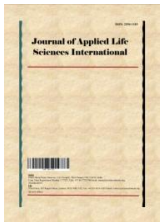

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Lipid Based Drug Delivery System: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Associated with the old/traditional of method of drug delivery are several limitation ranging from first-pass effect, low tolerance, minimal bioavailability, fluctuation of plasma drug concentration which result to less or no desired effect produced. This call for the demand for a more efficient drug administration technique. Lipid systems are biocompatible, inert and biodegradable, stable and deliver at the target with the desired effect. This paper attempt to describe several types of lipid particles used to deliver drug compounds and their applications as therapeutic agent in treating different clinical condition.

Keywords: Drug; biocompatible; biodegradable; bioavailability; lipids.

ABBREVIATION

AuNPs : Gold Nanoparticles
Bax : Bcl_2 Associated X Protein
BBB : Blood Brain Barrier

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CLSM : Confocal Laser Scanning Microscopy
CRC : Colorectal Cancer
DDS : Drug Delivery System
ED : Erectile Dysfunction
EO : Essential Oils
MMTPs : Mixed Monoterpenes Edge Activated PEGylatedTransfersomes
NP : Nanoparticles
PEG : Poly Ethylene Glycol
SiRNA : Small interfering RNA
SMAL : Self Micellizing Anticancer Lipid
TF : Transfersomes

1. INTRODUCTION

1.1 Conventional Drug Delivery

Drug delivery technique utilizes elegant chemical substances capable of crossing different animal system barriers to deliver a drug compound to a target tissue or cell in order to produce a needed therapeutic effect. The popular techniques for drug delivery follows the traditional means of administering drugs which includes; oral delivery, submucosal (tissues having mucosal lining such as mouth, anus, vagina, nose etc.) topical and intra-muscular. Dosing is preferred in the conventional delivery method as it enhance immediate release (IR) as soon as it get into systemic circulation [1].

Treatment related factors ranging from rate of drug administration and target site delivery as well as time frame of drug treatment have all been devised and improved for the past two decades. The traditional Drug Delivery System is an old technique for drug deliverance to a particular target site using one of the following means:

1. Through the Mouth (Oral)
2. Through the vein (Intravenous)
3. Via anus (Rectal)
4. Under skin (Subcutaneous)
5. Administered in the muscles (Intramuscular)
6. Under the tongue or between cheeks (Sublingual/ buccal)

- Mouth delivery of drugs mainly is characterized with swallowing drug compound in formulation of capsules, tablet or syrup which is absorbed and taken up for utilization by the Gastro-Intestinal Tract (GIT).
- Drug deliverance via vein is characterized with direct infusion of liquid drug compound into the blood via vein using an asceptic injector.
- Anal drug administration involves drugs in form of suppositories that naturally melt and get absorbed via the rectum, and thus, subsequently taken up to target site of action.
- Drug administered under the skin are liquid in form and injected under subcutaneous tissue.
- When liquid drugs are injected under muscle tissues using sterile injector, it is referred to as Intramuscular delivery.
- Sublingual/Buccal delivery of drugs involve chewing or placing of drug substances and rolled between cheeks or sucked with the tongue.

Associated with the old system of drug delivery are several limitations ranging from first-pass effect, low tolerance, minimal bioavailability, fluctuation of plasma drug concentration which result to less or no desired effect produced. Hence, these call for innovative means for drug delivering techniques to match current medical challenges. Trending issues include controlling toxic effect of drugs, pharmacodynamics, amount just needed to produce desired effect with low or no immune reactions. These novel methods needed to achieve these objectives are collectively called Drug Delivery System (DDS) and are a combination of several disciplines such as pharmacy, chemistry, bioconjugate science, polymer chemistry and subatomic
Science [1].

2. EXPANSE OF NANOTECHNOLOGY

Nanotechnology is a grossly interrelated field based on different scientific discipline such as physics, biochemistry, chemistry and material science that has great impact in medical deliverance of nanosized pharmaceutics, gene therapy and diagnostic, bio-sensing and targeted thermal ablation [2].

In the last two decades, the field of nanotechnology has positively influenced a great number of fields. It had a great impact in pharmaceutics as it had across several technical affiliations. An application of interest are drugs transported in form of colloids [3].

It is of immense application in the transport of pharmaceutical compounds for the treatment of different ailment. The merit of nanoparticles over other delivery systems is its distinct capacity to

administer the right dose of therapeutic formulation at the target site of malfunctiong tissues or cells with less or minimal toxicity to functional tissues or cells [1].

