1 Introduction to Nanoparticulate Drug Delivery Systems

Jayvadan Patel, Anita Patel, Mukesh Patel, and Govind Vyas

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Abstract

Nanotechnology is the innovatory technology of the twenty-first century, and nanoparticulates as drug delivery systems have created a considerable amount of attention from researchers. It is a promising interdisciplinary area of research wherever groups of atoms as well as molecules are handled at the nanometer levels. It can be defined as the systematic study of materials that have properties critically dependent on length scales on the order of nanometers. Such novel and improved properties make nanoparticulate materials promising candidates to provide the best scientific as well as technological progress in a number of fields in particular biology, communications, environment, energy, healthcare, information, medical care, and pharmacy. The use of nanotechnology in medicine and more explicitly drug delivery is set to spread speedily. The growing range of nanoparticulate-based drug delivery methods is assured of changing the formulation characteristics of new compounds and extending the lifecycle of existing compounds. In order to achieve this, the chapter deals with the definitions and classification of nanoparticulate materials, a fundamental understanding of their valuable properties, and different types of nanoparticulates employed as drug delivery systems.

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1 Introduction

The first technical revolution, at the end of the eighteenth century, has sparked the progression of industrial research and the attainment of novel materials. At present, the obstacles are the miniaturization of devices as well as instruments: lesser volume and lesser power consumption but better performance. The progress relies upon searching out novel pleasing materials and the capacity to construct minute structures with high accuracy. The development of novel technology is not very smooth and effortless task. One of the best splendid techniques created to answer such a condition is nanotechnology [1, 2]. In recent times, the study engaging nanoparticulate materials has created a substantial amount of attention from researchers. They believe nanotechnology is the innovatory technology of the twenty-first century.

The word nanotechnology is taken from the Greek word "nano," which stands for "dwarf" or "very small," and so it relates to materials of minute size ranges [3, 4]. The interdisciplinary science of nanotechnology is a brilliant field wherever a group of atoms as well as molecules are handled at the nanometer scale. In actual fact, it is the design of components, devices, materials, and/or systems close to atomic or molecular levels. Generally, one of the dimensions of nanomaterials is between 1 and 100 nanometers (nm) length in scale. This promising technology implies the imaging, handling, manufacturing, measuring, modification, modeling, and reduction of matter at the nanoscale with characteristic properties, for example, cost-effective, definite, eco-friendly, good strength, lighter, and specific for a variety of purposes [5, 6].

The definition of nanotechnology has been divided into two parts: one is the part about manufacturing at dimensions of 1–100 nm, and the other is about characteristics of materials at the nanometer scale that initiate their use for novel applications. The size range of particles that holds immense attention is characteristically from 100 nm down to the atomic level, for the reason that it is in this range that materials have fundamentally distinct properties from their bulk counterparts. The most important justifications for this revolutionize in performance are an increased significance of surface as well as the interfacial area [7]. At the same time, nanotechnology is a new-fangled paradigm in fundamental thoughts and understanding regarding the physical universe, where the bottom-up approach is the rule and not an exception. In this novel system, one has to imagine in terms of atoms and how they act together to create valuable materials, structures, devices, and systems [8–10].

Nanotechnology has been moving from the laboratory surroundings to applications and customer products for quite a while now [11]. Nanotechnology will create new perspectives for this world, and its promises have been noticed to provide the best scientific as well as technological progress in a number of fields in particular communications, electronics, energy, environment, information, health, and medical care [12]. Nanotechnology has also a wider perspective in the areas of biology, pharmacy, physics, and materials science which could merge to contribute to healthcare. The insight of nanotechnology has been investigated in healthcare research for the past three decades; it is still believed to be in the early stage of development as anticipated therapeutic advantages have not been totally understood [13, 14]. The educational as well as industrialized groups of people together are paying more attention along with money into the development of nanotherapeutics to conquer the superficial challenges and interpret the theoretically recognized benefits of nanoparticulate systems into clinical benefits. The exploit of nanotechnology in drug delivery is set to spread speedily. Although nanotechnology is at its early stages, however, it is expanding quickly, opening plentiful perspectives for the logical minds to utilize this enhanced technology for human well-being [15].

This chapter addresses to fill up-to-date understanding of manufactured nanoparticulates, by providing an extensive review of current progress in the nanotechnology field. It draws attention to the different definitions, classifications, fundamental properties, and different types of nanoparticulate materials employed for drug delivery.

2 Nanomaterials

Nanomaterials, previously called by Paul Ehrlich as "magic bullets" [16], are one of the major investigated materials of the century that gave birth to a novel branch of science referred to as nanotechnology [17]. Nanomaterials are chemical materials that can be produced or employed at a minute scale. Indeed, the word material speaks about an infinite number of components, jointly showing an averaged statistical performance. As a result, the performance of nanomaterials is affected by specific interface effects and demonstrates characteristics affected by the size and the restricted number of constituents [18].

Nanomaterials are a diverse class of substances that have structural constituents lesser than 100 nm in a minimum of one dimension. Nanomaterials consist of nanoparticles, which are particles, with at least two dimensions between about 1 and 100 nm [19]. However, a single globally recognized definition for nanomaterials does not present. Diverse groups have dissimilarities in belief in defining nanomaterials [20]. To be classified as nanomaterials, the material must be less than 100 nm in size in a minimum of one direction. The International Organization for Standardization (ISO) has explained nanomaterials as a "material with any external nanoscale dimension or having the internal nanoscale surface structure" [21]. As per the European Union Commission, nanomaterials means "a manufactured or natural material that acquires unbound, aggregated or agglomerated particles where external dimensions are between 1–100 nm size ranges" [22].

The exploit of different definitions throughout diverse authorities is referred to as the most important obstacle to regulatory efforts as it shows the way to legal uncertainty in applying regulatory approaches for indistinguishable nanomaterials. So, the requirement to convince diverging considerations is the main confront in developing a single international definition for nanomaterials.

