INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

CURRENT TRENDS ON ROLE OF NANO PARTICLES ON PULMONARY DISEASES

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ABSTRACT

In recent advances in nanotechnology engineering have given rise to rapid development of many novel applications in the biomedical field. The lung is one of the main route of entry for nano particles in to the body and hence a lightly site for accumulation of nanoparticles.In the present study the different types of nano materials for the preparation of nano particles and the use of nano particles in treatment of major pulmonary diseases like lung cancer.Pulmonary fibrosis Tuberculosis and Bronchial asthma and recent specific diagnostic test for lung cancer this article also includes about the present status in treatment of tuberculosis.

Keywords: Nano particles, nano materials, lung cancer, tuberculosis, pulmonary fibrosis.

1. INTRODUCTION

It is defined as a small object that behaves as a whole unit in terms of its transports and properties. Nanoparticles are particles that have one dimension that is 100 nanometers or less in size.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; this causes them to be more reactive to certain other molecules [1] .Nanoparticles used for a very long time probably the earliest use begin in glazes for early Chinese procelian.A roman cup called the Lycurges cup used nano sized gold clusters to create different colors depending on whether it was illuminated from the front or back. Carbon black is most famous example of a nano particulate material that has been produced in quantity for decades. Roughly1.5million ton of material is produced every year. Nanoparticles are currently made out of a very wide variety of materials the most common of the new generation of nanoparticles being ceramics which are the best splits in to metal oxides ceramics such as titanium zinc aluminium and iron oxides to name a prominent few and in the form of nano scale flakes of clay. According to the most widely accepted definitions at least one of their dimensions must be less than 100nm but some intresting new applications use particles of a few hundred nm so this report will not be overly strict about the 100nm limit.

2. NANO MATERIALS

2.1Carbon nanotube

Carbon nanotubes (CNTs) are allotropes of carbon with a cylindrical nanostructure. Nanotubes have been constructed with length-to-diameter ratio of up to 132,000,000:1[2-4] significantly larger than for any other material. These cylindrical carbon molecules have unusual properties, which are valuable for nanotechnology, electronics, optics and other fields of materials science and technology. Nanotubes are members of the fullerene structural family, which also includes the spherical buckyballs, and the ends of a nanotube may be capped with a hemisphere of the buckyball structure. Their name is derived from their long, hollow structure with the walls formed by one-atom-thick sheets of carbon, called graphene. These sheets are rolled at specific and discrete ("chiral") angles, and the combination of the rolling angle and radius decides the nanotube properties.

Nanotubes are categorized as single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs). Individual nanotubes naturally align themselves into "ropes" held together by van der Waals forces, more specifically, pi-stacking.

2.1a Single-walled

Most single-walled nanotubes (SWNT) have a diameter of close to 1 nanometer, with a tube length that can be many millions of times longer. The structure of a SWNT can be conceptualized by wrapping a one-atom-thick layer of graphite called graphene into a seamless cylinder. The way the graphene sheet is wrapped is represented by a pair of indices (*n*,*m*) . The integers *n* and *m* denote the number of unit vectors along two directions in the honeycomb crystal lattice of graphene. If *m* = 0, the nanotubes are called zigzag nanotubes, and if *n* = *m*, the nanotubes are called armchair nanotubes. Otherwise, they are called chiral. The diameter of an ideal nanotube can be calculated from its (n,m) indices as follows

$$d = \frac{a}{\pi}\sqrt{(n^2 + nm + m^2)}.$$

where *a* = 0.246 nm.

SWNTs are an important variety of carbon nanotube because most of their properties change significantly with the (*n*,*m*) value. Single-walled nanotubes are dropping precipitously in price, from around $1500 per gram as of 2000 to retail prices of around $50 per gram of as-produced 40–60% by weight.

2.1b Multi-walled

Multi-walled nanotubes (MWNT) consist of multiple rolled layers (concentric tubes) of graphite. There are two models that can be used to describe the structures of multi-walled nanotubes.In the *Russian Doll* model, sheets of graphite are arranged in concentric cylinders, e.g., a (0,8). In the *Parchment* model, a single sheet of graphite is rolled in around itself, resembling a scroll of parchment or a rolled newspaper. The interlayer distance in multi-walled nanotubes is close to the distance between graphene layer. s in graphite, approximately 3.4 Å. The Russian doll structure is observed more commonl**y.** Double-walled carbon nanotubes (DWNT) form a special class of nanotubes because their morphology and properties are similar to those of SWNT but their resistance to chemicals is significantly improved.

2.1c Synthesis

Techniques have been developed to produce nanotubes in sizeable quantities, including arc discharge, laser ablation, high-pressure carbon monoxide (HiPco), and chemical vapor deposition (CVD).

Most of these processes take place in vacuum or with process gases . Large quantities of nanotubes can be synthesized by these methods; advances in catalysis and continuous growth processes are making CNTs more commercially viable.

Arc discharge

During this process, the carbon contained in the negative electrode sublimates because of the high-discharge temperatures. Because nanotubes were initially discovered using this technique, it has been the most widely-used method of nanotube synthesis.

The yield for this method is up to 30% by weight and it produces both single- and multi-walled nanotubes with lengths of up to 50 micrometers with few structural defects.

Laser ablation

In the laser ablation process, a pulsed laser vaporizes a graphite target in a high-temperature reactor while an inert gas is bled into the chamber. Nanotubes develop on the cooler surfaces of the reactor as the vaporized carbon condenses. A water-cooled surface may be included in the system to collect the nanotube. The laser ablation method yields around 70% and produces primarily single-walled carbon nanotubes with a controllable diameter determined by the reaction temperature.

Chemical vapor deposition (CVD)

During CVD, a substrate is prepared with a layer of metal catalyst particles, most commonly nickel, cobalt, iron, or a combination. The metal nanoparticles can also be produced by other ways, including reduction of oxides or oxides solid solutions. The diameters of the nanotubes that are to be grown are related to the size of the metal particles. This can be controlled by patterned (or masked) deposition of the metal, annealing, or by plasma etching of a metal layer. The substrate is heated to approximately 700°C. To initiate the growth of nanotubes, two gases are bled into the reactor: a process gas (such as ammonia, nitrogen or hydrogen) and a carbon-containing gas (such as acetylene, ethylene, ethanol or methane). Nanotubes grow at the sites of the metal catalyst; the carbon-containing gas is broken apart at the surface of the catalyst particle, and the carbon is transported to the edges of the particle, where it forms the nanotubes. This mechanism is still being

studied. The catalyst particles can stay at the tips of the growing nanotube during the growth process, or remain at the nanotube base, depending on the adhesion between the catalyst particle and the substrate.
CVD is a common method for the commercial production of carbon nanotubes. For this purpose,
the metal nanoparticles are mixed with a catalyst support such as MgO or Al_2O_3 to increase the surface area for higher yield of the catalytic reaction of the carbon feedstock with the metal particles.

