ISSN: 2321-3760

Review Article

International Journal of Current Trends in Pharmaceutical Research

IJCTPR, 2014, Vol. 2(5): 646-656

www.pharmaresearchlibrary.com/ijctpr

Nanoparticles Based Therapeutics and Drug Delivery–A Review

Krishna moorthy S.B*, Rajalakshmi R, Rupangada V, Sravanthi R.R, Ramya sudha EM.

Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A. Rangampet, Tirupathi, Andhra Pradesh, India-517102

Received: 05 July 2014, Accepted: 16 August 2014, Published Online: 15 September 2014

Abstract

Nanocarriers are colloidal particulate systems which size ranges from 10-1000 nm. They have been successfully utilized in the diagnosis, treatment and monitoring of various diseases. Targeted delivery of drug molecules is one of the most interesting and challenging endeavours faced in pharmaceutical field, due to the critical and pharmacokinetically specific environment that exists. Nanoparticles are capable of self-assembly and maintaining stability and specificity, which are crucial to drug encapsulation and biocompatibility. Over these years, cancer targeting treatment has been greatly improved by new tools and approaches based on nanotechnology.

Keywords: Nanocarriers, targeted delivery, nanoparticles, biocompatibility

Contents

***Corresponding author**
Krishna moorthy S.B
Department of Pharmaceutics,
Sree Vidyanikethan College of Pharmacy,
Tirupathi, Andhra Pradesh, India-517102.
Manuscript ID: IJCTPR2203

PAPER-QR CODE

1. 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]. Some studies showed that it is possible to use nanoparticles for the targeting of highly hydrophobic drugs. The pharmacological studies were confirmed by clinical trials, and some of the formulations are in general use nowadays *i.e.*: in January 2005, FDA approved the use of Abraxane™, a suspension of paclitaxel loaded nanoparticles for breast cancer treatment). [2]

1.1 Advantages

- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
- 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.
- 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.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
- The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

1.2 Limitations

- 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. [3]

2. Nanoparticle Classification

a. 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.

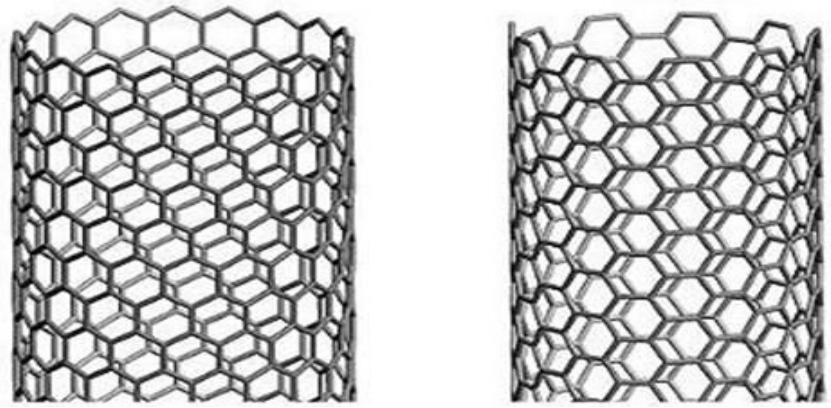

Figure 1: Structure of nanotubes

Table 1: Classification of nanoparticles

Category	Examples
Nanotubes	Carbon, (fullerenes)
Nanowires	Metals, semiconductors, oxides, sulfides, nitrides
Nanocrystals	Quantum dots insulators, semiconductors, metals, magnetic materials
Other nanoparticles	Ceramic oxides, metals
Nanobots	Biochip,nubots

b. 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., 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.

