Pharmaceutical Nano-Delivery Systems: A Review

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Abstract

Nanotechnology is the science that deals with the processes that occurs at molecular level and of nano-length scale size.Reduction of drugs toxicity and enhancement of their bioavailability, biocompatibility, stability and appropriate release are of high opportunities to be accomplished by size reduction, which make pharmaceutical field highly interesting in nanotechnology. Formulation and preparation of highly advanced nano-materials as drug delivery systems achieve the desired therapeutic objective. Current review will discuss in brief types of pharmaceutical nano-sized drug delivery systems by focusing on the specificity and the nature of each type.

Keywords: *nanotechnology, pharmaceutical nanotechnology, nanoparticles delivery systems.*

Introduction

Nanotechnology is still wide new science with advanced technologies and applications of different fields,nanomedicine and nano based drug delivery systems are very interesting applications of nanotechnology[1,2]. Nano is used as a scientific units to denote one-billionth part (10^{-9}) of the base unit, where the size of materials start from 1nm to 100nm highlyutilized or applied by nanomedicine such as biosensors and nano drug delivery such as liposome, nano suspension, dendrimers, carbon nanotubes, metal nano delivery systems and others[3,4,5.] Nanoparticles haveunique structural, chemical, physical and biological properties. Nano technology expected to have substantial applications in medicine in disease diagnostics and therapeutics. nano delivery systemes have become well appreciated in the last years where utilizing of nanostructures as delivery agents through incorporation of the drugin the nanocarriersor adsorption on them which promote high specificity and selectivityfor drug localization and targeting[6,7] . The first generation of nanoparticle-based drug delivery systems which are lipid based systems such as solid-lipid nanoparticles, liposomes and micelles[8,9,10].Nanostructures delivery systems help to deliverdrugs of low water-solubility and/or even low drug oral bioavailability and targeting it to the specified siteaction which lead to reduce dose required, enhance drug efficacy, decrease toxicity, decrease drug resistance, decrease patient to patient drug effect variability and increase the stability of the drug and formulation[11].Nanostructures stay in the blood circulatory system for a prolonged period and enable the release of drug as per the specified dose. Thus, they cause fewer plasma fluctuations with reduced adverse sideeffects; hence, they directly

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interact to treat the diseased cells with improved efficiency and reduced or negligible side effects[12].

Types of pharmaceutical Nanotechnology based on the systems:

Nano-materials and nano-devices play a key role in pharmaceutical nanotechnology. Nano-materials are also further classified into nano-crystalline and nano-structured materials[13]. Nano-crystalline materials are pure crystals of the drug which readily manufactured and then stabilized by thin coating of surfactant; their nano-sized lead to highly enhance the surface area to the volume ratio also lead to enhance the bioavailability of low solubility or insoluble drugs[14]. On the other hand; nano-structured are processed from nano-materials that provide special shapes and functionality in which at least external dimension is in the range 1-100nm[15]. Those multifunctional nano-materials can be broadly sub classified by their most applications as follow:-

1-Lipid-based Nano-Materials

Lipids based nano-materials are highly attractive choice nano delivery system due to their natural components and easily scaled up syntheses processes.

Liposomes:

Liposomes were the first nano-materials where it was applied as a drug delivery system. Liposomes are artificial vesicles composed from amphiphilic phospholipids and cholesterol which give self-association forming bilayer encapsulate an aqueous interiorly, liposomes still the most popular nanocarrier which used due to their ability to incorporate hydrophilic, hydrophobic and also amphiphilic drugs; where hydrophilic drugs incorporated in the aqueous compartment where the hydrophobic drugs are localized in the lipid membrane while the amphiphilic drug substances located at the lipid-aqueous interface, liposomes are biocompatible and biodegradable components[16,17]. Doxorubicin (Doxil®) was developed by Janssen Company is the first liposomal formula approved by FDA[18].

