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Solid Lipid Nanoparticles as Drug Delivery System for Water-Insoluble Drugs

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ABSTRACT – Solid lipid nanoparticles (SLNs) have emerged to combine the advantages of polymeric nanoparticles and lipid emulsions in early 1990s. SLNs can present several desirable properties derived from the solid state core. When formulating SLNs, there should be careful considerations about the physical state of the inner solid lipid core and its polymorphism and supercooling behavior. In this review, SLNs were compared to lipid emulsion and emulsion of supercooled melt to understand the unusual behaviors compared to lipid emulsions and to have insights into stability and release mechanism. SLNs have been regarded as biocompatible system because lipids are usually well-tolerable ingredients than polymers. Several studies showed good tolerability of SLNs in terms of cytotoxicity and hemolysis. Similar to various other nanoparticulate drug delivery systems, SLNs can also change biodistribution of the incorporated drugs in a way to enhance therapeutic effect. Most of all, large scale production of SLNs was extablished wihtout using organic solvents. Although there is no SLN product in the market till date, several advantagious properties of SLNs and the progress we have seen so far would make commercial product of SLNs possible before long and encourage research community to apply SLN-based formulations for water-insoluble drugs.

Key words – water-insoluble drug, solid lipid nanoparticles, parenteral delivery

Water-insoluble drugs have often resulted in low bioavailability when given orally due to the poor dissolution behavior, or have caused difficulties in the development of formulation into pharmaceutically acceptable vehicles (Chen et al., 2010). Various strategies to solubilize water-insoluble drugs have been tried, which include using cosolvent (Malick et al, 2007) or surfactants (Strickley, 2004), solid dispersion (Janssens and Van den Mooter, 2009), inclusion complex (Van de Manakker et al., 2009), salt formation (Elder et al., 2010) or colloidal systems such as microemulsion (He et al., 2010), micelles (Trivedi et al., 2010), polymeric nano-/micro-particles (Kumari et. al, 2009), liposomes (Cukierman and Khan, 2010), emulsions (Mirtallo et al., 2010) and solid lipid nanoparticles (SLNs) (Souto and Müller, 2010). Especially, colloidal systems have drawn attentions because they could be applied not only for solubilization of poorly-water soluble drugs, but also for the controlled delivery of the incorporated drugs.

Among various colloidal systems, polymeric nanoparticles, lipid emulsions and liposomes have been studied for a long period for the parenteral delivery of poorly water soluble drugs and for targeting and have paved the way for the development of more improved particulate systems to adopt their advantages and overcome their limitations which are described as follows. The solid matrix of polymeric nano- and micro-particles allows drug release over a few days. Disadvantages are; the relatively slow degradation of up to 4 weeks (Ogawa, 1988) which might possibly cause systemic toxic effects by impairment of the reticuloendothelial system (RES); cytotoxic effects observed *in vitro* after phagocytosis of polylactide (PLA) and polylactide/glycolide (PLA/GA) particles by macrophages (Smith and Hunneyball, 1986) and human granulocytes (Müller et al., 1993); toxic residues from the production (e.g., organic solvents when using solvent evaporation); the lack of production method on large industrial scale; incapability of autoclave. Sterilization needs to be performed by gamma irradiation possibly leading to the formation of radicals and subsequently toxic reaction products. Contrary to polymeric particulate systems, the degradation of liposomes is fast but there are still problems with the production as indicated by the small number of liposomal drug formulations on the market (e.g., drug incorporation, physical and chemical stability, partial lack of large-scale production methods). Lipid emulsions have been on the market for more than 65 years since World War II. They are used in large volumes in parenteral nutrition and proved to be non-toxic (e.g., Intralipid®, Lipofundin®). Large-scale production methods are available. How-

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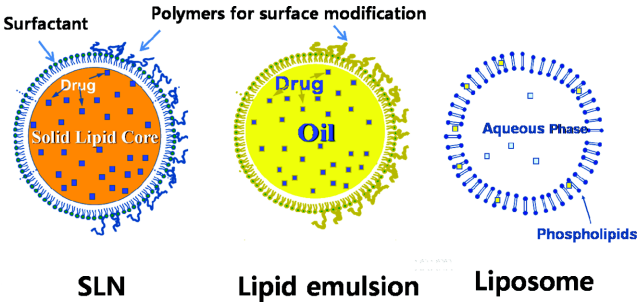

Figure 1. Schematic representation of SLN, liposome and lipid emulsion.

