Nanoparticles: Prominent Drug Delivery Strategy

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Abstract

Nanotechnology is the science that deals with the processes that occur at molecular level and of nanolength scale size. Pharmaceutical nanotechnology has emerged as a discipline having enormous potential as carrier for spatial and temporal delivery of bioactives and diagnostics and provides smart materials for tissue engineering. Pharmaceutical nanotechnology is now well-established as specialized area for drug delivery, diagnostics, prognostic and treatment of diseases through its nanoengineered tools. Metallic nanoparticles are emerging as good delivery carrier for drug and biosensor. Few nanotechnology based products and delivery systems are already in market. Nanoparticles production methods can be classified into the top down and bottom up categories. In the preparation of nanoparticles different types of matrix material are used such as polysaccharides, synthetic polymer and proteins. Various methods are used for preparation of nanoparticles viz; solvent evaporation, nanoprecipitation, salting out, solvent diffusion, spray drying and other more methods. Review article highlights introduction, opportunities and scope, advantages and disadvantages of nanoparticles, polymers used, methods of preparation, characterization and applications in detail. . Currently application of Nanoparticles is widely spread which are providing their service to humans. However, some suggested initiative must be taken in order to exploit the advantage of this very fascinating and ever growing potential technology.

Keywords - Nanotechnology, Nanoparticles, polymers, nanosize, spray drying

1. Introduction

Nanotechnology is one of the most significant research areas to emerge in the past decade or so. It is based on the concept of creating applications based on components built at the very small (nano-) scale. While only a relatively new field, the impact of nanotechnology is already being felt. Indeed, many believe that as nanotechnology matures as a technology and an increasing number of applications become commercially viable, it will fundamentally alter how societies function [1]. The word 'nano' is derived from Latin word, which means dwarf. Nano size refers to one thousand millionth of a particular unit thus nanometer is one thousand millionth of a metre (i.e. $1nm = 10^{-9}$ m). Nanoparticles are the manipulation of matter on an atomic and molecular scale. The earliest, widespread description of nanotechnology referred to the particular technological goal of precisely manipulating atoms and molecules for fabrication of macro scale products, also now referred to as molecular nanotechnology.

Nanotechnology is the science that deals with the processes that occur at molecular level and of nanolength scale size. There are numerous examples from nature like

DNA, water molecules, virus, red blood corpuscles (RBC) etc., which are of nanodimensions; even our history has numerous examples which prove that we have exploited the advantages of technology in one or other form. Figure 1 depicts various examples from nature and pharmaceuticals which are operated at various dimensions of nanolength scale. The term nanotechnology has been most commonly used in other fields of science like electronic, physics and engineering since many decades. Nanotechnology has shown tremendous progress in this fields [2].

Nanotechnology is a multidisciplinary field, convergence of basic sciences and applied disciplines like biophysics, molecular biology, and bioengineering. It has created powerful impact in various fields of medicine including cardiology, ophthalmology, endocrinology, oncology, pulmology, immunology etc., and to highly specialized areas like gene delivery, brain targeting, tumor targeting, and oral vaccine formulations. Nanotechnology provides intelligent systems, devices and materials for better pharmaceutical applications [3].
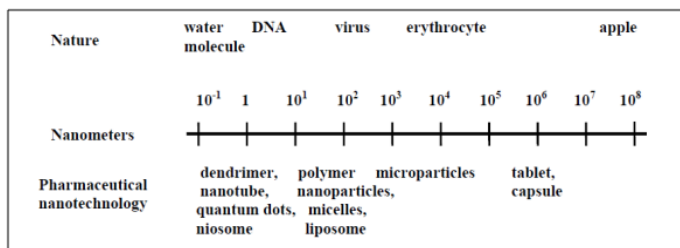

Fig. 1: Dimensions of Nanotechnology

2. Opportunities and Scope [4,5]

In the area of nanoelectronics and computer technology, nanotechnology will allow the construction of smaller circuits and computers. Smaller circuits will run faster enabling far greater computer speeds. New nanomaterials will mean that computers will have a much longer life. A laptop computer could therefore have its efficiency increased by millions living longer and working faster to give far better value for money.

