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Review Article

NANOTECHNOLOGY: A SAFE AND EFFECTIVE DRUG DELIVERY SYSTEM

NILESH JAIN*[1], RUCHI JAIN[1], NAVNEET THAKUR[1], BRHAM PRAKSH GUPTA[1], DEEPAK KUMAR JAIN[2], JEETENDRA BANVEER[1], SURENDRA JAIN[1]

[1]Sagar Institute of Research and Technology-Pharmacy, Bypass Road, Bhopal – 462036, MP, India. E-mail: nilujain01@yahoo.co.in
[2]Truba Institute of Pharmacy, Bypass Road, Bhopal, MP – 462 036, India.

ABSTRACT

Nanotechnology is relatively new, and although the full scope of contributions of these technological advances in the field of human health care remains unexplored, recent advances suggest that nanotechnology will have a profound impact on disease prevention, diagnosis, and treatment. Nanotechnology based delivery system would allow faster drug absorption, controlled dosage release into the human body and would have other unique properties of minimizing side-effects by eliminating requirement of co-solvent as used in conventional dosage form. Further, drugs that have side-effects due to triggering an immune system response can be wrapped in nanoparticle coating and prevent immune system from recognizing and reacting to a foreign substance. It is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation.

Key words: Nanotechnology, Nanoparticles, Solid lipid nanoparticles, Nano-emulsion.

INTRODUCTION

Nanotechnology is the science and technology of precisely manipulating the structure of matter at the molecular level. It is the use and manipulation of matter at a tiny scale. At this size, atoms and molecules work differently, and provide a variety of surprising and interesting uses. Nanotechnology deals with the creation of useful materials, device and systems and systems through control of matter on the nanometer length scale and exploitation of novel phenomena and properties at that length scale. With advancements in nano science and technology, a large number of materials and improved products may be available with a change in the physical properties when their sizes are shrunk. Nanotechnology-based delivery systems can also protect drugs from degradation. These properties can help reduce the number of doses required, make treatment a better experience and reduce treatment expenses. A number of nano-based systems allow delivery of insoluble drugs, allowing the use of previously rejected drugs or drugs which are difficult to administer e.g. paclitaxel. At present these systems are generally used for existing, fully developed off-patent drugs, the so-called "low-hanging fruit" of nanotechnology-based delivery.

These technologies include nanoarrays, protein arrays, nanopore technology, nanoparticles (NPs) as a contrivance in immunoassays and nanosensors, among others. Gold NPs and quantum dots (semiconductors) are the most widely used, but new materials are becoming available as more molecular entities are discovered as amenable to nanoscale design and fabrication. Crystal materials like those of gallium, phosphate, quartz, and ceramic are chosen for their durability and piezoelectric properties of developing and retaining an electric potential (charge) when subjected to mechanical stress. Another area of development is nanobiosensors, in which antibody-based piezoelectric nanobiosensors are well developed. Nanoparticles take advantage of their dramatically increased surface area to volume ratio. Their optical properties become a function of the particle diameter. When brought into a new material, Nanoparticles can vastly influence the material, like stiffness or elasticity. Nanotechnology should not be viewed as a single technique that only affects specific areas. It is more of a 'catch-all' term for a science which is benefiting a whole array of areas, from the environment, to healthcare, to hundreds of commercial products [1,2].

Nanotechnology is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation. Various nanosystems, as a result of their larger size, are accumulated at higher concentrations than normal drugs. In addition, the increased vascular permeability coupled with an impaired lymphatic drainage in tumors allows an enhanced permeability and retention effect of the nanosystems in the tumors or inflamed tissue. Thus, this pathophysiological opportunity allows extravasation of the nanosystems and their selective localization in the inflamed tissues. The tendency of nanosystems to specifically localize in the reticuloendothe-lial system also presents an excellent opportunity for passive targeting of drugs to the macrophages present in the liver and spleen. Thus, this natural system can be used for targeting drugs for intracellular infections [3]. The therapeutic value of many promising drugs for the treatment of various neurological disorders is diminished by the presence of the blood-brain barrier [4]. The blood-brain barrier is a unique membrane that tightly segregates the brain from the circulating blood. Thus, drug delivery to this organ is a challenge, because the brain benefits from very efficient protection. Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier. Nanoparticles can be effectively used to deliver relevant drugs to the brain [5].

