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Review Article

Smart Nanoparticles for Drug Delivery Application: Development of Versatile Nanocarrier Platforms in Biotechnology and Nanomedicine

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The study of nanostructured drug delivery systems allows the development of novel platforms for the efficient transport and controlled release of drug molecules in the harsh microenvironment of diseased tissues of living systems, thus offering a wide range of functional nanoplatforms for smart application in biotechnology and nanomedicine. This article highlights recent advances of smart nanocarriers composed of organic (including polymeric micelles and vesicles, liposomes, dendrimers, and hydrogels) and inorganic (including quantum dots, gold and mesoporous silica nanoparticles) materials. Despite the remarkable developments of recent synthetic methodologies, most of all nanocarriers' action is associated with a number of unwanted side effects that diminish their efficient use in biotechnology and nanomedicine applications. This highlights some critical issues in the design and engineering of nanocarrier systems for biotechnology applications, arising from the complex environment and multiform interactions established within the specific biological media.

1. Introduction

In the last decades, the development of novel approaches for the construction of nanoformulations (nanocarriers) for the efficient transport of drug molecules offers a wide range of biotechnology applications [1, 2]. Smart nanostructured materials can deliver drugs to the target sites with reduced dosage frequency and in a (spatial/temporal) controlled manner to mitigate the side effects experienced with traditional therapies. In particular, they allow resolving the main critical issues encountered with conventional pharmaceutical treatments such as the nonspecific distribution, rapid clearance, uncontrollable release of drugs, and low bioavailability [3–5]. The overall effect is a sensitive reduction in toxicity and/or adverse reactions. However, despite the remarkable developments of recent methodologies, most of all nanocarriers' action is associated with a number of unwanted side effects that diminish their efficient use in nanomedicine. This highlights some critical issues in the design and engineering of nanocarrier systems for biotechnology applications, arising from the complex environment and multiform interactions established within the specific biological media [6–8].

In this article, we highlight the recent development of nanostructured nanocarrier systems for drug delivery applications with a focus on the main properties and applications of the main organic nanocarriers (such as polymer-based micelles, liposomes, and dendrimers) and inorganic nanoparticles (such as carbon nanotubes, gold nanoparticles, and quantum dots). We analyse the main factors (and parameters) that strongly influence the design of nanostructure systems for the delivery of active drugs and chemotherapeutics.

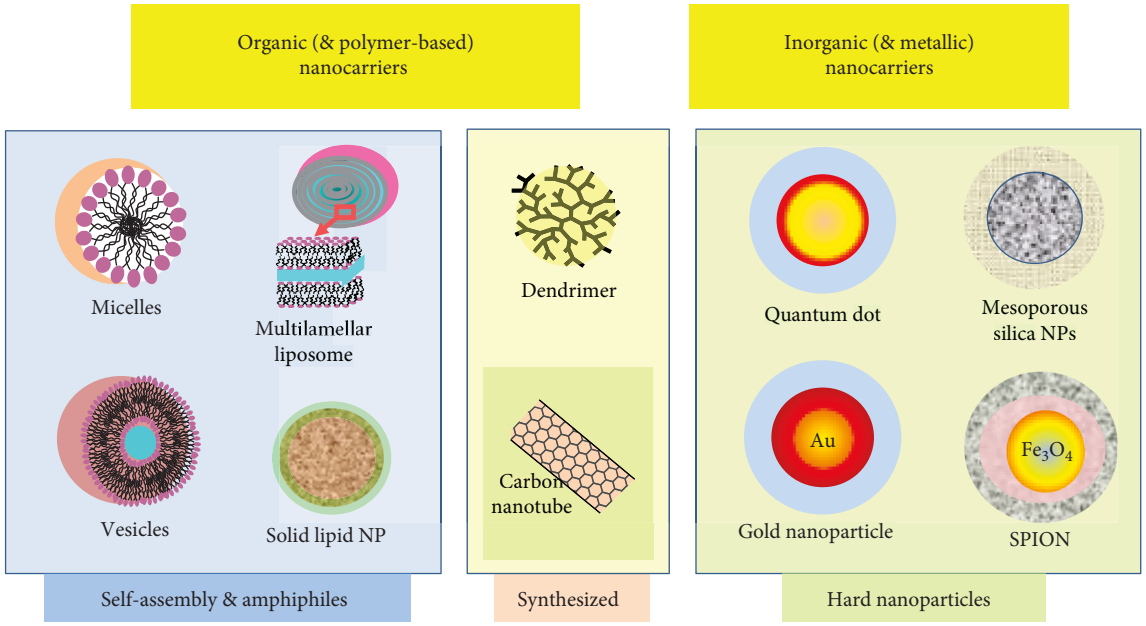

Figure 1: Example of the most employed organic and inorganic nanocarriers for smart application in drug delivery.

Furthermore, we put into evidence the current status (challenges and limitations) and emerging approaches of the nanoplatforms for therapeutic applications.

