IJPSR (2014), Vol. 5, Issue 3 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 August, 2013; received in revised form, 20 January, 2014; accepted, 12 February, 2014; published 01 March, 2013

PROTEIN NANOPARTICLES: FUTURE OF DRUG DELIVERY SYSTEMS

Alok Mahor *[1], Shashi Alok [1], Sunil Prajapati [1], Amita Verma [2], Poonam Yadav[1] and Madhuri Shringrishi[1]

Institute of Pharmacy, Bundelkhand University [1], Jhansi, Uttar Pradesh, India
Department of Pharmaceutical Sciences, Faculty of Health Sciences, Sam Higginbottom Institute of Agriculture, Technology and Sciences [2], Allahabad, Uttar Pradesh, India

Keywords:

Protein nanoparticles, Gelatin, Albumin, Site specific targeting

Correspondence to Author:

Alok Mahor

Assistant Professor, Institute of Pharmacy, Bundelkhand University, Jhansi, Uttar Pradesh, India

E-mail: alokmpharma@gmail.com

ABSTRACT: Nanoparticles have advantages, such as small size, high surface area, and modification using functional groups for high capacity or selectivity. Nanoparticles with Proteins are especially worthy of notice because they can be used for site specific targeting. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmaco-dynamic properties of various types of drug molecules. They have been used *in vivo* to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Nowadays active research is focused on the preparation of nanoparticles using proteins like albumin, gelatin, gliadin and legumin. Protein nanoparticles hold promise as drug delivery systems for parentral as well as oral. This article reviews the introduction of nanoparticles with especial focus on protein nanoparticles with preparation, characterization and applications of Protein Nanoparticles.

INTRODUCTION: In recent years, there has been a dramatic increase in research, technology, and production of nanoparticles. These nanoscaled particles have physico-chemical properties different from those of bulk material and, thus, offer opportunities for the development of new applications. Some of these engineered nano-particles are already in use in a diverse array of applications including medicine, food, clothes, personal care products, information technology, and construction materials, resulting in a wide range of exposure scenarios.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(3).790-98

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(3).790-98

Therefore, it has become important to determine the potential hazards of nanoparticles on human health. Nanoparticles can come in contact with the human body through inhalation but also through ingestion, dermal deposition, or by medical applications through injection. Nanoparticles having entered the body through inhalation can translocate into the systemic circulation, reach various remote organs, and affect their function [1].

The most important advantage of colloidal drug carrier systems is the possibility of drug targeting by a modified body distribution as well as the improvement of the cellular uptake of a number of substances. As a result undesired toxic side effects of the free drug can be avoided, for example with methotrexate. Proteins are a class of natural molecules that have unique functionalities and potential applications in both biological as well as material fields.

Nanomaterials derived from proteins, especially protein nanoparticles are biodegradable, non-antigenic, metabolizable and can also be easily amenable for surface modification and covalent attachment of drugs and ligands. Because of the defined primary structure of proteins the protein-based nanoparticles may suggest various possibilities for surface alteration and covalent drug attachment [2].

Challenges to Nano Drug Delivery: 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 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 [3].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties [4] and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen [5].

Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes.

For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties [6, 7].

The advantages of using nanoparticles as a drug delivery system include the following:

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.

3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.

5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

In spite of these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available.

The present review details the latest development of nanoparticulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles[8].

1. **Methodology in preparation of Nano particles:** Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including;

   (a) Size of nanoparticles required.

   (b) Inherent properties of the drug, e.g., aqueous solubility and stability.

   (c) Surface characteristics such as charge and permeability.

   (d) Degree of biodegradability, bio-compati bility and toxicity.

   (e) Drug release profile desired.

   (f) Antigenicity of the final product [9].

