Chapter

Nanomedicines: Nano based Drug Delivery Systems Challenges and Opportunities

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Abstract

Nanomedicine and nano delivery systems, although relatively recent but fast-developing technology is one where nanoscale materials are used to function as diagnostic tools or to deliver therapeutic agents to specifically targeted sites in a controlled manner. It also provides many advantages in the management of human diseases. Recently, there has been a range of excellent uses of nanomedicine as chemotherapeutic agents, biological agents, immunotherapeutic agents, etc., for treatment of different diseases. In this chapter we discuss the recent developments and insights obtained in the field of nanomedicine. It provides a review of the numerous nano-based drug delivery systems that enhance the efficacy of new and old drugs. The new opportunities and challenges arising in the area of nanomedicine from therapeutic viewpoint are also addressed.

Keywords: nanomedicines, nanoparticles, drug delivery systems, drug targeting, natural products added

1. Introduction

Human beings have been widely utilizing plant-based natural products as medicines against various diseases since ancient times. Many medicines are derived primarily from herbs, based on traditional knowledge and practices. Currently about 25% of the available therapeutic compounds and their derivatives are derived from natural resources [1, 2]. Natural compounds have impressive characteristics, such as exceptional chemical versatility, chemical and biological properties of macromolecular specificities and less toxicity. These thus constitute them as leads in the discovery of novel drugs [3]. In spite of several advantages, pharmaceutical companies are hesitant to commit to more in drug discovery and drug delivery systems based on natural compounds due to concerns associated with biocompatibility, toxicity, large size and targeted delivery, etc., and many natural compounds not even clearing the clinical trial phases [4, 5]. Hence, this presents a greater challenge of using them as medicine. Thus alternatively available libraries of chemical compounds are being explored to discover novel medicines. Various techniques like nanotechnology play substantial role in advancing drug formulations, targeting, efficient release and delivery with immense success. Nanotechnology bridges the barrier between physical and biological sciences by providing nanostructures with potential to fill the lacunae existing in various fields of sciences and in particular in the field of medicine.

The use of nanotechnology in the production of efficient medicines has been recognized as a key enabling technology, capable of delivering fresh and creative therapeutic approaches to address unmet medical demands [6]. The use of nanotechnology for medical purposes is referred to as nanomedicine [7] and nanomaterials are used for prevention, early diagnosis or treatment of a wide range of diseases with high specificity, efficacy, and personalization, to improve quality of life of patients. Owing to their small scale, nanomaterials have novel physicochemical properties, distinct from those of their traditional bulk chemical counterparts. Such properties significantly improve a range of opportunities in drug development. These physicochemical properties of nanoformulations can lead to pharmacokinetics/pharmacodynamics being changed, namely the delivery, absorption, removal and metabolism, the potential for more easily breaching biological barriers and their persistence in the environment and the human body.

The key component of nanomedicines are nanoparticles (NPs) and currently wide range of nanoparticle types exist depending on their structural features such as spheres [8], rods [9], wires [10], stars [11], sheets [12], multipodes [13], cages [14], etc. These particles can efficiently carry and deliver therapeutic agents as well as imaging and sensing agents to targeted sites. Nanoparticle carriers or nanocarriers have many advantages in medicine. First, they allow stable aqueous dispersions of active but poorly water-soluble therapeutic agents for delivery into the biological environment. Second, their structure, scale, shape and surface properties can be finely designed to protect the encapsulated agent when incorporated into the biological world and prevent it from degradation by various endogenous defense mechanisms including, immunodegradation, enzymatic degradation, reticuloendothelial system sequestration (RES) in the bloodstream, acid hydrolysis, lung mucociliary clearance, etc.

