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A REVIEW ON NANOPARTICLES

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ABSTRACT

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. It is a colloidal carrier, Particulate dispersions or solid particles with a size in the range of 10-100nm, in which the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix physically or chemically.

Key words: Nanoparticle, Nanoclusters, Nanospheres

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.

Nano capsules 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 fora prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes.

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 [1].

DEFINITION

It is a colloidal carrier, Particulate dispersions or solid particles with a size in the range of 10-100nm, in which the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix physically or chemically [2].

1st generation= ≤ 100 nm

2nd generation= ≤ 10 nm

Lower limit = 1 nm

CHARACTERISTICS OF NANO PARTICLES

- ✓ Self reassembling capacity
- ✓ Hole free structure
- ✓ High conduction
- ✓ Formation of new sub componentson rearranging

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CUTANEOUS EXPOSURE

Titanium dioxide (TiO2) is a substance contained in sunscreens2. Lademann*et al.* (1999) did not observe significant absorption of coated TiO2 nanocrystals (17 nm), beyond the stratumcorneum of the skin of human volunteers, except for a small quantity (< 1%), which had penetrated the hair follicles. Since the follicles are also isolated from livingtissue by a stratum corneum, the authors conclude that cutaneous absorption of TiO2 isabsent in living cutaneous tissues.

Schulz *et al.* (2002) did not observe cutaneous absorption of nanocrystalline TiO2 in the skin layers below the corneum stratum in humans, after testing the application of three formulations with different particulate characteristics (T805: 20 cubic nm; EusolexT200: 10-15 cubic nm, agglomerating into needle-shaped 100 nm nanoparticles; TioveilAQ-10P: 100 nm, in the form of coated needles of Al2O3 and SiO2 and particulate forms of TiO2; variable affinities for water and oil; coated or not). These results suggest a low probability of absorption of nanoparticulate TiO2 beyond the dermis and its transport to the bloodstream.

CLASSIFICATION

BASED ON NANO PARTICLES FOR DRUG DELIVERY

- ❖ Metal based nano particles
- ❖ Lipid based nano particles
- ❖ Polymer based nano particles
- ❖ Biological based nano particles

BASED ON DIMENSIONS

1) In one dimension
   - Thin films
   - Manufactured surfaces
2) In two dimensions
   - Carbon nano tubes
3) In three dimensions
   - Fullerenes
   - Dendrimers
   - Quantum dots

QUANTUM DOTS

Enhance imaging during surgical removal of lymph nodes associated with cancero

- ✓ Nanocrystals are Nanoscale crystals of semiconductor, insulators, metals magnetic materials.
- ✓ 1 to 10 nm in diameter
- ✓ Quantum dots have been called "artificial atoms".
- ✓ Used to
- ✓ Tag biological molecules
- ✓ Medical diagnostics,
- ✓ Targeted therapeutics,
- ✓ High-throughput drug screening.
- ✓ Direct imaging of cancer cells in degenerative eye

DENDRIMERS

Increasesthenumberof small branching molecules around central core molecule2-20 nanometers.

Core = amine core, sugars.

All core molecules share the characteristic of having multiple reaction sites that are identical.The core is mixed with an excess of the first monomer molecule which reacts with all of the core's reaction sites, giving rise to the first branches.

CARBON NANO TUBES

- Wound in a hexagonal network of carbon atoms,
- Hollow cylinders
- Diameters = 0.7 nm
- Each end can be opened or closed by a fullerene half-molecule.
- These Nanotubes - single layer (like a straw)
- several layers (poster rolled tube) [2]

Method of Preparation of Nanoparticles

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers [5]. The selection of matrix materials is dependent on many factors including:

- ➢ size of nanoparticles required
- ➢ Inherent properties of the drug

e.g., aqueous solubility and stability

- ➢ Surface characteristics such as charge and permeability
- ➢ Degree of biodegradability, biocompatibility and toxicity
- ➢ Drug release profile desired
- ➢ Antigenicity of the final product

Nanoparticles have been prepared most frequency by three methods:

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

However, other methods such as supercritical fluid technology and particle replication in non-wetting templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry.

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Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles 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

In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as 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 agent to form 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 ultra-sonication may be employed [6].

Spontaneous emulsification or solvent diffusion method

This is a modified version of solvent evaporation method. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase [6].

Polymerization method

In this method, monomers are polymerized to form nanoparticles 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. Nanocapsule formation and their particle size depend on the concentration of the surfactants and stabilizers used [6-9].