3 Why Are Nanoparticulate Materials So Special and Unique?

Nanoparticulate materials, which can be either stand-alone solids or subcomponents in other materials, are smaller than 100 nm in one or more dimensions. Putting this dimension in standpoint, a nanometer (nm) is one-billionth of a meter and one-millionth of a millimeter, approximately four times the diameter of an atom. For our macro-oriented brains, in fact, understanding the scale of the nanometer is not easy although real-life comparisons can help give us a good judgment. For example, the twinkling of an eye is to a year is what a nanometer is to a meter stick [23].

Nanoparticulate materials have a higher surface area-to-volume ratio in addition to the number of surface atoms, and their arrangement decides the size and properties of the nanoparticulate materials [24]. Size reduction of materials can bring about an entire range of novel physicochemical features and prosperity of prospective applications [25].

These features very much rely upon the size, shape, surface area, and structure of elements. Nanoparticulate materials can be present in single, compound, aggregated, or agglomerated structures with sphere-shaped, cylindrical, and asymmetrical shapes [26]. By the production of nanoparticulate structures, it is probable to manage the basic properties of materials, for instance, their charge capacity, magnetic properties, melting temperature, and even their color, without altering the chemical composition of the nanoparticulate structures. This will make possible novel, highly efficient materials and nanotechnologies that were impracticable in the past. The most important benefits of nanoparticulate materials against bulk material consist of a reduction in melting point as well as surface area and an enhancement in dielectric constant in addition to mechanical strength [27–30]. Additionally, the size of nanoparticulate materials facilitates them to absorb remarkably onto other materials [29, 31, 32]. At the nanoscale, the power of gravity gives van der Waals forces, surface tension, and additional quantum forces.

For differentiation of nanoparticulate materials from the bulk materials, it is essential to show the distinctive properties of nanoparticulate materials and their potential effects on science as well as technology. The size of the nanoparticulate materials has an enormous control on their properties (Fig. 1.1). When a particle is in its bulk state in comparison with its size in its microscale, there is not a large amount of dissimilarity in its properties. In contrast, when the particle achieves a size smaller than 100 nm, the properties revolutionize remarkably in comparison with its bulk state. In 1–100 nm, quantum size effects determine the properties of particles, like chemical, magnetic, optical, mechanical, electrical, and thermal properties [15, 23, 33].

Over the past few decades, the size-dependent properties of gold nanoparticles have been explicated well. Gold nanoparticles demonstrate the size-dependent color. At the nanoscale, the gold particle shows purple color diverse from the bulk, which was yellow-colored. This alteration in color is based on the alteration in their band type from continuous to discrete as a result of the confinement effect. These types of quantum effects in the nanometer scale are the elemental explanations behind the "tunability" of properties. By merely changing the particle size, we can alter the material property of our interest [15, 34].

Before talking about the properties of nanoscale substances, it may be beneficial to explain a case showing the basic effects of the minute size of nanoparticles [35]. The first and very important effect of smaller particle size is its huge surface area, and so as to get an idea of the significance of this geometric variable, the surface-over-volume ratio should be discussed. It is assumed that a particle is sphere-shaped, the surface a of one particle with diameter D is $a = \pi D^2$, and the corresponding volume v is $v = \frac{\pi D^3}{6}$. So, the surface/ volume ratio is

$$R = \frac{a}{v} = \frac{6}{D} \tag{1.1}$$

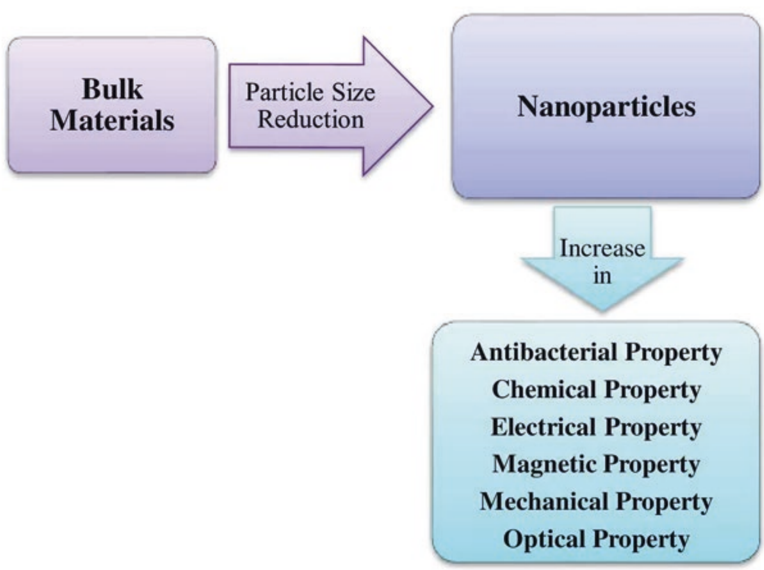

Fig. 1.1 Properties of nanoparticulate materials

This ratio is in opposite proportion to the particle size, and, accordingly, the surface enlarges with reducing particle size. Therefore, larger values of surface area are obtained for particles that are simply a few nanometers in diameter [36].

The distinctive properties and superior performance of nanoparticulate materials are established by their sizes, surface structures, and interparticle interactions. The role of particle size is incredibly analogous to the role of the particle's chemical composition, adding one more parameter for designing and managing the behavior of the particle. To entirely know the impacts of nanoparticulate materials in nanoscale science and technology, one requires to study why nanoparticulate materials are so special [36].

The excitation near nanoscale science as well as technology offers unique opportunities to build up innovatory materials. Nanoscale science and technology is a comparatively young field that includes almost all disciplines of science and engineering. Nanoparticulate structures are a novel branch of materials study drawing an immense deal of attention due to their impending application in chemical catalysis, computing, imaging, material synthesis, medicine, printing, and many other fields [36].

On account of all these inimitable behavior and properties, nanoparticulate materials have greater applications in cosmetics, electronics, and pharmaceutical industries. In addition, they are commonly employed for the advance of healthcare products and restoration of polluted environments [30]. Nanoparticulate materials stand for areas of scientific study and industrialized applications in the full expansion [37]. Nanoparticulate materials in addition play a very important role in drug delivery, imaging, and even in the surgical procedures as they have a size range comparable to that of biological molecules, for example, proteins, receptors, deoxyribonucleic acid, and ribonucleic acid (RNA) [38–42].