Nanoemulsion:

Nanoemulsion is the dispersed modern colloidal system having isotropically clear or transparent dispersion of two immiscible liquid phases as oil and water where their stabilization can be done using an interfacial film of surfactant molecules; the dispersed phase droplets size is about 50-200nm, nanoemulsion preparations used to deliver drugs to enhance their solubility, stability and also bioavailability such those preparations as vitamins nanoemulsionpreparations[19]. Taha et al. reported a two folds enhancement in the bioavailability of vitamin A through self-emulsifyingnanoemulsion in compare with the free vitamin A[20].Propofolnanoemulsion (Diprivan®) developed by Astra Zeneca where it was approved in 2001 by FDA[21].

Solid lipid Nanoparticles:

Solid lipid nanoparticles (SLN) are nanocarriers developed as a substitute colloidal drug delivey systems parallel to liposomes and lipid emulsion delivery systems, SLN are colloidal particles composed of solid lipid core which may contain triglyserides, glyserides mixtures or waxes, which being as solid in both human body temperature and room temperature, SLN are show distinctive features such as low toxicity, large surface area, prolonged drug release, superior cellular uptake in compare with the traditional colloidal carriers as well as compatibility to improve solubility and bioavailability of drugs. SLN can also further produced in powder form where it can be loaded in pellets, capsules or tablets for further enhancement of drug delivery[22,23]. PharmatecCompany developed in 2006 the first cyclosporine SLN formulation for oral administration[24].

Nano-Structure Lipid Carriers:

Nano-Structured Lipid Carrier (NLC) referred to the second generation of SLN where some limitations of SLN such low drug loading efficiency can be overcome by NLC, NLCs are biocompatible systems distinguished by a rigid morphology that contributes their unique properties compared to other lipid-based formulations. NLCs can prepare by blend of solid-phase and liquid phase lipids; which generally in solid state ate temperature above 40ºC. The lipid matrix of NLC has an imperfect crystal or amorphous structure which allow for loading in both molecular form and in clustered aggregates form at lattice imperfections [27]. SLN and NLC have the ability to protect liable molecules those are susceptible to hydrolysis such as peptides and proteins[25].

2-Polymer-Based Nano-Materials

Dendrimers:

Dendrimers are nano-sized radially symmetric molecules with well-defined, homogeneous and monodisperse structure consist of tree-like arms or branches three dimensional 3D structures of synthetic polymers[26].These hyperbranched molecules were first discovered by Fritz Vogtle in 1978, by Donald Tomalia and co-workers in the early 1980s[27]. Dendrimers are nearly monodisperse macromolecules that contain symmetric branching units built around a small molecule or a linear polymer core[28]. Polyamidoaminedendrimers were developed first in 1985; which produced by controlled polymerization and became the most popular one. Dendrimers can be used as nano-delivery system of drugs, vaccines and gene delivery[29].

Polymeric Nanoparticles:

Polymeric nanoparticles are colloid solid particles (nanospheres and nanocapsules) prepared by biocompatible and biodegradable polymers which offer complete drug protection. Drugs can be incorporated into nanoparticles by dissolution, adsorption entrapment, attachment or encapsulation; which provide controlled and sustained release of drugs for longer period of action as days or weeks. Stealth and surface modified polymeric nanoparticles can be used for passive and active delivery of bioactive[30]. Eligard® developed by Tolmar Company is leuprolide acetate and poly lactide co glycolide nanoparticles formulation approved by FDA[31].

Polymeric Micelles:

Polymeric Micelles (PMs) are nanocarriers that are formed by spontaneous arrangement of amphiphilic block copolymers in aqueous solutions. These nanoparticles have a hydrophobic core-hydrophilic shell architecture that facilitate the loading of hydrophobic drugs in the core lead to improve the solubility of these water insoluble drugs; PMs offer high entrapment efficiency, payload, stability in physiological condition, long circulating and target site accumulation[32]. Estrasorb® developed by Novavax Company is miceller estradiol formulation approved in 2003 by FDA[33].

