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# Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs

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***Importance of the field:*** Microemulsions have been studied extensively as potential drug delivery vehicles for poorly water-soluble drugs. An understanding of the physicochemical and biopharmaceutical characteristics of the microemulsions according to administration routes will provide guidance for designing the formulations of microemulsions.

***Areas covered in this review:*** In this paper, the use and the characteristics of microemulsions as drug delivery vehicles are reviewed. As the formulations of the microemulsion always include a great amount of surfactant and co-surfactant, which may cause hemolysis or histopathological alterations of the tissue, the potential toxicity or the irritancy of microemulsions is also discussed in this paper.

***What the reader will gain:*** Developments of microemulsions for poorly water-soluble drugs in recent years are included in this review. Several factors limiting the commercial or clinical use of microemulsions are also discussed.

***Take home message:*** Considering the potential in enhanced drug uptake/permeation and facing the limitations, their unique properties make microemulsions a promising vehicle for poorly water-soluble drugs.

**Keywords:** bioavailability, microemulsion, self-emulsifying drug delivery systems, solubility

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## 1. Introduction

It is estimated that >40% of new pharmacologically active chemical entities identified by high-throughput screening have a big problem with their water solubility [1]. Poor water solubility correlates with numerous issues such as impaired bioavailability and increased cost of drug product. For oral administration, poorly water-soluble drugs have slow drug dissolution rate and poor absorption in the gastrointestinal tract [1], whereas on intravenous administration, side effects and toxic effects might come as a result of the precipitation and aggregation of poorly soluble drugs. Therefore, great efforts have been made to improve the solubility of the drug candidates. The formulation strategies considered preferentially are the conversion of a drug to a salt form and pH adjustment. If the drug is intrinsically insoluble, there are still various strategies available, such as the use of co-solvents, inclusion complexes, nanosuspensions, micelles, liposomes, polymeric nanoparticles, microemulsions, and so on, and these approaches can be chosen according to drug octanol–water partition coefficient (P) and its melting point (MP), as well as the dose required [2]. Among these approaches, microemulsion is a promising one owing to its considerable capacity to improve the solubility of hydrophobic drugs.

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**Article highlights.**

- A microemulsion, which contains a large amount of surfactants and co-surfactants, is a promising formulation strategy to improve the solubility of the drug candidates.
- Pre-formulation solubility and phase diagram studies are required to obtain an optimal formulation of the microemulsion. During the formulation process of self-emulsifying drug delivery systems (SEDDS), the advantage of increasing solubilization with the risk of inducing drug precipitation on dilution must be balanced.
- With the emergence of new formulation techniques, SEDDS can be made in solid dosage forms and have been developed extensively as a more effective alternative to conventional liquid SEDDS.
- When delivered intravenously, microemulsions can be coated with hydrophilic polymers, such as PEG, PVA, hyaluronic acid and chitosan to prolong the residence in the blood and thus increase the accumulation of drugs in the target tissues.
- Transdermal delivery can be influenced by the interactions that may occur between the vehicle and the skin, and interactions between the active ingredient and the skin.
- As the formulations of the microemulsion always include a large amount of surfactant and co-surfactant, which may cause hemolysis or histopathological alterations of the tissue, the potential toxicity or the irritancy of the microemulsion should be evaluated.

This box summarizes key points contained in the article.



According to the most general definition provided by Danielsson and Lindman in 1981, a microemulsion is defined as 'a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution' [3]. With a droplet size usually in the range 20 – 200 nm, microemulsions are thermodynamically stable transparent (or translucent) Newtonian non-viscous liquids [4,5]. Nanoemulsions are also nanometric-sized emulsions, typically with a diameter of up to 600 nm [6,7]; but unlike microemulsions, nanoemulsions are thermodynamically unstable systems despite the fact that the long-term physical stability of nanoemulsions usually makes them unique [6]. Moreover, easy formation of microemulsions makes them more acceptable for exemplification in industry than conventional emulsions. In this paper, updates of self-emulsifying drug delivery systems (SEDDS) for oral administration and other forms used for intravenous or transdermal administration are reviewed.

## 2. Microemulsions by means of oral administration

SEDDS or self-emulsifying oil formulations (SEOF), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of microemulsions in order to improve the oral absorption of highly lipophilic drug compounds [8-11]. SEDDS, which contain the non-aqueous components of emulsions, offer some advantages over conventional emulsions [12-15]. These systems can emulsify rapidly under mild agitation and in the presence of aqueous media such as gastrointestinal tract (GIT) fluids to generate fine emulsion droplets, ranging in size from ~ 100 nm (SEDDS) to <100 nm for self-microemulsifying drug delivery systems (SMEDDS). After oral administration, SEDDS can maintain the poorly soluble drugs dissolved in the fine oil droplets when transiting through the GIT [16,17].

The use of SEDDS is limited, however, by their drug loading capacities and the use of excipients. Also, these systems are metastable and can be digested in the GIT. Therefore, the unique characteristics of these dosage forms present significant challenges to the pharmaceutical industry and regulatory agencies in many ways, such as the safety assessment, the precipitation of drug *in vivo*, digestibility of lipids in the formulation, intestinal efflux pumps and metabolizing enzymes, contribution of lymphatic transport of drug to absorption, and so on. Similarly, the problems of physical and chemical instability, as well as the unpredictable bioavailability and *in vivo* performance of these dosage forms, also limit the development of these systems [18].

This section thus begins with the excipient selection of SEDDS, the preparation techniques and dosage forms for SEDDS, and their *in vitro* and *in vivo* characterization, especially with respect to the biopharmaceutical aspects.

### 2.1 Excipient selection

A wide range of triglycerides, partial glycerides, semisynthetic oily esters and semisynthetic non-ionic surfactants esters are available from excipient suppliers [19]. As self-emulsification depends on the nature of the oil/surfactant pair, surfactant concentration and oil/surfactant ratio, and the temperature at which self-emulsification occurs, only very specific pharmaceutical excipient combinations lead to efficient self-emulsifying systems. Therefore, pre-formulation solubility and phase diagram studies are required in order to obtain an optimal formulation. Besides, several other factors including excipient properties, such as irritancy, toxicity, solvent capacity, miscibility, melting point, digestibility, purity, chemical stability, the cost, and so on, could affect our choice of excipient.

