

Chapter 2

Composition and Structure

Abstract Lipid nanoparticles, including solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), lipid-drug conjugates (LDC) and polymer-lipid hybrid nanoparticles (PLN), are colloidal carriers with a lipid matrix that is solid at body temperature. These colloidal carriers have attracted increasing interest for their use in therapeutic and cosmetic applications. The performance of lipid nanoparticle formulations is greatly influenced by their composition and structure. Lipid nanoparticles are generally composed of lipids, surfactants and co-surfactants. The lipid materials used in the production of lipid nanoparticles are usually solid at room temperature. Being well-tolerated in physiological conditions, lipid nanoparticles are typically biocompatible. Liquid lipids, or oils, are specifically used for production of NLCs. In most cases, lipid nanoparticles are produced as dispersions and surface-tailored with surfactants to improve dispersion stability. Polymers are often used to form polymer-lipid cores in the production of PLNs. Lipid nanoparticles are often used as sustained-release systems, with the structure of the lipid nanoparticles dictating their release properties. While the concentration of drug in lipid nanoparticle dispersions is quite well known, knowledge of the drug-lipid interaction in terms of the state and localization of the drug in the nanoparticle is still unknown. Several structural models of SLNs and NLCs have been proposed. The composition and structure of lipid nanoparticles—two critical factors that may influence their pharmaceutical performance—will be discussed in this chapter.

Keywords Composition • Lipids • Surfactants • Localization • Structure

2.1 Composition of Lipid Nanoparticles

SLNs are typically composed of solid lipid(s), surfactant(s), co-surfactant (optional) and active ingredients (typically drugs). The lipids used in the production of lipid nanoparticles are physiological lipids. Based on their structural

diversity, lipids used in the production are broadly categorized into fatty acids, fatty esters, fatty alcohols, triglycerides or partial glycerides. A few researchers have also reported the use of waxes in the preparation of lipid nanoparticles (Jenning and Gohla 2000). Lipid nanoparticles are surface-tailored with surfactants, which stabilize the colloidal system. They are sometimes used in combination with a co-surfactant, if necessary.

2.1.1 Lipids

The lipid, itself, is the main ingredient of lipid nanoparticles that influence their drug loading capacity, their stability and the sustained release behavior of the formulations. Lipid nanoparticle dispersions based on a variety of lipid materials including fatty acids, glycerides and waxes have been investigated (Blasi et al. 2013a, b; Doktorovova et al. 2014; Durán-Lobato et al. 2013; Dwivedi et al. 2014; Finke et al. 2012; Manjunath et al. 2011; Prombutara et al. 2012; Silva et al. 2011; Wang et al. 2012). Most of these lipids, with the notable exception of cetyl palmitate, are approved as generally-recognised-as-safe (GRAS) and are physiologically well-tolerated.

Selection of appropriate lipids is essential prior to their use in preparation of lipid nanoparticle dispersions. Although there are no specific guidelines, empirical values, such as the solubility of drug in the lipid have been proposed as suitable criteria for selection of an appropriate lipid (Bummer 2004). The solubility of the drug in lipid matrices is critical because it invariably influences the drug encapsulation efficiency and loading capacities, and subsequently the usefulness of the lipid nanoparticles in drug delivery (Kasongo et al. 2011). The solubility of drug can be easily quantified using UV-Visible spectroscopy or chromatographic techniques (Joshi et al. 2008; Joshi and Patravale 2008; Liu et al. 2012). The partitioning of drug between the lipid/oil and aqueous phases can also be predicted using mathematical equations. Such predictions are based on drug-lipid and drug-water interactions. Lipid nanoparticles with high drug loading can be prepared if the drug has high solubility in lipid or a high partition coefficient. Since the drug has different solubility in different lipid matrices, its apparent partition coefficients in those lipids also differ. This consequently leads to different loading capacities in different lipid matrices for the same drug. The complexity thus makes predictive models difficult; however they remain very useful as screening and prediction tools.

