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Synthetic mixed metal oxide nanoparticles in biomedical applications

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Abstract: *Mixed metal oxide (MMO) nanoparticles can play a considerable role in various areas of chemistry and physics. The unique electronic and magnetic property obtain when combine two metals in an oxide matrix have been well studied. Metal oxide nanoparticles have a unique structure, interesting and unusual redox and catalytic property, high surface area, good mechanical strength and are biocompatible. For these reasons, metal oxide nanoparticles have concerned extensive attention in the field of biomedical therapeutics, biological applications, bio-imaging and biosensing. This review aims to high light the major contributions of nanoparticles to modern medicine and also discussed biological applications. These materials have become significant mechanism in medical implant, cancer diagnosis and hiv/aids, tuberculosis, neurochemical monitoring. Titania, Silica Nanoparticles, Zinc oxide nanoparticles is the material of choice in medical implants; it provides an outstanding biocompatible surface for cell addition and production. More than a few other metal oxides have been used as gas sensing nanoprobes for cell labeling and separation, as contrast agents for magnetic quality imaging (MRI) and as carriers for targeted drug delivery. In this paper we also discuss Synthesis of nanoparticles, chemical precipitation and sol gel technique.*

Keywords: *Metal oxide Nanoparticle, Silica, Zinc oxide, Titanium Dioxide Nanoparticles, Synthesis of Nanoparticles, Drug Delivery, Biomedical Applications.*

1. INTRODUCTION :

A nanoparticles is a tiny object that behaves as a whole unit in terms of its transport and properties **.**The term "nanoparticles" is not usually applied to individual molecules; it usually refers to inorganic materials .The reason for the synonymous definition of nanoparticles and ultrafine particles is that, during the 1970s and 80s, when the first thorough fundamental studies with "Nanoparticles " were under way in the USA and Japan, they were called "ultrafine particles" (UFP). However, during the 1990s before the National Nanotechnology Initiative was launched in the USA, the new name, "Nanoparticles" had become more common Nanoparticles can exhibit size-related properties significantly different from those of either fine particles or bulk materials [1].

In terms of diameter, fine particles cover a range between 100 and 2500 nanometers, while ultrafine particles are sized between 1 and 100 nanometers. Nanoparticles may or may not exhibit size-related properties that are seen in fine particles. Despite being the size of the ultrafine particles individual molecules are usually not referred to as nanoparticles. Nanoclusters have at least one dimension between 1 and 10 nanometers and a narrow size distribution. Nano powders on the other hand are agglomerates of ultrafine particles, nanoparticles, or nanoclusters. Nanoparticles sized crystals are called nanocrystals.

Nanoparticles research is currently the most studied branch of science with the number of uses of nanoparticles in various fields. The particles have wide variety of potential applications in biomedical, optical and electronic field [2].

2. APPLICATIONS OF NANOPARTICLES :

The properties of many conventional materials change when formed from nanoparticles. This is typically because nanoparticles have a greater surface area per weight than larger particles which causes them to be more reactive to some other molecules. Nanoparticles are used in many fields. The list below introduces several of the uses under development [3].

SILICA NANOPARTICLES

In nature, silica makes up quartz and the sand. Silica aero gels are composed of silica nanoparticles interspersed with nonporous filled with air. As a result, this substance is mostly made up of air. Because air has very low thermal conductivity and silica has low thermal conductivity, they are great materials to use in insulators.

The functionalized silica nanoparticles attach to the cotton fiber and form a rough surface that is hydrophobic (water repellent),. Another type of silica nanoparticles is riddled with nano scale pores. Researchers are developing drug delivery methods where therapeutic molecules stored inside the pores are slowly released in a diseased region of the body, such as near a cancer tumor. Silicon dioxide nano films, a layer of silicon dioxide molecules that can be as thin as 1 nm, are used to provide electrical insulation between two parts of a device, such as a transistor. This method is used in making computer chips [4].

