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Review Article

SOLID LIPID NANOPARTICLES AND NANO LIPID CARRIERS: AS NOVEL SOLID LIPID BASED DRUG CARRIER

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ABSTRACT
Interest in lipid based drug delivery has developed over the past decade fuelled by a better understanding of the multiple roles lipids may play in enhancing oral bioavailability. Moreover, the emergence of novel excipients with acceptable regulatory and safety profiles coupled with advances in formulation technologies have greatly improved the potential for successful lipid based formulations. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles. SLN combine advantages of the traditional systems but avoid some of their major disadvantages. This paper reviews the present state of the art regarding production techniques for SLN/ nanostructured lipid carrier (NLC), drug incorporation method and types, stability. The potential of SLN/NLC to be exploited for the different administration routes is also highlighted.

KEYWORDS: Solid lipid nanoparticles, nanostructured lipid carrier, lipid based drug delivery, Application of SLN/NLC

INTRODUCTION
In the 1960s, the first safe parenteral fat emulsion (Intralipid) was developed by Wretlind for parenteral nutrition[1]. This was the beginning of a new delivery system for lipophilic drugs, which can be incorporated easily into the oil droplets. Successful market products are, e.g. Diazemuls and Diprivan. The main advantage of this carrier system is the reduction of side effects caused at the injection side[2]. A major disadvantage however is the critical physical stability of the drug containing emulsions due to a reduction ofthe zeta potential (ZP) which can lead to agglomeration, drug expulsion and eventually breaking of the emulsion[3].

Another interesting carrier systems are the liposomes. They have been described for the first time by Bangham et al. in the 1960[4,5]. Trade products (Ambisome, DaunoXome, Doxil and Alveofact) have been developed in order to reduce toxic side effects of the incorporated highly potent drugs and increase the efficacy of the treatment [6,7]. Major obstacles for the development of liposomal formulations were limited physical stability of the dispersions, drug leakage, low activity due to no specific tumour targeting, non specific clearance by the mononuclear phagocytic system (MPS) and difficulties in upscaling [6,8].

Polymeric nanoparticles made from non-biodegradable and biodegradable polymers are yet another innovative carrier system. Advantages of these particles are site-specific targeting and controlled release of the incorporated drugs[9]. However, the cytotoxicity of the polymers after internalization into cells is a crucial and often discussed aspect[10]. Also, large scale production of polymeric nanoparticles is problematic. Therefore, this carrier system has so far not been relevant for the pharmaceutic market.

In the middle of the 1990s, the attention of different research groups has focussed on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles (SLN or lipospheres or nanospheres) [11-14].

The SLN combine the advantages of other innovative carrier systems e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability, while at the same time minimising the associated problems. SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonar, rectal) have been developed and thoroughly characterised in vitro and in vivo[16–18].

SLN are produced by replacing the liquid lipid (oil) of an o/w emulsion by a solid lipid or a blend of solid lipids, i.e. the lipid particle matrix being solid at both room and body temperature[25]. SLN are composed of 0.1% (w/w) to 30% (w/w) solid lipid dispersed in an aqueous medium and if necessary stabilized with preferably 0.5% (w/w) to 5% (w/w) surfactant. The incorporation of cosmetic and pharmaceutical actives is feasible. The mean particle size of SLN is in the submicron rage, ranging from about 40 to 1000nm [25].

A first product has recently been introduced to the Polish market (Nanobase, Yamanouchi) as a topically applied moisturiser.

SLN have the chance to be exploited as delivery system in commercial products. However, there are also three limitations of the SLN system:

- drug expulsion phenomenon when lipid crystallizes to the stable b-form
- particle concentration in the aqueous dispersions ranging from about 1% to a maximum of only 30%.
- limitation of drug load by the solubility of the drug in the solid lipid.

These limitations was solved by creating a lipid particle with a controlled nanostructure, the nanostructured lipid carrier (NLC) [23,24]. 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.

