Review Article

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Nano-scale delivery: A comprehensive review of nano-structured devices, preparative techniques, site-specificity designs, biomedical applications, commercial products, and references to safety, cellular uptake, and organ toxicity

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Abstract: This review focuses on nano-structured delivery devices prepared from biodegradable and biocompatible natural and synthetic polymers, organic raw materials, metals, metal oxides, and their other compounds that culminated in the preparation of various nano-entities depending on the preparative techniques, and starting raw materials' utilizations. Many nanoparticles (NPs) made of polymeric, metallic, magnetic, and non-magnetic origins, liposomes, hydrogels, dendrimers, and other carbon-based nano-entities have been produced. Developments in nano-material substrate and end products' design, structural specifications, preparative strategies, chemo-biological interfacing to involve the biosystems interactions, surface functionalization, and on-site biomolecular and physiology-mediated target-specific delivery concepts, examples, and applications are outlined. The inherent toxicity, and safety of the design concepts in nanomaterial preparation, and their applications in biomedical fields, especially to the organs, cellular and sub-cellular deliveries are deliberated. Bioapplications, the therapeutic delivery modules' pharmacokinetics and medicinal values, nanopharmaceutical designs, and their contributions as nano-entities in the healthcare biotechnology of drug delivery domains have also been discussed. The importance of site-specific triggers in nano-scale deliveries, the inherent and induced structural specifications of numerous nanomaterial entities belonging to NPs, nano-scale composites, nano-conjugates, and other nano-devices of organic and inorganic origins, near biological systems are detailed. Modifications that provide nano-deliveries of their intrinsic therapeutic actions, through structural and physicochemical characteristics modifications, and the proven success of various nano-delivery

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devices and currently available commercial nanomedicinal and nanopharmaceutical products are also provided.

Keywords: nanomedicine, nanoparticles, hydrogels, liposomes, dendrimers, carbon nanotubes, drug delivery, biomedical applications, nano-products, toxicity

1 Introduction

1.1 Nanotechnology: concept, requirements, concurrent modes, and models in nano-delivery

Nanotechnology is a dynamic and functional field dealing with the process of synthesizing and utilizing materials, technically ranged between 1 and 100 nm in size, which are different in shapes, chemical composition, characteristics, reactivity, and functionalization potentials. The nanotech-originated materials for uploading, encapsulation, and delivery of drugs, genes, and other macromolecular entities are preferred to be in the size ranges of >100 nm for their ease of loading together with their inherent functional merits to meet the biosystem's demands and the biosystem's specifications for facile delivery at the intended site. Today, the nanotechnology-based deliveries to different sites of the biosystems represent state of the art in site-specific targeting of various types of cells, critical cellular masses, tissues, organs, cell-bound and embedded receptors, immunological, and skeletal sites, as well as drug delivery to the physiologically malfunctioning entities, locations, and conditions in the body. The payloads intended for delivery include small-molecule drugs, proteins, peptides, polypeptides, enzymes, antibodies, and other bio-based, and recombinant materials, genes, as well as macromolecular payloads with specific functions, and characteristics of choice. The delivery module design and preparations correspondingly utilize some of the naturally available and synthesized entities, and chemically suitable and structurally viable synthons, polymers, organic and inorganic originated metals, and carbon-based materials. The delivery entities by virtue of their structure and make-up provide desired site-specificity, and are prone to the induction of site-specific motifs as molecular identification tags, and on-demand designed and developed biocompatible and biodegradable as feasible delivery conjugates for target-specified deliveries and dispositions. The involved delivery modalities include nano-scale entities of various categories, including nanoparticles (NPs) of different origins, characteristics, physicochemical and biological potentials, lipidic nano-carriers, mesoporous nano-scale materials, molecular cages and other molecular templates, the carbon-based nano-scale entities of single and multiple dimensions (1D, 2D, and 3D), and the dendrimers of specifically designed characteristics and delivery potentials. The development and use of extremely small nano-scale entities have paved the way for key biotechnical advances in drugs and other payload delivery through the size, shape, and characteristics controls of the products intended for applications in various conditions *in vitro* and *in vivo*. The nano-biotechnical field has progressed exponentially over the last few decades, and currently, it deals with an interdisciplinary spectrum of potentials, characteristics, and functions through the involvement of various advancing levels of preparative methodologies in a generational manner of developments over the period. The preparative and delivery techniques and the recipe for building better nano-entities, nano-scale devices, nanovehicles, nanosystems, nanomachines, as well as nano gears are continuously being developed. Some of the products are in the conceptual stage, while some are in the market for different applications in biomedical fields. Nonetheless, the nanodelivery segment has assumed larger proportions in the discipline, and current technologies used for the preparation of products for various types of delivery on a nano-scale have provided purpose-built, nature-specific, end-site and characteristics based, and goal-specific bio-systems with assured levels of receptivity. The molecularly well guided nanoscale products with chronological control that attenuate physiological conditions are providing the needed expertise and edge to nanodeliveries. Furthermore, with new approaches continuously coming in, the advancements in methodology and applications in nanomedicines, nanosensors, nanodeliveries, nanodiagnostics, nano-biomaterials, tissue engineering at nano-scale initiatives, nano-scale implants, and stem cells, together with their intertwined and interfacial products and techniques, have evolved nearly up to clinical levels. The advances in techniques have attained the potential to design and produce nanobiomaterials for several biological uses in bones, hearts, lungs, livers, and other organs and to repair, replace, and regenerate the desired entities and to ameliorate undesired effects. Nonetheless, the applications of nanobiomedical technology in various biomedical fields, especially, in nanomedicine, diagnostics, therapeutics, and theranostics have improved the quality of healthcare [1,2]. However, the commercial products and their production are still limited and are in an evolving stage. The field is certainly wide open for innovations. It currently derives the thrust from the understanding of the complexities, and challenges on a minute scale that are effective in nature

to discover better and effective applications in therapeutic segments, diagnostics, imaging, sensing, and other biomedical and clinical fields relevant to human health.

The on-demand, accurate delivery of drugs and other payloads is of prime concern. The need for controlled drug delivery is obvious because of concerns about toxicity, and adverse reactions. The dose-controls, bioavailability at the site, membrane permeability of the drugs and other deliverables, as well as solubility in different media, proper holding of the drugs in the delivered medium, and overall superior on-site acceptability, which leads to the control of the delivery dynamics of the drug, are other concerns. Drug delivery, in essence, refers to the methods for transporting a drug into the body system according to requirements to effect, and assist the curing of diseases, and maintaining healthy physiology under various pharmacokinetic controls. It involves conventional and non-conventional drug administering routes, that is, oral, transdermal, rectal, intravenous infusion, intramuscular, topical, nasal, inhalation, otic, ophthalmic, sublingual, buccal, arterial, and subcutaneous [3–6]. The adopted routing modes deliver drugs in considerable quantities to provide, from satisfactory to the highest achievable levels of bioavailability with a play-out on a dose together with its needed frequency, wherein injunctions of bioavailability levels, and drug safety aspects are interplaying at the cellular and sub-cellular levels. The conventional drug routing methods have several disadvantages. The major disadvantages are pain, the likelihood of infection due to non-sterilized interventions, time constraints in delivery, sluggish absorption, as well as the variability of the doses. The first-pass metabolic effects, faster metabolic rates of the drugs, as well as their elimination by the liver before reaching the intended site, and undesired transport through systemic circulation to the unwanted locations, are also some of the other major bottlenecks. Drug deliveries, if not specified in design to reach the site through trigger and feedback of different factors of physiological and biological concerns, may further constrain and complicate delivery to the site. Here, the role of developments in nanomedicine and nanoscale delivery to fit the route specifications becomes important. The delivery modes, including nano-entity-based deliveries, also, at times, generate cellular toxicity, reticular endothelial system (RES) escape, lymphatic and fat accumulations, muscle damage, as well as blood flow variations. The changes in absorption rates, elicitations of toxic reactions, skin irritations, and variable blood flows to the skin, skin dehydration, abrasion, and rashes form a long list of pitfalls that may occur, although by adopting nano-module delivery they may be at lower levels. Moreover, among modern delivery modules, the injunctions for site-specificity, molecular-recognition capability, enzymatic interactions, chronology-based sustained and dose-controlled deliveries befitting the responses to and against the physiological conditions, pH-based performance with biocompatibility, and biodegradation characteristics have been at the forefront of the developments in nanomedicine and theranostic fields. The nanoscale delivery modules are being continuously developed, and improvements in the various processes in animal models, *in vitro* conditions, and clinical settings are intermittently showing up.

2 Nano-structured devices: nanomedicine, modern drug delivery, and pharmaceutical injunctions

The field of nanomedicine is remarkably efficient and capable of supporting appropriate changes in the healthcare sector compared to traditional delivery formats. The field has established newer applications and improvements in applications to end-users, especially in the therapeutics, and cellular, organ, gene, tissue engineering, implants, and drug delivery segments. The field of nanomedicine is replete with concurrent developments, and nano-bioengineering devices are under constant development and applications [7,8]. The current scenario in drug delivery system availability provides metal-based and polymeric NPs, synthetic and natural polymer-based NPs, magnetic and inorganic NPs, lipid-based NPs, hydrogels, dendrimers, buckyballs, carbon nanotube (CNT)-based materials, virus, and bacteria-based NPs. It also includes nano-admixtures (interfacial devices) as part of the nano-structured devices for a wide variety of drugs and other payload entities deliveries to different sites. Reports on delivery module efficacy, compatibility, site-specificity, various bioapplications, and development of commercial products are continuously coming. More developments are expected, and an overview of nano-structured devices and delivery modules of nano-scale structured systems are significant enough to be taken up to evaluate the impact and future directions in this field which has substantially evolved from the time of its inception.

2.1 NPs

NPs are the foremost delivery modules used in nano-scale delivery domains, especially in the oncology segment. The NPs have novel physico-chemical properties, as opposed to non-nano-scale particulate materials, as well as other entities together with materials of non-nano specifications. The small size, alterable surface specificity, surface area to volume ratio, enhanced solubility, and multi-functional characters of NPs have helped in constructing new nano-devices for biomedical uses, especially in therapeutics delivery. The nanosystems, especially the NPs, have gained much attention for their capabilities in detecting early-stage diseases, together with the delivery of pharmaceutical agents to cure ailing conditions. The NPs can target within, and on the cells within the body, for example, cancer cells, or other diseased cellular masses, and modify and terminate disease progression. The active ingredient(s) delivered by the NPs include releasing of the drug in and to a localized area to minimize the dose and its frequency, together with curtailing the potential systemic side effects caused by the use of the traditional drug therapy modalities. Oncological chemotherapy is one such prime application area for NP-based drugs as well as for other payloads' deliveries [9,10], including their site-specific targeted delivery. The NP-based products also stimulate and improve biological processes involving, for example, tissue engineering, infection control, and *de novo* synthesis of biomaterials. The developed nano-structured devices include functionalized CNTs, nanomachines, nano-assembly derived from transposable DNA fragments, DNA scaffolds, self-assembling polymeric nano-constructs, nanofibers, nano-devices of polymeric origins, protein-based nano-products, nanomembranes, nano-sized silicon chips, nano-arrays for drugs, nucleic acid, and peptide deliveries, as well as implants construed for nano-scale applications [11]. Abundant reports on the advances in preparative techniques of nanomaterials and NPs are available. Conventional techniques for NPs' production utilize

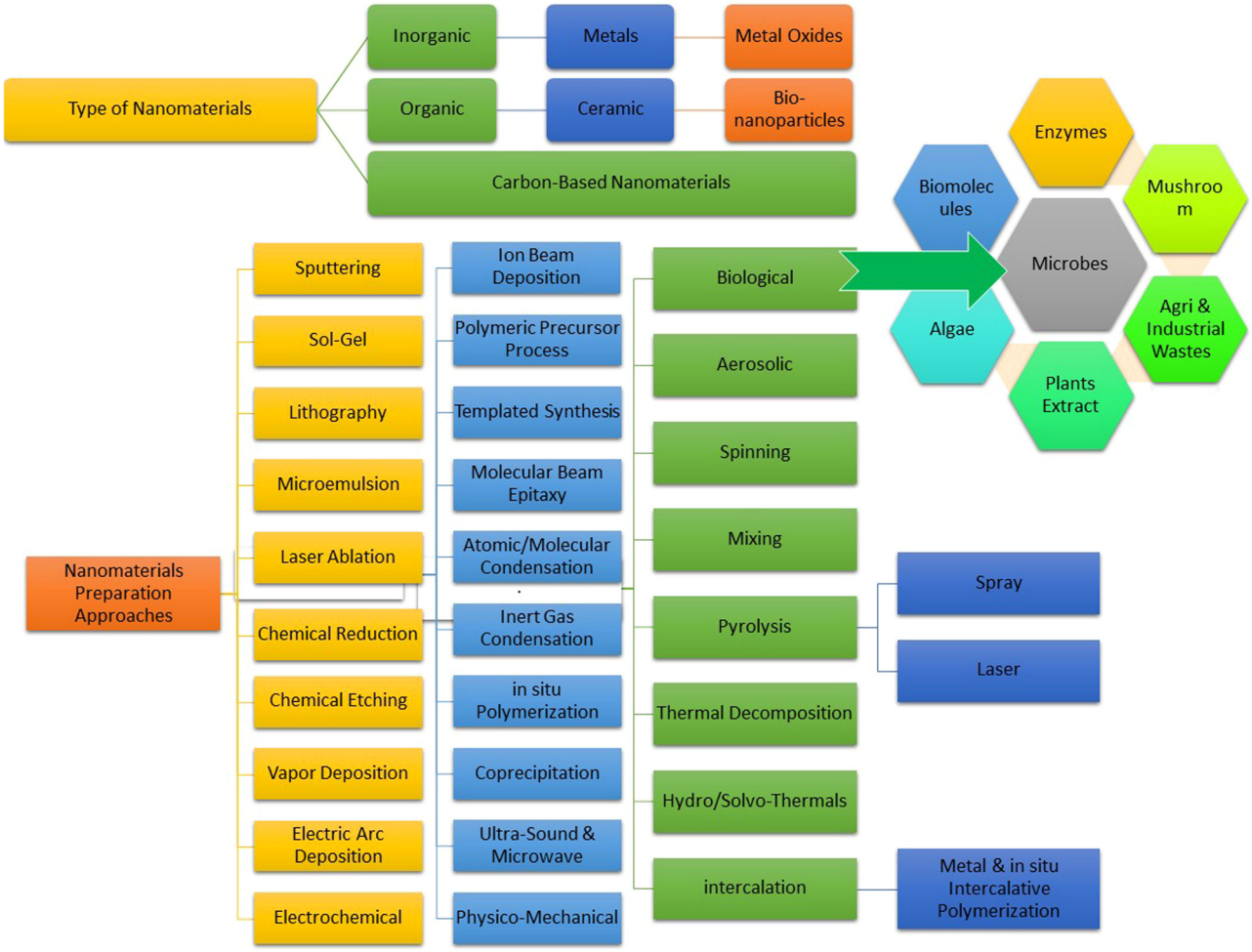

Figure 1: Various types of NP preparation methodologies.

chemical reduction methods, as well as natural, green, and bio-catalyst-based reduction methods to obtain high-density yields of naked and surface-capped NPs. The NP preparation techniques have utilized polymers of synthetic and natural origins, carbon sources, silica, metals, non-metals, as well as biological materials, that is, lipids, lactic acid, chitosan (CS), and phospholipids. A plethora of methods is available for purpose-defined, size-specified, and surface chemistry-controlled NP preparation. The current trends in the preparation of pre-designed, characteristics, and physico-chemical properties defined, and appropriately, functionalized NPs, owing to the advancements in synthesis, fabrication protocols/technologies, and characterization feasibility, have made the production of desirable NPs a reality [12,13]. Several techniques were used to prepare various types of NPs, and their different constructs through a set of chemical, physical, biological, and interfacial ways. A summative diagram depicting the preparation methods is presented in Figure 1.

2.1.1 Polymers-based NPs (PNPs)

PNPs are colloidal particles ranging from 10 to 1,000 nm and serve as drug delivery carriers of nano- to micro-scale ranges. PNPs offer better storage, encapsulation/entanglements, and transfer capacity with stability, due to the use of several types of surfactants in the formulation, which is maneuvered for embedding, and entrapping the drug and other payloads within its polymeric matrix, adsorbed, or conjugated onto its surface through its reactive functional groups, for efficient release from the matrix [14,15].

Several reports of PNPs preventing the degradation of sensitive drugs, and biomolecules of proteins, peptides, enzymes, antigens, antibodies, RNAs, and DNA origins are available. Protection is available from degradations caused by enzymatic and hydrolytic dilapidations [16], and many other environmental damaging factors [17–19]. Compared to free drugs, the PNP-encompassed drugs possess several benefits, for example, enhanced delivery, maximum bioavailability, optimized loading capacity, capability for controlled release, and choices of various administering routes. They also provide the ability to accumulate the intended drug in high concentrations for dealing with infections and inflammations through the integration of improved permeability, outreach, and distribution. The PNPs have also shown enhanced cells and tissue targeting when administered in conjugation with cell-specific moieties attached to the surface of the PNPs for specific and on-site targeting [20]. The PNPs possess several other properties, also by design obtained through preparation techniques, freedom of raw material choice, surface coating, and molecular tagging. Stability, tunable drug release properties, size distribution, and surface charge make them accordingly suitable and efficient drug delivery option materials [21] (Figure 2). The PNPs can be prepared as nanospheres and nanocapsules of different makes and matrices specifications depending upon their preparation methods. The nanocapsules are matrix systems with the medication compressed in an internalized cavity, usually, a thick polymeric-membrane wall, where the drug load is homogeneously distributed within the capsule. The nanospheres have the drug load scattered throughout the nanoentity's matrix (Figure 3). A number of techniques are used to prepare NPs, which include different methods like the emulsification process, salting out, solvent diffusion, solvent evaporation, dialysis, super-critical fluid technology, sol–gel, laser ablation, vapor deposition, polymerization, and nanoprecipitation (Figure 4) [22–24].

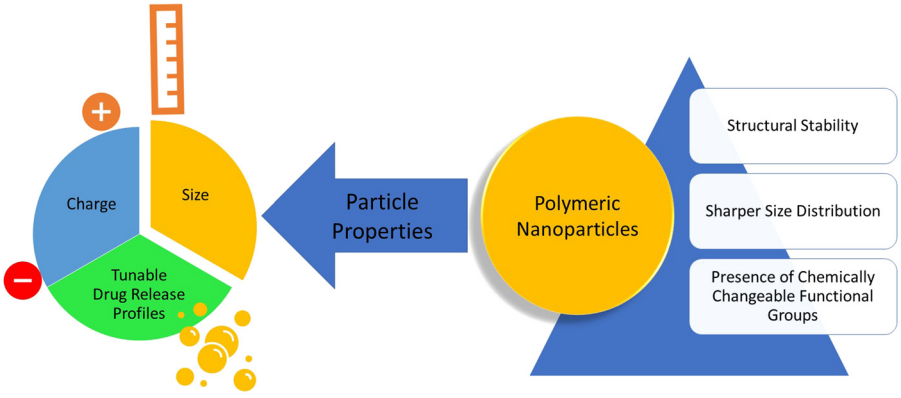

Figure 2: Physicochemical properties of PNPs.

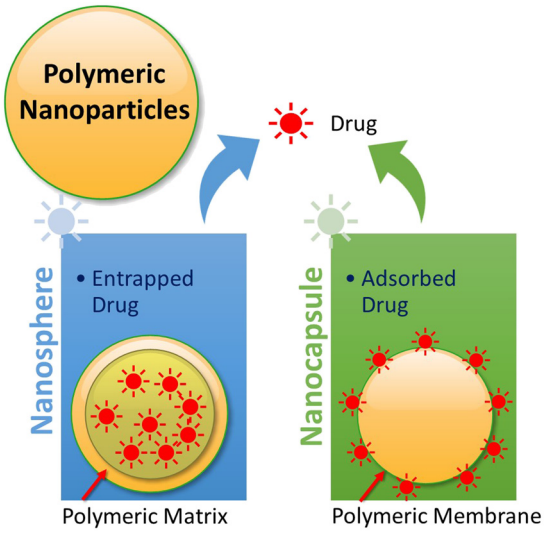

Figure 3: Types of polymeric NPs based on drug loadings.

2.1.2 Natural PNPs

The natural PNPs are prepared from biodegradable and biocompatible polymeric materials sourced from nature [25–28]. Among the most frequently used natural polymers used in preparing the formulations of PNPs are CS, alginate (ALG, sodium alginate), albumin (ALB), alginic acid, and gelatin [29–32]. A list of major natural polymers, together with their drug loading, delivery preferences, and characteristics inferred from the preparations, as well as pharmaceutical applications are summarized in Table 1.

2.1.2.1 CS-based NPs

CS is a non-toxic, biodegradable, and biocompatible carbohydrate class natural polymer, which makes it suitable for use in novel drug delivery systems, as they do not produce any adverse biochemical responses, irritation, and allergy. The CS NPs (CSNPs), colloidal in nature, entrap small molecular weight (MW < 500 Da) bioactive molecules through several mechanisms, that is, chemical and ionic cross-linking, covalent bonding, sequestration, conjugation, complexation, and physicochemical interactions that lead to the 3D-networked entity resulting in CSNPs. The CS and chemically modified-CS (mCS) are also useful in surface attaching and encapsulating the small MW drugs with higher encapsulation efficiency (ee). Different larger-sized bioactive molecules, proteinaceous products, macromolecular entities, genetic materials (all high MW) for different pharmacological backgrounds have been encapsulated in CS and its chemically modified (mCS) derivatives. The CS is also suitable for providing feasible structural and physicochemical characteristics to control the prepared nano-entities' capabilities to effectively transport, and safely deliver the payloads under different biosystem circumstances. CS, as a coating agent for other nano-carriers, for example, liposome, as a transfection agent, and as a carrier system for non-viral gene delivery are well known [33]. Several techniques, for example, emulsion formulations, ionic gelation [34–36], reverse micelle, and self-assembly [37–39] have been achieved for the preparation of CS-microparticles and CSNPs, but the ionic

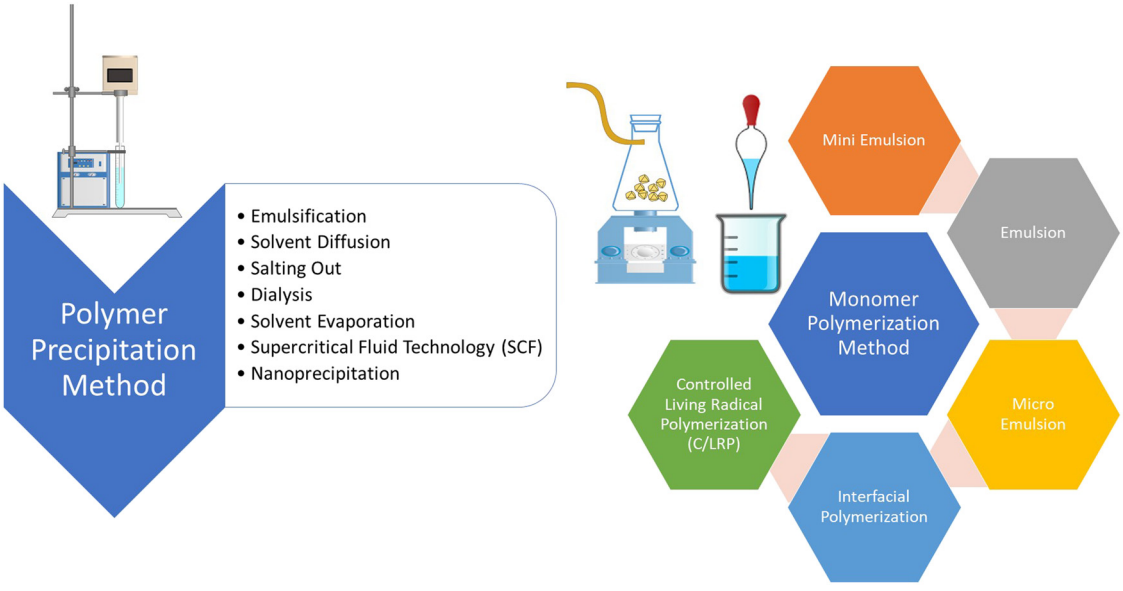

Figure 4: General methods of preparations and properties of PNPs.

