Solid Lipid Nanoparticles – characteristics, application and obtaining

Elwira LASON, Jan OGNOWSKI – Institute of Organic Chemistry and Technology, Cracow University of Technology, Cracow

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Introduction

Solid Lipid Nanoparticles (SLN), which were first mentioned in 1991, are colloidal lipid carriers, solid at room and body temperature [1]. SLN are obtained from GRAS (generally recognized as safe) lipids and surfactants, devoid of toxicity. SLN have a number of advantages over traditional colloidal systems, such as physical stability, protection of the active substance, controlled release of the active substance, biocompatibility, selective orientation, absence of organic solvents [2, 3].

Solid lipid nanoparticles (SLN) spur high interest, particularly in the pharmaceutical industry [4, 5], but also in cosmetics [6, 7] and food [8] industries.

SLN have been applied in the pharmaceutical industry for controlled drug release and increasing the bioavailability of trapped active substance by changing the dissolution rate in parenteral (intravenously, intramuscularly or hypodermically) [5, 9], oral [10] and rectal [11] therapies, in ophthalmology [12] and in external uses (dermatology, cosmetics) [13, 14].

SLN are considered promising carriers for active cosmetic ingredients due to many advantages over traditional forms. The SLN have a number of features determining their eligibility as carriers for cosmetic purposes, such as:

- Protection of unstable compounds against chemical degradations, e.g. retinoids [15]
- Controlled active ingredient release ability
- The ability to function as occlusal complexes
- Exhibited potential as UV blockers, capable of functioning as standalone sunscreens or in combination with other sun protection substances [6].

The continually emerging new diets related to circulatory system illnesses, obesity, hypertension or cancer have lead to the development by the food industry of the so-called bioactive food components. Clinical trials have confirmed the health benefits of including bioactive components in everyday diet. However, many of those beneficial components are strictly dependent on the carrier or are highly lipophilic and thus have low absorption and limited bioavailability in human organism. Furthermore, those components, when separated from plant or animal material, are simply unstable. This applies to various classes of bioactive components, such as carotenoids which are virtually insoluble in water. This causes a number of problems for the food industry, related to the inclusion of lipophilic biocomponents in nutrient carriers and this is an issue faced by special needs foods producers [8]. A perfect solution in this case proved to be the solid lipid nanoparticles.

Structure and properties of solid lipid nanoparticles

SLN are composed of a core of solid lipid with bioactive material constituting a part of the lipid matrix (Fig. 1). Such particle is stabilized by the surfactant layer (or a mixture of surfactants).

The term ‘lipids’ as used here is understood in a broader sense and includes triglycerides (e.g. tristearate), partial glycerides (e.g. the compound with trade name of Imwitor), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). As for emulsifiers, all classes can be used to stabilize lipid dispersion. It has also been proved that the combination of various emulsifiers can be more effective in preventing particle agglomeration.

An obvious advantage of SLN is the fact that the lipid matrix is obtained from physiological lipids, which reduces the risk of acute and chronic poisoning. The choice of emulsifier is determined by the method of administration and is more limited in parenteral application.

As previously mentioned SLN combine the advantages and are free of faults typical for other colloidal carriers with micro- and nanoparticles. The key advantages of SLN are:

- Controlled release and orientation of active substance
- Increase of the active substance stability
- The capability to include lipo- and hydrophilic substances
- No biotoxicity
- No necessity to use organic solvents
- No problems related to large-scale production and sterilizing
- High loading (drug loaded).

Methods of obtaining SLN

There are two basic methods of SLN production: high pressure homogenization (HPH) [1] and microemulsion technique [16]. Also, attempts have been made to obtain those compounds using less expensive and complicated methods, such as ultrasound technique (US) and solvent cast method. Unfortunately, those methods have a number of disadvantages. The basic methods of obtaining solid lipid nanoparticles are outlined below.