In the second generation of the lipid nanoparticle technology, the particles are produced using blends of solid lipids and liquid lipids (oils). To obtain the blends for the particles matrix, solid lipids are mixed with liquid lipids (oils), preferably in a ratio of 70:30 up to a ratio of 99.9:0.1. Due to the oil in these mixtures a melting point depression compared to the pure solid lipid is observed, but the blends obtained are also solid at body temperature. This second generation of nanoparticles is called nanostructured lipid carriers (NLC). The overall solid content of NLC could be increased up to 95%. These second generation of submicron particles can be loaded with cosmetic and pharmaceutical actives as well [9,26].

However, as a distinct advantage of SLN compared to polymeric nanoparticles, they can be produced by high pressure homogenization identical to parenteral O/W emulsions. This is a technique well established on the large scale since the fifties and already available in the pharmaceutical industry. The production lines for parenteral emulsions are in most cases equipped with temperature control units because an increased temperature facilitates emulsion production, this means that existing production lines can be used for producing SLN by the hot homogenization technique.

a) Solid Lipid Nanoparticle (SLN)

SLN are particles made from solid lipids (i.e. lipids solid at room temperature and also at body temperature) and stabilised by surfactant(s). By definition, the lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes[14]. The first patents have been granted in 1993 and 1996 and contain claims on different production methods of SLN[12,14].

The main features of SLN are the excellent physical stability, protection of incorporated labile drugs from degradation, controlled drug release (fast or sustained) depending on the incorporation model, good tolerability and site specific targeting. Potential disadvantages such as insufficient loading capacity, drug expulsion after polymorphic transition during storage and releatively high water content of the dispersions (70–99.9%) have been observed[9,13,26]. The drug loading capacity of conventional SLN is limited (generally up to approximately 25% with regard to the lipid matrix, up to 50% for special actives

such as Ubidecarenone) by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymorphic state of the lipid matrix[28–30].

If the lipid matrix consists of specially similar molecules (i.e. tristearin or tripalmitin), a perfect crystal with few imperfections is formed. Since incorporated drugs are located between fatty acid chains, between the lipid layers and also in crystal imperfections, a highly ordered crystal lattice cannot accommodate large amounts of drug[15]. Therefore, the use of more complex lipids (mono-, di-, triglycerides, and different chain lenghths) is more sensible for higher drug loading. The transition to highly ordered lipid particles is also the reason for drug expulsion. Directly after production, lipids crystallise partially in higher energy modifications with more imperfections in the crystal lattice [31–34].

The preservation of the a-modification during storage and transformation after administration (e.g. by temperature changes) could lead to a triggered and controlled release and has recently been investigated for topical formulations[35].

b) Nanostructured Lipid Carrier (NLC)

NLC have been introduced at the end of the 1990s in order to overcome the potential difficulties of SLN described above[20,21,34]. The goal was the development of a nanoparticulate lipid carrier with a certain nanostructure in order to increase the payload and prevent drug expulsion. This could be realised in three ways. In the first model, different lipids composed of different fatty acids are mixed this leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus to more room for the accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils). This model is called "imperfect type NLC". If higher amounts of oil are mixed with the solid lipid, a different type of nanostructure is present. Here, the solubility of the oil molecules in the solid lipid is exceeded; this leads to phase separation and the formation of oily nanocompartments within the solid lipid matrix[36,37].

NLC have only been exploited for the topical delivery, however their advantages over conventional SLN are also of interest for other application routes.

PREPARATION OF SLN/NLC

SLNs are made up of solid lipid, emulsifier and water/solvent. The lipids used may be triglycerides (tristearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), steroids (cholesterol) and waxes (cetyl palmitate). Various emulsifiers and their combination (Pluronic F 68, F 127) have been used to stabilize the lipid dispersion. The combination of emulsifiers might prevent particle agglomeration more efficiently.

A. High Pressure Homogenization Technique

In high pressure homogenization technique lipids are pushed with high pressure (100-200 bars) through a narrow gap of few micron ranges. So shear stress and cavitations are the forces which cause the disruption of particle to submicron range. Normally the lipid contents are in the range of 5-10%. In contrast to other preparation technique high pressure homogenization does not show scaling up problem[21].