2. Delivery system of nanoformulations

Delivery of nanomedicines can be by intracellular transport, epileptic transport and other types. Intercellular transport is facilitated and regulated through intracellularization, transporter mediated endocytosis, and permeation by interactions through particle size and/or cell surface [15, 16]. In addition, a smaller nanomedicine particle size improves intercellular transport which facilitates cell permeation and affects nanomedicine absorption, dissemination, and excretion. In fact, cell internalization by transporter-mediated endocytosis depends on the size of the nanomedicine molecule. Similarly in large particle sized nanomedicine, opsonization occurs quickly and its removal from the blood is facilitated by endothelial macrophages. The susceptibility of nanomedicinal cell surface transporters to nanomedicinal products has been reported to vary depending on the particle size of nanomedicinal products, and this can also impact the effective removal by macrophages of large particles from the blood. Nanomedicines composed of non-charged polymers, surfactants, or polymer coatings that degrade *in vivo*, associate with cell surface receptors or ligands because of their hydrophilicity to increase permeability or promote internalization of nanomedicines. In addition, through interacting with bioadhesive polymers or chelates, nanomedicines improve the intracellular transport of active pharmaceutical ingredients. Improved intracellular movement of active pharmaceutical ingredients coupled with various proteins, antibodies and other *in vivo* polymers is due to the opening of tight junctions and/or improved membrane permeability. In particular, the incorporation of anti-cancer agents with such a role would increase the effectiveness of chemotherapy, including the treatment of brain tumors that are immune to drugs associated with close junctions, the targeting of tumor cells and the routine targeting of cells. Using such a strategy

for nanomedicines, cytotoxicity against normal cells can be minimized and greater anti-cancer efficacy will be achieved. Decrease in intake of nanomedicines in the lungs through inhalation results in an improvement attributable to decreased deterioration and absorption by lung mucosa or macrophages, resulting in improved product processing period and product transfer to goal. The enhanced permeability and retention (EPR) effect improves anti-cancer efficacy by enhancing tumor permeation and retention time. The effect of the EPR also makes it possible to directly transmit nanomedicines to target tissue by combining an antigen, enzyme, peptide, or polysaccharide that can be used to modify the delivery of nanomedicines to target tissues via receptor/ligand interactions or other physiologically sensitive cell regulation interactions, drug efficacy modification or adverse reactions. There is improved longevity of hydrophilic-coated nanomedicines, preventing their opsonization or accumulation in the mucus. Nanomedicines can be retained *in vivo*, e.g. in the lung tissue for extended periods of time by particle size, by inhibiting macrophage-induced or mucosal disturbance and escape elimination by mucus ciliates, which may lead to deterioration or macroscopic consequences of lung mucosa [17]. Thus, a number of formulations have been designed that use delivery pathways that can regulate the pharmacokinetics and pharmacodynamics of nanomedicines.

3. Nanomaterial based delivery system

Nanotechnology in drug delivery has the potential to overturn the treatment of various diseases such as cancer, diabetes, neurodegenerative diseases, vascular diseases, etc. [18]. In the market for sale, nanotechnology based formulations are largely parenteral, with some intended for oral administration [19]. It is hoped that a significant number of preclinical and clinical trials would lead to the production of novel nanotherapeutics intended for non-parenteral delivery routes, such as pulmonary, nasal, vaginal, ocular, and dermal delivery routes. Of special concern to drug delivery systems (European Commission/ETP) [20] is the option of delivery and the obstacles to be addressed. Over time, various formulations based on nanoparticles have been developed to enhance the delivery mechanism of drugs, such as discussed below:

3.1 Polymeric nanoparticles

The most widely used chemical nanoparticles are constructed from synthetic polymers as natural polymers result in low reproducibility and controlled release actions for the trapped products, leading to variability in purity and batch-to-batch quality. At the other side, synthetic polymers with good to batch reproducibility and purity are available which facilitates the modification of the pattern of drug release from polymeric nanoparticles [21]. Nanoparticles formulated with synthetic polymers have been widely studied for drug distribution/delivery. In double emulsion methods hydrophilic moieties will encapsulate onto synthetic polymer-based nanoparticles, as it is not easy to maintain activity in unfavorable environment. Various synthetic polymers reported for drug delivery with biodegradable aliphatic polymers such as polylactide (PLA), poly lactide-co-glycolide, copolymers (PLGA) and poly (ε-carpolactone), as well as non-biodegradable polymers like polyacrylates and poly (methyl methacrylate) are used widely [22]. Polymer nanoparticles can efficiently shield unstable drugs from deterioration/degradation, thus avoiding the side effects of toxic medications. Natural polymeric nanoparticles consist of polymers of natural products like alginate, chitosan, albumin and gelatin [22]. Application of polymeric nanoparticles with therapeutic drugs such as dexamethasone or alpha-tocopheryl succinate can be used to avoid the cisplatin ototoxicity

