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Role of Nanoparticles in Drug Delivery System : A Comprehensive review

C.Karuppusamy, and P.Venkatesan
Department of Pharmacy, Faculty of Engineering & Technology,
Annamalai University, Annamalai Nagar, Tamilnadu, India 608 002

Abstract

Novel drug delivery systems have several advantages over conventional multi dose therapy. For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems using nanoparticles. Nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules. A well designed drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug. Polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their controlled and sustained release properties, subcellular size, biocompatibility with tissue and cells. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. The intent of the paper is to highlight the potential of nanoparticle formulation, characterization, advantages of nanoparticles and their applications in delivery of drug molecules.

Keywords: Nanoparticles, controlled release, sustained release, target site, therapeutic efficacy, novel drug delivery.

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. According to the definition from NNI (*National Nanotechnology Initiative*), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix “nano” is commonly used for particles that are up to several hundred nanometers in size.

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 nanosphares 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, application, health prospective and Pharmacological aspects of nanoparticles [2].

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bioactive compounds [3]. Liposomes, solid lipids nanoparticles, dendrimers, polymers, silicon or carbon materials, and magnetic nanoparticles are the examples of nanocarriers that have been tested as drug delivery systems (Fig. 1).

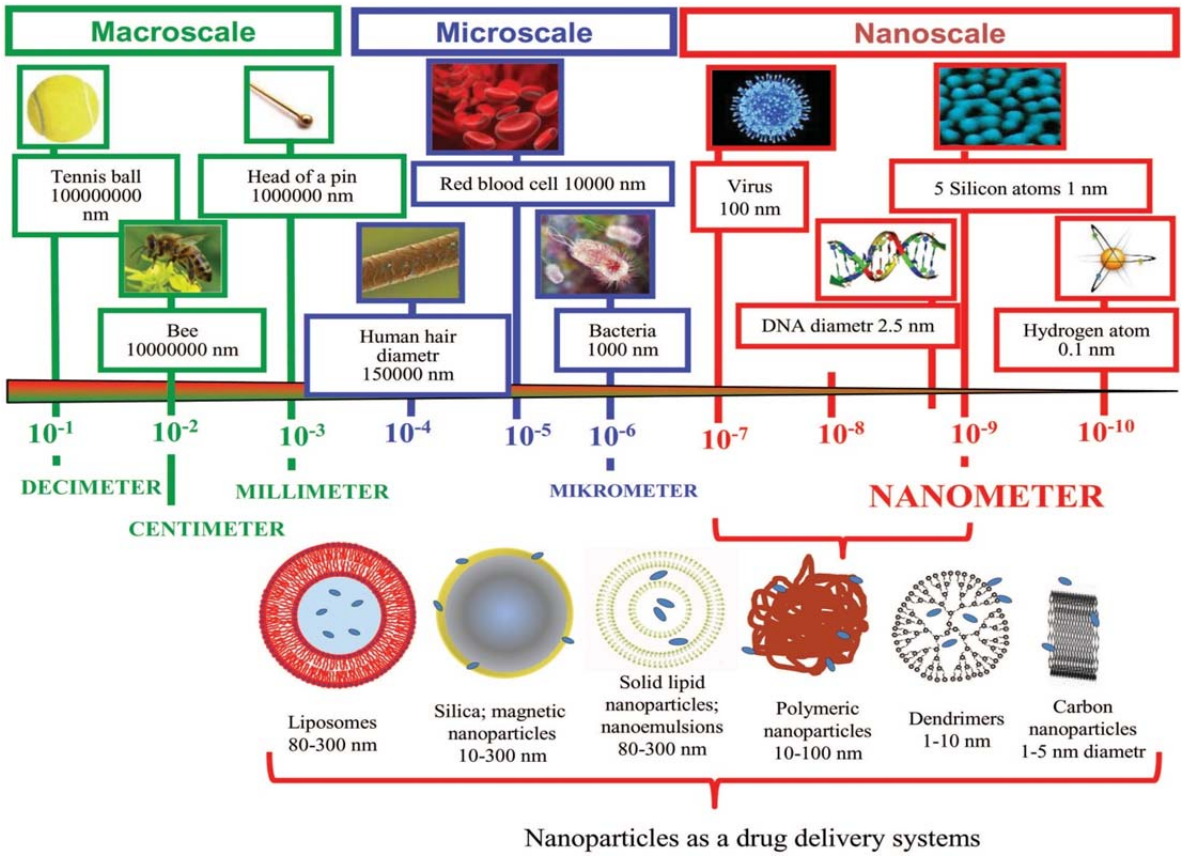

Fig 1. Nanoparticle drug delivery systems with relation to other scales

CLASSIFICATION OF NANOPARTICLES

There are various approaches for classification of nanomaterials. Nanoparticles are classified based on one, two and three dimensions [4].

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. This 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 [5]. 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.

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 [6].

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 [7]. 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 [8]. They are considered to be basic elements for large-scale synthesis of organic and inorganic nanostructures with dimensions of 1 to 100 nm [6]. 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 [9]. 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 [10]. Dendrimers may be toxic because of their ability to disrupt cell membranes as a result of a positive charge on their surface [11].

Quantum Dots (QDs):

Quantum dots are small devices that contain a tiny droplet of free electrons. Ds 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 ots (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 (Goldberg M et al., 2007). QDs also provide enough surface area to attach therapeutic agents for simultaneous drug delivery and in vivo imaging, as well as for tissue engineering [12].

