessi, H. (2004). Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. *International Journal of Pharmaceutics*, *280*(1), 241-251.

53. Chaudhary, H., Kohli, K., & Kumar, V. (2014). A novel nano-carrier transdermal gel against inflammation. *International Journal of Pharmaceutics*, *465*(1), 175-186.

54. Elnaggar, Y. S., El-Refaie, W. M., El-Massik, M. A., & Abdallah, O. Y. (2014). Lecithin-based nanostructured gels for skin delivery: an update on state of art and recent applications. *Journal of Controlled Release*, *180*, 10-24.

55. Bose S, Kohn BM. (2013) Bose, S., & Michniak-Kohn, B. (2013). Preparation and characterization of lipid based nanosystems for topical delivery of quercetin. *European*

Journal of Pharmaceutical Sciences, *48*(3), 442-452.

56. Kim, Y. H., Song, C. K., Jung, E., Kim, D. H., & Kim, D. D. (2014). A microemulsion-based hydrogel formulation containing voriconazole for topical skin delivery. *Journal of Pharmaceutical Investigation*, *44*(7), 517-524.
57. Jeirani, Z., Jan, B. M., Ali, B. S., Noor, I. M., Hwa, S. C., & Saphanuchart, W. (2012). The optimal mixture design of experiments: Alternative method in optimizing the aqueous phase composition of a microemulsion. *Chemometrics and Intelligent Laboratory Systems*, *112*, 1-7.
58. Bolzinger, M. A., Briançon, S., Pelletier, J., Fessi, H., & Chevalier, Y. (2008). Percutaneous release of caffeine from microemulsion, emulsion and gel dosage forms. *European Journal of Pharmaceutics and Biopharmaceutics*, *68*(2), 446-451.
59. Bshara, H., Osman, R., Mansour, S., & El-Shamy, A. E. H. A. (2014). Chitosan and cyclodextrin in intranasal microemulsion for improved brain buspirone hydrochloride pharmacokinetics in rats. *Carbohydrate Polymers*, *99*, 297-305.
60. Lv, F. F., Li, N., Zheng, L. Q., & Tung, C. H. (2006). Studies on the stability of the chloramphenicol in the microemulsion free of alcohols. *European Journal of Pharmaceutics and Biopharmaceutics*, *62*(3), 288-294.
61. Sintov, A. C., & Shapiro, L. (2004). New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability *in vivo*. *Journal of Controlled Release*, *95*(2), 173-183.
62. Kawakami, K., Yoshikawa, T., Moroto, Y., Kanaoka, E., Takahashi, K., Nishihara, Y., & Masuda, K. (2002). Microemulsion formulation for enhanced absorption of poorly soluble drugs: I. Prescription design. *Journal of Controlled Release*, *81*(1), 65-74.
63. Wang, X., Xue, M., Gu, J., Fang, X., & Sha, X. (2012). Transdermal microemulsion drug delivery system for impairing male reproductive toxicity and enhancing efficacy of Tripterygium Wilfordii Hook f. *Fitoterapia*, *83*(4), 690-698.
64. Nikumbh, K. V., Sevankar, S. G., & Patil, M. P. (2013). Formulation development, in vitro and in vivo evaluation of microemulsion-based gel loaded with ketoprofen. *Drug Delivery*, (0), 1-7.

