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Nanostructured Lipid Drug Carriers

New drugs can be tailor-made by biotechnological methods, however they also require "carriers" to deliver them in an optimized way. Intensive research demonstrated the potential of polymeric nanoparticles. However, despite almost 30 years of research, nanoparticulate products do practically not exist on the pharmaceutical market. To overcome problems of polymeric nanoparticles (e.g. lack of large scale production), nanoparticles based on solid lipids were developed. This paper describes the new generation of solid lipid carriers – NLC.

Particulate lipid matrices in the form of lipid pellets are known from the textbooks since many years, products are on the market (e. g. Mucosolvan retard, Boehringer-Ingelheim). After these lipid pellets as the first generation, P. Speiser developed so-called "lipid nanopellets for oral administration" in the middle of the eighties [1]. This system was not further developed, in many countries no patent protection exists anymore because the fees were not paid.

At the beginning of the nineties the third generation has been developed the so-called "solid lipid nanoparticles" (SLN) (Fig. 1).

SLN are produced by high pressure homogenisation of melted or solid lipids [2], the worldwide patent rights of this technology being currently held by SkyePharma/London. In parallel, a method was developed by Gasco to produce SLN using a microemulsion technique [3]. Licenses were given e. g. to Vectorpharma/Italy, a company pursuing the system further [4, 5].

After the development of SLN in 1991, increasing attention was given to lipid nanoparticles clearly documented by the increasing number of research groups and companies working with this carrier system. The two reviews published about SLN in 1995 and 2000 show this development [6, 7].

Industrial interests focussed on high sales drugs (e. g. cyclosporine) to be formulated with SLN. Pharmatec (Milan/Italy) developed a cyclosporine SLN formulation for oral administration as competitive product to Sandimmun Neoral [8]. The animal study published in the patent shows that the cyclosporine SLN combine the advantages of the old Sandimmun and the new Sandimmun microemulsion: avoidance of high plasma peak and low variability in plasma profile. The basis of this patent was extended in the PCT application [9].

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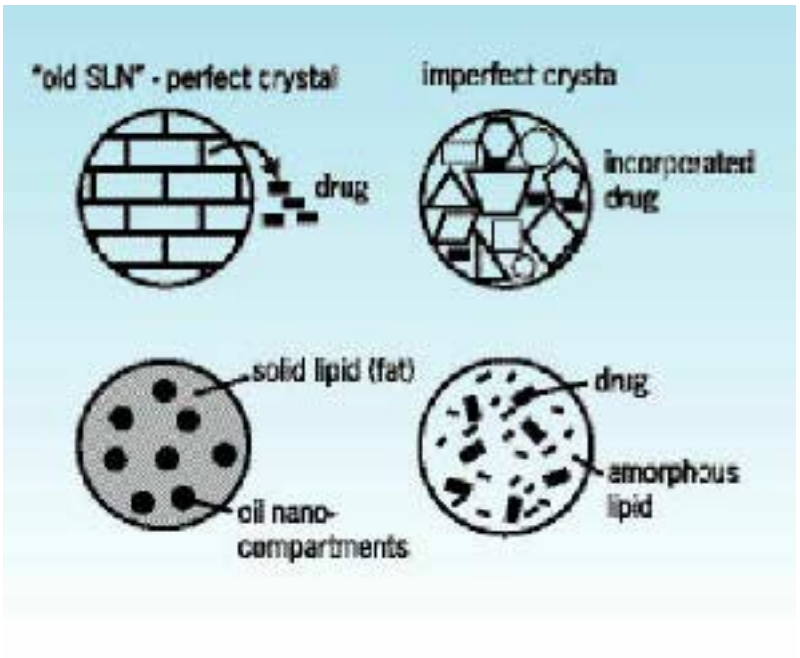
Another clear advantage of SLN compared to polymeric nanoparticles is the availability of large scale production units. An important point is also that these units can be qualified and validated. At Pharmatec a qualified production unit is available allowing the production of 10 kg dispersion in less than 30 minutes. dds GmbH (Kronshagen, Germany) has developed a system allowing the production of 50 to 150 kg dispersion per hour which can be extended by using high capacity homogenisers up to half a ton per hour.

To summarize, especially with regard to industrial production aspects, SLN have the chance to be exploited as delivery system in commercial products. However, there are also three limitations of the SLN system:

- limitation of drug load by the solubility of the drug in the solid lipid,
- drug expulsion phenomenon when lipid crystallizes to the stable β-form (Fig. 2, upper left),
- particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30%.

