World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 8, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

LIPID NANOPARTICULATE DRUG DELIVERY SYSTEMS

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Received on: 22-06-2019; Revised and Accepted on: 17-08-2019

ABSTRACT

Colloidal particles of size range between 10 and 1000 nm are known as nanoparticles. Over the last few years, lipid based drug delivery systems such as solid lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC) and lipid drug conjugate (LDC) have become the most promising drug delivery systems. Each preparation of the lipid based nanoparticles has advantages and disadvantages with respect to specific characteristics. The SLN is an excellent drug delivery system and has extensive prospects in the pharmaceutical field. Nanostructured lipid carriers (NLC), the second-generation lipid carrier is usually composed of solid lipids and liquid lipids together in a system. This mixing of solid lipids and liquid lipids causes depression in melting point of substrates and converts the mixture into solid form at body temperature. NLC exhibit a high drug loading with minimum expulsion of drug from matrix. Lipid–drug conjugates (LDC) are drug molecules that have been covalently modified with lipids. The conjugation of lipids to drug molecules increases lipophilicity and also changes other properties of drugs. The aim of present review is the most recent development of the lipid based nanocarriers according to the latest relevant literatures.

KEYWORDS: *Lipids, Nanocarriers, Lipophilic drugs, Nanostructured lipid carriers, Solid lipid nanoparticle.*

INTRODUCTION

Nanoparticulate drug delivery systems (DDS) have attracted a lot of attention because of their size-dependent properties. The last two decades have seen many nanoparticulate formulations being engineered using solid and liquid lipids as matrixes. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. Among the range of nanoparticles being currently investigated, lipid nanoparticles have taken the lead because of advantages of higher degree of biocompatibility and flexibility. These systems are commercially viable to formulate pharmaceuticals for topical, oral, pulmonary or parenteral delivery.

Advantages of Lipid Based Nanocarriers: [1]

The development of lipid-based drug carriers has attracted increased attention over the last decade. The following advantages among others, could be ascribed to lipid based nanocarriers:

- Ability to control and target drug release.
- Ability to improve stability of pharmaceuticals.
- Ability to encapsulate high drug content (compared to other carrier systems e.g. polymeric nanoparticles). the feasibility of carrying both lipophilic and hydrophilic drugs.
- Most of the lipids used are biodegradable, and as such they have excellent biocompatibility, are non-toxic, non-allergenic and non-irritating.
- They can be formulated by water-based technologies and thus can avoid organic solvents.
- They are easy to scale-up and sterilize.
- They are less expensive than polymeric/surfactant based carriers.
- They are easy to validate.

Types of Lipid Nanoparticulate Drug Delivery Systems:

Lipid nanoparticles are attractive for medical purposes due to their important and unique features, such as their surface to mass ratio that is much larger than that of other colloidal particles and their ability to bind or adsorb and carry other compounds. Lipid nano formulations produce fine dispersions of poorly water soluble drugs and can reduce the inherent limitations of slow and incomplete dissolution of poorly water soluble drugs (e.g. BCS II & IV drugs), and facilitate formation of solubilised phases from which drug absorption occurs. Furthermore, lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation, and hydrolysis [Figure 1] [2].

The most important types of lipid nanoparticles are:

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DOI: https://doi.org/10.5281/zenodo.3374087

1. Solid lipid nanoparticle (SLN) is colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid 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 the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials [3].

SLN are made up of solid lipids with a photon correlation spectroscopy mean diameter of approximately between 50 and 1000nm. General ingredients include solid lipid(s), surfactant(s), and water. The term lipid is used here in a broad sense and includes triglycerides (e.g., tristearin), partial glycerides, fatty acids (e.g., stearic acid), steroids (e.g., cholesterol), and waxes (e.g., cetyl palmitate). All classes of surfactants (with respect to charge and molecular weight) have been used to stabilize lipid dispersions [4].

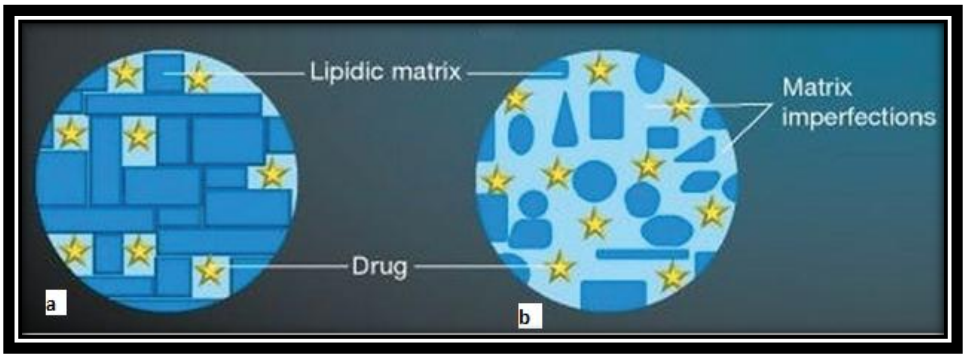

Fig. 1: Drug loading in solid-lipid nanoparticle matrix (a) versus nano-lipid carriers matrix (b)