Basically, there are two approaches for production by high pressure homogenization, hot and cold homogenization techniques[48]. For both the techniques the drug is dissolved or dispersed or solubilized in the lipid being melted at approximately 5-10°c above the melting point.

I. Hot Homogenization Technique

In hot homogenization technique the drug loaded melted lipid is dispersed under stirring by high shear device (e.g. Ultra Turrax) in the aqueous surfactant solution of same temperature. The pre-emulsion obtained is homogenized by using a piston gap homogenizer (e.g. Macron LAB 40/60 or APV-2000) and the produced hot o/w nanoemulsion is cooled down to room temperature. At room temperature the lipid recrystallizes and leads to formation of Nanoparticles.

II. Cold Homogenization Technique

Cold homogenization is carried out with the solid lipid containing drug. Cold homogenization has been developed to overcome the following problems of the hot homogenization technique such as: Temperature mediated accelerated degradation of the drug payload, Partitioning and hence loss of drug into the aqueous phase during homogenizationFirst step in between cold and hot homogenization is same

but they are differing from next steps. The melt containing drug is cooled rapidly using ice or liquid nitrogen for distribution of drug in the lipid matrix. Cold homogenization minimizes the thermal exposure of the sample.

B. Microemulsion Technique

The lipids (fatty acids and/or glycosides e.g. stearic acid) are melted; drug is incorporated in molten lipid. A mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipids and added under mild stirring to the lipid melt[20]. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratios for microemulsion formation. Thus the microemulsion is the basis for the formation of nanoparticles of a requisite size. This microemulsion is then dispersed in a cold aqueous medium under mild mechanical mixing in the ratio of hot microemulsion to water (1:25 -1:50). This leads to rapid recrystallization of the oil droplets on dispersion in cold aqueous medium.Thus Nanoparticles are formed due to precipitation. Production of SLNs at large scale is also feasible by the microemulsion technique.

C. Solvent Emulsification-Evaporation Technique

In solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug were dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then that is emulsified in an aqueous phase using high speed homogenizer[19]. To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the microfluidizer. Thereafter, the organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates Nanoparticles.

D. Solvent Emulsification-Diffusion Technique

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of both liquid . When heating is required to solubilize the lipid, the saturation step was performed at that temperature[22]. Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. Here the both the phase were maintain at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved[38]. Throughout the process constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization.

E Melting Dispersion Method (Hot Melt Encapsulation Method)

In melting method drug and solid lipid were melted in an organic solvent regarded as oil phase and simultaneously water phase was also heated to same temperature as oil phase. Then in second step, the oil phase added in to a small volume of water phase and the resulting emulsion was stirred at higher rpm for few hrs[32,33]. At last it was cooled down to room temperature to give Nanoparticles.

F. High Shear Homogenization and/or Ultrasonication Technique

This is a less frequently studied method for the production of lipid nanoparticles. The particles are prepared by melting the core material, adding phospholipids along with an aqueous medium and dispersing the melted material at increased temperature by mixing techniques, such as mechanical stirring or sonication[39,40]. Particle size reduction of the core lipid emulsion with soya lecithin is carried out with the help of ultrasonic energy.

G. Double Emulsion Technique

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to

sterically stabilize them by means of the incorporation of a lipid -PEG derivative[42,43]. A major drawback of this technique is the formation of high percentage of microparticles.

DRUG INCORPORATION MODELS AND TYPES OF SLN/NLC

A. Drug incorporation models of SLN are

I. Solid Solution Model

In the case of the solid solution model, the drug is molecularly dispersed in the lipid matrix when the particles are produced by the cold homogenization technique and using no surfactant or no drug-solubilizing surfactant[13].

II. Drug-Enriched Shell Model

The enriched shell model is characterized by drug selectively locating at the interface, either by fast solidification of the matrix lipid or by successful competition of the drug for the interface. Drug dispersed by such a model might exhibit a successful burst effect during drug. According to the drug-enriched shell model of drug incorporation, a solid lipid core forms when the recrystallization temperature of the lipid is reached. On reducing the temperature of the dispersion, the drug concentrates in the still liquid outer shell of the SLN[18-20].

