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Review Article

A brief review on basic fundamentals of nanoparticle (NPs)

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ABSTRACT: According to studies made by previous researchers there are various technical problems associated with liposomes which can be avoided by designing colloidal drugs carrier like nanoparticles with nanotechnology. Now a days they are beneficial in the field of agriculture, veterinary, pharmaceutical, textile technologies. Site specific delivery of encapsulated drugs can be formulated with a nanometer size range which can be injected into the general circulation. The objective of this review is to explain the potential of NPs and nanotechnology associated with their characters and classifications, synthesis and application as the emerging scopes for NPs, rather will attract everyone's attention. The aim of the present work is to characterize biodegradable nanoparticulate systems for oral controlled release, while numerous publications have appeared on this by international research teams, the research on polymeric nanoparticles has been primarily performed by a few research groups in Europe. Nanoparticles are being investigated as an alternative colloidal drug delivery system that could potentially avoid some of the technical problems observed with other drug delivery system.

KEYWORDS: nanoparticles and nanomaterials; advantages; disadvantages of nanoparticles; classification; characterization; property of nanoparticles; synthesis of nanomaterials

1. Introduction

Nanotechnology is defined as the technique by which particles of nano size (10^{-9} nm) can be designed or structured or device as a system with better developed characterized physicochemical properties than many class of microparticles[1].

Why and how can they enter into general circulation and act as a targeted/side specific drug delivery system in tumour complex and so other nanodrug delivery medicines are shown in **Figure 1**. NPs are nano size practically up to range 1–100 nm[2]. Due to its very small size is posse larger surface area and dominance of quantum effects. It can increase concentration in body with smaller size for a particular dose, it makes the particles soluble very easily by crossing the blood brain barriers too, it is providing enhanced pharmacokinetics and pharmacokinetics effects. Recent life systems are utilizing many medicines in form on NPs to treat tumor cancer like diseases[2]. Examples of nanotechnologies are polymer-based NPs, liquid based NPs [liposome nano emulsions solid-liquid NPs, cell assembling nanostructures]. e.g., micelles dendrimer based nano structures, though the nano carriers are the agent used in formulation of NPs have number of advantages like particle size, narrow size distribution, surface feature for target specific localization, protective in solution of a drug molecule to enhance stability, they can respond to physiological stimuli as well as distribution pattern upon systemic

administration. Some other inherent properties like multiple therapeutic agents can be combined to have a synergistic effect on the formulation, designing and development of NPs[3–5]. Along all these effects there smaller particles size and larger surface area to volume ratio potentiates them to cross through various biological barriers also[1–5]. Due to larger surface area NPs are held in suspension and oral route is widely accepted due to optimum absorption based on larger surface area present in the GIT. These parameters have profound effects on the biological environment. Apart from these surface charges, surface adsorption-like properties of nano carriers contribute to its usefulness as carrier platforms[1–5].

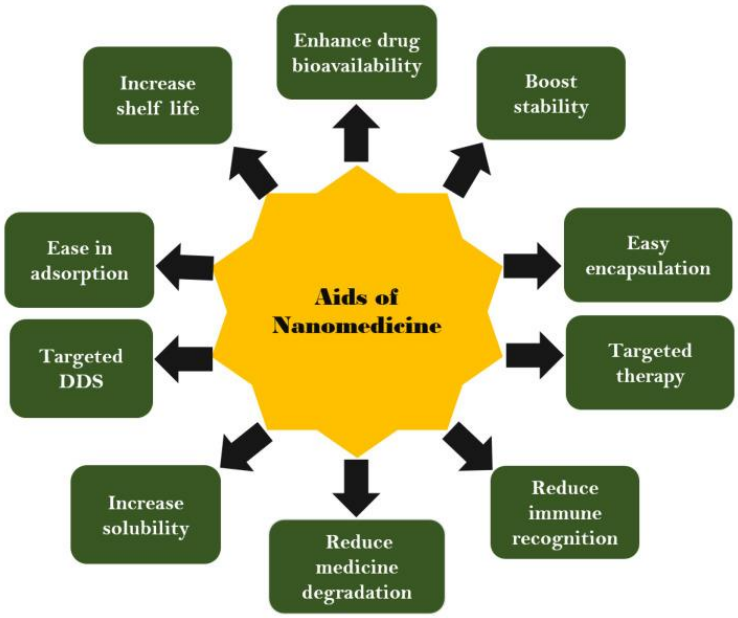

Figure 1. Aids of using nanomedicine platform for delivering drugs to the tumor complex[1].

What are the advantages of NPs that makes it superior from other drug delivery systems and thus challenges its potential, always hits the reader's/researcher's mind, e.g.,[6]

1) enters into tissue or lymphatic systems, biological barriers at molecular level. Diagnosis of cancers, Alzheimer's disease like applications.
2) accurate drug delivery of NPs, its selective interaction with cells makes them an efficient TDDS. It can avoid interaction with healthy cells.
3) characters like optical and magnetic properties nanoscale particle size range agents can pass through biological barriers with prolonged blood circulation time. It provides a selective binding to receptors. These properties had been taken out of scope for small organic molecules like peptides, nucleic acids and antibody application.

Nanotechnology offers an unprecedented opportunity in rational delivery of drugs and genes to solid tumors following systemic administration. Examples of nanotechnology applied in pharmaceutical product development include polymer-based nanoparticles, lipid-based nanoparticles (liposomes, nanoemulsions, and solid-lipid nanoparticles), self-assembling nanostructures such as micelles, and dendrimers-based nanostructures among others. These engineered nanocarriers offer numerous advantages: likes small particle size, narrow size distribution, surface features for target specific localization, protective insulation of drug molecules to enhance stability, opportunity to develop nanocarriers that respond to physiological stimuli, feasibility for delivery of multiple

therapeutic agents in a single formulation, combination of imaging and drug therapy to monitor effects in real time, and the opportunity to combine drugs with energy (heat, light, and sound) delivery for synergistic therapeutic effects. Regardless of the inherent properties of the drug candidates, the pharmacokinetics and distribution pattern upon systemic administration will be dictated by the properties of the nanocarrier system. For instance, particle size and surface charge of tailor-made nanocarriers regulate the biodistribution and pharmacokinetic properties of the nanosystems in the body. Specific engineering of the nanosystems can facilitate transport across a variety of biological barriers. Lastly, multifunctionalities of nanocarrier systems by inclusion of two or more therapeutic agents in a single platform for synergistic effects, combination of heat or light with drug therapy and the opportunity to add imaging contrast agents to therapy offer tremendous potential for the future of medicine. The oral route is widely accepted as the most common method of drug administration into the body due to accessibility, convenience, possibility of repeated self-administration by patients and the opportunity to achieve optimum adsorption based on the large surface area present in the GIT. The advantages of nanocarriers stem from the unique properties that result from their size. Compared to bulk material, nanomaterials have distinguishing characteristics which are largely the result of increased surface area to volume ratio. These properties change as the size of the particle changes. The large surface area allows nanoparticles to be held in suspension and increases frictional forces as well as surface adsorption. Additional material dependent changes include the generation of super plasticity, changes in optical properties, changes in solubility, increased catalytic activity, increased heat capacity, super magnetism in magnetic nanoparticles. Altering parameters such as size, conformation, and charge can have profound effects on how a nanoparticle interacts with and behaves in a biological environment. This versatility of nanoparticles along with appropriate surface chemistry contributes to their usefulness as carrier platforms[7–12].

2. Characteristics of NPs

Several physio-chemical properties characterize NPs as well as influence of its potential applications, so its very essential to have a clear focus on their properties. If we can set the properties as required then their applications can also be altered as per their requirement. NPs physical property influence its morphological features. Other properties like optical properties include color, light penetration, absorption, reflection capabilities, UV absorption in a solution[6,7]. When NPs are coated into a surface it includes the mechanical properties like elastic, ductile, tensile strength and flexibility. Other properties like hydrophobicity, hydrophilicity, suspension, diffusion, settling characteristics are used as and when required. Magnetic and electric properties like conductivity, semi conductivity and resistivity of NPs can open a new door for modern electronics. A range of literature are available supporting the recent study with many modern techniques viewed its physical properties, e.g., SEM technique for morphology study of NPs, e.g., SWNTS (single walled carbon tubes) dispersion in polymer matrix poly(butylene, terephthalate) (PBT) and nylon-6 by Saeed and Khan 2014, ZnO modified metal organic frameworks (MOFs) were studied through SEM technique, which indicates the ZnO NPs dispersion and morphologies of MOFs at different reaction conditions. TEM micrograph techniques are used to study the quadripolar hollow e-shell structure by Wang et al. One can study the XRD pattern of hollow shell structure also. Chemical properties of NPs such as reactivity with target stability and sensitivity towards moisture, atmosphere, heat, light manipulates its application. The antibacterial, antifungal, disinfection, toxicity properties are ideal for biomedical and environmental application. Corrosive, anticorrosive, oxidation-reduction and flammability characteristic of NPs determine their respective use. It is very difficult to study the chemical properties

of Np at the nanoscale ranging particle stage, so morphologic feature and inner structure studies are considered as important parameter[7–23].