2. Nanocarriers for Drug Delivery: Basic Properties

Conventional drug delivery systems of chemotherapeutic agents present a number of critical issues associated with the sensitive toxicity, poor specificity, and drug resistance induction, which sensitively decrease the therapeutic efficiency of many drug systems. Nanocarrier-based platforms are dedicated systems to the transport of chemotherapeutic active drugs composed of colloidal nanoparticles with submicron size (typically <500 nm) generally characterised by a high surface area to volume ratio. These nanostructured prototypes have enabled effective delivery of active (including anticancer) drugs into the diseased tissues. The overall goal of the employment nanocarriers in drug delivery applications is to treat a disease effectively with minimum side effects, thereby aiming at a sensitive improvement of the therapeutic outcomes by exploiting the (patho-)physiology of a diseased tissue microenvironment.

Modern smart nanostructured systems can be broadly divided into *organic* and *inorganic* nanocarriers (see Figure 1), while their physiochemical properties can be tuned by altering their compositions (organic, inorganic, or hybrid), dimensions (small or large sizes), shapes (sphere, rod, hyperbranched, multilamellar, or multilayered structures), and surface properties (functional groups, surface charge, PEGylation, coating processes, or attachment of targeting moieties). While a number of nanocarrier-based platforms have been approved for the treatment of various diseases (including tumors), many others are in different phases of clinical trials [9, 10]. In the following sections, we will discuss the main features of the different types of nanocarriers.

3. Organic and Polymer-Based Nanocarriers

The organic nanocarriers are carbon-based nanomaterials that are generally characterised by a high biocompatibility and improved drug loading capacity. They allow a versatile control of both morphology and chemical composition, while their colloidal stability and relatively large size allow incorporating and carrying a wide combination of different (hydrophilic/hydrophobic) drugs [11, 12]. Depending on the preparation methods, we can subdivide them into two main categories, namely, nanostructures that exploit the *self-assembly processes* (such as amphiphilic systems) and those that are obtained by specific *synthesis methods* (such as the dendrimers, hyperbranched polymers, chemical nanogels, and carbon nanotubes). It is worth noticing that the new generation of nanocarriers often is constructed by the suitable combination of the two methods by exploiting the *supramolecular approach* [13, 14].

3.1. Polymer-Based Amphiphilic Nanocarriers Obtained by Self-Assembly Processes. Many drug delivery nanocarrier systems are formed starting from basic building blocks that self-assemble under the effects of a number of driving (noncovalent) soft interactions, including van der Waals interactions, hydrophobic effect, hydrogen bonding, hydration and electrostatic forces, $\pi - \pi$ staking interactions, steric and depletion interactions, coordination bonding, and solvation [13–15]. In this respect, the amphiphilic macromolecules provide unique and still effective opportunities for designing novel materials for advanced application in drug delivery processes. Amphiphilic macromolecules possess both a *hydrophilic* portion, which can be uncharged or charged (anionic, cationic, or zwitterionic) and interacts favourably with the surrounding water, and a *lipophilic* (or *hydrophobic*) portion, which is usually composed of hydrocarbon chains that tend to minimize its exposure to water. In water

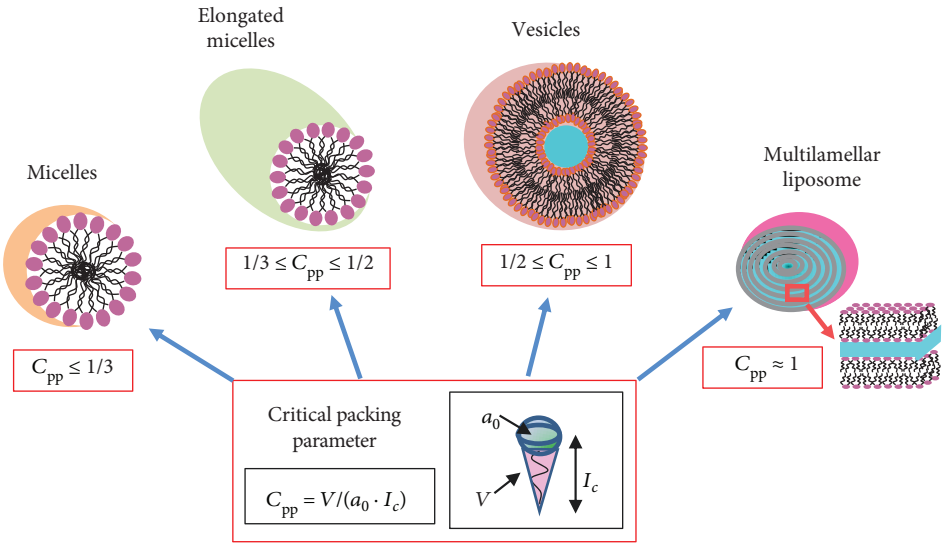

Figure 2: Analysis of the critical packing parameter C_{pp} and relevant shape factors that influence the amphiphilic nanocarrier morphology.

solutions, the hydration of the hydrophilic component as well as the collapsing hydrophobic association of the tail(s) causes a microphase separation with the formation of aggregates, when they exceed a given concentration (critical micelle concentration (CMC)) [15]. Control over the amphiphiles' shapes (by varying the *critical packing factor parameter* C_{pp}) gives the possibility to develop and manipulate nanostructure architectures (see Figure 2) ranging from spherical micelles ($C_{pp} \le 1/3$) to cylindrical micelles ($1/3 \le C_{pp} \le 1/2$), vesicles ($1/2 \le C_{pp} \le 1$) and lamellar structures ($C_{pp} = 1$) [15], while for larger values ($C_{pp} > 1$), the amphiphiles will assemble into "inverted" phases [14, 15]. Owing to their characteristic structure, *micelles* and *liposomes* (*vehicles*) offer special protection against degradation and a wide range of possibilities for targeted functionalization and combined therapy [2, 13, 14].