III. Drug-Enriched Core Model

The enriched core model is characterized by drug selectivity located at the core of the solid lipid nanoparticles, perhaps due to more rapid solidification of the drug relative to the matrix material. The enriched core model would be useful to produce a membrane controlled release pattern. Although the chemical stability and the release kinetics of drugs are largely related to localization of drugs within the aggregates. According to the drug-enriched core model of drug incorporation, cooling the nanoemulsion leads to a supersaturation of the drug which is dissolved in the lipid melt at or close to its saturation solubility and the drug precipitates prior to lipid recrystallization. Further cooling finally leads to the recrystallization of the lipid surrounding the drug as a membrane.

Factors affecting loading capacity of a drug in lipid are:

- solubility of drug in lipid melt,
- miscibility of drug melt and lipid melt,
- chemical and physical structure of solid matrix lipid,
- polymorphic state of lipid material.

In particular, there is an inverse relationship between solubility of the drug and loading capacity. Enhancement in aqueous solubility of drug leads lower to entrapment efficiency.

B. Drug incorporation models of NLC are

A SLN modified by incorporation of liquid lipid into the solid structure has been proposed as nanostructured lipid carriers (NLC) to overcome some limitations related to old generation SLN. Muller et al described NLC with a special structure for better drug accommodation in order to increase the payload and prevent drug expulsion during storage.

NLC combine controlled drug release characteristics with some advantages over SLN. NLC have so far been studied for topical use, but they offer all the advantages and production aims of SLN. Three types of NLC have been described which are summarized below.

I. Imperfect Type NLC (Imperfectly Structured Solid Matrix):

Spatially different lipids are mixed, and thus imperfections in the crystal order of lipid nanoparticles are provided. Therefore, the matrix contains imperfections to accommodate the drug in amorphous clusters. Mixing small amounts of chemically very different liquid lipids (oils) with solid lipids in order to achieve the highest incompatibility leads the highest drug payload.

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.

II. Amorphous Type (Structureless Solid Amorphous Matrix):

This kind of NLC can be achieved by mixing solid lipids with special lipids, eg, hydroxyoctacosanylhydroxystearate, isopropylmyristate or medium chain triglycerides such as Miglyol 822. Therefore, drug expulsion caused by the process of crystallization to β forms during storage is

prevented by the special structure of the lipid matrix since NLC are solids in an amorphous but not crystalline state (Radtke and Muller 2001).

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. 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.

III. Multiple Type (multiple oil in fat in water (O/F/W) carrier):

When lipids lack appropriate drug solubilities, addition of a higher amount of liquid lipid to the lipophilic phase displays the advantages of the solid matrix which prevented drug leakage while the liquid regions (oily nanocompartments) show comparatively high solubility for lipophilic drugs. In type III, lipids are mixed in a way that prevents them from crystallizing. The lipid matrix is solid, but in an amorphous state. The absence of crystallization avoids drug expulsion by crystallization.

STABILITY OF SLN/NLC DISPERSIONS

The physical stability of SLN dispersions has been investigated intensively, e.g. by measurements of particle size (photon correlation spectroscopy, PCS; laser diffraction, LD), charge (ZP) and thermal analysis (DSC)[46]. Physical stability of optimised aqueous SLN dispersions is generally more than 1 year[28,30] and Mu¨ller et al. could show stability for SLN made from glyceryl palmitostearate or tribehenate for up to 3 years by PCS[20]. The average diameter of the main population remained between 160 and 220 nm for the investigated period. Freitas and Mu¨ller investigated the effect of light and temperature on the physical stability of SLN dispersions composed of 10% tribehenate and 1.2% poloxamer 188[42]. They found that particle growth could be induced by an input of kinetic energy (light, temperature) to the system. Storage under artificial light lead to gelation of the system within 7 days of storage, under day light within 3 months and in darkness particle growth started after 4 months storage.

