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Review Article

DEVELOPMENT & SCREENING APPROACH FOR LIPID NANOPARTICLE: A REVIEW

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ABSTRACT

Since the beginning of the 1990s the lipid nanoparticles were getting a growing interest from the pharmaceutical technology research group's world wide. Nowadays solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugate (LDC) have been already investigated as carrier systems for many applications. This review article explains what was the need to develop new concept for lipid Nanoparticle. SLN have a lot of problem like drug loading as well as drug expulsion on long time storage due to β modification of solid lipid, To overcome this NLC were developed. SLN & NLC are basically use for loading of hydrophobic drug where LDC developed to overcome such problem. The approach used to select the solid as well as liquid lipid were discus in this article which help in selecting appropriate lipid for formulation of lipid Nanoparticle.

Keywords: *Nanoparticle, Lipid Nanoparticle, SLN, NLC, Screening Approach*

INTRODUCTION

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are two main types of lipid nanoparticles. SLN is a colloidal carrier system for controlled drug delivery, followed by the development of emulsion, liposomes, microparticles and nanoparticles based on synthetic or natural polymers. They combine the advantages of emulsions, liposomes and polymeric nanoparticles. The solid matrix can protect incorporated active ingredients against chemical degradation and provide the highest flexibilities in the modulation of the drug release profiles. Advantages of SLN and NLC include a potentially wide application spectrum (dermal, oral, intravenous), the use of biodegradable physiological lipids or lipidic stabilizers which are generally recognized as safe (GRAS) or have a regulatory accepted status.

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NLC composed of solid lipid matrix with certain content of liquid lipid are a new generation of lipid nanoparticles. The incorporation of liquid lipids into solid lipid matrix leads to great imperfections in the crystal lattice of nanoparticles, thus leading to improved drug loading capacity and reduced drug expulsion during storage[1,2]. SLN and NLC are suited for the incorporation of lipophilic actives, whereas the loading with hydrophilic molecules is relatively low. This is because hydrophilic molecules can only be solubilised in the lipid matrix. To overcome this lipid drug conjugate (LDC) were developed in 2001[3].

Basic criteria involve in the selection of lipids for production of lipid Nanoparticle are solubility study of drug in various lipids, partitioning behavior of drug in solid as well as liquid lipid & compatibility study of different lipid mixture [4].

WHY LIPID NANOPARTICLES? [1, 5]

- Better control over release kinetics of encapsulated compound

  - Engineering via size and lipid composition.
  - Melting can serve as trigger.
- Enhanced bioavailability of entrapped bioactive.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvents required.
- Wider range of base materials (lipids).
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility:
  - Can be subjected to commercial sterilization procedures.
  - Can be freeze-dried to produce powdered formulation.

ADVANTAGES OF LIPID NANOPARTICLE OVER CONVENTIONAL PARTICULATE CARRIERS [1, 5]

- Their small size and relatively narrow size distribution permits site-specific drug delivery.
- Controlled and Sustained release of active drug can be achieved.
- The incorporated drug is protected from the onslaughts of biochemical degradation.
- High drug payload.
- Incorporation of lipophilic and hydrophilic drugs feasible
- Can be sterilized by autoclave or gamma radiation.
- Can be lyophilizes and spray dried.
- Do not generate any toxic metabolites.
- Relatively cheap and stable.
- Easy of industrial scale production by hot dispersion technique.
- Surface modification can be easily performed.

DEVELOPMENT OF LIPID NANOPARTICLE

It was in 1990 when the first experiments in the production of lipid nanoparticles were performed in academic labs. The lipid nanoparticles were developed in parallel by M. R. Gasco in Turin/Italy, and by R. H. Muller/Berlin and J. S. Lucks, both at this time in Kiel/North Germany. The particle matrix of these novel carriers consisted of a solid lipid, therefore, to clearly differentiate these particles from nanoemulsions and fluid liposomes, they were called solid lipid nanoparticles (SLN). In 1999, the second generation of lipid nanoparticles was developed, the so called nanostructured lipid carriers (NLC). In these particles the matrix is composed not only of one solid lipid, but of a blend of a solid and a liquid lipid (e.g. oil). Advantages of NLC when compared to SLN are an increased loading capacity of actives. SLN and NLC are suited for the incorporation of lipophilic actives, whereas the loading with hydrophilic molecules is relatively low. To overcome this obstacle, in 2001 the so called lipid-drug-conjugates (LDC) were developed by Muller and Olbrich[3].