3. NANOPARTICLES

NPs can be defined as particulate matter ranging from 1 to 100 nm in size with a high specific surface area and specialized surface characteristics [4].

The nanoparticles are able to increase the bioavailability of the loaded drugs due to their ability to remain in systemic circulation for a longer period of time [2,5], by presenting a controlled drug release profile, resulting in steady-state plasma concentration, improved biocompatibility, multifunctional encapsulation of active agents, lesser degradation during blood circulation, effective delivery and reduced side effects [2].

Various kinds of materials have been carefully studied to explore their potential applications, which were mainly focused on the natural and artificial materials. Compared with artificial materials, the natural materials exhibit superiority in the biocompatibility, easy accessibility, and easy modification. Moreover, due to the reactive groups on the native natural materials, other functional groups could also be possibly introduced, thus endowing the newly obtained materials with tremendous functions, or adjusting their physical and chemical properties [6].

They usually consist of metals but they also could be protein and nucleic acid-based NPs or other biodegradable material-based NPs such as lipids (micelles, liposomes, phospholipids) or synthetic polymers (dextran, chitosan), silica, metal, and carbon [7].

Below, is an overview of different NP carriers; discovered in the last two decades

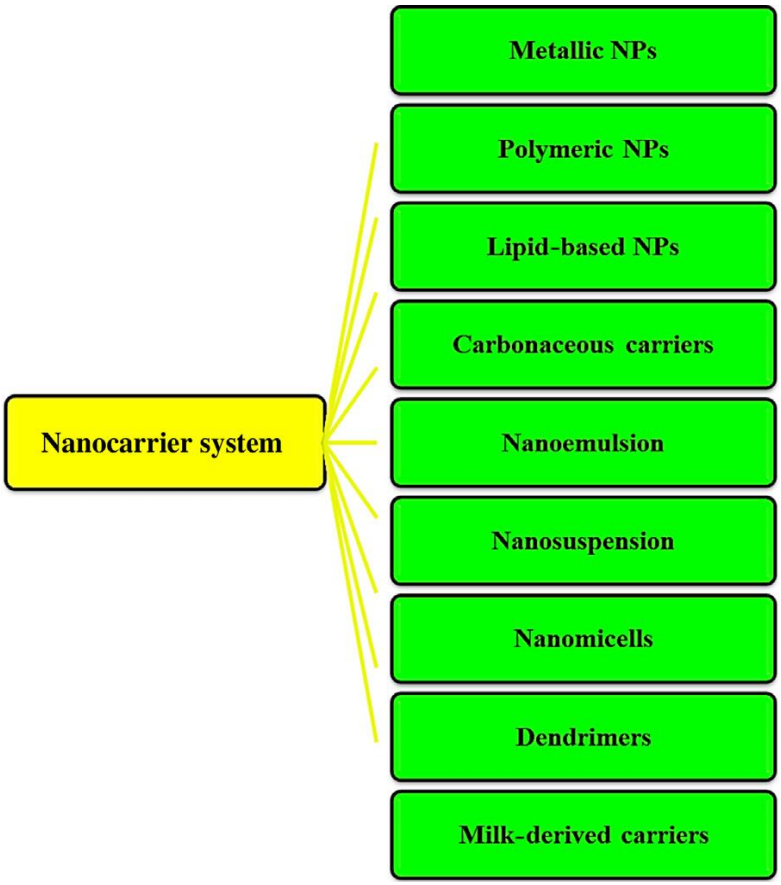

Fig. 1. Adapted from [1]
Schematic presentation of different types of Nanocarriers

4. MECHANISMS OF DRUG DELIVERY

Drugs are delivered via three major mechanisms:

1. Passive
2. Active
3. Physical targeting

The first approach (passive targeting) includes selective delivery by utilizing leaky vasculature and direct administration or implantation at the desired site [7]. The strategy of passive targeting has been successfully used to reach sites of leaky vasculature typical for tumors, sites of inflammation, infection or angiogenesis [8].

While in active delivery the therapeutic agent or a support system is conjugated to a tissue or a specific cell ligand, it involves the receptor and antibody-mediated targeting. As targeting ligands a broad variety of molecules including proteins, antibodies, antibody fragments, peptides, aptamers or small molecules has been explored in enhancing drug delivery [8,9]. It has been extensively investigated to overcome the barriers to drug delivery, for example, the blood brain barrier (BBB), cell membrane barrier [1,7].

Physical targeting method uses external fields such as magnetic or other sources (e.g. radiation) (Fig. 2) for guiding NPs to the target site and controlling the release process. This method was applied in photothermal therapy for killing cancer cells or inhibiting cell cycles. Thereby, different photothermal agents were used such as AuNPs carbon nanotubes and graphene [7].

