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Review Article

NANOPARTICLE: AN OVERVIEW OF PREPARATION, CHARACTERIZATION AND APPLICATION

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ABSTRACT

In the last 30 years, particle size reduction technologies turned from an exploratory approach into a mature commercial drug delivery platform. Nanonization technologies have gained a special importance due to a steadily increasing number of development compounds showing poor aqueous solubility. Many drug delivery companies and academic research groups have contributed to the currently existing large variety of different technologies to produce drug nanoparticles. These particles consist of pure active pharmaceutical ingredient (API) and are often stabilized with surfactants and/or polymeric stabilizers adsorbed onto their surface. The mean particle size ranges normally from 1 nm up to 1000 nm.

Here we review formulation aspects, characteristics and application of nanoparticle as drug delivery system.

KEYWORDS: Nanoparticles, polymeric nanoparticles, targeting, drug delivery, drug release.

INTRODUCTION

The prefix “nano” has found in last decade an ever-increasing application to different fields of the knowledge. Nanoscience, nanotechnology, nanomaterials or nanochemistry are only a few of the new nano-containing terms that occur frequently in scientific reports, in popular books as well as in newspapers and that have become familiar to a wide public, even of non-experts. The prefix comes from the ancient Greek νᾶνος through the Latin nanus meaning literally dwarf and by extension, very small. Within the convention of International System of Units (SI) it is used to indicate a reduction factor of 10^9 times. So, the nanosized world is typically measured in nanometers (1nm corresponding to 10^{-9} m) and it encompasses systems whose size is above molecular dimensions and below macroscopic ones (generally > 1 nm and < 100 nm).

Nanotechnology is the science of the small; the very small. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently, and provide a variety of surprising and interesting uses. Nanotechnology and Nanoscience studies have emerged rapidly during the past years in a broad range of product domains. It provides opportunities for the development of materials, including those for medical applications, where conventional techniques may reach their limits. Nanotechnology should not be viewed as a single technique that only affects specific areas. Although often referred to as the ‘tiny science’, nanotechnology does not simply mean very small structures and products. Nanoscale features are often incorporated into bulk materials and large surfaces. Nanotechnology represents the design, production and application of materials at atomic, molecular and macromolecular scales, in order to produce new nanosized materials.[1] Pharmaceutical nanoparticles are defined as solid, submicron-sized (less than 100 nm in diameter) drug carrier that may or may not be biodegradable. The term nanoparticle is a combined name for both nanospheres and nanocapsules. Nanospheres are matrix system in which drug is uniformly dispersed, while nanocapsules are the system in which the drug is surrounded by a unique polymeric membrane.

This systemic review focuses on Classification, method of preparation, Characterization, and applications of nanoparticles.

Need for developing nanoparticles

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents so as to achieve the site specific action of the drug at the rationale rate and dose.[2] Polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties.[3]

Advantages

Some of the advantages of using nanoparticles as a drug delivery system are as follows;

1. Ease of manipulation of the particle size and surface characteristics of nanoparticles so as to achieve both passive and active drug targeting after parenteral administration.
2. The nanoparticle surface can be modified to alter biodistribution of drugs with subsequent clearance of the drug so as to achieve maximum therapeutic efficacy with minimal side effects of the drug.[4]
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
4. 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.
5. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
6. Liposomes and polymer based nanoparticulates are generally biodegradable, do not accumulate in the body and so are possibly risk free.
7. Small sized nanoparticles can penetrate through smaller capillaries, which could allow efficient drug accumulation at the target sites.
8. Various routes of administration are available including oral, nasal, parenteral, intra-ocular etc.[5]

Limitations

In spite of these advantages nanoparticles do have limitations like,

1. Altered physical properties which lead to particle – particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size and larger surface area.
2. Smaller the particles size greater the surface area and this property makes nanoparticles very reactive in the cellular environment.
3. Small particles size results in limited drug loading and burst release. These practical problems have to be sorted out before nanoparticles can be used clinically or made commercially available.[6]

Toxicity

These tiny particles can easily get the entry inside the body through the skin, lungs or intestinal tract, depositing in several organs and may cause severe adverse biological reactions by altering the physiochemical properties of tissue. Non-biodegradable particles when used for drug delivery may show accumulation on the site of the drug delivery, leading to chronic inflammatory reactions. Most of the nanoparticulate toxicity reactions are observed due to inhalation of particulate matter leading to lung and cardiovascular diseases.

Types of Nanoparticles

Polymeric nanoparticles are colloidal structures composed of synthetic or semi synthetic polymers. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsule 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. The general synthesis and encapsulation of polymer are represented in Fig.1. Polymers such as polysaccharide Chitosan-Polylactic acid, Polylactic acid coglycolic acid, Poly-caprolactone, Chitosan nanoparticles have been used.