TITANIUM DIOXIDE NANOPARTICLES

Titanium dioxide is a molecule composed of one atom of titanium and two atoms of oxygen. Titanium dioxide absorbs ultraviolet light; this property makes titanium dioxide useful in sunscreens. Titanium dioxide nanoparticles are photo catalysts, which mean that they have the capability to use energy in light to catalyze reactions with other molecules at reduced temperatures. Titanium dioxide is reflects all colors in the visible light spectrum; therefore the light reflected from titanium dioxide is white. This characteristic makes it useful as a white pigment in paints. Titanium dioxide can be used in creams and coatings that absorb UV without causing a white coating. Titanium oxide nanoparticles as part of a film that uses the energy in light to start the chemical reaction that kills bacteria on surfaces. [5]

Researchers are also developing methods to use the photo catalytic properties of titanium dioxide nanoparticles to destroy cancer tumors. They are delivering titanium dioxide nanoparticles to cancer tumors using targeted drug delivery methods, and then shining light on the tumor. The titanium dioxide nanoparticles use the energy from the light to add an electron to oxygen molecules, which proceed to destroy cancer cells [6].

ZINC OXIDE NANOPARTICLES

Zinc oxide is use as a with (Fe2O3) is called calamine and is used in calamine lotion . When mixed with eugenol, a ligand, zinc oxide eugenol is formed, which has applications as a restorative and prosthodontic in dentistry [7].

ZnO, fine particles of the oxide have deodorizing and antibacterial properties and for that reason are added into materials including cotton fabric, rubber, oral care products, and food packaging. Zinc oxide is widely used to treat a variety of other skin conditions, in products such as baby powder and barrier creams to treat diaper rashes, calamine cream, anti-dandruff shampoos, and anti septic ointments. It is also a component in tape (called "zinc oxide tape") used by athletes as a bandage to prevent soft tissue damage during work outs [8].

Zinc oxide can be used in ointments, creams, and lotions to protect against sunburn and other damage to the skin caused by ultraviolet light. It is the broadest spectrum UVA and UVB reflector that is approved for use as a sunscreen by the U.S. Food and Drug Administration (FDA), When used as an ingredient in sunscreen, zinc oxide blocks both UVA (320–400 nm) and UVB (280–320 nm) rays of ultraviolet light. Zinc oxide and the other most common physical sunscreen, titanium dioxide, are considered to be non irritating, non allergenic [9]. [10], [11].

3. OTHER INORGANIC NANOPARTICLES :

METALS

Most metals have been produced in nanometric dimensions. Among them, gold NPs are studied in particular and show an optical resonance spectrum in the visible range, which is sensitive to the environmental conditions, size and shape of NPs. Their unique properties make it possible to envision a series of applications, particularly as optical markers for medical diagnosis or as cancer treatment agents. Nanometric silver is also produced in large quantities and is mainly used for its anti microbial properties. Nanometric platinum, palladium and rhodium are used in catalytic converters, iron, nickel and cobalt as catalysts, particularly for the synthesis of carbon nano materials, aluminium as a fuel, iron as a doping metal and copper in electronics. Gold, copper, silicon and cobalt nano wires, capable of being electrical conductors or semi conductors, have also been perfected and could be used to transport electrons in nano electronics. Finally, nano wires have been developed based on different metals, oxides, sulphides and nitrides [12], [13].

METAL OXIDES

Several metal oxides of nano metric dimensions have been created, but the most common ones, because they are produced on a large scale, are probably silica, titanium dioxide and zinc oxide. They are used either natural or coated, mainly in the fields of rheology, plastics and rubbers as active agents and additives (SiO_2), in sun creams (TiO_2, ZnO), and as pigment in paint (TiO_2). Different metal oxides have appeared in varied forms: nano tubes, nano rods, nano flakes, etc. In addition, certain structures show interesting properties for virtual applications in fields such as sensors, optoelectronics, transducers and medicine Other metal oxides are also produced, including cerium, iron, copper, zirconium, aluminum, nickel, antimony, yttrium, barium and manganese oxides, as well as nanoclays [14].

Fig:-1 Image of mixed metal oxide nanoparticles tandem catalyst.

QUANTUM DOTS

Quantum dots is an important field of research, quantum dots are typically composed of combinations of Group II and IV elements or Group III and V elements of the periodic table. Many researchers have been developed in the form of semi conductors, insulators, metals, magnetic materials or metallic oxides. The number of atoms in quantum dots, which can range from 1,000 to 100,000, makes them neither an extended solid structure nor a molecular entity [15] with smaller dimensions than the exaction Bohr radius; they display unique optical and electronic properties at diameters of about 1 to 10 nm. Because of their quantum confinement, they can, for example, absorb white or ultraviolet light and reemit it at a specific wave length a few nano seconds later [16]. Depending on the composition and size of the quantum dot, the light emitted may range from blue to the near infrared.

