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Nanoparticles as Drug Delivery Systems

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Abstract
For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Nanoparticles (NP) are defined as particles with a diameter smaller than 100 nm, are increasingly used in different applications, including drug carrier systems and to pass organ barriers such as the blood-brain barrier. Because of their unique properties Nanocrystals (quantum dots) and other nanoparticles (gold colloids, nanobars, dendrimers and nanoshells) have been receiving a lot of attention for potential use in Therapeutics, and therapeutics drug discovery. The use of nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Currently many substances are under investigation for drug delivery and more specifically for cancer therapy. Interestingly pharmaceutical sciences are using nanoparticles to reduce toxicity and side effects of drugs and up to recently did not realize that carrier systems themselves may impose risks to the patient. The present paper deals with all these aspects of NP.
Key-words: *Nanoparticles, Types, Drug delivery system*

INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon 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 carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes [1-4]. The reason why nanoparticles (NP) are attractive for such purposes is based on their important and unique features, such as their surface to mass ratio, which is much larger than that of other particles and materials, allowing for catalytic promotion of reactions, as well as their ability to adsorb and carry other compounds.

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties 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. 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 [5-8].

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.

TYPES OF NANOPARTICLES

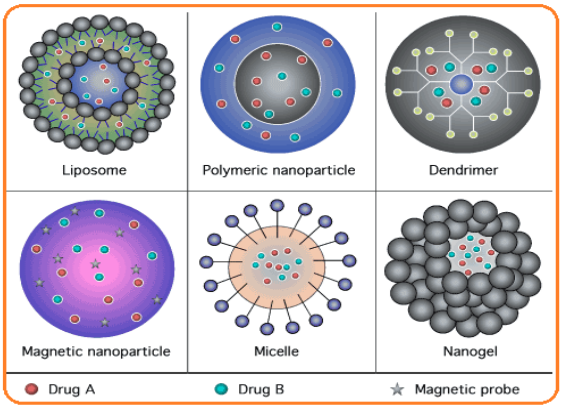

Figure 1: Schematic diagram representing the various types of nanoparticle use to develop MTIs. (1A) Liposome; (1B) Polymeric nanoparticle; (1C) Dendrimer; (1D) Magnetic nanoparticle; (1E) Micelle; (1F) Nanogel.

Liposomes

Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are characterized in terms of size, surface charge and number of bilayers. It exhibits number of advantages in terms of amphiphilic character, biocompatibility, and ease of surface modification rendering it a suitable candidate delivery system for biotech drugs. Liposomes have been used successfully in the field of biology, biochemistry and medicine since its origin. These alter the pharmacokinetic profile of loaded drug to a great extent especially in case of proteins and peptides and can be easily modified by surface attachment of polyethylene glycol-units (PEG) making it as stealth liposomes and thus increase its circulation half-life[9-11].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery. Main reason for their development is the combination of advantages from different carriers systems like liposomes and polymeric nanoparticles. SLN have been developed and investigated for parenteral , pulmonal and dermal application routes. Solid Lipid Nanoparticles consist of a solid lipid matrix, where the drug is normally incorporated, with an average diameter below 1 µm. To avoid aggregation and to stabilize the dispersion, different surfactants are used that have an accepted GRAS (Generally Recognized as Safe) status. SLN have been considered as new transfection agents using cationic lipids for the matrix lipid composition. Cationic solid lipid nanoparticles (SLN) for gene transfer can be formulated using the same cationic lipids as for liposomal transfection agents [12-17].

Polymeric nanoparticles

In comparison to SLN or nanosuspensions polymeric nanoparticles (PNPs) consists of a biodegradable polymer. The advantages of using PNPs in drug delivery are many, being the most important that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated in large quantities by a multitude of methods. Also, polymeric nanoparticles may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location[12-17]. Polymeric nanoparticles are a broad class comprised of both vesicular systems (nanocapsules) and matrix systems (nanospheres).

Nanocapsules

Nanocapsules are systems in which the drug is confined to a cavity surrounded by unique polymeric membrane whereas nanospheres are systems in which the drug is dispersed throughout the polymer matrix. The various natural polymers like gelatin, albumin and alginate are used to prepare the nanoparticles; however they have some inherent disadvantages like poor batch-to- batch reproducibility, prone to degradation and potential antigenicity. Synthetic polymers used for nanoparticles preparation may be in the form of preformed polymer e.g. polyesters like polycaprolactone (PCL), poly lactic acid (PLA) or monomers that can be polymerized *in situ* e.g. poly alkyl cyanoacrylate. The candidate drug is dissolved, entrapped, attached or encapsulated throughout or within the polymeric shell/matrix. Depending on the method of preparation, the release characteristic of the incorporated drug can be controlled. Polymeric nanoparticulate systems are attractive modules for intracellular and site specific delivery. Nanoparticles can be made to reach a target site by virtue of their size and surface modification with a specific recognition ligand. Their surface can be easily modified and functionalized [12-17].

Nanospheres

From its definition nanospheres are considered as a matrix system in which the matrix in uniformly dispersed. These are spheric vesicular systems.