The aim of the research was to overcome these limitations by creating a new lipid carrier, the NLC.



2 *"Old SLN" (upper left) and the three types of nanostructured lipid carriers: imperfect nanostructured solid matrix (upper right), multiple O/F/W carrier (lower left) and solid amorphous matrix (lower right).*

The four types of NLC

Overcoming these limitations was solved by creating a lipid particle with a controlled nanostructure, the nanostructured lipid carrier (NLC) [10, 11]. In the SLN the drug is mainly dispersed in molecular form, e. g. located in between the fatty acid chains of the glycerides. In the NLC very different lipids were blended to form the matrix, that means solid lipids and liquid lipids. Due to their differences in structure they cannot fit together very well to form a perfect crystal, the matrix contains a lot of imperfections to accommodate drug in molecular form and amorphous clusters. That means to say, the "perfect solution is the imperfection" (Fig. 2, upper right).

For many drugs the solubility in a liquid (melted) lipid is higher than in a solid lipid. This fact can lead to problems when producing SLN by the hot homogenisation technique. The drug is dissolved in the melted lipid and homogenised to form O/W nanoemulsion droplets. During the cooling process and especially during the crystallization process the solubility of the drug is continuously reduced leading to drug expulsion when drug concentration was selected too high. This feature that drugs might be better soluble in liquid oils was exploited in the second type of NLC. This type contains liquid oil nanocompartments within the lipid particle matrix (Fig. 2, lower left), that means it is an O/F/W system. By mechanical means it is not possible to create tiny oily nanocompartments in e. g. a 200 nm particle. This was achieved by the developed lipid-lipid precipitation technique.

1 *Atomic Force Microscopy (AFM) picture of spherical lipid nanoparticles made of lipids for dermal application.*

Melted solid lipid was mixed with a large amount of hot liquid oil, the droplets were formed by homogenisation at elevated temperature, during the cooling process a phase separation of the two lipids occurs. At a certain temperature they have a miscibility gap leading to the precipitation of the liquid oil in small droplets (similar to precipitating a drug from a solvent). The existence of the nanocompartments was proven by DSC (solidification of the liquid oil below 0°C), particles were also characterized by NMR and ESR.

The third type of NLC avoids drug expulsion by avoiding crystallinity [11]. If one has no crystalline matrix, there can be no drug expulsion due to progressing crystallization to stable ß forms. By controlled mixture of lipids particles were created which were solid, not crystalline but in an amorphous state (Fig.2, lower right). Of course, this amorphous state needs to be preserved.

3 *Appearance of lipid particle dispersions with increasing concentration of 20% and 30% (SLN, from left), more viscous NLC structure at 35% and high-viscous NLC dispersion (right) [after12].*

Production technology and scale up

For economical and technical (processing) reasons it is very often desirable to have a high solid content in lipid particle dispersions. For example liquid particle dispersions can be transferred to tablets by granulation using the particle dispersion as wetting agent. A similar approach is the production of pellets. For these processes it is not favorable at all when 70% or 80% of water need to be removed from the dispersion used.

Surprisingly it was found that under certain production conditions high pressure homogenisation can be used to produce particle dispersions with 50% or 60% solid content [10, 12]. The lipids used did not form an amphiphilic cream structure but remained as intact particles. The particle dispersions have a high consistency, they are cream-like or almost solid (Fig. 3).

Photon correlation spectroscopy (PCS), laser diffractometry and electron microscopy proved the existence of intact particles, size examples are given in Table 1.

lipid content	total solid	PCS size [nm]	Polydispersity index
20%	25%	180	0.128
30%	35%	208	0.072
35%	40%	266	0.210
40%	45%	283	0.244

