ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info/jasr

ISSN
0976-9595
Review Article

Nanoparticles – A Review

G.Maruthi, A.Anton Smith*, R.Manavalan
Department of Pharmacy, Annamalai University, Annamalai Nagar-608 002, Tamilnadu
**Corresponding author: auantonsmith@yahoo.co.in*

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 pharmaco-dynamic properties of various types of drug molecules. They have been used *in vivo* to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the site of action. Various polymers have been used in the formulation of nanoparticles for drug delivery research to increase therapeutic benefit, while minimizing side effects. Here, we review various aspects of nanoparticle formulation, characterization, effect of their characteristics and their applications in delivery of drug molecules and therapeutic genes.

Keywords: Nano-particles, Drug delivery, Targeting drug release

1. INTRODUCTION

Nanotechnology in short nanotech is the study of controlling of matter on anatomic size 100nm or even smaller in at least one dimension. It involves in developing sophisticated materials or devices with in that size.

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10/1000nm. The drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrix. Depending upon the method of preparation, nanoparticles, Nano-spheres or Nano-capsules can be obtained. Nano-capsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while Nano-spheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as long-circulating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver[1-4].

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen [5-6].

Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug, so as to drug achieve increase in therapeutic efficacy and reduction in side effects. 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. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc.

In spite of these advantages, nanoparticles do have limitations. For example, their small size and large surface area can lead to particle, particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before Nano-particles can be used clinically or made commercially available. The present review details the latest development of Nano-particulate drug delivery systems, surface modification issues, drug loading strategies, release control and potential applications of nanoparticles.

2. PHARMACEUTICAL ASPECTS OF NANOPARTICLES

Nano-particles in the point of view, three important process parameters are performed before releasing them for clinical-trails.

2.1. Purification of Nanoparticles

A new methodology knewas "cross flow filtration method" has been used and suggested for the purification of nanoparticles .In this method nanoparticles suspensionis filtered through membrane with direction of fluid being tangential to the surface of the membranes used.

2.2. Freeze drying of Nano-particles

This technique involves freezing of nanoparticle suspension sublimation of its water content under reduced pressure to get a free flowing powdered material.

2.3. Sterilization of Nano-particles

Nanoparticles intended for parenteral use should be sterilized product bepyrogenfree.Filtration through 0.22micron membrane cannot produce a complete sterilized product.Sterilization incase of nanoparticles is best achieved by using aseptic technique throughout their preparation and formulation and or by subsequent sterilizing treatment like autoclaving or irradiation.

2.4 Methodology in preparation of nanoparticles

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers. The selection of matrix materials is dependent on many factors including [7]; (a) size of nanoparticles required, (b) inherent properties of the drug, e.g., aqueous solubility and stability, (c) surface characteristics such as charge andpermeability, (d) degree of biodegradability, biocompatibility and toxicity, (e) Drug release profile desired, and (f) Antigenicity of the final product.

Nano-particles have been prepared most by five methods: (a) Nano-crystals and Nano-suspensions, (b)super critical fluid technology,(c)dispersion of performed polymers,(d) solidlipid nanoparticles,(e) polymerization of monomers, (f) preparation of co-polymerised peptide nanoparticles and (g) ionic gelation or co-acervation of hydrophilic polymers.

Methods such as, Nano-crystals Nano-suspensions, supercritical fluid technology [8],particle replication in non-wetting templates have also been described in the literature for production of nanoparticles. The latter was claimed to have absolute control of particle size, shape and composition, which could set an example for the future mass production of nanoparticles in industry.

2.4.1. Nano-crystals and Nano-suspensions

Recent investigations in drug delivery research have directed towards overcoming drug solubility problems of poorly soluble drugs.Nano-crystals and Nano-suspensions are two recently introduced aspects to the drug delivery research. The basic theme is to convert micronized drug powders to drug nanoparticles. There are various methods available of preparation of these particles. Table 1, shows various methods involved in the preparation of crystalline and nano-particles.

2.4.2. Production by super critical fluid process

Conventional methods such as solvent extraction-evaporation, solvent diffusion and organic phase separation methods require the use of organic solvents which are hazardous to the environment as well as to physiological systems.

