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AN OVERVIEW OF THE APPLICATIONS OF NANOMATERIALS AND DEVELOPMENT OF STENTS IN TREATING CARDIOVASCULAR DISORDERS

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Abstract. The applications of nanotechnology materials are rapidly advancing and will leave no field untouched by their ground breaking innovations. Nanoparticles are molecules with a diameter ranging from 10-100 nm and are available in different types such as spheres, rods, shells, cages and SERS particles which vary in shape, size and physical properties. The potential applications of nanomaterials include targeted drug and gene delivery, cancer diagnosis and therapy, determination of biological molecules and microorganisms, molecular probes for diagnosis of disease, immunoassay, and enzyme immobilization. Four types of stent devices include balloon angioplasty, bare metal stents, drug-eluting stents, and bioresorbable stents. Devices manufactured using nanotechnology materials have promising biomedical applications, and most noteworthy among them are the implantable non-woven nanofibrous stents for opening up narrowed blood vessels. The drug-eluting smart stents serve as reservoirs for delivery of medicines that prevent artery closure. The basic characteristics of a well-designed stent are that it must fit snugly in the blocked artery wall and form a scaffold to enhance blood flow without getting dislodged and/or drag-along further in the implanted blood vessel. In addition, the elastic and mechanical behaviour of a stent must match with the native tissue. Nano-robots constitute another important application of nanotechnology in health sciences. These devices may not only help to monitor and record detailed biomechanical and histopathological information of different tissues and organs in both humans and animal models, but also reduce the invasiveness risk and diagnostic cost of human diseases. Due to their specificity and site targeting properties, the nanomaterials may be a real boon for the diagnosis and treatment of diseases. However, several safety and regulatory questions remain to be addressed regarding the usefulness of conventional *in vitro* and *in vivo* methods employed for assessing short- and long-term consequences of nanoparticles and nanomaterials in humans, marine and wild animals as well as acute and chronic levels of exposure to environment.

1. INTRODUCTION

The risk of cardiovascular diseases (CVDs) such as coronary heart disease, myocardial infarction, atherosclerosis, and stroke is escalating in developed and developing countries. Narrowing of the arteries due to atherosclerosis is a serious condition in which calcium and fatty material build-up leads to plaque formation, and consequently reduce blood supply to the tissues and organs. Sometime the plaque rupture causes heart attack and stroke resulting in mortality and long-lasting morbidity. The treatment and prevention of CVDs is a major chal-

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lenge for basic researchers and health care professionals because the burden of premature mortality and morbidity due to CVDs is increasing worldwide. According to the World Health Organization, 40% of all deaths in the European Union countries are due to heart attacks and strokes, and the prevalence of coronary heart disease (CHD) is over 13 million in the US, however, nearly 80% of premature heart disease and stroke are preventable with heart healthy diets and lifestyle modifications [1,2]. A key trigger for heart attack (CHD) or brain attack (stroke) is plaque rupture or its dislodgement from atherosclerotic artery. The debris of the plaque may interrupt blood flow in the cardiac circulatory system leading to a heart attack, or cause a stroke if it obstructs a cerebral artery or other major blood vessels in the brain. Earlier diagnosis of CVDs, and ways to improve therapies constitute current challenges to health care providers and save lives. Therefore, it appears that the main priorities of cardiovascular research studies are determination of potential risk factors, early detection of disease aetiology, and cost-effective therapeutic measures to deal with CVD-related mortality and morbidity.