SLNs exhibit desirable physicochemical properties, biocompatibility, and the ability to encapsulate hydrophobic molecules [5,6]. Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions (70-99.9%) have been observed. The drug loading capacity of conventional SLN is limited by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix.

2. Nanostructured lipid carriers (NLC) are lipid nanoparticles that are characterized by a solid lipid core that consists of a mixture of solid and liquid lipid. Resulting lipid particle matrix exhibit melting point depression compared to the original solid lipid, but still the matrix is solid at body temperature. NLC are developed to overcome the potential difficulties with SLN[7-9] .Different types of NLC are obtained, imperfect, amorphous, and multiple-type, depending on the method of production and lipid blend composition. In the imperfect type, lipid crystallization is altered by small amounts of oils. In the amorphous type, the lipid matrix is solid, but not crystalline (amorphous state) - this can be achieved by mixing particular lipids. In the multiple type, the solid lipid matrix contains tiny oil compartments. This type is obtained by mixing a solid lipid with a higher amount of oil. The basic idea is that, by giving a certain nanostructure to the lipid matrix, the active compound payload is increased and the expulsion of entrapped compounds during storage is avoided [10].

3. Lipid-drug conjugate (LDC) nanoparticles were developed to overcome the low drug loading capacities of SLN and NLC for hydrophilic drugs. In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities of up to 33% have been developed [11]. "In a typical process, an insoluble drug-lipid conjugate bulk is prepared either via salt formation (e.g., with a fatty acid), or via covalent linking (e.g., esters or ethers). The obtained LDC is then processed to create a nanoparticle formulation, using HPH with the assistance of an aqueous surfactant solution" [12, 13]. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections [14].

The most frequent role of lipid-based formulations has traditionally been to improve the solubility of sparingly water soluble drugs especially Biopharmaceutics Classification System (BCS) Classes II & IV drugs.

Ingredients used in the Formulation of Lipid Nanoparticulate Drug Delivery Systems:

1. Emulsifiers:

Emulsifiers are essential to stabilize lipid nanoparticle dispersions and prevent particle agglomeration. The choice of the ideal surfactant for a particular lipid matrix is based on the surfactant properties such as charge, molecular weight, chemical structure, and respective hydrophile-lipophile balance (HLB). The HLB of an emulsifier is given by the balance between the size and strength of the hydrophilic and the lipophilic groups. The choice of the emulsifiers depends on the route of administration of the formulation, for e.g. for parenteral formulations, there are limits of the emulsifiers to be used [15]. Examples of emulsifiers are Lecithin, Poloxamer 188, Poloxamer 407, Polysorbate 20, Polysorbate 65, Polysorbate 80, Cremophor EL, Solutol HS 15**.**

2. Lipids:

The matrices for lipid nanoparticle preparation are natural, semi-synthetic or synthetic lipids which can be biodegradable, including triglyceride (tri-stearic acid, tri-palmitic acid, tri-lauric acid and long-chain fatty acid), steroid and waxes (e.g. beeswax, carnauba wax, etc) and phospholipids. They could be used singly or in combination. Lipids for the production of nanoparticles may be grouped into two: bilayer and non-bilayer lipids.

2.1. Bilayer lipids used in drug delivery: Some lipids are capable of adopting a certain orientation depending on the processing condition. Compounds that have approximately equal-sized heads and tails e.g. phospholipids tend to form

bilayers instead of micelles in aqueous system. In these structures, two monolayers of lipid molecules associate tail to tail, thus minimizing the contact of the hydrophobic portions with water and maximizing hydrophilic interactions.

Phospholipids with certain head groups e.g. phosphatidylcholine, can alter the surface chemistry of a lipid particle. The packing of phospholipid chains within the surface of the particle also affects its mechanical properties, including swelling, stretching, bending and deformability. These properties have been taken as benefit in the design of novel lipid particulate drug delivery systems such as surface modification for improved drug loading capacity. Bilayer lipids when present in lipid particulate DDS may define the boundaries of the particle and its environment (aqueous), and are often involved in many complex processes occurring at the interface.