For the recently developed SLN based on calixarenes, stability data of more than 1 year have been published. Shahgaldian et al. have further investigated the influence of the ionic strength on stability, observing strongest destabilisation by sulphate ions [24]. Apart from optimised storage conditions of labile SLN dispersions, they can also be spray-dried or lyophilised. Lyophilisation can be employed as an alternative very sensitive drying method. The process has been optimised with regard to operating conditions, lipid concentration, type and concentration of cryoprotectant and redispersing conditions [20,44].

Heiati et al. have investigated the effect of cryoprotective sugars on the size of neutral and negatively charged SLN after lyophilisation and reconstitution[45]. The azidothymidine palmitate (AZT-P) loaded SLN were composed of trilaurin, stabilised with lecithin and they were prepared by solvent emulsification–evaporation and subsequent HPH. They found that trehalose was the most effective cryoprotectant in a sugar/lipid ratio of 3:9 for neutral SLN and 2:6 for negatively charged SLN. Also, trehalose was most effective for preventing drug expulsion upon reconstitution.

For lecithin stabilised SLN formulations, autoclaving was possible. No increase in particle size was observed by PCS. Alternatively, SLN could be sterilised by gamma irradiation or (if the size is well below 200 nm) by filtration.[24,45,47]

APPLICATION OF SLN/NLC

A. Topical Applications

The biggest achievement by SLN technology is in the field of topical application. The continuous progress in the field of nanotechnology has allowed the scientists to develop the carriers of drug to improve the penetration of skin and also in targeting to specific skin layers.SLN ensure increased penetration of drug into the epidermis by close contact with the stratum corneum. However the drug free nanoparticles can be used to improve occlusive properties. SLNs are being considered as the next generation carriers after the liposomes. Similar to liposomes they are composed of well tolerated excipients and due to their small particle size they possess adhesive properties leading to film formation on the skin. SLNs have the potential to induce epidermal targeting which is derived by the studies on

topical glucocorticoids. On topical application glucocorticoids are first line drugs for acute exacerbations and calcineurin inhibitors for long term suppression of eczema. In one study by Schafer Korting *et. al.* 2002 has investigated that well tolerated lipid nanoparticles are suitable for glucocorticoids targeting to viable epidermis. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLC) have lipid matrix which might prevent the burst release obtained in conventional topical formulations. The anti-inflammatory activity of SLNs and microemulsion was compared and was found stronger than that of microemulsion in carrageenan induced rat paw edema. Solid lipid nanoparticles promoted the penetration of the drugs. The anti-inflammatory activity of SLNs was found to be two fold higher than the conventional formulations in carrageenan induced rat paw edema. Thus, the highest permeation rate, sustained effects, and the anti-inflammatory effects were observed with solid lipid nanoparticles.

SLNs used for topical application for various drug such as anticancers[35], vitamin-A[36], isotretinoin, flurbiprofen[37]. Using glyceryl behenate, vitamine A-loaded nanoparticles can be prepared. This method is useful for the improvement of penetration with sustained release. The isotretinoin-loaded lipid nanoparticles was formulated for topical delivery of drug.Production of the flurbiprofen-loaded SLN gel for topical application offer a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations.

B. Oral Administrations

Oral administration of SLNs is possible as aqueous dispersion or in a traditional dosage form i.e. tablets, pellets, capsules or powders in sachets. The poor absorption of certain drugs can be related to their poor wettability, so that incorporation of drugs into solid lipid nanoparticles provides completely wettable carriers. Solid lipid nanoparticles might be an interesting carrier system for per oral administration of poorly water soluble drugs with low per oral bioavailability. The lipid particles undergo digestion similarly to food lipids. Due to high dispersivity of solid lipid nanoparticles, they exhibit a high specific surface area for enzymatic attack by intestinal lipases[10,49,50]. This enzymatic degradation of the lipids leads to release of incorporated drugs in molecularly dispersed form. The bile salts facilitate their solubilization in the intestine and subsequent absorption.

Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance.

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. Various companies are interested in solid lipid nanotechnology for oral drug delivery. Pharmatec (Italy) developed a cyclosporine SLN formulation for oral administration. AlphaRx have also rifampicin-loaded SLN under preclinical phase.

