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Review Article

Nanomaterials in drug delivery—Promises and limitations

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ABSTRACT: The unprecedented upsurge of human suffering, whose canvas seems to broaden by the emergence of incurable diseases as a result of evolution of novel strains of microbes is further compounded by the development of antimicrobial resistance, growing urbanization and lifestyle. Nanomaterials are of nano size-ranging from 10–100 nm, and nowadays, they are finding immense applications in drug delivery owing to their advantages over the conventional drug delivery systems. This review article aims to discuss various types of nanomaterials including polymeric nanoparticles (polymersomes, dendrimers, polymer micelles, nanospheres, and nanogels), inorganic nanoparticles (SiNPs, quantum dots, MXenes, FeONPs, and AuNPs) and lipid-based nanomaterials (liposome, lipid nanoparticles, emulsions, and niosomes) in drug delivery applications. Besides this, the manuscript also discusses their limitations, suitability, theranostics, and safety concerns in drug delivery. From the discussion about their applications and limitations in drug delivery, it can be conclusively stated that because of their versatility, the nanomaterials are promising contenders in the field of nanomedicine and their utility in healthcare has convincingly endorsed the fact that however 'nano' the dimensions of nanomaterials are, they have colossal relevance.

KEYWORDS: nanomedicine; drug delivery; nanomaterials; biocompatibility; toxicity

1. Introduction

The fervor of scientific community to deliver better solutions for healthcare remains persistent, pertinent and needs to be made sustainable and economical to address the emergence of life-threatening diseases. Concerns also are due to the long-cherished miracle drugs, the antibiotics, which are losing their potency amidst rising anti-microbial resistance (AMR) and the origin of superbugs. With the lack of incentives, biopharma companies are deterred from undertaking further research into novel antibiotics. Under these conditions, of weaning hope, the use of nano-objects or nano structured surfaces that can either enhance antibiotics' efficacy or inhibit the attachment of bacteria or are lethal to bacteria (bactericidal/bacteriostatic) are the deliberate choice and would hold much significance[1]. Targeted drug delivery mediated by nano-carriers can facilitate intracellular drug transport and its retention[2]. Additionally, nanomaterials-based drug delivery systems can reinforce the pharmacological and restorative properties of traditional medicines[3].

A dosage of drug comprises the drug itself or API (Active Pharmaceutical Ingredient) and the non-drug component or excipient—wherein, the former aids in diagnostics, treatment and

prevention of diseases. The excipient is the pharmacologically inactive component that makes the drug more elegant and enhances stability, safety and palatability, along with providing for improved drug bioavailability and also acting as filler, binder, lubricant, disintegrating agent, flavor, anti-adherent or colorant. As a rule of thumb, while the drug reaches its target, its efficacy should not be lost. Further, upon reaching the target and binding to receptors, on the target cell or tissue, the entry of the drug at precise sites can be facilitated by the modulation of the chemistry of the drug and its design by taming the benefits emanating from nanotechnology research[4].

The long-established drug delivery systems suffer from several disadvantages. One of the problems of conventional drug delivery systems is that the drug might get metabolized before reaching the target or may display erratic absorption pattern and this has at least been demonstrated for the drug Levodopa, which finds extensive application in treatment of neurological disorders like the Parkinson's and hence leads to reduced efficacy of the drug[5]. After the drug reaches the target, therapeutic and pathological instances may initiate triggers such as lowering of the pH, over expression of reactive oxygen species (ROS) or existence of polypeptides of specific types[6]. Besides, cytosolic drugs followed by their entry into the cell compartment remain vulnerable to degradation via the endocytic pathways. However, nanoparticles of size of 20 nm escape endocytic degradation in lysosomes and endosomes[7]. Yet another disadvantage that emerges out of chemotherapy is caused due to repetitive and decked dosages of antineoplastic drugs resulting in distress to healthy cells and provocation of multidrug resistance. More often therefore, limitations like poor bioavailability, insolubility and elevated toxicity of drugs deter them from overcoming physiological and biochemical barriers of systemic nature[8]. Therefore, in the absence of precise delivery into selected cells, tissues and tumor microenvironment the result is poor efficacy and side effects of the drug.

The advantages of nano-based systems in drug delivery are tremendous. Engaging nanomaterials in drug delivery can conquer pharmacokinetic shortcomings by providing for uninterrupted release of drugs, prevention from degradation, entry even into the central nervous system and targeting the drug to precisely identified cells and particular intracellular pathways[5]. Nanomedicines can increase drug bioavailability, enhance its circulation time and sometimes also diminishes instances of recognition by immune system in breast cancer treatment[9]. It has been noted that nanotherapeutics in gastric cancers can also facilitate multimodal imaging along with targeted drug delivery that can well imply a theranostics (therapy plus diagnostics) approach[10]. Nano-carriers based formulations demon-strate better efficacy as compared to traditional medicines for the treatment of disorders of inner ear and this has been shown in animal models, however, for use in clinical procedures, challenges still need to be overcome[11]. Drug delivery by nanoparticles is an emerging field because of the decors arising out of their size and it can overcome the severity and after effects of surgery, radiotherapy and chemotherapy, the drawbacks frequently associated with conventional cancer treatment procedures[12,13]. **Table 1** gives a comparative account of the differences between conventional and nanomaterial-based drug delivery systems.

Although the translation of drug delivery systems into clinical outcomes may at present seem challenging due to scientific, curative and manufacturing impediments, however, the benefits in cancer therapy include avoidance of drugs entering into the non-cancer cells and entry only in the cancer cells, high drug payload, biocompatibility and efficacy cannot be overlooked[13]. However arduous it may appear, therefore, developing nanomedicines have tremendous potential in cancer treatment by chemotherapy[14]. Nanomaterials based drug carriers because of their physico-chemical and biological properties can

Table 1. Comparison of conventional and nanomaterial-based drug delivery

Conventional drug delivery	Nanomaterial based drug delivery
Loss of efficacy	Efficacy maintained
Erratic absorption pattern	Defined absorption
Endocytic degradation	Uninterrupted and sustained release
Multiple drug resistance	Targeting to tissue or organ concerned, EPR (Enhanced Permeability and Retention) effect
Toxicity and stress to healthy cells	Controlled release
Difficult to deliver drugs with sparing solubility	Can deliver even drugs with sparing solubility
Recognition by immune system	Lowering of recognition by immune system
Poor bio-availability	Drastically enhanced bioavailability

resolve issues related to drugs having sparing solubility under physiological conditions[15]. This can revamp performance of the therapeutic agent with diminished toxicity and is gaining immense popularity and impact in the medical field[16]. Quite recently, PEGylated halloysite/spinel ferrite nanocomposites sensitive to pH have been fabricated with the potential of delivering the drug dexamethasone in the lungs for the treatment of COVID-19[17]. Even for the treatment of life-threatening cardiovascular diseases like congestive heart failure, albumin-based nanoparticle formulation has been developed that an deliver the inotropic drug milrinone tagged with the targeting ligand angiotensin II and the results have demonstrated improved drug pharmacokinetics and functioning of the heart[18]. Additionally, unique drug delivery systems are offered by the development of nanorobots that upon surface functionalization with highly responsive chemical groups can generate customized responses in targeted cells and also, they can be tagged with immunoglobulins to target specific cells[4].