due to treatment with chemotherapy. Nanoparticles, trapping, transporting and ultimately spreading dexamethasone or alpha-tocopheryl succinate are capable of partially preventing large-dose ototoxicity of CDDP [23]. However, when administered systemically for long periods of time, these least soluble drugs have serious side effects. In the hydrophobic cavity of nanoparticles, the integration of such pharmaceutical products provides the requisite results *in vitro* and *in vivo.* Few popularly marketed formulations of the polymeric nanoparticles are Decapeptyl®, Gonapeptyl Depot®, Enantone Depot®, and Abraxane [24, 25].

3.2 Lipid nanoparticles

Lipid nanoparticles that are prepared with a solid matrix are called solid lipid nanoparticles (SLNs). These are constructed from nanoemulsions of oil in water with the utilization of a solid lipid. The first generations of SLNs were formed in the early 1990's [26]. The benefits associated with SLNs include cheap raw materials, usage of physiological lipids, avoidance of organic solvents, ease of scale-up, strong biocompatibility, enhancement of bioavailability, safety of vulnerable molds from environmental hazards and regulated drug release [27]. Using ultrasonic melt emulsification [28], ciprofloxacin (CIP)-loaded SLNs have recently been formulated with powerful antibacterial action. These were produced with a scale ranging from 165 to 320 nm and a polydispersity index with high trapping efficiency falling between 0.18 and 0.33. A controlled-release pattern of different lipids was shown by CIP release showing the full burst reaction, which contributes to the drug's rapid release. For 120 days this composition of CIPSTE was found to be stable at room temperature. SLNs for different routes of delivery, such as oral [29], dermal [30], pulmonary [31], ocular [32] and rectal [33], have been extensively tested *in vitro* and *in vivo*. Nano base and nano pearl are marketable SLN formulations [34].

3.3 Dendrimers

Dendrimers are special three-dimensional, hyper-branched, globular nano-polymeric structures. Attractive features such as water solubility, nano scaled size, narrow polydispersity index, modifiable molecular structure, internal cavity and several peripheral functional groups separate these from other nano systems. Terminal functionality serves as a platform for the conjugation and targeting of drugs. Such peripheral functional groups also provide them with tailor-made properties which improve their versatility [35]. The most commonly studied dendrimer for drug delivery is polyamidoamine. It's synthesis starts with the amine group, which interacts with methyl acrylate and contributes to the formation of two new branches of dendrimer terminated by ester. The amine-terminated dendrimer 'Full-generation' may be formed by subsequent amidation of the methyl ester with ethylene diamine. PAMAM dendrimers are non-immunogenic, biocompatible and water-soluble, and have functional terminal amine groups that can be altered to targeting drugs [35]. Dendrimers have been widely investigated for biodelivery via transdermal, nasal, ocular, and pulmonary pathways, in addition to improving solubility. Many of the synthetic cationic polymers such as amidised acid-labile allow different cargo delivery [36]. Changing their structure could solve toxicity-related problems [35]. A recent study showed that arginine terminated peptide dendrimers, along with sonophoresis, can significantly increase ketoprofen's transdermal penetration [37]. The findings revealed that the use of peptide dendrimer and application of ultrasound has worked synergistically. *In vitro* experiments have found that dendrimer and ultrasound-mediated drug permeation contributes to higher active drug plasma concentration as opposed to passive diffusion. Transdermal

administration of ketoprofen with A8 dendrimer demonstrated similar drug absorption and oral path plasma concentration [37]. Commercially available dendrimers of poly-propylenemine (PPI, AstromolR, DAB) [38] and polyamidoamine (PAMAM; Starburstk) have been the most usually explored for pharmacological use [38, 39].

