Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Nanocarriers as Novel Nose-to-Brain Targeted Drug Delivery Platforms

SAGAR PATEL, BRIJESH PATEL, ZARNA PATEL, CHANDRAKANTSING PARDESHI*

R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, India

ARTICLE DETAILS

Article history:
Received on 30 August 2012
Modified on 28 November 2012
Accepted on 07 December 2012

Keywords:
Nanoparticulate drug carriers,
Polymeric micelle,
Nanoemulsion,
Macroemulsion,
Carbon nanotubes (CNTs),
Dendrimer,
Solid lipid nanoparticles (SLNs),
Polymer-lipid hybrid nanoparticles (PLN),
Liposome.

ABSTRACT

The present review is designed to provide an insight on how nanoparticulate carriers are finding niche as promising drug vectors. In the era of controlled and site specific drug delivery systems, use of nanocarriers has became a revolutionary approach. Nanocarriers are at forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicines and research. The success of nanocarriers as targeted drug delivery platforms depends on their ability to incorporate drugs of different kinds, penetrate through several anatomical barriers, sustained release of incorporated drugs, and stability in nanoscale size. Such prototypic traits of nanocarriers offer a new breakthrough in drug delivery and therapeutics that holds great promise for achieving the goal of controlled and site-specific drug delivery. Delivery of drugs to the brain is a major challenge due to presence of physiological barriers that restricts the delivery of drugs to CNS. Thus, since last few decades, nasal route has been attracted a wide attention of researchers as a convenient, reliable, and safe, being non-invasive, route to achieve faster and higher levels of drug absorption in the brain. It is thought to do so through olfactory route of drug transport which bypass the blood-brain barrier (BBB) and allow the direct transport of drug from nose to brain. Herein, authors has tried to highlight over the frontline aspects relevant to nanoparticulate carriers and their potential as drug delivery systems for targeting the brain via nasal route of drug administration. The present discussion embodies the various nanocarriers and their utility as nose to brain targeted drug delivery vehicles, in the core areas of pharmaceutical sciences, thereby alarming the pharmaceutical industries to enhance their scale up.

© KESS All rights reserved

INTRODUCTION

The concept of designing specified delivery system to achieve selective targeting of drug has been originated from the perception of Paul Ehrlich, who proposed drug delivery to be as a 'magic bullet'. It was a very first report published on drug targeting. It is pertinent to discuss the concept and components, which are utilized in designing a targeted drug delivery system(s). A number of essential aspects that need to be considered while designing targeted drug delivery systems include carrier, target and targeting ligand. Carrier is a drug vector, which sequesters, transport and retain drug *en route,* while elute or deliver it within or in the vicinity of target. Targeting ligand is bounded to the carrier so as to negotiate its exclusive delivery to the specific pre-identified site [1].

Author for Correspondence:
Email: chandrakantpardeshi11@gmail.com

Brain is a delicate organ, isolated from general circulation and characterized by the presence of relatively impermeable endothelial cells with tight junctions, enzymatic activity and the presence of active efflux transporter mechanism (P-gp efflux). Because of theses formidable obstacles, many neurotherapeutics failed in treating CNS disorders since, they cannot be effectively delivered to brain. Excellent theoretical predictions and *in vitro* experimental data sometime follow the disappointing *in vivo* results leading to therapy failure, probably because the molecule cannot readily permeate into brain parenchyma in a sufficient concentration through systemic circulation. The mere consequence will be loss of molecule from market [2]. Delivery of drugs to the brain is a major challenge due to the presence of two physiological dynamic barriers that restricts the delivery of drugs to the CNS, the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) [3].

Conventionally, nasal route has been exploited for delivery of drugs for treatment of local diseases like nasal allergy, nasal infections and nasal congestion. But, since last few decades, the nasal route has been attracted a wide attention of researchers as a convenient, reliable, and safe, being non-invasive, route to achieve faster and higher levels of drug absorption [4].

Considering the potential hurdles in brain targeting through systemic route, alternative drug delivery route is needed to improve the therapeutic efficacy and bioavailability of biomolecules delivered via nose to brain drug delivery systems. Existence of direct transport pathway through olfactory region of nasal cavity may fulfill this demand. Animal and human investigations proved that, transport of exogenous materials directly from nose-to-brain is a potential route for bypassing the BBB. Last two decades have witnessed an unheralded explosion in research on the development of novel colloidal drug delivery systems. Most attractive area of research in drug delivery, now-a-days, is the design of nanocarriers, which are able to deliver drugs to the right place, at appropriate times, and at right dosage [5].

