Review Article

Nanoparticle: A Promising carrier for Novel Drug Delivery

Jaydip Kumbhani*, Chintan Tank, Jay Upadhyay, Ram Darshit, Thanki Nirali, Savaliya Hetal

Faculty of Pharmacy, Dr. Subhash Techanical Campus, Junagadh 362001, Gujarat, India.

ABSTRACT

For the past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like Nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Due to their small sizes, they exhibit unique physicochemical and biological properties like an enhanced reactive area as well as an ability to cross cell and tissue barrier, that make them a favourable carrier for novel drug delivery. They have been used to protect the drug entity in the systemic circulation, restrict access of the drug to the sites and to deliver the drug at a controlled and sustained rate to the site of action. Nanoparticles have been developed as an important strategy to deliver conventional drugs, recombinant proteins, vaccines and nucleotides. Therefore nanoparticles in the pharmaceutical biotechnology sector improve the therapeutic index and provide solutions for future delivery problems for new classes of so called biotech drugs including recombinant proteins and oligonucleotides. Various polymers have been used in the formulation of Nanoparticles for drug delivery to increase therapeutic benefit and minimizing side effects. This paper aims to review various aspects of Nanoparticle formulation, characterization, effect of their characteristics and applications of nanoparticles as carrier system in the field of pharmaceuticals.

Keywords: Carrier system, nanoparticles, polymer, particulate systems, targeting

Received 15 Sept 2015 Received in revised form 13 Oct 2015 Accepted 4 Jan 2016

***Address for correspondence:**
Jaydip Kumbhani,
Faculty of Pharmacy, Dr. Subhash Techanical Campus, Junagadh 362001, Gujarat, India.
E-mail: jkkumbhani56@gmail.com

INTRODUCTION

"Nanoparticles are sub-nanosized colloidal structures, composed of synthetic or semi-synthetic polymers with 10-1000nm Size range." Drug is dissolved, entrapped, encapsulated or attached to a nanoparticle. During last two decades, considerable attention has been given to the development of novel drug delivery system (NDDS), the rational for control drug delivery is to alter the pharmacokinetics and pharmacodynamic of drug substance in order to improve the therapeutic efficacy and safety through the use of novel drug delivery system. Besides more traditional matrix or reservoir drug delivery system, colloidal drug delivery system has gained popularity. The major colloidal drug delivery system includes liposome and polymeric nanoparticles. 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. These systems have been investigated primarily for site specific drug delivery, for controlled drug delivery, and also for the enhancement of dissolution rate/bioavailability of poorly water-soluble drugs. [1, 2]

Advantages of nanoparticles

- Ease of manipulation of the particle size and surface characteristics of nanoparticles so as to achieve both passive and active drug targeting after parenteral administration.
- Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents.
- Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an

important factor for preserving the drug activity.
- Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
- Ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics.
- Increases the stability of any volatile pharmaceutical agents, easily and cheaply fabricated in large quantities by a multitude of methods.
- Their sizes allow them to be administered intravenously via injection unlike other colloidal system, which occlude both needles and capillaries.
- Nanoparticle can act as controlled release system depending on their polymeric composition
- The nanoparticle surface can be modified to alter biodistribution of drugs with subsequent clearance of the drug so as to achieve maximum therapeutic efficacy with minimal side effects of the drug. [3,4]

Disadvantage of nanoparticles [5]
- High surface energy that may lead to high aggregation in biological system.
- Can be quickly scavenged by RES system of body resulting in low biological half – life.
- High immunogenicity or foreignnes*s.*
- 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.

Types of nanomedicines [6]**:**

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

1) Fullerenes

A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buck balls, and cylindrical ones are called carbon nanotubes or buckytubes. Fullerenes are similar in structure to the graphite, which is composed of stacked grapheme sheets of linked hexagonal rings, additionally they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules Bucky ball clusters or buck balls composed of less than 300 carbon atom commonly known as endohedral fullerenes. Mega tube larger in diameter than nanotubes and it is prepared with walls of different thickness which is potentially used for the transport of a variety of molecules of different sizes.

Table 1: Biomedical applications

Fullerenes composition	Application	References
Fullerene (C60)	HIV proteases	Friedman et al. (1993) and Sijbesma et al.
Fulleropyrrolidines	HIV-1 and HIV-2	Marchesan et al. (2005)
Dendrofullerene 1	HIV-1 replication	Brettreich and Hirsch (1998)
Amino acid derivatives of fullerene C60	HIV and human cytomegalovirus Replication	Kotelnikova et al. (2003)
(ADF) Buckminsterfullerene	Semliki forest virus (SFV, Togaviridae) or vesicular stomatitis virus (VSV, Rhabdoviridae	Kaesermann and Kempf (1997)

2) Solid Lipid Nanoparticle: [7]

SLNs mainly comprise lipids that are in solid phase at the room temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications. SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials. The typical methods of preparing SLNs include spray drying high shear mixing, ultra-sonication and high pressure homogenization Solid lipids utilized in SLN

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

3) Nanostructured lipid carriers (NLC)

Nanostructured Lipid Carriers are produced from blend of solid and liquid lipids, but particles are in solid state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate nanoparticles (LDC), which have been created to improve drug loading capacity. The NLC production is based on solidified emulsion (dispersed phase) technologi Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. NLCs accommodate the drug because of their highly unordered lipid structures. A desired burst drug release can be initiated by applying the trigger impulse to the matrix to convert in a more ordered structure. Major application areas in pharmaceutics are topical drug delivery, oral, and parenteral.