ADVANTAGES OF NANOTECHNOLOGY TECHNIQUES

1. Nanotechnology-based delivery systems can also protect drugs from degradation.
2. Improved products may be available with a change in the physical properties when their sizes are shrunk.
3. Reduce the number of doses required.
4. Make treatment a better experience and reduce treatment expenses.
5. Nano-based systems allow delivery of insoluble drugs.
6. Allowing the use of previously rejected drugs or drugs which are difficult to administer.
7. Drug targeting can be achieved by taking advantage of the distinct pathophysiological features of diseased tissues.
8. An ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site.
9. It should not lose its activity or therapeutic efficacy while in circulation.
10. Tumors allow an enhanced permeability and retention effect.
11. Passive targeting of drugs to the macrophages present in the liver and spleen.
12. Nanotechnology offers a solution for using the numerous chemical entities for treating brain disorders that are not clinically useful because of the presence of the blood-brain barrier.
13. Improve the oral bioavailability of the agents that are not effectively used orally.

DIFFERENT NANOTECHNOLOGY TECHNIQUES

1. Nanoparticles in Drug Delivery

Nanoparticles are colloidal particles having a size of 10 to 1000 nm. Nanoparticles and microparticles formulated using PLGA and PLA polymers are being investigated as a nonviral gene delivery system because of their sustained-release characteristics, biocompatibility, bio- degradability, and ability to protect DNA from degradation in endolysosomes. Although PLGA/PLA nanoparticles are under extensive investigation for drug and protein delivery, their application as a gene expression vector is recent. Nanoparticles can offer significant advantages over the traditional delivery mechanisms in terms of high stability, high specificity, high drug carrying capacity, ability for controlled release, possibility to use in different types of drug administration and the capability to transport both hydrophilic and hydrophobic molecules. The drugs may be enclosed inside the sphere of the nanoparticle or linked to the surface. Once they are at the target site, the drug payload may be released from the nanoparticle by diffusion, swelling, erosion or degradation. Active systems are also possible, e.g. drug release in response to the input of external energy such as targeted ultrasound, light or magnetic field. It has been demonstrated that rapid escape of nanoparticles takes place from the endolysosomal compartment to the cytoplasmic compartment following their intracellular uptake via an endocytotic process. The rapid escape of nanoparticles from the endolysosomal compartment could protect nanoparticles as well as the encapsulated DNA from the degradative environment of the endolysosomes [6, 7, 8, 9].

Nanoparticle-based drug delivery systems have considerable potential for treatment of tuberculosis (TB). Recently, the same group has demonstrated that nano- particles formulated using PLGA polymer demonstrated greater gene transfection than those formulated using PLA polymer in breast cancer (MCF-7) and prostate cancer cell lines (PC-3), and this was attributed to the higher DNA release from PLGA nanoparticles. PLGA with a higher molecular weight resulted in the formation of nanoparticles with higher DNA loading, which demonstrated higher gene expression than those formulated with lower molecular weight PLGA.

a. Protein nanoparticles

Albumin nanoparticle

The protein albumin has been modified to create novel nanostructures for applications in drug delivery. The surface of albumin has several groups available for covalent conjugation of biomolecules and drugs. Albumin-DNA–polyethylenimine (PEI) conjugates have been used for gene delivery, with reduced irritation, damage and toxicity. Albumin can also form nanoparticles which can be modified to alter size, polydispersity, surface charge, drug loading and release. Functionalised albumin nanoparticles have been shown to cross the BBB [10]. Similarly, bovine serum albumin nanoparticles loaded with sodium ferulate have been targeted to the liver [11].

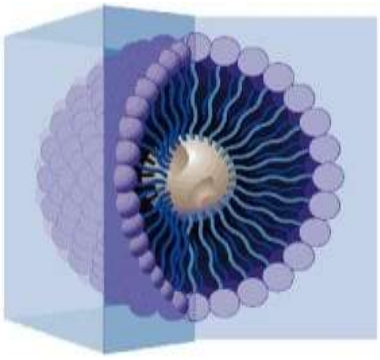

Figure 1: Albumin Nanoparticle

Chitosan and Lectin nanoparticles

Chitosan is a natural linear polysaccharide derived from the shells of crustaceans. Chitosan has the ability to clot blood and is used in bandages and other haemostatic agents. Its derivatives such as trimethylchitosan are used in non-viral gene delivery. It has also been used for the production of nanoparticles by ionotropic gelation with tripolyphosphate. Nanoparticles of chitosan and egg phosphatidylcholine (ePC) have been reported for the delivery of anticancer drug paclitaxel. The chitosan-ePC structure was found to be highly stable and biocompatible with these properties dependent on the ratio of the two materials. Lecithin is a lipid mixture of phospholipids mainly comprising phosphatid ylcholine which is normally extracted from egg yolk or soy beans, and is widely used as a food additive. It is alsoused for liposome and micelle formation. Chitosan is normally coated on the surface of lipid based nanostructures to improve the adhesive properties and increase stability [12].