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are structures with a diameter ranging from 10 to 100 nm. The PNPs are obtained from synthetic polymers, such as poly- £-caprolactone [13], polyacrylamide [14] and polyacrylate [15], or natural polymers, e.g., albumin [16], DNA [17], chitosan [17, 18] gelatin [19]. Based on *in vivo* behavior, PNPs may be classified as biodegradable, i.e., poly(L-lactide) (PLA) [20], poly- glycolide (PGA) [21], and non-biodegradable, e.g., polyurethane [22].

PNPs are usually coated with nonionic surfactants in order to reduce immunological interactions (e.g. opsonization or presentation PNPs to CD8 T-lymphocytes) as well as intermolecular interactions between the surface chemical groups of PNPs (e.g., van der Waals forces, hydrophobic interaction or hydrogen bonding) [23].

Drugs can be immobilized on PNPs surface after a polymerization reaction [24] or can be encapsulated on PNP structure during a polymerization step [25]. Moreover, drugs may be released by desorption, diffusion, or nanoparticle erosion in target tissue [23].

The application of biodegradable nanosystems for the development of nanomedicines is one of the most successful ideas. Nanocarriers composed of biodegradable polymers undergo hydrolysis in the body, producing biodegradable metabolite monomers, such as lactic acid and glycolic acid. Kumari et al. [26] re- ported a minimal systemic toxicity associated with using of PLGA for drug delivery or biomaterial applica- tions. Such nanoparticles are biocompatible with tis- sue and cells [27]. Drug-biodegradable polymeric nanocarrier conjugates used for drug delivery are stable in blood, non-toxic, and non-thrombogenic. They are also non-immunogenic as well as non-pro inflammatory, and they neither activate neutrophils nor affect reticuloendothelial system [28].

The field of polymer nanoparticles (PNPs) is quickly expanding and playing an important role in a wide spectrum of areas ranging from electronics, photonics, conducting materials, sensors, medicine, biotechnology, pollution control and environmental technology [29-37]. PNPs are promising vehicles for drug delivery by easy manipulation to prepare carriers with the objective of delivering the drugs to specific target, such an advantage improves the drug safety [38]. Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective permeation through cell membranes and stability in the blood stream. Polymers are very convenient materials for the manufacture of countless and varied molecular designs that can be integrated into unique nanoparticle constructs with many potential medical applications [39]. Several methods have been developed during the last two decades for preparation of PNPs, these techniques are classified according to whether the particle formation involves a polymerization reaction or nanoparticles form directly from a macromolecule or preformed polymer or ionic gelation method.

