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Review

Multifaceted Nanostructures in Drug Delivery

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Abstract

Nanotechnology can be employed in drug delivery applications and it overcomes many drawbacks that are encountered in conventional drug delivery. Drug loaded nanocarriers can be effectively used to mask the undesirable properties of drugs and promote the safe delivery of drugs. Nanostructures are designed with different properties which modify the properties of drugs and increase the therapeutic efficacy of drugs. They can be fabricated using wide range of materials and have shown different characteristics in drug delivery for various disease conditions. In this article, different multifaceted nanocarriers are reviewed for their drug delivery applications.

Keywords: Nanostructures, Nano medicine, Targeting, Nanotechnology

Introduction

Nanotechnology is the engineering and manufacturing of materials at nanoscale. The prefix of nanotechnology derives from ‘nanos’ – the Greek word for dwarf. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm in at least one dimension. However, the prefix “nano” is commonly used for particles that are up to several hundred nanometers in size. Among numerous applications of nanotechnology, the treatment, diagnosis, monitoring and control of biological systems has recently been referred to as ‘‘nanomedicine’’ by the National Institute of Health, USA.

In the conventional drug delivery systems, major problems encountered are limited effectiveness, poor biodistribution and lack of selectivity.(1) Aqueous solubility of hydrophobic drugs is also another problem encountered in conventional drug delivery and it results in less bioavailability. Delivering of drugs to target site at sufficient concentration is a major challenge in the effective treatment of diseases. Nanotechnology can be effectively applied in drug delivery applications to overcome many problems associated with conventional drug delivery and improve the efficacy of drugs in treating diseases.

Active and passive targeting

Nanoparticle drug delivery can be either an active or passive process. Due to smaller size of nanocarriers, they can be preferentially accumulated in the target area especially in the case of tumour tissues which contain leaky tumor capillary fenestrations.(2) It is

known as effective permeability and retention effect. This passive diffusion or convection of nanocarriers is known as passive targeting. Nanoparticles (NP) can be also be effectively used in active targeting. Active targeting involves drug delivery to a specific site based on molecular recognition. Coupling of a ligand to a NP is an example for it. This conjugated ligand in the surface of nanocarriers can interact with its receptor at the target cell site and thus ensure the drug release at the target site.(3)

Advantages of nano drug delivery

1. It modifies pharmacokinetics and biodistribution of therapeutic agents. Drugs which have less permeability can be entrapped into nanoparticles and drug loaded nanoparticles can be distributed into tissues.
2. Nanoparticles reduce the rate of elimination of drugs by encapsulating drugs into nanoparticles.
3. It minimizes toxicity of drugs by their preferential accumulation at the target site. Drug loaded nanoparticles can effectively release the drug to the target cells and reduce the exposure of free drug in non target organs and thus reduce the drug toxicity compared to free drug. Dose of drug can be minimized due to targeting efficiency.
4. It improves the solubility of poorly water-soluble drugs. Due to the nano size of drugs, surface area will by increased and thus enhance the solubility of drugs.
5. The circulation time of drugs can be increased using nanocarriers. Various techniques such as PEGylation can be employed for this.
6. Nanocarriers release the drugs at a sustained rate or in an environmentally responsive manner and thus lower the frequency of administration. Drug is entrapped or dispersed in polymer matrix and thus drug release can be controlled by limiting diffusion of drugs or erosion of polymer.
7. Encapsulation within nanocarriers protects the drugs from early inactivation and degradation.
8. It prevent drugs from prematurely interacting with the biological environment
9. It improve intracellular penetration of drugs.
10. Drug efflux proteins such as P-glycoprotein (P-gb) are present in the cell membrane. They decrease the transport of drugs into the cells. In case of tumour tissues, P-gp reduces the concentration anti cancer drugs. Encapsulation of drugs into nanoparticles with inhibiting agents for P-gp can overcome this problem.

Disadvantages of nano drug delivery

1. Nanotoxicity investigations have led to the speculation that nanomaterials may contribute to the formation of free radicals, damage brain cells, and cause undesirable penetration through the epidermis or other physiological barriers into areas of the body.
2. Nanoparticles easily penetrate biomembranes and interfere with basal metabolic reactions within the cell. Also these particles are easily translocated throughout the body not only through the circulatory system, but also the neural network.
3. Drugs incorporated into nanocarriers sometimes are not released into target area. This is observed in tumour tissues despite nanocarriers being accumulated into tumor tissues in sufficient quantity.
4. Nanoparticles could cause inflammatory effect due to smaller size and larger surface area when they are inhaled.

