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Review Article

Advancements in Microemulsion Based Drug Delivery Systems for Better Therapeutic Effects

Abstract

Recent progress in combinatorial drug has led to the generation of a large number of new compounds. microemulsions are versatile systems 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. A micro emulsion is a transparent, thermodynamically stable mixture of two immiscible liquid stabilized by surfactant (or mixture of surfactant). Microemulsions have many advantages for instance, more drug solubility, thermodynamic stability, manufacturing and permeation is easy over conventional formulations that convert them to important drug delivery systems. The design and development of microemulsions aimed at controlling or improving required bioavailability levels of therapeutic agents. Through this review an attempt has been made to focus on several recent developments occurred in the field of microemulsions based applications and which confirms its role as a suitable cargoes for delivery of drugs. In that note, the relevance of this paper and the truncated basic aspects and application on microemulsions are discussed.

Introduction

Recent progress in combinatorial chemistry has led to the generation of a large number of new compounds. Today, a large percent of these new chemical entities (NCEs) in addition to many existing drugs often show poor solubilization behavior which lead to poor oral bioavailability with wide intra- and inter- subject variation and present formulators with considerable technical challenges. The selection of an appropriate dosage form is critical because a dosage form with poor drug delivery can make a useful drug worthless. Bioavailability has important clinical implications as both pharmacologic and toxic effects are proportional to both dose and bioavailability [1]. A topical preparation pertain to medicaments applied to the surface of a part of the body and is 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, antibacterial, 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 [2,3].

Basic aspects of microemulsion

Micro emulsion is a colloidal dispersion composed of oil phase, aqueous phase, surfactant and co-surfactant at appropriate ratios, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10–100nm [4]. Microemulsions have been widely studied to enhance the bioavailability of the poorly soluble drugs. They offer a cost effective approach in such cases. Microemulsions have very low surface tension and small droplet size which results in high absorption and permeation. Interest in these versatile carriers is increasing and their applications have been diversified to various administration routes in addition to the conventional oral route. This can be attributed to their unique solubilization properties and thermodynamic stability which has drawn attention for their use as novel vehicles for drug delivery [5-7].

Microemulsions have advantages over both colloidal systems under investigation and conventional emulsions, suspensions and micellar solutions and may provide alternative drug carriers [8]. 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 [9,10].

Microemulsions are quaternary systems composed of an oil phase, a water system, surfactants and a cosurfactant [11]. These spontaneously formed systems possess specific physicochemical properties such as transparency, optical isotropic, low viscosity and thermodynamic stability. The observed transparency of these systems is due to the fact that the maximum size of the droplets of the dispersed phase is not larger than one-fourth of the wavelength of visible light approximately 150 nm. Droplet diameter in stable microemulsions is usually within the range of 10-100 nm (100-1000 °A), which means that the term 'micro emulsion' is misleading and these systems are actually Nano-sized emulsions. Many studies have shown that micro emulsion formulations possessed improved transdermal and dermal delivery properties, mostly *in vitro* [12-21] and several *in vivo* [22-24].

Types of microemulsion

Three types of microemulsions (Figure 1) are most likely to be formed depending on the composition:

1. Oil in water (O/W) microemulsions wherein oil droplets are dispersed in the continues aqueous phase.
2. Water in oil (W/O) microemulsions wherein water droplets are dispersed in the continuous oil phase.
3. Bi-continuous microemulsions wherein micro domains of oil and water are inter dispersed within the system.

In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and co-surfactants [25].

Comparison between emulsion, nanoemulsion and microemulsion

Emulsions and microemulsions are both stable dispersions of oil-in-water or water-in-oil. In emulsion systems, the structures are large enough to scatter light and as such they appear as cloudy colloidal solutions in comparison. The gross physical differences between micro emulsion and emulsion systems can be determined by visual examination- microemulsions show no tendency to phase separate and are usually optically transparent, whereas emulsions are opalescent or turbid and the phases inevitably separate (Table 1).

Formulation considerations

The challenges in formulating microemulsions are (Figure 2):

1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non-sensitizing.
2. Formulating cosmetically elegant microemulsions. The micro emulsion 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.

Construction of phase diagram

Pseudo-ternary phase diagram is constructed to obtain the appropriate components and their concentration ranges that can result in large existence area of micro emulsion. Once the appropriate micro emulsion components are selected, ternary pseudo phase diagram is constructed to define the extent and nature of the micro emulsion regions. To produce such diagrams, a large number of samples of different composition are prepared [31-39]. To study the phase behavior of simple micro emulsion systems comprising of surfactant, oil and water at fixed pressure and temperature ternary phase diagrams are used. Each corner of the ternary phase diagram represents 100% concentrations of a particular component. When four or more components are used pseudo-ternary phase diagrams are used to depict these systems in which each corner represents binary mixtures of two components such as surfactant/co-surfactant, surfactant/water, oil/drug, and water/drug mixtures [40].