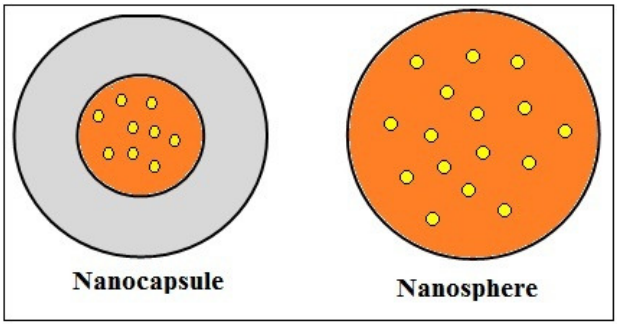

Figure 1: Schematic presentation of nanoparticulate drug carriers.

Nanocarriers are at forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicines and research, as well as in various allied fields of science. The successful implementation of nanocarriers for targeted drug delivery depends on their ability to incorporate different kinds to drugs, penetrate through several anatomical barriers, sustained release of incorporated drugs, and stability in nanometric size [6]. Such characteristics of nanocarriers offer a new prototype in drug delivery that holds great promise for achieving the goal of controlled and site-specific drug delivery. Thus, if appropriately investigated, these nanocarriers may open new vistas in the research and therapy of complex CNS disorders, as nose-to-brain drug delivery platforms. The schematic presentation of nanocarriers is depicted in Fig. 1.

Polymeric nanoparticles

Polymeric nanoparticles based on biodegradable polymers have been extensively studied as they offer improvement in nose-to-brain drug delivery by protecting the encapsulated drug from biological and/or chemical degradation, and extracellular transport by P-gp efflux system. This increases the CNS availability of drugs. Polymers approved by the U. S. Food and Drug Administration (FDA) for fabrication of polymeric nanoparticles and for administration in human beings are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactide-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(methyl methacrylate), and so on. These polymers are known to be biodegradable, biocompatible, and non-toxic and have been used for biomedical applications for more than two decades. Among these, PLGA has been widely explored for nanoparticulate formulations because of its biocompatibility, safety, ability to enhance mucoadhesion and enhanced drug stability. Seju *et al.*, (2011) have reported the PLGA nanoparticles loaded with olanzapine for the treatment of psychotic illness, schizophrenia, via nose to brain drug delivery system [7, 8].

Aquasomes

Aquasomes represents a new class of solid drug carriers, invented since last decade. Aquasomes are three-layered structures (core, coat, and drug) which are self-assembled through non-covalent bonds, ionic interactions and van der Waals forces. They consist of a ceramic core whose external surface is noncovalently engineered with carbohydrates to obtain a sugar ball, which is then rendered to adsorption of a therapeutic agent. The core provides structural stability to the immutable solids, while surface modification with carbohydrates creates a glassy molecular stabilization film that adsorbs therapeutic agent with minimum structural denaturation. Aquasomes offers an exciting mode of delivering therapeutic agents belonging to the class of proteins and peptides, since they are able to rectify some inherent problems associated with these molecules. These relevant problems include suitable route of drug delivery, physical and chemical instability, poor

bioavailability, and potent side effects. Aquasomes provides complete protections of an aqueous nature to the adsorbed therapeutics against the denaturing effects, like swelling or porosity changes, caused by external pH and temperature [9]. Aquasomes are not yet explored for nose-to-brain drug delivery of bioactives, but their potential application in delivering proteins and peptides could be exploited for targeting various potent molecules to the CNS.

Cubosomes

Cubosomes (cubs) are discrete, submicron, nanostructured particles of bicontinuous cubic liquid crystalline phase, which are able to incorporate large amounts of drugs of varying physicochemical properties and can be localized in body cavities, on the skin or on different mucosal surfaces. Cubosomes consisting of amphiphilic lipoid materials such as glyceryl monooleate (GMO), have a stiff, bioadhesive, and gel-like appearance and is biodegradable in nature. Therefore, modified nanovehicles with both mucoadhesive property and enhanced site specific delivery to the brain might eliminate the obstacles related to the brain drug delivery via nasal route and offers a feasible alternative. Wu *et al.*, (2012) reported the formulation of targeting ligand (odorranalectin) conjugated Cubosomes loaded with S14G-HN (humanin derivative) for the treatment of memory impairments caused by Alzheimer's disease in rats, as nose-to-brain drug delivery vehicles [10]. If further investigated, Cubosomes could be viewed as an excellent alternative to conventional dosage forms.