4) Nanoshells

Nanoshells are spherical cores of a particular compound (concentric particles) surrounded by a shell or outer coating of thin layer of another material, which is a 1–20 nm nanometers thick. Their properties can be modified by changing either the constituting materials or core-to-shell ratio. Nanoshell materials can be synthesized from semiconductors, metals and insulators. Usually dielectric materials such as silica and polystyrene are commonly used as core because they are highly stable Metal nanoshells are a novel type of composite spherical nanoparticles consisting of a dielectric core covered by a thin metallic shell which is typically gold. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. When a Nanoshell and polymer matrix is illuminated with resonant wavelength, nanoshells absorb heat and transfer to the local environment. This causes collapse of the network and release of the drug. In core shell particles-based drug delivery systems either the drug can be encapsulated or adsorbed onto the shell surface. The shell interacts with the drug via a specific functional group or by electrostatic stabilization method. When it comes in contact with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific antibodies for diseased tissues or tumors. Nanoshell materials have received considerable attention in recent years because of potential applications associated with them.

5) Quantum dots (QD)

The quantum dots are semiconductor nanocrystals and core shell nanocrystals containing interface between different semiconductor materials. The size of quantum dots can be continuously tuned from 2 to 10 nm, which, after polymer encapsulation, generally increases to 5–20 nm in diameter. Semiconductor nanocrystals have unique and fascinating optical properties, become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term

fluorescence imaging and detection QD core can serve as the structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisenseoligodeoxynucleotide(ODN)) and targeting biomolecules such as antibodies, peptides and a tamers can be immobilized on to the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds. This fully integrated nanostructure may behave like magic bullets that will not only identify, but bind to diseased cells and treat it. It will also emit detectable signals for real-time monitoring of its trajectory these benefits enables applications of QDs in medical imaging and disease detection.

6) Superparamagnetic nanoparticles

Superparamagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5–100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. The main advantages of super paramagnetic nanoparticles are that they can be visualized in magnetic resonance imaging(MRI) due to their paramagnetic properties; they can be guided to a location by the use of magnetic field and heated by magnetic field to trigger the drug release Superparamagnetic nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials (silica, gold) and organic (phospholipids ,fatty acids, polysaccharides, peptides or other surfactants and polymers There are several potential applications of super paramagnetic nanoparticles some of which are given in The following issues are not fully understood such as 1) the mechanisms utilized by cells to take up multifunctional SPIONs in human cells inculture, 2) specific adsorption of SPIONs to targeted sub cellular components after uptake, transport of drugs, plasmids or other substances to specific cells followed by controlled release, 3) prevention of uncontrolled agglomeration of modified SPIONs in physiological liquids,4) short and long-term impact on cell functions by loading cells of different phenotypes with such nanoparticles.

Formulation [8, 9]

Preparation of nanoparticle

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.

(i) Required nanoparticle size.
(ii) Permeability and surface charge of nanoparticle.
(iii) Level of biodegradability and biocompatibility must be optimum.
(iv) Material must be non toxic.
(v) Solubility profile and stability of drug should not be affected.
(vi) It should show desired drug release profile.
(vii) Must not be immunogenic.

Following are methods which are used in formulation of nanoparticles

1. Dispersion of preformed polymers.
2. Polymerization method.
3. Coacervation or ionic gelatin method.
4. Supercritical fluid technology

Method of preparation of nanoparticles from dispersion of preformed polymer

Dispersion of drug in preformed polymers is a common technique used to prepare biodegradable nanoparticles from Various Polymer. These can be accomplished by different methods described below.

a) Solvent evaporation
b) Nanoprecipitation
c) Emulsification/solvent diffusion
d) Salting out
e) Dialysis
f) Supercritical fluid technology (SCF)

Methods for preparation of nanoparticles from polymerization of monomers

a) Emulsion
b) Mini emulsion
c) Micro emulsion
d) Interfacial polymerization
e) Controlled/Living radical polymerization (C/LRP)

a) Solvent evaporation

Solvent evaporation was the first method developed to prepare PNPs from a polymer. In this method, polymer solutions are prepared in volatile solvents and emulsions are formulated. In the past, dichloromethane and chloroform preformed polymer 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 oil-in-water (o/w), 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.