### 2.2 Dosage forms and the preparation techniques

SEDDS are usually hard or soft shell capsules filled in by liquid forms, as many excipients used in SEDDS are not solids at room temperature. However, more sophisticated solid dosage forms (pellets/tablets) in particular are the preferred mode of drug delivery for patients. Fortunately, with the emergence of new formulation techniques, SEDDS is no longer limited to soft or hard gelatin capsules. Considering the advantages of SEDDS and solid dosage forms, solid SEDDS (S-SEDDS) have been extensively developed as a more effective alternative to conventional liquid SEDDS.

S-SEDDS are solid dosage forms with self-emulsification properties, which focus on the transformation of liquid or semisolid formulations into solid particles (powders, granules or pellets), which could subsequently be filled into capsules, sachets or compressed into tablets. The solidification techniques include adsorptions to solid carriers [20], spray drying [21,22], freeze drying [23], melt granulation [24], melt extrusion/extrusion spheronization [25,26], and so on. Capsules, tablets and pellets are usually the main solid dosage forms of S-SEDDS. Therefore, the properties of S-SEDDS are composed of both the corresponding properties of SEDDS and solid dosage forms.

### 2.3 *In vitro* and *in vivo* characterization

Studies of equilibrium phase behavior have been used since 1985 to explain the mechanisms of dispersion of SEDDS [27,28]. The formation of self-emulsification can be assessed by visual and instrumental observation. The self-emulsification efficiency could be estimated through the determination of the rate of emulsification and droplet size distribution. Photon correlation spectroscopy [13] is used for the determination of emulsion droplet size. The charge on the oil droplets of SEDDS is another property that needs to be assessed [29]. Melting properties and polymorphism of lipid or drug in SEDDS may be established by X-ray diffraction and differential scanning calorimetry.

Moreover, some authors [28,30] have paid much attention to the drug solubility in the lipid formulations when undergoing dilution and digestion in the GIT, which would influence the subsequent dispersion and absorption of drug. *In vitro* dispersion and digestion tests are of critical importance to the formulator with regard to predicting the fate of the drug in the intestinal lumen [31]. Also, many factors can also influence the drug absorption from SEDDS, such as lymphatic transport, enzymes metabolism and P-glycoprotein (P-gp) efflux.

### 2.4 Physicochemical and biopharmaceutical issues

#### 2.4.1 *Drug loading capacity and precipitation*

Lipid excipients are able to solubilize hydrophobic drugs within their matrix. However, different excipients have different solubilization capacity; for example, medium-chain triglycerides (MCT) generally have a higher solvent capacity on a weight basis than long-chain triglycerides (LCT) [32]. Poorly water-soluble drugs are hydrophobic but not necessarily lipophilic. Many poorly water-soluble drugs are poorly soluble in glycerides, as well as bile salt-lecithin mixed micelles. Such drugs (high melting point (>250°C) drugs with log P values of ~ 2 are poorly suited to these systems. Moreover, some poorly water-soluble drugs are much more soluble in co-solvents than oils, and such compounds also dissolve in the polyoxyethylene-rich environment present in water-soluble non-ionic surfactant materials. The total solvent capacity of mixtures of excipients is generally similar to the sum of the component parts.

Recently, much attention has been paid to the drug precipitation from SEDDS when diluted with water or dispersed in the GIT [9]. Drug precipitation from SEDDS is a consequence of concentration exceeding the equilibrium solubilization capacity. Therefore, systems formulated to have drug solubilization capacity much higher than the required concentration would be expected to show less propensity for precipitation *in vivo*. So, an understanding of factors influencing drug loading capacity while maintaining the capability of the system to undergo monophasic dilution with water and minimizing the tendency for drug precipitation in diluted systems is essential to the design of stable and appropriately low-volume systems for drug delivery applications.

The formulator must balance the advantage of increasing solubilization with the risk of inducing drug precipitation on dilution. One key factor to successful formulation of SEDDS is to avoid formulations that are so hydrophilic that they lose a considerable proportion of their solvent capacity on dispersion. However, long-chain digestion products remain extensively solubilized within mixed bile salt-lecithin micelles until they are absorbed [33]. This emphasizes the need for detailed studies on digestion and *in vitro–in vivo* correlation of these systems [34]. On the other hand, increasing the solubilization capacity of the formulation significantly over the desired drug concentration could help avoid *in vivo* drug precipitation. Formulations that can be diluted with water *in vitro* without drug precipitation are likely to be more stable under *in vivo* conditions than those that are not dilutable. Another approach in this direction is to promote the formation of supersaturated drug solution *in vivo* by the incorporation of hydrophilic polymeric ingredients in the formulation that act as precipitation inhibitors. The supersaturated drug solutions will eventually precipitate owing to the thermodynamic instability of the system, but if the precipitation is delayed long enough *in vivo* to cover the drug absorption time, bioavailability from these systems can be improved. Several common pharmaceutical excipients are acting as precipitation inhibitors, for example, methyl cellulose, hydroxypropyle methylcellulose (HPMC), HPMC phthalate (HPMCP), sodium carboxymethyl cellulose, and polyvinylpyrrolidone [35,36]. For example, Gao *et al*. developed a supersaturable SEDDS formulation using HPMC as precipitation inhibitor. The *in vivo* studies in rats demonstrated that SEDDS with HPMC could increase the bioavailability of paclitaxel greatly [37].

