Review Article

Microemulsions: A Novel Drug Carrier System

Bipin Sarvesh Katiyar[1]*, Sameer Sarvesh Katiyar[2], Preeti Satishchandra Mishra[1], Duvvuri Lakshmi Sailaja[2]
[1]Department of Pharmaceutics, PSIT, Bhauti, Kalpi road, Kanpur (UP), India-208020.
[2]Department of Pharmaceutics, NIPER, Balanagar, Hyderabad (AP), India-500037.
***Corresponding author's E-mail:** bipinkatiyar87@gmail.com

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ABSTRACT

Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a cosurfactant with a droplet size usually in the range of 20-200 nm. They can be classified as oil-in-water (o/w), water-in-oil (w/o) or bicontinuous systems depending on their structure and are characterized by ultra low interfacial tension between oil and water phases. These versatile systems are currently of great technological and scientific interest to the researchers because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains. These adaptable delivery systems provide protection against oxidation, enzymatic hydrolysis and improve the solubilization of lipophilic drugs and hence enhance their bioavailability. In addition to oral and intravenous delivery, they are amenable for sustained and targeted delivery through ophthalmic, dental, pulmonary, vaginal and topical routes. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability. While microemulsions are used in several fields, this article focuses on the reported investigations for topical and various other applications which exhibit minimal systemic absorption.

Keywords: Microemulsion, Bicontinous, Cosurfactants, Lipophilic drugs, Thermodynamic stability.

INTRODUCTION

The word microemulsion was originally proposed by Schulman et al. (1959)[1]. They prepared a quaternary solution of water, benzene, hexanol, and k-oleate which was stable, homogenous and slightly opalescent. These systems became clear as soon as a short chain alcohol was added. In the years between 1943 and 1965 Schulman and co-workers described how to prepare these transparent systems. Basically a coarse (or macro) emulsion was prepared and the system was then titrated to clarify by adding a co-surfactant (second surface active substance). When the combination of the four components was right, the system cleared spontaneously. Most of the work reported by Schulman dealt with four component systems. Hydrocarbons (aliphatic or aromatic), ionic surfactants, cosurfactants (generally 4–8 carbon chain aliphatic alcohol) and an aqueous phase. Schulman had previously published extensively in the field of monolayers and applied what he had learnt in that field to explain the formation of microemulsions. The surfactant and co-surfactant, when properly selected, form a mixed film at the oil/water interface, resulting in an interfacial pressure exceeding the initial positive interfacial tension. To summarize, the basic observation made by Schulman and co-workers was that when a co-surfactant is titrated into a coarse microemulsion composed of a mixture of water/surfactant in a sufficient quantity to obtain microdroplet, the result may be a system which is low in viscosity, transparent, isotropic, and very stable. The titration from opaque emulsion to transparent solution is spontaneous and well defined. It was found that these systems are made of spherical micro droplets with a diameter between 600 and 8000 nm. It was only in 1959 that Schulman proposed to call these systems microemulsions. Previously he used terms such as transparent water and oil dispersion, oleophatic hydromicelles or hydropathic oleomicelles. Since this time, microemulsions have found a wide range of applications, from oil recovery to synthesis of nanoparticles[2].

Topical preparations pertain to medicaments applied to the surface of a part of the body and are a term used to describe formulations that have effects only in a specific area of the body and are formulated in such a manner that the systemic absorption of the medicament is minimal. The methods involved in conventional topical drug delivery basically involve either assisting or manipulating the barrier function of the skin (topical antibiotics, antibacterials, emollients, sunscreen agents) or breaching the horny layer at the molecular scale so as to direct drugs to the viable epidermal and dermal tissues without using oral, systemic or other therapies.

There has been a revolution in the last two decades in the utilization of microemulsion systems in a variety of chemical and industrial processes. Microemulsions have shown a wide range of applications starting with enhanced oil recovery in the 70's, expanding to a wide range of chemicals and entering the pharmaceutical and cosmetic formulation area a decade ago[3].

Microemulsions have advantages over both colloidal systems under investigation and conventional emulsions, suspensions and micellar solutions and may provide alternative drug carriers. They are promising delivery systems which allow sustained or controlled drug release

for percutaneous, peroral, topical, transdermal, ocular and parenteral administration of medicaments. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability. Also, microemulsions that have inverse micellar structure may be less comedogenic than either creams or solutions[4].