The use of nanomaterials as drug delivery agents is on surge, however, concerns are raised because of their putative toxicity that results from their physico-chemical structure, surface attributes, buildup of the biological corona, particle agglomeration and biodegradability, which also limits the clinical translation of these platforms. Therefore, an in-depth understanding of nano-bio interactions would be beneficial in predicting the outcome of drug delivery using these platforms including mechanism and kinetics of toxicosis, trafficking, uptake and responses and synthesis of biocompatible nanomaterials for biomedicine[19]. The applicability of toxicity relates to all the stakeholders—from patients to labs and manufacturers (occupational exposure)[20]. This reinforces the fact that only biocompatible nanomaterials should be used in drug delivery. More promising contenders in this field, referred to as smart nanomaterials are used for drug delivery applications, that are selective and sensitive with fewer side effects for example, the use of smart nanomaterials in cancer treatment causes minimal to no side effects in non-cancer cells and response is generated only in the tumor microenvironment[21]. Usually, stimulation from inside or outside like temperature, pH or biological molecules can be used to initiate the release of the pharmaceutical component in such drug-nano combinations. Ranjha *et al*.[22] have pointed out that, sometimes biocompatible nanomaterials result upon combining it with nutraceuticals (also called functional or designer foods) and manipulation of the density and shape-size of the nanomaterials.

Nanotechnology has now become synonymous with sustainability among the scientific community and researchers across the globe are making prodigious use of green synthesis protocol more in conformity with the concept of circular economy. With this in mind, the phytochemistry of the common kitchen wastes or plant parts can be harnessed as reducing agents and/or capping agents for nanomaterials fabrication, which can themselves be used as antineoplastic agents. For example, AuNPs fabricated by green synthesis protocol using *Piper betle* leaves display anti-cancer effect against lung cancer cell line (A549) as demonstrated by MTT assay or metabolic as-

say[23]. The same group was successful in fabricating AgNPs using *Argemone mexicana* Linn., a medicinal plant and when used against SiHa cancer cell lines, the NPs showed growth inhibition up to almost 80% and the authors are of the view that fabrications like this hold immense potential in cancer therapeutics with bifold advantages-drug delivery and safety[24]. Significant growth inhibition of SiHa cancer lines was also noted using PtNP sol obtained when PtNPs were fabricated using *Oxalis*[25]. *Aloe vera* well known for its antiseptic properties was used in the synthesis of ZnO nanoparticles and it showed exceptional anti-neoplastic and anti-bacterial properties[23]. In yet another instance, ZnONPs fabricated using lemon grass showed toxicity against THP-1 human leukemia cells[26]. *Piper betle* leaves are widely used in ethnomedicine and cancer can be treated effectively by PtNPs fabricated using foliage of *Piper betle*[27]. Green synthesis of AgNPs was also undertaken using various medicinal plants like *Phyllanthus niruri*, *Achyranthes aspera* and *Azadirachta indica* and the nanoparticles hence fabricated were tested against THP-1 cell line, a human leukaemia cell line and the results clearly hinted that they could be used for cancer therapeutics[28]. Researches like these clearly illustrate clean and green fabrication prototypes of nanomaterials for treatment of cancer and other incurable diseases. However, the validation of long term and short-term effects of nanomedicines is mandatory and will require comprehensive clinical trials[29]. Nanoparticle based drug delivery systems fall into three categories—polymeric nanoparticles, inorganic nanoparticles and lipid-based nanoparticles[30]. The following section describes in detail the various types of nanoparticles in drug delivery.

2. Nanomaterial based drug delivery

2.1 Polymeric nanoparticles for drug delivery

Of all the drug delivery systems that exist, the polymeric nanoparticles contribute the maximum share[31]. These drug delivery systems offer advantages including drug targeting to the action site and also prolong drug circulation in the blood[6]. Although polymers of the synthetic type exist, they suffer from several shortcomings. However, in drug delivery applications, nano systems inspired by structural biology prove much helpful[4]. Polymer based nanoparticles can be made responsive to external stimuli such as ultrasound and at least in one case, drug delivery by ultrasound-responsive polymeric nanoparticles was found to be more efficient as compared to polymeric materials made responsive to other kinds of stimuli including ultraviolet, pH, temperature, etc. with better targeting sans any invasive procedural requirement[32].

a) Polymersomes—Polymersomes are unilamellar drug delivery systems of nano size with proven stability in colloidal state and displaying advantages such as limited permeation of aqueous fluids, because of enhanced bilayers thickness and providing for higher encapsulation and better adaptability[33]. Although liposome-based drug delivery systems are popular, polymersomes show better stability and are made using amphiphilic polymers[34]. Polymersomes can be made responsive to pH, temperature, changes in redox patterns, light, magnetic field, enzymes, etc. Even modification of polymersomes by peptides can enhance the efficacy of drug targeting and cellular uptake by cancer cells and often show comparatively reduced toxicity both *in vivo* and *in vitro* as compared to liposomes[35]. Polymersomes are totally synthetic analogues of liposomes that can encapsulate wide array of drugs because the properties of their membranes can be tailored, however the availability of pharmaceuticals based on polymersomes is almost nil in the market. The API L-asparaginase is used for the treatment of lymphoblastic leukemia and by using quality by design approach, a risk assessment matrix was generated, which could pave way for the development of nano encapsulated APIs utilizing polymer-