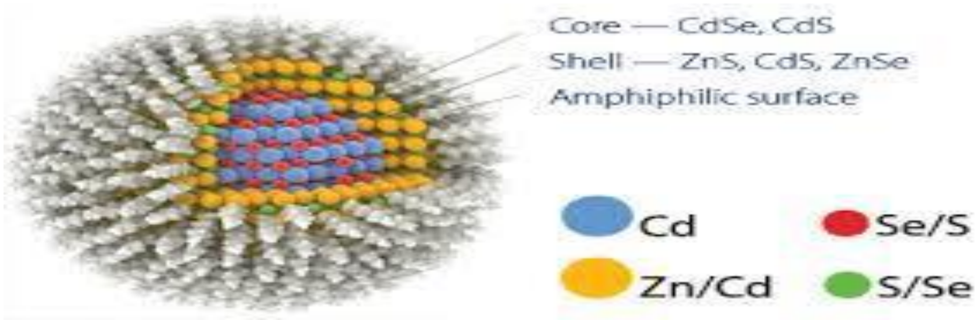

Fig-: 2 Schematicand Visual Representation of a Quantum Dot.

The flexibility of quantum dots and their associated optical properties make it possible to envision applications in fields such as multi color coding in the study of genetic expression, in high-resolution and high-speed screens and in medical imaging. Their high surface to volume ratio allows them to be combined with anti bodies, proteins and oligonucleides [17]. Some quantum dots are modified to produce drug vectors, diagnostic tools and inorganic solar batteries [18], [19].

4. SYNTHESIS OF NANOPARTICLES :

A nanoparticle involves breaking up a bulk material into atoms or ions and then allowing those atoms or ions to condense into nanoparticles. Equipment designed to produce nanoparticles makes the process more efficient by breaking down more of the raw material to the atomic level under controlled conditions to condense atoms together and form nanoparticles. Several types of systems are used to produce nanoparticles. A description of a few commonly used systems follows. In a plasma source system, an inert gas, such as argon, flows into a chamber. This gas carries macroscopic particles of the material from which you want to produce nanoparticles. A high-power radio frequency signal applied to the carrier gas produces plasma, which then flows into a cooled chamber, as illustrated in the ions then condense into nanoparticles. This method is often used for volume production of metallic Nanoparticles [20], [21].

CHEMICAL PRECIPITATION

In this strategy the size is control by arrested precipitation technique. The basic trick has been to synthesis and studies the nano material in situ i.e. in the same liquid medium avoiding the physical changes and aggregation of tiny crystallites. Thermal coagulation and Oswald ripening were controlled by double layer repulsion of crystallites using non-aqueous solvents at lower temperatures for synthesis. The synthesis involved reaction between constituent materials in suitable solvent. The dopent is added to the parent solution before precipitation reaction. Surfactant is used to maintain separation between the particles formed. Thus formed nano crystal are separated by centrifugation, washed and vacuum dried. The dried material was further subjected to UV curing for possible polymerization of surfactant capping film on the surface of nano cluster for imparting true quantum confinement [22][23][24].

SOL-GEL TECHNIQUES

In addition to techniques mentioned above, the sol-gel processing techniques have also been extensively used. Colloidal particles are much larger than normal molecules or nanoparticles. However, upon mixing with liquid colloids appear bulky where as the nano sized molecules always look clear. It involves the evolution of networks through the formation of colloidal suspension (sol) and gelatin to form a network in continuous liquid phase (gel). The precursor for synthesizing these colloids consists of ions of metal alkoxides and aloxysilanes. The most widely used are tetramethoxysilane (TMOS), and tetraethoxysilanes (TEOS) which form silica gels. Alkoxides are immiscible in water. They are organo metallic precursors for silica, aluminum, titanium, zirconium and many others. Mutual solvent alcohol is used. The sol gel process involves initially a homogeneous solution of one or more selected alkoxides. These are organic precursors for silica, alumina, Titania, zirconia, among others. **Mortia et al** [25]-[30]. A catalyst is used to start reaction and control PH. Sol-gel formation occurs in four stages. Hydrolysis, Condensation, Growth of particles, Agglomeration of particles.