Lipid polymorphism is another factor that influences the properties of a lipid nanoparticle system. The occurrence of multiple crystalline forms in solid lipids is particularly useful as they provide structural defects in which drug molecules can be accommodated. The perfect crystalline lattice, however, is more thermodynamically stable than the others. For example, the β -forms of triglycerides are more stable than the α -forms and β' -forms (Chapman 1962). Thermodynamically less stable or metastable forms eventually tend to transform to a more stable form. Such transitions pose a significant challenge in development of SLNs since drug molecules are accommodated in the crystal defects of the solid lipids. Their

disappearance with time thus creates an obvious issue to drug loading. This results in drug expulsion during storage or burst release after administration. Another factor that influences the selection of an appropriate lipid is thus its tendency to form perfect crystalline lattice structures or, at least, the rate at which metastable-to-stable transitions take place. No definitive guidelines exist for the choice of lipids based on these properties.

Generally, crystallisation in lipids with longer chains of fatty acids are slower than those with shorter fatty acid chains (Wong et al. 2007). Wax-based lipid nanoparticles are physically more stable, however they exhibit significant drug expulsion due to their more crystalline nature (Jenning and Gohla 2000). To avoid such problems with lipid crystallinity and polymorphism, a binary mixture of two spatially different solid lipid matrices, i.e. a solid lipid and a liquid lipid (or oil) was used to prepare lipid nanoparticle dispersions, now known as “nanostructured lipid carriers (NLC)” (Jenning et al. 2000d; Müller et al. 2002a; Souto et al. 2004).

Cationic lipids utilised in lipid nanoparticle preparation have been reported for use in gene delivery. The positive charge on the particle surface due to the use of a cationic lipid may enhance transfection efficiencies. Two-tailed (or branched) cationic lipids are preferred over one-tailed cationic lipids due to the cytotoxicity of the latter (Tabatt et al. 2004a, b). Examples of the lipids (including cationic lipids) which have been used in the preparation of lipid nanoparticles, both SLNs and NLCs, are listed in Table 2.1.

2.1.2 Surfactants

Surfactants (also known as surface-active agents or emulsifiers) form the other critical component of the lipid nanoparticle formulation. Surfactants are amphiphilic molecules that possess a hydrophilic moiety (polar) and a lipophilic moiety (non-polar), which together form the typical head and the tail of surfactants. At low concentrations, surfactants adsorb onto the surface of a system or interface. They reduce the surface or interfacial free energy and consequently reduce the surface or interfacial tension between the two phases (Corrigan and Healy 2006).

The relative and effective proportions of these two moieties are reflected in their hydrophilic lipophilic balance (HLB) value. Surfactants used in the preparation of lipid nanoparticle preparations play two quite distinct and important roles

- Surfactants disperse the lipid melt in the aqueous phase during the production process
- Surfactants stabilize the lipid nanoparticles in dispersions after cooling

Surfactants can be broadly categorized into three classes based on their charge: ionic, non-ionic and amphoteric. Table 2.2 lists a few surfactants from each class used in the preparation and stabilization of lipid nanoparticles. In all cases, the surfactants are surface tension lowering, which aids in the dispersion process required to form the product (first role). Ionic surfactants are traditionally thought

Table 2.1 Lipids used in the preparation of lipid nanoparticles

<i>Fatty acids</i>	<i>Waxes</i>
Dodecanoic acid	Cetyl palmitate
Myristic acid	Carnauba wax
Palmitic acid	Beeswax
Stearic acid	<i>Liquid lipids</i>
<i>Monoglycerides</i>	Soya bean oil
Glyceryl monostearate	Oleic acid
Glyceryl hydroxystearate	Medium chain triglycerides (MCT)/caprylic- and capric triglycerides
Glyceryl behenate	α -tocopherol/Vitamin E
<i>Diglycerides</i>	Squalene
Glyceryl palmitostearate	Hydroxyoctacosanylhydroxystearate
Glyceryl dibehenate	Isopropyl myristate
<i>Triglycerides</i>	<i>Cationic lipids</i>
Caprylate triglyceride	Stearylamine (SA)
Caprate triglyceride	Benzalkonium chloride (alkyl dimethyl benzyl ammonium chloride, BA)
Glyceryl tristearate/Tristearin	Cetrimide (tetradecyl trimethyl ammonium bromide, CTAB)
Glyceryl trilaurate/Trilaurin	Cetyl pyridinium chloride (hexadecyl pyridinium chloride, CPC)
Glyceryl trimyristate/Trimyristin	Dimethyl dioctadecyl ammonium bromide (DDAB)
Glyceryl tripalmitate/Tripalmitin	N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethyl ammonium chloride (DOTAP)
Glyceryl tribehenate/Tribehenin	

to infer electrostatic stability, whilst non-ionic surfactants are traditionally thought to infer steric repulsion stability. In reality, the situation is much more complex and many non-ionic surfactants used are too small to infer genuine steric stability, but probably result in stability through the Gibbs-Marangoni effect (Walstra 1993).

