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An introduction to medicinal, diagnostic and therapeutic uses of nanoparticles

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Abstract

Nanoparticles are the species i.e. atoms, molecules, polymers etc. which have overall size under 100 nm. The one-dimensional nanoparticle such as nanowires and nanotubes have one dimension larger than the nanoscale and two-dimensional nanomaterials such as self-assembled monolayer films have two dimensions larger than the nanoscale. The other nanoparticles are referred as zero dimensional nanomaterials because all of their dimensions are in nanoscale. The nanoparticles have emerged as important tools in medicine with wide range of clinical applications. In many cases they have been used in analyses and therapies where usual methods fail or remain ineffective. The applications of nanoparticles in diagnoses are important because when they are effective, their very less amounts can serve the purpose. In actual practice they help to detect the occurrence of disease on molecular scale. It is important to mention here that if at any stage it is detected that they are ineffective or are harmful they can be withdrawn without causing much damage. Their use provides freedom to the researchers to modify their properties such as appearance, taste, solubility etc. thereby improving the solubility of poorly soluble drugs, blood circulation, half life, drug release characteristics etc. The nanoparticles may provide more effective and more convenient route of administration because they allow targeted delivery and controlled release. This also reduces the side effects of the drugs. Their use may lower therapeutic toxicity and reduce health care costs. The imaging contrast agents based on nanoparticles have been shown to improve the sensitivity and specificity of magnetic resonance imaging. Considering the vast scope of nanomedicine we will focus on few medicinal applications of nanoparticles viz. diagnostic, therapeutic, imaging etc. The review article includes the synthesis of nanoparticles done by the researchers, their applications in medicine, their harmful effects if any and further prospects in this field.

Keywords: Diagnosis, imaging, nanomaterials, nanomedicine, therapeutic, toxicity.

Introduction

The scientists' community has become well aware of the importance of nanotechnology (Feynman, 1991). The nanotechnology deals with the structure, characteristics, utility of the substances of nanometer size. It deals with their applications in various fields' viz. food security, consumer products, medicines, fabrication, textiles, modern weapon etc. and their supremacy and advantages over the particles of normal size. Earlier scientists were interested in the properties both physical and chemical (Murray *et al.* 2000) which are size dependent. For example, the solutions of nanoparticles of a single substance show wide range of colours which changes with the change in the size of nanoparticles (Fig.3). However, other interesting properties were also luring the researchers. Therefore, now a day's scientists are exploring their commercial applications (Mazzola, 2003) in various fields. Nanotechnology has beneficial use in the field of medicine. It may be used to provide advance biomedical research tools. It can be useful in diagnostic tests and help to determine a certain individual's susceptibility to different disorders. The use of nanoparticles has been demonstrated for early diagnosis of infectious diseases. Here the nanoparticles attach to molecules in the blood stream indicating the start of infection. These nanoparticles enhance the Raman signal in Raman Scattering which indicates the occurrence of an infectious disease at very early stage. The nanotechnology has become a tool for noninvasive imaging for the internal organs of the human body and in drug delivery systems. The nanoparticles may be used in bone implants process because this would offer added durability and would be more

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compatible to human tissue.The purpose of this review is to give an idea of the uses of nanoparticles in medicine including their diagnostic, therapeutic and imaging applications. Scope for hybrid nanoparticles such as optoelectronics and memory devices (Yan *et al.*, 2003), (Keren *et al.*, 2003) is also there. In other words, the researchers are taking keen interest to explore this field of science and technology so that they can serve the community well. The optimum pace of the work done will be more beneficial.

Materials and Method

In present study nanoparticles of silver, gold, polymeric particles, metal oxides and some other particles of general interest have been considered. Their known synthetic methods, medicinal uses both diagnostic and therapeutic have been summarized. In some cases, for example silver nanoparticles, paclitaxel etc. the toxicity has also been listed.

1. Silver Nanoparticles

1.1 Synthesis of Silver Nanoparticles

The traditional preparation of Ag nanoparticles involves the chemical reduction of $AgNO_3$ (Guzman *et al.*, 2012) by glucose in the solution containing polyvinyl pyrrolidone (PVP). However, they can also be prepared by reduction of aq. Ag+ ions using bacteria like K. Pneumoniae and S. Aureus(Shahverdi *et al.*,2007). Even some fungus may be used for this purpose (Gajbhiye *et al.*, 2009), (Fayaz *et al.*,2010)and (Dar *et al.*,2013). This clearly shows that biological methods are also available for synthesis of nanoparticles of Ag.