Table I. *Potential advantages derived from the solid properties*

No particle coalescence
Improved physical stability
Reduced drug leakage
Avoidance of drug protruding into emulsifier film
Sustained/controlled drug release
Facilitated surface modification

ever, the release of most drug from fat emulsions is very fast (minutes) due to the distribution of the drug between oil droplets and the large volume of the blood. In early 1990s, a new idea was emerged; production of particles from solid lipids can combine the advantages of polymeric nanoparticles and fat emulsions (Müller and Runge, 1998). Particles from solid lipid possess a solid matrix allowing controlled drug release. The *in vivo* degradation of lipids is faster than that of PLA or PLA/GA particles and little or non-toxic effects are expected when using physiological lipids.

SLNs represent colloidal dispersions of non-polar lipids such as triglycerides (Lucks et al., 1992; Siekmann and Westesen, 1992) (Figure 1). The idea behind the use of solid lipids is to combine the superiorities of colloidal lipid carriers with the advantages of the solid physical state of polymeric nanoparticles. Lipid carriers are biodegradable, biocompatable and can be easily manufactured. Polymeric nanoparticles have the advantages with respect to size stability, drug leakage and sustained drug release due to their solid state. In the solid lipid matrix, the mobility of incorporated drugs is drastically reduced. A number of advantages can be theoretically deduced from the solid state of the dispersed lipid phase compared to the liquid state of lipid emulsions: no particle coalescence and improved stability due to solid core material (Table I). Owing to these potential advantages, SLNs have drawn attention as an alternative colloidal drug carrier system.

Table II. *Typical compositions of lipid emulsions*

Compound	Typical concentration (wt, %)
Oil (e.g. soya, safflower, MCT)	10-30 %
Phospholipids (egg + soya lecithin)	0.6-1.5 %
Isotonicity agent (glycerol, xylitol)	2.2-2.5 %
NaOH to adjust pH	q.s.
Water for injection	To 100 %

Comparison of SLNs and Lipid Emulsions

Lipid emulsions used in parenteral nutrition and drug delivery are composed of vegetable oils that are emulsified in an aqueous phase using fractionated egg or soya lecithins as emulsifying agents. Typical compositions are given in Table II. These emulsions are usually produced by high pressure homogenization, and they consist of submicron-sized oil droplets surrounded by a phospholipid monolayer. Lipid emulsions have been used as a calorie source in parenteral nutrition for decades. They are manufactured in large scale, and display an acceptable long-term stability. Lipid emulsions of this type have also been extensively investigated as drug carrier system (Collins-Gold et al., 1990; Prankerd and Stella, 1990). Incorporation of drugs might, however, result in a reduced stability of the product owing to perturbations of the stabilizing emulsifier film by drug cystals or diffusing drug molecules which have a high mobility in the liquid oil phase. These perturbations may induce instabilities of either mechanical nature due to reduction of film elasticity and film rupture, or electrochemical nature thus influencing the zeta potential. These unwanted effects may cause coalescence, particle growth and drug leakage. The high mobility of incorporated drug molecules also leads to a fast release of drug from the carrier in biological fluids so that it is hardly possible to achieve sustained release by an emulsion formulation (Magenheim et al., 1993).