#### 2.4.2 *In vitro dispersion and digestion tests*

The excipients such as dietary lipids can be digested and dispersed in the GIT. Therefore, one of the questions for a lipid-based oral formulation is whether the drug remains in solubilized form owing to lipid digestion of some components in the formulation following oral administration [28,38,39]. The

improvement of bioavailability requiring a hydrophobic drug in the solution or emulsion form can be compromised if the drug precipitates *in vivo*. With appropriate methods, *in vitro* dissolution can be correlated further with *in vivo* performance and used as a surrogate for bioequivalence studies. The main issue seems to stem from the concern that the absorption mechanism for lipid-based oral formulations is so complicated that it may not be feasible to create a single *in vitro* dissolution environment that mimics the physiological conditions [28].

As for SEDDS, one might contend that droplet size of the dispersed formulation could be more relevant and predictive of *in vivo* performance [40]. Actually, the conventional *in vitro* dissolution methods may not be appropriate for predicting *in vivo* performance of a complex lipid-based formulation because dissolution of the drug and gastrointestinal processing of the lipid vehicle (including digestion and dispersion) are intrinsically linked to each other. Truly, the *in vitro* release testing should incorporate the dynamics of lipid digestion, formation of various intermediate colloidal products, and solubilization of the drug under study [28]. In this case, *in vitro* 'dispersion' testing appears to be a more accurate description of the process of monitoring the ability of a formulation to maintain the drug in a solubilized state during dispersion in the stomach and subsequent processing of the formulation in the presence of pancreatic and biliary fluids. Considering the specificity of SEDDS, in recent years, *in vitro* dispersion tests and *in vitro* lipid digestion models that are more reflective of the GIT environment have been developed in order to predict better the fate of the formulation and drug in the intestinal lumen before absorption [41-44], because it is evident that the solvent capacity of SEDDS can be lost on digestion, which may lead to drug precipitation and bioavailability reduction. If the digestion experiment is followed by a centrifugation step, precipitated drug can be quantified by analyzing the contents of the pellet that sediments during centrifugation [39].

Rate of lipolysis of various lipids and formulations can be compared *in vitro*. Usually, lipolysis rate of MCT is higher than LCT, which has been shown to influence the bioavailability of hydrophobic drugs from lipid-based dosage forms. In previous research, SMEDDS formulations of danazol containing long-chain ($C_{18}$) lipids (LC-SMEDDS) and medium-chain ($C_8$ – $C_{10}$) lipids (MC-SMEDDS) were administrated orally to fasted beagle dogs, and the relationship between solubilization behavior on *in vitro* digestion and bioavailability has been described [45]. In the study, 69% of the drug dose precipitated on *in vitro* digestion for the MC-SMEDDS, whereas 94% of the dose was maintained in solution for the LC-SMEDDS. The oral bioavailability of danazol for LC-SMEDDS was significantly higher than that obtained from MC-SMEDDS, which reflected well the difference in the ability of the two formulations to retain drug in solution on *in vitro* digestion.

Cuiné *et al.* [46] also investigated the solubilization behavior of danazol self-emulsifying formulations containing relatively high quantities of surfactant during *in vitro* digestion, and evaluated the impact of surfactant digestion on their *in vivo* performance. A series of danazol microemulsion formulations composed of different proportions of Cremophor® EL (BASF, Parsippany, NJ, USA) (surfactant), ethanol (co-solvent) and a blend of soybean oil/Masine (1:1 w/w, the lipid phase) were taken. *In vitro* dispersion in water of all the formulations was rapid and no drug precipitation was observed. By contrast, drug solubilization was markedly affected by digestion and a reduction in lipid (and increase in surfactant) content resulted in increased drug precipitation. Consistent with these data, the bioavailability of danazol decreased significantly when the lipid content in the formulations was reduced. The results showed that a rank-order correlation was observed between the patterns of solubilization obtained during *in vitro* digestion and the *in vivo* performance of self-emulsifying formulations of danazol. In general, a decrease in the lipid content and an increase in the proportions of surfactant and co-solvent resulted in reduced danazol bioavailability.

Therefore, it appears that *in vitro–in vivo* correlation between differences in drug solubilization profiles during *in vitro* digestion and differences in *in vivo* exposure are evident for typical lipid-based self-emulsifying formulations. However, before more wide-ranging conclusions can be drawn with any confidence, considerably larger data sets are required, including drugs of varying lipophilicity and formulations with a broader range of lipidic excipient.

### 2.4.3 *Lymphatic transport*

The GIT is richly supplied with both lymphatic and blood vessels and therefore, after oral administration, drug can be absorbed across the enterocytes, potentially entering either lymphatic or blood capillaries. The absorbed drug is transported mainly into the portal blood. However, diffusion of high-molecular-mass or colloidal materials across the blood capillary endothelium is limited, and selective transport into the intestinal lymph may occur because the lymphatic capillaries are significantly more permeable than the neighboring blood capillaries [47].

Enhancing lymphatic drug transport is mostly dependent on drug association with developing lipoproteins in the enterocyte, which suggests that the provision of an appropriate lipid source to drive lipoprotein assembly is a useful strategy. Actually, the digestion efficiency, solubilization, uptake and transport of lipid in the intestinal lumen are likely to influence significantly the access of lipophilic drugs to the lymph. This subject, that the type and mass of co-administered lipid can alter the extent of lymphatic drug transport, has been reviewed previously [48]. Briefly, fatty acids with chain lengths of 14 or greater are more highly lymphatically transported than shorter chain fatty acids, and accordingly long-chain fatty acids and triglycerides composed of long-chain fatty acids more effectively support lymphatic drug transport than their medium- and

short-chain counterparts [49,50]. The degree of unsaturation of administered fatty acids also influences the extent of lymphatic lipid and drug transport. Generally, mono and polyunsaturated fatty acids promote lymphatic lipid transport more readily and effectively when compared with the equivalent saturated fatty acids [51].

