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Review Article

Nanoparticle - Novel Drug Delivery System.

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Abstract

In the recent past, the targeted drug delivery has gained more attention for various advantages. Amongst the plethora of Avenues explored for targeted drug delivery. Nanoparticles are 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. 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. Present review reveals the methods of preparation, characterization and application of several nanoparticulate drug delivery systems.

Keywords: Nano particle drug delivery system, nanospheres, nanocapsules.

Introduction

Nanotechnology, the term derived from Greek word 'Nano', meaning dwarf, applies the principles of engineering, electronics, physical and material science & manufacturing at a molecular and supra-micron level. 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.

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Need For Study

- At present 95% of all new potential therapeutics has poor pharmacokinetic and biopharmaceutical properties.
- Therefore, there is a need to develop suitable drug delivery systems that distribute the therapeutically active drug molecule only to the site of action, without affecting healthy organs and tissues, also lowering doses required for efficacy as well as increasing the therapeutics indices and safety profiles of new therapeutics.
- Different reasons are,

1) Pharmaceutical
   - Drug instability in conventional dosage form
   - Solubility

2) Biopharmaceutical

- Low absorption
- High membrane bounding
- Biological instability

3) Pharmacokinetic/ Pharmacodynamic
- Short half life
- Large volume of distribution
- Low specificity

4) Clinical
- Low therapeutic index

Objective

- 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
- To achieve a desired pharmacological response at a selected site without undesirable interactions at other site, thereby the drug have a specific action with minimum side effects & better therapeutic index.
- Ex: in cancer chemotherapy & Enzyme replacement therapy.

Ideal Characteristics

Targeted drug delivery system should be

- Biochemically inert (non-toxic), non-immunogenic
- Both physically & chemically stable in vivo & in vitro.
- Restrict drug distribution to target cells (or) tissues (or) organs & should have uniform capillary distribution.
- Controllable & predicate rate of drug release.
- Drug release does not effect drug action.
- Therapeutic amount of drug release.
- Minimal drug leakage during transit.
- Carriers used must be biodegradable (or) readily eliminated from the body without any problem & no carrier induced modulation of diseased state.
- The preparation of the delivery system should be easy (or) reasonably simple reproductive & cost effective.

Advantages and Disadvantages[2]

Advantages of nanoparticles:

1. They are biodegradable, non- toxic, site specific and capable of being stored for at least one year.
2. They are capable of targeting a drug to a specific site in the body by attaching targeted ligands to surface of particles or use of magnetic guidance.
3. They offer controlled rate of drug release and particle degradation characteristics that can be readily modulated by the choice of matrix constituents.
4. Drug loading is high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
5. They offer better therapeutic effectiveness and overall pharmacological response/unit dose.
6. The system can be used for various routes of administration including oral, nasal, parentral, intra-ocular etc.
7. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

Limitations

1. Presents bioacceptibility restrictions.
2. Difficult to manufacture in large scale.
3. Due to their small particle size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
4. Small particle 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 commercially made available.
    - The present work is a step towards development of nanoparticulate drug delivery system, surface modification

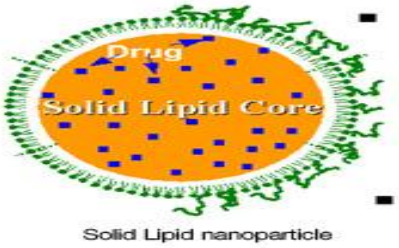
issues, drug loading strategies, release control and potential applications of nanoparticles.

Types of Nanoparticles[3]

The classes of nanoparticles listed below are all very general and multi-functional; however, some of their basic properties and current known uses in nanomedicine are described here.

1) Solid lipid nanoparticles (SLNs)
2) Liposomes
3) Nanostructured lipid carriers (NLC)
4) Fullerenes
5) Nanoshells
6) Quantum dots (QD)
7) Super paramagnetic nanoparticles

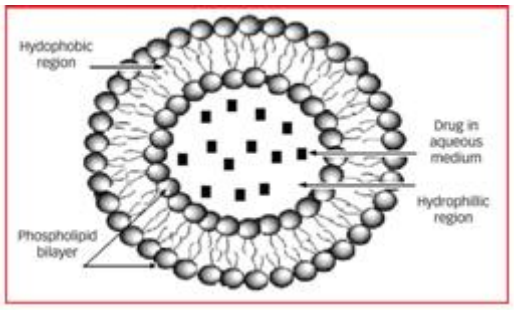
Solid lipid nanoparticles (SLNs)



SLNs mainly comprise lipids that are in solid phase at the room temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials The typical methods of preparing SLNs include spray drying high shear mixing ultra-sonication and high pressure homogenization (HPH) Solid lipids utilized in SLN formulations include fatty acids (e.g. palmitic acid, decanoic acid, and behenic acid), triglycerides (e.g. trilaurin, trimyristin, and tripalmitin), steroids (e.g. cholesterol), partial glycerides (e.g. glyceryl monostearate and gylceryl behenate) and waxes (e.g. cetyl palmitate).