Now days most of the industries have realized the potential applications of nanotechnology in pharmacy and are making their efforts in research and development in this area. Recent data depicts that global investment on nanotechnology reached US $ 12.4 billion in 2006. The data presented below suggests the global interest over nanotechnology investment and related issue (Fig. 2) (Riesch, 2007).
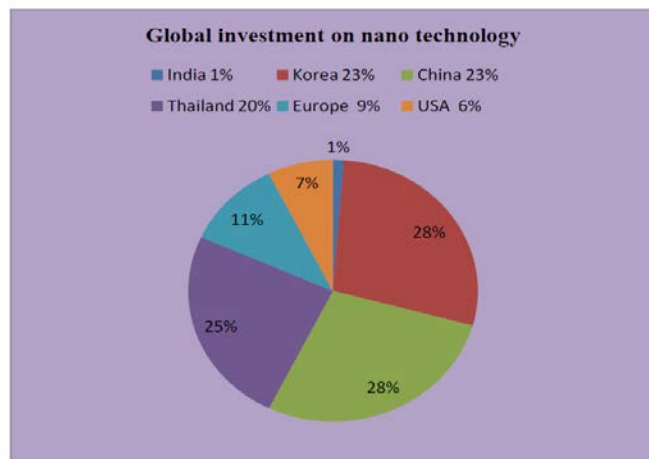

Figure 2: Global Investment in Nanotechnology

Novel drug delivery comprises of a number of features of nanotechnology, which make it a suitable tool to address major issues. The scope of pharmaceutical nanotechnology is very wide from smart material for tissue engineering to intelligent tools for delivery of drugs and diagnostics, and more recently, artificial RBC etc. Current applications of nanotechnology in pharmacy are development of nanomedicine, tissue engineering, nanorobots, advance diagnostic, as carrier of diagnostic and therapeutic modalities and as biosensor, biomarker, image enhancement device, implant technology, bioactive surfaces etc. A large number of nanosystems, which have been investigated in pharmacy to date, are liposomes, dendrimers, metallic nanoparticles, polymeric nanoparticles, carbon nanotubes, quantum dots, nanofibres etc.In health care and medicine biological nanosensors are being developed in the next 5 years and

will be used for fast and accurate diagnostics. Further ahead, nanotechnology may be used to build artificial muscle and 'lab on a chip' technology will develop more efficient drug discovery processes.

Fig.3: Pharmaceutical Nanotechnology Based Systems
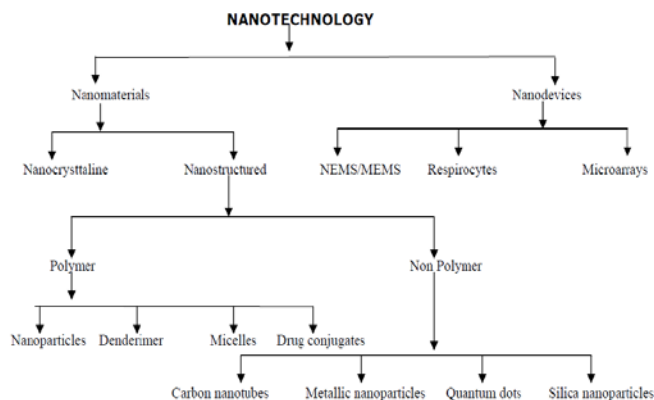
Nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 1-1000nm [6]. Drug nanoparticles are a formulation principle for all poorly soluble drugs for which the dissolution velocity is the rate limiting step for absorption and thus the reason for a too low oral bioavailability. The increase in surface area leads to an increase in the dissolution velocity according the Noyes- Whitney equation which describes the dissolution rate of the drug in a diffusion controlled process. A fact in the past often overlooked is the increase in the saturation solubility of nanonised compounds compared to micrometer particles, precisely the kinetic saturation solubility increases. Compared to micrometer crystals the nanocrystals lead to a supersaturated solution. This situation is metastable, that means as a function of time crystallization will be initiated, large crystals will precipitate and the system returns to the thermodynamically stable state of the saturation solubility of micrometer crystals. However, in general duration of this supersaturated state is sufficient for oral absorption [7].

