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International Journal of Pharmaceutics 355 (2008) 19–30
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Mini review

# Parenteral microemulsions: An overview

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Received 21 October 2007; received in revised form 27 December 2007; accepted 5 January 2008
Available online 12 January 2008

**Abstract**

Parenteral delivery of the hydrophobic drugs is a very challenging task. The conventional approaches such as use of co-solvents, oily vehicles and modern approaches such as mixed micelles, liposomes, complexation with cyclodextrins and emulsions have several limitations. Microemulsions have evolved as a novel vehicle for parenteral delivery of the hydrophobic drugs. Their interesting features such as spontaneity of formation, ease of manufacture, high solubilization capacity and self-preserving property make them the vehicle of choice. The review focuses on the excipients available for formulation of the parenteral microemulsions and describes the investigations reported for the various classes of therapeutic agents.


*Keywords:* Parenteral delivery; Hydrophobic drugs; Microemulsions; Paclitaxel

## 1. Introduction

Parenteral route is of utmost importance in the drug development and drug delivery research. In the process of generation and evaluation new chemical entities, development of the suitable parenteral formulation is required for pre-clinical studies in order to understand the behavior of the new chemical entities in the body. Furthermore, parenteral route is the only choice for the administration of the hydrophobic drugs such as amphotericin B and paclitaxel, which are poorly absorbed by the oral route (Vyas, 1995; Robbie et al., 1999). Parenteral route is also the most preferred route of administration in the case of emergency as it ensures very quick onset of action. However, design of parenteral drug delivery systems is a critical and challenging task as the number of excipients approved for parenteral delivery is considerably small. Furthermore, parenteral delivery systems have stringent regulatory requirements as the route of administration circumvents at least one protective barrier. The development of parenteral formulation is even more difficult in case of the hydrophobic drugs. Paradoxically, up to 40% of the new chemical entities discovered by the pharmaceutical industry today**,** are poorly soluble or lipophilic compounds and are difficult to formulate in a suitable parenteral dosage form for pre-clinical evaluation.

For the formulation of hydrophobic drugs, 'solubilization using co-solvent/s' is a conventional and most preferred approach. Co-solvents such as ethanol, propylene glycol and polyethylene glycol 400 are employed for this purpose (Akers, 2002; Strickley, 2004). However, co-solvent approach cannot be employed for parenteral administration of many drugs such as amphotericin B and artemether. Furthermore, the co-solvent based systems often lead to precipitation of the drug on dilution in several cases as reported for paclitaxel and tacrolimus (Vyas, 1995). The other disadvantages include severe pain at injection site and hemolysis which limits their utility and also patient acceptability in many cases (Krzyaniak and Raymond, 1997; Akers, 2002; Strickley, 2004). For extremely lipophilic drugs, solubilization using fixed oils and/or medium chain triglycerides (MCT) has been proposed. This approach has been useful for intramuscular depot formulae for the sustained release of the certain drugs like haloperidol (Fredholt et al., 2000; Akers, 2002). However, oily solutions cannot be administered by intravenous routes and are not suitable for quick onset of action. For example, onset of action and pharmacokinetics of artemether from oily solutions are reported to be erratic which limits their utility (Hien et al., 2004).

This scenario necessitates the application of novel delivery approaches to solubilize hydrophobic drugs and new chem-

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doi:10.1016/j.ijpharm.2008.01.004

ical entities to enable the development of parenteral dosage form.

## 2. Brief overview of the current strategies for parenteral delivery of hydrophobic drugs

Several strategies have been employed by the drug delivery scientists to tackle the problems associated with the parenteral delivery of hydrophobic drugs. Initially, solubilization of the hydrophobic drugs in the micelles of the suitable surfactant was attempted. Micellar formulations are still available in the market for vitamin D derivatives (Strickley, 2004) such as doxercalciferol (Hectorol®) and calcitriol (Calcijex®). However, micelles have very limited solubilization capacity and can be used for very potent drugs. Mixed micellar formulations (based on phospholipids and bile salts) have demonstrated some success and are utilized for the delivery of Amphotericin B (Fungizone®; Dupont, 2002). The bile salts are known to cause considerable hemolysis (Mrówczyńska and Bielawski, 2001; Zhang et al., 2001). Furthermore, the efficacy of the therapeutic agent is strongly influenced by its interaction with the mixed micelles. For example, mixed micellar approach proved to be successful for the delivery of diazepam whereas tetrazepam loaded mixed micelles failed to demonstrate desired effect due to very strong interaction of the drug molecule with the micellar structure. Liposomes are indeed interesting carrier systems for parenteral delivery of hydrophobic agents. However, complexity associated with the manufacturing process and enormous cost of the formulation often limits their commercial viability to very specific drug candidates such as doxorubicin (Doxil®) and Amphotericin B (AmBisome®). Use of cyclodextrins for the solubilization of hydrophobic drugs like itraconazole (Sporanox®) is another approach which has succeeded commercialization (Strickley, 2004). But the issues such as poor complexation and high cost of cyclodextrin derivatives like sulfobutyl ether-β-cyclodextrin often limits the utility of cyclodextrin complexation.

In comparison to aforementioned approaches, emulsions are preferred for the delivery of hydrophobic drugs due to advantages such as ability to solubilize considerable amount of drug, ability to prevent hydrolysis of the drugs such as barbiturates, ease of manufacture and scale-up and low cost as compared to other colloidal carriers such as liposomes (Floyd, 1999). Parenteral emulsions are being used for total parenteral nutrition for several years. The potential of emulsions in the effective parenteral delivery of several hydrophobic drugs is well documented in the literature (Floyd, 1999). Currently, propofol (a central anesthetic agent) is available as parenteral emulsion (Diprivan®, Astra-Zeneca) (Han et al., 2001). However, emulsions suffer from various disadvantages such as poor physical stability on long-term storage, risk of emboli formation, need for strict aseptic handling and rapid growth of microorganisms (Bennett et al., 1995).

