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Review Article

Nanoparticles: Classification, Method of Praparation, Characterization and Applications

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ABSTRACT

The most growing branch in the pharmaceutical science is "pharmaceutical nanotechnology". Pharmaceutical nanotechnologies have been gained a special recognition due to continuous increasing number of poor aqueous soluble compounds. Various pharmaceutical companies already manufactured the nanosized product which is available in market. Nanosized (10-1000nm) solid colloidal microscopic particles are called as nanoparticles. Nanoparticles are act as a drug delivering carrier for the small and large molecules. They have a potential to deliver the drug in a control rate. It has ability to target particular organs or tissues. Nanoparticles deliver the protein, peptide and genes also carriers of DNA in gene therapy. Various types of Nano pharmaceuticals systems like carbon nanotubes, quantum dots, dendrimers, etc have brought about revolutionary changes in drug delivery. TEM is microscopic technique to analyse nanoparticle size and shape, since it provides not only direct images of the sample but also the most accurate estimation of the nanoparticle homogeneity. This review article discussed the classification, various methods of preparation like Emulsion-Solvent Evaporation method, Double emulsion and evaporation method, Salting out Method, Emulsions-Diffusion Method, Solvent Displacement / Precipitation method, and their characterization techniques like, drug loading, drug release along with the application of nanoparticles. This article also include list of some relevant (polymer-based and lipid-based) organic and inorganic nanomedicines which is approved by the FDA and future aspects.

INTRODUCTION

Over past few decades the prefix "nano" has found an ever-increasing application to different fields of the knowledge. Nanotechnology refers the small; the very small. It means the use and manipulation of matter at a nano scale. It provides a variety of surprising and interesting use of matter due to small size. Over the conventional techniques, it provides the opportunities for the development of material, including those for medical applications. Nanotechnology represents the design, production of material at the macromolecular scale, to produce new nanosized material [1].

Nanoparticles are the colloidal microscopic particle that exist on a nanometer scale in the range of 10-1000nm.

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Nanoparticles has been considered as effective drug delivery device, in which drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix, and depending upon the method of preparation nanoparticles, nanocapsules, and nanospheres can be obtained. Nanocapsules are vesicular system in which the drug is confined to a cavity surrounded by a unique biodegradable polymeric membrane, while in case of nanospheres; the drug is physically and uniformly dispersed in a matrix (Fig. 1).

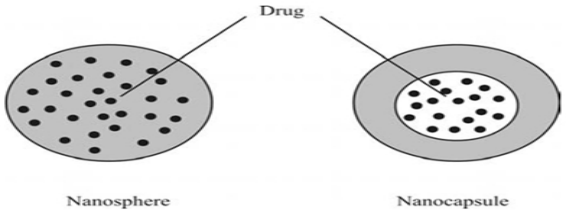

Figure 1: Difference between nanosphere and nanocapsules

Nanoparticles have a potential to deliver the drug in a control rate. It has ability to target particular organs/tissues. Nanoparticles deliver the protein, peptide and genes also carriers of DNA in gene therapy [2, 3].

Advantages

Some advantages of nanoparticles drug delivery system are:

1. Active and passive targeting can be achieved by manipulating the particle size, and surface characteristics of nanoparticles.
2. Surface of the nanoparticle can be modified to alter bio distribution of the drug with subsequent clearance of the drug to get maximum therapeutic efficacy with maximum side effects of the drug.
3. Particle degradation characteristics and controlled release can be easily modulated by the choice of matrix constituents.
4. Drug can be incorporated in to the system without any chemical reaction, and also drug loading is relatively high.
5. By attaching targeting ligand to surface of particle or use of magnetic guidance, specific sit of targeting can be achieved.
6. Polymer based nanoparticles do not accumulate in the body because used polymer are biodegradable, reduce the possibility of risk.
7. Nanoparticles can penetrate through smaller capillaries due to small size which could allow efficient drug release at the target site.
8. Nanoparticles can be delivered through various routes like oral, nasal, parenteral, and intraocular etc [4].

Limitations

1. Physical handling of nanoparticle is difficult due to small size and large surface area, and also chances of particle-particle aggregation it is due to alteration in physical properties of nanoparticles.

2. In cellular environment nanoparticles are very reactive because of small particle size and great surface area.

3. Burst release and drug loading is limited because of small particle size. These practical problems have to remove before nanoparticles can be used clinically or made commercially available [2].

Types of Nanoparticles

Polymeric nanoparticle is composed of synthetic or semi-synthetic polymer. Depending upon the method of preparation, nanocapsules, nanospheres can be obtained. Biodegradable polymer are used such as polysaccharides, chitosan-Polylactic acid, polylactic acid coglycolic acid, chitosan nanoparticles have been used.