Coacervation or ionic gelation method

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 nanoparticles 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 polyanionsodiumtripolyphosphate. In this method, positively charged amino group of chitosaninte racts with negative charged tripolyphosphateto form coacervates with a size in the range of nanometer. 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[1].

MECHANISMS REGULATING BODY DISTRIBUTION OIF NANO PARTICLES [10-14]

- Mono nuclear phagoositics system or reticuloendothelial system
- Tissular macrophages- MPS present at fixed site
- circulating monocytes- MPS circulating in blood stream
- Intravenously injected nanoparticles are extensively taken up by liver up to 90% &spleen 2-5%.
- Attachment of nanoparticles to macrophages is mediated through serum proteins called opsonins.
- Opsonins after adsorption onto the surface of the particles make any foreign material recognisable to the phagocytic cells of MPS.

SURFACE ENGINEERING OF NANO PARTICLES

To minimize opsonization and to achieve long circulating nanoparticles the following approaches are reported [6-8]

- bio-mimetic nanoparticles
- stericallystabilised nanoparticles

BIO-MIMETIC NANO PARTICLES

- Nanoparticles coated with sialic acids or polymers
- Prevents opsonin adsorption
- Protects against MPS phagocytosis

STERICALLY STABILISED NANO PARTICLES

Opsonization of nano particles can be prevented by:

- ✓ Coating with hydrophilic polymer
- ✓ Flexibility of the coating chains
- ✓ Molecular confirmations in aqueous solutions [6-8].

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Effect of Characteristics of Nanoparticles on Drug Delivery

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 the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles.

Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over micro particles as a drug delivery system. Generally nanoparticles have relatively higher intracellular uptake compared to micro particles and available to a wider range of biological targets due to their small size and relative mobility.

Drug loading [15-19]

Ideally, a successful nanoparticulate system should have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. Drug loading can be done by two methods:

• Incorporating at the time of nanoparticles production (incorporation method)

• Absorbing the drug after formation of nanoparticles by incubating the carrier with a concentrated drug solution (adsorption /absorption technique).

Drug release

To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on:

- Solubility of drug
- Desorption of the surface bound/adsorbed drug
- Drug diffusion through the nanoparticle matrix
- Nanoparticle matrix erosion/degradation; and
- Combination of erosion/diffusion process.

Applications of Nanoparticulate Delivery Systems

1) Tumor targeting using nanoparticulate delivery systems

The rationale of using nanoparticles for tumortargeting is based on

- Nanoparticles will beable to deliver a concentrate dose of drug in thevicinity of the tumor targets via the enhancedpermeability and retention effect or activetargeting by ligands on the surface of nanoparticles.

- Nanoparticles will reduce thedrug exposure of health tissues by limiting drugdistribution to target organ.Verdun *et al* demonstrated in mice treated withdoxorubicin incorporated into poly (isohexylcyanoacrylate) nanopsheres that higher concentrations of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

2) Long circulating nanoparticles

To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth". Particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes [16-19].

Amajor breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time.

3) Reversion of multidrug resistance in tumour Cells

Anticancer drugs, even if they are located in the tumourinterstitium, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop mechanisms of resistance. These mechanisms allow tumours to evade chemotherapy. Multidrug resistance (MDR) is one of the most serious problems in chemotherapy. MDR occurs mainly due to the over expression of the plasma membrane pglycoprotein (Pgp), which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells.

4) Nanoparticles for oral delivery of peptides and proteins

Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes.

5) Targeting of nanoparticles to epithelial cells in the GI tract using ligands

Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism.

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The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism. Different lectins, such as bean lectin and tomato lectin, have been studied to enhance oral peptide adsorption. Vitamin B-12 absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis.

6) Absorption enhancement using non-specific interactions

In general, the gastrointestinal absorption of macromolecules and particulate materials involves either Para cellular route or endocytotic pathway. The Para cellular route of absorption of nanoparticles utilizes less than 1% of mucosal surface area. Using polymers such as chitosan, starch or poly (acrylate) can increase the Para cellular permeability of macromolecules.

Endocytotic pathway for absorption of nanoparticles is either by receptor-mediated endocytosis, that is, active targeting, or adsorptive endocytosis which does not need any ligands. This process is initiated by an unspecific physical adsorption of material to the cell surface by electrostatic forces such as hydrogen bonding or hydrophobic interactions.