5. LIPID BASED DRUG DELIVERY SYSTEM

The majority of new drug candidates, intended for oral administration, often suffer from low oral bioavailability, and despite their pharmacological activity, they fail to proceed to advanced stages of research and development [10]. Therefore, require enabling DDSs to reach the desired bioavailability and thereby therapeutic effect. One group of enabling DDSs designed to bypass a slow dissolution process and increase the apparent drug solubility in the GI fluids, is LbDDSs. LbDDSs comprise a relatively wide range of physically different systems including lipid solutions, self-emulsifying DDSs (SEDDSs), and micellar systems. Most LbDDSs present the drug to the GI tract in solution, i.e. solubilized in lipids, surfactants, and co-solvents, or mixtures thereof [11].

Lipids are rightly being considered as safe and useful materials for drug delivery. Conventional lipid-based systems, consisting of emulsions and micro-emulsions, have been widely used to enhance bioavailability and the absorption. The stability of such systems is strictly related to particle size distribution, the lipid content, and the presence of a surfactant capable of stabilizing the dispersion [12].

6. LIPID BASED CARRIERS

Lipid-based carriers can be divided into various categories depending on their physicochemical properties and the method that is used for their fabrication [13]. The main lipid-based carriers include:

1. Micelles
2. Liposomes
3. Solid Lipid-Based Nanoparticles (SLN)
4. Nano Structured Lipid Carriers (NLC)
5. Lipid Drug Conjugates (LDC)
6. Nanoemulsions

Micelles: Micelles are therapeutic agent or a carrier to deliver a poorly water soluble drug having size of around 5-100 nm range. It consists of surfactants having a hydrophilic head and a lipophillic tail [14].

The drug is associated with the hydrophobic block of the co-polymer which is orientated toward the interior of the micelles while the hydrophilic blocks form an external shell. For applications by the oral route, pH-sensitive polymeric micelles are particularly interesting. These micelles are usually composed of block co-polymers with PEG as the hydrophilic part and a polymer derived from acrylic acid as the hydrophobic part. Such polymers self-aggregate at low pH, this protecting an encapsulated drug in the acid environment of the stomach, but dissociate at higher pH to allow drug release in the intestine. One such polymer is the PEG-b-poly(alkyl acrylate-co-methacrylic acid) [15].

Liposome: Liposomes are closed concentric bilayer membranes consisting of water-insoluble polar lipids. They are spherical vesicles (typically 50-500 nm in diameter), consisting of a lipid bilayer sustained through hydrophobic interactions that allow them to carry hydrophobic and hydrophilic molecules [16]. The amphiphilic

feature of liposomes explains why they are widely used to increase the penetration of hydrophilic molecules (in the aqueous core) and/or lipophilic molecules (within the membrane bilayer) [17]. They can encapsulate biomolecules and drugs for targeted delivery while protecting their bioactivity [18]. They are made up of phospholipids enclosing hydrophilic core 19 and were discovered by Bangham and co-workers in the 1960s [20].

A liposome surface decorated with PEG (PEGylated) can significantly improve the half-life of liposomes (>200 nm) in systemic circulation. Furthermore, the PEGylation approach can help to facilitate liposomal drug delivery by reducing multidrug resistance due to the over-expression of drug efflux transporter pumps such as P-glycoprotein [21].

Phospholipid vesicles demonstrate high biocompatibility, low toxicity, biodegradability, and can be produced on a large scale [22,23].

Cholesterol is sometimes added to the membranes of the liposomes for the purpose of increasing their stability and the rigidity of the lipid bilayer, reducing their permeability and inhibition of phospholipid acyl chain crystallization by modulating the bilayer fluidity. Phytosterols have been recently used as a substitute of cholesterol in the formulation of liposomes since cholesterol may cause health problems especially for consumers who are suffering from hypercholesterolemia [24].

Alcohol and surfactant are added to liposomes to render them more elastic transformable and flexible. They are composed of lipids and softeners (sodium cholate). This property of elasticity offers liposomes better skin permeation ability [25].

Liposomes have the ability to cross any cell membrane, the addition of other components to their surface to enhance their effectiveness is interesting in such a way, liposomes can include multiple brain cell membrane-targeting agents on their surface, enabling a specific interaction with target cells by molecular recognition mechanisms, and hence, improving the transport of the encapsulated Growth Factors through the BBB. RMP-7 is a molecule with the ability to increase the permeability of the BBB, when conjugated with liposomes enhances delivery of GFs [26].