Components of microemulsion formulations

Water phase: Depending upon the amount of water present in the system, water may form water pool or work as a dispersion medium in micro-emulsion systems [41].

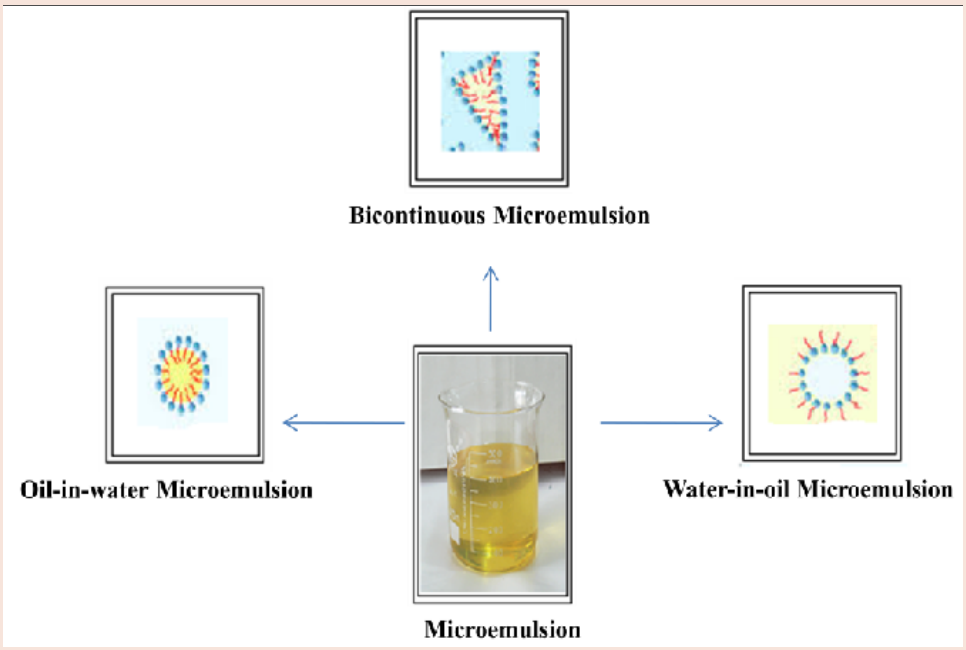

Figure 1: Different types of microemulsions formed depending on the composition.

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Table 1: Comparison between emulsion and microemulsion [26-30].

Sr. No.	Specification	Emulsion	Nanoemulsion	Microemulsion
1.	Appearance	Most emulsions are opaque (white) because bulk of their droplets is greater than wavelength of light and most oils have higher refractive indices than water.	Nanoemulsions are part of a broad class of multiphase colloidal dispersions. It is dispersions of nanoscale droplets formed by shear-induced rupturing.	Microemulsions are transparent or translucent as their droplet diameter are less than ¼ of the wave length of light, they scatter little light.
2.	Optical Isotropy	Anisotropic	Isptropic	Isotropic
3.	Microstructure	Static	Dynamic	Dynamic
4.	Droplet Size	>500nm	1-100nm	20-200nm
5.	Droplet Shape	Emulsions consist of roughly spherical droplets of one phase dispersed into the other.	Nanaoemulsion consist of spherical in shape due to that, small-sized droplet with its high surface area allowing effective transport of the active to the bioactive effects.	They constantly evolve between various structures ranging from droplet like swollen micelles to bicontinuous structure.
6.	Molecular Packing	Inefficient	Efficient	Efficient
7.	Stability	Thermodynamically unstable (Kinetically stable), will eventually phase separate.	Thermodynamically stable, long shelf-life	Thermodynamically stable, long shelf-life
8.	Phase	Biphasic	Monophase	Monophase
9.	Viscosity	High	Low	Low
10.	Interfacial tension	High	Low	Ultra low