somes[36]. It has been noticed that PEG when added as block co-polymers can extend the circulation of polymersomes in blood. Several novel applications are ascribed to polymersomes including drug delivery, medical imaging, electronics, and nanoreactors and by tagging biodegradable polymers, polymersomes can be made to release drugs in response to both external and internal stimuli[37]. The polymerization approach undertaken determines the quality of polymersomes. Their fabrication is done by amphiphilic block copolymers and the ratio of hydrophobic and hydrophilic blocks can be carefully manipulated for the polymersomes fabrication procedure[38]. Vesicles of polymersomes are made up of amphiphilic molecules and show better stability as compared to liposomes, nevertheless from the perspective of medical applications as drug delivery carriers, their functionalization is essential[39]. The diminished relaxivity of MRI contrast agents poses an obvious impediment in cancer theranostics. To overcome this disadvantage, Liu *et al*.[40] fabricated and characterized a novel MRI contrast agent based on diblock copolymer—folic acid-poly (L-glutamic acid)—block poly (ε-caprolactone) [FA-PGA-bPCL], magnetic in nature because of the use of super paramagnetic iron oxide NPs that could effectively encapsulate and deliver the antineoplastic drug to the site of tumor. Polymersomes include polymeric micelles and vesicles, and both hydrophilic and hydrophobic drugs can be loaded into their internal aqueous chambers which remain enveloped by membranes that are hydrophobic. Co-delivery polymersomes can deliver both hydrophilic and hydrophobic drugs together and demonstrate application in combination therapy. An offbeat example is the simultaneous delivery of paclitaxel and Doxorubicin (hydrophobic-hydrophilic drug pair) ingrained in unique co-delivery polymersomes, targeted by folate and exceedingly better results were obtained by this targeted combination therapy in contrast to non-targeted co-delivery polymersomes[41]. Various physiological and medicinal conditions implicate reactive oxygen, nitrogen and sulfur species (RONSS) that can be used in the fabrication of theranostics nanomaterials that are activatable, wherein RONSS can act as imminent provokes or triggers[42]. Spacer chemistry can be carefully tailored to fabricate ROS-responsive polymersomes with minimal side effects, including lessened toxicity to heart and weight loss that is evident in the administration of free Doxorubicin (DOX). It has been proposed that, TME (tumor microenvironment) responsive selective nanomedicines can be utilized to fabricate ROS-responsive polymersomes and they can hold immense application in treating diseases characterized with high ROS including aging, diabetes, cardiovascular diseases, obesity, and chronic inflammation[14]. The applications of amphiphilic block co-polymers in nanomaterials are quite common and can be used to fabricate stimuli responsive polymersomes and this strategy is holding the potential of fabricating resourceful and powerful drug delivery systems. In addition to drug delivery, applications such as bio-sensing, bio-detection, and nano/micro reactors are achievable using N-substituted poly amino acids that are biocompatible[43]. Blocks composed of PEG and copolymers of camptothecin (CT) and piperidine modified methacrylate were used to fabricate GOD (glucose-oxidase) polymersomes nanoreactors[44]. In comparison to liposomes, polymersomes are less toxic and more stable in the *in vivo* conditions. Certain ligands and peptides can be made to modify polymersomes to enhance efficacy of drug targeting and uptake by cancer cells and again methods like nanoprecipitation, film rehydration, electro formation, emulsification, etc. can make polymersomes responsive to pH, temperature, magnetic field, etc.[35]. Without any doubt, the synthetic polymersomes emerge as strong and promising contenders in the expanding field of nanomedicines[33].

b) Dendrimers—Dendrimers are polymeric systems for drug delivery possessing explicitly defined size, shape, molecular weight and monodispersity and were introduced for the first

time by Vogtle in 1978. The dendrimers by virtue of their physicochemical properties and architectural details impart lasting drug responses and enhanced adaptability and therefore hold great application in cancer therapeutics[45]. They have great potential in targeted drug delivery because of the steep proportion of chemical groups existing on their surface as compared to their molecular volume. Their spherical shape, nano size, monodispersity, lipophilic nature, hyper branching points and ability to penetrate walls of cells, confer them ideal candidature in drug delivery systems[46]. Although the toxicity posed by dendrimers limits their application in biological systems, they can be put to wide ranging applications by ligand coating[31]. Their ability to entrap and/or conjugate with hydrophobic or hydrophilic groups of high molecular weight facilitates their use as drug delivery agents. Antibodies and bioactive substances can be hooked to the terminal chemical groups to make them soluble, miscible and reactive. Delivery of therapeutics by dendrimers is however restrained due to regulatory concerns, however, one proposition that emanates is that the toxicity posed by cationic dendrimers can be overcome by PEGylation[47]. Cisplatin or cis-diamine platinum dichloride, the first platinated drug, forms cisplatin DNA-adducts and aids in its anti-neoplastic applicability in the treatment of testicular, lungs, head and neck, ovarian, colorectal and bladder cancers, however, low absorption and increased efflux from cisplatin resistant cell lines limits its applicability. The fabrication of dendrimers of MoS_2 and magnetic NPs, sensitive to pH and temperature, was attempted and it was observed that the release of cisplatin was 86 and 92% respectively, upon stimulation by near infrared laser light[48].

c) Polymer micelles—Targeted delivery of hydrophobic anticancer drugs is done by polymer micelles quite largely which can have on its surface certain targeting ligands[49]. Additionally, these micellar structures also find applications in diagnostics, gene delivery and imaging that can allow biodistribution of the drug *in vivo*. The micellar structure can be made to undergo controlled dissociation by making the block co-polymers sensitive to pH, temperature, light and ultrasound, etc., to cause triggered drug release[50]. Polymeric micelles are typically less than 100 nm, hence being of nano size they are discharged slowly in the renal secretion and also show EPR effect permitting its accumulation in tumor tissue. They are formed of amphiphilic block co-polymers that also find application in the fabrication of micelles, nanospheres, nano capsules and polymersomes[51]. Hydrophobic drugs like camptothecin, docetaxel and paclitaxel can be incorporated into its hydrophobic core, while the enclosing hydrophilic shell stabilizes and maintains the micellar structure in addition to aiding its solubilization in water and also prevents biological components from interacting non-specifically with it. Polymeric micelles are expensive options in terms of purity of the monomer, cost of synthesis, filling up the drug cargo, stability, biosafety, effortless functionalization, however they show up exceptional antineoplastic activity when loaded with the anticancer drug gemcitabine[52]. A novel polymeric micelle synthesized using triblock polymers of PEG-PCL-Ptyr (polyethylene glycol-polycapro-lactone-poly-L-tyrosine) would hold immense potential in delivery of the anticancer drug 10-hydroxycamptothecin and arrest cancer cells in the S phase and induce apoptosis[53]. The treatment of respiratory ailments was earlier done by administering the drugs via the oral or intravenous route but it suffered from disadvantages like drug side effects and snags associated with its entry into regional destinations in the lungs and hence led to reduced potency. However, polymeric micelles hold much applicability in treating respiratory ailments with reduced side effects and also effectively take care of drugs with poor solubility and can be administered even by inhalation[54]. The advantages of polymeric micelles as drug delivery systems are far superior as compared to other nano-carriers particularly because of their small

size, simple fabrication and sterilization and feature of good solubilization However, knowing the *in vivo* route would be immensely helped by techniques like dynamic light scattering, atomic force microscopy, cryo-TEM, X-rays scattering, FRET, symmetrical flow field fractionation and density ultracentrifugation[55]. The property of self-assembly of *in situ* generated ZnO leads to the formation of polymeric micelles and the study of Miao *et al*.[56] showed enhanced loading and unloading of the drug Doxorubicin, in the tumor and could effectively result in tumor suppression.