Small-sized liposomes enhance transitivity, but large-sized liposomes show a higher cell affinity compared with smaller ones. It therefore appears that large particles have a higher retention [27].

Classification of Liposomes: Liposomes can be categorized into different groups depending on their structural association, size and lamellarity, small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), double bilayer vesicles (DBVs), oligolamellar vesicles (OLVs), multi-lamellar vesicles (MLVs), giant unilamellar vesicles (GUVs), and multivesicular vesicles (MVV) [1,24,28].

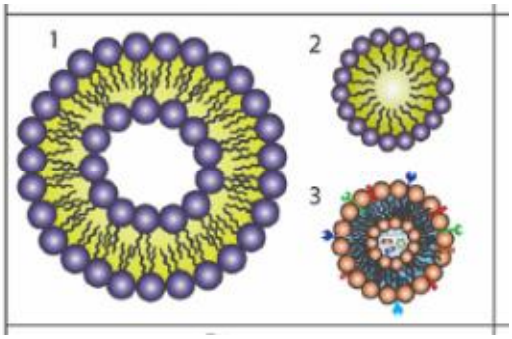

Fig. 2. Adapted from [29]

1. Lipid Nanoparticles:
2. Liposome
3. Micelle

Transfersomes: In order to overcome this inability of liposomes to permeate the skin, Cevc and Blume in the 1990s developed novel lipid vesicles known as deformable/elastic/flexible liposomes [17].Transfersomesrepresent not only the first generation of ultradeformable vesicles, but also one of the most successful carriers for skin delivery. The word Transfersome derives from the Latin word “transferre”, which means “to carry across”, and the Greek word “soma”, which means “body”[22**].**

Transferosomes are typically below 300 nm being more elastic and flexible than liposomes (typically five- eight times higher), which makes them highly suitable for skin penetration. They are mainly composed of phospholipids and edge activators. These edge activators interfere with the bilayer and confer ultra-flexibility to the vesicles which enhance their passage through small apertures of the skin. The concentration of the edge activator in the formulation (usually between 10-20 %) is crucial and ideally included in sub-lytic concentrations i.e. not able to cause destruction of vesicles [31,32]. Some widely used

edge activators of Transfersomes are: Tween, deoxycholate, spans, sodium cholate. However, enhanced permaeation is observed with monoterpenes as edge activator. Mixed monoterpenes (limonene-citral mixture) could significantly enhance the elasticity of Mixed Monoterpenes edge-activated PEGylated TFSs (MMPTs). CLSM analyses demonstrated that MMPTs were distributed in deep layers of the skin, indicating that MMPTs might transport deeper through the skin than conventional liposomes [32].

Ethosomes: Similar to transfersomes, ethosomes can improve the penetration through the stratum corneum barrier due to a quick permeation and greater transdermal flow [33]. The second generation of novel vesicular drug carriers are represented by these spherical, lipid blisters mainly composed of phospholipids, ethanol and water. The high alcohol content of up to 45% is the main distinguishing feature from liposomes enabling a decrease in size and elasticity when same method of preparation is used. In order to reach deeper tissues and cause a systemic action the penetration of the natural skin barrier and the magnitude of transdermal permeation are influenced. Further adjuvants added to the ethosomal formulation are cholesterol to improve stability or gel markers for increased residence time [34].

Cubosomes: Cubosomes are nano-structures composed mainly of amphiphilic polar lipid. When this amphiphilic substance dissolved in water with concentration above the critical micelle concentration, it forms micellar aggregations. At higher concentration, the formed micelles are forced to form cubic structure [35].

They are liquid crystalline particles in nano size range (100-300 nm), usually composed of lipids such as (Monoolein, and phytantriol) and with or without stabilizer/surfactant (Poloxomer 407) [36]. They are highly stable nanoparticles formed from the lipid cubic phase and stabilized by a polymer-based outer layer. The bicontinuous lipid cubic phases consist of a single lipid bilayer that folds in a tridimensional architecture forming a bicontinuous phase of lipid bilayered regions and aqueous channels [37]. The composition of the cubosome can be modified to control the pore sizes or to include specific types of lipids. Their outer polymer layer can be used to enhance targeting. They are highly stable forms under physiological conditions [38].

