

Review Article

REVIEW ON: EFFECT OF OIL, SURFACTANT AND COSURFACTANT ON MICROEMULSION

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ABSTRACT

Lipid dosage forms are the most preferred delivery system for hydrophobic drug molecules. Lipid dosage forms has many advantages of higher degree of biocompatibility and versatility and also lipid dosage form gained more importance in recent years because of their ability to improve the solubility and bioavailability of drugs with poor water solubility. Lipid formulation can be altered in various ways to provide wide range of product requirements as per the disease condition, route of administration, toxicity and efficacy. Lipid formulations are most reliable strategy for formulating pharmaceuticals, for topical, oral, pulmonary, or parenteral delivery. Due to their capability as therapeutic agents, ideally, these lipid-soluble drugs are incorporated into inert lipid carriers such as oil, surfactant dispersion, liposomes, emulsion etc. Emulsion is one of the known systems since many years. Pharmaceutical application of the emulsion is widely speeded after the microemulsion and nano emulsions appearance. Microemulsions are clear, stable and isotropic mixture of oil, surfactant and cosurfactant. Emulsions and nano emulsions are not thermodynamically stable, compared with microemulsions. The main objective of this review paper is to discuss about the effect of oil, surfactant and cosurfactant on the microemulsions.

Keywords: Emulsion, Microemulsion, Surfactant, Cosurfactant, Oil

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INTRODUCTION

Emulsion is a liquid dosage form consisting of two immiscible liquids such as water and oil, which are mixed using mechanical shear and surfactant. Surfactant is responsible for reducing naturally occurring attractive forces in the form of surface tension. Surfactant with low HLB value shows water in oil emulsion and high HLB values shows oil in water emulsion [1, 2]. Emulsion prepared without adding surfactant would be not stable, and the phases of the emulsion will be separated in different layers. Therefore, the addition of surfactant is necessary to make emulsion stable for long period of time [3, 4].

Emulgel is the combination of gel and emulsion. Both oil in water and water in oil types of emulsion is used as carrier to deliver the various drugs into the skin. Emulgel also have a great ability to penetrate through the skin. Gelling agent in the water phase converts the emulsion into an emulgel [5]. Emulgel dermatologically have many advantages such as greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, pleasing and transparent appearance [6].

Micro emulsion is clear, thermodynamically stable, isotropic liquid dosage form. It is formulated using oil, water, surfactant, and co-surfactant [7, 8]. Microemulsions are different from emulsion by their transparency, low viscosity, thermodynamic stability and spontaneity and at least 30% of water forms the spontaneous and thermodynamic stable dosage form [9]. Administration of the drugs using micro emulsions through the skin increase the local delivery of the drug by different mechanism [10].

Microemulgels, a dual drug delivery system, done by converting a liquid microemulsion into a semi-solid gel. Because of its dual action of emulsion and gel, it is considered as one of the most promising new drug delivery systems. Microemulsion dosage form is selected because of its good solubility and ability to penetrate into the skin, whereas gel can sustain the drug release and provide a lengthy drug residence time. For skin-related disorders, microemulgel is the best delivery technology which shows better efficacy with minimum amount of medicine [11, 12].

Emulsion

Emulsion is a biphasic liquid dosage form possessing two immiscible liquids; emulsifying agent is added, which form film around the

globules so that stable emulsion is formed. The globules size is 0.25 to 25 μm diameters [3, 4].

Ideal properties [3, 4]

- It must be stable at various temperature
- It must be not degraded by microbes on storage
- It must remain in its original type, without phase inversion.
- Must not rancid due to oxidation

Types of emulsion [3, 4]

Water in oil type (w/o)

Oil in water type (o/w)

Multiple emulsion

In water in oil type (w/o) emulsion, oil is in the dispersion phase and water is in dispersed phase. According to studies it is confirmed that stability plays major role in w/o emulsions and water in oil emulsions are stabilized using natural surfactants such as beeswax, resins and fat.

In oil in water emulsion, oil is in the dispersed phase and water is in the dispersion phase. Emulsifying agents used in the o/w emulsions is saponins, gum acacia and synthetic substance.