Solid lipid nanoparticles (SLN) have been proposed as a new type of colloidal drug carrier system suitable for intravenous administration. The system consists of spherical solid lipid particles in the nanometres range, which is dispersed in water or in surfactant solution.[7]

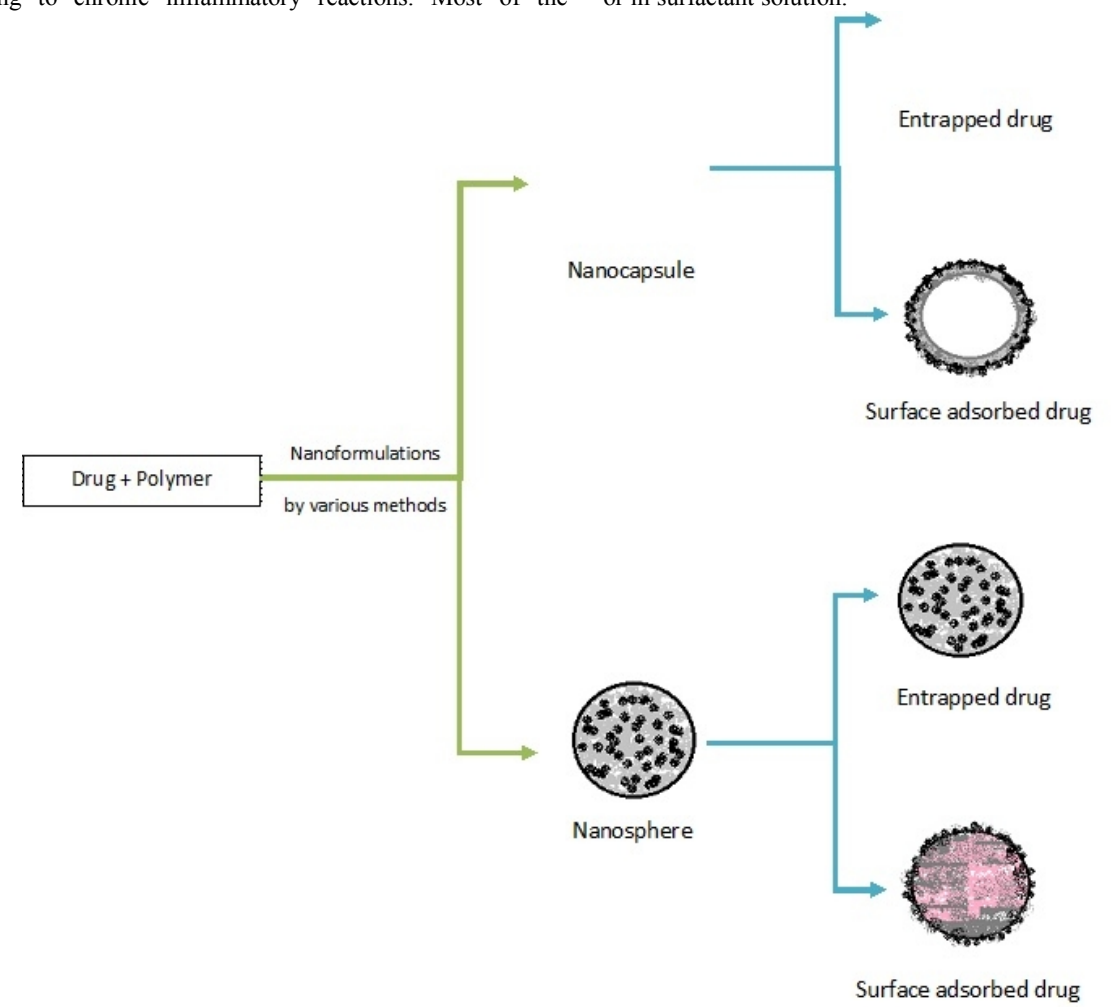

Figure 1: Types of polymeric nanoparticles: According to the structural organization biodegradable nanoparticles are classified as Nanocapsules and nanospheres. The drug molecules are either entrapped inside or adsorbed on the surface.

Classification of Nanoparticles

There are various approaches for classification of nanomaterials. Nanoparticles are classified based on one, two and three dimensions. [8]

One dimension nanoparticles

One dimensional system, such as thin film or manufactured surfaces, has been used for decades in electronics, chemistry and engineering. Production of thin films (sizes1-100 nm) or monolayer is now common place in the field of solar cells or catalysis. These thin films are using in different technological applications, including information storage systems, chemical and biological sensors, fibre-optic systems, magneto-optic and optical device.