Polymeric micelles

Advances in the syntheses of block copolymers have led to the formation of polymeric micelles that may serve as nanoscopic drug carriers. They are known as self-assemblies of block copolymers, and promising nanocarriers for drug and gene delivery. For drug delivery, polymeric micelles have been prepared from biodegradable and biocompatible block copolymers [11, 12]. Polymeric micelles were first proposed as drug carriers by Bader *et al.* in 1984. They have emerged as potential carriers for poorly water soluble drugs since they can solubilize those drugs in their inner core and offer attractive characteristics such as small size (< 100 nm) and propensity to evade scavenging by the mononuclear Phagocytic system (MPS) [13].

Amphiphilic diblock copolymers are generally used for the fabrication of polymeric micelles. However, triblock and graft copolymers can also be used. Polymeric micelles are characterized by core-shell structure. They consist of hydrophobic core and hydrophilic shell or block (Fig. 2). The hydrophilic shell forming copolymers includes: poly(ethylene oxide) (PEG), poly(N-vinyl-2-pyrrolidone) (PVP), poly[N-(2-hydroxypropyl)-methacrylamide] (pHPMA), poly(aspartic acid) (P-Asp), and so on. The lipophilic core forming copolymers includes: poly(propylene oxide) (PPO), poly(lactic acid) (PLA), poly(amino acid) (PAA), poly(lactide-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly (β-benzyl-L-aspartate) (PBLA), poly(DL-lactic acid) (PDLLA), and so on. The lipophilic core is responsible for loading of lipophilic drugs while hydrophilic shell is responsible for micellar stabilization. Several other polymers such as poly(N-isopropylacrylamide) (PNIPA) and poly(alky-lacrylic acid) impart temperature and pH-sensitivity to the micelles, and could be used to confer bioadhesive properties to the formulation [14].

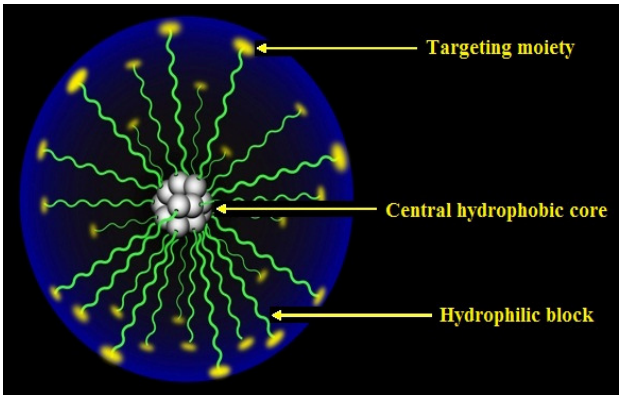

Figure 2: Structure of polymeric micelle

Jain *et al.*, (2010) have reported the formulation and evaluation of micellar nanocarriers for nose to brain delivery of zolmitriptan to treat migraine headache. Their results suggested the potential of micellar carrier as safe, stable and effective new generation vehicle for brain targeting [15].

Nanoemulsions

Emulsions with droplet size in the nanometric scale (typically in the range of 20-200 nm) are often referred as miniemulsions, nanoemulsions, ultrafine emulsions, or multiple emulsions, etc. These nanoemulsions appear transparent or translucent to the nacked eyes, and possess stability against sedimentation or creaming. The difference between nanoemulsion and

macroemulsion is shown in Fig. 3 (a) and 3 (b). These characteristics make nanoemulsions as carriers of vast interest for fundamental studies and practical applications in varied fields like chemical, cosmetic and pharmaceutical, etc. fields [16]. Kumar *et al.* (2008) proposed the intranasal nanoemulsions loaded with risperidone, as drug carriers for brain targeted drug delivery system. Their study demonstrated rapid and larger extent of transport of risperidone into the rat brain [17].

Figure 3: a) Nanoemulsion, b) Macroemulsion[16].