Solid-lipid nanoparticles have been a new type of colloidal drug carrier system which is suitable for intravenous administration. Shape of solid-lipid nanoparticle is spherical in the nanometer range, which is dispersed in water or in surfactant solution [5].

Classification

Nanoparticles are classified in various classes. Classification is based on the particle dimensions [6]. It may be one, two, and three dimension.

One Dimension Nanoparticles

A thin film or manufactured surfaces have been used in electronics; chemicals and engineering are known as one dimensional system. Thin film (size 1-100) or monolayer is now common place in the field of solar cells and catalysis offering, various technological application such as biological and chemical sensors, information storage system, magneto-optic, optical device and fiber optic systems.

Two Dimension Nanoparticles

Carbon Nanotubes

Carbon nanotubes are 1 nm in diameter and 100 nm in length, hexagonal network of carbon atoms, as a layer of graphite rolled up into cylinder. Single walled carbon nanotubes (SWCTNs) and multi walled carbon nanotubes (MWCNTs) are types of nanotubes. The small dimensions of carbon nanotubes are unique material with remarkable physical, mechanical, and electrical properties. They show metallic or semi conductive properties based on how the carbon leaf is wound on itself. The existing density that nanotubes can carry is much high and can reach one billion amperes per square meter to make it a superconductive.

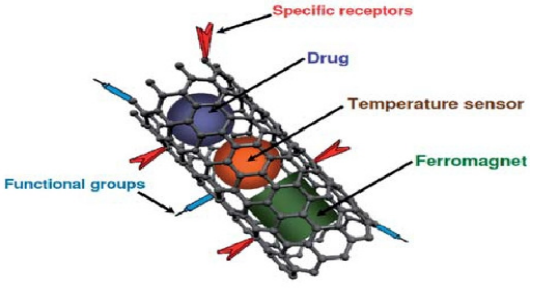

Figure 2: Schematic highlighting- the versatile functionalization possibilities of carbon nanotubes.

Carbon nanotubes have sixty times greater mechanical strength than the best steel. Molecular absorption capacity is high in carbon nanotubes and gives a three dimensional configuration besides this they are physically stable [7] (Fig. 2).

Three Dimensional Nanoparticles

Fullerenes (carbon 60)

28 to more than 100 carbon atoms make a round cage called as fullerenes (Fig. 3). Interconnected carbon pentagons and hexagons makes a hallow ball, looks like a soccer ball. Fullerenes are class of material with unique properties. Shape of the fullerenes can be changed under the extreme pressure and they regain their original shape when the pressure is released. These molecules do not connected with each other, thus giving them the major potential for use as lubricants. Because of having electrical properties they can be used in the electrical field, ranging from data storage to production of solar cells. Since fullerenes are blank structures with dimensions similar to many biological active molecules, they can be filled with diverse substances and give potential medical applications [8].

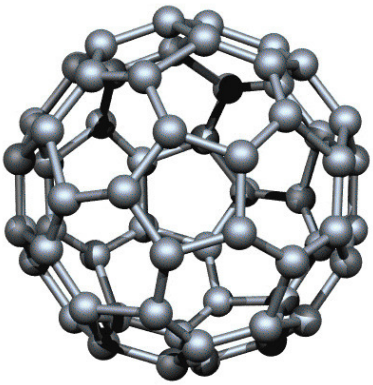

Figure 3: Three dimensional–Fullerenes nanoparticles (carbon 60)

Dendrimers

Dendrimers shows a new class of controlled-structure polymers with nanometric dimensions. Dendrimers are usually 10 to 100 nm in diameter with numerous functional groups on their surface depiction them ideal carriers for targeted drug delivery (Fig. 4). The structure and function of dendrimers has been welled deliberate. Existing dendrimers can be highly specialized, encapsulating functional molecules (i.e., therapeutic or diagnostic agents) inside their core. They are measured to be basic elements for large-scale synthesis of organic and inorganic nanostructures with dimensions of 1 to 100 nm. They are synchronized with organic structure such as DNA and also can be fabricated to metallic nanostructure and nanotubes or with the encapsulation capacity. Dendrimers have varied reactive surface groupings (nanostructure) and well-suited with organic structure such as DNA so their creative use is mainly 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. Dendrimers may be toxic because of their ability to interrupt cell membranes as a result of a positive charge on their surface. Dendrimers used in drug delivery studies typically integrate one or more of the following polymers: polyamidoamine (PAMAM), melamine, poly (L-glutamic acid) (PG), polyethyleneimine (PEI), poly (propylene imine), and poly (ethylene glycol) (PEG). Chitin and chitosan have also been incorporated with dendrimers Drug molecules can be incorporated into dendrimers via either complexation or encapsulation as shown in Fig. 5 [1, 7, 9].