C. Pulmonary Administrations

The nebulization of SLN/ NLC is a new and upcoming area of research. Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN/ NLC can be proposed as carriers of anticancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. A high rate of distribution in periaortic, axillar and inguinal lymph nodes was observed indicating that SLN could be effective colloidal carriers for lympho-scintigraphy or therapy upon pulmonary delivery.

SLN can be used for treating infections of the mononuclear phagocytic system. It is difficult to reach to particular parasites such as mycobacterium with a normal course treatment. Within the MPS macrophages, liver and spleen macrophages are more accessible than the parasites in the lung macrophages. Videira et al. 2002 developed SLNs (200 nm) as a carrier of drugs to the lungs, through alveolar airways to the lymphatic system thus minimizing MPS uptake and increasing the concentration at the tumor site.

D. In Cancer Chemotherapy

The effectiveness of cancer therapy in various solid tumors depends upon adequate delivery of therapeutic agent to tumor cells. Inadequate delivery of drugs to tumor cells leads to regrowth of tumor cells and even result in development of resistant cells. Current SLN-based anticancer drug delivery

systems have been shown to be superior to conventional drug solutions and are at least comparable to other encapsulated systems in almost every aspect such as drug efficacy, pharmacokinetics and drug biodistribution. A number of SLN systems also demonstrated abilities to treat cancers that are normally refractory to cytotoxic drug treatment. In the near future, it is expected that modified forms of SLN such as NLC, LDC, PLN, stealth SLN, targeted-SLN, and SLN loaded with drug combinations will be perfected and utilized to further improve the efficacies and side effect profiles of chemotherapeutic drugs for anticancer treatment.

E. In Cosmeceuticals

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers[38]. SLN and NLCs have proved to be controlled release innovative occlusive topicals. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations. NLC can easier be processed to cosmetics and because of the high particle concentration and cream-like consistency the NLC dispersions might be directly used[51].

F. For Nasal Vaccination

The use of nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. These represent key factors in the optimal processing and presentation of the antigen, and therefore in the subsequent development of a suitable immune response. Nasal administration is a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination

G. Parenteral Administrations

Peptide and protein drugs are usually available for parenteral use in the market. Their conventional oral administration is not possible due to enzymatic degradation in GI tract. Repeated parenteral administration is necessary since their half-lives are too short (a few minutes). To solve the problems, improve patient compliance and provide an effective treatment, researchers have studied non-parenteral administration routes such as transdermal and nasal for years.

SLN/NLC are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities, sufficiently small to circulate in the microvascular system and prevent macrophage uptake in case of hydrophilic coating.

Therefore, NLC have been suggested for viral and non-viral gene delivery. Cationic NLC has been demonstrated to bind genes directly via electrostatic interactions, and to have potential benefits in targeted gene therapy in treatment of cancer[48]. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules.

Moreover, coating of NLC with PEG increases stability and plasma half life of SLN in order to decrease phagocytic uptake, and therefore improves the biovailability of drugs[49]. Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass bloodbrain barrier (BBB), which is formed by the endothelium of the brain vessels, the basal membrane and neurological cells.

H. Ocular Administration

Ocular drug administration via SLN has been reported several times. Biocompatibility and muco-adhesive properties of SLN/ NLC improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. SLN were evaluated as carriers for ocular delivery of tobramycin in rabbit eyes[50]. Drug concentration in the aqueous humor was determined up to six hours. As a result SLN significantly enhanced the drug bioavalability in the aqueous humor.

CONCLUSION

Lipid based nano-carriers have the greater importance in the developing field of nanotechnology with several advantages apart from various carriers. Lipid based carriers are a promising nanoscaler delivery system for the pharmceutical industry. 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. Coating of SLN and NLC with hydrophilic substances is very promising in the treatment of various diseases such as cancer and tuberculosis. Reports on surface modification of SLN and NLC by PEG coating have distinctly increased attention of various research groups with the aim of improving drug bioavailability. The concept of surface modification is further increasing the importance of SLN and NLC among traditional colloidal drug carrier systems. SLN and NLC delivery are promising candidates that will enable efficient and targeted delivery of novel drug compounds. Sustained drug release and intracellular entry capability are properties of SLN and NLC drug delivery mechanisms will minimize side effects and allow for the direct treatment of the cause of the disease rather than the symptoms of the disease.

