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Biomedical Applications of Intelligent Nanomaterials

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Abstract

Intelligent nanomaterials can make dramatic changes in interdisciplinary medicine. They have versatile biomedical applications that are discussed in this chapter. Typically, this chapter focuses on five groups of intelligent nanoparticles and nanocomposites, including polymeric, lipid-based, carbon-based, metallic, and hybrid materials. In each group, available nanomaterials are introduced according to their ability to be controllably responsive to the alteration of pH, light, temperature, stress, moisture, electric/magnetic fields, and other external stimuli. Finally, the applications, limitations, challenges, and future trends of these nanostructured materials are discussed.

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1. Introduction

New materials are being developed at an increasing pace to lay the foundation for new advances within the realm of industry as well as medicine. Throughout history, biomaterials have been used to treat diseases and improve health. Some of the first biomaterials included gold for use in dentistry, while other examples include wooden teeth and glass eyes [1]. Also, with the development of research and technology, nanosized particles were developed. Nanoparticles are materials of 1—100 nm in size and have the potential to carry imaging agents, molecular drugs, nucleic acids, and other constituents [2, 3]. Ancient Egyptians exploited the use of nanotechnology, but the scientific experimentation and understanding of nanomaterials came to fruition in the late 1900s. At nanoscale proportions, materials will express different characteristics than their counterparts in larger dimensions, thus allowing for use in biomedical engineering applications such as drug delivery, DNA labeling, and cancer therapy [4]. On the other hand, intelligent nanomaterials were introduced, providing additional functionalities to the material and becoming more useful and desirable under specific circumstances. External stimuli can induce rapid and reversible changes in the nanostructure of the particle, such as the behavior in an aqueous environment. Once the stimulus is removed, the nanoparticle is able to return to its original state [5]. Thermo-sensitive and pH-responsive nanoparticles have been used extensively; also, the conversion of nanoparticles into nanocomposites makes their application in nanomedicine more valuable [6]. The addition of smart ingredients can ultimately transform the nanoparticles into permeation enhancers, guide site-specific accumulation, and provide dynamic control [7].

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Stimuli-responsive polymers have been of great interest in medicine for controlled drug release, cell adhesion mediators, and enzyme function controllers as well as gene expression. Solid lipid nanoparticles (SLNs) have also been used for controlled drug delivery, initiated by transformation from a- to ß-forms by means of a built in a trigger system [8]. Lipid-based nanostructures have shown the least toxicity for in vivo applications. A number of intelligent gels have been developed and can respond to prompts such as changes in pH, temperature, and even specific molecules in the body including glucose. Such systems may be valuable in areas of endocrinology and treatment of diseases such as diabetes. For instance, some provide a direct feedback, causing insulin to be delivered in response to detected excess in glucose [9]. Healthcare relies heavily on the development of new materials. Intelligent nanomaterials are being investigated for use in diagnoses, screening, imaging, and regenerative medicine. Biodegradable intelligent nanomaterials are being looked at for biomedical applications in vivo, including temporary implants, carriers for drug delivery and tissue engineering scaffolds. Polymer-based nanoparticles have been shown to be advantages in permeability and retention and thus are good candidates for drug delivery systems. Different polymeric systems exist including poly D,L-lactide-co-glycolide (PLGA), polylactic acid (PLA), polycaprolactone (PCL), chitosan, and gelatin.

Shape memory metallic alloys have also been considered as promising intelligent materials due to their function as sensors and actuators [10]. They can be integrated in textiles to provide multifunctional garments in several health care or common applications. One such example includes Nitinol wires used in recovering any shape and becoming superelastic. Nitinol has also been explored for use in medical, biomedical engineering and micro-electromechanical systems (MEMS) applications. Such intelligent metals have been

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recognized for use in orthodontic wires and vascular stents in addition to several other applications. Additionally, buckminsterfullerene (C60) and carbon nanotubes (CNTs) have been shown to undergo rapid, reversible changes in conformation and properties in response to minor changes in their surrounding environments [11]. Carbon nanostructures have benefits of low toxicity and biocompatibility. Thus, intelligent carbon nanomaterials have been used in various fields including biomedicine, bioimaging, energy conversion optical devices, and drug delivery.

Today, an important area of development is composite-nanostructured systems. One such example is incorporating shape memory materials into other functional materials to form hybrid composites, in which there would be benefits from each individual material. Shape memory alloys alone have an inferior dynamic response and low efficiency. However, ceramics such as piezoelectric have a superior dynamic response, although their displacements are small and many of them are very brittle. Thus, a system of shape memory alloys and piezoelectric ceramics can form smart hybrids that generate a larger displacement than the conventional piezoelectric ceramics and have the improved dynamic response, compared to monolithic shape memory alloys [12]. The design of such systems demands an optimized specificity to attain controlled functionality and biocompatibility [13]. Hybrid nanostructures as intelligent stimuli-responsive systems have been recognized for their use in nanomedicine as drug delivery carriers, theranostics, and imaging agents.

In this chapter, we focus on the introduction and medical applications of polymeric, lipid-based, carbon-based, metallic, hybrid, and composite nanostructures.

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2. Polymeric Nanoparticles

2.1. General Features

Several decades ago, drug delivery mechanisms were improved by nanoparticle encapsulation and delivery, which would result in sustained release and efficacy [14]. Because of primitive complications following delivery, such as rapid clearance, surface modification was necessary to improve clinical outcomes [15]. Surface modification is especially advantageous in oncological treatments because it can enhance the selective uptake capability of the delivery system in targeting of tumors [16]. In this regard, polymeric compositions help to reduce adverse physiological effects [17]. Ease of surface modification gives polymer-based nanoparticles a distinct advantage, which has drawn the attention of many scientists [18].

Enhanced permeability and retention (EPR) are a quality of nanocarriers, which has made them more suitable for certain medicinal areas [19]. Targeted accumulation, for example, can manifest a large concentration of therapeutic agents within the hydrophobic polymeric nanoparticles, due to localization near a specific site of pathology [20]. Water-insoluble agents can become encapsulated in the polymeric micelle surrounded by its hydrophilic shell, allowing the drug delivery system to travel through blood and other aqueous media [21].

Swelling also has a significant effect on drug release rate [22]. Mechanisms of drug release include swelling from the osmotic effects of the aqueous environment followed by enzyme-induced rupture, leading to drug release; however, the final end result of nanoparticle targeting depends on specific physical characteristics [23], where characterization of these systems are accomplished by advanced microscopy techniques [24]. Loading capacity and drug release are dependent on the chemical nature of both drug and polymer [25]. Scientists

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can deduce the binding rate from adsorption isotherms [26]. Moreover, the manipulation of polymer matrices can change the drug release action, and a direct proportion exists between loading and release [27]. Copolymer blending can similarly be used to control the release [28]. The overall goal of nanoparticle delivery should direct particle size and encapsulation efficiency [15].

The therapeutic potential of polymeric nanoparticles and evidences behind their clinical efficacy allow them to be widely focused on in both academic and industrial nanomedicine. Being the most prevalent nanoparticle in therapeutic applications, their promise is evident in oncology, immunology, endocrinology, orthopedics, and dentistry [29]. These biodegradable carriers have been frequently used as drug delivery systems [30]. The efficacy of anticancer drugs against tumors is enhanced by nanoparticle encapsulation [31]. The intelligent nature of these nanoparticles promotes structural self-assembly into a micellar form with polymers of different degrees of hydrophobicity [32]. The hydrophobic component of micelle functions in pharmaceutical delivery stabilizes the structure in blood as a result of steric protection [33]. Intelligent, polymeric nanocomposites can furthermore be stimulated for drug release as a result of external stimuli, such as pH or temperature change [29]. The co-delivery of multiple drugs or combination therapy is also possible, following polymeric nanoparticle synthesis [34]. Biodegradable polymeric systems exhibit controlled and sustained release, are safe and nonimmunogenic and can undergo encapsulation for nanodelivery [35—37].

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2.2. Poly-D,L-lactide-co-glycolide

PLGA is an effective, synthetic nanoparticle that undergoes enzymatic hydrolysis to produce metabolic products that are nontoxic [26]. Synthetic polymer nanoparticles have a dramatic effect on the improvement of sustained release compared to natural polymers [20]. They have demonstrably been incorporated in the development of bone implants and screws [38]. Nanoprecipitation is the most common method of synthesis for this type of polymeric nanoparticles [39]. This polymer is frequently blended with alginate or chitosan to form a composite which is useful for nanomedicinal purposes and commercialization [40-42]. PLGA was approved for human use by US Food and Drug Administration (USFDA), especially in therapeutic anticancer treatments [15]. Insulin-loaded PLGA nanoparticles as well as the incorporation of haloperidol, a drug used for acute psychosis, show a broad spectrum of therapeutic applications [43, 44]. Furthermore, bacterial infections, such as tetanus, and post-menopausal hormone therapy are relevant examples of PLGA nanoparticle encapsulation and drug delivery [45, 46].

2.3. Polylactic Acid

PLA is a biocompatible, polymeric nanoparticle that can be prepared by solvent evaporation [47]. Its role in antipsychotic drug encapsulation efficiency is notable, an increased efficiency of approximately 95%, and supported by both in vitro and in vivo neuroleptics [48]. PLA can drastically improve the blood circulation time of oridonin, which targets malignant lymphoid cells for apoptosis [49]. Although no considerable advantage was seen by its use, encapsulated PLA was used in pharmacological intervention in restenosis [50].

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2.4. Polycaprolactone (PCL)

PCL, which is commonly synthesized by nanoprecipitation, is the most profound case in long lasting implantable instruments, because of its slow rate of degradation [26]. Similar to the aforementioned polymeric nanoparticles, PCL is efficacious in cancer treatments and improves both drug release time and sustainability, in addition to the encapsulation efficiency of Tamoxifen [51]. It has been also used a carrier vehicle for insulin with a positive glycemic response that preserves the hormone's bioactivity, ultimately proving extremely useful for diabetics [52]. Amphotericin B (AmB) can cause fungal cell death, but may also induce toxicity. PCL nanoparticle encapsulation with AmB not only increases the effectiveness of the drug by sustained release but lowers also the associated toxic side effects [53].

2.5. Chitosan

Chitosan is a natural polymer derived from exoskeletal chitin from arthropods, and methods of its synthesis include ionotropic gelation and microemulsion [35]. It has been noted that chitosan remarkably increases the absorption of insulin from gastrointestinal tracts after encapsulation with hormone [54]. Nasal absorption of insulin was also enhanced in a rat model when delivered in encapsulated chitosan nanoparticles [55]. Gastrointestinal abnormalities, such as ulcerative colitis and Crohn's disease, can be targeted by cyclosporine A (Cy A) inhibition of T-cell activation and a subsequent autoimmune response. Chitosan has been effectively used in combination with the Cy A [56]. Furthermore, systemic immunological responses targeting Diphtheria toxoid (DT) were greatly enhanced during in vivo applications, as reported by van der Lubben et al. [57]. Chitosan-based nanoparticle

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applications in the literature are widespread and indicative of proven results in the treatment of various pathologies, including ocular delivery and anticancer therapy [58].

2.6. Gelatin

The nontoxic and bioactive behaviors of gelatin, in addition to its widespread use in food products, make it appealing for nanomedicinal uses [26]. It is derived from the degradation of collagen protein [59]. Gelatin is a hydrophilic polymer that can swell in an aqueous environment and is prepared with a variety of techniques, including desolvation and emulsion [60]. Drug loading is achieved by incubation in the gelatin solution for a certain period of time [61]. The biphasic drug release is characterized by initial, rapid burst release, followed by sustained release as a result of slow diffusion [15]. Bovine serum albumin (BSA) encapsulation maximizes the water absorption capability of gelatin nanoparticles to approximately 70% [62]. Anticancer and anti-HIV drugs have been also encapsulated in gelatin nanoparticles [63, 64]. These polymeric nanoparticles, in particular, are able to attach to tumorigenic cells in a specific ligand—receptor interaction [65]. Because of the abundance of collagen present in the eye, ocular drug delivery is another application of gelatin-based nanoparticles, improving both stability and corneal penetration because of the polymer's electrostatic interchange with mucin [59, 66]. It also holds tremendous promises in the delivery of genes and peptide drugs [62].

2.7 Potential and Challenges

Several other polymers have been synthesized as nanoparticles with the competence to serve as drug delivery systems. Despite not incorporated in humans due to its toxic byproducts,

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poly-alkyl-cyano-acrylates (PAC) encapsulation of antibacterial and anti-inflammatory drugs is possible [67, 68]. With respect to the anticancer drug Ftorafur, encapsulation leads to sustained release and larger loading capability [69]. Albumin is capable of encapsulating liphophilic drugs and was approved for treating metastatic breast cancer approximately a decade ago [70]. The histopathology of a tumor mediates uptake of nanocarriers [71]. The abundance of albumin in the circulatory system is advantageous in its use as a tumor detection vehicle and drug delivery in the central nervous system as it can cross the blood—brain barrier [72, 73].

Although many therapeutic advantages exist for polymeric nanoparticle delivery, limitations currently serve as an obstacle for the systems' maximum potential. For instance, problems with encapsulation efficiency and other physicochemical properties limit the full use of synthetic polymers, such as PLGA [74]. Loading efficiency, combination therapy, biocompatibility, potential toxicity, sustained release rate, and clinical applications are all factors that need to be taken into account when measuring drug suitability for patient uses. Despite potential challenges, the wide variability in physiological targeting gives polymeric nanocarriers tremendous attention.

Research is growing in the applications of polymeric nanoparticles in the treatment of disease. Surface modification remains a rampant technique to improve the polymer's applicability in the human beings. Surface modification has allowed these delivery systems to cross the blood—brain barrier [75]. Potential has been seen in the prevention of restenosis in postoperative recovery [76]. Vast anticancer therapy and lymphatic targeting have attracted attention [77]. Drug regimens given to eradicate pathogenic gastrointestinal bacteria can be lowered because nanoparticles can increase efficacy and mucoadhesivity [78]. Lastly,

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lungs can serve as an effective site of drug delivery in nanoparticle systems, given their vascularity, mucosal permeation, and surface area [79]. The versatility of the aforementioned systems and their desirable properties are continuing to improve the field of nanomedicine [15, 80].

3. Lipid-based Nanoparticles

3.1. Different Types

In the past decade, nanoparticle systems significantly influenced the development of pharmaceutical carriers. Liposomes [81], niosome [82], micelles [83], polymerosomes [84], dendrimers [85], nanoemulsion [86], aptamers [2], carbon-based nanostructure [87], metallic nanoparticle [88], etc. have been developed for therapeutic and diagnostic applications in a variety of diseases including cancer. Clinical success in drug delivery systems needs to include some important parameters: physical and biological stability, loading efficiency, drug release profile, and, most importantly, minimum toxicity. Among all types, lipid-based nanoparticles show the least toxicity for in vivo applications. Lipid-based nanoparticles mainly include: liposome, niosome, micelle, nanoemulasion, and SLNs.