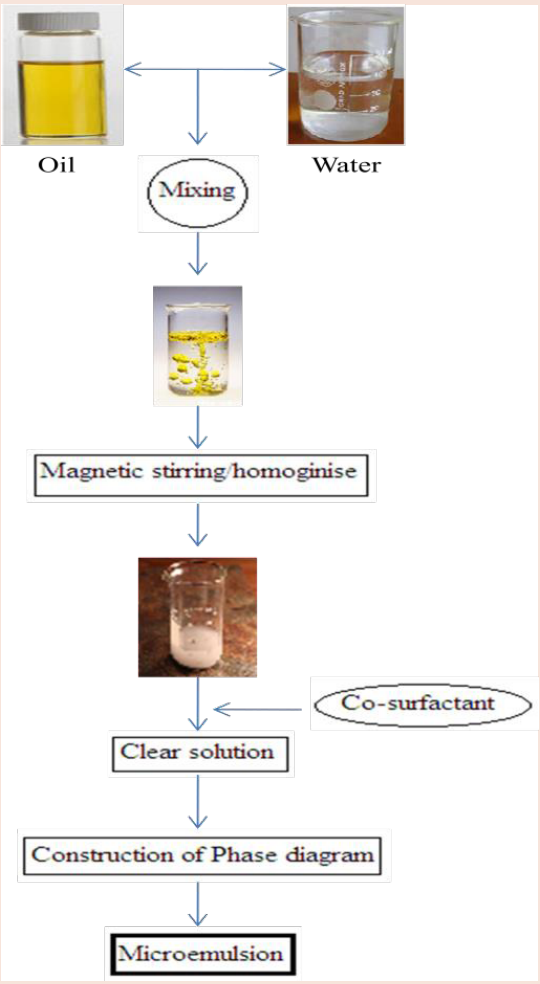

Figure 2: Schematic representation of formulation of Microemulsion.

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Oil phase: The oil phase must be chosen appropriately, since it governs the selection of the other ingredients for the micro emulsion and there are two main factors that need be considered before selecting the appropriate oil phase. Firstly, the solubilising potential of the oil for the selected substance must be seen. And secondly, the chosen must be such that the micro emulsion forming region is enhanced. Oils with shorter hydrocarbon chains are easier to micro-emulsify as compared to oils with long hydrocarbon chains. An oils ability to solubilise lipophilic groups is directly proportional to the chain length of the oil. Thus, the selected oil should be such that it is capable of solubilising the API, and facilitating the formation of microemulsions with desired characteristics [42,43].

Surfactants in microemulsions

Surfactants are molecules that typically contain a polar head group and an apolar tail [44]. They are surface-active and microstructure-forming molecules with a strong chemical dipole [45]. They can be ionic (cationic or anionic), nonionic, or zwitterionic. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, rod-shaped micelles, a hexagonal phase (consisting of rod-shaped micelles), lamellar (sheet) phases, reverse micelles, or hexagonal reverse micelles [46].

Cosurfactants

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a micro emulsion to form [47-50]. The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form micro emulsion over a wide range of composition. 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 [51-53] (Table 2).

Applications of microemulsion

During the last two decades, microemulsions have been extensively researched because of their tremendous potential in many applications. The role of microemulsions in various field are (Figure 3).

Microemulsion in pharmaceutical

Parenteral application: Parenteral administration (especially via the intravenous route) of drugs with limited solubility is a major problem in the pharmaceutical industry because of the extremely low amount of drug actually delivered to a targeted site. Micro emulsion formulations have distinct advantages over macro emulsion systems when delivered parenterally because of the fine particle, micro emulsion is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O micro emulsion can be used for parenteral delivery [55]. Rhee et.al formulated itraconazole containing parentral micro emulsion, using an o/w micro emulsion system. he average droplet size of the microemulsions was < 150 nm, and the hemolysis test showed this formulation to be nontoxic to red blood cells. The pharmacokinetic profiles of the ITZ-micro emulsion for itraconazole and its major metabolite, hydroxyitraconazole, were compared with those of a PEG 400 solution and cyclodextrin formulations in rats. Overall, these results highlight the potential of an ITZ-micro emulsion formulation for the parenteral route [56].

Oral administration

Oral administration of micro emulsion formulations offer the several benefits over conventional oral formulation for oral administration including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, micro emulsion has been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics [56].

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 shown in Table 3 and it takes into account contributions of three major factors, dissolution, solubility, and intestinal permeability, which affect oral drug absorption.

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

Table 2: Some commonly used components for microemulsions [54].