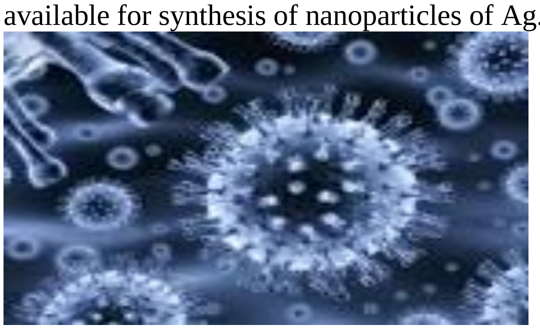

Fig. 1. Silver Nanoparticles
(Source: anthonyclavin.worldpress.com)

1.2 Applications in medicine

Diagnostic Uses

Silver nanoparticle based Surface Enhanced Raman Spectroscopy (SERS) has been used in early cancer detection (Brandt *et al.*, 2012). It is a well known fact that the early diagnosis of any disease results in a better chance to cure. In case of carcinoma, its early detection is a boon for the patients because at advanced stage it becomes incurable and even fatal to the patient suffering from cancer.

Therapeutic Uses

The Ag nanoparticles are used in wound healing. It has been shown that the Ag nanoparticles take lesser healing time and show better cosmetic after healing. In wounds treated with Ag nanoparticles better collagen alignment and greater mechanical strength has been reported (Lin *et al.*,2011). The Ag nanoparticles are used to kill bacteria in fabric, thus making the clothes infection and odour resistant.

1.3 Harmful effects of Ag nanoparticles

The Ag nanoparticles in general are non-toxic(Kwan *et al.*,2011). The Ag nanoparticles wound dressing is in use in the clinics for many years with no reports of toxicity. However some hypersensitivity reactions have been reported in burn patients who received ionic silver treatment.

2. Gold Nanoparticles

It is well known fact that gold is chemically inert for all biological processes. It remains unoxidized at nanoparticle size. However, there are wonderful variations in physical and chemical properties of gold nanoparticles. It is interesting to mention here that the variations in properties of gold nano particles are size dependent.

Fig. 2. Gold Nanoparticle
(Source: www.nanoprobes.com)

2.1 Synthesis of Gold Nanoparticles

The gold nanoparticles can be synthesized using surface adsorbate which can control the size of the particles. The gold nanoparticles can also be grown in the pores of silicate. The arrays of nanoparticles embedded in silicates can be used directly or they can be released by treating the silicates with thiols and hydrofluoric acid. These nanoparticles are then used for specific purposes. The gold nanoparticles can also be prepared by liquid chemical methods by reduction of chloroauric acid (H [$AuCl_4$]). Here the Au^{3+} ions are reduced to neutral gold atoms. The citrate synthesis (McFarland , 2004) of gold nanoparticles is colour dependent. It is known fact that in bulk at macroscale the element is gold coloured but at nanoparticle size it is red to purple in colour.Thus in this process the formation of nanoparticles can be observed by a change in colour.

2.2 Application in medicines

Cancer Imaging

A combination of gold nanoparticles and CAT scan technology has been used by researchers at the University of Missouri-Columbia to image early stage cancer in the lungs of pig. The researcher laced the nanoparticles with antibodies which form bonds with proteins expressed by cancerous lung cells. The rods are injected into the pig through intravenous needles which localize at the affected area and act as markers to establish a contrast medium for lung imaging. A CAT scan is then done on the pig to reveals the cancerous area.

Imaging Blood Flow

At Purdue University techniques have been developed to follow the track of blood flow throughout the ear of a mouse. In this technique gold nanoparticles have been attached to blood cells and these particles remained detectable for about half an hour before the kidneys finally filtered them out. It has been shown that angiogenesis i. e. the formation of new blood vessels is a first step for tumor growth. At this stage the ability to detect cancer would increase the chances for early treatment and easy recovery. Using conventional methods the targeting of angiogenesis is very difficult but the nanoparticles due to their size similarity are a good tool to probe all cellular components as well as angiogenesis. By mapping the angiogenesis, a physician could cut off the angiogenesis or the food chain of the tumor, and thus its growth is curtailed.

Therapeutic Uses

In 1997, the successful application of colloidal gold in a patient with rheumatoid arthritis was first reported (Abraham ,1997).Similar results were obtained upon subcutaneous introduction of gold nanoparticles into rats with collagen- and pristan-induced arthritis. Gold nanoparticles are also used in the diagnosis of heart diseases, cancers, and infectious agents (Peng , 2009). They are also common in lateral flow immunoassays, a common household example being the home pregnancy test.