Table 1: Natural polymer-based nano-carrier delivery systems

Drug or active entity	Nano-carrier	Data value	Inferences on the delivery system	Ref.
Insulin	CS	Drug loading (55%) Particle size (200–300 nm)	CSNPs improved insulin absorption in the nasal cavity more than CS aqueous solution	[30]
Linoleic acid-mCS		Particle size (200–600 nm)	Particle size was found to be larger in acidic solutions than in neutral and alkaline solutions	[37]
Trypsin		Particle size (523–1,372 nm)	Showed a higher kinetic constant value of trypsin NPs (71.9 mg/mL) than control	[38]
Curcumin		Drug loading (28–81%) Particle size (300 nm)	Developed formulation evaluation on cell viability HCT-116 colon cancer cells	[42]
Insulin	TMC	ee 80–90% Particle size (250 nm)	An *in vitro* study (Caco-2 cells) and an *ex vivo* study (excised rat duodenum, jejunum, and ileum) were studied	[48]
SP	CS	Particle size (50–400 nm)	NPs provided a continuous release of the entrapped SP release for 10 days	[49]
Insulin	CS, TECS	Drug loading (80%) Particle size (170–270 nm)	NPs showed enhanced colon absorption of insulin compared to free insulin in diabetic rats	[50]
Peptide	HSA–ALG	Particle size (60 µm)	The release of peptide-loaded microspheres was slower (release time >8 days) than that of uncoated microspheres	[67]
Yeast	ALG	ee 95%	Yeast microparticles showed potential as oral delivery systems	[68]
B225 gelatin	Gelatin	Particle size (200–250 nm)	The MW profile of gelatin in solution is critically affected in a time-dependent manner	[29]
Insulin		Particle size (250 nm) Zeta potential (−21.1 mV)	Insulin-loaded NPs under gelatin–poloxamer 188 ratio at 1:1 promoted insulin pulmonary absorption effectively	[80]
Ganciclovir	ALB	Drug loading (30%) Particle size (200–400 nm)	The biphasic pattern was shown with initial and rapid release *in vitro* profiles of the NPs	[89]
DOX	HSA	Drug loading (70–95%) Particle size (150–500 nm)	NPs were tested in two different neuroblastoma cell lines to influence cell viability	[90]

gelation technique and reverse micellar solubilization are among the most frequently used methods. In the former technique, the interactions of oppositely charged loading-intended materials readily generate the CSNPs. The tripolyphosphate (TPP) is used to prepare CSNPs, because of its non-toxicity, multivalent nature, and capacity to create nano-entities and gelation materials through ionic interactions. The concentrations of TPP and CS, through the pH of the solution, control the interactions, whereby the PNPs of smaller sizes are subsequently prepared with a limited size range. The technique dissolves surfactant in an organic solvent that forms reverse micelles. To avoid any turbidity, under steady agitation, an aqueous solution of CS is used. With additional water addition, the NPs of larger sizes are produced. The lower MW polymers are widely used for inverse micelle-based PNP preparations. Bovine serum albumin loading in comparatively low MW polymer resulted in producing approximately 140–430 nm size PNPs [40,41]. Micellar fatty acid (FA)-based solid lipid NPs (SLN–FA) have been prepared by Chirio *et al.* [42]. Stable polymers of different MW have been utilized in the presence of various non-ionic surfactants, for example, myristate, palmitic, and stearic acids. A 28% and up FA usage strongly affected the preparation of NPs. The SLNs of 300 nm diameter were also generated. An addition of CS·HCl (CS hydrochloride) to NP formulation produced positively charged bioadhesive NPs. The curcumin (CU) charged with FA produced CU–FA–SLN which affected the cell viability of the HCT-116 colon cancer cell lines. The CU–SLN–FA co-conditioning method used for the NP production of <300 nm size with the range of 28–81% use of FA on the medium to high MW and hydrolyzable polymers have been reported. The HCT-116 colon cancer cells treated with CU-NP colloidal nano-carrier, and which were able to treat HCT-116 cells with greater CU concentrations in the presence of lipid carriers with lowered toxicity observations are known [42]. The formulated CS–TPP–NPs, with the capability of peptide absorption throughout the mucosal surface, were reported by Grenha *et al.* [43]. A spray-drying process with mannitol as an excipient was used to produce the desired PNPs and CSNPs with appropriate characteristics of size and weight for pulmonary delivery. The phospholipid, which was termed as lipid–CS–NP complex (L–CSNPs), was also developed for insulin delivery. The aerodynamic properties of these spherical PNPs were essential for lung delivery. The structure of the phospholipid influenced the characteristics of the L–CSNP complexes. The phospholipid ensured the regulated release (~68%). It also effectively combined the scheme of an encapsulated protein (insulin). The developed microspheres with acceptable properties were offered for deep inhalation [43]. The *in vivo* capacity of the thiolated-CS NPs (T-CSNPs) to reduce allergic asthma was also investigated. Lee *et al.* [44] developed improved T-CSNPs for theophylline supply. The ovalbumin (OVA) challenged and OVA-sensitized BALB/c mice were induced with inflammatory allergic disease, and theophylline, CSNPs, and T-CSNPs were administered through the intranasal route to evaluate their efficacy, which showed superior performance of the T-CSNPs [44]. High-intensity ultrasonication induced considerable damage to the CSNPs, which affected their functioning as a drug carrier, as reported by Tang *et al.*, [45]. Another work analyzed the effects of acidity on the cross-linking between sodium-TPP and CS [46]. The antibacterial activity of positive, fixed-charged NPs, through minimum inhibitory concentration, was also reported [47]. The CSNPs and NPs loaded with copper against multiple microorganisms, for example, *Escherichia coli, Salmonella typhimurium,* and *Staphylococcus aureus* were evaluated for their antibacterial activity. Many organisms when tested against these, CSNPs, and copper-laden NPs, fully confirmed their antibacterial activity. Atomic force microscopy (AFM) showed that exposing *Salmonella choleraesuis* to CSNPs broke their cell membranes, and the cytoplasm leaked during the process [47]. Sandri *et al.* studied the penetrating effects of *N*-trimethyl CS NPs (TMCS-NPs). The outcome proposed that the mucoadhesive properties were the limiting factor for these PNPs' absorption, which caused increased contact time with the intestinal epithelium with compromise on an improved chance for internalization of these NPs [48]. Hu *et al.* produced and characterized CS–poly-(acrylic acid)-complexed NPs of sizes ranging from 50 to 400 nm by template polymerization of acrylic acid (AA) in CS solution, which produced positive charges on the NPs surface. The *in vitro* silk peptide (SP) release showed that the NPs entrapped SP effectively released the encapsulated material for 10 days. However, the peptide's release was affected by the medium's pH [49].

2.1.2.2 Modified CS-basedNPs

Among the modified CS-derivative (mCS), the dimethyl ethyl CS (DMEC) possesses antimicrobial, anticancer, and antioxidant activity. Another CS-derivative, diethyl methyl CS (DEMC, 79% quaternization), completely soluble in an aqueous medium, possesses a higher degree of antibacterial activity against *E. coli* than the CS, owing to its higher charge density, which was pH dependent, and were used for the preparation of NPs to enhance intestinal absorption of the insulin. NPs based on thiolated DMEC (DMEC-Cys) were also prepared for insulin delivery through buccal films, whereby the NPs enhanced (up to 97.18%)

insulin permeation through buccal mucosa of the rabbits, which exceeded the CS, and its derivative, DMEC [47] performances. The polyelectrolyte complexing technique, spherical morphology, and soft surface structures were created by Bayat *et al.* [50] by using a freshly quaternized derivative of CS from triethyl CS (TECS), and DMEC for insulin delivery to the colon through approximately 170–210 nm-sized, positively charged NP formulation. An exceeding 80% insulin was loaded and the loaded protein release was well demonstrated, both, in *ex vivo* and *in vivo* investigations. The *ex vivo* studies found better transport of insulin through the colon membrane for NPs, compared to the *in vivo* studies. The *in vivo* studies showed enhanced absorption of insulin in the colon using similar NPs, compared to the free insulin in the diabetic rats [50]. The tri ethyl chitosan's (TEC's) roles in NP preparation, and *ex vivo* condition assessed the uptake, which was enhanced in the colon-specific drug delivery. This was also true for the poorly absorbed drugs, as reported by Younessi *et al.* [51]. Their study showed a significant increase in the absorption of sodium fluorescein and brilliant blue in the presence of TEC, compared to the CS alone NPs [51]. The CSNPs prepared from different MW polymers, and the TMC-derived NPs for nasal immunization were prepared and characterized by Boonyo *et al.* The NP prepared from TMC-based material with a 40% degree of quaternization was the most effective in nasal supply [52]. Avadi *et al.* assessed the *in vivo* and *ex vivo* effects of DMEC polymer-based nanoformulation for use as an enhancer for intestinal para-cellular transport. In the presence of DMEC, in *ex vivo* conditions, the brilliant blue absorption concerning the polymer was significantly increased. The DEMC interacted with tight junctions of the colon epithelial cells with positive charges on them, and enhanced the permeability of the brilliant blue through the tight spaces [53] and demonstrated its effective application.

2.1.2.3 Alginate NPs

The ALG-NPs are sourced from ALG, which is a brown algae-sourced linear polysaccharide, composed of 1–4 interlinked α-L-glucuronic residues (G-block), and β-D-manuronic acid residues (M-block). The aqueous solubility, the tendency to gelate out in better shape, biocompatibility, and non-toxic nature are some of the benefits of this natural polymer [54–56]. Their primary ability, under mild conditions, to form a gel makes this polymer among one of the ideal candidates for the delivery of drugs, also at nano-scale levels. By responding to the divalent cations, the ALGs can form a gel with calcium ions, Ca^{2+}. The divalent calcium cations connected with the cross-linked matrix provided the material for further work on drug loading. ALG, as an anionic polymer, at decreased pH, forms an insoluble alginic acid [57–59]. The ALG matrix upon complex formation with other polymer changes, and with the coating of the prepared ALG particles, a controllable release of the drug triggers in. It also helped to avoid the drug degradation at higher pH, in which the surface coating has an important role to play [60]. Cedroxil® (Cefadroxil, a broad-spectrum first-generation cephalosporin class antibiotic) *in vitro* delivery, achieved through interpenetrating polymeric networks (IPNs) of sodium ALG with gelatin, and egg ALB, was cross-linked with glutaraldehyde [61]. Cefadroxil with a biological half-life of 1.2–2.0 h for a dose containing 0.5–1.5 g of the drug, wherein the short half-life was proposed to be enhanced through the developed IPN. The IPN also presented the prospect of oral delivery formulation design and its directives for the preparation [60]. In addition, various biological molecules, for example, heparin [62], hemoglobin [63], melatonin [64], and some vaccines [65,66] have been effectively entrapped using plain-beads synthesized from ALG, or as coated ALG-beads, as well as microcapsules. Furthermore, the *in vitro* analysis of the ALG microspheres coated with serum ALB showed effective peptide release [67]. For the intestinal provision of probiotic yeast based on pH differences, Hébrard *et al.* produced microparticulate materials of ALG–whey protein [68]. However, the coated microbubbles and microcapsules were comparatively more efficient than the smaller vesicles, given that the micro-entities were allowing more control over drug release for oral delivery systems and through ALG-matrix modifications [60]. The ALG-NPs, with antitubercular combination drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol), using the controlled cation-induced gelification technique, that was prescribed orally to mice infected with TB H37Rv, were prepared by Ahmad *et al.* [69]. The encapsulated drugs showed high efficiency, reaching up to 70–90% entrapments. A single oral dose of the drug persisted for 7–11 days in the plasma, and 15 days in the organs, that is, liver, spleen, and lungs [69]. Rajaonarivony *et al.* described a 250–850 nm-sized, ALG-NP formulation, based on gelification by the calcium ions for a doxorubicin (DOX) drug-loaded model. These results showed that the ALG-NPs are favorable carriers due to their high drug-loading capacity, which could reach over 50 mg DOX/100 mg ALG [70]. The ALG–CSNPs with low toxicity and biocompatibility, to improve transfection efficiency, were developed by Douglas *et al.* The presence of ALG diminishes the strength of the interaction between the CS and DNA, which produces

an enhancement in the transfection efficiency, as compared to the CSNPs alone [71]. An anti-sense oligonucleotide carrier system based on ALG-NPs was prepared to examine its ability to protect it from degradation in the presence of serum [72]. A polymeric composite (ALG, CS, and Pluronic F127) nanoformulation was prepared with ionotropic pre-gelation technique containing CU accompanied by the polycationic cross-links for cancer cell delivery. The encapsulation efficiency of the CU-showed a significant rise over ALG–CS non-Pluronic NPs, compared to composite NPs. The cytotoxicity test demonstrated that the composite NPs, when used against HeLa cells at a concentration of 500 μg/mL, were non-toxic. The green fluorescence within HeLa cells verified the internalization of the CU–composite–NPs. The half-maximal inhibitory concentration (IC_{50}) values for pure and free CU and encapsulated CU, were found to be at 13.28 and 14.34 μM, respectively [73]. Hyaluronic acid (HA) is another important natural and alternate polymer. HA is an anionic glycosaminoglycan structured polymer used in constructing delivery platforms [74,75]. The repeated carboxylic groups in each unit produce a response to pH changes, which were enhanced in a cross-linked hydrogel network [76]. For the release of blood clotting enzyme, thrombin, the study reported by Pitarresi *et al.* evaluated the pH-responsiveness of the photo-cross-linked HA-hydrogels [75]. Another derivative of HA, available with comparatively more abundant carboxylic groups, was used as a nanoformulation for delivery to the colon, and the pH-sensitive delivery of α-chymotrypsin [76] was demonstrated. The cellular pathways studied *in vivo* and *in vitro* conditions showed the pH-responsiveness of the HA-NPs. These observations were important factors for the development of an oral delivery system for insulin [77].

2.1.2.4 Gelatin-based NPs

Gelatin is a protein material that can be used with ease for NP production by controlled hydrolysis. It is biodegradable, non-toxic, easy to cross-link and modify chemically, thereby possessing an enormous potential to be used as a drug delivery carrier. Several methods have been described for formulating gelatin-based NPs, which included desolvation [78,79], thermodynamically driven self-assembled processing, emulsion formation [80], cross-linking with the polyethyleneimine (PEI) [81] and glutaraldehyde [82], nanoprecipitation [83], coacervation [84], and grafting of hydrophobic anhydrides to the amino groups of the pristine gelatin to form self-assembled micelles [85]. Novel emulsion techniques for preparing insulin-packed gelatin NPs for diabetes treatment with the help of glyceride as developed by Zhao *et al.* were found significantly effective. During the first 4 h after intratracheal stellation, the blood glucose levels in rat models decreased showing their fast-hypoglycemic effect and transitional stability [80]. Hypocrellin B, an agent for photodynamic cancer therapy, was also loaded onto modified poly-(ethylene glycol)-gelatin NPs. Solid tumor cells treated with the NPs resulted in significant tumor regression [86]. The cisplatin-loaded NPs prepared by Jain *et al.* showed higher input into the human breast cancer cells in comparison with the control [87]. Lu *et al.* described an intravesical delivery of paclitaxel-loaded gelatin NPs, achieved for bladder cancer. The absorption, positive tissue/tumor bladder targeting with 1 week retained supply was reported [88].

2.1.2.5 ALB NPs

The serum protein, ALB, available in pure form, is biodegradable in nature, non-toxic in action, and carries chemically reactive groups, that is, thiol, amino, and carboxyls. It is also non-immunogenic. These characteristics make it an attractive macromolecular carrier for preparing various nano-scale structures and devices, including the nanospheres and nanocapsules for various bioapplications. Different studies have demonstrated that human serum albumin (HSA) aggregates in solid tumors, which again makes it a potential macromolecular carrier as HSA-NPs for site-directed delivery of several drugs, including antitumor drugs, with enhanced bioavailability [89,90].

2.1.3 Synthetic PNPs

Synthetic PNPs have proven to be extremely attractive for biomedical applications in various roles. Synthetic polymers offer a viable and efficient transport and delivery vehicle for a wide variety of drugs, including peptides, proteins, lipids, and nuclear acids, and it is due to their tunable sizes, shape, surface properties, and chemical modification capabilities. Among the available synthetic polymers, poly-(L-lactic) acid (PLA), poly-D,L-lactic acid (PDLLA), poly-L-glycolic acid (PGA), poly(lactide-*co*-glycolic) acid (PLGA), polycaprolactone (PCL), polyanhydrides, polyorthoesters, polycyanoacrylates, poly-glutamic acid, poly malic acid, poly(*N*-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol) (PVA), poly(acrylic acid), polyacrylamide, poly(ethylene glycol) (PEG), poly (methacrylic acid), poly trimethylene carbonate (PTMC), and cellulose acetate phthalate (CAP) polymer [91–101] are worth mentioning. The most frequently used and

preferred synthetic polymers employed for drug delivery purposes are poly-L-lactide acid (PLA), PDLLA, PLGA, PCL, and PTMC. Another facile and successful method for the preparation of NPs was also developed which was based on the oxidative liquid phase polymerization technique, and it produced spherical-shaped, and functional, poly-(COOH)-poly-(carbazole) polymer from the carbazole-containing monomers. The produced microparticles were intensively examined by scanning electron microscopy. The microparticles were used to functionalize many polymeric and non-polymeric surfaces, matrices, and non-functional nanomaterials, due to the presence of dual-functional groups on them [102,103]. Mohsen *et al.* assessed the toxicity of novel fluorescent temperature/pH-responsive particles. The poly-*N*-iso-propyl acrylamide (p-NIPAM) based, p-NIPAM-*co*-5%-LY (p-NIPAM-*co*-(5%)-luciferin-yellow) was prepared using a surfactant-free emulsion polymerization method. The produced particles were found to be negatively charged with a size of roughly 250 nm at 15°C, which were de-swelled by increasing the temperature, leading to a decrease in the size of up to 100 nm. The toxicity testings were performed on two cell lines (HeLa and Vero), and their cell viability was found to be >80% for both the cell types with 0.3 mg/mL of the pNIPAM-*co*-5%-LY, while the NIPAM monomer exhibited cell viability at 80% at a concentration equal to or less than 3 mg/mL. The fluorescent property of these particles made them easily traceable, which made them suitable for cancer cell detection and targeting [104]. Paciotti *et al.* tested colloidal gold (cAu), as a cancer drug, as well as an immunodiagnostic marker. The group prepared a cAuNP as a vector in this experiment that aimed to deliver the tumor necrosis factor (TNF) to a solid tumor that grew in mice. The ideal vector, known as TP–cAu–TNF, consisted of thiol-derivatized PEG molecules. The recombinant human TNF, directly linked to the gold NP surface was used. The intravenous administration of TP–cAu–TNF was induced, which rapidly accumulated in the MC-38 colon carcinoma and showed little to no accumulation in other organs of the animals, that is, liver and spleen. The tumor cells were noticed due to modification in the color of the tumor because of the cAu sol (red/purple). The formulation was found to be less toxic and efficiently dropped the tumor burden when compared to native TNF [105].

2.1.4 Magnetic NPs

Iron oxide NPs (IONPs) are magnetic materials, superparamagnetic in nature. The iron oxide superparamagnetic NPs (SPION) consisted of Fe_2O_3 and Fe_3O_4. The particles communicate with external magnetic fields, thus provide wide-ranging possibilities through their magnetic character in nanomedicine fields where they have been used as an magnetic resonance imaging (MRI) contrast agent for magnetic hyperthermia-based anti-cancer therapies, and as a delivery option [106]. The magnetic NP-based drug delivery systems are tracked during their movement through the body. This significant property helped clinicians to monitor the drug movement to its targeted site [107]. Kafayati *et al.* [108] evaluated the toxicity of magnetic NPs with different surfactants, including oleic acid, and glycine, on bacterial cells. These magnetic NPs tend to accumulate at the targeted site [109]. However, it was recommended that the design of a magnetic drug delivery system should take into consideration the different factors, including the size and properties of the particles, drug loading capacity, target accessibility, the strength of the magnetic field, and the rate of the blood flow, which affect its performance [110]. As a nano-carrier system, Ye *et al.* developed biodegradable polymer-based vesicles to serve multimodal bioimaging and to deliver anti-cancer drugs. Several PLGA vesicles were prepared by encapsulating inorganic imaging agents of superparamagnetic nature, IONPs as PLGA–SPION, manganese-doped zinc sulfide (Mn:ZnS) quantum dots (QDs), and anti-cancer medication busulfan into PLGA-NPs using an emulsion-evaporation process [111]. Adams *et al.* studied formulations with PEI as PEI–alginic acid, oxidized-PEI (oxPEI), and oxPEI–alginic acid, that was tracing-enabled with the specific associations of the multifunctional metal NP on their surface, for use in the MRI scanning for brain stem cells gene delivery. It also showed that these two formulations prepared for use in combination with the oscillating magnetofection technology could be safely delivered to neural stem cells. After transfection, the intracellular particles were identified by histological procedures with labeled cells displaying contrast in the MRI for real-time cell tracking [112]. The polymeric materials, hydroxyethyl methacrylate (HEMA)–agar, and (HEMA–gelatin were also used to prepare the hydrogels, and their γ-irradiation as a stabilizer for magnetic NPs through radiation and co-precipitation loadings were successfully achieved. The hydrogel make-up and dispersion of the magnetic NPs in this gellish network were found to be smaller-sized, and lesser in the loadings that were achieved through the co-precipitation technique, when compared with the loadings in the irradiation technique alone. The HEMA–gelatin–Fe_3O_4 also had higher sizes than the HEMA–agar–Fe_3O_4 particles. The loading capacities and release patterns were dependent on pH and were worked out with the DOX·HCl anti-cancer drug [113].

2.1.5 Other inorganic NPs

The inorganic NPs are non-organic, non-living sourced material-based entities that can be prepared with different shapes, for example, spherical, rod-like, cylindrical, wire, triangular, prism, octahedron, and star-shaped. It also ranges from 1 to 100 nm in size [114]. The specific physicochemical characteristics of inorganic NPs made them a suitable tool in diagnostic biosensing, drug and gene delivery, and biomedical imaging [125]. The most commonly used inorganic NPs are gold, silver, iron oxide, zinc oxide, gadolinium, silica, titanium dioxide, nickel, cadmium, and at times, arsenic [115]. The NPs have, in contrast to bulk materials, unique properties, that is, high surface area, high surface-to-volume ratio, catalytic activity, optical, electronic, and magnetic properties. They also possess rich functionality ready to be utilized for various purposes. These NPs are biocompatible, monodisperse, amphiphilic, with safe-carrier capabilities, and have enhanced capability for targeted delivery among comparable various metal-based NPs. These NPs also have viable surface structures for various capping, conjugation, and tagging use, suitable charges for exploitation, aggregation proneness, and the capability to interact with biomolecules. Some of them also show anti-microbial activity [116–124]. The direct delivery of drugs and biomolecules, however, faces enzymatic and other degradation challenges, within the cells and during transport. Many inorganic materials, for example, calcium phosphate, gold, coal, silicon oxide, iron oxide, and layered dual-hydroxide have been used. Composites consisted of nickel–cobalt nano-needles have also shown lower toxicity. Therefore, these materials are supply alternatives to viral and cationic transporters [126,127], and their synthesis is frequently approached as a "top-down" or "bottom-up" strategy. The top-down approach starts with bigger, bulkier starting materials, and goes to downgrade/remove/reduce/diminish the material until the required-sized structure are obtained in a more or less controlled procedure depending on the exact method of preparation used. Most micro-manufacturing methods (lithography and milling methods) for preparing inorganic NP products are examples of this strategy. The bottom-up approach begins with lower, smaller-scale assembled ultra subunits with different control parameters to achieve the synthesis, which also depends upon the method used, for example synthetic techniques for polymerization [128]. The building up of a nanomaterial can start at a smaller scale to build the specified and differentiated nano-carrier. The preparation methods for NPs can be approached through physical, chemical, and biological methods.