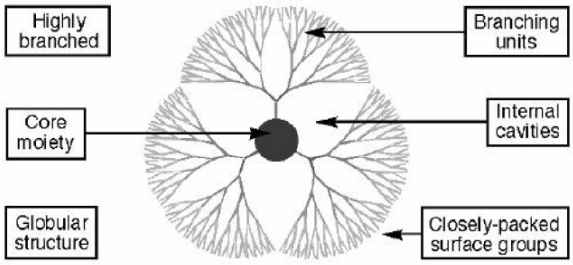

Figure 4: Schematic representation of a dendrimer showing core, branches, and surface.

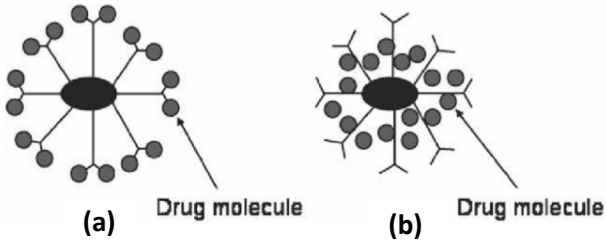

Figure 5: Schematic incorporation of drug within a dendrimer structure (a) Complexation: Covalent attachment to end groups (b) Encapsulation: Trapment inside dendrimer core

Quantum Dots (QDs)

Quantum dots are tiny devices that contain a small droplet of free electrons.QDs are colloidal semiconductor nanocrystals ranging from 2 to 10

nm in diameter. QDs can be synthesized from different types of semiconductor materials via colloidal synthesis or electrochemistry. Usually used QDs are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs). Quantum dots can have something from a single electron to a set of several thousands. The size, shape and number of electrons can be accurately controlled. They have been prepared in the form of semiconductors, insulators, metals, magnetic materials or metallic oxides. It can be used for optical and optoelectronic devices, quantum computing, and information storage. Colors oblique quantum dots are used for fast DNA Testing. Quantum dots (QDs) refer to the quantum captivity of electrons and holes carriers at dimensions lesser than the Bohr radiuos. QD nanocrystals are usually 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 additional initiate to avert the surface quenching of excitation in the emissive core and therefore increase the photostability and quantum yield of emission. QDs also offer adequate surface area to connect therapeutic agents for concurrent drug delivery and in vivo imaging, as well as for tissue engineering [10, 11].

Preparation of Nanoparticles

Various methods are used in the preparation of nanoparticles. They are

1. Emulsion-Solvent Evaporation Method
2. Double emulsion solvent method
3. Salting Out Method
4. Emulsions- Diffusion Method
5. Solvent Displacement / Precipitation method
6. Coacervation or Ionic gelation method
7. Desolvation method

1. Emulsion-Solvent Evaporation Method

This is one of the most commonly used methods for the preparation of nanoparticles. Emulsification-solvent evaporation involves two steps. In The first step polymer solution is emulsified into an aqueous phase and in the second step polymer solvent is evaporated, inducing polymer precipitation as nanospheres. The nano particles are collected by ultracentrifugation and washed with distilled water to remove stabilizer residue or any free drug and lyophilized for storage [12] (Fig. 6). Modified form of this method is known as highpressure emulsification and solvent evaporation method [13]. This method involves preparation of an emulsion which is then subjected to homogenization under high pressure followed by overall stirring to remove organic solvent .The size of the particle can be controlled by adjusting the stirring rate, type and amount of dispersing agent, viscosity of organic and aqueous phases and temperature. In spite of this method can be applied to liposoluble drugs and limitation are imposed by the scale up issue. Polymers used in this method is PLA, PLGA, EC, cellulose acetate phthalate [1], Poly (caprolactone) \ (PCL) [14], Poly (β-hydroxybutyrate) (PHB) [15].

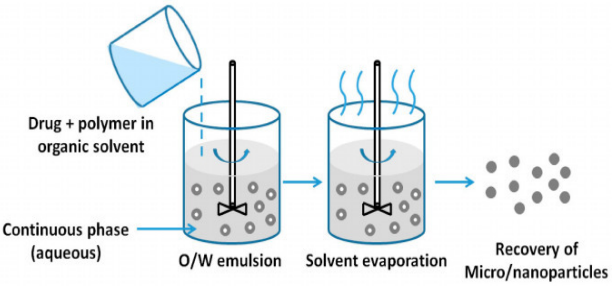

Figure 6: Emulsion-Solvent Evaporation Method

2. Double Emulsion and Evaporation Method

Limitation of the emulsion and evaporation method is the poor entrapment of the hydrophilic drugs. That is why; encapsulating hydrophilic drugs are encapsulated by the emulsion technique, in which addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form w/o emulsions. This w/o emulsion is added into second aqueous phase with continuous stirring to form the w/o/w emulsion. Then emulsion is subjected to solvent removal by evaporation and nanoparticles can be isolated by centrifugation at high speed. Isolated nanoparticles must be thoroughly washed before lyophilization [16]. In this method characterization of nanoparticles can be affected by the amount of hydrophilic drug to be incorporated, the concentration of stabilizer used, the polymer concentration and the volume of aqueous phase [17].