2.2 Quantum dot
A quantum dot is a portion of matter (e.g., semiconductor) whose excitons are confined in all three spatial dimensions. Consequently, such materials have electronic properties intermediate between those of bulk semiconductors and those of discrete molecules. They were discovered at the beginning of the 1980s by Alexei Ekimov in a glass matrix and by Louis E. Brus in colloidal solutions. The term "quantum dot" was coined by Mark Reed.
Researchers have studied quantum dots in transistors, solar cells, LEDs, and diode lasers. They have also investigated quantum dots as agents for medical imaging and hope to use them as qubits in quantum computing.

2.2a Production
It can be produced by following types.

Colloidal synthesis
A quantum dot is a portion of matter (e.g., semiconductor) whose excitons are confined in all three spatial dimensions.
Colloidal semiconductor nanocrystals are synthesized from precursor compounds dissolved in solutions, much like traditional chemical processes. The synthesis of colloidal quantum dots is based on a three-component system composed of: precursors, organic surfactants, and solvents. When heating a reaction medium to a sufficiently high temperature, the precursors chemically transform into monomers. Once the monomers reach a high enough supersaturation level, the nanocrystal growth starts with a nucleation process. The temperature during the growth process is one of the critical factors in determining optimal conditions for the nanocrystal growth. It may be high enough to allow for rearrangement and annealing of atoms during the synthesis process while being low enough to promote crystal growth.

Fabrication
Self-assembled quantum dots are typically between 5 and 50 nm in size. Quantum dots defined by lithographically patterned gate electrodes, or by etching on two-dimensional electron gases in semiconductor heterostructures can have lateral dimensions exceeding 100 nm.Some quantum dots are small regions of one material buried in another with a larger band gap. These can be so-called core-shell structures, e.g., with CdSe in the core and ZnS in the shell or from special forms of silica called ormosil. Quantum dots sometimes occur spontaneously in quantum well structures due to monolayer fluctuations in the well's thickness.Self-assembled quantum dots nucleate spontaneously under certain conditions during molecular beam epitaxy (MBE) and metallorganic vapor phase epitaxy (MOVPE), when a material is grown on a substrate to which it is not lattice matched. The resulting strain produces coherently strained islands on top of a two-dimensional wetting layer. This growth mode is known as Stranski–Krastanov growth. The islands can be subsequently buried to form the quantum dot. This fabrication method has potential for applications in quantum cryptography (i.e. single photon sources) and quantum computation. The main limitations of this method are the cost of fabrication and the lack of control over positioning of individual dots.Individual quantum dots can be created from two-dimensional electron or hole gases present in remotely doped quantum wells or semiconductor heterostructures called lateral quantum dots. The sample surface is coated with a thin layer of resist. A lateral pattern is then defined in the resist by electron beam lithography. This pattern can then be transferred to the electron or hole gas by etching, or by depositing metal electrodes (lift-off process) that allow the application of external voltages between the electron gas and the electrodes. Such quantum dots are mainly of interest for experiments and applications involving electron or hole transport, i.e., an electrical current. The energy spectrum of a quantum dot can be engineered by controlling the geometrical size, shape, and the strength of the confinement potential. Also, in contrast to atoms, it is relatively easy to connect quantum dots by tunnel barriers to conducting leads, which allows the application of the techniques of tunneling spectroscopy for their investigation.

Viral assembly
He reported using genetically engineered M13 bacteriophage viruses to create quantum dot

biocomposite structures. As a background to this work, it has previously been shown that genetically engineered viruses can recognize specific semiconductor surfaces through the method of selection by combinatorial phage display.[14] Additionally, it is known that liquid crystalline structures of wild-type viruses (Fd, M13, and TMV) are adjustable by controlling the solution concentrations, solution ionic strength, and the external magnetic field applied to the solutions. Consequently, the specific recognition properties of the virus can be used to organize inorganic nanocrystals, forming ordered arrays over the length scale defined by liquid crystal formation. Using this information, Lee et al. (2000) were able to create self-assembled, highly oriented, self-supporting films from a phage and ZnS precursor solution. This system allowed them to vary both the length of bacteriophage and the type of inorganic material through genetic modification and selection.

Electrochemical assembly

Highly ordered arrays of quantum dots may also be self-assembled by electrochemical techniques. A template is created by causing an ionic reaction at an electrolyte-metal interface which results in the spontaneous assembly of nanostructures, including quantum dots, onto the metal which is then used as a mask for mesa-etching these nanostructures on a chosen substrate.

Bulk-manufacture

Conventional, small-scale quantum dot manufacturing relies on a process called “high temperature dual injection” which is impractical for most commercial applications that require large quantities of quantum dots.A reproducible method for creating larger quantities of consistent, high-quality quantum dots involves producing nanoparticles from chemical precursors in the presence of a molecular cluster compound under conditions whereby the integrity of the molecular cluster is maintained and acts as a prefabricated seed template. Individual molecules of a cluster compound act as a seed or nucleation point upon which nanoparticle growth can be initiated. In this way, a high temperature nucleation step is not necessary to initiate nanoparticle growth because suitable nucleation sites are already provided in the system by the molecular clusters. A significant advantage of this method is that it is highly scalable.Recently a consortium of U.S. and Dutch companies reported a "milestone" in high volume quantum dot manufacturing by applying the traditional high temperature dual injection method to a flow system. However as of 2011, applications using bulk-manufactured quantum dots are scarcely available.

2.2b Cadmium-free quantum dots

Cadmium-free quantum dots are also called “CFQD”. In many regions of the world there is now a restriction or ban on the use of heavy metals in many household goods which means that most cadmium based quantum dots are unusable for consumer-goods applications.Cadmium and other restricted heavy metals used in conventional quantum dots is of a major concern in commercial applications. For Quantum Dots to be commercially viable in many applications they must not contain cadmium or other restricted metal elements.[5-7]A new type of CFQD can be made from rare earth (RE) doped oxide colloidal phosphor nanoparticles. Unlike semiconductor nanoparticles, excitation was due to UV absorption of host material, which is same for different RE doped materials using same host. Multiplexing applications can be thus realized. The emission depends on the type of RE, which enables very large stokes shift and is narrower than CdSe QDs[8] The synthesis is aqueous based, which eliminated issues of water solubility for biological applications. The oxide surface might be easier for chemical functionalizion more and chemically stable in various environments. Some reports exist concerning the use of such phosphor nanoparticles on biological targeting and imaging[9-12]

Fluorescence spectra of CdTe quantum dots of various sizes. Different sized quantum dots emit different color light due to quantum confinement. An immediate optical feature of colloidal quantum dots is their coloration. Qdots can be synthesized with larger (thicker) shells (CdSe qdots with CdS shells). The shell thickness has shown direct correlation to the lifetime and emission intensity.