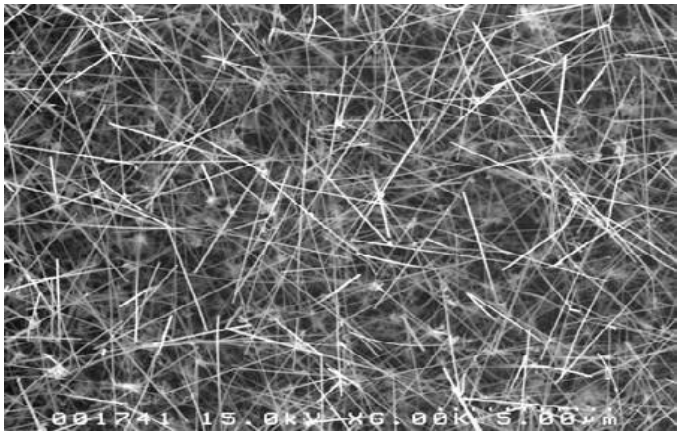

Figure 2: Structure of nanowires

c. Nanocrystals

Nanocrystal is any nanomaterial with at least one dimension ≤ 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 claims 12% 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.

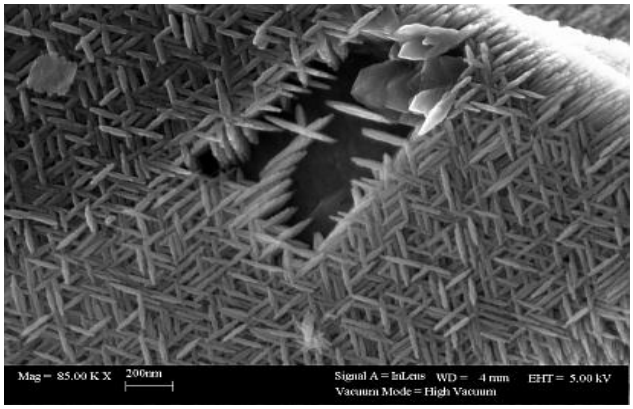

Figure 3: Structure of nanocrystals

d. Other Nanoparticles

A quantum dot is a semiconductor whose excitons are confined in all three spatial dimensions. As a result, they have properties that are between those of bulk semiconductors and those of discrete molecules. They were discovered at the beginning of the 1980s by Alexei Ekimov in a glass matrix and by Louis E. Brus in colloidal solutions. The term "Quantum Dot" was coined by Mark Reed. Researchers have studied quantum dots in transistors, solar cells, LEDs, and diode lasers. They have also investigated quantum dots as agents for medical imaging and hope to use them as qubits. In layman's terms, quantum dots are semiconductors whose conducting characteristics are closely related to the size and shape of the individual crystal. Generally, the smaller the size of the crystal, the larger the band gap, the greater the difference in energy between the highest valence bandand the lowest conduction band becomes, therefore more energy is needed to excite the dot, and concurrently, more energy is released when the crystal returns to its resting state. For example, in fluorescent dye applications, this equates to higher frequencies of light emitted after excitation of the dot as the crystal size grows smaller, resulting in a color shift from red to blue in the light emitted. The main advantages in using quantum dots is that because of the high level of control possible over the size of the crystals produced, it is possible to have very precise control over the conductive properties of the material. Quantum dots of different sizes can be assembled into a GML nanofilm.

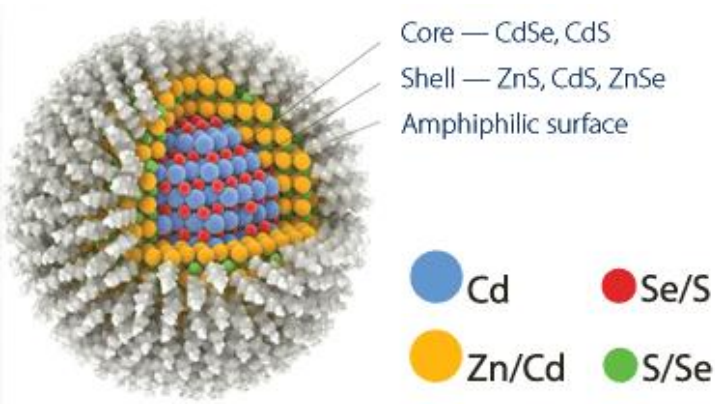

Figure 4: Structure of quantumdots

e. 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 ofdiabetes, 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.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. [4]