Two dimension nanoparticles

Carbon nanotubes (CNTs): Carbon nanotubes are hexagonal network of carbon atoms, 1 nm in diameter and 100 nm in length, as a layer of graphite rolled up into cylinder. CNTs are of two types, single walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) .The small dimensions of carbon nanotubes, combined with their remarkable physical, mechanical and electrical properties make them unique materials. They display metallic or semi conductive properties, depending on how the carbon leaf is wound on itself. The current density that nanotubes can carry is extremely high and can reach one billion amperes per square meter making it a superconductor. The mechanical strength of carbon nanotubes is sixty times greater than the best steels. Carbon nanotubes have a great capacity for molecular absorption and offering a three dimensional configuration. Moreover they are chemically and chemically very stable.[9]

Three dimension nanoparticles

Fullerenes (Carbon 60): Fullerenes are spherical cages containing from 28 to more than 100 carbon atoms, contain C_{60}. This is a hollow ball composed of interconnected carbon pentagons and hexagons, resembling a soccer ball. Fullerenes are class of materials displaying unique physical properties. They can be subjected to extreme pressure and regain their original shape when the pressure is released. These molecules do not combine with each other, thus giving them major potential for application as lubricants. They have interesting electrical properties and it has been suggested to use them in the electronic field, ranging from data storage to production of solar cells. Fullerenes are offering potential application in the rich area of nanoelectronics. Since fullerenes are empty structures with dimensions similar to several biological active molecules, they can be filled with different substances and find potential medical application. [10]

Dendrimers: Dendrimers represents a new class of controlled-structure polymers with nanometric dimensions. Dendrimers used in drug delivery and imaging are usually 10 to 100 nm in diameter with multiple functional groups on their surface, rendering them ideal carriers for targeted drug delivery.[11] The structure and function of dendrimers has been well studied. Contemporary dendrimers can be highly specialized; encapsulating functional molecules (i.e., therapeutic or diagnostic agents) inside their core.[12] They are considered to be basic elements for large-scale synthesis of organic and inorganic nanostructures with dimensions of 1 to 100 nm [11]. They are compatible with organic structure such as DNA and can also be fabricated to metallic nanostructure and nanotubes or to possess an encapsulation capacity.[13] Dendrimers have different reactive surface groupings (nanostructure) and compatible with organic structure such as DNA so their prolific use is particularly in the medical and biomedical fields. The pharmaceutical applications of dendrimers include nonsteroidal anti-inflammatory formulations, antimicrobial and antiviral drugs, anticancer agents, pro-drugs, and screening agents for high-throughput drug discovery.[14] Dendrimers may be toxic because of their ability to disrupt cell membranes as a result of a positive charge on their surface.[15]

Quantum Dots (QDs): Quantum dots are small devices that contain a tiny droplet of free electrons. QDs are colloidal semiconductor nanocrystals ranging from 2 to 10 nm in diameter. QDs can be synthesized from various types of semiconductor materials via colloidal synthesis or electrochemistry. The most commonly used QDs are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs). Quantum dots can have anything from a single electron to a collection of several thousands. The size, shape and number of electrons can be precisely controlled. They have been developed in a form of semiconductors, insulators, metals, magnetic materials or metallic oxides. It can be used for optical and optoelectronic devices, quantum computing, and information storage. Colour coded quantum dots are used for fast DNA Testing. Quantum dots (QDs) refer to the quantum confinement of electrons and hole carriers at dimensions smaller than the Bohr radiuos. QD nanocrystals are generally composed of atoms from groups II and VI (that is CdSe, CdS, and CdTe) or II and V (such as In P) at their core. A shell (that is ZnS and CdS) can be further introduce to prevent the surface quenching of excitons in the emissive core and hence increase the photostability and quantum yield of emission.[16] QDs also provide enough surface area to attach therapeutic agents for simultaneous drug delivery and in vivo imaging, as well as for tissue engineering.[17]

Preparation of Polymeric Nanoparticles

Nanoparticles can be prepared from a natural material such as proteins, polysaccharides and synthetic polymers. The selection of inert matrix material is depends on many factors like:[18] (a) final size of nanoparticles required; (b) drug properties like aqueous solubility and stability; (c) surface charge and permeability; (d) degree of biodegradability, biocompatibility and toxicity; (e) desired drug release profile; and (f) Antigenicity of the final product.