The primary aims of health related nanotechnology are to search for biocompatible and safe nanomaterials for the detection of disease aetiology, diagnosis, and to produce targeted drug delivery system to cure CVDs, stroke, cancer and other chronic diseases. Innovative Nano systems may also be helpful to identify patients at risk at early stage and to retard the growth of cardiovascular disease. Nanomaterials are available in different types such as spheres, rods, shells, cages, and particles which vary in shape, size, and physical properties. Such biocompatible nanomaterials have been used for the manufacture of stents which have saved millions of lives globally. The main focus of researchers working in the area of nanotechnology is to develop novel therapeutic materials those are safe and effective in different patients. As a matter of fact, nanoparticle-based materials have already made an impact in the pharmaceutical industry for the discovery of new therapies, cure for certain cancers, molecular probes for diagnostic purposes, gene carriers and drug delivery vehicles as well as development of stents. Due to the unique mechanical, electrical, chemical, and optical properties, the nanomaterials and nanostructures provide exciting new opportunities for basic and clinical research, diagnosis of disease, therapy of heart, lung, blood, and sleep disorders. Richard Feynman, winner of the 1959 Nobel Prize in Physics, emphasized in his address the future role of nanotechnology in cardiovascular sciences and envisioned the potential applications of nanotechnology in cardiovascular medicine [3]. With the multidisciplinary approach being undertaken by chemists, biomedical engineers, pharmacists, pharmacologists and physicians from a wide range of research institutions, small-to-medium-sized enterprises, and pharmaceutical companies from across the globe, some clinically proven effective remedies are being developed for treating CVDs, stroke, and the build-up of plaques in arteries [4]. To monitor the levels of different biochemical markers and to record the information in their internal memory in the human body, the nanorobots are a vital application of nanotechnology in medical research and diagnostics. These devices might be used to investigate detailed biomechanical and histometrical features of different tissues and organs. Nanotechnology may not only expand the ease, comfort, and effectiveness in medical applications but also help to reduce the diagnostic cost, and risk of invasiveness [5].

2. HISTORICAL PERSPECTIVE OF GOLD NANOPARTICLES

Gold (Au) is a unique metallic element which has a melting point of 1064 °C and a boiling point of 2970 °C. Several properties of gold such as its excellent conductive properties and its inability to react with water or oxygen have made it very useful to mankind over time [6]. In 1857, Michael Faraday explored the ruby gold nanoparticles and was astonished by the ruby color of the colloidal particles. His studies on these Au particles led to the birth of the modern day colloidal chemistry and the foundation of nanotechnology. Faraday laid stress on metallic Au being dispersed uniformly in both ruby glass and ruby fluid which was based upon some physical and chemical understandings. A 100 years later these ruby-coloured colloids were stable and their size was figured out to be in ranges of 2-6 nm from electron microscope [7,8].

Zsigmondy who started to investigate upon the opacity and colour of the ruby glass, tried to reproduce Au colloids through different methods. He combined Faraday's work and introduced a new procedure called, 'seed mediated method'. This method is still being used for the synthesis of nanoparticles. He also came up with an ultramicroscope for characterization of size, shape and structure of nanoparticles. Another scientist, Svedberg introduced ultra centrifuge and through it demonstrated the dependence of the motion of macromolecules (colloids) on their shape and size. During the simi-

