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NANOPARTICLES AS DRUG DELIVERY SYSTEMS – AN OVERVIEW

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ABSTRACT

One has to scan and focus on creativity of medicine in any form by using a suitable drug with mitigated side effects and should possess better therapeutic activity for the benefit of patients. Many dosage forms have been available with different particle size but this paper emphasis and congents on nanotechnology to overcome the problems of many conventional dosage forms. These particles plays a significant role in treatment of various diseases such as HIV, Diabetes, Obesity, Glaucoma, Leukemia's and many other disorders. The intended drug delivery system can be achieved by converting the particles into nanosize such as the nanocapsules, nanotubes, nanocrystals, polymeric nanoparticles and many more types of preprations which can bring a tremendous change and efficient remedy in many other conventional drug treatment methods.

INTRODUCTION:

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.

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In recent years, biodegradable polymeric nanoparticles, 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[1]. The wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment, and prevention. The iron oxide nanocrystals, cadmium selenide nanocrystals and carbon fullerene nanoparticle which are representative of the broad spectrum of nanoparticle presently being used by industry[2,3]. 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. Nanoparticles basically, help to increase the stability of drugs/proteins and possess useful controlled release properties[4]. Nanocrystals and other nanoparticles have been receiving a lot of attention recently and their utilization in cancer therapeutics is becoming a growing industry. The recent Food and Drug Administration approval of Abraxane (ABI-007), an albumin-taxol nanoparticle for the treatment of breast cancer which brought a tremendous development of other nanoscale drug delivery devices with the aim of landing more of a drug onto the target tissue and less onto healthy tissues. Here, we discuss the mechanism of nanoparticle drug delivery[5].

Characteristics of Nano-particles in Drug Delivery System

Nanomaterials fall into a size range similar to proteins and other macromolecular structures found inside living cells. As such, nanomaterials are poised to take advantage of existing cellular machinery to facilitate the delivery of drugs [6, 7]. Nanoparticles containing encapsulated, dispersed, absorbed or conjugated drugs have unique characteristics that can lead to enhanced performance in a variety of dosage forms. When formulated correctly, drug particles are resistant to settling and can have higher saturation solubility, rapid dissolution and enhanced adhesion to biological surfaces, thereby providing rapid onset of therapeutic action and improved bioavailability. In addition, the vast majority of molecules in a nanostructure reside at the particle surface, which maximizes the loading and delivery of cargos, such as therapeutic drugs, proteins and polynucleotides, to targeted cells and tissues. Highly efficient drug delivery, based on nanomaterials, could potentially reduce the drug dose needed to achieve therapeutic benefit, which, in turn, would lower the cost and/or reduce the side effects associated with particular drugs. Furthermore, Nanoparticles size and surface characteristics can be easily manipulated to achieve both passive and active drug targeting. Site-specific targeting can be achieved by attaching targeting ligands, such as antibodies or aptamers, to the surface of particles, or by using guidance in the form of magnetic Nanoparticles. Nanoparticles can also control and sustain release of a drug during transport at the site of localization, altering drug distribution and subsequent clearance of the drug in order to improve therapeutic efficacy and reduce side effects. Nanotechnology could be strategically implemented in new developing drug delivery systems that can expand drug markets. Such a plan would be applied to drugs selected for full-scale development based on their safety and efficacy data, but which fail to reach clinical development because of poor bio-pharmacological properties, for example, poor solubility or poor permeability across the intestinal epithelium, situations that translate into poor bioavailability and undesirable pharmacokinetic properties. The new drug delivery methods are expected to enable pharmaceutical companies to reformulate existing drugs on the market, thereby extending the lifetime of products and enhancing the performance of drugs by increasing effectiveness, safety and patient adherence, and ultimately reducing healthcare costs.

CLASSIFICATION

Nanoparticles are particles which are between 1 and 100 nanometers in size. Based on preparation methods the nano particles are generally classified into two major types [8]

- **Nanocapsules: -** The nanocapsules are vesicular systems which are made up of the polymeric membranes in which the inner core is encapsulated at the nanoscale level. The nanocapsules are generally made up of nontoxic polymer.
- **Nanospheres: -** Nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

NANOTUBE

Carbon nanotubes also known as buckytubes are allotropes of carbon with a cylindrical nanostructure. Nanotubes have been constructed with length-to-diameter ratio of up to 132,000,000:1, which is significantly larger than any other material. They may also have applications in the construction of body armor. They exhibit extraordinary strength and unique electrical properties, and are efficient thermal conductors. Chemical bonding in nanotubes is described by applied quantum chemistry, specifically, orbital hybridization. The chemical bonding of nanotubes is composed entirely of sp2 bonds, similar to those of graphite [17]. These bonds, which are stronger than the sp3 bonds found in diamonds, provide nanotubules with their unique strength. Moreover, nanotubes naturally held together by Van der Waals forces.