Suspensions of solid lipid nanoparticles have recently been suggested as an alternative drug delivery system that may circumvent the problems associated with lipid emulsions. Due to the solid core the particles cannot coalesce, and may therefore exhibit a better physical stability than liquid droplets. The mobility of incorporated drug molecules is drastically reduced in a solid phase. Therefore, drug leakage from the carrier and drug protrusion into the emulsifier film would be counteracted. Whereas drug release from an emulsion is a diffusion-controlled process that generally resultes in fast release from the carrier upon injection into the blood, drug release from solid particulate is matrix-dependent, and the degradation rate of the matrix lipids is assumed to determine drug release. It is there-

fore possible to control drug release from a solid lipid carrier to a certain extent by the choice of matrix constituents with different biological degradation rates. The presence of static interface might facilitate a surface modification of the carrier particles after solidification of the lipid matrix, e.g. by subsequent adsorption of nonionic surfactants. The latter might be of relevance to reduce carrier uptake by the reticuloendothelial system (RES) which is related to surface properties (Siekmann and Westesen, 1998). During the preparation of submicron solid lipid suspensions by melt homogenization, an emulsion of the lipid melt in the aqueous phase is intermediately created before the lipid droplets solidify to form SLNs. It is thus not surprising that emulsions of lipid melts behave physicochemically similar to the vegetable oil emulsions used in parenteral nutrition and drug delivery. However, it has been observed that the preparation of lecithin stabilized triglyceride suspensions with a composition similar to fat emulsions results in the formation of semisolid, ointment-like gels (Siekmann and Westesen, 1992). The gel formation can be avoided by the addition of co-surfactants. Many researchers have pointed out basic physicochemical differences between similarly composed lipid emulsions and lipid suspensions (Siekmann and Westesen, 1992). It is more difficult to obtain a stable SLNs than lipid emulsions and needs more extensive considerations on stabilizer, manufacturing process including shearing force and temperature, storage conditions and crystallinity of the solid lipids.

SLNs Versus Emulsions of Supercooled Melts

Although solid-lipid based carrier systems are produced from crystalline raw materials, it has to be considered that crystallization from the dispersed lipid melt might be different from that of the bulk phase. It may be due to the high dispersity, the small particle size, and the presence of emulsifying agents and drugs as well as the high surface-to-volume ratio. This may lead to differences in the crystallization behavior, the degree of cystallinity, and the polymorphism of the nanoparticulate lipids compared to the bulk materials. Indeed, thermoanalytical investigations of glycerides indicate that polymorphic transitions proceed faster in the dispersed state than in the bulk (Siekmann and Westesen, 1994). Moreover, it has been observed that the melting temperature and the recrystallization temperature of dispersed triglycerides are decreased compared with those of the bulk material (Siekmann and Westesen, 1994; Westesen and Bunjes, 1995; Bunjes et al., 1996). Thus, recrystallization of dispersed triglycerides requires significantly higher supercooling than that of the bulk. As a result of higher supercooling required for nucleation, recrystallization of melt-homogenized triglycerides may be considerably retarded or even prevented at a given temperature. Westesen and Bunjes (1995) found that nanoparticles prepared from triglycerides solid at RT did not necessarily recrystallize on cooling to common storage temperatures. Thus, melt-homogenized dispersions of trilaurin remain in the state of a supercooled emulsion at 4ºC over several months. A similar effect has also been observed for melt-homogenized dispersions of the lipophilic bioactive substance ubidecarenone (Siekmann and Westesen, 1995).

The physical state of the particles is very important from the technological as well as from the biopharmaceutical point of view. Stability problems that are related to the recrystallization process of the particles, e.g., the formation of gel-like systems (Westesen and Siekman, 1997) or significant particle growth due to inadequate stabilizer properties, do not occur in dispersions of supercooled melts which behave essentially as emulsions. Although the drug incorporation capacity of amorphous, liquid droplets might be higher than that of the crystal lattice of solidified particles, the supercooled state of the droplets is not thermodynamically stable. Though considerable kinetic stability was observed for the dispersions of supercooled melts, gradual recrystallization upon long-term storage cannot be excluded. In addition to stability, mechanisms of drug release are different between emulsions and solid lipid nanoparticles. Drug release from solid matrix is supposed to be degradation controlled and thus is slower than diffusion-controlled release from emulsions. It have been emphasized, therefore, the necessity of a comprehensive physicochemical characterization of colloidal drug carrier systems.