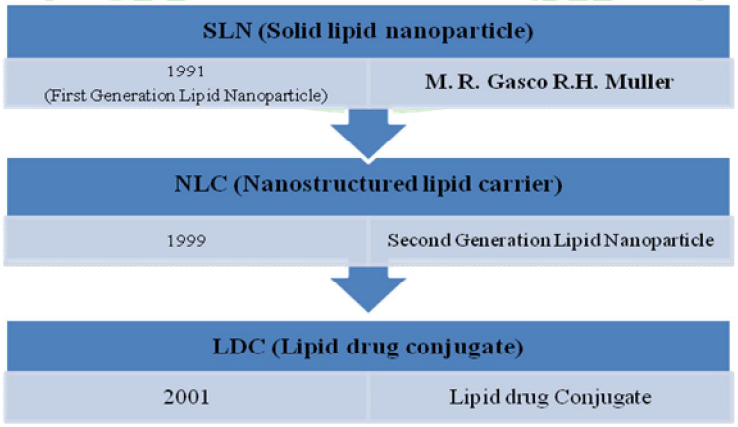

Figure 1: Development of lipid Nanoparticle

SLN & PROBLEM ASSOCIATED WITH IT

Different models have been described in the literature for how active molecules can be incorporated into SLN [6]. For each of the carriers, three basic types are described. The type of SLN depends on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production (hot vs. cold HPH), and the production temperature.

Therefore, three incorporation models have been proposed [7].

Types of SLN

- SLN Type I or homogeneous matrix model,
- SLN Type II or drug-enriched shell model and
- SLN Type III or drug-enriched core model.

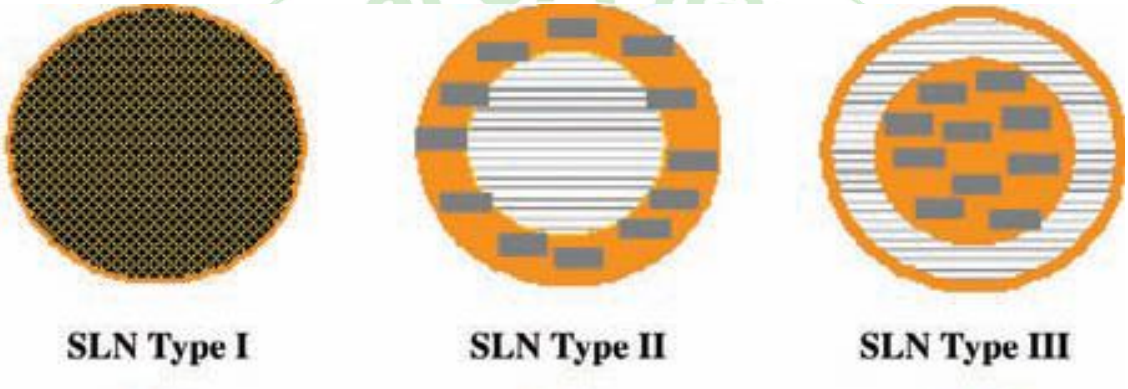

Figure 2: Basic types of solid lipid Nanoparticle

The SLN Type I:-

The SLN Type I corresponds to a homogeneous matrix model where the lipid and active ingredient are solidified (or crystallized) simultaneously and uniformly.

The SLN Type II:-

The SLN Type II or drug-enriched shell model is achieved when SLN are produced via the hot HPH technique and the active ingredient concentration in the melted lipid is low. During the cooling process of the hot o/w nano-emulsion, the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining lipid melt with increasing fraction of lipid solidified. An active-free lipid core is formed; when the active reaches its saturation solubility in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment in the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled way by altering the production parameters. A typical example of an active-enriched shell model is the incorporation of coenzyme Q10.

The SLN Type III:-

The SLN Type III or drug-enriched core model can take place when the active ingredient concentration in the lipid melt is high and at or relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt; when the saturation solubility is exceeded; active molecules precipitate leading to the formation of a drug-enriched core. The review by Mehnert high lights these aspects [1,5]. Pay-load for a number of drugs too low Drug expulsion during storage (Figure. 3) High water content of SLN dispersions