Microemulsions have evolved as second generation colloidal carrier systems and are being preferred over emulsions in several cases. Microemulsions are thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules. They include swollen micellar (oil-in-water, O/W), reverse micellar (water-in-oil, W/O) and bicontinuous structures (Tenjarla, 1999; Lawrence and Rees, 2000; Bagwe et al., 2001). The globule size of the micromeulsions is less than 150 nm. The various advantages such as spontaneity of formation (zero energy input), optical transparency, long-term physical stability, self-preserving nature (Al-Adham et al., 2000) give them an edge over conventional emulsions. The potential of microemulsions for various routes of administration is continuously being explored since last two decades. The utility of the microemulsions in dermal (Kreilgaard, 2002), oral (Gursoy and Benita, 2004) and ocular delivery (Vandamme, 2002) has been reviewed in the literature but there is no collective compilation about the applications of microemulsions in parenteral delivery. The present review would not focus on the basic aspects of the microemulsions such as structure, phase diagrams and characterization as they have been adequately reviewed by various authors (Tenjarla, 1999; Lawrence and Rees, 2000; Bagwe et al., 2001). Instead, the review presents discussion on the excipients available for the formulation of parenteral microemulsions, formulation considerations pertaining to parenteral delivery and the investigations reported till date. The main objective of the review is to accelerate the drug delivery research to extend applications of microemulsions in parenteral delivery which is still a niche area.

## 3. Formulation considerations and potential ingredients

Due to stringent requirements of the parenteral products, only few excipients are acceptable for parenteral delivery. The excipient selected for the parenteral systems should be biocompatible, sterilizable, available as non-pyrogenic grade, non-irritant to nerves and non-hemolytic. Very few excipients comply with all these requirements. For example, the sugar surfactants are biocompatible and have fairly good solubilization potential but they have been found to be hemolytic (Söderlind et al., 2003).

In general, the phenomenon of microemulsification is mainly governed by the factors such as (1) nature and concentration of the oil, surfactant, cosurfactant and aqueous phase, (2) oil/surfactant and surfactant/cosurfactant ratio, (3) temperature and pH of the environment and (4) physicochemical properties of the drug such as hydrophilicity/lipophilicity, p$K_a$ and polarity (Tenjarla, 1999; Lawrence and Rees, 2000; Bagwe et al., 2001). Hence, these factors should be given due consideration while formulation of the microemulsions. Formulation considerations with respect to the components of the microemulsions are discussed below.

### 3.1. Oily phase

Selection of an appropriate oily phase is very important as it influences the selection of the other ingredients of microemulsions, mainly in case of O/W microemulsions. Usually, the oil, which has maximum solubilizing potential for the selected drug candidate, is selected as an oily phase for the formula-

Table 1
Components available for parenteral microemulsions

| General class | Examples | Commercial name |
|---|---|---|
| Polysorbates | POE-20-sorbitan monooleate | Tween 80, Crillet 4 |
| | POE-20-sorbitan monolaurate | Tween 20, Crillet 1 |
| Sorbitan esters | Sorbitan monolaurate | Span 20, Crill 1 |
| PEO–PPO-block copolymers | Poloxamer 188 | Pluronic/Lutrol F 68 |
| POE alkyl ethers | POE-10-oleyl ether | Brij 96 V |
| POE castor oil | POE-35-castor oil | Cremphore EL, Etocas 35 HV |
| POE hydrogenated castor oil | POE-40-hydrogenated castor oil | Cremophore RH 40, HCO-40, Croduret 40 LD |
| | POE-60-hydrogenated castor oil | Cremophore RH 60, HCO-60 |
| POE-stearate | PEG-660-12-hydroxystearate | Solutol HS 15 |
| Phospholipids | Soybean lecithin | |
| | Egg lecithin | |
| | Diolelyl phosphatidyl choline | |
| | Distearoyl phosphatidyl glycerol | |
| | PEGylated phospholipids | |
| | Dimyristoyl phosphatidyl choline | |
| Fixed oils | Soybean oil, castor oil | |
| MCTs | Triglyceides of capric/caprylic acids | Miglyol 810, 812, Labrafac CC Croadamol GTCC, Captex 300, 355 |
| Fatty acid esters | Ethyl oleate | Crodamol EO |
| | Isopropyl myristate (IPM) | |
| | Isopropyl palmitate (IPP) | |
| Vitamins | Vitamin E | |
| Short chain alcohols | Ethanol, benzyl alcohol | |
| Alkane diols and triols | Propylene glycol (PG) | |
| | Glycerol | |
| Polyethylene glycols (PEG) | PEG 400 | |
| Glycol ethers | Tetrahydrofurfuryl PEG ether (tetraglycol or glycofurol) | |
| Pyrrolidine derivatives* | *N*-methyl pyrrolidone | Pharmasolve |
| | 2-Pyrrolidone | Soluphor P |
| Bile salts | Sodium deoxycholate | |

* Application in veterinary products only.

tion of microemulsions. This helps to achieve the maximal drug loading in the microemulsions. At the same time, the ability of the selected oil to yield systems with larger microemulsion existence region is also important. It is difficult for a single oily component to amalgamate both these requirements. It is known fact that oils with excessively long hydrocarbon chains (or high molecular volume) such as soybean oil are difficult to microemulsify whereas oils with shorter chain (or low molecular volume) such as medium chain triglycerides (MCT), fatty acid esters (like ethyl oleate) are easy to microemulsify (Malcolmson et al., 1998; Warisnoicharoen et al., 2000). On the contrary, the capacity of solubilization of lipophilic moieties usually increases with the chain length of the oily phase (Vandamme, 2002). The choice of the oily phase is often a compromise between its ability to solubilize the drug and its ability to facilitate formation of micromeulsions of desired characteristics. In certain cases, mixture of oils is also used to meet both the requirements. For example, a mixture of fixed oil and medium chain triglyceride is used in certain cases to have good balance between drug loading and emulsification (Jumaa and Mueller, 2002a). Recently, vitamin E (D-α-tocopherol) based emulsions are proposed in some investigations mainly due to its solubilizing potential (Constantinides et al., 2004). It has been reported that vitamin E can solubilize API such as itraconazole, saquinavir and paclitaxel which are difficult to solubilize by using conventional oily components (Constantinides et al., 2004). There are no reports on the vitamin E based microemulsions but there is a great scope to develop such systems. The oily components available for parenteral micromeulsions are listed in Table 1. Recently, microemulsions based on medium chain mono- and di-glycerides have also been reported (Nornoo et al., 2008; Nornoo and Chow, 2008). Medium chain mono- and di-glycerides such as Capmul® MCM have much higher solubilization potential than that of the fixed oils and MCT and they are easy to microemulsify. However, parenteral safety of these excipients on long-term administration needs to be established.