Structural/chemical characterization

The primary importance to study the composition and nature of bonding materials provides much information about bulk properties of related nanomaterials. XRD, energy dispersive X-ray (EDX), XPS, IR, Raman, BET and zeta size analyzer are commonly used techniques to study such properties. XRD revels information about crystallinity and its phase at single and multiphase NPs identification reported by Emery et al., but Ingham et al.[24] reported that it is difficult to study less than 100s of atom smaller NPs size to overcome problems related to such is made possible by XRD diffractogram. EDX is normally fixed with a TEM device which is widely used to get knowledge about elemental composition with approximate percentage weight, reported by Avasure et al.[25], Iqbal et al.[26]. They studied the individual ingredients energy radiation that are present in a single NPs sample. This technique is very helpful to the researchers as they can get confirmation about the elements present in their sample.

XPS is the most sensitive technique used to calculate the exact elemental ratio and bonding nature of the elements in the Np material. It can collect electronic images from electronic configuration, e.g., 1s, 2s, 2p, 3s reported by Lynch et al.[27]. It can study the depth of the electron transfer and become easy to study the analysis of dispersion engraved. It is again an evidence of successfully study of the dissolution of NPs in bulk of PEG. Wang et al.[28] quantified the NPs coating with help of XPS, SEM and TEM spectroscopy by help of SESSA software.

Vibration personalization of NPs is studied by FT-IR and Raman spectroscopy. XRD, XPS, EPS are the most feasible techniques to study the structural features of nanomaterials. The uneven electronic distribution in NPs lead to magnetic property which depend on synthetic protocols as well as co-precipitation and servo-thermal analysis results. Some relevant researchers are reported on these synthetic methods by Qi et al.[29]. Flame photometry synthesis, thermal decomposition, micro emulsion are useful method for its preparation reported by Wu et al. It is a very useful property that is applicable to biomedicines, data storage magnetic resonance imaging and environmental remediation by controlling water contamination. Riess and Hutten revealed the best effect of magnetic properties at 10–20 nm scale.

3. Classification of NPs

Nanoparticle is a nano sized particle is mainly divided by thirteen types, polymeric nanoparticles, solid lipid nanoparticles, nanosuspension, polymeric micelles, ceramic nanoparticles, liposome, dendrimers, magnetic nanoparticles, nanoshells coated with gold, nanowires, nanopores, quantum dots, ferrofluids.

3.1. Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLN) are nanostructures made from solid lipids such as glyceryl behenate (Compritol), stearic triglyceride (tristearin), cetyl palmitate and glycerol tripalmitate (tripalmitin) with a size range of 50 nm and 1000 nm. Research interest in SLN emerged about ten years ago due to their scalability potential. The lipids employed are well tolerated by the body; large scale production will be cost effective and simple by using high pressure homogenization. Some of the features of SLN include good tolerability, site-specific targeting, stability (stabilized by surfactants or polymers), controlled drug release and protection of liable drugs from degradation. However, SLN are known for insufficient drug loading, drug expulsion after polymorphic transition on storage and relative high water content of the

dispersions. SLN has been studied and developed for parenteral, dermal, ocular, oral, pulmonary and rectal routes of administration. To overcome the limitations of SLNs, nanostructured lipid carriers (NLC) were introduced. NLC is composed of solid lipids and a certain amount of liquid lipids with improved drug loading and increased stability on storage there by reducing drug expulsion. NLCs have been explored for dermal delivery in cosmetics and dermatological preparations. Lipid drug conjugate (LDC) nanoparticles were introduced to overcome the limitation of types of drugs incorporated in the solid lipid matrix. Lipophilic drugs are usually incorporated in SLNs but due to partitioning effects during production, only highly potent hydrophilic drugs effective in low concentrations are incorporated in SLNs. LDC enables the incorporation of both hydrophilic (e.g., doxorubicin and tobramycin) and lipophilic (e.g., progesterone and cyclosporine A) drugs. SLNs are submicron-sized carriers composed of a lipid solid matrix stabilized by a surfactant. SLNs have been used for carrying different therapeutic agents because they improve absorption and bioavailability. SLNs can be produced by many methods, although the following are the most common[15].

3.1.1. Hot high pressure homogenization (HPH) technique

HPH has emerged as a reliable and powerful technique for the preparation of SLN homogenizers of different sizes are commercially available[15]. It has been used for the production of nanoemulsions for parenteral nutrition. In contrast to other techniques, scaling up represents no problem in most cases. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 km/h) very high shear stress and vitiation forces disrupt the particles down to the submicron range. Typical lipid contents are in the range 5%–10% and represent no problem to the homogenizer. Even higher lipid concentrations (up to 40%) have been homogenized to lipid nanodispersions. Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device (ultra-turrax). The quality of the pre-emulsion affects the quality of the final product to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. HPH of the pre-emulsion is carried at temperatures above the melting point of the lipid. In general, higher temperatures result lower particle sizes due to the decreased viscosity of the inner phase. High temperatures may also increase the degradation rate of the drug and the carrier. This method increases the temperature of the sample (approximately 100 ℃ for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result of the high kinetic energy of the particle. The primary product of the hot homogenization is a nanoemulsion due to the liquid state of the lipid. Solid particles are expected to be formed by the following cooling of the sample to room temperature or to temperatures below. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a supercooled melt for several months.

3.1.2. Cold HPH technique

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to the increase in temperature during homogenization. It has been developed to overcome the following three problems of the hot HPH technique. a) Temperature induced drug degradation. b) Drug distribution into the aqueous phase during homogenization.

Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or supercooled melts. The first preparatory step is the same as in the hot HPH and includes the solubilization of dispersing the drug in the melt of the bulk lipid. However, the following steps are different. The drug containing melt is rapidly cooled (e.g., by means of dry ice or liquid nitrogen). The high cooling rate favors a homogeneous distribution of the drug within the lipid matrix. The solid, drug containing lipid is milled to microparticles. Typically particle sizes obtained by means of ball or mortar milling are in the range of 50–100 micrometers. Low temperatures increase the fragility of the lipid and favor particle commination. The solid lipid microparticles are dispersed in a chilled emulsifier solution. The pre-suspension is subjected to HPH at or below room temperature. In general, compared to hot homogenization, large particle sizes and broader size distribution are observed in cold homogenized sample. This method minimizes the thermal exposure of the sample but it does not avoid it due to the melting of the lipid/drug mixture in the initial step.

3.1.3. Solvent emulsification/evaporation (SEE)

Sjostrom and Bergenstahl described a production method to prepare nanoparticle dispersion by precipitation in o/w emulsions. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g., cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent a nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean particle size depends on the concentration of the lipid in the organic phase. Very small particles could only be obtained with low fat loads related to the organic solvent. With increasing lipid content the efficiency of the homogenization declines due to the higher viscosity of the dispersed phase. The advantage of this procedure over the cold homogenization process is the avoidance of thermal stress. Disadvantage is the use of organic solvents.

3.1.4. High shear homogenization (HSH)

High shear homogenization (HSH) and/or ultrasound are dispersing techniques which were initially used for production of soli lipid nanodispersions. Both methods are widespread and easy to handle. However, dispersion quality is often compromised by the presence of microparticles. Furthermore, metal contamination has to be considered if ultrasound is used. Ahlin et al. used a Lak Tek rotor-stator homogenizer (Omni International, Gaineville, USA) to produce SLN by melt emulsification. They cooling conditions on the particle size and the zeta potential. Lipids used in this study include trimystrin, tripalmitin and tristearin.

3.1.5. Microemulsion

Gasco and coworkers developed SLN preparation techniques which are based on the dilution of microemulsions. Gasco and other scientists understand microemulsions as two-phase systems composed an inner and outer phase (e.g., o/w-microemulsion)[15]. They are made by stirring an optically transparent mixture at 65–70 °C which is typically composed of a low melting fatty acid (e.g., stearic acid), an emulsifier (e.g., butanol, sodium monoactyl phosphate) and water. The hot-micro emulsion is dispersed in cold water (2–3 °C) under stirring. The dilution process is critically determined by the composition of the micremulsion[15]. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes.

3.2. Polymeric nanoparticles

Polymeric nanoparticles are colloidal solid particles with a size range of 10 nm to 1000 nm and they can be spherical, branched or shell structures. The first fabrication of nanoparticles was about 35

years ago as carriers for vaccines and cancer chemotherapeutics. They are developed from non-biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Drugs are incorporated into nanoparticles by dissolution, entrapment, adsorption, attachment or by encapsulation, and the nanoparticles provide sustained release of the drugs for longer periods, e.g., days and weeks. Nanoparticles enhance immunization by prevention of degradation of the vaccine and increased uptake by immune cells. One of the determinants of the extent of uptake by immune cells is the type of polymer employed. In a study comparing poly-(ε-caprolactone) (PCL), poly(lactide coglycolide) (PLGA) and their blend, PCL nanoparticles were the most efficiently taken up by immune cells due to their hydrophobicity. However, all polymeric nanoparticles elicited vaccine (diphtheria toxoid) specific serum IgG antibody response significantly higher than free diphtheria toxoid. To target drugs to site of action, the drug can be conjugated to a tissue or cell specific ligand or coupled to macromolecules that reach the target organs. To target an anticancer agent to the liver, polymeric conjugate nanoparticles which comprised biotin and diamine-terminated poly(ethylene glycol) with a galactose moiety from lactobionic acid were prepared. Some other applications of nanoparticles include possible recognition of vascular endothelial dysfunction; oral delivery of insulin; brain drug targeting for neurodegenerative disorders such as Alzheimer's disease; topical administration to enhance penetration and distribution in and across the skin barrier; and pH-sensitive nanoparticles to improve oral bioavailability of drugs such as cyclosporine A. Some polymers used in the fabrication of nanoparticles include chitosan, alginate, albumin, gelatin, polyacrylates, polycaprolactones, poly(D, L-lactide-co-glycolide) and poly(D, L-lactide). However, there are concerns about polymeric nanoparticles including cytotoxicity of by-products (although some, such as polyanhydrides, degrade into products that are biocompatible) and scalability.