7) Nanoparticles for gene delivery

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 [14-16].

8) *Nanoparticles for drug delivery into the brain*

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems.

It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the BBB.

Fig1. Nanoparticle

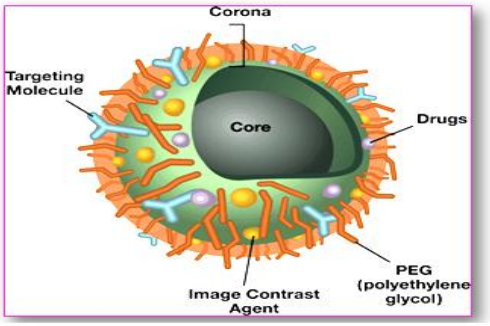

Figure 2. Nanospheres and Nanocapsules

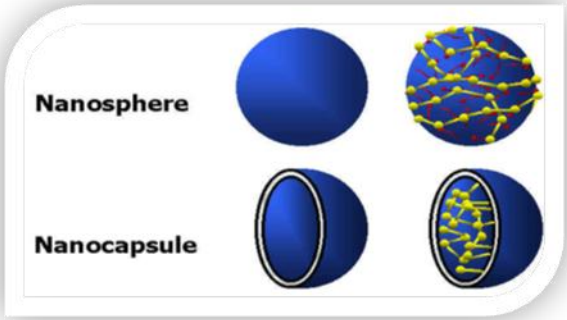

Figure 3. Nanocapsules

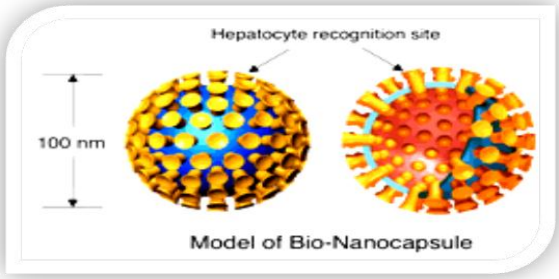

Figure 4. Inhalation

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Figure 5. Quantum Dots

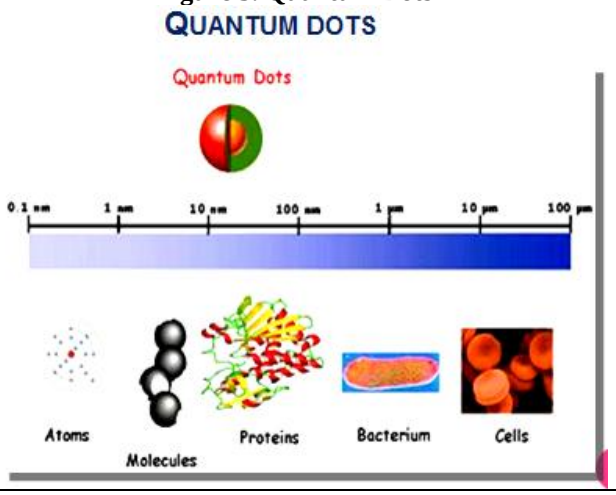


Figure 6. Dendrimers

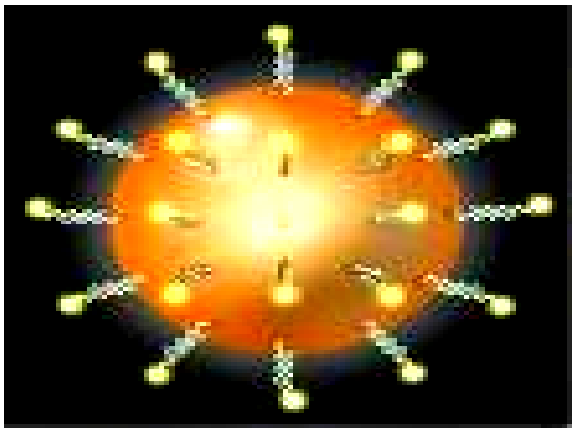


Figure 7. Carbon Nano Tubes

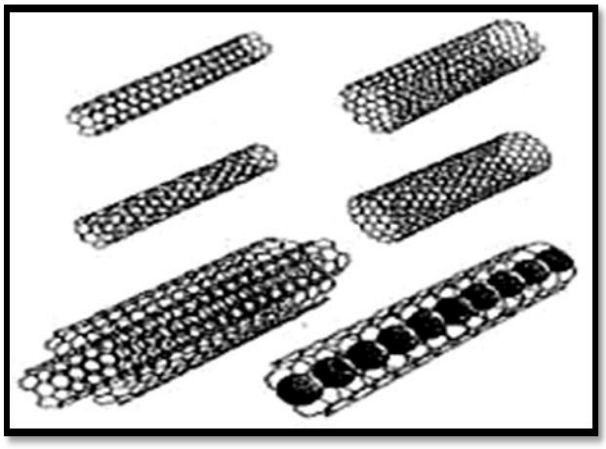


Figure 8. Heat Denaturation Process

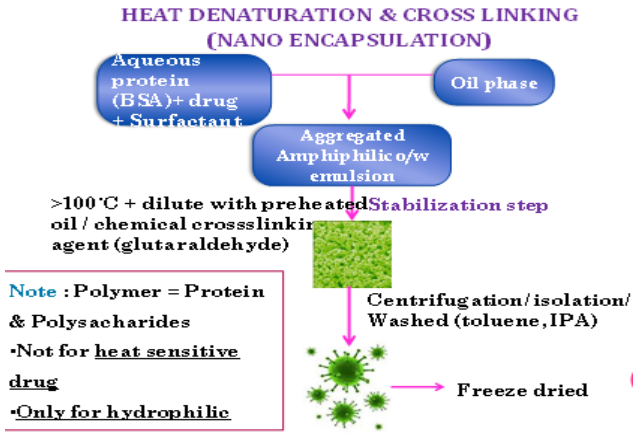


Figure 9. Solvation and Desolvation Method

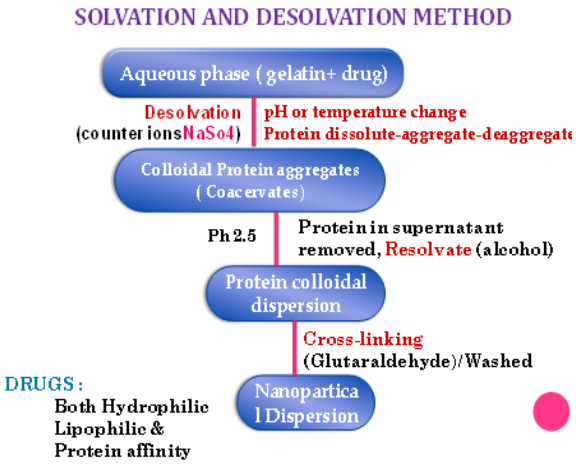
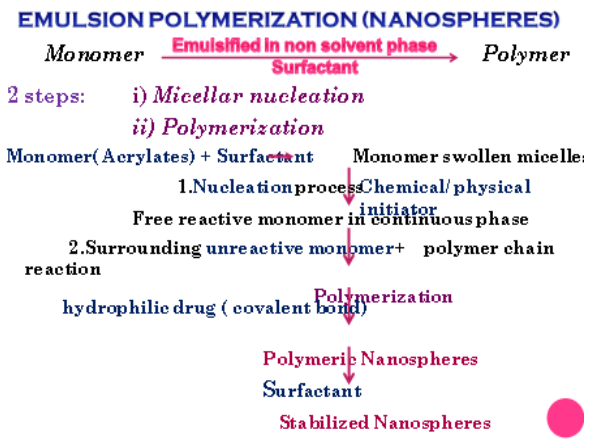


Figure 10. Emulsion Polymerization Method



CONCLUSION

The research hypothesis stated that if cells were treated with nanoparticles, the cell viability and morphology will be affected. The null hypothesis was accepted for all concentrations of graphite, titanium dioxide, and single walled carbon nanotubes on liver, neurons, heart, and skin cells. It was also accepted for multi walled carbon nanotubes on liver, neuron, and heart cells. The research hypothesis was supported for the low and high concentrations of multi walled carbon nanotubes on skin cells, but not for any other treatment. Those treatments showed a significant ability to encourage cell growth. High magnification of individual cells showed that nanoparticles did penetrate the cell wall and therefore affected the morphology.

The goal of this study (determine if nanoparticles have an effect on cells) was accomplished, and helped support that nanoparticles can be used in consumer products safely. The results showed that nanoparticles have no or positive effect on heart, liver, neuron, and skin cells. Other research on nanoparticles and their effect on living organisms showed detrimental effects. However, other studies used live organisms, such as mice, and tissues instead of cells. Also, the nanoparticles came in different states of matter.

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