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REVIEW

Nanoparticulate carriers for drug delivery

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Abstract: Drug delivery with nanoparticulate carriers is a new and upcoming research area that is making major changes within the pharmaceutical industry. Nanoparticulate carriers are discussed, particularly, engineered nanoparticulate carriers used as drug delivery systems for targeted delivery. Nanoparticulate carriers that are used for drug delivery systems include polymers, micelles, dendrimers, liposomes, ceramics, metals, and various forms of biological materials. The properties of these nanoparticulate carriers are very advantageous for targeted drug delivery and result in efficient drug accumulation at the targeted area of interest, reduced drug toxicity, reduced systemic side effects, and more efficient use of the drug overall. Nanoparticulate carriers are effective in passing various biological impediments and have a relatively high cellular uptake compared to that of microparticulate carriers, which allows for the drug agent to reach a targeted cell or tissue. The use of nanoparticulate carriers for drug delivery results in a prolonged and sustained release of the drug which ultimately reduces the cost and amount of doses that need to be administered to the patient. Currently, there is extensive research of nanoparticles as drug delivery carriers for challenging disease treatment cases such as cancer, HIV, and diabetes.

Keywords: drug delivery, pharmaceutical, nanoparticulate carriers, nanoparticles, polymers

1 Introduction

Nanotechnology is applied to many principles including engineering, electronics, manufacturing, physical and material science at molecular levels. Within the pharmaceutical industry, nanotechnology is applied to drug delivery systems for targeted drug delivery. Materials that are fabricated at nanoscale can either be created as a device or a system for drug delivery purposes. Nanoscale systems have had much attention in the past decade for advances in biomedical applications such as gene therapy, imaging, and drug delivery.

Drug delivery is a fundamental part of drug development and has become a major part of pharmaceutical research. Approximately 13% of the current global pharmaceutical market is accounted for by sales of products incorporating a drug delivery system [1, 2]. Currently, the sales of advanced drug delivery systems in the United States are approaching $20 billion annually [3]. The cost of discovering a new molecule is very high compared to the cost of drug delivery formulation research. Therefore, minimizing the amount used and the cost to make an expensive drug would reduce the cost of the product overall and make it more economical [4].

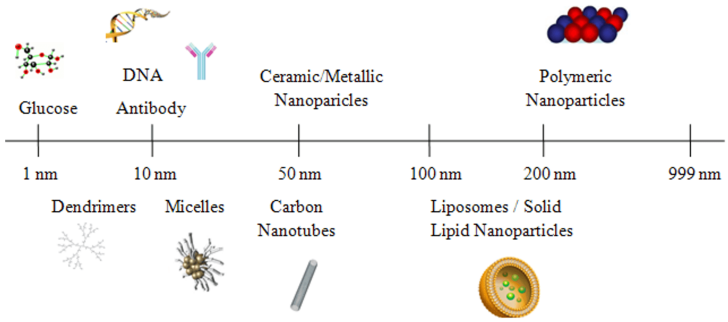
Today, there are many obstacles confronting drug delivery systems. Drug delivery systems act as a molecule in the blood system and distribute in the body according to its physicochemical properties, such as size, charge, surface hydrophobicity, and chemical structure of the surface [5]. Therapeutic agents alone exhibit poor physicochemical properties which expose them to degrading factors and lead to low drug solubility and poor biodistribution, which parallels to inefficient accumulation at the target site [6, 7]. Many therapeutic agents have not been successful because of their inadequate ability to overcome obstacles such as poor absorption, *in vivo* degradation, insufficient cellular uptake, toxicity to non-target tissues, systemic side effects, rapid elimination and are unable to reach the desired target area [2, 8–12]. With the use of nanoparticles as drug carriers, drug delivery systems have the ability to improve the physicochemical properties of therapeutic agents and achieve a maximum therapeutic effect at the site of action without the cause of many side effects and toxicity. Therefore, the main purpose of drug delivery system research is to increase the drug agent's therapeutic effect while decreasing the side effects through proper design and drug delivery system engineering. For this reason, drug delivery with nanoparticulate carriers is a major area of research that has recently been receiving much consideration.

