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Review Article

Engineered Nanocarriers: An Emerging Tool in Therapeutics and Diagnostics

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ABSTRACT

In present era nanoparticles have emerged as an efficient and promising tool in therapeutics and diagnostics. Nanotechnology is a multidisciplinary field it merges basic sciences and applied disciplines like biophysics, molecular biology and bioengineering. Nanotechnology has created impact in various fields of medicine comprising neurology, oncology, immunology, cardiology, endocrinology. Nanotechnology presents revolutionary opportunities for diagnosis and therapy of many diseases. The nanoparticles capable of diagnosis, drug delivery and monitoring of therapeutic response are expected to play a significant role in emergence of era of personalized medicine.

Keywords: Nanoparticles, Nanotechnology, Bioengineering, Diagnostics, Therapeutics, Drug delivery

INTRODUCTION

Nanocarrier engineering can be defined as technologies for making nanocarriers of therapeutic and imaging/diagnostic agents, nanoelectric biosensors, nanodevices with nanostructures. Nanocarriers in biomedical field are often referred to as particles with a dimension of few nanometers to 1000 nanometers unlike the definition of core nanotechnology in which nano means 1-100 nm in one dimension. Many techniques for making nanomaterials such as chemical synthesis, self assembly and coating are employed to prepare nanocarriers for delivering therapeutic and diagnostic agents.

Nanomedicine is the application of nanotechnology in the clinical field. There are two major medical applications of nanotechnology: medical imaging/diagnosis and therapeutic delivery. The latter faces more challenges due to strict requirement for therapeutic purpose. To achieve maximal therapeutic benefits the carrier must be designed so that the drugs can be delivered to the target sites at the right time with an optimal level and appropriate release kinetics.

The various pharmaceutical nanocarriers includes carbon nanotubes, quantum dots, dendrimers, polymeric nanoparticles, liposomes, polymeric micelles, polymeric drug conjugate, polyplexes/lipopolyplexes.[1]

ENGINEERING OF PHARMACEUTICAL NANOCARRIERS

Manipulations in size and surface of nanocarriers mentioned formerly by biocompatible polymers, hydrophilic polymers and some site specific ligands render them efficient delivery vehicles. These manipulations prevent their aggregation, opsonization and increase their specificity towards target. These manipulations are known as nanoparticle engineering as described below:

Modifying natural nanoparticles

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PHARMATUTOR
PHARMACY INFOPEDIA
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There are a variety of natural nanoparticles such as lipoproteins, viruses and ferritin. These natural nanoparticles can be loaded with contrast generating materials such as gallidium (Gd^{+3}) or manganese ion. These ions can be incorporated in phospholipid layer of lipoproteins and can be utilized for fluorescence imaging or unstable nuclei for positron emitting tomography.[2]

Organic monolayer and biomolecule coating of nanoparticles

To improve the stability and to prevent aggregation of nanoparticles synthetic organic ligands can be used. The synthetic organic ligands can be introduced on nanoparticles by chemical reactions. One of the popular methods includes reduction of chloroauric acid ($HAuCl_4$) by citrate producing gold nanoparticles with 20 nanometer diameter. In this approach citric acid acts as both reducing agent and stabilizer. Another method includes transfer of $AuCl_4^-$ to organic phase by surfactant tetraoctylammonium bromide followed by reduction using sodium borohydride ($NaBH_4$) in presence of alkanethiols.[3,4]

Consecutively nanoparticles can also be coated with biomolecules such as oligonucleotides, carbohydrates, lipids, peptides and proteins to minimize or avoid cytotoxicity. These biomolecules can be conjugated to nanoparticles by various techniques such as thiolated double stranded DNA can be directly conjugated to gold nanoparticles using ligase dependent strategy.[5,6]