2.2. Non-bilayer lipids used in drug delivery: In many biological systems, the major lipids are non-bilayer lipids, which in purified form cannot be arranged in a lamellar structure in the presence of aqueous systems. The structural and functional roles of these lipids in drug delivery are mainly in their utilization as matrix-forming lipids. They include such lipids as homolipids e.g. triglycerides and waxes. Their functional properties in lipid nanotechnology differs depending partly on their melting points, crystallinity and polymorphic characteristics. However, they may have absorption promoting properties especially for lipophilic drugs. Examples of some of the non-bilayer lipids used in the formulation of lipid micro- and nanoparticles.

Hard fats: *e.g*. Stearic acid Palmitic acid Behenic acid

Natural hard fats: *e.g* Goat fat Theobroma oil

Triglycerides: e.g. Trimyristin (Dynasan 114) Tripalmitin (Dynasan 116)

Waxes: *e.g*. Beeswax Cetyl palmitate Carnauba wax

Mono, di and triglycerides mixtures*: e.g.* Witepsol bases Glyceryl monostearate (Imwitor 900)

Challenges of Lipid Nanoparticle Drug Delivery System:

1. Interaction with the reticulo-endothelial system (RES): One major problem with the intravenous administration of colloidal particles is their interaction with the reticulo-endothelial system (RES). Nanoparticles for medical applications are frequently given via parenteral administration. As with any foreign material, the body mounts a biological response to an administered nanoparticle. This response is the result of a complex interplay of factors, not just the intrinsic characteristics of the nanoparticle. In particular, most materials, upon contact with biological matrices, are immediately coated by proteins, leading to a protein "corona" [16]. Certain components of the nanoparticle corona, known as opsonins, may augment uptake of the coated material by cells of the RES. The presence of opsonins on the particle surface creates a "molecular signature" which is recognized by immune cells and determines the route of particle internalization. The route of internalization affects the eventual fate of the nanoparticle in the body (i.e. its rate of clearance from the bloodstream, volume of distribution, organ disposition, and rate and route of clearance from the body). The cells of RES are capable of mopping up particles that they do not recognise as self i.e. particles they recognise as foreign. The negative effect can however, be remedied by linking of polyethylene glycol molecules to the lipid nanoparticles, thus increasing their hydrophilicity and the residence time of these particles in circulation. Alternatively, the lipid nanoparticles could be engineered to evade these RES cells by limiting the particle sizes to about 200 nm or less. It is believed that these cells do not recognise low nanometer-sized particles as foreign. Several other varied and unrelated challenges are encountered in lipid nanoparticle technology. These challenges constitute a serious research question which current strategies are targeted to address.

2. Formation of perfect crystalline structure during storage: Triglycerides crystallize in different polymorphic forms such as α, γ, β', and β- forms. Recrystallization from the melt results in the metastable α-polymorph which subsequently undergoes a polymorphic transition into the stable β-form via a metastable intermediate. The β-polymorph especially consists of a highly ordered, rigid structure with low loading capacity of drugs. Transition to the β-form via a metastable intermediate form leads to drug expulsion and inability to protect or prolong the release of the encapsulated drug.

3. Physical stability: The stability of lipid particulate systems is influenced by the size of the nanoparticles. Lipid nanoparticles are prevented from sedimentation by Brownian motion, but other instabilities like Ostwald ripening and aggregation may occur. Since nanoparticles have a large specific surface area, stabilization of the surface with sufficient amounts of emulsifier (s) is necessary. The formulation of the colloidal carriers themselves is a difficult task due to many problems that arise from their colloidal state and specific pharmaceutical demands on such formulations. Stability in a pharmaceutical sense refers to a shelf life of usually 3-5 years. Shorter shelf lives will only be accepted in very special cases. However, for most systems of pharmaceutical interest the colloidal state is at its best metastable. The colloidal state may cause several additional instabilities, for example, due to the presence of large interfaces (adsorption-desorption processes, interactions in the stabilizer layer, higher risk of chemical instabilities, etc.). Since many colloidal administration systems are intended for intravenous use, stability is very crucial. Ability to be sterilized is also an added advantage.