The lymphatic route of absorption offers a window of opportunity to enhance the bioavailability of highly lipophilic drugs (log P > 5) with high solubility in triglycerides (Cs > 50 mg/ml). Also, the lipid-based drug delivery systems consisting of alcohol esters of unsaturated long-chain fatty acids have been shown to enhance the bioavailability of certain drugs by facilitating the lymphatic route of uptake. Examples of successes include saquinavir with polyglyceryl oleate (Plurol® Oleique CC497; Gattefossé, France) or ethoxylated castor oil (Cremophor EL; BASF, USA) [52], ontazolast with glyceryl monooleate (Peceol™; Gattefossé, France) [53], and halofantrin with various triglycerides and derivatives [54]. Some highly lipophilic drugs administered orally have also been shown to gain access to the systemic circulation by means of intestinal lymphatic transport, avoiding the hepatic first-pass metabolism and resulting in a higher drug bioavailability [55]. However, the role of the intestinal lymphatic system in the processing of lipids and drugs from lipid-based oral dosage forms remains an area for further investigation.

#### 2.4.4 *Inhibition of drug efflux and enzymes metabolism*

In oral administration, many hydrophobic drug molecules entering the enterocyte are exposed to metabolizing enzymes, for example cytochrome P450 3A4 (CYP 3A4), or can be secreted back into the gastrointestinal lumen by P-gp efflux pumps on the enterocyte membrane, which will reduce their bioavailability. The involvement of P-gp transport and presystemic drug metabolism further complicates the absorption of a hydrophobic drug that is formulated in lipid-based formulation. In some cases, as shown recently, several lipid excipients and surfactants incorporated in SEDDS can inhibit the CYP 3A4 metabolism or intestinal efflux mediated by P-gp, resulting in an increased oral absorption of hydrophobic drugs [56-59]. The impact of formulation ingredients on the biopharmaceutical properties of drugs is also illustrated by the inhibition of drug efflux pumps by certain formulation ingredients. For example, common pharmaceutical excipients such as polyethylene glycol, Tween 80 and Cremophor EL have been shown to inhibit P-gp activity [60]. Their inclusion in the formulation, therefore, can be expected to increase the bioavailability of drugs that are known substrates of P-gp efflux pumps [61].

The interplay between certain excipients and enzymes/transporters has raised much concern about the predictability of drug absorption and bioavailability, as well as the possible drug–drug interactions when co-administered with other compounds. More studies are needed to elucidate these potential interactions during pharmaceutical development.

## 3. Microemulsions by means of intravenous and transdermal administration

### 3.1 Excipient selection

#### 3.1.1 *Oily phase*

The selection of oil is dependent on the nature of the drug as well as the administration route. The chosen oil should have solubilization potential for the drug, and the larger the existence region the microemulsion can form in the pseudo-ternary phase diagram with the selected oil, the better. For intravenous delivery, the organic solvent selected should be biocompatible, sterilizable, available as non-pyrogenic grade, non-irritant to nerves and non-hemolytic [62]. The oils commonly used for intravenous delivery include long-chain triglycerides (e.g., soybean oil, castor oils), medium-chain triglycerides, medium-chain mono- and di-glycerides, vitamin E, and unsaturated fatty acid and its ester (e.g., oleic acid, cholesteryl oleate). More excipients are available as the oil for transdermal drug delivery, and some of them also act as penetration enhancer, such as oleic acid. Other excipient that is often used as an oil phase in transdermal formulations is isopropyl myristate (IPM), isopropyl palmitate, isostearylic isostearate, triacetin, (+)-(*R*)-limonene, monoolein, ethyl oleate, and Mygliol 812®, and alcohols such as octanol, decanol, benzyl alcohol.

#### 3.1.2 *Surfactant*

Microemulsions are basically classified into four types, including oil-in-water (o/w, Winsor type I), water-in-oil (w/o, Winsor type II) and bicontinuous (Winsor type III or IV) systems [63], and the type of microemulsion formed is quite dependent on the surfactant type. The surfactant can be screened empirically according to its hydrophile–lipophile balance, as well as the critical packing parameter [64].

Naturally occurring surfactants are frequently used as the surfactant for microemulsions, of which lecithin is the most commonly used one owing to its excellent biocompatibility. Lecithin is typically purified from soy beans and egg and its major component is phosphatidylcholine, which has an amphiphilic structure and has low solubility in water. It is a versatile excipient because in aqueous solution it can have various forms such as liposomes, micelles, liquid crystals, microemulsions and organogels with the control of hydration, temperature, co-surfactant and so on. In most lecithin-based microemulsions, co-surfactant is generally included to prevent the formation of lamellar structures and other liquid-crystal phases. However, the introduction of co-surfactant may cause adverse effects. Recently, Yuan *et al.* prepared alcohol-free lecithin microemulsions for transdermal delivery of lidocaine [63]. In that formulation, instead of the co-surfactant, some so-called linker molecules, such as sorbitan monooleate, sodium caprylate and caprylic acid, were used to stabilize the microemulsion structure. It was found that lidocaine was highly soluble in these linker microemulsions, with relatively small aggregates (<10 nm in diameter) and low viscosity. Furthermore, these linker-based systems proved to be less

toxic than the alcohol-based lecithin microemulsion through MTT assay. It was hypothesized that hydrophilic linkers probably function through fluidizing the interstitial spaces between cells whereas the co-surfactant such as pentanol is more efficient at fluidizing the membranes of living cells, inducing cell lysis, hence the difference of the toxicity for linker-based alcohol-based lecithin microemulsion [63]. Despite those *in vitro* studies, investigations of *in vivo* efficacy and toxicity are needed to demonstrate the superiority of linker-based lecithin microemulsion.

Besides the zwitterionic surfactants, non-ionic, cationic, or anionic surfactants can also be used. Polysorbate 80, sorbitan monooleate (Span® 80), Poloxamers, Cremophor® EL, hexadecyltrimethyl-ammonium bromide, didodcecylammonium bromide and bis-2-ethylhexylsulphosuccinate are among the most well-known surfactants.