Nanogels

The submicron sized hydrogel particles that are confined to nanoscale dimensions are known as Nanogels. They have high water content, biocompatibility, and tunable size from submicrons to tens of nanometers, and an interior for incorporation of therapeutic agents. These unique characteristics offer great potential for the utilization of nanogels for application in tissue engineering, biomedical implants, bionanotechnology, and drug delivery. Biopolymer-based nanogels have attracted a great deal of interest in drug delivery and they are referred to as bionanogels. The naturally occurring biopolymers include polysaccharides like chitosan (CS), hyaluronan (HA), dextran (Dex), cellulose (CeL), pullulan (PuL), chondroitin sulfate (ChS), and alginate (Alg) [18].
Effective polysaccharide-based nanogels can be prepared by using various synthetic strategies, mainly based on chemical and physical cross-linking methods, like heterogenenous polymerization, continuous extrusion, precipitation in water, micromolding-microfluidic preparation, spray drying, supramolecular self-assembly, and self complexation. Various surface modification methods of biopolymers have also been explored and these includes methacrylation and covalent grafting by free radical polymerization (FRP), ring opening polymerization (ROP), and controlled/living radical polymerization (CLRP) [18].

For active drug targeting, the surface of nanogels could be modified with biospecific ligands. For this purpose, various coupling strategies can be used like covalent attachment of ligand moieties to the free surface functional groups of the nanogel formulations [19].

Nanogels have been utilized as potential carriers for oligonucleotide delivery to the brain by using polarized monolayers of bovine BMEC (Brain Microvessel Endothelial Cells), which forms the Blood-Brain Barrier (BBB). These studies have shown an increased transport of Ondansetron across the cell monolayers as a result of their incorporation into the nanogels. Further increase in oligonucleotide transport was observed when the nanogel carriers were modified with insulin or transferrin ligands [20, 21].

Azadi *et al.* (2012) have prepared surface modified Methotrexate-loaded nanogels for brain drug delivery. They observed that, Methotrexate-loaded nanogels surface engineered with polysorbate-80 may be a good candidate for the targeted delivery of this anticancer agent [22].

Carbon nanotubes (CNTs)

Carbon nanotubes consist exclusively of carbon atoms arranged in a series of condensed benzene rings, which are rolled up into a tubular structure. CNTs can be classified, on the basis of their structure, into two types: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). The SWCNTs consist of only one layer of cylinder graphene while MWCNTs contains several concentric graphene sheets (Fig. 4). CNTs have nanometric dimensions: SWCNTs have diameter in the range of 0.4-2.0 nm and lengths in the range of 20-10 nm, while MWCNTs have diameter in the range of 1.4-100 nm and lengths from 1μm to several microns [23].

CNTs have very interesting physicochemical properties such as: ordered structure with high aspect ratio, ultralight weight, high mechanical strength, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behavior, and high surface area. These unique characteristics of CNTs make them ideal candidate for potential diverse applications including pharmaceutical, engineering, biotechnological and biomedical [24].

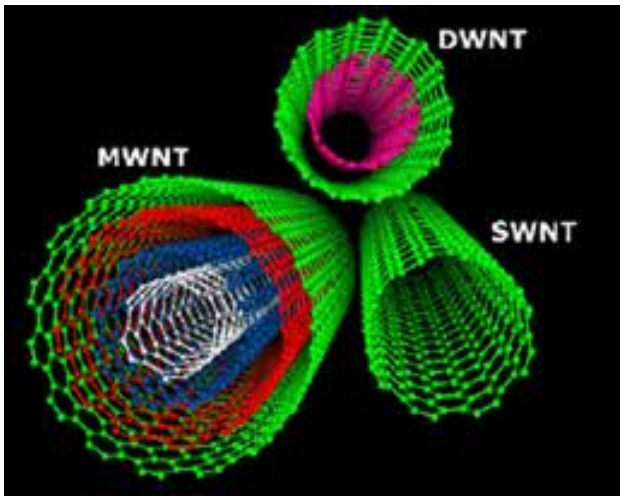

Figure 4: Different forms of carbon nanotubes (CNTs).

CNTs have attracted a vast attention of researchers around the world utilizing the various properties that CNT possess for applications ranging from sensors for detection of genetic abnormalities, to substrates for the growth of cells for tissue regeneration, and as drug delivery systems for a variety of diagnostic or therapeutic agents. To enhance the properties of CNTs, their surface can be functionalized with different molecules by adsorption, electrostatic interactions, or covalent bonding of molecules to the surface of CNTs [23].

Huang *et al.* (2011) prepared a folate-decorated CNTs loaded with doxorubicin for targeted delivery to the cancerous cell and proved high potential of developed system to address the current challenges in cancer therapy [25]. CNTs can also be explored for nose to brain targeted drug delivery by considering surface engineering approach so as to enhance the bioavailability and therapeutic efficacy of therapeutic agents that otherwise finds difficulty for delivery by any other route.