Microemulsions are thermodynamically stable isotropic systems in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. The short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Therefore microemulsions form spontaneously, with an average droplet diameter of 10 to 140 nm[5]. Microemulsions have the ability to deliver larger amounts of water and topically applied agents into the skin than water alone or other traditional vehicles such as lotions or creams because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization[6]. While microemulsions are used in several fields, in this review an attempt has been made to emphasize on the reported studies for topical applications which exhibit minimal systemic absorption.

ADVANTAGES OF MICROEMULSIONS

Microemulsions are potential drug carrier systems for various routes of administration. These are having advantages when compare to the other dosage forms.

a. These are thermodynamically stable and require minimum energy for formation.

b. Ease of manufacturing and scale-up.

c. Improved drug solubilization and bioavailability.

d. This system is reckoned advantageous because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release[7].

COMPONENTS OF MICROEMULSION FORMULATIONS

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions.

Oil Phase

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group region to a greater extent than long chain alkanes, and hence swell this region to a greater extent, resulting in increased negative curvature (and reduced effective HLB)[7]. Saturated (for example, lauric, myristic and capric acid) and unsaturated fatty acids (for example, oleic acid, linoleic acid and linolenic acid) have penetration enhancing property of their own and they have been studied since a long time. Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase. Lipophilic drugs are preferably solubilized in o/w microemulsions. The main criterion for selecting the oil phase is that the drug should have high solubility in it. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form.

Surfactants

The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. It is generally accepted that low HLB surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

Cosurfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form[8-11]. The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition[7, 12-14]. If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds). Short to medium chain length alcohols (C3-C8) are commonly added as cosurfactants which further reduce the interfacial tension and increase the fluidity of the interface.

STRUCTURE

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating[15]. Structurally, they are divided into oil-in-water (o/w), water-in-oil (w/o) and bicontinuous microemulsions. In w/o microemulsion, water droplets are dispersed in the continuous oil phase while o/w microemulsion is formed when oil droplets are dispersed in the continuous aqueous phase. In systems where the amounts of water and oil are similar, a bicontinuous microemulsion may result. In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants. The mixture of oil, water and surfactants is able to form a wide variety of structures and phases depending upon the proportions of the components. The flexibility of the surfactant film is an

important factor in this regard. A flexible surfactant film will enable the existence of several different structures like droplet like shapes, aggregates and bicontinuous structures, and therefore broaden the range of microemulsion existence. A very rigid surfactant film will not enable existence of bicontinuous structures which will impede the range of existence. Besides microemulsions, structural examinations can reveal the existence of regular emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the ratio of the components.

The internal structure of a microemulsion vehicle is very important for the diffusivity of the phases, and thereby also for the diffusion of a drug in the respective phases. Researchers have been trying zealously to understand the complicated phase behaviour and the various microstructures encountered in the microemulsion systems[16].

FACTORS AFFECTING THE MICROEMULSION

The formation of microemulsion will depend on the following factors are:

a. **Packing ratio**

The HLB of surfactant determines the type of microemulsion through its influence on molecular packing and film curvature. The analysis of film curvature for surfactant's association leadings to the formation of microemulsion, molecular packing and film curvature. The analysis of film curvature for surfactant association's leadings to the formation of microemulsion.

b. **Property of surfactant, oil phase and temperature**

The type of microemulsion depends on the nature of surfactant. Surfactant contains hydrophilic head group and lipophilic tail group. The areas of these groups, which are a measure of the differential tendency of water to swell head group and oil to swell the tail area, are important for specific formulation when estimating the surfactant HLB in a particular system. When a high concentration of the surfactant is used or when the surfactant is in presence of salt, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type. Diluting with water may increase dissociation and leads to an o/w system. Ionic surfactants are strongly influenced by temperature. It mainly causes increased surfactant counter-ion dissociation. The oil component also influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chains oils penetrate the lipophilic group region to a great extent and results in increased negative curvature. Temperature is extremely important in determining the effective head group size of nonionic surfactants. At low temperature, they are hydrophilic and form normal o/w system. At higher temperature, they are lipophilic and form w/o systems. At an intermediate temperature, microemulsion coexists with excess water and oil phases and forms bicontinuous structure.

c. **The chain length, type and nature of cosurfactant**

Alcohols are widely used as a cosurfactant in microemulsions. Addition of shorter chain cosurfactant gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favoured, while longer chain cosurfactant favours w/o type w/o type by alcohol swelling more in chain region than head region[7].

FORMULATION CONSIDERATIONS

The challenges in formulating topical microemulsions are:

1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non-sensitizing.