Table 2: 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(alkylcyanoacrylate)
Interfacial O/W polymerization	Hydrophobic	**Hydrophobic** Poly(alkylcyanoacrylate)
Solvent extraction evaporation	Hydrophilic and Hydrophobic Soluble in polar solvent	**Polyesters** Poly (lactic acid), poly(caprolactone)
Solvent displacement	Hydrophilic and Hydrophobic Soluble in polar solvent	**Polyesters** Poly (lactic acid), Poly(lactide-co glycolide),
Salting out	Soluble in polar solvent	**Polyesters** Poly (lactic acid),Poly (lactide-acid)

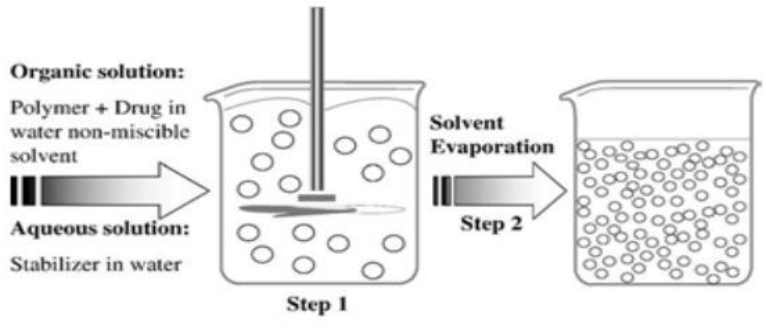

Figure 1 : Schematic representation of the Solvent evaporation technique

b) Nanoprecipitation

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. Considering the oil-based central cavities of the nanocapsules, high loading efficiencies are generally reported for lipophilic drugs when nanocapsules are prepared.

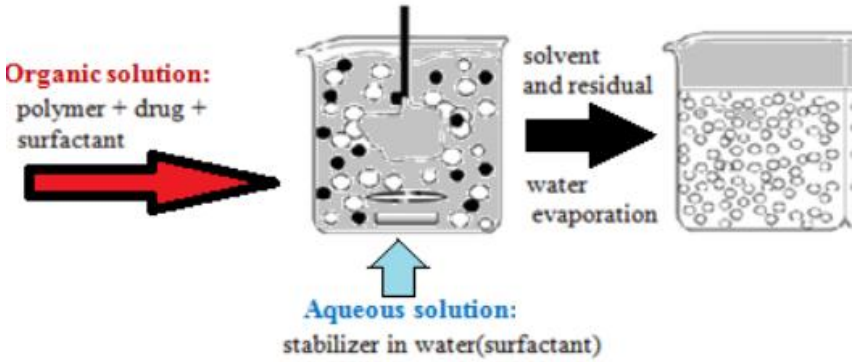

Figure 2: Schematic representation of the nanoprecipitation technique

c) Emulsification/solvent diffusion (ESD)
This is a modified version of solvent evaporation method. The encapsulating polymer is dissolved in a partially water soluble solvent such as propylene carbonate and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. In fact, to produce the precipitation of the polymer and the consequent formation of nanoparticles, it is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partly miscible with water or with another organic solvent in the opposite case. 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 liminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency.

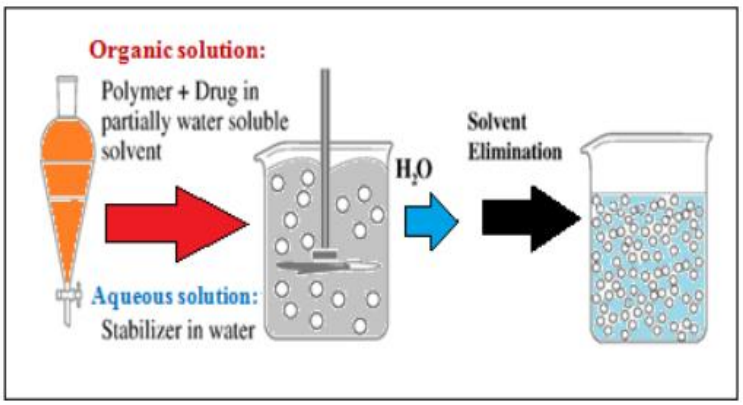

Figure 3: Schematic representation of the emulsification/solvent diffusion technique

d) Salting out

Salting out is based on the separation of a water miscible solvent from aqueous solution via a salting out effect. The salting out procedure can be considered as a modification of the emulsification/solvent diffusion. Polymer and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent (electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose) and a colloidal stabilizer such as polyvinylpyrrolidone or hydroxyethyl-cellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres the selection of the salting out agent is important, because it can play an important role in the encapsulation efficiency of the drug. Both the solvent and the salting out agent are then eliminated by cross-flow filtration. The main advantage of salting out is that it minimizes stress to protein encapsulates. 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 drugs.