Fig 3: Colours of various sized gold nanoparticles (Source: www.sigmaaldrich.com)

3. POLYMERIC NANOPARTICLES

A number of nanoparticles in the form of polymers have been developed which find applications in medicines. They are used as such or combined with other substances to fasten or improve their action. However due care is taken so that after combination with other particles their size remain under nano scale.

3.1 Nanosponges

These are polymeric nanoparticles coated with a red blood cell membrane. They mimic human blood cells and the membrane of red blood cell allows free movement of nanosponges in blood stream and helps to attract the toxins. They can circulate through our bloodstream soaking up bacterial infections and toxins. With a diameter of 85 nanometers, the nanosponges are 3000 times smaller than a human blood cell, so in a single infusion of nanosponges into the blood stream they would easily outnumber the red blood cells, and thus intercept most of the attacking toxins before they damage the actual blood cells. The toxins are absorbed in nanosponges and thus they are removed from the blood stream. These so-called 'nanosponges' are expected to be particularly effective in treating bacterial infections that have developed an immunity to antibiotic treatments—and also for treating venoms from snake bites (Nanosponges; New England Journal of Medicine-2013).

Fig. 4. Nanosponges
(Source: www.brightsideofnews.com)

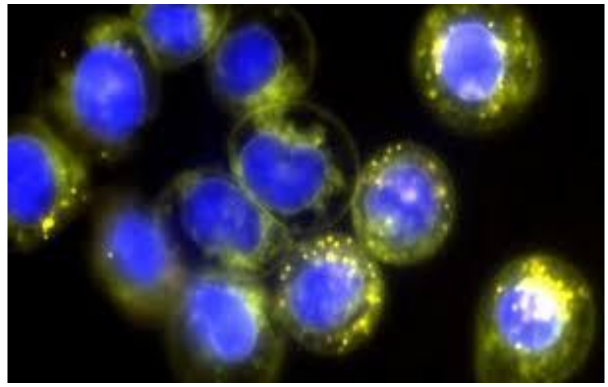

Fig.6. Cerium oxide nanoparticles
(Source: Research.unsw.edu.au)

3.2 Polyethylene glycol

The nanoparticles of polyethylene glycol-hydrophilic carbon clusters (PEG-HCC) are of spherical shape. They absorb free radicals at much higher rate than our body proteins. This helps to reduce the harm caused by the release of free radicals after a brain injury.

3.3 Nickel nanoparticles-polymer

A synthetic skin of nickel nanoparticles-polymer has been demonstrated with both self healing capability and the ability to sense pressure. It is used in prosthetics. When the material is held together after a cut it seals together in about 30 minutes giving it a self healing ability.

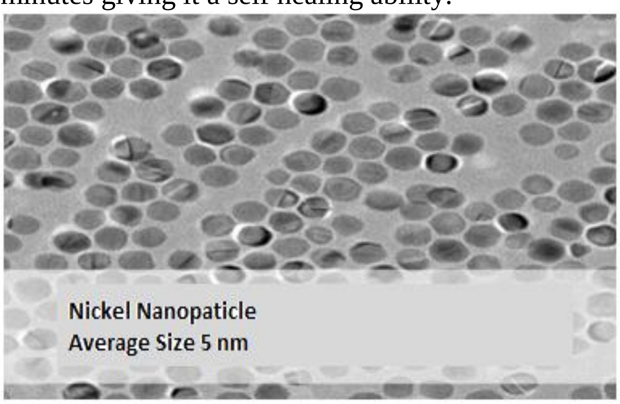

Fig. 5. Nickel nanoparticles
(Sources: www.boutiq.co.nz)

4. METAL OXIDES

4.1 **Cerium oxide**

The nanoparticles of cerium oxide act as antioxidant to remove oxygen free radicals which are present in blood stream of patients following a traumatic (physical) injury. These nanoparticles absorb the free radicals and then release the oxygen in less reactive state and the nanoparticles become free to absorb more free radicals (Lee , 2013).

4.2 Zinc oxide

The zinc oxide nanoparticles are used in preparation of popular calamine lotion. They are also used in other creams and ointments that are used to treat skin diseases. Zinc oxide nanoparticles can increase the antibacterial activity of ciprofloxacin. It has been shown that nano ZnO particles which have the average size between 20 nm and 45 nm can enhance the antibacterial activity (Nagarjan & Rajagopalan 2008) of ciprofloxacin against *Staphylococcus aureus* and *Escherichia coli* in Vitro.