2.3 Silver nanoparticles

Silver nanoparticles are nanoparticles of silver, i.e. silver particles of between 1 nm and 100 nm in size. While frequently described as being 'silver' some are composed of a large percentage of silver oxide due to their large ratio of surface-to-bulk silver atoms.

2.3a Synthesis

There are many different synthetic routes to silver nanoparticles. They can be divided into two broad categories: physical vapor deposition, ion implantation, or wet chemistry.

Ion implantation
Although it may seem counter-intuitive, ion implantation has been used to create silver nanoparticles. This process has been shown to produce silver particles embedded in glass, polyurethane, silicone, polyethylene, and polymethylmethacrylate. The particles grow in the substrate with the bombardment of ions. The existence of nanoparticles is proven with optical absorbance, though the exact nature of the particles created with this method is not known.

Wet chemistry
There are several wet chemical methods for creating silver nanoparticles. Typically, they involve the reduction of a silver salt such as silver nitrate with a reducing agent like sodium borohydride in the presence of a colloidal stabilizer. Sodium borohydride has been used with polyvinyl alcohol, poly(vinylpyrrolidone), bovine serum albumin (BSA), citrate and cellulose as stabilizing agents. Citrate and cellulose have been used to create silver nanoparticles independent of a reducing agent as well. An additional novel wet chemistry method used to create silver nanoparticles took advantage of ß-D-glucose as a reducing sugar and a starch as the stabilizer.

2.4 Colloidal gold
Colloidal gold is a suspension (or colloid) of sub-micrometre-sized particles of gold in a fluid usually water. The liquid is usually either an intense red colour (for particles less than 100 nm), or a dirty yellowish colour.

2.4a Synthesis
Turkevich method
Generally, it is used to produce modestly monodisperse spherical gold Nanoparticles suspended in water of around 10–20 nm in diameter. Larger particles can be produced, but this comes at the cost of monodispersity and shape. It involves the reaction of small amounts of hot chlorauric acid with small amounts of sodium citrate solution. The colloidal gold will form because the citrate ions act as both a reducing agent, and a capping agent. To produce larger particles, less sodium citrate should be added (possibly down to 0.05%, after which there simply would not be enough to reduce all the gold). The reduction in the amount of sodium citrate will reduce the amount of the citrate ions available for stabilizing the particles, and this will cause the small particles to aggregate into bigger ones (until the total surface area of all particles becomes small enough to be covered by the existing citrate ions.

Brust method
This method was discovered by Brust and Schiffrin in early 1990s,[13] and can be used to produce gold nanoparticles in organic liquids that are normally not miscible with water (like toluene). It involves the reaction of a chlorauric acid solution with tetraoctylammonium bromide (TOAB) solution in toluene and sodium borohydride as an anti-coagulant and a reducing agent, respectively. Here, the gold nanoparticles[14] will be around 5–6 nm. $NaBH_4$ is the reducing agent, and TOAB is both the phase transfer catalyst and the stabilizing agent.It is important to note that TOAB does not bind to the gold nanoparticles particularly strongly, so the solution will aggregate gradually over the course of approximately two weeks. To prevent this, one can add a stronger binding agent, like a thiol (in particular, alkanethiols), which will bind to gold covalently, producing a near-permanent solution. Alkanethiol protected gold nanoparticles can be precipitated and then re dissolved. Some of the phase transfer agent may remain bound to the purified nanoparticles, this may affect physical properties such as solubility. In order to remove as much of this agent as possible the nanoparticles must be further purified by soxhlet extraction**.**

Perrault Method
This approach, discovered by Perrault and Chan in 2009[15] uses hydroquinone to reduce $HAuCl_4$ in an aqueous solution that contains gold nanoparticle seeds. This seed-based method of synthesis is similar to that used in photographic film development, in which silver grains within the film grow through addition of reduced silver onto their surface. Similarly, gold nanoparticles can act in conjunction with hydroquinone to catalyze reduction of ionic gold onto their surface. The hydroquinone method complements that of Frens, as it extends the range of monodispersed spherical particle sizes that can be produced. Whereas the Frens method[16-17] is ideal for particles of 12-20 nm, the hydroquinone method can produce particles of at least 30-250 nm.

Sonolysis
Another method for the experimental generation of gold particles is by sonolysis. In one such process based on ultrasound, the reaction of an aqueous solution of $HAuCl_4$ with glucose], the reducing agents are hydroxyl radicals and sugar pyrolysis radicals (forming at the interfacial region between the collapsing cavities and the bulk water) and the morphology obtained is that of nanoribbons

with width 30 -50 nm and length of several micrometers. These ribbons are very flexible and can bend with angles larger than 90°. When glucose is replaced by cyclodextrin (a glucose oligomer) only spherical gold particles are obtained suggesting that glucose is essential in directing the morphology towards a ribbon.

Electron Microscopy

Colloidal gold and various derivatives have long been among the most widely-used contrast agents for biological electron microscopy.[18-22] Colloidal gold particles can be attached to many traditional biological probes such as antibodies, lectins, superantigens, glycans, nucleic acids,[18] and receptors. Particles of different sizes are easily distinguishable in electron micrographs, allowing simultaneous multiple-labelling experiments.

2.5 Nanoscale iron particles

Nanoscale iron particles are sub-micrometer particles of iron metal. They are highly reactive because of their large surface area. In the presence of oxygen and water, they rapidly oxidize to form free iron ions. They are widely used in medical and laboratory applications and have also been studied for remediation of industrial sites contaminated with chlorinated organic compounds[23-24].Research has shown that nanoscale iron particles can be effectively used to treat several forms of ground contamination, including grounds contaminated by polychlorinated biphenyls (PCBs), chlorinated organic solvents, and organochlorine pesticides.