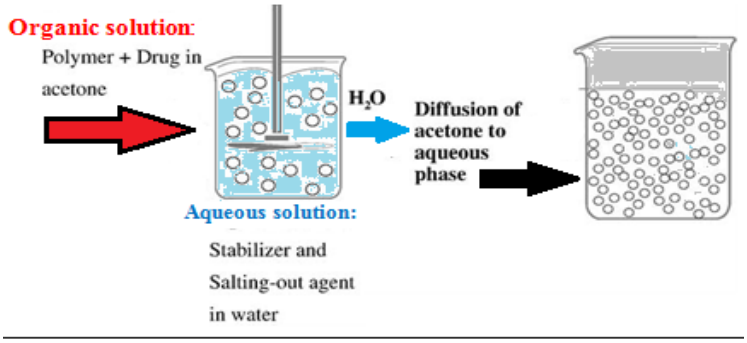

Figure 4: Schematic representation of the Salting out

e) Dialysis

Dialysis offers a simple and effective method for the preparation of small, narrow-distributed PN. Polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut off. Dialysis is performed against a non-solvent miscible with the former miscible. The displacement of the solvent inside the membrane is followed by the progressive aggregation of polymer due to a loss of solubility and the formation of homogeneous suspensions of nanoparticles.

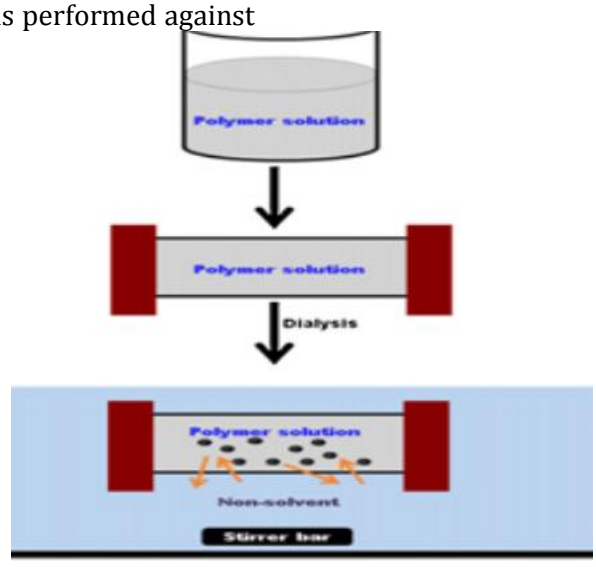

Figure 5: Schematic representation of osmosis based method for preparation of polymer nanoparticles

f) Supercritical fluid technology

The need to develop environmentally safer methods for the production of PNP has motivated research on the utility of supercritical fluids as more environmental friendly solvents, with the potential to produce PNPs with high purity and without any trace of organic solvent. Supercritical fluid and dense gas technology are expected to offer an interesting and effective technique of particle production, avoiding most of the drawbacks of the traditional methods.

Two principles have been developed for the production of nanoparticles using supercritical fluids:

1. Rapid expansion of supercritical solution (RESS)
2. Rapid expansion of supercritical solution into liquid preparation

Evaluation of nanoparticle [10-13]

1) Particle size

Particle size and size distribution are the most important characteristics of nanoparticle systems. The faster and most routine method of determining particle size is by

1. Photon-correlation spectroscopy.
2. Dynamic light scattering.
3. Brownian motion and light scattering properties*.*
4. Scanning or transmission electron microscopy (SEM or TEM)

2) Drug entrapment efficiency

The nanoparticles were separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 50C. Then the resulting supernatant solution was decanted and dispersed into phosphate buffer saline pH 7.4. Thus the procedure was repeated twice to remove the unentrapped drug molecules completely. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium.

Drug Entrapment efficiency (%) = Amount of released from the lysed nanoparticle X 100 Amount of drug initially taken to prepare the Nanoparticles.

3) 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. [15]

4) Zeta potential

The Zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (±) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. [16]

5) In vitro release studies

In vitro release studies were carried out by using dialysis tubes with an artificial membrane. The prepared nanoparticles were re-dispersed in 5 ml of phosphate buffer pH 7.4 and subjected to dialysis by immersing the dialysis tube to the receptor compartment Containing 150 ml of phosphate buffer pH 7.4. The medium in the receptor was agitated continuously using a magnetic stirrer and the temperature was maintained at37 ± 1˚C. 5ml sample of receptor compartment was take not various intervals of time over a period of 24 h and each time 5 ml fresh buffer was replaced. The amount of drug released was determined spectrometrically. it can also measured by centrifugation method, Agitation, Using biological or artificial membrane i.e. Side-by-side diffuse of cell.