### 3.2. Surfactants

Choice of the surfactant is critical for the formulation of microemulsions. The surfactant/s should favor microemul-

sification of the oily phase and should also possess good solubilizing potential for the drug. It should be noted that the surfactants are not innocuous. For example, Cremophore®EL (PEG-35-castor oil), a surfactant with very good parenteral acceptability causes several adverse-effects such as anaphylactic shocks and histamine release which limits its utility (Tije et al., 2003). Certain surfactants such as polyoxyethylene alkyl ethers, at higher concentration, may cause hemolysis on parenteral administration (Söderlind et al., 2003). These factors must be considered while choosing a type and the concentration of surfactant. Generally, surfactants of natural origin are preferred over synthetic surfactants, e.g. phospholipids are preferred over synthetic surfactants wherever possible. By and large, the surfactant concentration in microemulsions should be minimal as far as possible irrespective of its nature, origin and type. The choice of the surfactant would also be governed by the type of the microemulsion to be formulated. Low HLB surfactants such as Sorbitan monoesters are preferred for W/O microemulsion whereas high HLB surfactants such as polysorbate 80 are preferred for O/W microemulsion. In several cases, a mixture of lipophilic (low HLB) and hydrophilic surfactants (high HLB) may be required to obtain a microemulsion. The various classes of surfactants that are available for the pharmaceutical microemulsions are described in Table 1. Amongst various surfactants that are available, Lecithins, Poloxamers and Polysorbate 80 are most preferred (Strickley, 2004). Polyethoxylated castor oil derivatives (Cremophore®EL, Cremophore® RH 40 and Cremophore® RH 60) are used in some of the currently marketed co-solvent based formulations (Akers, 2002). However, in view of the adverse-effects associated with the Polyethoxylated castor oil derivatives, they should be used with caution for the formulation of microemulsion (Tije et al., 2003).

Lecithins should always be first choice due to their excellent biocompatibility. However, lecithins are too hydrophobic to form spontaneously the zero curvature lipid layers required for the formation of balanced microemulsions. Hence, in order to form phospholipid based microemulsions, it is necessary to adjust the HLB of phospholipids and to inhibit their tendency to form lamellar liquid crystalline phases. This is achieved by using auxiliary surfactant like polysorbate 80 (Moreno et al., 2003). Amongst poloxamers, poloxamer 188 should be preferred over poloxamer 407. Poloxamer 407 is known to cause hyperlipidemia on long-term administration (Palmer et al., 1997; Blonder et al., 1999). Recently, Solutol® HS 15 (PEG-660-12-hydroxystearate) has emerged as an alternative to Cremophore® EL. It has much better tolerance on parenteral administration than Cremophore® EL. It is being used in certain parenteral products such as Panitol® (Propanidid injection, Cryo Pharma, Mexico; Strickley, 2004). There are some reports on the formulation of parenteral microemulsions with the help of Solutol®HS 15 (Zhao et al., 2005; Rhee et al., 2007; Date and Nagarsenker, in press). It has been shown that the colloidal carriers based on Solutol®HS 15 can withstand freeze–thaw cycling very efficiently which would be of further advantage (Jumaa and Mueller, 2002b).

### 3.3. Cosurfactants

Most of the times, surfactant alone cannot lower the oil–water interfacial tension sufficiently to yield a microemulsion which necessitates addition of an amphiphilic short chain molecule or cosurfactant to bring about the surface tension close to zero. Short chain length ranging from $C_2$ and $C_{10}$ and amphiphilic nature of these agents enable them to interact with surfactant monolayers at the interface thereby affecting their packing (Lawrence and Rees, 2000; Vandamme, 2002). Liquid crystalline phases are formed when the surfactant film is too rigid. Cosurfactants penetrate into surfactant monolayer providing additional fluidity to the interfacial film and thus disrupting the liquid crystalline phases. Furthermore, cosurfactants also distribute themselves between aqueous and oily phase, thereby altering the chemical composition and hence the relative hydro/lipophilicity of the system. For parenteral microemulsions, short chain alcohols such as ethanol and benzyl alcohol can be employed as cosurfactants.

The short chain amphiphilic nature of ethanol enables formulation of microemulsions with a variety of oily phases and surfactants. The concentration of ethanol should preferably not exceed 10% (v/v) (Rowe et al., 2006a). Benzyl alcohol is a partially water miscible short chain amphiphile possessing local anesthetic and preservative properties. Like ethanol, it is also acceptable for parenteral delivery but its final concentration should not exceed 1% (w/v) (Rowe et al., 2006b). There are few of reports on the formulation of microemulsions using benzyl alcohol (Ryoo et al., 2005; Rhee et al., 2007). However, in most of the cases, it has been found to be inferior as compared to the ethanol.

Alkanediols such as propylene glycol and alkanetriol such as glycerol can also be used as a cosurfactant in the microemulsions. Usually, both of them have to be used at a high concentration to produce microemulsions which is attributed to their extreme hydrophilicity. However, it should be noted that higher concentrations of propylene glycol may result in pain on injection and hemolysis. Polyethylene glycols (PEG) such as PEG 400 can be employed as a cosurfactant (Lawrence and Rees, 2000; Bagwe et al., 2001; Vandamme, 2002). The pyrrolidone derivatives such as 2-Pyrrolidone (Soluphor® P) and *N*-methyl pyrrolidone (Pharmasolve®) can be used for parenteral microemulsions for veterinary applications (Akers, 2002). However, their potential in the formulation of microemulsions is yet to be explored to the fullest. Glycofurol (Tetrahydrofurfuryl alcohol PEG ether or Tetraglycol) is another amphiphilic liquid which has parenteral acceptability (Rowe et al., 2006c) and has potential to act as a cosurfactant in parenteral microemulsions (Ryoo et al., 2005; Kim et al., 2007; Rhee et al., 2007). The investigation by Kim et al. (2007) has indicated that glycofurol concentration of 5% (v/v) is tolerable in humans on I.V. administration. Recently, the use of sodium caprylate as a cosurfactant in parenteral micromeulsions has been reported (Morey et al., 2004, 2006a). Although sodium caprylate has potential to cause hemolysis, the microemulsions based on the sodium caprylate were safe to blood components (Morey et al., 2004).

This clearly demonstrates the beneficial effect of microemulsion structure.

### 3.4. Aqueous phase

Nature of the aqueous phase is also important for formulation of parenteral microemulsions. In case of parenteral microemulsions, the aqueous phase should be isoosmotic to the blood which is achieved with the help of additives such as electrolytes (sodium chloride), glycerol, dextrose and sorbitol. These additives can affect the area of existence of the microemulsions. Electrolytes such as sodium chloride decreases the phase inversion temperature (PIT) of the non-ionic surfactants (Tenjarla, 1999). The preparation of microemulsions is very sensitive to temperature, if the PIT is close to the operating conditions. Another important factor is pH of the aqueous phase which also has considerable influence on the phase behavior of the microemulsions. In case, of lecithin based microemulsions, adjustment of the initial pH at 7–8 is also important in order to minimize the hydrolysis of the phospholipids and the triglycerides to fatty acids, which can decrease the pH of the microemulsion and may affect the stability (Vandamme, 2002). Other additives in aqueous phase such as preservatives may also affect the microemulsion phase behavior and area of microemulsion existence. Preservatives like methyl paraben and propyl paraben are known to form complexes with surfactants like polysorbates. Such interactions may influence properties of microemulsion.