2. Formulating cosmetically elegant microemulsions.

The microemulsion formulation must have low allergic potential, good physiological compatibility and high biocompatibility.

The components involved in the general formulation of microemulsions include (a) an oil phase (b) an aqueous phase containing hydrophilic active ingredients [preservatives and buffers may be included] (c) a primary surfactant [anionic, non-ionic or amphoteric] (d) secondary surfactant or cosurfactants.

Generally non-ionic surfactants are chosen because of their good cutaneous tolerance, lower irritation potential and toxicity. Microemulsions can be formulated using single chain surfactants or double chain surfactants. Single chain surfactants do not lower the oil water interfacial tension sufficiently and hence cosurfactants are required. Double chained surfactants like sulfosuccinates can form microemulsions in the absence of cosurfactants but are too toxic for general pharmaceutical applications[17]. The cosurfactants even though being indispensable in the formulation of microemulsions, have exhibited toxicity e.g. medium chain length alcohols[18]. Hence judicious choice of surfactants and cosurfactants is of great importance. The use of polyoxyethylene alcohol ethers has been reported as cosurfacants[19-21]. Microemulsions prepared from phospholipids such as lecithins are preferred over synthetic surfactants from the toxicity point of view[22,23]. The biocompatibility requirements of the amphiphiles are fulfilled by lecithins and non-ionic surfactants[24]. The following examples are commonly used formulations components of microemulsions

- **Oil:** Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (Coconut oil, Safflower oil, Soyabean oil, Olive oil), Medium chain length triglyceride (Mygliol 812).

- **Surfactant:** Polysorbate (Tween 80 and Tween 20), Lauromacrogol 300, Lecithins, Decyl polyglucoside (Labrafil M 1944 LS), Polyglyceryl-6-dioleate (Plurol Oleique), Dioctyl sodium sulfosuccinate (Aerosol OT), PEG- 8 caprylic/capril glyceride (Labrasol).

- **Co-surfactant**: Sorbitan monooleate, Sorbitan monostearate, Propylene glycol, Propylene glycol monocaprylate (Capryol 90), 2-(2-ethoxyethoxy)ethanol (Transcutol P) and Ethanol.

METHOD OF PREPARATION

1. Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) 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 interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component Fig. (1).The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich. Observations should be made carefully so that the metastable systems are not included. The methodology has been comprehensively discussed by Shafiq-un-Nabi et al[25].

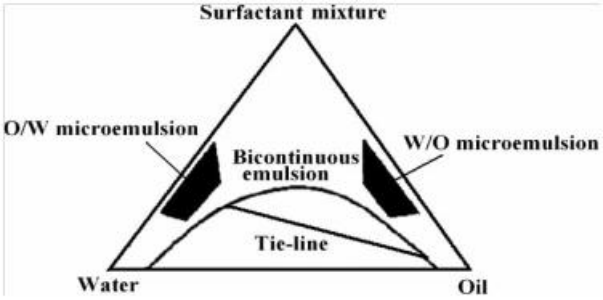

Figure 1: Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region

2. Phase Inversion Method

Phase inversion of microemulsions occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both in vivo and in vitro. These methods make use of changing the spontaneous curvature of the surfactant. For non-ionic surfactants, this can be achieved by changing the temperature of the system, forcing a transition from an o/w microemulsion at low temperatures to a w/o microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point of zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone.

Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus. Short-chain surfactants form flexible monolayers at the o/w interface resulting in a bicontinuous microemulsion at the inversion point.

Research Work carried out on Microemulsions:

Drug Name	Route	Purpose/Result
Flurbiprofen [26]	Parenteral	Increased the solubility
Apormorphine HCl [27]	Transdermal	Increased the permeability
Ketoprofen [28]	Transdermal	Enhancement of permeability
Prilocainne-HCL [29]	Transdermal	Increased the solubility
Estradiol [30]	Transdermal	Improvement in solubilization
Aceclofenac [31]	Dermatological	Increased the solubility
Piroxicam [32]	Oral	Increased the solubility
Diclofenac [33]	Transdermal	Permeability enhancement
Dexamethasone [34]	Topical Ocular	Enhanced the Bioavailability
Chloramphenicol [35]	Ocular	Increased the solubility
Ibuprofen [36]	Parenteral	Increased the solubility
Sumatriptan [37]	Intranasal	Enhanced the Bioavailability
Ibuprofen [38]	Topical	Increasing the solubility
Doxorubicin [39]	-	Increasing the Stability
Itraconazole [40]	Parenteral	For better absorption
Timolol [41]	Ophthalmic	For better absorption
Terbinafine [42]	Transdermal	Permeability enhancement
Fenofibrate [43]	Self-Micro emulsifying	Increasing the solubility
Progesterone [44]	Dermal	Increased chemical stability