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. The 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. 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. 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 [8].

Mechanisms of drug release

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.

Properties of Nanoparticles [8]

• Better dissolution

- Bioavailability Enhancement
- Physical Long Term Stability
- Increase in saturation solubility and dissolution velocity of drug
- Internal structure of nanoparticles.

Advantages of Nanoparticles [9, 10, 11]

- They are suitable for different routes of administration.
- Carrying capacity of nanoparticles is high.
- Shelf-stability of drug increases.
- Ability to sustain and control drug release patterns.
- Suitable for combination therapy where two or more drug can be co-delivered.
- Both hydrophobic and hydrophilic drug can be incorporated.
- System increases the bioavailability of drugs.
- Imaging studies can be done by utilizing them.
- It is used for targeted drug delivery of drugs.
- Development of new medicines which are safer.

Disadvantages of nanoparticles [12, 13]

- The manufacturing costs of nanoparticle are high which result in overall product cost.
- Solvents are toxic in nature which is used in the preparation process.
- Can start immune response and allergic reactions in body.
- Extensive use of poly (vinyl alcohol) as stabilizer may have toxicity issues.
- Nanoparticles are difficult to handle in physical form because particle-particle aggregation occurs due their small size and large surface area.

Preparation of Nanoparticles

Nanoparticles production methods can be classified into the top down and bottom up categories. Top down approaches involve the size reduction of large particles to the nanometer range. This can be achieved by milling or high pressure homogenization and has to been discussed in excellent reviews by Muller. The two major types of high pressure homogenization are micro-fluidization and piston gap homogenization. Micro-fluidization is essentially air jet milling in which the particles are fragmented by collision in a high pressure air jet. On the other hand, piston gap homogenization involves forcing a liquid suspension at high pressure through a narrow channel or gap inside a pipe.

In the preparation of nanoparticles different types of matrix material are used such as polysaccharides, synthetic polymer and proteins. Various factors are involved in selection of matrix material to be used in preparations which are as:

- Required nanoparticle size.
- Permeability and surface charge of nanoparticle.
- Level of biodegradability and biocompatibility must be optimum.
- Solubility profile and stability of drug should not be affected.
- It should show desired drug release profile.
- Must not be immunogenic.

Polymers used in preparation of nanoparticles

The polymers should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible.

Natural polymers: The most commonly used natural polymers in preparation of polymeric nanoparticles are:

❖ Chitosan

❖ Sodium alginate

❖ Gelatin

❖ Albumin

There are many synthetic polymers like Polylactides(PLA) , Polyglycolides(PGA) , Poly(lactide co-glycolides) (PLGA), Polyanhydrides, Polyorthoesters

Polycyanoacrylates ,Polycaprolactone , Poly glutamic acid Poly malic acid , Poly(N-vinyl pyrrolidone) , Poly(methyl methacrylate) ,Poly(vinyl alcohol) , Poly(acrylic acid) ,Poly acrylamide ,Poly(ethylene glycol) ,Poly(methacrylic acid)

Table 1: Polymer used for the preparation of nanoparticle.

Technique	Candidate drug	Polymer used
Heat denaturation and cross linking in w/o emulsion	Hydrophilic	**Hydrophilic** :Albumin ,Gelatin
Desolvation and cross linking in Water	Hydrophilic and protein affinity	**Hydrophilic** :Albumin ,Gelatin
Cross-linking in water	Hydrophilic and protein affinity	**Hydrophilic** :Alginates and chitosan
Polymer precipitation in an organic Solvent	Hydrophilic	**Hydrophilic** : Dextran
Emulsion polymerization	Hydrophilic	**Hydrophobic**:Poly (alkylcyanoacrylates)
Interfacial O/W polymerization	Hydrophobic	**Hydrophobic** :Poly(alkylcyanoacrylates)
Solvent extraction evaporation	Hydrophilic and Hydrophobic Soluble in polar solvent	**Polyesters** : Poly (lactic acid), poly caprolactone
Solvent displacement	Hydrophilic and ydrophobic Soluble in polar solvent	**Polyesters**: Poly (lactic acid), Poly (lactide-co-glycolide)
Salting out	Soluble in polar solvent	**Polyesters**: Poly (lactic acid),Poly (lactide-co-glycolide)