Nano-particles have been prepared most by following methods;

1. **Emulsification method [2]:** Initially, its method was set forth by Scheffel and his co-workers (1972) in order to prepare albumin sphere nanoparticles and then it was optimized by Gao and his co-workers [10]. The above process is shown in **Figure 1**. Gupta *et al*., 2004 prepared cross-linked gelatin nanoparticles encapsulating a fluorescent marker molecule fluorescein isothiocyanate-dextran to show Effect of cellular uptake of gelatin nanoparticles on adhesion, morphology and cytoskeleton organisation of human fibroblasts by using emulsification method [11].

2. **Desolvation method [2]:** The disadvantage of the emulsion methods for particles preparation is the need for applying organic solvents, for the removal both of the oily residues of the preparation process and of surfactants required for emulsion stabilization.

   Therefore, as an alternative method for the preparation of protein nanoparticles a desolvation process derived from the coacervation method of microencapsulation was developed (**figure 2**). Gelatin nanoparticles were prepared by the two-step desolvation Method [12]. Tseng CL *et al*., 2007, prepared gelatin nanoparticles with biotinylated EGF conjugation for lung cancer targeting by using this method [13].

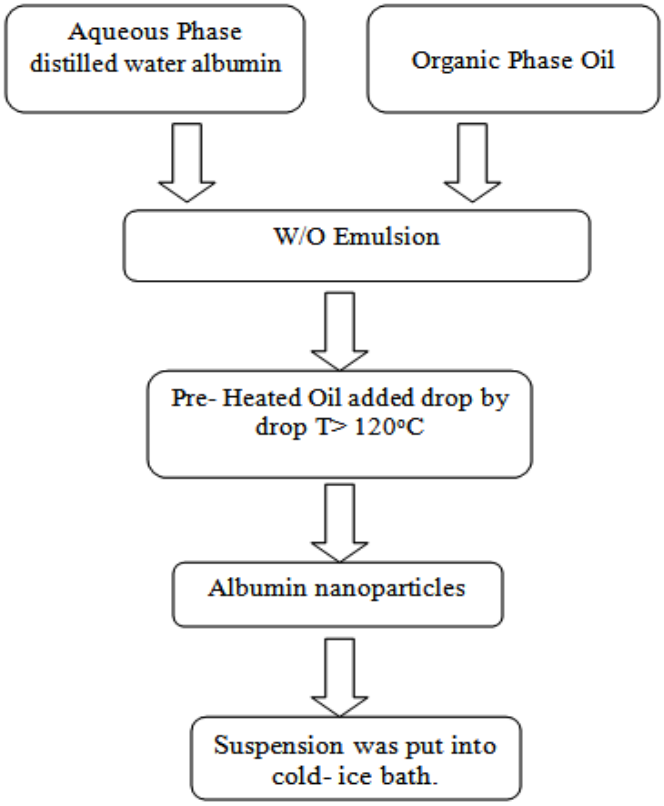

FIGURE 1: PREPARATION OF ALBUMIN NANO-PARTICLES WITH EMULSIFICATION METHOD [14]

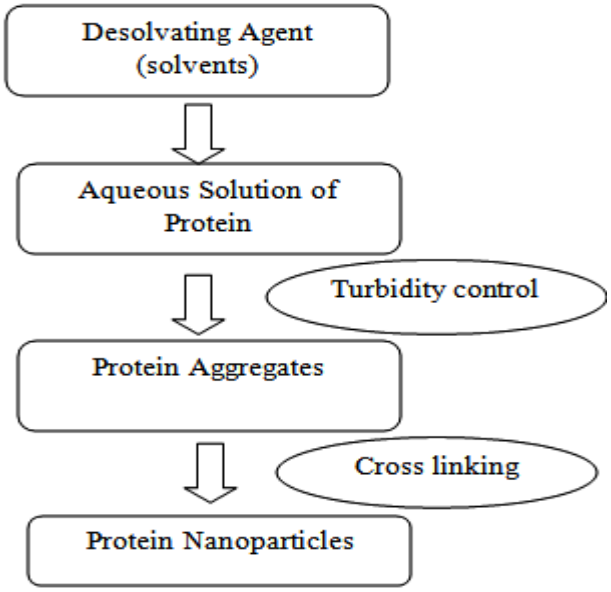

FIGURE 2: SHOWS PREPARATION OF ALBUMIN NANOPARTICLES BY USING DESOLVATING AGENT

3. **Preparation of co-polymerised peptide Nano-particles [9]:** A novel co-polymeric Nano-particulate drug delivery system, co-polymerized peptide particles has been developed as carrier for the oral uptake of therapeutic peptides. By using a copolymer delivery system using n-butyl cyanoacrylates as one of the monomer. The particle forming properties of the alkyl -2-cyno acrylates can be exploited.