For achieving high specificity the nanocarriers which may be of gold, silica, carbon nanotubes, magnetic nanoparticles, liposomes and micelles can be conjugated with aptamers. Aptamers are single-stranded oligonucleotides, DNA or RNA, with the ability to bind to non-nucleic acid target molecules, such as peptides, proteins, drugs, organic and inorganic molecules, or even whole cells, with high affinity and specificity. They are isolatedand chemically synthesized from 10^{12} to 10^{15} combinatorial oligonucleotide libraries by a process known as in vitro systematic evolution of ligands by exponential enrichment (SELEX). Over multiple rounds of selection (generally 6–18 rounds), quite large populations (>1013 different sequences) can be sieved, and the few nucleic acid species with specificity to the target can be isolated.[7,8,9,10,11]

Molecular self assembly

Molecular self assembly includes spontaneous organization of individual molecules into structurally defined stable arrangements through programmed non-covalent interactions such as hydrogen bonds, vander Walls forces, hydrophobic interactions, electrostatic interactions. This technique has been employed for creating nanofibres from small building blocks such as peptides and nucleic acids.[12,13]

Electrospinning

Electrospinning technique is also used primarily for production of nanofibre scaffolds. The electrospun nanofibre scaffold can be produced from natural macromolecules such as chitosan,[14] silk fibroin[15] and collagen[16] or from synthetic biodegradable polymers such as polyglycolic acid,[17] polylactic acid[18] and their co-polymers.[19] The electrospinning assembly includes a polymer solution or melt reservoir, grounded collector and a high voltage electric field in between. When the voltage is high enough to overcome the surface tension of the polymer solution or melt, a charged jet is generated towards the grounded collector, along which the solvent evaporates and melt solidifies to form solid state thin fibres.[20,21,22]

Phase separation

Phase separation is a process in which a homogeneous multicomponent system tends to separate into multiple phases to lower system free energy. Phase separation can be initiated

PHARMATUTOR
PHARMACY INFOPEDIA
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thermally or by nonsolvent addition, latter leads to formation of polymer rich and polymer lean phases. There are two cases for thermally induced phase separation firstly, if the solvent crystallization temperature is higher than the phase separation temperature solid-liquid phase separation occurs, where the solvent crystallizes to form pore shape after solvent sublimation. Secondly, if the solvent crystallization temperature is lower than the phase separation temperature used, a liquid-liquid phase separation takes place as the temperature of the solution is decreased. A thermally induced phase separation process generally involves five steps: polymer dissolution, liquid-liquid phase separation and gelation, solvent extraction, freezing and freeze drying. For example, poly(L-lacticacid) (PLLA) is dissolved in a selected solvent and thermally inducedto phase separate and gelwhen the temperature is decreased. The solvent of choice should have a low crystallization temperature to allow liquid–liquid phase separation, e.g., tetrahydrofuran, tetrahydrofuran–methanol, dioxane–methanol, and dioxane–pyridine.[23,24]

Co-precipitation

This technique is generally employed for production of metallic nanoparticles such as iron oxide nanoparticles. The aqueous solution of iron oxide nanaoparticles is prepared by co-precipitating Fe(II) and Fe(III) precursors. Hydrophilic polymer such as dextran, polyvinyl pyrrolidone during the particle formation process to ensure colloidal suspendability which passivate the nanocrystal surface and prevent particle aggregation.[25]

Programmed packaging

Programmed packaging is an innovative and novel concept for prejudicing the fate of nanoparticles. This concept involves three components: a programme for overcoming the barriers, the design of functional devices and their three dimensional assignment, the use of nanotechnology to assemble all devices into nano-sized structure. These nanocarriers have enhanced permeation and retention as well as specificity regarding target site.[26,27,28]

Hydrosol production by anti-solvent precipitation

Precipitation generally consists of following main steps: chemical reaction (and the subsequent supersaturation), nucleation, solute diffusion and particle growth. Anti-solvent precipitation can be employed for production of pharmaceutical hydrosols which are aqueous nanosuspensions of poorly water soluble drugs. On laboratory scale this can be achieved by simply mixing the ingredients in a beaker by the aid of magnetic stirrer at optimal experimental conditions. Three major steps are involved in this process firstly dissolution of the macromolecule in a suitable solvent, usually water; secondly precipitation of the macromolecule by adding an alcoholic desolvating agent or the aqueous solution containing multivalent cations like Ca^{+2}, SO_4^{2-} to the solution by the aid of burette to the magnetically stirred macromolecular solution; and thirdly addition of a hardening agent to trigger cross-linking of the macromolecule and fixing the nanoparticle matrix. The drug is dissolved in the alcoholic desolvating agent in step second before adding to the excipient solution.[29]