High Pressure Homogenization (HPH)

HPH has proved to be an effective and reliable method of SLN production. Homogenizers of various sizes are available on the market for relatively favourable prices and HPH has been used in the production of nanoemulsions for a number of years. Contrary to other technique, HPH usually does not pose any difficulties for large-scale production. High-pressure homogenizers force the liquid through very thin pipes (a few microns in diameter) under the pressure of 100-2000 bar. On very short distances, the liquid reaches very high velocity of over 1000 km/h. High turbulence and shear disintegrate

Fig. 1. Structure of solid lipid nanoparticles stabilized by surfactant layer

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the particles to submicron sizes. The typical lipid content is 5–10% and poses no difficulty for the homogenizer. Lipid nanodispersion has been achieved with lipid concentration as high as 40% [17].

HPH is further divided into hot and cold high pressure homogenization (Fig. 2). In both methods the preparatory stage involves the introduction of active substance into the lipids through dissolution or dispersion of those substances in liquefied lipid mass [18].

Hot HPH is conducted at temperatures higher than lipid melting point and can thus be considered homogenization in emulsion. Precrystallization of the active substance, melted lipid and water phase of the emulsifier is obtained in high speed mixer. The quality of pre-emulsions largely determines the quality of the end product. The desirable particle sizes are within a few micrometers. HPH of the pre-emulsion is conducted at temperature higher than lipid melting point. In general, the higher the temperature, the smaller the particle size, caused by viscosity reduction in the internal phase. However, too high temperature may cause the active substance and the carrier to decompose. The homogenization stage can be repeated a number of times. It should be noted that homogenization under increased pressure causes the emulsion temperature to rise by approx. 10°C for every 500 bar. In most cases 3 to 5 homogenization cycles under 500–1,500 bar are sufficient. The increase of homogenization pressure or the number of cycles often results in the increase in particle size due to coalescence which is the product of high kinetic energy of particles. The basis product of hot HPH is nanoemulsion in liquid state. Solid nanoparticles are obtained by cooling the sample to room temperature or lower. Due to small particle size and the presence of emulsifiers the crystallization of lipids can take very long (up to a few months) [18].

Cold homogenization is conducted with solid lipids (Fig. 2). Effective temperature control and regulation is required in order to maintain the solid state of lipids, since the temperature increases during homogenization. Cold HPH has been developed in order to overcome the three fundamental problems of hot homogenization:

- Decomposition of the active substance, caused by high temperature
- Decomposition of the active substance in the water phase during homogenization
- Complexity of the crystallization stage of the nanoemulsion, leading to multiple modifications.

**Microemulsion technique**

The use of microemulsion in SLN production was described first by Gasco et al. [20]. It should be noted, however, that the term ‘microemulsion’ is controversial and there is a variety of opinions in the scientific circles on the structure and dynamics of microemulsion. The matter was discussed in detail by Moulik & Paul [21].

In order to obtain microemulsion with lipids in solid state at room temperature, the process temperature must be higher than lipid melting point. Lipids (e.g. fatty acids and/or triglycerides) are melted and the mixture of water, emulsifiers and co-emulsifiers is heated to the temperature of the lipids and blended under mild conditions. If the procedure runs correctly, we will obtain a transparent, thermodynamically stable complex. The hot microemulsion is then dispersed in chilled water (2÷3°C) by smooth mechanical stirring, which ensures that the small particle size results from precipitation and not the mechanical stirring. The volume ratio of hot microemulsion to cold water should be from 1:25 to 1:50. The most popular emulsifiers are polysorbate 20, polysorbate 60 and soy lecithin. The most frequently used co-emulsifiers are usually alcohols, e.g. butanol. Technically, the precipitation of lipid particles in water is equivalent to diluting the complex, which leads to decrease in solid substance content in SLN dispersion. Due to diluting stage the achievable lipid content is lower than in formulations obtained through HPH [18, 19].

**High-speed homogenization and ultrasound dispersion technique**

The high-speed homogenization and ultrasound dispersion techniques [22, 23] are relatively well known and easily executed. However, the dispersion quality may be compromised by the presence of microparticles. Furthermore, in the case of ultrasound technique there is a risk of metal contamination.

**Solvent cast method of emulsification/evaporation**

Sjöström and Bergenståhl [24] described the method of nanoparticle dispersion production by precipitating o/w emulsion. The lipophilic material is dissolved in solvent that does not blend with water (e.g. cyclohexane), emulsified in the water phase. After
evaporating the solvent, the nanoparticle dispersion is created through precipitating the lipid in water phase. The diameter of obtained particles was 25 nm for cholesterol acetate as the model drug and the emulsifying mixture of lecithin/sodium glycolcholate. Reproducibility of the above results was confirmed by Sielman & Westesen [25].