Figure no: 5 Structure of nanobots

2.1 Properties of Nanoparticles

Nanoparticle Size

To put the size of nanoparticles in perspective, compares sizes of various objects. Because of the comparable size of the components in the human cells, nanoparticles are of great interest in drug delivery. It appears that nature, in making the biological systems, has extensively used nanometer scale. If one has to go hand in hand with nature in treating the diseases one needs to use the same scale, whether it is correcting a faulty gene, killing leprosy bacteria sitting inside the body cells, blocking the multiplication of viral genome, killing a cancer cell, repairing the cellular metabolism, or preventing wrinkles or other signs of aging. One cannot use a human arm to massage the hurt leg of an ant. Size matching is important in carrying out any activity. Drug delivery is aimed at influencing the biochemistry of the body. The basic unit of the biological processes is the cell and the biochemical reactions inside it. With the advent of nanoparticles it is now possible to selectively influence the cellular processes at their natural scales. [5-7]

Table 2: Size of nanoparticles

Object	Size (nm)
Carbon atom	0.1
DNA double helix (diameter)	3
Ribosome	10
Virus	100
Bacterium	1,000
Red blood cell	5,000
Human hair (diameter)	50,000
Resolution of unaided human eyes	100,000

3. Method of Preparation

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. 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. 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 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. [8-10]

3.1 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 ultrasonication may be employed. [11]

3.2 Double Emulsion and Evaporation Method

The emulsion and evaporation method suffer from the limitation of poor entrapment of hydrophilic drugs .Therefore to encapsulate hydrophilic drug the double emulsion technique is employed, which involves the addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the w/o/w emulsion. The emulsion then subjected to solvent removal by evaporation and nano particles can be isolated by centrifugation at high speed. The formed nanoparticles must be thoroughly washed before lyophylization. In this method the amount of hydrophilic drug to be incorporated, the concentration of stabilizer used, the polymer concentration, the volume of aqueous phase are the variables that affect the characterization of nanoparticles. [12]

3.3 Salting Out Method

Salting out based on the separation of a water-miscible solvent from aqueous solution via a salting-out effect. Salting-out is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent which is subsequently emulsified into an aqueous gel containing the salting out agent (electrolytes, such as magnesium chloride and calcium chloride, or non- electrolytes such as sucrose) and a colloidal stabilizer such as polyvinyl pyrrolidone or hydroxy ethylcellulose.

This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of solvent into the aqueous phase, thus inducing the formation of nanospheres. Several manufacturing parameters can be varied including stirring rate, internal/external phase ratio, concentration of polymers in the organic phase, type of electrolyte concentration and type of stabilizer in the aqueous phase .This technique used in the preparation of PLA, Poly(methacrylic) acids, and Ethyl cellulose nanospheres leads to high efficiency and is easily scaled up. Salting out does not require an increase of temperature and therefore may be useful when heat sensitive substances have to be processed. The greatest disadvantages are exclusive application to lipophilic drug and the extensive nanoparticles washing steps. [13]

3.4 Emulsions- Diffusion Method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point.

This technique presents several advantages, such as high encapsulation efficiencies (generally 70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency. Several drug- loaded nano particles were produced by the technique, including mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nano particles, doxorubicin-loaded PLGA nano particles, and cyclosporine (cy-A-); loaded sodium glycolate nanoparticles.

3.5 Solvent Displacement / Precipitation method

Solvent displacement involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of surfactant. Polymers, drug, and or lipophilic surfactant are dissolved in a semi polar water miscible solvent such as acetone or ethanol. The solution is then poured or injected into an aqueous solution containing stabilizer under magnetic stirring. Nano particles are formed instantaneously by the rapid solvent diffusion.The solvent is then removed from the suspensions under reduced pressure. The rates of addition of the organic phase into the aqueous phase affect the particles size. It was observed that a decrease in both particles size and drug entrapment occurs as the rate of mixing of the two phase increases. Nano precipitation method is well suited for most of the poorly soluble drugs. Nanospheres size, drug release and yield were shown to be effectively controlled by adjusting preparation parameters. Adjusting polymer concentration in the organic phase was found to be useful in the production of smaller sized nanospheres through restricted to a limited range of the polymer to drug ratio.