d) Nanosphere—The nanospheres as therapeutic molecule carriers have been thoroughly investigated and are spherical with the entire solid mass. In these matrix-type nanodevices, the drugs can be incorporated either uniformly into the core or onto the surface of the nanospheres where the drug diffuses into the target tissue. The benefits offered by nanospheres include high drug cargo poorly soluble drugs with sustained and targeted release of the therapeutic molecule[57]. Nanospheres show lesser uptake of drugs in the intracellular environments but quicker drug release as compared to nanorods, therefore indicating that shape affects intracellular drug delivery and release[58]. MTT assay revealed reduction in cell survival rate within 48 h after the delivery of the anticancer drug Paclitaxel into lungs by utilizing BSA protein based hollow nanospheres made of silica NP of precise dimensions[59]. Magnetic nanospheres were fabricated, based on κ-carrageenan and were made responsive to pH, temperature and magnetic field. The efficacy of these nanospheres in the delivery of the antineoplastic drug, 5-fluorouracil was reported by Geyik and Isiklan[60]. Using spherical mesoporous bioactive glass of 170.87 nm, the fabrication of pH stimulated nanospheres has been reported and they were used for the delivery of the model drug Daunomycin. This drug delivery system demonstrated better antimicrobial activity against *Pseudomonas aeruginosa* than *Bacillus subtilis*[61]. Uson *et al*.[62] fabricated nanospheres that incorporated palladium plasmonic nanosheets in its core and were made sensitive to NIR (near infrared) light stimulus that could find application in photothermal therapy. pH sensitive lignin nanospheres were fabricated for the oral delivery of Ibuprofen that released only 18% of the encapsulated drug at pH 1.2, while 90% at pH 7.5[63]. Boltnarova *et al*.[64] have reported that nano formulations utilizing experimental mental branched PLGA (poly lactic co-glycolic acid) showed better drug delivery in the macrophages when compared with commercially available PLGA. Even in orthopedics research and allied treatment procedures and diagnostics, transformational results by nano structure-based drug delivery systems cannot be denied[16]. In yet another example, pH responsive hollow and mesoporous nanospheres were fabricated making use of monodisperse Fe_3O_4 that exhibited trivial cytotoxic behavior even in lofty concentrations of drug and were able to load higher drug cargo[63]. Liu *et al*.[65] devised a novel strategy based on calcium-silicon nanoparticles co-encapsulated with miR-210 and angiogenic gene drug simvastatin to achieve improved osteogenic/angiogenic ability of bone graft materials. Utilizing Doxorubicin as a model drug, a unique drug delivery system was fabricated making use of hollow nanospheres encapsulated with polyacrylic acid that was both pH and temperature responsive without any cytotoxicity and improved drug loading capacity. Drug delivery systems of this type can have immense potential in therapies aimed at combating cancer[66]. The delivery of drugs like Ibuprofen and lysozyme including their absorption was achieved using templates based on rich content of geminal silanols containing nano cellulose materials having coarse surfaces. The attachment to one silicon atom of two hydroxyl groups gives it the nomenclature of geminal silanols[67]. Nanomaterials can overcome impediments due to bacterial resistance, high doses of drug and low bioavailability in the eyes and therefore can find applications in ocular drug delivery of the drug Levofloxacin for example, chitosan-cyclodextrin nanospheres were fabricated that could

effectively deliver Levofloxacin[68]. The assembly of DNA nanospheres by electrochemical transformation was found to be effective in atenolol-based drug delivery[69].

e) Nanogels—Nanogels, also referred to as the drug delivery systems of the next generation, are a kind of three-dimensional hydrogels sized around 1–1,000 nm. They are extensively used in drug delivery applications because of their stability, flexibility, and ability to respond to subsequent changes in the external environment. They are made up of swellable hydrophilic polymeric networks that are linked by various types of bonds including covalent, H-bonds and van der Waals interactions[70,71]. The nanogels because of their biocompatibility can be used in therapy as well as imaging and their responsiveness to stimuli can be manipulated by carefully choosing the polymer and crosslinker. Such distinctive features make nanogels better drug delivery agents when compared to remaining nanomaterials[71]. Besides they can carry high payloads and have tremendous water content and can ensure accurate delivery of the therapeutic molecule in cancer tissues. Using pH differences between the tumor and normal tissue (the pH of the non-cancerous tissues being higher as compared to the cancer tissue), pH sensitive nanogels were synthesized to ensure precise delivery followed by the release of anticancer drugs[72]. Using emulsions like hyaluronic acid and polyethyleneimine, nanogels were synthesized, and it showed excellent delivery of the drug doxorubicin in ovarian cancer cells[73]. In another study, nanogels responsive to both pH and temperature and functionalized with D galactose were synthesized and used for monitoring and release of drug in liver hepatocellular carcinoma[74].