Table 1: Various processes in the preparation of crystalline and nanoparticles

Process	Types of particles produced	Particle size
Single emulsion	Polymeric nano-particles	Size depends on the size of dispersion used
Double emulsion	Polymeric nano-particles	100-1000nm
Spray drying	Polymeric or lipidic	Typically less than 200nm
Gas anti solvent and precipitation.	Polymeric nano-particles	100-400nm
Nano precipitation	Polymeric or crystalline nano-particles	Down to 100nm
Wet milling	crystalline nano-particles	Down to 100nm
Micro precipitation	crystalline or nano-particles	Down to 100nm
High pressure homogenization	Polymeric,lipidic and crystalline nano-particles	Less than 100nm
High gravity precipitation	Polymeric nano-particles	Down 100nm

Therefore, the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro and nanoparticles because supercritical fluids are environmentally safe [9]. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure[9].Supercritical CO_2 (SC CO_2) is the most widely used supercritical fluid because of its mild critical conditions (T_c= 31.1 °C, P_c= 73.8 bars), nontoxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent (SAS) and rapid expansion of critical solution (RESS). The process of SAS employs a liquid solvent, eg., methanol, which is completely miscible with the supercritical fluid (SC CO_2), to dissolve the solute to be micronized; at theprocess conditions, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting the formation of nano-particles [8]. Thote and Gupta (2005) reported the use of a modifiedSAS method for formation of hydrophilic drug dexamethasone phosphate drug nanoparticles for micro-encapsulation purpose [10]. RESS differs from the SAS process in that itssolute is dissolved in a supercritical fluid (such as supercritical methanol) and then the solutionis rapidly expanded through a small nozzle into a region lower pressure, thus the solvent power of supercritical fluids dramatically decreases and the solute eventually precipitates. This technique is clean because the precipitateis basically solvent free. RESS and its modified process have been used for the product of polymeric Nano-particles [11]. Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment and is more expensive.

2.4.3. Dispersion of performed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly (lactic acid) (PLA); poly (D,L-glycolide) (PLG); poly (D, L-lactide-co-glycolide)(PLGA) and poly (cyanoacrylate) (PCA),[12-14]. This technique can be used in various ways as described below.
Solvent evaporation method: In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent toform anoil in water (o/w) emulsion.After the formation of stable emulsion,the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type and concentrations of stabilizer [15], homogenizer speed and polymer concentration. In order to produce small particle size, often a high-speed homogenization or ultra-sonification may be employed [17].

Spontaneous emulsification or solvent diffusion method:

This is a modified version of solvent evaporation method [18]. In this method, the water miscible solvent along with a small amount of the water immiscible organic solvent is used as anoil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. As the concentration of water miscible solvent increases, a decrease in the size of particle can be achieved. Both solvent evaporation and solvent diffusion methods can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug, a multiple w/o/w emulsion needs to be formed with the drug dissolved in the internal aqueous phase.

2.4.4. Solid lipid Nano-particles

Nanoparticles made from solid lipid type are attracting major attention as novel colloidal drug carriers. Solid lipid nanoparticles (SLNS) are submicron colloidal carriers (50/1000nm) which composed of physiological lipid dispersed in water or in an aqueous surfactant solution.

Preparation methods of SLN

There are two well established methods.
Hot homogenization technique: Homogenization of melted lipids at elevated temperature is termed as hot homogenization technique. This can be applied to lipophilic and insoluble drugs.

Cold homogenization technique: For hydrophilic drugs this technique is first choice. In case of too low solubility of the hydrophilic drugs in the melted lipid, surfactants can be used of solubilization of the drug. It is suitable for thermo-sensitive and thermo-liable drugs.

2.4.5. Polymerization method

In this method, monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified toremove various stabilizers and surfactants employed for polymerization by ultra-centrifugation andre-suspending the particlesan isotonic surfactant-free medium. This technique has been reported for making poly-butylcyanoacrylate or poly (alkyl-cyanoacrylate) nanoparticles [18-19]. Nano-capsule formation and their particle size depend on the concentration of the surfactantand stabilizers used [20].

2.4.6. Preparation of co-polymerised peptide Nano-particles:

A novel co-polymeric Nano-particulate drug delivery system, co-polymrisedpeptide particles has been developed as carrier for the oral uptake of therapeutic peptides.By using a copolymer delivery system using n-butyl cyanoacrylates as one of the monomer.The particle forming properties of the alkyl -2-cyno acrylates can be exploited.