5. USES AND ADVANTAGES OF NANOPARTICLES IN MEDICINE :

Some of the uses of nanoparticles in biology and medicine include:

- Creating fluorescent biological labels for important biological markers and molecules in research and diagnosis of diseases
- Drug delivery systems
- Gene delivery systems in gene therapy
- For biological detection of disease causing organisms and diagnosis
- Detection of proteins
- Isolation and purification of biological molecules and cells in research
- Probing of DNA structure
- Genetic and tissue engineering
- Destruction of tumors with drugs or heat
- In MRI studies
- In pharmacokinetic studies [31].

ADVANTAGES OF USING NANOPARTICLES AS A DRUG DELIVERY SYSTEM INCLUDE

The size and surface characteristics of nanoparticles can be easily manipulated. This could be used for both passive and active drug targeting. Nanoparticles can be made to control and sustain release of the drug during the transportation as well as the location of the release. Since distribution and subsequent clearance of the drug from the body can be altered, an increase in drug therapeutic efficacy and reduction in side effects can be achieved. Choosing an appropriate matrix also helps in increasing the efficacy and reducing side effects. Targeted drugs may be developed. Various routes of administration including oral, nasal, injection, intra-ocular (within the eyes) etc [32].

NANOMATERIALS USED IN MEDICAL INDUSTRY:

CANCER: Nanoparticles have made a tremendous impact in the treatment of various types of cancer, as evidenced by the numerous nanoparticles-based drugs and delivery systems that are in clinical use. Examples of numerous liposome- and polymer-based drugs. Paclitaxel is a well-known anti-cancer agent used to treat several types of cancer such as ovarian, skin, esophageal, and lung. This drug interferes with the functions of cancer cells by microtubule stabilization, resulting eventually in apoptosis [33], [34]. The most common mode of administration of this water-insoluble drug is as a solution in ethanol, administered together with a solvent, polyoxy ethylated castor oil [35]-[39]. A major short coming of this approach has been the side effects associated with Cremophor, including hyper sensitivity reactions, necessitating the administration of steroids and antihistamines as pre medications [40]-[41].

HIV/AIDS : De Jaeghere and coworkers investigated the delivery of an HIV-1 protease inhibitor, CGP 70726, using pH-sensitive nanoparticles made from a copolymer of methacrylic acid and ethyl acrylate. This copolymer is commercially available under the name Eudragit L100–55. The copolymer was chosen because of its pH-dependent solubility. CGP 70726 and other similar anti-viral agents are known to disrupt the replication cycle of HIV-1 [42]. A major challenge in delivering agents such as CGP 70726 is poor water solubility. De Jaeghere and colleagues synthesized nanoparticles by emulsifying a solution of the copolymer with a mixture of CGP 70726 and benzyl alcohol. The nanoparticles were administered orally to dogs and successful drug release was observed by analysis of blood samples. The HIV-1 Tat protein has recently emerged as a potential candidate for a prophylactic or therapeutic vaccine against HIV-1/AIDS [43], [44].

TUBERCULOSIS : Humans have been in a constant battle with tuberculosis (TB). Currently over use of antibiotics has resulted in the spread of multi drug resistant mycobacterium tuberculosis leading to antibiotic ineffectiveness at controlling the host cell and especially macrophages. Additionally, mycobacterium tuberculosis (Mtb) has developed methods to evade the immune system and survive with the discovery of nanoparticles (NPS) based drug, it is necessary to research their anti mycobacterium properties and bactericidal mechanisms in this study, we synthesized mixed metal oxide NPs and tested their ability to inhibit Mtb growth into macrophages and investigated the cytotoxic effects of Nps in THP-1 cells. Silver (Ag) Nps and zinc oxide (ZnO) Nps were synthesized by chemical Reduction and chemical deposition in aqueous solution and the diffraction light scattering scanning electron microscopy, transmission electron microscopy, and ultraviolet visible light absorption spectra were used to identify Nps properties Ag and ZnO Nps were mixed together at a ratio of BZnO /2Ag and diluted in to Lowenstein-Jensen medium followed by the addition for 28 days at $37^{o}C$. The toxicity of Nps to THP-1 cells was assessed by MTT test and macrophages were infected with Mtb for 4 h at $37^{0}C$ under 5% CO_2 [45], [46].