2.1.5.1 Gold NPs

Several reports are available dealing with the chemical and biological synthesis of AuNPs. Beveridge *et al.* [129] reported AuNP preparation by precipitation technique in various bacteria. Synthesis of gold nanowires from the extracted *Rhodopseudomonas capsulate* [130], which offered high control over the shape of the nanogold particles through exercising different concentrations of $HAuCl_4$ solution, was reported. Kaviya *et al.* [131] reported the use of the sun-dried peel of Citrus sinensis for the synthesis of silver and AuNPs in an aqueous medium, which achieved the production of spherical NPs with a size range between 14 and 20 nm. Moreover, the terpenoid functionalized alcohol, ketone, aldehyde, and amines were suggested to be the cause of NPs' stability. Several workers have reported multiple methods of different NPs, including AuNPs, syntheses with various sizes, shapes, and morphologies (nano-triangles, nano-prism, and octahedron). AuNPs using plant parts, for example, leaf extract of tamarind [132], *Pelargonium graveolens* (geranium) [133], neem (*Azadirachta indica*) [134], *Hibiscus rosa-sinensis* [135], coriander [136], *Magnolia kobus,* and *Dyopiros kaki* [137] have been reported. They have also been prepared from *Emblica officinalis* fruit extracts [138], using phyllanthin and apiin compounds [139,140], *Aloe vera* [141], mushroom extract [142], and honey [143]. AuNPs from the cell extract of endophytic fungus and *Colletotrichum* sp. [133] are also reported. The AuNPs present special characters like biocompatibility, large surface area to volume ratio, small size, high reactivity, and temperature stability, together with their ability to cross the cell membrane [144]. The 5-fluorouracil (5-FU) bound AuNPs were found to be more effective against fungal and bacterial organisms, compared to 5-FU alone [145]. In addition, the AuNPs can effectively conjugate with several antibiotics and can work more effectively against both types of bacteria, that is Gram-positive and Gram-negative, compared to the free antibiotic, 5-FU. These observations also suggested that the AuNPs could be utilized as an effective drug delivery system [146,147]. The AuNPs also proved to be effective in killing protozoa and bacteria [148]. Gu *et al.* [149] synthesized the vancomycin-coated, stable AuNPs, which showed enhanced anti-microbial activity compared to free vancomycin. In another publication, Ahangari *et al.* found that the gentamicin conjugated with AuNPs showed more antibacterial effects against *S. aureus* in comparison to the gentamicin alone [150]. In addition, the AuNPs have shown low cytotoxicity, and therefore served as a good scaffold for drug delivery, and they were utilized in medical imaging [151,152].

2.1.5.2 Silver NPs

The silver NPs (AgNPs) have various applications, especially in the fields of biomedical applications, which include anti-bacterial and anti-cancer engagements. They were also used as part of skin creams and ointments. The AgNPs can be prepared through chemical and physical methods, including electrochemical reduction, and solution irradiation [153]. AgNPs have been reported as being effective against infections of burns and wounds [154]. The most widely used AgNPs are silver oxide NPs, followed by zinc oxide NPs, and they have shown effective control against microorganisms, for example, bacteria, viruses, and small eukaryotes [155,156]. The mode of inhibiting the growth of these organisms is reported to be the inactivation of reproduction and protein synthesis and blockage of the electron transport chain reaction, which ultimately kills the bacteria [157]. The effectiveness of the anti-microbial activity depends upon the size of the AgNPs. The smaller the size, the greater the effect [157]. Several research groups have shown that the use of AgNPs in combination with antibiotics resulted in improved anti-microbial activity against both kinds of bacteria, that is, Gram-negative and Gram-positive [158–160]. The AgNPs also exert adverse effects on the host cells and initiate the production of reactive oxygen species (ROS) [161,162]. The AgNPs obtained from a bacterium, *Pseudomonas stutzeri* AG 259, were produced by the bio-reduction method. When the bacterium was challenged with the silver nitrate solution, well-defined AgNPs within the periplasmic area of the bacterium were produced [163]. The AgNPs were also produced in higher yields from the silver-tolerant yeast strains, MKY3 [164]. The fungi have also served as an efficient biocatalyst for the synthesis of metals and metal-sulfide NPs. The use of *Trichoderma harzianum, Colleotrichum* sp., *Rhizopus stolonifer, Trichoderma viride, Isaria fumosorosea, Guignardia mangifera, Duddingtonia flagrans, Trichoderma longibrachiatum, Epicoccum nigrum, Penicillium oxalicum, Arthroderma fulvum, Sclerotinia sclerotiorum* MTCC 8785, and *Rhizoctonia solani* is reported to produce AgNPs [165]. The fungus, *Fusarium oxysporum, Aspergillus flavus*, *Aspergillus niger*, *Aspergillus fumigates*, *Phanerochaete chrysosporium* (white-rot fungus), as well as *Rhizopus oryzae*, have also been found to produce stable AgNPs [165,166]. AgNPs were also obtained from *Pleurotus sajor-caju/Lentinus sajor-caju* (Oyster mushroom), which exhibited anti-microbial activity. The bacteria, for example, *Klebsiella pneumonia, Bacillus subtitles*, *E. coli*, *Bacillus licheniformis*, and *Pseudomonas aeruginosa*, were also successfully utilized for the preparation of AgNPs [167–169]. Another efficient bio-catalyzed synthesis used n-butanol extract of fresh *Buchanania axillaris* leaves' yielding high-density AgNPs [170]. Also, the synthesis of peptide-capped AgNPs, in the range of 10–25 nm sizes, utilized α-NADPH-dependent nitrate reductase and phytochelatin strategy, which were sourced from fungi, bacteria, nematodes, and plants [171].

2.1.5.3 Carbon-based nanomaterials (CBNs)

CBNs are materials-of-choice for targeted delivery owing to their structural properties, functionalization feasibility to attach different motifs for diversified delivery goals, and with minimal, or no toxicity to the biosystem. The graphenes, and their chemically transformed reduced, and oxidized graphenes, morphed graphenes, carbon dots, nano-diamonds, fullerenes, and CNTs of single and multiple-walled, forms the extended CBN family. Reports on carbon dots as nano-therapeutics, HA-functionalized carbon–dot–DOX-loaded NPs for targeted delivery to CD44, the nano-diamond-based pH-responsive delivery system through functionalization and DOX-loading, PEGylated nano-diamonds for gemcitabine delivery are some of the recent examples of CBNs' applications in nano-scale deliveries [172–176]. Graphene, graphene oxide (GO), reduced graphene, graphene sheets, and graphitic carbons have shown the ability to attach drug molecules, biomaterials, and implant motifs. The entities of hydrophobic nature, after proper functionalization, showed aqueous solubility and compatibility to the aqueous environment in the biological system, and CBNs have demonstrated this. The capability to interact with lipids in cell membranes, together with the nanomaterial-based characteristics of high surface-area-to-volume ratio of these materials have facilitated their participation as part of the desired nanovehicle for different types of payload deliveries, including small molecule drugs. The polyaromatic structure, and the ease with which various graphene-forms are functionalized (oxidized, reduced), composite-made, and conjugate-prepared, have offered the graphitic materials' another level of capability, and flexibility to upload different types of payload packings, transport, subsequent targeting, and delivery to cells, tissues, and organs with least observed toxicity. Graphene-based drugs and gene deliveries, delivery systems for tissue engineering, graphene-based electro-responsive implant materials, GO-based multifunctional platform for intracellular delivery, GO-based tumor-response release for DOX, and graphene–nanoribbon-based DNA delivery are some of the graphene applications in nano-delivery. Several recent reviews have covered the topic in detail [177–181].

Table 2: Preparation of different non-polymeric nanosystems from various bio-sources

Serial	Nanosystem	Biological sources	Part/medium	Ref.
1.	Gold	*Rhodopseudomonas capsulate*	Cell-free extract	[130]
		Citrus sinensis	Sun-dried peels	[131]
		Tamarindus indica	Leaf extract	[132–137]
		Pelargonium graveolens		
		Azadirachta indica		
		Hibiscus rosa sinensis		
		Coriandrum sativum		
		Magnolia kobus, Dyopiros kaki		
		Pelargonium graveolens	Cell extract	[133]
		Emblica officinalis	Fruit extract	[138]
		Phyllanthium	Plant extract	[139–141]
		Aloe vera		
		Volvariella volvacea	Mushroom extract	[142]
		Honey	Honey	[143]
		Epicoccum nigrum	Isolated fungus	[144]
2.	Silver	*Rhizopus oryzae*	Fungal cell filtrate	[165–171]
		Pseudomonas aeruginosa	Culture supernatant	
		Pseudomonas stutzeri	Microbial culture	
		Yeast strains MKY3	Culture extract	
		Fusarium oxysporum		
		Lentinus/Pleurotus sajor-caju		
		Bacillus licheniformis		
		Aspergillus fumigatus		
		Klebsiella pneumoniae	Culture supernatant	
		Bacillus subtilis		
		Escherichia coli		
		Aspergillus niger	Mushroom substrate	
		Aspergillus flavus	Cell-free filtrate	
		Buchanania axillaris	Leaf extract	
3.	Silica	*Cylindrotheca fusiformis*	Diatom	[187]

2.1.5.4 Silica NPs

Among different nanoparticulate materials, silica-made NPs (SiNPs) are an attractive choice as a carrier for cells and drugs. Their use in drug delivery and distribution, imaging, and controlled release, owing to their mesoporous nature, were found suitable for drug and gene encapsulations with a preference for loading of biomacromolecules with biocompatibility, retention flexibility, nontoxicity, and in larger quantities with low preparation costs. The SiNPs are among the most widely used nanoentities for several biomedical applications [182,183]. Nano-porous silica materials possessed several large pores with high surface areas, which made them capable of absorbing large quantities of drugs and allowed their accumulations in adequate concentrations at the site, thus enhancing localized delivery with the clear purpose of treatment, and other remediation. Furthermore, the silanol groups present on the SiNP surface allowed easy modifications of these NPs, which allowed proper control of the drug release, together with increased loading capacity [184]. Several researchers have reported the anti-bacterial activity of silicon nanoparticles (SiNPs) against *Staphylococcus* [185,186]. Well-organized, SiNPs of sizes varying between 50 and 100 nm from diatom species, *Cylindrotheca fusiformis* [187] were synthesized within a few hours at room temperature by Buckle *et al.* Thus, diatoms shells, after treating with magnesium vapors at elevated temperature, formed the Mg–Si oxide layer. The procedure was applied to prepare other metal-based NPs and disclosed the importance of the applications of diatoms in the synthesis of NPs [187]. Diverse ranges of bio-based materials have been utilized in the preparation of various non-polymeric, inorganic NPs (Table 2).

2.1.6 Lipid-based NPs

2.1.6.1 Liposomes

Liposomes are lipid-based vesicles, and the breakthrough preparation of liposomes was provided by Bangham *et al.* [188].

The liposomes have consisted of single and multiple concentric spheres of lipid bilayers, which are separated by compartments produced from natural and synthetic phospholipids. The liposomes have important properties of lessened toxicity, unique physical characteristics, comparatively better drug-loading capacity, and sustained drug release potential. These properties have made them the most desirable carrier for drug delivery purposes [189–192], and the majority of commercial nano-scale delivery modules are of liposomal origins. The liposomes are also more desirable in comparison to the SLN [193]. The compositional and preparative methods alterations for liposomes are diligently followed by a change in their surface charge and size. The liposomes are prepared as single or multiple bilayer vesicles, which are capable of conducting improved gene targeting, and efficient drug delivery [194]. Because of their rapid infusible lipid bilayer with the cell membranes, the liposomes have shown improved activity in anti-cancer and anti-microbial testings, which also provided enhanced drug delivery, drug stability, and drug outreach [195,196]. These characteristics have allowed the controlled accumulation of drug concentrations at the injection site (most common delivery mode for liposomal formulations) and their targeted localization with reduced toxicity [197]. Several researchers have reported liposome-encapsulated antibiotics for significantly improved elimination of intracellular bacterial infections [198,199]. Liposomes have specifically delivered drugs against lung tuberculosis [200], which were prepared by Deol and Khuller. Several ligands were prepared to lead liposomes to the target tumors that included antibodies [201–211], and small ligands, for example, folate [212–221]. Currently, the commercially available therapeutics (monoclonal) antibodies (mAbs) include Herceptin for breast cancer and epratuzumab for B-cell lymphoma. These mAbs have the advantages of stability with a high binding capacity [222–224], together with reduced immunogenicity in the subjects [225]. The liposomal insertion, scFvHER2 (human epidermal growth factor receptor 2-single-chain variable fragment), as anti-HER2 for anti-cancer DOX drug delivery [226,227], and anti-TfR scFv-lipoplexes (TfR is transferrin receptor) as a gene delivery platform have been reported [228,229].

2.1.6.2 Solid lipid NPs

The SLNs, a spherical, colloid entity, were discovered as a lipid-based carrier for controlled drug delivery, as well as gene carrier systems to replace emulsions, liposomes, and polymeric NPs [230]. The SLNs have a size ranging from 50 nm to 1 µm and are composed of physiological lipids dispersed in an aqueous surfactant solution, or aqueous media [231]. The SLNs were constituted as solid lipid matrix at 37°C or room temperature, and the drug loads inflated their size range up to 1 µm [232]. Since the SLN matrix was formed from physiological lipids, it reduced the hazard of acute and chronic toxicity [233]. The high-pressure homogenization or micro-emulsification processes mainly were used to prepare the SLNs. The SLNs prepared by any concurrent reported methods exist in dispersion form, which on long-term storage results in their instability, essentially due to the hydrolytic reactions, which severely affect their stability. The SLNs can also be altered into solid dry reconstitutable powder through lyophilization of the prepared formulation [234,235]. The advantages of the SLN outweigh its demerits and disadvantages (Figure 5).

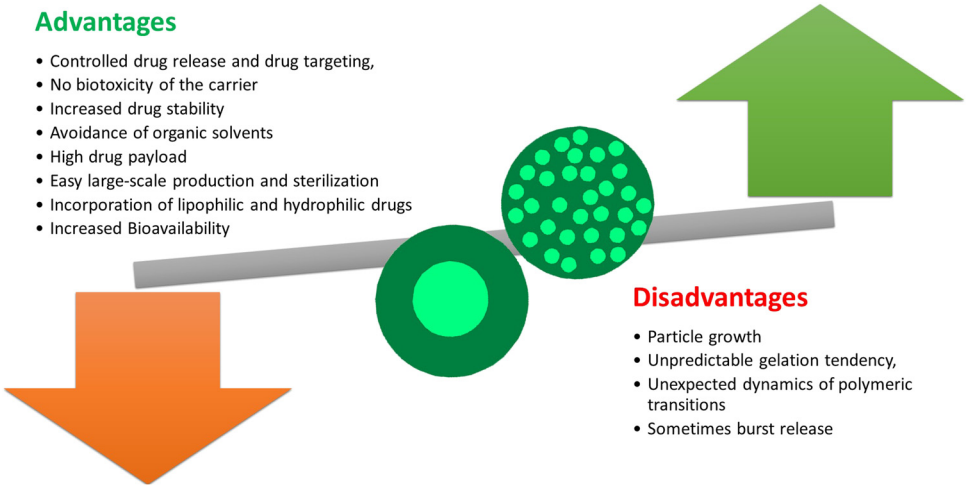

Figure 5: Advantages and disadvantages of SLNs.

SLNs have been recognized as an efficient carrier of drugs, especially lipophilic character drugs and for deliveries of other payloads of low and medium MW ranges [236]. To increase drug bioavailability, particularly in topical ocular delivery [237,238], and in anti-tubercular drug delivery to the lungs' alveolar tissue [239], as well as delivery to the lymphatic system with decreased side effects, the SLNs have been approached well [240].

2.2 Hydrogels

The first mention of the term "hydrogel" in the literature was made in 1894 [241]. A hydrogel is defined as a network of polymer-based hydrophilic chains, which exist as a colloidal gel in water, which is also the dispersion medium. The hydrogels are absorbent materials that can retain high water contents of up to over 90% of their weight [242]. The first synthetic hydrogel was prepared by Wichterle *et al.* using the copolymerization of ethylene methacrylate and 2-HEMA [243]. From its inception, the hydrogels have been used for biomedical purposes, for example, for contact lens fabrication, coatings on surgical gloves, in urinary catheters, for surgical drainage systems, in wound dressings, and as part of tissue engineering scaffolds material [244]. The drugs loaded inside the constituent polymer matrix of the hydrogel are diffused through the network with controlled-release patterns [245]. Hydrogels being extremely capable of retaining the loaded materials are viewed as efficient drug delivery systems due to their higher biocompatibility. The hydrogels' hydrophilic networks have been synthesized from synthetic as well as natural polymeric materials [246]. Their classification is based on their characteristics, including mechanical and structural (affine and phantom) characteristics, nature of the constituent polymers' side groups (neutral and ionic), physical forms of existence (amorphous, semi-crystalline, hydrogen-bonded, supramolecular, and hydrocolloid), methods of preparations (homo and co-polymerization based), and responsiveness to the physiologic and environmental stimuli (pH, ionic strength, temperature, and electromagnetic radiation) [247–250]. The classification is depicted in Figure 6.

The hydrogel/glass composite, nitric oxide-releasing NPs (NO-NPs) have been shown to have a high degree of effectiveness against methicillin-resistant *S. aureus* (MRSA) infection in various mouse models. In a previous study, Martinez *et al.* reported that the topical application of hydrogel/glass composite NO-NPs to skin wounds infected with MRSA significantly reduced bacterial infection compared to the control [251]. The limitations of the hydrogels, for example, low elasticity, and low load-bearing capacity results in the unwanted flow of drugs from the targeted site, but Peng *et al.* reported that the limitations would not affect the efficacy of the entrapped drug if it was injected subcutaneously [252]. The hydrogels possessed permeability for oxygen, nutrients, and water-soluble metabolites, and thus, were used in tissue engineering as bio-scaffolds [253]. The biopolymers, for example, collagen, fibrin, and matrigel-derived hydrogels had weak mechanical strength, and the potential for immunological reactions and a likelihood of animal virus contamination were observed [254]. The problem was tackled by developing synthetic polymer-based hydrogels [255]. The unique characteristics of the hydrogels, including their biocompatibility, available range of polymeric materials for their preparation, utilization of different synthetic protocols, and design achieved desirable physical characteristics, have made the hydrogels

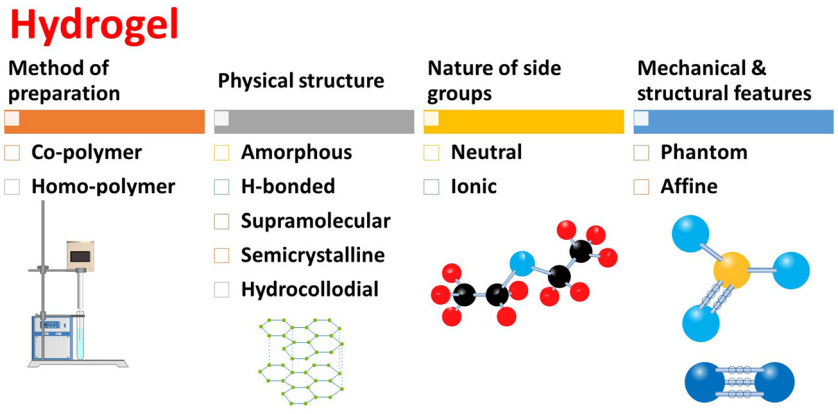

Figure 6: Classification of hydrogels based on their characteristics.

find immense applications in different biomedical fields. Stout and McKessor [256] prepared a cost-effective, antibacterial/fungal glycerin-based hydrogel formulation, which had a gel layer that absorbed the exudate from the wound, and simultaneously released the loaded material from the gel for wound healing. The hydrogel wound care products do not dry or make the wound dressing get bound to the wound and surrounding tissues. Additionally, the non-adhesive nature of the hydrogels does not cause any damage during the dressing removal process. This kind of hydrogel has provided a significant cushion and padding support over, around, and to the wound [257–259]. Elasto-Gel™ was FDA approved for all types of injuries, namely pressure ulcer, acute, and chronic injury, diabetic, and traumatic injury, and for use in other dermatological conditions, including first-grade burns as well as in cancers. The glycerin in Elasto-Gel™ acted as a skin-filler that tends to reduce the sore [260]. Another type of hydrogel, Aqua-form hydrogel, absorbed more fluid under conditions that simulated moist wounds and thereby indicated a more suitable clinical use for treating sluggish and necrotic wounds [261–265]. The electroconductive hydrogels were synthesized using semi-IPNs containing the novel electro-active polymer, PEI, and 1-vinyl imidazole(VI) polymer blend. The semi-IPNs are also systems constituted of PVA and polyacrylic acid. These systems reported successful electro-responsive drug release and suggested that the method is appropriate to be used for the development of safe and effective electro-responsive drug delivery systems. More than 2.6 and 0.7 mL of PEI and VI-based hydrogel products were found to be effective for the ideal therapeutic electro-responsive drug release (0.8 mg) system, wherein indomethacin was the experimental drug [266].

2.3 Dendrimers

Tomalia and co-workers discovered dendrimers in the late 1980s. The dendrimers are highly ordered, hyperbranched polymeric molecules that get an almost rounded shape as they increase in size and attain deliverable nanoscale sizes. Other names for dendrimers are arborols and cascade molecules. Dendrimers were prepared by a divergent synthesis approach. Dendrimers are shaped symmetrical, 3D rounded, and monodispersed entities that contain a single chemical group at their central, originating core. The dendrimers are also classified by their developmental generation wherein the number of repeated branching cycles on the core is counted, and each repeating cycle (generation) adds nearly double the MW of the previous cycle. The last cycle has comparatively more exposed functional groups. The starting core, which includes frequently used ammonia, ethylenediamine, polydiamine, and benzene tricarboxylic acid chloride has been reported, with more cores being continuously discovered, and established for drugs and other payload delivery purposes. The well-defined composition, shape, monodispersity, availability of abundant functional groups, and stability are among the main characteristics of dendrimers that render them appealing for drug loading and subsequent facile delivery. There is control of the number of functional groups available for attachment for drugs, imaging agents, and other moieties to the dendrimer, thus controlling the loading quantity in a more precise manner. Examples of dendritic loadings of drugs have been synthesized using different biocompatible materials that include PEI, polyethylene oxide (PEO), PEG, polyamidoamine (PAMAM), and polypropylene imine (PPI) [267–269] with several drugs fitted with the couplings on the dendritic end-groups. As a functional group, the PAMAM has primary amine, which allowed penetration of the cellular membrane and delivery of the anti-microbial drugs with high efficiency. Sulfamethoxazole (SMZ, sulfonamide) has low solubility and bioavailability, but when administered with PAMAM dendrimers in the *in vitro* condition, the SMZ-encapsulating PAMAM dendrimers caused the facile release of the drug and showed 4–8× folds increased antibacterial activity against *E. coli*, as compared to free SMZ. The gene transfection, attachments of non-steroidal anti-inflammatory drugs, anticancer agents, quinolones, and several other pharmaceuticals to various kinds of dendrimers have been reported [270–272]. The usefulness of dendritic systems and the auto-assembly of readily available amphiphilic *Janus* dendrimers achieved a varied framework. The amphiphilic *Janus* dendrimers, structurally composed of two dendrimeric wedges with the termination of two different functional groups, were self-assembled into a standardized onion-like layout with consistent size, varied shape, and known number of layers. Dendrimersomes and other complex structural architectures have also been reported. The *Janus* dendrimers have also been used for stabilizing drug suspensions [273,274]. It would be pertinent to mention along with dendrimers, the micelles, spongosomes, cubosomes, lipid–polymer hybrid nanostructures, discs, curved vesicles, and helical bands that have made drug and other payload deliveries including biomedical applications as the emerging alternatives [275,276] in parallel to other nano-entities and the dendrimers. A recent review on the preparation and bioapplications of dendrimers in nanomedicinal fields is available [277].

2.4 Buckyballs

Fullerenes are carbon materials that have formed in different caged-shaped structures. The lower volume, spherical structure, and void core have created a useful platform for drug delivery in the shape of buckyballs [278]. With 60 carbons, buckminsterfullerene [C60] is the most common example. The hydrophobic cleft of the protease enzyme from the human immunodeficiency virus (HIV)-1 could host a C60 molecule [279], as was reported by Friedman *et al.* Furthermore, many studies have approved the photodynamic inactivation of bacteria by C60 products. The hydrophobic split of the HIV-1 was also differentiated with the fullerene materials [280–285].