**Techniques for Preparation of Nanoparticles:**

I. Dispersion of preformed polymers

For the preparation of biodegradable nanoparticles from polymers such as poly (lactic acid) (PLA); poly (D, L-glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and Poly- (cyanoacrylate) (PCA), dispersion of preformed polymer method is used . This technique can be used in various ways as described below :

◆ **Solvent evaporation method** [14]

In this method, there is conventional formation of o/w emulsion between a partially water miscible solvent containing the polymer and the drug, and an aqueous phase containing the stabilizer. In this polymer is dissolved in an organic solvent such as dichloromethane, chloroform

or ethyl acetate. Oil in water (o/w) emulsion is prepared by emusification of drug and polymer

mixture in aqueous solution which contain emulsifying agent, which result in formation of stable

emulsion. After that by using pressure reduction method or continuous stirring, organic solvent is evaporated. The homogenizer speed, nature and stabilizer concentration along with the property of polymer effect size of nanoparticle. Usually high speed homogenizer or ultrsonication had been used to reduce the size of nanoparticle to an optimum size.
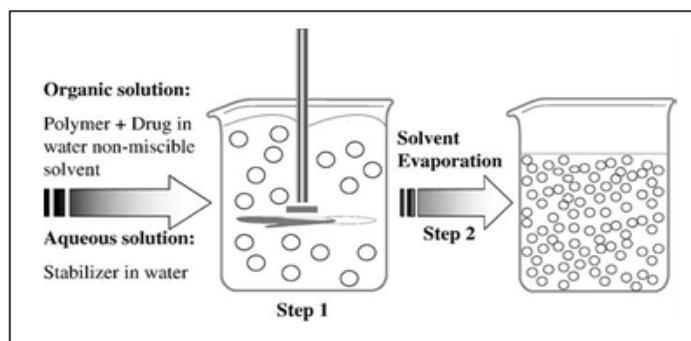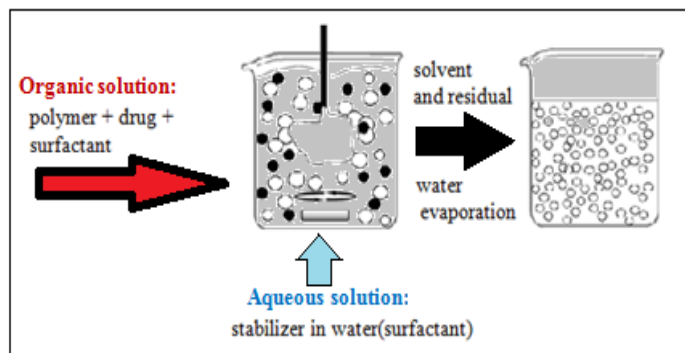

Fig 5: Schematic representation of the solvent-evaporation technique

◆ **Nanoprecipitation** [15]

Nanoprecipitation is also called solvent displacement method. It 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 a surfactant. The polymer generally PLA, is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension. To facilitate the formation of colloidal polymer particles during the first step of the procedure, phase separation is performed with a totally miscible solvent that is also a non solvent of the polymer. The solvent displacement technique allows the preparation of nanocapsules when a small volume of nontoxic oil is incorporated in the

organic phase. The usefulness of this simple technique is limited to water-miscible solvents, in which the diffusion rate is enough to produce spontaneous emulsification.

Fig 6: Schematic representation of the nanoprecipitation technique.

