Indian J. Applied & Pure Bio. Vol. 37(2), 537-546 (2022). **ISSN: 0970-2091**
A web of Science Journal

Conventional synthesis and applications of Nanoparticles

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Abstract

Recent advances in nanotechnology have offered wide new opportunities in medicine for the diagnosis and therapy of various diseases. Recent progress has made possible the engineering of nanoparticles to allow the site-specific delivery of drugs and to improve the pharmacokinetic profile of potent anticancer molecules with biomedical applications in treating cancer. Some of these drugs are generally ineffective when taken orally and also very toxic. Strategies with polysaccharide-based nanoparticles (polymeric nanoparticles) entrapping drugs can address these problems. This review covers some of the historical and recent advances in nanotechnology and concludes that polymeric nanoparticles show great promise as a tool for the development of drug delivery systems for potent anticancer drugs. The application of nanotechnology in different fields will comply with the need of human beings.

Nanoscale devices have led to the development of biodegradable self-assembled nanoparticles, which are being engineered for the targeted delivery of anticancer drugs and imaging contrast agents. Nanoconstructs serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of chemotherapeutic agents into malignant cells sparing the healthy cells. These smart multifunctional nanodevices hold out the possibility of radically changing the practice of oncology, allowing easy detection followed by effective targeted therapeutics at the earliest stages of the disease.

Nanoparticles are solid particles ranging in size from 10 nm to 1000 nm,[1]. They consist of macromolecular materials in which the active material or drug is dissolved, entrapped, or encapsulated, and/or to which the active material is adsorbed or attached. Nanoparticles hold significant promise as potential drug carriers due to their attractive physicochemical properties. Using the fundamental understanding of the biology of the diseased tissue *e.g.* cancer tissue, nanoparticles can be designed specifically so that they can target specific diseased cells, Ferrari[20], Alonso,[3], Couvreur and Vauthier[12], Duncan[18], Duncan *et al*.,[19], Farokhzad *et.al*.,[22], Farokhzad and Langer[21] and Gao *et.al*.,[23]. Nanotechnology deals with the production, manipulation, and use of material ranging in nanometres[35]. Human life gets an impact role

in all spheres mainly in the field of nanotechnology[33]. Nanotechnology mainly deals with the Nanoparticle having a size of 1-100nm in one dimension used significantly in medicinal chemistry, atomic physics, and all other known fields[4].n. Nanoparticles get produced by plants are more stable and the rate of synthesis is faster than that in other cases of the organism[68]. Mainly these methods for synthesizing nanoparticles have been developed in different methods in upcoming days because they are cost-efficient and require little or no maintenance[1].

Organic nanoparticles are carbon nanoparticles and inorganic nanoparticles are magnetic nanoparticles, and semiconductor nanoparticles[57].

Nanotechnology is already being used in numerous new kinds of batteries that are less flammable, quick recharging, more efficient, lighter weight, have a higher power density, and hold electrical charge longer[32,50,55]. One new lithium-ion battery type uses a common, nontoxic virus in an environmentally benign production process. Nanostructured materials are being pursued to greatly improve hydrogen membrane and storage materials and the catalysts needed to realize fuel cells for alternative transportation technologies at a reduced cost. Researchers are also working to develop a safe, lightweight hydrogen fuel tank. Various Nano science-based options are being pursued to convert waste heat in computers, automobiles, homes, and power plants, to usable electrical power[58,63].

Nanoparticles and vascular permeability :

Multicellular organisms develop new blood vessels for growth and repair through a process called angiogenesis which is regulated by a balance between pro-and antiangiogenic molecules. An imbalance in this process can be initiated by numerous angiogenetic diseases such as malignant tumors, inflammatory, ischaemic, infectious, and immune disorders, Carmeliet and Jain[9], Carmeliet[8] and Surolia, *et al*.,[69].

Angiogenic diseases cause the blood vessels surrounding the tissue to grow larger and become more permeable (leaky) than healthy vessels by increasing the porosity of the vasculature. Liposomes and nanoparticles (with sizes between 100 nm to 200 nm) get trapped in these larger than average porous regions of the blood vessels, Surolia, *et al*.,[69]. This discovery has been used as means for passively targeting angiogenic diseases with drugs encapsulated in nanoparticles (Figure 1), and the first applications reached the clinical trials in the mid-1980s According to Carmeliet and Jain[9], two most important aspects of nanoparticulate drug delivery must be:

1. the specific targeting of the diseased tissue with nanoparticles (appropriate size and functionalization with antibodies or other means of selective binding provides means of enhanced delivery of drugs and reduced non-specific toxicity); and
2. the time-dependent release of the drug (to prevent non-specific toxicity, the drug must not diffuse out of the particle while it is still in the circulatory system, and must remain encapsulated until the particle binds to the target).