NANOWIRE

A nanowire is a nanostructure, with the diameter of the 10^{-9} nanometers. Alternatively, nanowires can be defined as structures that have a thickness or diameter constrained to tens of nanometers or less and an unconstrained length. At these scales, quantum mechanical effects are important — which coined the term "quantum wires". Many different types of nanowires exist, including

metallic (e.g., Ni, Pt, Au), semiconducting (e.g., Si, InP, GaN, etc.), and insulating (e.g., SiO2, TiO2). Molecular nanowires are composed of repeating molecular units either organic (e.g. DNA) or inorganic (e.g. Mo6S9-xIx).The nanowires could be used, in the near future, to link tiny components into extremely small circuits. Using nanotechnology, such components could be created out of chemical compounds.

NANOCRYSTALS

Nanocrystal is any nanomaterial with dimension less than 100nm and that is single crystalline. More properly, any material with a dimension of less than 1 micrometre, i.e., 1000 nanometers, should be referred to as a nanoparticle, not a nanocrystal. Crystalline nanoparticles provide single-domain crystalline systems that can be studied to provide information that can help explain the behavior of macroscopic samples of similar materials, without the complicating presence of grain boundaries and other defects. Semiconductor nanocrystals in the sub-10nm size range are often referred to as quantum dots.

NANOBOTS

Nanorobotics is the technology of creating machines or robots at or close to the microscopic scale of a nanometer (10^{-9} meters). More specifically, nanorobotics refers to the still largely hypothetical nanotechnology engineering discipline of designing and building nanorobots, devices ranging in size from 0.1-10 micrometers and constructed of nanoscale or molecular components.

Potential applications for nanorobotics in medicine include early diagnosis and targeted drug-delivery for cancer, biomedical instrumentation surgery, pharmacokinetics monitoring of diabetes, and health care. In such plans, future medical nanotechnology is expected to employ nanorobots injected into the patient to perform work at a cellular level. Such nanorobots intended for use in medicine should be non-replicating, as replication would needlessly increase device complexity, reduce reliability, and interfere with the medical mission. Instead, medical nanorobots are posited to be manufactured in hypothetical, carefully controlled nanofactories in which nanoscale machines would be solidly integrated into a supposed desktop-scale machine that would build macroscopic products.

Fullerenes: A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buckyballs, and cylindrical ones are called carbon nanotubes or buckytubes. Fullerenes are similar in structure to the graphite, which is composed of stacked grapheme sheets of linked hexagonal rings, additionally they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules. Buckyball clusters or buckyballs composed of less than 300 carbon atoms are commonly known as endohedral fullerenes and include the most common fullerene, buckminsterfullerene, C60. Megatubes are larger in diameter than nanotubes and prepared with walls of different thickness which is potentially used for the transport of a variety of molecules of different sizes (Mitchell et al., 2001). Nano “onions” are spherical particles based on multiple carbon layers surrounding a buckyball core which are proposed for lubricants (Sano et al., 2001). These properties of fullerenes hold great promise in health and personal care application [8].

Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are generally recognized as safe to carry both hydrophilic and hydrophobic molecules through liposomes. The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes. Liposomes can vary in size, from 15 nm up to several μm and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes (multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) depending on their size range. The unique structure of liposomes, a lipid membrane surrounding an aqueous cavity, enables them to carry both hydrophobic and hydrophilic compounds without chemical modification. In addition, the liposome surface can be easily functionalized with ‘stealth’ material to enhance their in vivo stability or targeting ligands to enable preferential delivery of liposomes. These versatile properties of liposomes made them to be used as potent carrier for various drugs like antibacterials, antivirals, insulin, antineoplastics and plasmid DNA.