4. Gel formation: The change in morphology of lipid nanoparticles from spheres to platelets is responsible for the gelation of solid lipid nanoparticle dispersions. Depending on the composition, especially of the emulsifier (s) and the amount of lipid matrix, a gelation of the normally liquid dispersions can be observed on storage [17, 18]. By means of TEM and synchrotron measurements, the reason for the gelation was found. The gelation may derive from a reversible self-association of the particles due to a stacking of the platelets [19, 20]. This gellike feature of highly concentrated dispersions favours application as dermal drug delivery system since the viscoelastic features resemble those of semisolid creams. In contrast, the lipid nanoparticle formulations for intravenous and ocular administration have to remain fluid. Phase transitions that would lead to an unusual lamellar gel phase should be investigated for in parenteral formulations.

5. High water content of dispersions: The high water content of lipid nanoparticles (70-95%) could lead to drug degradation and high cost of energy input during lyophilisation. During lyophilisation, the integrity of the nanoparticles could be affected if adequate croprotectant or lyoprotectant was not included in the formulation. Water free nanoparticles could be used in tablet production or the nanoparticle dispersion used as

granulating fluid during production. SLN can be transformed into a powder by spray-drying. In any case, it is beneficial to have a higher solid content to avoid the need of having to remove too much water. For cost reasons, spray drying might be the preferred method for transforming SLN dispersions into powders, with the previous addition of a protectant.

6. Dosing problems: Selection of appropriate dosage form for lipid nanoparticle may be a problem. Outside injectables, there is need to package lipid nanoparticles in appropriate dosage units e.g. dispersible powders or hard/soft gelatine capsules especially for oral administration. Since the stomach acidic environment and its high ionic strength favour particle aggregation, aqueous dispersions of lipid nanoparticles might not be suitable to be administered orally as a dosage form. In addition, the presence of food will also have a high impact on their performance [21].

Packaging of SLN in a sachet for redispersion in water or juice prior to administration will allow an individual dosing by volume of the reconstituted SLN. This means additional step in packaging, which might result in introduction of additional technology and increase in the cost of the product.

7. Coexistence of other colloidal structures in the system (e.g. liposome and vesicles in SLN and NLC containing phospholipids): Considerable amounts of emulsifiers are needed for the stabilization of lipid nanoparticles. If the emulsifiers redistribute from the particles into the aqueous phase, they can form colloidal structures like micelles or liposomes or other vesicular structures by self-assembly. Drugs can be solubilized within these structures, affecting drug release as well as drug loading capacity. Hence the formation of additional colloidal structures has to be investigated for each formulation to enable further precautions to be taken to avoided it. The coexistence of liposomes and oil droplets was detected in an intravenous o/w nanoemulsion [22]. In solid lipid nanoparticle dispersion, additional liposomes were observed by means of cryo-TEM, although the amount was lower than in a corresponding emulsion [23]. In contrast to this, Schubert *et al.* [24] performed NMR, TEM and small angle X-ray scattering (SAXS) measurements and showed that no additional colloidal structures were formed. Drug nanocrystals could also be formed when the amount of the drug present far exceeds its solubility limit in the lipid matrix.

8. Supercooling of nanoparticles: Lipid nanoparticles prepared from triglycerides which are solid at room temperature may not necessarily crystallize on cooling to common storage temperatures. The particles can remain liquid for several months without crystallization (supercooled melt) [25].

Dispersions with lower melting points, in particular, monoacid triglycerides such as trilaurin or trimyristin, do not display melting transitions upon heating in differential scanning calorimeter or reflections due to crystalline nature in X-ray diffractometer after storage at room temperature. As confirmed by studies with quantitative 1H NMR spectroscopy, the matrix of the dispersed particles consists of liquid triglycerides in such particles. The particles have a high tendency toward supercooling. The critical crystallization temperature is mainly dependent on the composition of the triglyceride matrix and can also be modified by incorporated drugs. The degree of super cooling is much higher in the nanoparticles than for the bulk triglyceride. This supercooling could be taken advantage of and utilized as a delivery system of its own but this has to be planned for *ab initio*.

Applications of Lipid Nanoparticulate Drug Delivery Systems:

During the last decade, different substances have been entrapped into lipid nanoparticles ranging from lipophilic to hydrophilic molecules and including difficult compounds such as proteins and peptides.

1. Lipid nanoparticles as carriers for oral drug delivery: Lipid nanoparticles such as SLN can be administered orally as dispersion, SLN-based tablet, pellets or capsules or even as lyophilized unit dose powders for reconstitution for oral delivery. The stability of the particles in the GIT has to be thoroughly tested, since low pH and high ionic strength in the GIT may result in aggregation of the particles. In order to prove this, an investigation of the effect of artificial gastric fluids on different lipidic nanoparticle formulations was performed. The authors showed that a zeta potential of at least 8-9 mV in combination with a steric stabilization hinders aggregation under these conditions [26]. Additionally, for oral drug delivery, a release upon enzymatic degradation has to be taken into account [27].