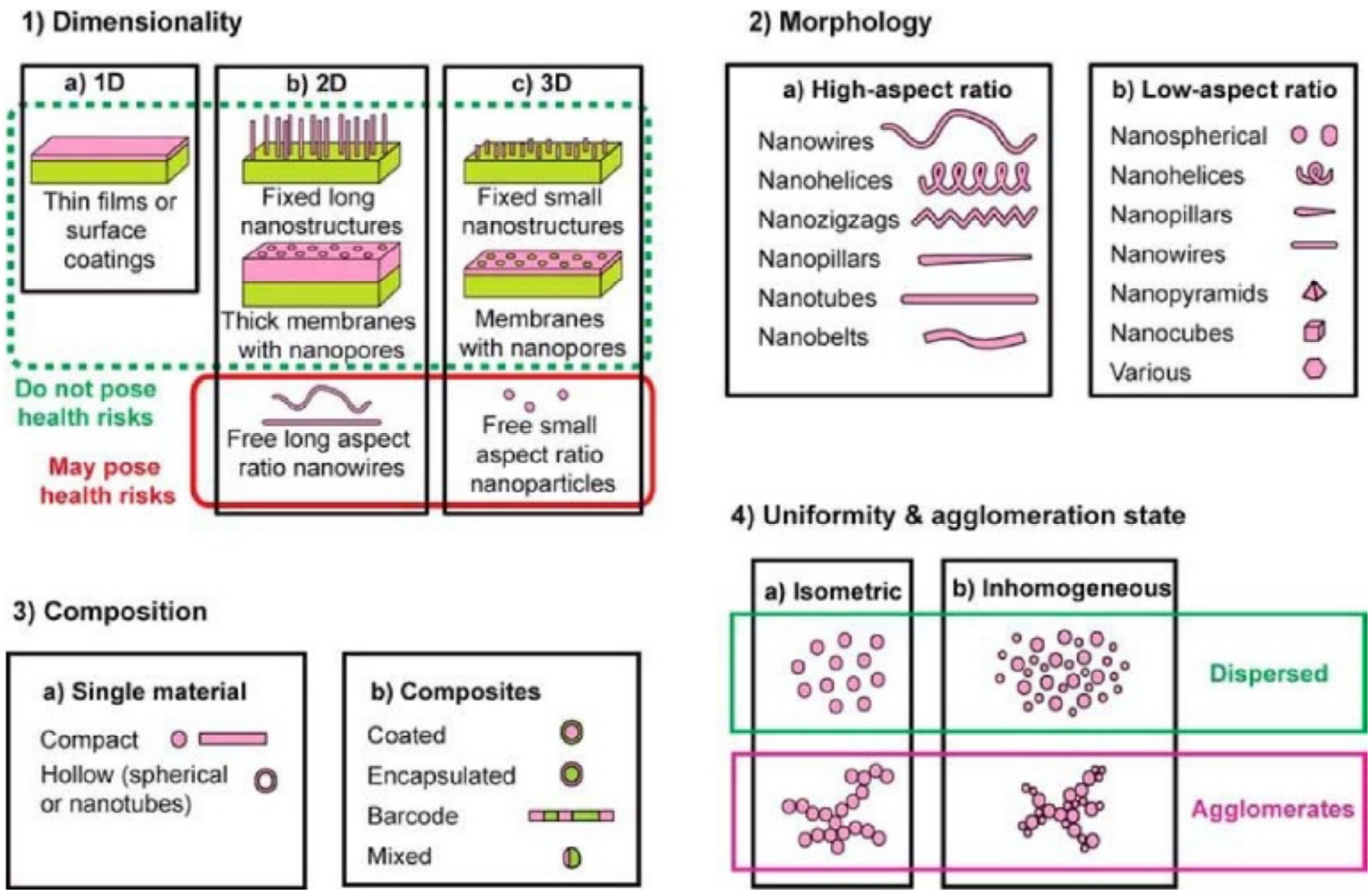

Fig. 1. Characterization of Nanomaterials on the basis of Dimensionality (a), Morphology (b), Composition (c) and Uniformity and agglomeration state (d).

lar period, G. Mie tried to find out the reason behind various colours of gold colloids [7].

In the middle ages, colloidal gold was used as a cure for diseases like arthritis and heart problems, epilepsy, dysentery, venereal diseases and tumours and also for the diagnosis of syphilis, a method which was used until the 20th century. Towards the end of 16th century, colloidal gold was routinely used to make ruby glass and for colouring ceramics by methods which are still used [6].

A brief description of nanomaterials used for making stents and nanomedicinal products is given in the following sections.

3. NANOTECHNOLOGY AND NANOMATERIALS

Nanotechnology consists of designing and producing devices or structures at molecular or miniscule scale, e.g., at the level of 10 -100 nm in diameter (one nanometer (nm) = one billionth or 10^{-9} of a meter) [9,10]. Nanomaterials are the main products of nanotechnologies, since they are characterized at nano-scale particles such as tubes, rods, fibres, spheres, shells, cages, and SERS *(Surface enhanced Raman scattering)* particles which vary in shape, size, and physical properties [11-13]. Nanoparticles are normally defined as being smaller than 100 nanometres in at least one dimension and are usually considered to be materials with at least one external dimension that measures 100 nanometres or less or with internal structures measuring 100 nm or less [14-17].

3.1. Types of nanomaterials

Shape or morphology of nanoparticles characterizes the type of nanomaterial, and it is helpful to classify them based on their number of dimensions (Fig. 1).