2.2 Inorganic nanoparticles for drug delivery

The major inorganic nanoparticles for drug delivery applications fall into the following classes.

a) Silica NPs (SiNPs)—The benefits of SiNPs in drug delivery are attributed to their biocompatibility, high surface area and ease of functionalization. SiNPs exist in three forms, namely non-porous, mesoporous, hollow mesoporous and finally, the core-shell silica (with or without surface modification). Among all these, mesoporous SiNPs (MSN) are preferred over others due to their adjustable pore-sizes and volumes, biocompatibility, comfortable functionalization, high drug cargo and antimicrobial drug delivery which minimizes drug after effects[2] and it has been proposed that the structure and geometry of MSN aids in drug delivery[75]. Polyacrylic acid based hollow hybrid mesoporous silica nanoparticles sensitive to both pH and temperature were fabricated and studied for the delivery of the drug Doxorubicin. The results showed excellent drug cargo and almost nil cytotoxicity and thus were found to be excellent for cancer therapy[76]. According to Wang *et al.*[77], MSNs find application in drug delivery—both controlled and targeted, where the drug can be released promptly or in a sustained manner, and MSN is used in bioimaging and as bioactive materials in tissue regeneration as well[77]. As drug delivery systems in cancer therapy, MSNs can carry multifunctional drugs due to excellent stability of their colloids[78]. Often, a therapeutic molecule for drug delivery can be attached to the surface of MSNs upon its surface functionalization by various additives[79]. Based on the availability and requirement, the drug may be made to release upon stimulation by external or internal stimuli[80]. According to Pada *et al.*[58], MSNs can be made responsive to pH for sustained release of drugs by coating them with polydopamine and they can be utilized to carry both hydrophilic and hydrophobic drugs. The model anticancer drug, Doxorubicin was released and targeted in a controlled manner by utilizing MSNs that carried a Y-shaped DNA structure and was made responsive to ATP[81]. MSN carrying pH sensitive lipids and also coated with polyacrylic acid was used to deliver two anti-

cancer drugs—arsenic trioxide and paclitaxel simultaneously and the result was improvement in overall therapeutic efficiency of the drug by increasing time of circulation and tumor targeting[76]. The limitation imposed by reduced bioavailability of the drug Ru-PIP (Ruthenium Polypridyl) drug was overcome by undertaking its release using mesoporous silica nanoparticle[82]. As previously stated, functionalization of MSN can result in enhanced therapeutic efficiency as observed by Murugan and Krishnan[83], in their fabrication of MSN functionalized with thiol groups that showed greater toxicity to MCF-7 cancer cells as compared to the MSN that lacked modifications. The fabrication of SiNPs can be an expensive affair when done using synthetic organic precursors which themselves in addition to being expensive, are non-biocompatible and also possess the ability to pollute. However, keeping in view the current role of circular economy in achieving sustainability the fabrication of homogenous SiNPs can also be made using agro residues like corn cob and husks (coffee, rice, wheat) and sugarcane bagasse. However, synthetic precursors are more in use in fabrication of SiNPs. Interestingly, face masks were made more effective in preventing SARS-CoV-2 infection by the incorporation of SiNPs[84].

b) Quantum dots (QDs)—Sized between 1–20 nm, QDs are nanomaterials of zero dimensions, with radius same as that of Bohr exciton and show spectra of absorption that is broad with outstanding brilliance and persistence for various applications because of the quantum confinement effect[85]. From applications ranging from tissue engineering, stem cell research and drug delivery, Graphene Quantum Dots (GQDs), are emerging as an important class of carbon-based nanomaterials[86]. GQDs possess less toxicity and better biocompatibility as compared to selenium or/tellurium/metal sulfide based QDs, and both doped and pure GQDs can be fabricated by using both bottom up and top-down approaches by the green synthesis protocol[87]. Only single layer of carbon is present in GQDs, although sometimes variations do exist and release of drugs is accomplished using EPR-pH, ligand-pH, core-shell photo thermal and magnetic thermal delivery platforms[88]. According to Badıllı *et al*.[89], QDs show characteristic absorption and emission spectra that is long lasting with immense brightness and these physico-chemical properties account for their use in fluorescent assays in disease detection and monitoring metabolism of drugs in the body. Within the core of the QD certain inorganic drug carriers or contrast agents with better biocompatibility can be incorporated. But in spite of this, the clinical translation of QD in drug delivery systems is problematic due to their probable toxicity[90]. GQDs can target the drug across the blood brain barrier and tumors and these carbon-based nanomaterials could solve therapeutic puzzles involved in the treatment of Parkinson's and Alzheimer's[91]. Li *et al*.[92] fabricated a drug delivery system comprising of Folic Acid-PEG-cGQDs (Folic Acid-Polyethylene Glycol-carboxylated Graphene Quantum Dots) that showed exceptional antitumor capability and reduced toxicity. In yet another experiment, Ghanbari *et al*.[93] have shown promising delivery of the hydrophobic anticancer drug curcumin against cancer of the breast in humans when curcumin was loaded into tryptophan conjugated GQDs. Wang *et al*.[94] fabricated a nano assembly constituted of GQD-FA to deliver anticancer drug Doxorubicin (DOX). They found that this nano assembly delivered the drug to the cancer cells and not to the non-cancer cells and that the drug delivery was efficient. DOX-GQD-FA could efficiently target the drug Doxorubicin to HeLa cells and the stable fluorescence released by GQDs was utilized for the real time monitoring of Doxorubicin release and its targeting. Utilizing nano materials and nasopharyngeal carcinoma, the tumor of the head and the neck was treated with drugs like cisplatin and Doxorubicin in which GQDs conjugated with GE11 (an EGFR antagonist peptide) facilitated monitoring of drug release[95]. GQDs can find applications in lung cancer theranostics—which

includes therapy—photolytic and hyperthermia and drug delivery as well[96].

Yet another promising agent in drug delivery is carbon dots that have dimensions of less than 10 nm and are fluorescent carbon-based nanomaterials. Their application as drug delivery agents is attributed to their excellent biocompatible nature, optical features, economical and eco-friendly attributes with plentiful diverse functional groups (like $–NH_2$, –COOH, –OH), stability and mobile electrons on their surface[97,98]. Das *et al.*[99] achieved excellent targeting of the anti-cancer drug capecitabine using carbon dots co-doped with nitrogen and sulphur, prepared from κ-carrageenan and folic acid. For the delivery of anticancer drugs, epirubicin and temozolomide to glioblastoma brain tumors the targeting ligand transferrin containing carbon dots were synthesized[100]. In yet another research, carbon dots synthesized using alginate were doped with nitrogen and used as carriers of drugs and for the toughening of hydrogels[101].