3. Salting Out Method

Salting out method is based on the separation of a water-miscible solvent from aqueous solution through a salting-out effect [18]. Firstly, polymer and drug are dissolved in a solvent which is then 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 also a colloidal stabilizer such as polyvinylpyrrolidone

or hydroxyethylcellulose. After this sufficient volume of water or aqueous solution is used for the dilution of oil/water emulsion because of improve the diffusion of solvent into the aqueous phase, hence leading the formation of nanospheres. In the organic phase several manufacturing parameters which can be varied including stirring rate, internal/external phase ratio, concentration of polymers, and in the aqueous phase, type of electrolyte concentration and type of stabilizer [19] PLA, Poly (methacrylic) acids, and Ethyl cellulose nanospheres is prepared by this technique leads to high efficiency and is easily scaled [20]. This method does not require an increase of temperature and thus may be useful when heat sensitive substances have to be processed [21].

4. Emulsions- Diffusion Method

This is also widely used method to prepare nanoparticles. Partially water-miscible solvent (such as propylene carbonate, benzyl alcohol) is used to dissolve the encapsulating polymer, and then saturated with water to ensure the initial thermodynamic equilibrium of both liquids, then in an aqueous solution containing stabilizer which emulsified the polymer-water saturated solvent phase, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to-polymer ratio. Finally according to boiling point, the solvent is eliminated by evaporation or filtration. In this technique no need for homogenization, and also have several advantages, such as high encapsulation efficiencies (generally 70%), high batch-to-batch reproducibility, and ease of scaleup, simplicity, and narrow size distribution. Disadvantage of this method is that a high volume of water is to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase, reducing encapsulation efficiency during emulsification [22]. By the technique several drugs- loaded nano particles were produced, including mesotetra hydroxyphenyl) porphyrin-loaded PLGA (p-THPP) nano particles [23], doxorubicin-loaded PLGA nano particles, and cyclosporine (CY-A-); loaded sodium glycolate nanoparticles [24].

5. Solvent Displacement / Precipitation Method

In the solvent displacement method an organic solution forms a precipitate of performed polymer. In the presence or absence of surfactant an organic solvent is diffused in the aqueous medium. Polymers, drug, and lipophilic surfactant are dissolved in an acetone or ethanol which are semi polar water miscible solvent. Then the solution is poured or injected into an aqueous solution containing stabilizer under magnetic stirring. Because of rapid solvent diffusion nano particles are formed immediately. After this, solvent is removed from the suspensions under reduced pressure. Due to the rates of addition of the organic phase into the aqueous phase affect the particles size. It was noticed that a decrease in both particles size and drug entrapment occurs as the rate of mixing of the two phase increases [25]. Nano precipitation method is well suited for most of the poorly soluble drugs. By adjusting preparation parameters a nanosphere size, drug release and yield were shown to be effectively controlled. polymer concentration is adjusted 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 [26].

6. Coacervation or Ionic Gelation Method

For the preparation of nanoparticles by coacervation method hydrophilic biodegradable polymers are used such as chitosan, sodium alginate and gelatin. This method can be used for the preparation of hydrophilic polymer based nanoparticles. Chitosan based hydrophilic nanoparticles prepared by ionic gelation method was first developed by calvo and co-worker [27, 28]. Two different aqueous phases are prepared, of which one is a polymer chitosan, adi-block copolymer ethylene oxide or propylene oxide and second is a polyanion sodium tripolyphosphate which are mixed, due to mixing positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a nanometer size. Formation of coacervates are when electrostatic interaction take place between two aqueous phases, and when two molecules interact due to ionic force, at room temperature resulting in transition from liquid phase to gel phase this is known as ionic gelation method [29].

7. Desolvation Method

Desolvation technique was adopted for the preparation of drug loaded polymer nanoparticles. The processing parameters like concentration of the drug and polymer, speed of rotation were optimized. Drug-polymer solution was prepared and its pH was adjusted to its isoelectric point. The desolvating agent is used for nanoparticle preparation. The addition of

desolvating agent to the drug-polymer solution was done by two methods, i.e.; continuous and intermittent respectively. The appearance of turbidity in the solution was considered as the end point. Then, few drops of Cross linking agent is added. For complete cross linking, the stirring was continued for 12 hours. The solvent and water were removed from the resultant solution by means of rotary evaporator. The obtained free flowing powder was then characterized for particle size distribution to ensure that they were within nanosize range. Further, it was evaluated for following parameters like zeta potential, entrapment efficiency and invitro drug release [29].