Members from the Pluronic[®] and Tween[®] families are the most commonly used non-ionic surfactants. As discussed, most of these surfactants contain a hydrophilic moiety (ethylene oxide) and a hydrophobic moiety (hydrocarbon chain).

Phospholipids and phosphatidylcholines are the common amphoteric surfactants employed in lipid nanoparticle preparation. These surfactants have both negatively and positively charged functional groups. They exhibit features of a cationic and an anionic surfactant at low and high pH conditions, respectively.

Selection of surfactants for nanoparticle preparation depends on a number of factors, including

- Intended route of administration
- HLB value of surfactant
- Effect on lipid modification and particle size
- Role in in vivo degradation of the lipid

Table 2.2 Surfactants and co-surfactants commonly used in the preparation of lipid nanoparticles

Surfactants	
<i>Ionic surfactants</i>	<i>Non-ionic surfactants</i>
Sodium cholate	Tween 20
Sodium glycocholate	Tween 80
Sodium taurocholate	Span 20
Sodium taurodeoxycholate	Span 80
Sodium oleate	Span 85
Sodium dodecyl sulphate	Tyloxapol
<i>Amphoteric surfactants</i>	Poloxamer 188
Egg phosphatidylcholine (Lipoid E PC S)	Poloxamer 407
Soy phosphatidylcholine (Lipoid S 100, Lipoid S PC)	Poloxamine 908
Hydrogenated egg phosphatidylcholine (Lipoid E PC-3)	Brij78
Hydrogenated soy phosphatidylcholine (Lipoid S PC-3,	Tego care 450
Phospholipon 80 H, Phospholipon 90 H)	Solutol HS15
Egg phospholipid (Lipoid E 80, Lipoid E 80 S)	<i>Co-surfactants</i>
Soy phospholipid (Lipoid S 75)	Butanol
	Butyric acid

Non-ionic surfactants are preferred for oral and parenteral preparations as they are less toxic and exhibit less irritation than ionic surfactants (McClements and Rao 2011). Amongst the ionic surfactants, cationic surfactants are more toxic than anionic or amphoteric surfactants. Therefore, the surfactants arranged in the decreasing order of toxicity are: cationic > anionic > non-ionic > amphoteric. Non-ionic surfactants effectively inhibit the in vivo degradation of lipid matrix. The poly (ethylene oxide) (PEO) chains on the non-ionic surfactants hinder the anchoring of the lipase/co-lipase complex that is responsible for lipid degradation. Adjusting the density of PEO chains on lipid nanoparticle surfaces can modify its in vivo degradation rate. Olbrich et al. studied the effects of surfactants on in vivo lipid degradation (Olbrich et al. 2002; Olbrich and Müller 1999). They suggested that Poloxamer 407 and sodium cholate have the most and least lipid degradation inhibitory effect amongst a selection of tested surfactants.

2.1.3 Other Agents

Apart from lipids and surfactants, lipid nanoparticle formulations can also contain a number of other ingredients including counter-ions and surface modifiers. The lipid nanoparticles engineered for encapsulation of cationic, water-soluble drugs may contain counter-ions such as organic anions or anionic polymers (Cavalli et al. 1995, 2002, 2003).

Table 2.3 Other agents used in the preparation of lipid nanoparticles

Counterions	Surface modifiers
<i>Organic salts</i>	Dipalmitoyl-phosphatidyl-ethanolamine conjugated with polyethylene glycol 2000 (DPPE-PEG ₂₀₀₀)
Mono-octyl phosphate	Distearoyl-phosphatidyl-ethanolamine- <i>N</i> -poly(ethylene glycol) 2000 (DSPE-PEG ₂₀₀₀)
Mono-hexadecyl phosphate	
Mono-decyl phosphate	
Sodium hexadecyl phosphate	Stearic acid-PEG 2000 (SA-PEG ₂₀₀₀)
<i>Ionic polymers</i>	α -methoxy-PEG 2000-carboxylic acid- α -lipoamino acids (mPEG ₂₀₀₀ .C-LAA18)
Dextran sulphate sodium salt	α -methoxy-PEG 5000-carboxylic acid- α -lipoamino acids (mPEG ₅₀₀₀ .C-LAA18)

Tailoring of the lipid nanoparticle surface with surface-modifiers such as hydrophilic polymers may reduce their uptake by the reticuloendothelial system (RES). The so-called “stealth” or long-circulating carriers stay longer in the systemic circulation and increase the residence of drug in blood (Fundarò et al. 2000; Zara et al. 2002). These “stealth” SLNs have been widely studied for delivery and targeting of anti-cancer cells as they are effectively and selectively taken up by tumor cells (Madan et al. 2013; Pignatello et al. 2013; Priano et al. 2011). Table 2.3 lists some of the counter-ions and surface-modifiers used in lipid nanoparticle preparation.