Multiple emulsions are the complexed mixtures where both oil in water and water in oil emulsion are existing simultaneously. They are stabilized using lipophilic and hydrophilic surfactants, respectively. Multiple emulsions are prepared by the re-emulsification of a primary emulsion or they can also prepare when an emulsion inverts from one type to another type. For example, w/o to o/w [3, 4].

Emulgel

Emulgel is the combination of gel and emulsion. Both oil in water and water in oil types of emulsion is used as carrier to deliver the various drugs into the skin. Emulgel also have a great ability to penetrate through the skin [5, 6].

Formulation consideration [13]

The challenges in the preparation of emulgel

- Finding systems which are non-irritating, non-toxic, non-comedogenic and non-sensitizing.
- Preparing accessorially effective emulgel
- The emulgel preparation should have low allergic properties, good physiological compatibility and high biocompatibility.

Preparation of emulgel [14]

Step 1: Preparation of emulsion

Step 2: Preparation of gel base

Step 3: Incorporation of an emulsion into gel base

Microemulsion

According to the literature survey, 40 % of the new drugs are poorly soluble in water, which shows poor dissolution for the drug through oral administration that leads to poor bioavailability and such drugs always a challenge to deliver through oral route. However, some of the researchers suggested that poorly water-soluble drugs can be enhanced by microemulsion formulation [7, 8].

Microemulsion is a clear, thermodynamically stable, isotropic liquid dosage form. It is formulated using oil, water, surfactant, and co-surfactant. Microemulsions are different from the emulsion by their transparency, low viscosity, thermodynamic stability and spontaneity. and at least 30% of water forms the spontaneous and thermodynamic stable dosage form. Administration of the drugs using microemulsions through the skin increase the local delivery of the drug by different mechanism [7-10].

When nanoemulsions are compared with microemulsions, nanoemulsions are not thermodynamically stable. Because nano emulsion undergoes degradation of the structure due to Ostwald ripening, flocculation, coalescence and gravitational separation, these results in particle size distribution change, physical properties change as well as chemical properties change. Whereas microemulsion will not undergo deformation on the long storage condition remains constant [15].

Microemulsion types (according to Winsor classification) [7, 16]

Type I (o/w): This type of microemulsion is formed when the surfactant is solubilized in water phase.

Type II (w/o): This type of microemulsion is formed when the surfactant is solubilized in oil phase.

Type III: This is one of the types of microemulsion where the surfactant is loaded in the interphase, which combines with both oil and water phase in this formulation, both oil and water phase are surfactant deficient which leads to the formation of three phase microemulsion.

Type IV: This is an extension of type III where a higher concentration of surfactant at interphase becomes single phase.

Methods of preparation of microemulsion

Phase titration method: Microemulsion was prepared by taking an appropriate amount of oil and surfactant: a cosurfactant mixture in a beaker, it was then mixed using sonication until the surfactant get solubilized and a clear solution is obtained. Then required amount of drug is dispersed (the amount of drug is determined by solubility studies) in oil and surfactant: cosurfactant mixture and dissolved with the help of a magnetic stirrer. Later on, the water phase is added dropwise until the system becomes transparent. Thus, the microemulsion is formed [7, 17, 18].

Phase inversion method: Phase inversion of the microemulsion is a conversion of o/w to w/o or vice versa. Phase inversion of the microemulsion is prepared by adding an excess amount of dispersed phase or by raising the temperature. This method results in extreme changes in particle size, which later shows change in *in vivo* and *in vitro* drug release profiles [19, 20].

Advantages [21, 22]

- Easy to solubilize hydrophobic or oil soluble drugs
- Most suitable system to increase the rate of absorption as well as bio availability by avoiding interfering variation.
- Microemulsions can be preferred to develop controlled and sustained release drug system.
- It is better choice system to minimize first pass metabolism.
- It can be used for different routes such as oral, parenteral and topical drug delivery.
- Suitable for long-term use since microemulsion is thermodynamically more stable compared to the conventional system

Disadvantages [23, 24]

- Expensive, if additional use of excess amount of surfactant and cosurfactant.
- Excess concentration of surfactant can lead to mucosal toxicity.