2.5 Virus-derived and bacteria-based NPs

The virus-derived NPs were among the latest entry into the nano-scale delivery modules. The viral NPs were derived from plant viruses, bacteriophages, and mammalian viruses. The development and applications of virus-derived NPs, and their genome-free versions, termed virus-like particles (VLPs) have been chemically conjugated to various ligands for specific deliveries. Fermentation and molecular farming have produced these VLPs. The particles are biodegradable and biocompatible in nature. The VLPs are used in cancer and immunological therapies, vaccines, gene transfers, and imaging, as well as for antimicrobial, cardiovascular agents' deliveries, and theranostics. The VLPs have shown both *in vitro* and *in vivo* applications, together with their functions as enzymatic nano-reactors. The ease of production in the system of choice owing to the superior capability to adapt and infect a wide range of organisms, and ability to customize for required modification, through chemical as well as genetic ways, have made the virus-based NPs an attractive choice for various types of deliveries of a wide range of materials like genes, drugs, and chemotherapeutic agents [286]. The (μ-glutamic acid)-based NPs were found to be good carriers of tumor vaccines for the proteins that have been used to provide antigenic proteins for the cells. These were used to develop potent immune responses as reported by Yoshikawa *et al.* who also proposed that the β-PGA poly-(γ-glutamic acid)-NP platform is sufficient to provide protein-dependent tumor vaccines reached out intracellularly [287]. Robertson *et al.* reported the T4 phage capsid developed-NPs without Hoc and Soc proteins (T4ΔHocΔSocNPs). They also documented the high efficiency of cell uptake in tumor cells of the T4-free Hoc-free Soc-NPs [288]. The West Nile Virus (WNV) was detected by a model paramagnetic NP (MNP)-based test for the detection of DNA oligonucleotides. Complemental oligonucleotide samples connected covalently to the manufactured MNPs, and Raman reporter tag-conjugated AuNPs for surface-enhanced Raman scattering sensing, with subsequent removal from the solution by the externally applied magnetic-origin of AuNP–WNV target sequence–MNP hybridization complexes, was also reported [289]. The nanomaterial induced viral infection in living cells using HIV-1 pseudo-type lentiviral particles. Cells were eventually exposed to different NPs and then the lentiviral infections were observed. The efficiency of transfection was shown to be improved by AuNPs, while the silver-based NPs decreased it, with a small or no impact on the infection rates of the virus [290]. Through molecular self-assembly, the viruses can form ordered structures, and the plants' virus systems are particularly advanced and have been utilized as bioinspired-engineered nanomaterials, and nano-vectors for future use. The plant virus-constructed NPs were physically uniform, biocompatible, biodegradable in nature, and facile to fabricate. They were also easily functionalized by alteration of the external surface, and loading of the cargo molecules into their internal cavity. Thus, these viruses can be utilized as targeted drug delivery systems [291]. Moreover, the multifunctional NPs holding promise as imaging and therapeutic delivery agents for the next generation of sensing development are being continuously verified for this purpose, especially incorporating the plant viral capsids. In this context, a previous study showed that the red clover necrotic mosaic virus could be loaded with high amounts of therapeutic molecules with MW of 600 Da and higher. Furthermore, it was also possible to conjugate the targeted peptides with less than 16 amino acids to the capsid using sulfosuccinimidyl-4-(N-maleimide-methyl)-cyclohexane-1-carboxylate as the chemical linker [292]. Moreover, subunit vaccine formulations based on isolated pathogens components (proteins and peptides) allowed the activation of highly specific and protective immune responses. Some researchers have tried to enhance the immunology and stability of the subunits by using genetically modified NPs of a plant virus as the carrier for transmission [293–295]. The *in vitro* and *in vivo* studies conducted to test unmodified potato virus X (PVX) toxicity, and the teratogenicity potential of tomato bushy stunt virus [296] was performed by Blandino *et al.* Various other groups investigated the biodiversity of PVX particles combined with different fluorescent dyes and PEGs of varying chain lengths. This masking eliminated the cell-like interactions with the NPs in plant viruses [297–299]. An A647 (AlexaFluor 647, dye)-labeled PVX-NP conjugated with a 12-amino acid peptide sequence with

correspondence to the epidermal growth factor receptor (EGFR) was effectively detected, and imaging was performed for the carcinoma cell lines.

3 Nano-structured delivery device pharmacokinetics

The success rate of a drug delivery carrier depends on important parameters defined by pharmacokinetics. The pharmacokinetics estimates the fate of the drug, active ingredient concentrations, and delivery status at the system, together with the underlying effects of hormones, nutrients, and toxins, thereby affecting the overall status of the drug in the body. Pharmacodynamics takes control over the biophysiological fate of the drug administered to the body. Current nano-drug delivery systems are employed to supply both the small molecules and various biomacromolecular entities, including peptides, proteins, DNA plasmids, and artificial oligonucleotides. To modify the release kinetics, it is desirable to configure the nano-scale drug delivery systems to monitor the distribution and thereby reduce the adverse side effects toward contributing to improving the therapeutic index, as some of the nanomaterials to be delivered have limited active-targeting, low bioavailability, and probable cytotoxicity, which affects the pharmacokinetics (PK). Moreover, current drug delivery systems offer controlled drug release at elevated global and local concentrations, wherein these abilities allow treating the affected area but also target the normal, un-diseased, and undefined locations in the body [300]. The particle size, an extremely important factor in delivery kinetics, plays a primal, decisive, first, and foremost role [301]. The smaller dimension NPs allow the nanostructures to pass cell membranes, reduce the chances of undesired clearance from the body, and minimize uptake by the reticulo-endothelium system (RES) [302,303]. The nano-structured delivery systems have a higher surface-area-to-volume ratio, and the small size is responsible for a better dissolution rate [304]. Undoubtedly, the drug loading capacity of the nano-carriers is comparatively lower than other non-nano procedures and devices. The nano systems' diameter has a significant role in the bioavailability and blood circulating time of the delivered nano-entities together with its entrapped/encapsulated payloads of drug and gene [305–307]. A number of nanoformulations have exhibited size-based characteristics (Table 3). The particulate material <100 nm is prone to be captured by the endocytic vesicles [308] and that led to the suggestion

Table 3: Pharmacokinetics relationship of nano-carrier performance and diameter ranges

Formulated module	Nano-carrier size	Composition	Inference	Ref.
AuNPs	<100 nm	Ag-colloidal solution	cAg toxicity is caused by the NPs themselves or Ag(+) that was formed during *in vivo* NP destabilization	[151]
Liposomes	100–200 nm	Distearoyl phosphatidylcholine, cholesterol, and distearoylphosphatidyl ethanolamine derivative of PEG	Most prolonged circulation time and the highest tumor accumulation	[305]
SiNPs	23 and 85 nm	Dye-doped imaging and internalization	Penetration at 58% for 23 nm-sized NPs as compared to 14% for the 85 nm-sized particles	[328]
	32–142 nm	Cationic, surface amine open, surface amine covered NPs	Monotonous reduction in systemic availability with liver and spleen accumulation, cationic amine-surface NPs showed lowered circulation, shielded amine surface SiNPs showed an increased clearance	[329]
PEGylated NPs	~75 ± 25 nm	PEG	Data showed the effects of particle diameter on targeting the mesangium of the kidney	[339]
Liposomal–DOX	100 nm	PEGylated	Liposomes AUC after a dose of 50 mg/mL was 300× greater than that with free drug	[351]

that the optimum size range is between 10 and 100 nm. The superior, controllable, actionable, and achievable properties of solubility, bioavailability, biodegradability, biocompatibility, encapsulation, retention, and release have made nano-structured devices and entities an ideal candidate for various delivery applications. However, a delivery model, best in all aspects may not be introduced, and the need for hybrid systems with case-by-case customizations may need to be developed for global and local deliveries [309].

3.1 Different NPs

Nano-structured delivery systems, and devices, for example, NPs, nanocapsules, nanotubes, nano-gels, *etc*., possess specified release patterns, peculiar release kinetics based on their constitution, pay-loads, and their corresponding characteristics as nanosystem, which are, for most of the parts, efficient, optimized, and specified in targeting behaviors [310,311]. The polyelectrolyte shells, produced by deposition through layer-by-layer structuring, have numerous advantages, including membrane thickness, the possibility to regulate surface property, and modulation of the release kinetics [312]. As both the inner and outer interfaces can be easily engineered, the shells are used in designated and permissible conditions of temperature and pH for easy loadings and releases [313]. Examples for that include drugs, enzymes, nucleic acids, dyes, *etc*. [314,315]. For certain typical applications, the nanotubes, similar to a microscopic-scale drinking straw, offer advantages over spherical NPs [316,317], according to their distinctive interior and exterior surfaces, in which the drug molecules are encapsulated within the vesicle, and thus the payloads are prevented from producing immunogenic reactions [317]. Additionally, the one-end open mouth structure of the nanotubes simplifies their mountings. The hydrogels or "nano jelly" offers simpler synthetic methods with relatively high potential for drug loading, which was also well applicable for topical delivery [318]. These hydrophilic polymer nets are cross-linked 3D networks and are swellable in an aqueous environment [319]. These nano-entities also react in response to several physiological stimuli, including ionic strength, pH, and temperature. Hybrid polymerizable nano-gels have been synthesized, which includes physically and chemically interconnectional motifs [320]. The nano-gel combines the features of gels, and the colloid properties, a large surface-to-volume ratio, a knitted microstructure, low-sizes, and heterogeneity. The architectonic design for the dendrimers is well regulated, thereby providing well-defined shapes, dimensions, and branch length, with predictable density and known surface functionality [321]. The medicinal loads were entangled physically in the dendrimer, or it was found to be chemically bound to the periphery through available functional groups. A number of drugs, that is, cisplatin [322], methotrexate [323], and 5-FU [324], allowed slower release for the higher buildup of solid tumors, with lowered toxicity than the corresponding free drugs to the normal tissue, and these steps were easily achieved particularly with PEGylated dendrimers [325]. The transverse cell membranes with PAMAM dendrimer were found to be combined with para-cellular transportation and adsorbent endocytosis [326]. The solubility of the dendrimers increased with length. The ester group-terminated dendrimers were comparatively more bioavailable for a given number of surface groups than their amino-end analogs. Among other nano-entities, the smaller-sized mesoporous SiNPs have shown better cellular uptake, cell membrane penetration, and drug retention for cancer cells [326–328]. The mesoporous SiNPs' bio-interaction properties predicted through mathematical modeling and observed through single-photon emission computerized tomography (SPECT)/computerized tomography (CAT) integrated imaging approaches for the effects of their size, surface chemistry, route of administration, linked biodistribution, and clearance in rat models were achieved. The increased particle sizes, from approximately 32 to 142 nm range increments provided lesser systemic bioavailability with lesser accumulation in the liver and spleen. The cationic mesoporous SiNPs with surface amine on them provided reduced circulation with enhanced clearance [329] (Table 3).

The pharmacokinetics, specificity of the PAMAM- and PLGA-based nanoformulations, showed sustained delivery with intraocular pressure reduced to 18% and up in eye deliveries [329]. Another brimonidine-loaded CSNP formulation provided longer-lasting effects than conventional eye drops [330]. The CS and HA-based NPs produced a considerable reduction in the intraocular pressure level in the eye when compared to the plain, free drug solution [331]. For the SPION, the NPs surrounding the tumor were checked through a histological test in CD31 expressed animal models [332], while the DOX-loaded lanthanide nano-scrolls inhibited tumor growth with insignificant cellular toxicity in both *in vitro* and *in vivo* conditions [333]. The application of gadolinium oxide NPs in magnetic theranostics [334] and the use of AuNP conjugates that showed 10× improved selectivity to the brain tumor with improved biocompatibility were also developed [335]. The PLGA and Mn-doped NPs increased delivery to the pancreatic cancer cells with reduced systemic toxicity [336–338]. Kidney mesangium targeting, ultra-small SPION for assessing the lymph nodes as an intravenous contrast agent with reduced signal intensity

for the normal but not the metastatic nodes, and tracking of transplanted bone marrow, and embryonic stem cells in rat brain and spinal cord by IONPs are known [339–341]. An efficient oral delivered nanoformulation consisting of Q10 coenzyme in PLGA was also developed [342]. For transdermal delivery, the PLGA nanovesicles exerted scalp-pore permeability from 2.0 to 2.5× higher than the control, while the CSNPs showed reduced irritation and toxicity [342–345]. NPs incorporating water-insoluble drugs, with the use of sodium dodecyl sulfate (SDS), were loaded into the NP framework without the need for post-synthetic modifications for their pharmacokinetics improvements [346]. The CS–TPP with acyclovir provided enhanced stability for sustained skin delivery of the drug, while the PEG-based NPs were found to have slipped through the human mucus barrier (Table 4) [347–349].

3.2 Liposomes

The liposomes are highly recommended drug delivery candidates due to their improved therapeutic index and better absorption rates. Compared to other drug-encapsulated liquid counterparts, they also prolonged the biological half-life, and reduced cytotoxicity to normal cells. Liposomal Doxil® and ALB-NP-based abraxane are available commercially. Their accuracy in the chemotherapy of prostate and breast cancers is documented [350]. Doxil, a DOX-liposomal drug, is RES resistant due to its PEGylated formulation. The pharmacokinetics profile characterized its prolonged blood circulation time with reduced distribution volumes, which thereby encouraged the absorption of the drug to the tumor with a removal half-life of 20–30 h. Its focus at the target site is at least 60-fold higher than free DOX [351].

The PEGylated-liposomal formulations of DOX [351], ciprofloxacin [352], and levofloxacin for contact-lenses anti-bacterial proposition [353], gene transfection [354], immunoliposomes based brain delivery [355], virosome-based immunization targets [356], double-liposome for peptic ulcer [357], active targeting to cancer [358], and toward transdermal diclofenac delivery [359] have been reported. The use of liposome-specific ligands directed against cancer cells' surface receptors is immensely important because their presence in cellular absorption processes tends to improve the therapeutic response at multiple times. The association by the internalization of liposomes with

Table 4: NPs' carriers targeting of body organs and their pharmacokinetics specificity

Site	Composition	Pharmacokinetics	Ref.
Eyes	PAMAM, PLGA	Developed NP formulation resulted in a sustained and effective intraocular pressure reduction (18% or higher) in 4 days	[326]
	Brimonidine tartrate and CS	*In vivo* tests revealed that brimonidine tartrate and CS-based NPs have a long-lasting effect than standard eye drops	[330]
	HA-mCS	CS and HA-based NPs resulted in a considerable reduction in intraocular pressure levels in comparison to plain drug solution	[331]
Brain	SPION	NPs revealed iron-tagged cells surrounding the tumor margin in animals expressing CD31, confirmed through histology	[332]
	Ultrathin lanthanide nano-scrolls	Developed NPs efficiently loaded (DOX, 80%) and significantly inhibited tumor growth with negligible cellular and tissue toxicity both *in vitro* and *in vivo*	[333]
	AuNPs conjugate	Showed 10-fold improved selectivity to the brain tumor by AuNP conjugates	[335]
		Surface plasmon resonance bands and biocompatibility improved with surface area to mass ratio	[336]
Pancreas	Mn-doped QDs	NPs showed para-magnetism and remained maintained with high photoluminescence	[337]
	PLGA-poloxamer	Developed NPs reduced the systemic toxicity of model anti-cancer drugs	[338]
Kidneys	SPION	Intravenously administered NPs reduce the signal intensity of normal but not metastatic nodes and was confirmed by magnetic resonance imaging of an animal model of nodal metastases	[340]
	PLGA	Histological examination indicated the existence of bromo-deoxy-uridine-positive cells as well as NP-labeled cells	[341]
		Therapeutic potential of a newly designed nanoparticulate formulation was tested (Gold Blatt 2K1C model) in renal hypertensive mice	[343]
Trans-dermal	PLGA	Encapsulated PLGA nanospheres exerted a scalp-pore permeability 2.0 to 2.5× higher than the control	[344]
	Polyacrylate, SDS	Observed that incorporated water-insoluble drugs with the use of SDS were directly loaded into the NP framework without the need for post-synthetic modifications	[346]

vascular cells also increased the concentration of the drug extracellularly and increased the amount of the drug that was distributed to the target cells. Receptor-specific ligands or anti-corps were the most common strategy for targeting surface cell receptors that were excessively expressed in cancer cells. The targeting by cell surface receptors had been widely studied in cancer as the upregulation of tumor-specific receptors in many types of cancer cells was previously demonstrated. For example, in response to growing metabolic demand, the TfRs and folate receptors were overexpressed by many types of tumor cells [359–362]. The obstacle to the delivery of liposomes by any tumor was overcome by direct targeting of the tumor cells through tumor vasculature/microenvironment. A system for selecting peptides that were specifically associated with the human tumor vasculature of xenografts of cancer [363] was developed by Chang *et al.* Connecting these peptides with a DOX-loaded liposome increased the drug's efficacy against several forms of severe combined immunodeficiency conditions. The peptides, IVO-8 (SNPFSKPYGLTV), and IVO-24 (YPHYSLPGSSTL) targeting tumors in neovasculature-specific phages, in general, connected the xenograft tumor vessels in animal models, and the six kinds of human solid tumor blood vessels, all of which were specifically delivered, were detected through dye tagging. The coupled IVO peptides in stealth liposomes with the PEG ends were shown to have increased therapeutic efficacy, enhanced cancer cell apoptosis, and decreased tumor angiogenesis in mice, consequently leading to decreased tumor growth.

A listing of liposome-based nano-carriers for different therapeutic purposes directed to various organs is summarized in Table 5.

4 Nano-delivery: bio-barriers, delivery modes, and devices

4.1 Delivery across the blood–brain barrier

Pharmacologically, central nervous system disorders are tough to treat, and one of the reasons for this is that the entry of drugs into the brain is restricted by the blood–brain barrier (BBB). It is a highly selectively permeable barrier consisting of brain endothelial cells, which are further interconnected by tight junctions (*zonula occludens*) with an electrical resistivity of approximately 0.1 mΩ [364]. The endothelial cells are biochemically assisted by star-shaped glial cells called astrocyte cell projections [365]. The BBB has a highly effective neuroprotective role, due to which almost 100% of macromolecular drugs and approximately 98% of small-molecule drugs are unable to pass through. Hence, only small lipophilic molecules (<500 Da) including amino acids, gases like CO_2, O_2, and glucose are known to be allowed to cross the barrier to the brain. For other substrates, the transport follows through carriers and receptor-mediated processes. Because of this, the transport of many diagnostics, and therapeutic agents

Table 5: Liposomal drug carriers' organ targetings and their major pharmacokinetic characteristics

Organ	Bioactive drug	Pharmacokinetics	Ref
Eyes	PEGylated-DOX	Reduced uptake by the RES, extended circulation time, and higher uptake at the site	[351]
	Ciprofloxacin	Positively charged liposomes showed superior entrapment efficiency (82.01 ± 0.52) over the negatively charged and neutral liposomes	[352]
	Levofloxacin	The liposome-coated lenses inhibited bacteria growth against *Staphylococcus aureus*	[353]
	Plasmid DNA cationic liposome complexes	Plasmid DNA cationic liposomes showed the highest transfection efficiency in eye tissues	[354]
Brain	Immunoliposomes (antibody-directed liposomes)	Immunoliposomes revealed that immunoliposomes accumulate in brain tissue over 24 h	[355]
	β-Amyloid	Virosomes triggered a dramatic decrease in both soluble β-amyloid (p = 0.01) and soluble β-amyloid (p = 0.03) in a double transgenic mouse model of Alzheimer's disease	[356]
Stomach	Ranitidine bismuth citrate, and amoxicillin	Dual loaded liposomes showed higher percent growth suppression against *Helicobacter pylori* than in the control sample	[357]
	DOX	Developed liposomes encapsulated with DOX improved stability and enhanced circulation time	[358]
Transdermal	Sodium diclofenac	An increased amount of liposome in-adhesive patch system enhanced the rate of skin permeation of the drug	[359]

of potential significance are prevented from reaching the brain. Mechanisms for drug delivery into the brain involve going "over," or "hind" the BBB [366]. The brain, which has a large surface area of about 20 m^2, allows successful administration of drugs through the trans-endothelial route. Improvements in drug delivery systems through transcytosis by targeting the local receptors existing on the surface of the BBB also provide a promising proposition. This target has been achieved by using nano-carriers that mimic the biosystem's structural, and functional specifications to permit the BBB-barred, restricted materials to cross over the BBB. The drugs cross the BBB disguised in these nano-scale carriers. The drugs, and other desirable materials loaded-NPs, and liposomes have gained access through the BBB. The resistance to degradative enzymes and coupling of certain antibodies that bind to the receptors on the surface membrane of the BBB have facilitated the task. However, another obstacle hindering the NP movement is the coverage of the NPs by opsonins, which allows the macrophages to recognize, phagocytose the NPs, leading to the elimination of the drug delivery device before it reaches the brain target, and cause therapeutic effects. The opsonization is avoided by using cell-specific ligands, and the coatings of the carrier by the hydrophilic polymers, for example, PEG. The mechanisms for delivering certain drugs to the brain include going either "through" or "behind" the BBB. This incorporates invasive and noninvasive procedures for drug delivery through various transport methods. One of the most important key players facilitating the successful targeting of the drug to the target site is the selection of the route of administration. A non-invasive drug administration to the brain section would be an ideal choice if it were uncomplicated, painless, and safe. The most common practices in medical and research studies are the intravenous application of drugs followed by the oral route, intranasal, and inhalation.

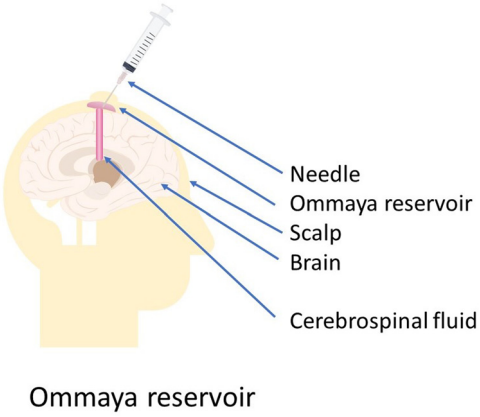

Figure 7: Ommaya reservoir.

The invasive interstitial and conventional techniques are for example, intrathecal/intraventricular, convection-enhanced diffusion, and intracerebral drug delivery systems. In invasive drug application, the delivery needs mechanical breakage of the BBB. In the following section, some of the examples of different invasive and non-invasive administration routes are described [367–369].

4.2 Invasive routes

4.2.1 Interstitial drug delivery

Several devices and techniques, for example, injections, catheters, and micro-pumps have been utilized for drug delivery purposes. The interstitial delivery provided minimum toxicity with the least systemic contacts. The delivery modules were subcutaneously implanted, and refilling of the drug took injections, also assisted by computation-aided functional supports. Through a skull-implanted reservoir, high concentrations of the drug were delivered for use in treating neurodegenerative disorders and brain tumors. Several examples of direct drug delivery to the brain interstitium-Ommaya reservoir (Figure 7), through aid-pump infusion generated by compressed Freon® to constantly deliver the drug, are available. The Medtronic SynchroMed® system used a peristaltic mechanism, and the MiniMed® PIMS (Programmable Implantable Medication System) utilized a solenoid pumping mechanism for the purpose.

Ommaya reservoirs have been used in numerous other clinical trials for constant and desired levels of drug delivery to treat patients with brain tumors by directly transporting the chemotherapeutic agents. BCNU (Carmustine), and its analogs, together with Adriamycin, bleomycin, methotrexate, cisplatin, interleukin-2 (IL-2), and fluorodeoxyuridine, which have also been characterized by a high intratumoral drug concentration, and mild-side effects, are reported to be delivered. However, this invasive technique presented different kinds of drawbacks when the catheter was clogged by tissue debris, thereby resulting in inadequate drug distribution in the tumor. In this context, the use of functionalized nano delivery entities has assumed much importance, and liposomal modules of drug delivery were sought in. The epidural delivery of multivesicular liposome (commercially available DepoFoam® technology) drug delivery system was applied. The morphine supply in dogs was activated through the system, which produced prolonged analgesia without any pathological effects after repeated administration of a 10 mg/mL dose to the animal [370].

4.2.2 Intracerebral delivery

The cerebrospinal fluids (CSFs) were demonstrated to play a definitive and major role in drug delivery. The CSF is in direct contact with the interstitial fluid of the brain. Therefore, drugs were sought to be delivered directly into the cerebral ventricles by avoiding the BBB. The intracerebral ventricular delivery has its particular advantages, and the drug half-life was manipulated, resulting in reduced systemic toxicity, as there are minimal or no proteins available for binding. Despite such an advantage, the drug generally drained into the systemic circulation, and efficacy level reached the same levels as that of an intravenously administered drug [370]. It happened because, in comparison to CSF, the clearance rate was slow. The rate of the drug's parenchymal diffusion from CSF, which produces intracranial pressure when the drug was infused into small ventricular volumes, was decreased. Therefore, the outcomes were marred by the high clinical prevalence of hemorrhage, CSF leaks, neurotoxicity, and central nervous system (CNS) infections. The nano delivery concept kicked in and liposomes laden with clodronate were tried [371]. Another strategy to bypass the BBB was to bring the drug directly into the parenchyma of the brain tissue, and this was achievable either through direct injection of the drug-using controlled discharge matrices, or by intrathecal catheteric device [372,373], or also through the intermediacy of the recombinant cells [374]. However, the only drawback observed was the slow movement of the drug from the initial injection site, which decreased exponentially, and the approach was not at all found feasible in acute brain injury, which provides a relatively short period for employing an effective therapy [375,376]. Use of the recombinant adeno-associated virus (rAAV, recombinant adeno-associated viral, adeno-associated virus serotype 2-neurturin, CERE-120) for expression of neurotrophic factors, for example, glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor, and the nurturin injected directly into the brain parenchyma for the treatment of Parkinson's disease, and atrophy of spinal neurons have been reported [377–379]. The limitations of the rAAV-mediated delivery which includes the host's stimulated immune responses, restricted brain transduction, low packaging capacity and rate-determining steps of transgene expression were controlled. The controlled rAAV delivery modules provide functional approaches to overcome these drawbacks. Coated nano-carriers have been proposed for this purpose. Nano-secondary ion mass spectroscopy analysis of iodine in intracerebral delivery of 5-iodo-2′-deoxyuridine for therapy of the F98 glioma has also been reported [380].

