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# NANOPARTICLES; A Review

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**Abstract:**

*Nanotechnology is related to design characterization, production and applications of structures, devices and systems by controlling shape and size at nanometer scale. Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers .Synthesis of nanoparticle done by different methods such as gas condestation* ***vacuum****, deposition and vaporization and other methods are involved. The Zeta potential of a nanoparticle is commonly used to characterized the surface charge property of nanoparticles. Particle size determines the in vivo distribution, biological fate, and toxicity and targeting ability of nanoparticle system. The advantages of using nanoparticles as a Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.*

**Key words**: *Nanoparticle, Polymers, Preparation, Synthesis, Characteristics, Evaluation.*

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## INTRODUCTION:

There is a great notice in the development of new biotechnological and nano biotechnological methods that can be used as either diagnostic or therapeutic equipment. Improving the efficiency of anticancer treatments is the goal of this research as it is also to minimize the distribution and toxic effects of these drugs in healthy tissues. There is a relatively recent boom in the improvement of nanobiological and nano technological platforms such as: polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanomaterials, super paramagnetic nanoparticles conjugated with DNA, RNA interference (RNAi), and antisense oligonucleotides (ASO). These nanotechnological platforms have diverse physical and chemical properties that give them with new biological distribution, availability and efficiency in anticancer treatment.

### Definitions

Important nano-definitions are described below:
**'Nanoscience'** can be defined as study of phenomenon and manipulation of materials at atomic and molecular scales.
**'Nanotechnology'** is related to design characterization, production and applications of structures, devices and systems by controlling shape and size at nanometer scale.
**'Pharmaceutical nanotechnology'**embraces applications of nanoscience to pharmacy as nanomaterials, and as devices like drug delivery, diagnostic, imaging and biosensor.
**Nanomedicine**'is defined as submicron size (<1um) modules, used for treatment, diagnosis, monitoring,and control of biological system.
Pharmaceutical nanotechnology has provided more fine-tuned diagnosis and fixed treatment of disease at a molecular level. Pharmaceutical nanotechnology is most innovative and highly specialized field, which will develop the pharmaceutical industry in near future. Pharmaceutical nanotechnology presents new opportunities to fight against many diseases. It helps in detecting the antigen associated with diseases such as cancer, diabetes mellitus, neurodegenerative diseases, as well as detecting the microorganisms and viruses associated with infections. It is expected that in next 10 years market will be filled with nanotechnology-devised medicine. [1-7]

## 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

(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, biocompatibility and toxicity;
(e) Drug release profile desired; and
(f) 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.
However, other methods such as supercritical fluid technology and particle replication in non-wetting templates (PRINT) 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.

### 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 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.[8-11]

### Polymerization method

In this method, monomers are polymerized to form nanoparticles in an aqueous solution . Drug is included 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 ultra-centrifugation 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 depends on the concentration of the surfactants and stabilizers used.[12]

## 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 control the drug loading, drug release and stability of nanoparticles. Many studies have established that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system. Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and available to a wider range of biological targets due to their small size and relative mobility. Desai et al found that 100 nm nanoparticles had a 2.5 fold greater uptake than 1 µm microparticles, and 6 fold greater uptake than 10 µm microparticles in a Caco-2 cell line. In a subsequent study, the nanoparticles penetrated throughout the submucosal layers in a rat in situ intestinal loop model, while microparticles were predominantly localized in the epithelial lining. It was also reported that nanoparticles can across the blood-brain barrier following the opening of tight junctions by hyper osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult-to-treat diseases like brain tumors . Tween 80 coated nanoparticles have been shown to cross the blood-brain barrier. In some cell lines, only submicron nanoparticles can be taken up efficiently but not the larger size microparticles . Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out . Smaller particles also have greater risk of aggregation of particles during storage and moving of nanoparticle dispersion. It is always a test to formulate nanoparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size. For instance, the rate of PLGA polymer degradation was found to increase with increasing particle size in vitro. It was thought that in smaller particles, degradation products of PLGA formed can spread out of the particles easily while in large particles, degradation products are more likely remained within the polymer matrix for a longer period to cause autocatalytic degradation of the polymer material. Therefore, it was hypothesized that larger particles will contribute to faster polymer degradation as well as the drug release. However, Panyam et al prepared PLGA particles with different size ranges and found that the polymer degradation rates in vitro were not substantially different for different size particles. Currently, the fastest and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).[13-14]