Microemulgel

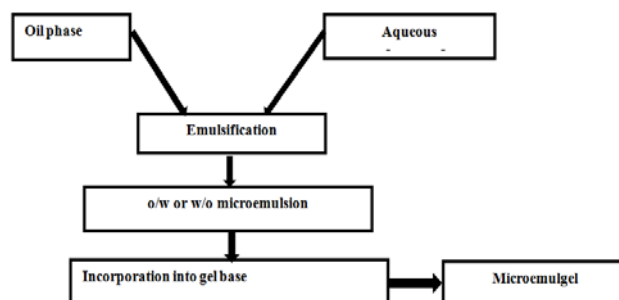
Microemulgel is a combination of emulsion and gels, exhibits characteristics of both. Microemulgel supports to deliver hydrophobic drugs by formulating oil in water microemulsion and this microemulsion can be incorporated into gel base [25, 26]. Microemulgel shows good patient acceptability. Due to its non-greasy in nature, it can be easily applied on to the skin as compared to the other topical dosage form such as ointments, creams which are very greasy, thick and excess amount required for rubbing [27].

Preparation process [28, 29]

Step 1: Preparation of o/w or w/o microemulsions by using values processed in oil and water step.

Step 2: Preparation of gel, using appropriate concentration of gelling agent and water.

Step 3: Incorporation of microemulsion in gel base with continuous stirring.



Major components of microemulgel [30, 31]

- Oil
- Surfactant
- Cosurfactant

Effect of oil, surfactant and cosurfactant on microemulsion

Oil

Oil shows the good solubility for the BCS class II drugs. The oil also acts as a penetration enhancer in a microemulsion based drug delivery system. Short chain oil enter tail group region to a greater extent than along the chain, which leads in the swelling of the tail group and hence an increase in negative curvature that minimize the effect of HLB balance [30, 31]. Oils also influence the area of the microemulsion region for example, Muhammad Asri Abd Sisak *et al.* 2017, total 18 phase diagrams were constructed successfully for both oleic acid and IPM. Each formulation showed a significant effect

on the area of microemulsion region, oleic acid-based system could not give large microemulsions region. IPM showed best choice in order to get larger microemulsions region with higher concentration of water with transition phase from w/o to o/w [32]. The increase in the oil concentration, increases in the size of the droplet. The oils which show higher solubility for the drug also shows higher droplet size, this effects of oil on the droplet size are studied by Omar sarheed *et al.* 2020 [33]. Molecular volumes of the oil also show its effect on the microemulsion. For example, IPM (molecular volume 528.2 g/cm³) based microemulsion system showed a smaller area of microemulsion as compared to system based on oleic acid (molecular volume 523.9 g/cm³)[34-36].

Surfactant

Surfactant is the second criteria to consider for the preparation of microemulsion and surfactant should be chosen in such a way that gives very best solubility for drug [37]. During the emulsification method, surfactant should quickly absorb within the interface and stop the droplets aggregation, there are 4 types of surfactants non-ionic, zwitterionic, cationic or anionic surfactants, which stabilizes the systems. Ionic and nonionic surfactants have a potential to extend the microemulsion region. Examples of non-ionic surfactant are brij-35, and tween 20/80 or span 80 [38]. Surfactant shows its effect on drug solubility for example, Handy M. Dawaba *et al.*-2010, stated his research work about the effect of surfactant tween 80, which show the greater solubility for the piroxicam drug [39]. Omar sarheed *et al.* 2020, concluded that increase in the surfactant concentration a decrease in the droplet size [33]. The ratio or HLB values of the surfactant mixture also influence the penetration of the microemulsion for example, Liangmei Chen *et al.* 2011 constructed 5 pseudo ternary phase diagrams using various mixed surfactants

(Cremophor EL/span 80) HLB values (8.4, 8.0, 7.6, 7.2, 6.8) out of 5 mixed surfactants with different HLB values, the flux and the amount of drug penetration increased with increasing content of the lipophilic surfactant span 80 and the skin retention was highest for mixed surfactant with HLB value of 7.6. Hence, it was suggested that the presence of mixed surfactant was beneficial in the formulation of microemulsions [40].