3.4 Nanoemulsion

Nanoemulsions are a fascinating colloidal drug delivery mechanism, thermodynamically stable and filtration-sterilizable [40, 41]. There are heterogeneous mixtures of oil droplets in aqueous media resulting in nano droplets with a small scale distribution. The resultant nanoemulsions are analyzed as translucent or clear, isotropic and supported by the suitable surfactant [42]. Three types of nanoemulsions can be developed:

a. water in oil nanoemulsion

b. oil in water nanoemulsion

c. bi-continuous nanoemulsion

The most detailed function of nanoemulsions is to mask the unpleasant taste of oily liquids. These also provide long-term drug action and prevention from hydrolysis and oxidation. These nanoformulations can therefore be identified as an efficient and impregnable delivery option with high bioavailability. Nanoemulsions are currently being explored extensively to target different photosensitizers, anticancer drugs, or therapeutic agents. Such nanoformulations propose a number of applications such as drug delivery, biologic diagnostics and chemical agents [43]. In 2016, Simion et al. developed targeted dexamethasone-loaded P-selectin lipid nanoemulsions to minimize vascular inflammation [44]. Prepared formulations have been described for physicochemical assays. In their study, nanoformulation was found to be efficient in both *in vitro* and *in vivo* experiments. It reduces the function of the endothelium activation selectively and thereby the inflitration of monocytes, resulting in a substantial reduction in inflammation of the lungs in a model animal mouse. Examples of nano-emulsion formulations are Norvir (Ritonavir), Restasis, Gengraf (Cyclosporin A), Etomidat-Lipuro (Etomidate), Ropion (Flurbiprofenaxtil), Diprivan, Troypofol (Propofol), Limethason (Dexamethasone) and Liple (Alprostadil palmitate) [45].

3.5 Nonstructured lipid carriers (NLC)

Nonstructured lipid carriers comprise the nanosystems of the second generation, consisting of solid lipid embedded into liquid lipids [46]. These nano carriers allow for a strong immobilization of therapeutic agents and avoid particle coalition of particles relative to emulsions [47, 48]. Therefore, because of the liquid oil droplets in a solid matrix, their drug loading potential is increased relative to SLNs. Biodegradability, lower toxicity, controlled release, drug tolerance and avoidance of organic solvents during manufacturing are among the beneficial effects of NLC on polymeric nanoparticles. NLCs have been extensively studied for hydrophobic and hydrophilic drug transport in recent years. The NLCs are developed to satisfy industrial specifications related to certification and registration, basic infrastructure, scale-up and low cost criteria [49]. The presence of multiple consumer goods reflects the carrier's success story. Numerous other NLC products, including NLC repair cream and NLC restoration cream, are commercially available. For the treatment of different diseases, NLCs

were explored through various routes of administration viz. oral, nasal, and parenteral [50]. Fluconazole-loaded NLCs were constructed using probe ultrasonication method and studied for antifungal activity on various *Candida species*. A substantial decrease in maximum inhibitory concentration (MIC) for all classes of *Candida* was observed using fluconazole NLCs. It is also mentioned that *Candida albicans* is more susceptible to fluconazole loaded NLCs than *Candida Parapsylosis, Candida glabrata* [51].

3.6 Nanogel

Nanogels, comprised of flexible hydrophilic polymers, can be prepared as plain gels [52]. Upon swelling, the drug can be randomly inserted into the nanogel. As a result, the gel collapses, resulting in the creation of solid, compact nanoparticles with reduced solvent amount. Nanogels provide novel applications for polymer-based drug carrier systems due to their biocompatibility, high moisture content and suitable mechanical properties. These gels have expanded polyvalent bioconjugation surface area and an internal network for biomolecule trapping. Physical encapsulation of bioactive compounds in the polymeric interlock along with their releasing pattern has been widely explored as a targeted mode of drug delivery [53]. Several approaches for the preparation of nanogels include micro-molding and photolithographic methods, continuous micro fluidics, modification of biopolymers, and heterogeneous living/controlled radical and free radical polymerizations [54]. Several criteria are required for designing and manufacturing of an efficient nanogel drug carrier system for therapeutic application. The consistency of nanogels for long-lasting blood circulation is one significant criterion. Another extraordinary novel feature that can detect receptors on infected cells is the bioconjugation of nanogel surfaces with particular ligands. Eventually, the biodegradability of nanogels should not only control the release of the drug for the required amount of time, but also make it possible to eliminate the empty system after the release of the drug [54]. In a recent study, topical delivery of chitin nanogel loaded with clobetasol is reported. This nanogel demonstrated exceptional toxicity against THP-1 and HaCaT cell lines by MTT assay. Nanoformulation demonstrated significant anti-inflammatory ability with an average inhibition of LOX and COX activities in THP-1 cells of 70 percent and 65 percent. Increased transdermal flux has been obtained from permeation studies of *in vitro* skin. Antipsoriatic activity conducted *in vivo* on imiquimod model demonstrated the value of nanogel for the topical application of clobetasol for psoriasis. Some selected and marketed nanogels are Sane Care Nanogel, Zyflex Nanogel, Augen Nanogel Eye-care Gel, Skin Beautiful Brightening Nanogel [55], and Oxalgin.