◆**Spontaneous emulsification or solvent diffusion method** [16]

This method also known as modified version of solvent evaporation method. In this method, two phase solvent is used, one is water miscible and other is water immiscible i.e. organic in nature which act as oil phase. In this method interfacial turbulence is created, by immediate diffusion between two solvents (which are differing in phase) which lead to the formation of small particles. A reduction in particle size can be gained by increasing the concentration of water miscible solvent both the above described method can be used for preparation of hydrophilic and hydrophobic drugs.
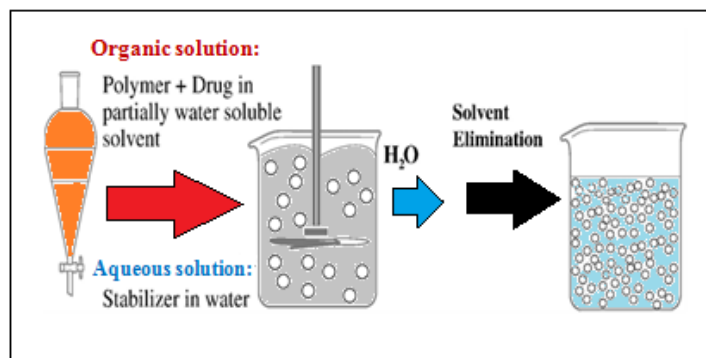
Fig 8: Schematic representation of the emulsification/solvent diffusion technique

◆ **Production of nanoparticles using supercritical fluid technology** [16]

Various conventional approaches like solvent diffusion, solvent extraction-evaporation and organic phase separtion require the use of organic solvent are hazardous to the environment as well as the physiological systems. Supercritical fluid technology thus has been invested as an alternative to prepare biodegradable micro and Nanoparticles. Solvent which remain fluid in a single phase regardless of pressure above critical temperature are known as supercritical fluid. Super critical CO_2 is the most widely used supercritical fluid. The most common processing techniques involves supercritical fluids are supercritical Antisolvent (SAS) and rapid expansion of critical solution (RESS). Formation of hydrophilic drug Dexamethsone phosphate by the use of modified SAS had been reported by Thote and Gupta (2005). RESS diffuse from SAS process in that its solute in dissolved in super critical fluid .Thus with solvent power of super critical fluid decrease and the solute eventually precipitate.
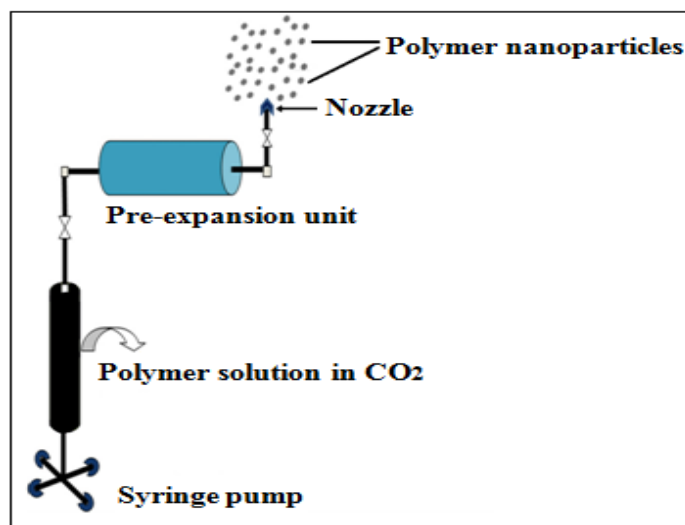
Fig 9: Experimental set-up for preparation of polymer nanoparticles by rapid expansion of supercritical fluid solution

Spray Drying

In spray drying, a drug solution (aqueous or organic) is atomized to fine droplets which are evaporated in a warm air current to form dry particles. However, conventional spray drying is not suitable for production of nanoparticles because they are too small to be collected by the cyclone (cutoff diameter ~1–2 μm) of the spray dryer.21 A higher drying air flow may potentially exceed the efficiency of the electrostatic collector. However, higher air flow will evaporate the droplets more rapidly, resulting in a less crystalline product due to insufficient time allowed for crystallisation. Thus, the usefulness of spray drying to prepare stable fine particles can be hampered. This becomes obvious since spray dried powders tend to be amorphous.