b. Gold nanoparticles

Colloidal gold nanoparticles have been used for a relatively long time for the treatment of diseases including cancer, rheumatoid arthritis, multiple sclerosis and neurodegenerative conditions such as Alzheimer's disease. The advantages of gold nanoparticles are their ease of preparation in a range of sizes, good biocompatibility, easily functionalised and their ability to conjugate with other biomolecules without altering their biological properties. Gold nanoparticles with diameters ≤ 50 nm have been shown to cross the BBB. PEGylated gold nanoparticles conjugated with TNF (tumour necrosis factor) can enter tumour cells through their leaky vasculature [13].

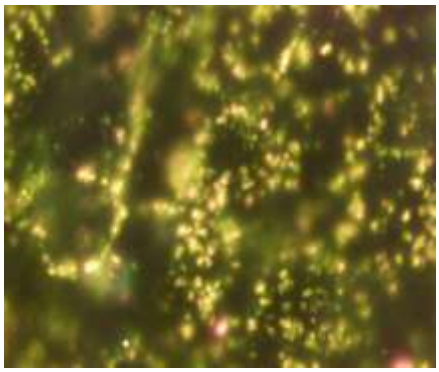

Figure 2: Gold nanoparticle

c. Magnetic nanoparticles

Magnetic nanoparticles have become one of the most studied and applied nanotechnology in the past few years. Applications involving magnetic nanoparticles include targeted drug delivery, as contrast agents in MRI (e.g. Feridex), gene delivery and cell separation, cell labelling. Iron oxide nanoparticles are widely studied due to their biodegradable nature, biocompatibility and superparamagnetic properties suited for MRI applications. Magnetic nanoparticles that can be loaded with drugs and still retain their MRI properties have been reported. The iron oxide nanoparticles were coated with oleic acid and loaded with anticancer agents doxorubicin and paclitaxel with a loading efficiency of up to 95% [14].

d. Ceramic nanoparticles

Nanoparticles of silica, titania, alumina etc. are normally classified under the heading ceramic nanoparticles. One of the advantages of these particles is that their preparation is very simple. They are unaffected by changes in pH or temperature. It is possible to manipulate many features of these nanoparticles, including size, shape, porosity, inertness etc., and they can easily be modified to attach different biomolecules. Their typical size is around 50 nm. Ceramic nanoparticles have been used to encapsulate hydrophobic drug molecules, the acidlabile model enzyme, serratiopeptidase and increase the transfection efficiency of DNA (used with a DNA-dendrimer conjugate).

Fabrication of these nanoparticles, however, is hindered by a number of factors including capture of the nanoparticles from the gas phase, or large volumes of solvents for synthesis. Researchers at the University of Florida have developed an improved method for the formation of ceramic nanoparticles that has the ability to produce a large quantity of nanoparticles which are of uniform size

and shape at a reduced cost and without many of the common drawbacks. Nanoparticle size is controlled by nucleation and growth and confined by the diameter of the nanofiber, resulting in the production of nanoparticles with uniform size [15].

2. Lipids in Drug Delivery

Lipid-based structures and formulations have been used as delivery systems for many years. Lipid nanostructures are capable of protecting their contents from the conditions within the body that could potentially cause degradation. They can be used to deliver insoluble drugs and targeting ligands can be attached.

a. Liposomes & Niosomes

Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a lipid bilayer. They are normally created by the extrusion of phospholipids. Solutes, such as a drug in the core, cannot pass through the hydrophobic bilayer although hydrophobic molecules can be adsorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules. The size of the liposomes can vary from 15 nm to several μm. Liposomes with nanometre sized cavities are also called nanoliposomes. PEGylated liposomes that avoid clearance by the RES are known as "stealth liposomes". Liposomes exploit the leaky nature of tumour vesicles which allow particles of less than 400 nm to pass through. Early research in this area has shown that liposomes remain in the tumour interstitial fluid in close vicinity to tumour vessels. Surface modification of liposomes with ligands like vitamins, antigens and antibodies for improved endocytosis by other cell types has also been proposed.