Nanoparticles Produced by Desolvation of Macromolecules

Another technology applicable to a wide range of polymers is based on desolvation by charge and pH changes, or by adding of a desolvating agent. The main advantage is that this process may be useful when heat-sensitive drugs are used because it does not require an increase in temperature and, therefore. Nanoparticles were prepared using the process of reversible swelling of macromolecules using gelatin, human serum albumin, bovine serum albumin, and casein as the macromolecular materials. By using this process nanoparticles can be directly produce in aqueous suspension, but the use of some potentially toxic compounds such as glutaraldehyde and desolvating agents requires subsequent purification [30].

Characterization of Nanoparticles

Characterization is necessary to understand the synthesis and application of nanoparticles [31]. The main parameters studied in the characterization of nanoparticles are particle size and shape. Size distribution, degree of aggregation, surface charge and surface area can also be studied [32]. Advanced microscopic techniques as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM) are used for characterization of nanoparticles. The physical stability and the in vivo distribution of the nanoparticles can be affected by average particle diameter, their size distribution and charge. Transmission electron microscopy and high resolution transmission electron microscopy are most powerful imaging tools which give detailed geometrical features and information about crystal structural, quality and orientation of nanoparticles [7].

Some Characterization Parameters of Nanoparticles are:

1. Particle size
2. Dynamic Light Scattering
3. Scanning Electron Microscopy
4. Transmission Electron Microscope
5. Particle Charge
6. Surface Hydrophobicity
7. Drug Release

1. Particle Size

Most parameters of the characterization of nanoparticles are Particle size distribution and morphology. Electron microscopy is used to measure the morphology and size. The main application of nanoparticles is in drug release and drug targeting. It has been found that particle size directly affects the drugs release. Smaller particles larger will be the surface area. As a result, most of the drug which loaded onto nanoparticles will be exposed to the particle surface which leads to fast drug release. On the other hand, if the drug is loaded in to large particles will be diffused slowly. As a drawback, there is a chanceof aggregation of small particles during storage and transportation of nanoparticle. That is why; there is a comparison between a small size and maximum stability of nanoparticles [33]. Particle size can also affect the Polymer degradation. For instance, the degradation rate of poly (lactic-co-glycolic acid) was found to increase with increasing particle size in vitro [34].

2. Dynamic Light Scattering (DLS)

Dynamic light scattering /photon-correlation is the fastest and the most popular method to determine particle size. This technique is widely used to determine the Brownian nanoparticles size in colloidal suspension in the nano and submicron ranges. When monochromatic light (laser) falls onto a solution of spherical particles in Brownian motion, then light hits the moving particle causes a Doppler shift, changing the wavelength of the incoming light. This change is determined the size of the particle [1]. This parameter assists in evaluation of the size distribution, particle's motion in the medium, which may further assists in measuring the diffusion coefficient of the particle and using the autocorrelation function. Dynamic light scattering (DLS) offer the most frequently used technique for accurate estimation of the particle size and size distribution [35].

3. Scanning Electron Microscopy (SEM)

Size, shape, and morphology of formed nanoparticles are determined by scanning electron microscope. SEM gives high resolution images a sample. The scanning electron microscope works as same principle as an optical [36]. Advantages of this technique are 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 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 [37]. The sample surface characteristics are obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to endure 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 [38].

4. Transmission Electron Microscope

Operating principle of Transmission electron microscope is different from scanning electron microscope; still it mostly brings same type of data. It can provide imaging, spectroscopic information, either simultaneously or in a serial manner, of the specimen with an atomic or a sub-nanometer spatial resolution. Sample for the TEM should be ultra-thin for the electronic transmittance that is why; preparation of sample is complex and time consuming. The nanoparticles dispersion is set down onto support grids or films. To form nanoparticles, they are secure 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 glassy ice. The sample surface characteristics of are obtained when a beam of electrons is transmitted through an ultra-thin sample, interacting with the sample as it passes through [38].

5. Particle Charge

Colloidal stability of the particle is determined by zeta potential. Surface charge of nanoparticles is very important to determines their interaction with the biological environment same as their electrostatics interaction with bioactive compounds. Storage stability of the colloidal dispersion is predicted by measuring the zeta potential. High positive or negative values of zeta potential should be achieved to ensure stability and avoid aggregation of the particles. Surface hydrophobicity of the particles can be predicted from the value of zeta potential [39].