Nanoparticulate systems are moderately small in size in comparison with cells but are larger than the majority of "small molecule"-type drugs, which could get better their residence time in circulation without any risk of clogging within the blood vessels, which sequentially can enhance the bioavailability and pharmacokinetic profile of a variety of drugs. Nanoparticles can make use of a natural process called endocytosis to go through cells, which offers a specific benefit in circumstances where normal penetration into cells would be difficult for a particular molecule [43]. This characteristic is also useful for the targeting of particular organelles within the cells like nuclei with gene knockdown by tiny interfering RNAs (siRNAs) [42, 44–46]. The higher surface-area-to-volume ratio is an additional interesting characteristic of nanoparticulate systems, which gives a huge substrate for adherence of definite moieties for active targeting [47]. Surface modification has been done to nanoparticles with specific antibodies or peptides to attain tissue targeting, which lessens the probability of distracted off-target toxicity [48, 49]. Consistent with therapeutic and diagnostic requirements, the surface features of nanotherapeutics can be customized with imparting stealth properties to avoid elimination by the reticuloendothelial system, which gets better the circulation time and raises drug concentration at the site of action [41, 50].

Nanoparticulate technology has opened up new opportunities in the early detection as well as management of different cancers, in biodetection of pathogens, and in the formulation of fluorescent biological labels as they receive both imaging and therapeutic aptitudes. Nanoparticulate technology is also beneficial in addressing solubility as well as stability problems of poorly soluble drugs and in modifying their pharmacokinetic profiles to get extended plasma half-life. Since the 1980s, the healthcare group of people has met clinical challenges where resistance has developed against antibiotics and chooses other conventional therapeutics. It is feasible that these problems can be tackled with nanoparticulate materials [40, 51]. As of 2014, more than 1800 consumer products containing nanoparticulate materials are on the market [52].

4 Classification of Nanoparticulate Materials

The manufacturing of traditional products at the nanoscale right now helps and will keep on helping the economic growth of various countries. To date, a variety of nanoparticulate products have been documented, and lots of other varieties of products are expected to come out in the future. Consequently, the requirement for their categorization has ripened. The first suggestion for nanoparticulate material classification was specified by Gleiter in 2000 [53]. A nanomaterial is a broad name given to every material existing at the nanometer scale. Numerous names have been presented to these novel materials like nanostructured, nanometer-sized, ultrafine-grained, etc. Nanoparticulate materials can be formed from one or more species of atoms or molecules and can demonstrate a broad range of size-dependent characteristics. In this range of size, nanoparticulate materials tie the gap among tiny molecules and bulk materials in terms of energy states [54, 55]. They can be found naturally or manufactured chemically, mechanically, physically, or biologically with a variety of structures [56]. Nanoparticulate materials can be categorized on the basis of special parameters including their origin, chemical composition, material-based, and their dimentions [57, 58].

4.1 Classification of Nanoparticulate Materials Based on Their Origin

Based on their origin, the nanoparticulate materials can be divided into two categories [59]:

Natural Nanoparticulate Materials
These types of materials speak about nanosized materials that belonged naturally to the environment (e.g., proteins, viruses, nanoparticles produced during volcanic eruptions, etc.) or that are formed by individual activity with no plan (e.g., nanoparticles produced from diesel combustion). These types of nanomaterials are formed in nature either by organic species or at some stage in human-induced activities. Manufacturing of the simulated surfaces with the best micro- as well as nano-patterns and properties for industrialized application is effortlessly accessible from natural origins. Naturally generated nanoparticulate materials are present through the Earth's spheres – to be precise, in the atmosphere, hydrosphere, and lithosphere which are comprised of rocks, soils, magma, or lava at particular stages of evolution and even in the biosphere which covers microorganisms and higher organisms, including humans, apart from anthropogenic activities. Globe is made up of nanoparticulate materials that are naturally formed and are also present in the oceans, lakes, rivers, groundwater, and hydrothermal vents [60–62].

Synthetic (Engineered) Nanoparticulate Materials
These types of nanoparticulate materials are manufactured with intent by means of a defined production procedure like mechanical grinding, engine exhaust, and smoke or are synthesized by physical, chemical, biological, or hybrid techniques. Synthetic nanoparticulate covers a wide range of materials counting both inorganic (elemental metals, metal oxides, and metal salts) and organic (fullerenes, micelle-like amphiphilic polyurethane particles, and dendrimers) materials [63]. The issue of the risk assessment approach has come into existence recently as there is increased manufacturing and succeeding release of engineered nanoparticulate in addition to their utilization in consumer products and industrial application. This risk assessment approach is very much helpful in the prediction of the behavior and fate of engineered nanoparticulate materials in different environmental media. The most important confront among engineered nanoparticulate materials is whether existing information is ample to predict their behavior or if they show a distinctive environment-related performance, diverse from natural nanoparticulate materials. At present, different sources concerned with possible applications are employed for the fabrication of engineered nanoparticulate materials [64].

4.2 Classification of Nanoparticulate Materials Based on the Chemical Composition

According to their chemical composition, nanoparticulate materials can be categorized as metal-based materials that are mainly made up of metals, like silver, gold, and copper. And metal oxide nanoparticulate materials are made of metal and oxygen, for example, titanium, silica, and alumina [57].

4.3 Material-Based Classification of Nanoparticulate Materials

The most recent nanoparticulate materials can be classified into four material-based categories:

Carbon-Based Nanoparticulate Materials

Generally, these carbon-based nanoparticulate materials cover up a wide range of compounds, counting fullerenes, carbon nanotubes, carbon nanofibers, carbon black, graphene, and carbon onions [63]. For manufacturing these carbon-based nanoparticulate materials, different methods are used like laser ablation, arc discharge, and chemical vapor deposition (except carbon black) [26].