3.2. Micelle and Vesicle Nanocarriers from Polymer-Based Amphiphiles. Polymers are widely used for drug delivery systems because of their biocompatibility and biodegradability as well as ease in the design and preparation and efficient delivery of the therapeutic active agents to the diseased tissues. The different polymers have specific properties that depend on the chemical-physical characteristics of their building block, while the versatile modification of their chemical groups has been employed for the functionalization and drug conjugation of many polymer-based nanoparticles [16]. According to Won et al. [17], by controlling the hydrophilic/hydrophobic balance (by the modulation of the weight fraction F_W of the hydrophilic block), it is possible to obtain a variety of shapes and morphologies of amphiphilic polymer nanocarriers in water solution, including spherical micelles ($F_W = 55$–70%), spherical vesicles ($F_W = 45$–55%), and vesicles ($F_W = 20$–40%).

Micelles-like nanocarriers obtained by the self-assembly of amphiphilic polymers have attracted much attention for drug delivery applications [18]. The micelles' hydrophobic core creates a microenvironment for the incorporation of lipophilic active compounds (drugs), resulting in significantly enhanced solubility of hydrophobic drugs to achieve improved bioavailability. At the same time, the hydrophilic shell provides a stabilizing interface between the hydrophobic core and the aqueous medium, with the aim at enhancing the colloidal stability and inhibiting aggregation and unwanted interactions with other components. On the other hand, *vesicles* prepared from amphiphilic polymers (called *polymersomes*) present a characteristic bilayer structure with an aqueous interior core, which is able to encapsulate hydrophilic molecules within the aqueous interior and also integrate hydrophobic drug molecules within the internal region of the bilayer membrane.

Recently, (tumor and intracellular microenvironment) responsive polymersomes with diverse functions, structures, and self-assembling morphologies have been discussed [5, 6]. Typical tumor (micro)environments can be utilized to construct responsive block copolymer-integrated nanoplatforms, allowing for a triggered payload release and enhanced imaging sensitivity. The main "endogenous stimuli" that can be used as internal triggers are the (weak) acidic pH, temperature gradients, a variety of specifically overexpressed enzymes, and redox species [5, 6]. The design of the hydrophilic shell could enhance the colloidal stability of the drug-loaded micelles in the bloodstream to achieve the long circulation in the body when the concentration of the polymer is higher than the CMC. Besides, the nanoscaled micelles with a small size (<200 nm) reduce nonselective uptake by the *reticuloendothelial system* (RES) and show the *enhanced permeability and retention* (EPR) effect at solid tumor tissue sites (passive targeting) [18].

Many *biodegradable polymers* show promising performances in the drug delivery applications by providing a high level of control over the complex structure-function relationship [15–19] and a controlled release of drugs by crossing the physiological (and pathological) barriers of the living systems. Natural polymers have been widely investigated for

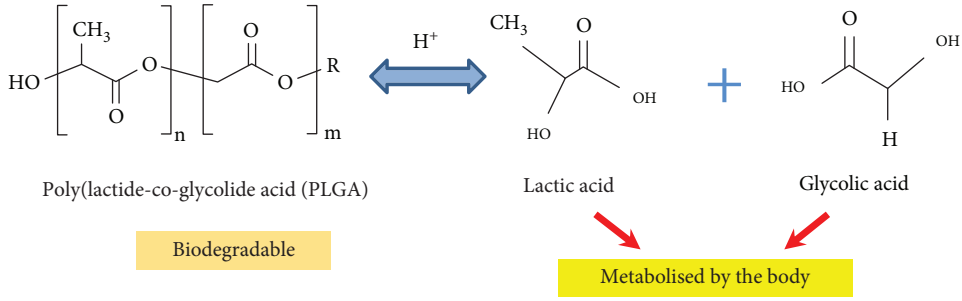

Figure 3: Biodegradability of the PLGA polymer. Polymer degradation is based on the hydrolysis of the copolymer, followed by the metabolization by the body.

drug delivery studies in the past years including chitosan, dextran, heparin, and hyaluronan [19]. However, recent research on the design of synthetic polymers to build various nanostructured delivery platforms is gaining particular attention in the field of nanomedicine. Polyesters, polycarbonates, polyamides, and polypeptides are among the most commonly used synthetic polymers.

In the next section, we briefly describe the most employed polymeric species and promising polymer candidates for the development of nanostructured drug delivery systems.