Among the various lipid-based formulations, liposomes are one of the most traditional. Liposomes and niosomes are self-assembled colloidal systems obtained by hydration of amphiphilic molecules above the phase transition temperature. To increase the bilayer stability and reduce aggregation, cholesterol and charged phospholipids are often added. Ihe commonly obtained type of vesicles includes: multilamellar vesicles, unilamellar vesicles, and multivesicular vesicles. Due to their biocompatibility and capability of loading both

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hydrophilic and lipophilic drugs, vesicular drug delivery systems are widely used in the pharmaceutical fields [89]. Another colloidal systems is micelles. Micelles are the simplest molecular assembly formed by amphiphilic molecules. Liposomes are composed of lipid bilayer, while micelles are closed lipid monolayers with a fatty acid core and polar surface. The micellar shape can be changed from spherical to ellipsoidal or rod like. Micelles can be mainly divided into three categories: lipid micelles, polymeric micelles, and lipid—polymeric hybrid micelles. Lipid micelles are formed from small amphiphilic molecules of surfactant [90]. Amphiphilic block copolymers can form polymeric micelles, and lipid-polymeric hybrid micelles are composed of amphiphilic lipids, which may be advantageous in both of them [83, 91, 92].

In comparison with liposomes, niosomes and micelle nanoparticles, SLNs introduced in the early 1990s represent an alternative carrier system to the traditional colloidal carriers discussed above. SLNs offer the following advantages: ease of preparation, low cost, long-term physical stability, and versatile chemistry. The preparation of SLNs can be achieved by micro-emulsion, high-pressure homogenization, W/O/W double emulsion, ultrasonication, and solvent-evaporation methods [93]. SLN mainly offers slower drug mobility than liquid systems like nanoemulsion. Eventually, nanoemulsions consist of a fine oil-in-water continuous phase, with nanosized droplets in the range of 10—100 nm in size [94]. Long-term stability, high solubility of drug molecules, and ease of preparation make them versatile as a drug delivery tool [95]. The methods of nanoemulsion formulation generally require a "high-energy" process, such as ultrasonication or high-pressure homogenization, to break down the large droplet to a smaller size [86].

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3.2. Applications

Stimuli-sensitive drug delivery nanocarriers have received a great deal of attention, due to the fact that they can deliver the cargo at the desired time and to the desired location. The mechanism of triggering, mainly due to the pathological changes, occurs in tissues [96]. Tumorigenic regions demonstrate a lowered pH [97], higher temperature [98], greater redox potential [99], and particular enzymes. These parameters are called "intrinsic stimuli" since there are local stimuli within the tumor tissue. On the other hand, drug delivery systems take advantage of induction in the desired region by externally applied stimuli, including temperature change, magnetic fields, ultrasounds or near-infrared (NIR) light, which are referred to as "extrinsic stimuli" [100].

3.2.1. Intrinsic Stimuli

The importance of pH-sensitive nanoparticles encompasses their ability to deliver the cargo drugs to the site of pathology. Diseases wherein pH-sensitive drug delivery systems are promising include: peptic ulcers, asthma, and cancer [101]. This can be achieved by two strategies: using polymers containing at least one ionizable group undergoing conformational or solubility changes in the response to environmental pH changes, and designing polymeric systems containing acid-sensitive bonds undergoing break-down to achieve pH-assisted on-demand control release [84]. Other pathological changes in tumorigenic regions alter the expression of some specific enzymes in the extracellular environment.

Enzyme-mediated drug delivery is mainly related to the change in the expression profile of specific enzymes in pathological conditions. The expression of specific enzymes like phospholipases, proteases or glycosidases is often greater in pathological tissues, such as the

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sites of inflammation or cancer [102]. This exploits the designed nanoparticles that respond to altered enzyme gradients in pathological tissues [102]. Enzyme-triggered systems exist in the microenvironment of tumor. Matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, are the most studied enzymes for on-demand enzymatic drug delivery [100]. Recent studies have reported the use of MMP's cleavable linker between polyethylene glycol (PEG) chains or transactivator of transcription (TAT)-functionalized liposomes [103].

Moreover, redox-sensitive systems relate to the breakage of disulfide bonds in the presence of glutathione. The triggering drug release depends on the amount of glutathione in intracellular and extracellular compartments. This may be achieved by designing disulfide links in the backbone of the hydrophobic polymeric component [104]. The other approach may be related to incorporated glutathione-sensitive agents in the core or in the shell of nanoparticles, such as micelles [105, 106]. Table 1 summarizes the most popular intrinsic stimuli-sensitive lipid-based nanoparticles.

Table 1. Examples of intrinsic stimuli sensitive lipid-based drug delivery systems.

Intrinsic Stimulus	Nanoplatforms	Components	Content	Results	Ref.
pH sensitive	Micelle	PDMA-b-PDPA di-block copolymers	Bcl-2 siRNA/ Paclitaxel	Overcoming MDR, Bcl-2 down regulation	[107]
pH sensitive	Micelle	DOPE–PEI	Doxorubicin/ siRNA	Enhanced the transfection efficacy/improved biocompatibility / Overcoming MDR	[108]
pH sensitive	Micelle	(ethylene glycol)-poly(aspartate hydrazone-adriamycin)	Doxorubicin	Triggering drug release under low pH condition/ greater in vivo antitumor efficiency	[109]
pH sensitive	Micelle	Folate conjugated–poly (aspartatehydrazone-adriamycin)	Doxorubicin	Hyrdazone bond cleaved at low pH/ enhanced cellular uptake and cancer cell toxicity	[110]

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pH sensitive	Liposomes	Dioleoylphosphatidylethanolamine / PEG	Doxorubicin	Enhanced intracellular drug delivery/ enhanced cell toxicity	[111]
pH sensitive	Liposomes	Egg phosphotidylcholine /transferrin /pH-sensitive fusogenic peptide	Mastoparan	Enhanced cellular uptake/ triggered drug release	[112]
Enzyme sensitive	Liposome	PEG2000-peptid sensitized to MMP-2, DODAG, DOPC, Chol	siRNA	Enhanced delivering nucleic acid to cell gene silencing	[113]
Enzyme sensitive	Micelle	PEG-pp-PEI-PE	Paclitaxel/ siRNA	High load of siRNA and paclitaxel, enhanced passive targeting, Efficient triggering release, enhanced cellular uptake	[114]
Enzyme sensitive	Liposome	DPPG,DPPC,DPPE-PEG2000	siRNA	enhance cellular uptake /Improved transfection of SiRNA	[115]
Redox sensitive	Micelle	poly-(ethylene glycol)-b-poly(lactide-co-2-methyl-2-carboxyl-propylene carbonate)	Daunorubicin/ Oxaliplatin	Lower systematic toxicity/ increase synergistic effect both in vivo and in vitro	[116]
Redox sensitive	Micelle	Poly (cystaminebisacrylamide-diaminohexane) with arginine grafted	Paclitaxel/ DNA	Low cell toxicity / increase cellular uptake	[117]
Redox sensitive	Micelle	Cationic amphiphiles synthesis from α-lipoic (6,8-thioctic) acid	Plasmid DNA	Increased transgene expression/ triggering DNA released	[118]
Redox sensitive	Micelle	siRNA-S-S-PE/PEG-PE	siRNA	Cytotoxicity decreased/ gene silencing increased	[119]

3.2.2. Extrinsic Stimuli

Thermo-sensitive drug delivery is one of the most investigated exogenous stimuli-responsive strategies. Thermo-responsivity of nanoparticles usually leads to a sharp change in at least one component of the nanoparticle upon temperature changes, resulting in triggered drug release. Ideally, the nanoparticles should be stable throughout blood circulation, but they also release drug cargo in a mildly hyperthermic state (~40-42 ºC) [100].

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Heat-triggered systems generally include liposomes, micelles, or polymers. Thermo-sensitivity for liposomes mainly arises from a gel-to-liquid phase transition of the constitute lipids, such as dipalmitoylphosphatidylcholine or lysolipids [100]. Another approach to sensitizing liposomal carriers to temperature is the incorporation of synthetic polymers in the membrane, where they act as a disruptive agent in a lower critical solution temperature (LCST) to 40 °c [120]. The following polymers have been added to sensitize liposomes to temperature: poly(N-substituted acrylamides), poly(N-vinylethers), and poloxamers [121]. Thermo-sensitive polymeric micelles are composed of self-assembled thermo-sensitive amphiphilic block copolymers. Moreover, iron oxide (10) nanoparticles, along with alternative magnetic fields, can induce hyperthermia-triggered drug release.

A magneto-response nanoparticle consists of a magnetically active component within a stable pharmaceutical formulation [122]. The magnetic nanosystem can serve as a magnetic guidance under externally applied permanent magnet or/and nano heat generator to control the drug release when an alternating magnetic field is applied. Sensitized magnetic fields are more often imparted by incorporating magnetite or maghemite to nanoparticles [123]. The biomedical application of magneto-responsive nanoparticles includes bioseparations, magnetofection, drug targeting, magnetic resonance imaging (MRI), and magnetic hyperthermia [122]. Magnetically responsive lipid-based nanoparticles consist of nanosized magnetic cores enwrapped by lipidic shells and include phospholipids, surfactants, and polymers.

One of the other extrinsic stimuli systems is light potential-sensitive systems. In the past few years, a variety of radiation-based drug delivery mechanisms have been developed. Photo-responsive drug delivery systems can be primarily divided into two categories. The first is

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the delivery of photosensitizers using conventional nanoparticles and the second is the design of light-assisted on-demand control release in response to a specific wavelength (in the visible, ultraviolet or NIR regions) [100]. Liposomal nanoparticles offer the ability to encapsulate hydrophobic photosensitize agents [124]. Photo-sensitive lipid molecules provide light-sensitive liposomal drug delivery systems with stable sustained release during circulation and localized photo-triggered drug release to desired sites [125] (Table 2).

Table 2. Examples of extrinsic stimuli sensitive lipid-based drug delivery systems.

Extrinsic Stimulus	**Nanoplatforms**	**Components**	**Content**	**Results**	**Ref.**
Thermo sensitive	Liposome	DPPC, DC-Chol, DOAB, cholesterol and magnetic fluid Fe_3O_4	DOX/ SATB1-shRNA	Enhanced in vivo and in vitro inhibition cell growth	[126]
Thermo sensitive	Liposome	DPPC/DSPC	Neomycin Methotrexate	Enhanced triggering drug release	[127]
Thermo sensitive	Liposome	DPPC/lyso-PC/DSPE-PEG2000	Doxorubicin/ Cisplatinum	Enhanced cell toxicity	[128, 129]
Thermo sensitive	Liposome	DPPC/DSPE-PEG2000/Chol/ELP	Doxorubicin	Triggered doxorubicin release/ Enhanced cell toxicity	[130]
Thermo sensitive	Micelle	polymer p(HPMAm)-b-p(AMPO)-b-p(HPMAm-Bz-co-HPMAm-Lac)	Paclitaxel	Increased drug stability during circulation	[131]
Light sensitive	Micelle	Anionic dendrimerphthalocyanine / PEG–PLL block copolymer	Doxorubicin	Increasing doxorubicin release during photoirradiation in vitro and in vivo	[111]
Light sensitive	Liposome	DPPC/ HSPC/ Cholesterol /DSPEPEG2000/ Au nanoparticles	Doxorubicin	Increased cell toxicity/ Increased antitumor efficiency	[132]
Light sensitive	Liposome	DSPC/ cholesterol/ Pyro-lipid/ DSPE-PEG-2K	Doxorubicin	High efficient cancer cell treatment	[133]
Light sensitive	Micelle	N-succinyl-N'-4-(2-nitrobenzyloxy)-succinyl-chitosan	Doxorubicin	Increased loading efficiency/ improved stability/ cell imaging	[134]

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		micelles		ability	
Magneto sensitive	Liposome	Transferrin conjugated-EPC/ cholesterol/ mPEG2000-DSPE	SPION	Enhanced transmigration to blood-brain barrier	[135]
Magneto sensitive	Liposome	DPPC	Doxorubicin/ SPION	Triggered drug release during exposure to the magnetic field	[136]
Magneto sensitive	Micelle	poly(2-vinylpyridine) / poly(ethylene oxide)/ poly(glycidyl methyl ether-co-ethyl glycidyl ether)	Maghemite	Efficient hyperthermia during AC magnetic fields exposure	[137]

3.3. Potential and Challenges

Nanocarrier design efficacy and payload delivery to desire cells are still a challenge in pharmaceutical researches. Compared to nonstimuli-sensitive drug delivery systems, stimuli-sensitive nanoparticles offer more advantages to efficiently control the drug release and enhance drug accumulation at desired sites. Despite the great progress in stimuli-sensitive drug delivery systems, there are still considerable problems to overcome, including low specificity and insufficient sensitization to the extrinsic and intrinsic stimuli [138].

Thus, the improved design and characterization of the nanoparticles are needed. By combining several stimuli-sensitive moieties and by functionalizing the nanoparticles with specific ligands, improvements in the efficiency of pharmaceutical drug delivery systems are possible.

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4. Carbon Nanostructures

4.1. General Feature

Carbon is unquestioningly one of the most abundant and useful elements in our universe. By altering the combination of sp, sp^2, and sp^3 carbon atoms, a broad extent of carbon allotropes including carbon structures and nanostructures would be accessible. Carbon nanostructures have attracted a great deal of attention as new materials with excellent properties and superior applications in a variety of fields over the last two decades. All of the carbon nanostructures could be structurally categorized in one group, which consists mainly of sp^2 carbon atoms settled in a hexagonal composition. However, they may have different morphologies, sizes, and shapes. Also, they generally have some ordinary properties due to the fact that they are made up primarily of a unique atomic arrangement.

Carbon nanostructures can be dimensionally divided into four main categories. The first group of carbon nanostructures is known as OD carbon nanostructures, which consist of fullerenes, carbon dots (CDs), and graphene quantum dots (GQDs). The second group is defined as ID carbon nanostructures, which is mostly comprised of CNTs and carbon nanofibers (CNFs). The third category of carbon nanomaterials can be called 2D carbon nanostructures, which is approximately, embraced graphene, graphene oxide (GO), reduced graphene (rGO), and multilayer graphitic sheets. Finally, there are some specific carbon nanostructures with three dimensional structures that are chiefly made up of CNTs and graphene hybrids, 3D carbon microspheres, and 3D graphenic superstructures.

In general, carbon nanostructures have several applications in different fields including biomedical engineering, biomedicine, drug delivery, biosensors, bioimaging, catalysis and

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photo catalysis, energy conversion and storage, solar calls, batteries, composites, and electrical and optical devices.