2 Methods

Literature was reviewed on drug delivery with nanoparticulate carriers such as polymeric particles, micelles, ceramic nanoparticles, metallic nanoparticles, liposomes, dendrimers, and carbon nanotubes. The literature used was clinical and review articles taken from various journals, such as Journal of Controlled Release and Nanomedicine, which were found in the OhioLINK database published between the years of 1997 to the year of 2008. Conclusions were made on the advantages that nanoparticulate carriers, especially polymeric nanoparticles, provide for drug delivery systems.

3 Nanoparticulate carriers

Over the past decade, there has been considerable interest in developing biodegradable nanoparticulate carriers as drug delivery systems. Nanoparticulate carriers that are utilized as drug delivery systems include carbon nanotubes, dendrimers, ceramic nanoparticles, metallic nanoparticles, micelles, liposomes, solid lipid nanoparticles, and polymeric nanoparticles. The nanoparticulate carriers offer a wide range of sizes from 0.4 nm to 1000 nm, in which the nanoscale is defined to be smaller than 1000 nm in diameter [8, 12, 13]. Nanoparticulate carrier systems are appealing for drug delivery, as described in Table 1, since they have the ability to carry therapeutic agents, such as small molecular weight drugs or macromolecules, like protein or DNA, safely to targeted areas across many biological obstacles that the therapeutic agent would confront alone. These nanoparticulate carriers are comparable in size to that of DNA, antibodies, and particles such as glucose (Figure 1).



Note: The mean ranges of nanoparticles and nanoparticulate carriers were utilized in orderto illustrate the size scale of nanoparticulate carriers. The particles have no bearing on whether or not they are suspendedin liquid or are separate particles.

Figure 1 The size scale of nanoparticulate cariers

Since nanoparticulate carriers are so small in size and exhibit advantageous surface characteristics, they are able to penetrate across biological barriers, such as the blood brain barrier, escape the reticuloendothelial system, prevent uptake by renal filtration, and enter through small capillaries into individual cells [1, 18]. The blood brain barrier (BBB) is a distinctive membrane that tightly segregates the brain from the circulating blood which, therefore, makes drug delivery a challenge [2, 19]. Some nanoparticulate carriers are unable to diffuse through the BBB. The ideal size of the nanoparticulate carrier to deliver therapeutic agents to the brain is less than 100 nm in diameter [20]. The reticuloendothelial system (RES) is the body's defense system that clears foreign particles which also makes drug delivery a difficulty. Nanoparticulate carrier systems that are generally larger than 400 nanometers in diameter are easily and rapidly captured by the RES, mainly by macrophages of the liver, spleen, lungs, bone marrow and lymph nodes [1, 15]. Nanoparticulate carriers in the range of 150-300 nm are usually taken up by the macrophages of the liver and spleen, while nanoparticulate carriers in the range of 30-150 nm are taken up by the bone marrow, heart, kidney and the stomach [12]. Since they are cleared by the RES they cannot circulate in the blood stream for long periods of time which inhibits their ability to deliver an efficient amount of the therapeutic agent to the targeted area. Nanoparticulate carriers that are not cleared by the RES have a prolonged circulation time and improvement of overall kinetic profile and therapeutic index of the drug delivered [21]. Macromolecules with diameters smaller than 20-30 nm are eliminated through renal filtration and therefore unable to circulate for long periods of time in the bloodstream [12]. Therefore, a nanoparticulate carrier needs to be able to be large enough to evade the renal filtration system yet small enough to avoid uptake by the RES and still have the ability to enter through small capillary blood vessels which are approximately 5 μm in diameter [15]. The ability to penetrate

across these biological obstacles allows for efficient delivery to targeted sites. Many therapeutic agents have not been successful because of untimely drug loss through rapid clearance and metabolism which limits their ability to reach target tissues and organs. Nanoparticulate carriers offer the ability to manipulate their physic-chemical properties, such as size and surface characteristics, for avoidance of certain biological systems that inhibit prolonged circulation.