Polymeric nanoparticles are prepared by using the techniques are generally classified in two groups. In the first group, nanoparticles are formed from preformed polymers. The polymers include both water-insoluble and soluble polymers of synthetic, semi-synthetic, or natural origin. Alternatively, nanoparticles are not prepared from preformed polymers but through various polymerization reactions of lipophilic or hydrophilic monomers. The techniques used for the preparation of nanoparticles based on water-insoluble polymers are primarily derived from methods developed for the preparation of aqueous colloidal polymer dispersions, which are used in the coating of solid dosage forms. Latexes are obtained by emulsion polymerization (e.g., acrylic latexesEudragits) and pseudolatexes through the emulsification of polymer solutions or melts (e.g., ethyl cellulose-Aquacoat, Surelease). The pharmaceutical industry adopted the colloidal polymer dispersions from other industrial applications including paints, varnishes, adhesives, and paper coatings. The aqueous colloidal polymer dispersions have been developed to avoid problems associated with the use of organic toxic solvents during the coating of solid dosage forms. The polymer dispersions allow the formation of water-insoluble coatings through the coalescence of the colloidal polymer particles into a homogeneous film from a completely aqueous coating medium. Drug-containing colloidal polymer particles (nanoparticles) can be obtained through the incorporation of a drug substance during or after the preparation of the polymer dispersions. As with microencapsulation methods, there is not one universal technique to prepare nanoparticles. The choice of a particular preparation method and a suitable polymer depends on the physicochemical properties of the drug substance, the desired release characteristics, the therapeutic goal, the route of administration, the biodegradability/biocompatibility of the carrier material, and regulatory considerations. From a technological point of view, the successful selection of a preparation method is determined by the ability to achieve high drug loadings, high encapsulation efficiencies, and

high product yields, and the potential for easy scale-up. For example, methods with high encapsulation efficiencies but with only low drug loading capacity are limited to very potent drugs. Methods that result in nanoparticles with drug loadings and high encapsulation efficiencies are preferred. The term nanoparticles often actually describe the suspended system of the nanoparticles in an aqueous phase, which is the colloidal polymer dispersion. Besides high drug loadings and encapsulation efficiencies, a preparation method should also be able to yield polymer dispersions with a high nanoparticle content, which also directly relates to the size of the dose that can be reasonably administered[7].

3.2.1. Emulsion polymerization

It is among the most frequently employed methods of producing nanoparticles[24]. The term "emulsion polymerization" is somewhat misleading because this process can be carried out without any emulsifier. This term was created because the monomer was emulsified in a nonsolvent by means of emulsifiers. After polymerization, a small polymer particle suspension was obtained. Initially it was assumed that these particles were produced by polymerization of the monomer emulsion droplets. Later it was realized that the resulting polymer particles were smaller than the emulsion droplets. The theory of emulsion polymerization was revised in that the location of polymerization was shifted to the emulsifier micelles. These micelles co-existed with single molecules that were absorbed at the emulsion/droplet interface. Thus stabilizing the emulsion droplets.

3.2.2. Polymerization in a continuous aqueous phase

Polymers used are poly(methyl methacrylate), poly(alkyl cyanoacrylate), acrylic copolymer, polystyrene, poly(vinyl pyridine), poly acrolein, polyglutaraldehyde, poly(alkyl methylidene maleonate) etc. Monomeric methyl methacrylate is soluble in water in water in concentrations up to 1.5%. After dissolution of the monomer, the polymerization is initiated either by high-energy radiation or chemically by addition of a polymerization initiator such as ammonium or potassium peroxodisulfate and heating to elevated temperatures.

3.2.3. Emulsion polymerization in a continuous aqueous phase

It was one of the first processes for the production of nanoparticles. In this process, the phases are reversed and very water soluble monomers are employed. Initially acrylamide and the cross linked N,N1-bisacrylamide were used as monomers. The monomers were solubilized by surfactants. The initiation of this polymerization can be carried out chemically using potassium peroxodisulfate as starters or by gamma or UV light radiation.

3.2.4. Interfacial polymerization

Polymerization of alkyl cyanoacrylates in an organic solvent containing water containing water-swollen micelles may lead to the formation of a polymer wall at the solvent-micellar-water interface. Electrocapillary emulsification method was used to prepare pol-y(N,N-L-Lysine-Diylterephthaloyl) nanoparticles. An electrical potential was applied between the oil and water phase. When this potential exceeds certain value, the interfacial tension is reduced to almost zero and spontaneous emulsification occurs and stable monodisperse emulsions of a particle less than 100 nm can be formed. Poly(alkyl cyanoacrylate) nanoparticles may be formed by this process in an aqueous surrounding phase.

3.2.5. Solvent deposition process

In this process poly(D,L-lactide) polymer as phospholipids are dissolved in acetone. A solution of the drug, indomethacin, dissolved in benzyl benzoate is added to the organic phase and the mixture is

subsequently poured into water containing 0.5% poloxamer 188 under moderate stirring. Nanocapsules with a poly(lactic acid) wall surrounding an oily core are formed instantaneously. This suspension is concentrated by the evaporation of acetone and partial evaporation of water under reduced pressure. Polycaprolactone and PLGA nanocapsules can be produced by this method.

3.2.6. Solvent deposition process

A preformed polymer is dissolved together with the drug in an organic solvent, which is then emulsified in water and subsequently evaporated by heating and/or reduced pressure. The particle size of the resulting polymer particles depends on the size of the emulsion droplets prior to the solvent evaporation. This method has also been used for the preparation of polyacrylic and ethylcellulose nanoparticles incorporating indomethacin as the model drug. While some of the polymers do not require any surfactants or polymer stabilizers, in other cases polysorbate 80, poloxamer 188, SLS, Brij 35, Brij 75, Myrj 52 are employed.

3.2.7. Desolvation from an organic polymer solution

Polyacrylic nanoparticles can be produced by the desolvation process after dissolution of relatively hydrophobic copolymers in water-miscible solvents such as acetone and ethanol. The solutions of the polymer and of the drug to be entrapped (such as ibuprofen, indomethacin) in the solvent were then poured into water, resulting in the spontaneous formation of nanoparticles of sizes between 90 nm and 205 nm. The drug entrapment efficiency was rather 73%–80%. The nanoparticles produced by this method, however were not dispersible in water after spray or freeze drying.

3.2.8. Nanoparticles in an oil emulsion

Nanoparticles consisting of albumin or other macromolecules may be produced by emulsification of aqueous solutions of these macromolecules and of the drug to be incorporated into the particles in oil. The resulting droplets can be hardened by cross-linking with aldehydes or other cross linkers or by denaturation of the molecules at high temperature. High efficiency homogenization or ultrasonication will result in the production of nanometer sized emulsion droplets after hardening nanoparticles. Yoshioka et al.[26] prepared gelatin nanoparticles containing mitomycin. Muramyl peptide and interferon were also incorporated into nanoparticles of gelatin.

3.2.9. Desolvation of macromolecules

Drugs like triamcinolone and doxorubicin were solubilized in water together with gelatin using polysorbate 80. Desolvation was then carried out with sodium sulphate solution and cross-linking was performed with glutaraldehyde solution. Gelatin, albumin, casein, and ethyl cellulose can also be used as the macromolecules for desolvation.

3.2.10. Carbohydrate nanoparticles

These consisting of acryolated dextran, maltodextrannor other starch derivatives were produced by polymerization of the acryolyl side after emulsification of the starch derivative in a toluene and chloroform solution. The drug is dissolved in the solution of acryolated starch derivative at a pH of 8.5. An alternative manufacturing method for this was employed by Schroder et al.

3.2.11. Nanoprecipitation

Fessi et al. proposed a new, simple, and mild method yielding nanometric and monodisperse polymeric particles without the use of any preliminary emulsification. Briefly, an organic solution of the polymer is prepared and added under moderate stirring to a nonsolvent liquid phase. Both solvent