High gravity controlled nanoprecipitation technology is the most efficient and popular method at industrial scale.[30]

Flash nanoprecipitation

Flash nanoprecipitation can be achieved by two techniques i.e. confined liquid impinging jets and multi-inlet vortex mixer. In confined liquid impinging jets, jets of antisolvent approaches a small chamber through two opposing nozzles, precipitation occurs in a region of extreme turbulence and intense mixing created by a jet of drug solution impinging a jet of antisolvent.

PHARMATUTOR
PHARMACY INFOPEDIA
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In this process the controlling factor is drug concentration and the velocity of the two impinging jets to prevent unbalanced flow and mixing. Particle size was found to decrease with increasing jet stream speed or drug concentration. The volume ratio of drug solution to anti-solvent is also expected to affect the precipitation process. Confined liquid impinging jets was applied to the precipitation of pharmaceutical compounds including salbutamol sulphate, ibuprofen, cyclosporine A, and amphotericin B. In this process the precipitation must be achieved as soon as the mixing takes place as this process is single pass process and in this mixing can be achieved only once.[31,32, 33, 34]

The multi inlet vortex mixer is a four stream device which provides the capability of controlling the supersaturation and solvent composition by varying the content and velocity of individual streams. The multi inlet vortex mixer assembly allows mixing of streams of unequal volumetric flows. This process avoids the constraints on the flow requirement of the liquid jets as in confined liquid impinging jet technology.[35,36]

Supercritical fluid technology

This technology eliminates the need of drying step for solvent which is necessary in other production techniques. this technology utilizes the the unique physical properties of supercritical fluid, i.e. low density and viscosity along with high diffusivity to attain rapid micro-mixing for precipitation. The most common supercritical fluid employed is CO_2. Supercritical CO_2 has critical temperature 31.1°C and pressure 72.9 atm.[37]

One of the process employing this technology is rapid expansion of supercritical solution. In this process hydrophobic drugs came out from a capillary tube into the ambient environment results in formation of fine particles.

Another process is supercritical antisolvent process, this process is generally employed for drugs that do not dissolve sufficiently in supercritical CO_2. In this case supercritical CO_2 acts as an antisolvent to precipitate the drugs from their polar solution. This is achieved either by passing the supercritical fluid through the drug solution or by introducing the drug solution in the supercritical fluid; by using capillary nozzles or by pressure differential atomizer.[38]

Sonoprecipitation

Sonoprecipitation is the the precipitation achieved by the aid of ultrasonic waves. The underlying principle behind this technique is the creation of voids followed by collapse of same releasing shock waves.Sonoprecipitation setup can be relatively simple, comprising an ultrasound probe in a mechanically stirred reaction tank where the anti-solvent is mixed with the drug solution to precipitate the fine drug particles. The ultrasound frequency is crucial and 20–25 kHz (or higher) was reported suitable for the process. Advantages associated with sonoprecipitation includes faster and more uniform nucleation throughout the sonicated volume leading to smaller and uniform sized particles and reduction in agglomeration by reducing the contact between the particles and controlling the number of nuclei.[39]

Controlled evaporation of droplets

This production strategy includes three techniques i.e. spray drying, aerosol flow reactor method and electrospraying.