Several types of surfactants are commonly used as emulsifiers to stabilize lipid dispersion, including soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate Advantages of these solid lipid nanoparticles (SLN) are the use of physiological lipids, the avoidance of organic solvents in the preparation process, and a wide potential application spectrum (dermal, oral, intravenous). Additionally, improved bioavailability, protection of sensitive drug molecules from the environment (water, light) and controlled and/or targeted drug release and improved stability of pharmaceuticals, feasibilities of carrying both lipophilic and hydrophilic drugs and most lipids being biodegradable SLNs possess a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year.

Liposomes



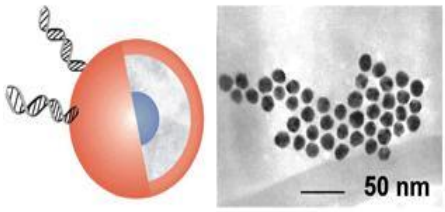
Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are GRAS (generally recognized as safe) ingredients, therefore minimizing the potential for adverse effects. Solutes, such as drugs, in the core cannot pass through the hydrophobic bilayer however hydrophobic molecules can be absorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules.

The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes. Liposomes can

vary in size, from 15 nm up to several lm and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes (multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) depending on their size range.

The unique structure of liposomes, a lipid membrane surrounding an aqueous cavity, enables them to carry both hydrophobic and hydrophilic compounds without chemical modification. In addition, the liposome surface can be easily functionalized with 'stealth' material to enhance their in vivo stability or targeting ligands to enable preferential delivery of liposomes. These versatile properties of liposomes made them to be used as potent carrier for various drugs like antibacterials, antivirals, insulin, antineoplastics and plasmid DNA.

Nanostructured lipid carriers (NLC)

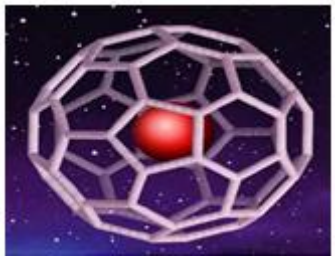


Nanostructured Lipid Carriers are produced from blend of solid and liquid lipids, but particles are in solid state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate nanoparticles (LDC) that have been created to improve drug loading capacity. The NLC production is based on solidified emulsion (dispersed phase) technologies.

NLC can present an insufficient loading capacity due to drug expulsion after polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules. Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures. A desired burst drug release can be initiated by applying the trigger impulse to the matrix to convert in a more ordered structure. NLCs of certain structures can be triggered this way. NLCs can generally be applied where solid nanoparticles possess advantages for the delivery of drugs.

Major application areas in pharmaceutics are topical drug delivery, oral and parenteral (subcutaneous or intramuscular and intravenous) route. LDC nanoparticles have proved particularly useful for targeting water-soluble drug administration. They also have applications in cosmetics, food and agricultural products. These have been utilized in the delivery of anti-inflammatory compounds, cosmetic preparation, topical cortico therapy and also increase bioavailability and drug loading capacity.

Fullerenes

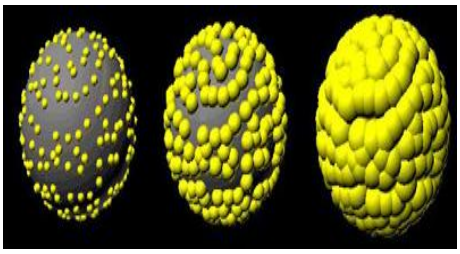


A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buck balls, and cylindrical ones are called carbon nanotubes or buck tubes. Fullerenes are similar in structure to the graphite, which is composed of stacked grapheme sheets of linked hexagonal rings, additionally they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules. Buckyballclusters or buck balls composed of less than 300 carbon atoms are commonly known as endohedral fullerenes and include the most common fullerene, buckminsterfullerene, C60.

Mega tubes are larger in diameter than nano tubes and prepared with walls of different thickness which is potentially used for the

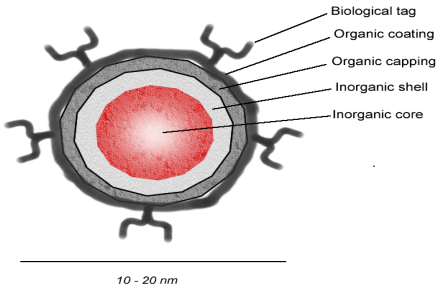
transport of a variety of molecules of different sizes Nano ‘‘onions’’ are spherical particles based on multiple carbon layers surrounding a buck ball core which are proposed for lubricants. These properties of fullerenes hold great promise in health and personal care application.