4.2.3 Convection-enhanced delivery (CED)

The CED included inserting a small-caliber catheter device into the micro-pump and infusing the drug into the brain parenchyma cells, penetrating through the interstitial spaces. The method allowed continuous infusion of the drug for several days. It showed a better response in drug diffusion and distribution than simple diffusion procedures. It was also observed for the drug with high MW. In a previous experiment, Bobo *et al.* used the CED technique to deliver proteins with high MW characteristics and found, after 2 h of continuous infusion, that the diffusion reached 2 cm from the injection site in the brain parenchyma cells. Thus, precise placement of catheters in the brain parenchyma and properly transmitted drug delivery are the important factors for successful drug reach using this method [381]. Convection-enhanced brain delivery, biofeedback pump for leptomeningeal carcinomatosis, and identification of hypothalamic neuron-derived neurotrophic factor have also been reported [382–384]. Liposome encapsulated DOX to brain delivery by CED is an example in point [385,386].

4.2.4 Intra-vascular delivery

Due to tight endothelial junctions, the BBB limits the passage of hydrophilic substances. Otherwise, as per routine the passing of only lipophilic drugs is allowed. For a transient opening of the tight junctions, different hyperosmolar substances including arabinose and mannitol have been injected into the cerebral circulation. The injections of pharmaceutical substances for facilitating the treatment of brain tumors were reported [387,388]. The strategy allowed uptake of the drug when the transport system was manipulated. The BBB surface receptor-mediated, carrier-mediated transports were the way out [389]. However, this strategy presented limitations after traversing the BBB. The drug encountered the basal lamina, which trapped opsonized particles and proteins, making the BBB opening less efficient, and nearly dysfunctional [390]. Leads into the intravascular nano delivery have been reviewed [391].

4.3 Non-invasive techniques

4.3.1 Olfactory pathway

The nasal pathway (Figure 8) also facilitates drug delivery to the CNS circumventing the BBB [392]. Nasal delivery is

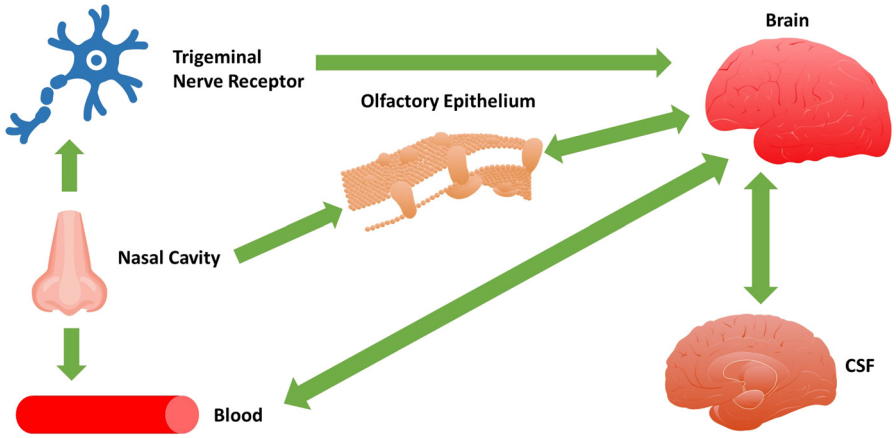

Figure 8: Drug delivery to CNS by olfactory pathway.

not typical for systemic administration; it may either be used intraneuronally or as extraneuronal. It was usually employed for the administration of drug molecules that functioned locally. The intranasal pathway is highly successful in administrating a large number of therapeutics and experimental molecules, including small lipophilic molecules, for example, cocaine, morphine, and proteins, for example, insulin (5.8 kD), leptin (16 kD), nerve growth factors (27.5 kD), selective oligonucleotides, and plasmid DNA [393–399]. Out of the four proposed pathways for transporting molecules by the intranasal cavity to CNS, the major pathway recommended is the olfactory nerve pathway. The olfactory nerves are connected with the trigeminal nervous system between the brain, and the exterior environment, and thereby provide the shortest pathway to delivery and transport of the drug to the brain, and the drug is transported to the CNS within minutes. The trigeminal nerve pathway innervates respiratory and olfactory epithelia, and helped in drug distribution to the brain, that is, brainstem and cerebellum areas [401,402]. The vascular pathway is the third route for delivering small and lipophilic drugs, while the fourth pathway for the intranasal CNS delivery is through CSF [400–402]. The intranasal delivery of glucagon-like peptide-1 antagonist, Exendin (9–39), brain uptake, quantitative analysis of olfactory-route delivered drug to the brain, and intrathecal delivery of pain medication to the brain has been achieved [403]. Nano formulations and other nanoparticulate systems for delivery through the intranasal route have been reported [404–407].

4.3.2 Focused ultrasound (FUS)

The FUS provided reversible BBB disruption with enhanced permeability by concentrating the acoustic energy to a focal spot, which could be used to target the brain. Various kinds of gas microbubbles were announced as cavitation nuclei to increase the BBB disturbance and minimize impairments to the surrounding normal brain cells. These focused microbubbles convert acoustic energy into mechanical power. In this way, the MRI analysis was used in combination with FUS to direct the FUS energy and to raise the local temperature, as well as to provide an opening for drug delivery [408–410].

4.4 Kidney-targeted drug delivery systems

Renal diseases are difficult to tackle due to their need for long-term medication and expensive dialysis including kidney transplants. In addition, the long-term medication/therapy is accompanied by serious side effects, which fails the clinical safety issues. Therefore, effective kidney-oriented nanosystem development represents promising advancements in treating renal disorders through improved drug delivery, enhanced therapeutic efficacy, and achieved safety. Such renal targeting systems provide powerful contributions in controlling pharmacokinetics and improvement in the efficacy increments of the drug. Attempts at achieving optimized renal supply through high MW CS, comparatively small MW proteins, poly(vinyl pyrrolidone-*co*-dimethyl maleic acid), and galectin-3-carbohydrate recognition domain (G3-C12) were pressed into action. Systems for proximal tubular cell delivery were designed. In multiple cases, mega line-mediated endocytosis due to the specific intake of the drug carriers by renal tubular proximal cells has been observed. In addition, the carrier's overall charge appears to be a major factor in the provision of kidney-specific drug delivery. On the other hand, mesangial cells are particularly appropriate for NPs and liposomal formulations considering their sizes

[411]. The delivery to the kidney through nano-structured devices and techniques, and involvement of modified nano-structures are commendable (Figure 9).

4.4.1 Macromolecular carriers

The low MW carriers improved water solubility, augmented oral absorption, and enhanced the bioavailability of the conjugated drugs. They also tend to provide sustained release of the drug and reduced extra-renal toxicity. These low MW glomerular proteins (LMWGPs) were also selectively accumulated in the kidneys. The LMWGP is part of the enzymes, immuno-proteins, peptide hormones, including lysozyme and insulin. From the glomeruli, low MW protein was shown to be transferred into renal tubules and reabsorbed. Due to their non-immunogenic property, some of these proteins were also used as a drug. A macromolecular drug–carrier conjugate also tends to be quickly removed, thereby maintaining drug levels within safe limits. This prevents extra-renal load and subsequent kidney damage [412,413].

4.4.2 Lysozyme conjugates

The low MW endogenous proteins (<20 kD) are among the most studied LMWGP. This includes lysozyme, which gets associated with drugs by forming peptide linkage with naproxen, ester linkage in triptolide-lysozyme [414–416], and disulfide bonding with captopril [417,418]. These linkages increased the performance by several folds when the uptake by renal proximal tubular cells occurred, that is, when compared to the free drugs, thereby significantly improving renal targeting. For example, naproxen-lysozyme was converted into naproxen-lysine to inhibit cyclooxygenase, and when naproxen was released from the conjugate its concentration increased to 70× higher than the naproxen itself. Similarly, anti-inflammatory and immunosuppressive triptolide, when conjugated with lysozyme, its renal concentration increased 20-folds in comparison to the equivalent dose of the free drug, as observed after 30 min of intravenous delivery. The renal targeting efficiency of the conjugate was enhanced from 11.7 to 95.5%. In addition, when free triptolide was administered, toxic effects were observed in the digestive, urogenital, circulatory, and reproductive systems. A lysozyme-conjugated triptolide showed a 22% lessened hepatotoxicity with no adverse effects on the immune system. The renal concentration of the conjugate of the ACE inhibitor, captopril with lysozyme was increased 6-folds in male Wistar rats, compared to the free drug. The drug conjugate was also found useful in reducing proteinuria with no systemic effects on blood pressure. Several other drugs have also been linked to lysozyme in various ways, for example, sunitinib analog 17864 through the platinum-based linker [419], sulfamethoxazole and DOX through cis-aconitic anhydride, and SB202190 through the platinum-[II]-based universal linkage system® (ULS) [420]. Advances in nano-module drug delivery to the kidney have been reviewed recently [421,422].

4.4.3 CS conjugates

The delivery of CS–prednisolone conjugate attached through succinic acid spacer increased the mean residence time of the conjugated drug, and the presence of 19 kD protein conjugate was 13-fold higher in the kidney, while 10% of the 31 kD protein–drug conjugate was retained in the kidney after 120 min of administration, compared to the free prednisolone. The conjugates were non-toxic to L929 and NRK-52E cell lines. The conjugates had a safer pharmacokinetics profile due to their faster uptake, and filtration from the kidney than the lysosome and its conjugate. The low MW polymeric conjugates, that is, CS and HECS (hydroxyethyl CS) with N-acetylation, have been used for safe and targeted transport, with polymers of different degrees of acetylation [423]. Rhein oral delivery for renal conditions and GLY-CS (glycol CS)-based site-

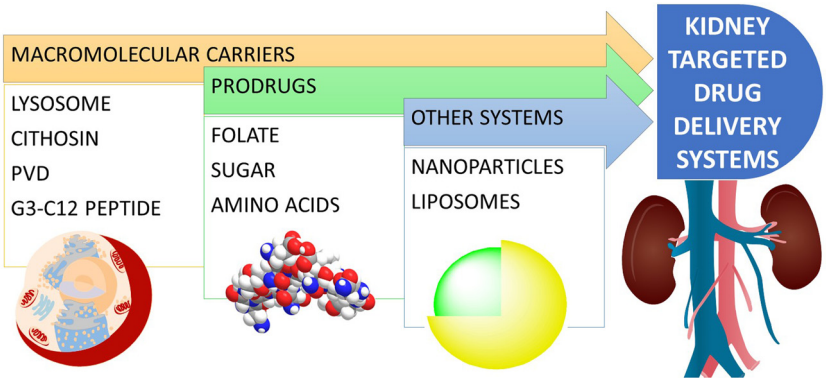

Figure 9: Kidney-targeted drug delivery systems.

specific renal delivery of biopolymeric Nano micelles as immunosuppressant have been recently reported [424,425].

4.4.4 Synthetic polymer-based conjugates

Poly(vinylpyrrolidone-*co*-dimethyl maleic acid), anionized PVP, and other polymeric-conjugates targeted the renal cells while specific uptake was mediated by megalin-based endocytosis. The mesangial cells were a suitable destination for particulate delivery modules. The polymer–drug conjugate delivery is affected by the carrier's MW and charges wherein the best renal targeting of ~80% of the administered dose being delivered to the kidney was preferred over polymeric MW averaging between 6 and 8 kDa with positive charge annotations [426–428].

4.4.5 Peptide conjugates

Galectin-3 (G3-C12), ε-poly-L-lysine derivatives, kidney-targeting peptide-derivatized elastin-like polypeptides, and carrier peptide $(KKEEE)_3K$ conjugates have been reported mainly for kidney-specific deliveries providing better pharmacokinetics, biodistribution, longer plasma half-life, and kidney accumulation, which was comparatively multi-folds higher than the free drugs in comparison with their accumulation in other organs. The peptide specific to the galectin-3 carbohydrate recognition domain [G3-C12] [ANTPCG-PVTHDCPVKR], identified using a combinatorial display technique, was shown to be specifically accumulated in (mouse) kidneys after intravenous delivery. Fluorescein isothiocyanate)-labeled G3-C12 peptide was reabsorbed in proximal renal tubular cells. When the sequence G3-C12 was conjugated to captopril, its renal concentration was increased by 2.7× folds as compared to the free drug [427–431].

4.4.6 Prodrugs

The chemically modified derivatives of parent drugs that are *in vivo* subjected to enzymatic, and other biochemical-based transformation to release the active drug, are termed prodrugs. The prodrugs exert desired pharmacological effects, improve the therapeutic efficacy, and reduce toxicity. Suzuki *et al.* [432] proposed glycoconjugates, a dual function entity, as a prodrug, and as a potential vector for renal targeting. The arginine–vasopressin glycosylated conjugates were introduced, and it was found that the structure of alkyl glucoside (Glc–S–C8–) was required to target the kidney. The effect was dependent on the chemical nature of the sugar that significantly altered targeting efficiency. The alky chain length, peptide structure, and type of chemical bondings, primarily ester, amide, and ether, together with the molecular size played the parts. Therapeutic substrates' conjugates with positive charged and low MW entities were developed [433,434].

The cytotoxicity and absorption tests in HK-2 and MDCK cell lines exhibited decreased cytotoxicity, together with 2.2×-multiplied intake by the cells compared to free prednisolone. The kidney concentration of the drug was increased 4.9-folds in comparison to the free prednisolone, as found in the *in vivo* tissue distribution tests. The authors concluded that 2-glucosamine could be the likely carrier for renal targeting [435,436]. Zidovudine-CS oligomeric conjugates were also prepared and tested for *in vivo* release of zidovudine in the mouse model through intravenous administration in a pharmacokinetics test procedure conducted by Liang *et al.* [437]. The results showed that the conjugate's residence time was 2.5× times higher than free zidovudine in the kidney. In addition, the uptake and distribution of prednisolone and its 2-deoxy-2-amino di-glucose conjugate demonstrated overall better performance. Atorvastatin delivery to the kidneys through ceria NPs for acute injury targeting the mitochondria with ROS responsiveness was also delivered [438].

4.4.6.1 Amino acid-modified prodrugs

Mice tissue distribution patterns of γ-glutamyl-dopamine (GGDA) were synthesized and analyzed by Wilk *et al.* [439]. The dopamine concentration in GGDA-treated kidneys was higher than the equivalent dose of dopamine, which suggested degradation of GGDA by renal enzymes. In the kidneys, the application of dopamine increased blood flow significantly without any significant effect on blood pressure and heartbeats. The concentration of free dopamine in plasma after oral administration of GGDA was very low, whereas the concentration in urine was relatively higher [440,441]. Such findings indicated that GGDA was a candidate for delivering dopamine to the kidneys. An *N*-acetyl-glutamyl prednisone prodrug material, prepared by Su *et al.* [442], and investigated for its *in vivo* distribution; together with its effects on bone density in rats was conducted to evaluate its adverse effects. The bone mineral densities (BMD) of the Wistar rats were assayed, and compared to the parent drug, prednisolone, the ACEP prodrug derivative showed improved kidney-targeting with lowered toxicity. The targeted renal prodrug exhibited increased drug concentration, and osteoporosis incidences induced by prednisolone were reduced.

4.4.6.2 Folate-modified prodrugs

The kidneys have important roles in the reduction of folate losses. The production of folate in the body starts with 5-methylenetetrahydrofolate. Thereafter, it is processed by the folate-binding protein, which is present on the proximal tubular epithelium, and it is reabsorbed during vascular circulation. Folic acid was coupled to diethylenetriaminepentaacetic acid (DTPA), using a spacer arm, ethylenediamine. This allowed a quick excretion of DTPA–folate conjugate. In the thymic tumor-bearing mice, after intravenous delivery of DTPA–folate, the conjugate was taken up by the tumor and transported to the kidneys. The fast deletion from FR-negative tissue of the DTPA–folate conjugate illustrated the critical role of the folate receptors in the absorption of conjugates [443]. The use of folate bindings has been limited, and the physicochemical properties of the conjugate are open to play a role in targeted and random deliveries since folate receptors were also expressed elsewhere.

4.4.7 NPs

The potential of NPs as drug delivery carriers to kidneys was emphasized as crucial since accumulation and toxicity are major concerns for renal tubules. An accumulation in the glomerular mesangial cells of high concentrations of actinomycin-D (AD)-loaded *iso*butyl acrylate NPs (ADNPs) were reported [444] in, both, *in vitro* and *in vivo* experiments. After the applications of ^{3}H-AD, or ^{3}H-ADNP into rats with experimental glomerulonephritis, the uptake ratios of [^{3}H-ADNP/^{3}H-AD] were, respectively, 6.9-folds increased after 30 min, and 4.0× levels increased after 120 min, compared to normal-conditioned rats. The *in vitro* experiments found out that the intakes by epithelial cells were 6-folds lower than the mesangial glomerular cells. The targeting of the glomerular mesangium is especially useful to treat glomerular inflammation with anti-inflammatory medications, for example, cortisone. The mesangium kidney could be targeted by NPs of sizes ~75 ± 25 nm in diameter. Thus the design criteria for NP-based treatments for renal diseases were established [445].

4.4.8 Liposomes

Small unilamellar vesicles (SUVs) linked to a mAb, Dal K29, entrapping methotrexate (MTX-SUVs) were more effective than the free drug, mAb (an IgG1 mAb), and normal mouse IgGs, or the non-specific mouse IgGl in renal cancer [446]. Dal K29-linked-(MTX-SUVs) showed, respectively, 6- and 8-folds increased binding than the unspecific (MTX-SUVs) and the unlinked (MTX-SUVs), following incubation with human kidney CaKi-1 cancer cells lines in 2 h duration. A colony inhibition experiment also found out that the Dal K29-related MTX-SUVs are 5- and 40-folds higher than that of the Dal K29-MTX, respectively, allowing the MTX to inhibit the growth of CaKi-1 cells. OX7 (OX7-mAb F(ab′)2 fragments)-coupled immuno-liposomes (OX7-IL) coupled liposomes attached with Fab fragments of OX7 mAb directed against the Thy1.1 antigen were prepared by Tuffin *et al.* [447]. The average diameters were 130 and 170 nm for the liposomes, and immuno-liposomes were generated. As the glomerular endothelium is corrugated, and as any base membrane does not divide the glomerular capillary, the mesangial cellulose was particularly a good choice for OX7-IL-based drug delivery. The OX7-IL was found to specifically target the mesangial cells following intravenous administering in rats, but the formulation was blocked in the case of the free OX7F(ab')2 fragment. The low-dose DOX injected rats had glomerular damage while the other kidney sections and body parts were spared, and most likely, it was thought to be caused by the conjugated OX7 antibody.

4.5 Drug delivery to pancreas

Among all the cancers, pancreatic cancer is the most deadly with the lowest survival rates statistics displayed so far. Pancreatic cancer is the third prominent reason for cancer deaths in the world. Lack of effective drug delivery has made it challenging because the pancreatic cells cluster in a nest of scar-like tissue with high resistance to chemo and radiation therapies. For the drugs to get to the pancreas, which is situated deep within the abdomen, specifically targeted delivery modules were deemed necessary. Recent advances in drug delivery systems provided higher prospects for improving the situation with respect to pancreatic cancer treatments. Drug delivery systems, for example, NPs, liposomes, CNTs, suicidal gene, siRNA, oncolytic virus, antibody, and small-molecule inhibitors, are worth-mentioning drug carriers.

4.5.1 NP- and QD-mediated delivery

Due to their unique structure and characteristics, NPs have been considered ideal carriers for therapeutic deliveries for the treatment of pancreatic cancer. Among many NPs-drug formulations, the PNPs encapsulating

rapamycin for oral nano-scale drug delivery with favorable pharmacokinetics had better therapeutic effects in inhibiting the growth of pancreatic cancer cells [448]. A drug delivery system for improving the treatment for MIA PaCa-2 (human pancreatic carcinoma) pancreatic cancer by encapsulating PHT-427 in single and double emulsions PLGA-NPs (SE–PLGA-427) and (DE–PLGA-427) were developed by Kobes *et al.* [449]. When studied in a mouse model, compared to SE-PLGA-427, the DE-PLGA-427 showed delayed drug release with a longer retention time in pancreatic cells. The MRI showed a significant decrease in cellularity with both forms of drug-loaded NPs during therapy. The tumor size decreased by 6- and 4-folds compared to untreated tumors. The primary pancreatic tumor was reduced by 68%. The AuNPs (~5 nm size) that were targeted *in vitro* and *in vivo* conditions of pancreas cancer were successful in delivering the intended drug [450]. The AuNP-based system delivered Cetuximab and a pro-epidermal growth factor (pro-EGF) antibody. It was well established that tyrosine kinase (TK), epidermal growth factor receptor (EGFR) (ErbB-1), which is overexpressed in pancreatic cancer, suggested a fair strategy for diagnosis and treating pancreatic cancer [451,452].

The mesoporous SiNPs, due to their robustness and biocompatibility, have demonstrated high potential as a drug delivery vehicle against pancreatic cancer. It is also well suited for use as a nano-theranostic agent for bioimaging and treatments. For the targeted delivery of gemcitabine using SiNPs, a previous study *in vitro* tested the therapeutic efficacy of the nanoformulation against Panc-1 cancer cells. The pancreatic cancer cells showed high levels of CD44 receptors on their surface, which made them insensitive toward chemotherapy and thus were considered responsible for cancer recurrence [453]. The application of another delivery system based on HA-conjugated NPs played an important role. The naturally available polysaccharide, HA, is also the ligand for CD44. The receptor is highly expressed on different cancer cells and has an important role in developing cancer, for driving the interactions between the extracellular matrix, the cancer cells, and cancer metastasis. HA with negative charge prohibits self-agglomeration and inhibits non-specific interactions, as well as binding to the cell surface. The other advantages of HA-sourced NP formulations are their multi-functionality because of HA, and their ability to target and accumulate in cancer cells due to improved endocytosis. The specificity of the endocytosis becomes possible only due to the interaction between HA and CD44 receptors. It resulted in decreased cytotoxicity compared to the free gemcitabine and un-functionalized NPs. Besides the specificity, the mesoporous SiNP nanoformulations also improved drug efficacy through their sustained release and protection against external stimulations. The progression was controlled through neural-drug-loaded ferritin NPs. The drug-loaded ferritin-NPs were targeted by the passive method. The NPs regulated the microenvironment to control the growth of pancreatic cancer cells. The ferritin-based NPs thus represented an effective and safe delivery route for pancreatic anti-cancer therapy [454]. Besides, the NPs were also recommended for cancer diagnosis as an imaging agent.

The QDs were also found promising in pancreatic cancer diagnosis. The manganese-doped QDs were stable, distributed into an aqueous environment, and quickly mixed with the targeting molecules. The multimodal QDs were identified as diagnostic agents for early pancreatic cancer detection through imaging, thereby suggesting the vital potential of QD as an efficient, safe, and novel imaging system for the early detection and diagnosis of pancreatic and several other cancers [455–457].