**Surface properties of nanoparticles**

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation . Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the in vivo fate of nanoparticles . Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as
it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs. Generally, it is IgG, compliment C components that are used for recognition of foreign substances, especially foreign macromolecules. Hence, to increase the likelihood of the success in drug targeting by nanoparticles, it is necessary to minimize the opsonization and to prolong the circulation of nanoparticles in vivo. This can be achieved by

(a) Surface coating of nanoparticles with hydrophilic polymers/surfactants;

(b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamine and polysorbate 80 (Tween 80). Studies show that PEG conformation at the nanoparticle surface is of

utmost importance for the opsonin repelling function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation whereas PEG surfaces in mushroom-like configuration were potent complement activators and favoured phagocytosis . The zeta potential of a nanoparticle is commonly used to characterise 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. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface [15-25].

## SYNTHESIS OF NANOMATERIAL

It is classified as bottom-up manufacturing which involves building up of the atom or molecular constituents as against the peak method which involves making smaller and smaller structures through design from the bulk material as exemplified by the semiconductor industry.

### Gas Condensation

Gas condensation was the first technique used to synthesize nanocrystalline metals and alloys. In this technique, a metallic or inorganic material is vaporized using thermal evaporation sources such as a Joule heated refractory crucibles, electron beam evaporation devices, in an atmosphere of 1-50 m bar. In gas evaporation, a high residual gas pressure causes the formation of ultra fine particles (100 nm) by gas phase collision. The ultra fiine particles are formed by collision of evaporated atoms with residual gas molecules. Gas pressures greater than 3 mPa (10 torr) are required. Vaporization sources may be resistive heating, high energy electron beams, low energy electron beam and inducting heating. Clusters form in the area of the source by homogenous nucleation in the gas phase grows by incorporation by atoms in the gas phase. It comprises of a ultra high vacuum (UHV) system fitted evaporation source, a cluster collection device of liquid nitrogen filled cold finger scrapper assembly and compaction device. During heating, atoms condense in the super saturation zone close to Joule heating device. The nano particles are separate by scrapper in the form of a metallic plate. Evaporation is to be done from W, Ta or Mo refractory metal crucibles. If the metals react with crucibles, electron beam evaporation technique is to be used. The method is extremely slow. The method suffers from limitations such as a source-precursor incompatibility, temperature ranges and dissimilar evaporation rates in an alloy. Alternative sources have been developed over the years. For instance, Fe is evaporated into an inert gas atmosphere. Through collision with the atoms the evaporated Fe atoms loose kinetic energy and condense in the form of small crystallite crystals, which collect as a loose powder. Sputtering or laser evaporation may be used in its place of thermal evaporation. Sputtering is a non-thermal process in which surface atoms are physically ejected from the surface by momentum transfer from an energetic bombarding kind of atomic/molecular size. Typical sputtering uses a glow discharge or ion beam. Interaction events which occur at and near the target surface during the sputtering process in magnetron sputtering has advantage over diode and triode sputtering. In magnetron sputtering, most of the plasma is confined to the near target region. Other alternate energy sources which have been successfully used to produce clusters or ultra fine particles are sputtering electron beam heating and plasma methods. Sputtering has been used in low pressure environment to produce a variety of clusters including Ag, Fe and Si.[26-27]

### Vacuum Deposition and Vaporization

Before proceeding to the other methods, it is important to understand the terms vacuum deposition and vaporization or vacuum evaporation. In vacuum deposition process, elements, alloys or compounds are vaporized and deposited in a vacuum . The vaporization source is the one that vaporizes materials by thermal processes. The process is carried out at pressure of less than 0.1 Pa (1 m Torr) and in vacuum levels of 10 to 0.1 MPa. The substrate temperature ranges from ambient to 500°C. The saturation or equilibrium vapor pressure of a material is defined as the vapor pressure of the material in equilibrium with the solid or liquid surface. For vacuum deposition, a reasonable deposition rate can be obtained if the vaporization rate is fairly high. A useful deposition rate is obtained at a vapour pressure of 1.3 Pa (0.01 Torr). Vapour phase nucleation can occur in dense vapour cloud by multi body collisions, the atoms are passed through a gas to provide necessary collision and cooling for nucleation. These particles are in the range of 1 to 100 nm and are called ultra fine particles or clusters. The advantages associated with vacuum deposition process are high deposition rates and economy. However, the deposition of many compounds is difficult. Nanoparticles produced from a supersaturated vapour are usually longer than the cluster.[28-30]