Inorganic-Based Nanoparticulate Materials

These inorganic-based nanoparticulate materials include metal and metal oxide nanoparticles. These nanoparticulate materials can be synthesized into metals like gold nanoparticles or silver nanoparticles, metal oxides like titanium dioxide and zinc oxide nanoparticles, and semiconductors such as silicon and ceramics [59].

Organic-Based Nanoparticulate Materials

Organic-based nanoparticulate materials consist of nanomaterials prepared generally from organic matter, exclusive of carbon-based or inorganic-based nanomaterials. The exploitation of non-covalent interactions for the self-assembly and blueprint of molecules assists to renovate the organic nanoparticulate materials into most wanted structures, for instance, dendrimers, micelles, liposomes, and polymeric nanoparticles [59].

Composite-Based Nanoparticulate Materials

Composite nanoparticulate materials are multi-phase nanoparticles with one phase on the nanoscale dimension that can either join nanoparticles with other nanoparticles or nanoparticles attached with bigger or with bulk-type materials (e.g., hybrid nanofibers) or very complex structures, for example, metalorganic frameworks. The composites may be any combinations of carbon-based, metal-based, or organic-based nanoparticulate materials with any form of metal or polymer bulk materials. Nanoparticulate materials are fabricated in diverse morphologies contingent on the essential properties for the desired application [59].

4.4 Classification of Nanoparticulate Materials Based on Their Dimensions

Nanoparticulate materials with structural characteristics at the nanoscale can be created in various forms. In 2007, Pokropivny and Skorokhod formed a new idea of classification for nanoparticulate materials which listed the newly developed composites, for example, zero-dimensional (0-D), one-dimensional (1-D), two-dimensional (2-D), and three-dimensional (3-D) nanoparticulate materials [65]. This classification is greatly reliant on the electron association along the dimensions in the nanomaterials. For instance, electrons in 0-D nanoparticulate materials are captured in a dimensionless space, while 1-D nanoparticulate materials have electrons that can shift along the *x*-axis, which is less than 100 nm. Similarly, 2D and 3D nanoparticulate materials have electron associations along the *x- and y*-axis and *x*-, *y*-, and *z*-axis in that order. The ability to forecast the properties of nanoparticulate materials decides the classification value of the nanoparticulate materials. The categorization of nanoparticulate materials given by researchers suggested that the features of nanoparticulate materials are ascribing to the particle shape as well as dimensionality, as per the "surface engineering" conception, and therefore class of nanomaterials [65, 66].

In accordance with this conception, nanoparticulate materials can be classified as follows:

Zero-Dimensional (0-D)

They are crystalline bunches of a few hundred to a few thousand atoms with sizes ranging from 2 to 100 nm [67]. All the dimensions of the materials present in the nanometer scale are called 0-D nanoparticulate materials. Nanoclusters are forms that are 1 to 100 nm in all space-based dimensions. These are in most cases sphere-shaped nanostructures, while their length, breadth, and heights are controlled at a single point. 0-D nanomaterials are either amorphous or crystalline in nature. In recent times, widespread investigation is in development to fabricate nanoparticles for a variety of applications [68].

One-Dimensional (1-D)

The second class of nanoparticulate materials, subjected as 1-D nanoparticulate materials, is held in reserve for those materials that have nanoscale dimensions that are equal in all but one direction [69]. The nanoparticulate materials have one of the dimensions, which are exterior, the nanoscale, and are called 1-D nanoparticulate materials. It has only a single parameter, either length or breadth or height. These are commonly needlelike nanostructures that include nanotubes, nanowire, nanofibers, and nanorods having a diameter between 1 and 100 nm and a length that could be much larger and are classified as 1-D nanostructures. These types of nanomaterials are either amorphous or crystalline in nature. These nanoparticulate materials present momentous benefits over bulk or thin-film planar devices [70]. Nanofibers are to some extent bigger in diameter than the characteristic nanomaterial definition, though still too small to see to the naked eye. They are generally manufactured by electrospinning technique in the case of inorganic nanofibers or catalytic synthesis method for carbon nanotubes and exhibit size ranges between 50 and 300 nm in diameter. Nanofibers can be aligned biochemically and electrostatically [26]. Nanowires are similar to nanofibers. In these systems, one dimension surpasses by an order of magnitude the other two dimensions, which are in the nano-range [71].

Two-Dimensional (2-D)

In this class of nanoparticulate materials, only one dimension is in the nanometer scale, while another two are out of the nanoscale [71]. It has simply length and breadth. 2-D nanostructures display plate-like shapes [72]. Examples of 2-D nanostructures are nanotubes, dendrimers, nanowires, nanofibers, nanofilms, nanolayers, nanotextured surfaces or thin films, and nanocoatings. 2-D nanoparticulate materials can be amorphous or crystalline. They are fabricated from different chemical compositions. They are utilized as a single layer or multilayer structure [73]. The properties of 2-D systems are not as much understood, and their manufacturing capabilities are less advanced. 2-D systems are applied to structural bulk materials for the purpose of improving the desired properties of the surface, for example, corrosion resistance, wear resistance, friction, and holding the bulk properties of the material unchanged [74].

Three-Dimensional (3-D)

Three-dimensional (3-D) structures are materials having three random dimensions beyond the nanoscale [57]. 3-D nanostructures have all parameters like breadth, height, and length. These materials acquire a nanocrystalline nature [75]. Examples of these types of nanomaterials are quantum dots or nanocrystals, fullerenes, particles, precipitates, and colloids. A number of 3D systems, for example, natural nanomaterials, metallic oxides, and carbon black, are widely known, whereas others, for example, dendrimers, fullerenes, and quantum dots, portray the maximum confronts with regard to manufacturing and understanding of properties. 3-D nanoparticulate materials consist of the dispersion of nanoparticles, bundles of nanowires, and nanotubes as well as multi-nanolayers [66, 76].

5 Properties: The Physics at the Nanoscale

Recently, the materials science investigation is paying attention to the discovery of novel materials with new-fangled and superior properties and novel synthesis methods to deal with the augmented technological requirement. Nanoparticulate materials are the center of interest attributable to their remarkable application and fascinating properties [77, 78].