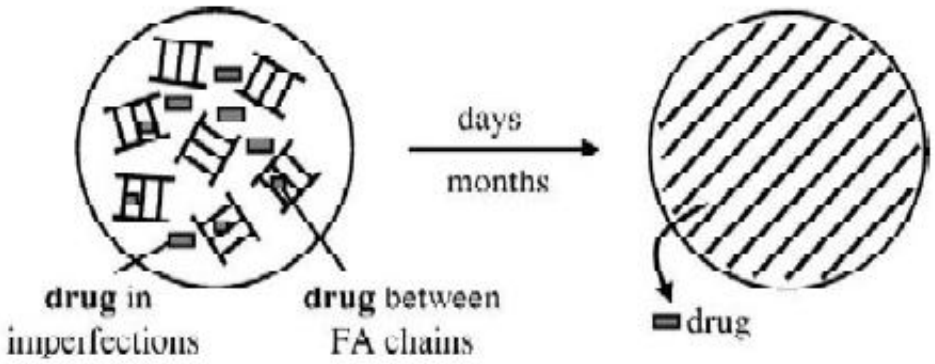

Figure 3: Mechanism of drug expulsion during storage of SLN dispersions, transition to highly ordered lipid crystal [8].

DEVELOPMENT OF NLC

NLC have been developed to overcome the drawbacks associated with SLN. They are considered to be the second generation of lipid nanoparticles. Compared to SLN, NLC show a higher loading capacity for active compounds by creating a less ordered solid lipid matrix, i.e. by blending a liquid lipid with the solid lipid, a higher particle drug loading can be achieved. Therefore, the NLC have an increased drug loading capacity in comparison to SLN and the possibility of drug expulsion during storage is less [8,9].

THE NEW CONCEPT OF NLC

The three types of NLC can be summarized

- The imperfect type
- The amorphous type
- The multiple type

A potential problem in SLN is the formation of a perfect crystal, which can be compared to a dense 'brick wall'. Using different molecules, i.e. different 'stones' to build the matrix or 'wall' leaves enough imperfections to accommodate the drug. Drug load in SLN is limited due to the formation of the lipid crystal. Drug expulsion is caused by an ongoing crystallization process towards a perfect crystal. Thus, by avoiding crystallization, one can avoid these obstacles—which is realised in the NLC type 2. The lipid matrix is solid but not crystalline it is in an amorphous state . This can be achieved by mixing special lipids, e.g. hydroxyoctacosanylhydroxystearate with isopropylmyristate. The solid character of the particles was proven by NMR measurements and the lack of crystallinity by DSC analysis[10]. The third type of NLC is a multiple system, being comparable to w/o/w emulsions. In this case it is an oil-in-solid lipid-in-water dispersion. The solid lipid matrix contains tiny liquid oil nanocompartments This NLC type uses the fact that for a number of drugs, the solubility in oils is higher than their solubility in solid lipids.

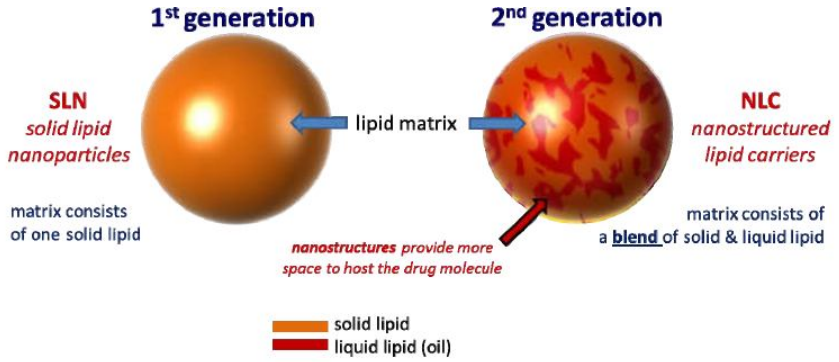

Figure 4: Difference between an SLN and an NLC particle matrix structure

LIPID DRUG CONJUGATE (LDC)

The lipid drug conjugates (LDC_S) a novel lipid based nanoparticles which has been extensively employed for the delivery and targeting of drugs. These have been exploited for many features in the field of pharmaceutical technology. SLN and NLC are suited for the incorporation of lipophilic actives, whereas the loading with hydrophilic molecules is relatively low. This is because hydrophilic molecules can only be solubilised in the lipid matrix or adsorbed on the surface. Thus, for hydrophilic drugs, a sufficient loading can only be achieved for very potent drugs,To overcome this obstacle, in 2001 the so called lipid-drug-conjugates (LDC) were developed by Muller and Olbrich.The lipid drug conjugates have the potential to act as a delivery system for hydrophilic and lipophilic drugs, which makes the delivery system suitable for brain targeting. Serum protein adsorption on lipid drug conjugate nanoparticles is a new carrier system for I. V. application. The particles were surface modified to target them to the brain which makes the lipid drug conjugates a promising delivery system [3].