## 4. Advantages of microemulsions in parenteral delivery

The nanostructure of the micromeulsions ensures that the probability of emboli formation in the blood is insignificant. Furthermore, the small size of the microemulsions may result in higher blood circulation time which would be useful in certain cases. The excellent thermodynamic stability, high solubilization capacity, low-viscosity and ability to withstand sterilization techniques make microemulsions an interesting delivery system. Furthermore, micromeulsions were found to be less painful on injection as compared to the co-solvent based formulations (Lee et al., 2002). Microemulsions have also been shown to reduce the toxicity potential of the certain drugs like Amphotericin B by means of encapsulation (Moreno et al., 2001). The W/O microemulsions can be used for the controlled delivery of the hydrophilic therapeutic actives such as aminoglycoside antibiotics. With the use of suitable excipients such as PEGylated phospholipids, it is possible to improve the circulation time of the therapeutic agents in the blood which is mainly useful for infections like malaria and in the cancer treatment.

The microemulsions can also be stored in the form of anhydrous preconcentrates. Such systems are referred to as self-microemulsifying drug delivery systems (SMEDDS). SMEDDS can be diluted with the IV fluids such as 0.9% saline or 5% dextrose just before the administration to spontaneously yield microemulsions. The preconcentrates can be employed for the drugs susceptible to hydrolysis and can easily be autoclaved if the therapeutic agent is heat stable.

## 5. Potential explored

As mentioned earlier, development of parenteral microemulsions is a niche area and the number of research papers published is significantly less as compared to dermal and oral micromeulsions. Nonetheless, appreciable number of investigations has been reported and some of them clearly demonstrate the advantage of microemulsions as parenteral delivery systems. The overview of some of the important investigations related to the parenteral microemulsions and their *in vivo* advantages are listed in Table 2.

Corswant et al. (1998) were amongst the first to report development of parenteral microemulsions based on Solutol® HS 15, Soybean lecithin, ethanol, PEG 400 and MCT. The bicontinuous microemulsions with varying oil content were formulated. The hemodynamic studies in rats indicated that the microemulsions had no significant effect on the acid–base balance, blood gases, plasma electrolytes, arterial blood pressure or heart rate. The microemulsions could successfully solubilize drugs like felodipine.

### 5.1. Delivery of anti-cancer agents

Several anti-cancer agents are required to be administered by parenteral route. However, poor water-solubility and high degree of toxic side effects limit their parenteral delivery. Most of the anti-cancer agents are formulated as a mixture of co-solvents and surfactants and suffer from common problems associated co-solvent based parenteral formulations as described earlier. Microemulsions would be an attractive alternative for delivery of cytotoxic agents. Amongst various cytotoxic agents, paclitaxel has received maximum attention by various research groups for the development of parenteral microemulsions.

Paclitaxel is a plant-derived anti-neoplastic agent that demonstrates impressive clinical activity against ovarian, breast, non-small cell lung carcinomas and AIDS-related Kaposi's sarcoma (Wall and Wani, 1996). Due to its limited aqueous solubility (10.8 g/ml) and high lipophilicity ($K_{O/W} = 311$) paclitaxel has very low oral bioavailability. Hence, it is administered as an intravenous (i.v.) infusion to patients as Taxol® (Trissel, 1997). Taxol® is a co-solvent based product that contains Cremophor® EL (polyoxyethylated castor oil) and ethanol. This formulation is chemically stable at room temperature for 27 days once diluted with IV fluids. However, precipitation of paclitaxel is evident after 3 days; hence in-line filters with IV sets were used (Vyas, 1995). Furthermore, adverse-effects associated with the Cremophore® EL severely limit the clinical utility of the product in several cases. The attempts have been directed to develop parenteral formulations with minimal or no Cremophore® EL content.

Parenteral paclitaxel microemulsion was first reported by He et al. (2003) which contained lecithin, ethanol, poloxamer 188 and a very small amount of Cremophore® EL as compared to that used in Taxol®. The microemulsion and Taxol® were evaluated

Table 2
Overview of parenteral micromeulsions and their *in vivo* advantages

| Drug | Composition | *In vivo* advantages | Reference |
|---|---|---|---|
| Paclitaxel | Lecithin, Poloxamer 188, Cremophore EL, Ethanol | Less hyersensitivity reaction, higher AUC value and prolonged circulation as compared to Taxol | He et al. (2003) |
| | Cremophore EL, Glycofurol, Labrafil 1944 CS, PLGA | Anti-tumor effects observed for prolonged time | Kang et al. (2004) |
| | Lecithin, Poloxamer 188, Ethanol, Tricaproin, Tributyrin | Higher AUC values and mean residence time as compared to Taxol | Zhang et al. (2006) |
| | Capmul MCM, Myvacet 9-45 Lecithin, Butanol | Higher AUC values and mean residence time as compared to Taxol | Nornoo et al. (2008) and Nornoo and Chow (2008) |
| Vincristine | PEGylated phospholipid, Vitamin E, Cholesterol, Oleic acid | Higher efficacy, survival rate and lesser side-effects as compared to free drug | Junping et al. (2003) |
| Norcanthridine | Ethyl oleate, lecithin, ethanol | Higher concentrations in liver and AUC values as compared to commercial formulations. The drug is used for liver metastases. Hence, higher liver concentrations would be useful | Zhang et al. (2005) |
| | Isopropyl myristate, lecithin, Tween 80 | Higher efficacy, survival rate and lesser nephrotoxicity as compared to Fungizone | Moreno et al. (2001) and Brime et al. (2003, 2004) |
| Amphotericin B | Solutol HS 15, Peceol, Myrj-52 | Higher $LD_{50}$ value as compared to Fungizone | Darole et al. (in press) |
| Itraconazole | POE-50-hydrogenated castor oil, benzyl alcohol, MCT, Ethanol | Higher AUC values as compared to the cyclodextrin based formulation | Rhee et al. (2007) |
| Flurbiprofen | PEGylated phospholipid, Ethanol, Ethyl oleate, lecithin | Prolonged circulation and higher AUC values as compared to the solution | Park et al. (1999) |
| Clonixic acid | Tween 85 and 20, castor oil | Less painful as compared to marketed formulation | Lee et al. (2002) |
| Ibuprofen eugenol ester | Solutol HS 15, ethanol, MCT | Prolonged circulation and higher AUC values as compared to the solution | Zhao et al. (2005) |
| Propofol | Solutol HS 15, Tween 80 | Less painful as compared to marketed emulsion of propofol (propovan) | Date and Nagarsenker (in press) |
| Artemether | Lecithin, labrasol, ethanol, Poloxamer 188, ethyl oleate | Significant improvement in anti-malarial activity as compared to the conventional oily solution | Tayade (2006) |
| Quercetin | Tween 20, clove oil | Significant improvement in anti-leishmanial activity as compared to the free drug | Gupta et al. (2005) |
| Bassic acid | Tween 20, clove oil | Significant improvement in anti-leishmanial activity as compared to the free drug | Lala et al. (2006) |