3.7 Nanocapsule

Nanocapsule consists of either liquid or solid core in which drug is loaded and encapsulated by membrane of synthetic or natural polymers [56, 57, 58]. Lipid core nanocapsules are prepared by the precipitation method. Prepared nanoparticles have been tested for physical, chemical and biological characteristics. The most important characteristics to note during their synthesis are particle size and distribution. This can be calculated through multi-angle laser light scattering in a superconducting quantum interference instrument through X-ray diffraction, X-ray photoelectron spectroscopy, Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) [57]. Chemically stable, biocompatible and readily reproducible are industrial bioactive nanocapsules. Because of their coating, which protects the encapsulated material from unenviable effects, such as dissolving the liquid and avoiding the release of active components, they have captured the attention of research groups. In biomedical research, agrochemicals, sanitizing materials, cosmetics and water treatment, nanocapsules have

a wide range of biomedical applications. In addition, the effectiveness of such medications has also been studied for cancer treatment [59], radiotherapy [60], self-healing, contagion [78] and for use in food and agriculture. New developed nanocapsules will open new avenues of research and development for the delivery of bioactive compounds to target tissues in the future [57, 58]. Due to their ability to destroy colon cancer cells, resveratrol-charged lipid-core-nanocapsules (RSV-LNC) were developed and characterized. Constant and controlled drug release has been confirmed by the RSV-LNC. Increased anticancer activity in HT29 cancer cells compared to free RSV resulted in RSV incorporated in the nanocapsule. RSV-loaded nanocapsules have a promising potential for enhancing therapeutic effectiveness in colon cancer cells based on *in vitro* evaluation. In order to authenticate the improved behavior of RSV nanoformulations, more experiments on animal models are nevertheless proposed. SOLUDOTS-PTX (Lipid Nanocapsules of Paclitaxel) is currently in clinical trials.

3.8 Nanosponges

Nanosponges have drawn the interest of drug delivery scientists in pharmaceutical science as they have the capacity to load both hydrophilic and lipophilic moieties [61, 62]. These are thin, non-toxic, porous colloidal structures of scaffolds that have multiple cavities where drug molecules can be stuck. In the processing of these nanocarriers, α-cyclodextrins are the most commonly used. It is possible to investigate different crosslinkers in their development, such as hexamethylene di-isocyanate, carbonyl di-imidazole, pyromellitic dianhydride, diphenyl carbonate, etc. In water as well as in organic solvents, these structures are insoluble [63], self-sterile [64, 65] and stable up to 300° C and pH range of 2–11. Using ultrasound-assisted synthesis techniques, Trotta and colleagues produced cyclodextrin nanosponges [86] and examined them for anti-tumor drugs [66]. Efavirenz is a class II drug, a non-nucleoside reverse transcriptase inhibitor widely used for HIV [67]. This medicine, however, exhibits less solubility and reduced bioavailability. Beta-cyclodextrin cross linking with carbonates in variable ratios was performed to increase the solubility and dissolution of this compound. Some of the advertised formulations of nanosponge are Glymasason, Prostavastin, Brexin and Mena-gargle [68, 69].