6) Kinetic modeling

In order to understand the kinetic and mechanism of drug release, the result of *in vitro* drug release study of nanoparticles were fitted with various kinetic equation like zero order (cumulative% release *vs.* time), first order (log % drug remaining *vs.* time), Higuchi's model (cumulative % drug release *vs*. square root of time), Peppas plot (log of cumulative% drug release *vs*. log

time). *R*2 (coefficient of correlation) and *k* (release rate constant) values were calculated for the linear curve obtained by regression analysis of the above plots. [17]

7) Stability studies

The stability study was carried out using the optimized Formulation. Formulation was divided into 3 sets of samples and stored at 4˚C in refrigerator, room temperature (29˚C), 45 ± 2˚C/75% RH in humidity control ovens. After 60 d drug content of all samples were determined by the method as in drug content. *In vitro* release study of optimized formulation was also carried out after 60 d of storage. [18]

Characterization of nanoparticles:

To understand synthesis and application of nanoparticle, characterization of nanoparticle is Necessary.

1) Particle size

Most of the properties of nanoparticle like drug loading and release pattern , in vivo distribution ,tissue targeting, toxicity and biological fate are concerned with the size and size distribution of Nanoparticles so they had become an important parameter in characterization of product[15]. It has been reported that micro particles are less effective drug delivers than particle having size ranging in between nanometers for e.g. Nanoparticles having size range greater than 230 nm acquire in the spleen shown by body distribution studies. [19]

2) Surface properties of nanoparticles

The nature and intensity of the surface charge of nanoparticle is very important as it determine their interaction with its biological environment as well as their electrostatic interaction with bioactive compounds. After the intravenous administration of nanoparticles, body immune system recognizes these, followed by phagocytic removal from body by blood circulation.And if once, surface non-modified nanoparticles (conventional nanoparticles) reached in the blood stream they undergo rapid opsonization and cleared by the macrophages of MPS rich organs. [20]

Phagocytes can be prevented by-

(1) Coating the surface of nanoparticles with by using hydrophilic polymers/surfactants which coat the surface of nanoparticle.

(2) With the help of biodegradable copolymers having hydrophilic segments like polyethyleneglycol (PEG), polyethylene oxide, poloxamine and polysorbate 80 (Tween 80) which are used to prepare Nanoparticles.

3) Drug loading [21]

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.

4) 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.

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

Nanoparticle Applications in Medicine

1) Biomedical application of solid lipid nanoparticles [22]

Biomedical Application of solid lipid nanoparticles is listed below.

Nanotechnology for brain drug delivery

The blood brain barrier (BBB) is a structure formed by a complex system of endothelial cells, as troglia, pericytes, and perivascular mast cells, preventing the passage of most circulating cells and molecules. [23] Among the different nano devices, nanosize drug delivery systems between 1 and 100 nm work as a whole unit in terms of transport to cross BBB.[24] Nanosize brain drug

delivery systems may promote the targeting ability of drug in brain and at the same time enhance the permeability of molecules through BBB. However crossing of BBB by the nano rug carriers will depend completely on the physicochemical and biomimetic features and does not depend on the chemical structure of drug, inside the nanoparticles. [25]

Table 3: Different parameters and characterization methods for nanoparticles

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)

Table 4: Biomedical application of solid lipid nanoparticles

SLN composition	Drug	Application
Stearic acid	Rifampicin ,isoniazid, Pyrazinamide	Mycobacterium Tuberculosis
Stearic acid, soya Phosphatidylcholine, and Sodiumtaurocholate Glyceryltripalmitate and tyloxapo.	Ciprofloxacin, Hydrochloride Tobramycin, Clotrimazole	Gram-negative bacteria, gram positive bacteria and mycoplasma Fungi (e.g. yeast, aspergilli, dermatophytes)
Glycerylbehenate, propyleneglycol, tween80, and Glycerylmonostearate	Miconazole nitrate	Fungi
Glycerol palmitostearate	Econazole nitrate	Fungi
Cetylpalmitate	Insulin	Type 1 diabetes
Lecithin, SODIUM taurocholate	Nimesulide	Inflammation
Oleic acid	Ibuprofen	Inflammation
Stearic acid, soyaphosphatidylcholine, and sodium taurocholate	Tobramycin	Pseudomonas aeruginosa
Soyabean-oil	Doxorubicin	Breast cancer
Hyaluronic acid–coupled chitosan	Oxaliplatin	Colorectal cancer
Cholesteryl butyrate	Doxorubicin, paclitaxel	Colorectal cancer
SLN	Tamoxifen,	Breast cancer

Nanosize drug carriers in ocular drug delivery [26-30]

Drug loaded nanoparticles with favorable biological properties include prolonging the residence time, decreasing toxicity and high ability of drug penetration into the deeper layers of the ocular structure and minimizing precorneal drug loss by the rapid tear fluid turnove*.* Nanoparticles could target at cornea, retina and choroid

by surficial applications and intravitreal injection. Nanoparticles can deliver ocular drugs to the target sites for the treatment of various diseases such as glaucoma, corneal diseases, diabetic retinopathy etc. The uses of nanotechnology based drug delivery systems like nanosuspensions, SLNs and nanoliposomes have greater effect for ocular therapeutic efficacy. Contact lenses loaded with nanoparticles can be effective for topical administration of ophthalmic drugs. Drug loaded contact lenses can also provide continuous drug release because of slow diffusion of the drug molecules through the lens matrix.