Nanoshells



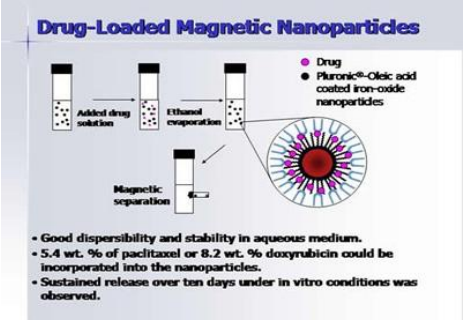
Nanoshells are also notorious as core-shells, nanoshells are spherical cores of a particular compound (concentric particles) surrounded by a shell or outer coating of thin layer of another material, which is a few 1–20 nm nanometers thick Nanoshell particles are highly functional materials show modified and improved properties than their single component counterparts or nanoparticles of the same size. Their properties can be modified by changing either the constituting materials or core-to-shell ratio Nanoshell materials can be synthesized from semiconductors (dielectric materials such as silica and polystyrene), metals and insulators. Usually dielectric materials such as silica and polystyrene are commonly used as core because they are highly stable. Metal nanoshells are a novel type of composite spherical nanoparticles consisting of a dielectric core covered by a thin metallic shell which is typically gold. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. Nanoshells offer other advantages over conventional organic dyes including improved optical properties and reduced susceptibility to chemical/thermal denaturation. Furthermore, the same conjugation protocols used to bind biomolecules to gold colloid are easily modified for nanoshells .When a nanoshell and polymer matrix is illuminated with resonant wavelength, nanoshells absorb heat and transfer to the local environment. This causes collapse of the network and release of the drug. In core shell particles-based drug delivery systems either the drug can be encapsulated or adsorbed onto the shell surface. The shell interacts with the drug via a specific functional group or by electrostatic stabilization method. When it comes in contact with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific antibodies for diseased tissues or tumors.

Quantum dots (QD)



The quantum dots are semiconductor nanocrystals and core shell nanocrystals containing interface between different semiconductor materials. The size of quantum dots can be continuously tuned from 2 to 10 nm, which, after polymer encapsulation, generally increases to 5–20 nm in diameter. Particles smaller than 5 nm are quickly cleared by renal filtration. Semiconductor nanocrystals have unique and fascinating optical properties; become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection. QD core can serve as the structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisense oligodeoxynucleotide (ODN)) and targeting biomolecules such as antibodies, peptides and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds. This fully integrated nanostructure may behave like magic bullets that will not only identify, but bind to diseased cells and treat it. It will also emit detectable signals for real-time monitoring of its trajectory.

Superparamagnetic nanoparticles



Super paramagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5–100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. The main advantages of superparamagnetic nanoparticles are that they can be visualized in magnetic resonance imaging (MRI) due to their paramagnetic properties; they can be guided to a location by the use of magnetic field and heated by magnetic field to trigger the drug release. Super paramagnetic nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials (silica, gold) and organic (phospholipids, fatty acids, polysaccharides, peptides or other surfactants and polymers). In contrast to other nanoparticles, superparamagnetic nanoparticles based on their inducible magnetization, their magnetic properties allow them to be directed to a defined location or heated in the presence of an externally applied AC magnetic field. These characteristics make them attractive for many applications, ranging from various separation techniques and contrast enhancing agents for MRI to drug delivery systems, magnetic hyperthermia (local heat source in the case of tumor therapy), and magnetically assisted transfection of cells. Already marketable products, so-called beads, are micron sized polymer particles loaded with SPIONs. Such beads can be functionalized with molecules that allow a specific adsorption of proteins or other biomolecules and subsequent separation in a magnetic field gradient for diagnostic purposes. More interesting applications, like imaging of single cells or tumors, delivery of drugs or genes, local heating and separation of peptides, signalling molecules or organelles from a single living cell or from a living (human) body are still subjects of intensive research. The transdisciplinarity of basic and translational research carried out in superparamagnetic nanoparticles during the last decades lead to a broad field of novel applications for superparamagnetic nanoparticles.

Methods

- **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 various factors which include:

a. Size of nanoparticle required
b. Inherent properties of the drug, e.g., aqueous solubility and stability
c. Surface characteristics such as charge and permeability
d. Degree of biodegradation, biocompatibility and toxicity
e. Drug release profile desired
f. Antigenicity of the final product.

- **Methods of preparation[4]**

The various methods are as follows:

1. Emulsion Polymerization
2. Desolvation method
3. High Pressure Homogenization
4. Controlled Gellification Method
5. Controlled Nanoprecipitation without Surfactants
6. Solvent Evaporation Method
7. Solvent Emulsification or Solvent Diffusion method
8. Supercritical Fluid Extraction
9. Melt Emulsification and Homogenization following Spray drying of nanodispersions.

1. Emulsion Polymerization

Chitosan Nanoparticles were prepared by emulsion polymerization in a closed 100ml flask. Chitosan was dissolved in 100ml 1

% acetic acid solution under magnetic stirring at 400-500 rpm; the pH value was adjusted to 4-5. One percent (w/v) of the monomer methyl metharcylate was dissolved in the above mixture at 75^0C and APS solution was added. The reaction was completed after 5 hrs. The resulting nanoparticles suspensions were dialyzed through a semi-permeable membrane with an exclusion diameter of 14,000 Da. After purification, characterization was carried out.

2. Desolvation Method

Glidian Nanoparticles were prepared by a Desolvation procedure. Glidian and clarithomycin were dissolved in 20ml of a ethanol: water phase (7: 3v/v) and this solution was poured into a stirred physiological saline phase (NaCl 0.9 % w/v in water), containing 0.5 % Pluronic F-68 as a stabilizer. Then ethanol was eliminated by evaporation under reduced pressure and the resulting nanoparticles were purified by centrifugation at 15,000rpm for 1 hr. The supernatant was removed and the pellets were resuspended in water. The suspension was passed through a 0.45 micrometer pore size membrane filter and the filtrate was centrifuged again and finally the nanoparticles were freeze dried using 5 % glucose solution as a cryoprotector. Nanoparticles were hardened by the addition of 2mg glutaraldehyde per mg and stirred for 2hr at room temperature before purification and freeze drying.