in rabbits for their potential to produce hypersensitivity reactions. Interestingly, paclitaxel microemulsion demonstrated significantly less hypersensitivity reactions as compared to Taxol® owing to their very low Cremophore® EL content. Furthermore, pharmacokinetic evaluation of paclitaxel microemulsion and Taxol® showed that AUC values for paclitaxel were significantly higher for microemulsion (34.98 $\mu g\,ml^{-1}\,h$) as compared to that of Taxol® (21.98 $\mu g\,ml^{-1}\,h$). This clearly demonstrates that the improvement in tolerability and efficacy of the therapeutic agent can easily be achieved by appropriate design of microemulsion systems.

Zhang et al. (2006) have successfully developed paclitaxel SMEDDS devoid of Cremophore® EL. The SMEDDS contained tributyrin, tricaproin, ethanol, lecithin and poloxamer 188. The SMEDDS formulation on dilution with saline yielded microemulsions with globule size as small as 16 nm. Comparative evaluation of the pharmacokinetic parameters of paclitaxel SMEDDS and Taxol® indicated that paclitaxel SMEDDS yielded significantly higher AUC values and longer circulation time than that of Taxol®.

Nornoo et al. (2008) and Nornoo and Chow (2008) have recently investigated the potential of Cremophor-free W/O microemulsions of paclitaxel. The authors also evaluated the potential of medium chain mono- and di-glycerides such as Capmul® MCM and Myvacet® in the development of parenteral microemulsions. The developed microemulsions were found to be safer as compared to Taxol® with respect to erythrocyte toxicity. The pharmacokinetic studies indicated that paclitaxel microemulsions exhibited 2- to 5-fold higher circulation time, and 3- to 8-fold wider tissue distribution as compared to that of Taxol®.

The feasibility of development of controlled release SMEDDS of paclitaxel has also been established by Kang et al. (2004). The paclitaxel SMEDDS were formulated by using Cremophore® ELP, glycofurol, Labrafil 1944 CS. The controlled release paclitaxel SMEDDS were developed by solubilizing biodegradable polymers such as Polylactide-co-glycolide (PLGA) in these systems with the help of glycofurol (a solvent for PLGA). It was hypothesized that the controlled release SMEDDS, after contact with body fluid, would form a microemulsion gel (due to presence of PLGA) containing paclitaxel in solubilized form and would release paclitaxel at a slower rate. Interestingly, the controlled release SMEDDS demonstrated sustained release of paclitaxel in dissolution studies and also sustained cytotoxic action in human breast cancer cell line MCF7 and SKOV-3 human ovarian cancer cell line as compared to that of PLGA free microemulsion preconcentrate. *In vivo* studies indicated that controlled release paclitaxel SMEDDS

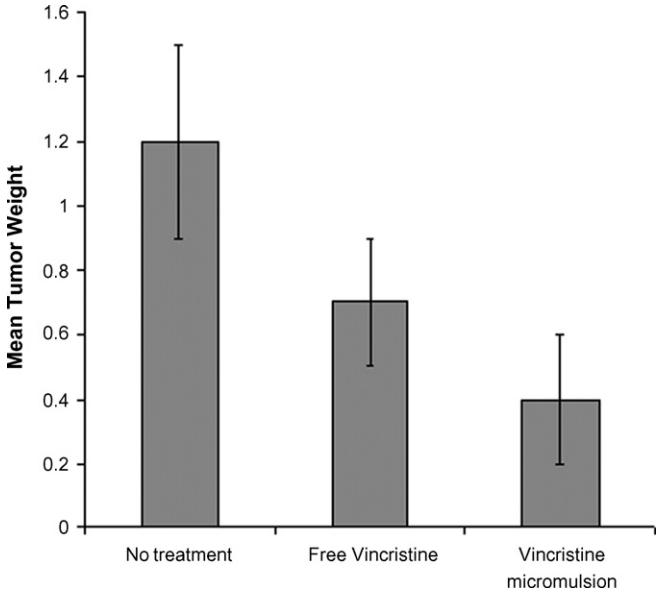


Fig. 1. Comparative anti-tumor efficacy of free vincristine and its microemulsion in M5076 solid tumor model in C57BL/6 mice (Junping et al., 2003). Vincristine microemulsion demonstrated higher efficacy than the free vincristine ($P < 0.05$).

were more effective than that of PLGA free microemulsion preconcentrates with respect to reduction in the tumor volume.

Vincristine is a hydrophobic cytotoxic alkaloid obtained from *Catharanthus roseus* and is employed in the treatment of leukaemia, Hodgkin's disease, non-Hodgkin's lymphomas and breast and lung cancer. Junping et al. (2003) formulated microemulsion of vincristine by using PEGylated phospholipids, vitamin E, cholesterol and oleic acid. The pharmacokinetic parameters of the microemulsion were compared with that of the free drug in the tumor bearing mice. The microemulsions resulted in significantly higher efficacy (Fig. 1), tolerability and survival rate as compared to that of free drug. Furthermore, the vincristine microemulsion group showed significantly lower vincristine concentrations in the heart, spleen and liver than that of the free drug indicating that microemulsions could reduce the incidences of adverse-effects. Concentrations of the vincristine in tumor were significantly higher in the case of microemulsions and so was the residence time of the vincristine in the body. This investigation clearly demonstrates the potential of microemulsions in improving the delivery of anti-cancer agents. From this investigation, it can be inferred that that the PEGylated phospholipid based microemulsions may serve as an alternative to long-circulating liposomes though comparative studies are required to be done.

