Polymeric nanoparticles have been intensely investigated since their introduction by Speiser and co-workers in the mid-seventies. Despite their interesting properties, not many products made it to market because of the presence of solvent residues left over from production, the cytotoxicity of the polymers, and the lack of low-cost, qualified large-scale production units yielding a product of a quality acceptable by the regulatory authorities. As an alternative, solid lipid nanoparticles (SLNs) were developed in 1991 (Figure 1),1 a technology now owned by the drug delivery company SkyePharma. The matrix is a blend of solid lipids. SLN formulations that have been developed, for example, for the oral delivery of cyclosporine (Pharmatec/Eurand, Milan)2,3 and the intravenous delivery of Paclitaxel. Vectorpharma/Trieste followed a similar route by developing SLNs from microemulsions.4,5

A new generation of nanostructured lipid carriers (NLCs) consisting of a lipid matrix with a special nanostructure has been developed.6-8 This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%.

Types of NLC
It is well known from the study of suppositories that highly ordered crystalline lipid matrices will lead to drug expulsion. Lipid nanoparticles and microparticles made from blends of solid lipids can experience this, especially when nanoparticles are prepared from highly purified lipids, for example, tristearin.9 The formation of highly ordered β1 or β modifications, particularly during storage, leaves little space for drug molecules, and the expulsion of drugs leads...
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Figure 1 Atomic force microscopy (AFM) graph of lipid nanoparticles.

Figure 2 Different types of NLC: I – highly imperfect matrix; II – multiple O/F/W type; III – non-crystalline amorphous NLC (versus SLN with high crystallinity).

to drug crystals in suspensions and solid dosage forms. To avoid this problem, the particles should have a controlled nanostructure that offers enough space to accommodate the drug. Four different approaches were taken for an optimized nanostructure of NLCs.

In type I, solid lipids and liquid lipids (oils) are blended. The difference in the structures of the lipids and special requirements in the crystallization process lead to a highly disordered, imperfect lipid matrix structure offering space for drug molecules and amorphous clusters of drugs (Figure 2, I).

In general, drug solubility is higher in liquid lipids than in solid lipids. Based on this, particles were produced with a high content of liquid lipids (oils). During the production process, the liquid lipid particles (nanoemulsions) are cooled from the molten state to room temperature to crystallize and form solid particles. At high oil concentrations a miscibility gap of the two lipids (solid lipid plus oil) occurs during the cooling phase, leading to phase separation, that means precipitation of tiny oily nanocompartments (Figure 2, II). In this multiple oil/fat/water, type II drug can be accommodated in the solid, but at increased solubility in the oily parts of the lipid matrix.

In type III, lipids are mixed in a way that prevents them from crystallizing. The lipid matrix is solid, but in an amorphous state (Figure 2, III). The absence of crystallization avoids drug expulsion by crystallization. Lipid particles are preferentially suited to incorporate lipophillic drugs; hydrophilic drugs can only be incorporated at a low percentage (however, this is still sufficient for highly potent peptides and proteins).

In a further variation of the lipid matrix, water-soluble drugs were conjugated with a lipid, thus forming a water-insoluble lipidic conjugate. The lipid conjugate powder was melted and processed in the same way as the other types to yield a lipid drug conjugate (LDC) nanoparticle. Depending on the conjugate, this lipidic conjugate has a drug loading of up to 30–50% for water-soluble drugs. Conjugation is performed by salt formation or covalent linkage.

Modulation of Drug Release
Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally this release should be triggered by an impulse when the particles are administered.

NLCs accommodate the drug because of their highly unordered lipid structures. By applying the trigger impulse to the matrix to convert in a more ordered structure, such a desired burst drug release can be initiated. NLCs of certain structures can be triggered this way; for example, when applying the particles to the skin incorporated in a cream. Increase in temperature and water evaporation leads to an increase in drug release rate (Figure 3). Based on these cyclosporine-lipid particles are under development to treat psoriasis. The cream itself is saturated with cyclosporine, as well as a cyclosporine-loaded NLC contained in the cream. After application to the skin, accelerated release from the lipid particles should lead to a supersaturated system (similar to microemulsions, but without high surfactant concentration) leading to an improved penetration of cyclosporine into the skin.