3. High Pressure Homogenization

The Drug is first subjected to premilling low pressure homogenization to decrease the particle size of the powder. Then the drug in powder form is added to an aqueous surfactant solution (5%w/v suspension of drug) under magnetic stirring (500rpm). After dispersion, a first size reduction step is achieved using Ultra Stirrer at 24,000 rpm for 10minutes (in an ice bath to prevent sample temperature increase). Nanosuspension were then prepared using high pressure homogenizer, all this operation should be done under heat exchanger by maintaining the system temperature at 10 ± 1^0 C.

4. Controlled Gellification Method

Alginate Nanospheres were obtained by including the Gellification of Sodium alginate solution with calcium Chloride. The pH of the solution was adjusted to 9 using 0.05M NaOH, and the drug, Methotrexate (10 mg) was dissolved in the sodium alginate solution.12ml of Poly-1-lysine (0.1 %) solution was added to get a final suspension of alginate nanoparticles. The suspension was kept for overnight and Nanospheres were centrifuged at a speed of 40,000 rpm for half an hour. The Nanospheres were collected and stored in acetone water mixture.

5. Controlled Nanoprecipitation without Surfactants

Water insoluble drug was dissolved in the solvent at definite concentration. The solution was filtered through 0.45 micrometer pore size membranes to remove the possible particulate impurities. The drug nanoparticles were then prepared by the controlled nanoprecipitation. Briefly, 5ml drug solution was quickly poured into the antisolvent under magnetic stirring and the precipitation was formed immediately upon mixing. The freshly formed nanoparticles were then filtered and dried under vaccum at 50^0C for 12 hrs.

6. Solvent Evaporation Method

Nanoparticles of this type are prepared by dissolving Poly (D, L- lactic acid-co-glycolic acid) PLAGA in methylene chloride and the drug is dissolved in DMSO were mixed. This mixture is emulsified with 0.5% w/v poly vinyl alcohol using homogenous under pressure, then methylene chloride is removed under reduced pressure. The phase ratio between organic/total volume is 0.24.

7. Solvent Emulsification or Solvent Diffusion Method

This is a modified method of Solvent evaporation. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used in the oil phase. Due to 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 particles can be achieved.

8. Supercritical Fluid Extraction

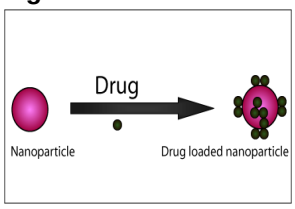
A supercritical fluid can be generally defined as a solvent at a temperature above critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 ($SCCO_2$) is the most widely used supercritical fluid because of its mild critical conditions (T_c=31.1^{0}C, P_c= 73.8 bars), non toxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical antisolvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, e.g., methanol, which is completely miscible with the supercritical (SC CO_2), to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid, leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles.

9. Melt emulsification and Homogenization

Nanoparticles were prepared by melt emulsification and homogenization followed by spray drying of nanodispersions. They were prepared with glyceride lipids, which was melted and then homogenized with the drug to form an emulsion. This nanoemulsion was then spray dried. By spray drying method powder nanoparticles can be obtained with excellent redispersibility and minimal increase in the particle size (20-40nm).

Drug Loading and Release

Drug Loading[1]



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 loading and entrapment efficiency very much depend on the solid-state drug solubility in matrix material or polymer (solid dissolution or dispersion), which is related to the polymer composition, the molecular weight, the drug polymer interaction and the presence of endfunctional groups (ester or carboxyl) 39 40 41. The PEG moiety has no or little effect on drug loading The macromolecule or protein shows greatest loading efficiency when it is loaded at or near its isoelectric point when it has minimum solubility and maximum adsorption 19 For small molecules, studies show the use of ionic interaction between the drug and matrix materials can be a very effective way to increase the drug loading.

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:

a. solubility of drug;
b. desorption of the surface bound/adsorbed drug;
c. drug diffusion through the nanoparticle matrix;
d. nanoparticle matrix erosion/degradation; and
e. Combination of erosion/diffusion process.

Thus solubility, diffusion and biodegradation of the matrix materials govern the release process. In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or ‘burst’ is mainly attributed to weakly bound or

adsorbed drug to the large surface of nanoparticles 45. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better sustained release characteristics 46. If the nanoparticle is coated by polymer, the release is then controlled by diffusion of the drug from the core across the polymeric membrane. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect 43; whereas if the addition of auxillary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in drug release could be observed 20. Various methods which can be used to study the
in vitro release of the drug are:

- **a.** side-by-side diffusion cells with artificial or biological membranes;
- **b.** dialysis bag diffusion technique;
- **c.** reverse dialysis bag technique;
- **d.** agitation followed by ultracentrifugation/centrifugation
- **e.** Ultra-filtration or centrifugal ultra-filtration techniques.

Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

Factors which govern drug release rate

1. Release mechanism
2. Diffusion coefficient
3. Bio-degradation rate

CHARACTERIZATION[5]

Adequate and proper characterization of the nanoparticles is necessary for its quality control. However, characterization of nanoparticles is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters which need to be evaluated for the nanoparticles are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, super cooled, melts, drug nanoparticles), time scale of distribution processes, drug content, *in vitro* drug release and surface morphology.