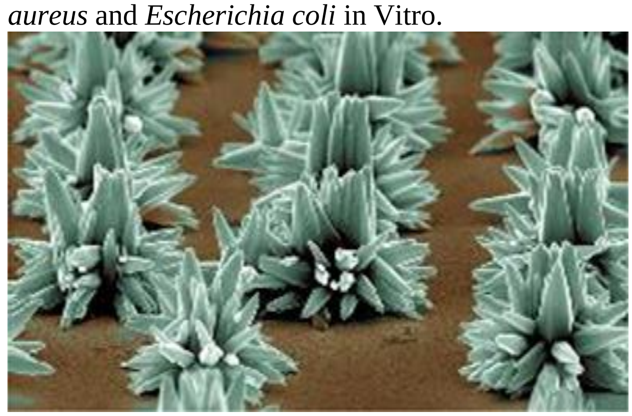

Fig.7. Zinc Oxide Nanoparticles(Source: pixgood.com)

4.3 Silicon oxide

The nanoparticles of silicon oxide are used as a stable, non-toxic platform for biomedical applications such as drug delivery and theranostics. In pharmaceutical products, silica aids powder flow when tablets are formed. They are used to form stable antioxidants because in most of the cases the

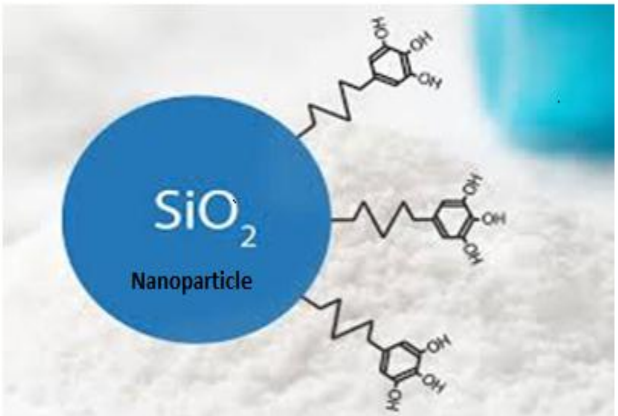

Fig. 8. Gallic acid coupled with Silicon Oxide nanoparticles to increase antioxidant effect (Source: www.ethlife.ethz.ch)

antioxidants are oxidized in presence of oxygen and gradually lose their antioxidant effect.

4.4 Iron oxide

Super paramagnetic iron oxide nanoparticles (SPIONs) can be prepared by thermal decomposition of iron acetylacetonate. The particles are made water-soluble by binding with 2, 3-dimercaptosuccinic acid. The SPIOn have been used in human patients with prostate cancer to detect small metastases in the lymph node (Harisinghani, 2003). These SPIOn nanoparticles can also be used to detect cancer in vivo.They bound directly to luteinizing hormone releasing hormone (LHRH) and show high efficiency for intracellular uptake to breast cancer cells. The inclusion of a small spacer molecule such as glutamic acid in between SPION and LHRH increases further receptor mediated intracellular uptake(Challa, 2007).

5. Other nanoparticles

5.1 Paclitaxel

It is obtained from the bark of a tree named Taxus Brevifolia. Earlier it was used under trade mark Taxol.It is an important anti-cancer agent. It is used to treat several types of cancer viz. ovarian, skin, esophageal, and lung cancer (Abratt,2006), (Chao *et al.*,2006), (De *et al.*,2006) and(Kikuchi *et al.*,2005). Paclitaxel is approved in the UK for ovarian, breast and lung, bladder, prostate, melanoma, esophageal, and other types of solid tumors.

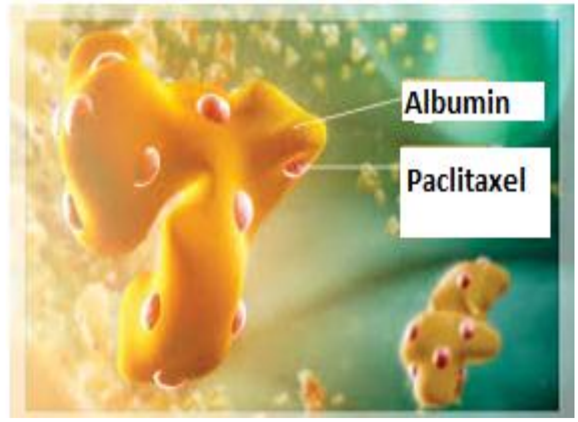

Fig. 9.Albumin bound paclitaxel nanoparticles In treatment of metastatic Breast cancer and lung cancer (Source: trialx.com)

Side Effects

The use of paclitaxel has some side effects including female infertility as a result of ovarian damage (Ozcelik *et al.*, 2010) The side effects include vomiting, loss of appetite, thinned or brittle hair, chest pain, fever, pain in the joints of arms or legs etc.