In spray drying, a drug solution is atomised to fine droplets which are evaporated in a warm air current to form dry particles. The drug solution may be of aqueous or organic nature. For production of nanoparticles Buchi Nano Spray Dryer B-90 in which piezoelectrically driven vibration mesh atomizer is used which produces fine droplets which are then collected by electrostatic collector, in which conventional spray dryer fails.[40,41]

PHARMATUTOR
PHARMACY INFOPEDIA
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In aerosol flow reactor method the solution is atomized with the aid of ultrasonic or collision-type air jet nebulizer. The droplets thus produced are suspended in a carrier gas are then fed into a turbular flow reactor housed in a constant temperature oven for evaporation. In this process the temperature history and residence time is controllable, since the feed rate and temperature can be adjusted.[42]

In electrospraying liquid flowing out from a capillary under the influence of an electric field will acquire charges close to the Rayleigh limit (the maximum amount of charge a droplet can carry) which overcome the surface tension causing the liquid jet to breakup into droplets. The liquid coupled with a drying gas will evaporate to form dry nanoparticles. This method can be employed for liquids having surface tension below 50 mN/m.[43]

ROLE OF NANOPARTICLES IN THERAPEUTICS

Oncology

Cancer is a disease with a very high mortality rate worldwide. It is a fatal disease, but can be cured if detected at early stage, and then treated in a proper way. Cancer occurs due to mutation in the DNA by mutagenic agents or by viral infection. In the past few years, the applications of nanotechnology have been realized in clinical laboratory analysis, imaging and therapeutics. In cancer therapy, targeted delivery in a localized way is one of the key challenges. Nanotechnology has the potential to play a significant role to achieve such a goal. In cancer therapeutics, nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage of the drugs with better specificity, low toxicities, and better bioavailability.[44] Since the nanoparticles are very small in size (hundred to thousand times smaller than the human cell) therefore nanoscale devices (50 nm or less) can enter cells and the organelles easily and interact with DNA, proteins, enzymes and cell receptors extracellularly and intracellularly. Again, smaller nanoparticles (≤20 nm) can move out of blood vessels and circulate throughout the body. Since biological processes, including events that lead to cancer, occur at the nanoscale and inside the cells, nanotechnology offers tools that may be able to detect disease in a very small volume of cells or tissue.[45] For example a multifunctional envelope type nanodevice can be used for gene delivery to tumours. The ideal multifunctional envelope type nanodevice (MEND) consist of a nucleic acid core condensed or complexed with a polycation and a lipid envelope structure equipped with the various functional devices, such as polyethylene glycol, specific target ligands and cell-penetrating peptides. R8-MEND was applied *in vivo* topically for delivery of gene to hair follicles. The R8-MEND formulation result in an extension of hair growth period.[46]

Opthalmology

There are a number of challenges associated with ocular drug delivery due to the innate protective characteristic property of eye to protect against the entry of foreign compounds. The major problem associated with ocular delivery is is to maintain the appropriate drug concentration at the site of action for optimal time period to elicit maximum pharmacological response. The nanocarriers have proved themselves excellent carrier for ocular drug delivery as they protect the encapsulated material and also offers the opportunity to control drug delivery.[47,48,49] To improve stability and interaction with mucosa of eye the nanocarriers are coated with hydrophilic coating by hydrophilic materials such as chitosan and polyethylene glycol; or hydrophilic materials in combination with cyclodextrins or hyaluronic acid. Examples include Cationorm® (Novagali Pharma, France), is a cationic emulsion used to treat dry eye syndrome; Refresh dry eye therapy developed by Allergen is an anionic emulsion used for lubrication,

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Durezol™ developed by Sirion Therapeutics contains Difluprednate, is an anionic emulsion used to treat pain and inflammation associated with ocular surgery.[49]

Neurology

Delivery of drug to central nervous system (CNS) is a great challenge for pharmacy personnel since the drug has to pass through the blood brain barrier, blood cerebral spinal fluid barrier, and blood tumour barrier (in case of delivery of drug to CNS for treatment of brain tumour). Engineered nanocarriers such as linear polymers, hyperbranched polymers,dendrimers, liposomes and micelles have proved themselves successful in overcoming these limitations. The various mechanisms for nanoparticle mediated CNS delivery include temporarydisruption of the BBB to increase permeability, the use of impregnatedpolymers for local drug administration, convection-enhanceddelivery (CED), and intranasal delivery. Generally nanoparticles are employed to treat brain tumours and in some cases of brain infection. One of the gold standard of intra-cerebral drug therapy includes Gliadel® consists of bischloroethylnitrosourea(carmustine) polymer wafers that are placedin the resection cavity after tumor excision.Clinical trialshave indicated that Gliadel® as a successful adjunct to surgery andradiation increasing survival of glioblastoma multiforme (is a devastating form ofcancer that appears rapidly without much warning of prior symptomsor antecedent lower grade pathology) patients up to two months.[50,51]