In reality, the fundamental properties of matter transform at the nanoscale and nanoparticulate materials manifested fascinating and valuable properties. The chemical and physical properties of nanoparticulate materials can be quite diverse from those of larger particles of the same material. They are nearer in size to single atoms and particles over bulk materials, and to clarify their performance, it is essential to make use of quantum mechanics [26]. At the same time, practically all microstructured materials have identical properties to the corresponding bulk materials. This is mostly attributable to the nanometer size of the materials which make them (a) large fraction of surface atoms, (b) high surface-to-volume ratio and quantum confinement effects, (c) spatial confinement, and (d) reduced imperfections, which do not exist in the corresponding bulk materials [79]. Changed properties can comprise but are not restricted to color, solubility, material strength, electrical conductivity, magnetic performance, mobility, biological activity, and chemical reactivity (Fig. 1.2) [23, 80].

Size effects make up a peculiar and attractive aspect of nanoparticulate materials. The effects are taken into consideration by size pertaining to the advancement of chemical, electronic, electromagnetic, spectroscopic, structural, and thermodynamic properties of these predetermined systems with varying sizes [25]. The properties of material basically rely on the type of motion its electrons can execute, which depends on the gap available for them. Therefore, the properties of a material are characterized by an explicit length scale, usually on the nanometer dimension. If the physical size of the matter is decreased below this length scale, subsequently there is a transformation of its properties that turn out to be susceptible to size along with shape. Attributable to our capacity of atom manipulation, we can formulate nanoparticulate materials suitable for specific applications [81].

In any matter, the considerable variation of basic electrical and optical properties with decreased size will be seen when the energy spacing between the electronic levels goes beyond the thermal energy. In tiny nanocrystals, the electronic energy levels are not constant as in the bulk but are discrete: on account of the captivity of the electronic gesture function to the physical lengths of the particles. This observable fact is called quantum confinement, and, consequently, nanocrystals are also referred to as quantum dots [82]. Furthermore, nanocrystals attain a higher surface area and a great fraction of the atoms present on their surface. Since, this fraction depends largely on the size of the particle (30% for a 1 nm crystal, 15% for a 10 nm crystal); it can give rise to size effects in chemical and physical properties of the nanocrystals.

5.1 Confinement Effect

Quantum size effects are correlated to the "dimensionality" of a system in the nanometer range [83]. The quantum effects are an outcome of quantum mechanics and of the particle-wave duplicity. These come about in cases where the size of the system is proportionate with the de Broglie wavelengths of the electrons, phonons, or excitons circulating in them [84]. In actual fact, electrons are active as particles and waves; seeing as waves, they voyage around the whole space in which they are free to move about. The nanograin acts similar to a type of box, in which a definite property may or may not be present. Below a specific critical size, characteristics of the matter straightforwardly and exactingly rely upon the size of the grain. This is known as the confinement effect [85]. Quantum size effects play a fun-

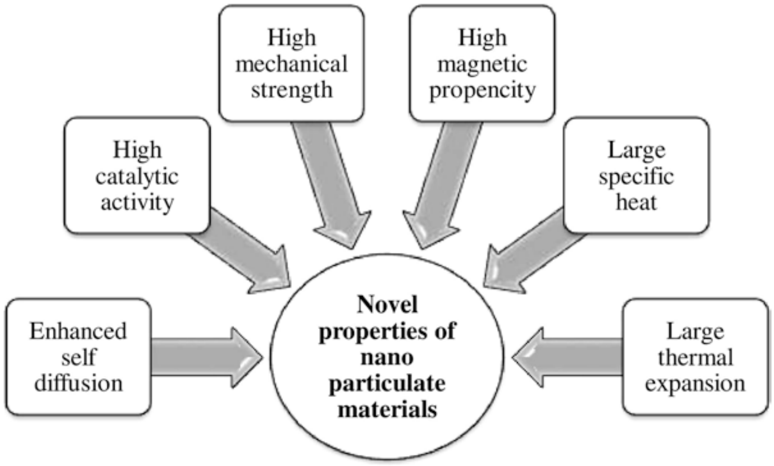

Fig. 1.2 Size-dependent properties of nanoparticulate materials

damental role in deciding the physical and chemical properties, e.g., charge-transport mechanisms and electronic structure. Optical as well as electron-tunneling spectroscopies are crucial for learning these systems [79, 86].

5.2 Surface Effects

Atoms present at surfaces have fewer neighbors as compared to atoms in the bulk. As a consequence of this lesser coordination and unsatisfied bonds, surface atoms are little stabilized compared with bulk atoms [79]. If the particle is very small in size, it has a large fraction of atoms at the surface and a great average binding energy per atom. The surface-to-volume proportion scales with the contrary size, and, as a result, there are plentiful properties that comply with the identical scaling law. Edge and corner atoms have even lesser coordination and attach foreign atoms and molecules more strongly. The coordination number is also restricted in small pores [87].

The influence of size reduction is not exclusive of outcomes for the atomic arrangement and the physical properties of substances. In fact, if the structure of the superficial region of a particle is exaggerated over the range of the particle size, a surface layer cannot be specified precisely [88]. It is acknowledged that the composition or the structure of the crystal is customized at the free surface of the material. The volume of this surface layer turns out to be noteworthy in nanoparticulate materials. The surface layer of nanoparticulate materials, in that case, can be specified as the outer region where the composition or the structure of the crystal is diverse from those of the particle interior [89].

5.3 Mechanical Properties

Nanostructures demonstrate advanced mechanical properties than the bulk materials, for example, mechanical hardness, elastic modulus, tensile stress, fatigue strength, scratch resistance, fracture toughness, etc. [90]. The aforementioned augmentation in the mechanical properties of nanoparticulate material is ascribing to the structural flawlessness of the material. The microscopic-sized matters get free of internal structural deficiencies like dislocations, microtwins, and impurity precipitations. Repeated mechanical failure is caused by multiplying imperfections in the nanoparticulate materials, which are more lively and move to the surface, under annealing, purifying the material. This repositioning of defects to the surface departs perfect material structures within the nanoparticulate materials. The exterior surface of nanostructure materials is incredibly small or free from imperfections in comparison to that of bulk materials. Materials with fewer defects will give out superior mechanical properties [91].