5. Large scale production of nanopharmaceuticals is complex and expensive.

Types of nanostructures

Different types of nanostructures have been designed with varying sizes and shapes. A wide range of materials that are biodegradable and non biodegradable in nature have been employed for the fabrication of different nanostructures. Characteristics of such nanostructures are different in drug loading capacity, release rate of drugs, targeting efficiency, circulation time and stability. These nanostructures have been evaluated in animal studies and some of them are successfully used clinically for treating diseases. Here different nanostructures that can be used in the drug delivery applications are discussed.

Polymeric nanoparticles

Polymeric nanoparticles are solid colloidal particles with diameters ranging from 1 to 1000 nm. In the polymer matrix of nano size, drug is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Binding of drug to the carrier leads to the suppression of its unwanted physicochemical properties (e.g. low solubility) and to the increasing circulation time in blood. The polymer matrix prevents drug degradation and may also provide management of drug release from these nanoparticles. Polymeric nanoparticles can be prepared by a wide range of polymers including natural and synthetic polymers. Natural polymers that are widely used in nanoparticle synthesis include chitosan, dextran, albumin, heparin, gelatin, and collagen. A variety of synthetic biodegradable polymers is employed for fabrication of nanostructures. Synthetic polymers such as polyethylene glycol (PEG), polyglutamic acid (PGA), poly-D,L-lactide-co-glycolide (PLGA), polycarprolactone (PCL) and poly-lactic acid (PLA) have been widely used to prepare nanoparticles and encapsulate drugs for cancer therapy.(4)

Core-shell nanoparticles

Core-shell nanoparticles have a core made of a material coated with another material on top of it. The coating of a benign material on top of the core makes the nanoparticles much less toxic and bio-compatible. Sometimes the shell layer not only act as nontoxic layer, but also improve the core material property.(5) They can be made by a wide range of different combinations in close interaction, including inorganic/inorganic, inorganic/organic, organic/inorganic, and organic/organic materials. This novel carrier can be used to increase the residence time, reduction of dosing quantity and frequency of drugs. In the biomedical field, these core-shell nanoparticles can be employed for bioimaging, controlled drug release, targeted drug delivery, cell labeling and tissue engineering applications.(6) Polyethylene glycol (PEG) can be used as a shell material in designing of novel core/shell type colloidal carriers for drug delivery applications.(7)

Liposomes

Liposomes are concentric bilayered vesicles made by a phospholipid membrane which contain one or more double layers of phospholipids. They are composed of phospholipids and steroids (e.g., cholesterol), and/or other surfactants. They form spontaneously when certain lipids are dispersed in aqueous media.(8) The amphiphilic nature of liposomes, their ease of surface modification, and a good

biocompatibility profile leads to increased circulation time. Both hydrophilic and hydrophobic drugs can be encapsulated in liposomes. Hydrophobic molecules are inserted into the bilayer membrane, and hydrophilic molecules can be entrapped in the aqueous center.(9) Liposomes offer several advantages including biocompatibility, ability to carry large drug payloads and wide range of physicochemical and biophysical properties that can be modified to control their biological characteristics.(10)

Polymersomes

They are bilayered vesicles which are comprised of amphiphilic block copolymers which contain chemically linked hydrophilic and hydrophobic polymer chains. Polymersome is constructed of amphiphilic block copolymers with a molecular weight up to 100 kDa. This higher molecular weight of the building blocks manifests itself in a tougher, less permeable and less fluidic membrane and as a result superior physical and chemical stability are obtained. They are often considered to be more stable than liposomes.(11) The hydrophobic part of the block copolymer mainly constitutes of non-biodegradable polymers like poly (ethyl ethylene) (PEE), poly (butadiene) (PBD) poly (dimethylsiloxane)(PDMS), poly (styrene) (PS) and biodegradable polymers like poly (lactide) (PLA) and poly caprolactone. The hydrophilic part is formed by polymers like poly (ethylene glycol) (PEG), poly (acrylic acid) (PAA) and poly (L-glutamic acid) (PGA).(12)

Polymeric micelles

Polymeric micelles (PMs) are nanoscopic core-shell structures created by spontaneous self-assembly of individual amphiphilic di/tri-block co-polymers, with hydrophobic core and hydrophilic surface shells. Block copolymers can be made of hydrophilic and hydrophobic blocks and form self-aggregates in water.(13) Formations of micelles in aqueous solution occur when the concentration of the block copolymer increases above a certain concentration named the critical micelle concentration (CMC). These block copolymers may be di or tri block co polymers. Poly (styrene)-b-poly (ethylene oxide), poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) are few examples of block co polymers that are used to prepare polymeric micelles.(14) Depending upon the polarity, drug molecules can be entrapped in the core (non polar molecules), shell (polar molecules) and in-between the core and shell (intermediate polarity). They improve the solubility of poorly water soluble drugs.