EVALUATION OF MICROEMULSIONS

The microemulsions are evaluated by the following techniques. They are:

Phase behavior studies

Visual observations, phase contrast microscopy and freeze fracture transmission electron microscopy can be used to differentiate microemulsions from liquid crystals

and coarse emulsions. Clear isotropic one-phase systems are identified as microemulsions whereas opaque systems showing bifringence when viewed by cross polarized light microscopy may be taken as liquid crystalline system.

Rheology

Change in the rheological characteristics help in determining the microemulsion region and its separation from other related structures like liquid crystals. Bicontinuous microemulsion are dynamic structures with continuous fluctuations occurring between the Bicontinuous structure, swollen reverse micelle, and swollen micelles.

Scattering Techniques

Scattering techniques such as small angle neutron scattering, small angle X-ray scattering and light scattering have found applications in studies of microemulsion structure, particularly in case of dilute monodisperese spheres, when polydisperse and/or concentrated systems such as those frequently seen in microemulsions.

MICROEMULSIONS IN DRUG DELIVERY

During the last two decades, microemulsions have been extensively researched because of their tremendous potential in many applications. The role of microemulsions in drug delivery shall be discussed comprehensively herein.

Oral Delivery

The development of the effective oral delivery systems has always been the main goal because drug efficacy can be severely limited by instability or poor solubility in the gastrointestinal fluid. Biopharmaceutical Classification System (BCS) is a useful guidance by US FDA and it takes into account contributions of three major factors, dissolution, solubility, and intestinal permeability, which affect oral drug absorption. According to the BCS, drug substances are classified as follows:

Class I - High Permeability, High Solubility

Class II - High Permeability, Low Solubility

Class III - Low Permeability, High Solubility

Class IV - Low Permeability, Low Solubility

Knowledge of BCS help the formulation scientists to develop a dosage form based on mechanistic, rather than empirical approaches. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250 mL of water over a range of pH from 1.0 to 7.5 and highly permeable when they show >90 percent absorption of the administered dose[45,46]. In contrast, compounds with solubility below 0.1mg/mL provide significant dissolution related problems, and often, even compounds with solubility below 10mg/mL present difficulties related to solubilization during formulation. A major technological hurdle for routine clinical use of many drugs is their very poor solubility in water.

Microemulsions have the potential to enhance the solubilization of the poorly soluble drugs and overcome the dissolution related bioavailability problems. This is particularly important for the BCS class II or class IV drugs. The successful formulation of such drugs is highly dependent on the performance of the formulated product. Microemulsions act as super solvent of these drugs and can be optimized to ensure consistent bioavailability. In addition, they can be used for the delivery of hydrophilic drugs including macromolecules such as proteins and peptides. This is due to the existence of polar, nonpolar and interfacial domains which allow encapsulation of drugs with varying solubility. Moreover, these systems have been reported to protect the incorporated drugs against oxidation, enzymatic degradation[47] and enhance the membrane permeability[48]

a) Bioavailability Enhancement of Poorly Water Soluble Drugs.

Paclitaxel, an anticancer drug, has poor aqueous solubility and therefore, formulation of paclitaxel has proven to be difficult. Gao et al., disclosed self emulsifying compositions that generated a supersaturated paclitaxel microemulsion upon contact with water in vivo that permitted its rapid and efficient absorption resulting in improved oral bioavailability[49]. The composition comprised of a solvent, a surfactant, a substituted cellulosic polymer (e.g. hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, etc.), and optionally a Pglycoprotein inhibitor. Paclitaxel and surfactant were present in a ratio of from about 1:3 to about 1:20 by weight; and the substituted cellulosic polymer and paclitaxel were present in a ratio of from about 50:1 to about 0.1:1 by weight. The oral administration of a commercial product, Taxol® (Bristol Myers Squibb) showed approximately 10-fold lower Cmax than that obtained with their composition in rats.

b) Controlled and Sustained Release of Drugs

A sustained-release dosage form for the delivery of a progestogenic steroid comprising of a capsule, a self-emulsifying drug formulation contained within a first portion of the capsule, an expandable layer contained within a second portion of the capsule[50]. The expandable layer was so positioned that the self-emulsifying drug formulation could be expelled from the capsule upon expansion of the expandable layer and a semipermeable membrane is formed over at least a portion of an outer surface of the capsule Fig. (2). The semipermeable membrane comprised of a thermoplastic polymer composition having a softening point of 40- 180C. The aqueous fluid dissolved the gelatin capsule and the imbibed fluid caused the push-displacement layer to expand and push the emulsified formulation through an orifice at a controlled rate. The dosage form comprising the liquid formulation provided various advantages such as improved solubility, improved bioavailability, sustained

release and inhibition of crystal growth during storage thereby providing improved stability.