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Table 1: Comparison between Hot and Cold Homogenisation

Steps	Hot Homogenization	Cold Homogenization
Step 1.	Melt lipid; dissolve or solubilize active ingredients in the lipid.	
Step 2.	Disperse melted lipid in hot aqueous surfactant solution.	Cooling and recrystallization of the active lipid mixture using liquid nitrogen or dry ice.
Step 3.	Preparation of a pre-emulsion by means of a rotor-stator homogenizer.	Milling of the active lipid mixture by means of a ball mill or a jet mill.
Step 4.	High-pressure homogenization above the melting point of the lipid.	Disperse lipid microparticles in cold aqueous surfactant solution.
Step 5.	Cooling and recrystallization.	High-pressure homogenization at or below room temperature

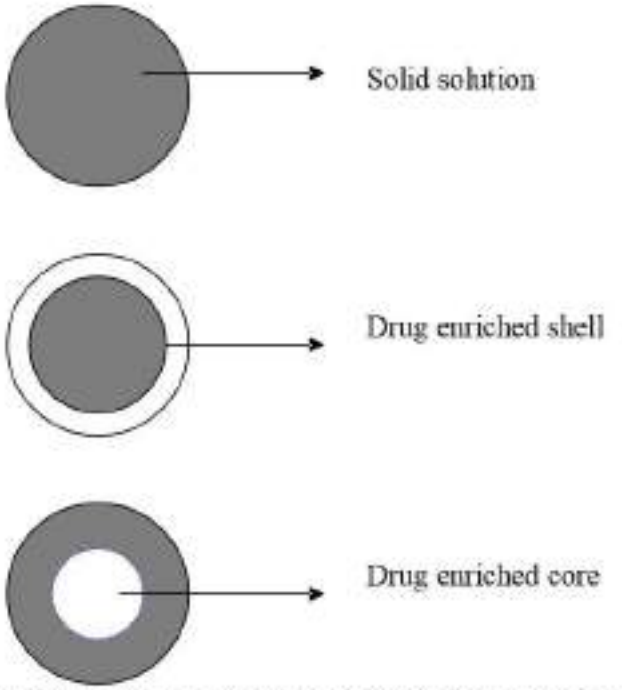


Figure 1: Proposed structural models for drug-containing SLN

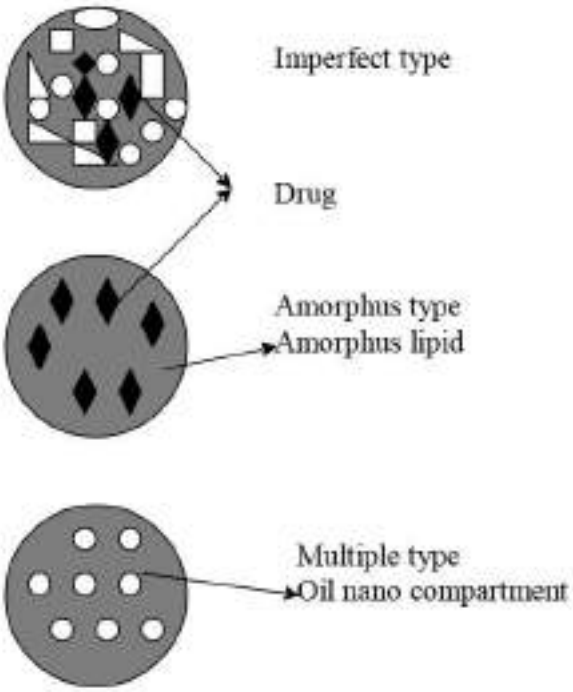


Figure 2: Proposed structural models for drug-containing NLC