Recently, biocompatible MXene based QDs are gaining popularity in cancer theranostics. They have the general formula $M_{n+1}X_nT_x$, and are transition metal carbides, carbonitrides and nitrides and have two dimensional planar structures. They bear on their surface discrete surface terminations and abundant functional groups. They find use as nano drugs and in biomedicines as biological sensors, bioimaging, theranostics, and photothermal drug delivery[102,103]. By careful manipulation of their optical and electronic properties MXene systems like Ti_3C_2, Nb_2C, Ti_2C are used as sensoring probes and photothermal therapy in studying drug delivery in *in vitro* and *in vivo* cancer models[104]. However, apprehensions sometimes still prevail regarding their biological compatibility, which can be achieved by adopting suitable strategies for their functionalization and synthesis protocols[105]. Mxenes are also utilized in non-invasive theranostics like photomedicines, wherein photons are used for cancer/tumor ablation. They are known for their ease of synthesis, high drug loading capacity, photothermal transformation, and magnificent photodynamic efficiency[106]. Currently, the synthesis protocols of Mxenes are tiresome and are usually undertaken using hazardous etchants or fluoride-containing reagents, however, it is expected that switch green chemistry-based protocols and milder conditions will further help in enhancing its biocompatibility and biosafety. Further, research in this area should focus also on scaling up the synthesis to achieve enhanced yields, functionalization processes, cost effectiveness and environment friendly procedures[107].

c) Iron oxide nanoparticles (IONPs)—Drug delivery by iron oxide nanoparticles to their respective sites is brought about by magnets and is helpful in enhancing the drugs' activity under physiological conditions. The popularity of magnetic nanoparticles stems from their ability to be managed in magnetic field; with the benefits of biocompatibility and the ease of their surface modification to link the drug molecule[3]. They do so by adsorbing and releasing the drug in a manner that is controlled. Cationic peptides like Lasioglossin, known for its anti-microbial behavior, from bee venom are easily carried as drugs by bare IONPs[108]. IONPs conjugated with the anticancer drugs can effectively be targeted by magnets to gliosarcomas and it was found that the drug accumulated at the tumor site and further its quantification was done by MRI[109]. Often the bare IONPs aggregate and create impediment in drug delivery, under these circumstances they are coated with stabilizing agents. The need for a separate stabilizing agent can be warded off by using zwitterionic drugs like Norfloxacin—that plays dual role, first in stabilization of the nanoparticle and second their inherent antibiotic activity[110]. The clearance of nanoparticles from the circulatory system is because of their recognition by mononuclear phagocytes. To achieve synergistic photothermal and chemotherapeutic effect IONPs were fabricated that mimicked the tumor exosome and released the anticancer drug upon NIR irradiation (Near Infra-Red) followed by rapid drug release by es-

caping recognition by macrophages and immune clearance[111]. As Nedyalkova *et al*.[112] pointed out that super conducting magnets, local implantation of magnets and magnetic stents can generate suitable magnetic field gradient for *in vivo* delivery of drug using superparamagnetic IONPs. Therefore, it would not be wrong to say that in the fight against cancer, leading platform technology is provided by super magnetic IONPs and that they are emerging candidates with excellent theranostic capacity with the ability to simultaneously deliver and image drug delivery. However, sometimes the delivery suffers from disadvantages such as development of oxidative stress and cellular targeting that is unpredictable. Hydrogels made up of chitosan-IO nanocomposites sensitive to pH and external magnetic field were super magnetic and used to deliver the model drug Doxorubicin that showed slow release under *in vitro* conditions[113]. 5-aminolevulinic acid, an anticancer drug was studied for its delivery by carbon nano tubes (CNTs) and, carboxyl-functionalized CNTs and IONPs, and it was found that drug delivery by functionalized CNT and IONP were suitable and notably, the functionalization was found to take place through hydrogen bonds and van der Waals interactions[114]. The *in-situ* synthesis of active cisplatin II led to sustained death of ovarian cancer cells when IONPs loaded with cis-diamminetetrachloroplatinum IV was used for targeting[115]. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) was developed as a quantitative tool for the analysis of drug delivery of cisplatin IV, prodrug conjugated to IONPs into isolated cells[116].

d) Gold nanoparticles (AuNPs)—AuNPs are excellent systems for drug delivery applications because the surface of AuNPs can be loaded with different kinds of therapeutic ligands. Additionally, they can also be used in photothermal and anti-angiogenic therapy, and radiotherapy. Additionally, features such as biocompatibility, low cytotoxicity and optical properties make them suitable for use in cancer theranostics, however, their effectiveness might be limited sometimes due to toxicity issues arising out of interaction with the human physiology[117,118]. The uptake of AuNPs is faster because of their size and stability, and the fabrication is easy and reproducible[119]. Often the AuNPs may lose efficacy before reaching their target. To prevent this, and make drug delivery more efficacious polymeric networks can be made to load AuNPs for instance, AuNPs can be combined with thermo responsive hydrogels that release the drug upon stimulation by suitable temperature. In HeLa cell lines, DOX was selectively targeted by gold nano- and micro-particles functionalized with silk conjugated with folic acid and fluorescein markers[120]. AuNPs of mean size around 5 nm could form transient and reversible holes on the stratum corneum and hence protein drugs-AuNPs could be used for needleless and self-administrable transcutaneous vaccination[121]. Sulaiman *et al*.[122] reported hesperidin loaded AuNPs tagged with pH sensitive linkers to carry the drug Doxorubicin across the nuclear membrane resulting in apoptosis or cytotoxicity to cancer cells[123]. In malignant tumors, AuNPs can enable delivery of drugs as they possess physicochemical properties and photonic properties that are unique[124]. The anticancer drug methotrexate was loaded onto AuNPs coated with gelatin to target the drug in MCF-7 breast cancer cell lines[125]. Hassanen *et al*.[126] have reported that the risk of renal toxicity in cancer therapy was reduced, when anti-cancer drug was delivered using AuNPs. Besides, the synthesized nanomaterials can themselves be cytotoxic to the cancer cells as reported by Jha *et al*[127].

2.3 Lipid based nanomaterials for drug delivery

Drug delivery platforms bearing one or more lipid bilayers have the ability to self-assemble, carry large drug cargoes, and possess high bioavailability, biocompatibility and candor of formulation[12,128]. Lipid based platforms for drug delivery comprise the most common class of

FDA-approved medicines of the nano size and include liposomes, lipid nanoparticles and emulsions[30].