1D Nanomaterials

One-dimensional nanomaterials at the nanometer scale are thin films or surface coatings that includes the circuitry of computer chips and the anti-reflection and hard coatings on eyeglasses. Thin films of nanomaterials have been developed and used for decades in various fields such as electronics, chemistry, and engineering. Thin films can be deposited by various methods and can be manufactured controllably to be only one atom thick, a so-called monolayer film [18].

2D Nanomaterials

Two-dimensional nanomaterials have two dimensions in the nanometer scale. These include 2D nanostructured films, with nanostructures firmly attached to a substrate, or nanopore filters used for small particle separation and filtration. Free particles with a large aspect ratio, with dimensions in the

nanoscale range, are also considered 2D nanomaterials. Asbestos fibers is an example of 2D nanoparticles.

3D Nanomaterials

Materials that are nanoscaled in all three dimensions are considered 3D nanomaterials. These include thin films deposited under conditions that generate atomic-scale porosity, colloids, and free nanoparticles with various morphologies such as gold nanorods [19].

3.2.Categories of new nanotechnology materials

Nanotechnology is an innovative technology that allows the usage of nanoscale material to develop new devices with applications across diverse fields, e.g., medicine, cosmetics, engineering, biotechnology, food and agriculture, environment sciences, biomedical-textiles, and military protection clothing etc. Nanomaterials in the size range of 0.1 – 100 nm have increased efficacy in targeting cellular and tissue specific clinical applications in order to maximize therapeutic effects [19-22]. They have structural features and properties in between those of single atoms and bulk material which include clusters [23,24]. Nanoparticles [25-31], quantum dots [17,31-33], nanotubes [15,35] as well as collection or organization of these individual structures in 2 or 3 dimensional assemblies. The shape, size and surface functional groups of nanomaterials can be manipulated for chemical and mechanical properties in order to develop new products, medical devices, stents, and nanotechnology scaffolds to grow stem cells [36-40]. Nanomaterials are also used to develop targeted drug delivery systems that are engineered in a way to link with specific proteins and nucleic acids associated with the disorder, thereby protecting it from biodegradation, immune system attack, and to cross over various cellular barriers.

Nanomaterials used in medicine

Because of their role in determining enzyme action, cell cycle, cell signalling damage repair, nanomaterials can be used to create analytical tools for analysing the structure of cells and tissues at the atomic and cellular levels, and to design biocompatible materials for novel therapies as well as targeted drug delivery, and diagnostic purposes. Due to their unique capabilities and purported minimal side effects in treating variety of ailments, nanomaterials have a wide range of biomedical applications. Among the vast array of nanomaterials, one example is of the biocompatible super-paramagnetic iron oxide with properly oriented surface architecture and semiconductor crystals called quantum dots (QDs) have been developed for analyses of biological systems as QDs when attached to biological molecules, emit specific colours and offer quick and extensive screenings [41].

Nanosensors are used for monitoring *in vivo* biological processes in single living cells that can help to improve our current understanding of cellular functions. Nanosized liposomes are currently used to encapsulate anticancer drugs [42-51]. Magnetic nanoparticles (NPs) are employed in analysing blood, urine, and other body fluids to speed up the separation and improve selectivity of the analytical methods used [1-4,42,53,54-65].Various fluorescent nanomaterials (NMs) have formed the basis for new detection techniques for infectious and genetic disease diagnosis and treatment [3,17,66-77]. NMs have also proven effective in delivering various vaccine antigens/epitopes with increased antibody and cellular responses [5,52,53,69,78-80].

Herbal Nanomedicines

Plant-derived herbal medicines have been used for curing a number of aliments for centuries. The active ingredients of herbal remedies can be attached with nanomaterials for wound and burn healing purposes. Novel drug delivery systems (NDDS) are newer approaches to deliver the targeted substances to achieve maximum therapeutic effects. Slow release nano-dosage forms such as polymeric nanoparticles, liposomes, proliposomes, solid lipid nanoparticles, nanoemulsions, etc., are being developed as NDDS for target drug delivery, improved bioavailability, enhanced absorption, reduce dose and reduce elimination. Some herbal nanomedicines currently tested are listed in Table 1.