Solid lipid nanoparticles (SLN)

They are generally made up of a solid hydrophobic core of lipids containing the drug that is dissolved or dispersed.(15) The SLNs are submicron colloidal carrier which is composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. They are a comparatively stable colloidal carrier system. The liquid lipid used in emulsions is replaced by a solid lipid at room temperature in SLN. Solid lipids include high melting point glycerides and waxes.(16) They have many advantages such as good biocompatibility, and low toxicity. Lipophilic drugs can be effectively encapsulated in SLNs.

Self nanoemulsifying drug delivery

Self-emulsifying drug delivery systems (SEDDS) or self emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or

more hydrophilic solvents and co-solvents/surfactants.(17) Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil−in−water (o/w) emulsions. For lipophilic drugs that exhibit dissolution rate−limited absorption, these systems may offer an improvement in the rate and extent of absorption.

Magnetic nanoparticles

Nanoparticles of iron oxide with diameters in the 5–100 nm range is known as magnetic nanoparticles. Magnetic nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials or organic materials.(18) By applying external magnetic field, nanoparticles are directed to target area. They can be used as contrast agents for magnetic resonance imaging (MRI)(19) and as carriers for drug delivery.(20)

Metal and inorganic nanoparticles

Various metals, such as gold (Au), copper (Cu), and silver (Ag), and inorganic carriers, such as silica or alumina, have been used for the preparation of nanoparticles, among which gold nanoparticles are most promptly used due to their excellent optical and photoelectric properties. Moreover, gold exhibits some specific advantages, like inertness and nontoxicity, higher stability, ease of preparation, and possibility of bioconjugation and biomodification with thiol, disulfide and amine functional groups. Gold nanoparticles are highly effective contrast agents in cancer diagnosis and photodermal cancer therapy.(21)

Dendrimers

Dendrimers are polymer-based macromolecules formed from monomeric or oligomeric units, such that each layer of branching units doubles or triples the number of peripheral groups. The structure of dendrimers consists of three distinct architectural regions as a focal moiety or a core, layers of branched repeat units emerging from the core and functional end groups on the outer layer of repeat units. The drug may be encapsulated in the internal structure of dendrimers(22) or it can be chemically attached or physically adsorbed on dendrimer surface.(23)

Carbon nanotubes

Carbon tubes are cylindrical molecules formed by rolling single layer or multiple layers of graphene sheets into cylinder.(24) Based on their structure, they can be classified into single walled, double walled and multi walled carbon nano tubes. Among these, single walled CNTs can readily penetrate into the cell and this property makes them a suitable carrier for drugs to be delivered in to the cells.(25)

Nanocrystals

Dissolution rate of poor water soluble drugs can be improved by reducing the drug particle to nano size.(26) Nanocrystals are aggregates of molecules that can be combined into a crystalline form of the drug surrounded by a thin coating of surfactant. They can be prepared by reducing the drug particle size to nanometer range and stabilizing the nanocrystal's surface with a layer of nonionic surfactants or polymeric macromolecules which form a thin hydrophilic layer around the hydrophobic drug particle.(27) These layers of thin coating prevent aggregation of the crystalline drug material.

Niosomes

They are bilayer structures and are formed by self-association of nonionic surfactants

and cholesterol in an aqueous phase. Non ionic surfactants are more stable and biocompatible and less toxic compared to their anionic, amphoteric, or cationic surfactants.(28) They can be used for entrapment of a large number of drugs with a wide range of solubility.(29) They allow entrapment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be incorporated into niosomes. Niosome surfaces can be conjugated with small molecules and/or macromolecular targeting ligands to enable cell specific targeting.

Drug conjugates

Polymer-drug conjugates

Polymer drug conjugates offer several significant advantages over traditional small molecule therapeutics. First, the aqueous solubility of a drug can be dramatically improved following conjugation to a water soluble polymers.(30) Polymer drug conjugates offer the potential for a drug to be delivered in a controlled manner from the conjugates. Polymer conjugates are useful for drugs which exhibit a short blood plasma half-life due to rapid metabolism or clearance or for drugs which exhibit off target toxicities. Also targeting moieties can be included in the polymer drug conjugates for the site specific drug delivery. Most widely investigated polymers used for conjugates are poly (ethylene glycol) (PEG)(31) and *N*-(2-hydroxypropyl) metha crylamide (HPMA)32 copolymers. PEG-protein conjugates have gained particular importance due to the ability of PEG to protect against protein enzymatic degradation and reduce uptake by the reticuloendothelial system (RES) due to simple steric hindrance.