Dendrimers

Dendrimers, a unique class of polymers, are highly branched macromolecules whose size and shape can be precisely controlled. Dendrimers are fabricated from monomers using either convergent or divergent step growth polymerization. The well-defined structure, mono dispersity of size, surface functionalization capability, and stability are properties of dendrimers that make them attractive drug carrier candidates. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation. Dendrimers are being investigated for both drug and gene delivery, as carriers for penicillin, and for use in anticancer therapy [18-23].

Nanotube

Carbon nanotubes (CNTs; 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. These cylindrical carbon molecules have novel properties which make them potentially useful in many applications in nanotechnology, electronics, optics, and other fields of materials science, as well as potential uses in architectural fields. They may also have applications in the construction of body armor. They exhibit extraordinary strength and unique electrical properties, and are efficient thermal conductors. Nanotubes are members of the fullerene structural family, which also includes the spherical bucky balls. The ends of a nanotube may be capped with a hemisphere of the bucky ball structure. Their name is derived from their size, since the diameter of a nanotube is on the order of a few nanometers (approximately 1/50,000th of the width of a human hair), while they can be up to 18 centimeters in length (as of 2010). Nanotubes are categorized as single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs).Chemical bonding in nanotubes is described by applied quantum chemistry, specifically, orbital hybridization. The chemical bonding of nanotubes is composed entirely of sp^2 bonds, similar to those of graphite. These bonds, which are stronger than the sp^3 bonds found in diamonds, provide nanotubules with their unique strength. Moreover, nanotubes naturally align themselves into "ropes" held together by Van der Waals forces.

Nanowire

A nanowire is a nanostructure, with the diameter of the order of a nanometer (10^{-9} meters). 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., SiO_2, TiO_2). Molecular nanowires are composed of repeating molecular units either organic (e.g. DNA) or inorganic (e.g. $Mo_6S_{9-x}I_x$).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 at least one dimension $\leq$ 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. For example, any particle which exhibits regions of crystallinity should be termed nanoparticle or nanocluster based on dimensions. These materials are of huge technological interest since many of their electrical and thermodynamic properties show strong size dependence and can therefore be controlled through careful manufacturing processes. Crystalline nanoparticles are also of interest because they often 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. Crystalline nanoparticles made with zeolite are used as a filter to turn crude oil onto diesel fuel at an ExxonMobil oil refinery in Louisiana, a method cheaper than the conventional way. A layer of crystalline nanoparticles is used in a new type of solar panel named SolarPly made by Nanosolar. It is cheaper than other solar panels, more flexible, and claims12% efficiency. (Conventionally inexpensive organic solar panels convert 9% of the sun's energy into electricity.) Crystal tetrapods 40 nanometers wide convert photons into electricity, but only have 3% efficiency. (Source: National Geographic June 2006) The term NanoCrystal is a registered trademark of Elan Pharma International Limited (Ireland) used in relation to Elan's proprietary milling process and nanoparticulate drug formulations.

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 Nano robots injected into the patient to perform work at a cellular level. Such Nano robots 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. The most detailed theoretical discussion of nanorobotics, including specific design issues such as sensing, power communication, navigation, manipulation, locomotion, and onboard computation, has been presented in the medical context of nanomedicine by Robert Freitas. Some of these discussions remain at the level of unbuildable generality and do not approach the level of detailed engineering.

Nanoparticles as drug carrier vehicle

- It helps in improving solubility and bioavailability, reducing toxicity, enhancing release and providing better formulation opportunities for drugs.
- Major advantages of nano-sizing include (i) increased surface area, (ii) enhanced solubility, (iii) increased rate of dissolution, (iv) increased oral bioavailability, (v) more rapid onset of therapeutic action, (vi) less amount of dose required, (vii) decreased fed/fasted variability, and (viii) decreased patient-to-patient variability.
- 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.
- 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.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
- Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and are available to a much wider range of biological targets due to their small size and relative mobility. 100 nm nanoparticles had a 2.5 fold greater uptake than 1 μm microparticles, and 6 fold greater uptake than 10 μm microparticles.
- Nanotechnology offered numerous smart materials that are used for tissue repair and replacement, implant coatings, tissue regeneration scaffolds, structural implant materials, bone repair, bioresorbable materials, some implantable devices (sensory aids, retina implants etc.), surgical aids, operating tools, and smart instruments.

Nanoparticles Applications

Healthcare/medical [24-38]

- Targeted drug delivery
- Alternative drug and vaccine delivery mechanisms (e.g. inhalation, oral in place of injection).
- Bone growth promoters
- Cancer treatments
- Biocompatible coatings for implants
- Sunscreens (e.g. using ZnO and TiO2) / cosmetics
- Bio labeling and detection (e.g. using Au)
- Carriers for drugs with low water solubility
- Fungicides (e.g. using ZnO)
- MRI contrast agents (e.g. using superparamagnetic iron oxide)
- New dental composites
- Biological binding agents (e.g. for high phosphate levels)
- Antiviral, antibacterial (e.g. Ag), anti-spore non-chemical creams and
- powders (using surface tension energy on the nanoscale to destroy biological particles)

CONCLUSION

Nanotechnology is expected to bring a fundamental change in manufacturing in the next few years and will have an enormous impact on life sciences, including drug delivery, diagnostics, nutraceuticals and production of biomaterials. Engineered nanoparticles (NP) (<100 nm) are an important tool to realize a number of the above applications. The use of Nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. For decades pharmaceutical sciences have been using nanoparticles to reduce toxicity and side effects of drugs. The nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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