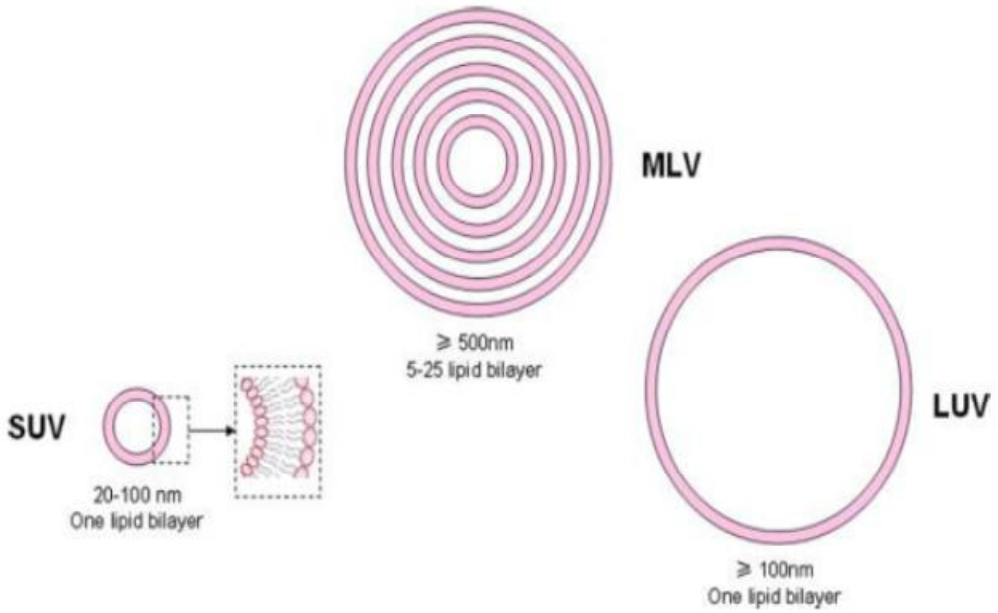

Fig. 3. Adapted from [30]
Unilamellar, Multilamellar, Oligolamellar Liposomes

Phytosome: Phytosomes, also known as herbosomes, are complexes of natural bioactive materials (plant extracts or water soluble phytoconstituents) and phospholipids (phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine). In fact, there is no difference between phytosomes and liposomes. The former are liposomes loaded with phyto-compounds and hence phytosomes are a special case of liposomes [24].

Niosomes: Niosomes have a multi-thin-layer vesicular structure and contain basically nonionic surfactants, a hydration medium, and lipids such as cholesterol [38].

Niosomes are a hydrated mixture of cholesterol and nonionic surfactants such as alkyl-ether, esters, and amides. Also called nonionic surfactant vesicles. They have great advantages, such as low cost, high stability, wide availability of nonionic surfactants, and mild storage conditions. Niosomes are similar to liposomes but the bilayers are formed by nonionic surfactants. Compared with liposomes, Niosomes have greater stability over a long period of time. Liposomes and Niosomes are not able to transport into deeper skin, but Ethosomes have the capability to reach the deep skin layer [28].

Niosomes have already conquered the cosmetic industry and are now being explored to determine the potential for further commercial applications [34].

7. SOLID-LIPID NANOPARTICLES

In the early 1990s, the attention of three research groups of Müller, Gasco and Westesen has focused on the development of alternative carrier system to liposomes, emulsions and polymeric nanoparticles, the so-called solid lipid nanoparticles (SLNs) [34,39]. Solid lipid nanoparticles (SLNs) are lipid-based DDSs that represent an evolution of emulsions; the oil of the fat emulsion is replaced by solid lipids [40].

SLNs are formulated with lipids or lipid mixtures which are in a solid state at room and also at body temperature [41**].** Their solid lipid core provides the opportunity for solubilizing Essential oils (stearic acid and palmitic acid; triglycerides, such as tristearin and tripalmitin; partial glycerides, such as glycerylbehenate and glycerylpalmitostearate;) and protect them against degradation [24]. These EOs are physiological substances which are classified as Generally Recognized as Safe (GRAS) category [41]. Compritol®888 ATO, Precirol® ATO5, cetyl alcohol, cetylpalmitate, glycerylmonostearate, trimyristin/Dynasan®114, tristearin/Dynasan® 118, stearic acid, Imwitor®900 are brand names used in formulation of SLNs, and appear to be well tolerated physiologically when administered in vivo [42].

SLNs is (around 10 to 200 nm) and narrow size range (100 to 200 nm) permits them to cross tight endothelial cells of the blood- brain-barrier (BBB) also in the digestion It escapes from the reticuloendothelial system and bypass the liver [43]. The average diameter of SLNs is in the submicron range from 50 to 1000 nm. They are composed of physiologically tolerated lipids dispersed in an aqueous surfactant phase. Over the last two decades, SLNs have attracted increasing attention as a colloidal carrier system for cosmetic active ingredients and biologically active food components. Particularly, these nanoparticles exhibit great potential as suitable drug delivery system.