a) Liposome—Nanovesicles, as they can be called, both liposomes and polymersomes can carry drugs, however, major challenges in their application in drug delivery are caused due to their degradation and delivery to healthy targets[129]. Liposomes and also the micellar structures are formed of amphiphilic molecules like surfactants, phospholipids and block co-polymers and as excellent drug delivery agents show properties like bioavailability, and are biodegradable, biologically compatible, and also show enhanced compliance with the patient body[130]. Structurally, liposomes can be unilamellar and multilamellar and their stability can be controlled both *in vitro* and *in vivo* by regulating nanoparticle size, surface charge, lipid composition, number of lamellae and their surface modification with ligands[131]. The stability of liposomes can be enhanced by PEGylation and PEGylated liposomes have demonstrated augmented anti-cancer effects. Increased anti-cancer effect was seen when Doxorubicin was targeted to treat cancers of mammary glands and ovarian cancers that were found to be resistant to platinated drugs[132]. Liposomes can entrap both hydrophilic and lipophilic molecules simultaneously in the same system endearing these systems the usage flexibility[133]. The ease of degradation of liposomes inside the body at physiological pH and ability to encapsulate hydrophilic agents inside the aqueous environment and lipophilic drugs in outer layers of lipids make them magnificent drug delivery agents[134]. When aiming for drug delivery and targeting, it may be required to prolong persistence of the drug by subjecting liposomes to surface modifications. Active targeting of the drug to designated regions in the body can be mediated by attachment to the surface of nanomaterials certain surface ligands and targeting feature depends on its valency, which corresponds to the numerical value of ligands attached[135]. Feng *et al*.[136] have highlighted the fabrication of immunoliposomes, that could *in vivo* perform dual functions—drug delivery and imaging, for example, for the treatment of Alzheimer's disease PEGylated liposomes with two antibodies were used—OX26 and 19B8[137]. In yet another instance, for the treatment of renal diseases, promising results in mice were achieved when drug Doxorubicin was encapsulated in OX-7 monoclonal antibody coupled with immunoliposomes[138]. The antigen-antibody dependent toxicity to cells was higher when Doxorubicin was encapsulated within liposomes conjugated with antihuman-CD71 monoclonal antibody[139]. For the therapy of B chronic lymphocytic leukemia cells anti-CD37 monoclonal antibodies conjugated to liposomes were used and could be a more preferred approach for personalized nanomedicines in the B cell malignancy treatment[140].

b) Niosomes—Niosomes are another vesicle-based drug delivery systems that are spheroidal and bi-layered and are formed by the self-assembly of non-ionic surfactants in aqueous environment. Cholesterol forms a major component of the membrane of niosomes and the size of the niosomes is influenced by the cholesterol content, HLB value of surfactant and the methods used for size reduction[141,142]. In comparison to liposomes, niosomes are preferred because of their stability and economical preparation procedure. It has been understood that the drug delivery by niosomes improves the pharmacological potential of the drug by putting off the drug's clearance from circulation, protecting the drug from the biological environment, and limiting the effects to the targeted cells only[143]. Niosomes lie in the nanometer size range and just like liposomes they can carry both hydrophilic as well as hydrophobic payloads for topical and targeted delivery of drugs[144]. By the coupling of desired ligands on the surface of niosomes, drugs can be targeted to suitable drug receptors[145]. Niosomes can be injected via ocular and transdermal routes and find application in the treatment of cancer, for instance, to address the poor stability and solubility of curcumin for cancer treatment was

improved by niosomal delivery[146]. Impairment in the cardiovascular functioning caused by myocardial ischemia reperfusion was overcome by the niosomal delivery of simvastatin[147].

c) Lipid nanoparticles (LNPs)—The uniqueness of LNPs lies in their ability to form within the core of the particle structures like the micelles and their morphology can be varied by regulating their synthesis and formulation specifications[148]. However, their appropriateness as drug carriers is limited as they carry diminished drug cargo because of their uptake by liver and spleen[149]. LNPs can find applications in gene therapy as they can deliver nucleic acids in an effective manner. Interestingly, LNPs are neutral at pH 7 but in endosomes become acidic—this leads to their delivery within the cell by promoting endosomal escape[150,151]. Limitations of drug delivery to specific sites in body do exist, for example to those sites where drugs cannot reach and still there are drugs that have low therapeutic index. Lipid nanoparticles hold much promise as drug delivery agents as they can carry drugs across daunting barriers such as blood-brain or plasma membrane, with protracted pharmacokinetics and diminished side effects and can even be used to deliver siRNA, CRISPR complex and sometimes even vaccines in liposomes[152]. The benefits sought from lipid nanoparticles range from enormous biological compatibility, simple fabrication, spontaneous scale up, delivery to required targets and toxicity that is null. Generally speaking, the lipid nanoparticles can be used for delivery via oral or the parenteral route and have GRAS status approved by FDA. Geometrically they are spherical, uniformly sized with good stability, enhanced cellular penetration efficiency and positive zeta potentials[153]. The emergence of solid lipid nanoparticles as putative drug delivery vehicles as biomimetic agents with potential to carry active therapeutics across blood-brain-barrier and find applications in the treatment of neuropathological problems like, Alzheimer's disease, Parkinson's disease, Huntington's disease, brain tumor, multiple sclerosis, epilepsy, and brain tumor[154]. The pharmacokinetic fluctuations especially related to absorption of Erlotinib HCl for the treatment of metastatic lung cancer showed poor oral bioavailability and it was improved by the use of solid lipid nanoparticles in the delivery[155]. Wiemann and Keck[156] found that LNPs based drug formulations were better than the traditional formulations including nano emulsion with pure oil containing active ingredient, etc. in dermal drug delivery. A concern that limits its use is the lipolysis of the lipid nanoparticle of the LNPs. Hence, the urge to develop a better drug delivery system continues and it has been highlighted that in oral drug delivery solid LNPs hold much promise as potential therapeutics[157].

d) Emulsion—With size well in nano range, from 10–100 nm, nano emulsion application in drug delivery cannot be denied and it can be produced by dispersing liquid phase as droplets in another liquid phase. These are said to be liquid emulsions and can be stabilized by surfactants like peptide and protein surfactants, phospholipids[158]. Nano emulsions are advantageous as drug delivery systems as they can allow controlled release of drugs, and can embody and carry drugs to suitable targets without causing their degradation and exhibit wonderful bio availability. Although toxicity of high drug administration via the parenteral route has been noted, oral administration is treated as secure[159]. Oil in water or water in oil dispersion, could bring about ocular delivery, when these heterogeneous nano emulsions were used along with surfactants and co-surfactants[160]. However, the pharmacological profile of the drug, fabrication, functionalization along with the administration route could facilitate clinical translation of drug delivery systems based on nano emulsion[161]. The studies on the delivery of a local anesthetic lidocaine via the transdermal route were carried out by oil-water nano-emulsion based on alginate and studies were carried out to understand the role of oil phase and surfactant on drug delivery[162]. To reduce the side effects of drugs and to

enhance the therapeutic efficiency of the drugs for the treatment of Alzheimer's disease, *in situ* hydrogels, nano emulsions and nanostructure carriers were fabricated, that could intra-nasally deliver the drug to the brain[163]. For the treatment of dementia, Alzheimer's, delivering a stilbenoid and also for reusing an FDA-approved drug, bio-obased nano emulsions could be synthesized[164]. For the delivery of aluminum pthalocyanine chloride to glioblastoma in human beings, cholesterol rich nano-emulsion was formulated[165]. For cancer treatment, MRI, insulin oral delivery, therapy in case of spinal injury, healing of bacterial skin infections, nano emulsion was fabricated utilizing the colloidal nature of dextran, a natural polysaccharide[166]. For the topical delivery of drugs to the skin *Pterodon pubescens* nano-emulsion was incorporated with hyaluronic acid, which imparted properties that were favorable for these nano-emulsion as topical drug carriers[167]. The administration of high doses of nano emulsions by the parenteral route can lead to toxicity issues, however their oral administration can be considered safe[159].