Nanoparticles in cancer [31-37]

Nanoparticulate delivery systems in cancer therapies provide better penetration of therapeutic and diagnostic substances within the cancerous tissue in comparison to conventional cancer therapies. Nanoparticulate drug delivery systems are being developed to deliver smaller doses of chemotherapeutic agents in an effective form and control drug distribution within the body. Nanoparticulate delivery systems utilize specific targeting agents for cancer cells minimizing the uptake of the anticancer agent by normal cells and enhance the entry and retention of the agent in tumor cells. Nanocarriers may actively bind to the specific cancer cells by attaching targeting agents with the help of ligands molecules to the surface of the Nanocarriers that bind to specific receptor antigens on the cell surface. Nanocarriers will recognize and bind to target cells through ligands receptor interactions. It is even possible to increase the drug targeting efficacy with the help of antibodies by conjugating a therapeutic agent directly to it for targeted delivery. Thus the drug Nanocarriers are of great hope for future cancer therapy.

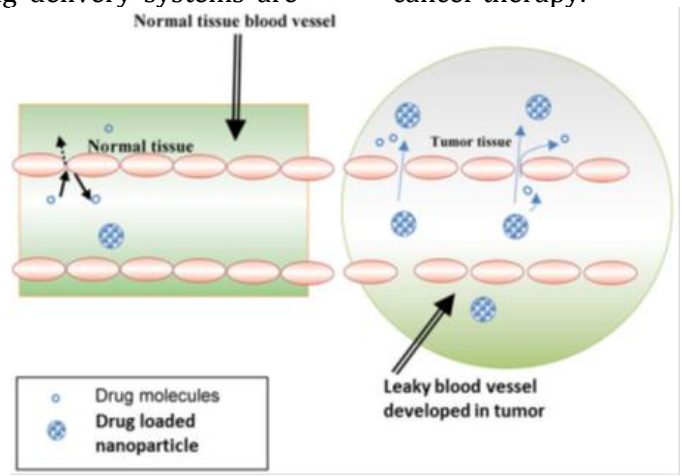

Figure 6: Schematic diagram of nanoparticle permeation and retention effect in normal and tumour tissues

Gene delivery

Transfer of genetic material in Nanocarriers may be an approach for the treatment of various genetic disorders such as diabetes mellitus, cystic fibrosis, and alpha 1 antitrypsin deficiency and may more. A number of systemic diseases are caused by lack of enzymes factors that are due to missing or defective genes.[38] Previously gene therapy which was used to treat genetic disorders nowadays being contemplated as carrier systems which could be implanted for combating diseases other than genetic disorder like malignant form of cancer, heart diseases and nervous diseases. [39] Nanoliposomes can be used to deliver genetic materials into cells. Nanoliposomes incorporated with PEG and galactose target liver cells effectively due to their rapid uptake by liver Kupffer cells. Cationic nanoliposomes have been considered as potential non-viral human gene delivery system. [40] The negatively charged genetic material (e.g. plasmid) is not encapsulated in nanoliposomes but complexed with cationic lipids by electrostatic interactions. Plasmid liposome complexes can enter the disease cells by infusion with the plasma or end some membrane. Allovectin-7 (gene transfer

product) is composed of a plasmid containing the gene for the major histocompatibility complex antigen HLA-B7 with B2 micro globulin formulated with the cytofectin. [41]

Table 5: Recent Nanodrug Carriers in Clinical Trials (Source: Clinicaltrials.gov)

Product name	Delivery material	Phase	Condition	Therapeautic delivered
Genexol-PM	Amphilicdiock Copolymer forming Micelle	I	Non small Cell lung cancer	Paclitaxel
Docetaxel-PNP	Polymeric Nanoparticles	I	Advanced solid malignancies	Docetaxel
Paclitaxel Poliglumex	Drug Polymer Conjugate	II	Prostate cancer	Paclitaxel
Long-circulating liposomal prednisolone disodium phosphate	Liposome	I	Rheumatoid Arthritis	Prednisolone
Cisplatin and LiposomalDoxorubicin	Liposome	I	Advanced cancer	Cisplatin and doxorubicin
Liposomal doxorubicin and bevacizumab	Liposome	II	Kaposi's sarcoma	Doxorubicin and bevacizumab

Marketed products:

Some of the products which are used are described (**Table 6**).