Curcumin liposomes

Curcumin is widely purported for its anti-microbial effects, but due to its lower solubility and permeability, its pharmacological actions have not been determined. Nanoparticles have made it possible for exploring the wide range of effects of curcumin. Curcumin liposomes are now under investigation for diversity of application. It was reported that curcumin liposomes have better permeability and solubility as compared to the non-coated curcumin [81]. Curcumin therapy is being considered for a wide range of applications such as anti-cancer, anti-oxidant, antiplatelet aggregation, etc., [82-85]. In addition, curcumin liposomes are now being tried for their application to decrease the risk of cardiovascular diseases [86].

Table 1. Plant-derived herbal nanomedicines.

Herbal nanomedicine	Formulation	Pharmacological activity
Curcumin	Curcumin liposomes	Antioxidant, antitumor, antiplatelet aggregation
Quercetin	Quercetin liposomes	Antioxidant, anticancer
Podophyllum peltatum	Solid lipid nanoparticles	Antiviral, anticancer
Silybum marianum	Silymarin liposomes	Hepatoprotective
Camptothec acuminate	Camptothein nanoparticle	Lung and breast cancer
Ginkgo biloba	Ginkgo biloba nanoparticles	Brain function activation

Quercetin

It is a flavonoid present in plants and foods such as red wine, onions, green tea, apples and berries. Quercetin has been used for long-time to lower the blood levels of high cholesterol, and to decrease the incidence of heart disease, diabetes, cataracts, hay fever, peptic ulcer, schizophrenia, inflammation, asthma, gout, viral infections etc. It is also used for treating prostate cancer [87]. Studies are under way to evaluate the quercetin liposomes effects on COX-2, NF-κB, hepatotoxicity, and wound healing [88-91].

Podophyllum peltatum

Podophyllum belonging to the family *Berberidaceae* commonly known as mayapple or ground lemon. It is traditionally used as emetic, cathartic and anti-helminthic [92]. The active ingredient podophyllotoxin has purgative and cytostatic properties [89,93]. Some investigators consider podophyllum as an anticancerous plant [16], and podophyllotoxin-loaded solid lipid nanoparticles are being studied for site specific anti-tumor effects [91,92].

Silybum marianum

This plant belongs to the family *Asteraceae* commonly known as cardus marianus, milk thistle and Saint Mary's thistle. It is traditionally used in Chinese medicine as antihepatotoxic agent in order to clear heat, relieve toxic material by soothing the liver and promoting bile flow [93]. Mechanochemical activation and spray congealing methods are used to treat the dry extracts of *Silybum marianum* so as to enhance its oral bioavailability [94]. Silymarin liposomes show better results for hepatoprotective action because their bioavailability is enhanced by such formulation [95].

Camptotheca acuminate

This plant belongs to the family Nyssaceae commonly known as happy tree, cancer tree, or tree of life. The pharmacologically active constituent camptothecin is a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase I, which is believed to be the mechanism of action for its anti-cancer treatment for treatment of patients with solid tumours [96]. Human phase I trials with camptothecin nanoparticles have shown some success for the treatment of patients with solid tumours [97]. Hydrophobically modified glycol chitosan nanoparticles of camptothecin have enhanced the drug stability and tumor targeting in cancer patients [98].

Ginkgo biloba

It is traditionally used in Chinese and Japanese medicine for the enhancement of cognitive functions. In a few studies, *Ginkgo biloba* has shown positive results in the improvement of dementia and Alzheimer's disease [99,100]. Ginkgo biloba nanoparticles are purported for the treatment of Alzheimer's disease and site targeting for brain degenerative disorders [101].

Parentral injection routes with nanomaterial-based vaccine show efficacy in a range of 40 -800 nm size nanomaterials [69-72]. Small size nanomaterials are rapidly cleared from body [5,102-107]. However, nanomaterials larger than 10 nm avert single pass renal clearance and the presence of negative charges minimize their non-specific interaction with proteins and cells to achieve pharmacokinetic manipulations [10]. Recognition capabilities of biomolecules when combined with nanomaterials can lead to novel tissue substitutes, biosensors and controlled drug delivery systems with improved therapeutic performances.