#### 3.1.3 Co-surfactant

The co-surfactant is also often included in the formulation of the microemulsion used for systemic or transdermal delivery. Owing to its amphiphilic nature, a co-surfactant accumulates substantially at the interfacial layer, increasing the fluidity of the interfacial film by penetrating into the surfactant monolayer. Co-surfactants include short-chain alcohol and medium-chain alcohol. For transdermal drug delivery, some of the co-surfactants are also known as penetration enhancers, such as ethanol, alkanols and propylene glycol [65]. As reviewed by Williams and Barry [65], ethanol affects the penetration of the drug through various mechanisms. On the one hand, ethanol functions through changing the state of the drug. For example, ethanol can enhance the flux of permeation by increasing the solubility of the drug and the evaporation of the ethanol can increase the drug concentration, providing a supersaturated state with a greater driving force for permeation. On the other hand, ethanol can alter the structure of the stratum corneum, extracting some of the lipid fraction from within the stratum corneum when used at high concentration for prolonged times. Other co-surfactants that are often used for parenteral microemulsions include propylene glycol and glycerol, PEG400, 2-pyrrolidone (Soluphor® P) and glycofurol (tetrahydrofurfuryl alcohol PEG ether or tetraglycol).

#### 3.1.4 Aqueous phase

Water served as the aqueous phase in most of the studies. The pH of the aqueous phase always needs to be adjusted as it has considerable influence on the phase behavior of the microemulsions. For example, adjustment of the initial pH at 7 – 8 is important for lecithin-based microemulsions, in order to minimize the hydrolysis of the phospholipids and the triglycerides to fatty acids and improve the stability [66]. As for parenteral microemulsions, the aqueous phase should be isoosmotic to the blood, which can be achieved with the addition of agents such as sodium chloride, glycerol, dextrose and sorbitol.

### 3.2 Stability of microemulsions

One of the advantages of the microemulsion over the traditional emulsion is its excellent thermodynamic stability. However, the physical stability and chemical stability of the drug-loaded microemulsions for intravenous or transdermal delivery still need to be examined because drugs tend to precipitate and crystallize as large crystals on storage [67]. The stability of drug-loaded microemulsions can be affected by intrinsic properties of the microemulsions, such as the type and levels of surfactant used, the phase volume ratio, and the internal storage conditions such as the temperature and the light.

The diallyl trisulfide microemulsion reported by Chengwen Mao *et al.* [68] showed a good stability at 4°C during 3 months of storage. All the formulations have high negative zeta potentials and such electrostatic repulsive forces may contribute to the stability of the DT microemulsions. In another study, the microemulsion also acted as a protector for all-*trans*-retinoic acid (ATRA) [69], which is readily degraded on exposure to light [70]. Within 1 h, <30% of ATRA remained intact in methanol solution, whereas 9% of ATRA incorporated in microemulsion was degraded, and after 7 h of incubation ~ 59% of ATRA was found intact. When the samples were protected from light, the concentration of ATRA remained constant in any samples. The stability of ATRA in microemulsion is considered to be due to the presence of protective films surrounding ATRA, which were provided by phospholipid layers.

The stability of theophylline microemulsion was investigated by storage at -4°C, 60°C and ambient temperature. All microemulsion formulations showed excellent stability at ambient temperature, whereas the phase separation and turbidity were observed when vehicles were stored at -4°C and 60°C [71]. The coagulation of the internal phase at low temperature and the cloud point of surfactant mixture at high temperature might lead to this instability; but these were easily recovered by storing at ambient temperature for a while.

### 3.3 Bioavailability of microemulsions

#### 3.3.1 Through the intravenous route

Various nanocarriers including microemulsions effectively accumulate in many tumors predominantly by means of the enhanced permeability and retention (EPR) effect. The EPR effect, which was first observed by Matsumura and Maeda, is caused by abnormally high permeability of tumor blood vessels combined with poor lymphatic drainage in tumor tissues [72]. To increase the accumulation of drugs in the tumors, the nanocarriers need to be long-circulating. Coating the nanocarriers with hydrophilic polymers such as PEG is the most frequent way to impart *in vivo* longevity to drug carriers. The presence of PEG with appropriate conformation and density sterically hinders interactions of blood components with their surface and slows down their fast capture by the reticuloendothelial system [73].

In injectable microemulsions of vincristine (M-VCR), the oil phase was a vitamin E solution of oleic acid and VCR, and

PEG-DSPE and cholesterol were used as the surfactants. The particle size of M-VCR ranged from 90 to 150 nm. Compared with free VCR solution (F-VCR), the plasma AUC of M-VCR was significantly increased and the spleen and liver $AUC_{0.08-12\,h}$ of M-VCR were significantly decreased. Such a difference of the pharmacokinetics between M-VCR and F-VCR may be due to the steric barrier of the surface-grafted PEG chains of M-VCR. Besides, the tumor $AUC_{0.08-12\,h}$ of M-VCR was significantly greater than that of F-VCR owing to the EPR effect, showing greater potential antitumor effects than F-VCR in M5076 tumor-bearing C57BL/6 mice.

To achieve targeting of folate receptor (FR)-positive tumor cells, Yukino Ohguchi *et al.* [74] synthesized folate-PEG-DSPE and formulated the aclacinomycin A (ACM)-loaded microemulsion with it as the surfactant. *In vitro* study indicated that KB cells that overexpress FR showed selective FR-mediated uptake, but it was not the case in FR-negative HepG2 cells. However, there was no significant difference in the antitumor effect between folate-PEG-DSPE microemulsion and non-folate microemulsion following intravenous injection, although both of them inhibited tumor growth more significantly than ACM solution on day 24 following tumor inoculation. Compared with non-folate microemulsion, a greater amount of folate-modified microemulsion accumulated in the spleen, which may be an explanation for the deficient targeting of folate-PEG-DSPE microemulsions to the KB tumors. Therefore, further study is needed to optimize the formulations of the microemulsion to achieve tumor targeting.