Components	Examples	
Oil	MCTs	Glyceryl tricaprylate/caprate: Captex 355, Miglyol 810, Neober M-5 etc
	LCTs	Corn oil, soyabean oil, safflower oil, olive oil etc
	Mono/diglyceride	Glyceryl caprylate/caprate (Capmul MCM), Glycerol monooleate (Capmul GMO) etc
	Fatty acids	Oleic acid
	Propylene glycol ester	Capmul PG-8, Propylene glycol monolaurate (Lauroglycol)
Surfactant	HLB > 10	Tween-20, Tween-80, Polyoxyl 35 castor oil (Cremophore EL), PEG-8 caprylic/ capric glycerides (Labrasol), Polyoxyl 40 hydrogenated caster oil (Cremophore RH 40) etc.
	HLB < 10	Phosphatidylcholine, Unsaturated polyglycolized glycerides (Labrafil M 2125), Span-40, Span-80 etc
Co-surfactant	Propylene glycol, Polyethylene glycol, Ethanol, Isopropyl alcohol, Isopropyl myristate, ethanol, propanol, isopropanol, etc.	

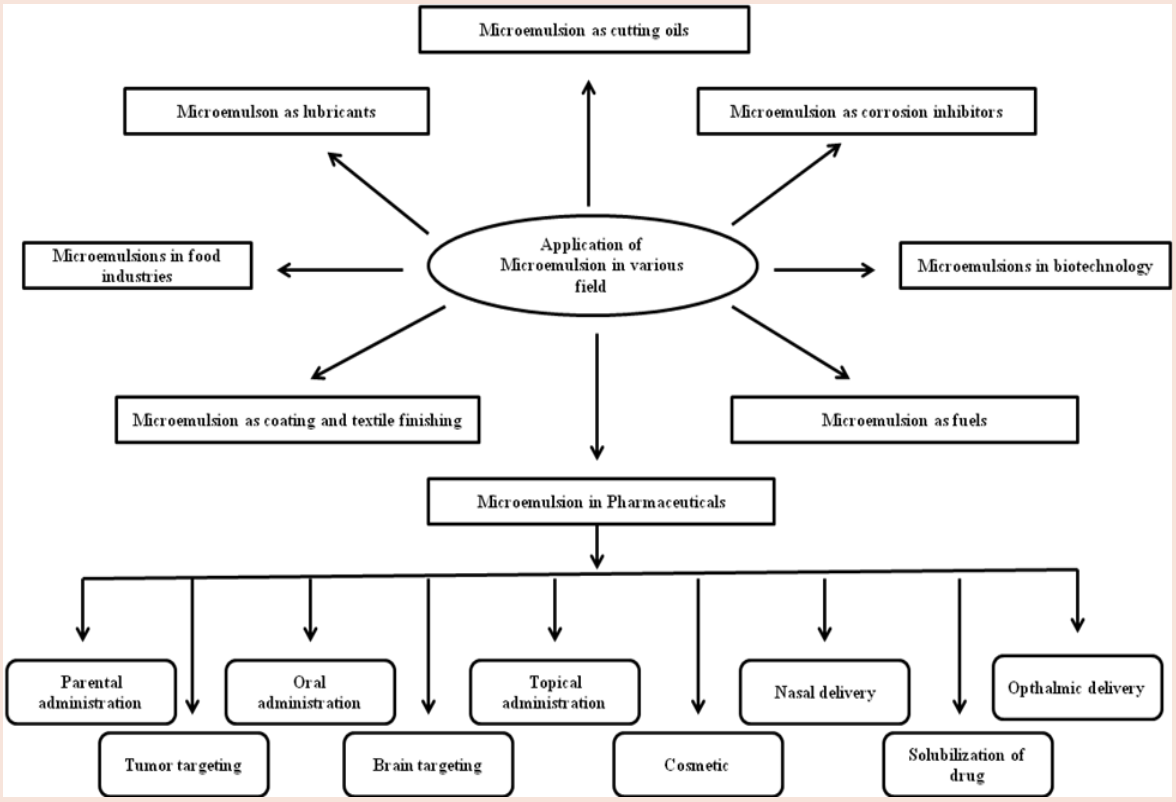

Figure 2: Application of microemulsion in various fields.

Table 3: According to the BCS, classification of drug substances.

Sr. No.	Class	Permeability	Solubility
1.	I	High	High
2.	II	High	Low
3.	III	Low	High
4.	IV	Low	Low

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 [57,58].

Topical administration

Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drug and related toxicity effects. Another is the direct delivery and targetability of the drug to affected area of the skin or eyes [58].

Due to the small micelles size and large amount of inner phase in microemulsions, the density of droplets and their surface area are assumed to be high. Therefore, micelles settle down to close contact with the skin providing high concentration gradient and improved drug permeation. Moreover, low surface tension ensures good contact to the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration gradient over the skin for a long time [59].