6. Surface Hydrophobicity

Several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption of probes, contact angle measurements etc are used for the determination ofSurface hydrophobicity. Recent advancement in research offers several analytical techniques are reported in literature for surface analysis of nanoparticles [40].

7. Drug Release

It's very essential to determine extent of the drug release and in order to obtain such information most release methods require that the drug and its delivery vehicle be separated. Drug loading capacity of the nanoparticles is defined as the amount of drug bound per mass of polymer or in another term it is the moles of drug per mg polymer or mg drug per mg polymer or it could also be given as percentage relative to the polymer. Various techniques such as UV spectroscopy or high performance liquid chromatography (HPLC) after ultracentrifugation, ultra filtration, gel filtration, or centrifugal ultra-filtration are used to determine this parameter. Methods that are employed for drug release analysis are also similar to drug loading assay which is more often assessed for a period of time to evaluate the drug release mechanism [41, 42].

Future Aspect

Currently, the science of nanomedicine is the most fascinating areas of research. A lot of research in this field in the last two decades has already led to the filling of 1500 patents and completion of several dozens of clinical trials [45]. Without disturbing the physiology of the normal cells such as the cancer/tumour cells various types of nanoparticles can be deliver the accurate amount of drug to the affected cells. More research on materials with more consistent uniformity, drug loading and release capacity would be the further area of research. Metals-based nanoparticles will be used for diagnostic purposes. In future the application of these metals including gold and silver both in diagnosis and therapy is an area of research that could

potentially lead to wider application of nanomedicines. One major enthusiasm in this direction includes the gold-nanoparticles that appear to be well absorbed in soft tumour tissues and making the tumour susceptible to radiation based heat therapy for selective elimination. As nanomedicines gain popularity, their affordability would be another area of research that needs more research input [46].

Table 1: Different Parameters to be Characterized Along with their Characterization Method are Presented Below [43].

Parameter	Characterization method
Particle size and distribution	Photon correlation spectroscopy(PCS), Laser defractometry, Transmission electron microscopy, Scanning electron microscopy, Atomic force microscopy
Drug stability	Chemical analysis of drug, Bioassay of drug extracted from nanoparticles
Release profile	*In vitro* release characteristics under physiological and sink condition
Chemical analysis of surface	Static secondary ion spectroscopy
Carrier-drug interaction	Diffential scanning calorimetry
Nanoparticle dispersion solubility	Critical flocculation temperature(CFT)
Surface Hydrophobicity	Water contact angle measurement, X-ray photoelectron spectroscopy
Charge determination	Laser doppler anemometry, Zeta potential

Table 2: Applications of Various Nanosystems in Cancer Therapy [7]

Nanosystems	Applications in Cancer Therapeutics
Carbon nanotubes	DNA mutation detection, protein biomarker detection
Dendrimers	Controlled release drug delivery, image contrast agents
Nanoparticles	MRI and ultrasound image contrast agents, targeted drug delivery, permeation enhancers, reporters of apoptosis, angiogenesis, etc.
Quantum dots	Optical detection of genes and proteins in animal models and cell assays, tumour and lymph node visualization

Table 3: List of Relevant Marketed (Polymer-based and Lipid-based) Organic and Inorganic Nanomedicines Approved by the FDA [44], Marketed Preparation of Polymer-based Nanoparticles

Clinical product	Formulation	Indication	Company	Year
Renagel	Poly(allylamine hydrochloride)	kidney disease	Sanofi	2000
Eligard	Leuprolide acetate and polymer (poly (DL-lactide-co-glycolide))	Prostate cancer	Tolmar	2002
Estrasorb	Micellar estradiol	Menopausal therapy	Novavax	2003
Adynovate	Polymer-protein conjugate	Hemophilia	Baxalta	2015
Cimzia/ certolizumab pegol	PEGylated antibody fragment (certolizumab)	Crohn's disease, Rheumatoid /psoriatic arthritis, Ankylosing spondylitis	UCB	2008-2013
Genexol-PM	paclitaxel loaded mPEG-PLA micelle	Metastatic breast cancer	Samyang Corporation	2007

Table 4: Marketed Preparation of Lipid-based Nanoparticles

Clinical product	Formulation	Indication	Company	Year
Doxil/Caelyx	Liposomal doxorubicin	Ovarian, breast cancer, Kaposi's sarcoma	Janssen	1995-2008
Onivyde	Liposomal irinotecan	Pancreatic cancer	Merrimack	2015
Marqibo	Liposomal vincristine	Acute lymphoblastic leukemia	Talon Therapeutics Inc.	2012
AmBisome	Liposomal amphotericin B	Fungal/protozoal infections	Gilead Sciences	2012
Myocet	Liposomal doxorubicin	in metastatic breast cancer with cyclophosphamide	Elan Pharmaceuticals	2000
Visudyne	Liposomal verteporfin	Choroidal neovascularisation, macular degeneration, wet age-related, myopia, and ocular histoplasmosis	Bausch and Lomb	2000

CONCLUSION

Nanoparticulate systems have great potentials, to convert low soluble, poorly absorbed and labile biologically active substanceinto promising deliverable drugs. This review provides an overview of characterization methods, types and, application of nanoparticles. This article concludes that nanoparticle has a tremendous growth in recent years. For example nanoparticle synthesis using plant sources is largely adopted due to its eco-friendly nature and cost effectiveness etc.