The preparation method of nanoparticles can be classified in different ways:

In the first, it can be classified as:

- Bottom-up technique
- Chemical reaction technique
- Top-down technique
- Combination technique

Nanoparticles can be obtained by using bottom-up processes, i.e. precipitation starting from molecular solutions. Furthermore, comminution of larger particles down to nanoparticles (top-down) can be performed. Another way is the combination of both principles (combination techniques). The last way leads via a chemical reaction step directly to nanoparticles (chemical reaction approach).

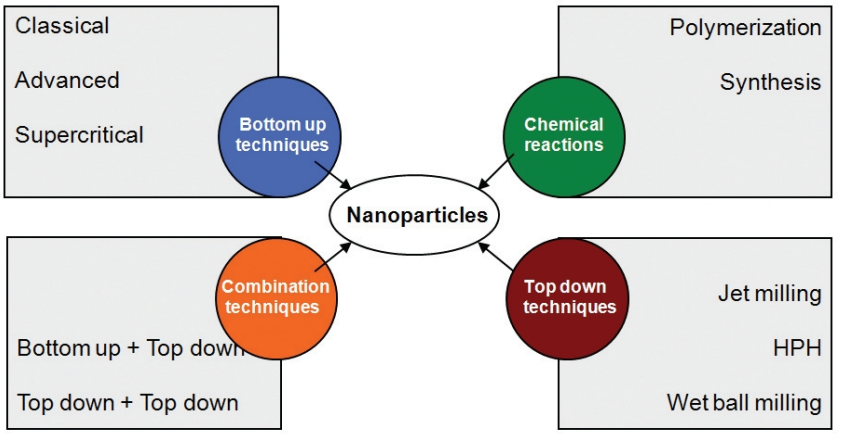

Figure 2: Overview of various principles to produce nanoparticles

Chemical Reactions

Chemical reactions, like polymerizations, are one way to produce nanoparticles; however they are normally not used for the production of drug nanoparticles consisting of pure API.

These techniques are commercially very important e.g. for the production of pharmaceutical coating materials in the form of latex dispersions. Chemical reactions can also be used to manufacture polymeric nanoparticles consisting of a matrix forming polymer in which the API is embedded. The drug load of such particles is normally significantly lower than 100% therefore they have to be distinguished from drug nanoparticles produced via standard particle size reduction techniques.

Bottom-up Approaches

Bottom-up approaches start with drug molecules in solution. By changing the conditions of the system in solution, the drug molecules start to precipitate in larger formations. In the classical precipitation process, the poorly soluble API is dissolved in a water miscible organic solvent. The precipitation is induced by mixing the drug solution with an aqueous phase. This is often referred to as the "solvent/ antisolvent" approach. One approach was already developed in the 1980's by Sucker and colleagues. The principle of classical precipitation has been then further developed by several academic and industrial research groups. Later also more and more advanced precipitation technologies have been introduced. These technologies are also referred to as particle engineering technologies. One interesting approach is known as Evaporative Precipitation into Aqueous Solution (EPAS). For this process, the API is dissolved in an organic solvent which is not miscible with water. The drug solution is sprayed into heated water resulting in an immediate evaporation of the organic solvent, thus drug nanoparticles are formed instantaneously. Spray-freezing into liquid (SFL) and ultrarapid freezing (URF) are alternative particle engineering processes developed by the same research group.

Top-down Approaches

In contrast to the bottom-up technologies, one can also start with large API particles and break them down to small drug nanoparticles. Therefore, this process type is regarded as top-down technology. Currently particle size reduction technologies of this type are by far commercially the most important and successful. A very important technology is based on wet ball milling (WBM). In order to produce nanocrystalline dispersions, a milling chamber is charged with milling media (e.g. zirconium dioxide beads, silicium nitride beads, polystyrene beads), aqueous stabilizer/ surfactant solution and micronized API. The moving milling media causes high shear forces and thus attrition of the drug particles. For large scale production, the mill can be run in circulation mode, which means that the suspension is continuously pumped through the milling chamber until the desired particle size of the drug nanocrystals is obtained. The drug particles are separated from the milling media by a separating gap or a filter cartridge. The WBM technology is by far the most important particle size reduction method at the moment. Currently there are 5 products on the market using this technology; many others are still in development. High pressure homogenization (HPH) is another very important top-down technology. One can distinguish several process types. The first technology that was developed based on HPH with a piston-gap homogenizer is a process performed in aqueous media at room temperature. During the homogenization step, a coarse suspension is forced through a very tiny homogenization gap. The particle size reduction is mainly caused by cavitation forces, shear forces, and particle collision. Later, this principle was further development as a process, which can be also performed in water-reduced and non-aqueous media. Drug nanoparticles can be also generated by a high shear process using jet stream homogenizers. In this case the collision of two fluid streams under high pressures up to 1700 bar leads to particle collision, shear forces and also cavitation forces. To preserve the particle size, stabilization with phospholipids or other surfactants and stabilizers is required. A major disadvantage of this process is the required production time. In many cases, time consuming 50 to 100 passes are necessary for a sufficient particle size reduction. This technology is now also used for one product on the market.