3. Safety evaluation of the nanoparticle formulations for drug delivery

The endeavors of nanotechnologists continue but as per figures, safety concerns lead to the acceptance of only 80% of them and remaining that fail to comply with the safety guidelines and efficacy get rejected[168]. Nanotoxicology of drugs has often been overlooked, and whenever attempts at drug delivery are initiated, compliance with regulatory guidelines framed along with the ethical concerns need to address the safety of human subjects, environment and other organisms on the planet earth[169]. Nanomaterials for use as drug delivery agents require FDA and EMA approvals before getting a final nod[170]. The size, shape and surface chemistry and conjugation with polysaccharides affect the pharmacokinetics of nanocarriers and often, the incorporation of surface coatings like polyethylene PEG, PVP, PVA, dextran, chitosan, poly (carboxybetaine), poly (sulfo-betaine) can result in desired fate and improve stability of the colloid post administration into the physiological milieu of the body and cells. For inorganic NP, it has been observed that doping by titanium oxide (TiO_2) can reduce the toxicity of silver nanoparticles[170]. Concern also emerges with respect to the use of PEG as it can lead to immune response[171], for instance, Doxil®, a Doxorubicin containing liposomal formulation that has been granted approval for treatment of Kaposi's sarcoma and cancer of mammary glands leads to hand-foot syndrome and cutaneous squamous cell carcinoma[172,173]. Further concern that can definitely address toxicity issues includes nanomaterials fabrication and characterization in clean rooms. This can be scaled up from the laboratory to large scale to be utilized by the pharma industry and therefore the final products coming up from the laboratory also need to be re-evaluated for their potential toxicity. The incorporation of next generation lipids can decrease the toxicity issues of lipid based nanoparticles that gets eliminated quickly from the plasma imparting enhanced toleration in pre-clinical studies and *in vivo* potency and a novel class of next generation drug delivery platforms that includes cell based extracellular vesicles are gaining popular at par with the synthetic nano-carriers, and show compelling advantages as compared to traditional synthetic carriers for drug delivery[174]. Thus, for the safe use of nanomaterials encouragement should be backed by justified ethical and regulatory guidelines to ensure safety during fabrication, scale up, adoption and clearance or dumping[169]. **Figure 1** illustrates the different steps involved in nanomaterial-based drug delivery system from fabrication, characterization, functionalization, toxicity assessment, approval by the regulatory bodies, drug loading and finally targeting.

4. Future perspectives

What emanates from the above discussion is that nanomaterials are promising carriers of

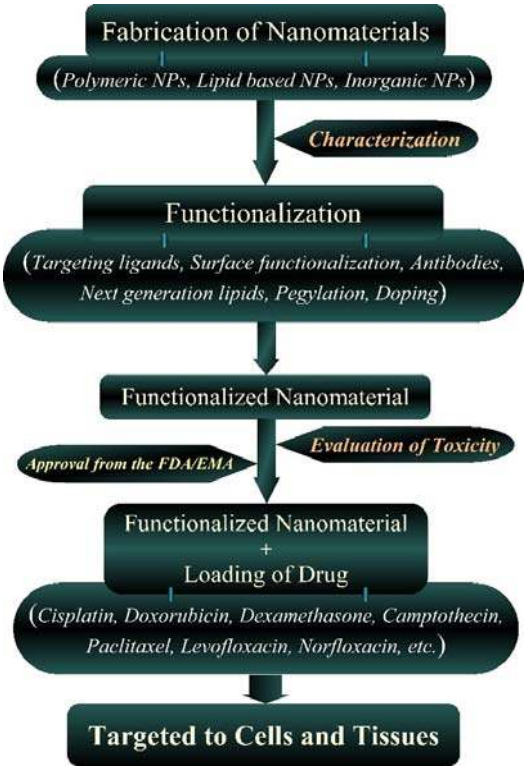

Figure 1. The schematic highlights various steps involved in nanomaterial-based drug delivery system.

drugs to treat various pathological conditions associated with eyes, ears, skin, heart, lungs, central nervous systems, to name just a few. Despite overcoming the obstacles of conventional drug delivery, the nanomaterials display various useful properties like biocompatibility, targeted delivery, high drug payload, etc., toxicity issues may crop up which needs to be dealt with stringent care and prudence. Although emergence of unforeseen impurities during fabrication procedures was obvious and cannot be warded off, science and its disciplines need to collaborate for better products in the health care, and in particular drug delivery. The following recommendations need to be highlighted to ensure secure fabrication of nanomaterials for drug delivery:

a) Nanomaterials fabrication by green synthesis protocol should be emphasized that can take care of plenty of cheap wastes from the environment and hence reduce the load of biodegradable pollutants.

b) Careful choice of agents for surface functionalization of nanomaterials.

c) Careful toxicity analysis when scaling up from laboratory to pilot plant and finally to industrial scale.

d) Nano material fabrication and characterization utilizing using Clean Room Facility.

e) Grant of GRAS status by FDA before final application in nanotherapeutics.

5. Conclusion

Nanomaterial based drug delivery systems are recently gaining much popularity because of their ability to target a therapeutic molecule to desired bodily targets by precise alteration of their rate, timing and area of release. Despite their novel uses in biomedicines, concerns related to toxicity, improved immune response and detrimental effects on the GI tract should be addressed. This interdisciplinary field would require further technological interventions within the limits of approvals by the statutory bodies to generate biocompatible nanomaterials by providing valuable inputs from material science, microelectronics and green synthesis protocols. It is expected that suffering caused to the mankind by incurable diseases like cancer can be addressed by following closely these novel platforms through collaborative efforts between research labs across the globe having outstanding infrastructure, manpower and scientific intellectual temperament.

Conflict of interest

The authors declare no conflict of interest.

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