Medical applications of nanomaterials are summarized in Table 2.

Another focus of this review is on the development of nanofibrous stents which are surgically implanted for opening up the completely or partially blocked arteries in different cardiovascular disorders. A brief description of stent technology is given in the following section.

Development of stents is a significant milestone in opening up blocked vessels. Implantation of stents has emerged as effective treatment to open the passageways which are obstructed by a variety of

Table 2. Medical applications of nanomaterials.

Nanomaterial	Application	References cited
Gold nanoparticles and Gold Biosensors	Pregnancy test	[4,111,112]
Hydroxyapatite	Tissue regeneration	[18,113,114]
Iron oxide	Drug and vaccine delivery	[52,54,69,114]
Iron oxide	Separation	[115]
Titanium oxide	Protein adsorption	[110]
Titanium and ceramics	Implants	[116,117]
Titanium	Biosensor	[110]
Iron oxide	Magnetic resonance imaging	[52,113]
Quantum dots	Fluorescence, IR Imaging	[3,66,71]
Quantum dots	Vaccine delivery	[5,69]
Quantum dots	Biosensors	[67,75,77,115]
Chitosan	Drug and gene delivery	[119-123]
Liposome	Drug delivery	[42,44,48]
PLGA	Drug delivery	[124-127]
Carbon nanotubes	Tissue regeneration	[128-130]
Carbon nanotubes	Biosensors	[127]

CVDs. During the past two decade, surgical implantation of stents has virtually become a routine procedure for opening up arteries blocked with plaque, esophageal cancer, airways blocked due to lung cancer, scar inflammation or weakening of the airway wall. It is estimated that more than one million stents are implanted each year worldwide, and in the United States alone around 60% stenting procedures are carried out annually in about 600,000 heart patients. The main advantage of stenting is that they do not require major surgery as they are implanted directly through the arteries. To date, a variety of stents (over 40-types) are commercially available or in development composed of different materials such as metal, metal-alloys, platinum, polymer, plastics, coated, un-coated, drug eluting, balloon-expandable and self-expandable. Therefore, over the past two decades the quality of life of patients suffering from arterial blockage has improved immensely. Four generations of stent treatment include balloon angioplasty, bare metal stents, drug-eluting stents, and bioresorbable stents as illustrated in Fig. 2.

A new era of stents started at the beginning of 2011 with world's first drug-eluting-bioresorbable coronary stents. To open the blockage due to the formation of plaques, fatty materials, and cholesterol-induced atherosclerosis in the arteries, the concept of remodelling of the artery was introduced in 1964, which entered into mainstream in 1977 through a procedure called angioplasty to restore blood flow. However, angioplasty has shortcomings because the opening created by this procedure was not very smooth and because the balloon did not evenly expand in all areas of the arterial wall [128-131]. Also, some of the compressed material tends to "spring back", since the recoil causes the channel to become narrow shortly after being enlarged by balloon expansion. Moreover, balloon angioplasty caused restenosis in about 40% of all treated patients [132]. Thus, the concept of stent was developed as a means to mitigate elastic recoil of the artery, control restenosis, strengthen the artery wall, and to hold arterial channels permanently open [133,134].

The other potential benefit of stenting is shorter recovery time over the artery bypass surgery. Therefore, the stent implantation has become the treatment of choice among patients compared to simple balloon angioplasty [135]. However, restenosis occurs in stenting too which is called thrombosis if tissue damage happens right after the stent insertion and in-stent-restenosis if inflammation and scar formation appears within 3-6 months of implantation due to the response of stent presence and native tissue [134,135]. The chances of restenosis are

Fig. 2. Starting from balloon angioplasty to further developed stages of stents.