The last production principle is a relatively new one. The combinative approach describes a process where at least two different particle size reduction principles are combined. The most common combination is a bottom-up process which is combined with a top-down step.[19]

In an another way the preparation of nanoparticles can be classified as: [20]

A) Dispersion of preformed polymers

1. Solvent evaporation method

2. Spontaneous emulsification or solvent diffusion method

B) Polymerization of monomers

C) Ionic gelation or coacervation of hydrophilic polymers
D) Supercritical fluid technology
However, other methods such as particle replication in non-wetting templates (PRINT) [21] have also been described in the literature for production of nanoparticles.

A) Dispersion of preformed polymers: It is the most 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 (cyanoacrylates) (PCA). [22, 23]

1. Solvent evaporation method: Organic solvents such as dichloromethane, chloroform or ethyl acetate are used to dissolve the polymer which is also used as the solvent for dissolving the hydrophobic drug. The drug dissolved or dispersed in polymer solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form oil in water emulsion. Once stable emulsion is formed, the organic solvent is evaporated either by reducing the pressure or by continuous stirring. For preparation of the small uniform sized particle size, High-speed homogenizer or ultrasonication may be employed.[24]

2. Spontaneous emulsification or solvent diffusion method: This is a modification of solvent evaporation method. This technique involves the use of water miscible solvent along with a small amount of the water immiscible organic solvent as an oil phase. An interfacial turbulence is generated between the two phases due to spontaneous diffusion of immiscible solvents leading to the formation of small particles. By increasing the concentration of water miscible solvent decrease in the particle size can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. For hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.[25]

B) Polymerization method: In this method, monomers are polymerized to form nanoparticles in an aqueous solution in which drug may be dissolved. Drug may also be incorporated by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactants employed for polymerization by ultracentrifugation and resuspending the particles in an isotonic surfactant-free medium. This technique has been reported for making polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles. [26, 27]

C) Coacervation or ionic gelation method: The method involves a mixture of two aqueous phases, of which one is the polymer Chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. In this method, positively charged amino group of Chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometre. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature. [28, 29]

D) Supercritical fluid technology: Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of enormous amounts of organic solvents which are hazardous to the environment as well as to human beings. Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro- and nanoparticles. Supercritical fluids are environmentally safe.[30] A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 (SC CO_2) is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bars), nontoxicity, non-flammability and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent (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 fluid (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 the formation of nanoparticles. The solvent power of supercritical fluids dramatically decreases and the solute eventually precipitates. This technique is clean because the precipitate is basically solvent free. RESS and its modified process have been used for the product of polymeric nanoparticles.[31, 32] Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.

Characterization of Nanoparticles

Nanoparticles are generally characterized by their size, morphology and surface charge, using such advanced microscopic techniques as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). The average particle diameter, their size distribution and charge affect the physical stability and the in vivo distribution of the nanoparticles. Electron microscopy techniques are very useful in ascertaining the overall shape of polymeric nanoparticles, which may determine their toxicity. The surface charge of the nanoparticles affects the physical stability and redispersibility of the polymer dispersion as well as their in vivo performance.

Particle size

Particle size distribution and morphology are the most important parameters of characterization of nanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affects the drug release. Smaller particles offer larger surface area. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to fast drug release. On the contrary, drugs slowly diffuse inside larger particles. As a drawback, smaller particles tend to aggregate during storage and transportation of nanoparticle dispersion. Hence, there is a compromise between a small size and maximum stability of nanoparticles.[33]

Polymer degradation can also be affected by the particle size. For instance, the degradation rate of poly (lactic-co-glycolic

acid) was found to increase with increasing particle size in vitro. [34]

There are several tools for determining nanoparticle size as discussed below:

Dynamic light scattering (DLS)

Currently, the fastest and most popular method of determining particle size is photon-correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is widely used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges. Shining monochromatic light (laser) onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light. This change is related to the size of the particle. It is possible to extract the size distribution and give a description of the particle's motion in the medium, measuring the diffusion coefficient of the particle and using the autocorrelation function. . The photon correlation spectroscopy (PCS) represent the most frequently used technique for accurate estimation of the particle size and size distribution based on DLS. [35]

Scanning Electron microscopy

Scanning electron microscopy (SEM) is giving morphological examination with direct visualization. The techniques based on electron microscopy offer several advantages in morphological and sizing analysis; however, they provide limited information about the size distribution and true population average. For SEM characterization, nanoparticles solution should be first converted into a dry powder, which is then mounted on a sample holder followed by coating with a conductive metal, such as gold, using a sputter coater. The sample is then scanned with a focused fine beam of electrons.[36] The surface characteristics of the sample are obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to withstand vacuum, and the electron beam can damage the polymer. The mean size obtained by SEM is comparable with results obtained by dynamic light scattering. Moreover, these techniques are time consuming, costly and frequently need complementary information about sizing distribution.