Nanoscale iron particle are easily transportable through ground water, allowing for in situ treatment. Additionally, the nanoparticle-water slurry can be injected into the contaminated area and stay there for long periods of time. These factors combine to make this method of cheaper than most currently used alternative. Researchers have found that although metallic iron nanoparticles remediate contaminants well, they tend to agglomerate on the soil surfaces. In response, carbon nanoparticles and water-soluble polyelectrolytes have been used as supports to the metallic iron nanoparticles. The hydrophobic contaminants adsorb to these supports, improving permeability in sand and soil. In field tests have generally confirmed lab findings. However, research is still ongoing and nanoscale iron particles are not yet commonly used for treating ground contamination.

2.6 Platinum nanoparticles

Platinum nanoparticles are usually in the form of a suspension or colloid of sub-micrometre-sized particles of platinum in a fluid, usually water. A colloid is technically defined as particles which remain suspended without forming an ionic, or dissolved solution. The platinum nanoparticle[25-26] sizes range between 2-3 nanometres (nm). Trillions of platinum nanoparticles are suspended in the brownish red or black colored colloidal solution. Nanoparticles come in wide variety of shapes including spheres, rods, cubes, and caps. Due to the antioxidant properties of the platinum nanoparticles, they are the subject of substantial research with applications in a wide variety of areas, including nanotechnology, medicine.

2.6a Synthesis

Platinum nanoparticles are fabricated by reduction of hexachloroplatinate. After dissolving hexachloroplatinate, the solution is rapidly stirred while a reducing agent is added. This causes platinum ions to be reduced to neutral platinum atoms .As more and more of these platinum atoms form, the solution becomes supersaturated and platinum gradually starts to precipitate in the form of sub-nanometre particles. The rest of the platinum atoms that form stick to the existing particles, and, if the solution is stirred vigorously enough, the particles will be fairly uniform in size. Various procedures employed to attain platinum nanoparticles include heating, reflux, cooling, stirring, filtration and filling, examinations & tests and packaging. To prevent the particles from aggregating, some sort of stabilizing agent or stabilizer that sticks to the nanoparticle surface is usually added. They can be functionalized with various organic ligands to create organic-inorganic hybrids with advanced functionality

Nano particles for cancer detection

Today nanoparticles are being studied and used for detecting and destroying cancer cells in mice. A couple of these new cancer detecting nanoparticles are gold nanoparticles and magnetic iron oxide nanoparticles encased in a biocompatible material. Gold nanoparticles can be used as both detecting and destroying cancer cells. Cancer cells have a protein called Epidermal Growth Factor Receptor (EGFR) which the gold nanoparticles attach themselves to. “If you add this conjugated nanoparticle solution to healthy cells and cancerous cells and you look at the image, you can tell with a simple microscope that the whole cancer cell is shining,” The

healthy cell doesn't bind to the nanoparticles specifically, so you don't see where the cells are. With this technique, if you see a well defined cell glowing, that's cancer."Similar to gold nanoparticles is quantum dots. These use cadmium selenide nanoparticles which glow when under ultraviolet light which makes it easier to extract the tumor. Magnetic iron oxide nanoparticles encased in a biocompatible material can make detecting cancer cells easier, even if the cancer cells are small and clearer so there is less mistakes in the detecting process. These particles stick to the tumor cells turning them into little magnets which are then attracted to the tip of a biopsy needle. "It might also be possible to detect cells from breast, prostate, and ovarian cancers that have spread to other parts of the body in amounts too tiny to sample with an ordinary needle. Instead of using biopsies, MRI's can be used to distinguish malignant lymph nodes which can help in telling how far prostate cancer has spread. "Researchers in the Netherlands and Boston, Massachusetts, recently reported in the New England Journal of Medicine that an MRI contrast agent consisting of highly lymphotropic iron oxide nanoparticles enabled clinicians to detect small nodal metastases that otherwise would have gone undetected in 33 of the 80 patients with prostate cancer. Therefore, cancer patients can get the ideal treatment for there specific case.

Treatment of pulmonary diseases with the help of nanoparticles will be seen as follows.

LUNG CANCER

Diagnosis

A simple new technique could help improve diagnosis and treatment options for sufferers of lung cancer (Fig :1)

A new technique that may help improve diagnosis and treatment options for sufferers of lung cancer involves counting the number of tumour cells in blood samples. It involves counting the number of tumour cells in blood samples before and after chemotherapy, allowing doctors to establish how well patients are responding to treatment. The technique is said to represent an improvement on a current diagnosis test that is invasive and can only be carried out once. To be able to detect and count these rare tumour cells circulating through the blood, and the link this has to the progress of the disease, opens an incredibly exciting new area of research. We could now look at the genetic faults that are behind the disease and start to develop drugs that target these. In a new paper published in the Journal of Clinical Oncology, researchers detail how they studied the number of circulating tumour cells (CTCs) in 101 lung cancer patients before and after one cycle of chemotherapy. The team discovered that patients who had five or more CTCs were much less likely to survive the disease. They believe that by counting CTCs, doctors will be able to monitor how well patients are responding to chemotherapy soon after starting it and so move them on to different treatments if the number of cells rises.

By sniffer dogs

According to new research published in the *European Respiratory Journal*, sniffer dogs could be used for the early detection of lung cancer Researchers from the Schillerhoehe Hospital in Germany were the first to discover that sniffer dogs can reliably detect lung cancer Because current methods of detection are unreliable, scientists have been examining the use of exhaled breath specimens from patients for future screening tests. The method identifies volatile organic compounds (VOCs) that are associated to the presence of cancer. Even though various different technological programs have been developed, this method is still difficult to apply in clinical settings, as it requires patients not to eat and smoke prior to testing. This new study was designed to examine whether sniffer dogs could be used to identify a VOC in the breath of patients. Using dogs with specific training, researchers conducted a study comprising of 220 participants, including lung cancer patients, chronic obstructive pulmonary disease (COPD) patients and healthy volunteers.The researchers conducted a series of tests to evaluate whether the dogs were capable to reliably identify lung cancer compared with healthy volunteers, volunteers with COPD and whether the results were still detected with the presence of tobacco. The result reveled, that the dogs managed to correctly identify 71 samples with lung cancer out of a possible 100 and also successfully detected 372 samples that did not have lung cancer out of a possible 400.The dogs were able to detect lung cancer independently from COPD and tobacco smoke and therefore substantiate the method as a valid indicator for lung cancer that is independent of COPD and also detectable in the presence of tobacco smoke, food odors and drugs.