Mechanisms of drug release [40]

The polymeric drug carriers deliver the drug at the tissue site by any one of the three general physico-chemical mechanisms.

- By the swelling of the polymer nanoparticles by hydration followed by release through diffusion.
- By an enzymatic reaction resulting in rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core.
- Dissociation of the drug from the polymer and its de adsorption/release from the swelled nanoparticles.

Preparation of nanoparticles

The properties of PNPs have to be optimized depending on the particular application. In order to achieve the properties of interest, the mode of preparation plays a vital role. Thus, it is highly advantageous to have preparation techniques at hand to obtain PNPs with the desired properties for a particular application. Different techniques like polymerization, preformed polymers or ionic gelation etc are used. The selection of appropriate method for the preparation of nanoparticles depends on the physicochemical character of the polymer and the drug to be loaded. The primary manufacturing methods of nanoparticles from preformed polymer includes:

Emulsion-Solvent Evaporation Method

This is one of the most frequently used methods for the preparation of nanoparticles. Solvent evaporation was the first method developed to prepare PNPs from a. In this method, polymer solutions are prepared in volatile solvents and emulsions are formulated. In the past, dichloromethane and chloroform preformed polymer[40] were widely used, but are now replaced with ethyl acetate which has a better toxicological profile. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods utilize high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. Afterwards, the solidified nanoparticles can be collected by ultracentrifugation and washed with distilled water to remove additives such as surfactants. Finally, the product is lyophilized [41]. Lemoine *et al* [42] prepared PLGA nanoparticles of about 200nm by utilizing dichloromethane 1.0% (w/v) as the solvent and PVA or Span 40 as the stabilizing agent. Song *et al.*[43] prepared nanoparticles of PLGA with a typical particle size of 60–200nm by employing dichloromethane and acetone (8:2, v/v) as the solvent system and PVA as the stabilizing agent. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultra-sonication may be employed.

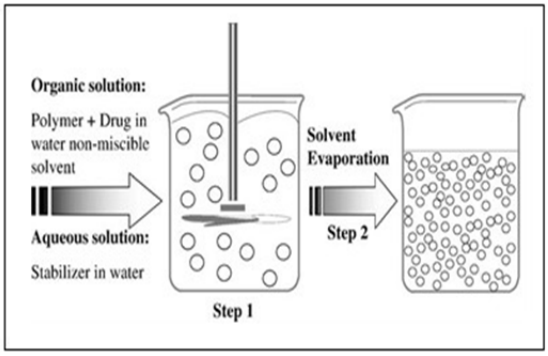

Fig. 2. Schematic representation of the solvent-evaporation technique

Salting Out Method

Salting out based on the separation of a water-miscible solvent from aqueous solution via a salting-out effect [45]. Salting-out is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. Polymer and drug are initially dissolved in a solvent which is subsequently emulsified into an aqueous gel containing the salting- out agent (electrolytes, such as magnesium chloride and calcium chloride, or non-electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethylcellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of solvent into the aqueous phase, thus inducing the formation of nanospheres. Several manufacturing parameters can be varied including stirring rate, internal/external phase ratio, concentration of polymers in the organic phase, type of electrolyte concentration and type of stabilizer in the aqueous phase [46]. This technique used in the preparation of PLA, Poly(methacrylic) acids, and Ethyl cellulose nanospheres leads to high efficiency and is easily scaled up [47,48]. Salting out does not require an increase of temperature and therefore may be useful when heat sensitive substances have to be processed. The greatest disadvantages are exclusive application to lipophilic drug and the extensive nanoparticles washing steps.