### Mechanical Attrition

Unlike many of the methods mentioned above, mechanical attrition produces its nanostructures not

by cluster assembly but by the structural decomposition of coarser grained structures as a result of plastic deformation. Elemental powders of Al and β-SiC were prepared in a high energy ball mill. More recently, ceramic/ceramic nanocomposite WC-14% MgO material has been fabricated. The ball milling and rod milling techniques belong to the mechanical alloying process which has received much attention as a powerful tool for the fabrication of several advanced materials. Mechanical alloying is a unique process, which can be carried out at room temperature. The process can be performed on both high energy mills, centrifugal type mill and vibratory type mill, and low energy tumbling mil.

High energy mills include:
Attrition Ball Mill
Planetary Ball Mill
Vibrating Ball Mill
Low Energy Tumbling Mill
High Energy Ball Mill

**Attrition Ball Mill**
The milling procedure takes place by a stirring action of a agitator which has a vertical rotator central shaft with horizontal arms (impellers). The rotation speed was later increased to 500 rpm. Also, the milling temperature was in greater control.

**Planetary Ball Mill**
Centrifugal forces are caused by rotation of the supporting disc and autonomous turning of the vial. The milling media and charge powder alternatively roll on the inner wall of the vial and are thrown off across the bowl at high speed (360 rpm).

**Vibrating Ball Mill**
It is used mainly for production of amorphous alloys. The changes of powder and milling tools are agitated in the perpendicular direction at very high speed (1200 rpm).

**Low Energy Tumbling Mill**
They have been used for successful preparation of mechanically alloyed powder. Theyare simple to operate with low operation costs. A laboratory scale rod mill was used to prepare homogenous amorphous Al30Ta70 powder by using S.S. cylinder rods. Single-phase amorphous powder of AlxTm100-x with low iron concentration can be formed by this technique.

**High Energy Ball Mill**
High-energy ball milling is an already established technology, however, it has been considered dirty because of contamination problems with iron. However, the use of tungsten carbide component and inert atmosphere and /or high vacuum processes has reduced impurity levels to within acceptable limits. Common drawbacks include low surface, highly poly disperse size distribution, and partially amorphous state of the powder. These powders are highly reactive with oxygen, hydrogen and nitrogen. Mechanical alloying leads to the fabrication of alloys, which cannot be produced by conventional techniques. It would not be possible to produce an alloy of Al-Ta, because of the difference in melting points of Al (933 K) and Ta (3293 K) by any conventional process. However, it can be fabricated by mechanical alloying using ball milling process.

**Chemical Precipitation**
In this strategy the size is control by arrested precipitation technique. The basic trick has been to synthesis and studies the nano material in situ i.e. in the same liquid medium avoiding the physical changes and aggregation of tiny crystallites. Thermal coagulation and Oswald ripening were controlled by double layer repulsion of crystallites using non-aqueous solvents at lower temperatures for synthesis. The synthesis involved reaction between constituent material in suitable solvent . The dopent is added to the parent solution before precipitation reaction. Surfactant is used to maintain separation between the particles formed . Thus formed nano crystal are separated by centrifugation, washed and vacuum dried. The dried material was further subjected to UV curing for possible polymerization of surfactant capping film on the surface of nano cluster for imparting true quantum confinement.[31-33]

## EVALUATION OF NANOPARTICLES

**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 influnced 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.[34]

**Particle Shape**
SEM characterizes the nanosuspension before going for evaluation; the nanosuspension is lyophilized to form solid particles. The solid particles are coated with platinum alloy using a sputter coater.[35]

**Particle size**
Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate,and 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).[36]

**Drug Entrapmaent Efficiency**

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 50C. 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.

Drug Entrapment efficiency (%) = Amount of released from the lysed nanoparticle X 100 Amount of drug Initially taken to prepare the Nanoparticles.[37]

**Advantages of Nanoparticles**

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

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

b) 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.

c) Sitespecific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.

d) 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.

e) The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.[38-39]

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