There are also microemulsions for parental delivery that do not incorporate PEG in the formulations. A cholesterol-rich microemulsion termed LDE that contains cholesteryl oleate, egg phosphatidylcholine, triolein and cholesterol has been used to carry anticancer drugs to the target tissues in various tumor models [75-77], based on the properties of the microemulsion, to concentrate in the tumors where low-density lipoprotein (LDL) receptor is upregulated. LDE concentrates paclitaxel oleate, a paclitaxel lipophilic derivative, in the tumor roughly fourfold relative to the normal adjacent tissues [76]. The association of paclitaxel oleate with LDE results in remarkable changes of the pharmacokinetics of the drug compared with commercial paclitaxel. The LDE-paclitaxel oleate also shows better antitumor activity than the commercial paclitaxel, as indicated by the reduction in tumor growth, increase in survival rates and percentage cure of treated.

To avoid reticuloendothelial system trapping, nanocarriers may be covered with a hydrophilic barrier to escape recognition. Apart from synthetic hydrophilic polymers frequently used for this purpose, such as poly(ethylene glycol), polyvinyl alcohol and poly (amino acid) [78-80], in the preparation of liposomes and nanoparticles, the nature-derived hydrophilic polymer such as hyaluronic acid chitosan has also been used to coat the nanocarriers [81]. In an attempt to enhance the circulation time of the nobiletin-loaded microemulsion, weakly positively charged hyaluronic acid chitosan (HAC) was added and expected to adsorb to the external surface of the negatively charged microemulsion. Both microemulsion and HAC-coated microemulsion showed a prolonged residence in the blood compared with the free drug, and the retention time of HAC-coated microemulsion in the blood circulation was markedly longer than that of the microemulsion group, which may help to explain the fact that the presence of HAC in the microemulsions resulted in an increased concentration of nobiletin in the brain. Owing to the mucoadhesive activity of hyaluronic acid, hyaluronic acid has been reported to be able to inhibit the phagocytosis of the macrophages in a dose and molecular mass-dependent manner [82]. Moreover, the components in the formulation, Cremophor EL 35 and labrasol, which have been shown to be able to inhibit the multidrug resistance phenotype and increase the permeability of tight junctions in Caco-2 cells, may also play a role in overcoming the blood–brain barrier.

### 3.3.2 *Through the transdermal route*

Human skin is an important target site for the application of drugs. Compared with oral routes, the transdermal route of drug administration has the advantages of minimizing the first-pass effect and providing an alternative to hypodermic injection [4]. It has been recognized that transdermal delivery can be influenced by the interactions that may occur between the vehicle and the skin, and interactions between the active ingredient and the skin [83]. The influence of the type of microemulsion used on the transdermal adsorption and permeation has been evaluated recently with the model drug lidocaine [63,84]. Results showed that type II (water-in-oil) and type IV (bicontinuous) linker-based vehicles produce larger transdermal lidocaine flux, larger lidocaine skin absorption and larger lidocaine permeability than type I (oil-in-water) microemulsion and pentanol-based type II microemulsion. The superior flux obtained with linker microemulsions was demonstrated to result from the use of hydrophilic linkers, sodium caprylate and caprylic acid, which accelerate the interfacial mass transfer by reducing the interfacial rigidity of the systems [63]. Moreover, the release profiles of types I and II microemulsions were also investigated [84]. It was demonstrated that the release of drug from type I microemulsions is slower than type II microemulsions and the mass transfer coefficient of type II systems was larger than that of type I. The lower rate of penetration for type I systems may be related to the higher viscosity of these systems. All of these results suggest that the morphology of the microemulsion plays an important role in the drug release kinetics.

## 4. Toxicity of microemulsions

As the formulations of the microemulsion always include a large amount of surfactant and co-surfactant, which may cause hemolysis or histopathological alterations of the tissue, the potential toxicity or the irritancy of the microemulsion should be evaluated. To evaluate the safety of the

intravenous microemulsion, the *in vitro* red blood cell hemolysis experiment can be undertaken instead of the *in vivo* test [85,86]. *In vitro* studies evaluating the potential hemolytic activity of microemulsions prepared with varying types of surfactant and oil and different ratios of aqueous to non-aqueuos indicate that the highest hemolytic activity of microemulsions may be attributed to the excipient used in the formulations. The most hemolytic microemulsions corresponded to those containing the surfactant Labrasol®, with or without butyl lactate, so the use of high amounts of Labrasol and butyl lactate should be avoided in microemulsions [86].

For the topical use of microemulsions on the skin, the skin redness test to judge the extent of erythema and edema and histological analysis to examine the epidermis thickening and infiltration of inflammatory cells are often used to evaluate the irritancy of the microemulsion [87,88]. For intact skins after a single application or multiple applications, neither microemulsion-based hydrogel (MBH) nor microemulsion formulation of penciclovir irritated the skin. However, after a single application or multiple applications to injured skins, slight skin irritation occurred for the microemulsion, but not for MBH. It was possible that the decrease of the metabolic capability for damaged skins induced accumulation of surfactant mixture and oil phase, which induced irritation reaction. The SEM in skin showed that, compared with MBH, microemulsion could change the structure of stratum corneum to a greater extent, and this change could be beneficial to the permeation of drugs through skins.

The choice of surfactants also greatly influences the toxicity of SEDDS for oral delivery of drugs. Generally, polysorbates and polyethoxylated vegetable oils are less toxic than single-chain surfactants, and esters are less toxic than ethers (which are non-digestible). Non-ionic surfactants are generally considered to be acceptable for oral administration, and the emergence of several successful marketed products has given the industry confidence in lipid-based products [89]. The oral and intravenous $LD_{50}$ values for most non-ionic surfactants exceed 50 and 5 g/kg, respectively, so 1 g surfactant in a formulation is well tolerated for uses in acute oral drug administration [90]. More careful consideration should be given to the formulation for chronic use, and it is noteworthy that marketed lipid products for chronic use generally do not tend to include surfactants [89]. However, the marketed HIV protease inhibitor products (Agenerase, Kaletra and Norvir) contain a considerable quantity of surfactants in each capsule, and several capsules are administered 2 – 4 times daily, so that patients ingest 2 – 3 g Cremophor or D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) a day. It is generally believed that the clinical indication benefit outweighs the risk in this case, so such a formulation is still acceptable as a whole.