The particle size/size-distribution may be studied using photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM) atomic force microscopy (AFM), scanning tunneling microscopy (STM), or freeze fracture electron microscopy (FFEM).

Measurement of particle size and zeta potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by the particle movement. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger microparticles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear

advantage of LD is the coverage of a broad size range from the nanometer to the lower millimeter range. The development of polarization intensity differential scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. However, despite this progress, it is highly recommended to use PCS and LD simultaneously. It should be kept in mind that both methods do not 'measure' particle size. Rather, they detect light scattering effects which are used to calculate particle size. For example, uncertainties may result from non–spherical particle shapes. Platelet structures commonly occur during lipid crystallization and have also been suggested in the SLN. Further, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of microparticles (microparticles of unit form or microparticles consisting of aggregates of smaller particles). Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artifacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape. Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter.

Dynamic light scattering (DLS)

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant(s) being related to the diffusion coefficient(s). Using standard assumptions of spherical size, low concentration, and known viscosity of the suspending medium, particle size is calculated from this coefficient. The advantages of the method are the speed of analysis, lack of required calibration, and sensitivity to submicrometer particles.

Static light scattering / Fraunhofer diffraction

Static light scattering (SLS) is an ensemble method in which the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. The method is fast and rugged, but requires more cleanliness than DLS, and advance knowledge of the particles' optical qualities.

Acoustic methods

Another ensemble approach, acoustic spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information on surface charge.

Nuclear magnetic resonance (NMR)

NMR can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Electron microscopy

SEM and TEM provide a way to directly observe nanoparticles, physical characterization of nanoparticles 113 with the former method being better for morphological examination. TEM has a smaller size limit of detection, is a good validation for other methods, and affords structural required, and one must be cognizant of the statistically small sample size and the effect that vacuum can have on the particles.

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the subtechniques. That ultrahigh resolution is obtainable with this approach, which along with the ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool.

X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)

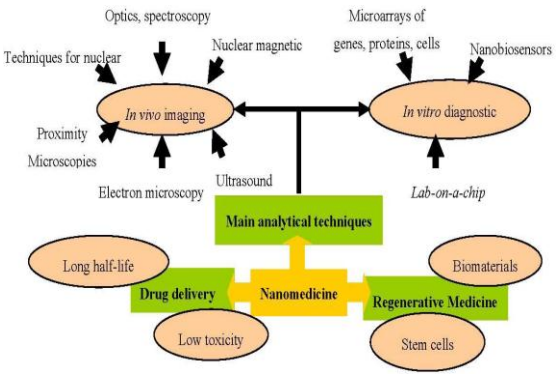
The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus permitting the degree of crystallinity to be assessed. Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies.

Application

Nanomedicine Applications[6]

Nanomedicine applications are grouped below in three interrelated areas:

1. analytical/diagnostic tools,
2. drug delivery and
3. regenerative medicine



Analytical Diagnostic Tools

The limitations of current diagnostic technology mean that some diseases can only be detected when at a very advanced stage. Nanodiagnostics, defined as the use of nanotechnology for clinical diagnostic purposes, were developed to meet the demand for increased sensitivity in clinical diagnoses and earlier disease detection.

The application of micro and nanobiotechnology in medical diagnostics can be subdivided into two broad categories:

1. *In vitro* diagnostic devices and
2. *In vivo* imaging.

***In Vitro* Diagnostic Devices**

- The use of these devices in research has become routine and has improved our understanding of the molecular basis of disease and helped to identify new therapeutic targets.
- *In vitro* diagnostic devices include nanobiosensors, microarrays, biochips of different elements (DNA, proteins or cells) and lab-on-a-chip devices.

Nanobiosensor

- A Nanobiosensor is defined as a compact analysis device that incorporates biological (nucleic acid, enzyme, antibody, receptor, tissue, cell) or biomimetic (macrophage-inflammatory proteins, aptamers, peptide nucleic acids) recognition elements.
- Interaction between the compound or microorganism of interest and the recognition element produces a variation in one or more physical-chemical properties (e.g., pH, electron transfer, heat, potential, mass, optical properties, *etc*.) that are detected by the transducer. The resulting electronic signal indicates the presence of the analyte of interest and its concentration in the sample. These sensors can be electronically gated to respond to the binding of a single molecule. Prototype sensors have been successfully used to detect nucleic acids, proteins and ions. They can operate in liquid or gas phase, opening up an enormous variety of downstream applications.

- These detection systems use inexpensive low-voltage measurement methods and detect binding events directly, so there is no need for costly, complicated and time-consuming chemical labelling, e.g., with fluorescent dyes, or for bulky and expensive optical detection systems. As a result, these sensors are inexpensive to manufacture and portable. Hence,
- nanobiosensors are revolutionizing the *in vitro* diagnosis of diseases and have major implications for human health. They allow healthcare professionals to simultaneously measure multiple clinical parameters using a simple, effective and accurate test. These devices are also ideal for high-throughput screening and for the detection of a single disease in various samples or of various diseases in a single sample.