4.2. Zero-dimensional Carbon Nanostructures

Generally, zero-dimensional carbon nanostructures are usually made up of sp^2 carbon atoms. However, they may contain some sp^3 carbon atoms at edge planes or defect structures. Fullerenes are one of the most well-known zero-dimensional carbon nanostructures, which has commenced the discovery of other carbon nanostructures. Fullerenes can be considered as the smallest carbon nanostructure. They are synthesized from graphite by different methods, such as laser irradiation, plasma discharges, chemical vapor deposition (CVD), and arc discharge [139-141]. Other important OD carbon nanostructures are called CDs, which contains carbon nanodots, GQDs, and polymer dots. CDs were discovered by Xu et al. [142] during synthesizing single-walled CNTs (SWCNTs) by means of the arc discharge method. Respecting the earlier mentioned consideration, fullerenes as zero-dimensional carbon nanostructures have extraordinary conduction in a wide range of temperatures due to its crystallinity [142]. Moreover, because of its proper functionalization, fullerenes have been lately utilized in biomedical applications, liquid crystals, and hydrogen storage [139-142]. Carbon quantum dots, GQDs, and polymer quantum dots as another kind of the OD carbon nanostructures have been extensively studied recently [143]. These attractive carbon nanostructures have countless features such as low toxicity and biocompatibility compared to metallic quantum dots, have easy synthesis approaches, excellent solubility in water and other solvents, superior optical properties with low photobleaching, facile functionalization, and so forth [139-141]. It has been shown that, because of strong fluorescence and

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photoluminescence which can be achieved by these nanostructures, they can be used in a variety of fields, especially those that are related to optical properties such as bioimaging, photo catalysis, and biological labeling. For instance, superior optical and fluorescence properties of CDs make them attractive to produce TiO /C-dots and SiO /Cdots in order to convert the sunlight spectrum to a desired wavelength for the degradation of pollutants such as poly aromatic hydrocarbons (PAHs) [140]. Also, owing to its strong selectivity, sensitivity, and photostability, CDs and GQDs are used as novel and extremely accurate probes for the detection of heavy metals such as Hg, Ni, Cr, and Pb. Furthermore, this type of OD carbon nanostructure has been widely utilized for bioimaging, due to its low toxicity and excellent emission—excitation behavior in living cells [139-142].

Drug delivery is another important applications of the CDs family. Due to its various chemical functional groups, the combination of CD nanostructures with magnetic nanostructures such as Fe304 and Fe203 can be used as an applicable structure in order to improve a drug's release, control, and delivery [142]. Energy-related harnesses are another significant application of CDs, which broadly includes organic photovoltaic cells (OPVs) and solar cells. As aforementioned, CDs and GQDs absorb a wide range of wavelengths and convert it to a desired wavelength. This potential application provides an opportunity for researchers to focus on these nanostructures as smart materials for energy conversion in solar cells. Also, tunable band gap characteristics of CDs and GQDs make them alluring nanostructures for OPVs [140, 142, 143].

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4.3. One-dimensional Carbon Nanostructures

One-dimensional carbon nanostructures are mainly comprised of cylindrical or tubular nanostructures with sp^2 carbon atoms in a hexagonal network. CNTs are one of the well-known ID carbon nanostructures, discovered in 1991. CNTs are made up of graphene sheets which are combined to form a tubular or cylindrical shape with diameters about 0.5—10 nm and micrometer length [143]. This feature increases the aspect ratio (L/D) of CNTs. With respect to the number of graphene like sheets in the CNTs, they are divided into three main categories: SWCNTs, double-walled CNTs (DWCNTs), and multi-walled CNTs (MWCNTs). CNFs are another group of carbon nanostructures [144—146]. Due to the fact that CNFs are mainly based on sp^2 carbon atoms, they are structurally like CNTs except in diameter [147]. The diameters of CNFs are ranged between 50 and 200 nm; however, CNFs have a high aspect ratio. Furthermore, CNTs have a hollowed composition and are vacant cylinders. On the contrary, CNFs do not have these properties, as a principal difference between these carbon nanostructures [147, 148].

CNTs as the main member of the one-dimensional carbon nanostructures have tremendous applications. Because of their high strength and suitable electrical properties, CNTs and CNFs have been used for producing composite materials and in the electronic industry, respectively. Regarding their high aspect ratio, CNTs are convenient nanostructures as polymer additives to make nanocomposites, enhancing physical and chemical characteristics. Environmental applications such as air and water purification have been successfully reported. Considering their high surface area and adsorbent capacity, CNTs can be used as adsorbents for the removal of organic and inorganic pollutants [145—147]. CNTs have been greatly applied as catalysis supports in different chemical reactions such as gas to liquid

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reactions (GTL), desulfurization, oxygen reduction reactions, and so on. CNTs have also broadened a new horizon in biomedical applications, such as gene and drug delivery, bioimaging, and in biosensors. Energy storage and energy conversion are another application of the one-dimensional carbon nanostructures, such as lithium batteries, fuel cells, solar cells, and super capacitors.

4.4. Two-dimensional Carbon Nanostructures

The most prominent two-dimensional carbon nanostructure is graphene. Graphene is known as the thinnest and strongest substance that has been ever discovered. Graphene sheets are composed of a two-dimensional sheet, in which sp^2 carbon atoms are bonded to form a honeycomb lattice. Graphene has a numerous physical and chemical properties such as high surface area, appropriate electrical conductivity, suitable transparency, proper biocompatibility, high mechanical strength and so forth [149—151]. Owing to its extraordinary and unique characteristics, scientific researches on graphene have been conducted in various fields.

One of the most important issues in synthesizing carbon nanostructures is aggregation. Graphene sheets tend to stick toward each other through weak van der Waals interactions. If graphene sheets aggregate, the properties will be changed. Thus, it would be very essential to prevent aggregation by means of mechanical exfoliation. Graphene could be produced by different methods. In a general manner, the synthesis of graphene can be classified into three main techniques, as briefly described below. The first and common method is chemical-based techniques, one of the most well-known approaches is called Hammer's method. Also, there are many different modifications or improvements on this method, which makes it

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attractive for researchers. Briefly, in this method, graphite as the carbon precursor is used and oxidized in concentrated sulfuric acid with KMnO4 as another oxidant. In addition, after holding the reaction at a desired temperature for a period, the GO sheets are separated by adding water and oxygen peroxide. Consequently, the GO should be washed by hydrochloric acid in order to remove any manganese residue and finally should be washed with the copious amounts of water to reach the neutral pH value [152]. Chemical-based approaches can be used to produce a large amount of graphene, although some of these techniques need especial and precious materials. rlhe second method is called CVD, in which graphene is usually synthesized with graphite target. The greatest advantage of the CVD method is the lack of any metallic residue that is an issue in chemical-based methods. The third method for the preparation of graphene is named exfoliation. As mentioned earlier, in order to maintain the superior properties of graphene, the sheets should be individually separated. Therefore, due to the fact that the graphite is naturally made up of graphene sheets which are held together with van der Waals' interactions, exfoliation separates graphene sheets by breaking these weak interactions [153, 154].

Owing to the striking characteristics of graphene and its by-products, it has an extended scope of applications and is utilized from technological applications to medical ones. Some important applications include field effect devices, energy storage and conversion systems, sensors including bio and electrochemical sensors, transparent electrodes, solar cells and fuel cells, nanocomposites, and biomedicine. lhe technological applications of graphene are preliminary comprised of electrical and optical properties. For example, there are numerous reports on field-effect transistors (FET) biosensors, which can be used as precise biosensors, rather than electrochemical biosensors that have become obsolete [153—155]. There are

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several kinds of transistors that are affected by the discovery of graphene, including photosensitive transistors, spin transistors, ballistic transistors, etc. Transparency of graphene sheets is another crucial feature of this kind of the superstructure material. The combination of graphene sheets with transparent polymers, such as polymethyl methacrylate (PMMA), can lead to appropriate nanocomposites with a multitude of applications in electronic devices and transparent electrodes.

From medical and biomedical perspectives, graphene, GO, functionalized graphene, and other derivatives of graphene have exhibited practical applications, including disease diagnostics, bioimaging, cancer targeting, tissue engineering, drug delivery, cancer therapy, gene delivery, antibacterial and antiviral materials, and so forth. For instance, due to its high specific surface area and excellent chemical functional groups, GO and functionalized GO has shown promising results for the delivery of water insoluble anticancer drugs. Furthermore, extraordinary optical characteristics of graphene and its family members inaugurates a novel method for cancer therapy. For example, the appropriate absorption of wavelength in NIR range introduces graphene and its derivatives as promising photothermal carbon nanostructures which can be used for in vivo cancer therapy. The existence of edge planes and defect structures on graphene sheets makes it thoroughly outstanding and effective as antibacterial materials. It is believed that, the antibacterial behavior of graphene sheets is provided by a possible interaction between bacteria and graphene sheets. In addition to these considerations, graphene sheets are a unique candidate for sensors and biosensors, because of its exceptional selectivity, sensitivity, and conductivity. Since graphene has demonstrated a great potential for surface modification and manipulation, it has shown that

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the biocompatibility of graphene and its related production is much more than other carbon nanostructures such as CNTs, CNFs, and fullerenes [152-155].

4.5. Three-dimensional Carbon Nanostructures

Three-dimensional carbon structures mainly contain diamonds and graphite. Three-dimensional carbon nanostructures are usually synthesized with graphene sheets as 2D plates and CNTs, CNFs, carbon nanohorns, and other ID carbon nanostructures [156]. Owing to the fascinating chemical and physical characteristics of these nanostructures, numerous works have been reported on hybridized CNTs and graphene as three-dimensional carbon nanostructures. Three-dimensional carbon nanostructures have higher surface area because of an additional dimension [156], and chemical vapor is commonly used for its production. It is believed that if the one-dimensional carbon nanostructures are placed vertically onto graphene sheets, it would be more desirable for specific applications such as drug delivery and catalysis.

Three-dimensional carbon nanostructures are based on hybridizing zero-, one-, and two-dimensional carbon nanostructures which represent a novel structure with the characteristics of their components. Three-dimensional carbon nanostructures like other types of the carbon nanoallotropes have multiple applications in various fields of science and technology. The combination of graphene and fullerenes has been recently investigated as convenient superstructures for photovoltaic cells. Hybridizing graphene sheets with one-dimensional carbon nanostructures including CNTs and CNFs provides an opportunity for electronic industry to increase the performance of transistors, light-emitting diodes (LED), and composite materials. On the other hand, there are numerous publications which indicate the

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application of 3D carbon nanostructure as support catalysis for energy conversion in fuel cells. The small size of CDs and GQDs makes them striking candidates for combination with other carbon nanostructure to improve their performance in biological and technological applications [156].

4.6. Potential and Challenges

Considering the earlier discussion regarding carbon nanostructures and their related applications, it is found that the potential usage of these precious materials has been regarded to a great extent in science and technology. As the number of carbon nanostructures and their derivatives increases, the probability of replacing obsolete materials with carbon nanostructures will be raised. However, there are some barriers which have hindered the comprehensive exploitation of these smart materials. One of the most important challenges is the purification and large-scale production of carbon nanostructures. Nonetheless, there are some attempts to produce carbon nanostructure, especially CNTs and graphene in an enormous scope for different applications. It is noteworthy that the future of science and technology relies heavily on the development and utilization of sophisticated materials including carbon nanostructures.

5. Nanostructured Metals

5.1. Nitinol

Shape memory alloys as intelligent materials in reconstructive surgery are gaining growing interest [157]. Among them, NiTi shape memory alloy has outstanding sensing-actuating

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behaviors. Suitable biocompatibility, fine corrosion resistance and promising osteoconductivity have been reported particularly for NiTi porous alloys [158]. NiTi alloys show a combination of shape memory and superelasticity, making this alloy especially promising for cardiovascular stents. NiTi stents are able to elastically recoil to their original shape after being crushed entirely with no variation of the lumen diameter, because the elasticity of NiTi is approximately 10 times higher than that of the stainless steel material currently used in medical devices [159, 160]. This alloy is being used in the form of powder, wire, bulk, surface treated bulk, and porous scaffolds. Here, we aim to discuss the aforementioned structures and the effect of nanotechnology on the improvement of their biological characteristics.

Micro- and nanostructured features on the surface of dental implants and stents commonly present particular behaviors. Samaroo et al. [161] synthesized NiTi alloys with different micron to nanometer surface roughness by using different particle sizes of NiTi powder. The results of endothelial cell culture indicated that endothelial cells adhered much better on fine grained compared with coarse grained NiTi compacts. Moreover, cells proliferated more on NiTi with greater sub-micron and nanoscale surface roughness, compared with coarse grained NiTi. It was also confirmed by using molecular dynamics simulations that certain single-crystal face centered cubic (FCC) metal nanowires can show both shape memory as well as pseudo elastic properties [162]. Ihe mentioned properties are for nanoscale phenomena that are not detected for bulk metal, showing that metal nanowires may be employed in future nano- and microscale structures as self-healing materials. Shape memory nanowires would comprise an improvement over bulk alloys in multiple respects, including

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the ability to sustain larger tensile stresses, having more than 40% reversible strains, as compared to about 10% for bulk alloys [163].

Mechanical alloying and sintering processes are production techniques for making nanostructured materials [164—182], which have been used for NiTi alloys. Highly crystalline ultra-pure nanoparticles developed by mechanical alloying—combustion synthesis give a high surface area, desirable for enhanced osteoconductivity. High energy milling is an innovative approach to producing nanocrystalline NiTi materials. During the milling process, nanometer-scale component interactions are carried out at atomic planes. Biological characteristics including biocompatibility, bioactivity and biodegradability seem to be controllable with milling speed/ time, compression pressure, and sintering temperature/times. NiTi shape memory alloys can be developed from both elemental and mechanically alloyed aggregate compacts [158]. Also, laser ablation in liquid is known as a technique to create colloidal shape memory alloy nanoparticles. The generation of NiTi shape memory alloy nanoparticles for surface coatings was demonstrated as an effective tool giving access to nanomaterials for biomedical usages. Cell adhesion has been observed on a surface coated with laser generated NiTi nanoparticles [157].

Due to the shape memory effect, superelasticity, biocompatibility and a high damping capacity, intelligent metals are being used in several applications, in particular for biomedical engineering and MEMS [183]. They have attracted much attention for orthodontic wires, vascular stents, orthopedic implants, and eyeglass frames. Additionally, the application of nanotechnology can improve success rates of implants for orthopedic and dental applications. NiTi possesses both mechanical and thermal shape memory behavior; thus, NiTi vascular stents can unfold once exposed to the convective heat flow of blood. Moreover, the elasticity

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of NiTi presents a high flexibility, which is beneficial for delivering the stent to the vascular site [161].

5.2. Other Metallic Nanoparticles

Metallic nanoparticles such as gold (Au) or silicon dioxide—gold (Si02—Au) nanoshells have been incorporated into temperature-responsive interpenetrating polymer networks as new intelligent therapeutic nanocomposite systems, where the nanoparticles or nanoshells absorb light, and then convert it to heat and transmitted locally to the surrounding intelligent therapeutic nanocomposite [184]. Au nanoparticles were incorporated inside a polyacrylamide/poly(acrylic acid) shell via an in situ inverse emulsion polymerization and its surface was then treated by PEG via covalent grafting. Depending on the type and size, the metallic nanoparticle core can be tuned to absorb visible-to-NIR with 530—1200 nm wavelengths of light. By increasing temperature, the polymer swelling begins and releases any encapsulated useful agents within the polymer network [185]. Using metals, intelligent therapeutic systems are able to revolutionize drug delivery and disease treatments based on thermally responsive metal—polymer nanocomposites [184].

Metallic nanowires have been widely investigated for the past decade because of their better mechanical, electrical, and optical properties due to their nanometer size scale. Park et al. [163] also showed that silver nanowires can display both shape memory and pseudoelastic properties. Silver nanoparticles are also well known to cause antiproliferative effects [186]. Because of the mentioned properties, it appears that nanowires could potentially be employed as next-generation structural materials, biosensors, and circuitry, and

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interconnectors in future nanoscale devices to fill the critical need for nanoscale self-healing materials in future nanomedicine applications [163].