4. **Coacervation or ionic geleation method [9]:** Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as, chitosan, gelatin and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan Nano-particles by ionic gelation. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly-anion sodium tri-polyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged tri-polyphosphate to form coacervate with a size in the range of Nano-meter. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

Characterization of Nanoparticles [9]: There are many methods for the characterization of nanoparticles, but some important methods are mentioned below.

1. **X-ray characterization of Nano-particles:** X-ray methods of characterization represent a powerful approach to the study of Nano-phase materials. The advantage of these techniques is to provide meaningful ensemble averaged information about both medium range and local atomic structure in Nano-systems.

2. **Transmission Electron Microscopy and Spectroscopy of Nano-particles:** One of the typical characters of Nano-phase materials in the small particle sizes. Although some structural features can be revealed by x-ray and neutron diffraction, direct imaging of nanoparticles is only possible using transmission electron microscopy (TEM) and scanning probe microscopy. TEM is unique because it can provide a real space image on the atom distribution in the Nano-crystals on its surface.

Today`s TEM is a versatile tool that provides not only atomic resolution lattice images but also chemical information at spatial resolution of 1nm or better, allowing direct identification the chemistry of a single Nano-crystal.

3. **Scanning Probe Microscopy of Nano-nucleus:** The basic idea of scanning probe microscopy (SPM) is relatively simple. A probe susceptible to the property that has to be measured, then it has to bring into the vicinity of a surface and the reaction of the probe can be measured. As one is interested in microscope information the probe has to be sufficiently small and its movements have to be controlled on a length scale comparable to its size. Depending on the specific property measured in the type of probe and the way in which the reaction of probe is amplified all existing SPM methods can be differentiated.

4. **Dynamic Light Scattering (DLS):** DLS also known as photon correlation spectroscopy or quasi elastic light scattering (QELS) records the variation in the intensity of scattered records the micro second time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion and is quantified by completion of an autocorrelation function. Using standard assumption of spherical size low concentration, and know viscosity of the suspending medium particle size is calculated from this co-efficient.

5. **Zeta potential:** Zeta potential is used as a sure gate for surface change and is often measured by which is achieved, mostly using a Doppler shift, and the user should familiarize themselves in their particular approach implemented in their equipment [9].

6. **Drug loading** [2]**:** Drug may be bound to nanoparticles either;

    a. By polymerization in the presence of the drug- in most cases in the form of a solution (incorporation method) or;

    b. By adsorbing the drug after the formation of nanoparticles by incubating them in the drug solution.

Depending on the affinity of the drug to the polymer, the drug will be surface adsorbed, dispersed in the particle polymer matrixin the form of a solid solution [15] or solid dispersion, or in some case, the drug may be covalently bound to the polymer.

Therefore, it is apparent that a large amount of drug can be entrapped by the incorporation method when compared to the adsorption [16]. The macromolecule or protein shows greatest loading efficiency when it is loaded at or near its isoelectric point when it has minimum solubility and maximum adsorption. The drug loading of the nanoparticles is generally defined as the amount of drug bounded per mass of polymer (usually moles of drug per mg polymer or mg drug per mg polymer) it could also be given on a percentage basis based on the polymer.

7. **Determination of Drug entrapment:** Binding of drug to the protein nanoparticles was measured by centrifuging part of the particle suspension. For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (*w*) by UV-spectrophotometry, fluorescence spectrophotometer or by a validated HPLC method. A standard calibration curve of concentration versus absorbance was plotted for this purpose.