Antibody-drug conjugates

Antibody-drug conjugates utilize the antibody as a delivery vehicle for highly potent cytotoxic molecules with specificity for tumor-associated antigens for cancer therapy. Targeted therapy for the tumor-specific antigens has become an invaluable tool in cancer therapy. In particular, antibody-based immunotherapies using monoclonal antibodies (mAbs) and antibody fragments have been the focus of the development of strategic anticancer drugs. First human clinical trial followed less than a decade later, with the antimitotic vinca alkaloid vindesine as the cytotoxic payload.(33) FDA approved many antibody-drug conjugates for clinical use.

Lipid-drug conjugates

Drugs can be linked with lipids covalently to form lipid drug conjugates which improve oral bioavailability, enhanced tumour targeting, reduced toxicity and drug loading into carriers. Various types of lipids such as fatty acids (stearic acid, docosahexaenoic acid), steroids (cholesterol, cholic acid), glycerides and phospholipids have been investigated as drug conjugates.(34)

Nanogel

They have cross linked networks of hydrophilic polymers.(35) They can be prepared by physical self-assembly of interactive polymers and chemical cross-linking of preformed polymers.(36) Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Although the hydrophilic nature of nanogels may offer limitation for

encapsulation of hydrophobic drugs, suitable engineering of the polymer structure allows high encapsulation of poorly soluble anticancer drugs.(37)

Nanofibres

They are ultra-fibers with diameters less than 100 nanometers. Due to the internal architecture, nanofibers are well suited for various medicinal applications, such as carriers for cell cultivation, tissue engineering scaffolds or wound dressings. The incorporation of biologically or pharmacologically active compounds into the nanofibers may be very useful for these applications. Among the several methods of preparations, electrospinning technique can be considered as a simple and versatile method for the production of continuous polymeric nanofibrous mats that are formed by nano- to micro-sized fibers.(38)

Quantum dots

Quantum dots (QDs) are colloidal semiconductor nanocrystals (up to 2 to 10 nm), composed of atoms from groups II–VI or III–V of the periodic table, having unique optical and fluorescent properties. Those most commonly used are cadmium selenide (CdSe), cadmium telluride (CdTe), and indium arsenide (InAs).(39) Owing to their small size, they can be used for the tagging of biological macromolecules, such as nucleoside and proteins.

Clinically approved nano-pharmaceuticals

Numerous nanostructures are investigated for drug delivery applications, and few types of nanostructures have got approval in clinical use. Toxicity caused by nano drug delivery is a major concern in getting approval for clinical use. However the number of nanopharmaceuticals being approved has gradually increased as it showed good efficacy compared to conventional drug delivery systems. Here some nanopharmaceuticals that are approved in clinical use, is listed in the Table 1.

Conclusion

Pharmaceutical nanotechnology is a rapidly expanding technology in drug delivery applications. Numerous types of nanostructures have been investigated as drug delivery systems and some of them are successfully used clinically. Multifaceted nanocarriers can be effectively employed to encapsulate drugs with different properties and can be used to maximize drug efficacy in treating diseases. Even though they showed good efficacy in treating diseases than conventional drug delivery, toxicity caused by them restrict their usage. Upto now, few numbers of nanopharmaceuticals are approved in clinical use. Since the discovery of new drugs is time consuming, and huge funds are necessary for bringing them into clinical use, the efficacy of existing drugs can be improved for treating diseases by making them into nanopharmaceuticals. Further research should be focused on reducing toxicity of nanopharmaceuticals.

Table 1: Nanopharmaceuticals in clinical use

Drug	Brand name	Nano-carrier	Indication
Amphotericin B	AmBisome	Liposome	Systemic fungal infection
Daunorubicin citrate	DaunoXome	Liposome	HIV-related Kaposi's sarcoma
Doxorubicin hydrochloride	Doxil	Liposome	AIDS-related Kaposi's sarcoma, multiple myeloma, ovarian cancer
Adagen	Adenosine deaminase	PEG conjugates	Adenosine deaminase deficiency – severe combined immunodeficiency disease
Emend	Aprepitant	Nanocrystals	Antiemetic
Tricor	Fenofibrate	Nanocrystals	Hypercholesterolemia
Eligard	Leuprolide acetate	PLGH copolymer nanoparticles	Advanced prostate cancer
Genexol	Paclitaxel	Polymeric micelles	Metastatic breast cancer, pancreatic cancer
Abraxane	Paclitaxel	Albumin bound nanoparticles	Metastatic breast cancer, non-small-cell lung cancer

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