Transmission electron microscope

TEM operates on different principle than SEM, yet it often brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultra thin for the electron transmittance. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles withstand the instrument vacuum and facilitate handling, they are fixed using either a negative staining material, such as phosphotungstic acid or derivatives, uranyl acetate, etc, or by plastic embedding. Alternate method is to expose the sample to liquid nitrogen temperatures after embedding in vitreous ice. The surface characteristics of the sample are obtained when a beam of electrons is transmitted through an ultra thin sample, interacting with the sample as it passes through.[37]

Atomic force microscopy

Atomic force microscopy (AFM) offers ultra-high resolution in particle size measurement and is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale.[38] Instrument provides a topographical map of sample based on forces between the tip and the sample surface. Samples are usually scanned in contact or noncontact mode depending on their properties. In contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe hovers over the conducting surface in non-contact mode. The prime advantage of AFM is its ability to image non-conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures.[39] AFM provides the most accurate description of size and size distribution and requires no mathematical treatment. Moreover, particle size obtained by AFM technique provides real picture which helps understand the effect of various biological conditions.[40]

Surface Charge

The nature and intensity of the surface charge of nanoparticles is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. The colloidal stability is analyzed through zeta potential of nanoparticles. This potential is an indirect measure of the surface charge. It corresponds to potential difference between the outer Helmholtz plane and the surface of shear**.** The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion. High zeta potential values, either positive or negative, should be achieved in order to ensure stability and avoid aggregation of the particles. The extent of surface hydrophobicity can then be predicted from the values of zeta potential. The zeta potential can also provide information regarding the nature of material encapsulated within the nanocapsules or coated onto the surface.[41]

Surface hydrophobicity

Surface hydrophobicity can be determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, contact angle measurements etc. Recently, several sophisticated analytical techniques are reported in literature for surface analysis of nanoparticles. X – Ray photon correlation spectroscopy permits the identification of specific chemical groups on the surface of nanoparticles.[42]

Drug loading

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 end functional groups (ester or carboxyl).[43]

Drug Release

A central reason for pursuing nanotechnology is to deliver drugs, hence understanding the manner and extent to which the drug molecules are released is important. In order to

obtain such information most release methods require that the drug and its delivery vehicle be separated. The drug loading of the nanoparticles is generally defined as the amount of drug bound per mass of polymer (usually moles of drug per mg polymer or mg drug per mg polymer); it could also be given as percentage relative to the polymer. The technique used for this analysis is classical analytical methods like UV spectroscopy or high performance liquid chromatography (HPLC) after ultracentrifugation, ultra filtration, gel filtration, or centrifugal ultrafiltration. Quantification is performed with the UV spectroscopy or HPLC. Drug release assays are also similar to drug loading assay which is assessed for a period of time to analyze the mechanism of drug release.[44]

Methods of evaluation for release of drugs

Various methods which can be used to study the in vitro release of the drug from nanoparticles are:

(i) Side-by-side diffusion cells with artificial or biological membranes.
(ii) Dialysis bag diffusion technique.
(iii) Reverse dialysis bag technique.
(iv) Agitation followed by ultracentrifugation/ centrifugation.
(v) Ultra-filtration or centrifugal ultra-filtration techniques.

Commonly release study is carried out by controlled agitation and centrifugation. As the method is time consuming and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

There are five possible mechanisms for drug release: (a) desorption of drug bound to the surface, (b) diffusion through the nanoparticle matrix, (c) diffusion through the polymer wall of nanocapsule, (d) nanoparticles matrix erosion, or (e) a combined erosion–diffusion process.[45] The kinetic analysis of drug release from nanoparticles can be described by a biexponential function

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

Where C is the concentration of drug remaining in the nanoparticles at time t, A and B are system characteristic constants (A is used for diffusion control system and B for erosion control system) and α, β are rate constants that can be obtained from semi logarithmic plots.[45] In general drug release rate depends upon solubility, diffusion and biodegradation of the matrix materials.

