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Review Article

Lipid nanoparticles: A modern Formulation Approach in Topical drug Delivery Systems

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ABSTRACT

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals.lipid nanoparticles are known as solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers, which are attracting wide attention of formulators world-wide. SLNs and NLCs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsion, liposomes and polymeric nanoparticles).Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are composed of a solid matrix once they are derived from o/w emulsions simply replacing the liquid lipid (oil) by a lipid being solid both at room and body temperature.The important parameters which need to be evaluated for the SLNs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, in vitro drug release and surface morphology.Lipid carriers has bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility. SLN and NLC offers an economical and patient-friendly device for administration of drugs by topical routes.

Keywords: Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLC), Topical Drug Delivery, Topical Applications

INTRODUCTION

Solid lipid nanoparticles (SLN) combining the advantages of colloidal carriers, had attracted increased attention as a drug delivery system when it was introduced in 1991[1]. To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs) and Nanostructured lipid carriers, which are attracting wide attention of formulators world-wide. SLNs and NLCs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsion, liposomes and polymeric nanoparticles). They are new a generation of submicron-sized lipid emulsion where the lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at interfaces, and are

attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials.[2]

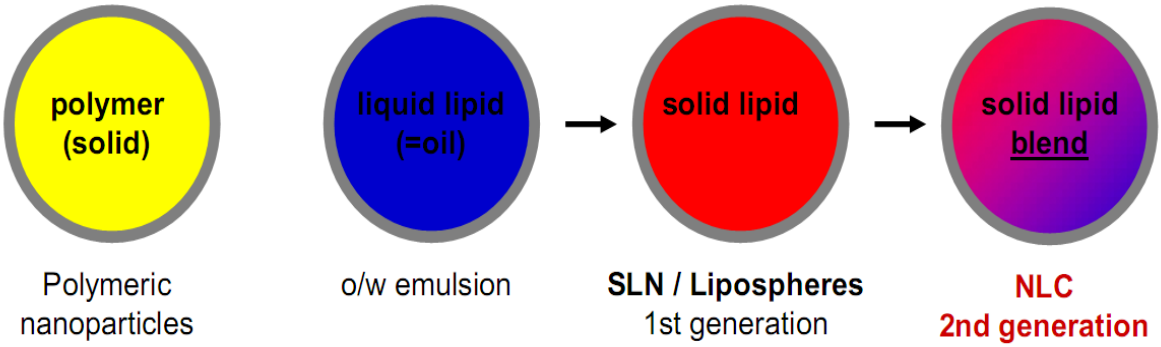

Fig.I. Traditional Carriers And Lipid Nanoparticles

The term colloid is broadly applicable to systems consisting of at least 2 components; one dispersed in the other as fine particles in any state of matter.
As pharmaceutical carriers, colloidal drug delivery systems can be subdivided into:

- Polymer systems (micelles, dendrimers, etc),
- Self-assembled lipid systems (liposomes, emulsions, solid lipid nanoparticles, etc),
- Drug nanoparticle systems and pro-colloidal systems (self-emulsifying oral delivery systems and liquid crystalline systems).[1]

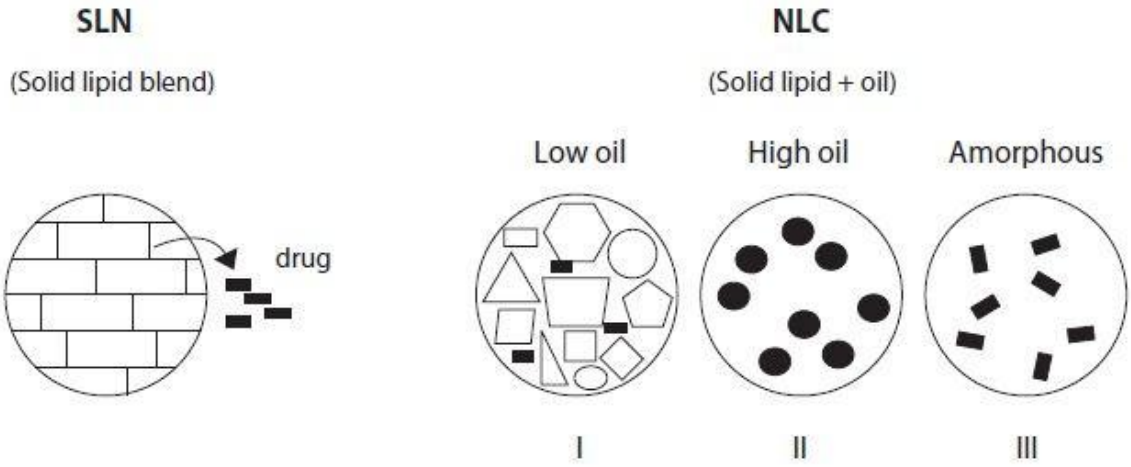

Fig.II. Different type of NLC: I-highly imperfect matrix; II-multiple O/F/W type; III-non crystalline amorphous NLC. (Versus SLN with high crystallinity)[3].