REFERENCES

[1] Sovan Lal Pal, Utpal Jana, P. K. Manna, G. P. Mohanta, R. Manavalan. Nanoparticle: An overview of preparation and characterization. Journal of Applied Pharmaceutical Science.2011: 228-234

[2] Mohan V.J, Chen Y. Nanoparticles a review. Tropical Journal of Pharmaceutical research. 2006: 5; 562.

[3] Lee M, Kim SW. Polyethylene glycol-conjugated copolymers for plasmid DNA delivery. Pharm Res 2005; 22: 1-10.

[4] Konwar Ranjit., Ahmed Abdul baquee, Nanoparticles: An overview of preparation, characterization & application. International research journal of pharmacy. 2013; 4[4], 47-48.

[5] Yadav C., Kumari A., Yadav SK., Subhash C. Biodegradable polymeric nanoparticles based drug delivery systems review. Colloids and surfaces B: Biointerfaces. 2010; 75:1-18.

[6] Hett A. Nanotechnology: small matters, many unknown. Swiss Re, Risk Perception series, Zurich 2004.

[7] Ashish Kumar Varma, Ashish Srivastava, Swatantra Kushwaha. Nano Particulate Carriers in Drug Delivery System: A Review. Journal of Drug Discovery and Development. 2018; 2(2), 19-25.

[8] Tomalia DA. Birth of a new macromolecular architecture: Dendrimers as quantized building blocks for nanoscale organic chemistry. Aldrichimica Acta.2004; 37: 39 -57.

[9] 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.

[10] Goldberg M., Langer R., Jia X. Nanostructured materials for applications in drug delivery and tissue engineering. J Biomater Sci Polym.2007; 18:241-68.

[11] 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.

[12] Song CX., Labhasetwar V., Murphy H., Qu X., Humphrey WR. Shebuski R J., Levy R J. Formulation and characterization of biodegradables nanoparticles for intravascular local drug delivery.J Control Release.1997; 43:197- 212.

[13] Jaiswal J., Gupta SK., Kreuter J. Preparation of biodegradable cyclosporine nanoparticles by high-pressure emulsification solvent evaporation process. J Control Release.2004; 96:1692-178.

[14] Lemarchand C., Gref R., Passirani C., Garcion E., Petri B., Muller R. Influence of polysaccharide coating on the interactions of nanoparticles with biological systems. Biomaterials.2006; 27:108-18.

[15] Koosha F., Muller RH., Davis SS., Davies MC. The surface chemical structure of poly (-hydroxybutyrate) microparticles produced by solvent evaporation process. J Control Release.1989; 9:149-57.

[16] Vandervoort J., Ludwig A. Biodegradable stabilizers in the preparation of PLGA nano particles: a factorial design study. Int J Pharm. 2002; 238:77-92.

[17] Ubrich N., Bouillot P., Pellerin C., Hoffman M., Maincent P. Preparation and characterization of propanolol hydrochloride nanoparticles: A comparative study. J Control release. 2004:291-300.

[18] 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.

[19] Allemann E., Gurny R., Doekler E. Drug-loaded nanoparticles preparation methods and drug targeting issues. Eur J Pharm Biopharm. 1993; 39:173-91.

[20] 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.

[21] Lambert G., Fattal E., Couvreur P. Nanoparticulate system for the delivery of antisense oligonucleotides. Adv Drug Deliv Rev. 2001; 47:99-112.

[22] Takeuchi H., Yamamoto Y. Mucoadhesive Nanoparticulate system for peptide drug

delivery. Adv Drug Del Rev. 2001; 47: 39-54

[23] 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.

[24] El-shabouri MH. Positively charged nano particles for improving the oral bioavailability of cyclosporine-A.Int J Pharm. 2002; 249:101-8.

[25] Fessi H., Puisieux F., Devissaguet J-P., Ammoury N., Benita S. Nano capsule formation by interfacial deposition following solvent displacement. Int J Pharm. 1989; 55:R1-R4.