Dendrimers

Dendrimers are one of the most researched macromolecules of the recent times. Since the last decade, Dendrimers have emerges as highly promising drug delivery modules because of their unique structure and properties. Dendrimers are a unique class of macromolecules having highly branched, three dimensional, nanoscale architectures with high surface functionality and low polydispersity.

Structurally dendrimers consist of hydrophobic core and hydrophilic exterior functional moieties. The groups present in inner channels of dendrimers are called as endo-receptors while those present on the surface are called as exo-receptors. A dendrimers is a hyperbranched ordered, monodisperse, high molecular weight polymers possessing a central core with void spaces, radially extending repeating units and terminal functional groups. Dendron is a segment of the dendrimers. Thus, dendrimers are composed of three distinct regions; as shown in Fig. 5:

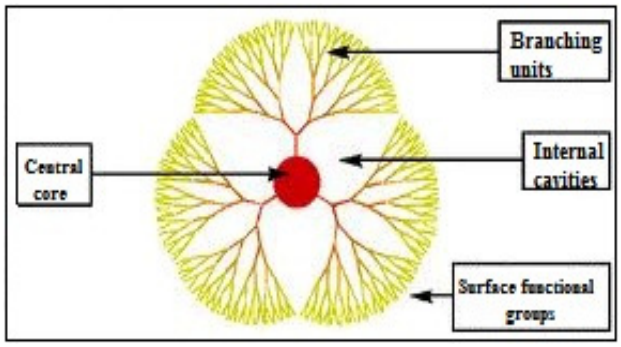

Figure 5: Dendrimer structure (modified from 27).

i. An initial core.
ii. A series of inner microdomains or internal cavities made up of repetitive molecular units, and
iii. Terminal moieties from which further branching and surface modification can be performed to enhance the characteristics of native dendrimers [26, 27].

The therapeutic efficacy of any drug is often diminished due to its inability to gain access to the site of action. Dendrimers can be used to deliver drugs to the specific sites in the body. Tansey and co-workers (2004) have developed branched poly(l-glutamic acid) centered PAMAM dendrimers to create new biodegradable polymers with improved biodistribution and targeting abilities. These constructs were surface functionalized with poly(ethylene glycol) to enhance their biocompatibility and folic-acid receptors specificity to introduce cell-specific targeting [28].

Lipid-based nanoparticles

In the era of nanoparticulate controlled and site specific drug delivery systems, use of solid lipids to produce lipid nanoparticles has became a revolutionary approach in early nineties. Based on the generations of lipid nanoparticles evolved, they are categorized in following types:

i. Solid lipid nanoparticles (SLN)

ii. Nanostructured lipid carriers (NLC)
iii. Polymer-lipid hybrid nanoparticles (PLN)
iv. Lipid-drug conjugate (LDC)

The most widely accepted problems associated with traditional drug delivery systems include:

a. Poor drug solubility
b. Poor absorption, rapid metabolism and excretion
c. Drug distribution to non-targeted sites combined with high drug toxicity
d. High fluctuations in drug plasma levels

To troubleshoot these formidable problems, a novel, promising first generation solid-lipid based nanoscale drug delivery system was brought in, in early nineties, called as solid-lipid nanoparticles (SLN). SLNs are one generation next to the sub-micron sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid and are mainly composed of physiological lipid dispersed in water or in aqueous surfactant solution (Fig. 6). Replacement of liquid oil with solid lipid has presented a most important milestone in a direction to achieve controlled drug release because, mobility of drug in solid lipid is usually lower as compared to liquid oil which made them attractive for their potential use in improving the performance of pharmaceuticals, nutraceuticals and other such materials [29, 30]. Kaur *et al.*, (2008) highlighted the potential of solid lipid nanoparticles in targeting the brain [2].

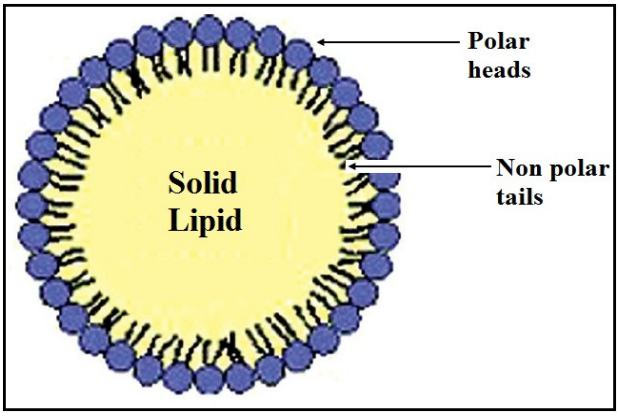

Figure 6: Solid lipid nanoparticles (SLNs)

Nanostructured Lipid Carriers (NLCs), introduced at the turn of millennium, represents a new and improved generation of SLNs and are made of a solid lipid matrix entrapping liquid lipid nanocompartments, the blend being solid at body temperature [31]. This new generation of lipid nanocarriers was introduced to overcome the existing problems associated with SLNs such as limited drug loading capacity, drug expulsion during storage, long-term physical stability, etc.