SCREENING APPROACH

Selection of solid lipid:

Solubility Study:

Solid lipid selection was based on the solubility of drug to give a visually clear solution in lipid melt under normal light when seen with naked eye. The lipids used for the production of lipid Nanoparticle were selected such as Glyceryl behenate, Stearic acid, Cetyl palmitate, Tristearin, Tripalmitin, Tricaprin, Glyceryl monostearate etc. the drug and varying quantities of selected lipid in 15 ml of glass vials were heated above the melting point of lipid in controlled temperature water bath. After melting the lipid in vials the solubility of drug was observed visually in the melt [11, 12, 13]. solubility of drug in the lipid is a determinant of the encapsulation efficiency of lipid nanoparticle. It is expected that high lipid solubility would result in high encapsulation efficiency of the final formulation [4,11]. Dilip et al. found that Stearic acid having the highest potential to solubilize iaceclofenac as compare with the other lipid like Glceryl behenate, tristearin & cetyl palmitate. Quantity of solid lipid required to solubilize 10 mg of aceclofenac given in figure 5.

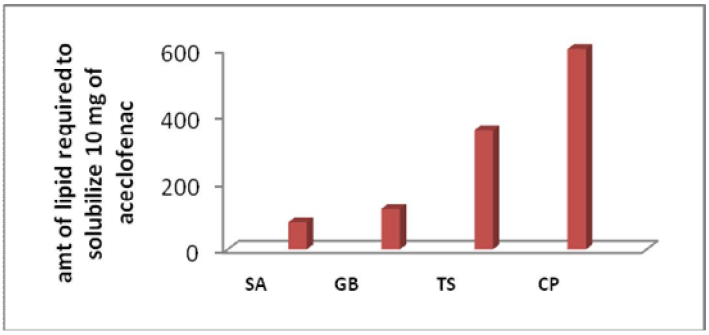

Figure 5: Solubility of aceclofenac in different solid lipids (SA- Stearic acid: GB- Glyceryl behenate: TS- Tristearin: CP- Cetyl palmitate) [4].

Partitioning Behavior:

Partition coefficients (ratio of the amount of drug in lipid to the amount of drug in aqueous phase) are another tool for the selection of solid lipid. Ten milligrams (Approximately) of drug was dispersed in a mixture of melted lipid (1 g) and 1 ml of hot distilled waterand shaken for 30 min in a hot water bath. Aqueous phase was separated after cooling by ultracentrifugation and analyzed for drug content. Bhalekar et al. showed that Partition coefficients (ratio of the amount of miconazole nitrate in lipid to the amount of miconazole nitrate in aqueous phase) obtained by analyzing drug content in aqueous phase were 37±2.14, 72.54±1.85, and 46±1.58 for Emulcire 61, compritol 888 ATO, and Precirol ATO 5, respectively. Compritol 888 ATO in which miconazole nitrate exhibited higher partition coefficient was selected for preparation of SLN[14] .

Selection of liquid lipid

The solubility of drug in different liquid lipids (oils), was determined by using shake flask method. Briefly, an excess of drug was added individually to the oils in screw capped tubes. Mixtures were then shaken for 24 hours in a water bath shaker maintained at 25^0C±2 ^{0}C. After 24 hour, each sample was centrifuged at 5000 rpm for 10 minute; supernatant was diluted suitably. The amount of drug solubilized in the vehicles was analyzed by HPLC or UV-VISIBLE spectrophotometer [15, 16]. Dilip et al. found solubility of aceclofenac is higher in oleic acid followed by isopropyl myristate, Oleic acid selected as liquid lipid for NLC formulation because it belonging to the frequently used penetration enhancers in the semisolid vehicle applied to the skin may enhance drug uptake further [4].

Solid lipid liquid lipid compatibility

After selection of solid lipid and liquid lipid a compatibility study of both lipid were performed, solid lipid and liquid lipid in 9:1 were taken and put in glass vials & heated at 100^0C. The mixture were checked after 1 hour immediately after solidification and after 24 hours, mixture creating one single phase only were selected [12,15].

CONCLUSION

Solid lipid nanoparticles and nanostructured lipid carriers developed to overcome stability problems of liposomes may result in approved drugs with improved stability, LDC were developed to overcome the problem associated with SLN & NLC. The article further explains about basic preformulation strategies for selection of solid & liquid lipid for lipid Nanoparticle dispersion.

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