Most commonly studied Nonionic surfactant are Cremophor EL and Cremophor RH40 [44]. Poloxamers, polysorbates, lecithins, polyvinyl alcohol, and bile salts are the most frequently used to provide the stabilization of the lipid nanodispersion. The intended administration route of SLNs is an important issue for selection of the surfactant type. Conversely, using the combination of surfactants could have a positive impact on preventing particle agglomeration [41].

SLNs formulations for various application routes have been developed such as parenteral, oral, dermal, ocular, pulmonary, and rectal and systematically also characterized in in-vitro and in-vivo studies [43].

The main advantage of SLNs is that they provide the collective benefits of both liposomes and polymeric NPs, as well as substantial space for loading both lipophilic and hydrophilic candidates 45.

8. NANOSTRUCTURED LIPID CARRIERS

NLCs are considered to be an upgraded version of SLNs, where the compact arrangement of the uniformly structured solid lipids has been replaced with an unstructured lipid matrix established by blending both solid and liquid lipids, which eventually provide more space for

loading drug candidates [45]. NLCs offer special advantages: sustained release, good biocompatibility and biodegradable properties[46].

NLC have been introduced at the end of the 1990s in order to overcome the potential difficulties of SLN described above. The goal was the development of a nanoparticulate lipid carrier with a certain nanostructure in order to increase the payload and prevent drug expulsion [47]. This could be comprehended in three ways: (1) the imperfect type, (2) the multiple type, and (3) the amorphous type [48].

Different types of NLCs such as plain NLCs, multifunctional NLCs, PEGylated NLCs and ligand-attached NLCs were explored for lung targeting [49].

8.1 Lipid Drug Conjugates (LDC)

SLN are useful for the incorporation of lipophilic drugs. Due to partitioning effects during the production process, only highly potent hydrophilic drugs which are effective in low concentrations (e.g. LHRH or EPO) can be firmly incorporated in the solid lipid matrix. In order to overcome this limitation, the so- called LDC nanoparticles with drug loading capacities of up to 33% have been developed at the turn of the millennium. Here, an insoluble drug-lipid conjugate bulk is prepared either by salt formation with a fatty acid, i.e. lipid-drug bioconjugates through grafting of the carboxylic groups of the fatty acids (e.g., stearic acid, oleic acid) with the functional groups (e.g., amine group) of drug molecules or by covalent linking (e.g. to esters or ethers). In the salt formation process, the free drug base and fatty acid are dissolved in a suitable solvent. The solvent is then consequently evaporated under reduced pressure. For the covalent linking, the drug (salt) and a fatty alcohol react in presence of a catalyst and the LDC bulk is then purified by recrystallization [42,47].

8.2 Nanoemulsions

Nanoemulsions are fine emulsions, either water in oil or oil in water, prepared by using two immiscible phases, with the help of one or more suitable surfactants. The range of the droplet size of these forms varies approximately between a few to 200 nanometers, which makes them appear in a transparent-to-milky-white appearance to the naked eye [38].

These novel formulations enhance drug delivery when given orally, parenterally and dermally. In contrast to microemulsions, nanoemulsions diluted with water remain stable without changing the droplet size distribution; this stability is influenced by changes in temperature and pH [21]. Lesser toxic formulation, kinetically stable systems, targeting applications, and aesthetic features forced the pharmaceutical researchers to work on nano-emulsion [50].