- **Characterization of nanoparticles** [17, 18, 19]
- To understand synthesis and application of nanoparticle, characterization of nanoparticle is necessary. Size determination is the primary parameter for characterization of nanoparticle. Various techniques had been used for this purpose as below:

1. **Method of determining particle size is by**
2. Photon-correlation spectroscopy.
3. Dynamic light scattering.
4. Brownian motion and light scattering properties.
5. Scanning or transmission electron microscopy (SEM or TEM).

2. Particle Size Distribution

Particle size distribution (also known as polydispersity index) being an important aspect during the formulations of nanosystems, efforts are made to achieve a system with lowest polydispersity index. Some techniques to determine the particle size distribution are dynamic light scattering, which is used to measure particles ranging from a few nanometers to about 3 μm, while laser diffraction is used to detect microparticles or possible aggregates of drug nanoparticles.

3. Particle Charge / Zeta Potential

Zeta potential is used to determine the charge at particle surface. Zeta potential measurement is made to optimize formulation parameters and to make predictions regarding the storage stability of the **colloidal dispersion**. Currently principal technique involved in zeta potential determination is laser doppler anemometry.

4. Structural characterization

Structural characterization is a parameter that plays important role in determining various attributes of a nanosystem like shape, size, surface morphology, structural arrangement spatial distribution, density, geometric feature etc. Development of electron microscopy tool improves accessibility and feasibility to determine these attributes at nanometer scale. Scanning electron microscopy (SEM) produces the image down to length scales of 10 nm and provides valuable information regarding structural arrangement, spatial distribution as well as surface morphology of nanoparticles. Transmission electron microscopy (TEM) and high resolution TEM are more powerful imaging tools than SEM and give more detailed geometrical features and information like crystal structure, quality, and orientation of nanoparticles. Moreover, scanning tunneling probe such as scanning tunneling microscope (STM), electrical field gradient microscopy (EFM), and scanning thermal microscopy, combined with atomic force microscopy(AFM) have been employed to illustrate structural, electronic, magnetic and thermal properties besides topographical properties of nanosystems.

5. Particle Morphology

Differential Scanning Calorimetry (DSC) determines the crystalline structure. When nanoparticles are prepared drug particles get converted to amorphous form. Hence it

is essential to measure the extent of amorphous drug generated during the production of nanoparticles. The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug.

6. Drug loading

A high drug- loading capacity is the measure of successful nanoparticulate system because it reduces the amount of matrix material for administration. Drug loading can be done by two methods:

a) Incorporation method: - In this drug is incorporated during the formation of   nanoparticle.

b) Adsorption/absorption method: - In this method drug is made to be adsorbed on nanoparticle.

In this formed nanoparticle is kept in concentrated solution of drug and adsorption phenomenon take place.

7. Saturation Solubility and Dissolution Velocity

The nanosuspensions increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium Kelvin equation and the Ostwald- Freundlich equations can explain increase in saturation solubility.

8. Drug release

Another Factor for a formulation of successful nanoparticulate system, study of parameter such as both drug release profile and polymer biodegradation is concern. In general, drug release rate depends on:

(a) Solubility of drug.

(b) How far the Drug is diffused through the nanoparticle matrix.

(c) Combination of erosion/diffusion process.

(d) Degree of material matrix erosion/degradation and

(e) Time taken by the drug for desorption through surface.

Loading of drug by incorporation method produce system which has small burst effect and good sustained release characteristics [20]. Coating the nanoparticle with polymer, release is affected by movement of drug from core across the polymeric membrane. In this case polymeric membrane becomes release determining factor because it affects the solubility and diffusivity of drug. A number of methods can be used to determine in vitro release of drug

(a) Reverse dialysis bag technique

(b) Dialysis bag diffusion technique.

(c). centrifugal ultra-filtration techniques

(d) Agitation.

(e) Using biological or artificial membrane i.e. Side-by-side diffusion of cells.