3.1 Targeting and delivery of nanoparticulate carriers

Nanoparticulate carriers containing therapeutic agents are delivered to targeted cells and tissues by either active or passive targeting. Passive targeting is achieved by utilizing the physical and chemical properties of the nanoparticulate carrier and the disease pathology [19,22]. Passive targeting allows the nanoparticulate carrier to passively target highly vascular tissues through the enhanced permeability and retention (EPR) effect. The EPR effect allows the nanoparticluate carriers to pass through extravascular spaces and accumulate in tissues such as tumor tissues [19]. By adjusting the physical and chemical properties of the nanoparticulate carrier, there will be efficient therapeutic delivery to the target without delivery to non-target areas causing toxicity and systemic side effects. The influential chemical and physical property factors include hydrophilicity/hydrophobicity, positive/negative charge, size, and mass [15]. Active targeting is achieved by conjugating the therapeutic agent of the nanoparticulate carrier system to an antigen or ligand, which directs them to the targeted tissue or organ by antigen-antibody and ligand-receptor binding interactions [1, 15, 18, 23]. This type of targeting refers to efforts to create a therapeutic concentration of the drug at the targeted site through the use of specific interactions that will be recognized by the cells present at the disease site, which maximizes therapeutic efficacy and reduces its systemic side effects. Active targeting of drug delivery systems with nanoparticulate carriers provides an ideal targeting system which provides for prompt delivery to the target tissues, efficient drug accumulation at target sites, reduced drug toxicity, reduced systemic side effects, and more efficient use of the therapeutic agent [1, 18, 24].

For efficient targeted drug delivery to occur, the degradative pathway that the nanoparticulate carrier encounters must be avoided. During circulation throughout the blood, the nanoparticulate carriers with no surface modifications are usually taken up by the RES or renal filtration system depending on their size and surface characteristics [19]. If the nanoparticulate carrier clears these obstacles, the nanoparticulate carrier systems are able to reach their targeted area of interest. Once the nanoparticulate carrier system has found the targeted cell, cellular uptake occurs through various processes such as clathrin-coated pits, caveoli, phagocytosis, fluid-phase pinocytosis, or receptor mediated endocytosis which is illustrated in Figure 2 [23, 25–27]. As soon as the drug delivery system is within the cell, it is delivered to sub-cellular organelles [22]. It has been primarily seen that the nanoparticulate carriers are delivered to early endosomes and continues its path to late endosomes and lysosomes (endo-lysosomes) where degradation otherwise takes place [28]. For more efficient drug delivery, the degradation of the lysosomes has to be avoided. This degradation can be avoided by endosomal escape which then leads to delivery to other intracellular organelles such as the golgi apparatus, endoplasmic reticulum (ER), and nucleus or compartment such as the cytoplasm [2, 11]. The ability for nanoparticulate carriers to escape from the endosomes is dependent on the material and surface characteristics of the carrier. Nanoparticulate carriers that escape into the cytoplasm could act as intracellular reservoirs for sustained release to target areas within the cytoplasm [11].

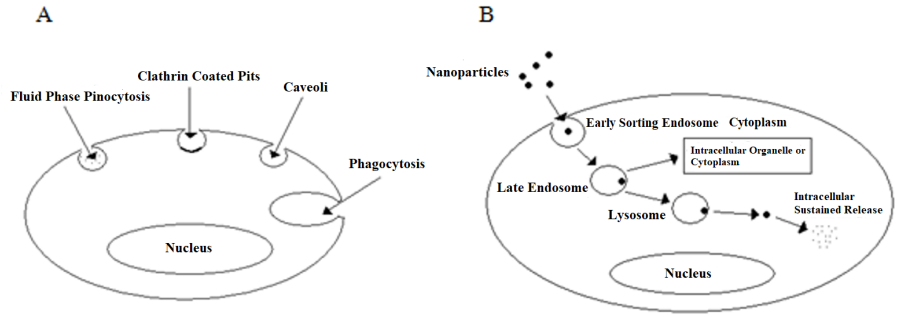


Figure 2 Schematic representation of (A) different intracellular uptake pathways, and (B) intracellular trafficking of nanoparticles.

It has been seen that drug delivery systems with nanoparticulate carriers have a relatively higher uptake compared to microparticulate carriers [23, 29, 30]. Nanoparticulate carriers have the ability of escaping the endosomes, continue their pathway to targeted organelles, and

have an efficient therapeutic effect. This was demonstrated in a study in which 100 nm size nanoparticulate carriers showed 2.5 fold greater uptake compared to 1 μm and 6 fold higher uptake compared to 10 μm microparticles in Caco-2 cell line [23, 30]. Another study performed demonstrated similar results when the use of nanoparticulate carriers and microparticulate carriers were tested in rat in situ intestinal loop model. In this study it was found that the uptake of nanoparticulate carriers was 15-250 fold greater than the uptake of larger size microparticles (1 μm and 10 μm) [23, 29]. In these studies, particle size significantly affected the uptake of the particulate carrier.