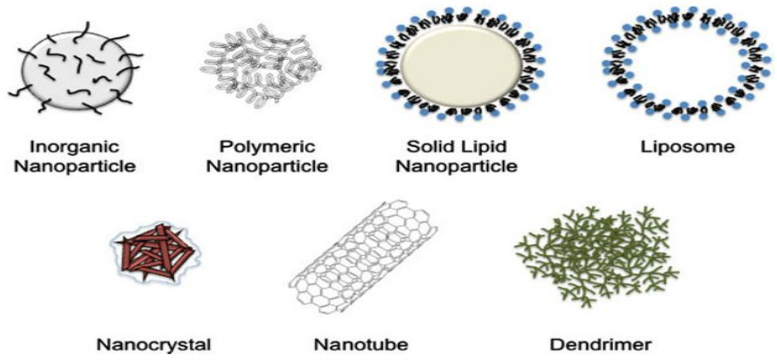

Fig 1: various forms of nano preparations [4]

Fullerenes composition	Application
Fullerene (C_{60}) 34 methyl radicals	Free radicals and oxidative stress
Fullerene (C_{60})	HIV proteases
C3-Fullero-tris-methanodicarboxylic acid	Apoptosis of neuronal cells
Carboxyfullerene	Apoptosis of hepatoma cells
Metallofullerol	Leukemia and bone cancer

Table 1: Biomedical application of fullerenes [8].

Liposome composition	Drug
1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol	Polymyxin B
Hydrogenated Soya phosphatidylcholine (PC) and cholesterol	Ampillicin
Phosphatidylcholine, cholesterol and Phosphatidylinositol	Netilmicin
Phosphatidyl glycerol, phosphatidyl choline and cholesterol	Streptomycin
Stearylamine (SA) and dicetyl phosphate	Zidovudine
Hepatically targeted liposomes	Insulin

Table 2: Biomedical application of Liposomes [8].

Superparamagnetic nanoparticles composition	Application
SPIONs coated with organic molecules showing an overall median diameter of less than 50–160 nm	MRI contrast agents for detecting liver tumors.
Superparamagnetic iron oxide nanoparticles	Identify dangerous arteriosclerotic plaques by MRI
Colloidal dispersions of superparamagnetic (subdomain) iron oxide nanoparticles	Magnetic fluid hyperthermia (MFH) in cancer treatment
Nanosized superparamagnetic nanoparticles (Fe O) coated with the multivalent cationic agent (PEI)	Purification of plasmid DNA from bacterial cells

Table 3: Biomedical application of super paramagnetic nanoparticles[15].

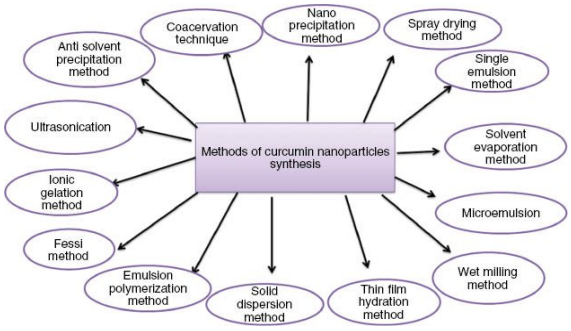

Fig 2:Methods for synthesis of Nanoparticles [10]

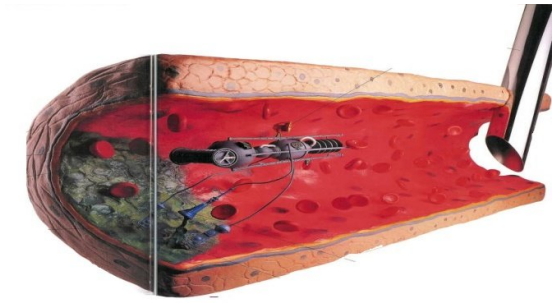

Fig 3: Nano robot [11]

Superparamagnetic nanoparticles

Superparamagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5–100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. The main advantages of superparamagnetic nanoparticles are that they can be visualized in magnetic resonance imaging (MRI) due to their paramagnetic properties; they can be guided to a location by the use of magnetic. Superparamagnetic nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials (silica, gold) and organic (phospholipids, fatty acids, polysaccharides, peptides or other surfactants and polymers). Red blood cells coating to nanoparticles can be effective in preventing the immune system adverse reactions. [7]

Preparation of Nanoparticles

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 frequently by three methods:-

- Dispersion of preformed polymers
- Polymerization of monomers
- Ionic gelation or coacervation of hydrophilic polymers.