Orthopaedics

Bone fracture healing engages both intramembranous and endochondralossification processes, with the latter involving cartilaginouscallus formation. The callus formation is dependent on the recruitmentof progenitor cells from the surrounding tissues, and the formed callusundergoes vascularization, calcification and remodeling into normalbone restoring biomechanical properties. A nanofibre biomimetic scaffold can be constructed to provide temporaryphysical support before the neo-tissue takes over, which could be accomplishedby using biodegradable materials. The surface architecture and chemistry of the scaffold canbe engineered to encourage its positive interactions with cells. Collagen is the major organic component of the bone extracellular matrix, which is present in the form of a fibrous network with fiberdiameters ranging from 50 to 500 nm. It has been found by various studies that collagen fibers promoted osteogenesis. Therefore, scaffoldswith nanofibrous architecture were developed to mimicthe structural features and hopefully the pro-osteogenic properties of collagenous extracellular matrix of the bone. These scaffolds were indeedfound to enhance osteogenesis. Various bioactive agents required for osteogenesis can be delivered through this nanofibre scaffolds in a three dimensional controlled manner. Nanofibres also eliminates the risk of graft rejection and infection associated with allografts and problems linked with permanent metallic implants such as stress shielding, infection and chronic pain.[52,53,54]

Immunology

Nanocarriers can be used as vaccine adjuvants due to their unique properties. There are a number of advantages associated with using nanocarriers as vaccine adjuvants. Nanocarriers are the only adjuvants that can effectively increase the amount of antigen reaching systemic circulation, also nanocarriers can control the release of antigen over prolonged period of time which in result determine the immune response. Nanocarriers can also perform other function along with the primary delivery of antigen which includes immunomodulation or immunostimulation. Examples include Synthetic Biomimetic Supramolecular Biovector (SMBV ™) is

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

aproprietary technology developed by the French company BiovectorTherapeutics S.A. and is particularly aimed at nasal vaccination.SMBV™
Carriers are comprised of a polysaccharide core surrounded by aliposome membrane. SMBV™ are spherical and have structures comparable to virus. SMBV™can be easily formulated in the form of sprays that can distribute the vector in the nasal cavity.[55,56]

Acquired Immuno Deficiency Syndrome (AIDS)
The lack of effective vaccines against pathogensthat cause sexually transmitted diseases (STDs) has stimulated greatinterest in the development of topical microbicides as one of the means ofcurbing the epidemic of STDs. Microbicides are compounds designedfor vaginal (and possibly rectal) administration that are envisaged toput safe, affordable and accessible protection against Human Immunodeficiency Virus (HIV). Microbicides are designed to inhibit HIV infection by directlyinactivating the virus or interrupting its attachment, entry, orreplication. It has been found that the efficacy ofnanoscale systems lies in their comparable size to proteins, and thepresentation of multiple protein-binding ligands that may be effectiveat disrupting protein–protein interactions that drive disease pathogenesis. Examples include SPL 2923 (antiviral dendrimer compound) which contain PAMAM branching unit and a core of ammonia and surface of naphthalenedisulfonic acid groups are attached by athiourea linker; inhibits reverse transcriptase, integrase and HIV attachment/fusion.[57,58]