Treatment

Inhalable nano particles to treat lung cancer in mouse model (Fig :2)

Doxorubicin-loaded nanoparticles (NPs) were incorporated into Inhalable effervescent and

non-effervescent carrier particles using a spray-freeze drying technique[27]. The prepared inhalable powders were tested in a tumor bearing Balb/c mouse model. Control mice were treated with blank inhalable NPs, inhalable lactose powder containing free doxorubicin, and intravenous injections of a suspension of doxorubicin NPs, doxorubicin solution, or saline solution. The survival of treatment groups was plotted with Kaplan-Meier curves.Animals treated with inhalable effervescent nanoparticle powder containing 30µg doxorubicin showed a highly significant improvement in survival compared to all other treatment groups. Mice in control groups treated with doxorubicin solution or doxorubicin NPs as intravenous injection, died in less than 50 days. Inhalable free doxorubicin showed high cardiac toxicity.Pathological samples showed large tumor masses in the lungs of animals not treated or treated with i.v. injections of doxorubicin NPs or doxorubicin solution. The lungs of animals treated with inhalable effervescent doxorubicin NPs showed fewer and much smaller tumors compared to the control groups, as visualized by MRI imaging which confirmed the observed pathology results. The present study demonstrates that inhalable effervescent doxorubicin NPs is an effective way to treat lung cancer. This non-invasive route of administration might change the way lung cancer is treated in the future.

Formulation and in vivo evaluation of effervescent inhalable carrier particles for pulmonary delivery of nanoparticles

The purpose of this study was to evaluate the safety of a new inhalable effervescent carrier preparation containing model nanoparticles. Spray-freeze drying was used to prepare inhalable powders containing butyl cyano acrylate nanoparticles**.** The particle size of the nanoparticles before incorporation into the effervescent carrier and after dissolving the carrier powder was measured using laser light scattering. The particle size distribution of the effervescent carrier aerosol particles was measured using a cascade impactor. The prepared powder was tested in vivo using five Balb/c nude mice**.** The animals were treated with 1 mg of inhalable powder every week for 4 weeks. The body weight and morbidity score of the mice were observed over an 8-week period. The effervescent activity of the inhalable nanoparticle powder was observed when the powder was exposed to humidity. The particle size of the nanoparticles did not change significantly after spray-freeze drying. The mass median aerodynamic diameter (MMAD) of the prepared powder was 4.80 +/- 2.12 microm, which is suitable for lung delivery. The animals that were treated with effervescent powder tolerated the administration without any changes in their morbidity scores. Our pilot study demonstrates that pulmonary nanoparticle delivery via effervescent carrier particles appears safe in the present animal model.

Formulation and cytotoxicity of doxorubicin nanoparticles carried by dry powder aerosol particles

Regional drug delivery via dry powder inhalers offers many advantages in the management of pharmaceutical compounds for the prevention and treatment of respiratory diseases. In the present study, doxorubicin (DOX)-loaded nanoparticles were incorporated as colloidal drug delivery system into inhalable carrier particles using a spray-freeze-drying technique. The cytotoxic effects of free DOX, carrier particles containing blank nanoparticles or DOX-loaded nanoparticles on H460 and A549 lung cancer cells were assessed using a colorimetric XTT cell viability assay.The mean geometric carrier particle size of 10 ± 4 µm was determined using confocal laser scanning microscopy. DOX-loaded nanoparticles had a particle size of 173 ± 43 nm after re-dissolving of the carrier particles. Compared to H460 cells, A549 cells showed less sensitivity to the treatment with free DOX**.** The DOX-nanoparticles showed in both cell lines a higher cytotoxicity at the highest tested concentration compared to the blank nanoparticles and the free DOX. The cell uptake of free DOX and DOX delivered by nanoparticles was confirmed using confocal laser scanning microscopy. This study supports the approach of lung cancer treatment using nanoparticles in dry powder aerosol form.

Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung:

Spray-drying is a common practice of powder preparation for a wide range of drugs. Spray-dried powders can be used to deliver particles to the lungs via a dry powder inhaler (DPI). The present study investigated the feasibility of developing a platform for aerosol delivery of nanoparticles. Lactose was used as the excipient and spray-dried with two different types of nanoparticles: gelatin and polybutylcyanoacrylate nanoparticles. Results showed that some carrier particles were hollow while others had a continuous matrix. Gelatin nanoparticles were incorporated

throughout the matrix and sometimes accumulated at one end of the lactose. Polycyanoacrylate nanoparticles mostly clustered in different spots within the lactose carriers. The mean sizes of both nanoparticle types were characterized at two different times: before they were spray-dried and after they were redissolved from the spray-dried powders. Both nanoparticle types remained in the nano-range size after spray-drying. The mean nanoparticle sizes were increased by approximately 30% after spray-drying, though this increase was statistically significant only for the gelatin nanoparticles. Dispersion of the powder with an in-house passive dry powder inhaler and subsequent cascade impaction measurements showed that incorporation of the nanoparticles did not affect the fine particle fraction (FPF) or mass median aerodynamic diameter (MMAD) of the powders.FPF was approximately 40% while MMAD was 3.0±0.2 μm, indicating the present formulations yield aerosols of a suitable particle size for efficient lung delivery of nanoparticles. The present work demonstrates that nanoparticles can be delivered to the lungs via carrier particles that dissolve after coming in contact with the aqueous environment of the lung epithelium. This opens the way for new drug-targeting strategies using nanoparticles for pulmonary delivery of drugs and diagnostics.

Peptides in the therapeutic delivery of nanoparticles

The most commonly used peptides that have been employed for the cellular delivery of NPs. TAT & TAT-like peptides.The TAT peptide was one of the first cell-penetrating peptides (CPPs) to be described[28-37].Interest in this peptide stemmed from two independent reports demonstrating that the 86-residue transcriptional activator protein Tat (encoded by HIV-1) could be efficiently internalized by cells when present in the surrounding tissue culture media. Subsequent studies to determine the domain responsible for cellular uptake localized the activity to residues 47–57 within the native Tat protein. The corresponding 11-mer peptide sequence (YGRKKRRQRRR) bears six arginines and two lysine residues and these positively charged residues have been identified as the key determinants of cellular uptake as they mediate the initial interactions of the peptide with the negatively charged cell surface. While it has been firmly established that the positively charged residues are responsible for uptake, the exact mechanism of cellular uptake remains somewhat less clear. Indeed, a number been proposed. Evidence exists for two types of endocytosis: classical clathrin-mediated endocytic uptake and caveolae-mediated clathrin-independent endocytosis. Other evidence points to caveolae-mediated endocytosis involving the formation of membrane invaginations composed chiefly of cholesterol and sphingo lipids. Regardless of the ultimate mechanism of internalization, it is clear that electrostatic interactions between the positively charged residues of the TAT peptide and the negatively charged residues of heparan sulfate proteoglycons (and other cell surface receptors) are essential for initial membrane binding followed by uptake. Typically the endocytosed NPs remain sequestered within endocytic vesicles, although in some instances nuclear entry has been noted. The TAT peptide and its derivatives have been used for the cellular delivery.