2.2 Structure of Solid Lipid Nanoparticles

SLNs have three different morphologies, based on the location of the incorporated drug molecule (Fig. 2.1),

- Drug-enriched shell model
- Drug-enriched core model
- Homogenous matrix model

These structures have been described based on the results observed by Müller and co-workers (Müller et al. 2002b).

2.2.1 Drug-Enriched Shell Model

A schematic of the drug-enriched shell model is depicted in Fig. 2.2a. A drug-enriched shell is a lipid core enclosed by a drug-enriched outer shell. Such a structure is obtained when hot liquid droplets cool rapidly to form lipid nanoparticles as a result of phase separation. The drug-enriched shell morphology can

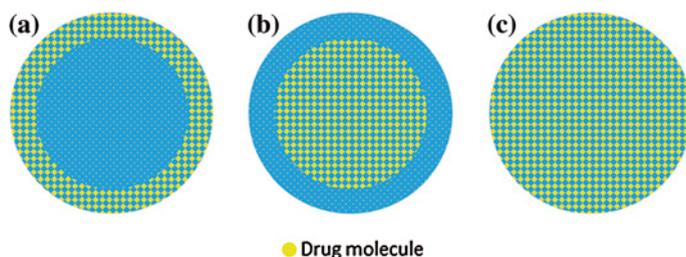


Fig. 2.1 Drug incorporation models of solid lipid nanoparticles. **a** Drug-enriched shell model. **b** Drug-enriched core model. **c** Solid solution (homogenous matrix) model

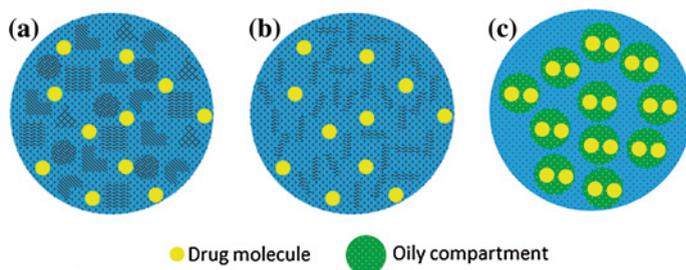


Fig. 2.2 Drug incorporation models of nanostructured lipid carriers. **a** Type I or the imperfect crystal type NLC. **b** Type II or the multiple type NLC. **c** Type III or the amorphous type NLC

be explained by a lipid precipitation mechanism that occurs during production and by repartitioning of the drug that occurs during the cooling stage. After hot homogenization, each droplet is a mixture of melted lipid and drug. Rapid cooling accelerates lipid precipitation at the core with a concomitant increase in drug concentration in the outer liquid lipid. Complete cooling leads to precipitation of a drug-enriched shell. This structural model is suitable for incorporation of drugs that are released as a burst. Such a rapid release is highly desirable for dermatological SLN formulations that require increased drug penetration, in addition to the occlusive effect of the SLN (Muchow et al. 2008). The controlled release of clotrimazole from a topical SLN formulation was due to its drug-enriched shell structure (Souto et al. 2004).

The solubility of the drug in the surfactant-water mixture at elevated temperatures is another factor that can influence precipitation of drug in the shell. During the hot homogenization process, drug partially moves out of the lipid core due to its increased solubility in the surfactant solution. However, solubility of the drug in the surfactant solution decreases as the dispersion is cooled. This leads to drug enrichment in the shell, in cases where lipid core solidification has already started (Muchow et al. 2008).