The routes for particle uptake after oral application are transcellular (via the M cells in the Peyer's patches or enterocytes) or paracellular (diffusion between the cells). However, theuptake via M cells is the major pathway, resulting in the transport of the particles to the lymph [28].

Uptake into the lymph and the blood was demonstrated by means of TEM and gamma counting of labelled SLN. It was found that uptake to the lymph was considerably higher than to the plasma [29], and as such, a reduced first pass effect concludes, as the transport via the portal vein to the liver is bypassed [30]. SLN containing the antituberculosis drugs rifampicin, isoniazid and pyrazinamide have been studied in animals model and it was found that administration every 10 days could be successful for the management of tuberculosis [31].

2. Lipid nanoparticles for parenteral drug delivery: Lipid nanoparticles can be formulated for subcutaneous, intramuscular or intravenous administration. For intravenous administration, the small particle size is a prerequisite as passage through the needle and possibility of embolism should be considered. SLN offer the opportunity of a controlled drug release and the possibility to incorporate poorly soluble drugs. Additionally, especially for intravenous application, drug targeting via modification of the particle surface is possible, and for SLN formulation with a controlled release, higher plasma concentrations over a prolonged period of time can be obtained. Such systems form an intravenous depot. Further studies with different drugs such as idarubicin, doxorubicin, tobramycin, clozapine or temozolomide also showed a sustained release as described in a review paper by Harms and Müller-Goymann [32].

3. Lipid nanoparticles as carriers for peptides and proteins drugs: Lipid nanoparticles have been extensively studied for the delivery of proteins and peptides. Therapeutic application of peptides and proteins is restricted by their high molecular weight, hydrophilic character and limited chemical stability, which cause low bioavailability, poor transfer across biological membranes and low stability in the bloodstream. Most of the available peptides and proteins are delivered by injection, but their short half life demands repeated doses that are costly,

painful and not well tolerated by patients. Lipid nanoparticles could be useful for peptide and protein delivery due to the stabilizing effect of lipids and to the absorption promoting effect of the lipidic material that constitute this kind of nanoparticles [33].

4. Lipid nanocarriers for nasal vaccination: The use of lipid nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. Besides improved protection and facilitated transport of the antigen, nanoparticulate delivery systems could also provide more effective antigen recognition by immune cells. These represent key factors in the optimal processing and presentation of the antigen, and therefore in the subsequent development of a suitable immune response. In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination.

5. Lipid nanoparticles as carriers in cosmetic and dermal preparation: Lipid nanoparticles can be incorporated into a cream, hydrogel or ointment to obtain semisolid systems for dermal applications. Another possibility is to increase the amount of lipid matrix in the formulation above a critical concentration, resulting in semisolid formulations [34]. The substances used for the preparation of dermal SLN are rather innocuous since they are mostly rated as GRAS and many of them are used in conventional dermal formulations. This resulted in the first dermal formulations containing SLN for cosmetic purposes entering the market [35]. Due to the adhesiveness of small particles, SLN adhere to the stratum corneum forming a film as these films have been shown to possess occlusive properties [36]. It was shown that the degree of crystallinity has a great impact on the extent of occlusion by the formulation. With increasing crystallinity the occlusion factor increases as well [37].

This explains why liquid nanoemulsions in contrast to SLN do not show an occlusive effect and why the extent of occlusion by NLC compared to SLN is reduced. Other parameters influencing the occlusion factor are the particle size and the number of particles. Whilst with increasing size the factor decreases, an increase in number results in an increase in the extent occlusion [38]. The occlusive effect leads to reduced water loss and increased skin hydration. Highly crystalline SLN can be used for physical sun protection due to scattering and reflection of the UV radiation by the particles. A high crystallinity was found to enhance the effectiveness and was also synergistic with UV absorbing substances used in conventional sunscreens [39].

Similarly synergism was observed on the sun protection factor and UV-A protection factor exhibited by the incorporation of the inorganic sunscreen, titanium-dioxide in NLC of carnauba wax and decyl oleate [40].

6. Lipid nanoparticles for ocular application: The eye possesses unique challenges with respect to drug delivery especially with respect to the posterior segment and treating vision threatening diseases. Poor bioavailability of drugs from ocular dosage form is mainly due to the pre-corneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and relative impermeability of the corneal epithelial membrane. Due to the adhesive nature of the small nanoparticles, these negative effects can be reduced. For ocularly administered SLN an increase in bioavailability was observed in rabbits by Cavalli *et al.* [41] using tobramycin ion pair as the model drug. Various *in vitro* studies show a prolonged and enhanced permeation when the drug is incorporated in lipid nanoparticles. For systems containing phospholipids, a further improved permeation of diclofenac sodium was observed [42].