Long-Term Stability
During long-term storage of dispersions, particle aggregation can occur. Aggregation and shell formation were reported for SLNs. Single particles diffuse in the dispersion medium; collision of particles can lead to perikinetic flocculation (Figure 4a).
In the highly concentrated NLC dispersions the particles form a ‘pearl-like network’, thus the particles are in a fixed position and cannot undergo collision and perikinetic flocculation. After administration of the particles and dilution with fluids (gastrointestinal fluids, for example), the network is destroyed releasing single, nonaggregated particles (Figure 4b).

Lipid particle dispersions were produced at identical surfactant concentration, but with low lipid content (below 30%, outside patent coverage) and with 35% lipid. The low particle dispersion aggregated during storage time, the gel-like NLC dispersion remained stable during storage and, after dilution, single particles were obtained showing no size increase.13

**Production of NLCs**

NLCs can be produced by various traditional dispersion techniques. The preferred production method is high-pressure homogenization. Up to approximately 60% solid content, high-pressure homogenization can be applied alone to achieve solid contents of, for example, 80% when the multistep process is applied.

First the lipid phase is melted. Then the drug is dissolved in the molten lipid thereby, preparing a drug-containing lipid melt. This melt is then dispersed in an aqueous surfactant solution heated at the same temperature, using a high-speed stirring. The obtained pre-emulsion is then homogenized using a piston-gap homogenizer. Small lab-scale batches of 40 mL are produced using a discontinuous LAB 40 (APV Homogenizer GmbH, Germany). Larger batches up to a 0.5 L dispersion are produced using a modified continuous LAB 40 homogenizer tower and the two product vessels possess temperature control jackets.

The highly concentrated NLC dispersions are highly viscous, gel-like or pasty. These systems have no flowability — the difference to conventional emulsions and SLN dispersions is shown in Figure 5.

To produce an 80% NLC dispersion, a multistep production process is applied. First, a 50% SLN dispersion is produced by high-pressure homogenization. One hundred grams of such a dispersion contains 50 g of lipid and 50 g of water. In the next step, 10 g of lipid is added, which is dispersed by high-speed stirring in the remaining 50 g of water. This results in 110 g of dispersion containing 60 g of lipid (55%) and again 50 g of water. In the next step, another 10 g of lipid is dispersed in this 50 g of water phase and so on until a lipid content of 80% is reached.

Large-scale production of NLC is easily possible. High-pressure homogenizers are available to process one ton and more per hour. There are also no regulatory hurdles because these machines are accepted in production lines for parenterals, in parenteral emulsions for nutrition, for example.

**Application Areas**

Oral administration of NLCs is definitely a very interesting and easy-to-realize area. The basic usefulness of lipid particles for oral delivery has been shown by the SLN-cyclosporine patents — NLCs have the potential to do an even better job. In addition, lipids promote the absorption of a range of drugs, also supporting the use of lipid particles for oral delivery. Of special interest for oral delivery are lipid–drug conjugate (LDC) nanoparticles providing high-loading capacities for hydrophilic drugs. Primary drugs of interest are compounds undergoing chemical degradation in the gastrointestinal tract. NLCs can be incorporated...
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into traditional dosage forms such as tablets and pellets using the NLC dispersion as granulation fluid or wetting liquid for the pellet mass. NLCs produced in oil or polyethylene glycol (PEG) 400 can be filled directly into soft gelatin capsules.

The second easy-to-realize area is topical application. All the lipids and surfactants used in traditional pharmaceutical creams can be employed, thus leaving little regulatory hurdles. Data are available showing delivery advantages of lipid particles compared to normal creams and ointments. Because of the high consistency of NLC dispersions, they can be used as topical dosage forms without further processing.

First lines in parenteral delivery are controlled release forms (subcutaneous or intramuscular, for example) and the intravenous route. LDC nanoparticles have proved particularly useful for targeting water-soluble drugs to the brain.

**Perspectives**

NLCs can generally be applied where solid nanoparticles possess advantages for the delivery of drugs. Major application areas in pharmaceuticals are topical drug delivery, oral and parenteral administration. They also have applications in cosmetics, food and agricultural products.

**References**

7. R.H. Müller et al., extended patent on the basis of (6), PCT application PCT/EP00/04112 (2000).