6. REVIEW OF LITERATURES :

In recent years, many researchers worked for the development and exponential interest in the novel drug delivery system using nanoparticles in this connections **pal and his co-workers (2011).** Synthesized nanoparticles which they applied as drug delivery system with great success. Nanoparticles provide great significances of advantages regarding drug involvement in the transportation or correct position of a part (targeting), delivery and with their potential for combine diagnosis and therapy and one of the major tools on Nano-medicine and drug delivery in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release , many researchers worked that the possibility to use in different route of administration and the capability to deliver both hydrophilic and hydrophobic drug molecules [47].

The current nano technology applications in the agro-food production chain are focused on the development of nano sized or nano encapsulated food ingredients and additives, delivery systems for bioactive compounds, bioavailability, and innovative food packaging **(Bouwmeester *at al.* 2009) (Sekhon 2010).** In addition, nano technology can lead to increase food productivity and to supply fresher and healthier foods. Furthermore, it is possible to enhance the utilization of nutrition and nutraceuticals "Classification of nano-delivery systems." "Review of Health Safety Aspects of Nano technologies in Food Production" Regulatory Toxicology and Pharmacology with the aid of nano delivery systems **(Xu 2010).** Nano technology analysts estimated that between 150- 600 nano foods and 400-500 nano food packaging applications are already on the market **(Sekhon *el at*. 2011) [48].**

Nanoparticles can be applied as reactive particles in packaging materials. They are nano sensors which are designed to respond to environmental change, such as temperature or moisture in storage rooms, degradation products of the food commodities, or contamination by micro or geneses **(Bouwmeester *el al.* 2009s).**

Also, there are nanoparticles such as nanoclays which are incorporated into plastic beer bottles. The nanoclays increase the strength of the bottle, making them more shatter proof. In addition, the nanoclay extends the self life by acting as a barrier to keep oxygen outside the bottle and carbon dioxide inside **(Busby *at al.* 2010) [49].**

A negative surface charge for the WC NPs is in agreement with literature findings for such particles in pure water Observed data in this study (approx. -20 mV) was less negative compared with approx -60 mV of larger-sized WC particles reported in **(Anderson and Bergstrom, 2000€)** and approx 35 mV of smaller sized WC NPs in **(Bastian *et al.* 2009).** A near-neutral charge in SW for the Cu NPs is expected from earlier reports of other Cu NPs **(Hedberg *et al.* 2016).**

In this study, we have performed detailed sedimentation measurements that also allow measurements of the released metal fraction. It was shown important in this and in earlier studies to be aware of and understand artifacts introduced from several experimental steps. These artifacts can be introduced during membrane filtration, the sonication procedure (**Pradhan *et al.* 2016),** and during measurements of the added dose **(Hedberg *et al.* 2016).** In the case of the Cu NPs, the total amounts of released Cu were actually higher than the measured amount of Cu in solution, both due to a loss of Cu during membrane filtration and due to precipitation of released Cu. As all NPs investigated in their study rapidly sedimented from solution, which resulted in a loss of some particles after sonication of the particle dispersion, it was hence important to measure the actual added dose. Digestion procedures for the WC and the WC-Co NPs were not trivial. It was shown crucial to use an alkaline pH both during digestion and for accurate solution analysis of W. We hope that elaborated procedures are employed in future studies of similar NPs of relevance for e.g. traffic environments in order to assess their environmental fate, ecotoxicity, and possible synergistic / antagonistic effects with different molecules [50].

Nano-sized particles are generally of higher concern compared with micron-sized particles in terms of their environmental and health risks due to an increased ability to reach the alveolar region of the lung **(Kastury *et al.* 2017),** an increased ability of cell up take and adverse health effects, and an increased environmental mobility [51].