2.4.7. Coacervation or ionic geleation method

Much research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as,chitosanm,gelatin and sodium alginate. Calvo and co-workers developed a method for preparing hydrophilic chitosan Nano-particles by ionic gelation [21-22]. The method involves a mixture of two aqueous phases, of which one is the polymer chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a poly-anion sodium tri-polyphosphate. In this method, positively charged amino group of chitosan interacts with negative charged tri-polyphosphate to form co-acervateswith a size in the range of Nano-meter. Co-acervates are formed as a result of electrostatic interaction between two aqueous phases, whereas, ionic gelation involves the material undergoing transition from liquid to geldue to ionic interaction conditions at room temperature.

3. CHARACTERIZATION OF NANOPARTICLES

The three key steps of nanoparticles in nanotechnology is particledevelopment, characterization and fabrication.In which characterization is a critical area and currently most challenging task. There are many methods, but some important are mentioned below.

3.1. X-ray characterization of Nano-particles

X-ray methods of characterization represent a powerful approach to the study of Nano –phasematerials. The advantage of these techniques is to provide meaningful ensemble averaged information about both medium range and local atomic structure in Nano-systems.

3.2. Transmission electron microscopy and spectroscopy of Nano-particles

One of the typical characters of Nano-phase materials in the small particle sizes. Although some structural features can be revealed by x-ray and neutron diffraction, direct imaging of nanoparticles is only possible using transmission electron microscopy (TEM) and scanning probe microscopy. TEM is unique because it can provide areal space image on the atom distribution in the Nano-crystals on its surface. Today`s TEM is a versatile tool that provides not only atomic resolution lattice images but also chemical information at spatial resolution of 1nm or better, allowing direct identification the chemistry of a single Nano-crystal.

3.3. Scanning probe microscopy of Nano-nucleus

The basic idea of scanning probe microscopy (SPM) is relatively simple. A probe susceptible to the property that has to be measured, then it has to bring into the vicinity of a surface and the reaction of the probe can be measured. As one is interested in microscope information the probe has to be sufficiently small and its movements have to be controlled on a length scale comparable to its size. Depending on the specific property measured in the type of probe and the way in which the reaction of probe is amplified all existing SPM methods can be differentiated.

3.4. Dynamic light scattering (DLS)

DLS also known as photon correlation spectroscopy or quasi elastic light scattering (QELS) records the variation in the intensity of scattered records the micro second time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion and is quantified by completion of an autocorrelation function. Using standard assumption of spherical size low concentration, and know viscosity of the suspending medium particle size is calculated from this co-efficient.

3.5. *Turbidemetry*

For non–absorbingparticles,turbidity is the complement to light scattering because it represents the amount of incident radiation not reaching a detector that it light lost to scattering. Hence the turbidity spectrum is also described by Mie theory and thus can be used to the data are normalized for concentration.

3.6. Zeta potentials

Zeta potential is used as a suregate for surface change and is often measured by which is achieved, mostly using a Doppler shift, and the user should familiarize themselves in their particular approach implemented in their equipment.

4. VARAITIONS OF CHARACTERISTICS OF NANOPARTICLES ON DRUG DELIVERY

4.1. Particle size

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity and the targeting

ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over micro-particles as a drug delivery system[23]. Generally nanoparticles have relatively higher intracellular uptake compared to micro-particles and available to a wider range of biological targets due to their small size and relative mobility. Desai *et al.,* found that 100 nm nanoparticles had a 2.5 fold greater uptake than1 μm sized micro-particles, and 6 fold greater uptake than 10 μm sized micro-particles in a Caco-2 cell line [24]. In a subsequent study [25], the nanoparticles penetrated throughout the sub-mucosal layers in a rat in situ intestinal loop model, while micro-particles were predominantly localized in the epithelial lining. It was also reported that nanoparticles can across the blood-brain barrier following the opening of tight junctions by hyper osmotic mannitol, which may provide sustained delivery of therapeutic agents for difficult to treat diseases like brain tumors [26]. Tween 80 coated nanoparticles have been shown to cross the blood-brain barrier [27]. In some cell lines, only submicron nanoparticles can be taken up efficiently but not the larger size microparticles [28]. Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out [29]. Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability. Polymer degradation can also be affected by the particle size. For instance, the rate of PLGA polymer degradation was found to increase with increasing particle size *in vitro* [30]. It was thought that in smaller particles, degradation products of PLGA formed can diffuse out of the particles easily while in large particles, degradation products are more likely remained within the polymer matrix for a longer period to cause autocatalytic degradation of the polymer material. Therefore, it was hypothesized that larger particles will contribute to faster polymer degradation as well as the drug release. However, Panyam*et al*., prepared PLGA particles with different size ranges and found that the polymer degradation rates *in vitro* were not substantially different for different size particles [31]. Currently, the fastest and most routine method determining particle size is by photon-correlation spectroscopy or dynamic light scattering. Photon-correlation spectroscopy requires the viscosity of the medium to be known and determines the diameter of the particle by Brownian motion and light scattering properties [32]. The results obtained by photon-correlation spectroscopy are usually verified by scanning or transmission electron microscopy (SEM or TEM).