Microarrays

- The microarray is another diagnostic device that is becoming a standard technology in research laboratories worldwide.
- Microarray-based studies have enormous potential in the exploration of diseases such as cancer and in the design and development of new drugs.
- Microarrays have been widely applied in the study of various pathological conditions, including inflammation, atherosclerosis, breast cancer, colon cancer and pulmonary fibrosis . As a result, functions have been assigned to previously unannotated genes, and genes have been grouped into functional pathways.
- Several types of microarray have been developed for different target materials, which can be DNA, cDNA, mRNA, protein, small molecules, tissues or any other material that can be quantitatively analyzed.
- The main applications of microarrays in human health are listed below.
    - **i.** *Gene expression analysis*, used to determine gene expression patterns and simultaneously quantify the expression of a large number of genes, permitting comparison of their activation between healthy and diseased tissues.
    - **ii.** *Detection of mutations and polymorphisms,* allowing the study of all possible polymorphisms and the detection of mutations in complex genes.
    - **iii.** *Sequentiation*, used to sequence short DNA fragments (sequencing of long DNA fragments has not yet proven possible, although they can be used as quality controls).
    - **iv.** *Therapy follow-up*, allowing evaluation of genetic features that may affect the response to a given therapy.
    - **v.** *Preventive medicine,* developing knowledge on the genetic features of diseases in order to treat and prevent them before symptom onset.
    - **vi.** *Drug screening and toxicology,* analyzing changes in gene expression during the administration of a drug, as well as localizing new possible therapeutic targets and testing for associated toxicological effects.
    - **vii.** *Clinical diagnosis*, allowing the rapid identification of pathogens by employing the appropriate genetic markers.

In conclusion, molecular diagnosis is a fast-growing field. Analysis of global expression by microarray techniques simultaneously reveals the state of thousands of genes of diseased cells. These approaches offer a more accurate diagnosis and risk assessment for various diseases, leading to a more precise prognosis and new therapeutic approaches. The ultimate reach of microarray technology will be achieved with its entry into the physician‘s clinic as a routine diagnostic tool.

Lab-on-a-Chip

- The latest *in vitro* diagnostic development derives from the integration of several functions in a single device.
- Lab-on-a-chip integrates one or several laboratory functions on a single chip ranging from only a few millimeters to a square centimeter in size and incorporates sample preparation, purification, storage, mixing, detection and other functions.
- Its development was based on advances in microsystem technologies and in the field of micro fluidics on the design of devices that use microscopic volumes of sample.
- The chips use a combination of phenomena, including pressure, electroosmosis, electrophoresis and other mechanisms to move samples and reagents through microscopic channels and capillaries, some as small as a few dozen nanometers.
- Lab-on-a-chip has many applications in medicine and biology.
- Advantages of their use include the extremely rapid analysis of samples containing fluid volumes that can be less than a picoliter, the high degree of automation, cost savings due to the low consumption of reagents and samples and their portable and disposable nature.
- Lab-on-a-chip is used in real-time polymerase chain reaction and immunoassays to detect bacteria, viruses and cancers.
- It can also be used in blood sample preparation to crack cells and extract their DNA.
- Lab-on-a-chip may soon play an important role in efforts to improve global health, especially with the development of point-of-care testing devices.
- The goal is to create microfluidic chips that will allow healthcare providers in poorly-equipped clinics to perform diagnostic tests (e.g., immunoassays and nucleic acid assays) with no laboratory support.
- One active research line on the lab-on-a-chip addresses the diagnosis and management of HIV infections. Around 40 million people are infected with HIV in the world, yet only 1.3 million receive antiretroviral treatment and around 90% of HIV-infected individuals have never been tested for the disease. This is largely because its diagnosis requires measurement of the number of CD4+ T lymphocytes in the blood by means of flow cytometry, a complicated technique that requires trained technicians and expensive equipment that are not available in most developing regions.

***In Vivo* Imaging**

- Nanotechnology has produced advances in imaging diagnosis, developing novel methods and increasing the resolution and sensitivity of existing techniques. Although these systems have emerging recently only some of them are in clinical and preclinical use, they have made it possible to study human biochemical processes in different organs *in vivo*, opening up new horizons in instrumental diagnostic medicine.
- These systems include positron-emission tomography (PET), single-photon-emission CT (SPECT), fluorescence reflectance imaging, fluorescence-mediated tomography (FMT), fiber-optic microscopy, optical frequency-domain imaging, bioluminescence imaging, laser-scanning confocal microscopy and multiphoton microscopy.
- Imaging diagnosis has gained importance over the years and is now an indispensable diagnostic tool for numerous diseases, including cancer, cardiovascular diseases and neurological syndromes.
- The main benefits of molecular imaging for *in vivo* diagnosis lie in the early detection of disease and the monitoring of disease stages, e.g., in

cancer metastasis, supporting the development of individualized medicine and the real-time assessment of therapeutic and surgical efficacy.