Applications of Nanoparticulate Delivery Systems

a) Nanoparticle as drug delivery systems

The use of pharmacological agents is frequently limited by drug resistance at the target level owing to physiological barriers cellular mechanism is encountered. In addition, many drugs have a poor solubility, low bioavailability and they can be quickly cleared in the body by the reticuloendothelial system. Furthermore, the efficacy of different drugs, such as chemotherapeutical agents, is often limited by dose- dependent side effects.

Gastrointestinal tract: Other portals for entry are GI and Skin. It is known that the kinetics of particle uptake in GI tract depends on diffusion and accessibility through mucus initial contact with enterocytes, cellular trafficking and post-translocation events. The smaller the particle diameter is, the faster they could diffuse through GI secretion to reach the colonic enterocytes Following uptake by GI tract nanoparticles can translocate to the blood stream and distribute all over the body. Targeting strategies to improve the interaction of nanoparticles with adsorptive sites (enterocytes and M-cells of Peyer's patches) in the GI tract utilizes specific binding to ligands or receptors and nonspecific adsorptive mechanism. The surface of enterocytes and M cells shows cell-specific carbohydrates, which can serve as binding sites to nanoparticle drug carriers with appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism.

Brain: The brain is probably one of the least accessible organs for the delivery of drugs due to the presence of the blood–brain barrier (BBB) that controls the transport of endogenous and exogenous compounds, thus providing the neuroprotective function. Drugs normally unable to cross the BBB could be delivered to the brain after binding to the surface-modified poly (butyl cyanoacrylate) (PBCA) nanoparticles.[46]

Tumor cell targeting: Anticancer drugs, which usually have large volume of distribution, are toxic to both normal and cancer cells. Therefore, precise drug release into highly specified target involves miniaturizing the delivery systems to become much smaller than their targets. With the use of nanotechnology, targeting drug molecules to the site of action is becoming a reality resulting in a personalized medicine, which reduces the effect of the drug on other sites while maximizing the therapeutic effect. This goal is mainly achieved by the small size of these particles, which can penetrate across different barriers through small capillaries into individual cells. In addition, nanoparticles can be prepared to entrap, encapsulate, or bind molecules improving the solubility, stability and absorption of several drugs, as well as avoiding the reticulo-endothelial system, thus protecting the drug from premature inactivation during its transport. In fact, it has been shown that nanoparticles have the ability to carry various therapeutic agents including DNA, proteins, peptides and low molecular weight compounds. Among all of them, liposome and polymer-based nanoparticulates are the most widely used nanoparticles as drug delivery systems, as these compounds are generally biodegradable, do not accumulate in the body and they are possibly risk-free. For instance, several anticancer drugs, including paclitaxel, 5-fluorouracil, doxorubicin, have been successfully formulated using polymers and liposomes as drug delivery systems.

Respiratory tract: One of the most common entry passages for nanoparticles is respiratory tract. Nanoparticles could avoid normal phagocytic defences therein respiratory tract and gain access to systemic circulation and may reach to CNS. Aerosol therapy using nanoparticles as drug carrier is gaining importance for delivering therapeutic compounds. The lung is an attractive target for drug delivery due to non-invasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases and the availability of a huge surface area for local drug action and systemic absorption of drug. Colloidal carriers (i.e., nanocarrier systems) in pulmonary drug delivery offer many advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous

solubility, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects and the potential of drug internalization by cells.[47]

b) For gene delivery

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. 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 endo-lysosomal compartment to the cytoplasmic compartment.[48] Following the 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.[46]

c) For Diagnosis and Bioimaging

A number of molecular imaging techniques are available, such as optical imaging (OI), magnetic resonance imaging (MRI), ultrasound imaging (USI), positron emission tomography (PET) and others have been reported for imaging of in vitro and in vivo biological specimens.[49, 50] The current development of luminescent and magnetic nanoparticles advances bio imaging technologies.[51] Two different types of nanoparticles have been widely used for imaging: luminescent nanoprobes for OI and magnetic nanoparticles for MRI. There are also dual-mode nanoparticles for simultaneous imaging by OI and MRI.[52] Nanobiotech scientists have successfully produced microchips that are coated with human molecules. The chip is designed to emit an electrical impulse signal when the molecules detect signs of a disease. Special sensor nanobots can be inserted into the body under the skin where they check blood contents and warn of any possible diseases. They can also be used to monitor the sugar level in the blood. Advantages of using such nanobots are that they are very cheap and easy to produce.[53] Gold nanoparticles are being used for detection of cancer. Gold nanoparticles have been used as ultrasensitive fluorescent probes to detect cancer biomarkers in human blood. The method is very sensitive and could also be employed in direct detection of viral or bacterial DNA. Gold nanoparticles are promising probes for biomedical applications because they can be easily prepared and, unlike other fluorescent probes such as quantum dots or organic dyes, don't burn out after long exposure to light.[54]