4.2. Surface properties of Nano-particles

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation [33]. Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (Opsonins). This in turn influences the *in vivo* fate of nanoparticles [33-34]. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between a Nano-particles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. Indeed, once in the blood stream, surface non-modified nanoparticles (conventional nanoparticles) are rapidly opsonized and massively cleared by the macrophages of MPS rich organs [35]. Generally, it is IgG, compliment C components that are used for recognition of foreign substances, especially foreign macromolecules. Hence, to increase the likelihood of the success in drug targeting by nanoparticles, it is necessary to minimize the opsonization and to prolong the circulation of nanoparticles *in vivo*. This can be achieved by (a) surface coating of nanoparticles with hydrophilic polymers/surfactants; (b) formulation of nanoparticles with biodegradable copolymers with hydrophilic segments such as polyethylene glycol (PEG), polyethylene oxide, polyoxamer, poloxamineand polysorbate 80 (Tween 80). Studies show that PEG conformation at the nanoparticle surface is of utmost importance for the opsonin repelling function of the PEG layer. PEG surfaces in brush-like and intermediate configurations reduced phagocytosis and complement activation whereas PEG surfaces in mushroom-like configuration were potent complement activators and favoured phagocytosis [2-36]. The zeta potential of a nanoparticle is commonly used to characterise the surface charge property of nanoparticles [37]. 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. The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the Nano-capsule or adsorbed onto the surface.

4.3. Drug loading

Ideally, a successful Nano-particulate system should have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. Drug loading can be done by two methods: Incorporating at the time of nanoparticles production (incorporation method). Absorbing the drug after formation of

nanoparticles by incubating the carrier with a concentrated drug solution (adsorption/absorption technique).

Drug loading and entrapment efficiency very much depend on the solid-state drug solubility in matrix material or polymer (solid dissolution or dispersion), which is related to the polymer composition, the molecular weight, the drug polymer interaction and the presence of end functional groups (ester or carboxyl)[38,39,40]. The PEG moiety has no or little effect on drug loading [41]. The macromolecule or protein shows greatest loading efficiency when it is loaded at or near its isoelectric point when it has minimum solubility and maximum adsorption for small ionic molecules, studies show the use of interaction between the drug and matrix materials can be a very effective way to increase the drug loading [42-43] .

4.4. Drug release

To develop a successful Nano-particulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on: (1) solubility of drug, (2) desorption of the surface bound/adsorbed drug, (3) drug diffusion through the nanoparticle matrix, (4) nanoparticle matrix erosion/degradation, and (5) combination of erosion/diffusion process. Thus solubility, diffusion and biodegradation of the matrix materials govern the release process. In the case of Nano-spheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion of the matrix under sink conditions. If the diffusion of the drug is faster than matrix erosion, the mechanism of release is largely controlled by a diffusion process. The rapid initial release or 'burst' is mainly attributed to weakly bound or adsorbed drug to the large surface of Nanoparticles. It is evident that the method of incorporation has an effect on release profile. If the drug is loaded by incorporation method, the system has a relatively small burst effect and better sustained release characteristics. If the nanoparticle is coated by polymer, the release is then controlled by diffusion of the drug from the core across the polymeric membrane. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect ; whereas if the addition of auxillary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in drug release could be observed. Various methods which can be used to study the *in vitro* release of the drug are: (1) side-by-side diffusion cells with artificial or biological membranes, (2) dialysis bag diffusion technique; (3) reverse dialysis bag technique, (4) agitation followed by ultracentrifugation/ centrifugation, (5) Ultra-filtration or centrifugal ultra-filtration techniques. Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

5. DRUG DELIVERY APPLICATIONS OF NANOPARTICLES:

There are many applications but here it is dealing with injectable nanoparticles.