The release of the therapeutic agent from a nanoparticulate carrier drug delivery system can achieve a certain kinetic profile. Cytotoxic drugs typically show a steep dose-response curve and high does intensity is required to ensure therapeutic success [5]. Three of the most common kinetic profiles are zero order, first order and Higuchi [25, 31].

Zero order: $D_t = D_0 + k_0 t$

First order: $ln\ D_t = ln\ D_0 + k_1 t \rightarrow D_t = D_0\ e^{k1t}$

Higuchi: $D_t = D_0 = k_H\ t^{1/2}$

where D_t is the amount of drug released at time t, D_0 is the initial amount of drug released, result of initial rapid release, k_0 is the zero-order release constant, k_1 is the first-order release constant, and k_H is the Higuchi release constant. In Figure 3, the three different kinetic profiles of the release of the drug agent plotted versus time are shown with 2 mg/kg initial amount of drug released. For experimental purposes, the release constants were chosen randomly ($k_0 = 0.5$ and $k_1 = 0.2$). The most advantageous kinetic profile for drug delivery is the zero order, which will allow for a steady and prolonged release rate so that the levels of the therapeutic agent at the targeted area would remain constant [25, 31]. Drug delivery through oral administration or by injection follows the first order kinetic profile. Drug delivery through more current transdermal drug delivery mechanisms follows the Higuchi kinetic profile. Drug delivery systems utilizing nanoparticulate carriers have the ability to achieve a zero order kinetic profile by having a steady release rate so the drug levels remain constant within the body without causing toxicity and damaging side effects. Nanoparticulate carriers' pharmacokinetic profiles are still in the process of being further research in which another article will accompany this journal article.

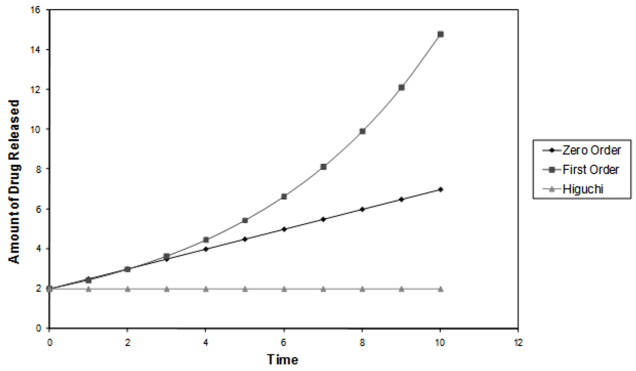


Figure 3 Drug release kinetic profiles from zero order, first order, and Higuchi.

3.2 Polymeric nanoparticles

The most common nanoparticulate carriers used for drug delivery systems are polymeric nanoparticles, which have a wide range of sizes from 10 to 1000 nanometers [2, 11]. Polymeric nanoparticulate carriers are developed and prepared into two different polymeric structures: nanospheres and nanocapsules [4, 7, 11, 13, 17]. Nanospheres are matrix-like structures in which therapeutic agents can be firmly adsorbed into the surface, entrapped, or dissolved within the matrix for drug delivery purposes. Nanocapsules contain a polymeric shell and an inner core. Drug agents are usually dissolved into the core of the nanocapsule but can also be adsorbed at the surface of the nanocapsule. Polymeric nanoparticle structures are excellent for drug delivery because they have the ability to be biodegradable, depending on the polymer, and their size allows them to penetrate through small capillaries. These characteristics help achieve efficient cellular uptake allowing for effective drug accumulation at targeted sites within the body.

Biodegradable polymeric nanoparticles do not accumulate in the body and have the ability for sustained drug release within the target site over a long period of time without any harmful side effects and optimum therapeutic efficacy [8, 11]. Without the use of nanocarriers, large doses of the therapeutic agent are administered to compensate for degradation and the dilution by the blood [21]. With the use of hydrophilic polymeric nanocarriers, a decreased dose of