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 [60,61]. Sheetal et al. in 2013, Prepared and evaluated transnasal micro emulsion of carbamazepine. Oleic acid was selected as oil while Tween 80 and propylene glycol were selected as surfactant and cosurfactant respectively based on solubility results. Optimized ratio of Tween 80: propylene glycol was selected after developing pseudoternary phase diagrams for different ratio and microemulsions were prepared. The prepared microemulsions were evaluated for globule size, viscosity, pH, conductivity and % transmittance. Ex-vivo diffusion study for optimized micro emulsion was performed through sheep nasal mucosa wherein diffusion flux and permeability coefficients were determined. Further pharmacodynamics performance was evaluated in rats by electrically induced seizures. It was found that optimized micro emulsion was stable and transparent with average globule size of 190 nm and diffusion flux of 75.77 μg cm−2 min−1 and showed no toxicity during histopathological evaluation on sheep nasal mucosa.

Opthalmic 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. microemulsions have emerged as a promising dosage form for ocular useful in achieving improved patient compliance and favorable for ophthalmological use [62]. Okur et al. 2014, studied the effect of Novel ofloxacin-loaded micro emulsion formulations for ocular delivery and found that OFX microemulsions could be offered as a promising strategy for ocular drug delivery.

Tumor targeting

The utility of microemulsions as vehicles for the delivery of chemotherapeutic or diagnostic agents to neoplastic cells while avoiding normal cells. A method for treating neoplasms, wherein neoplasms cells have an increased number of LDL (low density, lipoprotein) receptors compared to normal cells. The micro emulsion 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. 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 [69,70].

Microemulsions in cosmetics

In many cosmetic applications such as skin care products, emulsions are widely used with water as the continuous phase. It is believed that micro emulsion formulation will result in a faster uptake into the skin. Cost, safety (as many surfactants are irritating to the skin when used in high concentrations), appropriate selection of ingredients (i.e. surfactants, cosurfactants, oils) are key factors in the formulation of microemulsions [77,78].

Solubilization of drug in microemulsion

Microemulsion possesses interesting physicochemical properties, i.e. transparency, low viscosity, thermodynamic stability, high solubilization power. Because of these specific properties of micro emulsion can be useful as a drug delivery system. The different categories of drugs solubilized in micro emulsion systems for their better therapeutic efficacy [79] (Table 4).

Conclusion

Microemulsions are an attractive technology platform for the pharmaceutical formulators as it has excellent transparency and relatively simple formulation process. The role of micro emulsion 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. Microemulsions have proved their efficiency in oral administration of cyclosporine (Neoral). But the main concern is that the applicability and effectiveness of micro emulsion based drug delivery systems should not be limited to oral routes only. They can be easily used for developing novel cargoes for phytoactives and extracts also. The current scenario potentiate the targeting aspects of microemulsions due to their tremendous capability of carrying lipophilic drugs. Several targeting cargoes have been developed in recent years with the concept of microemulsions at its base. It can be hoped that in near future microemulsions will

Table 4: Research envisages of microemulsion in different route of administration.

Sr. No.	Delivery System	Drug	Category	Application	Ref.
1.	Nasal Delivery	Diazepam	Anticonvulsant or antiepileptic drug	Nasal route for administration of diazepam is useful approach for the rapid onset of action during the emergency treatment of status epilepticus.	[61]
2.	Opthalmic Delivery	Dexamethasone	Antiallergic	It showed better tolerability and higher bioavailability. The formulation showed greater penetration in the eye which allowed the possibility of decreasing the number of applications per day.	[63]
3.	Parentral Application	vitamins E, A, D, and K	Supplements	It suitable for fat soluble vitamins and hydrophobic drugs	[64]
4.	Oral administration	Paclitaxel	Anticancer	Microemulsion permitted its rapid and efficient absorption resulting in improved oral bioavailability.	[65]
5.	Topical administration	miconazole, ketoconazole, itraconazole	Antimycotics	microemulsions impart to them increased drug loading, enhanced penetration through the biological membranes, and increased bioavailability.	[66,67]
6.	Tumor targeting	Aclacinomcycin	Antitumor agent	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 tumour cells.	[68]
7.	Brain targeting	Clonazepam	Anticonvulsant or antiepileptic drug	Mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher indicating larger extent of distribution of the drug in the brain.	[76]
8.	Cosmetic	-	Moisturizing, soothing agents, sunscreens, antiperspirants, body cleansing agents, hair conditioners.	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.	[79]

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become a versatile system for drug delivery not only for conventional but also for phytoactive and that the potential of microemulsions as novel compartmentalized liquids will be even more significant in upcoming era.

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