4.5.2 Liposomes

The photo-actable multi-inhibitor liposome (PMIL) doped in carrying cabozantinib and a photo-actable chromophore (benzo-porphyrin derivative) were prepared. The antagonist multikinase was used to exhibit light-induced cytotoxicity associated with the photo-initiated continuous release of the drug, and it was employed to inhibit tumor growth and arrest treatment-escaped signaling pathways. The photodynamic disruption to tumor cells and microvessels was found to be triggered by intravenous PMIL administration. The subsequent release of XL184 (cabozantinib, a kinase inhibitor) inside the tumor was initiated, and a single PMIL treatment achieved prolonged tumor reduction in mouse models which also suppressed metastasis in an orthotropic pancreatic tumor model [458]. For improving second-line treatment for metastatic pancreatic cancer, a liposome called MM-398 consisting of around 80,000 irinotecan molecules was used to disrupt the proper functioning of the DNA in cancer cells [459]. A global, randomized, and open-labelled, phase-III clinical trial consisting of nano-liposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer, after previous gemcitabine-based therapy (NAPOLI-1), was conducted. This delivery system improved the pharmacodynamic and pharmacokinetic features of the drug. However, besides that, 5-FU leucovorin (folinic acid) alone increased the overall survivability dramatically than a mixture of M-398 + 5-FU. A “smart” injectable nano-therapeutics entity scheduled to selectively deliver pharmaceutical products was shown to improve the effectiveness of the drug by

200-fold increments. It was based on their ability, both to resist oxidation and to focus at key target locations, that is, to pancreatic regions comprising the cells that produce insulin. The dramatic increase in effectiveness allowed the use of smaller quantities of drugs, significantly reducing toxic side effects and lowering treatment costs. Due to poor delivery, and systemic toxicity many cytotoxic drugs, that is, folinic acid (leucovorin) (folfirinox), FU, irinotecan, and oxaliplatin, have only limited usefulness in treating pancreatic cancer. The localized delivery of chemotherapeutic agents using iontophoretic instruments inserted directly into the pancreas has become feasible. The iontophoretic therapy-based use of folfirinox for the diagnosis of pancreatic cancer in an orthotropic patient-derived xenograft model was described [460]. The growth suppression of mouse-tumor with controls for 7 weeks with folfirinox iontophoretic delivery in contrast to intravenous delivery was significantly greater. Another device for localized, targeted, time and release-controlled drug delivery systems was found to be 12× more effective than the free drug delivered intravenously. The delivery was also compared with two groups of mice carrying transplanted human pancreatic tumors. The device helped in slowing down the tumor progression, and the tumor size effectively shrank. The thin, flexible film made up of PLGA polymer was easy to implant to the site with a minimally invasive surgical procedure. Being flexible, it took a near-spherical shape. Drugs like paclitaxel were embedded into the film, which was released over a pre-programmed interval. The delivery minimized the side effects. Such a film was also used to open the blocked bile duct, be used as a coating for a stent, and was found to help prevent cancer cells from spreading in the duct, and blocking the duct again [460].

4.6 Drug delivery across the placenta

The human placenta is a complex disc-shaped organ, which acts as a connection between the fetus and mother. It is responsible for performing functions like transferring gasses (O_2 and CO_2), supply of nutrients (glucose, amino acids, FAs, electrolytes, vitamins, and water), and waste removal from the fetus and maternal plasma. As the placenta is an endocrine organ, it produces different steroid hormones like the human chorionic gonadotropin, human placental lactogenic peptides, human growth hormone variant, estrogens, and progesterone. Immunoglobulins also cross from the mother to the fetus by pinocytosis to provide passive immunity in the first months of life.

Nearly all the drugs cross the placenta to reach the fetus [461]. However, some drugs had higher concentrations in the fetal blood, compared to maternal blood. Succinylcholine has an incomplete transfer to the placenta resulting in a higher concentration in maternal *versus* fetal blood. The drugs transferred from the mother to the fetal blood are carried into the intervillous space and pass through the syncytiotrophoblast, fetal connective tissue, and the endothelium of fetal capillaries. Multiple factors regulate the drug transport through the placenta, that is, thickness, surface area, the presence of drug carriers, metabolism, uteroplacental blood flow, pH gradient of the fetal and maternal blood across the placenta, MW of the drug, and its lipid solubility. Nonetheless, major transport effects were observed for the polar drugs, and their elimination was accelerated. In contrast, the elimination of lipophilic drugs was slowed, and the effect on the structures of amphiphilic drugs was variable. The polar drugs were found to cross the placenta slowly, gets accumulated in the amniotic fluid, where they were found accumulated in the fetal gut lumen. Lipophilic drugs crossed the placenta rapidly, and their trans-placental distributions were dependent on their affinity to the maternal and fetal affinity, which was mainly dependent upon the drug–protein binding on either side of the placenta. The fetus and neonate disposed of all drugs slowly than adults. The most efficient elimination processes involved the drugs' biotransformations as sulfate conjugate, together with active renal excretion [461,462].

4.6.1 Placental drug transfer mechanism

The transfer of drugs to the placenta takes place both through active and passive transporting mechanisms. The drugs, for example, midazolam and paracetamol, were diffused through passive moving, following Fick's law of diffusion. This makes the rate of diffusion/time directly proportional to the surface area of the placenta and the concentration level across it, and *vice versa*, which is proportional to the membrane's thickness. According to the formula, the rate of diffusion Q is, $Q = k \times \mathrm{SA} \times (C1 - C2)/d$. Here, k is the diffusion constant, Q is the rate of drug diffusion through the placenta/time, SA is the surface area of the placental membrane, $C1$ is the maternal drug concentration, $C2$ is the concentration of free drug in the fetus, and d is the thickness of the placental membrane. Small MW drugs readily diffuse if the drug is also lipophilic in nature. This opens the way for SLNs, and other lipid-coated vesicles, and carrier systems for facilitated delivery across the placenta. The size of the nanoparticulate material also plays a role. NPs and nanomaterials of size up to 500 nm have been shown to cross the placental barrier in mouse while for the human

placenta the size limit was observed only up to 240 nm [463,464]. The diffusion was also influenced by the pH and pKa of the maternal blood, which further influences the degree of the drug's ionization. Only the non-ionized part of a partially ionized drug passes through the placenta membrane. Most anesthetic medications are improperly ionized in the blood, and thus, easily, unwittingly spread across the placenta. The exception is the strongly ionized neuromuscular blocks, which are also marginal in transmission. An increase in the rate of drug ionization was observed when the pH of the maternal blood varies. The protein-bound drugs do not spread to the placenta. The cell membranes were crossed free and by unbound drugs in a facilitated diffusion transfer, for example, the cephalosporins and glucocorticoids transferred through facilitated diffusion. Transfer of molecules, for example, norepinephrine and dopamine require some energy input like ATP, as it takes place against a concentration gradient. On both sides of the placental membrane, active drug carriers were found which allowed the transport of drugs from mother to fetus and inversely. The distribution and expression of the active drug carriers within the placenta could vary according to gestation. Early studies discovered different active carriers on the placenta including the multidrug resistance proteins 1–3 (for the transport of drugs like HIV protease inhibitors and MTX), and p-glycoprotein (involved in the transport of drugs, *e.g.*, dexamethasone, digoxin, cyclosporin-A, and chemotherapeutic substrates like vinblastine and vincristine). Another strategy for drug transport between fetus and mother is termed pinocytosis in which drugs were completely enveloped into a membrane and were then removed to the other side of the cells [465,466]. Nanodeliveries across the placenta have provided outreach to the fetus with safe drug delivery options during pregnancy through control of placental interaction with the drugs [467].

5 Smart nanodevices: combination of functional variability and site specificity

5.1 Smart drug delivery systems

Smart drug delivery systems (SDDSs) adjust and match the biological environment-driven responses, and function in the body as well as the systems they interact with. These systems also overcome biological barriers for uninterrupted delivery. The SDDS increases the solubility and stability of controlled payload delivery and facilitates on-site release in a desired, chronological pattern. The systems build and maintain adequate drug concentration at the required site along with the reduction in localized and systemic cytotoxicity. New generation transport systems use smart substrates, that is, shape memory polymers with glass transition temperature called switching temperature (T), which needs to be close to body temperature together with the shape-changing capability intact and actionable at desired conditions. Self-folding polymers, which were buildup from multilayers with hinges, or different thermal expansion coefficients, allowed folding upon being triggered in the delivery situations designed for the purpose. The environment-responsive polymers were used for the preparation of delivery polymers with predefined functions and properties to match any single polymer or every polymer in the blend adjusts independently. Different criteria, that is, aqueous environment, drug loading capacity, release kinetics, and degradation influence the suitability of the polymer through its shape-memory polymeric action and other inherent characteristics. The systems are optimized for being minimally invasive upon implanting through the incision and are designed to release the drug payload based on self-anchoring. Shape memory polymers were developed for use as potential drug-eluting stents, for example, double-layer systems made of L-lactide, glycolide, and tri-methylene carbonate loaded with anti-cancer, paclitaxel, the biodegradable polymeric cross-linked poly-(ε-caprolactone), and poly(sebacic anhydride) polymer-based delivery platforms. The oligo-(caprolactone-*co*-glycolide)-methacrylate combined with the drug, and the delivery started at a temperature range between 28 and 42°C as part of the temperature stimulus device. Wischke *et al.* [468] observed that the diffusion-controlled drug releases separately than the polymer degradations. SDDS has gained ground as a platform of choice for drug delivery to specific sites. The approaches of targeted drug delivery systems including active, passive, inverse, double, dual, combination, and physical targetings are being used very often in therapy, together with temperature, shape, pH, enzyme, physiological conditions responsiveness, and *Janus* nanosystems and devices, as part of SDDS [469–472].

5.1.1 Passive targetings

For passive targeting, the nano-carrier needs to be antiphagocytic to enable the drug-loaded nanosystems to stay in circulation for a longer period. Normally NPs of

size range 10–100 nm layered with PEG were used as a carrier. The passive targeting additionally integrates targeted preparation delivery to the malignant bed area throughout several invasive modalities. The polymer NPs have shown signs of improved retention and permeability upon targeted release in tumor cells. Moreover, the leaky vasculature, in many ways, improves the delivery of anticancer drugs, and the loaded nanosystems. The lymphatic drainage, which was missed in the tumor bed results in drug buildup, thereby supporting the tumor-targeting strategies to enable the nanosystem-loaded drug to accumulate from 10 to 100× in additional concentrations than the free drug. However, locally administered drugs led to increased concentrations at the targeted tumor site with reduced toxicity to normal cells. The E1B-55 kDa gene was expanded by attenuating onyx-0115 of type 2/5 adenovirus [473]. It is a complex, and the p53 gene was inhibited by other protein connections. The medication was administered in various ways directly to the malignant cells. The Onyx-0115 has undergone clinical trials through intra-tumoral administration for head and neck cancers [474], by intra-tumoral delivery through endoscopic ultrasound for pancreatic cancer [475], by hepatic artery to metastatic colorectal cancer [476], through intraperitoneal administration to ovarian cancer [477], and by intra-tumoral administration under radiographic leads for advanced sarcomas [478]. Direct delivery has surpassed other modes and has provided benefits in cancer management. The passive targeting (enhanced permeability and retention [EPR] effect) has provided the nano-scale carrier facilitated route to the tumor wherein NPs, liposomes, and SLNs have been employed [479–481].

5.1.2 Active targetings

The active targeting provided precise ligand–receptor interaction for intracellular localizations following the transport and extravasation [482–486]. The active targeting of tumors was achieved through several means. It was targeted through capillary action, specifically to certain tissues and organs, thereby delivering the drug to the specific malignant cell types, tissues, and organs *sans* the normal healthy cells. Delivering (nano) medication to Kupffer cells is one such example. The approach controls the NPs for targeted delivery to specific sites. The carbohydrate-holding sites required specific receptor antigens. In carbohydrate targeting, an interaction between the tumor cells' binding glycoproteins, selectins, and the cell surface of carbohydrate were used for delivery purposes [487]. NPs holding carbohydrates motifs on their surface interact with the cancer cells mediated through selectins, and in the process, the normal healthy cells were spared. The NPs uptake through endocytosis, and receptors, and antigens overexpression allowed specific targetings. The surface functionalization by interaction-by-design approach provided the desired targeting. The ligand–receptor enhanced the delivery kinetics. The drug-coated NPs were internalized by the cells through cytosolic action and were procured in the cells through lysosomal enzymes [488]. The antigens or receptors were also re-processed to the cells' surface after delivery has been complete. The targeted drug delivery system included key biomolecules of antigenic nature, surface proteins, receptors, and other biomolecular motifs. Chemotherapeutic drugs and traditional as well as other/herbal drugs had been targeted through the active targeting approach [489]. Figure 10 represents the major drug targeting strategies.

5.2 Stimuli responsive nano-carriers

The premature release of drugs, and other payloads from the loaded, and tagged nanosystems have been prevented through targeted release controls. The nanosystems incorporating the characteristics to release their load upon the stimuli were designed for the de-loading process to start and function. NPs and other nano delivery platforms responding to endogenous or exogenic stimuli have been designed on a large scale and tested. The identified endogenous triggers were pH change, charge reversal, enzyme level alterations, and small organic molecules, for example, glucose presence, as well as changes in redox gradient situations, and exposure to the targeted receptor and other biomolecules present at the intended physiological condition sites that are linked to the pathological characteristics of the disease. Opioid peptide-based releases were also observed to activate and intensify in the diseased areas by the exogenous stimuli, for example, temperature, presence of magnetic field, ultrasonication, photo-illuminance, energy pulsation, and high power radiations [490–492]. A number of stimuli-responsive drug delivery techniques are presented in Figure 11.

5.2.1 pH-responsive nano deliveries

The pH is the most frequently used trigger for drug delivery. Different organs have different pH values, and designed carriers are capable of sensitively differentiating between

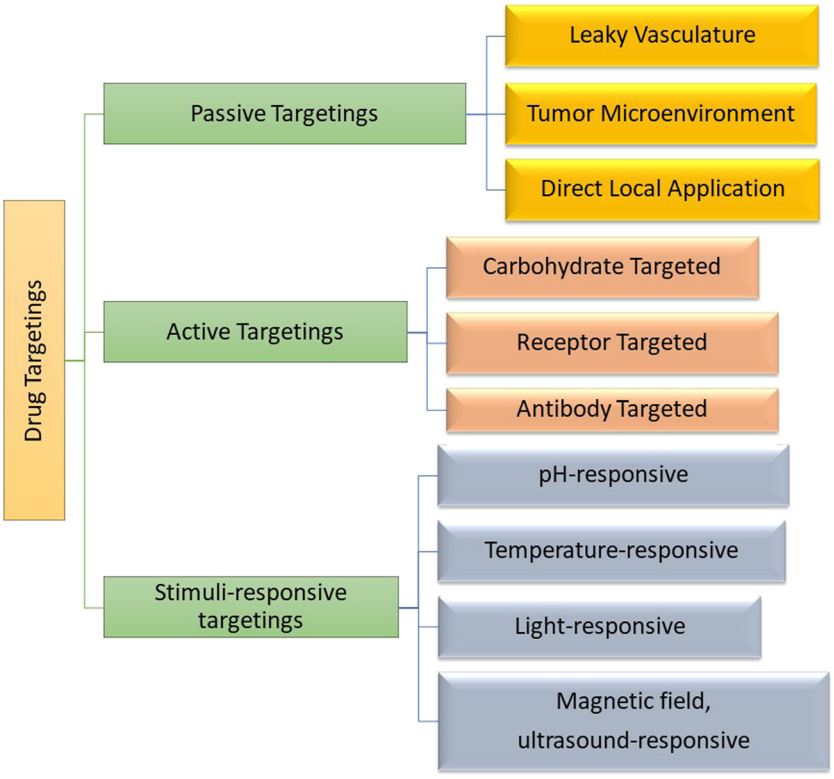

Figure 10: Different types of drug targetings.

delicate pH changes at specific sites, for example, inflammatory, ischemic, and tumor tissue sites. Polymeric micellar delivery platforms were pH-sensitive and were used to improve the effectiveness of cancer chemotherapy. The pH trigger caused the release of the drug after accumulation at the site in response to a slight change in the observed acidic pH of the extracellular tissue fluids. Ternary grafted copolymers, for example, polystyrene, poly(ethylene glycol) methyl ether, and poly-(acrylic acid) were specifically synthesized, and at pH 7.4, stabilized the DOX-containing benzyl benzoate nanoemulsion in water constituting the compact polymeric layer to inhibit any early DOX release. At lower pH 5, the hydrophilic and hydrophobic balance was disturbed to release DOX from its platform [493]. Acetal-containing pH-responsive polymer-based nano-drug delivery systems have also been developed [494]. High-stability polymers with pH-responsive mechanisms for nano-drug delivery were also reported [495].

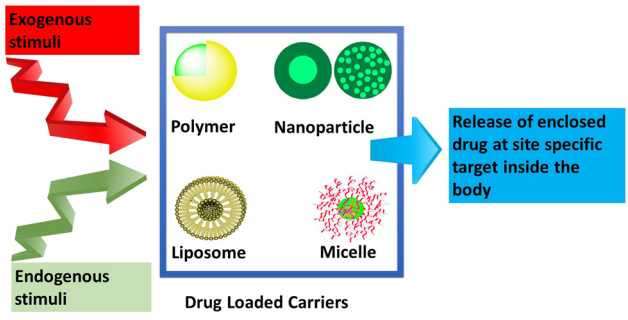

Figure 11: Stimuli responsive/triggered drug release systems.

5.2.2 Redox-responsive nano-carriers

The redox potential of various tissues in microenvironments is multivariate in nature and was used to model redox-reactive drug delivery systems. Glutathione (GSH)-based deliveries were an outstanding approach to optimize the delivery of drugs utilizing the NPs. Such redox signals had been commonly used in the intracellular drug delivery system. A well-known redox mechanism reported for cancer cells is GSH reduction. In contrast, the blood levels of GSH and the usual extracellular matrices redox vary from 2–20 μM to 100- to 500-folds greater than the typical GSH rates inside the cell cancer cells at the same time. A number of approaches including multi-functional nano-carrier, stimuli, and enzyme responsive triggered, and passive and active tumor targetings of nano-carriers to exploit the tumor microenvironment and the on-site redox had been proposed and developed [496].

5.2.3 Temperature and enzyme-triggered nano-carriers

Certain enzymes, for example, glycosidase, lipase, phospholipase, and proteases were manipulated to trigger the biocatalytic function in cancer and inflammatory conditions. The major challenge in an enzymatic drug delivery system was to accurately control the system's initial response time. Another challenge was the higher temperature of the pathophysiological disorders site and biosystem than the normal tissue temperatures, which were utilized as a useful and effective variable to monitor the drug release. Temperature-sensitive nano-platforms of NPs of metallic and polymeric origins, nano-emulsion, and other nano-entities capable of temperature trigger were designed and are reported. The temperature response between 40 and 45°C was also utilized for cancer hyperthermia-related drug delivery through external stimuli of a magnetic field, and ultrasonication energy supply for the trigger release of the drug [497–499]. Additionally, the photosensitive carriers trigger drug release at a single, or repeated light irradiation, as it "opens" and "closes" the nano-platform under programmable command through exposures to the external magnetic field. The spatial regulation with non-invasive stimuli paved the way for targeted, site-specific, time-defined, temperature-sensitive, and payload release control [500–502] delivery options. The regulated release of drugs provided better penetration, bioavailability, biochemical and chemical stability, and increased and adequate drug concentration at the target site on demand through the stimuli adjustments by different types of nano-carriers [503–512].

Based on specific triggers, biocompatible and biodegradable polymers released the entrapped drugs at the designated site according to the pre-fixed delivery cycle and frequency. The phenomenon was maneuvered by the biosystem's specifications for responding to the triggered changes at the site. In this context, the frequently used polymers in developing controlled-release NPs were aliphatic polyesters, for example, PGA, PLA, and PLGA. In addition, the CS and its derivatives were also found suitable for the purpose. CSNPs and mCSNPs, which directed the delivery through tagging of antibodies, and the magnetically driven nanostructures and aptamers, were also used for the purpose. Mesoporous SiNPs also responded as stimuli-responsive nanomaterials to produce smart delivery systems. The biomolecular capping of the NPs pores provided extra reactivity for the biosystem. The intracellular and internal stimuli were used for the removal of the capping to respond to the release of drugs, and other payloads, at the site. The deliveries were met in response to the built-in functional demands from the NPs. In addition, the optical contrast and magnetic imaging agents were also used to drive the multipurpose drug delivery systems as well as performing the diagnosis through the NP applications [513,514].

The micellar nanostructures, SLNs, and conjugated delivery of anti-cancer agents, that is, DOX, paclitaxel, and MTX, as part of the enhanced performance nano-carriers were reported [515–522]. The immunoliposomal delivery, functionalized PLGA, PLA, and PLGA-PEG NPs for bone delivery were recorded. Lipid-coated, TNF functionalized NPs, prostate cancer-targeted nanosystems, deliveries to the brain, and delivery of antigens, use of dendritic cells, siRNA therapy with sterically stabilized NPs, galactose-carrying polystyrene coated PLGA-NPs for receptor-mediated *trans*-retinoic acid delivery to the hepatocyte, and poly(hydroxyethyl aspartamide) (PHEAC)-based micellar formulations for ocular drug delivery were some of the smart nano-carriers developed for the precise and controlled drug delivery [523–535] options. A list of different drugs delivered through smart nano-carriers is summarized in Table 6.

6 Site-specific organ delivery

6.1 Organ targeting

Targeted delivery dealing with drugs to target-specific organs required a pre-work-out plan on preparation. It also needed to take into consideration the characteristic properties for the site-specificity design of the nano-structured entity, to specifically reach the intended organ's site, and de-load the loaded mass according to the set parameters, and in association with the internal or external stimuli. The feat is considered an additional advantage. The selective drug delivery to specific body sites required exclusively prepared nanosystems after consideration of the selected route. Each body organ has its specific characteristics, requirements, functioning, and biology to deal with the nano-scale drugs and other payload deliveries, as and when that happened.

6.1.1 Eyes

The conventional methods of topical and systemic administration of drugs to the eye are primitive, and the need for controlled and continuous release, particularly for conditions that influence the ocular posterior segment, has profound importance. Different non-implanted and

Table 6: Smart drug delivery nano-carriers used for the treatment of cancers

Drug/active moiety	NP carrier	Cancer/tumor site	Ref.
Adriamycin	Novel pH-sensitive polymeric mixed micelles, PLA, and PEG	Solid tumor	[515]
DOX	Polymer-lipid hybrid NPs	Murine solid tumor model	[516]
	Poly(*N*-ε-(3-diethylamino)propyl-isothiocyanato-L-lysine)-β-poly(ethylene-glycol)-β-poly(L-lactide)	Solid tumor	[518]
MTX	HSA	Solid tumor	[517]
Paclitaxel	Trimyristin, phosphatidylcholine, and PEGylated phospholipid	Ovarian and breast cancer	[519]
	PEG-distearoyl phosphoethanolamine conjugate (PEG–PE), solid triglyceride (ST), and cationic lipofectin lipids	Ovarian carcinoma	[520]
Daunorubicin	Biotinylated immunoliposomes, non-covalent (biotin-streptavidin)	Brain tumor	[521]
Ellipticine	Methoxy(polyethylene glycol)-*b*-poly(5-benzyloxy-trimethylene carbonate	Solid tumor	[523]
MTX, tritium	Non-targeted polymer, folate-conjugated	Epidermoid carcinoma	[524]
Alendronate	PLGA and PEG	Solid tumor	[525]
Docetaxel	Carboxy-terminated PLGA–PEG	Prostate cancer	[526]
Paclitaxel	PLA–PEG	Xenograft tumor model	[527]
Rhodamine-dextran	PLA–PEG	Prostate cancer	[529]
Antigens	PLGA	Bone cancer	[531]

implantable materials and devices have been developed where medications are equipped to deal with specific pre-corneal, fluidic, and other barriers for ocular tissue release of the drug. New, effective, and patient-oriented products and technologies to overcome such barriers and sustain the required levels of drug release to the eyes have been developed. In this context, many nano-carriers were formed, for example, nano-suspensions, NPs, nanomicelles, liposomes, and dendrimers. Nano-micelles for ocular anterior segment drug delivery as dexamethasone-loaded nanomicelles made up of copolymers of PHEAC, and PEGylated–PHEAC were introduced [536]. The copolymer of poly[ethylene oxide]–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) as a micellar delivery for transferring plasmid DNA with LacZ gene in rabbit and mice ocular tissues were designed and developed [537]. For posterior ocular drug delivery, cyclosporin-loaded nano micelles for delivery to the rabbit eye were also prepared. Owing to their size, NPs were sought in for the purpose and present an important nano-entity. The use of biocompatible polymeric NPs led to low irritation, allergy, and sustainable drug release avoiding repeated administrations. However, the NPs were quickly cleared from the pre-corneal sacks, and to avoid premature cleaning, the mucoadhesive NPs were introduced to increase the pre-corneal stopover time [538]. HA, CS, and PEGNPs were commonly used as they provided better pre-corneal habitation times. The quaternized CS, positively charged polymer, has an affinity to bind negatively charged corneal surface, thereby improving the pre-corneal retention time with increased availability of the drug. In the rabbit eye, Musumeci *et al.* [539] showed that melatonin-loaded PLGA–PEG–NPs had a significant intraocular pressure-lowering effect, and the NPs were more effective as compared to the aqueous solution of an equivalent concentration of melatonin-loaded PLGA-NPs. In a study using Sprague-Dawley rats, 20 nm of particles were rapidly removed from periocular tissues shortly after the application. The fast clearance was considered to be caused by the removal of episcular, conjunctival, and/or other circulatory periodic systems. On the contrary, the particles with a size range between 200 and 2,000 nm were maintained for 2 months after the administration. Hence, NPs with small size were not recommended to be used for delivery, and also for the extended trans-scleral drug delivery to the back of the eye [540,541]. Glucocorticoids, that is, dexamethasone prednisolone and hydrocortisone, widely used for treating eye inflammation were formulated as nanosuspension for better bioavailability [542]. The hydrocortisone (Hc) nanosuspension was prepared (300 nm) by the precipitation and milling process which provided better AUC (0–9 h) values of 28.06 ± 4.08 and 30.95 ± 2.2, respectively, significantly ($P < 0.05$) higher than that of the HC solution (15.86 ± 2.7). Prolonged drug action, observed through changes in intraocular pressure, was maintained for 9 h as compared to the 5 h action of the drug's solution. The milled formulation was stable for 2 months and showed no change in size whereas the precipitated formulation yielded 440 nm particle size [543]. Nonetheless, the liposomes provided

near-perfect nano delivery for the ophthalmic application because of their excellent bioavailability, lipidic structure, and capacity to accept both hydrophilic and hydrophobic drugs. The liposomes showed better efficacy for both the frontal and posterior parts of the eye. In the rabbit eye, a single subconjunctival injection of latanoprost-liposomal combination produced a sustained intraocular pressure-lowering effect over a period of 50 days compared to the use of the conventional dye drop formulation. The cationic liposomes were more active than the negatively charged liposomes due to the binding of the corneal layer with the later type of liposomes [544]. In an alternate study, in the rabbit eye, liposomes loaded with coenzyme Q10 (CoQ10) and coated with mucoadhesive TMCS, resulted in 4.8-fold improvement in the pre-corneal residence time for tests on delaying selenite-induced cataract, which was observed to be delayed with the coated liposomes [545]. Also, the posterior segment delivery showed liposomes' decreased cleaning from the vitreous humor and prolonged drug release from the liposome-bound cyclosporine [546]. Tacrolimus (FK506) and infliximab liposomal formulation showed improved effectiveness in the suppression of uveoretinitis compared to the medication alone and reduced sensitivity in internal retinal cells [547,548]. Different preparations of liposomal NPs have been investigated for ocular drug delivery, and some are now commercially available, while others are in clinical and pre-clinical trials. PAMAM dendrimers are also widely used as ocular drug transport platforms for the transport of tropicamide and pilocarpine nitrate for miotic and mydriatic activity in albino rabbits [549]. Ocular gene delivery through liposomes [550], the role of viscosity, and particle size of ophthalmic suspension have also been investigated [551]. A recent review summarizing the formulation approaches, and state-of-the-art on patents is also available [552]. Figure 12 presents the different nano-structures involved in ocular drug delivery.