PULMONARY FIBROSIS

Pulmonary fibrosis is the formation or development of excess fibrous connective tissue (fibrosis) in the lungs. It is also described as "scarring of the lung".[38-40]

Traetment

The immune system is felt to play a central role in the development of many forms of pulmonary fibrosis. The goal of treatment with immune suppressive agents such as corticosteroids is to decrease lung inflammation and subsequent scarring. Responses to treatment are variable. Once scarring has developed, it is permanent. Those whose conditions improve with immune suppressive treatment probably do not have idiopathic pulmonary fibrosis. Pulmonary fibrosis causes decreased oxygen levels in the blood. A decrease in blood oxygen level (hypoxia) can lead to elevated pressure in the pulmonary artery (the vessel that carries blood from the heart to the lungs to receive oxygen), a condition known as pulmonary_hypertension which can in turn lead to failure of the right ventricle of the heart. Therefore, patients with pulmonary fibrosis are frequently treated with supplemental oxygen to prevent pulmonary hypertension. In some cases, new agents used to lower the blood pressure in the pulmonary artery.

TUBERCULOSIS

Tuberculosis, MTB, or TB (short for *tubercle bacillus*) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* [41] Tuberculosis usually attacks the lungs but can also affect

other parts of the body. It is spread through the air when people who have an active MTB infection cough, sneeze, or otherwise transmit their saliva through the air. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progress to active disease, which, if left untreated, kills more than 50% of those infected.

General Diagnosis (Fig : 3)

Tuberculosis is diagnosed definitively by identifying the causative organism (*Mycobacterium tuberculosis*) in a clinical sample (for example, sputum or pus) a tuberculin skin test (Mantoux test),[42] or a, Interferon Gamma Release Assay[43] (IGRA) was also used to diagnosis.Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from *M. tuberculosis*. Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common. Hodgkin's lymphoma, malnutrition, or most notably active tuberculosis disease .The newer interferon release assays (IGRAs) such as T-SPOT.TB and Quanti__FERON-TB Gold In Tube overcome many of these problems. IGRAs are *in vitro* blood tests that are more specific than the skin test. IGRAs detect the release of interferon gamma in response to mycobacteria proteins such as ESAT-6. These are not affected by immunization or environmental mycobacteria, so generate fewer false positive results. There is also evidence that IGRAs are more sensitive than the skin test.

New TB tests have been developed that are fast and accurate. These include polymerase chain reaction assays for the detection of bacterial DNA. One such molecular diagnostics test gives results in 100 minutes and is currently being offered to 116 low- and middle-income countries. Another such test, which was approved by the FDA in 1996, is the amplified mycobacterium tuberculosis direct test (MTD, Gen-Probe). This test yields results in 2.5 to 3.5 hours, and it is highly sensitive and specific when used to test smears positive for acid-fast bacilli (AFB).

Treatment

Nanotechnology in treatment of tuberculosis

Treatments with improved sustained release profiles and bioavailability can increase compliance through reduced drug requirements and there in minimize MDR-TB. The micro-encapsulation of pharmaceutical substances in biodegradable polymers used in controlled drug delivery has seen as an emerging technology. Carrier or delivery systems such as liposomes and microspheres have been developed for the sustained delivery of anti-TB drugs and have found better chemotherapeutic efficacy when investigated in animal models[44-46].The following are among the important technological advantages of nanoparticles as drug carriers: high stability (i.e., long shelf life); high carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix); feasibility of incorporation of both hydrophilic and hydrophobic substances; and feasibility of variable routes of administration, including oral administration and inhalation. These carriers can also be designed to enable controlled (sustained) drug release from the matrix.Indian research group from Postgraduate Institute of Medical Education and Research (India) has reported increased bioavailability and "undetectable bacterial counts in the lungs and spleens of *Mycobacterium tuberculosis*-infected mice" 21 days post-inoculation. Sharma *et al.* (2004)[47], conducted a study to explore lectin-functionalized poly (lactide-co-glycolide) nanoparticles (PLG-NPs) as bio adhesive drug carriers against tuberculosis (TB), in order to reduce the drug dosage frequency of anti-tubercular drugs and thus improve patient compliance in TB chemotherapy.In this study they observed the presence of drugs in plasma for 6–7 days for rifampicin and 13–14 days for isoniazid and pyrazinamide after administration of lectin coated PLG-NPs through the oral/aerosol route. They also observed that upon administration of uncoated PLG-NPs (oral/aerosolized) rifampicin was detectable in plasma for 4–6 days, whereas isoniazid and pyrazinamide were detectable for 8–9 days. All three drugs were present in lungs, liver and spleen for 15 days. Obtaining these results they concluded that WGA-functionalized PLG-NPs could be potential drug carriers for antitubercular drugs through the oral as well as aerosol route for effective TB control.

Present Status of Nanoparticle Research for Treatment of Tuberculosis

Liposomes (Fig : 4)

Liposomes are small spherical vesicles formed of amphiphilic lipids enclosing an aqueous

core. They are widely studied as carrier systems for hydrophilic drugs[48-53].Gentamicin incorporated liposomes were evaluated for antibacterial activity in M. avium infected mouse model. The drug encapsulated liposomes significantly reduced the bacterial count in spleen and liver as compared to free drug. A dose-related reduction in bacterial load was observed, but no sterilization was found .Similar results were reported in literature for second-line antibiotics liposomes. Deol and Khuller[54] developed Stealth liposomes for the targeted delivery of anti-TB drugs to the lung. Liposomes were composed of mixture of phosphatidylcholine, cholesterol, dicetylphosphate, O-steroyl amylopectin and monosialogangliosides / distearylphosphatidylethanolaminepoly (ethylene glycol) 2000. *In vivo* biodistribution after intravenous administration in healthy and tuberculosis infected mice showed pronounced increase in accumulation from 5.1% for contional liposome's to 31% for PEGylated liposomal systems after 30 min. The accumulation extent was mainly associated to the composition of the liposomal vesicles.103 uptake levels in the lungs increased to approximately 40% for the PEGylated nanocarriers when administered to pretreated infected animals only after 30 min. whereas, 30– 50% reduction in uptake was observed for modified liposomes for accumulation in the liver and spleen. Drug-loaded nanocarriers showed a significant decrease in the toxic effects when evaluated for cytotoxicity in peritoneal macrophages compared to free drugs.