and nonsolvent must have low viscosity and high mixing capacity in all proportions. As an example, acetone and water meet these conditions. The only complementary operation following the mixing of the two phases is to remove the volatile solvent by vaporization under reduced pressure. Further concentration of the aqueous suspension can be carried out under the same conditions or by freeze-drying. The mean diameter of the particles is about 200 nm with a low dispersity. It was observed that the size of the particles was mainly related to the type of the polymer used and less to the experimental conditions. This method has been successfully applied to various biodegradable preformed polymers such as poly(lactide), poly(glycolide), poly(lactide-co-glycolide), poly(e-caprolactone), poly(alkylcyanoacrylate), and other nonbiodegradable preformed polymers such as poly(acrylic), poly(vinylchloride-co-acetate), ethylcellulose, cellulose acetophthalate, and poly(styrene). Small amounts of surfactants, either lipophilic or hydrophilic, can be added to the solvent or to the nonsolvent (for an injectable suspension, phospholipids and Synperonic PE/F68 can be used). However, it was observed that surfactants were not necessary to obtain the colloidal dispersion (which forms spontaneously) but only to stabilize it and to facilitate its dispersion following caking by sedimentation. It was also noteworthy that the sense and the rate of mixing of the two phases had no influence, the organic solution of the polymer being slowly added to the non-solvent or vice versa, with or without the aid of additional stirring. In fact, the most critical conditions for obtaining the spontaneous formation of colloidal particles alone, avoiding any bulk precipitation of the material, were the low concentration of the polymer in the organic phase and the 1/2 ratio of solvent to non-solvent volumes. One of the most interesting and practical aspect of this method is its capacity to be scaled up from laboratory to industrial amounts. This technique presents numerous advantages, in that it is a straightforward technique, rapid and easy to perform. The nanoparticle formation is instantaneous and the entire procedure is carried out in only one step. Briefly, it requires two solvents that are miscible. Ideally, both the polymer and the drug must dissolve in the first one (the solvent), but not in the second system (the non-solvent). Nanoprecipitation occurs by a rapid desolvation of the polymer when the polymer solution is added to the non-solvent. Indeed, as soon as the polymer-containing solvent has diffused into the dispersing medium, the polymer precipitates, involving immediate drug entrapment. The rapid nanoparticle formation is governed by the so-called Marangoni effect, which is due to interfacial turbulences that take place at the interface of the solvent and the non-solvent and result from complex and cumulated phenomena such as flow, diffusion and surface tension variations. Nanoprecipitation often enables the production of small nanoparticles (100–300 nm) with narrow unimodal distribution and a wide range of preformed polymers can be used, such as poly(d,l-lactic-coglycolic acids), cellulose derivatives or poly-caprolactones. This method does not require extended shearing/stirring rates, sonication or very high temperatures, and is characterized by the absence of oily-aqueous interfaces, all conditions that might damage a protein structure. Moreover, surfactants are not always needed and unacceptable toxic organic solvents are generally excluded from this procedure. However, the original nanoprecipitation method suffers from some drawbacks. This technique is mostly suitable for compounds having a hydrophobic nature such as indomethacin, which is soluble in ethanol or acetone, but displays very limited solubility in water. Consequently, reduced or even zero drug leakage toward the outer medium led to nanoparticles with entrapment efficiency values reaching 100%[24].

Figure 2. A schematic representation of the nanoprecipitation method applying dialysis **(A)** in a membrane; and **(B)** the dropping technique under stirring respectively.

NPs are also classified into various categories depending on their morphology, size and chemical properties, characters, e.g., carbon based organic/inorganic based, dendrimers, micelles, liposomes. They are biodegradable, nontoxic. Some particles, e.g., micelles, liposomes are known as nanocapsules, because they have hollow cores within themselves and are sensitive to thermal and electromagnetic radiation[8]. These unique character makes them an ideal choice for drug delivery. The drug charring capacity, its stability determines their efficiency apart from other properties like size, composition and surface morphology[12,17,23].

Carbon based NPs are completely made up of carbon. It is classified into fullerenes. Graphene, carbon nanotubes (CNT), carbon nanofibers and carbon black and something activated carbon nano size fullerenes (C60) is a carbon molecule that is spherical in shape and made up of carbon atom held together by sp^2 hybridization. About 28–1500 carbon atoms forms the spherical structure with diameter up to 8.2 nm, for a single layer. Graphene, an allotrope of carbon is a hexagonal structure of honeycomb lattice is of carbon atom in two dimensional plane. Grapheme sheet thickness is around 1 nm. CNT is a graphene nano foil along with a honeycomb lattice of carbon atom is packed into hollow cylinders to form nanotubes of diameter 0.7 nm for single layer and 100 nm for multilayer of varying length[17,19,21]. Its ends are either hollow or closed by half fullerenes molecules. Carbon nano fibers are produced by the same graphene nanofoils as CNT but poured into a cone or cup shape instead of a regular cylindrical tubes. Carbon black is made up of carbon amorphous in nature with a 20–70 nm diameter sphere. Its agglomerates are bound with ± 500 nm size. Organic NPs are used in TDDS which can be injected into different parts of body. Inorganic NPs are made up of carbon, e.g., metal and nonmetal based NPs[15,17,21,22].

Metal based NPs or inorganic based NPs are made up of metals of nanometric size by destructive or constructive method. All metals can be synthesized into their own NPs, e.g., Al, Cd, Co, Cu, Au, Fe, Pb, Ag, Zn. They possess exceptional properties when compared to their metal counterparts, e.g., ferrous instantly oxidized to iron oxide (FeO) in the presence of oxygen at RT (room temperature} increases its reactivity compared to iron NPs[1].

Dendrimers are nanostructures produced from micromole cules such as poly amidoamine (PAMAM), polypropyleneimine and polyaryl ether; and are highly branched with an innercore. The particle size range is between 1 to 100 nm although their sizes are mostly less than 10 nm. About 20 years ago, dendrimer studies centred on their synthesis, physical and chemical properties while exploration of their biological applications was initiated about thirteen years ago. The uniqueness of dendrimers is based on their series of branches, multivalency, well defined molecular weight and globular structure with controlled surface.

4. Approaches for the synthesis of nanomaterials

Two main approaches are used for the synthesis of nanomaterials (**Figure 3**): top-down approaches and bottom-up approaches.

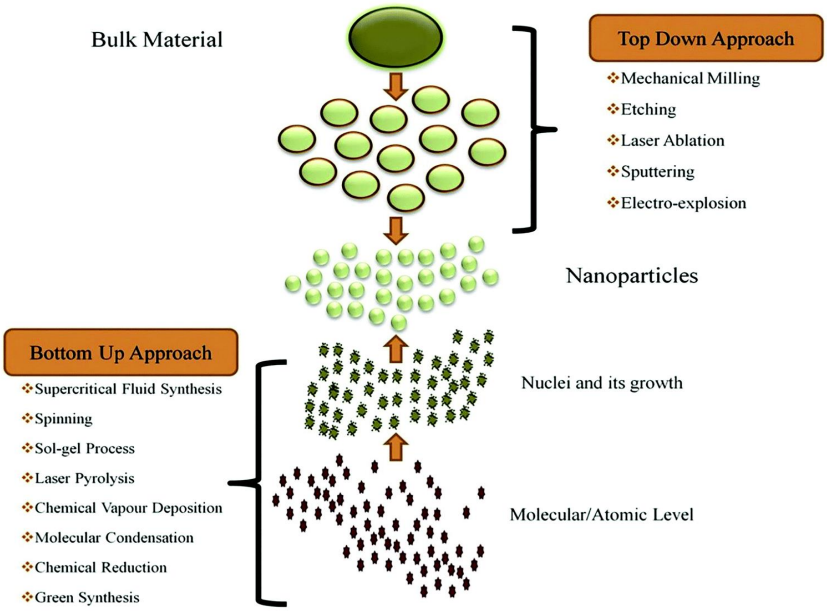

Figure 3. Typical synthetic methods for NPs for the (a) top-down and (b) bottom-up approaches.

4.1. Top-down approaches

In top-down approaches, bulk materials are divided to produce nanostructured materials. Top-down methods include mechanical milling, laser ablation, etching, sputtering, and electro-explosion.

4.1.1. Mechanical milling

Mechanical milling is a cost-effective method for producing materials at the nanoscale level from bulk materials. Mechanical milling is an effective method for producing blends of different phases, and it is helpful in the production of nanocomposites. The principle of the ball milling method is shown in **Figure 4**[25]. Mechanical milling is used to produce oxide- and carbide-strengthened aluminum alloys, wear-resistant spray coatings, aluminum/nickel/magnesium/copper-based nanoalloys, and many other nanocomposite materials[26]. Ball-milled carbon nanomaterials are considered a novel class of nanomaterial, providing the opportunity to satisfy environmental remediation, energy storage, and energy conversion demands[27].

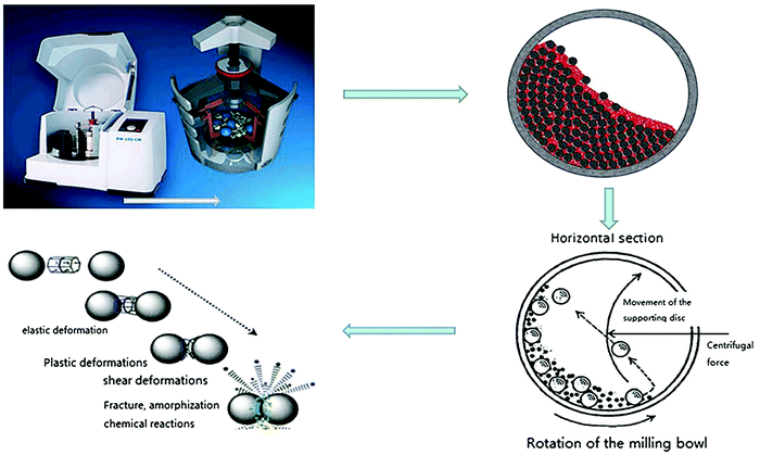

Figure 4. The principle of the ball milling method[25]. [Reprinted with permission. Copyright: ©2016, John Wiley & Sons, Ltd.]

4.1.2. Electrospinning

Electrospinning is one of the simplest top-down methods for the development of nanostructured materials. It is generally used to produce nanofibers from a wide variety of materials, typically polymers[28]. One of the important breakthroughs in electrospinning was coaxial electrospinning. In coaxial electrospinning, the spinneret comprises two coaxial capillaries. In these capillaries, two viscous liquids, or a viscous liquid as the shell and a non-viscous liquid as the core, can be used to form core-shell nanoarchitectures in an electric field. Coaxial electrospinning is an effective and simple top-down approach for achieving core-shell ultrathin fibers on a large scale. The lengths of these ultrathin nanomaterials can be extended to several centimeters. This method has been used for the development of core-shell and hollow polymer, inorganic, organic, and hybrid materials[29]. A schematic diagram of the coaxial electrospinning approach can be seen in **Figure 5**[30].