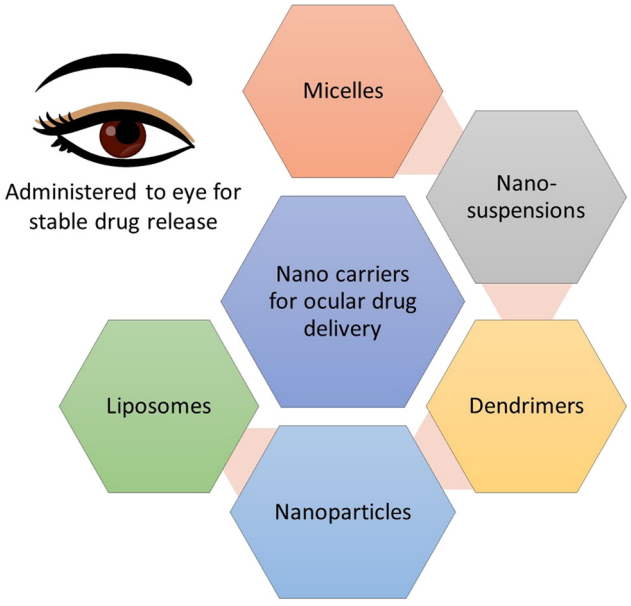

Figure 12: Smart nano-carriers for ocular drug delivery.

6.1.2 Dental area

Polymer and microparticulate hydrogels have so far been used. Their physicochemical characteristics and the properties gained as constituents of the formulation, influence the drug's distribution, availability, and release profile. Compared to microspheres, microparticles, and emulsion-based drug delivery systems, the NPs provide several benefits, including strong aqueous dispersibility, availability, absorption, controlled release profile, and greater stability. NPs penetrate inaccessible dense periodontal pits due to their size and reduce the drug administration frequency. PNPs synthesized using micellar polymerization resulted in a nanoparticulate powder suitable for dental applications [553]. NPs penetrate inaccessible dense periodontal pits due to their size and reduce the drug administration frequency. Another dental delivery nanosystem using emulsification–-diffusion preparation method providing triclosan-loaded polymeric PLGA, PLA, and cellulose acetate phthalate NPs were developed, which crossed the junctional epithelium for use in periodontal defects in dogs. Triclosan delivery was achieved for a longer period. The site-directed and site-specific deliveries using micro/NP solutions to the root canal cavity and periodontal pocket allowed the reduction of therapy sessions for clinicians and acted as an adjuvant for surgical events for teeth protection [554–556].

6.1.3 Heart

For treating cardiovascular diseases, the endothelium is considered a vital target for drug delivery. Several pharmacological interventions for endothelium treatment are available, which also include nano-scale interventions. There are many heart-targeted nano-scale drug delivery systems, for example, dendrimers, liposomes, and NPs made from materials like TiO_2, cerium, polymeric, and SiNPs. Polymeric drug conjugates, microbubbles, nano-coated stents, and micelles have also been used [557–563]. Cardiac-targeted ligands when conjugated on dendrimers' surface resulted in therapeutic entities, for example, poly-amidoamine dendrimer-based polymeric material in

conjugation with chemically functionalized nucleosides, which were found to enhance cardioprotective potency by the activation of the A3 adenosine receptor (A3AR) that exists on the cardiomyocyte surface [564]. *S*-Nitroso-*N*-acetyl penicillamine-modified polyamide amine fourth-generation dendrimers (G4-SNAP) were prepared to decrease I/R (ischemia/reperfusion) injury in rat hearts. It was found that GSH increased the production of NO resulting in the protection of the heart tissue from radical oxidation [565]. The dendrimer complexes were also conjugated to the DNA using the electroporation technique to increase the transfection efficiency in mouse cardiac grafts [566]. The development of liposomal carriers for heat treatment, upon preparation, yielded liposomes loaded with ATP and intended for anti-myosin antibodies. In rat hearts before global ischemia–reperfusion, the formulation delivery resulted in improvement of contractile recovery [567]. Treatment with immuno-liposomes containing vascular endothelial growth factor and conjugated with anti-P-selectin resulted in significant improvement of cardiac functions and vascularization due to the overexpression of P-selection in the damaged myocardium [568–570]. The liposomes were also modified to target angiotensin II type-1. The results showed that after systematic administration *in vivo*, the NPs were able to transport the active substrate to the affected heart tissue [571]. The functionalized SiNPs were used to target drugs to the heart [572]. Stable magnetic NPs and adenoviral vectors were delivered into the infarcted heart for treating acute myocardial infarction. Nanomaterials using cerium oxide, CeO_2, NPs for protection of the heart against inflammatory and oxidative injury caused by monocyte chemotactic protein-1 were prepared and tested [573]. The atherosclerotic burden related to exposure to standard diesel fuel was treated with CeO_2 NPs [574]. The biodegradable polymer-based stents were engineered to prevent re-stenosis before implantation, and stents were *in situ* degraded after the repair has been performed [575,576]. The PLA stents provided reduced inflammation and long-lasting results in a porcine model [577]. However, the polymer-based stents have poor structural strength, and to remedy this shortcoming, the bio-resorbable stents are now preferably synthesized from metallic and plastic alloy (plastic bends) materials. The magnesium stent was accepted and adopted within the first 3 weeks of implantation [578]. The ceramic nanoporous aluminum oxide coating and its suitability as a carrier for immunosuppressive drug tacrolimus delivery were established. The spongy aluminum oxide-coated stents encapsulating the drug inhibited neo-intimal growth [579]. Moreover, the ultrasound-targeted microbubble destruction technique was proved as an excellent proprietor for gene and drug transport on an experimental basis [580,581]. Deep venous thrombosis, acute coronary syndromes, the remission of arterial ischemia, and acute ischemic strokes were treated using microbubbles [582–584]. The roles of synthetic polymers have grown exponentially due to their versatile nature and capability to provide on-demand nanocarriers with desirable properties for delivery to almost all organs, and areas of the body. The size-control, inherent characteristics incorporated in the nanosystems, and surface modifications are comparatively feasible in synthetic polymers due to their structural specifications when compared to natural origin polymers, and this has made these polymers polymers-of-choice for preparing different kinds of nanosystems, delivery, and diagnostics uses [585,586]. Computational and numerical simulations on nano-hemodynamics, and nano-drug delivery, respectively, have also been recently attempted [587,588]. The nano-designed entities including nano-scale biomaterials prepared for the purpose have demonstrated their preventive and therapeutic advantages for diagnosing and treating cardiovascular disorders. The designed delivery platforms have targeted and removed coronary artery plaques, protected arterial damages caused by stenosis as well as arterial occlusion. The NPs have successfully minimized reperfusion-related injuries and have contributed to myocardium recovery through the targeting of cells, biochemicals, and paracrine factors delivery after the myocardial infarction [589]. Figure 13 represents nanocarriers employed for drug delivery to the heart. A listing of metals and major synthetic polymer-based nano-carrier systems are provided in Table 7.

6.1.4 Lungs

The pulmonary/nasal route is amply favored by the fact that the lungs can provide a vast (100 m^2) but extremely thin (0.1–0.2 μm), absorbing mucosal membrane area, together with an adequate supply of blood. The route is a non-invasive procedure for the delivery of treatment agents, and also for peptides and proteins. Nevertheless, recent developments have shown high potential. Nonetheless, the pulmonary distribution of proteins and peptides is hindered by the impact of the respiratory temperament, and the complicity of the human respiratory system's anatomic forms. The drugs were delivered to the pulmonary route using two techniques, that is, intratracheal instillation and aerosol inhalation which was used in intranasal applications. The increased distribution, with a deeper penetration in the alveolar region, or the periphery of the lungs was reached by aerosol technology. However, this is more expensive and makes it difficult to measure

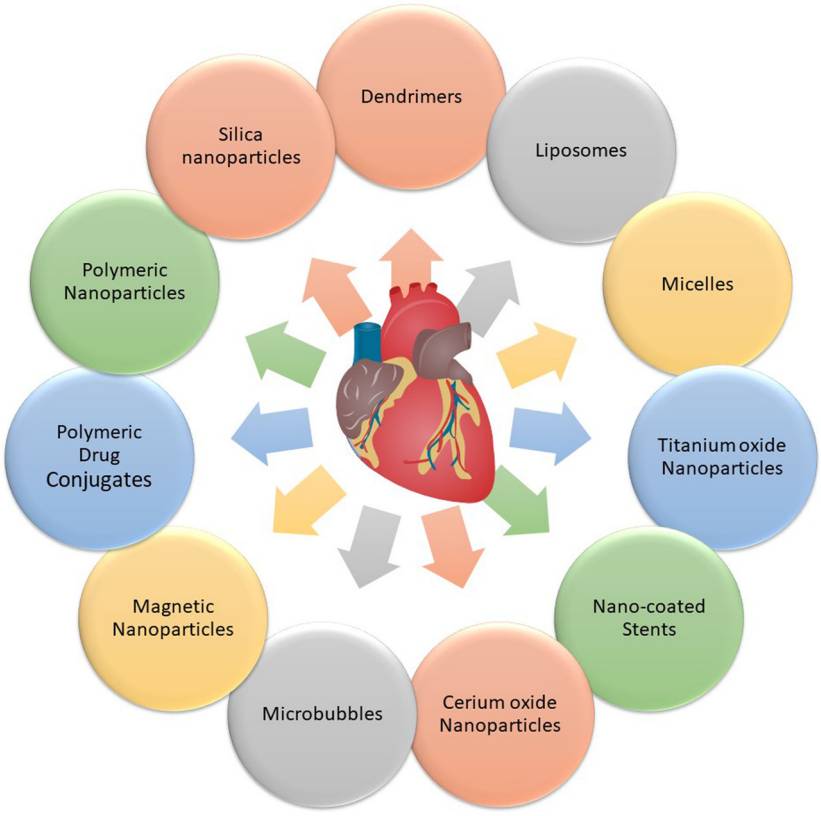

Figure 13: Nano-carriers for drug delivery to the heart.

the exact dose inside the lungs. By comparison, the production is much smooth, less costly, and the delivery of medications is not standardized. There are three common ways to deliver aerosols, jet or ultrasound nebulizer, inhalation metered doses, and inhaling of dry powder. For aerosol delivery, metered-dose inhalers are commonly used. The dry powder inhalers were designed to deliver drug/excipient powder into the lungs. Most aerosols use a chlorofluorocarbon (CFC) propellant. However, in the mid-nineties, efforts were made to use enviro-friendly hydro fluoroalkanes (HFAs: HFA-134a, and HFA-227), an alternative to ozone-depleting CFC. Advances in pulmonary and nasal delivery employing nano and microparticles, hydrogels, liposomes, and dry-coated powders have been recently reviewed [590,591].

6.1.4.1 Intra-tracheal inhalation

The NPs intratracheal noninvasive delivery provides deep alveolar reach to the delivered drug with better biodistribution, drug deposition, and residence time. The NPs, by their physicochemical characteristics and surface modifications, provide favored drug bindings leading to enhanced therapeutic effects at the cellular and molecular levels. The site-specificity provides higher drug concentrations, amplified signals for imaging purposes, and protection against secondary organs exposure [580]. The successful delivery of AuNPs, supported the delivery of temozolomide (TMZ), also as liposomes against induced lung cancer which demonstrated the superior drug distribution, deeper penetration of the dose, and probable synergistic actions of the AuNPs, TMZ, and the liposomes to produce therapeutic effects [592,593].

7 Nanovaccine delivery: COVID-19

NPs have been used for the delivery of anti-viral medications. Examples of AuNPs conjugated to certain viruses that successfully activate macrophages, interferon production, and enhanced anti-viral immunity are well known. The RNA and ferritin-based NPs were used as molecular chaperons to elicit strong T-cell responses toward promoting interferon production. The developed polymeric NPs injectable hydrogel system had the capability for sustained antigen release [594]. The hydrogel, which stabilizes

Table 7: Metals and synthetic polymer-based nanosystems

Payload	Carrier	Data value	Inferences on drug delivery	Ref.
Lucifer yellow	*p*-NIPAM	Particle size (250 nm)	NP monomer showed cell viability over 80% at a concentration equal to or less than 0.3 mg/mL	[104]
$FeCl_2{\cdot}4H_2O$	Magnetic NPs	Particle size (10–50 nm)	Magnetite NPs showed less toxicity on the living bacteria cells compared to control	[108]
Yeast strain, MKY3	Silver oxide	Particle size (10–50 nm)	AgNPs were confirmed by optical absorption, transmission electron microscopy, X-ray diffraction, and X-ray photoelectron	[117]
Fungal strain	Silver oxide	Particle size (20–50 nm)	Developed NPs produced high anti-bacterial potential	[118]
Cells-free extract	Gold	Particle size (10–20 nm)	Gold nanowires formed at the higher concentration of gold ions in the aqueous solution	[130]
Strain *Bacillus*	Silver	Particle size (10–60 nm)	Performed sequencing of 16S rRNA gene demonstrated the strain of isolated *Bacillus* as *megaterium*	[154]
Escherichia coli	Zinc oxide	Particle size (70 nm)	Increased inhibitory effect as the concentration of ZnO NPs increased	[156]
Nitrate Reductase	Silver	Particle size (10–25 nm)	Nitrate reductase-mediated synthesis of AgNPs from $AgNO_3$ was developed	[171]
Bacitracin Kanamycin	Silica	Particle size (50–100 nm)	Significantly improved the anti-*Staphylococcal* activity of bacitracin and kanamycin sulfate	[186]
Melatonin	PLGA, PEG	Drug loading (44–80%) Particle size (100–400 nm) Zeta potential (–32 mV)	The optimized NPs showed higher ocular tolerability in rabbit eyes using bio-microscopy	[539]
Triclosan	PLGA, PLA, CAP, PVAL	Drug loading (6.04 wt%) Particle size (82.4 nm) Zeta potential (–19 mV)	Triclosan released fast from NPs for periodontal treatment in dogs	[555]
Calcium phosphate	PLA–PLGA	Particle size (100–200 nm)	Significantly reduced the inflammatory cell infiltration in the vessel walls of rabbit iliac arteries relative	[577]

the antigen, was suggested to be made of a mixture of hydroxypropyl methylcellulose derivatives, HPMC-C12, and poly-(ethylene glycol)-*b*-poly(lactic acid). The antibody titers remained high against two common variants, B.1.351 (South Africa) and B.1.1.7 (United Kingdom). The single-dose vaccine doubled the dose of all the components and produced higher titers than the double-dose and two-dose single-component hydrogel group. The hydrogel-based vaccine has potential and the dose sparing will be helpful in difficult global transportation. In this context, it would be pertinent to discuss the development of a high-density microarray patch for delivering the SARS-CoV-2 vaccine through the skin patch, which resulted in stable and effective vaccine formulation [595]. Moreover, the prospects of QD and other nano-structured entities have the potential to be developed as biosensors to detect COVID-19 instead of the slow polymerase chain reaction technique. Toxicity-related issues are also at the forefront in the diagnosis and therapy of COVID-19 infections through nanotechnical means [596–599].

8 Safety and toxicological concerns

The understanding of the hazards and safety issues due to the use of nanomaterials has started to emerge explicitly. Both *in vivo* and *in vitro* toxicity evaluation methods are available. Functional and viability *in vitro* assays gauge the effects on cellular processes while the *in vivo* methods check for cellular level fatalities, mitochondrial damage, BBB destruction, cell viability, histocompatibility, tissue and organ damages, allergy, skin rashes, and overall adverse effects. The *in vivo* methods utilize animal models, that is, mice, rats, guinea pig, zebrafish, including oyster, fish, bacteria, and microalgae. The DNA synthesis and DNA damage, altered gene expression, immunogenicity, cell proliferation effects, exocytosis, hemolysis, apoptosis, necrosis, and metabolic and oxidative states changes, together with dose and LD_{50} effects are some of the *in vivo* conditions and parameters to evaluate the toxicity of nanomaterials [600].

The inherent characteristics of size, charge, high surface area to volume ratio, ability to pass through the cell membrane, ability to evade the immune system, enter the circulatory apparatus, reach organs and interact with biosystems have posed an enormous threat concerning toxicity generation and elicitation by nanomaterials. These materials and nano-scale metal entities are more toxic, and this includes arsenic, cadmium, other hazardous elements, and material nanostructures. Exposure to nanomaterials is almost unavoidable. The nanomedicinal and nanopharmaceuticals' threats are inherent in their latent toxicity, also resulting from dose mismanagement, drug adverse reactions, and nano-scale implications of the formulation. The understanding of the nanomaterials' effects on the body is critical before its clinical use. Nanotoxicology research has gained momentum and answers to safety and toxicity are being continuously investigated. The inhalation, dermal contact and ingestion, intravenous delivery, implants, and skin penetration for therapeutic purposes have provided nanomaterials entry to the body, to a maximal extent through the bloodstream, from where it reaches all vital organs, lymphatic areas, circulatory system, brain, lungs, liver, kidneys, gastrointestinal tract, tissues, and gonads (Figure 14). However, the extent and outreach concentration may differ based on affinity and accumulation of the nanomaterials in specific organs. The encountered biomolecules adhere to the surface of the exposed nanomaterials and generate protein corona, which was investigated with fluorescence correlation spectroscopy and AFM. The protein corona was formed by interactions of metal NPs, that is, gold, silver, and proteins. The metal oxide NPs induce oxidative stress, immuno-response, and apoptosis [601]. The polymeric nanomaterials, especially the nano-encapsulated, and the constituent polymers' toxicity is dependent upon the size, shape, dispersity, tunable properties, surface coating on the nanomaterial, shell's characteristics, and pay-load delivery mode and carrier [602,603]. There are ways to detect and determine the nanomaterials' cellular toxicity, oxidative stress, immuno-toxicity, genotoxicity, and cell death induced by the *in vitro* present NPs [604]. Among the suspected and serious toxicity, cellular and genotoxicity are prime concerns. In this context, the extra hazardous role of NPs, especially metal NPs cannot be overlooked, due to their catalytic character and high reactivity. The potential of toxicity and extent of exposure determines the risk assessment paradigm through the dose–response relationship [605].

8.1 Nano-entity sizes, cellular-uptake, and toxicity

The normal protective mechanisms of the biosystem do not provide an effective defense against nanomaterials. The macrophagic cells uptake larger PEGylated nano-entities more efficiently than smaller-sized nanomaterials. The accumulation of these nanomaterials is responsible for much of the nanotoxicity. The size of an NP has substantial effects on their interactions with living cells and

influences the absorption efficiency, and intracellular localization of the nanomaterial leading to adverse reactions and cytotoxicity. Despite extensive efforts, the reliable correlation between the cellular response(s) and NPs' size is not possible. Drawing broad inferences from a wide array of NPs and a complicated mix of biological probes is still untenable. However, the NPs' endocytosis occurs regardless of the particle size. The NPs' uptake differs based on the NPs' size and the cell type as well as the surface features of the cell. NPs in general are more likely to be internalized by passive uptake [606].

The size of NPs affects their circulation, biodistribution, and clearance. The size facilitates better intracellular absorption by passing through the openings of the tight junctions, and consequently, NPs have been delivered across the BBB to treat brain diseases, that is, Parkinson's, Alzheimer's, and gliomas. The medications encapsulated or tagged to NPs were quickly released, also owing to their concentration at or near the particle surface, in addition to their other encapsulation models, that is, core–shell. The smaller NPs have a longer $t_{1/2}$ than the larger ones [607]. The activation in the bloodstream cleared them from the body in a faster manner, which was being collected in the liver and spleen. A 50 nm size is the observed optimal size for cellular uptake as experimented in the thermodynamic models and several experimental tests. Additionally, NPs less than 20 nm penetrated the tumor. According to the observations on cellular uptake, 37 nm size had been suggested as the optimal requirement for MRI core diameter [608]. Figure 15 shows the reported optimum NPs' sizes for cellular uptake. Lipidic and polymeric NPs have a diameter range of ~100 nm entailed for internalization. The metal-based and polymeric NPs were recorded to have the size of 3–50 nm for cellular uptake [609–613].

The SPION were demonstrated to disrupt and suppress stem cell differentiation and activate the synthesis of signaling molecules, tumor antigens, formation of lysosomes, disturbed cell functioning, and are known to stimulate the synthesis of IL-8, an inflammation mediator. The SiNPs were also implicated in enhanced expressions of IL-1β and TNFα [614].

Another category of nanomaterials, the QDs are nano-sized (2–10 nm) particulate material, also considered artificial atoms, are semiconducting in nature, and possess fluorescent properties. The QD bonding through covalent and non-covalent interaction to the drug molecule for delivery and therapeutic purposes was achieved by passive transport, facile delivery, and active transport. The QD outer shell surface provided conjugation increases aqueous solubility and reduces the toxicity of the QDs. The QD toxicity was found to be dependent upon the size, material used for production, dose, mode of administration, and the chemical composition of the outer capping.