Nano emulsions

Nanoemulsion, many times referred as miniemulsions or sub-micronemulsions by dispersing mainly oil in water[55].Thermodynamically stable nanoemulsion (mean particle size of 80.9 nm and polydispersity index of 0.271) of ramipril, were developed for oral administration. *In vitro* drug release showed that drug release till 24 h from nanoemulsion and was highly significant ($p<0.01$) bas compared to marketed capsule formulation and drug suspension. The relative bioavailability of ramipril nanoemulsion to that of conventional capsule was 229.62% and to drug suspension was 539.49 suggesting the use of developed ramipril nanoemulsion for pediatric and geriatric patients

Polymeric nanoparticles

In Polymeric nanoparticles, the drug is attached, entrapped or encapsulated in polymeric core and depending upon the method of preparation, they are called as nanoparticles, nanospheres or nanocapsules .(Fig :6) Polymeric nanoparticles represent an attractive alternative to liposomes. Pandey et al., developed sustained release RIF, INH and PYZ loaded poly (lactideco- glycolide) (PLG) nanoparticles for oral delivery. In mice, the drugs could be detected in the plasma up to 4 days for RIF and 9 days for INH and PYZ; therapeutic concentrations in the tissues were detected till 9 to 11 days after single oral dose administration of nanoparticles whereas free drugs after administration were cleared within 12 to 24 h from the plasma.

Five oral doses every 10 day of nanoparticles were sufficient to achieve complete bacterial clearance from the organs of TB bacillus infected mice, whereas free drugs took 46 doses to get the same results.

Solid lipid nanoparticles (SLN)

Nanoparticles showed similar results when tested in guinea pigs.

In SLN, the drug is mainly entrapped in solid lipid matrix to produce lipid nanoparticles of size range 50-1000 nm and they produced using hot or cold high pressure homogenization technique.[56]. It is noteworthy that the solid lipid nanoparticles display important advantages, such as the composition (physiologic compounds) and the possibility of large-scale production favored by the feasibility to avoid organic solvents in the manufacturing process. A sterilizing effect was achieved after administration of solid lipid nanoparticles. No tubercle bacilli could be detected in the lungs/spleen after seven doses of treatment of infected guinea pigs with drug loaded solid lipid nanoparticles.Pandey[57-60] R., developed RIF, INH and PYZ loaded SLN by using emulsion solvent diffusion technique and tested against experimental tuberculosis.

SLN formulations following a single oral administration to mice maintained therapeutic drug concentrations in plasma till 8 days and in the organs rich in MPS (lungs, liver and spleen) for 10 days as compared to free drugs which were cleared within 1–2 days. In M. tuberculosis H37Rv infected mice, 5 oral doses at every 10^{th} day of drug loaded SLNs were sufficient to completely suppress bacterial load in the lungs/spleen whereas free drug required administration of 46 daily oral doses to get same effect. SLN incorporated antitubercular drug significantly reduced the dosing frequency and improved bioavailability[61].Nano suspensions Nano suspensions, poor water soluble drugs are dispersed in aqueous phase containing

stabilizing agent. Presently more than 8 candidates are in clinical trials . Clofazimine was formulated as a nanosuspension (385 nm) and administered to mice intravenously. It resulted in a considerable reduction of bacterial loads in the liver (72.5 mg/kg tissue), spleen (81.4 mg/kg tissue), and lungs (35.0 mg/kg tissue) of mice infected with M. avium when compared with pharmacokinetic data, drug concentrations in these organs reached high concentrations, well in excess of the minimal inhibitory concentration for most M. avium strains.The effects of clofazimine nanocrystals were comparable to those of the liposomal formulation used as a control in this study. This study was specially planned to overcome the poor solubility and toxicity.(Fig :5)

Micelles

Micelles are submicroscopic aggregates (20-80 nm) of surfactant molecules resulting in liquid colloid[62-64].They can be used for development of drug depot system. The sol–gel transition temperature was optimized by selecting optimized GA/CL ratio and length of the hydrophobic segments.RIF sustained release was obtained over 32 days from 25% gel matrix. INH-poly (ethyleneglycol)–poly (aspartic acid) conjugates were studied for sustain release of the drug.

A 5.6-fold increase in anti-tuberculosis activity against M. tuberculosis was found for micelle-forming prodrug as compared to the free drug . Similar attempts were made to incorporate PYZ and RIF in micelles (<100 nm) aiming to minimize renal filtration and prolonging mean residence times in the blood stream with improved antimicrobial activity.

Niosomes

Niosomes has similarity to that of liposomes and they are mainly composed of non-ionic surfactant and with or without incorporation of lipids[65].

Niosomes (1–2 μm) were prepared using sorbitan esters (Span 20, 40, 60, 80 and 85) and cholesterol in a 50:50 percent mol fraction ratio. They showed increase in entrapment efficiency with increase in hydrophobicity of the surfactant. *In vivo* biodistribution showed, higher RIF concentrations in thoracic lymph nodes via the intraperitoneal route (46.2% of the administered dose) for Niosomal formulations as compared to free drug (13.1%). These findings suggested that compartmentalization of the drug took place in the lymphous tissue.

Dendrimers

Dendrimers represent a novel class of structurally controlled three dimensional macromolecules that radiate from a central core and are mainly derived from a branches-upon-branches structural design. Dendrimers are well defined, highly branched macromolecules. Kumar et al. developed mannosylated fifth generation (5G) PPI dendrimeric nanoparticles for delivery of RIF to macrophages. Drug encapsulations mainly depend on hydrophobic interactions and hydrogen bonding contributing to the physical binding of the drug to the core.

BRONCHIAL ASTHMA

Asthma (from the Greek άσθμα, *asthma*, "panting") is the common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm.