2.2.2 Drug-Enriched Core Model

A drug-enriched core model is obtained when the recrystallization mechanism is the opposite of that described for the drug-enriched shell model. Figure 2.2b shows a schematic representation of a drug-enriched core model. This morphology is obtained when the drug has a tendency to crystallize prior to the lipid. The drug is solubilized in the lipid melt close to its saturation solubility. Subsequent cooling of the lipid emulsion causes super-saturation of the drug in the lipid melt; this leads to the drug recrystallizing prior to lipid recrystallization. Additional cooling leads to lipid recrystallization that forms a membrane around the already crystallized drug-enriched core. This structural model is suitable for drugs that require prolonged release over a period of time, governed by Fick's law of diffusion (Müller et al. 2002b).

2.2.3 Solid Solution Model

A solid solution model, also referred to as the homogenous matrix model, is obtained when the drug is homogeneously dispersed within the lipid matrix in molecules or amorphous clusters. This model is usually described for lipid nanoparticles prepared by a cold homogenization technique, or when highly lipophilic drugs are incorporated such that a hot homogenization technique can be employed without the use of surfactants or drug-solubilizing molecules. When a cold homogenization technique is employed, the solubilized drug is dispersed in the bulk lipid. When subjected to high pressure homogenization, mechanical agitation leads to the formation of lipid nanoparticles with a homogenous matrix. A similar result is obtained when the lipid droplets produced by a hot homogenization technique are rapidly cooled; droplets tend to crystallize and there is no phase separation between the drug and the lipid. Such models are suitable for incorporation of drugs that exhibit prolonged release from particles (Muchow et al. 2008). An example of such a model is a prednisolone-loaded SLN system that exhibits slow release of prednisolone, usually from 1 day to 6 weeks (Jenning and Gohla 2000).

2.3 Structure of Nanostructured Lipid Carriers

Like SLNs, NLCs have been proposed to possess three different morphologies, based on the location of incorporated drug molecules (Jenning et al. 2000a, b, c)

- NLC type I or “imperfect crystal” type
- NLC type II or “multiple” type
- NLC type III or “amorphous” type

2.3.1 NLC Type I or “Imperfect Crystal” Type

Imperfect crystal type NLCs have an imperfectly structured solid matrix. Such imperfections can be increased by using glycerides composed of different fatty acids. Good drug accommodation can be achieved by increasing the number of imperfections. In order to achieve “maximum imperfections”, rather than using solid lipids only, the imperfect type of NLC is prepared by mixing spatially different lipids, resulting in imperfections in the crystal lattice. The disordered crystal accommodates more drug molecules, either in molecular form or as amorphous clusters. Using a mixture of glycerides with varying fatty acid chains forms a solid matrix with variable distances. Addition of a small amount of liquid lipid further increases drug-loading (Müller et al. 2002a).

2.3.2 NLC Type II or “Multiple” Type

The second type of NLC is the oil-in-lipid-in-water type. The solubility of lipophilic drugs in liquid lipids (oils) is higher than that in solid lipids. This principle can be used to develop the “multiple” type NLC. In this type of NLC, higher amounts of oil are blended in solid lipids. At low concentrations, oil molecules are easily dispersed into the lipid matrix. Addition of oil in excess of its solubility leads to phase separation producing tiny oily nano-compartments surrounded by the solid lipid matrix. Such models allow controlled drug release and the lipid matrix prevents drug leakage (Jenning et al. 2000d). Lipophilic drugs can be solubilized in the oils and multiple types of NLCs are formed during the cooling process of a hot homogenization process.

2.3.3 NLC Type III or “Amorphous” Type

The phenomenon of crystallization often leads to drug expulsion. To minimise this, NLCs can also be prepared by carefully mixing solid lipids with special lipids such as Hydroxyoctacosanylhydroxystearate, isopropyl palmitate or MCT. Solid, but non-crystalline lipid nanoparticles are formed. The lipid core congeals in an amorphous nature. This type of NLCs, called “amorphous” type NLC, and minimizes drug expulsion by maintaining the polymorphicity of the lipid matrix.

2.4 Conclusions

The physicochemical characteristics and stability of lipid nanoparticles are dependent on the composition of the lipid nanoparticle formulations. The lipid nature of these carrier systems is one of the major features that have attracted the

interest of many researchers. Based on the organisation of lipids and drugs in the particles, a wide variety of structural models have been described for SLNs and NLCs. The drug release from lipid nanoparticles is a compromise between the composition and the structural model obtained for each formulation.