3.9 Inorganic nanoparticles

Silver, gold, iron oxide and silica are included in inorganic nanoparticles. Nevertheless, only a few nanoparticles have been approved for clinical use, while most of them are still in the clinical trial stage. Metal nanoparticles, silver and gold, have different properties such as SPR (surface plasmon resonance) that liposomes, dendrimers, micelles do not exhibit. They show a variety of benefits when it comes to surface durability, such as decent biocompatibility and flexibility. Studies of their delivery-based actions have not been able to establish whether their toxicity is based to the particulate or ionized form; and while two mechanisms, such as paracellular transport and transcytosis, have been suggested, there is inadequate evidence on their *in vivo* transmission and uptake mechanisms [70]. Drugs can be conjugated by ionic or covalent bonding and physical absorption to gold nanoparticles (AuNPs) surfaces and can be transmitted and regulated by biological stimulation or light activation [71]. Silver nanoparticles display antimicrobial activity however, as far as drug distribution is concerned, very few experiments have been performed, e.g. Prusty and Swain [72] synthesized a spongy polyacrylamide/dextran nano-hydrogel hybrid structures with covalently attached silver nanoparticles for ornidazole production, resulting in an *in vitro* release of 98.5 percent [72]. Likewise, in another study, iron oxide nanoparticles were synthesized using a laser pyrolysis process and

protected by Violamycin B1 and antracycline antibiotics and tested against MCF-7 cells for their cytotoxicity and anti-proliferation properties, compared with commercially available iron oxide nanoparticle and showing promising results [73].

3.10 Quantum dots

Quantum dots (QDs) are regarded as semiconductor nanocrystals with a diameter ranging from 2 to 10 nm with their optical characteristics, such as absorbance and photoluminescence being size-dependent [74]. QDs have received significant interest in the field of nanomedicine, because, unlike traditional organic dyes, QDs pose emissions in the near-infrared region (< 650 nm), a very advantageous phenomenon in the field of biomedical imaging, due to low tissue absorption and decreased light dispersion [75]. Furthermore, the same light source can excite QDs with different sizes and/or compositions resulting in separate emission colors over a wide spectral range [76, 77]. In this way, QDs are quite attractive to multiplex imagery. QDs have been extensively studied in the field of medicine as targeted delivery of drugs, sensoring and imaging agents. A large number of studies on the use of QDs as contrast agents for *in vivo* imaging are currently available in the literature [78, 79]. Han et al. [80] have produced a novel fluorophore for intravital cytometric imaging based on QD conjugate antibodies coated with norborne-displaying polyimidazole ligands. This fluorophore has been used for the *in vivo* marking of bone marrow cells. The investigators found that fluorophore has been able to diffuse across the bone marrow and mark rare cell types, such as hematopoietic stem and progenitor cells [80]. Shi et al. (2015) [79] have produced a multifunctional biocompatible graphene oxide quantum dot protected by a magnetic nanoplatform for the detection/diagnosis of specific tumor cells of liver cancer (glypican-3-expressing hep G2). According to the scientists, the adhesion of an anti-GPC3 antibody to the nanoplatform resulted in a systematic isolation of hepG2 hepatocellular carcinoma cells from blood samples [79]. The continuous and/or controlled release of therapeutic agents can also have benefits from QDs. This behavior can be achieved by active stimuli by light, wind, radio frequency or magnetic fields [81, 82] as far as controlled release is concerned. Olerile et al. [83] have developed a theranostic framework as a multi-functional parenteral system that focuses on the co-loading of QDs and anti-cancer drugs in nanostructured lipid carriers. The nanoparticles were spherical with a higher paclitaxel encapsulation potential (80.7 ± 2.11 percent) and a 77.85 percent tumor growth inhibition score. The authors observed that the device was able to monitor and identify H22 tumor cells precisely [83]. Cai et al. [84] have produced pH-responsive quantum dots based on ZnO quantum dots coated with PEG and hyaluronic acid to be stable under physiological conditions and for targeting specific HA-receptor CD44 cells. This nanocarrier was also assessed for doxorubicin's (DOX) sustained release. At physiological pH, these carriers were stable and DOX was loaded into the carrier and the complex form of Zn^{2+} ions or PEG conjugation. DOX was only released from the tumor cells under acidic intracellular conditions due to disturbance of ZnO QDs. The investigators found that the combination of DOX and ZnO QD [84] enhanced the anticancer function.

