IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2016 Vol.:6, Issue:3

Challenges of Nano Drug Delivery and its Safety Issues

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

***Bijay Kumar Sahoo, Sidheswar Prasad Pattajoshi**

PG Dept. of Pharmaceutics, College of Pharmaceutical Sciences, Marine Drive Road, Puri, Odisha, India.

Submission: 10 June 2016
Accepted: 15 June 2016
Published: 25 June 2016

Keywords: Nanotechnology, Nanoparticles, Solid lipid nanoparticles, Nano-emulsion, Drug delivery, Nanomaterials

ABSTRACT

Nanotechnology is the science and technology of precisely manipulating the structure of matter at the molecular level. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently and provide a variety of surprising and interesting uses. Nanotechnology deals with the creation of useful materials, device and systems and systems through control of matter on the nanometer length scale and exploitation of novel phenomena and properties at that length scale. Nanotechnology is one approach to overcome challenges of conventional drug delivery systems based on the development and fabrication of nanostructures. Various nanostructures employed in drug delivery, their methods of fabrication and challenges of nano drug delivery are reviewed. The present subject matter is mainly conferred on different nanostructures and its challenges and possible safety issues. Some challenges associated with the technology as it relates to drug effectiveness, toxicity, stability and drug regulatory control.

INTRODUCTION

With advancements in nanoscience and technology, a large number of materials and improved products may be available with a change in the physical properties when their sizes are shrunk. Nanotechnology-based delivery systems can also protect drugs from degradation. These properties can help reduce the number of doses required, make treatment a better experience and reduce treatment expenses. A number of nano-based systems allow delivery of insoluble drugs, allowing the use of previously rejected drugs or drugs which are difficult to administer e.g. paclitaxel. The fabrication of nanostructures is able to provide superior drug delivery systems for better management and treatment of diseases. The nanostructures employed as drug delivery systems have multiple advantages which make them superior to conventional delivery systems. The benefits account for the extensive research that has been undertaken into the development of nanostructures such as liposomes, nanocapsules, nanoemulsions, solid lipid nanoparticles, dendrimers, polymeric nanoparticles, etc, for delivery of drugs. The materials employed in the fabrication of nanostructures determine the type of nanostructures obtained and these nanostructures, in turn, determine the different properties obtained and the release characteristics of incorporated drugs. The therapeutic value of many promising drugs for the treatment of various neurological disorders is diminished by the presence of the blood-brain barrier. The blood-brain barrier is a distinctive membrane that tightly segregates the brain from the circulating blood. Thus, drug delivery to this organ is a challenge, because the brain benefits from very efficient protection.

Nanotechnology offers a solution for using the copious chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier. Nanoparticles can be effectively used to deliver relevant drugs to the brain.

TYPES OF NANO-STRUCTURES

Polymeric nanoparticles:

Polymeric nanoparticles are colloidal solid particles with a size range of 10 to 1000nm and they can be spherical, branched or shell structures. The first fabrication of nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics. They are developed from non-

biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Drugs are incorporated into nanoparticles by dissolution, entrapment, adsorption, attachment or by encapsulation, and the nanoparticles provide sustained release of the drugs for longer periods, e.g., days and weeks. Nanoparticles enhance immunization by prevention of degradation of the vaccine and increased uptake by immune cells. One of the determinants of the extent of uptake by immune cells is the type of polymer employed.

Some polymers used in the fabrication of nanoparticles include chitosan, alginate, albumin, gelatin, polyacrylates, polycaprolactones, poly(D, L-lactide-co-glycolide) and poly (D, L-lactide).

Liposomes:

Liposomes were first developed about 40 years ago. They are small artificial vesicles (50 – 100nm) developed from phospholipids such as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, and phosphatidylserine, which have been used in biology, biochemistry, medicine, food, and cosmetics. The characteristics of liposomes are determined by the choice of lipid, their composition, method of preparation, size and surface charge. Liposomes have been applied as drug carriers due to their ability to prevent degradation of drugs, reduce side effects and target drugs to the site of action. However, limitations of liposomes include low encapsulation efficiency, rapid leakage of a water-soluble drug in the presence of blood components and poor storage stability. Applications of liposomes include transdermal drug delivery to enhance skin permeation of drugs with high molecular weight and poor water solubility; drug delivery to the lungs by nebulisation; ocular drug delivery and in the treatment of parasitic infections.