5.3. Potential and Challenges

Risks and uncertainties are associated with the use of NiTi alloys in biomedical applications. The corrosion resistance of NiTi is controversial. Ihe corrosion resistance of NiTi alloy is due to the naturally formed titanium dioxide (Ti02) on its surface. However, this layer is too thin (typically 5-10 nm thick) and is easy to deteriorate. Pitting corrosion is the primary mechanism of NiTi implants in the human body. Chloride ions (Cl-) in the body fluid have high diffusivity and interfere with the passive layer, leading to the breakdown of the oxide layer and eventually pitting corrosion [160]. Severe pitting corrosion and fractures have been detected in NiTi stent wires of explanted aortic endovascular grafts. The occurrence of corrosion and fracture in NiTi stents may induce the release of toxic nickel (Ni), subsequent inflammations and possible carcinogenic effects. Cytotoxicity of released Ni ions on endothelial cells has been observed in regard to the NiTi alloy [187]. In addition, the inert surface of NiTi does not allow for the easy attachment of endothelial cells and the formation of a monolayer. In long-term cell culture tests, cells did not grow well on NiTi with larger grain size, because the coarse particles had large voids on the surface, whereas the existence of a superior amount of homogeneous inter particulate voids on fine grained NiTi seems to be more helpful for endothelial cell attachment and proliferation, leading to the creation of an endothelial cell monolayer [188]. Moreover, data from laboratory experiments confirmed that the endothelialization of NiTi alloy at present could be enhanced by surface micro-/nanopatterning [189].

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Different kinds of surface treatments have been reported, such as chemical or electrochemical processes, heat treatment, ion implantation, etc. Anodization has also been proven to be efficient informing a compact Ti-enriched oxide layer, notably decreasing Ni release from the material surface [190]. Another concern over the use of NiTi is lack of surface osteoconductivity, which is a characteristic among metallic biomaterials, but has been less addressed for NiTi and can be improved by the existence of a bioactive layer on the surface. For example, hydroxyapatite and other calcium phosphate coatings have been developed to encourage the bone tissue attachment and increase the interface bonding of Nitinol surfaces for orthopedic applications [191]. Although these coatings could enhance the surface bioactivity, a low bonding strength with the substrate and deformation capacity are major concerns in long term. On the other hand, it may be possible to increase the surface osteointegrity by changing the surface roughness, for example hybrid micro-to-nanoscale structures, which avoids the use of coatings with weak adhesion strengths. Such a technique follows to the idea of biomimetics, which proposes that the designed micro- and nanotopographies would present biologically appropriate surfaces for biomaterials. Such findings state that a micro-to-nanoscale surface treatment is a proficient route, which can improve the surface biofunctionality of titanium alloys [1901.

Nanograined NiTi microtubes have currently been utilized to produce medical devices such as stents designed for less invasive operations [192]. Any improvement in practical procedures for making highly surfaced NiTi implants enhances the success rate and decreases the healing time after surgery. Good flexibility, fatigue life and super elastic properties at or near the body temperature allow to decrease the size of medical devices made of nanograined NiTi material [193]. Furthermore, it has been recently found that the

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introduction of porosity in the structure of NiTi has great applications, since porosity is believed to be beneficial for osteointegration. Although, making porous NiTi encourages tissue-ingrowth through the pores, the surface area of NiTi exposed to the body corrosive media increases, leading to the higher corrosion rate of NiTi. However, nanocrystal formation in NiTi improves the mechanical properties. Controlling the amount of porosity in the structure of NiTi in order to have optimized biological, mechanical and corrosion properties should be considered in further studies.

Regarding production techniques, these alloys are conventionally made by arc melting or induction melting, followed by a hot or cold treatment to reach their final shapes. However, these processes require several re-melting processes to ensure enough homogeneity. Casting processes usually have technical obstacles such as oxidation and diffusion of contaminants from the crucible as well as difficulty in working or mechanically machining.

To produce NiTi components at an industrial scale, near net shape fabrication methods are ideal with limited machining. For this reason, there has been significant interest in powder metallurgy routes. This process can evade troubles relevant with casting, such as segregation or grain growth, and has the advantages of an accurate control of composition and simple realization of complex shapes. However, difficulties inherent in the powder metallurgy process include high porosity and tendency to form other Ni-Ti phases, including Ni3Ti, Ti2Ni, Ni4Ti3, etc. Spark plasma sintering is a relatively innovative technique for sintering powders with uniform heating to high densities at lower temperatures. The refinement of NiTi particles is beneficial for the sintering process [183]. However, so far, there are few reports on the development of NiTi using nanosized NiTi powders, perhaps because of their high surface reactivity and susceptibility to oxygen contamination. Shearwood et al. [183]

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focused on the characterization of NiTi alloy prepared by spark plasma sintering of NiTi nanopowder produced by the electro-explosion of wire process.

In summary, intelligent nanostructured metals that are powder, wire, bulk, and porous have attracted much attention due to the combination of shape memory and superelasticity properties. Present investigations in this field show greater propensities for having nanostructured metals. Nanostructured intelligent metals have presented an improved interaction with various cell lines, higher mechanical properties and intelligent therapeutic behavior. If the production techniques and corrosion rates are well controlled, these nanostructures metals may be a promising selection for dental, orthopedic, cardiovascular, and drug delivery systems.

6. Hybrid Nanostructures

The development of smart composite and hybrid nanomaterials has gained great attention in recent years because they present unique remarkable physicochemical characteristics. These nanomaterials are designed via hybridization of both inorganic and organic components to provide improved functions and attributes. One of their general features is their ability to respond to various internal or external stimuli, including; pH, temperature, redox potential, light and magnetic fields. Accordingly, these intelligent stimuli-responsive systems, as promising platforms, offer numerous opportunities in many different fields including nanomedicine as drug delivery carriers, theranostics and imaging agents. In other words, nanoplatforms have emerged to overcome the restrictions associated with conventional methods and to attain both therapeutic and diagnostic purposes in the same platform.

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Hereupon, this section reviews recent advances and developments in potential biomedical applications of metal and carbon-based smart nanocomposites.

6.1. Smart Nanostructured Platforms for Drug Delivery

Intelligent stimuli-responsive nanostructures are widely used as drug delivery carriers for targeting and controlled releasing of drugs, genes and other therapeutic components, a phenomenon known as smart drug delivery. Specific delivery nanosystems display important advantages, such as optimizing the efficacy of curative drugs, reducing undesirable side-effects on normal tissues and organs, protecting compounds against enzymatic and proteolytic degradations, delivering therapeutic agents more selectively to a target site and, consequently, decreasing the dosing frequency. A major obstacle in cancer treatments is the drug resistance and the efficient delivery of therapeutic agents. To inhibit the drug resistance and effectively treat disease, novel approaches are used.

6.1.1. Metal-based Smart Composite and Hybrid Nanostructures

Intrinsic properties of gold (Au) and 10 magnetic nanoparticles have led to the development of a wide variety of smart composite and hybrid nanostructures for theranostic applications. Transference vehicles for drugs and nucleic acids based on gold nanoparticles (AuNPs) have received great attention in the last few years, due to advantages such as simple preparation, ease of surface functionalization, facile bioconjugation, and biocompatibility [194]. To achieve tumor-targeted delivery, AuNPs should be modified by molecules that show high affinity to cancer cells and interact with cell surface receptors over-expressed [195]. The gold nanoparticles can be functionalized by thiolated ligands using Au—S link formation, and

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many molecules can be covalently attached to Au by this approach [196]. For instance, pH-sensitive composite nanostructures with a gold core, a hydrophobic poly(L-aspartate-doxorubicin) inner shell, and a hydrophilic poly(ethylene glycol) and folate-conjugated poly(ethylene glycol) outer shell (PEG-OH/FA) have been successfully prepared [197]. Acidcleavable hydrazone binding covalently links anticancer drug doxorubicin to the hydrophobic inner shell. The carrier exhibited a higher cytotoxic effect on the 4T1 mouse mammary carcinoma cell line with pH-triggered drug releasing and targeting ability. Another approach to controlling the drug release is to use the exchange reaction of biodegradable disulfide bonds of Au—S-R in the presence of intracellular glutathione (GSH) [198].

Braun et al. [199] demonstrated the pulsed NIR laser-dependent release of siRNA from gold nanoshells as a light-responsive delivery system. Besides covalent linking, noncovalent functionalization to carry nucleic acids can be obtained via electrostatic interactions. Han et al. [200] introduced a photo labile gold nanoparticle system to deliver DNA using o-nitrobenzyl ester linker with a positive charge. An and his co-workers [201] fabricated a thermosensitive liposome—AuNP hybrid to release drug.

Freeman et al. [202] used magnetic carriers to deliver drugs to specific target sites for the first time. Core-shell NPs may consist of magnetic Fe_3O_4 NPs (IONPs) as the core and a polymeric or nonpolymeric (silica or metals) structure as the shell. The drug can be covalently bound to the surface or entrapped or adsorbed within pores of the vehicle (polymer or mesoporous silica). For drug release using a pH-dependent behavior, Chen et al. [203] prepared Fe_3O_4@SiO_2 core-shell nanostructures to deliver anticancer agent doxorubicin (DON). Kim and co-workers [204] applied a layer of temperature-sensitive polymers onto the surface of IONPs (IONP/polymer) for controlled drug release using

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temperature as a trigger. In another study, Hayashi et al. [205] designed magnetic field-responsive smart NPs by combining DOX and clustered IONPs core within a polymer with a glass-transition temperature (T) of 44 ºC for cancer treatments. P(EO-co-LLA) functionalized Fe_3O_4@$mSiO_2$ nanocomposites were also employed by Guo et al. [206] for thermo and pH-sensitive drug-controlled release and hyperthermia.

6.1.2. Carbon-based Smart Composite and Hybrid Nanostructures

Over the past few years, carbon-based nanostructured materials, such as CNTs and graphene with sp^2-hybridized carbon atoms, have made significant advances on clinical therapeutics. Functionalized CNTs exhibit unique properties, which enable a wide range of biomedical areas and can be used as drug carriers for in vitro and in vivo delivery. Covalent and noncovalent strategies can be employed for surface processing of CNTs, affecting toxicity and water solubility [207]. Tie high surface area and high loading capacity, cellular internalization, and biocompatibility of CNTs help for applications in drug delivery [208]. Biomolecules (e. g. DNA and proteins) can also be attached to functional groups on modified CNTs via electrostatic binding [209, 210].

FA-MWCNT@Fe nanocomposites were prepared of MWCNTs difunctionalized with folate and iron for biological (active) and magnetic (passive) targeting, respectively. External magnetic fields increased to deliver DOX to six-fold compared to free DOX [211]. A targeted drug delivery system triggered by a change in pH by using SWCNTs has been reported [212]. It was also modified with carboxylate groups and processed by a polysaccharide coating, so that it is be able to be loaded with the anticancer agent DOX. A composite with dual pH and electro-responsive release behavior was prepared by Yun et al.

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[213] using MWCNTs, poly(acrylic acid) and poly(vinyl alcohol). MWCNTs were employed to enhance electro-responsive characteristics. In another study [214], the same group developed an electro-responsive transdermal drug delivery system by electrospinning of poly(vinyl alcohol)/poly(acrylic acid)/MWCNTs nanocomposites. Spizzirri et al. [215] synthesized spherical gelatin/CNTs hybrid microgels as an electro-responsive system to deliver drug. Also, Ghosh and colleagues [216] also reported a novel drug delivery system composed of pH-sensitive CNT for the target specific release of DOX to cancer cells.

Graphene, GO and rGO, owing to their key interesting features, offer opportunities for theranostic applications. In this regard, pH-sensitive linkers, biodegradable polymers, tumor targeting ligands and magnetic carriers can be conjugated to graphene derivatives. Also, drug delivery using GO-Fe304 nanocomposites was served for the first time by Yang et al. [217]. The hybrid material displayed magnetic properties and pH responsiveness behavior for controlled targeted drug delivery. A novel nanohybrid of hyaluronic acid (HA)-decorated GO was produced as a pH-responsive nanocarrier for controlling the release of anticancer drug DOX (HA—GO—DOX) for cancer therapy [218]. In other research, Hu and co-workers [219] reported a pH-dependent release of DOX from graphene-based nanocarriers with a nonionic surfactant, (PF127/graphene) hybrid. Besides pH-dependent behaviors, Wen and collaborators [220] introduced a biodegradable and redox-responsive nanocarrier using a PEGylated nanographene oxide that could transport an encapsulated payload to tumor areas, with elevated glutathione (GSH) levels. GO-poly (N-isopropyl acrylamide) composite is a thermo-responsive material that was prepared by Pan et al. [221] to efficiently deliver camptothecin and to kill off cancer cells.

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6.2. Smart Nanostructures for Diagnostic Imaging

Given that the early detection and diagnosis of disease has a vital role in curing and most cancers are asymptomatic in the early stages, conventional imaging methods like X-ray and MRI do not have adequate spatial resolution for early detection. Thus, new approaches are required for accurate diagnosis. Nanohybrid platforms have unique properties that can be utilized as promising materials for bioimaging applications. Diagnostic imaging agents can be attached to the surface of nanostructured materials. Image contrast and spatial resolution are important for diagnostic techniques in biomedicine, and imaging agents have been developed to provide robust imaging signals and to improve diagnostic accuracy.

6.2.1. Metal-based Smart Composite and Hybrid Nanostructures

Metallic nanomaterials, like gold (Au) and 10, can serve as contrast agents and cancer nanodiagnostics for a variety of imaging techniques, because of their unique properties compared to current agents. Gold-based hybrid nanostructures provide tunable optical characteristics, exhibit strong native fluorescence, and display excellent anti photobleaching behaviors, that makes them attractive components for medical imaging. Also, through both passive and active targeting strategies, these nanostructures can be delivered to tumor sites and enhance imaging quality. Day et al. [222] developed NIR resonant antibody-conjugated gold-gold sulfide nanosized particles as contrast and therapeutic agents for breast cancer.

Hou et al. [223] manufactured Fe304 nanoparticles labeled with a NIR fluorophore, IRDye800CW-Fe304 that can be used as an effective probe for cell-labeling and in vivo imaging. Feng and colleagues [224] prepared Fe304 nanoparticles coated with PEG diacid and (3-aminopropyl) triethoxysilane (F%04/APTES/PEG) for MRI. nanocomposite was also

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designed by Lai and co-workers [225] for MRI, luminescence imaging, and photodynamic therapy.

6.2.2. Carbon-based Smart Composite and Hybrid Nanostructures

CNTs display remarkable mechanical and optical properties that make them a favorable tool for early cancer detection. Moreover, graphene-based nanocomposites can be used for imaging due to functionalizability of their surface that provides a material with interesting optical and magnetic properties. Zerda et al. [226] demonstrated that SWCNTs attached with cyclic Arg—Gly—Asp (RGD) peptides can be utilized as a contrast agent for photoacoustic imaging of tumors in living mice. Wu and co-workers [227] loaded Fe304 nanoparticles on the surface of MWCNTs and suggested the potential application of the hybrid as an excellent MRI contrast agent. Selective imaging and probing of cells by using SWCNTs as NIR fluorescent tags were reported by Welsher and colleagues [228].