Co-surfactant

The cosurfactant is generally used with the surfactant in the preparation of microemulsion, which decreases the interfacial tension between the two immiscible liquids to the transient negative value. At this negative value fine droplets are formed due to the interphase expansion and much surfactant/cosurfactant get absorbed on the surface until the bulk condition is source enough to make the interracial tension positive again. Cosurfactant of short medium chain length alcohols also ensures that interfacial film is flexible enough to misshape readily around droplets, as the interaction between primary surfactant molecules decrease both polar head group interaction and hydrocarbon chain interaction [41]. Research work of Muhammad asriabdisak *et al.* 2017 the effect of co-surfactant depends on its chain length, where only an appropriate chain length is suitable for good microemulsion formation. PEG400 (long chain), Transcutol (medium chain), propylene glycol (short chain), were used in his study to evaluate the effect of co-surfactant on the preparation of microemulsion. In his study, he concluded that medium chain length surfactant is most suitable co-surfactant in combination with single chain surfactant [32]. The surfactant having HLB value more than 20 often requires the presence of a cosurfactant to reduce surfactant effective HLB value within range of required microemulsion formulation [42-44].

Table 1: Examples for oil, surfactant and cosurfactant in research study [45-50]

Oils	Surfactant	Cosurfactant
Propylene glycol	Tween 80	Propylene glycol400
Karanj oil	Span 20	Capryol90
Oleic acid	Tween 20	Propylene glycol
Capryol90	Tween 80	PEG400
Palm oil	Tween 80	N-butanol
Orange oil	Tween 80	Propylene glycol
Oleic acid	Tween 80	Ethanol
Capryol™90	Tween 80	Transcutol p

Table 2: Microemulgel marketed formulation

Name the product	Active ingredients	Company
Voltrarenmicroemulgel	Diclofenac diethyl ammonium	Novartis pharma
Avindo gel	Azithromycin	Cosme pharma laboratories
Zorotene gel	Tezarotene	Elder pharmaceuticals
Clinagel	Clindamycin phosphate allantoin	Stiefel pharma
Acent gel	Aceclofenac, Methyl salicylate, capsaicin	Intra labs IndiaPvt Ltd
Topinate gel	Clobetasol propionate	Systopicpharma
Kojivitgel	Kojicacid, Dipalmitatearbutin, Octinnoxate	Micro gratia pharma
Exceexgel	Clindamycin, Adapalene	Zee laboratories
Lupigylgel	Metronidazole	Lupin pharma
Pernox gel	Benzoyl peroxide	Cosme remedies Ltd
Clobengel	Clotrimazole, Beclomethasonedipropionate, Neomycin	Elder pharmaceuticals
Miconaz-H-microemulgel	Miconazole-nitrate, Hydrocortisone	Medical union pharmaceuticals

Table 3: Patented formulation [51-55]

S. No.	Formulation	Patent no.
1	Gel-microemulsion formulation	US20030083314 A1
2	Microemulsion gel preparation of oxiconazole nitrate	CN102423293 B
3	Composition for microemulsion gel having bleaching and antiseptic properties	US5336432 A1
4	Microemulsion based gel	EP0760651 B1
5	Granisetron HCL Microemulsion based gel	CN101933902 A

CONCLUSION

Microemulsion is a potential drug delivery system, mostly used for the delivery of hydrophilic and lipophilic drug. Microemulsion have good characteristics such as improved drug solubilization, longer shelf life and improvement of bioavailability of poorly soluble drugs. According to the literature evidence the oil, surfactant and cosurfactant present in the microemulsion show their effect on microemulsion, i.e. type of oil, concentration and molecular volume influence the area of microemulsion and droplet size. Surfactants with a single chain increase the microemulsion region. Type of surfactant like ionic and nonionic extends the microemulsion region compared to other types of surfactants. The ratio of surfactant shows its effect on microemulsion penetration. Cosurfactant with medium chain length gives good microemulsion and cosurfactant reduces surfactant effective HLB value within the range of required microemulsion formulation.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors have no conflict of interest regarding this review.

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