significantly reduced to 25% in stenting procedure when compared to angioplasty (40%). Later on, drug-eluting stents were developed for the prevention of in-stent-restenosis which carry special drug on their surface to controls scar formation [136,137]. As mentioned earlier, a new era for stent technology started at the beginning of 2011 with world's first drug-eluting bioresorbable coronary stent that dissolves within approximately two years, leaving patients with a treated artery free of a permanent implant [138]. To date, a variety of stents of metals, polymer and plastic in various designs are fabricated. Commonly used metals in stent fabrication include stainless steel, tantalum and nitinol alloys due to their strength, elasticity and flexibility and shape memory, whereas polymers are convenient for drug loading [139-143]. It is estimated that by 2020, global stent device market for USA alone will be six billion USD, where 900,000 stent procedures are performed annually [144]. Though coronary stenting has emerged over the years for the treatment of myocardial infarction, unfortunately 20% to 40% cases develop stent restenosis after stenting, whereas drug eluting stents lead to late stent-induced thrombosis. The market for clinical use, particularly drug-eluting stents has reduced due to early and delayed complications with stenting and the restenosis rate by 80 percent [144]. Optimizing stent design parameters and manufacturing technologies are of great importance because of the increased demand by the ageing population and escalating CVDs which happen to be one of the major killers in the 21st century. Since last few years, nanotechnology is poised to revolutionize biotechnology for medical applications [145], particularly, in developing the next generation of cardiovascular stents using coating of nanoparticles, nanocomposite polymers and nanofiber [146,147]. High-performance flexible [148-150], bioresorbable [151,152], advanced therapeutics via functionalized nanoparticles [153-159] and inorganic nanoparticles have been explored as futuristic therapeutic platforms because of their high surface-to-volume ratio, ability to scavenge reactive oxygen species (ROS), and photo activation properties [160,161]. Fabrication and characterization of bioresorbable and bioinert nanomaterials, designs and their integration strategies with a bioresorbable electronic stent (BES), fitted with nanomembrane-based flexible flow/temperature sensors and memory storage devices, anti-inflammatory nanoparticles, and drug-loaded core/shell nanospheres that are activated by an external optical stimulus has been reported [162]. It is also anticipated [163] that the next generation cardiovascular stent could involve coating with special nanocomposite polymers such as polyhedral oligomeric silsesquioxane poly-caprolactone (POSS-PCU) to enhance endothelialization, endothelial progenitor cell (EPC)-specific antibodies could be attached to the polymer, nitric oxide (NO)-eluting polymers for maintaining a healthy endothelium and preventing thrombosis, and multiple drugs could be incorporated using layer by layer coating technology. Also, polyhedral oligomeric silsesquioxane poly-(carbonate-urea) urethane (POSS-PCU) is non-biodegradable, and so is used as the base coat to prevent bare metal from coming into contact with circulating blood, whereas polyhedral oligomeric silsesquioxane poly caprolactone (POSS-PCL) is biodegradable, and can be used together with drugs for controlled release.

4. SUMMARY AND CONCLUSIONS

The demand for nanotechnology engineered materials is increasing globally and their impact is being felt in a wide variety of biomedical sciences, agriculture and food industry, and physical disciplines, including military applications. Due to their specificity and site targeting properties, the nanomaterials may be a real boon for the diagnosis and treatment of diseases. Here, in the cardiovascular arena, the course of the treatment remains dual in nature, where the stents are implanted mechanically and the therapeutic entities are administered separately. However, nanoparticles imbibed onto the stents can make treatment a one way method, where drugs need not be administered separately but through the medium of stents. Such engineering technique could be one of the most convenient and the compliance reliable method for the patients suffering from cardiovascular ailments. As nanoparticles are known to increase the solubility and permeability of the drugs, the imbibition of drugs on nanoparticles or the stents will not only improve the bioavailability of the therapeutic agents but will also affect their predetermined release profiles. Nevertheless, several issues and concerns are being raised regarding the long-term environmental impact of nanoscale particles, toxicity evaluation of nanomaterials, and cellular and genotoxicity of nanomedicines. Presently, several important safety and regulatory questions remain unanswered: namely, are conventional *in vitro* and *in vivo* methods used for assessing short- and long-term adverse effects of nanoparticles or nanomaterials sufficient, considering their higher surface area, acute and chronic levels of exposure to environment, humans, marine life, and wild ani-

mals? Do similar nanoparticles display differential short- and long-term toxicity once introduced in the body?

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