To summarize different parameters to be characterized along with their characterization method are presented in table below:

Parameter	Characterization method
Particle size and distribution	Photon correlation spectroscopy(PCS)
	Laser defractometry
	Transmission electron microscopy
	Scanning electron microscopy
	Atomic force microscopy
Surface hydrophobicity	Water contact angle measurement
	Rose Bengal(dye) binding
	X-ray photoelectron spectroscopy
Charge determination	Laser Doppler Anemometry
	Zeta potentiometer
Carrier-drug interaction	Diffential scanning calorimetry
Chemical analysis of surface	Static secondary ion mass spectrometry
	Sorptometer
Nanoparticle dispersion stability	Critical flocculation temperature(CFT)
Release profile	In vitro release characteristics under physiologic and sink conditions
Drug stability	Bioassay of drug extacted from Nanoparticles
	Chemical analysis of drug

Table 2: Different parameters and characterization methods for nanoparticles [21].

Applications of Pharmaceutical Nanoparticles [22, 23]

Miniaturization is often beneficial in pharmaceutical technology. Although it has increased complexity yet it imparts large number of benefits in drug delivery and diagnostic. Miniaturization is helpful in overcoming various physiological, biochemical and pharmaceutical barriers. Pharmaceutical nanotechnology provides wide

array of systems or device of nanosize, which offer numerous benefits.

There are various pharmaceutical and biomedical areas where pharmaceutical nanosystems have achieved remarkable breakthrough and realized their market applications. Some important applications areas are discussed here:

1. As nanomaterials for tissue engineering

Nanotechnology offered numerous smart materials that are used for tissue repair and replacement, implant coatings, tissue regeneration scaffolds, structural implant materials, bone repair, bioresorbable materials, some implantable devices (sensory aids, retina implants etc.), surgical aids, operating tools, and smart instruments.

2. As drug carrier system

Conventional drug delivery systems or dosage forms suffer from many limitations such as lack of target specificity, high rate of drug metabolism, cytotoxicity, high dose requirement, poor patient compliance etc. Nanotechnology enabled drug delivery system with optimized physical, chemical and biological properties can serve as effective delivery tools for currently available bioactives. Some nanobased drug delivery tools are polymeric nanoparticles, liposome, dendrimer, polymeric micelles, polymer-drug conjugates, antibody- drug conjugates, which can broadly be classify as

➢ sustained and controlled delivery system,

➢ stimuli sensitive delivery system,

➢ functional system for delivery of bioactives,

➢ Multifunctional system for combined delivery of therapeutics, biosensing and diagnostic, and (iv) site specific targeting (intracellular, cellular, tissue)

3. Implantable delivery systems

Nanotechnology is opening up new opportunities in implantable delivery systems by virtue of its size, controlled and approximately zero order release which otherwise may cause toxicity when compared to intravenous administration (due to first order drug kinetics). Some pharmaceutical novel nano drug vascular carriers like liposome, ethosome and trnasferosome and some implant chips have been envisaged recently, which may help in minimizing peak plasma levels and reduce the risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance.

1. Site specific drug delivery

Several approaches are now being tested for better site-specific delivery using liposomes, polymeric micelles, dendrimers, iron oxide, proteins using manipulation in passive and active uptake of drug. The tumor targeting of drugs with passive delivery using enhanced permeation and retention (EPR) effect is thought to be one intelligent approach using these carrier system taking the advantages of leaky vasculature of tumor. Some surface modification approaches using various site-specific ligands via covalent binding or adsorption with carrier system enhanced their site specificity and make them intelligent tools for active delivery. The conjugations of these carriers with ligands provide them site specificity at various levels. In the chemotherapy of tuberculosis with active delivery to lung cells is reported to have improved drug bioavailability, reduction in dose frequency and overcoming the non-adherence problem encountered in the control of TB.

Conclusion

Pharmaceutical nanotechnology offers new tools, opportunities and scope, which are expected to have a great impact on many areas in disease diagnostics and therapeutics. The foregoing review shows that therapeutic agents which are poorly soluble absorbed poorly and that are labile can be converted into promising forms which can be delivered through different routes of administration. It has various advantages simultaneously

and also has some limitation such as can be immunogenic and others. The physio-chemical parameters of the drug play an important role in the selection of the nanoparticle material that has to be employed. Various methods can be used for the preparation of nanoparticles depending upon need. Characterization of them is must for better therapeutic response. Currently application of Nanoparticles is widely spread which are providing their service to humans.

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