## 5. Expert opinion

Microemulsions have been paid extensive attention owing to their potential to be used as effective drug delivery vehicles for a large range of drugs. The excipient, characteristics, bioavailability and pharmacodynamic effects of representative microemulsions used in oral/intravenous/transdermal administration are summarized in **Table 1**. However, there is still a considerable amount of fundamental work that needs to be performed before the microemulsions can be used as multipurpose drug delivery vehicles. Up to now, special attention has been paid to the physicochemical and biopharmaceutical characteristics of the formulations, which will affect the *in vivo* performance of the formulation. More mechanistic studies should be encouraged to facilitate a better understanding of the pharmaceutical characteristics of such lipid formulations and complex interactions between lipid excipient, drug and the physiological environment.

Poorly water-soluble drugs are a broad class of drugs that represent a real challenge for the design of appropriate formulations aimed at enhancing oral bioavailability. For oral delivery, formulators need to have a good understanding of gastrointestinal digestion and to set up standardized predictive *in vitro* tests to predict the fate of the formulation after oral administration. Also, more attention should be paid to the drug precipitation from SEDDS when diluted with water or dispersed in the GIT. Moreover, traditional preparations of SEDDS are usually prepared as liquids and orally administered in soft or hard gelatin capsules that produce some disadvantages, such as high production costs, low drug incompatibility and stability, drug leakage and precipitation, and capsule ageing. Then incorporation of liquid SEDDS into a solid dosage form is compelling and desirable, and some solid self-emulsifying dosage forms have been initially explored, such as self-emulsifying tablet and pellets. Furthermore, SEDDS encompass a wide range of compositions and show a broad character and functionality, how the choice of excipients is likely to influence the fate of the formulation and drug *in vivo*. A large quantity of surfactant might irritate the GIT with chronic use. Thus, the safety aspect of the surfactant vehicle should be carefully considered in each case and the method of how to decrease its quantity in formulation also should be experimented. Finally, the advanced solidification techniques and some new solid dosage forms of SEDDS will emerge and be used in the near future.

Although there are some systematic and mechanistic studies and several model drugs addressing the critical area of microemulsions, and microemulsions have demonstrated potential as a commercially feasible and new vehicle for parenteral delivery hydrophobic drugs, relatively few *in vivo* studies in humans by means of intravenous injection have been reported in the literature when compared with conventional dosage forms. The lack of surfactants and co-surfactants significantly hindered successful development of formulations of new injectable microemulsions with satisfactory stability and curative effect both *in vitro* and *in vivo*. Moreover, a long-term safety evaluation of new excipients needs to be undertaken to widen the scope of the microemulsions used for systemic administration.

On the other hand, as is well known, the main challenge to transdermal drug delivery is to overcome the barrier of

**Table 1. Summary of representative microemulsions used in oral/intravenous/transdermal administration.**

| Drug | Oil | Aqueous phase | Surfactant | Co-surfactant | Mean particle size (nm) | Pharmacokinetics | Pharmacodynamic characteristics | Ref. |
|---|---|---|---|---|---|---|---|---|
| *Intravenous delivery* | | | | | | | | |
| 10-alkoxy-9-nitrocampto-thecin (MONCPT) | Soybean oil | Water | PEG 400, lipoid E80, Cremophor EL | Glycerol, glycerol formal, Ethanol | 67 | NA | 93.6% tumor suppression rate in S180-bearing mice, and MONCPT injection was only 24.2% at the same dosage | [91] |
| Vincristine (VCR) | Oleic acid and vitamin E | 0.9% NaCl aqueous solution, pH 7.4 | PEG-DSPE | Cholesterol | 138 | Decreased uptake by the mononuclear phagocytic system of liver and spleen, increased accumulation in tumor | In the solid M5076 tumor model, the tumor weight inhibition rate of microemulsion of VCR was 67%, significantly higher than that of free VCR (42%) | [92] |
| Aclacinomycin A (ACM) | Vitamin E | 0.9% NaCl aqueous solution | Folate-PEG5000-DSPE, PEG2000-DSPE | Cholesterol | 120 | In each organ, the ACM concentration of microemulsion of ACM was significantly higher than that of free ACM, mainly ACM accumulation in the spleen rather than the tumor | Microemulsion of ACM showed significantly higher tumor suppression than ACM solution on day 24 following tumor inoculation | [74] |
| Paclitaxel | Vitamin E | Water | PEG 400, TPGS, Poloxamer 407 | | 62 | | A threefold increase in the maximum-tolerated dose over Taxol, a significant reduction in tumor growth | [93] |
| Paclitaxel oleate | Cholesteryl oleate | Water | Egg phosphatidylcholine, triolein | Cholesterol | | High accumulation in liver and tumor | The reduction of tumor growth, increase in survival rates and % cure of treated mice of the complex is pronouncedly greater than that of commercial paclitaxel | [76] |
| *Transdermal delivery* | | | | | | | | |
| Cyclosporin A (CysA) | IPM | Water | AOT, Tween 85 | | NA | High local concentrations and minimal distribution to other organs via the circulation | | [94] |