In a lot of nanoparticulate materials, hardness is noticed as the most common mechanical property. A variety of superhard nanocomposites manufactured using borides, carbides and nitrides [92]. Extraordinary production methods were employed to produce such nanocomposites, in particular plasma-induced chemical technique and physical vapor deposition technique [93]. The nanoparticulate materials are created containing excellent mechanical properties for impending applications in macro-, micro-, and nanoscales. Nanocrystalline copper is three times more resistant as compared to usual copper; they are also more flexible [94]. Carbon nanotubes and nanowires are employed to make high-frequency electromechanical resonators that can be utilized as nanoprobes or nanotweezers to control nanomaterials on a nanometer scale [95, 96].

Elasticity conception deals with the small, continue and reversible deformations of isotropic elastic materials [97]. An elastic material exhibits the following three properties: It distorts under stress and comes back to its original shape when the stress withdraws. It is uniform, isotropic, and homogeneously distributed in its occupied volume. Materials are normally not isotropic as they are polycrystalline, with grains having diverse shapes and orientations. Conversely, as the lengths of the materials are very big to correspond to the mean grain, homogeneity and isotropy hypothesis are occasionally more or less satisfied. Therefore, the elasticity hypothesis is as well employed for polycrystalline materials [98].

5.4 Structural Properties

The reduction in particle size of material results in the transformation in interatomic spacing, and so surface and surface energy increase [33]. The structural alterations are noticed when the particle size reduces predominantly in the nanoscale range. Gold nanoparticles can accept a polyhedral shape, for example, cuboctahedral and multiply twinned decahedra [99]. Aforesaid shapes can be explored and understood by the enlargement of crystalline along with a variety of crystallographic directions and energies of different crystallographic planes. Crystalline solid acquires long-range episodic structure of atoms and distinct prototypes. The fundamental factor of nanoparticulate materials is their shape, size, and morphological constitution. The surface morphology of nanoparticulate materials can be adjusted by means of a chemical agent named surfactant. The morphologies of nanoparticles are adjustable, and by scheming them, we can investigate their properties [100].

5.5 Thermal Properties

Several properties of materials can be customized by managing their nanoscale dimensions. Such customized nanostructures can be employed to meet the demands of various applications. The thermodynamics of nanosystem is different from the thermodynamics of macroscopic systems, where the number of particles has a tendency to perpetuate [101]. Higher surface energy will change monotonically with size and can be taken care of within the structure of thermodynamics [102]. Among them is the melting and other phase transition temperatures that exemplify the common experimental difference of melting point of gallium nitride spherical nanoparticles aligned with the size of the particles [103]. Its physical starting point is the raise of surface energy, the augment of the amplitude of atomic vibrations, and the supplementary surface growth of thermal vibration energy in the consequence [65]. It has been stated that the specific heat raised with the reduction in particle size, while the melting entropy, as well as enthalpy, diminished as the particle size reduces [104].

The exploit of nanofluid to improve the thermal transfer is a hopeful application of the thermal properties of nanoparticulate materials. Nanofluids are in general said to be solid-liquid composite materials, which contain nanoparticulate materials of size in the range 1–100 nm suspended in a liquid [105]. Nanofluids grasp greater than ever interests in both research and practical applications because of their very much superior thermal properties in comparison with their base fluids. A great deal of nanoparticulate materials can be employed in nanofluids counting nanoparticles of oxides, nitrides, metals, metal carbides, and nanofibers such as single-wall and multiwall carbon nanotubes, which can be discrete into different base liquids dependent on the potential applications, for example, water, ethylene glycol, and oils [106].

The most significant attributes of nanofluids are the momentous increase of thermal conductivity proportionate to liquids exclusive of nanoparticulate materials, which have been proven by numerous investigational works [107]. Nanofluid-based devices will facilitate the expansion of real-time, plainly invasive medical diagnostic systems to observe astronaut health and assist in diagnosing and treating sickness [108]. As a result, investigators are facing problems for the hypothetical analysis of thermal transport in nanoparticulate materials [109]. The thermal properties of nanoparticulate materials can be tailored by numerous factors like the small size of particles, the shape of the particle, the huge interface area, etc. Hence, the thermal properties of nanoparticulate materials are fairly diverse in comparison to the bulk materials. As the length of the material lessens to the nanometer range, it is quite similar to the wavelength and means a free path of phonon, which results in the noteworthy transform in phonon transport in the material. As a consequence of the transform in phonon confinement and quantization of phonon transport, thermal properties without human intervention get customized [110].

5.6 Optical Properties

The optical properties are based on electronic structure, and an alteration in zone structure results in an alteration in absorption and luminescence spectra. Their distinctiveness, such as spectral width and position, and sensitivity to light polarization rely not only on the inherent properties of the nano-objects (e.g., composition, structure, size, shape) but also on their surroundings [85].

The diminution of material dimension as well has an effect on the optical properties of the materials. The optical properties of nanomaterials depend on the size of particles which can be clarified in two ways. One is due to the more confined structure, energy level spacing increases and another is related to surface plasmon resonance (SPR). The optical properties of metallic nanoparticles are measured by the SPR phenomenon [111]. The SPR is resultant from the steady motion of the conduction band electrons from one surface of the particle to the other, upon communication with an electromagnetic field. The reduction in size beneath the electron mean free path (distance the electron moves between scattering collisions with the lattice centers) brings about intense absorption in the UV-visible range. Optical excitation of the SPR causes surface plasmon absorption [112].