3.2.1. Poly(lactic Acid) (PLA) and Poly(lactic-co-glycolide) (PLGA) Copolymers. Among all the commonly used biodegradable synthetic polymeric (bio)materials, the most employed for drug delivery applications are the saturated poly(α-hydroxy esters), including *poly(lactic acid) (PLA)*, *poly(glycolic acid) (PGA)*, and *poly(lactic-co-glycolide) (PLGA)* copolymers [20–24]. Due to their excellent safety profile, good biocompatibility, low levels of immunogenicity and toxicity, and the tuneable rate of biodegradation in vivo, these polymers have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as effective carriers for drug delivery in humans.

The biodegradability of PLGA is based on the hydrolytic degradation through de-esterification of the polymers (Figure 3) to generate the lactic and glycolic acid monomeric components, which are metabolized and then removed by the body by natural pathways (such as the Krebs cycle). Their physicochemical and mechanical properties can be tailored via the selection of the polymer molecular weight, copolymerization, and functionalization. Polyethylene glycol (PEG) is the most popular hydrophilic polymer for surface modification of both (hydrophobic) PLA and PLGA to form an amphiphilic block copolymer [20, 21]. Their applications have focused on drug delivery systems mainly involving nanoparticles, micelles, and hydrogels. Poly(ethylene glycol)–poly(lactic-co-glycolide) (PEG–b-PLGA) diblock copolymer micelles represent one of the most promising platforms for drug delivery, where the hydrophobic PLGA core can efficiently encapsulate many therapeutic agents, while the hydrophilic PEG shell prevents the adsorption of proteins and phagocytes, thus extending the blood circulation periods [23]. Copolymer conformation and critical packing factor parameter C_{pp} regulate the morphology of the self-assembled structures, thus influencing the specific biomedical application. Different structures with different properties have been used in different copolymer combinations including A–B diblock type, A–B–A or B–A–B triblock type, and alternating multiblock, multiarmed block, and star-shaped block types (where A and B are representative of the PEG hydrophilic and the PLGA hydrophobic segments, respectively) [20–24]. In Figure 4 are reported the PEG-PLGA diblock (and PEG-PLGA-PEG triblock) copolymers' micellar structures and (hydrophilic/hydrophobic) drug encapsulation characteristics.

PEG–PLGA diblock copolymer micelles have been tested extensively in humans for the incorporation and (controlled) delivery of small molecule drugs and many hydrophobic anticancer compounds [21–23]. Recent researches evidenced the development of PLGA nanocarriers for the delivery of therapeutic biomacromolecules which are able to maintain their colloidal stability (and to maximize their loading efficiency) even in the harsh physiological environment condition of the diseased tissues [24–26].

Chemical conjugation of the PEG–PLGA copolymer facilitates a high drug loading, characterised by a forced localization of the drug in the inner hydrophobic chains. Recently, doxorubicin- (DOX-) conjugated PLGA–PEG micellar nanocarriers with a higher DOX loading displayed a more sustained drug release behavior compared with physically incorporated DOX in PEG–PLGA micelles [25]. Moreover, up to 50% release of conjugated DOX–PLGA–PEG micelles was obtained over 2 weeks while a total release of physically entrapped PEG–PLGA micelles took only 3 days. PEG-PLGA nanocarrier encapsulation of proteins and peptide drugs, such as insulin, calcitonin, and DNA, has been reported in several studies [23]. Finally, the suitable combination of imaging and functionalized nanoparticles has enabled concurrent diagnosis and therapy of diseased tissues through the development of theranostic nanocarriers. Recently, a PLGA-PEG-folate theranostic system was combined with dual imaging tracers (namely, near infrared and 19F magnetic resonance imaging) with the chemotherapeutic agent doxorubicin DOX [27]. The in vitro cytotoxicity assay also showed that folate-targeted PLGA-PEG nanoparticles were able to kill cancer cells more efficiently than were non-folate conjugated particles [27].

Finally, various preliminary animal studies have displayed the great potential of these PLA and PLGA-based nanocarriers in the treatment of various diseases including diabetes, cancer, cardiac disorder, bacterial/viral infection, autoimmune diseases, and cartilage damage [20–24].