Yang et al. [229] offered anrGO-IOnanoparticle-polyethylene glycol nanocomposite (RGO—IONP—PEG) with excellent physiological stability, intense NIR optical absorbance, and superparamagnetic characteristics. In another study [230], a multifunctional superparamagnetic graphene

oxide-IO hybrid nanocomposite (GO-IONP) was synthesized, then functionalized by PEG polymer, and used for in vivo MRI applications. Chen and co-workers [231] introduced composites of aminodextran-coated Fe_3O_4 nanoparticles and GO that can be used as a contrast agent for cellular MRI. Using 10 nanoparticles into PLA microcapsules and surface functionalization with GO, Li et al. [232] fabricated a novel multifunctional theranostic agent and employed it as a hyperthermic and imaging contrast agent for ultrasound, photoacoustic

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and MRI. Quantum dot (QD)-tagged rGO(RGO—QD) nanocomposites were also developed for fluorescent cell imaging and photothermal therapy [233].

From the above surveys, it is clear that hybrid nanoplatforms have emerged for a multitude of applications to overcome the limitations associated with conventional methods and to attain both therapeutic and diagnostic purposes in the same platform.

7. Concluding Remarks

In this chapter, an overview was provided on the structure, preparation, and biomedical applications of polymeric, lipid-based, carbon-based, metallic, hybrid, and composite intelligent nanostructures, particularly nanoparticles. Also, challenges associated with the further development of each category were addressed. Overall, it was concluded that biomedical requirements for the aforementioned materials are improved by nanostructuring, as compared to conventional, coarse-sized structures for both therapeutic and diagnostic purposes. In the polymer group, particularly enhancements in the effectiveness of drug delivery by PLGA, PLA, PCL, chitosan, and gelatin were the main area of focused. In this regard, surface modification can be deemed as an effective approach to overcoming this group's possible limitations, including toxicity, encapsulation efficiency and other physicochemical properties. Lipid-based nanoparticles, including liposome, niosome, micelle, nanoemulasion, and SLNs, having the minimum in vivo toxicity, were also regarded in enzyme-, pH-, and redox-sensitive, as intrinsic stimuli-sensitive, and thermo-, light- and magneto-sensitive, as extrinsic stimuli-sensitive, drug delivery areas. Insufficient sensitization to extrinsic and intrinsic stimuli was noted to be the main challenge of this group, as can be addressed by combining several stimuli-sensitive moieties and by

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functionalizing the nanoparticles with specific ligands. Furthermore, zero-, one-, two-, and three-dimensional carbon nanostructures in biomedical engineering, biomedicine, drug delivery, biosensors, and bioimaging were also addressed, where purification and large-scale processing are their main limitations. Intelligent nanometals mainly benefit from shape memory and superelasticity properties, developed for dental, orthopedic, cardiovascular and drug delivery applications, with the challenge of corrosion behavior. Eventually, the most advanced group, i. e. hybrid and composite nanoplatforms which overcome the limitations of the former groups were introduced for both therapeutic (drug delivery) and diagnostic purposes.

References

1. B.D. Ratner, A.S. Hoffman, F.J. Schoen, J.E. Lemons, Biomaterials Science: An Introduction to Materials in Medicine, Amsterdam, Academic Press, 2004.

2. D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, Nanocarriers as an emerging platform for cancer therapy, Nature Nanotechnology, 2, 751-760, 2007.

3. S. xu, Y. Luo, R. Graeser, A. Warnecke, F. Kratz, P. Hauff, K. Licha, R. Haag, Development of pH-responsive core—shell nanocarriers for delivery of therapeutic and diagnostic agents, Bioorganic & Medicinal Chemistry Letters, 19, 1030-1034, 2009.

4. A. Tiwari, A.K. Mishra, H. Kobayashi, A.P. Turner, Intelligent Nanomaterials, Hoboken, NJ, John Wiley & sons, 2012.

5. I.Y. Galaev, M. Gupta, B. Mattiasson, Use smart polymers for bioseparations, Chemtech, 26, 19-25, 1996.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

6. S.K. Sahoo, T.K. De, P. Ghosh, A. Maitra, pH-and thermo-sensitive hydrogel nanoparticles, Journal of Colloid and Interface Science, 206, 361—368, 1998.

7. M. Elsabahy, K.L. Wooley, Design of polymeric nanoparticles for biomedical delivery applications, Chemical Society Reviews, 41, 2545—2561, 2012.

8. V. Jenning, K. Mäder, S.H. Gohla, Solid lipid nanoparticles (SLN^{TM}) based on binary mixtures of liquid and solid lipids: a 1 H-NMR study, International Journal of Pharmaceutics, 205, 15—21, 2000.

9. N.A. Peppas, Hydrogels and drug delivery, Current Opinion in Colloid & Interface Science, 2, 531-537, 1997.

10. M. Haldopoulos, F. El Feninat, D. Mantovani, Encyclopedia of Biomaterials and Biomedical Engineering, Shape Memory Metals, 2004.

11. L. Dai, Intelligent Macromoleculesfor Smart Devices: From Materials Synthesis to Device Applications, Berlin, Springer Science & Business Media, 2004.

12. Z. Wei, R. Sandstroröm, S. Miyazaki, Shape-memory materials and hybrid composites for smart systems: Part I: shape-memory materials, Journal of Materials Science, 33, 3743-3762, 1998.

13. R. Lehner, X. Wang, S. Marsch, P. Hunziker, Intelligent nanomaterials for medicine: carrier platforms and targeting strategies in the context of clinical application, Nanomedicine: Nanotechnology, Biology and Medicine, 9, 742— 757, 2013.

14. M. Aprahamian, C. Michel, W. Humbert, J. Devissaguet, C. Damge, Transmucosal passage of polyalkylcyanoacrylate nanocapsules as a new drug carrier in the small intestine, Biology of the Cell, 61, 69—76, 1987.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

15. M. Hans, A. Lowman, Biodegradable nanoparticles for drug delivery and targeting, Current Opinion in Solid State and Materials Science, 6, 319—327, 2002.

16. T. Betancourt, J.D. Byrne, N. Sunaryo, S.W. Crowder, M. Kadapakkam, S. Patel, S. Casciato, L. Brannon-Peppas, PEGylation strategies for active targeting of PLA/PLGA nanoparticles, Journal ofBiomedical Materials Research Part A, 91, 263-276, 2009.

17. L. Illum, S.S. Davis, Polymers in Controlled Drug Delivery, New York, John Wright, 1987.

18. R. Herrero-Vanrell, A. Rincon, M. Alonso, V. Reboto, I. Molina-Martinez, J. Rodriguez-Cabello, Self-assembled particles of an elastin-like polymer as vehicles for controlled drug release, Journal of Controlled Release, 102, 113—122, 2005.

19. R. Singh, J.W. Lillard, Jr., Nanoparticle-based targeted drug delivery, Experimental and Molecular Pathology, 86, 215—223, 2009.

20. S.M. Moghimi, A.C. Hunter, J.C. Murray, Long-circulating and target specific nanoparticles: theory to practice, Pharmacological Reviews, 53, 283-318, 2001.

21. M. Yokoyama, Block copolymers as drug carriers, Critical Reviews in Therapeutic Drug Carrier Systems, 9, 213—248, 1991.

22. E. Dashtimoghadam, H. Mirzadeh, F.A. Taromi, B. Nyström, Microfluidic self-assembly of polymeric nanoparticles with tunable compactness for controlled drug delivery, Polymer, 54, 4972—4979, 2013.

23. R. Gref, Y. Minamitake, M.T. Peracchia, V. Trubetskoy, V. Torchilin, R. Langer, Biodegradable long-circulating polymeric nanospheres, Science, 263, 1600-1603, 1994.

24. S. Sundar, J. Kundu, S.C. Kundu, Biopolymeric nanoparticles, Science and Technology ofAdvanced Materials, 11, 014104, 2010.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

25. D.B. Shenoy, M.M. Amiji, Poly (ethylene oxide)-modified poly (e-caprolactone) nanoparticles for targeted delivery of tamoxifen in breast cancer, International Journal of Pharmaceutics, 293, 261—270, 2005.

26. A. Kumari, S.K. Yadav, S.C. Yadav, Biodegradable polymeric nanoparticles based drug delivery systems, Colloids and Surfaces B: Biointerfaces, 75, 1—18, 2010.

27. Y. Chen, V.J. Mohanraj, J.E. Parkin, Chitosan-dextran sulfate nanoparticles for delivery of an anti-angiogenesis peptide, Letters in Peptide Science, 10, 621-629, 2003.

28. J. Matsumoto, Y. Nakada, K. Sakurai, T. Nakamura, Y. Takahashi, Preparation of nanoparticles consisted of poly (L-lactide)—poly (ethylene glycol)—poly (L-lactide) and their evaluation in vitro, International Journal of Pharmaceutics, 185, 93—101, 1999.

29. O.C. Farokhzad, R. Langer, Nanomedicine: developing smarter therapeutic and diagnostic modalities, Advanced Drug Delivery Reviews, 58, 1456—1459, 2006.

30. M.J. Fonseca, J.C. Jagtenberg, H.J. Haisma, G. Storm, Liposome-mediated targeting of enzymes to cancer cells for site-specific activation of prodrugs: comparison with the corresponding antibody-enzyme conjugate, Pharmaceutical Research, 20, 423—428, 2003.

31. M. Yokoyama, M. Miyauchi, N. Yamada, T. Okano, Y. Sakurai, K. Kataoka, S. Inoue, Characterization and anticancer activity of the micelle-forming polymeric anticancer drug adriamycin-conjugated poly (ethylene glycol)poly (aspartic acid) block copolymer, Cancer Research, 50, 1693—1700, 1990.

32. V.P. Torchilin, Micellar nanocarriers: pharmaceutical perspectives, Pharmaceutical Research, 24, 1—16, 2007.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

33. F.X. Gu, R. Karnik, A.Z. Wang, F. Alexis, E. Levy-Nissenbaum, S. Hong, R.S. Langer, O.C. Farokhzad, Targeted nanoparticles for cancer therapy, Nano Today, 2, 14—21, 2007.

34. L. Zhang, A.F. Radovic-Moreno, F. Alexis, F.X. Gu, P.A. Basto, V. Bagalkot, S. Jon, R.S. Langer, O.C. Farokhzad, Co-delivery of hydrophobic and hydrophilic drugs from nanoparticle-aptamer bioconjugates, ChemMedChem, 2, 1268-1271, 2007.

35. W. Tiyaboonchai, Chitosan nanoparticles: a promising system for drug delivery, Naresuan University Journal: Science and Technology, 11, 51—66, 2013.

36. J. Panyam, V. Labhasetwar, Biodegradable nanoparticles for drug and gene delivery to cells and tissue, Advanced Drug Delivery Reviews, 55, 329—347, 2003.

37. A. des Rieux, V. Fievez, M. Garinot, Y.-J. Schneider, V. Préat, Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach, Journal of Controlled Release, 116, 1—27, 2006.

38. S. Hanafusa, Y. Matsusue, T. Yasunaga, T. Yamamuro, M. Oka, Y. Shikinami, Y. Ikada, Biodegradable plate fixation of rabbit femoral shaft osteotomies: a comparative study, Clinical Orthopaedics and Related Research, 315, 262-271, 1995.

39. C.P. Reis, R.J. Neufeld, A.J. Ribeiro, F. Veiga, Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles, Nanomedicine: Nanotechnology, Biology and Medicine, 2, 8—21, 2006.

40. L. Liu, Y.J. won, P.H. Cooke, D.R. Coffin, M.L. Fishman, K.B. Hicks, P.X. Ma, Pectin/poly(lactide-co-glycolide) composite matrices for biomedical applications, Biomaterials, 25, 3201—3210, 2004.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

41. R. Di Toro, V. Betti, S. Spampinato, Biocompatibility and integrin-mediated adhesion of human osteoblasts to poly(DL-lactide-co-glycolide) copolymers, European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences, 21, 161—169, 2004.

42. R.C. Mundargi, V.R. Babu, V. Rangaswamy, P. Patel, T.M. Aminabhavi, Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-co-glycolide) and its derivatives, Journal of Controlled Release: Official Journal of the Controlled Release Society, 125, 193—209, 2008.

43. A. Budhian, S.J. Siegel, K.I. Winey, Production of haloperidol-loaded PLGA nanoparticles for extended controlled drug release of haloperidol, Journal of Microencapsulation, 22, 773—785, 2005.

44. P.S. Kumar, S. Ramakrishna, T.R. Saini, P.V. Diwan, Influence of microencapsulation method and peptide loading on formulation of poly(lactideco-glycolide) insulin nanoparticles, Die Pharmazie, 61, 613—617, 2006.

45. R.S. Raghuvanshi, Y.K. Katare, K. Lalwani, M.M. Ali, O. Singh, A.K. Panda, Improved immune response from biodegradable polymer particles entrapping tetanus toxoid by use of different immunization protocol and adjuvants, International Journal of Pharmaceutics, 245, 109—121, 2002.

46. G. Mittal, D.K. Sahana, V. Bhardwaj, M.N. Ravi Kumar, Estradiol loaded PLGA nanoparticles for oral administration: effect of polymer molecular weight and copolymer composition on release behavior in vitro and in vivo, Journal of Controlled Release: Official Journal of the Controlled Release Society, 119, 77-85, 2007.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

47. H. Fessi, F. Puisieux, J.P. Devissaguet, N. Ammoury, S. Benita, Nanocapsule formation by interfacial polymer deposition following solvent displacement, International Journal ofPharmaceutics, 55, RI—R4, 1989.

48. J.-C. Leroux, E. Allémann, F. De Jaeghere, E. Doelker, R. Gurny, Biodegradable nanoparticles—from sustained release formulations to improved site specific drug delivery, Journal of Controlled Release, 39, 339—350, 1996.

49. J. Xing, D. Zhang, T. Tan, Studies on the oridonin-loaded poly (D,L-lactic acid) nanoparticles in vitro and in vivo, International Journal of Biological Macromolecules, 40, 153—158, 2007.

50. A. Levitzki, Tyrphostins: tyrosine kinase blockers as novel antiproliferative agents and dissectors of signal transduction, 7he FASEB Journal, 6, 3275-3282, 1992.

51. H. Gao, Y. Wang, Y. Fan, J. Ma, Synthesis of a biodegradable tadpole-shaped polymer via the coupling reaction ofpolylactide onto mono (6- (2 -aminoethyl) amino-6-deoxy)-ß-cyclodextrin and its properties as the new carrier of protein delivery system, Journal of Controlled Release, 107, 158—173, 2005.

52. C. Damgé, P. Maincent, N. Ubrich, Oral delivery of insulin associated to polymeric nanoparticles in diabetic rats, Journal of Controlled Release, 117, 163-170, 2007.

53. M. Espuelas, P. Legrand, P. Loiseau, C. Bories, G. Barratt, J. Irache, In vitro antileishmanial activity of amphotericin B loaded in poly (e-caprolactone) nanospheres, Journal ofDrug Targeting, 10, 593—599, 2002.

54. B. Sarmento, A. Ribeiro, F. Veiga, P. Sampaio, R. Neufeld, D. Ferreira, Alginate/ chitosan nanoparticles are effective for oral insulin delivery, Pharmaceutical Research, 24, 2198-2206, 2007.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

55. R. Fernandez-Urrusuno, P. Calvo, C. Remufiån-L6pez, J.L. Vila-Jato, M.J. Alonso, Enhancement of nasal absorption of insulin using chitosan nanoparticles, Pharmaceutical Research, 16, 1576—1581, 1999.