Dendrimers:

Dendrimers are nanostructures produced from macromolecules such as polyamide amine (PAMAM), polypropyleneimine and poly aryl ether; and are highly branched with an inner core. The particle size range is between 1 to 100nm although their sizes are mostly less than 10nm. About 20 years ago, dendrimer studies centred on their synthesis, physical and chemical properties while exploration of their biological applications was initiated about thirteen years

ago. The uniqueness of dendrimers is based on their series of branches, multivalency, well defined molecular weight and globular structure with controlled surface functionality, which enhances their potential as carriers for drug delivery. Dendrimers have been reported to provide controlled release from the inner core. However, drugs are incorporated both in the interior as well as attached on the surface. Due to their versatility, both hydrophilic and hydrophobic drugs can be incorporated into dendrimers.

Solid lipid nanocarriers:

Solid lipid nanoparticles (SLN) are nanostructures made from solid lipids such as glyceryl behenate (Compritol), stearic triglyceride (tristearin), cetyl palmitate and glycerol tripalmitate (tripalmitin) with a size range of 50 and 1000nm. Research interest in SLN emerged about ten years ago due to their scalability potential. The lipids employed are well tolerated by the body. Large scale production will be cost effective and simple by using high-pressure homogenization. Some of the features of SLN include good tolerability, site-specific targeting, stability (stabilized by surfactants or polymers), controlled drug release and protection of liable drugs from degradation. However, SLN is known for insufficient drug loading, drug expulsion after the polymorphic transition on storage and relatively high water content of the dispersions. SLN has been studied and developed for parenteral, dermal, ocular, oral, pulmonary and rectal routes of administration.

Polymeric micelles:

Micelles are formed when an amphiphilic surfactant or polymeric molecules spontaneously associate in an aqueous medium to form core-shell structures or vesicles. Polymeric micelles are formed from amphiphilic block copolymers, such as poly(ethylene oxide)-poly(_-benzyl-Laspartate) and poly(N-isopropyl acrylamide)-polystyrene, and are more stable than surfactant micelles in physiological solutions. They were first proposed as drug carriers about 25years ago. The inner core of a micelle is hydrophobic which is surrounded by a shell of hydrophilic polymers such as poly (ethylene glycol). Their hydrophobic core enables incorporation of poorly water soluble and amphiphilic drugs while their hydrophilic shell and size (<100nm) prolong their circulation time in the blood and increase accumulation in tumoural tissues.

Polymeric micelles are able to reach parts of the body that are poorly accessible to liposomes; accumulate more than free drugs in tumoral tissues due to increased vascular permeability. Thus, polymeric micelles can be employed to administer chemotherapeutics in a controlled and targeted manner with a high concentration in the tumoural cells and reduced side effects. Polymeric micelles have been employed for targeted and intracellular delivery, sustained release, and parenteral delivery

Nanocapsules:

Nanocapsules are spherical hollow structures in which the drug is confined in the cavity and is surrounded by a polymer membrane. They were developed over 30 years ago. Sizes between 50 and 300nm are preferred for drug delivery and they may be filled with oil which can dissolve lipophilic drugs. They have low density, high loading capacity and are taken up by the mononuclear phagocyte system, and accumulate in target organs such as liver and spleen. Nanocapsules can be employed as confined reaction vessels, protective shell for cells or enzymes, transfection vectors in gene therapy, dye dispersants, carriers in heterogeneous catalysis, imaging, and drug carrier. Encapsulation of drugs such as ibuprofen within nanocapsules protects liable drugs from degradation, reduces systemic toxicity, provide controlled release, and mask unpleasant taste.