5.2 Bismuth nanoparticles

The bismuth nanoparticles are used in radiation therapy to concentrate radiation for treatment of cancer tumors. Results indicate that the bismuth nanoparticles increased the radiation dose to the tumor by 90 percent. By enhancing the amount of radiation in the tumour the initial dose given in radiotherapy may be decreased. This will have fewer side effects for the patient suffering from cancer.

5.3 Carbon nanotubes

The sensor using carbon nanotubes embedded in a gel are used to monitor the level of nitric oxide in the bloodstream. The monitoring of level of nitric oxide is important because it helps to diagnose the inflammation caused by inflammatory diseases. The sensors are injected under the skin to monitor the level of nitric oxide. It has been found that the sensors remained functional for over a year in mice.

5.4 Graphene oxide

The sheets of graphene oxide attached to molecules containing an antibody that attaches to the cancer cells. These cancer cells are then tagged to fluorescent molecules so that that they can stand out in a microscope. This technique can detect a very low level of cancer cells, as low as 3 to 5 cancer cells in a one milliliter in a blood sample.

Results and discussion

The study of nanomaterials is finding its application in every field of modern science and technology.

Among a variety of Nanomaterials, the silver nanoparticles are easy to synthesize and are non-toxic. They act as good tool in early detection of cancer. Their use takes less time in wound healing.

The gold nanoparticles possess unique properties viz. small size, colour variations, low toxicity etc. These features find applications of gold nanoparticles in biomedical, biological processes, biosensors, drug delivery etc. The polymeric nanoparticles such as nanosponges, polyethylene glycol and nickel nanoparticles-polymer show wide range of applications including removal of toxic materials, free radicals, treatment of bacterial infections etc. The nickel nanoparticles-polymer can be used as synthetic skin. Thus polymer-based nanoparticles are of much importance because they are cheap and there is large scope for the researchers to apply them for the benefit of mankind. Some metal oxides nanoparticles such as cerium oxide, zinc oxide, silicon oxide and iron oxide have been included in this article. They act as antioxidants to remove free radicals, in preparation of lotions and ointments, as filler in tablets, in treatment of cancer etc. They can also be combined with other substances to increase their antibacterial, antifungal and antioxidant properties. Therefore lot of work can be done to explore the further applications of metal oxides nanoparticles. The Paclitaxel obtained from the bark of a tree is used to treat various types of cancers including skin, ovarian, breast, lung, bladder, prostate, melanoma, esophageal etc. However, it's some side effects also have been observed. Though, till date it is the most important weapon to curb the menace of deadly disease cancer. The bismuth nanoparticles, carbon nanotubes, graphene oxide etc. are useful in radiation therapy, detection of inflammatory diseases and cancer cells. Most of the nanoparticles discussed above are useful in detection and treatment of cancer. The application of nanomaterials in biomedicine is currently increasing owing to growing evidence of its benefits in cancer prevention and treatment. As this disease is wide spread it means lot of work is required to be done in this field. This article will be beneficial to the researchers to peep in this vast field. Besides medicinal uses the nanoparticles can be used in modern food technology, textiles, weapons, polymers, robotics, coating of materials, catalysis, pollution control etc. The nanowires of silicon are recognized as next-generation sensors, battery electrodes, solar cells etc. The nanotubes made of carbon are stronger than steel but very flexible and lightweight. In addition to the remarkable mechanical properties, nanotubes can replace copper as an electrical conductor or with a very small change in structure, replace silicon as a semiconductor. The nanotechnology can play a key role in pollution prevention technologies. For example, nanotechnology-based home lighting can reduce energy consumption and reduce carbon emission. In catalysis nanoparticles can be used for reducing pollutants.The nanostructure catalysts can make chemical manufacturing more efficient by providing higher selectivity for desired reaction products. The nanoparticle based fabrics will be highly durable and more wear and tear resistant. It means the field of nanotechnology is a vast and an important field and it require a lot of work particularly in the area of medicinal application which is yet to be explored in this field.

Conclusion

Nanotechnology has emerged as an important branch of technology covering almost each and every field of science. Besides their applications in medicine, the nanoparticles can be used in electronics, as sensors, better quality insulating materials, tougher and harder cutting tools, high power magnets, better and future weapons, etc. There is large scope in these fields because all these fields are interdisciplinary. However it may be pointed that we still have a lot to learn about the synthesis and behavior of nanoparticles. There are already many natural and manmade sources of nanoparticles. At the same time many methods have been developed for their synthesis. In the above study emphasizes has been given to the medicinal utility of nanoparticles. A few substances have been considered and it has been realized that their nanoparticles are more effective and economical in nanoparticle size. Moreover due to their lesser quantities in use the environmental pollution caused by their release will be less damaging.

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