References

- Blasi P, Schoubben A, Romano G, Giovagnoli S, Di Michele A, Ricci M (2013a) Lipid nanoparticles for brain targeting II. Technological characterization. *Colloid Surf B* 110:130–137
- Blasi P, Schoubben A, Traina G, Manfroni G, Barberini L, Alberti P et al (2013b) Lipid nanoparticles for brain targeting III. Long-term stability and in vivo toxicity. *Int J Pharm* 454(1):316–323
- Bummer P (2004) Physical chemical considerations of lipid-based oral drug delivery—solid lipid nanoparticles. *Crit Rev Ther Drug* 21(1):19
- Cavalli R, Bargoni A, Podio V, Muntoni E, Zara G, Gasco M (2003) Duodenal administration of solid lipid nanoparticles loaded with different percentages of tobramycin. *J Pharm Sci* 92(5):1085–1094
- Cavalli R, Gasco M, Chetoni P, Burgalassi S, Saettone M (2002) Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. *Int J Pharm* 238(1–2):241–245
- Cavalli R, Morel S, Gasco M, Chetoni P (1995) Preparation and evaluation in vitro of colloidal lipospheres containing pilocarpine as ion pair. *Int J Pharm* 117(2):243–246
- Chapman D (1962) The polymorphism of glycerides. *Chem Rev* 62(5):433–456
- Corrigan O, Healy A (2006) Surfactants in pharmaceutical products and systems. In: Swarbrick J (ed) *Encyclopedia of pharmaceutical technology*, 3rd edn. Informa Healthcare, NY, USA, pp 3583–3596
- Doktorovova S, Shegokar R, Fernandes L, Martins-Lopes P, Silva A, Müller R et al (2014) Trehalose is not a universal solution for solid lipid nanoparticles freeze-drying. *Pharm Dev Technol* 19(8):922–929
- Durán-Lobato M, Enguix-González A, Fernández-Arévalo M, Martín-Banderas L (2013) Statistical analysis of solid lipid nanoparticles produced by high-pressure homogenization: a practical prediction approach. *J Nanopart Res* 15(2):1–14
- Dwivedi P, Khatik R, Khandelwal K, Shukla R, Paliwal S, Dwivedi A et al (2014) Preparation and characterization of solid lipid nanoparticles of antimalarial drug Arteether for oral administration. *J Biomater Tissue Eng* 4(2):133–137
- Finke J, Schur J, Richter C, Gothsch T, Kwade A, Büttgenbach S et al (2012) The influence of customized geometries and process parameters on nanoemulsion and solid lipid nanoparticle production in microsystems. *Chem Eng J* 209:126–137
- Fundarò A, Cavalli R, Bargoni A, Vighetto D, Zara G, Gasco M (2000) Non-stealth and stealth solid lipid nanoparticles (SLN) carrying doxorubicin: pharmacokinetics and tissue distribution after i.v. administration to rats. *Pharmacol Res* 42(4):337–343
- Jenning V, Gohla S (2000) Comparison of wax and glyceride solid lipid nanoparticles (SLN®). *Int J Pharm* 196(2):219–222
- Jenning V, Gysler A, Schäfer-Korting M, Gohla S (2000a) Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Eur J Pharm Biopharm* 49(3):211–218
- Jenning V, Mäder K, Gohla S (2000b) Solid lipid nanoparticles (SLNTM) based on binary mixtures of liquid and solid lipids: a ¹H-NMR study. *Int J Pharm* 205(1–2):15–21
- Jenning V, Schäfer-Korting M, Gohla S (2000c) Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. *J Control Release* 66(2–3):115–126