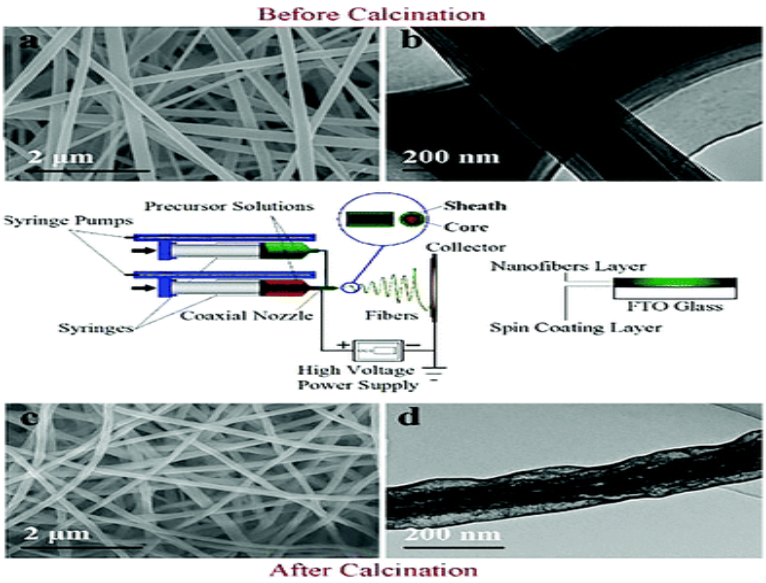

Figure 5. A schematic diagram of the coaxial electrospinning technique (center), and (**a**) and (**c**) FESEM; and (**b**) and (**d**) TEM images of fibers before and after calcination[30].

4.1.3. Lithography

Lithography is a useful tool for developing nanoarchitectures using a focused beam of light or electrons. Lithography can be divided into two main types: masked lithography and maskless lithography[31]. In masked nanolithography, nanopatterns are transferred over a large surface area using a specific mask or template. Masked lithography includes photolithography[32], nanoimprint lithography[33] , and soft lithography[16]. Maskless lithography includes scanning probe lithography[34], focused ion beam lithography[35], and electron beam lithography. In maskless lithography, arbitrary nanopattern writing is carried out without the involvement of a mask. 3D freeform micro-nano-fabrication can be achieved via ion implantation with a focused ion beam in combination with wet chemical etching, as shown in **Figure 6**[36].

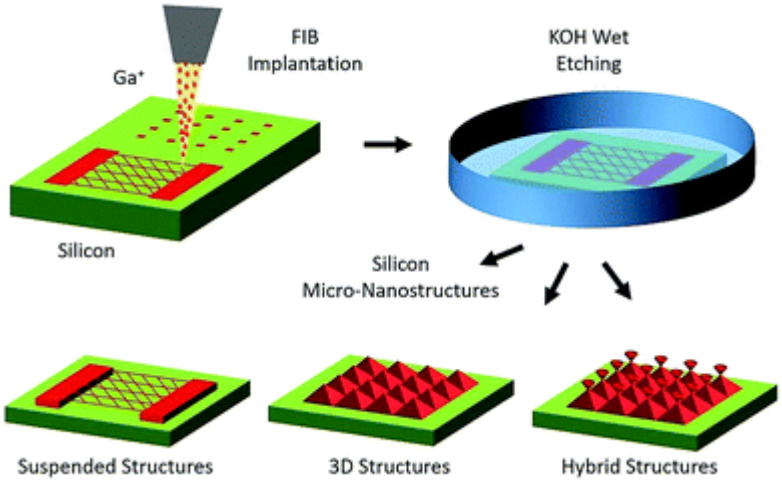

Figure 6. A schematic diagram of the fabrication of 3D micro-nanostructures with an ion beam through bulk Si structuring. This involves implantation in Si through Ga FIB lithography and mask-writing at nanometer resolution, subsequent anisotropic wet etching in KOH solution, and the fabrication of Si micro-nanostructures via the selective removal of the unimplanted region. [Reprinted with permission. Copyright: ©2020, Elsevier B.V. All rights reserved.]

4.1.4. Sputtering

Sputtering is a process used to produce nanomaterials via bombarding solid surfaces with high-energy particles such as plasma or gas. Sputtering is considered to be an effective method for producing thin films of nanomaterials[37]. In the sputtering deposition process, energetic gaseous ions bombard the target surface, causing the physical ejection of small atom clusters depending upon the incident gaseous-ion energy (**Figure 7**)[38,39]. The sputtering process can be performed in different ways, such as utilizing magnetron, radio-frequency diode, and DC diode sputtering[39]. In general, sputtering is performed in an evacuated chamber, to which the sputtering gas is introduced. A high voltage is applied to the cathode target and free electrons collide with the gas to produce gas ions. The positively charged ions strongly accelerate in the electric field towards the cathode target, which these ions continuously hit, resulting in the ejection of atoms from the surface of the target[40]. Magnetron sputtering is used to produce WSe_2-layered nanofilms on SiO_2 and carbon paper substrates[18]. The sputtering technique is interesting because the sputtered nanomaterial composition remains the same as the target material with fewer impurities, and it is cost-effective compared with electron-beam lithography[41].

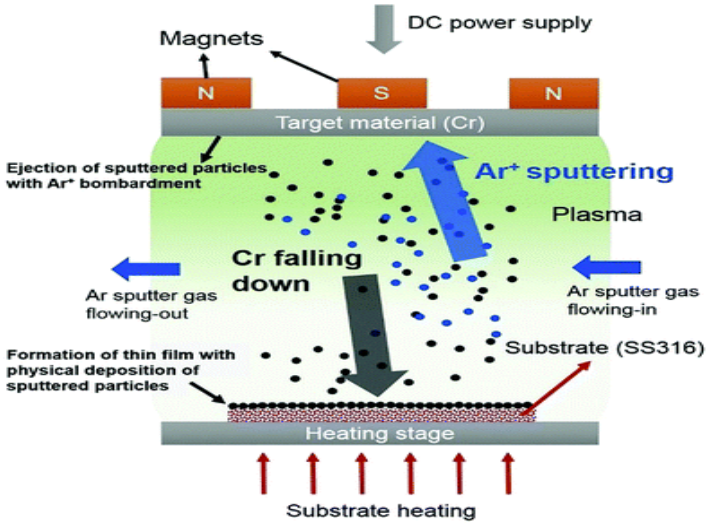

Figure 7. A schematic diagram of the DC magnetron sputtering process. [Reprinted with permission. Copyright: ©2017, Elsevier Ltd. All rights reserved.]

4.1.5. The arc discharge method

The arc discharge method is useful for the generation of various nanostructured materials. It is more known for producing carbon-based materials, such as fullerenes, carbon nanohorns (CNHs), carbon nanotubes, few-layer graphene (FLG), and amorphous spherical carbon nanoparticles[42]. The arc discharge method has great significance in the generation of fullerene nanomaterials. In the formation process, two graphite rods are adjusted in a chamber in which a certain helium pressure is maintained. Filling the chamber with pure helium is important as the presence of moisture or oxygen inhibits fullerene formation. Carbon rod vaporization is driven by arc discharge between the ends of the graphite rods[43].

The conditions under which arc discharge takes place play a significant role in achieving new forms of nanomaterials. The conditions under which different carbon-based nanomaterials are formed via the arc discharge method are explained in **Figure 8**. Various carbon-based nanomaterials are collected from different positions during the arc discharge method, as their growth mechanisms differ[42]. MWCNTs, high-purity polyhedral graphite particles, pyrolytic graphite, and nano-graphite particles can be collected from either anode or cathode deposits or deposits at both electrodes[44–46]. Apart from the electrodes, carbon-based nanomaterials can also be collected from the inner chamber. Different morphologies of single-wall carbon nanohorns (SWCNHs) can be obtained under different atmospheres. For example, 'dahlia-like' SWCNHs are produced under an ambient atmosphere, whereas 'bud-like' SWCNHs are generated under CO and CO_2 atmospheres[47]. The arc discharge method can be used to efficiently achieve graphene nanostructures. The conditions present during the synthesis of graphene can affect its properties. Graphene sheets prepared via a hydrogen arc discharge exfoliation method are found to be superior in terms of electrical conductivity and have good thermal stability compared to those obtained via argon arc discharge[48].

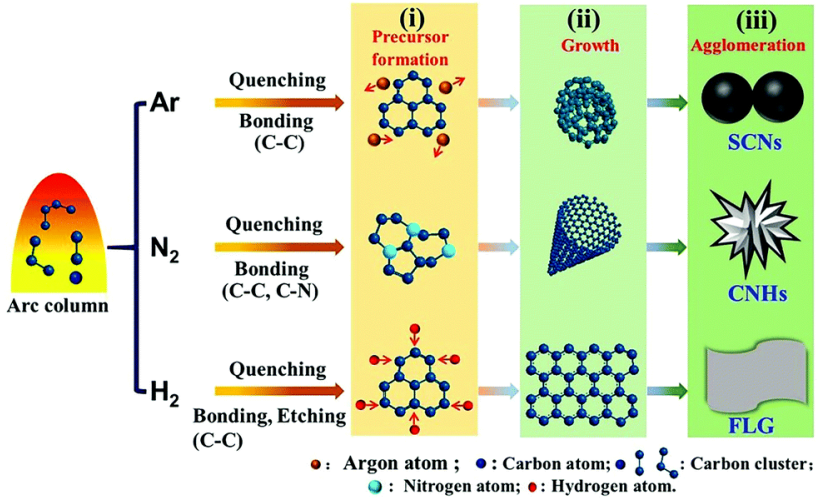

Figure 8. A schematic illustration of the formation mechanisms of carbon nanomaterials on the inner wall of the chamber using different gases via a DC arc discharge approach.