    The amount of drug in supernatant was then subtracted from the total amount of drug added during the formulation (*W*). Effectively, (*Ww*) will give the amount of drug entrapped in the pellet. Then percentage entrapment is given: Drug entrapment (%) Finally, the encapsulation efficiency refer to the ratio of the amount of drug encapsulated/absorbed to the total (theoretical) amount of drug used, with regard to the final drug delivery system of the dispersion of nanoparticles.

8. **Drug release:** Release profiles of the drugs from nanoparticles depend upon the nature of the delivery system. In the case of nanospheres, drug is uniformly distributed/ dissolved in the matrix and the release occurs by diffusion or erosion of the matrix. If the diffusion of the drug is faster than matrix degradation, then the

mechanism of drug release occurs mainly by diffusion, otherwise it depends upon degradation. Many theoretically possible mechanisms may be considered for the release drug from protein nanoparticles:

(a) Liberation due to polymer erosion or degradation,

(b) Self-diffusion through pores,

(c) Release from the surface of the polymer,

(d) Pulsed delivery initiated by the application of an oscillating magnetic or sonic field [17].

In many case, some of these processes may coexist, so that the distinction between the mechanisms is not always trivial. When drug release occurs by a self-diffusional process, a minimum drug loading is necessary before drug release is observed. This is easy to understand since the process involves diffusion through aqueous channels created by the phase separation and dissolution of the drug itself. This mechanism rarely occurs with drug loaded nanoparticles since, as explained before, the encapsulation efficiency of most drugs is generally too low. In fact, release from the surface and erosion or bulk polymer degradation is usually the most important processes affecting the liberation of drug from nanoparticles.

Methods for quantifying drug release *in vitro* are:

a. Side by- side diffusion cells with artificial or biological membranes;

b. Equilibrium dialysis technique;

c. Reverse dialysis sac technique;

d. Ultracentrifugation;

e. Ultrafiltration; or

f. Centrifugal ultrafiltration technique [5].

Potential and promising applications of Protein Nanoparticles:

1. **Oral delivery of Protein:** Oral delivery of protein has become a pressing goal in recent years due to the increased availability of novel therapeutics through the advent of recombinant DNA technology. One of the holy grails of oral drug delivery is to deliver proteins, such as insulin, with the efficacy similar to the parenteral formulations. The increasing importance of proteins can be attributed to three main developments. First, improved analytical methods have promoted discovery of numerous hormones and peptides that have found applications as biopharmaceuticals. Second, molecular biology and genetic engineering have enabled large-scale production of polypeptides previously available only in small quantities.

   Lastly, there is a better understanding of the role of regulatory proteins in the pathophysiology of human diseases. Consequently, pharmaceutical companies around the world have developed protein oral delivery technologies for producing therapeutically active ingredients in commercial scales, as listed in **Table 1**[18]**.**

   Proteins have become the drugs of choice for treatment of numerous diseases as a result of their exquisite selectivity and their ability to provide effective and potent action. Protein drug development, however, continues to be a formulation challenge to pharmaceutical scientists. Many protein drugs are currently used as parenteral formulations because of their poor oral bioavailability. This is due to several unfavorable physicochemical properties, such as large molecular size, susceptibility to enzymatic degradation, poor stability in the gastric low pH environment, poor penetration of the intestinal membrane, short plasma half-life, immunogenicity, and the tendency to undergo aggregation, adsorption, and denaturation.

   Enzymatic degradation and poor penetration of the intestinal membrane induce low oral bioavailability of biological molecules. The challenge here is to improve the oral bioavailability from less than 1% to at least 30–50%. These problems also remain unsolved.

Unfavorable physicochemical properties of proteins present monumental challenges to pharmaceutical formulation scientists. Designing and formulating a protein drug for delivery through the gastrointestinal (GI) tract requires innovative and practical strategies. Various strategies currently under investigation include chemical modification, formulation vehicles, protease inhibitors, absorption enhancers and muco-adhesive polymers. Among them, nanoparticles as a carrier or a device have become the focus of attention in this field recently. The nanoparticles possess certain advantages such as greater stability during storage, stability *uy53zs* after administration and ease of scale-up without an aseptic process for oral administration.