56. A.M. De Campos, A. Sånchez, M.A.J. Alonso, Chitosan nanoparticles: a new vehicle for the improvement of the delivery of drugs to the ocular surface, Application to Cyclosporin A: International Journal of Pharmaceutics, 224, 159-168, 2001.

57. I.M. van der Lubben, G. Kersten, M.M. Fretz, C. Beuvery, J.C. Verhoef, H.E. Junginger, Chitosan microparticles for mucosal vaccination against diphtheria: oral and nasal efficacy studies in mice, Vaccine, 21, 1400—1408, 2003.

58. S.A. Agnihotri, N.N. Mallikarjuna, T.M. Aminabhavi, Recent advances on chitosan-based micro-and nanoparticles in drug delivery, Journal of Controlled Release, 100, 5—28, 2004.

59. W. Friess, Collagen—biomaterial for drug delivery, European Journal of Pharmaceutics and Biopharmaceutics, 45, 113—136, 1998.

60. R. Oppenhiem, Paclitaxel loaded gelatin nanoparticles for intravesical bladder cancer therapy, International Journal ofPharmaceutics, 8, 217, 1981.

61. N. Sahoo, R.K. Sahoo, N. Biswas, A. Guha, K. Kuotsu, Recent advancement of gelatin nanoparticles in drug and vaccine delivery, International Journal of Biological Macromolecules, 81, 317—331, 2015.

62. J.K. Li, N. Wang, X.S. Wu, Gelatin nanoencapsulation ofprotein/peptide drugs using an emulsifier-free emulsion method, Journal ofMicroencapsulation, 15, 163-172, 1998.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

63. Z. Lu, T.-K. Yell, M. Tsai, J.L.-s. All, M.G. Wientjes, Paciitaxel-loaded gelatin nanoparticles for intravesical bladder cancer therapy, Clinical Cancer Research, 10, 7677-7684, 2004.

64. A. Kaur, S. Jain, A. Tiwary, Mannan-coated gelatin nanoparticles for sus tained and targeted delivery of didanosine: in vitro and in vivo evaluation, Acta Pharmaceutica, 58, 61—74, 2008.

65. G. Young Lee, K. Park, J.H. Nam, S.Y. Kim, Y. Byun, Anti-tumor and antimetastatic effects of gelatin-doxorubicin and PEGylated gelatin-doxorubicin nanoparticles in SCC7 bearing mice, Journal ofDrug Targeting, 14, 707—716, 2006.

66. G.K. Zorzi, J.E. Pårraga, B. Seijo, A. Sånchez, Hybrid nanoparticle design based on cationized gelatin and the polyanions dextran sulfate and chondroitin sulfate for ocular gene therapy, Macromolecular Bioscience, 11, 905—913, 2011.

67. B. Seijo, E. Fattal, L. Roblot-Treupel, P. Couvreur, Design of nanoparticles of less than 50 nm diameter: preparation, characterization and drug loading, International Journal ofPharmaceutics, 62, 1—7, 1990.

68. A. Gürsoy, L. Eroélu, S. Ulutin, M. Tayürek, H. Fessi, F. Puisieux, J.-P. Devissaguet, Evaluation of indomethacin nanocapsules for their physical stability and inhibitory activity on inflammation and platelet aggregation, International Journal ofPharmaceutics, 52, 101—108, 1989.

69. J. Arias, V. Gallardo, M. Ruiz, A. Delgado, Ftorafur loading and controlled release from poly (ethyl-2-cyanoacrylate) and poly (butylcyanoacrylate) nanospheres, International Journal ofPharmaceutics, 337, 282-290, 2007.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

70. F. Kratz, Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles, Journal of Controlled Release, 132, 171—183, 2008.

71. N. Desai, V. Trieu, Z. Yao, L. Louie, S. Ci, A. Yang, C. Tao, T. De, B. Beals, D. Dykes, Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel, Clinical Cancer Research, 12, 1317-1324, 2006.

72. H. Sinn, H. Schrenk, E. Friedrich, U. Schilling, W Maier-Borst, Design of compounds having an enhanced tumour uptake, using serum albumin as a carrier. Part I, International Journal of Radiation Applications and Instrumentation. Part B. Nuclear Medicine and Biology, 17, 819—827, 1990.

73. J. Kreuter, T. Hekmatara, S. Dreis, T. Vogel, S. Gelperina, K. Langer, Covalent attachment of apolipoprotein Al and apolipoprotein B-100 to albumin nanoparticles enables drug transport into the brain, Journal of Controlled Release, 118, 54-58, 2007.

74. F. Danhier, E. Ansorena, J.M. Silva, R. coco, A. Le Breton, V. Préat, PLGAbased nanoparticles: an overview of biomedical applications, Journal of Controlled Release, 161, 505-522, 2012.

75. J. Kreuter, Nanoparticulate systems for brain delivery of drugs, Advanced Drug Delivery Reviews, 47, 65-81, 2001.

76. I. Fishbein, M. Chorny, L. Rabinovich, S. Banai, I. Gati, G. Golomb, Nanoparticulate delivery system of a tyrphostin for the treatment of restenosis, Journal of Controlled Release, 65, 221-229, 2000.

77. Y. Nishioka, H. Yoshino, Lymphatic targeting with nanoparticulate system, Advanced Drug Delivery Reviews, 47, 55—64, 2001.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

78. R. Müller, C. Jacobs, O. Kayser, Nanosuspensions as particulate drug formu lations in therapy: rationale for development and what we can expect for the future, Advanced Drug Delivery Reviews, 47, 3—19, 2001.

79. H. Takeuchi, H. Yamamoto, Y. Kawashima, Mucoadhesive nanoparticulate systems for peptide drug delivery, Advanced Drug Delivery Reviews, 47, 39-54, 2001.

80. A.Z. Wang, R. Langer, O.C. Farokhzad, Nanoparticle delivery of cancer drugs, Annual Review ofMedicine, 63, 185—198, 2012.

81. R.E. Eliaz, F.C. Szoka, Liposome-encapsulated doxorubicin targeted to CD44 a strategy to kill CD44-overexpressing tumor cells, Cancer Research, 61, 2592-2601, 2001.

82. H. Dehaghi, S.D. Zadeh, H. Keshvari, P. Abasian, Preparation and characterization of dorzolamide HCI loaded in niosome in order to study the amount of its realese, Research in Pharmaceutical Sciences, 7, S290, 2012.

83. H. Önyüksel, E. Jeon, I. Rubinstein, Nanomicellar paclitaxel increases cytotoxicity of multidrug resistant breast cancer cells, Cancer Letters, 274, 327—330, 2009.

84. E. Fleige, M.A. Quadir, R. Haag, Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications, Advanced Drug Delivery Reviews, 64, 866—884, 2012.

85. I.J. Majoros, A. Myc, T. Thomas, C.B. Mehta, J.R. Baker, PAMAM dendrimerbased multifunctional conjugate for cancer therapy: synthesis, characteriza tion, and functionality, Biomacromolecules, 7, 572—579, 2006.

86. C. Solans, P. Izquierdo, J. Nolla, N. Azemar, M. Garcia-Celma, Nanoemulsions, Current Opinion in Colloid & Interface Science, 10, 102—110, 2005.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

87. V.S. D.A. Prendergast, G. Pastorin, S. Jain, Carbon-Based Nanomaterials for Targeted Drug Delivery and Imaging, Targeted Drug Delivery: Concepts and Design, Springer, pp. 615—645, 2015.

88. J. Wang, D. Xu, A.N. Kawde, R. Polsky, Metal nanoparticle-based electrochemical stripping potentiometric detection of DNA hybridization, Analytical Chemistry, 73, 5576-5581, 2001.

89. R.B. Campbell, S.V. Balasubramanian, R.M. Straubinger, Influence of cationic lipids on the stability and membrane properties ofpaclitaxel-containing liposomes, Journal ofPharmaceutical Sciences, 90, 1091—1105, 2001.

90. L. Arleth, B. Ashok, H. Onyuksel, P. Ihiyagarajan, J. Jacob, R.P. Hjelm, Detailed structure of hairy mixed micelles formed by phosphatidylcholine and PEGylated phospholipids in aqueous media, Langmuir, 21, 3279—3290, 2005.

91. A. Krishnadas, I. Rubinstein, H. Önyüksel, Sterically stabilized phospholipid mixed micelles: in vitro evaluation as a novel carrier for water-insoluble drugs, Pharmaceutical Research, 20, 297—302, 2003.

92. R.D. Dabholkar, R.M. Sawant, D.A. Mongayt, P.V. Devarajan, V.P. Torchilin, Polyethylene glycol—phosphatidylethanolamine conjugate (PEG—PE)-based mixed micelles: some properties, loading with paclitaxel, and modulation of P-glycoprotein-mediated efflux, International Journal ofPharmaceutics, 315, 148-157, 2006.

93. S. Wissing, O. Kayser, R. Müller, Solid lipid nanoparticles for parenteral drug delivery, Advanced Drug Delivery Reviews, 56, 1257—1272, 2004.

94. M.J. Lawrence, G.D. Rees, Microemulsion-based media as novel drug delivery systems, Advanced Drug Delivery Reviews, 45, 89—121, 2000.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

95. A. Azeem, M. Rizwan, F.J. Ahmad, Z. Iqbal, R.K. Khar, M. Aqil, S. Talegaonkar, Nanoemulsion components screening and selection: a technical note, AAPS PharmSciTech, 10, 69-76, 2009.

96. Y. Li, G.H. Gao, D.S. Lee, Stimulus-sensitive polymeric nanoparticles and their applications as drug and gene carriers, Advanced Healthcare Materials, 2, 388-417, 2013.

97. H. Wu, L. Zhu, V.P. Torchilin, pH-sensitive poly (histidine)-PEG/DSPE-PEG co-polymer micelles for cytosolic drug delivery, Biomaterials, 34, 1213—1222, 2013.

98. G. Li, Y. Meng, L. Guo, T. Zhang, J. Liu, Formation of thermo-sensitive polyelectrolyte complex micelles from two biocompatible graft copolymers for drug delivery, Journal of Biomedical Materials Research Part A, 102, 2163-2172, 2014.

99. A. Russo, W. DeGraff, N. Friedman, J.B. Mitchell, Selective modulation of glutathione levels in human normal versus tumor cells and subsequent differential response to chemotherapy drugs, Cancer Research, 46, 2845—2848, 1986.

100. S. Mura, J. Nicolas, P. Couvreur, Stimuli-responsive nanocarriers for drug delivery, Nature Materials, 12, 991—1003, 2013.

101. V. Balamuralidhara, T. Pramodkumar, N. Srujana, M. Venkatesh, N.V. Gupta, K. Krishna, H. Gangadharappa, pH sensitive drug delivery systems: a review, American Journal of Drug Discovery and Development, 1, 24—48, 2011.

102. J.B. Park, C.S. Lee, J.H. Jang, J. Ghim, Y.-J. Kim, S. You, D. Hwang, P.G. suh, S.H. Ryu, Phospholipase signalling networks in cancer, Nature Reviews Cancer, 12, 782-792, 2012.

103. L. Zhu, P. Kate, V.P. Torchilin, Matrix metalloprotease 2-responsive multifunctional liposomal nanocarrier for enhanced tumor targeting, ACS Nano, 6, 3491-3498, 2012.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

104. Y. Sun, X. Yan, T. Yuan, J. Liang, Y. Fan, Z. Gu, X. Zhang, Disassemblable micelles based on reduction-degradable amphiphilic graft copolymers for intracellular delivery of doxorubicin, Biomaterials, 31, 7124—7131, 2010.

105. A.N. Koo, H.J. Lee, S.E. Kim, J.H. Chang, C. Park, C. Kim, J.H. Park, S.C. Lee, Disulfide-cross-linked PEG-poly (amino acid) s copolymer micelles for glutathione-mediated intracellular drug delivery, Chemical Communications, 48, 6570-6572, 2008.

106. Li, K. Xiao, J. Luo, W. Xiao, J.s, Lee, A.M. Gonik, J. Kato, T.A. Dong, K.S. Lam, Well-defined, reversible disulfide cross-linked micelles for ondemand paclitaxel delivery, Biomaterials, 32, 6633—6645, 2011.

107. H. Yu, Z. Xu, X. Chen, L. Xu, Q. Yin, Z. Zhang, Y. Li, Reversal of lung cancer multidrug resistance by pH-responsive micelleplexes mediating co-delivery of siRNA and paclitaxel, Macromolecular Bioscience, 14, 100—109, 2014.

108. G. Navarro, R.R. Sawant, S. Biswas, S. Essex, C. Tros de Ilarduya, V.P. Torchilin, P-glycoprotein silencing with siRNA delivered by DOPE-modified PEI overcomes doxorubicin resistance in breast cancer cells, Nanomedicine, 7, 65—78, 2012.

109. Y. Bae, N. Nishiyama, S. Fukushima, H. Koyama, M. Yasuhiro, K. Kataoka, Preparation and biological characterization of polymeric micelle drug carriers with intracellular pH-triggered drug release property: tumor permeability, controlled subcellular drug distribution, and enhanced in vivo antitumor efficacy, Bioconjugate Chemistry, 16, 122—130, 2005.

110. Y. Bae, W.-D. Jang, N. Nishiyama, S. Fukushima, K. Kataoka, Multifunctional polymeric micelles with folate-mediated cancer cell targeting and pHtriggered drug releasing properties for active intracellular drug delivery, Molecular BioSystems, 1, 242—250, 2005.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

111. H.L. Lu, W.J. Syu, N, Nishiyama, K. Kataoka, P.S. Lai, Dendrimer phthalocyanine-encapsulated polymeric micelle-mediated photochemical internalization extends the efficacy of photodynamic therapy and overcomes drug-resistance in vivo, Journal of Controlled Release, 155, 458—464, 2011.

112. Y. Yamada, Y. Shinohara, T. Kakudo, S. Chaki, S. Futaki, H. Kamiya, H. Harashima, Mitochondrial delivery of mastoparan with transferrin liposomes equipped with a pH-sensitive fusogenic peptide for selective cancer therapy, International Journal of Pharmaceutics, 303, 1—7, 2005.

113. P. Yingyuad, M. Mével, C. Prata, C. Kontogiorgis, M. Thanou, A.D. Miller, Enzyme-triggered PEGylated siRNA-nanoparticles for controlled release of siRNA, Journal ofRNAi and Gene Silencing: An International Journal ofRNA and Gene Targeting Research, 10 (2014) 490.

114. L. Zhu, F. Perche, T. Wang, V.P. Torchilin, Matrix metalloproteinase 2-sensitive multifunctional polymeric micelles for tumor-specific co-delivery of siRNA and hydrophobic drugs, Biomaterials, 35, 4213—4222, 2014.

115. C. Foged, H.M. Nielsen, S. Frokjaer, Liposomes for phospholipase A 2 triggered siRNA release: preparation and in vitro test, International Journal of Pharmaceutics, 331, 160-166, 2007.

116. H. Xiao, W. Li, R. Qi, L. Yan, R. Wang, S. Liu, Y. Zheng, Z. Xie, Y. Huang, X. Jing, Co-delivery of daunomycin and oxaliplatin by biodegradable polymers for safer and more efficacious combination therapy, Journal of Controlled Release, 163, 304-314, 2012.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

117. K. Nam, H.Y. Nam, PH. Kim, S.W. Kim, Paciitaxel-conjugated PEG and argi nine-grafted bioreducible poly (disulfide amine) micelles for co-delivery of drug and gene, Biomaterials, 33, 8122—8130, 2012.