For semiconducting materials, the quantum size effect is most studied. By reduction of the particle size of semiconducting material, interband transition is shifted to the higher frequency, which results in the increase in bandgap. The bandgap of semiconducting materials is within a few electron volts, which rises quickly with reducing particle size. Quantum confinement results in a blue shift in the bandgap [113]. The optical properties of nanostructured semiconductors powerfully rely upon particle size. Hence, the optical properties of such materials are effortlessly adjustable by changing the size of particles. The nanostructured semiconducting materials acquire excellent transporter confinement and energy density states, which assemble it most appropriate and resourceful for laser devices [114]. When the particle size of metal nanostructures is lesser than the wavelength of incident radiation, a SPR is created. By commencing the above discussion, it is understandable that the optical properties of materials are very much affected by the particle dimension. By changing the dimension of materials in nanometer, we can modify sophisticated optical materials for devices [115].

5.7 Magnetic Properties

Nanomagnetism is a vibrant and very interesting topic of current solid-state magnetism and nanotechnology [116]. It is of foremost scientific attention and high technological importance. Ferromagnetic nanoparticulate materials encompass prospective benefits over present materials in various applications in hard magnets, soft magnets, magnetic recording, etc. It is well recognized that the coercivity of magnetic substances has an outstanding reliance on their size. Magnetic coercivity rises with the decrease in particle size in the nanometer range going through a highest at the solitary domain size and afterward reduces once more time for very tiny particles on account of thermal effects and turns into zero at the superparamagnetic particle size. An iron, which is a soft magnetic material with coercivity of about 20 Oersted (Oe) at room temperature, could be formed "hard" with a coercivity of 540 Oe [117]. An additional example is the amazing phenomenon of giant magnetoresistance of magnetic multilayers that has been developed to enhance the capability of hard discs by over a factor of a hundred in a few years [118].

The magnetic properties are exploited in drug delivery [119]. The magnetic characteristics of the nanoparticles can also be different from those of the related bulk material. Attributable to a smaller size of the particle, the surface area increases, and magnetic coupling with neighboring atoms also increases, which leads to the varied magnetic properties.

Ferromagnetism takes place even for the smallest dimensions. The magnetic torques are improved atom-like for clusters with not more than around 100–200 atoms. The magnetic torque diminishes and moves toward the bulk limit, as the size is raised up to 700 atoms, with vibrations probably resulting from surface-induced spin-density waves or structural alterations. Ferromagnetism is referred to a worldwide aspect of nanoparticles of the nonmagnetic oxides [120]. When the particle size diminishes beneath a definite size, ferromagnetic particles turn out to be unstable. Such instability is a result of the spontaneous polarization of domains and the adequately elevated surface energy. Owing to this property, ferromagnetic grows to be paramagnetic at the nanometer scale, but it acts in a different way from the conventional paramagnetic, and therefore it is named superparamagnetism [121].

A bulk ferromagnetic substance generally includes multiple magnetic domains, while nanostructured ferromagnetic substances have minute magnetic nanoparticles and have simply one domain. These domains of different particles are arbitrarily dispersed as a result of thermal fluctuation and develop into aligned in the presence of an externally applied magnetic field [122].

6 Types of Nanomaterials

Nanomaterials are one of the key products of nanotechnology. Nanomaterials have a higher surface-to-volume ratio, and they preserve properties notably different from the bulk material as at this stage quantum effects might be noteworthy. Basically, we can say the electrical, electronic, magnetic, mechanical, optical, etc., properties of solids are considerably changed with a big decline in the particle size. Applications of nanotechnology in drug delivery take place through the use of designed nanomaterials as well as forming delivery systems from nanoscale molecules such as liposomes, polymeric micelles, polymeric nanoparticles, nanocapsules, nanocrystals, nanotubes, nanocages, dendrimers, quantum dots, etc. There are different types of nanomaterials utilized as drug delivery systems which are briefly discussed in this section.

6.1 Liposomes

Liposomes are concentric bilayer spherical-shaped vesicle systems in which an aqueous volume is totally enclosed by a lipidic bilayer membrane made up of phospholipids as well as steroids generally in the size range of 50–450 nm. The structure of the liposomal membrane is similar to that of cell membranes and for the reason that they make easy inclusion of drugs in them. Liposomes are employed as excellent drug delivery vehicles for biotechnological drugs because of various advantages like amphiphilic character, biocompatibility, and simplicity of surface modification. Due to their size, hydrophilic as well as hydrophobic features, and biocompatible and biodegradable character, liposomes are promising systems for drug delivery [123].

6.2 Polymeric Micelles

Polymeric micelles are nanoparticulate systems made of amphiphilic block copolymers that get together by themselves in the aqueous solution to create a nanoscale supramolecular core-shell arrangement under 100 nm sizes. Polymeric micelles because of their hydrophilic surface defend their nonspecific uptake by the reticuloendothelial system. The hydrophobic core of polymeric micelles can be laden with hydrophobic drugs like camptothecin and paclitaxel; however, the hydrophilic part makes the whole system soluble in water as well as stabilizes the core. Polymeric micelles have a strong potential for hydrophobic drug delivery seeing as their center core structure allows the incorporation of these kinds of drugs ensuing in the improvement of bioavailability as well as stability [124, 125].

Polymeric micelles have provided evidence as an excellent novel drug delivery system attributable to higher and adaptable loading capacity, steadiness in physiological circumstances, slow rate of dissolution, the higher buildup of drugs at the target site, and likelihood of end group functionalization for conjugation of targeting ligands [126].

6.3 Metallic Nanoparticles

Metallic nanoparticles are submicron size structures generally made of pure metals like cerium, gold, platinum, silver, titanium, and zinc or their compounds like chlorides, fluorides, hydroxides, oxides, and sulfides. Recently, the use of metallic nanoparticles has been growing in different medical applications, for instance, bioimaging, biosensors, targeted drug delivery, and photoablation therapy [127, 128]. Additionally, the surface modification, as well as functionalization of metallic nanoparticles with definite functional groups, lets them attach to antibodies, drugs, and other ligands, rendering these systems more hopeful in biomedical applications [127–129].