A variety of biological and drug compounds have been delivered using liposomes. These include antibiotics, antioxidants (retinoids, carotenoids, tamoxifen, urate, glutathione etc.), vitamins (Vitamins A, C and E), haemoglobin, ATP, NSAIDs (indomethacin and naproxen) and genetic materials (plasmid DNA). Several formulations including amphotericin B and daunorubicin have been successfully commercialized [16, 17].

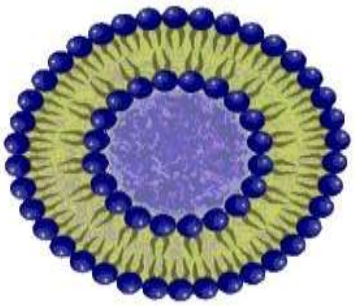

Figure 3: Bilayer structure of liposomes

Niosomes

Niosomes are non-ionic surfactant vesicles with a similar structure to liposomes. They can encapsulate aqueous solutes and act as drug carriers. Niosomes are formed by the self assembly of non-ionic amphiphiles in aqueous media. The application of heat or physical agitation helps the process to attain a closed bilayer structure. Their uptake by organs such as the liver and spleen make niosomes best suited as drug delivery agents in diseases affecting these organs. They are also used in targeting cancer cells. Since niosomal antigens are potent stimulators of the cellular and humoral immune responses they are also useful as adjuvants in vaccine delivery. High levels of drugs were found in the target location when administered via Niosomes compared to conventional routes. They have also been used with anti-inflammatory agents and anti-infective agents. PEGylated cationic niosomes have been used for the cellular delivery of oligonucleotides. Niosomes improve percutaneous passage of 5-fluorouracil (5-FU) through human stratum corneum and epidermis, and are non-toxic. Niosomes of frusamide have been reported, that increased skin permeability and sustained drug levels [18].

b. Micelles

Micelles are also spherical lipid nanostructures but they do not have a bilayer or inner cavity. The hydrophobic ends of the phospholipids point inwards and the hydrophilic ends face the outside, forming a spherical structure. Reverse micelles have this polarity the opposite way. The typical size of micelles for pharmaceutical applications ranges from 10-80 nm. Compared to liposomes, micelles have a short circulation time within the body due to their smaller size. However, this gives them the advantage of being able to enter tumour cells more easily, because of the EPR effect. Micelles can also be made from polymers. Polymeric micelles are formed by block-copolymers consisting of hydrophilic (e.g. PEG) and hydrophobic monomer units with longer hydrophilic blocks and shorter hydrophobic blocks. They have a hydrophobic core stabilised by hydrophilic units. These micelles are more stable than conventional micelles and are preferred for drug delivery applications as the circulation time is longer and they offer better biodistribution.

Lipid-polymer conjugate micelles can also be made. They can carry different types of chemicals like paclitaxel, diazepam and captothecin. They also exhibit good longevity and stability. Micelles with improved solubility and intracellular delivery have been prepared using PEG-phosphatidylethanolamine (PEG-PE) conjugates. Micelles conjugated with transferrin can target cancer cells and deliver DNA. Similarly folate residues attached to micelles have been used to deliver adriamycin to cancer cells. The advantage of such agents is enhanced target penetration due to the smaller size and easy movement to the target location [19, 20].

c. Lipid Nanoparticles (SLNs, NLCs & lipid drug conjugates)

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are particles of nanometre dimensions with a solid lipid matrix. They are oily droplets made from lipids which are solid at room temperature and stabilised by surfactants. The advantage of SLNs is that there is no need for organic solvents in the preparation, they provide protection from water and can be used for controlled drug release. Solid lipid nanoparticles (SLN) are particulate systems for parenteral drug administration with mean particle diameters ranging from 50 up to 1000 nm. SLN were produced by high pressure homogenization of aqueous surfactant solutions containing the drug-loaded lipids in the melted or in the solid state (500/1500 bar, 3/10 cycles). They also have applications in cosmetics. Stealth and nonstealth SLNs have been used to deliver paclitaxel. Sustained release of doxorubicin has been reported using SLCs. Although SLNs are promising they suffer some drawbacks. Their loading capacity is low and there is a tendency to expel the contents during storage. These problems are caused by the tendency for the particle matrix to form a perfect crystal lattice when solid lipids are used. The high water content of SLN dispersions can also be problematic [21].