Nanoscale systems of delivery :

Several varieties of nanoparticles are available, different polymeric and metal nanoparticles, liposomes, micelles, quantum

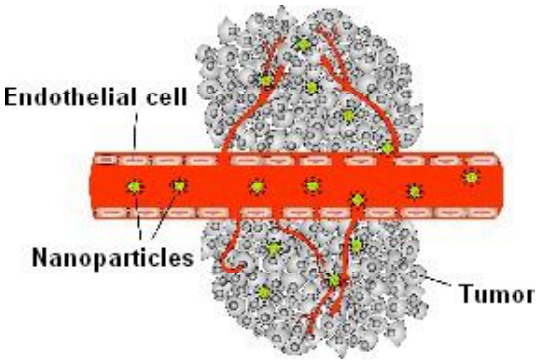

Figure 1 The schematic representation of the passive targeting of nanoparticulate drug carriers through the leaky vasculature.

dots, dendrimers, microcapsules, cells, cell ghosts, lipoproteins, and many different nanoassemblies. All of these nanoparticles can play a major role in diagnosis and therapy (Table 2.1). Polymeric nanoparticles, allow the encapsulation of drugs inside a polymeric matrix, Carmelie[8], Surolia[69], and Guo *et al.*,[27]. The nanoparticles can also be coupled with targeting ligands to provide site-specific delivery in treating diseases.

Drug nanoparticles consist of the drug and a biocompatible polymer, either biodegradable or non-biodegradable, Allémann[2] and Kreuter[43]. Nanoparticles can be further classified into nanocapsules and nanospheres based on their structure, Couvreur *et al.*,[13] Kreuter[42], and Legrand[48]. A nanocapsule consists of an oily core containing the lipophilic drug surrounded by a shell composed of the polymer and a nanosphere has a matrix consisting of a homogeneous distribution of the drug and the polymer (figure 2). The drug is either solubilized in the polymer matrix to form an amorphous particle or embedded in the polymer matrix as crystallites.

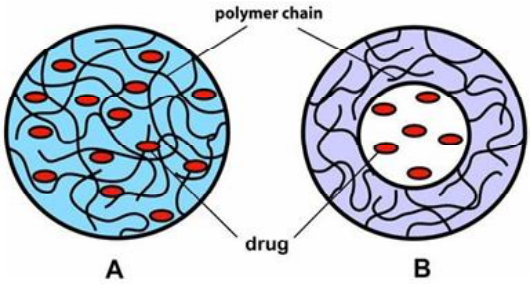

Figure 2**:** Drug encapsulated polymer nanoparticles: **A.** Nanosphere: drug molecules are dispersed in the solid polymer matrix, **B.** Nanocapsule: drug molecules are present in the corecovered with the polymer shell.

The principle of nanoparticles as drug delivery systems is based on the following facts, Bender[6]:

1. During transit *in vivo* they prevent the degradation and retard the release of the drug by minimizing the interaction of loaded drug with blood components.

2. They control and sustain the release of the drug during transportation and at the site of localization, altering the organ distribution of the drug. Thus, subsequent clearance of the drug can be manipulated to achieve a reduction in undesired side effects and an increase in drug therapeutic efficacy.

3. Their particle size and surface characteristics can be manipulated to achieve both passive and active drug targeting after parenteral administration.