[26] Chorney M., D Aneuberg H., and Golomb G. Lipophilic drug loaded nanospheres by nano precipitation: effect of the formulation variables on size, drug recovery and release kinetics. J Control release 2002; 83: 389- 400.

[27] Calvo P, Remunan-Lopez C, Vila-Jato JL, Alonso MJ. Novel hydrophilic chitosan polyethylene oxide nanoprticles as protein carriers.J Appl Polym Sci. 1997; 63:125–32.

[28] Calvo P, Remunan-Lopez C, Vila-Jato JL, Alonso MJ. Chitosan and chitosan/ethylene oxidepropylene oxide block copolymer nanoparticles as novel carriers for proteins and vaccines. Pharm Res. 1997; 14:1431–6.

[29] Abhishek Garg*, Sharad Visht, Pramod Kumar Sharma and Nitin Kumar.Formulation, Characterization and Application on Nanoparticle: A Review. Pelagia Research Library. 2011, 2 (2): 17-26.

[30] Serpe L, Catalano MG, Cavalli R et al. Cytotoxicity of anticancer drugs incorporated in solid lipid nanoparticles HT-29 colorectal cancer cell line. *Eur J Pharm Biopharm* 2004; 58: 673-680.

[31] J. Panyam, V.Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev, 2003, 55, 329-47.

[32] C.Minelli, talk on 'Measuring nanoparticle properties: are we high and dry or all at sea?' at 'Nanoparticle Characterisation – Challenges for the Community' event – IOP (Institute of Physics), book of abstracts, July 2016, London. , talk on 'Measuring nanoparticle properties: are we high and dry or all at sea?' at 'Nanoparticle Characterisation – Challenges for the Community' event – IOP (Institute of Physics), book of abstracts, July 2016, London

[33] Redhead H M., Davis SS. and Illum L. J. Control. Release.2001; 70: 353.

[34] Betancor L. and Luckarift HR. 2008 Trends Biotechnol. 26 566 Dunne M, Corrigan

[35] DeAssis DN, Mosqueira VC, Vilela JM, Andrade MS, Cardoso VN. Release profiles and morphological characterization by atomic force microscopy and photon correlation spectroscopy of 99m Technetium— fluconazole nanocapsules.Int J Pharm. 2008; 349:152–60.

[36] P. Heera and S. Shanmugam, Nanoparticle Characterization and Application: An Overview Int.J.Curr.Microbiol.App.Sci (2015) 4(8): 379-386.

[37] Jores K., Mehnert W., Drecusler M., Bunyes H., Johan C., MAder K. Investigation on the stricter of solid lipid nanopartuicles and oil-loaded solid nanoparticles by photon correlation spectroscopy, fieldflow fractionasition and transmission electron microscopy. J Control Release.2004; 17: 217- 227.

[38] Molpeceres J., Aberturas MR., Guzman M. Biodegradable nanoparticles as a delivery system for cyclosporine: preparation and characterization. J Microencapsul.2000; 17: 599-614.

[39] Pangi Z., Beletsi A., Evangelatos K. PEG-ylated nanoparticles for biological and pharmaceutical application. Adv Drug Del Rev. 2003; 24: 403- 419.

[40] 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; 59:261–78.

[41] Kreuter J. Physicochemical characterization of polyacrylic nanoparticles. Int J Pharm. 1983; 14:43–58.

[42] Magenhein B, Levy MY, Benita S. A new in vitro technique for the evaluation of drug release profile from colloidal carrier's ultra- filtration technique at low pressure.Int J Pharm. 1993; 94:115–23.

[43] S. P. Vyas, R. K. Khar, Targeted and controlled drug delivery. CBS Publishers and Distributers, New Delhi, 2002, 1, 331-343.

[44] Domenico Lombardo, Mikhail A. Kiselev and Maria Teresa Caccamo. Smart Nanoparticles for Drug Delivery Application: Development of Versatile Nanocarrier Platforms in Biotechnology and Nanomedicine. Journal of Nanomaterials.Volume 2019, Article ID 3702518, 26 pages. https://doi.org/10.1155/2019/3702518.

[45] Pandit A, Zeugolis DI. Twenty-five years of nano-bio-materials: have we revolutionized healthcare? Fut Med. 2016; 11(9):985–7.

[46] Jayanta Kumar Patra, Gitishree Das, Leonardo Fernandes , Estefania Vangelie Ramos Campos, Maria del Pilar Rodriguez-Torres, Laura Susana Acosta-Torres, Luis Armando Diaz-Torres, Renato Grillo, Mallappa Kumara Swamy, Shivesh Sharma, Solomon Habtemariam & Han-Seung Shin .Nano based drug delivery systems: recent developments and future prospects. Journal of Nanobiotechnology. 71 (2018).