4.1.6. Laser ablation

Laser ablation synthesis involves nanoparticle generation using a powerful laser beam that hits the target material. During the laser ablation process, the source material or precursor vaporizes due to the high energy of the laser irradiation, resulting in nanoparticle formation. Utilizing laser ablation for the generation of noble metal nanoparticles can be considered as a green technique, as there is no need for

stabilizing agents or other chemicals[49]. A wide range of nanomaterials can be produced through this technique, such as metal nanoparticles[50], carbon nanomaterials[51,52], oxide composites[53], and ceramics[54]. Pulsed laser ablation in liquids is an exciting approach for producing monodisperse colloidal nanoparticle solutions without using surfactants or ligands. The nanoparticle properties, such as average size and distribution, can be tuned via adjusting the fluence, wavelength, and laser salt addition. It can be seen in **Figure 9** , that the sizes of as-synthesized Pd nanoparticles are substantially affected by the wavelength and fluence of the pulsed laser[55].

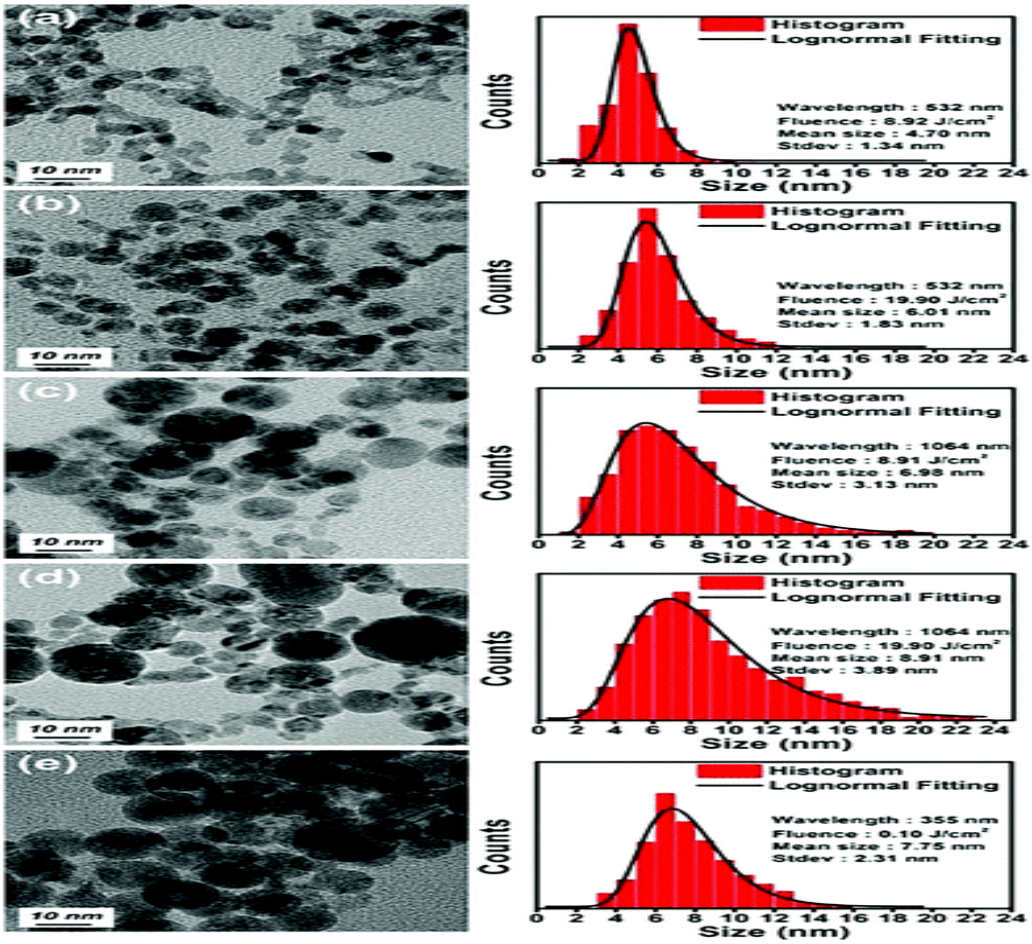

Figure 9. TEM images, corresponding mean sizes, and standard deviations of palladium nanoparticles synthesized via laser ablation in water for 10 min at laser wavelengths and fluences of (a) 532 nm and 8.92 J cm^{-2}, (b) 532 nm and 19.90 J cm^{-2}, (c) 1064 nm and 8.92 J cm^{-2}, (d) 1064 nm and 19.90 J cm^{-2}, and (e) 355 nm and 0.10 J cm^{-2}.

4.2. Bottom-up approaches

4.2.1. Chemical vapor deposition (CVD)

Chemical vapor deposition methods have great significance in the generation of carbon-based nanomaterials. In CVD, a thin film is formed on the substrate surface via the chemical reaction of vapor-phase precursors[56]. A precursor is considered suitable for CVD if it has adequate volatility, high chemical purity, good stability during evaporation, low cost, a non-hazardous nature, and a long shelf-life. Moreover, its decomposition should not result in residual impurities[56]. For instance, in the generation of carbon nanotubes via CVD, a substrate is placed in an oven and heated to high temperatures. Subsequently, a carbon-containing (such as hydrocarbons) gas is slowly introduced to the system as a precursor. At high temperatures, the decomposition of the gas releases carbon atoms, which

recombine to form carbon nanotubes on the substrate[57]. However, the choice of catalyst plays a significant role in the morphology and type of nanomaterial obtained. In the CVD-based preparation of graphene, Ni and Co catalysts provide multilayer graphene, whereas a Cu catalyst provides monolayer graphene[58]. Overall, CVD is an excellent method for producing high-quality nanomaterials[59], and it is well-known for the production of two-dimensional nanomaterials (**Figure 10**)[60].

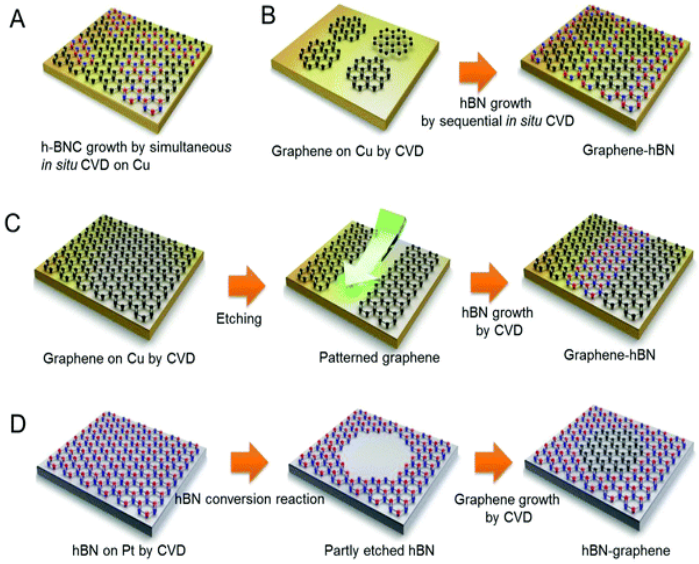

Figure 10. A schematic diagram of the growth of in-plane graphene and hBN heterostructures via various techniques: (**A**) Simultaneous in situ CVD growth, (**B**) sequential in situ CVD growth, (**C**) lithography-assisted growth, and (**D**) conversion growth[60].

4.2.2. Solvothermal and hydrothermal methods

The hydrothermal process is one of the most well-known and extensively used methods used to produce nanostructured materials[61,62]. In the hydrothermal method, nanostructured materials are attained through a heterogeneous reaction carried out in an aqueous medium at high pressure and temperature around the critical point in a sealed vessel[63]. The solvothermal method is like the hydrothermal method. The only difference is that it is carried out in a non-aqueous medium. Hydrothermal and solvothermal methods are generally carried out in closed systems[64]. The microwave-assisted hydrothermal method has recently received significant attention for engineering nanomaterials, combining the merits of both hydrothermal and microwave method. Hydrothermal and solvothermal methods are exciting and useful methods for producing various nano-geometries of materials, such as nanowires, nanorods, nanosheets, and nanospheres[65–67].

4.2.3. The sol-gel method

The sol-gel method is a wet-chemical technique that is extensively used for the development of nanomaterials. This method is used for the development of various kinds of high-quality metal-oxide-based nanomaterials. This method is called a sol-gel method as during the synthesis of the metal-oxide nanoparticles, the liquid precursor is transformed to a sol, and the sol is ultimately converted into a network structure that is called a gel[68]. Conventional precursors for the generation of nanomaterials using the sol-gel method are metal alkoxides. The synthesis process of nanoparticles via the sol-gel method can be completed in several steps. In the first step, the hydrolysis of the metal oxide takes place in water or with the assistance of alcohol to form a sol. In the next step, condensation takes place, resulting in an increase in the solvent viscosity to form porous structures that are left to age.