Table 6: Marketed products of Nanoparticle

Product	API	Indication	Company	Nanoparticle technology
RAPAMUE*	Sirolimus	Immunosuppressant	Wyeth	Elan drug delivery nanocrystals
EMEND*	Aprepitant	Antiemetic	Merck	Elan drug delivery nanocrystals
TriCor*	Fenofibrate	Treatment of hypercholesterolemia	Abbott	Elan drug delivery nanocrystals
MEGACE*ES	Megestrolacetate	Appetite stimulant	PAR pharmaceutical	Elan drug delivery nanocrystals
Triglide™	Fenofibrate	Treatment of hypercholesterolemia	First Horizon pharmaceutical	Skye pharmaIDD-P technology

CONCLUSION

Last few years several new technologies have been developed for the treatment of various diseases. The use of nanotechnology in developing Nanocarriers for drug delivery is bringing lots of hope and enthusiasm in the field of drug delivery research. Nanoscale drug delivery devices present some advantages which show higher intracellular uptake than the other conventional form of drug delivery systems. Nanocarriers can be conjugated with ligands such as antibody to favor a targeted therapeutic approach. The empty virus capsids are also being tried to use for delivering drugs as a new therapeutic strategy. Thus, nano size drug delivery systems may revolutionize the entire drug therapy strategy and bring it to a new height in near future. However, toxicity concerns of the nanosize formulations should not be ignored. Full proof methods

should be established to evaluate both the short-term and long term toxicity analysis of the nanosize drug delivery systems.

REFERENCES

1. Tamizhrasi, S., Shukla, A., Shivkumar, T., Rathi, V., Rathi, J. C., Formulation and Evaluation of Lamivudine Loaded Polymethacrylic acid Nanoparticles. Int.J. Pharm. Tech. Res., 2009, 1(3), 411-415.
2. Gaur A., Mindha A., Bhatiya A.L. Nanotechnology in Medical Sciences. Asian J. of Pharmaceutics. 2008, 2(2), 80-85.
3. Konwar, R., Baquee A.A., Nanoparticle: An Overview of Preparation, Characterization and Application. Int. Res. J. Pharm. 2013, 4 (4), 47-57.
4. Garg, A., Visht, S., Sharma, P.K., Kumar, N., Formulation, Characterization & Application on Nanoparticle, Pelagia Res. Library, 2011, 2 (2), 17-26
5. Kumar, P., Kulkarni, P.K., Srivastava, A.A., Pharmaceutical application of nanoparticles in drug delivery system. J. of Chem. & Pharmaceutical Res., 2015, 7(8), 703-712.
6. Mudshinge, S.R., Deore, A.B., Patil, S., Bhalgat, M.C., Nanoparticles: Emerging Carriers for Drug Delivery. Saudi Pharm. J., 2011, 19, 129–141.
7. Neeta Rai, Abhishek Kumar Jain, Jobin Abraham. Formulation and evaluation of herbal antidandruff shampoo containing garlic loaded solid lipid nanoparticles. International Journal of Pharma Research and Review. 2013, 2(10), 12–24.
8. Nagavarma, B.V., Yadav, K.S., Ayaz, A., Vasudha, L.S., Shivakumar, H.G., Different Techniques for Preparation of Polymeric Nanoparticles. Asian. J. Pharma. & Clinical Res. 2012, 5(3), 16-23.
9. Galindo-Rodriguez S., Allemann E., Fessi H., Doelker E., Physicochemical parameters associated with nanoparticle formation in the salting-out, emulsification-diffusion, and nanoprecipitation methods. Pharm. Res. 2004, 21(14), 28- 39.
10. Nesalin, A.J., Smith, A.A., Preparation & Evaluation of Chitosan Nanoparticles Containing Zidovudine. Asian J. Pharma. Science, 2012, 7(1), 80-84.
11. J. Panyam, M.M. Dali, S. K. Sahoo, Ma. W, S.S.Chakravarthi, G.L. Amidon, RJ Levy, V. Labhasetwar. *J Control Release, 2003*, 92, 173-187.
12. V. Subramani, J. Jerome Jeyakumar, M. Kamaraj, B. Ramachandran. Plant Extracts Derived Silver Nanoparticles. International Journal of Pharma Research & Review, 2014; 3(3):16-19.
13. M. Chitra A. Josephine Anbarasi. Potential of Silver Nanoparticles Using Melia azedarach L. Against Some Bacterial Pathogens. International Journal of Pharma Research & Review, 2012; 1(3):10-14.
14. Swarbrick, S., Boylan, J., Encyclopedia of pharmaceutical technology. 2nd ed., New York MarcelDekker, 2002, 369–394.
15. Brigger, C. Dubernet, P. Couvreur, Nanoparticles in cancer therapy and diagnosis. Adv. Drug Deliv.Rev.2002, 54, 631-651.
16. Couvreur, P., Barratt, G., Fattal, E., Legrand, P., Vauthier, C., Nanocapsule terchnology a review. Ther. Drug. Carrier Syst, 2002, 19(2), 99-134.
17. Jahanshahi, M., Babaei, Z., Protein nanoparticle: A unique system as drug delivery vehicles. Afr. J. Bio.technol. , 2008, 25, 4926-4934.
18. Fresta, M., Puglisi, G., Giammona, G., Cavallaro, G., Micali, N., Furneri P.M., Pefloxacine mesilate- and ofloxacin-loaded polyethylcyanoacrylate nanoparticles: characterization of the colloidal drug carrier formulation. J. Pharm. Sci, 1995, 84, 895-902.
19. Chen, Y., McCulloch, R.K., Gray, B.N., Synthesis of albumin-dextran sulfate microspheres possessing favourable loading and release characteristics for the anti-cancer drug doxorubicin. J Control Release, 1994, 31, 49-54.
20. Gavandi, S., Recent Trends of Nanotechnology In Drug Delivery And Their Application-An Overview. Asian J. of Pharma. Tec. & Innovation, 2015, 3(10), 63 -74.
21. Chen, Y., Mohanraj, V.J., Parkin, J.E., Chitosan-dextran sulfate nanoparticles for delivery of an antiangiogenesis peptide. Letters in Peptide Science 2003, 10, 621-627.
22. Mehnert, W., Mäder, K., Solid lipid nanoparticles: production, characterization and applications. Adv. Drug Deliver Rev. 2001, 47(2–3), 165–196.
23. Petty, M.A., Eng, H.L., Junctional complexes of the blood brain barrier: permeability changes in neuro inflammation. Progress in Neurobiology. 2002; 68(5): 311-323.
24. Rabanel, J.M., Aoun, V., Elkin, I., Mokhtar, M., Hildgen, P., Drug loaded Nanocarriers: passive targeting and crossing of biological barriers. Curr. Med. Chem. 2012, 19(19), 3070-3102.
25. Gabathuler, R., Approaches to transport therapeutic drugs across the blood- brain barrier to treat brain diseases. Neurobiology of Disease, 2010, 37(1), 48-57.
26. Youns, M., Hoheisel, J.D., Efferth, T., Therapeutic and diagnostic applications of