7. CONCLUSION :

Mixed metal oxide (MMO) nanoparticles can play an considerable role in various areas of chemistry and physics. The unique electronic and magnetic property obtain when combine two metals in an oxide matrix have been well studied. Metal oxide nanoparticles have a unique structure, interesting and unusual redox and catalytic property, high surface area, good mechanical strength and are biocompatible. For these reasons, metal oxide nanoparticles have concerned extensive attention in the field of biomedical therapeutics, biological applications, bio-imaging and biosensing. This chapter discusses property and biomedical applications of select nanometer size metal oxides. These materials have become significant mechanism in medical implant, cancer diagnosis and hiv/aids, tuberculosis, neurochemical monitoring. Titania, Silica Nanoparticles, Zinc oxide nanoparticles is the material of choice in medical implants; it provides an outstanding biocompatible surface for cell addition and production. more than a few other metal oxides have been used as gas sensing nanoprobes for cell labeling and separation, as contrast agents for magnetic quality imaging (MRI) and as carriers for targeted drug delivery. In this paper we also discuss Synthesis of nanoparticles, chemical precipitation and sol gel technique. New and emerging applications of nanoceria as neuro protective agents possessing antioxidant/free radical scavenge property are emerging in the biomedical field, and ceria-based nanoparticles may be used as therapeutic agents in the treatment of medical diseases related to reactive oxygen species, such as spinal cord repair, stroke and degenerative retinal disorders. Issues related to biocompatibility and toxicity of these nanoparticles for in vivo biomedical applications remains to be fully explorsed.

REFERENCES :

1. Langer, R. (2000). Biomaterials in drug delivery and tissue engineering: one laboratory's experience. *Accounts of Chemical Research*, *33*(2), 94-101.
2. Bhadra, D., Bhadra, S., Jain, P., & Jain, N. K. (2002). Pegnology: a review of PEG-ylated systems. *Die Pharmazie*, *57*(1), 5
3. Murray, C. B., Kagan, A. C., & Bawendi, M. G. (2000). Synthesis and characterization of monodisperse nanocrystals and close-packed nanocrystal assemblies. *Annual review of materials science*, *30*(1), 545-610.
4. Salata, O. V. (2004). Applications of nanoparticles in biology and medicine. *Journal of nanobiotechnology*, *2*(1), 3.
5. Paull, R., Wolfe, J., Hébert, P., & Sinkula, M. (2003). Investing in nanotechnology. *Nature biotechnology*, *21*(10), 1144-1147.
6. Taton, T. A. (2002). Nanostructures as tailored biological probes. *TRENDS in Biotechnology*, *20*(7), 277-279.
7. DiMaio, D., & Liao, J. B. (2006). Human papillomaviruses and cervical cancer. *Advances in virus research, 66,* 125-159.
8. Levrero, M. (2006). Viral hepatitis and liver cancer: the case of hepatitis C. *Oncogene*, *25*(27), 3834-3847.
9. Kusters, J., van Vliet, A., & Kuipers, E. (2006). Pathogenesis of Helicobacter pylori Infection Clin Microbiol Rev 19: 449-490. *Crossref Google Scholar*.
10. Burgos, J. S. (2005). Involvement of the Epstein-Barr virus in the nasopharyngeal carcinoma pathogenesis. *Medical oncology*, *22*(2), 113-121.