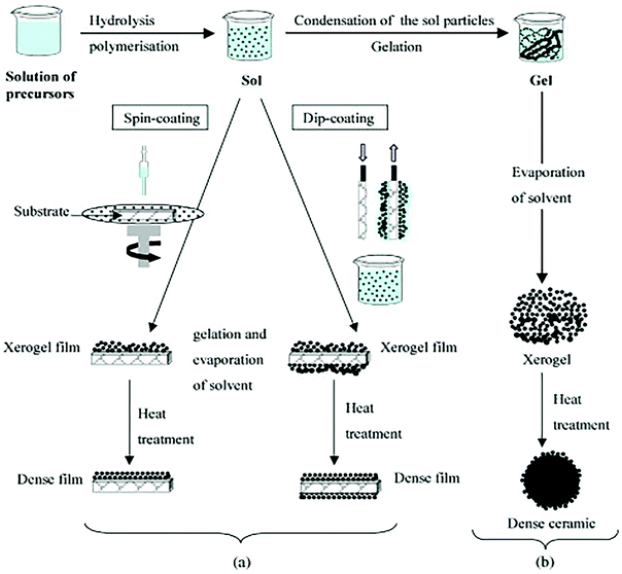

Figure 11. An overview showing two sol–gel method synthesis examples: (**a**) films from a colloidal sol and (**b**) powder from a colloidal sol transformed into a gel.

During the condensation or polycondensation process, hydroxo-(M–OH–M) or oxo-(M–O–M) bridges form, resulting in metal-hydroxo- or metal-oxo-polymer formation in solution[69]. During the aging process, polycondensation continues, with changes to the structure, properties, and porosity. During aging, the porosity decreases, and the distance between the colloidal particles increases. After the aging process, drying takes place, in which water and organic solvents are removed from the gel. Lastly, calcination is performed to achieve nanoparticles[70]. **Figure 11** shows film and powder formation using the sol-gel method[71]. The factors that affect the final product obtained via the sol-gel method are the precursor nature, hydrolysis rate, aging time, pH, and molar ratio between H_2O and the precursor[72]. The sol-gel method is economically friendly and has many other advantages, such as the produced material being homogeneous in nature, the processing temperature being low, and the method being a facile way to produce composites and complex nanostructures[72].

4.2.4. Soft and hard templating methods

Soft and hard template methods are extensively used to produce nanoporous materials. The soft template method is a simple conventional method for the generation of nanostructured materials. The soft template method has been considered advantageous due to its straightforward implementation, relatively mild experimental conditions, and the development of materials with a range of morphologies[73]. In the soft templating method, nanoporous materials are produced using plenty of soft templates, such as block copolymers, flexible organic molecules, and anionic, cationic, and non-ionic surfactants[74]. Most prominent interactions between the soft templates and the precursors occur through hydrogen bonding, van der Waals forces, and electrostatic forces[75]. Soft templates of 3D specifically arranged liquid crystalline micelles are used to synthesize 3D ordered mesoporous structures. One of the classic examples involves mesoporous solids, such as lamellar (MCM-50), cubic (MCM-48), and hexagonal (MCM-41) ordered mesoporous silicas, being produced using alkyltrimethylammonium surfactant[76,77]. Generally, for the synthesis of ordered mesoporous materials via a soft templating method, two processes called cooperative self-assembly and "true" liquid-crystal templating are adopted[78]. Several factors can affect the mesoporous material structures derived from 3D arranged micelles, such as the surfactant and precursor concentrations, ratio of surfactant to precursor, surfactant structure, and environmental conditions[79]. The nanoporous material pore sizes can be tuned via

varying the surfactant carbon chain-length or introducing auxiliary pore-expanding agents. A range of nanostructured materials, such as mesoporous polymeric carbonaceous nanospheres[80], single crystal nanorods[81], porous aluminas[82], and mesoporous N-doped graphene[83], can be produced via the soft template method.

The hard template method is also called nano-casting. Well-designed solid materials are used as templates, and the solid template pores are filled with precursor molecules to achieve nanostructures for required applications (**Figure 12**)[76]. The selection of the hard template is critical for developing well-ordered mesoporous materials. It is desirable that such hard templates should maintain a mesoporous structure during the precursor conversion process, and they should be easily removable without disrupting the produced nanostructure. A range of materials has been used as hard templates, not limited to carbon black, silica, carbon nanotubes, particles, colloidal crystals, and wood shells[84]. Three main steps are involved in the synthetic pathway for obtaining nanostructures via templating methods. In the first step, the appropriate original template is developed or selected. Then, a targeted precursor is filled into the template mesopores to convert them into an inorganic solid. In the final step, the original template is removed to achieve the mesoporous replica[85]. Via using mesoporous templates, unique nanostructured materials such as nanowires, nanorods, 3D nanostructured materials, nanostructured metal oxides, and many other nanoparticles can be produced[86]. From this brief discussion, it can be seen that a wide range of unique structured nanomaterials can be produced using soft and hard template methods.

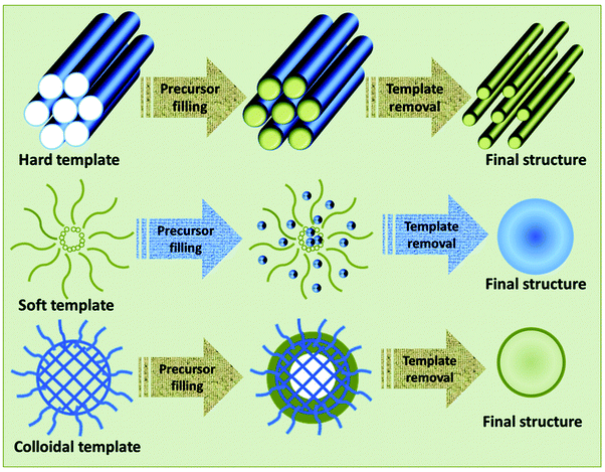

Figure 12. A schematic representation of the synthesis of materials using different types of templates[76].

4.2.5. Reverse micelle methods

The reverse micelle method is also a useful technique for producing nanomaterials with the desired shapes and sizes. An oil-in-water emulsion results in normal micelles, in which hydrophobic tails are aimed towards a core that has trapped oil droplets within it. However, reverse micelles are formed in the case of a water-in-oil emulsion, in which the hydrophilic heads are pointing towards a core that contains water[87]. The core of the reverse micelles acts as a nanoreactor for the synthesis of nanoparticles. It acts as the water pool for developing nanomaterials. The size of these nanoreactors can be controlled by varying the water-to-surfactant ratio, ultimately affecting the size of the nanoparticles synthesized through this method. If the water concentration is decreased, this results in smaller water droplets, resulting in the formation of smaller nanoparticles[88]. Thus, the reverse micelle method provides a facile route for synthesizing uniform nanoparticles with precisely controlled size.

Nanoparticles developed through the reverse micelle method are amazingly fine and monodispersed in nature[89]. **Figure 13** demonstrates the synthesis of magnetic lipase-immobilized nanoparticles via the reverse micelle method[90].

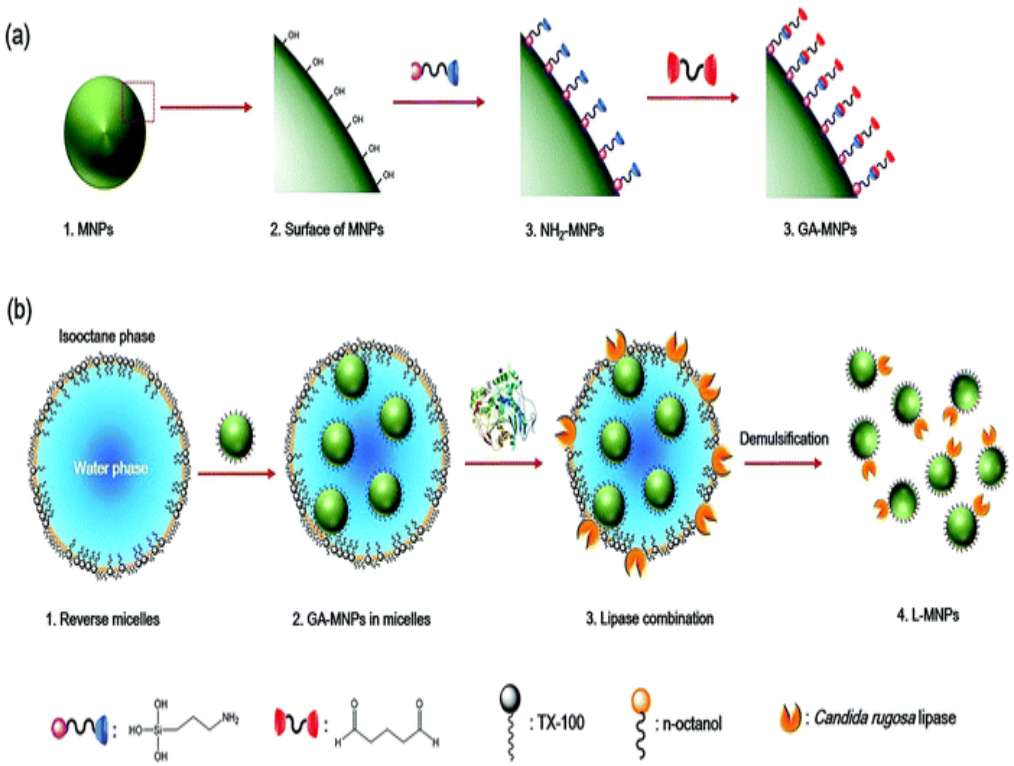

Figure 13. (**a**) A schematic diagram showing the synthetic steps to GA-MNPs. (**b**) The synthesis of L-MNPs through a non-ionic reverse micelle method.