Preparation

Compositions

SLNs usually consisted of solid core and stabilizers similar to lipid emulsion. Saturated monoacid triglycerides, saturated fatty acids and hard fats were investigated as solid core as shown in Table III. Usually, SLN can be stabilized using phopholipids, nonionic surfactants such as poloxamer, Tweens, bile salts and so on.

Manufacturing methods

SLNs can be produced by spray drying, melt homogenization, cooling down of hot microemulsions or solvent evaporation.

Lipid micropellets were prepared from glycerides and phospholipids to improve the intestinal absorption of lipophilic

Table III. *Solid lipids used as core of SLNs*

Solid lipids
Saturated monoacid triglyceride
Tricaprin (m.p. 31ºC)
Trilaurin (Dynasan 112, m.p. 46ºC)
Trimyristin (Dynasan 114, m.p. 56ºC)
Tripalmitin (Dynasan 116, m.p. 64ºC)
Tristearin (Dynasan 118, m.p. 73ºC)
Glycerol behenate (Compritol® ATO 888; m.p. 72ºC)
Di- and tri- glycerides
Monostearate monocitrate diglyceride (Acidan N12; m.p.)
Propyleneglycol palmito-stearate (Monosteol; m.p. 33-36ºC)
Polyoxyethyleneglycol 300 mono, distearate (Superpolystate; m.p. 32-36ºC)
Saturated fatty acids
Stearic acid
Behenic acid
Hard fats
Witepsol W35
Witepsol E85 (m.p. 44.4ºC)
Softisan 142 (m.p. 45.9ºC)
Others
Cholesteryl acetate

drug (Eldem et al., 1991). But, the spray-dried micropellets were too large for i.v. application. Lipid nanopellets prepared by sonication of melted lipids are described for peroral application only (Speiser, 1990). Sonication cannot efficiently reduce the number of large particles to be within the specification for i.v. injectables, e.g., particulate matter (USP).

Production of SLN by high pressure homogenization yielded particle dispersions suitable for i.v. injection (Schwatrz et al., 1994). There are two basic homogenization techniques of homogenization for SLN, homogenization of melted lipids at elevated temperature (hot homogenization technique) and homogenization of a suspension of solid lipids at room temperature or below (cold homogenization technique) (Müller and Runge, 1998). In hot homogenization technique, the lipid matrix material is melted and drug can be incorporated by dissolving in the melted lipid. Alternatively, insoluble drugs can be dispersed in the melted lipid in the form of nanocrystals. In the next production step the drug-containing lipid is dispersed in its molten state in a hot aqueous surfactant solution possessing a temperature slightly above the melting point of the lipid. Dispersion is performed using a rotor-stator stirrer. The obtained coarse pre-emulsion is then homogenized using high

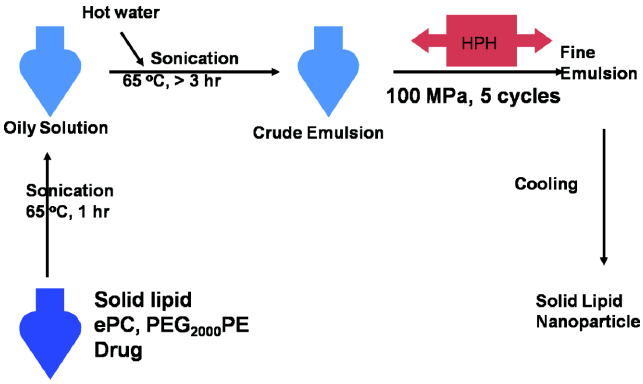

Figure 2. A representative lab-scale manufacturing process of SLNs by hot melt homogenization using trimyristin as core solid lipid.

pressure homogenizer. The obtained product is an oil-in-water emulsion. Cooling down of this emulsion to room temperature (or below) would lead to lipid recrystallization and formation of the SLNs. We applied rapid cooling by dipping into liquid nitrogen followed by thawing in water bath to make sure solidification of the core lipid as shown in Figure 2. The hot homogenization technique can be applied to lipophilic and insoluble drugs. Even many heat-sensitive drugs can be processed because time to higher temperature is relatively short. The technique is not suitable for incorporating hydrophilic drugs into SLN. During the homogenization of the melted lipid phase the drug partitions to the water phase resulting in very low entrapment efficiency.