- An ideal imaging modality should be non-invasive, sensitive, and provide objective information on cell survival, function and localization. MRI, CT, PET) and SPECT are the most widely used and studied modalities in cancer patients Overall, nuclear imaging by PET or SPECT offers greater sensitivity (>5 × 103 cells) but is limited by the lack of anatomical context, whereas MRI provides accurate anatomical detail but no data on cell viability and shows poor sensitivity (>105 cells).
- Although none of these modalities is ideal, MRI is the preferred option for cellular tracking by detecting proton relaxations in the presence of a magnetic field (1.5 Tesla [T]-3 T for clinical imaging), it yields tomographic images with excellent soft tissue contrast and can locate the cells of interest in the context of the surrounding milieu (oedema or inflammation) without the use of harmful ionizing radiations (the case with CT, PET or SPECT).
- In addition, MRI offers a longer tracking window in comparison to PET and SPECT, which are limited by the decay of the short-lived radioactive isotopes.
- In parallel to the development of imaging techniques, intense research has been fuelled by the need for practical, robust and highly sensitive and selective detection agents that can address the deficiencies of conventional technologies. New contrast agents, used to increase the sensitivity and contrast of imaging techniques are increasingly complex and formed by synthetic and biological nanoparticles. Nanoparticles possess certain size-dependent properties, particularly with respect to optical and magnetic parameters, which can be manipulated to achieve a detectable signal.
- The primary event in most nanoparticle-based assays is the binding of a nanoparticle label or probe to the target biomolecule that will produce a measurable signal characteristic of the target biomolecule. A probe that is to function in a biological system must be water-soluble and stable and have minimal interaction with the surrounding environment.
- For fluorescence readouts, the probe should ideally have a high fluorescence quantum yield and minimal photobleaching rates in order to generate a detectable signal. The most promising nanotechnologies for clinical diagnosis include quantum dots (QDs),

Drug Delivery

- One of the most important nanotechnology applications developed over the past decade have been nanovehicles, nanoscale compounds used as a therapeutic tool and designed to specifically accumulate in the sites of the body where they are needed in order to improve pharmacotherapeutic outcomes.
- The main objective of this application is to increase therapeutic effectiveness while obtaining lower toxicity rates. Hence, nanodrugs and nanodiagnostics have been developed to increase bioavailability profiles, enabling the administration of lower doses and thereby minimizing the adverse reactions found with conventional drugs in clinical practices and increasing the quality of patient health.
- In the field of cancer therapy there are a lot of clinical applications based on nanotechnologies, with a major development in drug delivery systems.
- The reason for the rise in nanotechnology applications in medicine is the prospect of improving

effectiveness by the biological targeting of drugs in current clinical use.

- In cancer treatments, nanoparticles are usually administered by intravenous injection, travelling in the blood stream and passing through biological barriers (cell membranes) of the organism in order to reach and activate their molecular targets.
- One of the main objectives of nanotechnology is overcome the shortcomings of classical chemotherapy, including the multiple drug resistance mechanisms that make this treatment ineffective in a high percentage of cancer cases.
- The other problem of conventional anticancer therapies is the non-specific action of the drugs, leading them to damage both tumor and non-tumor cells in a state of division.
- Nanoparticles can overcome the side effects of conventional therapies by the following means:
    - **i.** sustaining drug release over time;
    - **ii.** so-called passive enhanced permeability, targeting the effect to tumor tissue;
    - **iii.** targeting the cell surface with the use of ligands related to endosomal uptake and membrane disruption;
    - **iv.** Permitting release of the drug in the cell cytoplasm; and (5) protecting the drug from enzymatic degradation.

- The main goals of drug delivery design are:
    - **i.** to decrease the side effects of conventional therapy by decreasing drug concentration in normal tissues;
    - **ii.** to enhance the pharmacokinetics and pharmacodynamics profiles;
    - **iii.** to allow intravenous drug administration by increasing drug solubility;
    - **iv.** to minimize drug loss in transit and maximize drug concentration in the tumor;
    - **v.** to improve drug stability by avoiding drug degradation;
    - **vi.** to achieve optimal cellular uptake and intracellular delivery
    - **vii.** To ensure biocompatibility and biodegradability.

- The achievement of these drug concentrations in the tumor requires nanoparticles to possess the following characteristics:
    - **i.** (a) nanoparticle size between 10 and 100 nm;
    - **ii.** (b) a neutral or anionic nanoparticle surface charge to prevent elimination by the kidneys; and
    - **iii.** (c) The ability to avoid opsonization and phagocytosis, which destroy foreign material *via* the reticuloendothelial system.
- Active targeting using nanoparticles as the delivery system allows a specific area of the body to be targeted, avoiding one of the drawbacks of current chemotherapy, *i.e.*, toxic effects in non-malignant organs. Studies are being carried out on the attachment of targeting ligands on the nanoparticle surface, enabling specific binding of the nanoparticle to receptors on the tumor cell surface.

Regenerative Medicine

- Tissue engineering brings together principles and innovations from

engineering and the life sciences for the improvement, repair or replacement of tissue/organ function.