Nanoemulsions:

Nanoemulsions are emulsions with droplet size below 1μ but usually between 20 and 200nm. Unlike microemulsions which are white in colour due to their light scattering ability, nanoemulsions whose nano size is often smaller than the visible wavelength, are transparent. Nanoemulsions are biodegradable, biocompatible, easy to produce, and used as carriers for lipophilic drugs which are prone to hydrolysis. They are employed as a sustained release delivery system for depot formation via subcutaneous injection. They enhance gastrointestinal absorption and reduce inter- and intra-subject variability for various drugs. Due to their very large interfacial area, they exhibit excellent drug release profile. Stability against sedimentation is attained based on the nano size of the droplets because the sedimentation rate due to gravity is less than Brownian movement and diffusion. Unlike microemulsions, nanoemulsions are metastable and can be destabilized by Ostwald ripening whereby the small droplets dissolve and

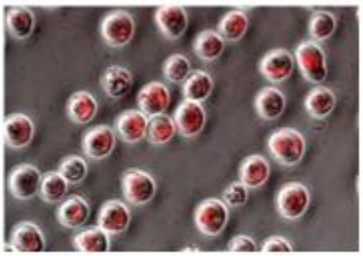
their mass is taken up by the large droplets and depletion induced flocculation due to the addition of thickening polymers. When this happens, the nanoemulsion becomes opaque and creaming will occur. However, the addition of a small amount of second oil with low solubility into the aqueous phase and addition of a second surfactant may reduce Ostwald ripening.

Metallic nanoparticles:

Metallic nanoparticles include iron oxide, gold, silver, gadolinium, and nickel which have been studied for targeted cellular delivery. Gold exhibits favourable optical and chemical properties at the nanoscale for biomedical imaging and therapeutic applications. It can be manipulated to obtain the desired size in the range of 0.8 to 200nm. The surface can be modified with different functional groups for gene transfection, modified into gene delivery vector by conjugation and also modified to target proteins and peptides to the cell nucleus. Gadolinium has been studied for enhanced tumour targeted delivery by modification of the nanoparticles with folate, thiamine, and poly (ethylene glycol). Metallic nanoparticles have large surface area thereby incorporating a high drug dose. However, the toxicity of metallic nanoparticles is of concern.

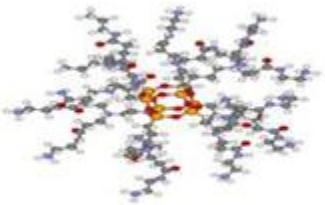
Carbon nanomaterials:

These include carbon nanotubes and fullerenes. Fullerenes are carbon allotrope made up of 60 or more carbon atoms with a polygonal structure. Nanotubes have been used for their high electrical conductivity and excellent strength. These materials are being studied for therapeutic applications. Fullerenes can be functionalized for delivery of drugs and biomolecules across the cell membrane to the mitochondria. Carbon nanotubes unique properties including low cytotoxicity and good biocompatibility attract their use as vector system in target delivery of drugs, proteins, and genes. However, the toxicity of carbon nanotubes is of great concern. Carbon nanotubes may cause inflammatory and fibrotic reactions.



Nano-Capsule

Liposomes



Dendrimers

CHALLENGES AND SAFETY ISSUES

Although nanotechnology in drug delivery has been successful, as evidenced by some nano drug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges which have to be surmounted. However some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting. Another challenge of research and development (R&D) of nanomaterials for drug delivery is large scale production.

There is always a need to scale up laboratory or pilot technologies for eventual commercialization. A number of nano drug delivery technologies may not be scalable due to the method and process of production and high cost of materials employed. The challenges of scaling up include a low concentration of nanomaterials, agglomeration, and the chemistry process – it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale. Maintaining the size and composition of nanomaterials at large scale is also a challenge. Despite the number of patents for nano drug delivery technologies, commercialization is still at its early stage. This is partially due to the fact that most of the research studies in nano drug delivery are carried out by researchers in academia. Therefore, for these technologies to get to the market there has to be increased partnership with the pharmaceutical companies. Unfortunately, a number of the major pharmaceutical industries are yet to consider nanotechnology as one of their priorities due to lack of regulatory guidelines and challenges of scaling up. However, it is envisaged that with the expiration of more patents and market loss, more pharmaceutical industries will take up the production of nano drug products in order to compete favourably. Advances in nano drug delivery technology also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products. The United States' Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have taken the initiative to identify some possible scientific and regulatory challenges. Furthermore, the International Organization for Standardization has set up a technical committee (TC 229) for the field of nanotechnologies to

develop standards pertaining to terminology and nomenclature; measurement and characterization; and health, safety and environment amongst other standards. These standards are still under development.