4. Natural product based drug delivery system

Natural product-based materials are currently considered to be the key ingredients in the preparation and processing of new nanoformulations as they have interesting features such as biodegradability, biocompatibility, availability, renewability and low toxicity [85–87]. In addition to the aforementioned properties, biomaterials are largely capable of undergoing chemical modifications, ensuring unique and desirable

properties for potential nanomedicine uses [88, 89]. For example, nanoparticles of metals, metal oxide and sulfides have been recorded to be synthesized using different microorganisms, including bacteria, fungi, algae, yeast, etc., [90] or plant extracts. Microorganism that assists the synthesis process is prepared in the adequate growth medium and then mixed with a metal precursor and left for incubation to form the nanoparticles either intracellularly or extracellularly [91–93]. Similarly, plant extracts are used for synthesis in which the extract is mixed with the metal precursor and incubated further at room temperature or boiling temperature for a definite time or exposed to light as an external stimulus [94]. Currently, natural product-based materials are considered essential ingredients in the preparation and production of nanoformulations as they have fascinating characteristics such as biodegradability, biocompatibility, sustainability, renewable energy and low toxicity [85, 86, 95]. In addition to the above mentioned properties, biomaterials are, for the most part, capable of undergoing chemical modifications, guaranteeing them special and attractive properties for future applications in the field of nanomedicine [89, 96, 97]. Nanoparticles, especially the silver nanoparticles have been prolifically studied *in vitro* for their antibacterial, antifungal, and cytotoxicity potential [98, 99]. Nanocarriers such as crystal nanoparticles, liposomes, micelles, polymeric nanoparticles, solid lipid nanoparticles, superparamagnetic iron oxide nanoparticles and dendrimers are formulated for natural product based drug delivery. Gupta et al. [100] synthesized chitosan-based nanoparticles loaded with Paclitaxel (Taxol) extracted from *Taxus brevifolia* for cancer therapy applications, and used them to treat various forms of cancer. The drug loaded with nanomedicines exhibited better efficacy with sustained release, high cell absorption and decreased hemolytic toxicity compared to pure Paclitaxel [100]. Chang et al. [101] developed a heparin/berberine conjugate to improve the suppressive development of *Helicobacter pylori*, thus reducing cytotoxic effects in infected cells. In a study conducted by Dian et al. [102], polymeric micelles were used to deliver Quercetin (polyphenol) and the results showed that these micelles could provide continuous release for up to 10 days *in vitro*, with continuous plasma levels and increased complete *in vivo* drug accessibility. Spillmann et al. proposed a multifunctional liquid crystal nanoparticles device as intracellular fluorescent imaging and doxorubicin distribution in which nanoparticles were functionalized with transferrin. Daunorubicin is a natural product extracted from a number of wild strains of *Streptomyces,* doxorubicin (DOX) is a hydrolated version of it used in chemotherapy [103]. Within the endocytic vesicles of HEK 293 T/17 cells, cellular uptake and continuous liberation have been achieved. For intracellular transport, perylene was used as a chromophore to chase particles and encapsulated compounds [104]. Liposomes are studied mostly, and have been used in various formulations for the delivery of natural products like Resveratrol, Curcumin, etc. [105, 106].

In addition, it can be seen that the sustained release mechanisms of naturally occurring therapeutic agents are a crucial method for increasing the biological efficacy of these agents and addressing their drawbacks by introducing new options for chronic and terminal disease management [107–110].

The global demand for plant-derived pharmaceuticals will rise from $29.4 billion (as in 2017) to around $39.6 billion in 2022 with a compound annual growth rate (CAGR) of 6.15% in this timeframe (BCC-Data), according to BBC Report. Any of the nanostructure-based materials included in this section have already obtained FDA clearance.

5. Challenges and opportunities

While there have been a large number of nanomedicine-related studies and tests, only a handful have advanced to market-related review and once again a

