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Review Article

NANOPARTICLES AS A NOVEL DRUG DELIVERY SYSTEM: A REVIEW

Prabhjot kaur*, Loveleenpreet kaur and MU. Khan

Department of Pharmaceutics, Sri Sai College of Pharmacy, Badhani, Pathankot, Punjab, india.

ABSTRACT

For the past few years, there has been a considerable research on the basis of Novel drug delivery system, using particulate vesicle systems as such drug carriers for small and large molecules. Nanoparticles, Liposomes, Microspheres, Niosomes, Pronisomes, Ethosomes, Pro-liposomes have been used as drug carrier in vesicle drug delivery system. Various polymers have been used in the formation of Nanoparticles. Nanoparticles have been improving the therapeutic effect of drugs and minimize the side effects. Basically, Nanoparticles have been prepared by using various techniques as such dispersion of preformed polymers, polymerization of monomers and ionic gelation or co-acervation of hydrophilic polymer. In a past research of work of nanomedicines these have been particularly used for cell repair, anti-microbial techniques, anticancer therapy, gene delivery system, vector cell repair, nanorobot for chromosome repair therapy. Sometimes the Nanoparticles are likely to be unsafe for the biological system. Nanoparticles have been evaluated by using parameters of drug entrapment efficiency, particle shape, drug release study.

Keywords: Nanoparticles, polymerization, dispersion, nanorobot.

INTRODUCTION [1-4]

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug dissolved, entrapped, encapsulated or attached to a nanoparticles matrix. Depending upon to the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly (ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carrier of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.

The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment, and prevention. These technological innovations, referred to as nanomedicines by the National Institutes of Health have the potential to turn molecular discoveries arising from genomics and proteomics into widespread benefit for patients. Nanomedicines is a large subject area and includes nanoparticles that act as biological mimetic (e.g. functionalized carbon nanotubes) ,"nanomachics"(e.g. those made from interchangeable DNA parts and DNA scaffolds such as octahedron and stick cube) , nanofibers and polymeric nanoconstructs as biomaterials (e.g. molecular self- assembly and nano-fibers of peptides and peptideamphiphiles for tissue engineering) , shape memory polymers as molecular switches, nanoporous membranes) , and nanoscale micro-fabrication based devices (e.g. silicon microchips for drug release and micro machined hollow needles and

two dimensional needles assay from single crystal silicon), sensors and laboratory diagnostics[5].

The focus of various researches is to assess the nature of interaction between manufactured nanoparticles and the skin; including dermal absorption, cutaneous toxicity as well as the ability to distribute to the skin after systemic exposure. The skin is a primary route of potential exposure to toxicants including novel nanoparticles. However, there is no information on whether particles are absorbed across the stratum corneum barrier or whether systemically administered particles can accumulate in dermal tissue. Our laboratory has developed a well validated humane alternative animal model that is predictive of in vivo human dermal absorption that is ideally suited to assess both the dermal absorption of nanoparticle as well as there potential accumulation in skin after systemic exposure. These studies will utilize iron oxide nanocrystals, cadmium selenide nanocrystals and carbon fullerene nanoparticle which are representative of the broad spectrum of nanoparticle presently being used by industry. Eight particle types selected from these commercially relevant manufactured nanoparticles will be studied to allow assessment of size, shape and composition on absorption, distribution or toxicity to the skin. These data would provide a preliminary but relevant assessment of both systemic exposure after topical administration as well as cutaneous hazard after both topical and systemic exposure, the two essential components of any risk assessment. We postulate that should carbon nanoparticle be accidentally modified or if exposure occurs before cleansing, they could have untoward consequences if they gain entry to tissues.

Presently, there are minimal data available on the interaction between manufactured nanoparticles and biological tissues. The basic requirement for any risk assessment includes information on hazard (e.g. toxicity) and exposure (e.g. absorption). This proposal focuses on the health effects of nanoparticle interactions with the skin. This integrated research program will generate data on the ability of nanoparticles to be toxic to keratinocytes as well as assess the ability of nanoparticles to either be absorbed into skin after topical exposure, or distribute into skin as would occur after systemic exposure by an alternate route of administration. At the conclusion of the research, the boundaries of a dermal risk assessment for manufactured nanoparticle exposure will be available[6].

Polymeric micelles for delivery of water soluble compounds[7]

Amphiphillic polymers assemble into nanoscopic supramolecular core-shell structures, termed polymeric micelles, which are under extensive study for drug delivery. There are several reasons for this growing interest. Polymeric micelles maybe safe for parenteral administration relative to existing solubilizing agents (for instance, Cremophor EL), permitting an increase in the dose of potent yet toxic and poorly water soluble compounds. Polymeric micelles solubilize important poorly water-soluble compounds, such as amphotericin B (AmB), propofol, paclitaxel, and photosensitizers. A major factor in drug solubilization is the compatibility of a drug and a core of a polymeric micelle. In this context, we may consider Pluronics, poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly(ester)s, and PEG-b-poly(L-amino acid)s for drug delivery. Polymeric micelles may circulate for prolonged periods in blood, evade host defenses, and gradually release drug. Thus, they may show a preferential accumulation at sites of disease such as solid tumors. Polymeric micelles inhibit p-glycoprotein at drug-resistant tumors, gastrointestinal tract, and blood/brain barrier, perhaps providing a way to overcome drug resistance in cancer and increase drug absorption from the gut and drug absorption into the brain. Lastly, polymeric micelles may reduce the self-aggregation of polyene antibiotics, key membrane-acting drugs used to combat life-threatening systemic fungal diseases. In this way, they may reduce its dose-limiting toxicity without a loss of antifungal activity.