Nanostructured lipid carriers (NLCs)

In order to overcome some of the drawbacks of SLNs, a second generation of lipid particles have been developed by mixing solid lipids with liquid lipids. They are called nanostructured lipid carriers (NLCs). Compared to SLNs, NLCs usually have a distorted structure which makes the matrix structure imperfect, creating spaces to accommodate active compounds. NLCs can be produced by various traditional dispersion techniques. The preferred production method is high-pressure homogenization. Up to approximately 60% solid content, high-pressure homogenization can be applied alone to achieve solid contents of, for example, 80% when the multistep process is applied. They have been investigated for the topical delivery of drugs, including anti-fungals and non-steroidal anti-inflammatories and have been recently reviewed. These structures also have applications in cosmetics [22].

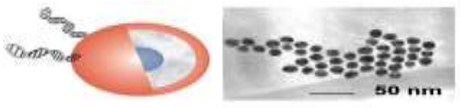

Figure 4: Nanostructured lipid carriers

Lipid-drug conjugates nanoparticles

In order to overcome the limitations of SLNs, drug-lipid conjugates have been developed with an observed loading capacity of up to 33 % 85. Mehnert *et al.* investigated the structure of lipid based nanoparticles and reported that SLNs and other nanostructured lipid carriers did not show any advantage with respect to incorporation rate compared to conventional nanoemulsions.

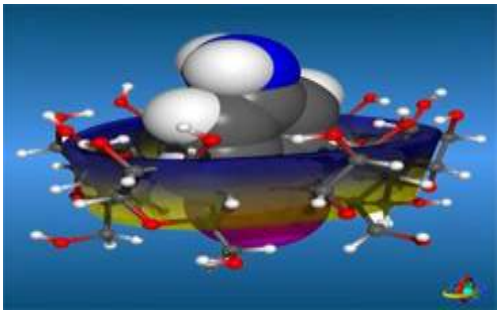

Figure 5: Lipid-drug conjugates nanoparticles

Nanoemulsions

Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The terms sub-micron emulsion (SME) and mini-emulsion are used as synonyms. Emulsions which match this definition have been used in parenteral nutrition for a long time. Usually, SMEs contain 10 to 20 per cent oil stabilized with 0.5 to 2 per cent egg or soybean lecithin. Nanoemulsions are dispersions of nanoscale droplets of one liquid within another. There are a number of high and low-energy methods of formation. Nanoemulsions have a number of advantages over larger scale emulsions. They can be stabilised to increase the time before creaming occurs. They are transparent or translucent, and have a larger surface area due to the small particle size [23].

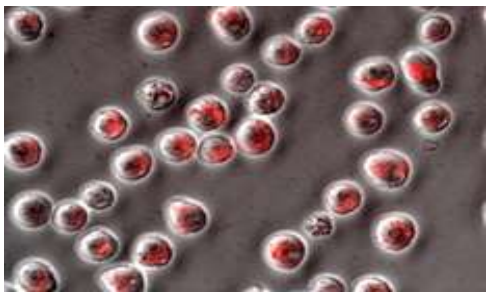

Figure 6: Lipid nanocapsules

Lipid nanocapsules (LNCs)

These systems can be thought of as a cross between liposomes and nanoemulsion particles. Their outer wall is thicker than a traditional nanoemulsion particle allowing functionalisation and more controlled delivery. LNCs are composed of a liquid, oily core (medium-chain triglycerides) surrounded by hydrophilic and lipophilic surfactants. Stealth LNCs have also been synthesised using PEG to improve circulation time. LNCs have been used to deliver anticancer drugs LNCs have been used to deliver therapeutic molecules and radionuclides across the blood brain barrier by conjugation of antibodies or antibody fragments. Their structure is a hybrid between polymeric nanocapsules and liposomes because of their oily core which is surrounded by a tensioactive rigid membrane. They have a lipoprotein-like structure. Their size can be adjusted below 100 nm with a narrow distribution [24].

3. Nanosuspensions & Nanocrystals

Nanosuspensions are colloidal dispersions of nanoparticles of an insoluble molecule, which are stabilized by surfactants. Nanosuspensions can be used to maintain these drugs in a preferred crystalline state of sufficiently small size for intravenous administration. Their advantages are similar to those of nanoemulsions. They can also achieve even higher levels of drug loading because the drug is in the solid state. Several studies have demonstrated the use of nanosuspensions for drug delivery with improved efficacy and release [25].