the therapeutic agent can be administered which reduces uptake by the organs of the RES and prolongs circulation time. Currently there is extensive research of many polymers for drug delivery systems such as hydrophobic polylactides (PLA), hydrophilic poly (glycolic) (PGA), poly (lactide glycolide) (PLGA), and polyethylene glycol (PEG) because of their characteristics that provide for sustained release such as biocompatibility and biodegradability [2, 32]. The hydrophilic polymers, such as PGA, protect the therapeutic agent from capture of macrophages of the RES and enhance the biocompatibility [19]. Synthetic polymers have a greater advantage since they have a sustained delivery that can last for days to even weeks and months while natural polymers such as albumin, gelatin, alginate, collagen, and chitosan have a shorter duration [1, 11, 32]. Synthetic polymers also offer a greater advantage versus natural polymers in that they can be fabricated to have a wide range of properties [33]. Since these polymers have many beneficial characteristics such has biocompatibility and sustained release, they are very beneficial for drug delivery systems.

Since polymeric nanoparticles have such characteristics as sustained targeted drug release and small size, these particles are advantageous for the delivery on anticancer drugs [6]. The problem with anticancer agents is that they damage both the malignant and normal cells. If these drugs can be targeted to the malignant cells only, there would not be such a systemic side effect. Doxorubicin is an FDA-approved anticancer agent that has life-threatening side effects and toxicity which are related to the cumulative dose. When the doxorubicin anticancer agent is attached to the polymer polyethylene glycol (PEG), it has shown in patients improved penetration to the malignant cells [6]. The pegylated doxorubicin allows for sustained delivery and more biocompatibility which results in fewer dosages or reduced dose. Research performed by Fahmy et al loaded the polymeric PLGA nanoparticles with doxorubicin which allowed for targeted delivery to T-cells to kill cytotoxic T lymphocytes to compare with doxorubicin loaded liposomes. The PLGA nanoparticle was loaded with doxorubicin, attached to the antibody Biotin-Anti-CD3 to target T-cells, and coupled with the Biotin-BSA-Gd-DTPA contrast agent for visualization of the location of the drug dose as seen in Figure 4 [32]. The doxorubicin anticancer agent was released from 10-mg nanoparticles under simulated physiological conditions (1 x phosphate-buffered saline, 37° C) and showed a sustained and controlled release that reached a peak around 10 days for a prolonged period of time (Figure 5). From these results, polymeric nanoparticles exhibit the ability to be very effective for sustained and biocompatible delivery for the treatments of many infectious diseases compared to the doxorubicin-loaded liposomes in which there were high intracellular concentrations even though the in vitro efficacy of the doxorubicin was not necessarily improved. Research has shown that attachment of polymeric nanoparticles to other forms of drug delivery carriers have the ability to serve as a barrier, preventing degradation, and results in prolonged drug delivery to target areas.

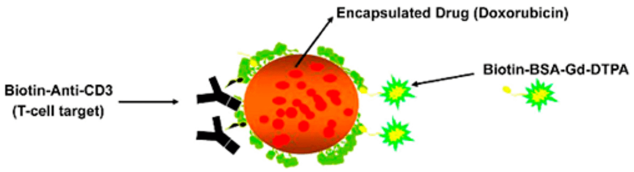


Figure 4 PLGA polymeric nanoparticle encapsulated with the therapeutic agent Doxorubicin, attached to T-cell antibodies andimaging contrast agents. [31]

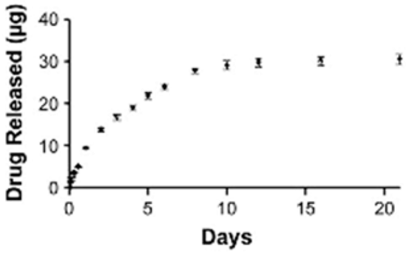


Figure 5 Cumulative release of Doxorubicin from 10-mg nanoparticles under simulated physiological conditions [31]

3.3 Polymeric micelles

Polymeric micelles are an assembly of amphiphilic block copolymers that are ideal drug carriers generally ranging in size from 15 to 80 nanometers (Figure 6). Polymeric micelles