TABLE 1: PROTEIN ORAL DELIVERY TECHNOLOGIES UNDER DEVELOPMENT BY COMPANIES [18]

Company	Product	Systems	Characteristics and advantages	Products currently available or under development
Emisphere	Eligen®	Carrier molecules	Facilitates the absorption of small molecules without altering chemical form, biological integrity or pharmacological properties, Passive transcellular transport enables drug molecules of all sizes to cross the cell membrane	Calcitonin, GPL-1, PYY, insulin, growth hormone, parathyroid hormone, heparin
Altus	CLEC®	Protein crystallization	Catalysts containing the enzyme alcohol dehydrogenase (ADH). Protein stabilization against proteolysis and self-digestion	Calcitonin, other polypeptides, lipases, esterases, and proteases
Generex	Oral-Lyn™	Spray device and aerosol particles	Penetrate the buccal epithelium Treatment of type 1 and 2 diabetes	Insulin, macrotonin
NOBEX/ Biocon	HIM2	Amphiphilic oligomers	Resist enzyme digestion and increase membrane permeation	Insulin, enkephalin, calcitonin, parathyroid hormone
Apollo Life Sciences	Oradel™	Nanoparticles	Protection of the drug payload from digestive enzymes and transport of protein-based drugs and antibodies across the intestinal wall transporting both small and large molecules (up to 150 kDa in size) for protein-based drugs and antibodies	Insulin and oral delivery of anti-inflammatory. Proteins (TNF blocker)
Autoimmune Incorporated/ Eli-Lilly	AI-401	Oral formulation	Protect proteins from enzyme digestion. Oral tolerance therapy. Treatment of Type 1 diabetes but also for prevention of progression	Insulin
Provalis PLC	Macrulin™	Lipid-based water-in-oil microemulsion	Protect proteins from proteolysis or acidic degradation, and enhance the protein absorption in GIT treatment of Type 2 diabetes	Insulin, salmon, calcitonin
Endorex	Orasome™	Polymerized liposomes	Protect proteins from the stomach and upper GIT	Insulin and growth hormone, vaccines

2. **Parenteral delivery of Protein [19]:** Now a day self-administered injectables are available that are in expensive and easy to deliver protein drug. But human aspects are critically important in this equation when insulin delivery is considered. It was practically seen that around 65% of patient with type 1 and type 2 diabetes, were not confident in their ability to effectively self-manage their disease and as many as 25% of folks described anxiety with respect to self-injection. Another problematic area is the paediatric drug administration as there is lack of age appropriate drug formulation that leads to the off-label use of adult drug delivery approaches.

3. **Antibiotics with Protein nanoparticles:** Antibiotics are other drugs that were shown to yield an increase in efficacy or a decrease in toxicity after binding to protein nanoparticles. Amoxicillin and gliadin nanoparticles-bearing amoxicillin (AGNP) both showed anti–*Helicobacter pylori*, but the required dose for complete eradication was less in AGNP than in amoxicillin.

   AGNP eradicated *H. pylori* from the gastrointestinal tract more effectively than amoxicillin because of the prolonged gastrointestinal residence time attributed to mucoadhesion.

A dosage form containing mucoadhesive nanoparticles bearing a potential antibiotic should be useful for the complete eradication of *H. Pylori* [20].

4. **Protein nanoparticles as carriers for ophthalmic drugs:** Protein nanoparticles exhibit a considerably longer half–life in the eye than eye-drops. Pilocarpine bound to gelatin nanoparticles substantially prolonged the intraocular pressure reduction in rabbits with experimental glaucoma as well as the miosis time [21] in comparison to a pilocarpine eye-drop solution.