d) Tissue repair

Tissue repair using iron oxide nanoparticle is accomplished either through welding, apposing two tissue surfaces then heating the tissues sufficiently to join them, or through soldering, where protein or synthetic polymer-coated nanoparticles are placed between two tissue surfaces to enhance joining of the tissues. Temperatures greater than 50°C are known to induce tissue union induced by the denaturation of proteins and the subsequent entanglement of adjacent protein chains.[55] This is believed to be nanoparticles that strongly absorb light corresponding to the output of a laser are also useful for tissue-repairing procedures. Specifically, gold- or silica-coated iron oxide nanoparticles have been designed to strongly absorb light.[56] The nanoparticles are coated onto the surfaces of two pieces of tissue at the site where joining was desired. This technique affords methods to minimize tissue damage by using the least harmful wavelengths of light and/or lower powered light sources. Stem cells are the body's master cells and have a unique ability to renew them and give rise to other specialized cell types.

Some of the selected Drugs as Nano Drug Delivery System

Name of the drug	Purpose
Clonazepam	To determine the drug loading capacity & drug release. [59]
Morphine	To study antinociceptive activity and blood brain delivery. [60]
Adriamycin	To enhance effective delivery of Adriamycin. [61]
Dexamethasone	To increase the amount of drug release with respect to pure drug. [62]
Tamoxifen	To increase the local concentration of tamoxifen in estrogen receptor positive breast cancer cells. [63]
Cyclosporin A	To form stable suspension of submicron particles of Cyclosporin A. [64]
Praziquantel	To study the effect of formulation variables on size distribution. [65]
Aspirin	Capable of releasing the drug in a slow sustained manner. [66]
Docetaxel	For effective delivery of drug to solid tumors. [67]
Estradiol	To increase oral bioavailability of Estradiol. [68]
Cyproterone	To improve skin penetration of the poorly absorbed drug Cyproterone. [69]
Curcumin	For coating curcumin onto a metal stent by electrophoretic deposition thereby avoiding problem with restenosis after percutaneous coronary intervention.[70]
Ropivacaine	To decrease the systemic toxicity of ropivacaine. [71]
Didanosine	For sustained release of Didanosine. [72]
Lamivudine	Increased bioavailability of lamivudine is observed when tested in AIDS patients. [73]
Simvastatin	To enhance effective delivery of poorly water soluble drug simvastatin. [74]
Doxorubicin	To improve oral bioavailability of Doxorubicin. [75]
Amphotericin B	To improve oral bioavailability and to show reduced nephrotoxicity compared to intravenous fungizone. [76]
Rifampicin	To formulate Rifampicin for aerosol delivery in a dry powder, which is suited for shelf stability, effective dispersibility and extended release with local lung and systemic drug delivery. [77]
Curcumin	To enhance the transport of curcumin to brain and to enhance the delivery system to cross the BBB. [78]

Some Marketed Nanoformulations

Brand Name	API	Company
Daunoxome	Doxorubicin	Gilead Sciences.
Ambisome	Amphotericin B	Gilead Sciences
Amphotec	Amphotericin B	Alza
Abelect	Amphotericin B	Elan
Rapamune	Sirolimus	Elan/Wyeth
Emend	Aprepitatnt	Elan/Merck
Tricor	Fenofibrate	Elan/Abbot.
Triglide	Fenofibrate	First Horizon Pharmaceuticals

These cells, therefore, have the potential to be used for transplantation purposes, for example, to replace degenerated cells or repairing of a damaged tissue, providing signals so that the stem cells can yield the appropriate cell types for the development of a tissue.[57] In addition, various proteins, growth factors, etc., could be bound to these nanoparticles that might be delivered at the damaged tissue, where it would play a role in tissue development. Magnetic nanoparticles can also be used to target the stem cells and activate at required sites of injury and repair in diseases such as diabetes, cancer, heart disease, Alzheimer's and Parkinson's disease.[58] Biodegradable nanoparticle-based vaccines, for oral vaccination, are also in development and may allow targeting of antigens to specific dendritic cell receptors.

Future Opportunities and Challenges

Nanoparticles and nanoformulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumor therapy, gene therapy, AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood - brain barrier.

CONCLUSION

Nanoparticles present a highly attractive platform for a diverse array of biological applications. The surface and core properties of these systems can be engineered for individual and multimodal applications, including tissue engineering, therapeutic delivery, biosensing and bioimaging. 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. Nanotechnology-enabled drug delivery is opening prospective future in pharmaceutics. 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.

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