The NLCs have mostly been extensively investigated for topical and dermatological preparations in the delivery of clotrimazole [32], celecoxib [33], ascorbyl palmitate [34], fluticasone [35] and so on. NLCs are not yet explored for CNS targeting however, one can utilize this novel carrier as nose to brain targeted drug delivery vehicle.

Clinical success of polymeric nanoparticles and liposomes leads to the hypothesis of the development of polymer-lipid hybrid nanoparticles (PLN) that takes advantage of the unique strengths of polymeric nanoparticles and liposomes. The hybrid nanoparticles can be a robust drug delivery platform with high drug encapsulation efficiency, tunable and sustained drug release profile, excellent serum stability, and potential for differential targeting of cells or tissues. Structurally, PLNs are composed of three distinct components; as presented in Fig. 7:

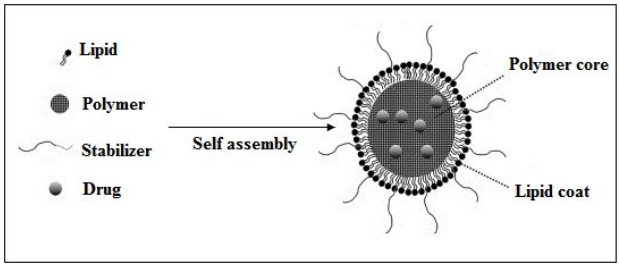

Figure 7: Polymer-lipid hybrid nanoparticles (PLN)

i. A hydrophobic polymeric core which can encapsulate the poorly water soluble drugs;
ii. A hydrophilic polymeric shell which enhances the stability and systemic circulation half-life of drugs; and
iii. A lipid monolayer at the interface of core and shell that acts as a molecular fence to promote retention of drug inside the polymeric core, thereby enhancing the drug encapsulation efficiency, increasing drug loading, and controlling drug release [36].

Wong *et al.*, (2006) have developed polymer-lipid hybrid nanoparticles loaded with anticancer drug doxorubicin hydrochloride, for the treatment of multidrug-resistant breast cancer and demonstrated an efficient approach to deliver a cytotoxic drug for improved treatment of drug-resistant breast cancer [37].

Although there is no formal study underwent on the structure of lipid-drug conjugate nanoparticels (LDCs), however they are thought to be similar to classical SLNs. In LDCs, drug is evenly distributed within the lipid matrix due to ion-activated complex formation between charged drug and lipid molecules. To our knowledge, LDCs are not yet explored for CNS targeted drug delivery via nasal route. In 2006, Olbrich and co-workers had developed lipid-drug conjugate nanoparticles of diminazine diaceturate and stearic acid/oleic acid [38].

Liposomes

Liposomes are lyotropic liquid crystals composed of relatively biocompatible and biodegradable materials and consist of an aqueous core entrapped by one or more bilayers of natural and/or synthetic lipids (Fig. 8). Liposomes have been widely investigated since 1970s as drug carriers for improving the delivery of therapeutic agents to specific sites in the body. The success of liposomes as drug carriers has been reflected in a number of liposome-based formulations, which are commercially available [39]. Liposomes (In Greek, fat bodies) are mainly of three types:

i. Small unilamellar vesicles (SUV): contain only one lipid layer and 20-25 nm in diameter;
ii. Large unilamellar vesicles (LUV): contain single lipid layer and 100-300 nm in diameter;
iii. Multilamellar vesicles (MLV): contain several (upto 14) lipid layers and several hundred nanometers (> 500 nm) in diameter [40].