CONCLUSION: The above discussed literature postulates that the protein nanoparticles are the future of drug delivery systems adhering to the basics of delivering therapeutics with efficacy, optimum bioavailability, minimizing side effects, target oriented and time release fundamentals (**tables 2 and 3**). Therefore, in near future, drug delivery systems will be seen using more and more biodegradable polymers such as proteins eradicating the use of toxic and harmful polymers and helping mankind.

TABLE 2: EXAMPLES OF SOME THERAPEUTIC PROTEINS AND THEIR PHARMACEUTICAL APPLICATIONS

Protein	Pharmaceutical Applications
Erythropoietin	Anaemia associated with kidney failure
Granulocyte colony stimulating factor	Neutropenia caused by cytostatic treatment
Growth hormone	Growth hormone deficiency in children
Insulin	Diabetes mellitus
Interferon alpha-2b	Hepatitis A, Hepatitis B and some types of cancer
Interferon beta	Multiple Sclerosis
Interleukin-2	Kidney cancer
Platelet-derived Growth Factor	Neuropathic ulcers in lower limb of diabetic patients
Streptokinase	Acute myocardial infraction

TABLE 3: POTENTIAL APPLICATIONS FOR NANOTECHNOLOGIES IN DRUG DELIVERY [22]

Material/technique	Characteristics	Medical applications
Ligands attached to nanoparticles	Surface modification with functional groups high degree of engineering precision control the size of the nanoparticles.	Labeling, tracing and imaging, sensing and detection, recognition and attachment to damaged or diseased tissue followed by release of therapeutic compound
Quantum dots	Emit different wavelengths over abroad range of the light spectrum from visible to infrared, depending on their size and chemical composition. Influence the fluorescence properties of the particles.	Fluorescent probes, detection and targeting
Nanocapsules	Consists of a shell and a space Can be made in specific sizes, shapes, and in reasonable quantities. Control the release of substances or protect them from the environment. Higher safety and efficacy, evasion of the host immune system and delivery of therapeutic agent to target sites.	Slowly release loading drugs. Lipid nanocapsules as nanocarriers e.g. Buckyball-based treatment for AIDS
Nanoporous materials	Ability of nanopores of certain sizes to let some substances pass and others not, or to force molecules	Nanoporous membranes for molecules like DNA and RNA can be coupled to sensors or used for drug-delivering implants
Polymers	Allow for judicious selection for targeting and delivery can be used to improve the function of the nanoparticle High degree of engineering precision.	Drug carrying devices or implants Combining multi-modal therapy and imaging
Sorting biomolecules and precise sorting	Nanopores capable of rapid and precise sorting.	Gene analysis and sequencing

ACKNOWLEDGEMENT: The authors wish to extend their gratitude to the authorities of Bundelkhand University, Jhansi and Sam Higginbottom Institute of Agriculture, Technology and Sciences, Allahabad, for their continuous support during the preparation of this manuscript.

REFERENCES:

1. Bihari P, Vippola M, Schultes S, Praetner M, Khandoga AG and Reichel CA: Optimized dispersion of nanoparticles for biological *in vitro* and *in vivo* studies. BioMed Central Ltd. Particle and Fibre Toxicology 2008; 5:14.
2. Jahanshahi M and Babaei Z: Protein nanoparticle: A unique system as drug delivery vehicles. African Journal of Biotechnology 2008; 7 (25): 4926-4934.
3. Ochekpe NA, Olorunfemi PO and Ngwuluka NC: Nanotechnology and Drug Delivery Part 2: Nanostructures for Drug Delivery. Tropical Journal of Pharma ceutical Research 2009; 8(3): 275- 287.
4. Jahanshahi M, Aghajani H and Ling TC: Assembly and purification of nanostructure bioproducts: protein nanoparticle characteri zations and non-stick exterior coating adsorbents. Int. J. Nanosci. Nanotech 2005; 1: 9-19.
5. Soppimath KS, Aminabhavi TM, Kulkarni AR and Rudzinski WE: Biodegradable polymeric nanoparticles as drug delivery devices. J. controlled release 2001; 7: 1-20.
6. Vila A, Sanchez A, Tobio M, Calvo P and Alonso MJ: Design of biodegradable particles for protein delivery. J Control Release 2002; 78: 15-24.
7. Mu L and Feng SS. A novel controlled release formulation for the anticancer drug paclitaxel (Taxol(R)): PLGA nanoparticles containing vitamin E TPGS. J Control Release 2003; 86: 33-48.
8. Mohanraj VJ and Chen Y: Nanoparticles- A Review. Tropical Journal of Pharmaceutical Research 2006; 5 (1): 561-573.
9. Maruthi G, Smith AA and Manavalan R: Nanoparticles–A Review. Journal of Advanced Scientific Research 2001; 2(4); 12-19.
10. Gao Z, Shukla AJ, Johnson JR and Crowley WR: Controlled release of contraceptive steroids from biodegradable and injectable gel formulation: *in vitro* evaluation. Pharm. Res 1995; 12: 857-863.
11. Gupta AK, Gupta M, Yarwood SJ, Adam SG and Curtis ASG: Effect of cellular uptake of gelatin nanoparticles on adhesion, morphology and cytoskeleton organisation of human fibroblasts. Journal of Controlled Release 2004; 95: 197– 207.
12. Coester CJ, Langer K, Von Briesen H and Kreuter J: Gelatin nanoparticles by two step desolvation-a new preparation method, surface modifications and cell uptake. Journal of Microencapsulation 2000; 17(2): 187-193.
13. Tsenga CL, Wanga TW, Guo-Chung Dongb GC, Wua YH S, Younga TH and Shieha MJ: Development of gelatin nanoparticles with biotinylated EGF conjugation for lung cancer targeting. Biomaterials 2007; 28: 3996–4005.
14. Jahanshahi M: "Molecular Nanotechnology & Nanobiotechnology", Book: Academic University (Mazandaran) publications.ISBN 2005; 964-2571-10-2.
15. Harmin T, Speiser P and Kreuter J: A solid colloidal drug delivery system for the eye: encapsulation of pilocarpin in nanoparticles. J. Microencapsul 1986; 3: 3-12.
16. Breitenbach MA, Kamm W, Hungere KD, Hund H and Kissel T: Oral and nasal adminis tration of tetanus toxoid loaded nanoparticles consisting of novel charged biodegradable polyesters for mucosal vaccination. Proc. Intern. Symp. Control. Release. Bioact. Mater 1999 26: 348-349.
17. Couvreur P and Puisieux F: Nano and micro particles for the delivery of poly peptides and proteins. Adv. Drug Del. Rev 1993; 10: 141-162.
18. Park K, Kwon IC and Park K: Oral protein delivery: current status and future prospect. React. Funct. Polym 2011; 71: 280–287.
19. Prusty AK and Sahu SK: Biodegradable Nanoparticles- A novel approach for oral administration of biological products. International Journal of Pharmaceutical sciences and nanotechnology 2009; 2(2): 503-508.
20. Umamaheshwari RB, Ramteke S and Kumar Jain N: Anti–Helicobacter Pylori Effect of Mucoadhesive Nanoparticles Bearing Amoxicillin in Experimental Gerbils Model. AAPS Pharm. Sci. Technol 2004; 5(2): 32.
21. Diepold R, Kreuter J, Himber J, Gurny R, Lee VHK and Robinson JR et al: Comparision of different models for the testing of pilocarpine eyedrops using conventional eyedrops and a novel depot formulation (nanoparticles). Graefe's Arch. Clin. Exp. Ophthalmol 1989; 227: 188-193.
22. Carino GP, Jacob JS and Mathiowitz E: Nanosphere based oral insulin delivery. J. Control. Release 2000; 65: 261–269.

How to cite this article:
Mahor A, Alok S, Prajapati SK, Verma A and Yadav P and Shringrishi M: Protein Nanoparticles: Future of Drug Delivery Systems. *Int J Pharm Sci Res* 2014; 5(3): 790-98.doi: 10.13040/IJPSR.0975-8232.5(3).790-98

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)