5. Applications of nanoparticle

Applications in drugs and medications Nano-sized inorganic particles are important material in the development of novel nanodevices and can be used in numerous physical, biological, biomedical and pharmaceutical application[91,92]. Many literatures proves that PEG, PLA has efficiency as a carrier in preparation of nanoparticles. It has been proved as a gift system for IV administration. The present day has used high magnetization values with particle size smaller than 100 nm[1], that inhibit tumor growth. Silver NPs are used in wound dressing, catheters, household products due to their antimicrobial activity. Superparasmagnetic iron oxide NPs are raising its head against tissue repair, immunoassays, detoxification of biological fluids like biomedical application[93] .

5.1. Applications in manufacturing and materials

Jia Ling Tsong, Rodney Robert, Sook Mei Khor et al have applications including chemical sensors and biosensors.

Noncrystalline materials display physicochemical characteristics that induce unique electrical, mechanical, optical and imaging properties which have certain applications in the medical, commercial, and ecological sectors[94].

5.2. Application in the environment

To save environment from contaminant of nano materials that release from industrial and

household applications super paramagnetic iron oxide NPs are effective material for the toxic soft material of NPs[95]. For photodegradation reactions of toxic nano materials present in the environment can be removed by NiO/ZnO NPs modified silica gel with <10 nm particle sizes are used to clean it. Due to small size it has a larger surface area and facilitates photo degradation reaction[96–97].

5.3. Applications in the electronics

Printed electronics with various functional inks containing metallic NPs, organic electronic molecules, CNTS and ceramic NPs for new type of electronic equipment[96].

5.4. Applications in energy harvesting

NPs also use in energy storage applications to reserve the energy into different forms at nanoscale level[90–96].

5.5. Applications in mechanical industries

Many nano devices are used for various industrial purposes. It has been applied in coating, lubricating and adhesives purposes. Others with purpose are mentioned in **Table 1**.

Table 1. Therapeutic application of nanoparticles[5,7,8,16–18].

Application purpose	Application/purpose
Cancer therapy	Targeting, reduced toxicity, enhanced up take of antitumor agents, improved invitro and in vivo stability
Intracellular	Target reticuloendothelial systems for intracellular
Targeting	Infections
Prolonged systemic circulation	Prolong systemic drug effect, avoid uptake by the reticuloendothelial system
Vaccine adjuvant	Enhances immune response, alternate acceptable adjuvant
Peroral absorption	Enhanced bioavailability, protection from gastrointestinal enzymes.
Ocular delivery	Improved retention of drug or reduced washout.
DNA delivery	Enhanced delivery and significantly higher expression levels.
Oligonucleotide delivery	Enhanced delivery of oligonucleotide
Other application	Crosses blood-brain barrier. Improved absorption and permeation. Radio-imaging, oral delivery of peptides.

5.6. Challenges of nanodrug delivery

Although nanotechnology in drug delivery has been successful, as evidenced by some nanodrug products in the market, not all approaches have met with the same success. New nanomaterials being developed come with challenges which have to be surmounted. However, some of the challenges encountered have been and are still being tackled by modification of the physicochemical characteristics of the nanomaterials to improve on properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barrier sand site-specific targeting.

Another challenge of research and development (R&D) of nanomaterials for drug delivery is large scale production. A number of nanodrug delivery technologies may not be scalable due to the method and process of production and high cost of materials employed. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process—it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale. Maintaining the size

and composition of nanomaterials at large scale is also a challenge.

Despite the number of patents for nanodrug delivery technologies, commercialization is still at its early stage. This is partially due to the fact that most of the research studies in nanodrug delivery are carried out by researchers in academia. Unfortunately, a number of the major pharmaceutical industries are yet toconsidernanotechnologyasoneoftheirprioritiesduetolackofregulatoryguidelines and challenges of scaling up. However, itis envisaged that with the expiration of more patents and market loss, more pharmaceutical industries will take up the production of nanodrug products in order to compete favorably.

Advances in nanodrug delivery technology also provide new challenges for regulatory control. The increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nanodrug products, which are different from conventional drug products. The United States' Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) have taken the initiative to identify some possible scientific and regulatory challenges. Furthermore, the International Organization for Standardization has set up a technical committee (TC 229) for the field of nanotechnologies to develop standards pertaining to terminology and nomenclature; measurement and characterization; and health, safety and environment amongst other standards. These standards are still under development.

5.7. Safety issues

With increased R&D work on nanodrug delivery, emerges concerns about the safety of the nanotechnologies in humans. Some of the nanomaterials are biodegradable while some are not; furthermore, the side effects of the by-products present a huge concern. Materials which may be safe at macroscale may not be at nanoscales in there may be changing physicochemical characteristics of nanoscale preparations. These nanomaterials may not clear completely from the body and their accumulation may have several possible effects.

Safety and possible impact nanomaterials should not be considered for the patient population alone but also for the entire manufacturing and disposal processes. Conventional safety measures in a pharmaceutical factory may not be appropriate for the development and fabrication of nanomaterials. Also extra measures are to be taken to protect the environment from increased envisaged negative impacts of nanomaterials. There is also the general public reluctance to embrace nanotechnology based on the unavailability of documented safety guidelines. However, despite these challenges, nanodrug delivery is a development that can't be ignored and so the challenges will be tackled with time.

6. Conclusion

The degradation of these nanoparticles was found to be a surface erosion process, because the particle size decreases immediately after incubation and does not show any lag period. This observation is in agreement with an earlier finding that the release rate of drugs such as dactinomycin depends on the cyanoacrylate side chain ester length. Here in the review, we presented an overview of NPs, their types, characterizations, physicochemical properties applications, and synthesis through different characterization techniques such as SEM, TEM and XRD, it divulged a clue that NPs have size ranges from few nanometer to 500 nm with use of nanomaterial like dendrimers and others. Because of its nano size, NPs have large surface area, which make them suitable candidate for various applications. Beside this, the optical properties are also dominant at those nano sizes, which further increases the importance of nanomaterials in photocatalytic applications. Various synthetic techniques are useful to

control the specific morphology, size and magnetic properties of NPs. The molecular weights of nanoparticles are mainly determined after the dissolution of the particles in an appropriate solvent and the subsequent gel permeation chromatography. The validation of the obtained results is a however. So far, mainly polystyrene and some poly(methyl methacrylate) standards are available that are only of limited use for the molecular weight determination of other polymers. Though NPs are useful for many applications, but still there are some health hazard concerns due to their uncontrollable use and discharge to natural environment, which should be consider for make the use of NPs more convenient and environmental friendly so that it can clean environment by providing safer air and water, and clean renewable energy for a sustainable future, which is made possible now a days. Nanotechnology attracts a lot of attention where more investment is made for the research and development by top institutions, industries and organizations. It has also been established to be an advanced field of science where extensive research is carried out to implement the technology. This is being tested for various new applications (**Table 1**) to increase the efficiency and performance of the object or process and subsequently reduce the cost so that it is accessible for everyone. Nanotechnology has a great future due to its efficiency and environmental friendly properties.

Nanotechnology-based nanomedicine is a diverse field for disease treatment. Nowadays, in every sort of disease, nanotechnology is emerging as the best therapeutic to cure disease. At California University, researchers are developing methods to deliver cardiac stem cells to the heart. They attached nanovesicles that directly target injured tissue to increase the amount of stem cells there. Thus, the involvement of stem cells with nanotechnology will develop many solutions for the disease-based queries in the medical arena. However, nanomedicine and nanodrugs deal with many doubts. Irregularities and toxicity and safety valuations will be the topic of development in the future. Nanotechnology will be in high demand. Nowadays, drug-targeted delivery through nanoparticles is catching the attention of pharmaceutical researchers all over the world. Nanomedicine will overcome all the side effects of traditional medicines. This nanoscale technology will be incorporated in the medical system to diagnose, transport therapeutic drugs, and detect cancer growth, according to the National Cancer Institute. Experts are trying to treat SARS-CoV-2 with nanomedicine, as nanoparticles with 10–200 nm size can detect, for site-specific transfer, SARS-CoV-2, exterminate it, and improve the immune system of the body. Nanotechnology could help to combat COVID-19 by stopping viral contamination. Highly accurate nano-based sensors will be made in the future that will quickly recognize the virus and act by spraying to protect frontline doctors and the public. Furthermore, many antiviral disinfectants are being developed through nanobiotechnology to stop virus dissemination. In the future, nanotechnology will evolve to develop drugs with high activity, less toxicity, and sustained release to target tissue. Therefore, personalized medicine and nanomedicine both will be potential therapies to treat COVID-19 successfully, as well as to treat upcoming diseases in future.

Future challenges of nanoparticles as nanomedicines:

In the field of nanomedicine, there are many innovations which show its importance in clinical and other medical aspects. Many scientists have investigated in their research how nanomedicine is involved in treating malignancies and reducing mortality and morbidity rates. However, there are also future challenges that nanomedicines have been facing until now. The implementation of nanomedicine in clinical practice will face many issues with insurance companies, regulatory agencies, and the public health sector. Until now, the FDA has not developed any specific regulation for the products containing nanomaterials. Due to a lack of nanomaterial standardization and other safety issues, US agencies, such

as the EPA European pharmaceutical association) and NIOSH (National institute for occupational safety and health), are giving less funding to these research endeavors.

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Conflict of interest

The authors declare no conflict of interest.

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