With increased R&D work on nano drug delivery, emerge concerns about the safety of the nanotechnologies in humans. Some of the nanomaterials are biodegradable while some are not; furthermore, the side effects of the by-products present a huge concern. Materials which may be safe at macro scale may not be at nanoscale since there may be a change in physicochemical characteristics at the nanoscale. These nanomaterials may not clear completely from the body and their accumulation may have several possible effects. Safety and possible impact nanomaterials should not be considered for the patient population alone but also for the entire manufacturing and disposal processes.

Conventional safety measures in a pharmaceutical factory may not be appropriate for the development and fabrication of nanomaterials. Also, extra measures are to be taken to protect the environment from increased envisaged negative impacts of nanomaterials. Although reduced cost to the patients is envisaged to be one of the advantages of nanotechnology since fewer materials are expected to go into production as compared to bulk production; it is doubtful if this will be so as successful commercialization will be expensive.

CONCLUSION

There is the general public hesitation to cuddle nanotechnology based on the unavailability of documented safety guidelines. However, in spite of these challenges, nano drug delivery is a development that cannot be ignored and so the challenges will be embarking upon with time.

The increasing awareness of R&D in the area of nano drug delivery would continue to change the whole concept of medicines including aspects such as product characteristics, bioavailability, pharmacokinetics, stability, drug use, and toxicity in human as well as animal and plant diseases. This in itself possess enormous challenges to the formulation scientist who has to keep abreast of rapid developments in this field. A whole segment of R & D has opened up, posing great challenges to equipment manufacturers, material scientists, pharmaceutical researchers and regulatory agencies. It is anticipated that better understanding and application of nanotechnology

for effective drug delivery would ultimately enhance the efficacy of treatment and patient compliance in drug use. It would be difficult to refute the potential benefits of nanotechnology and stop development of research related to it since it has already begun to break through many different fields of research. However, nanotechnology can be developed using guidelines to assure that the technology does not become too potentially harmful.

REFERENCES

1. Vasir JK, Reddy MK, Labhasetwar V. Nanosystems in drug targeting: opportunities and challenges. Curr Nanosci 2005; 1: 47-64.
2. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 1986; 46: 6387-92.
3. Pardridge WM. Vector-mediated drug delivery to the brain. Adv Drug Deliv Rev 1999; 36: 299-321.
4. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 2002; 54: 631-51.
5. Prabha S, Zhou WZ, Panyam J, Sahoo SK, Labhasetwar V. Sizedependency of nanoparticle-mediated gene transfection: studies with fractionated nanoparticles. Int J Pharm 2002;244:5-15
6. Mishra V, Mahor S, Rawat A, Gupta PN, Dubey P, Khatri K, et al. Targeted brain delivery of AZT via transferrin anchored PEGylated albumin nanoparticles. J Drug Target 2006; 14(1) 45- 53.
7. Li FQ, Su H, Wang J, Liu JY, Zhu QG, Fei YB, et al. Preparation and characterization of sodium ferulate entrapped bovine serum albumin nanoparticles for liver targeting. Int J Pharm 2008; 349(1-2): 274-82.
8. Sonvico F, Cagnani A, Rossi A, Motta S, Bari Di MT, Cavatorta F, Alonso MJ, Deriu A, Colombo P. Formation of self-organized nanoparticles by lecithin/chitosan ionic interaction. Int J Pharm 2006; 324: 67–73.
9. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumor tropic accumulation of proteins and the antitumor agent smancs. Cancer Res 1986; 46: 6387-92.
10. Pardridge WM. Vector-mediated drug delivery to the brain. Adv.Drug Deliv Rev 1999; 36: 299-321.