are nanoparticle systems that contain a hydrophobic core surrounded by a hydrophilic shell, which make them great carriers for hydrophobic drugs, or water insoluble agents [4, 10, 11, 15, 16]. Therapeutic agents are incorporated into the core of the polymeric micelle by chemical conjugation and physical entrapment. Their hydrophobic core prevents interaction with blood components, hydrophilic shell minimizes uptake by the RES and their small size prevents recognition by the immune system and renal excretion, which allows for enhanced endothelial cell permeability by diffusion and long circulation times in the blood stream [21]. Since micelles can solubize hydrophobic drugs, they can be used for intravenous administration of different water-insoluble drugs [1, 7, 11]. Polymeric micelles are favored for drug delivery over conventional surfactant micelles since they have good thermodynamic stability in physiological solutions, which prevents rapid dissociation in vivo and longer circulation in the body [1, 11]. To enhance targeted drug delivery, micelles are capable of being attached to ligands such as antibodies or peptides which direct the micelle or drug carrier to the desired target area. A study performed by Yoo and Park encapsulated the anti-cancer agent doxorubicin in PEG-PLGA micelles modified with folic acid to actively target tumors. After intravenous administration of these modified micelles, the drug was detected up to 96 hours. The free doxorubicin was seen to be cleared by 24 hours. This difference between the free drug and the drug encapsulated within the polymeric micelle nanocarrier indicated that selective targeting of the drug into the tumor occurred in a timely manner [34].

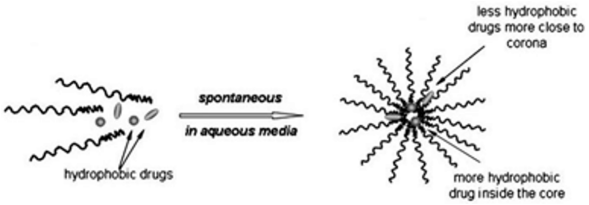


Figure 6 Micelle loading with hydrophobic drugs [15]

3.4 Dendrimers

Dendrimers are a new class of nanoparticles that were first discovered in the 1980's. They have a distinctive star-shaped structure with a series of branches symmetrically formed around an inner core (Figure 7) [2, 8, 11]. Each layer of branching corresponds to a generation; therefore, dendrimer size depends on the amount of generations which is related to their layers or branching units [8]. Dendrimers are promising carriers for drug delivery since they have a very small range of size, from 3 to 5 nanometers, have a ease of preparation and functionalization, and their branching structure creates a core that is ideal for entrapment of therapeutic agents [1]. As dendrimer molecular weight and generation increases, the terminal groups become more tightly packed, therefore, achieve a concentrated delivery of the therapeutic agents. By modifying their terminal groups, the inner core of the dendrimer may be made hydrophilic while the outer surface is hydrophobic, or vice versa [1, 4, 11]. Water-soluble dendrimers are capable of being attached to solubizing macromolecules and can be used as coating agents to protect or deliver drugs to specific sites in the body. Common types of dendrimers are polyamidoamines, polyamines, polyamides (polypeptides), poly (aryl ethers), polyesters, carbohydrates and DNA. Currently, the Polyamidoamine (PAMAM) dendrimers are commonly used for drug delivery [2, 35]. PAMAM are synthesized by repetitive addition of branching units around an amine core such as ammonia or ethylene diamine [4, 32]. The amine core has the ability to function as a drug reservoir and have been studied as carriers for small therapeutic agents. It has been found that dendrimers' surface charge and molecular weight are very influential in the kinetic behavior of the dendrimers. Regarding surface charge, cationic PAMAM dendrimers showed increased toxicity and rapid uptake from circulation compared to anionic dendrimers [21, 36].

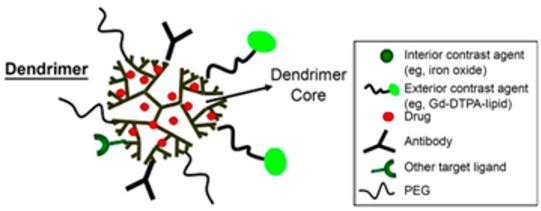


Figure 7 Dendrimer loaded with a drug and attached to ligands, antibodies, and PEG for enhanced targeted drug delivery. [31]