For a hydrophilic drug the cold homogenization technique is the method of first choice. The hydrophilic drug is dissolved in the melted lipid. In case of a extremely low solubility of the hydrophilic drug in the lipid, surfactants can be used for solubilization of the drug. In the next production drug, the drug-containing melted lipid is solidified in dry ice or liquid nitrogen and milled using e.g., a mortar mill. Dry ice or liquid nitrogen is used to increase the brittleness of the lipid and to ease the milling procedure. The obtained lipid microparticles (approximately 50 to 100 μm) are dispersed in a cold aqueous surfactant solution and this lipid suspension is homogenized at room temperature or below. The cavitation and shear forces in the homogenization gap are sufficiently high to break the microparticulates and to yield SLNs. This homogenization technique avoids or minimizes melting processes of the lipid. Temperature peaks occurring inside the homogenizer during the homogenization process obviously do not possess a sufficiently high energy to melt the lipid. In case of an inlet temperature of about 20ºC, the outlet temperature of the product is typically about 40ºC. The oulet temperature can be reduced by cooling the homogenization tower. SLN produced by the cold

homogenization technique possesses a slightly higher polydispersity in size distribution than particles obtained by hot homogenization and the mean particle size is only slightly higher than that by hot processing the same lipid at identical homogenization parameters (pressure, temperature, number of homogenization cycles). To further reduce the mean particle size and to minimize the polydispersity, a high number of homogenization cycles can be applied. Alternatively, the homogenization can be performed slightly below the melting point of the lipid (e.g. 5 to 10ºC) which seems to lead to a softening of the lipid during the homogenization process. The softened lipid can be more easily dispersed resulting in a more uniform product of small mean particle size. The homogenization temperature needs to be carefully selected because otherwise the loss of hydrophilic drugs to the water phase is too high (Müller and Runge, 1998).

Sjöström prepared SLN by solvent evaporation method (Sjöström et al. 1993) as follows. The solid core is dissolved in organic solvent. The organic solvent is added to water. The surfactants are dissolved in the water and/or the organic solvent. The o/w mixture is emulsified to an o/w emulsion. Emulsification (homogenization) is accomplished by treatment in a colloid mill followed by high pressure homogenization with cooling by an iced water bath. The organic solvent in the emulsions is removed at room temperature by evaporation in a rotary evaporator at reduced pressure to form particles in an aqueous suspension.

Another method for preparation of SLN is dispersing warm o/w microemulsions in cold water under stirring (Cavalli et al., 1996). The internal phase of the microemulsions is composed of lipophilic substances with low melting points. In this method, a droplet structure is already present in the warm microemulsion system. Thus no energy is required for the formation of the nanoparticles. Rapid cooling in a cold aqueous medium is sufficient to obtain a dispersion of the SLN.

Melt homogenization technique is mostly preferred in many SLN research groups due to resulting homogeneous particle size and capability of large-scale production. Recently, industrial scale production by high pressure homogenization was reported and long term stability over 1 yr was monitored comparing with lab scale and medium scale production (Shegokar et al., 2010). They used APV Micron LAB 40, a piston-gap homogenizer (APV Systems, Unna, Germany) for lab scale production, a modified version of Micron LAB 60 for medium-scale batch (10 kg) production, and APV Gaulin 5.5 which has three pistons and two homogenization valves, or Avestin C50 (Avestin Inc., Ottawa, Canada) for large-scale production.

In vitro and *in vivo* Toxicity

For parenteral, especially intravenous administration, it will be necessary to perform a toxicity study despite the fact that the lipids are composed of physiological compounds. As an *in vitro* test system, the human granulocytes and human promyelotic cell line HL60 were employed (Müller et al., 1997). HL60 cells were differentiated *in vitro* having characteristics of mature granulocytes by treatment with retinoic acid. The SLNs (trimyristin and glycerol behenate SLN) showed a lower cytotoxicity than polyalkylcyanoacrylate and polylactic/glycolic acid (PLA/GA) nanoparticles. The nature of the lipids, differing in degradation velocity, had no effect on viability.