7. Pulmonary application of lipid nanoparticles: Pulmonary drug application offers the advantage of minimizing toxic side effects if a local impact is intended. Systemic delivery can be achieved through pulmonary delivery, offering the advantage of bypassing the first pass effect, as well as offering a large absorptive area, extensive vasculature, easily permeable membrane and low extracellular and intracellular enzyme activities. A problem of this method of administration is the low bioavailability. SLN can easily be nebulized to form an aerosol of liquid droplets containing nanoparticles for inhalation. *In vivo* studies showed that the administered drugs (rifampicin, isoniazid and pyrazinamide for the treatment of tuberculosis) resulted in a prolonged mean residence time and a higher bioavailability than the free drug.

8. Application of liquid crystal drug delivery systems: The spontaneous self assembly of some lipids to form liquid crystalline structures offers a possible new class of sustained release matrix. The nanostructured liquid crystalline materials are highly stable to dilution. This means that they can persist as a reservoir for slow drug release in excess fluids such as the GIT or subcutaneous space, or be dispersed into nanoparticle form, while retaining the parent liquid crystalline structure. The rate of drug release is directly related to the nanostructure of the matrix. The particular geometry into which the lipids assemble can be manipulated through either the use of additives to modify the assembly process, or through modifying conditions such as temperature, thereby providing a means to control drug release.

Liquid crystal depot could be injected as a low-viscosity solution. Once in the body, it selfassembles and encapsulates the drug in a nanostructured, viscous liquid crystal gel. The drug substance is then released from the liquid crystal matrix over a time period, which can be tuned from days to months. The liquid crystal depot system is capable of providing *in vivo* sustained release of a wide range of therapeutic agents over controlled periods of time.

Liquid crystal nanoparticles can be combined with controlled-release and targeting functionalities. The particles are designed to form *in situ* at a controlled rate, which enables an effective *in vivo* distribution of the drug. The system has been shown to give more stable plasma levels of peptides in comparison to competing microsphere and conventional oildepot technologies [43].

Oral liquid crystal DDS are designed to address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. Compared with conventional lipid or non-lipid carriers, these show high drug carrier capacity for a range of sparingly water-soluble drugs. For drugs susceptible to *in vivo* degradation, such as peptides and proteins, liquid crystal nanoparticles protect the sensitive drug from enzymatic degradation. The system also addresses permeability limitations by exploiting the lipid-mediated absorption mechanism. For watersoluble peptides, typical bioavailability enhancements range from twenty to more than one hundred times. In an alternative application large proteins have been encapsulated for local activity in the GIT. Liquid crystal nanoparticle systems

can be designed to be released at different absorption sites (e.g., in the upper or lower intestine) which is important for drugs that have narrow regional absorption windows.

With regards to topical application, liquid crystal systems form a thin surface film at mucosal surfaces consisting of a liquid crystal matrix, whose nanostructure can be controlled for achieving an optimal delivery profile. The system also provides good temporary protection for sore and sensitive skin. Their unique solubilizing, encapsulating, transporting, and protecting capacity is advantageously exploited in liquid and gel products used to increase transdermal and nasal bioavailability of small molecules and peptides.

CONCLUSIONS

Drug carrier systems utilizing lipid particles has been favoured recently as result of the GRAS status of the excipients and their conventional use in pharmaceutical and food products. Lipids and lipid nanoparticles are promising delivery systems for oral administration of small molecule drugs like proteins and peptides. Based on the composition and organization of lipids and drugs in the particles, a wide collection of structural forms have been illustrated for SLNs and NLCs. Lipid formulations of drugs are able to control the release of drugs and reduce absorption variability. The oral administration of lipid nanoparticles is possible as aqueous dispersion or alternatively changed into a conventional dosage forms such as tablets, pellets, capsules, or powders in sachets. The ability to incorporate drugs into lipid nanocarriers offers a new model in drug delivery that could be used for passive and active drug targeting. With the development and interest in lipid particulate drug delivery systems shown by pharmaceutical formulation scientists, a future full of lipid nanoparticle products in the market is envisaged.