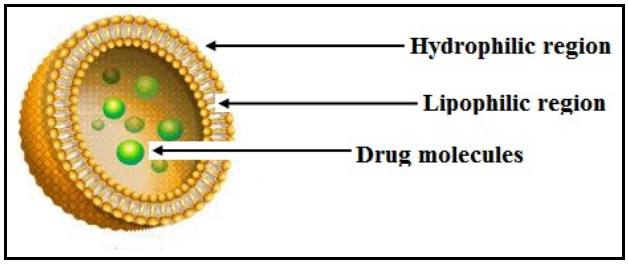

Figure 8: Structure of liposome

Liposomes can be used for targeting and introduction of therapeutic agents to specific site by conjugation or cross linking of targeting moiety to the native liposome or by surface modification of the fabricated liposomal formulation. Nishioka and Yoshino (2001) have highlighted over the efficiency of liposomes in lymphatic targeting [41]. Lymphatic uptake of liposomes of various sizes, lipid compositions, and surface characteristics has been investigated, which in turn suggests the feasibility of liposomes in brain targeting through nasal drug delivery platform.

CONCLUSION

Colloidal nanocarriers, in their various forms, have potential of providing endless opportunities in the field of drug delivery. They have a bright future in the delivery of therapeutic and diagnostic agents. These colloidal nanoparticulate carriers have potential of achieving broad objectives of controlled drug release, enhanced therapeutic efficacy, enhanced targeting abilities, and enhanced bioavailability.

To explore the broad applications of nanoparticulate formulations, it is essential that the pharmaceutical industries specialized in development of new drug delivery systems should engage themselves in novel formulation technologies to foster their scale up and bring them into pharmacist's shelf.

REFERENCES

[1] Vyas SP, Khar RK. Molecular basis of targeted drug delivery. In: SK Jain and VK Jain. Targeted and controlled drug delivery: Novel carrier systems, 1st Ed. New Delhi: CBS publishers and distributors; 2011. 38-80.
[2] Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. J Control Release. 2008; (127):97-109.
[3] Alam MI, Beg S, Samad A, Baboota S, Kohli K, Ali J, Ahuja A, Akbar M. Strategy for effective brain drug delivery. Eur J Pharm Sci. 2010; (40):385-403.
[4] Pardeshi CV, Rajput PV, Belgamwar VS, Tekade AR. Formulation, optimization and evaluation of spray dried mucoadhesive microspheres as intranasal carriers for valsartan. J Microencapsul. 2011; (29):103-114.
[5] Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm. 2009; (379):146-157.
[6] Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J Pharm Sci. 2009; (3):349-358.
[7] Seju U, Kumar A, Sawant KK. Development and evaluation of olanzapine-loaded PLGA

nanoparticles for nose-to-brain delivery: In vitro and in vivo studies. Acta Biomaterialia. 2011; (7):4169-4176.

[8] Mishra B, Patel BB, Tiwari S. Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. Nanomedicine. 2010; (6):9-24.

[9] Umashankar S, Sachdeva RK, Gulati M. Aquasomes: a promising carrier for peptides and protein delivery. Nanomedicine. 2010; (6):419-426.

[10] Wu H, Li J, Zhang Q, Yan X, Guo L, Gao X, Qiu M, Jiang X, Lai R, Chen H. A novel small Odorranalectin-bearing cubosomes: Preparation, brain delivery and pharmacodynamic study on amyloid- β_{25-35}-treated rats following intranasal administration. Eur J Pharm Biopharm. 2012; (80):368-378.

[11] Kwon GS, Okano T. Polymeric micelles as new drug carriers. Adv Drug Del Rev. 1996; (21):107-116.

[12] Nishiyama N, Kataoka K. Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacol Ther. 2006; (112):630-648.

[13] Jones MC, Leroux JC. Polymeric micelles - a new generation of colloidal drug carriers. Eur J Pharm Biopharm. 1999; (48):101-111.

[14] Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine. 2010; (6):714-729.

[15] Jain R, Nabekar S, Dandekar P, Patravale V. Micellar Nanocarriers: Potential Nose-to-Brain Delivery of Zolmitriptan as Novel Migraine Therapy. Pharm Res. 2010; (4):655-664.

[16] Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. Curr Opin Colloid Interface Sci. 2005; (10):102-110.

[17] Kumar M, Mishra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm. 2008; (358):285-291.

[18] Oh JK, Lee DI, Park JM. Biopolymer-based microgels/nanogels for drug delivery applications. Prog Polym Sci. 2009; (34):1261-1282.

[19] Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. Colloidal carriers and blood–brain barrier (BBB) translocation: A way to deliver drugs to the brain? Int J Pharm. 2005; (298):274-292.

[20] Vinogradov SV, Batrakova EV, Kabanov AV. Nanogels for oligonucleotide delivery to the brain. Bioconjug Chem. 2004; (15):50–60.