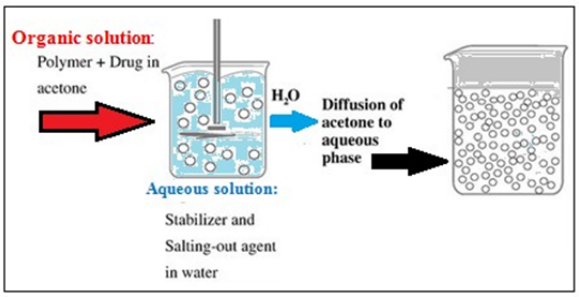

Fig. 3. Schematic representation of the salting out technique Dialysis

Emulsions- Diffusion Method

This is another widely used method to prepare nanoparticles. The encapsulating polymer is dissolved in a partially water-miscible solvent (such as propylene carbonate, benzyl alcohol), and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. This technique presents several advantages, such as high encapsulation efficiencies (generally 70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale- up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing

encapsulation efficiency [49]. Several drug- loaded nano particles were produced by the technique, including mesotetra (hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nano particles[50] doxorubicin-loaded PLGA nano particles [51], and cyclosporine (cy-A-); loaded sodium glycolate nanoparticles [52].

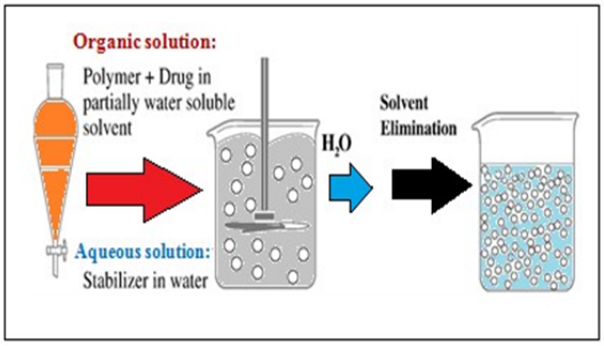

Fig. 4. Schematic representation of the emulsification/solvent diffusion technique

Solvent Displacement / Precipitation method

Solvent displacement involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of surfactant. Polymers, drug, and or lipophilic surfactant are dissolved in a semipolar water miscible solvent such as acetone or ethanol. The solution is then poured or injected into an aqueous solution containing stabilizer under magnetic stirring. Nano particles are formed instantaneously by the rapid solvent diffusion.

The solvent is then removed from the suspensions under reduced pressure. The rates of addition of the organic phase into the aqueous phase affect the particles size. It was observed that a decrease in both particles size and drug entrapment occurs as the rate of mixing of the two phase increases. Nano precipitation method is well suited for most of the poorly soluble drugs. Nanosphere size, drug release and yield were shown to be effectively controlled by adjusting preparation parameters. Adjusting polymer concentration in the organic phase was found to be useful in the production of smaller sized nanospheres through restricted to a limited range of the polymer to drug ratio [53].

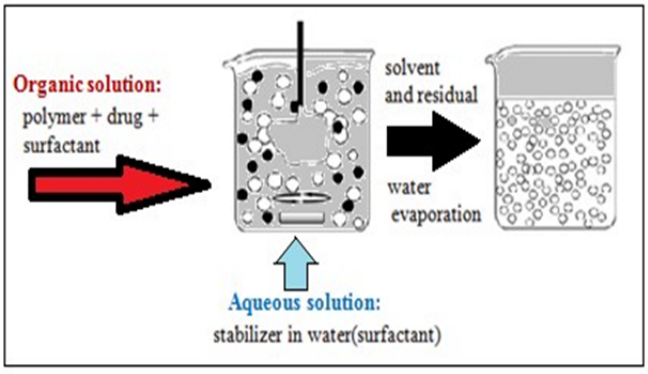

Fig. 5. Schematic representation of the nanoprecipitation technique. Surfactant is optional.

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. 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 [53-55].

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 [56].

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. 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 [57-59].

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 [60].

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**.** Instrument provides a topographical map of sample based on forces between the tip and the sample surface. Samples are usually scanned in contact or non- contact 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. 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 [61].

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 [62].

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 [63].

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, ultrafiltration, 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 [64-68].