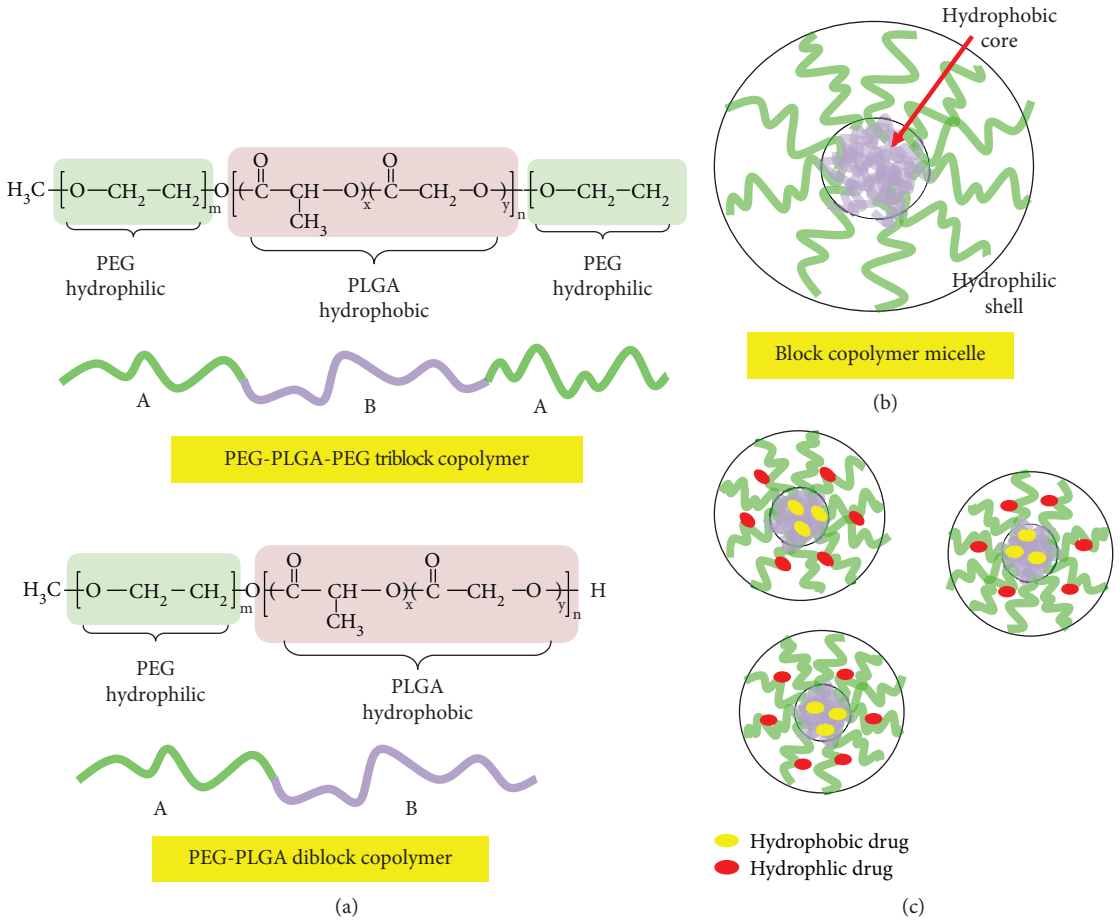

Figure 4: Main characteristics of PEG–b-PLGA (diblock and triblock) copolymers (a). Micellar self-assembly (b) and hydrophilic/hydrophobic drug encapsulation characteristics (c).

3.2.2. Chitosan. Chitosan is a biodegradable and biocompatible polymer with chemical functional groups (that typically have positive surface charges) that can be easily modified to perform specific functions, suitable for a wide range of potential applications [25]. Chitosan-based nanoparticles have been investigated in various drug delivery applications, following different (parental and nonparental) routes of administration, including treatment of dermatologic and gastrointestinal diseases, pulmonary diseases, and drug delivery to the brain and ocular infections [25]. Polymeric micelle nanoparticles based on amphiphilic chitosan derivatives obtained by grafting hydrophobic long acyl chains have been recently prepared via self-aggregation in water [26]. Moreover, self-assembled amphiphilic micelles based on chitosan (CS) and polycaprolactone (PCL) were produced and used as carriers of paclitaxel (PTX) to improve its intestinal pharmacokinetic profile [27]. Experimental results indicated that chemical modification of chitosan nanoparticles can improve their targeting and bioavailability. Recent advances highlight the use of chitosan nanoparticles for tumor targeting [28], imaging and therapy (theranostic) applications [29], and construction of targeted drug delivery systems. A chitosan-based nasal formulation of morphine (RylomineTM) is currently in phase 3 clinical trials in the US and phase 2 clinical trials (UK and EU).

3.2.3. Temperature-Sensitive Polymeric Nanocarriers. Recent investigations have focused on stimulus-sensitive (smart) nanocarriers for drug delivery, due to the possibility to control the delivery and release of drugs to a specific site at the desired time. Many prototypes of (internal and external) stimulus-responsive nanosystems have been developed, including physical (e.g., temperature, light), chemical (e.g., redox, pH), and biological (e.g., enzymes) smart delivery systems [30, 31].

Temperature is one of the most widely explored stimuli for drug delivery application in cancer. Thermosensitive micelles are comprised of polymers having thermoresponsive blocks, which undergo a sharp change in their aqueous solution properties [32, 33] that destabilize the micellar structure thus allowing the controlled triggering of the drug release [33, 34]. The first generation of thermosensitive polymers micelles was based on mere hydrophobic interactions between polymer blocks, while more recently shell or core crosslinking was introduced, in order to improve their stability in the circulation after intravenous administration. Various nanoformulations of drug-loaded micelles based on thermosensitive polymers have shown promising results in vitro, as well as in vivo [33, 34]. Many polymers are incompletely soluble below a certain temperature, known as *lower critical solution temperature* (LCST), where the polymer

retains water by forming hydrogen bonds. Above LCST, the hydrogen bonds between water and the polymer chains are disrupted rendering the polymer hydrophobic to precipitate out. This phase change can be exploited for a controlled destabilization of the polymeric micellar structure [33, 34].