4. Nanoparticle Characterization

4.1 Particle size and zeta-potential measurements, and surface topography

NP suspensions were prepared at a final concentration of 0.1 mg ml ¯1 in filtered phosphate buffer saline (PBS) and the particle size distribution was measured using dynamic light scattering with a Nano-ZS Zetasizer (Malvern Instrument Ltd., Malvern, Worcestershire, UK) at 37°C in back-scattering mode. The zeta potential of the NP suspensions was measured in triplicate at 37°C using the Zetasizer. Surface imaging was carried out in tapping mode using a multimode AFM equipped with a NanoScope IIIa controller (Digital Instruments, Santa Barbara, CA). The NPs were deposited by spreading a 20 ml suspension droplet on a freshly cleaved mica surface and stored in 30% relative humidity (RH) atmosphere 2 h prior to AFM analysis. All images were obtained in air and at room temperature using commercial etched silicon cantilevers with a tip of radius ranging from 5 to 10 nm and a spring constant of 20–100 N m_1. Image analysis was performed using the NanoScope III software (version 512r2).

4.2 Immobilization of the nanoparticles on mica surfaces

To determine their mechanical properties, the NPs were grafted onto modified mica surfaces as described elsewhere.15 Briefly, large sheets (1.5 - 4 cm) of freshly cleaved mica surfaces were first plasma treated to activate OH groups on their surface as described in detail elsewhere. Plasma activation was performed for 5 min at 40 W using argon and water vapors at a partial pressure of 80 mTorr and 300 mTorr respectively. After the plasma treatment, the mica surfaces were left in the plasma chamber under vacuum (0.5 mTorr) for 5 min. Then, the surfaces were transferred to an evaporation chamber and stored under vacuum (1.6 mmHg). The evaporation chamber was connected via a valve to a small glass reservoir containing 100 ml of APTES. After purging the evaporation chamber for 15 min, the valve was opened allowing APTES vapors to react with the activated mica surfaces. Evaporation was allowed to proceed for 4 h.

The valve was closed and remnant APTES vapors were pumped out for 2 h. The grafting reaction of APTES was completed by annealing the surfaces for 30 min at 90°C under atmospheric pressure. Then, the surfaces bearing grafted APTES molecules were immersed overnight in a 1% (w/w) water solution of glutaraldehyde where the coupling reaction between APTES amine function and glutaraldehyde carbonyl functional groups took place in presence of the catalytic agent NaBH3CN. The resulting glutaraldehyde-functionalized mica surfaces were thoroughly rinsed with Milli-Q water prior to NP deposition. Deposition was performed using the horizontal convective evaporation method.18 A small drop (25 ml) of a NP suspension (0.1% w/w in DMEM) was placed between a glass applicator and the functionalized mica surface prior to substrate translation. As the surface was translated at a fixed velocity, the NP suspension drop could spread on the substrate forming a uniform monolayer of nanoparticles. The final concentration of grafted NPs on the surfaces was 2.6 - 0.4 NPs/mm2 as determined by AFM imaging. [14]

4.3 Mechanical properties of the nanoparticles

The mechanical properties of the NPs grafted on mica surfaces were measured in PBS at 37°C using a Bioscope AFM equipped with a G-type piezotube scanner, Nanoscope IIIa controller, and version 4.43r8 of the Nanoscope software (Veeco Metrology, Santa Barbara,CA). Silicon nitride microlevers with spring constant k ¼ 0.01 N m¯1 were used. Mica substrates bearing grafted NPs were immersed in PBS at 37°C 1 h prior to measurement. Localization of the NPs was realized by scanning the surface in contact mode over a 3x3 μm^2 area. The scanning area was progressively decreased to visualize only one NP in the scanned area. Force profiles were measured by approaching the tip to the NP on the surface at a fixed velocity and recording the cantilever deflection. Young moduli were extracted from experimental curves by fitting the force
profiles with the Hertz model for a conical indenter:

$$F = 2Etan\theta \,/\, \pi(1 - v2) \times \delta 2$$

where F is the indentation force, E and n are the Young modulus and the Poisson ratio of the NPs respectively, d is the indentation and q is the half-opening angle of the indenter. One monolayer of NPs was prepared for each of the different NP batches. Five to ten force profiles were recorded on one single NP and six different NPs were analyzed for all surfaces. The Young moduli reported in this study represent the average value obtained from all recorded force profiles. [15]