Malaria
Malaria is a protozoal disease caused by four species of genus *Plasmodium* i.e. *Plasmodiumfalciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale.* These protozoans are transmitted by bite of female mosquito vector of *Anopheles* genus. As there are a lot of side effects of combination therapy for malaria and also poor patient compliance due to high cost and lot of drug interactions. Thedevelopment of drug resistance bymalaria parasitesmay also be due tothe use of ineffective pharmaceutical dosage forms of antimalarials. Thus there is need of an effective technique for overcoming these drawbacks. Thus nanotechnology serves as better option by targeting drugs specifically to their site of action, furthermore nanotechnology has the potential to restore the use of oldand toxic drugs bymodifying their biodistribution and reducing toxicity. The aimof using nanocarriers as drug delivery systems is to promotedrug or vaccine protection against extracellular degradation, to improveselectivity in relation to the target, to reduce the frequency ofadministration and the duration of the treatment and to improve thepharmacokinetic profile of the drug. Also long circulating nanocarriers improve the bioavailability and reduce the dose required due to enhanced selectivity. The most important property of a nanocarrier in the context ofmalaria is the ability to remain in the blood stream for a long period oftime in order to improve the interaction with infected red blood cells (RBCs) and parasite membranes. Other useful properties of nanocarriers include protection of unstable drugs, cell-adhesion properties, and the abilityto be surface-modified by conjugation of specific ligands. In case of cerebral malaria colloidal nanocarriers are used that fit intravenous administration. Two main strategies are used for targeting the antimalarial drugs to hepatocytes and erythrocytes, is active and passive targeting. Conventional nanocarriers such as liposomes can be used for passive targeting, whereas for active targeting surface modified nanocarriers such as PEGylated nanocarriers are used. Recently an oil and water nanoemulsion prepared with Miglyol® and used to encapsulate primaquine for oral administration. A self

PHARMATUTOR
PHARMACY INFOPEDIA
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microemulsifying drug delivery system of artemether has been prepared which has significantly improved the antimalarial activity of artemether against *P. berghei* infected mice.[59,60]

Tuberculosis

Tubeculosis (TB) is the disease caused by *Mycobacterium tuberculi* which affects respiratory system. After AIDS it is the second most deadly disease all over the world. It is estimated that almost 30% of the global population is infected with the *Mycobacterium tuberculi.* It is a communicable disease which spreads by droplet infection. TB is often associated with drug resistance and multi drug resistance (MDR-TB) is very difficult to treat. Even though TB appears as achronic disease with relatively slow progression, multi-resistantstrains can kill immune-compromised patients in extremely shortperiods of time. Also the toxicity and low solubility of anti-tubercular drugs needs an innovative drug delivery system for the treatment of TB. Thus nanotechnology offers the best alternative to conventional dosage form. A nanocrystalline suspension of clofazimine has been developed which improves the solubility of clofazimine as well as reduces its toxicity. Currently continuous efforts are in progress to develop nanocarriers for safe and effective treatment of TB.[61,62]

ROLE OF NANOPARTICLES IN DIAGNOSTICS/IMAGING

Contrast agents for medical imaging

Nanoparticles can be very useful as contrast generating agents as various advantages associated with them such as improved contrast, high payload carrying capacity, long circulation time and the ease of including multiple properties. In magnetic resonance imaging (MRI) the contrast generating materials should be of supermagnetic or paramagnetic nature. Thus MR-active nanoparticles are generally labeled with Gd^{+3} or contain iron oxide core.[63,64] For fluorescence based imaging techniques quantum dots possess excellent properties. Furthermore on the basis of specificity of nanoparticles they can be used as contrast media for certain diseases such as low density lipoproteins (LDL) can be incorporated with the contrast generating materials to detect cancer as LDL receptor is over expressed in some type of cancer. Contrast generating atoms, unstable nuclei like ^{123}I (for MRI) and fluorophores (for fluorescence imaging techniques) can be attached to protein constituent of lipoproteins.[65]

Virusesmay be modified to carry contrast within their cavity, at the interfaceof their subunits and on their outer faces. The shells of viruses without nucleic acid is called capsid, for many viruses this capsid form is stable and it is these non-infectious forms that can be used as contrast agents. The cowpea chlorotic mottle virus (CCMV) was the first virus to be adopted as MRI contrast agent. This virus contains 180 metal binding sites between its protein subunits which normally binds calcium ions. From these sites some of the calcium ions are replaced by Gd^{+3} ions generating a contrast agent of very high relaxivity, where relaxivity is a measure of contrast generating efficacy.[66]