5.1. Injectable Nano-particles for efficient drug delivery

Types of carriers:

Injectable nanoparticles dosage forms can be classified into three main categories 1) Crystalline drug Nano-suspensions,wherein the drug is available in stable crystalline form. 2) Polymeric Nano-particles, wherein the drug is en-capusulated within a polymer matrix in an amorphous state. 3) Solid lipid Nano-particles, in this drug is encapsulated within a lipid matrix in an amorphous state.

5.2. Crystalline drug Nano-suspensions

Crystalline nanoparticles of drugs are typically provided either by controlled crystallization or by a high energy particle size reduction process. It includes wet milling and high pressure homogenization [44-45]. A third approach was reported recently, where in crystallization and particle sizes were combined to produce injectable Nano-suspensions[46]. Seen through scanning electron micrograph later, the final suspension typically consists of as much as 90% drug surrounded by a layer of surfactants. Because of this feature, crystalline drug Nanosuspensions can provide high drug loading. Furthermore, as very low levels of excipients are used, concerns regarding excipients related toxicity are reduced.

5.3. Polymeric Nano-particles

Polymeric Nano-particles consist of the drug dispersed in an amorphous form within a polymer matrix,such particles could be prepared as Nano-spheres,wherein the drug is dispersed uniformly by throughout the matrix of the particle, or as Nano-capsules.Polymeric nano particles aretypically prepared from bio-degradable polymers to avoid accumulation of the polymer matrix on respect dosing.Early reports of injectable polymeric nanoparticles typically involved

polylactide (PLA) or tis co- polymeric with glycolide (PLGA) [47].

Polymeric nanoparticles are typically prepared using conventional emulsion based process.The nanoparticles produced using thisprocess are uniformly spherical in nature has come to known by scanning electron micrograph.

5.4. Lipid Nano Particles

Lipidic nanoparticles use bio-compatible lipids as carriers. The principles of preparation and stabilization of such carriers are similar to polymeric nanoparticles [48].Until recently these carriers were considered mainly in none therapeutic applications. Other types of inorganic nanoparticles are those which are used in conjunction with a externally triggered systemsuch as magnetic(nanoparticles).Ithe tab 2, given below shows some list of drugs incorporated into nano-particles for targeted drug delivery.

Table 2: A representative list of drugs incorporated into nano particles for targeted drug delivery

Drug	Class	Target organ/cells	Technology
Camptothein	Chemotherapeutic	Solid tumour	PEG – PLA nano particles
Paclitaxe	Chemotherapeutic	Arterial neoinlima	Albumin nano particles
SN -38	Chemotherapeutic	Tumour	Crystalline nano particles
Indinavil	antiviral	brain	Crystalline nano particles
Doxorubicin	Chemotherapeutic	Brain	Poly sorbate coated nano particles
Dalargin	Analgesic	Brain	Poly sorbate coated nano particles
Itraconazole	Antifungal	Macrophages	Crystalline nano particles

6. NANOPARTICLES AND THE BLOOD-BRAIN BARRIER

One of the promising alleys of nanotechnology is organ or cell specific drug delivery mediated by nanoparticles. It is expected that transport of nanoparticles across the blood-brain barrier (BBB) is possible by either passive diffusion or by carrier-mediated endocytosis. Coating of particles with polysorbates (e.g., polysorbate-80) results in anchoring of apolipoprotein E (apo E) or other blood components. Surface modified particles seem to mimic LDL particles and can interact with the LDL receptor leading to uptake by endothelial cells. Hereafter, the drug (which was loaded in the particle) may be released in these cells and diffuse into the brain interior or the particles may be trans-cytosed.

Also, other processes such as tight junction modulation or P-glycoprotein (Pgp) inhibition also may occur. Oberdörster*et al.*, 2002 reported the translocation of inhaled nanoparticles via the olfactory nerves. Drug delivery systems crossing the BBB are certainly welcome, but this also implicates that unintended passage through the BBB is possible; therefore good safety evaluations are needed.

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