smaller handful have earned final clearance. The conversion of fundamental science into clinical practice was less than 10 percent, based on some reports [111, 112]. Thus, drugs that travel through what is known as the 'valley of death' do not seem convenient. This will lead to a time-consuming, lengthy, futile series of reviews, escalating the expense of health care as a whole [113]. Perhaps the reasons for such an undesirable state of affairs lie in multiple fields and procedure facets. One of the key problems involves nanoparticles' *in vivo* behavior, which is expected to be somewhat different from their *in vitro* behavior. The key problems that need to be extensively explored using various animal *(in vivo*) models are cellular interactions, tissue transfer, diffusion, and biocompatibility. It is not simple or cheap to perform such tests to provide adequate proof of effectiveness and protection. Another obstacle for tumor-targeted nanoformulations in particular is the heterogeneity and heterogeneous nature of tumors. Different gene expression profiles, molecular patterns and degree of drug resistance between different tumors may impede penetration and decrease the efficacy of tumor-targeted NPs [114, 115]. This challenge could lead to an unsuccessful clinical trial (despite promising animal preclinical data) and to rejection of the nanoformulations examined. Relevant drug penetration into tumors, the efficacy of the release of drugs into the target cells, and the quality of the drug loaded nanoparticles, are other factors that involve a precise professional experimentation [114]. Owing to time and money problems, this comprehensive research may not be possible in all biomedical laboratories which itself is another concern. The multifunctional structure and operation of some nanoformulations could be another obstacle on the road to nanoformulation acceptance. Many investigative nanoformulations have a hybrid structure and contain separate diagnostic and therapeutic components. Different experiments are required to demonstrate the protection of such systems, and the long-term biocompatibility of such systems is not yet clear [116, 117]. Regarding this issue, the regulatory authorities have different restrictions, and it will take time-consuming and costly regulatory studies to be sure of the long-term safety of these theranostic nanoformulations. Many of the classical approaches for nanoformulation synthesis are already incomplete and need to be more developed and optimized. Batch-to-batch variance is another problem that can hamper the development of enough stocks of nanoformulations for market approval to be achieved. The updating of production methods and the highly accurate characterization of nanoformulations are expected to be laborious, time-consuming and expensive [116, 118].

In spite of all the above-mentioned obstacles, the demand for nanopharmaceuticals and nanomedicines will continue to expand over the next few years, primarily thanks to developments in bionanotechnology and nanoengineering, the implementation of explicit guidelines on new nanotechnology-based products, more support from government organizations, more consensus on environmental issues and the creation of collaborations between nanomedicines startups and leading pharmaceutical companies [119]. In other words, in order to convince investors about the value of nanopharmaceuticals and to improve the overall health and well-being of society, intellectual property and regulatory agencies need to change their approach to meeting the specific needs of nanomedicine and shorten their time to regulatory approval. However, in the case of nanodrugs, it is particularly important to consider the risks to health and the environment *vis a vis* it's short-term gains. Another similarly significant aspect that has drawn researchers and companies' interest is the increasing role that cancer plays in mortality and morbidity statistics worldwide As in 2018, FDA earned the most approvals for oncology drugs [120, 121]. This, and the large number of other cancer-related pharmaceuticals licensed over the past few years, shows not just the patients' desperate need for better cancer treatment, but also the massive cancer care market. There is still tremendous hope for the application of chemotherapy and photothermal or photodynamic treatment. These, though, are variations of products, which could be

easier to progress to complete clearance. Diseases affecting the immune system are also very important for the pharmaceutical industry. These applications include stimulating the immune system to combat infections and cancer, but also to down-regulate the immune system to combat autoimmune diseases and allergies. Overall, it is believed that the rising rate of cancer-related deaths will be driving the anticipated increase in the size of the global nanomedicine market in the coming years.

6. Conclusion

Initially, the use of nanotechnology was mostly based on improving the solubility, absorption, bioavailability and controlled release of drugs, but now a wide range of nanodimensional tools are included that can be used to diagnose, precisely deliver at target, sense or activate material in the living system. By using nanocarriers formulated with gold, silver, cadmium sulphide, and titanium dioxide polymeric nanoparticles along with solid lipid nanoparticles, nanogels, liposomes, micelles, iron oxide nanoparticles, and dendrimers, the efficacy of the natural products has greatly improved. One of the major interests in the advancement of nanomedicine in recent years is the convergence of therapy and diagnosis (theranostic) as an example of cancer as a disease model. Since the 1990s, there has been a remarkable growth in the number of FDA-approved nanotechnology-based products and clinical trials, including synthetic polymer particles; liposome formulations; micellar nanoparticles; nanocrystals and many others frequently associated with drugs or biologics. Although regulatory frameworks for nanomedicines along with safety/toxicity tests will be the focus of further research in the future, the way we discover and deliver drugs in biological systems has already revolutionized nanomedicine. Thanks to advances in nanomedicine, the ability to deliver, and even targeted delivery, has also become a reality.

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