[21] Kabanov AV, Batrakova EV, Melik-Nubarov NS, Fedoseev NA, Dorodnich TY, Alakhov VY, Chekhonin VP, Nazarova IR, Kabanov VA. 1992. New clases of drug carriers: micelles of poly(oxyethylene)–poly(oxypropylene) block copolymers as microcontainers for drug targeting form blood in brain. J Control Release. 22, 141–158.

[22] Azadi A, Hamidi M, Khoshayand MR, Amini M, Rouini MR. Preparation and Optimization of Surface-treated Methotrexate-loaded Nanogels Intended for Brain Delivery. Carbohydr Polym. 2010; DOI:10.1016/j.carbpol.2012.05.066.

[23] Lacerda L, Bianco A, and Prato M, Kostarelos K. Carbon nanotubes as nanomedicines: From toxicology to pharmacology. Adv Drug Del Rev. 2006; (58):1460-1470.

[24] Bianco A, Kostarelos K, Partidos CD, Prato M. Biomedical applications of functionalised carbon nanotubes. Chem Commun. 2005; (5):571-577.

[25] Huang H, Yuan Q, Shah JS, Misra RDK. A new family of folate-decorated and carbon nanotube - mediated drug delivery system: Synthesis and drug delivery response. Adv Drug Del Rev. 2011; (63):1332-1339.

[26] Jain NK, Prajapati RN, Agrawal A, Gupta U, Asthana A. Dendrimers-Reflection on host-guest interaction mechanism towards solubility enhancement. Asian J Pharm. 2009; (3):188-196.

[27] Singh SK, Lohiya GK, Limburkar PP, Dharbale NB, Mourya VK. Dendrimer a versatile polymer in drug delivery. Asian J Pharm. 2009; (3):178-187.

[28] Tansey W, Cao XY, Pasuelo MJ, Wallace S. Synthesis and characterization of branched poly(l-lutamic acid) as a biodegradable drug carrier. J control release. 2004; (94):39-51.

[29] Mehnert W, Mader K. Solid lipid nanoparticles Production, characterization and applications. Adv Drug Del Rev. 2001; (47):165-196.

[30] Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug

delivery- a review of the state of the art. Eur J Pharm Biopharm. 2000; (50):161-177.

[31] Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Del Rev. 2002; Suppl-1, (54):S131-S155.

[32] Souto EB, Wissing SA, Barbosa CM, Muller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm. 2004; (78):71-77.

[33] Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm. 2008; (346):124-132.

[34] Teeranachaideekul V, Muller RH, Junyaprasert VB. Encapsulation of ascorbyl palmitate in nanostructured lipid carriers (NLC)-Effects of formulation parameters on physicochemical stability. Int J Pharm. 2007; (340):198-206.

[35] Doktorovova S, Araujo J, Garcia ML, Rakovsky E, Souto EB. Formulating fluticasone propionate in novel PEG-containing nanostructured lipid carriers (PEG-NLC). Col Surf B: Biointerfaces. (2010); (75):538-542.

[36] Zhang L, Chan JM, Gu FX, Rhee JW, Wang AZ, Radovic-Moreno AF, Alexis F, Langer R, Farokhzad OC. Self-Assembled Lipid Polymer Hybrid Nanoparticles: A Robust Drug Delivery Platform. ACS nano. 2008; (8):1696-1702.

[37] Wong HL, Bendayan R, Rauth AM, Wu XY. Simultaneous delivery of doxorubicin and GG918 (Elacridar) by new Polymer-Lipid Hybrid Nanoparticles (PLN) for enhanced treatment of multidrug-resistant breast cancer. J Control Release. 2006; (116):275-284.

[38] Olbrich C, Gessner A, Schroder W, Kayser O, Muller RH. Lipid-drug conjugate of the hydrophilic drug diminazine-cytotoxicity testing and mouse serum adsorption, J Control Release. 2004; (96):425– 435.

[39] Goyal P, Goyal K, Kumar SGV, Singh A, Katare OP, Mishra DN. Liposomal drug delivery systems – Clinical applications. Acta Pharm. 2005; (55):1-25.

[40] Kozubek A, Gubernator J, Przeworska E, Stasiuk M. Liposomal drug delivery, a novel approach: PLARosomes. Acta Biochim Pol. 2000; (3):639-649.

[41] Nishioka Y, Yoshino H. Lymphatic targeting with nanoparticulate system. Adv Drug Del Rev. 2001; (47):55-64.