Zhang et al. (2005) have reported the formulation of W/O microemulsion of norcanthridin, an anti-cancer agent employed in the treatment of hepatomas. The microemulsions contained lecithin, ethanol, ethyl oleate and exhibited droplet size less than 75 nm. The pharmacokinetics and body distribution of the norcanthridin after the parenteral administration of the microemulsion were evaluated and compared to that of the marketed formulation. The mean residence time, area under the curve (drug availability) and the liver concentrations of norcanthridin were significantly higher for the microemulsions as compared to that of the marketed formulation.

### 5.2. Delivery of anti-fungal agents

Increasing incidences of systemic fungal infections in immunocompromised patients has necessitated development of parenteral dosage forms of anti-fungal agents. Several approaches such as liposomes, mixed micelles, lipid complexes and cyclodextrin complexation have been employed for improving the parenteral delivery of anti-fungal agents such as amphotericin B, and itraconazole. The potential of microemulsions in parenteral delivery of anti-fungal agents has been established very recently.

Amphotericin B is an extremely potent anti-fungal agent used in the treatment of invasive fungal infections such as aspergillosis, systemic candidiasis and histoplasmosis. The oral delivery of amphotericin B is very difficult due to its negligible absorption through gastrointestinal tract which necessitates its parenteral delivery (Robbie et al., 1999). However, parenteral delivery of amphotericin B is associated with several disadvantages such as hemolysis and nephrotoxicity (Dupont, 2002). Currently, amphotericin B is commercially available as mixed micellar formulation, liposomes and lipid complexes (Dupont, 2002). Though liposomes and lipid complexes have succeeded in reducing the adverse-effects of amphotericin B, the enormous cost of these formulation restrict their clinical utility. On the contrary, mixed micellar formulation is cost-effective but cannot improve the tolerability of the amphotericin B.

Moreno et al. (2001), in a series of investigations, evaluated the impact of the microemulsions on the acute toxicity, efficacy and *in vivo* tolerability of amphotericin B. Biocompatible amphotericin B microemulsions based on polysorbate 80, lecithin and isopropyl myristate could successfully be formulated. The acute toxicity of amphotericin B micromeulsions was evaluated in comparison to the mixed micellar formulation (Fungizone®). Interestingly, the $LD_{50}$ value of amphotericin B microemulsion was 4-fold higher than that of the mixed micellar formulation (Moreno et al., 2001). This clearly indicates the advantage that may be derived from microemulsion structures. In another investigation, the authors evaluated the *in vivo* potential of the lecithin based amphotericin microemulsions in the immunocompetent and neutropenic mice infected with systemic candidiasis. Studies indicated that there was 3-fold increase in the tolerated dose of the amphotericin when it was administered as microemulsion as compared to that of marketed formulation. Furthermore, the microemulsions were superior to marketed formulation with respect to ability to reduce fungal load and mortality of the mice (Brime et al., 2004). Later on, the *in vivo* tolerability of amphotericin B microemulsions on repeated administration was evaluated with respect to nephrotoxicity and hemolysis. Microemulsions were very well tolerated at 3-fold higher doses as compared to mixed micellar formulation. There were no signs of renal lesions and hemolysis when amphotericin B microemulsions were administered at the dose of 3 mg/kg whereas mixed micellar formulation at the dose of 1 mg/kg showed considerable lesions (Brime et al., 2003).

Table 3
Hemolytic potential of Amphotericin B microemulsion and Fungizone® (Darole et al., in press)

| Concentration (μg/ml) | %Hemolysis of Amphotericin B microemulsion | %Hemolysis of Fungizone® |
|---|---|---|
| 5 | 0.139 ± 0.24 | 1.986 ± 3.44* |
| 10 | 0.139 ± 0.24 | 5.819 ± 1.43* |
| 15 | 3.957 ± 1.84 | 27.315 ± 1.09* |
| 20 | 5.692 ± 0.52 | 42.067 ± 2.8* |
| 25 | 7.832 ± 1.67 | 100* |

* $P < 0.05$; hemolysis caused by microemulsions is significantly lesser than that of the Fungizone®.

Recently, Darole (2005) and Darole et al. (in press) have reported the formulation of Amphotericin microemulsion based on different components such as Solutol® HS 15, Myrj® 52 and Peceol®. The microemulsions were significantly less hemolytic as compared to the Fungizone® (Table 3). The $LD_{50}$ value of the microemulsions was 2-fold higher than that of Fungizone®.

Itraconazole is a poorly water-soluble triazole anti-fungal agent indicated in the treatment of invasive fungal infections. The current parenteral product of itraconazole (Sporanox®) is based upon inclusion complex of itraconazole with hydroxylpropyl-β-cyclodextrin (HPBCD). However, for the solubilization of itraconazole, a considerably high amount of cyclodextrin has to be employed which leads to considerable increase in the product cost.

Rhee et al. (2007) successfully developed itraconazole microemulsions with the help of benzyl alcohol, MCT, ethanol and Cremophore® EL. The comparison of the pharmacokinetic parameters of the microemulsion with that of the Sporanox® and PEG solution revealed that the microemulsion was superior to the Sporanox® and was bioequivalent to the PEG solution. However, the microemulsion would be preferable than PEG solution if the pain on injection aspects are concerned although they were not evaluated by the investigators. The microemulsions were found to safe to the blood components.

### 5.3. Delivery of anti-inflammatory agents

Anti-inflammatory agents are often required to be administered by parenteral route in case of severe pain and in certain emergencies. A parenteral formulation yielding quick onset of action and longer duration would be desirable for optimal treatment. Park and Kim (1999), in two subsequent investigations, evaluated the potential of flurbiprofen microemulsions in parenteral delivery. In the first study, microemulsions based on Tween 20 and ethyl oleate were formulated and the effect of aqueous phases such as 5% dextrose, 0.9% saline, 2.5% glycerol and 5% sorbitol was evaluated. The pharmacokinetic studies in the rats indicated that the microemulsions were not different than the solutions with respect to the *in vivo* behavior. However, in the other study, they formulated lecithin based microemulsions with PEGylated phospholipid, ethanol and ethyl oleate. The pharmacokinetic studies indicated that the half-life, area under the curve (AUC) and mean residence time of flurbiprofen from microemulsions was considerably higher (1.5- to 2-fold) than that of the solution. Furthermore, the RES uptake of the flurbiprofen microemulsions was considerably lower than that of the solutions (Park et al., 1999). This indicates that PEGylated phospholipids based microemulsions can give prolonged circulation of the drugs resulting in prolonged therapeutic effect.