PURPOSE OF TOPICAL PREPARATION[4]

In order to formulate an effective and efficient topical preparation, consideration must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the

preparation. Topical preparations may be used for:

- Surface effects: cleansing (removal of dirt and germs), cosmetic (enhancement of appearance), protective (prevention of moisture loss, sunscreen), antimicrobial (reduction of infection).
- Stratum corneum effects: protective (e.g. sunscreens that penetrate this layer), keratolytic (a sloughing of the skin, useful in the treatment of psoriasis), protective (moisturizing).
- Viable epidermal and dermal effects: several classes of drugs may penetrate to these layers (anti-inflammatory, anesthetic, antipruritic, antihistamine). Although it is difficult for drugs to penetrate the stratum corneum, once they are in the dermis, they can diffuse into the general circulation. It is difficult to formulate a drug with only a local effect without subsequent uptake by the blood.
- Systemic effects: a few drugs, such as scopolamine, nitroglycerin, clonidine, and estradiol, have been formulated in a manner to achieve systemic effects.
- Appendage effects: some classes of drugs are intended to exert their action in these portions of the skin (depilatory, exfolient, antimicrobial, and antiperspirant). Infection remains major cause of morbidity and mortality following the shock phase in the burn patient. Measures to reduce the risk of wound infection and subsequent sepsis include early excision where possible, and the use of topical antimicrobial creams such as silver sulphadiazine. The patient suffering major burns is at risk from both cutaneous and systemic infection.

PRINCIPLES OF TOPICAL DRUG RELEASE

The common principles of drug release from lipid nanoparticles can be explained below; drug release is inversely proportional to the partition coefficient of the drug. Surface area increases due to smaller particle size in nanometer range which results in higher drug release. Slow release of drug could be accomplished when the drug is equally dispersed in the lipid matrix. This phenomenon of drug dispersion depends on type of SLN and drug entrapment (set up) model of SLN.

Crystalline form of the lipid carrier substance and high flexibility of the drug result into the fast drug release from system. Crystallization degree and mobility of drug are inversely proportional to each other. The drug incorporation model of solid lipid nanoparticles is crucial to the drug release pattern.

Fast primary drug release (burst effect) happens in the first 5 minutes in the drug-enriched shell model (i.e., about 100% within <5 min) as because of the outer most layer of the particles due to the larger surface area of drug (i.e. smaller particle size) decomposition on the particle surface. The burst release phenomenon can reduces with increasing the particle size and continuous release of drug obtained when the particles size will be adequately larger, i.e. lipid microparticles. The nature of surfactant used in the system and its concentration i.e. which will interact with the outer most shell to affect its structure, should be observed as the further significant factor, because a lower surfactant concentration results into a minimum burst and prolonged drug release. In the drug-enriched core model, the release of drug will be membrane controlled and is governed by the Flicks law of diffusion since the lipid surrounds to the drug as a membrane.[5]