NANOPARTICLES APPLICATIONS

Healthcare/medical

- Targeted drug delivery
- Alternative drug and vaccine delivery mechanisms (e.g. inhalation, oral in place of injection).
- Bone growth promoters
- Cancer treatments
- Biocompatible coatings for implants
- Sunscreens (e.g. using ZnO and TiO2) / cosmetics
- Bio labeling and detection (e.g. using Au)
- Carriers for drugs with low water solubility
- Fungicides (e.g. using ZnO)
- MRI contrast agents (e.g. using superparamagnetic iron oxide)
- New dental composites
- Biological binding agents (e.g. for high phosphate levels)
- Antiviral, antibacterial (e.g. Ag), anti-spore non-chemical creams and
- powders (using surface tension energy on the nanoscale to destroy biological particles)

Future opportunities and challenges

Nanoparticles have already been applied as drug delivery

systems with great success. Nanoparticles provide massive advantages regarding drug targeting, delivery and with their potential for combine diagnosis and therapy and one of the major tools in Nanomedicine. These are many technical, challenges in developing the following techniques:- Virus-like systems for intracellular systems, Architecting of biomimetic polymers, control of sensitive drugs, functions (of active drug targeting, bioresponsive triggered systems, systems interacting with me body smart elivery), nanochips for nanoparticle release, carriers for advanced polymers for the delivery of therapeutic peptide / proteins. Drug delivery techniques were established to deliver or control the amount & rate. Most major and established internal research programmes on drug delivery that are formulations and dispersion containing components down to nano sizes [5,68].

CONCLUSION

Nanocarriers as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. 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. The present pharmaceutics is often characterized by poor bio-availability which far too often results in higher patient costs and inefficient treatment but also, more importantly, increased risks of toxicity or even death. Nanotechnology focuses on the very small and it is uniquely suited to creating systems that can better deliver drugs to tiny areas within the body. Nano-enabled drug delivery also makes it possible for drugs to permeate through cell walls, which is of critical importance to the expected growth of genetic medicine over the next few years. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