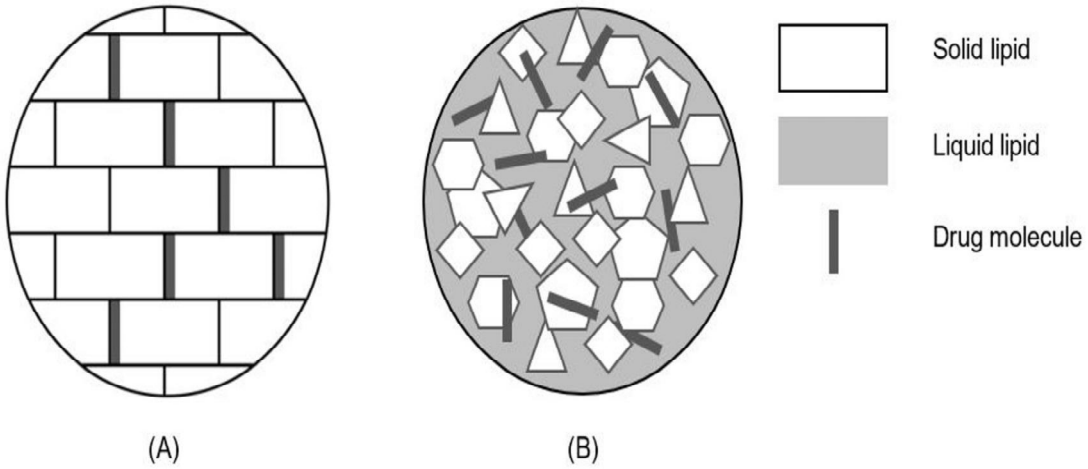

Fig. 4. (A) and (B) Adapted from [34]
Features the two major types of Solid Lipid Based Nanoparticles;
(A) Solid Lipid Nanoparticles.
(B) Nanostructured Lipid Carriers

8.3 Self-Emulsifying Drug Delivery System (SEDDS)

In 1943, Hoar and Schulman hypothesized the existence of microscopic emulsion-like structures in a transparent mixture of oil, alcohol, water and a cationic surfactant. About fifteen years later, the presence in these systems of small emulsion-like structures was confirmed by electron microscopy and coined the term "Micro-emulsion" to define a system consisting of water, oil and surfactants, which is a transparent, optically isotropic and thermodynamic stable Newtonian non-viscous liquid [51].

A readily dispersible isotopic mixture of oil, drug, surfactant, and co-surfactant, which forms an oil-in-water emulsion with a droplet size below 1000 nm in the presence of agitation, is called a self-micro-/nanoemulsifying drug-delivery system [52]. Self-emulsifying drug-delivery systems (SEDDSs) enhance the bioavailability of APIs with low water solubility. SMEDDSs (microemulsifying) are different from SNEDDSs (nanoemulsifying) only in terms of droplet size. Compared with SMEDDSs, SNEDDSs are more effective in enhancement of bioavailability because of the high interface surface area for drug absorption due to the nanosized droplets. All components reach the GIT, which provides a suitable environment for the emulsification process, whereas preparations of SLNs, NLCs, and liposomes need external energy. Different parameters affect the SEDDS properties such as size, bioavailability, and drug release [28].

8.4 Application of Lipid Based Delivery Systems

8.4.1 Lipid-based nanoparticles in erectile dysfunction treatment

Lipid-based drug delivery systems are an emerging technology in pharmaceutical development owing to their ability to improve the solubility and bioavailability of poorly water-soluble drugs. In addition, they have gained considerable attention due to the obvious advantages of biocompatibility and versatility. Lipid-based nanoparticles are composed of physiological lipids and hence, are well-tolerated, usually non-toxic, and produce non-toxic degradation products. These drug delivery systems are commercially viable to formulate pharmaceuticals for topical, oral, parenteral, or pulmonary and can penetrate the skin in the transdermal delivery of drugs. Therefore, as lipid-based drug delivery systems provide a vast array of formulation possibilities, they have also been extensively studied in the delivery of ED drugs via the oral and transdermal route of administration. Recently, research has focused on newer approaches using novel lipid-based nanocarriers including liposomes, ethosomes, transfersomes, nanostructured lipid carriers, solid lipid nanoparticles, and lipid nanoemulsions for the safe and effective delivery of ED therapeutics [53].

8.4.2 Application in NSAIDS (Lipid nanoparticles in topical drug delivery)

Ketoprofen and naproxen are other two widely studied NSAIDs used for the treatment of chronic inflammatory pathologies such as the osteoarthritis and the rheumatoid arthritis. Puglia and co-workers formulated NLC loaded with these anti-inflammatory compounds and determined their permeation profiles through the skin. Nanoparticle behavior on human skin was assessed, in vitro, to determine the drug percutaneous absorption (Franz cell method) and, in vivo, to establish the active localization (tape-stripping technique) and the controlled release abilities (UVB induced erythema model). The results demonstrated that the particles were able to reduce the penetration of the drugs with respect to the reference forms, increasing yet the accumulation in the stratum corneum of ketoprofen and naproxen. The accumulation and the consequent formation of a drug depot were responsible of an interesting anti-inflammatory prolonged effect [51].