(1) Thermosensitive Poly(N-isopropylacrylamide) (PNIPAm). The most widely used thermoresponsive polymer is poly (N-isopropylacrylamide) (PNIPAm). This polymer, which has a LCST at 33°C, is then water-soluble below the LCST, while it becomes hydrophobic at body temperature [35, 36]. Based on the thermosensitive property of PNIPAm, a wide range of thermosensitive micelle nanocarriers can be developed, where the LCST of PNIPAm-based polymers can be easily modified via copolymerization with hydrophilic or hydrophobic monomers. The strategy to use thermosensitive polymeric micelles aims at achieving drug delivery control by changing the temperature of the environment slightly above or below the LCST, thus resulting in destabilization of the micelle's structure and triggering a release of the encapsulated drug [35, 36]. With this approach, the drug release could be controlled by local heating (or cooling) during a given time period.

Dedicated PNIPAM-based nanoplatforms can also respond to further stimuli, including light and electric field stimuli [37]. Due to their distinct properties, responsive microgels have been employed in various applications including sensing, catalysis, drug delivery, optical devices, cell attachment and culturing, radiotherapy, and optics [37]. Refined control of thermoresponsive swelling/deswelling and drug release properties of poly(N-isopropylacrylamide) hydrogels have been recently obtained by using poly(ethylene glycol) (PEG) with varying chain lengths as polymer crosslinkers [38]. Compared with PNIPAm hydrogels crosslinked with a conventional small molecular crosslinker, N,N′-methylenebisacrylamide, a greater degree and range of thermoresponsive swelling/deswelling as well as tunable LCST are demonstrated for PNIPAm-PEG hydrogels [38].

(2) Thermoresponsive (Pluronic) PEO-PPO-PEO Triblock Copolymers. Thermoresponsive linear AB-type diblock and ABA-type triblock copolymer architectures obtained by versatile synthesis processes have attracted enormous interest and have already found broad application in biomedicine as tissue engineering and drug/protein delivery and stimulate the route for the rational design and engineering of materials with desired properties [39–41]. In thermoresponsive ABA triblock copolymers, the temperature can be used as a trigger to form flower-type micelles or/and hydrogels at the higher concentrations.

A special class of ABA triblock copolymers are represented by the commercially available Pluronic-type class of amphiphilic poly(ethylene oxide)-poly(propyleneoxide)-poly(ethylene oxide) PEO_m-PPO_n-PEO_m triblock copolymers. In those systems, the hydrophilic poly(ethyleneoxide) (PEO) block assures the requested biocompatibility and the desired "stealth" characteristic that minimize possible unwanted interactions with cellular components. Moreover, the possibility of molecular control by tuning the desired polymer composition and architecture makes these systems a versatile tool to study, in a convenient way, the rich and complex phenomenology in the field of colloidal science [41–44]. A relevant number of studies involving Pluronic block copolymers as drug delivery systems or bioformulations for (pre)clinical use or trials are present in literature [44–46].

As recently evidenced by Pitto-Barry and Barry [44], the encapsulation of the DOX anticancer drug in the Pluronic micelles strongly influences its biodistribution and leads to a better accumulation of the micellar drug in the tumors compared to the free drug. Moreover, it exhibits a superior antitumor activity over DOX in a wide range of doxorubicin-sensitive and -resistant human solid (and hematopoietic) malignancies [44].

In conclusion, polymeric micelles have demonstrated particular strength in solubilizing hydrophobic drugs in relevant doses without the inclusion of toxic organic solvents or surfactants, while the hydrophobic block can be tailored to encapsulate drug molecules with a wide variety of structures. Moreover, anticancer efficiency can be obtained by modifying the micelle's surface with targeting ligands for specific recognition of receptors (overexpressed on the surface of tumor cells) [46, 47].

3.2.4. Polymeric Nanogels. Polymer-based micelles and vesicles maintain their structure above the CMC. Below the CMC, with the dissociation of their self-assembled nanostructures into single polymer chains, they lose the function as drug carriers. To overcome this problem, the employment of chemically (or physically) crosslinked polymer networks to obtain *nanogels* has become a common and effective approach to obtain more stable nanocarriers in different biological conditions [48].

Polymer-based nanogels are three-dimensional networks consisting of chemically (or physically) crosslinked polymer containing both hydrophilic (or polar) and hydrophobic monomers. They are generally dispersed in aqueous media where they form semi-solid states (hydrogels) that may be swollen by a large amount of water (hydrogels). The properties of hydrogels can be tuned to match the needs of specific applications by the choice of a specific polymer (molecular structure and segments length), the crosslinking mechanism, and the eventual presence of acidic (or basic) polymer moieties, whose state of protonation can be easily controlled with pH or salt concentration. Stimulus-responsive (smart) hydrogels can undergo structural transitions in response to external stimuli or (internal) environment changes of the physical properties of the system such as its temperature, electric field, and exposure to light [49, 50].