REFERENCES

1. Hahens WI., Oomen AG., deJong WH., Cassee FR. What do we (need to) know about the kinetic properties of nanoparticles in the body? Regulatory Toxicology and Pharmacology. 2007; 49:217-229.
2. Couvreur P., Dubernet C., Puisieux F. Controlled drug delivery with Nano particles:current possibilities and future trends. Eur J Pharm Biopharm. 1995; 41:2-13.
3. Suri SS, Fenniri H, Singh B: Nanotechnology-based drug delivery systems. J Occup Med Toxicol, 2007, 2, 16.
4. Hett A. Nanotechnology: small matters, many unknown. 2004
5. Lachman, Liberman, Kaing “Theory and practice of Industrial Pharmacy”, 3rd edn: 26-30.
6. Tomalia DA. Birth of a new macromolecular architecture: Dendrimers as quantized building blocks for nanoscale synthetic organic chemistry. Aldrichimica Acta. 2004;37(2):39-57
7. Wiener EC., Brechbiel MW., Brothers H., Magin RL., Gansow OA.,Tomalia DA. Dendrimer-based metal chelates: a new class of magnetic resonance imaging contrast agents. Magn Reson Med. 1994; 31:1-8.
8. Li Y., Cheng Y., Xu T. Design, synthesis and potent pharmaceutical applications of glycodendrimers: a mini review. Curr Drug Discov Technol. 2007; 4:246-54.
9. Fu HL., Cheng SX., Zhang XZ., Zhuo RX. Dendrimers/DNA complexes encapsulated in a water soluble polymer and supported on fast degrading star poly (DL-lactide) for localized gene delivery. J ControlRelease. 2007; 124:181-8.
10. Cheng Y., Wang J., Rao T., He X., Xu T. Pharmaceutical applications of dendrimers: promising nanocarriers for drug delivery. Front Biosci. 2008; 13:1447-71.
11. Mecke A., Uppuluri S., Sassanella TM., Lee DK., Ramamoorthy A., Baker Jr JR. Direct observation of lipid bilayer disruption by poly (amidoamine) dendrimers. Chem Phys Lipids. 2004; 132:3-14.
12. Larson DR., Zipfel WR., Williams RM., Clark SW., Bruchez MP., Wise FW. Water-soluble quantum dots for multiphoton fluorescence imaging in vivo. Science. 2003; 300:1434-6.
13. Bilensoy E, Sarisozen C, Esendagl G, Dogan LA, Aktas Y, Sen M, Mangan AN: Intravesical cationic nanoparticles of chitosan and polycaprolactone for the delivery of Mitomycin C to bladder tumors. Int J Pharm, 2009, 371, 170–176.
14. Bai J, Li Y, Du J, Wang S, Zheng J, Yang O, Chen X: One-pot synthesis of polyacrylamide-gold nanocompos- ite. Mater Chem Phys, 2007, 106, 412–415.
15. Turos E, Shim JY, Wang Y, Greenhalgh K, Reddy GS, Dickey S, Lim DV: Antibiotic-conjugated polyacrylate nanoparticles: New opportunities for development of anti-MRSA agents. Bioorg Med Chem Lett, 2007, 17, 53–56.
16. Martinem A, Iglesias I, Lozano R, Teijon JM, Blanco MD: Synthesis and characterization of thiolated alginate-albumin nanoparticles stabilized by disulfide bonds. Evaluation as drug delivery systems. Carbohydr Polym, 2011, 83, 1311–1321.
17. Mao HQ, Roy K, Troung-Le VL, Janes KA, Lin KY, Wang J, August JT, Leong KW: Chitosan-DNA nanopar- ticles as gene carriers: synthesis, characterization and transfection efficiency. J Control Release, 2001, 70, 399–421.
18. Rejinold NS, Chennazhi KP, Nair SV, Tamura H, Jayakumar R: Biodegradable and thermo-sensitive chitosan-g-poly(N-vinylcaprolactam) nanoparticles as a 5-fluorouracil carrier. Carbohydr Polym, 2011, 83, 776–786.
19. Saraog GK, Gupta P, Gupta UD, Jain NK, Agrawal GP: Gelatin nanocarriers as potential vectors for effective management of tuberculosis. Int J Pharm, 2010, 385, 143–149.
20. Mainardes RM, Khalil NM, Gremião MPD: Intranasal delivery of zidovudine by PLA and PLA–PEG blend nanoparticles. Int J Pharm, 2010, 395, 266–271.
21. Park J, Fong PM, Lu J, Russell KS, Booth KJ, Saltzman WM, Fahmy TM: PEGylated PLGA nanoparticles for the improved delivery of doxorubicin. Nanomedicine, 2009, 5, 410-418.
22. Fritzen-Garcia MB, Zanetti-Ramos BG, Schweitzer de Oliveira C, Soldi V, Pasa AA, Creczynski-Pasa TB: Atomic force microscopy imaging of polyurethane nano- particles onto different solid. Mater Sci Eng C, 2009, 29, 405–409
23. Torchilin V: Multifunctional Pharmaceutical Nanocarri- ers, Springer Science + Business Media, LLC, NY, 2008.
24. Luo G, Yu X, Jin C, Yang F, Fu D, Long J, Xu J et al.: LyP-1-conjugated nanoparticles for targeting drug deliv- ery to lymphatic metastatic tumors. Int J Pharm, 2010, 385, 150–156.
25. Mora-Huertas CE, Fessi H, Elaissari A: Polymer-based nanocapsules for drug delivery. Int J Pharm, 2010, 385, 113–142.
26. Kumari A, Yadav SK, Yadav SC: Biodegradable poly- meric nanoparticles based drug delivery systems. Col- loids Surf B Biointerfaces, 2010, 75, 1–18.
27. Panyam J, Labhasetwar V: Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev, 2003, 55, 329–347.
28. Des Rieux A, Fievez V, Garinot M, Schneider YJ, Préat V: Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Con- trol Release, 2006,116, 1–27.
29. Schmid G. Nanoparticles: from theory to applications. Weinheim, Germany: Wiley-VCH Publishers; 2004.
30. Geckeler KE, Rosenberg E, editors. Functional nanomaterials. Valencia, USA: American Scientific Publishers; 2006.
31. Hosokawa M, Nogi K, Naito M, Yokoyama T. Nanoparticle technology handbook. Amsterdam, Netherlands: Elsevier; 2007.
32. Geckeler KE, Nishide H, editors. Advanced nanomaterials. Weinheim, Germany: Wiley-VCH Publishers; 2010.
33. Wang X, Summers CJ, Wang ZL. Large scale hexagonal patterned growth of aligned ZnO nanorods for nano-optoelectronics and nanosensor arrays. Nano Lett 2004, 4:423– 6.
34. Jang JS, Oh JH. Novel crystalline supramolecular assemblies of amorphous polypyrrole nanoparticles through surfactant templating.