Lee et al. (2002) evaluated the potential of polysorbate and castor oil based microemulsion preconcentrates in the delivery of another anti-inflammatory agent, clonixic acid. The pharmacokinetics of clonixic acid microemulsion preconcentrates were no different than the marketed clonixic acid formulation based on the co-solvents. However, the microemulsions caused significantly less pain at injection site than the marketed formulation when evaluated by rat paw-lick test (Fig. 2). This clearly demonstrates the advantage of the microemulsions over co-solvent based formulations. Recently, Zhao et al. (2005) have fabricated ibuprofen eugenol ester loaded microemulsions based on Solutol HS 15, lecithin, ethanol and medium chain triglycerides. The pharmacokinetic parameters of ibuprofen from micromeulsion were compared to that of ibuprofen solution. Interestingly, the mean residence time (MRT) and half-life of ibuprofen from microemulsion were significantly higher (2- to 3-fold) than that of the solution indicating that micromeulsions may have prolonged effect.

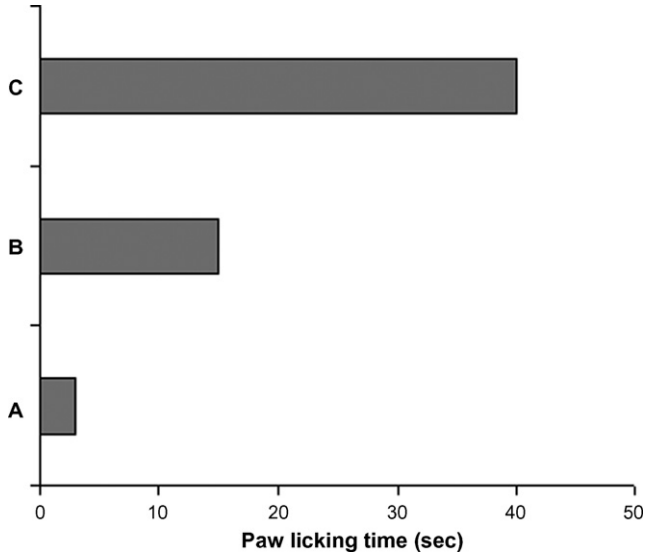


Fig. 2. Pain on injection of clonixic acid microemulsion and solution (rat paw-lick test; Lee et al., 2002). (A) Clonixic acid microemulsion diluted with saline, (B) clonixic acid solution diluted with saline and (C) clonixic acid solution diluted with co-solvents; microemulsion was significantly less painful as compared to the solution ($P < 0.05$).

### 5.4. Delivery of propofol

Propofol (2,6-diisopropylphenol) is a short-acting hypnotic agent which is administered by intravenous route during short surgical procedures and mechanical ventilation in the intensive care unit (White and Negus, 1991; McKeage and Perry, 2003). It offers various advantages such as favorable pharmacokinetic profile (rapid distribution and high metabolic clearance), rapid onset and recovery even after long periods of anesthesia and low incidence of post-operative nausea and vomiting (Langley and Heel, 1988; Bryson et al., 1995). In spite of such attractive clinical advantages, the successful development of injectable propofol formulation is very difficult due to its poor aqueous solubility (154 μg/ml) and high lipophilicity ($\log P = 3.8$; Babu and Godiwala, 2004). Currently, it is marketed as an oil-in-water emulsion (1%, w/v) that contains soybean oil, glycerol, and purified egg phosphatide (Diprivan®, Astra-Zeneca, USA, and the generic Propofol emulsion from Baxter International, USA; Han et al., 2001). However, these formulations lead to pain at the site of injection which strongly limits their clinical utility. Being a lipid-based emulsion, they also suffer from a number of limitations, such as poor physical stability, potential for embolism, and need for strictly aseptic handling, rapid growth of microorganisms (Bennett et al., 1995) and hyperlipidemia after long-term infusion due to presence of soybean oil (Bryson et al., 1995; Morey et al., 2006a). The formulation of microemulsions using propofol as an oily phase seemed to be a viable option as propofol exists as a liquid at room temperature. Furthermore, the excellent physical stability, self-preserving nature of micromeulsions and absence of the soybean oil in the microemulsion would be of great advantage.

Ryoo et al. (2005), first reported the formulation of propofol microemulsions using Solutol HS 15 and ethanol. However, Ryoo and coworkers mainly focused on the accelerated stability testing and *in vitro* hemolysis of the propofol microemulsions. The microemulsions could withstand the accelerated temperature conditions (40 °C/75% RH) and resulted in less than 1% hemolysis. We have recently have recently established the in vivo advantages of the Solutol based propofol microemulsions. We have fabricated three microemulsions using Solutol HS 15 as a surfactant and propylene glycol, glycofurol and polysorbate 80 as cosurfactants (Date, 2006; Date and Nagarsenker, in press). The microemulsions were found to be significantly less painful as compared to the currently marketed propofol emulsion, Propovan®, Bharat Serums Ltd., India (Table 4) and it was observed that microemulsions do not compromise the pharmacodynamic effects of propofol in rats (Table 5). Currently, Solutol HS 15 and glycofurol based microemulsion of propofol (Aquafol®) has been introduced in the market by Daewon Pharmaceutical Co. Ltd., Seoul, Korea. Kim et al. (2007), in a recent study, evaluated the pharmacodynamics of Aquafol in humans. It was observed that the Aquafol® does not alter the pharmacodynamics of propofol in comparison to the propofol emulsion Dirprivan®.

Table 4
Pain on injection of propofol microemulsion and emulsion (Rat paw-lick test; Date and Nagarsenker, in press)

| Formulation | Duration of paw-lick (s) mean ± S.D. |
|---|---|
| Propovan® | 24.918 ± 3.0 |
| Propofol microemulsion[a] | 13.738 ± 2.590[**] |

[a] Microemulsion used in the study contains Solutol HS 15 and polysorbate 80.
[**] $P < 0.05$; pain on injection caused by microemulsion is significantly lesser than that of the marketed emulsion (Propovan®).

Table 5
Anesthetic efficacy of propofol microemulsions and marketed emulsion (Date and Nagarsenker, in press)

| Formulation | Duration of LORR[*] (min) mean ± S.D. |
|---|---|
| Propovan® | 12.918 ± 2.699 |
| SHS-PG microemulsion | 15.358 ± 2.136 |
| SHS-GF microemulsion | 14.575 ± 2.038 |
| SHS-T80 microemulsion | 14.085 ± 1.9 |

SHS: Solutol HS 15, PG: propylene glycol, GF: glycofurol, T80: Polysorbate 80.
[*] LORR: Loss of righting reflexes which is a measure of anesthetic efficacy; statistical evaluation (ANOVA) indicates that microemulsions do not compromise anesthetic effect of propofol ($P > 0.05$).