Treatment

Titanium and gold nanoparticles in asthma

In the current issue of the European Respiratory Journal, report for the first time, on the effects of two ENMs, titanium dioxide (TiO2) and gold (Au) NPs, in a murine model of toluene-2,4-diisocyanate-induced asthma.NPs were administered by oro pharyngeal aspiration after repeated dermal sensitization to diisocyanate. The day after NP administration, animals were oro pharyngeal challenged with diisocyanate, and the next day, airway reactivity to metacholine was measured and bronchoalveolar lavage (BAL) inflammation and lung histological features were analyzed. The dose of NPs, based on the current time-weighted average (TWA) values for a single shift in TiO2 level, was 16 mg for a mouse weighing 20 g.The main results of the study can be classified into three groups: 1) effects of diisocyanate sensitization and challenge not modified by either one of the two NPs (increase in matrix metalloproteinase-9 in BAL, increase in serum immunoglobulin E levels, increase in BAL eosinophils, and increase in airway hyper responsiveness (AHR; only in the case of TiO2); 2) effects

Induced by both NPs in diisocyanate-sensitised and –challenged animals (increase in macrophage inflammatory protein-2 in BAL, increase in macrophages and neutrophils in BAL, lung macrophages infiltration); and 3) effects induced only by Au NPs in diisocyanate-sensitised and -challenged animals (potentiation of the increase in AHR, diminished tumour necrosis

Factor (TNF) secretion in BAL, and lung tissue edema and epithelial damage). The last two types of effects of NPs were not observed in animals not exposed to diisocyanate. The last two types of effects were not observed in animals not exposed to diisocyanate.Therefore, both NPs modified some features of the diisocyanate-induced asthma model: TiO2 NPs induced lung macrophage and neutrophil recruitment without affecting AHR, whereas Au NPs induced these effects along with lung tissue edema, epithelial damage and potentiation of AHR. Neither NP induced biological responses in non sensitised and challenged animals. Taken together, these results are very interesting and open new areas of research in the field of nano toxicology

Nanoparticles and their Applications are summarized in table 1

CONCLUSION

In the present article the use of nano particle for the treatment of several major pulmonary diseases like Lung cancer Tuberculosis Pulmonary fibrosis and Bronchial asthma were discussed. The nano particles are highly advantageous for treatment of pulmonary diseases because of the ease of nano particle penetration in to pulmonary cavity and its of production along with targeting of nano particle to specific site. Inhalable doxorubicin nano particle is an non invasive approach to treat lung cancer provides a further scope for the study of nano particle use on lung cancer. There is a chance of further investigation on the use of nano particles for several major pulmonary diseases.

Fig. 1: New technique for diagnosis of lung cancer . It involves counting the no.of tumor cells in blood sample after chemotherapy

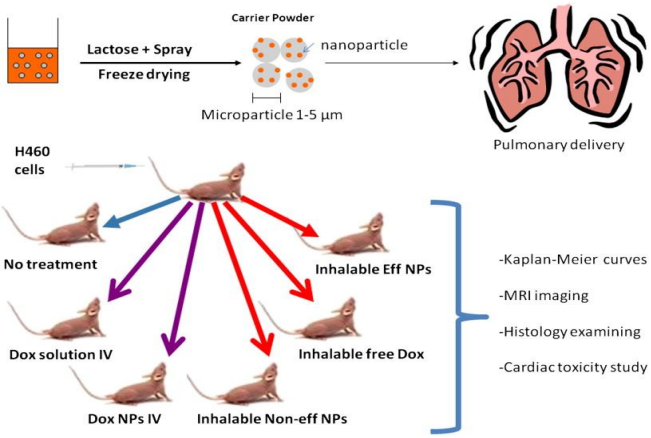

Fig. 2: Inhalable nano particles to treat lung cancer in mouse model

Fig. 3: tuberculin test sample

Table 1:

Property	Application
Optical	Anti-reflection coatings. Tailored refractive index of surfaces. Light based sensors for cancer diagnosis.
Magnetic	Increased density storage media. Nanomagnetic particles to create improved detail and contrast in MRI images.
Thermal	Enhance heat transfer from solar collectors to storage tanks. Improve efficiency of coolants in transformers.
Mechanical	Improved wear resistance. New anti-corrosion properties. New structural materials, composites, stronger and lighter.
Electronic	High performance and smaller components, e.g, capacitors for small consumer devices such as mobile phones. Displays that is cheaper, larger, brighter, and more efficient. High conductivity materials.
Energy	High energy density and more durable batteries. Hydrogen storage applications using metal nanoclusters. Electrocatalysts for high efficiency fuel cells. Renewable energy, ultra high performance solar cells. Catalysts for combustion engines to improve efficiency, hence economy.
Environmental	Clean up of soil contamination and pollution, e.g. oil. Biodegradable polymers. Aids for germination. Treatment of industrial emissions. More efficient and effective water filtration.
Surfaces	Dissolution rates of materials are highly size dependant. Activity of catalysts. Coatings for self cleaning surfaces, Pilkington's glass for example.
Personal care	Effective clear inorganic sunscreens

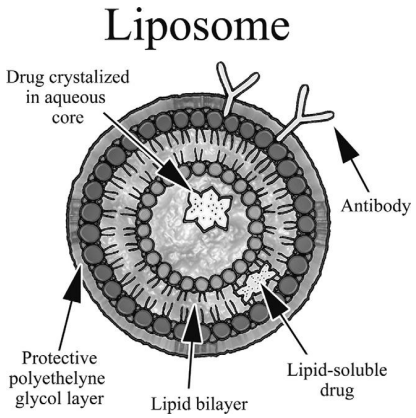

Fig. 4: liposome action

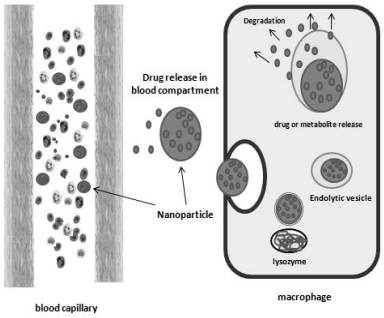

Fig. 5: Mechanism by which nanoparticles encapsulated drug can be released in infected macrophages for anti tubercular treatment

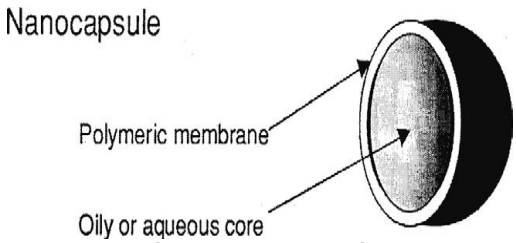

Fig. 6: nano capsule

ABBREVATIONS

VATS- videoscopic assisted thracoscopic wedge biopsy
MMAD-mass median aero dynamic diameter
FPF-fine particle fraction
DPI-dry powder inhaler
COPD-chronic obstructive pulmonary disease
VOCS-volatile organic compound
CTS-circulating tumor cells

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