Aptamer nanomaterial conjugates in diagnostics

For use of nanocarriers as clinical probes it is necessary for them to possess target recognition capability, this can be achieved by functionalizing the nanocarriers with biomolecules, such as deoxyribonucleic acid (DNA). Aptamers are functionalized DNA molecules which can be considered as nucleic acid analogue of antibodies. Aptamers possess high binding affinity and specificity towards a wide range of targets such as viruses, small molecules like nucleotides to macromolecules like proteins and cell.[67]

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Quantum dots (QD) or semiconductor nanoparticles are fluorescent nanomaterials with unique optical properties. As compared to organic fluorescent dyes, quatum dots are more photostable and the wavelength of emitted light can be controlled by changing their size and composition of materials. QDs functionalized with DNA have been used for thedetection of DNA and real time monitoring of hybridization procedure. The first aptamer-QD conjugate was based on detection of thrombin. In this the QDs were functionalized with thrombin aptamers and these aptamers are conjugated with complementary DNA with quencher at the end. In the absence of thrombin the fluorescent signal from QDs was quenched due to charge transfer from QDs to quencher, but the presence of thrombin leads to release of complementary DNA and the quenching of signal do not occur. It was recently reported that carbon nanotubes (CNT) also havefluorescence in the near-IR (near-infra red) rangewhich is advantageous for cell imagingby avoiding the high background fluorescence fromthe organelles in thecells.[68]

For colorimetric detection novel metallic nanoparticles such as gold and silver can be employed. Gold nanoparticles have very high extinction coefficient, making their colors distinguishablewithout any instrument at only a few nanomolar concentration. Dispersed gold nanoparticles smaller than 100 nm in solution originally have reddish color. When gold nanoparticles aggregate, their color changes from red toblue due to a shift of their surface plasmon resonance to a higherwavelength. So aptamers can be incorporated in them for fluorescent reporter.[69]

Nanocarrier based diagnostics for infectious diseases

Nanocarriers can be used to construct sensors for diagnosis of infectious disease. These sensors includes nanoparticle labels in immunochromatographic tests (ICT) assays, nanoparticle aggregation assays, nanoparticle labels of whole pathogens.

In immunochromatographic tests gold nanoparticles can serve as contrast agents in lateral flow tests which is visible to naked eye. Example is malarial test strip which gives fast results even with low pathogen count.[70]

In nanoparticle aggregation assays the nanoparticles which have strong optical absorption such as gold and silver can be used, which on aggregation shows red shift providing a convenient optical signal. These interaction strategies rely on interaction between nanostructure-bound antibodies and the target molecule.[71]

Direct labeling of pathogen is also useful in detecton of infectious disease. For example Lieber and co-workers used boron-doped silica nanowires to detectinfluenza A. In this study, the authors attached an antibody specific tothe virus to the nanowires and analyzed the change in nanowireconductivity after antigen–antibody interaction.[72]

CONCLUSION

Nanoparticles are extremely promising delivery systems and constitutean extraordinary field of research at the interface betweenchemistry, biophysics, biochemistry, molecular biology, pharmacyand medicine. Their characterization is complicated because of theirmulticomponent formulation, their macromolecular structures andthe rapid exchanges that occur with their changing microenvironmentwhen they are injected in vivo.However, the amount of work currently underway is astonishing,and nanoparticles will abundantly and rapidly enter the routine formulationof many drugs and as diagnostic aids in the next few years. Several passive, stealthnanoparticles have already been successfully used in the clinic for theimproved formulation of highly toxic drugs.

These nanotechnology innovations applied to diagnostics arepromising with immense

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

humanitarian benefits. However, whenapplying these innovations to developing countries or low resourcesettings, the user requirement needs understanding. A nanotechnologybased TB diagnostic kit, designed by the Central ScientificInstruments Organization of India and currently in the clinical trialphase, does not require skilled technicians for use and offersefficiency, portability, user-friendliness and availability for use for aslittle as 30 rupees.

Besides all these active targeting of nanoparticles is an issue, and this technology isnot ready yet. The generation of highly sophisticated particles with coordinatedand multifunctional properties should be obtained. Thus, the true challenge is to define a simple, robust, safeand reproducible method to produce complicated nanocarriers.

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PHARMATUTOR
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