nanoparticles. Curr. Drug Targets. 2011, 12(3), 357-365.
27. Kesavan, K., Balasubramaniam J., Kant, S., Singh, P.N., Pandit, J.K., Newer approaches for optimal bioavailability of ocularly delivered drugs: review. Curr. Drug Delivery, 2011 8(2), 172-193.
28. Yasukawa, T., Drug delivery systems for vitreoretinal diseases. Prog. Retin Eye Res., 2004, 23(3), 253-281.
29. Behar-Cohen, F., Drug delivery to target the posterior segment of the eye. Med. Sci., 2004, 20(6-7), 701-706.
30. Gulsen, D., Chauhan, A., Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci., 2004, 45(7), 2342-2347.
31. Surendiran, A., Sandhiya, S., Pradhan, S.C., Adithan, C., Novel applications of nanotechnology in medicine. Indian J Med. Res. 2009, 130, 689-701.
32. Malam, Y., Loizidou, M., Seifalian, AM., Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci., 2009, 30(11), 592-599.
33. Byrne, J.D., Betancourt, T., Brannon-Peppas, L., Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv. Drug Delivery Rev., 2008, 60, 1615-1626.
34. Ruoslahti, E., Bhatia, S.N., Sailor, M.J., Targeting of drugs and nanoparticles to tumors. J. Cell Biol., 2010, 188(6), 759-768.
35. Praetorius, N.P., Mandal, T.K., Engineered nanoparticles in cancer therapy. Recent Pat. Drug Deliv. Formulation, 2007, 1(1), 37-51.
36. Peer, D., Karp, J.M., Hong, S., Farokhzad, O.C., Margalit, R., Langer, R., Nanocarriers as an emerging platform for cancer therapy. Nature Nanotech, 2007, 2, 751-760.
37. Lammers, T., Hennink, W.E., Storm, G., Tumor-targeted nanomedicines: principles and practice. British Journal of Cancer, 2008, 99, 392-397.
38. Davis, P.B., Cooper, M.J., Vectors for airway gene delivery. AAPS J. 2007, 9, E11-E17.
39. Alex, S.M., Sharma, C.P., Nanomedicine for gene therapy. Drug Deliv. Transl. Res., 2013, 3, 437-445.
40. Pathak, A., Vyas, S.P., Gupta, K.C., Nano-vectors for efficient liver specific gene transfer. Int. J. Nanomed., 2008, 31-49.
41. Boettger, M., Zaitsev, S., Cartier, R., Haberland, A., Sukhorukov, G., Moehwald, H., Zastrow, H., Schneider, M., Preparation and use of dna-polyelectrolyte nanoparticles for gene transfer. WO03087384A1. 2003.