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Review Article

Nanostructured Lipid Carriers: An Alternative to Solid Lipid Nanoparticles as Potential Second Generation Carrier for Topical Delivery of Antibiotics

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Abstract

As compared to emulsion, liposomes and polymeric microparticulate systems, Nanostructured Lipid Carriers (NLC) has emerged as a novel colloidal drug carrier system which has gained a lot of popularity among researcher due to its applicability for various routes such as oral, topical and parenteral with embedded properties of site specific and controlled drug delivery with reduced side effects. Along with their advantages, some challenges such as low drug loading and drug expulsion from Solid Lipid Nanoparticles SLN during storage were needed to be addressed. These limitations were overcome in Nanostructured lipid carriers (NLC), which are second generation SLN. NLC accommodate the drug because of their highly unordered lipid structures. NLC can be administered via oral, ocular, pulmonary and intravenous routes. The present reviews correlate the types of NLC, preparation methods and characterisation of SLN and NLC. The review covers in brief the comparative study of SLN and NLC of some drugs by researchers.

Keywords: Solid lipid nanoparticles, Nanostructured lipid carriers, lipid matrix, drug carriers.

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Introduction

Solid lipid nanoparticles (SLN) are of several potential applications in drug delivery and research. Due to their unique size dependent properties, lipid nanoparticles offer possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could use for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. SLN are the new generation of nanoparticulate active-substance vehicles and are attracting major attention as novel colloidal drug carriers for topical use. Compared with other vehicles such as creams, tinctures, and emulsions, SLN combine such advantages as controlled release, negligible skin irritation, and protection of active compounds.[1]

Although SLN have numerous advantages of controlled and targeted drug delivery increased stability of incorporated drug, there are some limitations too. During storage it was observed that drug was expelled out of SLN. The reason behind expulsion of drug was the highly ordered crystalline lipid matrix which was leaving very little space for drug molecules. To overcome the said problem nanostructured lipid carriers (NLC) were introduced. The first report on the use of SLN for oral delivery is by Speiser who termed them as nanopellets. As the science of SLN technology progressed, different methods of production for them were developed and stable formulations of SLN were discovered.[2]