118. M. Balakirev, G. Schoehn, J. Chroboczek, Lipoic acid-derived amphiphiles for redox-controlled DNA delivery, Chemistry & Biology, 7, 813—819, 2000.

119. T. Musacchio, O. Vaze, G. D'Souza, V.P. Torchilin, Effective stabilization and delivery of siRNA: reversible siRNA-phospholipid conjugate in nanosized mixed polymeric micelles, Bioconjugate Chemistry, 21, 1530—1536, 2010.

120. S.B. La, T. Okano, K. Kataoka, Preparation and characterization of the micelle-forming polymeric drug indomethacin-incorporated poly (ethylene oxide)—poly (ß-benzyl L-aspartate) block copolymer micelles, Journal of Pharmaceutical Sciences, 85, 85—90, 1996.

121. T. Ta, T.M. Porter, Thermosensitive liposomes for localized delivery and triggered release of chemotherapy, Journal of Controlled Release, 169, 112—125, 2013.

122. V.P. Torchilin, Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery, Nature Reviews Drug Discovery, 13, 813—827, 2014.

123. A. Akbarzadeh, M. Samiei, S. Davaran, Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine, Nanoscale Research Letters, 7, 1-13, 2012.

124. R.F. Donnelly, P.A. McCarron, D.I. Morrow, S.A. Sibani, A.D. Woolfson, Photosensitiser delivery for photodynamic therapy. Part 1: Topical carrier platforms, Expert Opinion on Drug Delivery, 5, 1241—54, 2008.

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https://doi.org/10.1002/9781119242628.ch8

125. A. Yavlovich, B. Smith, K. Gupta, R. Blumenthal, A. Puri, Light-sensitive lipid-based nanoparticles for drug delivery: design principles and future considerations for biological applications, Molecular Membrane Biology, 27, 364-381, 2010.

126. Z. Peng, C. Wang, E. Fang, X. Lu, G. Wang, Q. Tong, Co-delivery of doxorubicin and SATB 1 shRNA by thermosensitive magnetic cationic liposomes for gastric cancer therapy, Plos One, 9, e92924, 2014.

127. M.B. Yatvin, J.N. Weinstein, W.H. Dennis, R. Blumenthal, Design of liposomes for enhanced local release of drugs by hyperthermia, Science, 202, 1290-1293, 1978.

128. D. Needham, G. Anyarambhatla, G. Kong, M.W. Dewhirst, A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model, Cancer Research, 60, 1197-1201, 2000.

129. J. Woo, G.N. Chiu, G. Karlsson, E. Wasan, L. Ickenstein, K. Edwards, M.B. Bally, Use of a passive equilibration methodology to encapsulate cisplatin into preformed thermosensitive liposomes, International Journal of Pharmaceutics, 349, 38—46, 2008.

130. S.M. Park, M.S. Kim, s.-J. Park, E.S. Park, K.-S. Choi, Y.-S. Kim, H.R. Kim, Novel temperature-triggered liposome with high stability: formulation, in vitro evaluation, and in vivo study combined with high-intensity focused ultrasound (HIFU), Journal of Controlled Release, 170, 373—379, 2013.

131. W.E. Hennink, C.F. van Nostrum, Y. Shi, Interfacially hydrazone crosslinked thermosensitive polymeric micelles showed de-crosslinking and accelerated paclitaxel release at acidic pH, ACS Biomaterials Science & Engineering, 1, 585-592, 2015.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

132. J. You, P. Zhang, F. Hu, Y. Du, H. Yuan, J. Zhu, Z. Wang, J. Zhou, C. Li, Nearinfrared light-sensitive liposomes for the enhanced photothermal tumor treatment by the combination with chemotherapy, Pharmaceutical Research, 31, 554-565, 2014.

133. D. Luo, K.A. Carter, A. Razi, J. Geng, S. Shao, D. Giraldo, U. Sunar, J. Ortega, J.F. Lovell, Doxorubicin encapsulated in stealth liposomes conferred with light-triggered drug release, Biomaterials, 75, 193—202, 2016.

134. S. Huang, D. Yin, Y. Zhao, Y, Gu, Optimization and characterization of the photosensitive N-succinyl-N'-4-(2-nitrobenzyloxy)-succinyl-chitosan micelles, Twelfth International Conference on Photonics and Imaging in Biology and Medicine (PIBM 2014), International Society for Optics and Photonics, pp. 92300c-92312C, 2014.

135. H. Ding, V. Sagar, M. Agudelo, S. Pilakka-Kanthikeel, V.S.R. Atluri, A. Raymond, T. Samikkannu, M.P. Nair, Enhanced blood—brain barrier transmigration using a novel transferrin embedded fluorescent magnetoliposome nanoformulation, Nanotechnology, 25, 055101, 2014.

136. M. Babincova, P. Ciémanec, V. Altanerova, C. Altaner, P. Babinec, AC-magnetic field controlled drug release from magnetoliposomes: design of a method for site-specific chemotherapy, Bioelectrochemistry, 55, 17—19, 2002.

137. S. Reinicke, S. Döhler, S. Tea, M. Krekhova, R. Messing, A.M. Schmidt, H. Schmalz, Magneto-responsive hydrogels based on maghemite/triblock terpolymer hybrid micelles, Soft Matter, 6, 2760—2773, 2010.

138. L. Zhu, R.I. Mahato, Targeted delivery of siRNA to hepatocytes and hepatic stellate cells by bioconjugation, Bioconjugate Chemistry, 21, 2119-2127, 2010.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

139. X. Yang, C. Cheng, Y. Wang, L. Qiu, D. Li, Liquid-mediated dense integration of graphene materials for compact capacitive energy storage, Science, 341, 534-537, 2013.

140. M. Nurunnabi, Z. Khatun, K.M. Huh, S.Y. Park, D.Y. Lee, K.J. Cho, Y.-K. Lee, In vivo biodistribution and toxicology of carboxylated graphene quantum dots, ACS Nano, 7, 6858-6867, 2013.

141. Q. Liu, B. Guo, Z. Rao, B. Zhang, J.R. Gong, Strong two-photon-induced fluorescence from photostable, biocompatible nitrogen-doped graphene quantum dots for cellular and deep-tissue imaging, Nano Letters, 13, 2436—2441, 2013.

142. Y. Dong, J. Lin, Y. Chen, F. Fu, Y. Chi, G. Chen, Graphene quantum dots, graphene oxide, carbon quantum dots and graphite nanocrystals in coals, Nanoscale, 6, 7410-7415, 2014.

143. P.J.F. Harris, Carbon Nanotube Science: Synthesis, Properties and Applications, Cambridge, Cambridge University Press, 2009.

144. L. Qu, L. Dai, M. Stone, Z. Xia, Z.L. Wang, Carbon nanotube arrays with strong shear binding-on and easy normal lifting-off, Science, 322, 238—242, 2008.

145. M. Endo, T. Hayashi, Y.-A. Kim, Large-scale production of carbon nanotubes and their applications, Pure and Applied Chemistry, 78, 1703—1713, 2006.

146. K. Gong, F. Du, Z. Xia, M. Durstock, L. Dai, Nitrogen-doped carbon nanotube arrays with high electrocatalytic activity for oxygen reduction, Science, 323, 760-764, 2009.

147. J.M. Lee, J.S. Park, S.H. Lee, H. Kim, S. Yoo, S.O. Kim, Selective electron-or hole-transport enhancement in bulk-heterojunction organic solar cells with N-or B-doped carbon nanotubes, Advanced Materials, 23, 629—633, 2011.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

148. A.D. Franklin, M. Luisier, S.-J. Han, G. Tulevski, C.M. Breslin, L. Gignac, M.S. Lundstrom, W. Haensch, Sub-IO nm carbon nanotube transistor, Nano Letters, 12, 758-762, 2012.

149. D.W. Wang, F. Li, J. Zhao, W. Ren, Z.G. Chen, J. Tan, Z.S. wu, 1. Gentle, G.Q. Lu, H.M. Cheng, Fabrication of graphene/polyaniline composite paper via in situ anodic electropolymerization for high-performance flexible electrode, ACS Nano, 3, 1745-1752, 2009.

150. I.V. Lightcap, T.H. Kosel, P.V. Kamat, Anchoring semiconductor and metal nanoparticles on a two-dimensional catalyst mat. Storing and shuttling electrons with reduced graphene oxide, Nano Letters, 10, 577—583, 2010.

151. K. Novoselov, A.K. Geim, S. Morozov, D. Jiang, M. Katsnelson, I. Grigorieva, S. Dubonos, A. Firsov, Two-dimensional gas of massless Dirac fermions in graphene, Nature, 438, 197—200, 2005.

152. K.S. Novoselov, A.K. Geim, S. Morozov, D. Jiang, Y. Zhang, S.A. Dubonos, I. Grigorieva, A. Firsov, Electric field effect in atomically thin carbon films, Science, 306, 666-669, 2004.

153. A.A. Balandin, S. Ghosh, W. Bao, I. Calizo, D. Teweldebrhan, F. Miao, C.N. Lau, Superior thermal conductivity of single-layer graphene, Nano Letters, 8, 902-907, 2008.

154. C. Berger, Z. song, T. Li, X. Li, AX Ogbazghi, R. Feng, Z. Dai, A.N. Marchenkov, E.H. Conrad, P.N. First, Ultrathin epitaxial graphite: 2D electron gas properties and a route toward graphene-based nanoelectronics, The Journal ofPhysical Chemistry B, 108, 19912-19916, 2004.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

155. T. Thompson, E. Falardeau, L.R. Hanlon, The electrical conductivity and optical reflectance of graphite-SbF 5 compounds, Carbon, 15, 39—43, 1977.

156. L. Peng, Y. Feng, P. Lv, D. Lei, Y. Shen, Y. Li, W. Feng, Transparent, conductive, and flexible multiwalled carbon nanotube/graphene hybrid electrodes with two three-dimensional microstructures, 7he Journal of Physical Chemistry C, 116, 4970-4978, 2012.

157. A. Hahn, S. Barcikowski, Production of bioactive nanomaterial using laser generated nanoparticles, Journal of Laser Micro/Nanoengineering, 4, 51—54, 2009.

158. S. Sadrnezhaad, H. Arami, H. Keivan, R. Khalifehzadeh, Powder metallurgical fabrication and characterization of nanostructured porous NiTi shapememory alloy, Materials and Manufacturing Processes, 21, 727—735, 2006.

159. D. Stoeckel, Nitinol medical devices and implants, Minimally Invasive Therapy & Allied Technologies, 9, 81—88, 2000.

160. T. Zhao, Y. Li, Y. Xia, S.S. Venkatraman, Y. Xiang, X. Zhao, Formation of a nano-pattering NiTi surface with Ni-depleted superficial layer to promote corrosion resistance and endothelial cell-material interaction, Journal of Materials Science: Materials in Medicine, 24, 105—114, 2013.

161. H.D. Samaroo, J. Lu, T.J. Webster, Enhanced endothelial cell density on NiTi surfaces with sub-micron to nanometer roughness, International Journal of Nanomedicine, 3 (2008) 75.

162. H.S. Park, K. Gall, J.A. Zimmerman, Shape memory and pseudoelasticity in metal nanowires, Physical Review Letters, 95, 255504, 2005.

163. H.S. Park, C. Ji, On the thermomechanical deformation of silver shape memory nanowires, Acta Materialia, 54, 2645—2654, 2006.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

164. R. Amini, M. Hadianfard, E. Salahinejad, M. Marasi, T. Sritharan, Microstructural phase evaluation of high-nitrogen Fe—Cr—Mn alloy powders synthesized by the mechanical alloying process, Journal ofMaterials Science, 44, 136-148, 2009.

165. R. Amini, H. Shokrollahi, E. Salahinejad, M. Hadianfard, M. Marasi, T. Sritharan, Microstructural, thermal and magnetic properties of amorphous/nanocrystalline FeCrMnN alloys prepared by mechanical alloying and subsequent heat treatment, Journal of Alloys and Compounds, 480, 617-624, 2009.

166. E. Salahinejad, M.J. Hadianfard, D.D. Macdonald, S. Sharifi-Asl, M. Mozafari, K.J. Walker, A.T. Rad, S.V. Madihally, L. Tayebi, In vitro electrochemical corrosion and cell viability studies on nickel-free stainless steel orthopedic implants, PLOS One 8, e61633, 2013.

167. E. Salahinejad, R. Amini, M. Marasi, M.J. Hadianfard, The effect of sintering time on the densification and mechanical properties of a mechanically alloyed Cr—Mn—N stainless steel, Materials & Design, 31, 527—532, 2010.

168. E. Salahinejad, R. Amini, E.A. Bajestani, M. Hadianfard, Microstructural and hardness evolution of mechanically alloyed Fe-Cr—Mn—N powders, Journal ofAlloys and Compounds, 497, 369-372, 2010.

169. E. Salahinejad, R. Amini, M. Marasi, M. Hadianfard, Microstructure and wear behavior of a porous nanocrystalline nickel-free austenitic stainless steel developed by powder metallurgy, Materials & Design, 31, 2259—2263, 2010.

170. E. Salahinejad, R. Amini, M. Hadianfard, Structural evolution during mechanical alloying of stainless steels under nitrogen, Powder Technology, 215, 247-253, 2012.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

171. E. Salahinejad, R. Amini, M. Hadianfard, Effect of milling time on structure and mechanical properties of porous nickel-free austenitic stainless steels processed by mechanical alloying and sintering, Materials Science and Engineering: A, 527, 5522-5527, 2010.

172. E. Salahinejad, R. Amini, M. Hadianfard, Contribution of nitrogen concentration to compressive elastic modulus of 18Cr—12Mn—xN austenitic stainless steels developed by powder metallurgy, Materials & Design, 31, 2241-2244, 2010.

173. E. Salahinejad, M. Hadianfard, M. Ghaffari, S.B. Mashhadi, A. Okyay, Liquidphase sintering of medical-grade P558 stainless steel using a new biocompatible eutectic additive, Materials Letters, 74, 209—212, 2012.

174. S. Izadi, K. Janghorban, G. Akbari, M. Ghafari, E. Salahinejad, Effects of boron addition on mechanical alloying and ordering behaviors of Fe—Al—(B) alloy powders, Journal ofAlloys and Compounds, 493, 645—648, 2010.

175. E. Salahinejad, M. Hadianfard, M. Ghaffari, S.B. Mashhadi, A. Okyay, Compositional homogeneity in a medical-grade stainless steel sintered with a Mn—Si additive, Materials Science and Engineering: C, 32, 2215—2219, 2012.

176. R. Amini, E. Salahinejad, E.A. Bajestani, M. Hadianfard, On the general outline of physical properties of amorphous-nanocrystalline Fe—Cr—Mn—N alloy powders prepared by mechanical alloying under nitrogen, Journal of Alloys and Compounds, 509, 3252-3256, 2011.