5. Applications

5.1 Tumor Targeting Using Nanoparticulate Delivery Systems

The rationale of using nanoparticles for tumor targeting is based on following characteristics

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 targeting by ligands on the surface of nanoparticles. Nanoparticles will reduce the drug exposure of healthy tissues by limiting drug distribution to target organ. Studies show that the polymeric composition of nanoparticles such as type, hydrophobicity and biodegradation profile of the polymer along with the associated drug's molecular weight, its localization in the nanospheres and mode of incorporation

technique, adsorption or incorporation, have a great influence on the drug distribution pattern in vivo. The exact underlying mechanism is not fully understood but the biodistribution of nanoparticles is rapid, within ½ hour to 3 hours, and it likely involves mononuclear phagocytic system (MPS) and endocytosis/phagocytosis process. Such propensity of MPS for endocytosis/phagocytosis of nanoparticles provides an opportunity to effectively deliver therapeutic agents to these cells. This biodistribution can be of benefit for the chemotherapeutic treatment of MPS-rich organs/tissues localized tumors like hepatocarcinoma, hepatic metastasis arising from digestive tract or gynaecological cancers, brochopulmonary tumors, primitive tumors and metastasis, small cell tumors, myeloma and leukemia. [16]

5.2 Ligand Attached Nanoparticles

To be successful as a drug delivery system, nanoparticles must be able to target tumors, which are localized outside MPS-rich organs. [17] In the past decade, a great deal of work has been devoted to developing socalled "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes. [18] A major 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. [19] These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface, which repel plasma proteins. [20-21]As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time and hence called as long circulating nanoparticles. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles. Studies show nanoparticles containing a coat of PEG not only have a prolonged half-life in the blood compartment but also be able to selectively extravasate in pathological sites such as tumors or inflamed regions with a leaky vasculature. As a result, such long-circulating nanoparticles have increased the potential to directly target tumors located outside MPSrich regions.

The sizes of the colloidal carriers as well as their surface characteristics are the critical to the biological fate of nanoparticles. A size less than 100 nm and a hydrophilic surface are essential in achieving the reduction of opsonisation reactions and subsequent clearance by macrophages. Coating conventional nanoparticles with surfactants or PEG to obtain a longcirculating carrier has now been used as a standard strategy for drug targeting in vivo. Extensive efforts have been devoted to achieving "active targeting" of nanoparticles in order to deliver drugs to the right targets, based on molecular recognition processes such as ligandreceptor or antigen-antibody interaction. Considering that fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion molecules such as selectins and integrins are involved in metastatic events, nanoparticles bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins. [22] Targeting with small ligands appears more likely to succeed since they are easier to handle and manufacture. Furthermore, it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles.

5.3 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. Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. For instance, it has been found that insulin-loaded nanoparticles have preserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration. [23, 24]. The surface area of human mucosa extends to 200 times that of skin48. The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g., (a) proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin; (b) proteolytic enzymes at the brush border membrane (endopeptidases); (c) bacterial gut flora; and (d) mucus layer and epithelial cell lining itself. The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelia cells in the GI tract.

5.4 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. [25] The key ingredient of polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. Hence, polynucleotide vaccines are set to supersede many conventional vaccines particularly for immunotherapy. However, there are several issues related to the

delivery of polynucleotides, which limit their application. These issues include efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of these cells, and ensuring that the integrity of the polynucleotide is maintained during delivery to the target site. Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endolysosomal compartment to the cytoplasmic compartment. [26] Hedley et al. [27] reported that following their intracellular uptake and endolysosomal escape, nanoparticles could release DNA at a sustained rate resulting in sustained gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein.