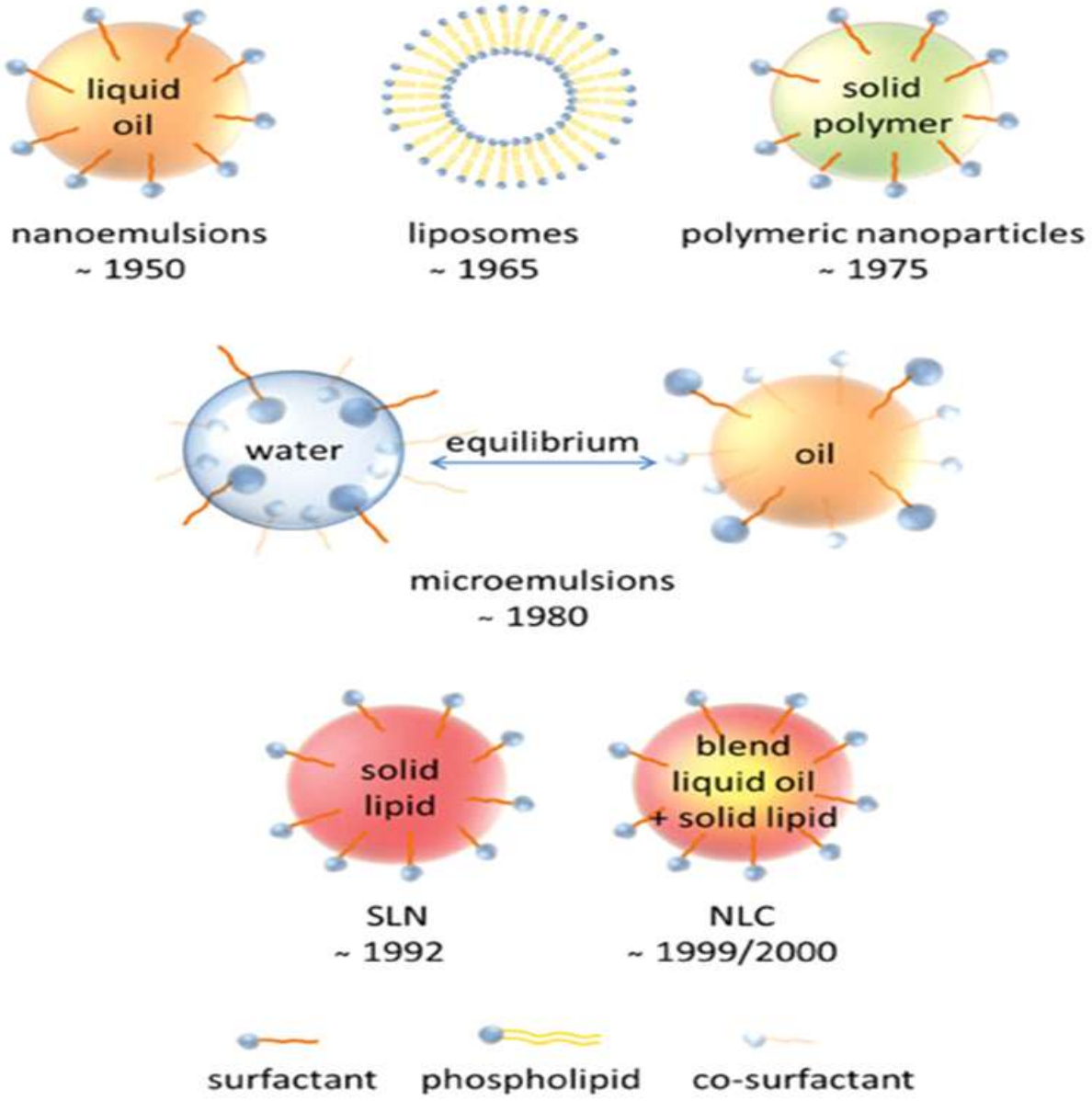

Fig. 1: Different generations of carrier dosage forms utilized for different drug delivery systems.

Earlier, the utilization of SLN for Parenteral drug delivery with focus on the definition of lipid nanoparticles and their different types such as SLN, NLC, and Lipid Drug Conjugates, their production techniques, scale-up feasibilities, stability of the incorporated drug, release and the biological and biopharmaceutical aspects have been discussed.

NLC are the second generation SLN, NLC are composed of binary mixture of solid lipid and a spatially different liquid lipid as the carrier. This consists of a lipid matrix with a special nanostructure and this nanostructure improves drug loading and firmly incorporates the drug during storage. NLC can be administered, e.g., via the oral, ocular, pulmonary and the intravenous route. NLC accommodate the drug because of their highly unordered lipid structures.[3]

Types of NLC

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. 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.[4]

Type II

The multiple oil/fat/water, drug can be accommodated in the solid, but at increased solubility in the oily parts of the lipid matrix. 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.[5]

Type III

Lipids are mixed in a way that prevents them from crystallizing. The lipid matrix is solid, but in an amorphous state.[6]

Table 1: Comparison of states between SLN and NLC along with their different subtypes.

Solid Lipid Nanoparticles	Nanostructured Lipid Carriers (Solid Lipid + Oil)
Drug With Solid Lipid Blend	Type I- Low Oil (Imperfect Matrix)
	Type II- High Oil (Multiple O/F/W Type)
	Type III-Amorphous (Noncrystalline Amorphous Nlc)

Methods of preparation for SLN and NLC

1. Homogenization Method.
   a) Hot homogenization
   b) Cold Homogenization
2. Solvent evaporation method.
3. Solvent emulsification-diffusion Method.
4. Microemulsion based method
5. Supercritical fluid method
6. Spray drying method
7. Double emulsion method
8. Precipitation technique
9. Film-ultrasound dispersion
10. High-speed homogenization followed by ultrasonication method

Hot homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A preemulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. High pressure homogenization of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.[7]

Cold homogenization

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as temperature induced drug degradation, drug distribution into the aqueous phase during homogenization. In cold homogenization the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a presuspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.[8]

Solvent evaporation

SLN can also prepared by solvent evaporation method. The lipophilic material is dissolved in a

water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar).[9]

Microemulsion based method

Microemulsion based method Gasco and co-workers developed NLC preparation techniques which are based on the dilution of microemulsions.They are made by stirring an optically transparent mixture at 65-70 0 which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), coemulsifiers (sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3 0) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic cosolvents of the microemulsion might play a similar role in the formation of lipid nanoparticles as the acetone for the formation of polymer nanoparticles. [10]

Spray drying method

It's an alternative procedure to lyophilization in order to transform an aqueous NLC dispersion into a drug product. It's a cheaper method than lyophilization. But his method can cause particle aggregation due to high temperature, shear forces and partial melting of the particle.[11]

Models for incorporation of active compounds into SLN

There are basically three different models for the incorporation of active ingredients into SLN

I. Homogeneous matrix model

II. Drug-enriched shell model

III. Drug-enriched core model

Release of active compounds from SLN

The effect of formulation parameters and production conditions on the release profile from SLN was intensively investigated by Mehnert, Müller and zur Mühlen. They investigated the release profile as a function of production temperature. It can be summarised from their findings that the release profiles were often biphasic—an initial burst release was followed by a prolonged release.