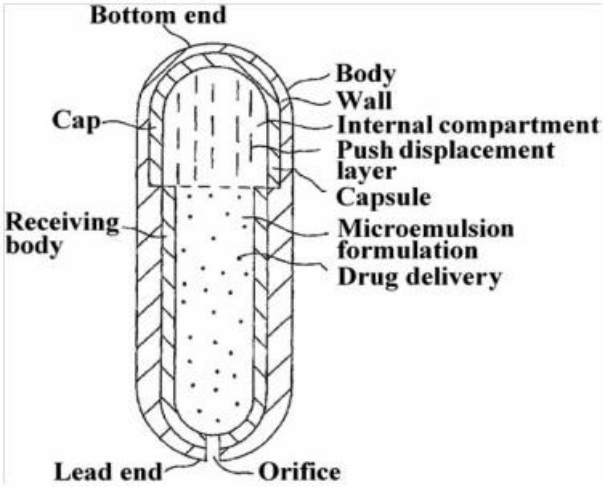

Figure 2: Dosage form comprising a capsule made of two parts consisting of a body portion and a cap portion in which capsule contains a drug microemulsion formulation and an expandable composition.

Parenteral Delivery

The formulation of lipophilic and hydrophobic drugs into parenteral dosage forms has proven to be difficult. O/w microemulsions are beneficial in the parenteral delivery of sparingly soluble drugs where the administration of suspension is not desirable. They provide a means of obtaining relatively high concentration of these drugs which usually requires frequent administration. Other advantages are that they exhibit a higher physical stability in plasma than liposomes or other vesicles[51] and the internal oil phase is more resistant against drug leaching. Several sparingly soluble drugs have been formulated into o/w microemulsion for parenteral delivery[52-59]. Microemulsions can also be used as intravenous delivery systems for the fat soluble vitamins and lipids in parenteral nutrition[59].

Dennis et al., patented an intravenous microemulsion delivery system for water insoluble or sparingly water soluble drugs that comprised an oil phase comprising the drug, a long polymer chain surfactant (e.g. lecithin, gelatin casein, tweens, macrogol ethers, etc.) component and a short fatty acid surfactant (e.g. stearic acid, glyceryl monostearate, sorbitan esters, etc.) component and an aqueous phase[60]. The droplet size ranged from 10-100 nm. They had found the composition to be useful for propofol, a short-acting intravenous anesthetic. Micromulsion would emulsify or partition propofol into the non-aqueous phase and preclude (or markedly reduce) stinging and allow painless injection.

Microemulsions are generally not dilutable with aqueous fluids, such as certain bodily fluids and buffer solutions, and form emulsions upon contacting such fluids. Various microemulsions are also sensitive to temperature and are not stable outside of room temperature conditions. US Patent 6245349 provided drug delivery compositions in both concentrated and diluted forms for use as vehicles in the administration of various active agents[61]. The concentrated drug delivery compositions were formulated with a phospholipid component, a component selected from propylene glycol or certain polyethylene glycol compounds, a high HLB surfactant, and the drug component, with water and/or an optional oil component. The concentrated drug delivery compositions could be diluted with an aqueous fluid to form an o/w microemulsion. These o/w microemulsions were characterized by their small particle size and their wide range of temperature stability, typically from about -20o-50oC. They could be administered by intravenous, intraarterial, intrathecal, intraperitoneal, intraocular, intraarticular, intramuscular or subcutaneous injection.

Ophthalmic Delivery

In conventional ophthalmic dosage forms, water soluble drugs are delivered in aqueous solution while water insoluble drugs are formulated as suspensions or ointments. Low corneal bioavailability and lack of efficiency in the posterior segment of ocular tissue are some of the serious drawbacks of these systems. Recent research efforts have therefore focused on the development of new and more effective delivery systems. Microemulsions have emerged as a promising dosage form for ocular use[62].