REFERENCES:

1. Attama AA, Momoh MA and Builders PF. Lipid nanoparticulate drug delivery systems: a revolution in dosage form design and development. In: Sezer AD, editor. Pharmacology, Toxicology and Pharmaceutical Science. Croatia: InTech **2012** Open Access Publisher.
2. Müller RH, Runge SA and Ravelli V. German Patent Application **1998** DE 19819273A1.
3. Cavalli R, Caputo O andGasco MR. Solid lipospheres of doxorubicin and idarubicin. Int J Pharm **1993**;89:R9-R12.
4. Mehnert W and Mader K. Solid lipid nanoparticles: production, characterization, and applications. Advanced Drug Delivery Reviews **2001**;47(3):165–196.
5. Dingler A and Gohla, S. Production of solid lipid nanoparticles (SLN): Scaling up feasibilities. J Microencapsul **2002**;19:11–16.
6. Barbosa RM, Da Silva CM, Bella TS, De Araújo DR, Marcato PD, Durán N, De Paula and E. Cytotoxicity of solid lipid nanoparticles and nanostructured lipid carriers containing the local anesthetic dibucaine designed for topical application. J Phys Conf Ser **2013**; 429:1–8.
7. Muller RH, Radtke M and Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drug. Int J Pharm. **2002**;242:121-8.
8. Radtke M and Muller RH. Comparison of structural properties of solid lipid nanoparticles (SLN) versus other lipid particles. Proc Int Symp Control Rel Bioact Mater **2000**;27(3):09-10.
9. Uner M. Preparation, characterization and physico-chemical properties of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC): their benefits as colloidal drug carrier systems. Pharmazie **2006**;61: 375-86.
10. Battaglia L, Gallarate M and Panciani PP. Techniques for the preparation of solid lipid nano and microparticles," in Application of nanotechnology in drug delivery **2014** IntechOpen, London, UK.
11. Muller RH, Radtke M and Wissing SA. Solid lipid nanoparticles (SLN) an nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev **2002**; 54:S131-55.
12. Onuigbo EB, Okore VC, Ngene AA, Esimone CO and Attama AA. Preliminary Studies of a Stearylamine-based Cationic Liposome. J Pharm Res **2011**;10(1):25-29.
13. Olbrich C, Gessner A, Kayser O and Müller RH. Lipid--drug-conjugate (LDC) nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazenediaceturate. J Drug Targeting **2002**;10(5): 387–396.
14. Olbrich C, Gebner A, Kayser O and Muller RH. Lipid–drug conjugate (LDC) nanoparticles as novel carrier system for the hydrophilic antitrypanosomal drug diminazenediaceturate. J Drug Target **2002**;10:387-96.
15. Severino P, Andreani T, Sofia-Macedo A, Fangueiro JF, Santana M-H A, Silva AM and Souto EB. Current State-of-Art and New Trends on Lipid Nanoparticles (SLN and NLC) for Oral Drug Delivery. J Drug Deliv **2012**; doi:10.1155/2012/750891.
16. Aggarwal P, Hall JB, McLeland CB, Dobrovolskaia MA and McNeil SE. Nanoparticle Interaction with Plasma Proteins as it Relates to Particle Biodistribution, Biocompatibility and Therapeutic Efficacy. Adv Drug Deliv Rev **2009**;61:428–437.
17. Westesen K and Siekmann B. Investigation of the Gel Formation of Phospholipid- stabilized Solid Lipid Nanoparticles. Int J Pharm **1997**;151:35-45.
18. Lippacher A, Müller RH andMäder K. Investigation on the Viscoelastic Properties of Lipid Based Colloidal Drug Carriers. Int J Pharm **2000**;196(2):227-230.
19. Unruh T, Westesen K, Bösecke P, Lindner P and Koch MHJ. Self-assembly of Triglyceride Nanocrystals in Suspension. Langmuir **2002**;18(5):1796-1800.
20. Illing A, Unruh T and Koch MHJ. Investigation on Particle Self Assembly in Solid Lipidbased Colloidal Drug Carrier Systems. Pharm Res **2004**;21(4):592-597.
21. Mehnert W andMäder K. Solid Lipid Nanoparticles: Production, Characterization and Applications. Adv Drug Deliv Rev **2001**;47(2-3):165–196.
22. Westesen K and Wehler T. Physicochemical Characterization of a Model Intravenous Oil in-water Emulsion. J Pharm Sci **1992**;81:777-786.
23. Heiati H, Phillips NC and Tawashi R. Evidence for Phospholipid Bilayer Formation in Solid Lipid Nanoparticles Formulated with Phospholipid and Triglyceride. Pharm Res **1996**;13:1406-1410.
24. Schubert MA, Harms M and Müller-Goymann CC. Structural Investigations on Lipid Nanoparticles Containing High Amounts of Lecithin. Eur J Pharm Sci **2006**;27(2-3):226-236.
25. Westesen K, Bunjes H. Do Nanoparticles Prepared from Lipids Solid at Room Temperature Always Possess a Solid Lipid Matrix. Int J Pharm **1995**;115: 129-131.