5.5 Gene Therapy Using Nano-Delivery Systems [28]

Gene therapy involves the delivery of one or more genes and the sequences controlling their expression into the target cell or tissue. These newly delivered genes can then replace a defective gene or add genes, which "rewrite" certain aspects of the cell's functions, thus producing new proteins. The delivery of genes to the cell or tissue needs to be carried out using a vehicle, approved for clinical applications, which facilitates the gene's entrance into the cell. We have developed two new vehicles for gene delivery: Nanoparticles and ultrasound waves. The nanoparticles containing the new gene are injected into the site of interest where they are taken up by the cells and release their gene contents in the cells. The ultrasound energy, which is given from outside the body, forces the entrance of genes into the organ without the need of invasive surgery. Both technologies are used to deliver genes, which encode for the anticancer drugs

5.6 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 watersoluble 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. [29] 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. For example polysorbate 80/LDL, transferring receptor binding antibody (such as OX26), lactoferrin, cell penetrating peptides and melanotransferrin.

Table 3: Application of nanotechnology in the different field [30]

Applied field	Application
Nanomedicines	Nano drugs, Medical devices, Tissue engineering
Chemical and Cosmetics	Nanoscale chemicals and compounds, paints, coatings etc
Materials	Nanoparticles, carbon nanotubes, biopolymers, points, coatings
Food Sciences Environment and Energy	Processing, nutracetical food, nanocapsules. Water and air purification filters, fuel cells, photovoltaic
Military and Energy	Biosensors, weapons, sensory enhancement
Electronics	Semiconductors chips, memory storage, photonica, optoelectronics
Scientific Tools	Atomic force, microscopic and scanning tunneling microscope
Agriculture	Atomic force, microscopic and scanning tunneling microscope.

6. Conclusion

The foregoing show that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. 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.