Polymer-Drug Conjugates:

Polymer-drug conjugates act as a prodrug, site-specific drug delivery nanocarriersformed by the conjugation of low molecular weight drugs with polymer which cause drastic change in pharmacokinetic of drug in whole body and at cellular level. They are designed to increase the overall molecular weight which facilitate their retention in cancer cells as well as enhance drug activity of multidrug resistance cells[34,35], also these conjugatesoffers drug protection from degradation and reduce the premature drug release and harmful side effects on healthy cells. Oncaspar® developed by Sigma-Tau Company is polyethylene glycol pegaspargase conjugate approved by FDA in 1994[36].

3-Carbon-Based Nano-materials

Carbon Based Nanomaterials (CBNs) have drawn significant interest in diverse areas due to their distinctive structural dimensions and physicochemical properties , based on the structure of CBNs are categorized as carbon nanotubes, graphene, mesoporous carbon, nanodiamond and fullerens, these materials demonstrated higher drug-loading capacity, improve biocompatability and lower immunogenicity. CBNs are extremely useful in various biological applications as novel carriers to deliver drugs or vaccines with loading capacity and extended blood circulation time[37]. Yang et al. developed epirubicine-loaded carbon nanoparticles, which have the ability to release the drug slowly and found that significantly ($p<0.001$) enhanced the drug concentration in the metastatic lymph nodes in patients with breast cancer[38].

4-Inorganic-Based Nano-Materials

Ceramic Nanoparticles:

Ceramic nanoparticles are primerly made up of oxides, carbides, phosphates and carbonates of metals and metalloids such as calcium, titanium, silicon, etc. ceramic nanoparticles are mesoporous particles have high mechanical strength with highly resistant to environmental changes. Ceramic nanoparticles are biocompatible in nature and easily engineered to desired size and porosity in addition to high heat resistance and chemical inertness that make ceramic nanoparticles have a wide range of applications[39]. Ceramic nanoparticles are considered to be excellent carriers for drugs, genes, proteins, imaging agents etc. which provide the complete protection to these entrapped molecules against the denaturating effects of external pH and temperature. The first successful ceramic drug loading was performed by Mattie et al. in 1988 the study reports the delivery of several drugs such as (danazol and dihydrotestosterone) loaded aluminocalcium phosphorous oxide nanoparticles, which demonstrating that the nanoparticles can release the steroidal drug uninterruptedly for one year[40].

Quantum Dot:

Quantum dot nanoparticles are semiconductor nanomaterial's with intrinsic chemical and physical properties, these nanoparticles have particular optical and electronic properties such as size-tunable absorption bands and emission colors due to quantum confinement effect. Quantum dot nanoparticles can artificially synthesized from II to IV and III to V elements such as Cd, Te, Zn, Se, etc. these nanoparticles have physical dimension of 2-10nm that make them a more reliable and influential candidate in most of industrial applications also these nanoparticles are widely used in biological applications that require fluorescence including DNA array technology, cell biology and immuno-fluorescence assays, particularly in immuno-staining of proteins, actins, microtubules and nuclear antigens for cancer cell detection[41].

Metallic Nanoparticles:

Metallic Nanoparticles are particulate materials have novel electrical, optical, physical chemical and magnetic properties such as gold, silver, copper, iron, platinum, cobalt, nickel and palladium[42]. Metal nanoparticles have prime importance for various biomedical applications due to unique Plasmon absorption peak at visible region, surface functionalization ability and high stability; which can be used for delivery of drugs and genes, diagnostic assay with high sensitivity, magnetic resonance imaging, radiotherapy enhancement, protein bioseparation and thermal ablation. Recently metal nanoparticles are universally considered as a promising multifunctional platform for wide purposes particularly in the case of cancer[43]. INFed®developed by Sanofi Aventis Company, is the first nano-structured material approved by FDA in 1974 for the

iron deficiency in chronic renal disease[44].

Conclusion

Since the discovery of nanotechnology and development in nano-scale products enable highly growth in several fields especially pharmaceutical nanotechnology and drug nano delivery systems which lead to enhance the therapeutic efficacy of the drug with reduction of their toxicity, also observed a significant improvement for drug selectivity and specificity at the targeted site of action of numerous diseases and infections from cancer to other several diseases and gene therapy and vaccination.

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