Nanocrystals

Nanocrystals are aggregates comprising several hundred to tens of thousands of atoms that combine into a "cluster". Typical sizes of these aggregates are between 10-400 nm and they exhibit physical and chemical properties somewhere between that of bulk solids and molecules. By controlling the size and surface area, other properties such as bandgap, charge conductivity, crystalline structure and melting temperature can be altered. The crystals must be stabilised to prevent larger aggregates from forming. Nanocrystals are produced by nanosonication. First, a nanosuspension is formed by high speed stirring, followed by wet milling, high pressure homogenisation, nanocrystallisation and spray drying to create nanosized crystals. The advantages of nanocrystallisation are the ability to solubilise poorly soluble drugs, high bioavailability, major decrease in dosage volume, and an increase in tolerated dose.

Figure 7: Nanocrystals

4. Polymer therapeutics

Polymer therapeutics is an umbrella term to describe polymeric drugs, polymer-drug conjugates, polymer-protein conjugates, polymeric micelles to which drug is covalently bound, and multi-component polyp lexes being developed as non-viral vectors. One of the biggest advantages of using polymers in drug delivery is that it is possible to manipulate their properties (e.g. molecular weight, linkers etc.) to adapt to the drug delivery requirements. Conjugating nanoparticles and other nonmaterials to polyethylene glycol (PEG), known as PEGylation, is used widely as it offers a number of advantages. These include increased protein solubility and stability, reduced immunogenicity, prevention of clearance by the reticuloendothelial system (RES) and increased plasma half-life - leading to less frequent dosing.

a. Polymer-protein conjugates

Polymers conjugated with proteins can then be administered parenterally can increase protein solubility and stability. PEGylation has been used to treat several diseases including hepatitis B and C, [26] acute lymphoblastic leukaemia (PEG–L-Asparaginase) [27], neutropaenia associated with cancer chemotherapy (PEG–GCSF) [28] and different cancers [PEG–glutaminase combined with a glutamine anti-metabolite 6-diazo-5-oxo-norleucine (DON].

b. Polymer-drug conjugates

Polymer drug conjugates can improve the targeting ability, reduce the associated toxicity and overcome drug resistance. Hydrophilic polymers can be conjugated with hydrophobic drugs to increase their solubility. Polymer-drug conjugates have become a fast-growing field, with nearly a dozen polymeric conjugates advancing to the clinical trial stage. Results from early clinical trials of these polymer-drug conjugates have demonstrated several advantages over the corresponding parent drugs, including fewer side effects, enhanced therapeutic efficacy, ease of drug administration, and improved patient compliance. Increased therapeutic efficacy is achieved primarily through an enhanced permeability and retention (EPR) effect of long-circulating polymers.

c. Polyketal nanoparticles

Polyketals are readily-synthesized, biocompatible, hydrophobic polymers with biodegradable ketal linkages in their backbone. They can form nanoparticles for encapsulating hydrophobic drugs or proteins. They can undergo acid-catalysed hydrolysis to release their therapeutic payload in acidic environments such as tumours, inflammatory tissues etc. There are no acidic byproducts produced during degradation, unlike other polymers (e.g. polyester), that can cause inflammation. Polyketal nanoparticles (PKNs) represent a novel and effective drug delivery vehicle, which appear to target macrophages selectively.

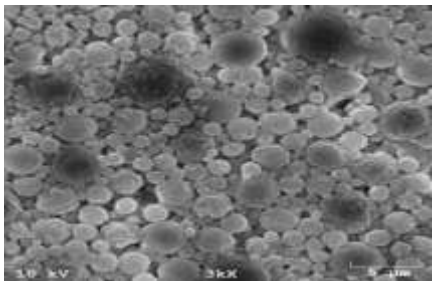

Figure 8: Polyketal nanoparticles

d. Nanogels

Nanogels are cross-linked nanoscale particles made of flexible hydrophilic polymers. They are soluble in water and allow spontaneous loading of drugs in aqueous media. The nanogel collapses to form dense nanoparticles after adding the drug molecules. Nanogels possess large surface area, tuneable size and a network to allow incorporation of molecules. They have been used to incorporate drugs, DNA/RNA and inorganic molecules such as quantum dots. Nanogel particles comprised of PEG and polyethylenimine (>100nm) have been used to cross the blood-brain barrier (BBB) and deliver oligonucleotides to the brain. Nanogels have also been used for pH-dependant release of doxorubicin and incorporation of an insoluble small molecule anticancer drug [29].