6.4 Polymeric Nanoparticles

Polymeric nanoparticles are tiny particles within the size range from 1 to 1000 nm and can be laden with active pharmaceutical ingredients entrapped inside or surface-adsorbed onto the polymeric central part. The term "nanoparticle" includes both nanocapsules and nanospheres, which are different with regard to their morphology. Nanocapsules are made up of an oily interior portion in which the drug is dissolved, enclosed by a polymeric shell that manages the drug release from the core. On the other hand, nanospheres are continuous polymeric networks in which the drug is retained in the interior or adsorbed onto their surface [130–132]. Benefits of polymeric nanoparticles as drug carriers include their potential use for controlled release, the ability to guard drug and other molecules with biological activity against the environment, improve their bioavailability and therapeutic index. Polymeric nanoparticles have shown great potential for targeted delivery of drugs for the treatment of several diseases [133, 134].

6.5 Nanocapsules

Nanocapsules are nanoparticulate systems in which the drug is confined to a hollow space enclosed by a distinctive polymeric membrane which provides a unique nanostructure. A nanocapsule has magnetized enormous attention, owing to the protective coating, which is generally pyrophoric and simply oxidized and provides sustained release of active ingredients [135]. Nanocapsules as drug delivery systems can improve the bioavailability of drugs and also help to attain targeted delivery. Similarly, by loading the drug within polymeric nanocapsules, it can defend the drug from breakdown or degradation done by the biological environment. Meanwhile, nanocapsules can successfully decrease the detrimental effects between drug and tissue environments [136].

6.6 Nanocrystals

Nanocrystal is a nanoparticulate carrier-free drug delivery system with at least one dimension ≤100 nm and that is solitary crystalline. However, even with the definition that points out nanocrystals as a "carrier-free" system, surfactants or polymeric steric stabilizers are indispensable to avert colloidal particle aggregation and as a consequence improve stability [137, 138]. Nanocrystals are of interest to researchers nowadays as they provide special features including enhancement of saturation solubility, dissolution velocity, and adhesiveness to surface/cell membranes, and so nanocrystals are employed as a means of achieving colloidal particles with customized biological properties that permit modifying the drug delivery as well as targeting [139].

6.7 Nanotube

Carbon nanotubes are tube-like cylindrical nanostructures having less than 100 nm diameter generally made up of carbon allotrope graphene with sp^2 hybridized carbon atoms. Nanotubes are categorized as single-wall nanotubes as well as multiwall nanotubes. Nanotubes show sparkling electrical, mechanical, optical, and synthetic characteristics, gaining widespread eagerness for their potential application in different fields like nanotechnology, electronics, optics, and other fields of materials science. Carbon nanotubes, has attracted incredible interest in the biomedical field due to their unique features like ability to deliver drugs at targeted sites, biocompatibility, higher drug loading capacity, higher surface area, great strength, and flexible interaction with payload, excellent optical and electrical features [140–142].

6.8 Nanocages

Nanocages are nanoparticulate-based drug delivery systems that have a hollow structure that can put in a nutshell large amounts of drugs inside. The term "cage" means that it can be unlocked, and so nanocages are frequently intended to be stimulus-responsive, taking benefit of definite physical or chemical differences in the environment at their target to alter their molecular structure [143]. Nanocages have a higher loading capacity than other nanoparticles and so can be loaded with hundreds or even thousands of drug molecules. As a result, a lesser dose of nanoparticles is needed to deliver a therapeutically effective dose of the drug, and, therefore, the overall cytotoxicity of the nanocages is reduced. A different main feature of nanocages is the aptitude to encapsulate and defend the drugs from the environment fully so that nanocages can be utilized as carriers of highly lipophilic drugs and stay stable in hydrophilic environments like the bloodstream. As soon as the nanocages get to the target tissue, the more lipophilic environment facilitates drug release [144, 145].

6.9 Dendrimers

Dendrimers are highly bifurcated, monodisperse, symmetric molecules with well-defined and three-dimensional nanostructures whose size and shape can be accurately controlled. Dendrimers are highly defined nanoparticles with sizes ranging from 1 to 15 nm [146–148]. The well-defined globular-shaped nanostructure, which is hyperbranched, with high compatibility with a biological system and capability for surface functionalization without difficulty, makes dendrimers outstanding candidates for photodynamic therapy, gene delivery, small interfering RNA delivery, oligonucleotide delivery, medical and biomedical application, and vaccine delivery and as drug delivery agents [149].

6.10 Quantum Dots

Quantum dots are known as semiconductor nanocrystals with size ranging from 2 to 10 nm, and their optical properties, for example, absorbance and photoluminescence, are size-dependent. The quantum dots have achieved immense attention in the field of nanomedicine, since, unlike conventional organic dyes, the quantum dots give emission in the near-infrared region (<650 nm), an incredibly attractive characteristic in the field of biomedical images, thanks to the low absorption by the tissues and decline in the light scattering [150]. Additionally, quantum dots with diverse sizes and/or compositions can be excited by the same light source resultant in separate emission colors over a broad spectral range [151, 152]. In this sense, quantum dots are awfully interesting for multiplex imaging. Quantum dots have been widely studied as targeted drug delivery, sensors, and bioimaging in the medical field.

7 Conclusion

Nanotechnology can be characterized as the understanding, control, and manipulation of materials, having dimensions approximately within the 1–100 nm range, where conventional physics breaks down. Scientists consider nanotechnology as the innovatory technology of the twenty-first century. Nanomaterials refer to natural, incidental, or manufactured materials containing particles in unbound or agglomerated/aggregated states. It has been observed that nanomaterials are totally different from their bulk moieties and cannot be studied as same as bulk or small molecules because of their distinguishing properties in nanometer scale. These distinguishing properties of nanomaterials are dependent on the composition, chemistry, particle dimension, and interactions with other materials. The exploit of nanotechnology in developing nanoparticulate carriers for drug delivery is bringing lots of hope and eagerness in the field of drug delivery research. Nanoparticulate materials as a drug delivery present a number of benefits that demonstrate high intracellular uptake than the other conventional form of drug delivery systems. Additionally, nanoparticulate materials can be coupled with a ligand-like antibody to help a targeted therapeutic strategy. Hence, nanoparticulate drug delivery systems may modernize the entire drug therapy approach and carry it to a new height in the nearest future.

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