**Table 1. Summary of representative microemulsions used in oral/intravenous/transdermal administration (continued).**

| Drug | Oil | Aqueous phase | Surfactant | Co-surfactant | Mean particle size (nm) | Pharmacokinetics | Pharmacodynamic characteristics | Ref. |
|---|---|---|---|---|---|---|---|---|
| Tolterodine tartrate | IPM | Water | Labrasol | Plurol | 25.3 | Significantly lower $C_{max}$, delayed $T_{max}$ and higher mean residence time value when compared with oral delivery | A sustained activity was observed over a period of 72 h after transdermal application of microemulsion to human volunteers | [95] |
| Penciclovir | Oleic acid | Water | Cremophor EL | Ethonal | 36.5 | Significant increase of the permeation of penciclovir into both epidermis and dermis in microemulsion-based hydrogel compared with the commercial cream | | [88] |
| Quercetin | Canola oil | Water | Span 80, Tween 80 | Propylene glycol | NA | | Quercetin microemulsion significantly prevented the UV-B irradiation-induced endogenous reduced glutathione depletion and secretion/activity of metalloproteinases | [87] |
| Progesterone | Tributyrin | Water | Polyoxyethylene-10-dodecyl ether | Polymeric additives (silicon dioxide and polymeric emulsifier) | 5.5 | Improved skin permeation and decreased skin retention by the addition of polymeric agents compared with the pure microemulsion | | [96] |
| Theophylline | Oleic acid | Water | Cremophor RH 40, Labrasol | | Range from 22.3 to 78.5 | Higher $AUC_{0\rightarrow\infty}$ of transdermal administration than that of oral solution administration | | [71] |
| *Oral delivery* | | | | | | | | |
| Itraconazole | Tocopherol acetate | | Pluronic L64 | Transcutol | 246 | Greatly enhanced bioavailability of itraconazole, and influenced by food intake or not | | [14] |

**Table 1. Summary of representative microemulsions used in oral/intravenous/transdermal administration (continued).**

| Drug | Oil | Aqueous phase | Surfactant | Co-surfactant | Mean particle size (nm) | Pharmacokinetics | Pharmacodynamic characteristics | Ref. |
|---|---|---|---|---|---|---|---|---|
| Probucol | Sesame oil | | Cremophor RH40, Maisine 35-1 | Ethonal | 45.0 | The bioavailability from the surfactant solution and the oil solution were slightly lower compared to the self-nanoemulsifying drug delivery system | | [40] |
| Paclitaxel | Glycery dioleate Cremophor EL | | Cremophor EL | Ethanol, PEG 400 | NA | The paclitaxel S-SEDDS formulation shows 10-fold higher $C_{max}$ and fivefold higher oral bioavailability compared with that of the orally dosed Taxol formulation | | [37] |
| Danazol | Soybean oil | | Cremophor EL, Maisine 35-1 | Ethanol | 40.4 | LC-SMEDDS formulations significantly enhanced the oral bioavailability of danazol when compared with fasted administration of the powder formulation | | [45] |
| Curcumin | Ethyl oleate | | Cremorphor EL, emulsifier OP | PEG 400 | 31.5 | SMEDDS significantly increased the oral absorption of curcumin compared with its suspension | | [97] |
| Acyclovir | Sunflower oil | | Tween 60 | Glycerol | 17.9 | SMEDDS increased the oral bioavailability of acyclovir by 3.5-fold compared with the pure drug solution | | [98] |
| Vinpocetine | Ethyl oleate | | Solutol HS | Transcutol® P, | Range from 23.5 to 75.1 | Oral bioavailability of vinpocetine of SMEDDS was 1.72-fold higher as compared with that of the commercial tablet | | [99] |
| Silymarin | Glyceryl monooleate | | Polysorbate 20, HCO-50 | Transcutol | 67 | Oral bioavailability of silymarin from the SMEDDS was 3.6 times higher than the reference capsule | | [100] |

**Table 1. Summary of representative microemulsions used in oral/intravenous/transdermal administration (continued).**

| Drug | Oil | Aqueous phase | Surfactant | Co-surfactant | Mean particle size (nm) | Pharmacokinetics | Pharmacodynamic characteristics | Ref. |
|---|---|---|---|---|---|---|---|---|
| Exemestane | Capryol 90 | | Cremophor ELP | Transcutol P | Within 100 | The relative bioavailability of exemestane of SMEDDS was enhanced by 287.32% | | [101] |
| Oridonin | Maisine 35-1, Labrafac CC, | | Cremophor EL | Transcutol P | Range from 23 to 25 | The oridonin SMEDDS showed a 2.2-fold increase in relative bioavailability compared with that of the suspension | | [102] |
| 9-Nitrocamptothecin (9-NC) | Ethyl oleate | | Tween 80 (T-form) or Cremophor EL (C-form) | PEG-400, Ethanol | 30.8 for T-form and 39.8 for C-form | | The 9-NC SMEDDS produced significantly more tumor shrinkage when compared with 9-NC suspension in nude mice bearing human ovarian cancer xenografts | [103] |
| Nimodipine | Ethyl oleate | | Labrasol, Cremophor® RH 40 | | 44.1 | AUC and $C_{max}$ after oral administration of the solid SMEDDS were 2.6- and 6.6-fold higher, respectively, compared with those of the conventional tablet | | [104] |

the stratum corneum, which hampers the achievement of therapeutic drug levels in either topic or systemic circulation. Owing to their penetration-enhancing properties, microemulsions can find application in several clinical areas. Several encouraging studies on the enhanced dermal drug uptake by microemulsions have been reported and several fields such as site-specific treatment of dermatological diseases and topical genetic immunization using microemulsions should be paid more attention. Anti-acne drugs, local anesthetics and drugs such as cyclosporine A to treat psoriasis vulgaris appear to be useful through the skin route when encapsulated in microemulsions because a fast penetration and, hence, a fast occurring effect can be reached. Also, microemulsions offer a high solubilization capacity for poorly soluble drugs such as some hormones and beta-blockers, and combined with their permeation-enhancing effect, high flux rates and high concentration of drug in blood can be obtained. Investigators are now making great efforts to improve the convenience and compliableness in the clinic, using approaches such as adding thickening agents or making patches to combine the microemulsion with other polymers, which can increase drug fluxes similar to the fluid microemulsion at the same time to improve the drug disposition into the dermis layer. On the other hand, topical genetic immunization using vaccine-containing microemulsions is a highly innovative approach because the skin represents the body's front line for immunosurveillance.

In conclusion, considering the potential in enhanced drug uptake/permeation and facing the limitations, their unique properties make microemulsions a promising vehicle for multifunctional drug delivery.

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## Declaration of interest

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