The extent of burst release could also be controlled by the amount of surfactant used in the formulation. High surfactant concentration leads to high burst release, low surfactant concentration to minimisation of the burst. This was explained by redistribution effects of the active compound between the lipid and the water phase during the heating up process and subsequently the cooling down process after production of the hot oil-in-water emulsion during the hot homogenization process. Heating the lipid / water mixture leads to an increased solubility of the drug in the water phase, the drug partitions from the melted lipid droplet to the water phase. After homogenization, the oil in water emulsion is cooled, the lipid core starts crystallizing with still a relatively high amount of active drug in the water phase. Further cooling leads to supersaturation of the drug in the water phase, the drug tries to partition back into the lipid phase; a solid core has already started forming leaving only the liquid outer shell for drug accumulation. From this it can be summarised that the higher the solubility of drug in the water phase during production, the more pronounced is the burst effect.[12]

The solubility increases with increasing production temperature and increasing surfactant concentration (the latter only when the surfactant solubilises the active compound). Consequently, little or no burst will be obtained when producing at low temperatures, low surfactant concentration or surfactant in free medium.

Conclusion

To overcome the stability and drug expulsion problems of SLN, the NLC (known as second

generation) had emerged. The highly unordered lipid matrix structured of NLC improved drug encapsulated and stability also presenting controlled and targeted drug release made them popular in nanopharmaceutical research field. NLC are attractive alternatives to micro and nanoemulsion, liposomes and

nanoparticles, but a detail study of possibility of meeting industrial needs such as process scale up, equipment qualification and validation is required. We hope in near future a number of drugs will be presented as their NLC.

References

1. Gasco MR. Method for producing SLN of narrow size. United state patent.1993;5,250,236.
2. Relkin P , Shukat R , Bourgaux C , Meneau F. Procedia Food Science.2011;1: 246 – 250.
3. Singhal G, Patel R, Prajapati B G, Solid Lipid Nanoparticles: A Review. Scientific Reviews & Chemical Communications. International Research Journal of Pharmacy.2011;2(2): 40-52.
4. Ekambaram P, Abdul H S and K.Priyanka. Solid Lipid Nanoparticles: A Review. Scientific Reviews & Chemical Communications.2012; 2(1):83-87.
5. Patel D, Dasgupta S, Dey S , Ramani Y R, Ray S, Mazuder B. Nanostructured Lipid Carriers (NLC)-Based Gel for the Topical Delivery of Aceclofenac: Preparation, Characterization, and In VivoEvaluation. Science Pharma 2012;80: 752.
6. Muller R H, Radtke M, Wissing S A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advanced Drug Delivery Reviews 2002; 1(54): S134 –S136.
7. Waghmare A.S, Grampurohit N.D, Gadhve N.D, Gadhve M.V, Gaikwad D.D, Jadhav S.L. Solid Lipid Nanoparticles: A Promising Drug Delivery System. International Research Journal of Pharmacy. 2012; 3(4):106.
8. M. Schäfer-Korting and Wolfgang Mehnert. Lipid nanoparticles for improved topical application of drugs for skin diseases. Advanced Drug Delivery Reviews.2007; 59:427–443
9. Souto EB, Muller RH. SLN and NLC for topical delivery of ketoconazole. Journal of Microencapsulation. Aug 2005;22(5): 501-10.
10. Elnaggar SR, Magda A El-Massik, Abdallah OY. Fabrication, appraisal, and transdermal permeation of sildenafil citrate-loaded nanostructured lipid carriers versus solid lipid nanoparticles. International Journal of Nanomedicine. 2011; 6:3195-205.
11. Wang JJ, Liu KS, Sung KC, Tsai CY, Fang JY. Skin permeation of buprenorphine and its ester prodrugs from lipid nanoparticles: lipid emulsion, nanostructured lipid carriers and solid lipid nanoparticles. Journal of Microencapsulation. Dec 2009 ;26(8):734-47.
12. Souto EB, Muller RH. Investigation of the factors influencing the incorporation of clotrimazole in SLN and NLC prepared by hot high-pressure homogenization. Journal of Microencapsulation. June 2006; 23(4):377-88.
13. Souto EB; Muller RH. The use of SLN and NLC as topical particulate carriers for imidazole antifungal agents. Phamazie. May 2006; 61(5):431-7.
14. Pathak P and Nagarsenkar M. Formulation and Evaluation of Lidocaine Lipid Nanosystems for Dermal Delivery. AAPS Pharma Science Technology.2009;10(3):985-992.
15. Steacova J, Wolfang M, Blaschke T. Pharmaceutical Research.2007; 24(5): 991-1000.
16. Souza LG, Silva EJ, Martins AL, Mota MF, Braga RC, Lima E, Valadares MC, Taveira SF, Marreto RN. Development of topotecan loaded lipid nanoparticles for chemical stabilization and prolonged release. European Journal of Pharmaceutics and Biopharmceutices.