8.4.3 Lipid Nanocapsules in treatment of Brain Diseases

The central nervous system (CNS), namely the brain, still remains as the hardest area of the human body to achieve adequate concentration levels of most drugs, mainly due to the limiting behavior of its physical and biological defenses. Lipid nanocapsules emerge as a versatile platform to tackle those barriers, and efficiently delivery different drug payloads due to their numerous advantages. They can be produced in a fast, solvent-free and scalable-up process, and their properties can be fine-tuned for to make an optimal brain drug delivery vehicle. Moreover, lipid nanocapsule surface modification can further improve their bioavailability towards the central nervous system. Coupling these features with alternative delivery methods that stem to

disrupt or fully circumvent the blood-brain barrier may fully harness the therapeutic advance that lipid nanocapsules can supply to current treatment options [54]. Surfactants are also employed to increase brain targeting. Commonly used surfactants like polysorbate 80 (PS 80 or Tween 80) and poloxamer 188 can induce the adsorption of proteins from the bloodstream that interact directly with receptors and transporters on the BBB surface [55].

8.4.4 Application of Micelles in Treatment of Colorectal Cancer (CRC)

Bioactive lipids such as sphingolipids play an important role in signal transduction pathways, especially growth arrest, cell proliferation and pro-apoptotic effects in cancer cells. They control various membrane-associated signaling pathways, which are actively involved in growth and apoptosis of cancer cells. Moreover, sphingolipids have been reported to induce apoptosis by generating reactive oxygen species (ROS), caspase expression and Bax translocation. Recently, it has been established that sphingolipid-based novel self-micellizing anticancer lipid (SMAL) could selectively induce cell death via the activation of apoptosis and autophagy in CRC cell lines. SMAL-based Nano-DDS can serve the dual function of a drug delivery agent with antitumor activity [56].

8.4.5 Application of *Liposomes* as Antigen Carriers

To achieve cross-presentation by "cytosolic pathway", cytoplasmic delivery of antigen is crucially important. For this purpose, pH-sensitive liposomes have been widely used because of their pH-responsive content release properties and destabilization ability of endosomal membrane. One strategy for obtaining pH-sensitive liposomes is conjugation of pH-sensitive materials to antigen- loaded liposomes [57].

8.4.6 Application of *Nanoemulsion in* Cancer Treatment

Paclitaxel nanoemulsions (22 nm) composed of labrasol, d-α-tocopheryl polyethylene glycol 1000 succinate and labrafil, when administered orally at a dose of 10 mg/kg paclitaxel, were rapidly absorbed reaching a steady-state value in half an hour, which were constant up to 18 h and amounted to an absolute bioavailability of 70.62%. This increase in bioavailability could be due to the inhibition of P-glycoprotein efflux by d-α-tocopheryl polyethylene glycol 1000 succinate and labrasol, which have contributed to the enhanced peroral bioavailability of paclitaxel [21].

8.4.7 Therapeutic Small interfering RNA in lipid *nanoparticles* with anti-cancer effect

The efficacy of lipid carriers has a tremendous impact on cancer treatment in clinics. Exponentially growing evidence suggests that conventional drugs used in cancer treatment are highly dependent on pharmacological interventions that exert undesirable toxic effects that are of continuous concern. In this regard, silencing the cancer-promoting genes through siRNA-LNPs could be a viable alternate option in cancer therapy. Considerable attention has been devoted recently to the development of chemically diverse LNPs formulation for targeting cancer cells. Intriguingly, the first-in-human trial examined the efficacy of siRNA in LNP targeted against vascular endothelial growth factor (VEGF) and kinesin spindle protein (KSP) in cancer patients of liver metastasis. This formulation markedly inhibited tumor growth by displaying greater bioavailability and well-tolerated at clinically relevant dosages [33].

Cationic-SLN reconstituted with protein-free low-density lipoprotein (LDL), conjugated to PEG and c-Met siRNA significantly reduced the tumor growth by decreasing c-Met expression level in U-87MG glioma cells and glioblastoma xenograft tumor model [33].

9. CONCLUSION

Of the various techniques of drug delivery, lipid systems stand out to be merited with less toxic effect to animals with a good treatment efficacy, safe distribution and utilization by tissues and cells coupled to stable release at target site. In addition, combined action of short peptides, aptamers, ligands and genes with lipid particles have enhanced the increase uptake and utilization of drug substances by target tissues to achieve maximal therapeutic effect. Nonetheless, this system is demerited with the likely formation of "protein corona" a complex formed when serum substrate interacts with ligands, aptamers or short peptides, resulting to a reduced uptake of NPs across target site [45]. The possible accumulation of lipid NPs at the RES sites, i.e., the liver, subsequently restricts or lowers the dose of NPs that reaches the systemic

circulation. These limitations have been effectively overcome by altering the physicochemical properties of NPs and by making surface modifications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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