For the first assessment of *in vivo* toxicity, SLNs were injected into mice (Müller and Runge, 1998). Multiple high dosed bolus injections were administered into the tail vein every 2 days (3 times, 1.33 g lipid/kg body weight). The lipid matrices injected were cetylpalmitae and Compritol®. The injections were well tolerated without any signs of acute toxicity. By the end of the injection period, the animals were sacrificed, the organs weighed and histologically examined. Little change was found for the high dosed cetylpalmitate-SLN. A distinct increase in liver and spleen weight including infiltration of macrophages and the presence of fat was observed with the high dosed Compritol nanoparticles. However, the changes proved to be reversible. This could be explained by the slower *in vivo* degradation of Compritol-SLN compared to cetylpalmitate-SLN. The metabolizing capacity of the body was just not sufficient to cope with the administered high dose of lipid. It should be pointed out, that the injected dose would be equivalent to a bolus injection of 100 g pure lipid in man (75 kg body weight). Reduction in the dose of Compritol SLN administered to the mice could avoid these side effects.

There have been considerations on erythrocyte hemolysis by SLNs because SLNs showed distinct affinity to red blood cells depending on the surfactant used. According to a recent study, percentage of hemolysis was less than 5% in all nanoparticles tested such as SLNs made of Precirol or Compritol, NLC (nanostructured lipid carriers) made of a mixture of Precirol and squalene, and lipid emulsion of squalene (Huang et al., 2008). Although all the nanoparticles showed good tolerability in hemolysis assay, the percentage of hemolysis was higher in nanoparticles made of Precirol than those of Compritol SLNs suggesting cellular binding is dependent on the composition of inner phase.

From the *in vitro* cytotoxicity and *in vivo* toxicity reported, the SLN appears to be a very well tolerated drug carrier system. They seem to be even better tolerated than nanoparticles

produced from accepted polymers.

Biodistribution

SLNs have been applied to many drugs including water-insoluble agents such as many anticancer drugs and some NSAIDs as well as water-soluble peptides such as insulin and others as shown in Table IV. Most biodistribution studies of SLN formulations were performed for anticancer agents and all the studies reviewed here demonstrated significant alterations in drug distribution when delivered using SLNs.

Comptothecin SLN, consisted of camptothecin(0.1%), stearic acid(2%), soybean lecithin (1.5%) and poloxamer 188 (0.5%), was highly taken up by brain, heart and reticuloendothelial systems in mice (Yang et al., 1999). The mean residence time of Camptothecin SLN increased about 18 times in plasma compared with the same doses of camptothecin solution, which may be due to the coating of the surface of SLN with poloxamer 188 and the sustained release of camptothecin from SLN.

The pharmacokinetics of doxorubicin incorporated as ion-pair into SLNs was compared with that of the commercial solution of the drug, Adriablatina®, in rats (Zara *et al*., 1999). The anthracycline concentration in the blood was markedly higher at each time point with the SLN than with the commercial solution. The drug concentration was also higher in the lung, spleen and brain. SLN-treated rats showed a lower doxorubicin concentration in liver, heart and kidney. This could be related to a slow drug release from SLN to the blood or to the targeted organs. The high lipophilicity of SLN could account for the unusual presence of doxorubicin in the brain that does not occur with the commercial doxorubicin solution. The lower uptake into liver, reticuloendothelial system, may be due to the small particle size (<100 nm).

Paclitaxel was also formulated into pegylated SLNs and the biodistribution was compared with the commercially available micellar formulation, Taxol, in rats. (Lee et al, 2007; Li et al., 2010). Paclitaxel in pegylated SLNs showed plasma disposition profile similar to that in Taxol and significantly higher uptake into liver and spleen compared to that in Taxol (Li et al., 2010).