- Jenning V, Thünemann A, Gohla S (2000d) Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. *Int J Pharm* 199(2):167–177
- Joshi M, Pathak S, Sharma S, Patravale V (2008) Design and in vivo pharmacodynamic evaluation of nanostructured lipid carriers for parenteral delivery of artemether: Nanoject. *Int J Pharm* 364(1):119–126
- Joshi M, Patravale V (2008) Nanostructured lipid carrier (NLC) based gel of celecoxib. *Int J Pharm* 346(1–2):124–132
- Kasongo W, Pardeike J, Müller R, Walker R (2011) Selection and characterization of suitable lipid excipients for use in the manufacture of didanosine-loaded solid lipid nanoparticles and nanostructured lipid carriers. *J Pharm Sci* 100(12):5185–5196
- Liu W, Tian R, Hu W, Jia Y, Jiang H, Zhang J et al (2012) Preparation and evaluation of self-microemulsifying drug delivery system of baicalein. *Fitoterapia* 83(8):1532–1539
- Madan J, Pandey R, Jain V, Katare O, Chandra R, Katyal A (2013) Poly (ethylene)-glycol conjugated solid lipid nanoparticles of noscapine improve biological half-life, brain delivery and efficacy in glioblastoma cells. *Nanomed Nanotechnol* 9(4):492–503
- Manjunath K, Venkateswarlu V, Hussain A (2011) Preparation and characterization of nitrendipine solid lipid nanoparticles. *Die Pharm Int J Pharm Sci* 66(3):178–186
- McClements D, Rao J (2011) Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. *Crit Rev Food Sci* 51(4):285–330
- Muchow M, Maincent P, Müller R (2008) Lipid nanoparticles with a solid matrix (SLN®, NLC®, LDC®) for oral drug delivery. *Drug Dev Ind Pharm* 34(12):1394–1405
- Müller R, Radtke M, Wissing S (2002a) Nanostructured lipid matrices for improved microencapsulation of drugs. *Int J Pharm* 242(1–2):121–128
- Müller R, Radtke M, Wissing S (2002b) Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev* 54:S131–S155
- Olbrich C, Kayser O, Müller R (2002) Lipase degradation of Dynasan 114 and 116 solid lipid nanoparticles (SLN)—effect of surfactants, storage time and crystallinity. *Int J Pharm* 237(1–2):119–128
- Olbrich C, Müller R (1999) Enzymatic degradation of SLN—effect of surfactant and surfactant mixtures. *Int J Pharm* 180(1):31–39
- Pignatello R, Leonardi A, Pellitteri R, Carbone C, Caggia S, Grazian A et al (2013) Evaluation of new amphiphilic PEG derivatives for preparing stealth lipid nanoparticles. *Colloid Surf A* 434:136–144
- Priano L, Zara G, El-Assawy N, Cattaldo S, Muntoni E, Milano E et al (2011) Baclofen-loaded solid lipid nanoparticles: Preparation, electrophysiological assessment of efficacy, pharmacokinetic and tissue distribution in rats after intraperitoneal administration. *Eur J Pharm Biopharm* 79(1):135–141
- Prombutara P, Kulwatthanasal Y, Supaka N, Sramala I, Chareonpornwattana S (2012) Production of nisin-loaded solid lipid nanoparticles for sustained antimicrobial activity. *Food Control* 24(1–2):184–190
- Silva A, González-Mira E, García M, Egea M, Fonseca J, Silva R et al (2011) Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. *Colloid Surf B* 86(1):158–165
- Souto E, Wissing S, Barbosa C, Müller R (2004) Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. *Int J Pharm* 278(1):71–77
- Tabatt K, Kneuer C, Sameti M, Olbrich C, Müller R, Lehr C-M et al (2004a) Transfection with different colloidal systems: comparison of solid lipid nanoparticles and liposomes. *J Control Release* 97(2):321–332
- Tabatt K, Sameti M, Olbrich C, Müller R, Lehr C-M (2004b) Effect of cationic lipid and matrix lipid composition on solid lipid nanoparticle-mediated gene transfer. *Eur J Pharm Biopharm* 57(2):155–162

- Walstra P (1993) Principles of emulsion formation. *Chem Eng Sci* 48(2):333–349
- Wang S, Chen T, Chen R, Hu Y, Chen M, Wang Y (2012) Emodin loaded solid lipid nanoparticles: preparation, characterization and antitumor activity studies. *Int J Pharm* 430(1–2):238–246
- Wong H, Li Y, Bendayan R, Rauth M, Wu X (2007) Solid lipid nanoparticles for anti-tumor drug delivery. In: Amiji M (ed) *Nanotechnology for cancer therapy*. Taylor and Francis, Hoboken, pp 741–776
- Zara G, Cavalli R, Bargoni A, Fundarò A, Vighetto D, Gasco M (2002) Intravenous administration to rabbits of non-stealth and stealth doxorubicin-loaded solid lipid nanoparticles at increasing concentrations of stealth agent: pharmacokinetics and distribution of doxorubicin in brain and other tissues. *J Drug Target* 10(4):327–335



<http://www.springer.com/978-3-319-10710-3>

Lipid Nanoparticles: Production, Characterization and Stability

Shah, R.; Eldridge, D.; Palombo, E.; Harding, I.

2015, IX, 97 p. 30 illus., 18 illus. in color., Softcover

ISBN: 978-3-319-10710-3