The choice of the hydrogel composition depends on the specific biomedical application and may require specific properties such as biocompatibility, transport/mechanical properties, chemical stability and the ability to respond to microenvironment changes [51–53]. Another crucial factor for hydrogel performance is the nature of the involved (chemical or physical) crosslink interaction, as it influences many of the network properties, like swelling, elastic modulus, and transport properties [54, 55]. In Figure 5(a) is reported the

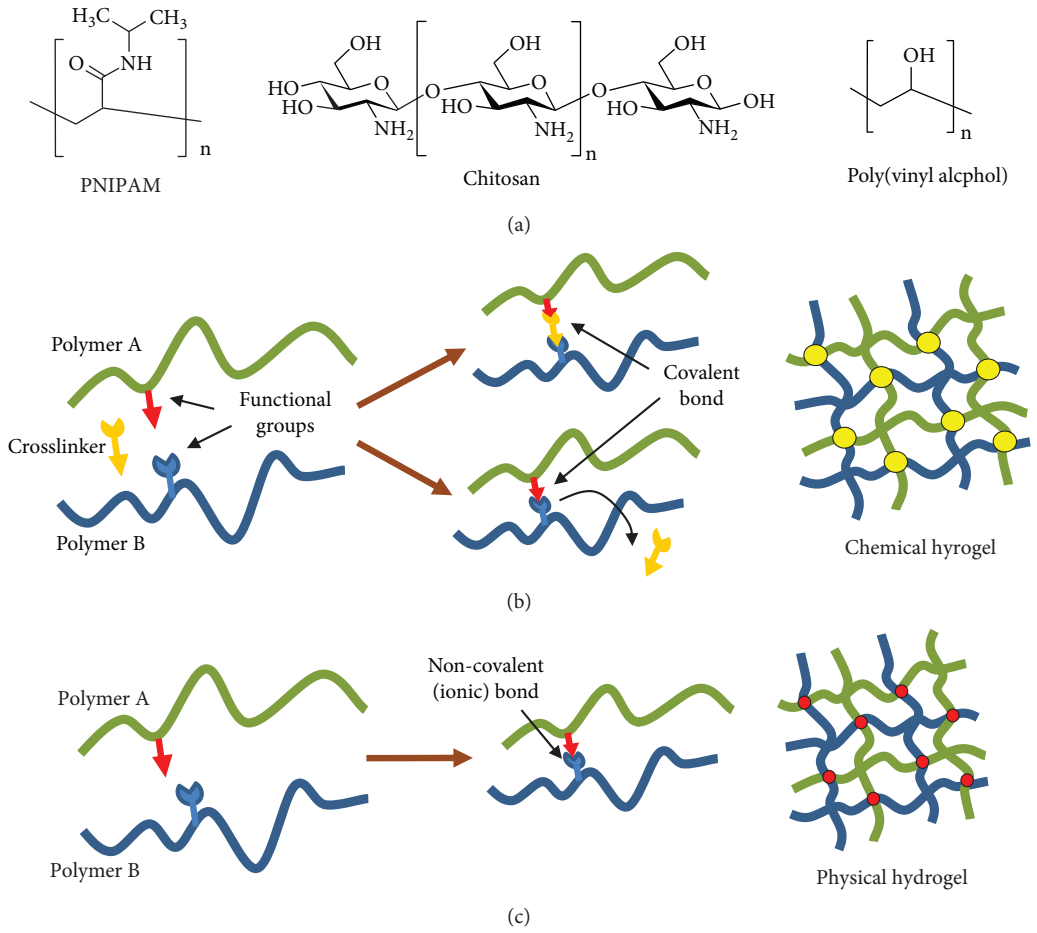

Figure 5: Chemical composition of PNIPAM, chitosan, and poly(vinyl alcohol) hydrogels. Schematic representation of the main crosslinking approaches employed for the construction of chemical (b) and physical hydrogels (c).

chemical composition of some of the main hydrosoluble (i.e., PNIPAM, chitosan, and polyvinyl alcohol) hydrogels.

In *chemical crosslinked hydrogels*, a bifunctional (or multifunctional) crosslinking agent is added to a dilute solution of a hydrophilic polymer. Chemically crosslinked hydrogels are developed by chain growth polymerization, addition, and condensation polymerization and through irradiation techniques (using high-energy ionizing radiation, like electron beam, gamma, or X-ray). One common way to create a covalently crosslinked network is to polymerize end-functionalized polymers. The permanent linking (covalent bonds) produced by chemical crosslinking will not break, and this may limit the ability to control the hydrogel drug release characteristics. Among the numerous chemical crosslinkers used, glutaraldehyde is one of the most employed, as it can react with both proteins and carbohydrate functional groups and can provide substantial improvement of the hydrogel mechanical properties [51–53]. Chitosan (gel) nanoparticles (<100 nm) crosslinked with glutaraldehyde evidenced an increased particle size with increasing levels of crosslinking. However, an in vivo evaluation of glutaraldehyde-crosslinked materials is necessary in order to understand possible cytotoxicity effects and potential in medical applications. Recent investigations have shown that carboxylic acids (such as citric acid) are able to crosslink the biopolymer in wet and dry conditions, thus improving the mechanical properties and stability of biomaterials, without the need for a potentially cytotoxic catalyst. Moreover, poly(carboxylic acids) can react with hydroxyl and/or amine groups and therefore crosslink both proteins and polysaccharides. Proteins crosslinked with carboxylic acids have proved to be biocompatible and to provide the desired improvements in properties for both protein- and carbohydrate-based biomaterials [54].