Chem Commun 2002, 19:2200–1.
35. Fudouzi H, Xia Y. Photonic papers and inks: color writing with colorless materials. Adv Mater 2003, 15:892–6.
36. Brahim S, Narinesingh D, Elie GA. Amperometric determination of cholesterol in serum using a biosensor of cholesterol oxidase contained within a polypyrrole hydrogel membrane. Anal Chim Acta 2001, 448:27–36.
37. Zhang Q, Chuang KT. Adsorption of organic pollutants from effluents of a kraft pulp mill on activated carbon and polymer resin. Adv Environ Res 2001, 5:251–8.
38. Shokri N, Akbari Javar H, Fouladdel Sh, Khalaj A, Khoshayand MR., Dinarvand. R *et al*. Preparation and evaluation of poly (caprolactone fumurate) nanoparticles containing Doxorubicin Hcl. DARU (19) 1, 2011.
39. Peer D, Karp J.M, Hong S, Farokhzad O.C, Margalit R, Langer R, 2007. Nanocarriers as an emerging platform for cancer therapy. Nat. Nanotechnol. 2, 761–770.
40. Ghosh. PK Hydrophilic polymeric nanoparticles as drug carriers. Indian J Biochem Biophys 2000 (37), 273-282.
41. PrasadRao.J, KurtE.Geckeler Polymer nanoparticles: Preparation techniques and size control parameters , Progress in Polymer Science G Model. J Pharm Pharmaceuti Sci -674.
42. Catarina Pinto Reis, Ronald J. Neufeld, Antonio J. Ribeiro, Francisco Veiga. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles Nanomedicine: Nanotechnology, Biology, and Medicine 2 (2006) 8– 21.
43. Lemoine D, Preat V. Polymeric nanoparticles as delivery system for influenza virus glycoproteins. J Control Release 1998;54: 15–27.
44. Song CX, Labhasetwar V, Murphy H, Qu X, Humphrey WR, Shebuski RJ *et al*. Formulation and characterization of biodegradable nanoparticles for intravascular local drug delivery. J Control Release 1997, 43:197–212.
45. Catarina PR., Ronald JN., Antonio JR. Nano capsulation 1. Method of preparation of drug – loaded polymeric nanoparticles: Nano technology, Biology and medicine. 2006; 2:8-21.
46. Allemann E., Gurny R., Doekler E. Drug-loaded nanoparticles-preparation methods and drug targeting issues. Eur J Pharm Biopharm. 1993; 39:173-91.
47. Quintanar-Guerrero D., Allemann E., Fessi H., Doelker E. Preparation techniques and mechanism of formation of biodegradable nanoparticles from preformed polymers. Drug Dev Ind Pharm. 1998; 24:1113-28.
48. Jung T., Kamm W., Breitenbach A., Kaiserling E., Xiao JK., Kissel T. Biodegradable nano particles for oral delivery of peptides: is there a role for polymer to affect mucosal uptake? Eur J Pharm Biopharm. 2000; 50:147-60.
49. Vargas A., Pegaz B., Devefve E., Konan- Kouakou Y., Lange N., Ballini JP. Improved photodynamic activity of porphyrin loaded into nano particles: an in vivo evaluation using chick embryos. Int J Pharm. 2004; 286: 131- 45.
50. Yoo HS., Oh JE., Lee KH., Park TG. Biodegradable nanoparticles containing PLGA conjugates for sustained release. Pharm Res. 1999: 16: 1114-8.
51. El-shabouri MH. Positively charged nano particles for improving the oral bioavailability of cyclosporine-A. Int J Pharm. 2002; 249:101-8.