7. References

1. Vj Mohanraj and Y Chen, Nanoparticles – A Review, Tropical Journal of Pharmaceutical Research, **2006**, vol 5 (1): 561-573.
2. Lucretiu cismaru and marcel popa, polymeric nanoparticles with biomedical applications, *rev. Roum. Chim.,* **2010**, vol *55*(8): 433-442.
3. Kreuter J. Nanoparticles. In Colloidal drug delivery systems, J, K., Ed. Marcel Dekker: New York, **1994**, vol 1(1): 219-342.
4. Chow TS., Size-dependent adhesion of nanoparticles on rough substrates. J Phys: Condens Matter, **2003**, vol 15(2):L83–L87.
5. Lamprecht A., Schafer U, Lehr C-M., Size-dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa. Pharm Res**, 2001**, vol 18(6:)788–793.
6. Kelly L., Coronado E., Zhao LL., Schatz GC., The optical properties of metal nanoparticles: the influence of size, shape, and dielectric environment. J Phys Chem B. **2003**, vol 107:668–677.
7. Kreuter J., Nanoparticles. In Colloidal drug delivery systems. J. K. Ed. Marcel Dekker: New York, **1994**, vol 3(3): 219- 342.
8. Reverchon E. and Adami R., Nanomaterials and supercritical fluids. The Journal of Supercritical Fluids , **2006**, vol 37:1-22.
9. Rolland J.P., Maynor B.W., Euliss L.E., Exner A.E., Denison G.M. Direct fabrication and harvesting of monodisperse, shape-specific nanobiomaterials. J. Am. Chem. Soc, **2005**, vol. 127:10096-10100.
10. Amit s. Manmode, dr.dinesh m. Sakarkar, nilesh m. Mahajan, nanoparticles-tremendous therapeutic potential: a review, International Journal of PharmTech Research, **2009**, Vol.1(4): 1020-1027
11. Vandervoort J., Ludwig A. Biodegradable stabilizers in the preparation of PLGA nano particles: a factorial design study. Int J Pharm. **2002**, vol 238:77-92.
12. Catarina PR., Ronald JN., Antonio JR. Nano capsulation 1. Method of preparation of drug–loaded polymeric nanoparticles: Nanotechnology, Biology and medicine. **2006**, vol 2(1):8-21.
13. Sovan Lal Pal, Utpal Jana, P. K. Manna, G. P. Mohanta, R. Manavalan, Nanoparticle: An overview of preparation and characterization, Journal of Applied Pharmaceutical Science, **2011**, vol 1(6): 228-234.
14. Xavier Banquy,a Fernando Suarez,b Anteneh Argaw,c Jean-Michel Rabanel,a Peter Grutter,b Jean-Franc¸ois Bouchard,c Patrice Hildgenab and Suzanne Giasson*adef, Effect of mechanical properties of hydrogel nanoparticles on macrophage cell Uptake, Soft Matter, **2009**, vol 5(2): 3984 -3991
15. Couvreur P., Kante B., Lenaerts V., Scailteur V., Roland M., Speiser P., Tissue distribution of antitumor drugs associated with polyalkylcyanoacrylate nanoparticles. J Pharm Sci, **1995**, vol 69: 199-202.
16. Moghimi S.M., Hunter A.C., Murray J.C., Longcirculating and target-specific nanoparticles: theory to practice. Pharmacol Rev, **2001**, vol 53: 283-318.
17. Storm G., Belliot S., Daemen T., Lasic D., Surface modification of nanoparticles to oppose uptake by the mononuclear phagocyte system. Adv. Drug Deliv. Rev, **1995**, vol 17: 31-48.
18. Torchilin V., Trubetskoy V., Which polymer can make nanoparticulate drug carriers long circulating Adv. Drug Deliv. Rev, **1995**, vol 16: 141-155.
19. Jeon S.I., Lee J.H., Andrade J.D., De Gennes P.G., Protein--surface interactions in the presence of polyethylene oxide : I. Simplified theory. J. Colloid Interface Sci., **1991**, vol 142: 149-158.
20. Jeon S.I, .Andrade J.D. Protein--surface interactions in the presence of polyethylene oxide: II. Effect of protein size. J. Colloid Interface Sci., **1991**, vol 142:159-166, 1991.
21. Stella B., Arpicco S., Peracchia M. , *et al.* Design of folic acid-conjugated nanoparticles for drug targeting. J. Pharm. Sci., **1991**, vol 89: 1452-1464.
22. Damge C., Michel C., Aprahamian M., Couvreur P., Devissaguet J.P., Nanocapsules as carriers for oral peptide delivery. J. Control. Release, **1990**, vol 13:233-239.
23. Brandtzaeg P., Berstad A., Farstad I., *et al.* J. Mucosal immunity – a major adaptive defense mechanism. Behring Inst. Mitt,**1997**, vol 98: 1-23.
24. Lee V., Yamamoto A., Penetration and enzymatic barriers to peptide and protein absorption. Adv. Drug Deliv. Rev, **1990**, vol 4: 171-207.
25. Gurunathan S., Wu C., Freidag B., DNA vaccines: a key for inducing long-term cellular immunity. Curr. Opin. Immunol , **2000**, vol 12: 442-447.
26. Panyam J., Zhou W.Z., Prabha S., Sahoo S.K., Labhasetwar V., Rapid endo-lysosomal escape of poly (DL-lactide-co-glycolide) nanoparticles: implications for drug and gene delivery. Faseb J, **2002**, vol 16: 1217-1226.
27. HedleyV, Curley J., Urban V., Microspheres containing plasmid-encoded antigens elicit cytotoxic Tcell responses. Nat Med, 4: 365-368, **1998**.

28. Chen Y., Dalwadi G., Benson H., Drug delivery across the blood-brain barrier. Current Drug Delivery, **2004**, vol 1: 361-376.
29. Pangi Z., Beletsi A., Evangelatos K. PEG-ylated nanoparticles for biological and pharmaceutical application. Adv Drug Del Rev. **2003**, vol 24: 403- 419.