Fialho et al., prepared microemulsion based dexamethasone eye drops which showed better tolerability and higher bioavailability[63]. The formulation showed greater penetration in the eye which allowed the possibility of decreasing the number of applications per day. This might be useful in achieving improved patient compliance.

Habe et al., formulated water-continuous microemulsions for ocular application of pilocarpine[64]. In vitro Studies showed a prolonged pilocarpine release from the microemulsions with lecithin. The authors found microemulsions to be favourable for ophthalmological use.

Nasal Delivery

Microemulsions are now being studied as a delivery system to enhance uptake across nasal mucosa. Addition of a mucoadhesive polymer helps in prolonging the residence time on the mucosa. Nasal route for administration of diazepam might be a useful approach for the rapid onset of action during the emergency treatment of status epilepticus. For this microemulsion was formulated comprising of ethyl laurate (15%), Tween 80: propylene glycol: ethanol at 1:1:1 weight ratio (70%) and water (15%). The nasal absorption of diazepam was found to be fairly rapid at 2 mg kg-1 dose with maximum drug plasma concentration reached within 2-3 min. The bioavailability (0-2 h) after nasal spray compared to i.v. injection was about 50% [65].

Periodontal Delivery

Periodontal disease is a collective term for a number of progressive oral pathological afflictions like inflammation and degeneration of the gums, periodontal ligaments, cementum and its supporting bone. It is a major cause of tooth loss. The invention of Brodin et al., included a novel pharmaceutical composition comprising local anaesthetic in oil form, surfactant, water and optionally a taste masking agent[66]. The composition was in the form of an emulsion or microemulsion and had thermoreversible gelling properties i.e. it was less viscous at room temperature than after introduction onto a mucous membrane of a patient. The surfactant in the formulation imparted the thermoreversible gelling properties. Preferred surfactants were Poloxamer 188®, Poloxamer 407® and Arlatone 289®. The composition could be used as a local anaesthetic for pain relief within the oral cavity in conjunction with periodontal scaling and root planning and overcame the problem with the existing topical products (jelly, ointment or spray) such as lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

Drug Targeting

Drug targeting has evolved as the most desirable but elusive goal in drug delivery. By altering the pharmacokinetics and biodistribution of drugs and restricting their action to the targeted tissue increased drug efficacy with concomitant reduction of their toxic effects can be achieved. Drug targeting to diseased cells can be achieved by exploiting the presence of various receptors, antigens/proteins on the cell membrane which may be uniquely expressed or over expressed in these cells as compared to the normal cells. Specific antibodies to the surface proteins and ligands for the receptors can be used to target specific cells. Submicron size range of these systems confers excellent opportunities to overcome the physiological barriers and enables efficient cellular uptake followed by intracellular internalization.

1) *Cellular Targeting*

Nucleic acids delivered to cells are promising therapeutics. The invention of Monahan et al. included insertion of nucleic acid into a reverse micelle for cell delivery[67]. They referred w/o microemulsions to as reverse micelles. The reverse micelle had the property to compact the nucleic acid for easier delivery. To further enhance the delivery, other molecules such as a surfactant having a disulfide bond or a polyion might be added to the nucleic acid-micelle complex. Another advantage of the invention was the use of reverse micelles for gene delivery to the cells. The micelle containing the compacted polynucleotide could be utilized as a reaction vesicle in which additional compounds such as polycation could be added to the DNA. Additionally, the polynucleotide/reverse micelle system was used as a vesicle for template polymerization of the DNA or caging of the DNA in which the polycation was crosslinked. Another advantage was that the micelle might be cleaved under physiological conditions involved along the transfection (process of delivering a polynucleotide to a cell) pathway. Better recovery and purification of the biomolecules could be achieved by utilizing cleavable reverse micelles which was difficult earlier.

The invention of Wheeler et al. was related to cell delivery of hydrophobic compounds in microemulsion carrier[68]. Microemulsion was comprised of a mixture of oil, a hydrophobic compound, and a polyethylene glycollinked lipid. The purpose of polyethylene glycol-linked lipid was to enhance the stability of the microemulsion compositions. The hydrophobic compound resided in an oil environment which was surrounded by a monolayer of a polar lipid. The polar head of the lipid faced outwards to provide compatibility with the external aqueous environment and the nonpolar tail faced the internal oil environment. A targeting moiety such as biotin, avidin, streptavidin or antibodies might be covalently or noncovalently attached to the lipid monolayer. The composition could also be used for diagnostic and therapeutic purposes.