Preparation of Nanoparticles[8]

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: Size of nanoparticle required; inherent properties of the drug, e.g., aqueous solubility and stability; surface characteristics such as charge and permeability; degree of biodegrability, biocompatibility and toxicity, drug release profile desired; and Antigenicity of the final product. Nanoparticles have been prepared most frequency by three methods; (1) dispersion of preformed polymers; (2) polymerization of monomers; and (3) ionic gelation or coacervation of hydrophilic polymers.

Dispersion of preformed polymers[9, 10]
Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticle from poly (lactic acid) (PLA); poly (D,L-glycolide),PLG; poly (D,L-lactide-co-glycolide) (PLGA) and poly(cyanoacrylate) (PCA), This technique can be used in various ways as described below.

Solvent evaporation method[11]
In this method, the polymer is dissolved in an organic as solvent such as dichloromethane, chloroform or ethyl acetate which is also used the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agents to form an oil in water (o/w) emulsion. After the formation of stable emulsion, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.

Polymerization method[12, 13, 14]
In this method, monomers are polymerized to form nanoparticle in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles.

Coacervation or ionic gelation method[15]
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 nanoparticles by ionic gelation. In this method, positively charged amino-group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer.

Evaluation of Nanoparticles
Drug Entrapmaent Efficiency[16]
The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 5°c. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium.

$$\text{Drug Entrapment efficiency (\%)} = \frac{\text{Amount of released from the lysed nanoparticle}}{\text{Amount of drug Initially taken to prepare the nanoparticles}} \times 100$$

Particle Shape[17]
The nanoparticles were subjected to microscopic examination (SEM) for characterization size. The nanosuspension was characterized by SEM before going for evaluation; the nanosuspension was lyophilized to form solid particles. The solid particles were coated with platinum alloy using a sputter coater.

Particle size[18]
Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

Zeta potential[19]
The Zeta potential of a nanoparticle is commonly used to characterized the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the

composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (±) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

Nanoparticle Properties and Safety[20, 21]

The nanoparticles are likely to be unsafe for the biological system. The research on toxicity of nanoparticles indicates that some of these products may enter the human body and become toxic at the cellular level in the tissues and organs. The impact of nanoparticles interactions with the body is dependent on their size, chemical composition, surface structure, solubility, shape and how the individual nanoparticles accumulate together. Due to small size and hence higher specific surface area of the nanoparticles, these can easily bind with the transport toxic pollutants, which when inhaled can cause a number of pulmonary disease in mammals. Inhaled nanoparticles have the ability to translate in the body as much the nanoparticles enter the body these can travel freely in the blood throughout the body and reach the organ like liver or brain. It can get deeper into the lungs and bloodstream may cross the blood brain barrier. Skin contact could easily occur during handling of the nanoparticles. Fullerencs and bucky balls, which are known to attract electrons, cause generation of damaging free radicals. Nan toxicity studies of carbon-based materials as well as quantum dots have been conducted. Literature shows that low-solubility ultrafine particles are more toxic than larger particles on a mass for mass basis.

Applications of Nanoparticles

Tumor targeting using Nanoparticulate delivery system[22]

The rational of using nanoparticles for tumor targeting is based on (1) nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active nanoparticles. (2) Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ. Verdun et al demonstrated in mice treated with doxorubicin incorporated into poly (isohexylcynoacrylate) nanospheres that higher concentration of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

Nanoparticles for Gene delivery[23]

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.

Nanotechnology in Medicine Application: Anti-Microbial Techniques[24]

One of the earliest nanomedicine applications was the use of nanocrystalline silver which is as an antimicrobial agent for the treatment of wounds, A nanoparticle cream has been shown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection.

Burn dressing that is coated with nanocapsules containing antibotics. If a infection starts the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibotics. This allows much quicker treatment of an infection and reduces the number of times a dressing has to be changed. A welcome idea in the early study stages is the elimination of bacterial infections in a patient within minutes, instead of delivering treatment with antibiotics over a period of weeks.

Nanotechnology in Medicine Application: Cell Repair

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. Read about design analysis for one such cell repair nanorobot in this article: The Ideal Gene Delivery Vector: Chromallocytes, Cell Repair Nanorobots for Chromosome Repair Therapy.

Nanotechnology in Medicine: Company Directory

Company	Product
BioDelivery_Sciences	Oral drug delivery of drugs encapuslated in a nanocrystalline structure called a cochleate
CytImmune	Gold nanoparticles for targeted delivery of drugs to tumors
Invitrogen	Qdots for medical imaging
Smith_and_Nephew	Antimicrobial wound dressings using silver nanocrystals
Luna_Inovations	Bucky balls to block inflammation by trapping free radicals
NanoBio	Nanoemulsions for nasal delivery to fight viruses (such as the flu and colds) or through the skin to fight bacteria
NanoBioMagnetics	Magnetically responsive nanoparticles for targeted drug delivery and other applications

CONCLUSION

Nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biological active substance into promising deliverable drugs. Generally nanoparticle have relatively higher intracellular uptake compared to microparticles and available to a wide range of biological targets due to their small size and relative mobility.

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