- Since its inception, this multidisciplinary field has been governed by the generic concept of combining cell, scaffold (artificial extracellular matrix) and bioreactor technologies in the design and fabrication of neo-tissues/organs.
- Every tissue or organ in our body is composed of parenchymal cells (functional cells) and mesenchymal cells (support cells) contained within an extracellular matrix to form a microenvironment, and these microenvironments collectively form our tissues and organs.
- In terms of the development and maintenance of tissues and organs, our body is the bioreactor, exposing the microenvironment of the cell and extracellular matrix to biomechanical forces and biochemical signals.
- The ultimate goal is to enable the body (cellular components) to heal itself by introducing a tissue engineered scaffold that the body recognizes as self and uses to regenerate neo-native functional tissues.
- Furthermore, the demand for organs for transplantation far exceeds the supply, and the construction of organs by regenerative therapy has been presented as a promising option to address this deficit. Nanotechnology has the potential to provide instruments that can accelerate progress in the engineering of organs.
- Achievement of the more ambitious goals of regenerative medicine requires control over the underlying nanostructures of the cell and extracellular matrix.
- Cells, typically microns in diameter, are composed of numerous nanosized components that all work together to create a highly organized, self-regulating machine. Cell-based therapies, especially those based on stem cells, have generated considerable excitement in the media and scientific communities and are among the most promising and active areas of research in regenerative medicine .
- The pace of research could be accelerated by the creation of multi-functional tools to improve the monitoring and modification of cell behavior.
- While nano medicine is primarily focused on cancer-related research, the application of nanotechnology has considerable potential in cell-based therapies for regenerative medicine, e.g., in localizing, recruiting and labelling stem cells to begin the regeneration process.

Marketed Products of Nanomedicine

1. Nanoparticle
2. Nanocrystal
3. Nanotube
4. Superparamagnetic iron oxide
5. Liposomes
6. Micelle

Some Indian Technologies

1. First produced smart hydrogel nanoparticles for drug delivery applications(US Patent 5847111)
2. Tumor Targeted Delivery of Taxol using nanoparticles (US Patent 6,322,817)
3. Inorganic Nanoparticles as non-viral vectors for targeted delivery of genes (US Patent 6555376); Technology transferred to a California based Pharm Com
4. Once in 48 hours dose Ophthalmic delivery (US Patent 6579519) (Another improved formulation patent on ophthalmic gels is being submitted in India)
5. Oral Insulin Delivery (Patent Pending)

Conclusion

- Nanoparticles represent a promising drug delivery system of controlled and targeted release.

- The emergence of nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from oral to injectable. And the payoff for doctors and patients should be lower drug toxicity, reduced cost of treatments, improved bioavailability, and an extension of the economic life of proprietary drugs.
- The foregoing show that nano particulate 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 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 nanoparticles technology into a realistic practical application as the next generation of drug delivery system.
- This would allow earlier and more personalized diagnosis and therapy, improving the effectiveness of drug treatments and reducing side effects. In addition, nanoparticles are a promising platform technology for the synthesis of molecular-specific contrast agents.

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Table 1: Comparison of quantum dots (QDs), cantilevers and gold nanoparticles.

. **Feature**	**QDs**	**Cantilevers**	**Gold nanoparticles**
Structure	Semiconductor nanocrystals typically composed of a semiconductor core encapsulated by another semiconductor shell with a larger spectral band-gap; a third silica shell can be added for water solubility	Nano-machined silicon or a piezoelectric material such as quartz similar to those used in atomic force microscopy	Gold particles in the nanometre size domain; gold nanoshells consist of concentric sphere nanoparticles with a dielectric core (typically gold sulfide or silica) surrounded by a thin gold shell
Size	2–10 nm	Nanoscale	2–150 nm (changes in optical properties as a function of size)
Diagnostic applications	- *In vitro* diagnosis: immune histochemistry, infectious agent detection, fluoro immunoassays, immunoassays, intracellular imaging and tissue imaging. - *In vivo* imaging	DNA and protein (various biomarkers) detection and quantification.	Detection of DNA and proteins (including antibodies)
Method for detecting	Fluorometry and several types of microscopy, such as fluorescence, confocal, total internal reflection, wide-field epi fluorescence, atomic force, and multiphoton microscopy	Operate either statically, by measuring absolute cantilever deflection, or dynamically, by measuring resonance frequency shifts	Surface plasmon resonance microscopy. Gold particles coated with silver have strong light-scattering properties and can easily be detected by standard dark-field microscopy with white light illumination
Advantage	- Their optical tunability, resistance to photobleaching, excitation of various QDs by a single wavelength of light (for multiplexing), narrow emission band, and exceptional stability of optical properties after conjugation to a biomolecule. - They do not need lasers for excitation. - The instrumentation needed for detection is simple.	- Their sensitivity, compatibility with silicon technology, and capacity for microfluidic integration. - Good potential for high throughput protein screening	Their optical properties, useful for imaging and photothermal therapy. Their surfaces, functionalized using various well-characterized chemical moieties (thiols, disulfides, amines)
Toxicity	Risk of leakage of toxic core semiconductor materials into host system or into the environment on disposal	No particular toxicity concerns	No particular toxicity concerns

Table 2: Some drugs using nanocarriers and their administration routes.

. **Compounds**	**Nanocarrier**	**Application**
CPX-1 irinotecan	Liposome	Systemic
DNA (gene therapy)	Solid lipid nanoparticles	Systemic
Tamoxifen citrate	Solid lipid nanoparticles	Systemic
Pilocarpine hydrochloride	Polymeric nanoparticles	Systemic
Ibuprofen	Solid lipid nanoparticles	Topical
Insulin	Solid lipid nanoparticles	Systemic
Clobetasol propionate	Nanostructured lipid carriers	Systemic
Vitamin A	Solid lipid nanoparticles	Topical