2) *Tumour Targeting.*

Maranh suggested the utility of microemulsions as vehicles for the delivery of chemotherapeutic or diagnostic agents to neoplastic cells while avoiding normal cells[69]. They claimed a method for treating neoplasms, wherein neoplasms cells have an increased number of LDL (low density, lipoprotein) receptors compared to normal cells. The microemulsion comprised of a nucleus of cholesterol esters and not more than 20% triglycerides surrounded by a core of phospholipids and free cholesterol and contained a chemotherapeutic drug. Microemulsions were similar in chemical composition to the lipid portion of low density lipoprotein (LDL), but did not contain the protein portion. These artificial microemulsion particles incorporated plasma apolipoprotein E (apo E) on to their surface when they were injected in the bloodstream or incubated with plasma. The apolipoprotein E served as a linking element between the particles of the microemulsion and the LDL receptors. The microemulsions could then be incorporated into cells via receptors for LDL and delivered the incorporated molecules. Thus, higher concentration of anticancer drugs could be achieved in the neoplastic cells that have an increased expression of the receptors. In this way toxic effects of these drugs on the normal tissues and organs could be avoided. In human subjects, they observed no change in the plasma kinetics of the radioactively labeled microemulsion containing carmustine or cytosine-arabinoside thereby confirming that the incorporation of these drugs did not diminish the capacity of the microemulsion to incorporate apo E in the plasma and bind to the receptors.

Shiokawa and coworkers reported a novel microemulsion formulation for tumour targeted drug carrier of lipophilic

antitumour antibiotic aclacinomycin A (ACM)[70]. Their findings suggested that a folate-linked microemulsion is feasible for tumour targeted ACM delivery. The study showed that folate modification with a sufficiently long PEG chain on emulsions is an effective way of targeting emulsion to tumour cells.

3) *Brain Targeting.*

Intranasal administration confers a simple, practical, cost effective, convenient and noninvasive route of administration for rapid drug delivery to the brain[71-74]. It allows a direct transport of drugs to the brain circumventing the brain barriers. Vyas et al.,[75-77] prepared mucoadhesive microemulsion for an antiepileptic drug clonazepam. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8h following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2- fold higher indicating larger extent of distribution of the drug in the brain.

Antifungal

Antifungal agents e.g. miconazole, ketoconazole, and itraconazole being lipophilic in nature have been formulated as microemulsions to impart to them the advantages like ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability compared to conventional dosage forms[78-79].

Microemulsions of poorly water soluble antifungal drugs miconazole, ketoconazole, and itraconazole were designed and developed by Puranajoti et al.,[80] using either mineral oil or olive oil as an oil phase. Various combinations of surfactant and cosurfactant were used, including Labrafil M 1944 CS and Plurol Oleique (1:1); Labrafil M 1944 CS and Plurol Oleique (1:2); or Labrafil M 1944 CS, Capmul MCM C-8, Pluro Oleique, and dehydrated ethyl alcohol (3:3:1:1).

Antiviral

A study was done to investigate and evaluate microemulsion and microemulsion-based hydrogel as a topical delivery system for penciclovir in comparison with a commercial cream. The results of permeation test in vivo in mice showed that as compared with the commercial cream, microemulsion based hydrogel and microemulsion could significantly increase the permeation of penciclovir into both epidermis and dermis. Stability tests showed that microemulsion-based hydrogel stored at 4 °C for 3 months had no significant change in physicochemical properties. Skin irritation test in rabbits demonstrated that single application or multiple applications of microemulsion-based hydrogel did not cause any erythema or edema. Thus, it can be concluded that microemulsion based hydrogel could be a promising vehicle for topical delivery of penciclovir[81].

Antiacne

Novel drug delivery strategies like microemulsions can play a pivotal role in improving the topical delivery of antiacne agents by enhancing their dermal localization with a concomitant reduction in their side effects[82]. Microemulsions of azelaic acid, a bioactive molecule used in many skin disorders, prepared using its monosodium salt (AZA-Na) has been evaluated as delivery vehicles. Dialysis membrane experiments showed decreasing permeability to AZA-Na, and this was related to its partition at the microemulsion interface. The results suggested that microemulsions containing AZA-Na could be used to optimize drug targeting in acne treatment[83].

Antioxidants

Antioxidants have been used in dermatological and cosmetic products because of their property of scavenging and destroying aggressive oxidizing agents and free radicals that are involved in various skin conditions.

In animals, topical application of alpha-tocopherol has shown to exert photo protective effects by reducing the number of sunburn cells, UV induced damage and inhibiting photo carcinogenesis. An o/w or w/o microemulsion of vitamin E delivered the vitamin predominantly to the epidermis avoiding accumulation in organs other than the skin. The cream or lotion prepared with the same amount of vitamin results in excessive accumulation in the organs[84].