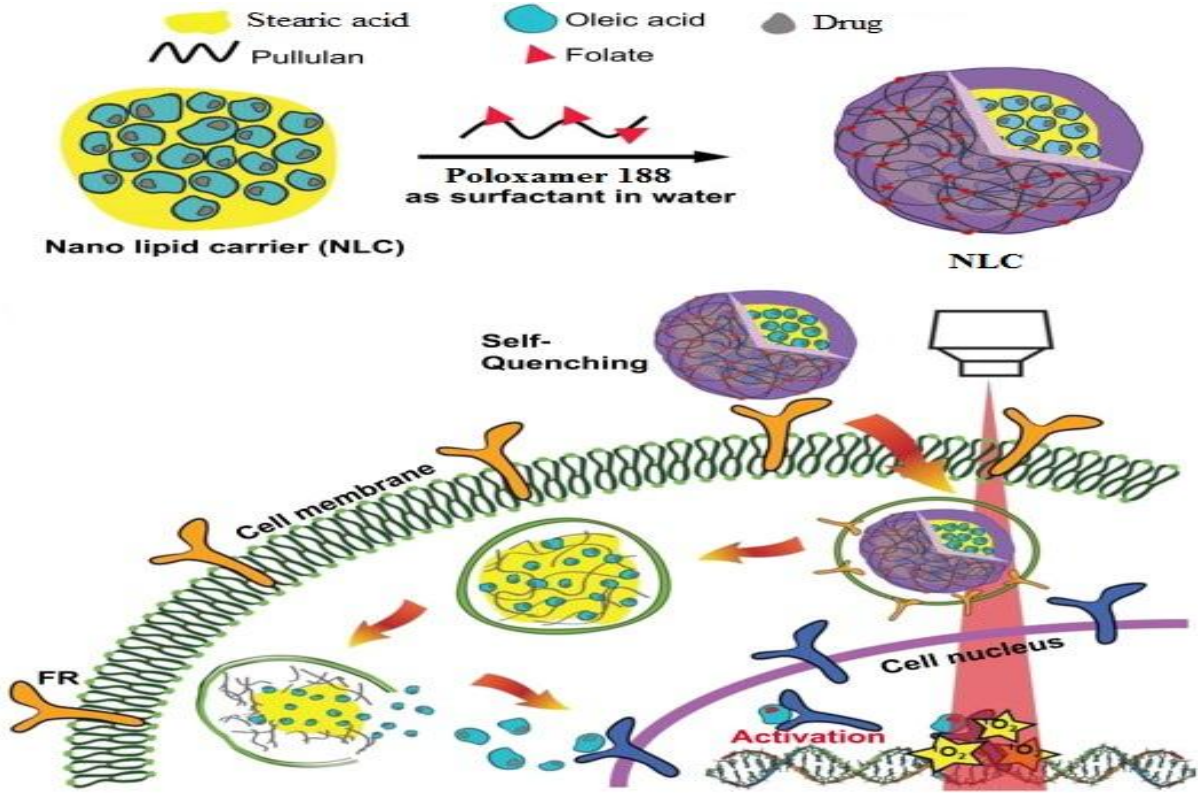

Fig.III. Principles of drug release from lipid nanoparticles.

DERMATOLOGICAL BASES[4]

Generally, topical preparations meant for systemic or local effect are classified as

- Solids – Dusting powder
- Semi-solids – Creams, Gel, Ointments, Paste and other
- Liquids – Solution, Emulsion, Liniments, Suspension, Soaps, Shakes, Collidons, Lotion, Paints and other.
-

COMPOSTIONS

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are composed of a solid matrix once they are derived from o/w emulsions simply replacing the liquid lipid (oil) by a lipid being solid both at room and body temperature. Being the particle matrix is in a solid state, its melting point which varies between 50ºC (122ºF) and up to almost 100ºC (212ºF) can be adjusted by the choice of the lipid. SLN are the first generation of the lipid nanoparticles, consisting of a matrix which is produced solely from a solid lipid. The lipid can be a highly pure lipid e.g. tristearin or a less defined mixture of acylglycerols, such as Compritol® or Imwitor®. NLC are produced from a lipid blend, consisting of a mixture of a solid lipid with a liquid lipid (oil). This mixture is chosen in order to obtain a particle matrix which is in a solid state at the anticipated melting point. Relatively high amounts of oil can be incorporated when choosing a mixture with a high melting lipid, e.g. blending the oil with a wax of high melting point (80-90ºC).[6]

Enlisted Methods of preparation for SLN and NLC [3]

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

CHARACTERIZATION

Adequate and proper characterization of the SLNs and NLCs are necessary for its quality control. However, characterization of SLN and NLC is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters which need to be evaluated for the SLNs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, *in vitro* drug release and surface morphology. The particle size/size-distribution may be studied using photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM) atomic force microscopy (AFM), scanning tunnelling microscopy (STM), or freeze fracture electron microscopy (FFEM)[2].

TOPICAL APPLICATIONS[2]

SLNs and NLCs have been used for topical application for various drugs such as tropolide, imidazole antifungals, anticancers, vitamin A, isotretinoin, ketoconazole, DNA, flurbiprofen and glucocorticoids. The penetration of podophyllotoxin-SLN into stratum corneum along with skin surface lead to the epidermal targeting. By using glycerylbehenate, vitamine A-loaded nanoparticles can be prepared. The methods are useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipid nanoparticles was formulated for topical delivery of drug. The soyabean lecithin and Tween 80 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin. Production of the flurbiprofen-loaded SLN gel for topical application after a potential advantages of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Polyacrylamide, glycerol and water were used for the preparation of this type of SLN gel.

LIMITATIONS OF THE SOLID LIPID NANOPARTICLES

- Drug expulsion phenomenon (when lipid crystallizes to the stable b-form).
- Particle concentration in the aqueous dispersions range from about 1% to 30%.
- Limitation of drug load by the solubility of the drug in the solid (lipid).[5]

These limitations were solved by a lipid particle with the controlled nanostructure, the nanostructured lipid carrier (NLC). In the NLC, very different lipids were blended to form the matrix, i.e. solid lipids and liquid lipids. Due to their change in structure they cannot fit together very fine to form a perfect crystal form, the matrix containing a lot of imperfections to accommodate drug in molecular form and amorphous clusters form.

ADVANTAGES OF TOPICAL LIPID NANOPARTICLES

- Increase of skin occlusion[7.8]
- Increase of skin hydration and elasticity[9,10]
- Enhancement of skin permeation and drug targeting[11,12]
- Improve benefit/risk ratio[13,14]
- Enhanced chemical stability of chemically liable compounds[15,16]

CONCLUSION

Lipid carriers has bright future, because of their intrinsic property to improve the bioavailability of lipophilic drugs with low aqueous solubility. SLN and NLC offers an economical and patient-friendly device for administration of drugs by topical routes.Technologically, the straightforward production of nanocarriers avoiding organic solvents should be a relevant criterion for industrial scale-up (e.g. Solid Lipid Nanoparticles and Nanostructured Lipid Carries) conditioning the becoming of topical formulations for the 21st century's dermatological practices.

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