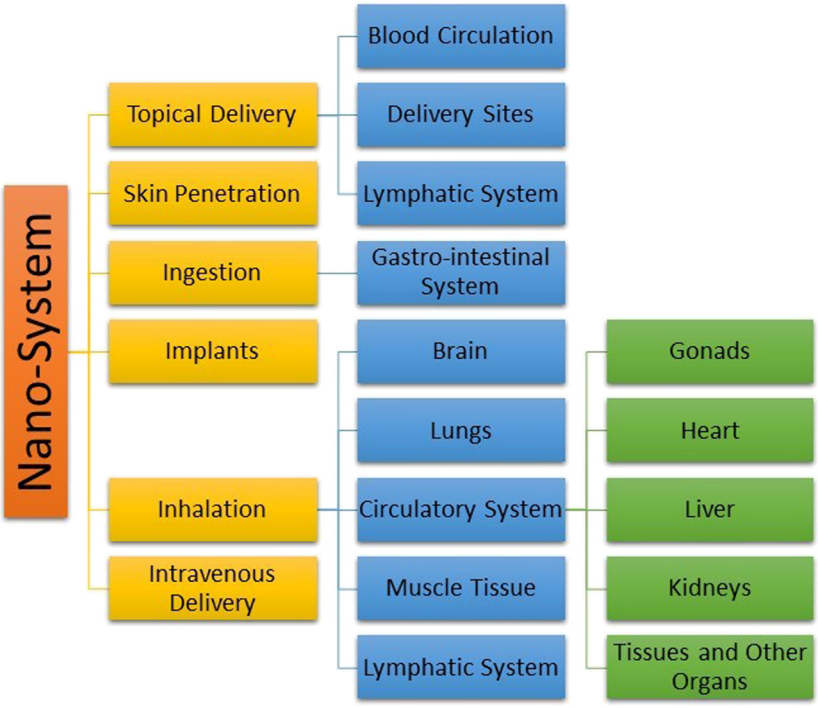

Figure 14: Nanosystem exposure routes and uptake organs.

The QD toxicity was considered to be generated due to the leakage of free metal ions, for example, cadmium, and arsenic, upon oxidative stress. The QDs were absorbed by mitochondria, cause changes in organ histology, and malfunction [615,616].

The toxicity of CBNs, single and multiple-walled CNTs, graphene, reduced GO, and other graphene-based nanomaterials have also been conjectured of probable adverse reactions and were investigated for interactions with the biological environment, toxicity in Caco-2 and MCF-7 cell lines, and their involvements in organ toxicity [617–624]. Formation of protein corona on the graphenes materials' surface, flocculation and aggregation in the tissue and organs' site owing to the colloidal nature of this genre of nanomaterials, and immunological and inflammatory responses by biological entities, organs, and tissues to the graphenes entities, membrane toxicity, disruptions, mutagenicity and suspected genotoxicity, and accumulation in organs were recorded. The graphene toxicity depends on their lateral size, dose, and surface charge. The toxicity has been contained with polymeric conjugation, coating, imprinting, and embedding in biocompatible polymers, that is, CS, PEG, ethylene-diamine-modified-poly-isobutylene-maleic-anhydride, polyurethane, PEI, PPI, and PAMAM and their derivatives, wherein some of these polymers supplement in the delivery of the drugs and gene, and are uptaken by cells for therapeutic purposes [625–631]. The materials also promote cell growth, attachment, and damage. The GO caused a decrease in cell viability and was responsible for inducing mutagenesis [632] and lung injury through autophagy [633]. Doses >10 mg/mL were suggested to lead to acute lung injury and cause chronic pulmonary fibrosis [634]. Critical analysis of graphene materials' toxicity [635], reviews observing the toxicity [636,637], and recent information (ca. 2020) on toxicity data [638] are available to chart further course in nanomaterial toxicity and adverse impact in conjunction with the delivery of the material and targeting in therapeutics and diagnosis in the biomedical field.

8.2 Nanomaterials and organ toxicity

The organs outreach and biodistribution of the nanomaterials to different sites produce a number of disease conditions. Neurological disorders including Alzheimer's and Parkinsonism's, asthma, bronchitis, emphysema, and cancers in the brain and lungs are suspected. The circulatory system and heart were pointed for atherosclerosis, vasoconstriction, and arrhythmia, and death, respectively. Kaposi's sarcoma of the lymphatic system, glomerular swellings, renal cells necrosis, Basilar membrane thickening in the kidneys, allergy, itching, dermatitis, and auto-immune diseases are suspected to have developed from the skin and topical implants nanomaterials interactions. Crohn's disease and colon cancer in the gastrointestinal tract, tissue degeneration, stromal cells damage in bones, ovarian lesions, sperm abnormality in gonads, and sequestration, accumulation, sub-cellular damage, inflammation, oxidative damages to the liver are known (Figure 16) [639–641]. As for the nanomaterial toxicity to reproductive organs is concerned, the liver and reproductive system toxicity have been studied in detail. Females

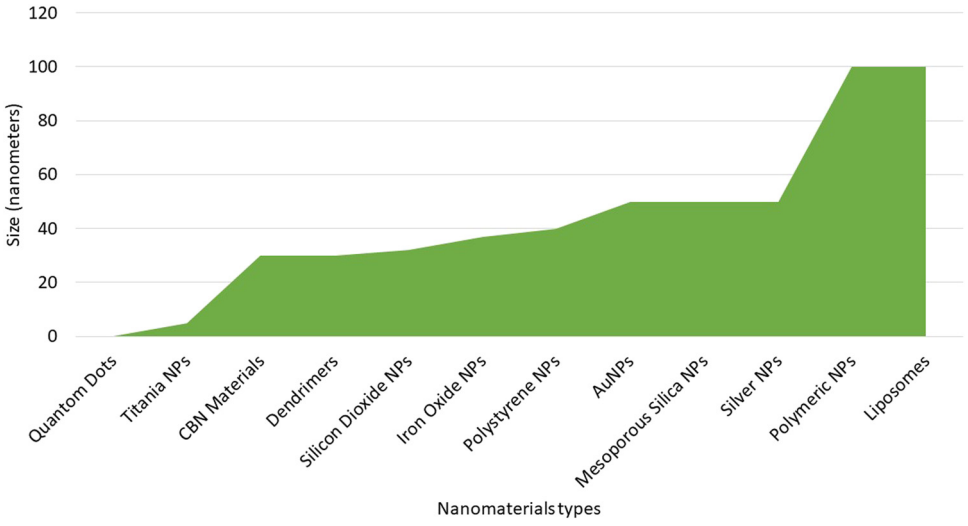

Figure 15: Comparative nano-scale (optimum) sizes of various nano-carriers for cellular uptake.

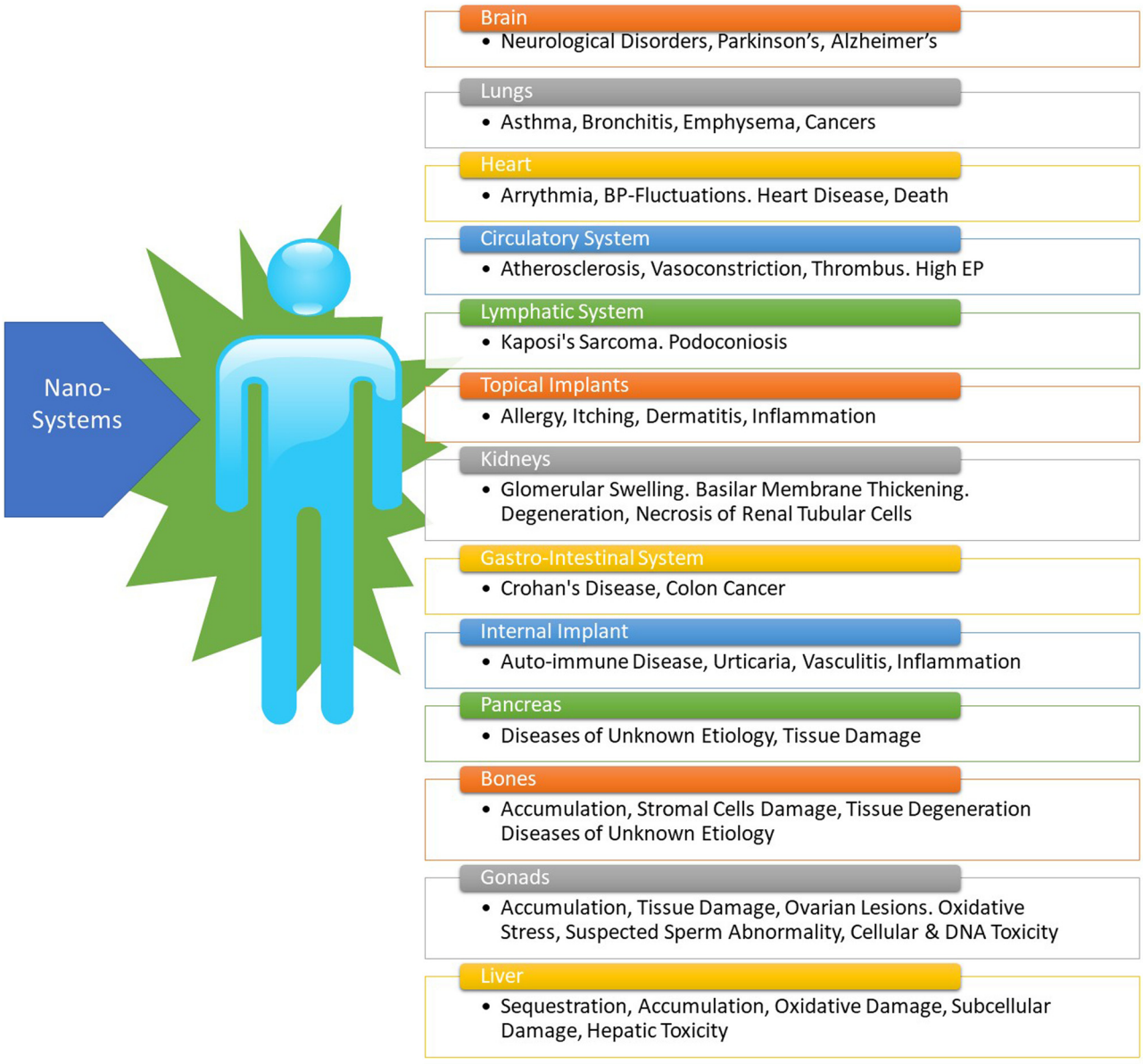

Figure 16: Suspected and confirmed diseases from nanomaterial uptake.

were reported to be more vulnerable to toxicity affecting the reduction capacity and fetal development. The germ cells in men were particularly affected which included the testis. As for the nanomaterials' toxicity to reproductive organs is concerned, liver and reproductive system toxicity were studied in many details, and the females were reported to be more vulnerable to toxicity affecting fetal development. The germ cells in men are particularly affected. The toxicity was related to the nanomaterial types, their concentration, route to reaching the reproductive system, and the animal species. The impact on the primary target organs (first encounter and impact) and the secondary organs is decisive in the toxicity elicitations. Toxicity generated with metal and metal oxides and polymeric nano-entities is well-recorded [642–644].

The toxicity of lungs by nanomaterials leading to bronchitis, emphysema, cell necrosis, and cancer is thought to be caused by alveolar-I type cells membrane perforation, inflammation, nano-particulate matter's cell entry, membrane lipid peroxidation, cell membrane high fluidity, and generation of ROS. The nano-entities ~50 nm sizes and the QDs perforate the membrane much easier and cause severe damage. The nanomaterial toxicity leads to interferences with cell differentiation and protein synthesis,

disrupts intracellular transport, cell migration, tubulin polymerization, formation of adhesive complexes, damage to the cytoskeleton, and neovascularization [645].

The primal involvement with the liver which accumulates and sequesters up to 30–99% of all the administered larger-sized (>100 nm) NPs through the systemic circulation, in turn, lowers the nanomedicine, nano drug-delivery quotients to the intended organ, and thereby introduces liver toxicity. Typically, a ratio of under 5% nanomaterials, especially NPs, was delivered to the intended diseased site. The Kupffer cells, endothelial, hepatocyte, and other cellular masses of the liver were found to be involved in producing liver toxication [646]. The liver damage is caused by elimination of Kupffer cells, increase in cytokine release, TNF-α, and IL-1 involvement. The engagement of various receptors and biomolecules including the hepatic proteins and disturbances to the hepatic metabolism are undertaken during the process involving the nanomaterial interaction. Internal toxicity removal involves renal, hepatic, and mononuclear phagocytic systems. Depending upon the type and composition of the nanomaterial, which includes zinc, gold, silica, manganese, iron, and cadmium, silver citrate and gadolinium were variably excreted into the bile, and from there are transited through the bile ducts, and to the small intestine for excretion. The metal and metal oxides inorganic NPs with biocompatible surface chemistries with and without biodegradable, nearly surface interaction neutral nanomaterials were eliminated intact. The degradable nanomaterials form aggregates, reduced-sized remnants, ionic disposition as well as metal–protein complex to be removed [647]. The contribution of polymeric nanomaterials, including

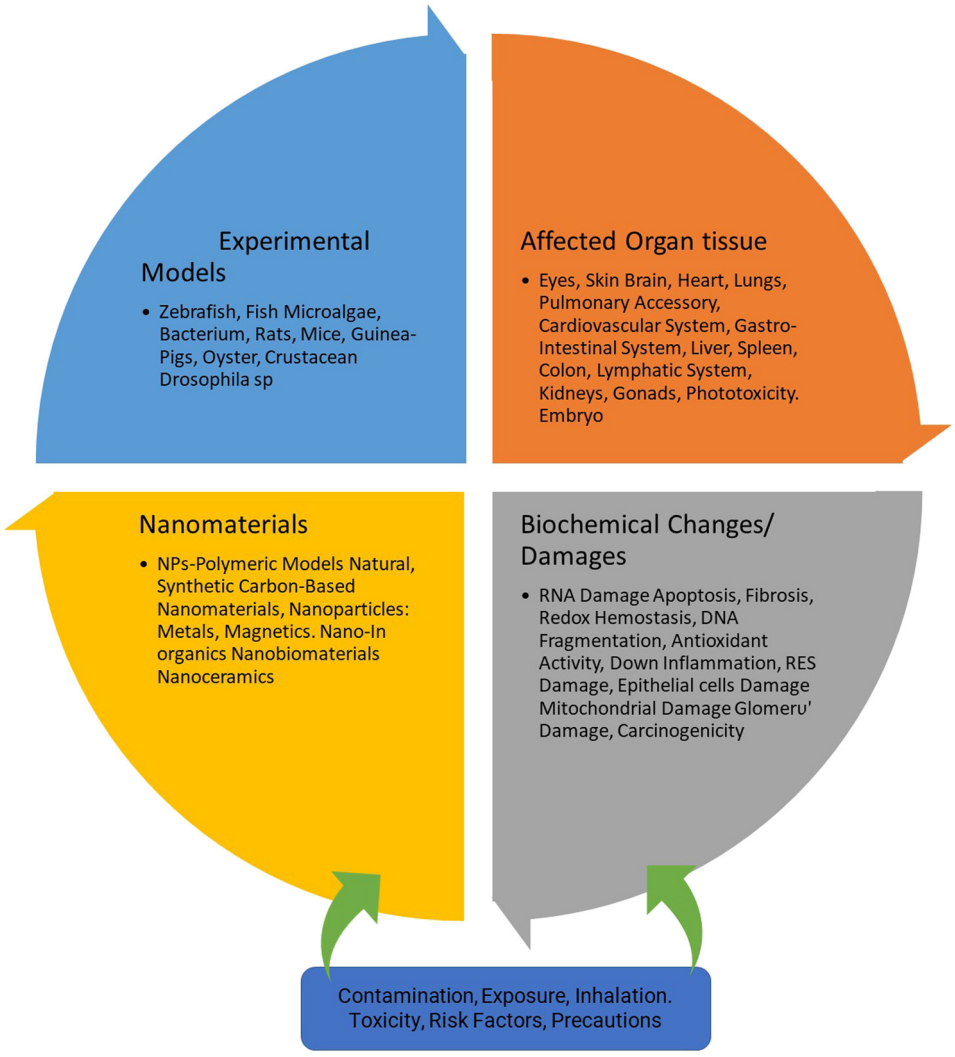

Figure 17: Toxicity cycle components for nanotoxicity causative factors, experimental evaluation vehicles, organs, and tissues toxicity, and probably effected biochemical changes and observed damages.

Table 8: Major commercial nano-products

Company	Product	Drug and carrier	Therapy	Significance
AMAG	Feraheme™	*Ferumoxytol*: SPION–PGSCME	Iron-deficient chronic kidney failure	Prolonged, and decreased dose release
Amgen	Neulasta®	Filgrastim: PEG–GCSF protein	Neutropenia in oncotherapy	Plus protein stability
Acorda	Zanaflex®	Tizanidine HCl: nanocrystals	Muscle relaxant	Increased availability, decreased dose
Biogen	Plegridy®	Interferon-β1a: PEG	Multiple sclerosis	Improved stability
Bausch & Lomb	Visudyne®	Verteporfin: liposome	Myopia	Enhanced site-directed photosensitive delivery
	Macugen®	PEG-Aptanib: PEGylation	Macular degeneration; neovascular-aging vision loss	Improved stability
Celgene	Abraxane®	Taxol®: ALB NPs	Breast cancer; non-small cell lung and pancreatic cancers	Enhanced site-specific delivery
Chiesei Farma	Curosurf®	Proteins SP-B and SP-C: liposome	Stress disorder, respiratory distress syndrome	Decreased toxicity, increased delivery
Enzon	Oncaspar®	L-Asparaginase: PEG	Acute lymphoblastic leukemia	Improved stability
Eagle Pharma	Ryanodex®	Dantrolene sodium: nanocrystals	Malignant hypothermia	Higher dosing
Galen	DaunoXome®	Daunorubicin: liposomes	Kaposi's sarcoma	Increase delivery, decrease toxicity
Genetech	Pegasys®	*Interferon*-α2a: PEG	Hepatitis B and C	Improved stability
Gilead Sciences	AmBisome®	Amphotericin B: liposomes	Infections; fungal, protozoal	Reduced nephrotoxic
Hoffman-La Roche	Mircera®	Meth-PEG: β-epoetin	Anemia due to renal failure	Improved stability
Janssen	Doxil®	DOX–liposome	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	Increase delivery, less toxicity
	Invega®	Paliperidone palmitat: nanocrystals	Schizophrenia	Controlled release
Lupin Atlantis	Tricor®	Fenofibrate: nanocrystals	Hyperlipidemia	Increased availability
MagForce	Nanotherm®	IONPs: amino silane coat	Brain tumor	Heat therapy to destroy tumor cells
Merck	PegIntron®	*Interferon*-α2b: PEG	Hepatitis C	Improved stability
	Emend®	Aprepitant: nanocrystals	Anti-emetic	Increased absorption, and bioavailability
Merrimak	Onivyde®	Irinotecan: liposomes	Pancreatic cancer	Increased delivery
Nanopharm Cermisphere	Nanocomposite Patch	Lidocaine: SiNPs	Topical delivery, wound management	Faster pain relief
Novavax	Estrasorb™	Estradiol: micelle	Menopause hormonal therapy	Sustained release
Onco TCS	Marqibo®	Vincristine: liposomes	Acute lymphoblastic leukemia	Increase site-specific delivery, less toxicity
Pacira Pharma	DepoDur®	Morphine sulfate: liposomes	Prolonged release	Post-operative loss of pain
Pfizer	Somavert®	PEG-visomant HGH receptor antagonist	Acromegaly	Improved stability
QLT Ophthalmics	Visudyne®	Verteporfin: liposome	Ocular diseases, macular degeneration	Improved retention time
Sanofi	Renagel®	Sevelamer HCl/CO_3-poly(allylamine) HCl	Chronic renal diseases	Increase delivery and circulation time

(*Continued*)

Table 8: *Continued*

Company	Product	Drug and carrier	Therapy	Significance
Sanofi Aventis	INFeD® Iron; Dexferrum® Iron	Iron dextran (low and high MW)	Chronic kidney failure with iron deficiency	Increased dose-load
Sigma-Tau	Abelset	Amphotericin-B: lipid liposome	Anti-fungal	Reduced toxicity
	DepoCyt©	Cytarabine–liposome	Lymphomatous meningitis	Increase site-specific delivery, lesser toxicity
	Adagen®	Pegademase bovine–PEG–adenosine deaminase enzyme	Immunodeficiency disease	Improve circulation time lesser immunogenicity
Stryker	Vitoss®	Calcium phosphate–nanocrystals	Substitute for bone	Bone structure mimic by cell adhesion, growth
Teva	Copaxone®	Glatopa–AA copolymer	Multiple sclerosis	Regulated clearance
Tolmar	Eligard®	Leuprolide acetate: PLGA	Prostate cancer	Prolonged delivery and circulation time
UCB	Cimzia®	Certolizumab: PEG	Crohn's disease, rheumatoid arthritis, spondylitis	Increase stability and circulation time
Wyeth	Rapamune®	Sirolimus: nanocrystal	Immunosuppressant, transplant rejection	Increased bioavailability

AA copolymer: L-glutamate, L-alanine, L-lysine, and L-tyrosine random copolymer; GCSF, granulocyte colony-stimulating factor; nanocryst, nanocrystal; PGSCME, poly gluco-sorbitol carboxymethyl ether.

synthetic and naturals, to oxidative stress, inflammation, genotoxicity, reproductive gonadal toxicity, and hemocompatibility is mediated through various biochemical route disturbances, receptor interactions, and enzymatic reactivity at the polymeric nanomaterials interaction sites. Both *in vivo* with different animal models and *in vitro* toxicity evaluations against a number of cell lines, biochemical substrates, and corresponding biomarkers have been reported [602–604].

Toxicity evaluations, concepts and requirements in preparative designs, size and shape control, materials' characterizations, biodistribution, metabolism, degradation, and degradant interactive potential, pharmacokinetics interactive trends in toxicity elicitations, the toxicokinetics, interactions at the site and during transport, and systemic and body clearance are among the details that contribute toward designing safer nanomaterials. The starting springboard to formulation development is embedded in the toxicity generation understanding whereby the safety-by-design approach, molecular modeling, computational assessment, and methodically safe-by-design approach are worth mentioning [648–650].

The RES blockages by nanomaterial design-approach preparation, especially for liposomes, have been reported to increase the nanomedicine's efficacy [651].

A toxicity cycle depicting components of nanotoxicity causes, experimental evaluation vehicles, organs, and tissues toxicity, and probably effected biochemical changes and observed damages from the nanomaterial exposure are illustrated in Figure 17.

9 Nano-based biomedical commercial products

Nanotechnology has tremendous commercial value, and the global nanomedicine market is expected to reach US $261 billion by 2023. Major nano-medicinal and nanopharmaceuticals segments are drug delivery and therapeutics, imaging, implants, nano-devices, regenerative medicine, topical formulations, and vaccines. The category of products represents all pathological classes including for oncology, cardio-vascular system (CVS), infections, orthopedics, neuronal diseases, urology, ophthalmology, and immunity boosters. A number of major products available in the market are listed (Table 8), which is not a comprehensive listing since products are continuously under development, clinical trials, and patenting where the liposomal formulations are a major share [652–654]. About 1,121 products from 414 companies and 45 countries are listed at the nanotechnology product database [655] either under nanomedicine categories, which are approved or under clinical evaluations. The emulsion, liposome, and oncological products dominate the market share. Diagnostics and bone substitutes form the major part of applications for commercialization purposes [656].

10 Conclusions and prospects

Nanostructured materials vary in characteristics and applications due to their inherent starting raw materials' physicochemical properties, intricate preparation methodologies, and on-demand designated surface functionalization to impart the designed characteristics and site-directedness, together with biocompatibility and biodegradability to the nano-scale functional materials. The use of natural and synthetic polymeric raw materials has immensely contributed to the biocompatibility and biodegradable behavior of nano-carriers. The metallic, non-metallic, and hybrid, that is, metal-polymer and non-metal-polymer, nano-structured entities have provided properties-by-design characteristics to specifically targeted, singular, and multiple-use nanomaterials, both in delivery for diagnosis and treatments. The first generation (simpler, non-functionalized), and second-generation (singularly functionalized) nano-carrier have gained ground in advancements with the preparation and bioapplications on experimental and clinical settings. The third generation nano-carriers (doubly functionalized) for simultaneous site-specific and trigger-response mechanisms upon delivery are coming of age, and extensive preparation techniques modification and developments have taken place, together with bioapplications which are in an advanced stage of improvement and expansions. The multiply functionalized dual-use, both for therapeutic and diagnostics purposes nano-carriers are starting to take shape in the realm of preparation, functionalization, and applications. The fourth-generation nano-carriers have attained the characteristic of crossing over bio-barriers, which is a critical future need.

Further developments for various types of nano-carriers, that is, CNTs, graphene roll-up, molecular cages, proteins, antigen–antibody, and hetero and homo polymer-based attached and embed, as well as encapsulating nano-structured materials are the areas needing further attention according to the delivery specifics for the tissue, organs, and disease conditions. Another area needing attention is to address the development drawbacks of reproducible bulk synthesis of nanomaterials, much required for clinical evaluations, and subsequent commercialization.

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