e. Dendrimers & Hyperbranched Polymers

Dendrimers are unimolecular, monodisperse, micellar nanostructures with a well-defined, regularly branched symmetrical structure and a high density of functional end groups. They are robust, covalently fixed, 3D structures possessing both a solvent-filled interior core (nanoscale container) that can carry molecules, e.g. drugs, and a homogenous, defined, exterior surface functionality (nano-scaffold) that can be functionalised. The first and most widely studied dendrimers are poly (amidoamine) (PAMAM) dendrimers. Dendrimers can be created using a divergent method where the dendron originates from a central core and branches out. Alternatively, a convergent method where the dendrimers grow inwards to a focal point may be used. One of the advantages of dendrimers is that they are similar in size to many proteins and biomolecules like insulin, cytochrome C and haemoglobin. Second generation dendrimers have a width similar to that of DNA (2.4 nm), and 5th and 6th generation PAMAM dendrimers have similar widths to cellular lipid membranes (~5.5 nm). The loading capacity of dendrimers can be manipulated by the addition of different guest molecules onto the surface of dendrimers. Dendrimers have also been effective against bacterial and viral infection.

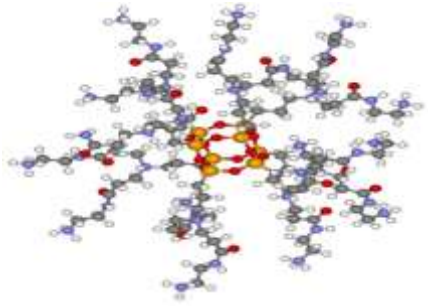

Figure 9: Dendrimers

5. Carbon Nanostructures in Drug Delivery

a. Carbon nanotubes (CNTs)

CNTs have the ability to transport drug molecules, proteins and nucleotides. Due to their size and shape, carbon nanotubes can enter living cells without causing cell death or obvious damage. Molecules can be covalently or non-covalently attached to the surface. The hollow structure of CNTs allows encapsulation of molecules but as yet there are very few examples of this for drug delivery. For biological applications CNTs require covalent or non-covalent [30, 31] functionalisation to prevent aggregation and increase their solubility. Several drugs have been successfully delivered, including amphotericin B [32], which is normally insoluble and toxic due to its tendency to aggregate. When delivered using CNTs there was increased solubility, low aggregation (and therefore lower toxicity) and increased anti-fungal action. A number of therapeutic applications of CNTs have been reported, including boron neutron capture therapy (BNCT), inducing immunoresponse, gene and siRNA delivery. A recent review details biological applications of CNTs [33].

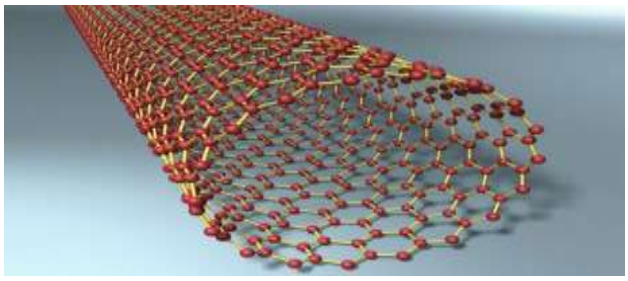

Figure 10: Carbon nanotubes

b. Carbon nanohorns

Carbon nanohorns have a structure similar to CNTs except they are closed at one end, forming a cone-shaped cap, or 'horn'. They have a tendency to form spherical dahlia-flowerlike aggregates, roughly <100 nm. They have been used to deliver cisplatin and dexamethasone. Carbon nanohorns can behave like a conductive metallic or semiconductor depending on their structure, which is useful for nanoscale electronic devices and in electrically conductive films in coatings, plastics, nanowire, nanofiber and in certain bioscience applications. Carbon Nanohorns are generally immediately available in most volumes.

c. Nanodiamonds

Diamond nanoparticles, or nanodiamonds have the capability for surface functionalisation. This has been used to immobilise proteins and deliver drug molecules. Recently, Nanodiamonds bound to doxorubicin were embedded into a polymer microfilm to achieve slow release of the drug over one month. This system could potentially be used for tumour patches. Fluorescent nanodiamonds can enter cells, and may have applications in cell tracking and imaging. The nanodiamond-insulin clusters hold promise for wound-healing applications and could be integrated into gels, ointments, bandages or suture materials.