Morey et al. (2006a,b) have been working on the microemulsions of propofol in a parallel manner. However, their propofol microemulsions are based on the poloxamer 188 and sodium caprylate. The microemulsions exhibited particle size less than 50 nm and were found to be very stable after 4 months of storage (Morey et al., 2006a). The *in vivo* efficacy of the microemulsions was tested in rats and dogs and microemulsions did not compromise the anesthetic effect of propofol. Hemodynamic studies carried out in the dogs indicated that the micromeulsions were safe to the blood components (Morey et al., 2006b). Authors, through these investigations, established the utility of sodium caprylate for the formulation of the parenteral microemulsions which was not reported so far. However, long-term studies are required to be carried out.

### 5.5. Miscellaneous examples

Artemether is a potent and rapidly acting anti-malarial agent available for the treatment of severe multiresistant malaria and is included in WHO List of Essential medicines (Pink et al., 2005). It is active against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* and is also indicated in the treatment of cerebral malaria. As described earlier, artemether is currently marketed as an oily solution for intramuscular administration. However, the therapeutic potential of artemether is considerably hampered due to its erratic absorption from parenteral oily solution (Hien et al., 2004).

The microemulsions would be an attractive approach for achieving quick onset of artemether on parenteral delivery. Considering this fact, Tayade and Nagarsenker (2004) fabricated artemether microemulsion based on lecithin, ethanol, poloxamer 188, Labrasol® and ethyl oleate. The efficacy of the microemulsion was evaluated in the *Plasmodium berghei* infected mice and was compared to that of the oily solution. The artemether microemulsion resulted in significant reduction in percent parasitemia on the days 8 and 12 (Fig. 3) as compared to that of oily

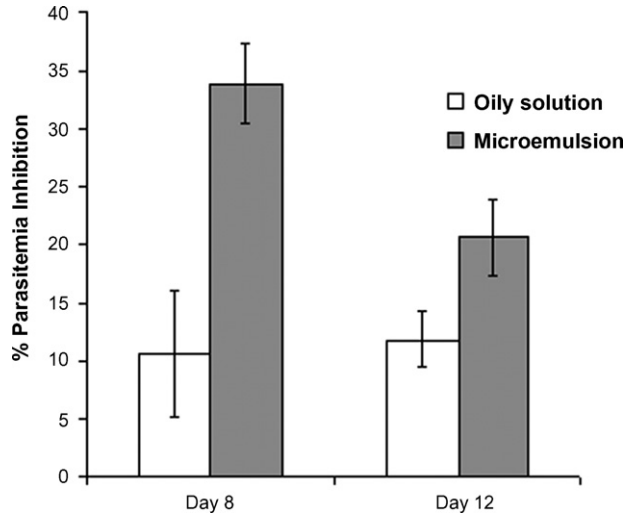


Fig. 3. Comparative efficacy evaluation of artemether oily solution and artemether microemulsion in *P. berghei* infected mice (Tayade, 2006). Microemulsion exhibits higher anti-malarial activity than the oily solution ($P < 0.05$).

solution (Tayade, 2006). Moreover, microemulsion resulted in higher number of survivals than that of oily solution.

Gupta and coworkers, in three consecutive investigations, have evaluated potential of clove oil based microemulsion formulations in the delivery of natural anti-leishmanial agents viz. quercetin, diospyrin and bassic acid (Gupta et al., 2005, 2006; Lala et al., 2006). Interestingly, they observed that microemulsions with size less than 50 nm can be easily formed with Tween 20, clove oil and water. The single dose (0.05 ml) acute toxicity study of this vehicle showed 100% survival rate in mice and no signs of hepatotoxicity were observed (Gupta et al., 2006). The efficacy of the quercetin loaded microemulsions was tested in comparison to the quercetin solubilized in dimethylsulfoxide (DMSO) in the hamsters infected with *Leishmania donovani* (Gupta et al., 2005). It was observed that the reduction of the parasite load in the mice was significantly more for the microemulsion formulations as compared to that of the free drug (Fig. 4). The similar results were obtained for the bassic acid micromeulsions (Lala et al., 2006). These observations are indeed interesting but the long-term safety of this formulation is questionable because there are no reports on the use of clove oil in the parenteral formulations. Furthermore, the formulations were injected intra-peritonially and not by intravenous route which is a usual clinical practice.

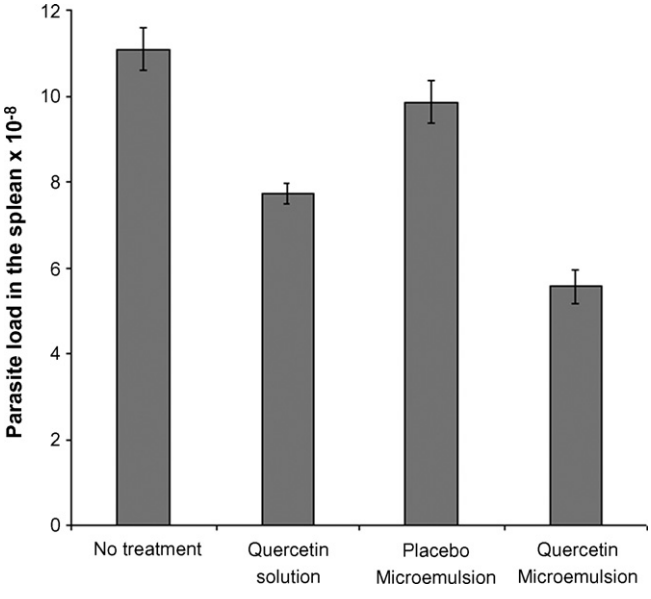


Fig. 4. Comparative efficacy of quercetin solution and its microemulsion in hamsters infected with *Leishmania donovani* (Gupta et al., 2005). Quercetin solution was prepared in dimethylsulfoxide; Microemulsion is more active than the free quercetin ($P < 0.05$).

## 6. Conclusion

Microemulsions have demonstrated potential as a commercially feasible and novel vehicle for parenteral delivery hydrophobic drugs. With the appropriate selection of the excipients, it is also possible to design a parenteral microemulsion with desired characteristics such as sustained release and prolonged blood circulation. The utility of cosurfactants such as sodium caprylate and oily phase such as medium chain mono- and diglycerides have recently been explored for the formulation of parenteral microemulsions. The long-term safety evaluation of such a novel excipients needs to be undertaken to widen the scope of the parenteral microemulsions.

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