Table 1

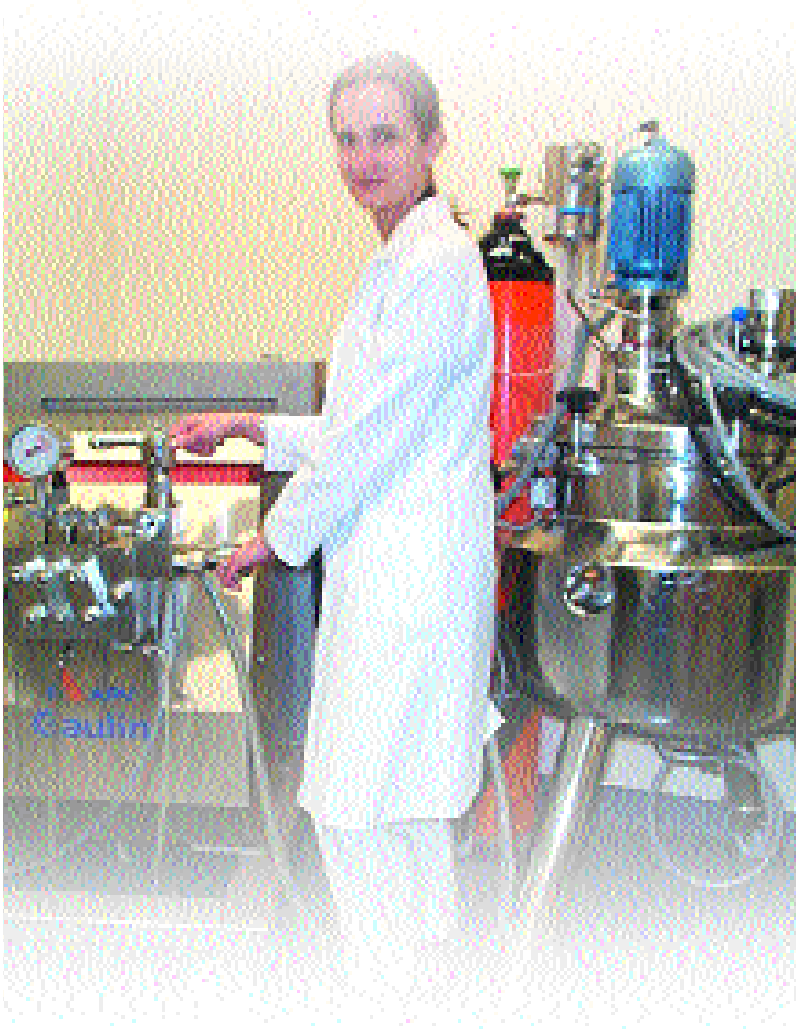
By a special multi-step production process the solid concentration could be increased to more than 80%, of course the dispersions are not cream-like anymore, they are more or less in a solid form. Details of the technology are described and covered by the German patent application [10] and the PCT application [11].

Large scale production can be performed using high pressure homogenisers from the shelf, i.e. low-cost equipment. Figure 4 shows an APV Gaulin 5.5 with a capacity of 150 kg dispersion per hour. Such machines are accepted in production lines for parenterals (e.g. emulsion for infusion), therefore easy going from the regulatory aspect.

Application: oral drug delivery

NLC can exploit all the advantages known from lipid nanoparticles for oral administration. Compared to the other systems, drug loading can be increased, drug inclusion is improved. NLC can easier be processed to traditional dosage forms well known by the patient, e. g. tablet, capsule or pellet. Because of the high particle concentration and cream-like consistency the NLC dispersions might be directly filled into capsules when producing the particles in a suitable dispersion medium, e. g. PEG 600, oil.

The high particle concentration facilitates the use of these dispersions for granulation or as wetting agent in the pellet production.



4 *APV high pressure homogeniser (left) with a production capacity of 150 kg dispersion per hour, a product container for medium scale (right),*

It appears also feasible that the cream-like particle dispersion can be filled into tubes. The patient can dose the required amount of drug on a spoon by using a special dosing mechanism. This would be a simple and versatile system for individual dosing of e.g. cyclosporine SLN.

Other routes of delivery

Another very attractive route is delivery of drugs to the skin. High concentrated NLC are already cream-like and can directly be applied to the skin. Improved delivery could be achieved by effects like occlusion and creation of supersaturated systems (similar to microemulsions but without a high surfactant content, e.g. for cyclosporine to treat psoriasis) [13].
A broad application is parenteral delivery ranging from s.c. depots to i.v. and also i.m. As an i.v. system, the NLC can be loaded with paclitaxel avoiding critical solubilizers like Cremophor EL.

Perspective

The lipid nanoparticles – SLN and NLC – are carrier systems with good perspectives to be marketed very successfully. The reason for this is that they were developed considering industrial needs, e.g. scale up, qualification and validation, simple technology, low cost, regulatory excipient status (e.g. GRAS), tolerability etc.

The smart NLC as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectables.

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