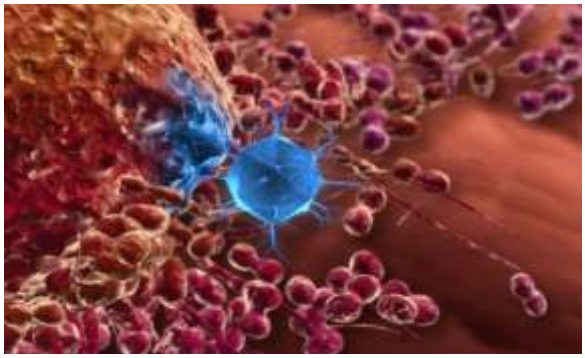

Figure 11: Nanodiamonds

6. Other Nanotechnologies for Drug Delivery

a. Cyclodextrin Nanosponges

Cyclodextrin nanosponges are complex networks of cross-linked cyclodextrins cross-linked and formed into a roughly spherical structure, about the size of a protein, with channels and pores inside. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponges have been used for removal of organic impurities in water.

b. Drug Carrying Implantable Thin films

These are nanoscale thin films that can be precisely controlled to release chemical agents by applying an electrostatic field. Hammond et al. reported the development of a thin film of approx. 150 nm thickness using a layer by layer approach. It is made up of the negatively charged material Prussian Blue and a positively charged drug molecule, or a positively charged molecule enclosing a drug. The advantages of the layer by layer approach include ease of preparation, versatility, capability of incorporating high loading of biomolecules into films, fine control over the structure, and robustness of the products under ambient and physiological conditions. The film can be implanted in the body and can carry discrete packets of drugs that can be released separately, which could be particularly useful for chemotherapy.

PARTICLE SIZE FOR DIFFERENT NANOTECHNOLOGY TECHNIQUES

Particle size range for different nanotechnology techniques are shown in Table 1.

Table 1: Particle size range for different Nanotechnology techniques

Techniques	Size range
Nanoparticles	10 to 1000 nm.
Liposomes	15 nm to several µm.
Micelles	10-80 nm.
Solid Lipid Nanoparticle	50 nm to 1000 nm.
Nanoemulsion	50 to 1000 nm.
Lipid Nanocapsule	Less than 100 nm.
Nanocrystals	10-400 nm
Carbon nanohorns	Less than 100 nm.

APPLICATION OF NANOTECHNOLOGY

The importance of nanotechnology in therapeutics and the role played by it in combating some of the chronic diseases, such as cancer. Areas in drug delivery where nanotechnology can make a difference include:

1. Developing systems that improve the solubility and bioavailability of hydrophobic drugs.
2. Designing delivery vehicles that can improve the circulatory presence of drugs.
3. Eliminating or minimising toxicity.
4. Increasing specificity.
5. Targeting drugs to specific cells or tissues.
6. Developing delivery systems for slow release.
7. Improving vaccine adjuvants and delivery.
8. Developing novel nanostructures that can be used in specific applications, e.g. ocular, cancer therapy, neurology, orthopaedics.
9. Delivery of repaired genes or the replacement of incorrect genes is fields in which nanoscale objects could be introduced successfully.

FUTURE PROSPECTIVE

Over the next couple of years it is widely anticipated that nanotechnology will continue to evolve and expand in many areas of life and science, and the achievements of nanotechnology will be applied in medical sciences, including diagnostics, drug delivery systems, and patient treatment. For the pharmaceutical industry the field of drug delivery represents a strategic tool for expanding drug markets, because new delivery technologies could repackage classical drugs, offering a competitive edge after the expiry of patents and avoiding competition from generics.

CONCLUSION

The multidisciplinary field of nanotechnology is bringing the science of the almost incomprehensibly small device closer and closer to reality. Nanotechnology offers the ability to build large numbers of products that are incredibly powerful by today's standards. This possibility creates both opportunity and risk. It would be difficult to deny the potential benefits of nanotechnology and stop development of research related to it since it has already begun to penetrate many different fields of research. However, nanotechnology can be developed using guidelines to insure that the technology does not become too potentially harmful.

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