3.5 Liposomes

Liposomes are small spherical vesicles that are composed of cholesterol and phospholipid bilayers (Figure 8) [2,8,11]. Properties of liposomes vary depending on the size, the composition of the lipid, surface characteristics, method of preparation, and route of administration [8,11,21]. They range in size from 20 to 150 nanometers. Liposomes are very attractive for nanoparticulate carrier systems because of their size, biocompatibility, hydrophilic and hydrophobic characteristics [1]. Liposomes are made from biological material, therefore, harmless to the body and are capable of circulating in the blood stream for a long period of time [8]. Liposomes are formed with either a single lipid or multiple lipid bilayers. A single lipid bilayer is classified as small unilamellar vesicles (SUV) or large unilamellar vesicles (LUV) depending on their size and is primarily used to encapsulate water soluble drugs. Multiple lipid bilayers are classified as multilamellar vesicles (MLV) and are primarily used to entrap lipid soluble drugs. Recently, it has been found that if the liposome bilayer is attached to a polymer, such as polyethylene glycol (PEG), it reduces the rate of uptake by macrophages of the RES and has a pro-longed circulation in the blood stream [2,11,21,37,38]. These types of liposomes are known as "stealth" liposomes which have been used to successfully load the anti-cancer agent doxorubicin, described earlier with loaded PLGA nanoparticles, that currently is used for the treatment of solid tumors [39]. Recently, there have been improvements with corticosteroid-loaded liposomes in experimental arthritic models for the treatment of arthritis [32]. Also, liposome drug delivery systems can be attached to antibodies or ligands to enhance target specific drug delivery.

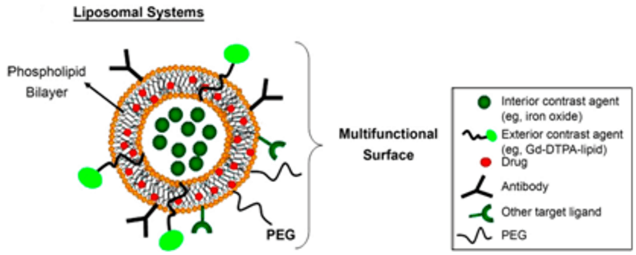


Figure 8 Liposomal systems loaded with a drug agent and attached to ligands, antibodies, and PEG for enhanced targeted drug delivery. [31]

3.6 Solid lipid nanoparticles

Solid lipid nanoparticles are a new class of drug carrier system that were developed in the 1990's as an alternative to emulsions and liposomes for drug delivery systems. The solid lipid nanoparticle systems range from 10 to 215 nanometers in size [40, 41]. Solid lipid nanoparticles have a matrix form composed of solid lipids, which are solid at room temperature and body temperature, and stabilized with surfactants. Solid lipid particles are more favored than liposomes such that they have good tolerability and are biodegradable. Surfactant coated solid lipid nanoparticles have the potential of penetrating across the blood brain barrier, which is a unique membrane that tightly segregates the brain from the blood circulation [7,41]. Several nanoparticle systems have been developed for effective brain targeting such as surfactant coated poly (alkyleyanoacrylate) nanoparticles. Solid lipid nanoparticles provide lower cytotoxicity, higher drug loading capacity, and best production scalability as compared to the polymeric nanoparticle systems for targeted drug delivery to the brain [40,41]. Targeting drugs to the brain is a major challenge in drug delivery. Drugs alone are incapable of crossing the blood brain barrier; therefore nanoparticulate carriers, such as surfactant coated solid lipid nanoparticles, have the potential to provide sustained delivery of therapeutic agents to the brain. Solid lipid nanoparticles are also emerging in the field of anti-cancer drug delivery. The emergence of newer forms of solid lipid nanoparticles, such as polymer-lipid hybrid nanoparticles, nanostructured lipid carriers, and long-circulation solid lipid nanoparticles, expand the function of solid lipid nanoparticles in cancer therapies [42].

3.7 Carbon nanoparticles

Carbon nanotubes are attractive for drug delivery systems because of their size (diameters of nanometers and lengths of micrometers), geometry, and surface characteristics [43]. Carbon nanotubes are high aspect ratio hollow cylinders of carbon atoms that have either a single wall or multi wall carbon structure that range 0.4 to 100 nanometers in size [8, 14]. Carbon nanotubes have the ability to encapsulate drug agents inside their cavities for drug delivery.