11. Kajander, E. O., & Çiftçioglu, N. (1998). Nanobacteria: an alternative mechanism for pathogenic intra-and extracellular calcification and stone formation. *Proceedings of the National Academy of Sciences*, *95*(14), 8274-8279.
12. Falkner, R., & Jaspers, N. (2012). Regulating nanotechnologies: risk, uncertainty and the global governance gap. *Global environmental politics*, *12*(1), 30-55.
13. Hansen, S. F. (2009). Regulation and risk assessment of nanomaterials: Too little, too late?
14. Stefaniak, A. B., Hackley, V. A., Roebben, G., Ehara, K., Hankin, S., Postek, M. T., ... & Thünemann, A. F. (2013). Nanoscale reference materials for environmental, health and safety measurements: needs, gaps and opportunities. *Nanotoxicology*, *7*(8), 1325-1337.
15. Maynard, A. D., & Kuempel, E. D. (2005). Airborne nanostructured particles and occupational health. *Journal of nanoparticle research*, *7*(6), 587-614.
16. Schulte, P. A., Trout, D., Zumwalde, R. D., Kuempel, E., Geraci, C. L., Castranova, V., ... & Halperin, W. E. (2008). Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: state of the science. *Journal of occupational and environmental medicine*, *50*(5), 517-526.
17. Michalet, X., Pinaud, F. F., Bentolila, L. A., Tsay, J. M., Doose, S. J. J. L., Li, J. J., ... & Weiss, S. (2005). Quantum dots for live cells, in vivo imaging, and diagnostics. *science*, *307*(5709), 538-544.
18. Åkerman, M. E., Chan, W. C., Laakkonen, P., Bhatia, S. N., & Ruoslahti, E. (2002). Nanocrystal targeting in vivo. *Proceedings of the National Academy of Sciences*, *99*(20), 12617-12621.
19. Michalet, X., Pinaud, F. F., Bentolila, L. A., Tsay, J. M., Doose, S. J. J. L., Li, J. J., ... & Weiss, S. (2005). Quantum dots for live cells, in vivo imaging, and diagnostics. *science*, *307*(5709), 538-544.
20. Kahn, J. S. (2006). The widening scope of coronaviruses. *Current opinion in pediatrics*, *18*(1), 42-47.
21. Kol, A., & Santini, M. (2004). Infectious agents and atherosclerosis: current perspectives and unsolved issues. *ITALIAN HEART JOURNAL.*, *5*, 350-357.
22. Konrad, A., Herr, U., Tidecks, R., Kummer, F., & Samwer, K. (2001). Luminescence of bulk and nanocrystalline cubic yttria. *Journal of applied Physics*, *90*(7), 3516-3523
23. Andrievskii, R. A. (1994). The synthesis and properties of nanocrystalline refractory compounds. *Russian Chemical Reviews*, *63*(5), 411.
24. Godwin, M. A., Shri, K. M., & Balaji, M. (2015). Engineering and Bioscience. *Int. J. Res. Eng. Biosci.*, *3*(5), 11-29.
25. Bhargava, R. N., Gallagher, D., Hong, X., & Nurmikko, A. (1994). Optical properties of manganese-doped nanocrystals of ZnS. *Physical Review Letters*, *72*(3), 416.
26. Yu, Z. Q., Chang, D., Li, C., Zhang, N., Feng, Y. Y., & Dai, Y. Y. (2001). Blue photoluminescent properties of pure nanostructured γ–Al 2 O 3. *Journal of Materials Research*, *16*(7), 1890-1893.
27. Lu, C. H., & Jagannathan, R. (2002). Cerium-ion-doped yttrium aluminum garnet nanophosphors prepared through sol-gel pyrolysis for luminescent lighting. *Applied physics letters*, *80*(19), 3608-3610.
28. Morita, M., Rau, D., Kajiyama, S., Sakurai, T., Baba, M., & Iwamura, M. (2004). Luminescence properties of nano-phosphors: metal-ion doped sol-gel silica glasses. *Materials Science-Poland*, *22*(1), 5-15.
29. Lee, M., & Kim, S. W. (2005). Polyethylene glycol-conjugated copolymers for plasmid DNA delivery. *Pharmaceutical research*, *22*(1), 1-10.
30. Feynman, R. P. (1960). There's plenty of room at the bottom. *California Institute of Technology, Engineering and Science magazine*.
31. Allen, T. M., & Cullis, P. R. (2004). Drug delivery systems: entering the mainstream. *Science*, *303*(5665), 1818-1822.
32. Duncan, R. (2003). The dawning era of polymer therapeutics. *Nature reviews Drug discovery*, *2*(5), 347-360.
33. Abratt, R. P., Lee, J. S., Han, J. Y., Tsai, C. M., Boyer, M., Mok, T., ... & Lehnert, M. (2006). Phase II trial of gemcitabine-carboplatin-paclitaxel as neoadjuvant chemotherapy for operable non-small cell lung cancer. *Journal of Thoracic Oncology*, *1*(2), 135-140.
34. Kikuchi, A., Sakamoto, H., & Yamamoto, T. (2005). Weekly carboplatin and paclitaxel is safe, active, and well tolerated in recurrent ovarian cancer cases of Japanese women previously treated with cisplatin-containing multidrug chemotherapy. *International Journal of Gynecologic Cancer*, *15*(1), 45-49.
35. Chao, Y., Li, C. P., Chao, T. Y., Su, W. C., Hsieh, R. K., Wu, M. F., ... & Cheng, A. L. (2006). An open, multi-centre, phase II clinical trial to evaluate the efficacy and safety of paclitaxel, UFT, and leucovorin in patients with advanced gastric cancer. *British journal of cancer*, *95*(2), 159-163.
36. De Giorgi, U., Giannini, M., Frassineti, L., Kopf, B., Palazzi, S., Giovannini, N., ... & Marangolo, M. (2006). Feasibility of radiotherapy after high-dose dense chemotherapy with epirubicin, preceded by dexrazoxane, and

paclitaxel for patients with high-risk stage II-III breast cancer. *International Journal of Radiation Oncology* Biology* Physics*, *65*(4), 1165-1169.