177. E. Salahinejad, R. Amini, M. Ghaffari, M. Hadianfard, Crystal interstitial sites contribution to nitrogen supersaturation in mechanically alloyed Fe—Cr—Mn—N alloys, Journal of Alloys and Compounds, 505, 584—587, 2010. 178. E. Salahinejad, M.J.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

Hadianfard, M. Ghaffari, S.B. Mashhadi, A.K. Okyay, Fabrication of nanostructured medical-grade stainless steel by mechanical alloying and subsequent liquid-phase sintering, Metallurgical and Materials

178. Transactions A, 43, 2994-2998, 2012.

179. E. Salahinejad, M. Hadianfard, M. Ghaffari, R. Amini, S.B. Mashhadi, A. Okyay, Microstructural characterization of medical-grade stainless steel powders prepared by mechanical alloying and subsequent annealing, Advanced Powder Technology, 24, 605—608, 2013.

180. M. Javanbakht, M. Hadianfard, E. Salahinejad, Microstructure and mechanical properties of a new group of nanocrystalline medical-grade stainless steels prepared by powder metallurgy, Journal of Alloys and Compounds, 624, 17-21, 2015.

181. R. Amini, E. Salahinejad, M. Hadianfard, E.A. Bajestani, M. Sharifzadeh, A novel approach to quantify nitrogen distribution in nanocrystalline amorphous alloys, Journal of Alloys and Compounds, 509, 2248—2251, 2011.

182. M. Javanbakht, E. Salahinejad, M. Hadianfard, The effect of sintering temperature on the structure and mechanical properties of medical-grade powder metallurgy stainless steels, Powder Technology, 289, 37—43, 2016.

183. C. Shearwood, Y. Fu, L. Yu, K. Khor, Spark plasma sintering of TiNi nanopowder, Scripta Materialia, 52, 455—460, 2005.

184. M. Caldorera-Moore, N.A. Peppas, Micro-and nanotechnologies for intelligent and responsive biomaterial-based medical systems, Advanced Drug Delivery Reviews, 61, 1391-1401, 2009.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

185. D.E. Owens, J.K. Eby, Y. Jian, N.A. Peppas, Temperature-responsive polymer—gold nanocomposites as intelligent therapeutic systems, Journal of Biomedical Materials Research Part A, 83, 692-695, 2007.

186. F. Heidenau, W. Mittelmeier, R. Detsch, M. Haenle, F. Stenzel, G. Ziegler, H. Gollwitzer, A novel antibacterial titania coating: metal ion toxicity and in vitro surface colonization, Journal of Materials Science: Materials in Medicine, 16, 883-888, 2005.

187. J. Wataha, P. Lockwood, M. Marek, M. Ghazi, Ability of Ni-containing biomedical alloys to activate monocytes and endothelial cells in vitro, Journal of Biomedical Materials Research, 45, 251—257, 1999.

188. H.l. Yell, S.K. Lu, T.Y. Tian, R.C. Hong, W.H. Lee, C.H. Tsai, Comparison of endothelial cells grown on different stent materials, Journal of Biomedical Materials Research Part A, 76, 835—841, 2006.

189. Y. Shen, G. Wang, L. Chen, H. Li, P. Yu, M. Bai, Q. Zhang, J. Lee, Q. Yu, Investigation of surface endothelialization on biomedical nitinol (NiTi) alloy: effects of surface micropatterning combined with plasma nanocoatings, Acta Biomaterialia, 5, 3593—3604, 2009.

190. Z. Huan, L. Fratila-Apachitei, I. Apachitei, J. Duszczyk, Synthesis and characterization of hybrid micro/nano-structured NiTi surfaces by a combination of etching and anodizing, Nanotechnology, 25, 055602, 2014.

191. J. Choi, D. Bogdanski, M. Köller, S.A. Esenwein, D. Müller, G. Muhr, M. Epple Calcium phosphate coating of nickel—titanium shape-memory alloys. Coating procedure and adherence of leukocytes and platelets, Biomaterials, 24, 3689-3696, 2003.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

192. S. Kujala, J. Ryhänen, A. Danilov, J. Tuukkanen, Effect of porosity on the osteointegration and bone ingrowth of a weight-bearing nickel—titanium bone graft substitute, Biomaterials, 24, 4691—4697, 2003.

193. W. Ni, Y. T. Cheng, D.S. Grummon, Microscopic shape memory and superelastic effects under complex loading conditions, Surface and Coatings Technology, 177, 512-517, 2004.

194. S. Rana, A. Bajaj, R. Mout, V.M. Rotello, Monolayer coated gold nanoparticles for delivery applications, Advanced Drug Delivery Reviews, 64, 200—216, 2012.

195. S. Manju, K. Sreenivasan, Gold nanoparticles generated and stabilized by water soluble curcumin—polymer conjugate: blood compatibility evaluation and targeted drug delivery onto cancer cells, Journal of Colloid and Interface Science, 368, 144-151, 2012.

196. M.E. Stewart, C.R. Anderton, L.B. Thompson, J. Maria, S.K. Gray, J.A. Rogers, R.G. Nuzzo, Nanostructured plasmonic sensors, Chemical Reviews, 108, 494-521, 2008.

197. M. Prabaharan, J.J. Grailer, S. Pilla, D.A. Steeber, S. Gong, Gold nanoparticles with a monolayer of doxorubicin-conjugated amphiphilic block copolymer for tumor-targeted drug delivery, Biomaterials, 30, 6065—6075, 2009.

198. R. Hong, G. Han, J.M. Fernåndez, B.-J. Kim, N.S. Forbes, V.M. Rotello, Glutathione-mediated delivery and release using monolayer protected nanoparticle carriers, Journal of the American Chemical Society, 128, 1078-1079, 2006.

199. G.B. Braun, A. Pallaoro, G. Wu, D. Missirlis, J.A. Zasadzinski, M. Tirrell, N.O. Reich, Laser-activated gene silencing via gold nanoshell-siRNA conjugates, ACS Nano, 3, 2007-2015, 2009.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

200. G. Han, C.C. You, B.J. Kim, R.S. Turingan, N.S. Forbes, C.T. Martin, V.M. Rotello, Light-regulated release of DNA and its delivery to nuclei by means of photolabile gold nanoparticles, Angewandte Chemie, 118, 3237—3241, 2006.

201. X. An, F. Zhan, Y. Zhu, Smart photothermal-triggered bilayer phase transition in AuNPs—liposomes to release drug, Langmuir, 29, 1061—1068, 2013.

202. M. Freeman, A. Arrott, J. Watson, Magnetism in medicine, Journal ofApplied Physics, 31 (1960) S404-S405.

203. F. Chen, Q. Gao, J. Ni, The grafting and release behavior of doxorubincin from Fe304@ Si02 core—shell structure nanoparticles via an acid cleaving amide bond: the potential for magnetic targeting drug delivery, Nanotechnology, 19, 165103, 2008.

204. G.C. Kim, Y.Y. Li, Y.F. Chu, S.X. Cheng, R.X. Zhuo, X.Z. Zhang, Nanosized temperature-responsive Fe304-UA-g-P (UA-co-NIPAAm) magnetomicelles for controlled drug release, European Polymer Journal, 44, 2761—2767, 2008.

205. K. Hayashi, M. Nakamura, H. Miki, S. Ozaki, M. Abe, T. Matsumoto, W. Sakamoto, T. Yogo, K. Ishimura, Magnetically responsive smart nanopar ticles for cancer treatment with a combination of magnetic hyperthermia and remote-control drug release, Theranostics, 4, 834, 2014.

206. W. Guo, C. Yang, H. Lin, F. Qu, P (EO-co-LLA) functionalized Fe304@ mSi02 nanocomposites for thermo/pH responsive drug controlled release and hyperthermia, Dalton Transactions, 43, 18056—18065, 2014.

207. Z. Liu, S. Tabakman, K. Welsher, H. Dai, Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery, Nano Research, 2, 85-120, 2009.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

208. G. Cirillo, S. Hampel, U.G. Spizzirri, 0.1. Parisi, N. Picci, F. lemma, Carbon nanotubes hybrid hydrogels in drug delivery: a perspective review, BioMed Research International, 2014, 17, 2014.

209. S. Marchesan, M. Prato, Under the lens: carbon nanotube and protein interaction at the nanoscale, Chemical Communications, 51, 4347—4359, 2015.

210. M. Ito, T. Kobayashi, Y Ito, T. Hayashida, D. Nii, K. Umemura, Y. Homma, Intense photoluminescence from dried double-stranded DNA and singlewalled carbon nanotube hybrid, Applied Physics Letters, 104, 043102, 2014.

211. R. Li, R.A. wu, L. Zhao, Z. Hu, S. Guo, X. Pan, H. zou, Folate and iron difunctionalized multiwall carbon nanotubes as dual-targeted drug nanocarrier to cancer cells, Carbon, 49, 1797—1805, 2011.

212. X. Zhang, L. Meng, Q. Lu, Z. Fei, P.J. Dyson, Targeted delivery and controlled release of doxorubicin to cancer cells using modified single wall carbon nanotubes, Biomaterials, 30, 6041—6047, 2009.

213. J. Yun, J.s. 1m, Y.S. Lee, T.S. Bae, Y.M. Lim, H.l. Kim, pH and electroresponsive release behavior of MWCNT/PVA/PAAc composite microcapsules, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 368, 23-30, 2010.

214. J. Yun, J.S. Lm, Y.S. Lee, H.I. Kim, Electro-responsive transdermal drug delivery behavior of PVA/PAA/MWCNT nanofibers, European Polymer Journal, 47, 1893-1902, 2011.

215. U.G. Spizzirri, S. Hampel, G. Cirillo, F.P. Nicoletta, A. Hassan, O. Vittorio, N. Picci, F. lemma, Spherical gelatin/CNTs hybrid microgels as electroresponsive drug delivery systems, International Journal of Pharmaceutics, 448, 115-122, 2013.

This is the accepted manuscript (postprint) of the following article:
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https://doi.org/10.1002/9781119242628.ch8

216. M. Ghosh, S. Brahmachari, P.K. Das, pH-responsive single walled carbon nanotube dispersion for target specific release of doxorubicin to cancer cells, Macromolecular Bioscience, 14, 1795—1806, 2014.

217. X. Yang, X. Zhang, Y. Ma, Y. Huang, Y. Wang, Y. Chen, Superparamagnetic graphene oxide—Fe304 nanoparticles hybrid for controlled targeted drug carriers, Journal of Materials Chemistry, 19, 2710—2714, 2009.

218. E. song, W. Han, C. Li, D. Cheng, L. Li, L. Liu, G. Zhu, Y. song, W. Tan, Hyaluronic acid-decorated graphene oxide nanohybrids as nanocarriers for targeted and pH-responsive anticancer drug delivery, ACS Applied Materials & Interfaces, 6, 11882-11890, 2014.

219. H. Hu, J. Yu, Y. Li, J. Zhao, H. Dong, Engineering of a novel pluronic F 127/ graphene nanohybrid for pH responsive drug delivery, Journal of Biomedical Materials Research Part A, 100, 141—148, 2012.

220. H. wen, C. Dong, H. Dong, A. Shen, W. Xia, X. Cai, Y. song, X. Li, Y Li, D. Shi, Engineered redox-responsive PEG detachment mechanism in PEGylated nano-graphene oxide for intracellular drug delivery, Small, 8, 760-769, 2012.

221. Y. Pan, H. Bao, N.G. Sahoo, T. Wu, L. Li, Water-soluble poly (N-isopropylacrylamide)-graphene sheets synthesized via click chemistry for drug delivery, Advanced Functional Materials, 21, 2754—2763, 2011.

222. E.S. Day, L.R. Bickford, J.H. Slater, N.S. Riggall, R.A. Drezek, J.L. west, Antibody-conjugated gold-gold sulfide nanoparticles as multifunctional agents for imaging and therapy of breast cancer, International Journal of Nanomedicine, 5, 445, 2010.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

223. Y. Hou, Y. Liu, Z. Chen, N. Gil, J. Wang, Manufacture of IRDye 800 CW-coupled Fe304 nanoparticles and their applications in cell labeling and in vivo imaging, Journal of Nanobiotechnology, 8, 25, 2010.

224. B. Feng, R. Hong, L. Wang, L. Guo, H. Li, J. Ding, Y. Zheng, D. Wei, Synthesis of Fe304/APTES/PEG diacid functionalized magnetic nanoparticles for MR imaging, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 328, 52-59, 2008.

225. C.W. Lai, Y.H. Wang, C.H. Lai, M.J. Yang, C.Y. Chen, P.T. Chou, C.S. Chan, Y. Chi, Y.C. Chen, J.K. Hsiao, Iridium-complex-functionalized Fe304/SiO2 core/shell nanoparticles: a facile three-in-one system in magnetic resonance imaging, luminescence imaging, and photodynamic therapy, Small, 4, 218-224, 2008.

226. A. De La Zerda, C. Zavaleta, S. Keren, S. Vaithilingam, S. Bodapati, Z. Liu, J. Levi, B.R. Smith, T.J. Ma, O. Oralkan, Carbon nanotubes as photoacoustic molecular imaging agents in living mice, Nature Nanotechnology, 3, 557—562, 2008.

227. H. wu, G. Liu, Y Zhuang, D. wu, H. Zhang, H. Yang, H. Hu, S. Yang, The behavior after intravenous injection in mice of multiwalled carbon nanotube/Fe304 hybrid MRI contrast agents, Biomaterials, 32, 4867-4876, 2011.

228. K. Welsher, Z. Liu, D. Daranciang, H. Dai, Selective probing and imaging of cells with single walled carbon nanotubes as near-infrared fluorescent molecules, Nano Letters, 8, 586—590, 2008.

229. K. Yang, L. Hu, X. Ma, S. Ye, L. Cheng, X. Shi, C. Li, Y. Li, Z. Liu, Multimodal imaging guided photothermal therapy using functionalized graphene nanosheets anchored with magnetic nanoparticles, Advanced Materials, 24, 1868-1872, 2012.

This is the accepted manuscript (postprint) of the following article:
M. D. Fahmy, H. E. Jazayeri, M. Razavi, M. Hashemi, M. Omidi, M. Farahani, E. Salahinejad, A. Yadegari, S. Pitcher, L. Tayebi, *Biomedical applications of intelligent nanomaterials*, Intelligent Nanomaterials, 2 (2016) 199-245.
https://doi.org/10.1002/9781119242628.ch8

230. X. Ma, H. Tao, K. Yang, L. Feng, L. Cheng, X. Shi, Y. Li, L. Guo, Z. Liu, A functionalized graphene oxide-iron oxide nanocomposite for magnetically targeted drug delivery, photothermal therapy, and magnetic resonance imaging, Nano Research, 5, 199—212, 2012.

231. W. Chen, P. Yi, Y. Zhang, L. Zhang, Z. Deng, Z. Zhang, Composites of aminodextran-coated Fe304 nanoparticles and graphene oxide for cellular magnetic resonance imaging, ACS Applied Materials & Interfaces, 3, 4085—4091, 2011.

232. X.D. Li, X.L. Liang, X.L. Yue, J.R. Wang, C.H. Li, X.J. Deng, L.J. Jing, L. Lin, E.Z. Qu, S.M. Wang, Imaging guided photothermal therapy using iron oxide loaded poly (lactic acid) microcapsules coated with graphene oxide, Journal of Materials Chemistry B, 2, 217—223, 2014.

233. S.H. Hu, Y.W. Chen, W.T. Hung, I.W. Chen, S.Y. Chen, Quantum-dot-tagged reduced graphene oxide nanocomposites for bright fluorescence bioimaging and photothermal therapy monitored in situ, Advanced Materials, 24, 1748-1754, 2012.