The surface characteristics of carbon nanotubes are very helpful for achieving targeted drug delivery with reduced drug toxicity and side effects. Carbon nanotubes are chemically inert and are not attacked by strong acids or alkali, which is appealing for drug delivery systems. Also, carbon nanotubes have high mechanical strengths (up to 60 GPa), high Young's moduli (up to 1 TPa), and high thermal and electrical conductivities [14]. When first discovered in the 1990's, carbon nanotubes were found ineffective because of their insolubility and incompatibility with polymers under physiological conditions. There have only been very few reports describing biological applications, but recently it has been found that functionalization of carbon nanotubes increases solubility and compatibility with polymers. There are two types of functionalization, covalent and non-covalent attachment of bioactive molecules such as lipids or proteins [44, 45]. Non-covalent functionalization is more preferred since it preserves wall integrity and certain properties of the carbon nanotubes [46]. Through functionalization research, cells have been grown on carbon nanotubes [14]. Since cells have grown on the carbon material, carbon nanotubes appear to have no cytotoxic effect and are appealing for drug delivery in the future.

3.8 Ceramic nanoparticles

Ceramic nanoparticles with entrapped therapeutic agents are a newly emerging nanoparticulate carrier and have a great potential for future development of drug delivery systems. These types of nanoparticulate carriers are inorganic systems that can be engineered to have a desired size, shape, and porosity, which is a great advantage for the production of drug delivery systems [1, 11]. Ceramic nanoparticles are designed and fabricated to be less than 50 nanometers in size [7]. Biocompatible ceramic particles that are currently being researched for drug delivery are: silica, titania, and alumina [1, 4, 11]. The main advantage of using ceramic nanoparticles is that they are more effective in evading the uptake of the reticuloendothelial system because of their ultralow size [2, 11]. Recently, there has been a study entrapping insulin in the ceramic hydroxyapatite nanoparticle for orally administered insulin instead of injection for diabetes [8]. Like many other nanoparticulate carriers, ceramic nanoparticles can be easily modified with different functional groups for enhanced targeted delivery.

3.9 Metallic nanoparticles

Metallic nanoparticles are not as developed as other nanoparticulate carriers but show great aspects for future development [8]. Metallic nanoparticles are appealing for drug delivery since they are synthesized in extremely small sizes that are less than 50 nanometers [8] Their small size creates a large surface area and, therefore, has the ability to carry relatively high drug amounts within the nanoparticle system. Functionalizing the surface of the metal to create a nanoparticulate carrier is still under extensive research [8]. Currently, research is being performed for releasing metallic nanoparticles loaded with drug agents into targeted locations by an external exciting source such as an infrared light or a magnetic field [25]. Typical metals that are used in the metallic nanoparticle systems are gold, silver, platinum, and palladium [25]. One of the most widely used forms of metallic nanoparticles is gold since they are an excellent candidate for bioconjugation with biological materials [47, 48]. A study performed by Bhumkar et al demonstrated oral and nasal administration of insulin loaded chitosan reduced gold nanoparticles has led to improved therapeutic effect. The studies were performed *in vivo* with diabetic male Wistar rates using insulin loaded chitosan reduced gold nanoparticles. The nanoparticles in this study showed prolonged stability in terms of aggregation for about 6 months and the blood glucose levels lowered by 30.41 and 20.27% for oral (50 IU/kg) and nasal (10 IU/kg) after 2 hours after administration [48]. This study shows the development of metallic nanoparticles as promising nanoparticulate carriers for therapeutic agents. Further research is being performed on other forms of metallic nanoparticles as drug delivery systems such as the effects and safety of those forms used in the human body.

4 Conclusions

Nanoparticulate carriers improve many features of the targeted drug delivery such that it lowers drug toxicities, improves bioavailability, reduces economic costs of treatment, and most importantly increases patient adherence to treatment. Nanoparticulate carriers have very promising future in implantable drug delivery devices which will allow for an extended duration of action, reduced frequency of re-dosing and improved patient acceptance. The nanoparticulate carriers discussed in this paper include carbon nanotubes, dendrimers, ceramic nano-particles, metallic nano-particles, micelles, liposomes, solid lipid nanoparticles, and polymeric. The authors have found extensive examination of the polymeric nanoparticles due mainly to their

biocompatibility, biodegradable kinetics, and have been found applicable for prolonged drug delivery at the targeted sites. Some challenges include loading of the therapeutic agents into the nanoparticulate carrier, controlling the drug release profile, guiding the nanoparticulate carrier to the desired target, and the concern of using non-biodegradable nanoparticulate carriers and their accumulation in the body. A high level of non-biodegradable particles that accumulate in the body might reach a harmful boundary and cause undesirable effects. Therefore, the toxicology of many nanoparticulate carriers needs to be further researched and evaluated.

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