37. Roof, K. S., Coen, J., Lynch, T. J., Wright, C., Fidias, P., Willett, C. G., & Choi, N. C. (2006). Concurrent cisplatin, 5-FU, paclitaxel, and radiation therapy in patients with locally advanced esophageal cancer. *International Journal of Radiation Oncology* Biology* Physics*, *65*(4), 1120-1128.
38. Worden, F. P., Moon, J., Samlowski, W., Clark, J. I., Dakhil, S. R., Williamson, S., ... & Southwest Oncology Group, the Head and Neck Working Group. (2006). A phase II evaluation of a 3-hour infusion of paclitaxel, cisplatin, and 5-fluorouracil in patients with advanced or recurrent squamous cell carcinoma of the head and neck: Southwest Oncology Group study 0007. *Cancer*, *107*(2), 319-327.
39. Koziara, J. M., Whisman, T. R., Tseng, M. T., & Mumper, R. J. (2006). In-vivo efficacy of novel paclitaxel nanoparticles in paclitaxel-resistant human colorectal tumors. *Journal of controlled release*, *112*(3), 312-319.
40. Zhang, J. A., Anyarambhatla, G., Ma, L., Ugwu, S., Xuan, T., Sardone, T., & Ahmad, I. (2005). Development and characterization of a novel Cremophor® EL free liposome-based paclitaxel (LEP-ETU) formulation. *European journal of pharmaceutics and biopharmaceutics*, *59*(1), 177-187.
41. Zhang, W., Yang, H., Kong, X., Mohapatra, S., San Juan-Vergara, H., Hellermann, G., ... & Mohapatra, S. S. (2005). Inhibition of respiratory syncytial virus infection with intranasal siRNA nanoparticles targeting the viral NS1 gene. *Nature medicine*, *11*(1), 56-62.
42. Robins, T., & Plattner, J. (1993). HIV protease inhibitors: their anti-HIV activity and potential role in treatment. *Journal of acquired immune deficiency syndromes*, *6*(2), 162-170.
43. Cafaro, A., Caputo, A., Fracasso, C., Maggiorella, M. T., Goletti, D., Baroncelli, S., ... & Borsetti, A. (1999). Control of SHIV-89.6 P-infection of cynomolgus monkeys by HIV-1 Tat protein vaccine. *Nature medicine*, *5*(6), 643-650.
44. Caputo, A., Gavioli, R., & Ensoli, B. (2004). Recent advances in the development of HIV-1 Tat-based vaccines. *Current HIV research*, *2*(4), 357-376.
45. Lourenco, M. C., de Souza, M. V., Pinheiro, A. C., Ferreira, M. D. L., Gonçalves, R. S., Nogueira, T. C. M., & Peralta, M. A. (2007). Evaluation of anti-tubercular activity of nicotinic and isoniazid analogues. *Arkivoc*, *15*, 181-191.
46. Du Toit, L. C., Pillay, V., & Danckwerts, M. P. (2006). Tuberculosis chemotherapy: current drug delivery approaches. *Respiratory research*, *7*(1), 118
47. Pal S.L., JanaU. Manna P.K., Mohanta G.P., Manavalan R. (2011). Nanoparticles An overview of preparation and characterization. *Journal of Applied Pharmaceutical Science* vol. 01, Issue 06, pp228-234.
48. Sekhon, R. S., Lin, H., Childs, K. L., Hansey, C. N., Buell, C. R., De Leon, N., & Kaeppler, S. M. (2011). Genome-wide atlas of transcription during maize development. *The Plant Journal*, *66*(4), 553-563
49. Buzby, J. C., Hyman, J., Stewart, H., & Wells, H. F. (2011). The value of retail-and consumer-level fruit and vegetable losses in the United States. *Journal of Consumer Affairs*, *45*(3), 492-515.
50. Hedberg, Y. S., & Odnevall Wallinder, I. (2016). Metal release from stainless steel in biological environments: A review. *Biointerphases*, *11*(1), 018901
51. Kastury, F., Smith, E., & Juhasz, A. L. (2017). A critical review of approaches and limitations of inhalation bioavailability and bioaccessibility of metal (loid) s from ambient particulate matter or dust. *Science of The Total Environment*, *574*, 1054-1074.