Newer studies show that combined applications of various antioxidants can increase their potency as compared with a single antioxidant alone. Branka Rozman et al have developed a temperature-sensitive microemulsion gel as an effective and safe delivery system suitable for simultaneous topical application of a hydrophilic vitamin C and a lipophilic vitamin E. By changing water content of liquid o/w microemulsion, a gel like microemulsion with temperature sensitive rheological properties was formed. The temperature-driven changes in its microstructure were confirmed by rotational rheometry, viscosity measurements and droplet size determination. The release studies have shown that the vitamin release at skin temperature from gellike microemulsion were comparable to those from o/w microemulsion and were much faster and more complete than from o/w microemulsion conventionally thickened with polymer (carbomer)[85].

Ocular

Eye drops account for 90% of the available ophthalmic formulations due to their simplicity and convenience. However, rapid precorneal loss caused by drainage and high tear fluid turnover is amongst the major problems associated with topical ophthalmic drug delivery. Only 5% of the applied drug in eye drops penetrates the cornea and reaches the intraocular tissues with the rest of the dose undergoing transconjunctival absorption or drainage via the nasolacrimal duct before transnasal absorption.

This results in loss of drug into the systemic circulation and provides undesirable systemic side effects Accordingly, microemulsions provided a promising alternative with improved ocular retention, increased corneal drug absorption and reduced systemic side effects whilst maintaining the simplicity and convenience of the dosage form as eye drops.

Judy Chan et al [85] evaluated microemulsion based phase transition systems for ocular delivery of pilocarpine hydrochloride (a model hydrophilic drug). They used two non-ionic surfactants sorbitan mono laurate and polyoxyethylene sorbitan mono-oleate with ethyl oleate (oil component) and water. These systems undergo phase change from microemulsions to liquid crystalline and to coarse emulsion with a change in viscosity depending on water content. Incorporation of pilocarpine hydrochloride did not affect the phase behaviour. Thus, phase transition microemulsion is promising for ocular drug delivery as it provides the fluidity with its viscosity being increased after application and increasing ocular retention while retaining the therapeutic efficiency.

Spermicidal

O.D'Cruz[86] described a formulation of novel gelmicroemulsions (GM) as nontoxic, dual-function intravaginal spermicides, which could be used as delivery vehicles for lipophilic drug substances targeting sexually transmitted pathogens. These GMs comprising oil-in-water microemulsion and polymeric hydrogels were designed to solubilize lipophilic antiviral/antimicrobial agents and exhibited rapid spermicidal activity in human semen and was compared against nonoxynol-9-based detergent spermicide (Gynol II). Spermicidal GM has shown unprecedented potential as dual function microbicidal contraceptives to improve vaginal bioavailability of poorly soluble antimicrobial agents without causing significant vaginal damage.

Cosmetics

There is growing recognition of the potential benefits of microemulsions in the field of cosmetics in addition to drug delivery. They are now being widely investigated for preparing personal care products with superior features such as having improved product efficiency, stability, appearance and minimal irritation. They are well suited for the preparation of various cosmetic products such as moisturizing and soothing agents, sunscreens, antiperspirants, body cleansing agents, hair conditioners and after shave formulations. Microemulsions are also suitable in perfumery so as to minimize the quantity of organic solvents[87].

CURRENT & FUTURE DEVELOPMENTS

The full potential of microemulsion systems is yet to be realized. A lot of innovations are expected to come in the field of microemulsion technology. The role of microemulsion systems is of paramount importance in providing novel solutions to overcome the problems of poor aqueous solubility of highly lipophilic drug compounds and provide high, more consistent and reproducible bioavailability. Furthermore, these formulations can be easily scaled up which is important from industrial standpoint considering the relative cost of commercial production. In addition to oral drug delivery, a lot of topical products employing the microemulsion technology are likely to emerge. This is significant not only from the view point of drug delivery but also from the huge and lucrative cosmetic market prospects. Microemulsions can also be used to achieve drug targeting however challenges remain, primarily because of the layers of barriers that these systems need to overcome to reach to the target. Recent research work is focused on the production of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles. A considerable amount of work still needs to be performed to characterize the physicochemical behavior of the microemulsions. Despite the caveat associated with this therapeutic system, the current scientific interest seems to be directed at recognizing its full potential as a novel drug delivery tool.

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