26. Zimmermann E and Müller RH. Electrolyte-and pH-stabilities of Aqueous Solid Lipid Nanoparticle (SLN) Dispersions in Artificial Gastrointestinal Media. Eur J Pharm Biopharm **2001**;52(2):203-210.
27. Olbrich C and Müller RH. Enzymatic Degradation of SLN-Effect of Surfactant and Surfactant Mixtures. Int J Pharm **1991**;180(1):31-39.
28. Des Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V. Nanoparticles as Potential Oral Delivery Systems of Proteins and Vaccines: A Mechanistic Approach. J Control Rel **2006**;116(1):1-27.
29. Bargoni A, Cavalli R, Caputo O, Fundaro A, Gasco MR and Zara GP. Solid Lipid Nanoparticles in Lymph and Plasma after Duodenal Administration to Rats. Pharm Res **1998**;15(5):745-750.
30. Souto EB and Doktorovova S. Solid Lipid Nanoparticle Formulations, Pharmacokinetic and Biopharmaceutical Aspects in Drug Delivery. Methods Enzymol **2009;** 464(C):105-129.
31. Pandey R, Sharma S and Khuller GK. Oral Solid Lipid Nanoparticle-based Antitubercular Chemotherapy. Tuberculosis **2005**;85(5-6):415-420.
32. Harms M, Müller-Goymann CC. Solid Lipid Nanoparticles for Drug Delivery. J Drug Del Sci Tech **2011**;21(1):89-99.
33. Del Pozo-Rodriguez A, Delgado D, Solinís MA and Gascón AR. Lipid Nanoparticles as Vehicles for Macromolecules: Nucleic Acids and Peptides. Recent Pat. Drug Deliv Formul **2011**;5:214-226.
34. Hussein R. Charakterisierung von Hartfettmatrices und Lipid nanosuspensionen mit Phospholipon 90H. Ph.D. thesis. TU Braunschweig, Braunschweig. **2009**.
35. Müller RH, Petersen RD, Hommoss A and Pardeike J. Nanostructured Lipid Carriers (NLC) in Cosmetic Dermal Products. Adv Drug Del Rev **2007**;59(6):522-530.
36. Pardeike J, Hommoss A and Müller RH. Lipid Nanoparticles (SLN, NLC) in Cosmetic and Pharmaceutical Dermal Products. Int J Pharm **2009**; 366(1-2):170-184.
37. Wissing SA and Müller RH. The Influence of the Crystallinity of Lipid Nanoparticles on their Occlusive Properties. Int J Pharm **2002**;242(1-2):377-379.
38. Wissing SA and Müller RH. Cosmetic Applications for Solid Lipid Nanoparticles (SLN). Int J Pharm **2003**; 254(1):65-68.
39. Villalobos-Hernandez JR and Müller-Goymann CC. Sun Protection Enhancement of Titanium Dioxide Crystals by the Use of Carnauba Wax Nanoparticles: The Synergistic Interaction between Organic and Inorganic Sunscreens at Nanoscale. Int J Pharm **2006**;322(1-2): 161-170.
40. Villalobos-Hernandez JR and, Müller-Goymann CC. *In vitro* Erythemal UV-A Protection Factors of Inorganic Sunscreens Distributed in Aqueous Media Using Carnauba Wax-Decyl Oleate Nanoparticles. Eur J Pharm Biopharm **2007**;65(1):122-125.
41. Cavalli R, Gasco MR, Chetoni P, Burgalassi S and Saettone MF. Solid Lipid Nanoparticles (SLN) as Ocular Delivery System for Tobramycin. Int J Pharm **2002**; 238(1-2):241-245.
42. Bur M, Henning A, Hein S, Schneider M and Lehr CM. Inhalative Nanomedicine Opportunities and Challenges. Inhalat Toxicol **2009**;21(Suppl. 1):137-143.
43. Pandey R and Khuller GK. Solid Lipid Particle-based Inhalable Sustained Drug Delivery System Against Experimental Tuberculosis. Tuberculosis **2005**;85(4): 227-234.

How to cite this article:

Jaswinder Singh. LIPID NANOPARTICULATE DRUG DELIVERY SYSTEMS. J Pharm Res 2019;8(8):557-563.
DOI: https://doi.org/10.5281/zenodo.3374087

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nils