4. They can be used as long-acting depot preparations.

Table-2. Nanoscale systems of delivery

Drug delivery systems	Stage of development	Drug applied	References
Liposomes	Marketed	Amphotericin B, Daunorubicin, Doxorubicin	Legrand,[47]
Micelles			
Phospholipid	Preclinical	Paclitaxel, Camptothecin, Diazepam	Davidson *et. al.*,[16], Krishnadas, *et. al.*,[45] and Koo *et. al.*,[40]
Pluronic	Clinical Preclinical	Doxorubicin (SP1049C) Paclitaxel, Tamoxifen, Etoposide	Ashok *et.al.*,[5]; Danson *et.al.*,[15]; Kim *et.al.*,[38];Cavallaro *et.al.*,[10]
Poly (L-aminoacid)	Clinical *In vitro*	Doxorubicin (NK911) Antisense oligonucleotides	Le Garrec *et.al.*,[47] and Lee[46]
Polyester	Preclinical	Paclitaxel Doxorubicin	Matsumura *et.al.*,[52]; Kakizawa[34]; Kim *et.al.*,[38]
Nanoemulsions	Preclinical	Amphotericin B Paclitaxel Dexamethasone Benzathine penicillin G	Shuai[67]; Yoo and Park[76]; Brime *et.al.*,[7]; He *et.al.*,[29]
Nanoparticulate systems			
Drug nanocrystals	Preclinical	Amphotericin B Etoposide, camptothecin, Paclitaxel	Seki *et.al.*,[64] and Santos-Magalhaes *et. al.*,[65]
Polymer-based nanoparticles	Preclinical	Tamoxifen Cyclosporin-A Theophylline	Kayser *et.al.*,[64]; Merisko-Liversidge *et.al.*,[53]; Shenoy and Amiji[66]; Molpeceres *et.al.*, [54]
Lipid-based nanoparticles	Preclinical	Doxoribicin Camptothecin	Radwan *et.al.*,[59]; Zara *et.al.*,[77]
Ceramic-based nanoparticles	*In vitro*	2-divinyl-2-(1- hexyloxyethyl) pyropheophorbide	Yang[75]
Albumin nanoparticles	*In vitro* DNA and antisense	Paclitaxel oligonucleotides	Roy *et.al.*,[62]; Ibrahim *et.al.*,[31] Rhaese *et.al.*,[61]
Nanogels	Preclinical	Oligonucleotides	Wartlick[73]
Dendrimers	Preclinical	Indometacin *In vitro* 5- fluorouracil Antisenseo-ligonucleotides	Vinogradov *et.al.*,[72]; Chauhan *et.al.*,[11]; Tripathi *et.al.*,[71]

Polysaccharide-based delivery systems for anticancer drugs :

It is desirable that the drug after administration (oral, intravenous, local, transdermal, *etc*) reaches the site of action in sufficient concentrations. Scientists are facing the challenge of achieving the required concentration of the drug at the tumor site for a desired period due to the rapid clearance of such particles from the bloodstream by the macrophages of the reticuloendothelial system (RES), mainly in the liver and spleen, Gregonadis and Neerunjun[25]. As a result, high doses of drugs are applied which eventually lead to drug resistance and toxicity. Thus, one of the main goals of nanomedicine is to develop safe and effective drug carriers that are systemically applied but will selectively deliver cytotoxic drugs to tumor cells without harming normal cells, Gullotti and Yeo[26]. Among the available potential drug carrier systems in the nanoscale range, the polysaccharide-based nanoparticles play an important role and their use with some anticancer drugs shows promising results.

Mitoxantrone included in polysaccharides:

Mitoxantrone is one of the commonly used drugs in the treatment of breast cancer. The challenge in the therapy with this drug is that prolonged treatment results in some side effects, such as heart toxicity and myelosuppression, *etc*. One of the known methods of preparation of a nanoformulation of Mitoxantrone is the ion gelation method using sodium TPP as a gelation agent, and obtaining an encapsulation efficacy of 98%. Tests for *in vitro* release in physiological saline or physiological saline containing 0.5% (w/v) ascorbic acid by a dialysis bag showed sustained release with an initial burst effect, (Lu)[49].

Doxorubicin (DOX) included in polysaccharides :

Doxorubicin (DOX) has been successfully entrapped into oleoyl-chitosan nanoparticles prepared by the o/wemulsification method with a high encapsulation efficiency of 53%. The drug was completely released from nanoparticles in the buffer medium of Na_2HPO_4– citric acid (pH3.8), whereas in PBS (pH 7.4) 65% of doxorubicin was released after 6 hours, followed by a sustained release until 72 hours. Approximately 72% of DOX was released for 3 days, showing the potential of the nanoparticles as a sustained drug delivery system, suggesting that the nanoparticles might act as a barrier against the release of entrapped DOX. This result indicated that the nanoparticles contributed to an extended circulation of DOX and thus an improvement in therapeutic efficacy (Zhang)[78].

Paclitaxel included in polysaccharides:

Paclitaxel, one of the potent anticancer drugs and most widely studied limits its use due to side effects such as hypersensibility, hypotension, or breast pain after its intravenous administration. Hu and coworkers have obtained paclitaxel-loaded nanoparticles by self-crosslinkingstearic- grafted chitosan and using glutaraldehyde as a cross-linker to stabilize the systems. These formulations showed high encapsulation efficiency which ranged from95% to 99%. When the surfaces of micelles were cross-linked by glutaraldehyde, the burst release of the micelles at an earlier

stage was highly improved and the drug release time was prolonged. By controlling the amino substitution of stearic-grafted chitosan and the crosslinking degree, the prolonged and controlled release could be achieved, (Zhang)[78].

Applications of nanoparticles in food :

Nanofood is a term used to describe foods that use nanotechnology techniques, tools, or manufactured nanomaterials that have been added during cultivation, production, processing, or packaging. There are several purposes for the development of nano food. These include improvement of food safety, enhancement of nutrition and flavor, and cutting production and consumer costs. In addition, nanofood provides various benefits which include health-promoting additives, longer shelf lives, and new flavor varieties The application of nanotechnology in food is rapidly emerging and is involving all areas of the food chain from agricultural applications to food processing and enhancing the bioavailability of nutrients.