Solvent evaporation method

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 oil in water (o/w) emulsion [10, 11]. 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.

Coacervation or ionic gelation method

The preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. 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.

Dispersion of preformed polymers

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).

Polymerization method

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.

Evaluation of Nanoparticles

The various evaluation parameters are available for the determination of the efficacy and safety of the prepared nanoparticle dosage form which are as described below: -

Drug Entrapmaent Efficiency

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.

SPECTROSCOPIC METHODS [12]

There are various spectroscopic methods available for the analysis of the nanoparticles. The spectroscopic techniques which provide information on nanoparticle size and also offer a quick method to aid in the optimization of particle size and buffer pH. The various types of the spectroscopic methods used in evaluation of nanoparticles are:-

- Transmission electron microscopy (TEM): - Easier method & Permits differntiation among nanocapsule & nanoparticle.
- FTIR spectroscopy: - To monitor and chatacterize gold nanoparticle conjugated systems.
- UV-Visible spectroscopy: - Provide information about the nanoparticle size in the conjugated systems.

Particle Shape

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.[15,16,17]

Particle size

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). [18, 19]

Zeta potential

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. [20]

Surface Hydrophobicity

The measurement of hydrophobicity is the important evolution parameter in which provides

information about the interaction of the nanoparticles with the biological environment. The generally used methods for the estimation of hydrophobicity:-Hydrophobic interaction chromatography, Two-phase partition. Contact angle measurement

APPLICATIONS

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.

LIMITATIONS

Thus, the nanoparticles has many advantages compared to the conventional dosage form it as possess some of the disadvantages at the movement due to nanoparticles might become dangerous for humans, even nanoparticles that naturally occur in our body can have a serious effect on both our short term and long term health. If nanomedicine was expanded to nanorobotics, then we would need to consider the possible effects of a glitch in the programming, and how sever the effects must be. This reminds us that before nanomedicine can be used extensively, it will need to go through a rigorous process of testing to make sure it doesn't do more harm than good. Some of the other major limitations of nanoparticles are: -

- Very costly formulation with no low yield.
- Reduced ability to adjust the dose.
- Highly sophisticated technology, which requires skills to manufacture.
- Stability of dosage form is big issue owing to its nano - size.

FUTURE SCOPE [11]

Nanoscience or nanotechnology that promises to hold the key to overcoming some of humanity's challenges. By engineering nanomedicine may help in diagnosing diseases at an early stage in order to provide optimal treatment to patients. Single cell detection can be achieved through nanotechnology. In the past several decades, it is been able to increase the sensitivity of our imaging techniques, by a variety of means. Nanotechnology has inevitably given birth to molecular imaging (e.g. PET, molecular magnetic resonance imaging, etc.). A new drug-delivery system developed by nanotechnology researchers promises to solve the challenge of the poor water solubility of today's most promising anti-cancer drugs and thereby increases their effectiveness. Another invention as a result of nanotechnology has been the use of nanoemulsions to help treat cystic fibrosis. Those who suffer with cystic fibrosis get bacterial infections in their lungs and through the use of these nanoemulsions these bacteria can be killed thus leading to an improved way of life. Nanotechnology should also be applied to weight loss and body-image enhancers. Advances in nanosensors, nanodevices, genomics and bioinformatics along with selective drug delivery and regenerative medicine would thrust healthcare beyond bounds mankind could actually imagine, especially in development of personalized medicine. In terms of the world's ever increasing energy requirements - a diminishing source of fossil fuels and threats of major climate changes due to global warming has called immediate attention to deliver long term solutions and alternative forms of energy. Nanoporous membranes or nanofibers can be designed to remove organic/inorganic salts, pollutants and various biological contaminants from any available source of water. Thus, the importance of nanotechnology can vary in fields as diverse as materials engineering, medicine, information technology, defense, environmental remediation, energy production, and agricultural technology upholding the need for more exploration.

With respect to technological applications, there are currently many nanoparticle research projects devoted to:

(i) Developing means of combating cancer by developing nanomaterials like nanoshells and nanopolymers for targeted drug delivery;
(ii) Engineering materials to replace diseased organs, repair nerve damage, and improve prosthetic limbs;
(iii) Building cost-effective solutions for water purification.

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