The comparison of SLN obtaining methods should be made by the same researcher, using the same compounds stored under identical conditions, and the particle size should be measured on the same equipment. Otherwise, the data will not be completely reliable. Nevertheless, the researchers have proved HPH to be the most effective method of obtaining solid lipid nanoparticles [1, 26].

SLN stability

The physical and chemical stability of SLN is regulated by two visibly different processes, i.e. the SLN suspension’s ability to retain homogeneity (suspension stability) and preventing the carrier from recrystallization (carrier stability). The instability of the above processes causes the uniform suspension to stratify by processes typical for other dispersions, such as: flocculation and sedimentation, as well as creaming and coalescence. Furthermore, the recrystallization process may lead to cross-linking of crystallized particles, thereby causing the suspension to behave like gel [27].

Releasing active substance from SLN

Thus far, numerous studies have been conducted on the introduction of various active substances into SLN systems, particularly in medicine (Table 1). Data on the mechanisms of releasing active substances from SLN are much more scarce. Considerable data on the release mechanisms in in-vitro tests were collected by Menhert et al., who used the following model drugs: tetracaine, detomidine or prednisolone [19, 28, 29, and 30].

In most cases the active substance is released by rupturing the SLN capsule. For instance, SLN obtained by both methods, i.e. hot and cold HPH, released tetracaine and detomidine almost immediately [30]. Compared to that, it was proved possible to delay the release of prednisolone by using the cold HPH technique [28]. The choice of appropriate homogenization temperature enabled the change of active substance release profile.

Due to colloidal size of particles, the studies on active substance release from SLN systems are difficult. Moreover, such experiments are conducted under different conditions (samples may be separated by filtering, centrifuging or dialysis), which provides a further obstacle for result comparison.

Table 1

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>[31, 32, 33]</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>[33, 34]</td>
</tr>
<tr>
<td>Risperidone</td>
<td>[2]</td>
</tr>
<tr>
<td>Clofazimine propionate</td>
<td>[35]</td>
</tr>
<tr>
<td>Insulin</td>
<td>[36]</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>[37]</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Cortisone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cosmetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoic acid</td>
<td>[38]</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>[39]</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>[40, 41]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Food industry</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-carotene</td>
<td>Lutein</td>
</tr>
<tr>
<td></td>
<td>Lycopene</td>
</tr>
</tbody>
</table>

Conclusion

There is no doubt about the importance of effective delivery of medical substances to our organism, regardless whether the product in question is of pharmaceutical, cosmetic or food origin. The selection of appropriate carrier, marked by non-toxicity and neutral to our organism and, crucially, compatible with the active substance, is not an easy task. In recent years the solid lipid nanoparticles have proved to be the ideal solution to this problem and an alternative to traditional liposomes and other systems. The SLN are exciting carrier systems for encapsulating bioactive substances with considerable potential for application. The obvious advantages of SLN are firstly: composition (physiological compounds), rapid and effective obtaining, including large-scale production capability, no necessity to use solvents and the ability to obtain highly concentrated lipid suspensions. Unfortunately, those systems have disadvantages as well. Those include: low active substance load capacity of the carrier, problematic stability in storage, combined with the possibility of occurrence of processes such as: gelation, particle size increase or decreasing active substance.

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Elwira LASOŃ - M.Sc.,(Eng), graduated from the Faculty of Chemical Engineering and Technology of the Cracow University of Technology in 2008, specializing in: “Light organic technology”. Currently employed at the Institute of Organic Chemistry and Technology of the Cracow University of Technology. Specialization: organic technology, biotechnology, catalytic processes.

Jan OGOŃOWSKI - Professor (Ph.D., Eng) is a graduate of the Faculty of Chemistry of the Silesian University of Technology (1996). Currently He is employed as head of the Organic Technology and Refining Processes Chair on the Faculty of Chemical Engineering and Technology, Cracow University of Technology. Specialization: organic technology, biotechnology, catalytic processes.