52. Chorney M., DAneuberg H., Golomb G. Lipophilic drug loaded nanospheres by nano precipitation: effect of the formulation variables on size, drug recovery and release kinetics. J Control releas.e 2002; 83: 389- 400.
53. Betancor L. and Luckarift HR. 2008 Trends Biotechnol. 26 566
54. P. Venkatesan, V. SreeJanardha nan, C. Muralidharan, and K. Valliappan. Acta Chim. Slov., 2012; 59: 242–248.
55. P.Venkatesan, R. Manavalan, and K. Valliappan. Preparation and evaluation of sustained release loxoprofen loaded microspheres. Journal of Basic and Clinical Pharmacy
56. De Assis DN., Mosqueira VC., Vilela JM., Andrade M.S., Cardoso VN. Release profiles and morphological characterization by atomic force microscopy and photon correlation spectroscopy of 99m Technetium – fluconazole nanocapsules. Int J Pharm. 2008; 349: 152 – 160.
57. Molpeceres J., Aberturas MR., Guzman M. Biodegradable nanoparticles as a delivery system for cyclosporine: preparation and characterization. J Microencapsul. 2000; 17: 599-614.
58. P. Venkatesan et al. / International Journal on Pharmaceutical and Biomedical Research (IJPBR) Vol. 2(3), 2011, 107-117
59. R.Sathiya Sundar, A.Murugesan, P.Venkatesan, and R.Manavalan, Formulation Development and Evaluation of Carprofen Microspheres. Int.J. Pharm Tech Research. 2010 Vol.2, No.3, 1674-1676.
60. Soppinath KS., Aminabhavi TM., Kulkurni AR., Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release. 2001; 70:1-20.
61. Polakovic M., Gorner T., Gref R., Dellacherie E. Lidocaine loaded biodegradable nanospheres. II. Modelling of drug release. J Control Release. 1999; 60: 169 -177.
62. Pangi Z., Beletsi A., Evangelatos K. PEG-ylated nanoparticles for biological and pharmaceutical application. Adv Drug Del Rev. 2003; 24: 403- 419.
63. Scholes PD., Coombes AG., Illum L., Davis SS., Wats JF., Ustariz C., Vert M., Davies MC. Detection and determination of surface levels of poloxamer and PVA surfactant on biodegradable nanospheres using SSIMS and XPS. J control Release. 1999; 59: 261 - 278.
64. Kreuter J. Physicochemical characterization of polyacrylic nanoparticles. Int. J. Pharm. 1983; 14: 43 -58.
65. Magenhein B., Levy MY., Benita S. A new in vitro technique for the evaluation of drug release profile from colloidal carriers-ultrafiltration technique at low pressure. Int. J. Pharm. 1993; 94: 115-123.
66. P.Venkatesan, R.Manavalan and K.Valliappan Microencapsulation: A Vital Technique In Novel Drug Delivery System. J. Pharm. Sci. & Res. Vol.1(4), 2009, 26-35
67. A. Arunkumar et al.,: Formulation, Evaluation and Optimization of Sustained Release Bilayer tablets of Niacin and Green Tea extract by employing Box-Behnken design, J. Sci. Res. Phar., 2016; 5(2): 23-28.
68. A. Arunkumar et al.,: Development and Validation of New Analytical methods for Simultaneous estimation of Epigallocatechin gallate, a component of Green Tea extractand Niacin in a Pharmaceutical dosage form, J. Pharm. Res., 2016; 5(2): 21-24.