Application of nanoparticles in Gene delivery :

It is a technique that plays a vital role that can efficiently introduce a gene of interest to express its encoded protein in a suitable host or host cell. Now a day, there are different types of primary gene delivery systems that mainly employ viral vectors like retroviruses and adenoviruses, nucleic acid electroporation, and nucleic acid transfection[14].

Applications in manufacturing and materials :

Nanocrystalline materials provide very interesting substances for material science since their properties deviate from respective bulk materials in a size-dependent manner. Manufacture NPS displays physicochemical characteristics that induce unique electrical, mechanical, optical, and imaging properties that are extremely looked for in certain applications within the medical, commercial, and ecological sectors[17]. NPS focus on the characterization, designing, and engineering of biological as well as non-biological structures < 100 nm, which show unique and novel functional properties. The potential benefits of nanotechnology have been documented by many manufacturers at high and low levels and marketable products are already being mass-produced such as in microelectronics, aerospace, and pharmaceutical industries (Weiss *et al*.,)[73].

Applications in the environment :

The increasing area of engineered NPs in industrial and household applications leads to the release of such materials into the environment. Assessing the risk of these NPs in the environment requires an understanding of their mobility, reactivity, Ecotoxicity, and persistency[60,79]. The engineering material applications can increase the concentration of NPs in groundwater and soil which presents the most significant exposure avenues for assessing environmental risks[24,51]. Due to the high surface to mass ratio, natural NPs play an important role in the solid/water partitioning of contaminants that can be absorbed to the surface of NPs, co-precipitated during the formation of natural NPs, or trapped by aggregation of NPS which had contaminants adsorbed to their surface. The interaction of contaminants with NPS is dependent on the

NP's characteristics, such as size, composition, morphology, porosity, aggregation/disaggregation, and aggregate structure. The luminophores are not safe in the environment and are protected from environmental oxygen when they are doped inside the silica network[70].

Applications in electronics :

There has been growing interest in the development of printed electronics in the last few years because printed electronics offer attractive to traditional silicon techniques and the potential for low cost, large-area electronics for flexible displays, and sensors. Printed electronics with various functional inks containing NPs such as metallic NPs, organic electronic molecules, CNTs, and ceramics NPs have been expected to flow rapidly as a mass production process for new types of electronic equipment[41].

The important characteristics of NPs are facile manipulation and reversible assembly which allow for the possibility of incorporation of NPs in electric, electronic or optical devices such as "bottom-up" or "self-assembly" approaches are the benchmark of nanotechnology[56].

In situ Application of Nanoparticles :

The method of application for nanoparticles is usually site-specific and is dependent on the type of geology found in the treatment zone and the form in which the nanoparticles will be injected. The most direct route of injection utilizes existing monitoring wells, piezometers, or injection wells. Recirculation is a technique that involves injecting nanoparticles in upgradient wells while downgradient wells extract groundwater. The extracted groundwater is mixed with additional nanoparticles and re-injected in the injection well. The wells keep the water in the aquifer in contact with the nZVI and also prevent the larger agglomerated iron particles from settling out, allowing continuous contact with the contaminant. Research is ongoing into methods of injection that will allow nanoparticles to better maintain their reactivity and increase their access to recalcitrant contaminants by achieving wider distribution in the subsurface. Creating nZVI on-site reduces the amount of oxidation the iron undergoes, thereby reducing loss in reactivity. Researchers in green chemistry have successfully created nZVI in soil columns using a wide range of plant phenols, which, according to the researchers, allows greater access to the contaminant and creates less hazardous waste in the manufacturing process[28].

Nanoparticles are particularly useful for formulating new drugs because they can provide protection from degradation in biological fluids and promote penetration into cells. As shown in this review, there is a great deal of interest in the properties of nanoparticles and their potential applications in medicine as well as other applied fields for the welfare of human beings.

Nanoparticles, because of their sustained-release properties, subcellular size, and biocompatibility with tissue and cells, seem to hold promise for the achievement of these important objectives. Nanoparticles permit alterations in the bioavailability of drugs and improve the pharmacokinetic profile of numerous drugs with biomedical purposes.

Finally, if nanoparticulate systems show great promise as a tool for the development of potent anticancer molecule delivery without any toxic effects, their final success will depend heavily on the will of the pharmaceutical industry to develop new polymers, test their potential in therapeutics, and demonstrate their safety. Nanoparticulate systems able to improve the efficacy of both established drugs and new molecules will likely be available shortly.

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