Several studies reported the increased AUC (Zara et al., 2002; Reddy et al, 2005; Yang et al, 1999), enhanced uptake into brain (Zara et al., 2002; Reddy et al, 2005; Fundaro et al., 2000), tumor (Reddy et al, 2005), liver (Reddy et al, 2005; Yang et al., 1999), lung (Reddy et al, 2005; Yang et al., 1999), spleen (Reddy et al, 2005; Yang et al., 1999), kidney (Reddy et al, 2005; Yang et al., 1999). However, these studies also showed that SLNs delivered reduced amount of drugs into

Table IV. *Drugs incorporated into solid lipid nanoparticles*

Drug	Reference
10-hydroxycamptothecin	Liu, 2008; Zhang, 2008
5-FU	Yu, 2000
actarit	Ye, 2008
all trans retinoic acid	Lim 2004
arthemeter	Joshi, 2008
bromocriptine	Esposito, 2008
buprenorphine	Wang, 2009
calcitonin	Martins, 2009
camptothecin	Huang, 2008; Yang 1999, Yang 2002
carvedilol	Faisal, 2008; Sanjula 2009
chlorambucil	Sharma, 2009
cholesteryl butyrate	Brioschi, 2007, 2008; Serpe, 2004; Pellizaro, 1999
ciprofloxacine	Jain, 2008
cisplatin	Tian, 2008
cyclosporin A	Müller, 2008; Ugazio, 2002
diazepam	Abdelbary, 2009
docetaxel	Xu, 2009
doxorubicin	Serpe, 2006; Ying, 2008; Wong, 2004, 2006a, 2006b; Cavalli, 1993, 2000
etoposide	Reddy, 2005
ferrulic acid	Bondi, 2009
flavones	Wang, 2007
FudR(derivative of 5-FU)	Wang, 2002
floxuridinyl diacetate	Lian, 2008
flurbiprofen	Bhaskar, 2009; Han, 2008
ibuprofen	Casadei, 2006; Paolicelli, 2008
idarubicin	Cavalli, 1993; Zara, 2002
insulin	Battaglia, 2007; Bi, 2009; Gallarate, 2008; Liu 2008,a,d,; Sarmento, 2007
magnetite	Hsu, 2008
methotrexate	Paliwal, 2008; Ruckmani, 2006
mitoxanthrone	Lu, 2006
nimesulide	Bondi, 2009
nitrendipine	Bhaskar, 2009b; Kumar, 2007; Manjunath, 2006
olanzapine	Vivek, 2007
oridonin	Zhang, 2005
oxymatrine	Sun, 2007
paclitaxel	Dong, 2008; Lee, 2007; Yuan, 2008; Cavali, 2000; Stevens, 2004; Serpe, 2004; Chen, 2001
pranziquantel	Yang, 2009
quercetin	Li, 2009
saponins	de Ven, 2009
saquinavir	Kuo, 2009; Kuo, 2007
silibin	Zhang, 2007
SN-38 (irinotecan analog)	Williams, 2003
tamoxifen	Fontana, 2005; Reddy, 2006
tashione II A	Liu, 2005
tobramycin	Bargoni, 2001
vinorelbine bitartrate	Wan, 2008

heart, lung, spleen, liver and kidney (Zara et al, 2000; Fundaro et al, 2000; Yang, et al, 1999), which suggest that biodistribution of drugs in SLNs can vary depending on the composition of SLNs.

Conclusion

The emergence of SLNs has led to development of carriers for water-insoluble drugs and showed potentials for parenteral and oral delivery to enhance bioavailability. There should be careful considerations on the physical state and polymorphism of inner phase of SLNs. The parenteral acceptance of the lipids and other particle stabilizers can be a hurdle in their successful commercilization and more extensive *in vivo* safety studies should be performed. Although biodistribution of SLNs are quite similar to that of other particulate carriers, composition of inner core and stabilizers play a major role in addition to particle size, surface charge, surface modification and physicochemical properties of drugs. Most of all, it is very attractive carriers because large-scale produciton has been successfully established. Although there is no SLN product in the market till date, several advantagious properties of SLNs and the progress we have seen so far would make commercial product of SLNs possible before long.

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