Physically crosslinked hydrogels, on the other hand, can be developed by hydrogen bond; ionic, van der Waals, and hydrophobic interactions; stereocomplex formation; and crystallization [53, 54]. The hydrogen bonding between polymer chains of the hydrogels may be used to control drug release through various factors including polymer concentration (and molar ratio), type of solvent, solution temperature, and degree of association of polymer functionalities. Crosslinking by ionic interactions can be performed under gentle conditions, at room temperature and physiological pH [53, 54]. Anionic polymers crosslinked with the employment of metallic ions produce stronger hydrogels. Complexation of polyanions with polycations has also been exploited in several drug delivery applications [51–53].

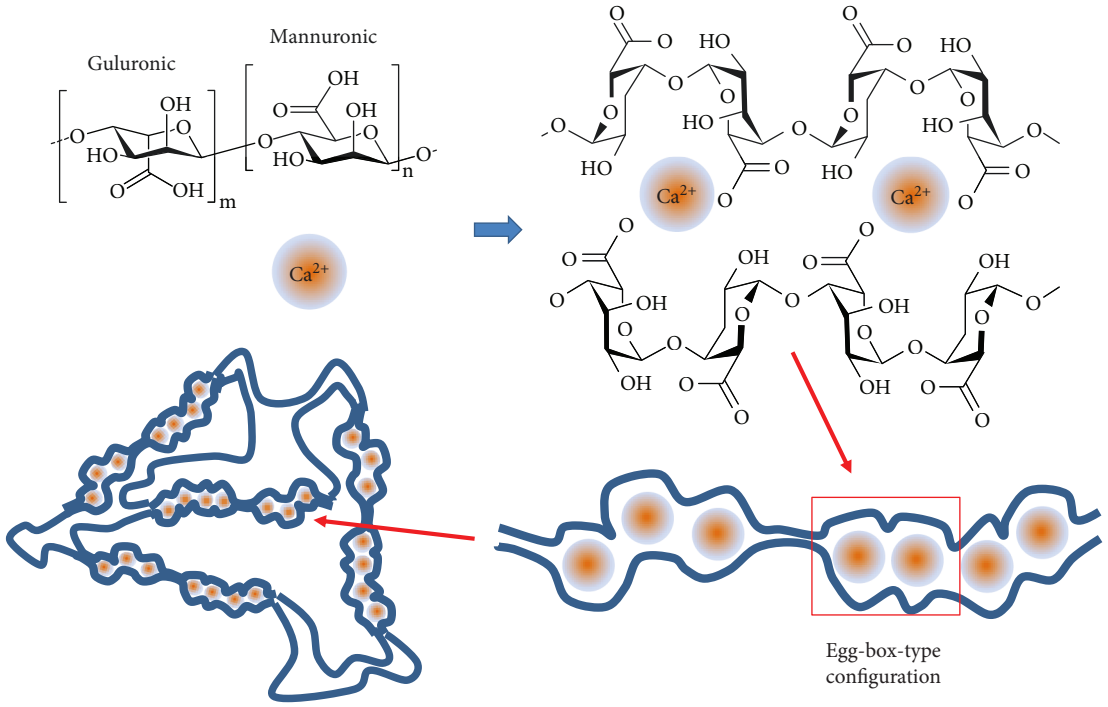

Figure 6: Schematic representation of the calcium-alginate-based hydrogels. Ionic-type crosslinking of alginate is caused by chelation of metal cation Ca^{2+} by carboxylate groups of β-D-mannuronate and α-L-guluronate residues of alginate. The alginate chains are arranged around a metal cation Ca^{2+} in an "egg-box" (2 : 1) helical structure configuration.

Ionically crosslinked chitosan hydrogels are produced via complex formation of chitosan and polyanions, like dextran sulfate or polyphosphoric acid. A relevant number of investigations on the self-assembling preparation of chitosan nanoparticles in drug delivery applications have been proposed in recent years. In particular, the nanoparticle preparations by polyelectrolyte complexation and by the self-assembly of hydrophobically modified chitosans are able to encapsulate various typologies of different drugs (including doxorubicin, paclitaxel, and amphotericin B) under different conditions while preserving their stability and biocompatibility. Therefore, chitosan-based self-assembled nanoparticles have great potential, as well as multiple applications for the future in the design of novel drug delivery systems [55]. In Figure 5, the schematic representation of the main crosslinking approaches employed for the construction of chemical (b) and physical hydrogels (c) is reported.

Alginate represents another important example of a polymer that can be crosslinked by ionic interactions and can be employed as nano-matrix for the encapsulation of living cells and for protein release. It consists of a natural polysaccharide having mannuronic and glucuronic acids which remain complexed with calcium ions and which generate a crosslinked gel (at room temperature and physiological pH) (Figure 6) [52].

The gels can be destabilized by extraction from the gel of Ca ions (via chelating agent). Due to its biocompatible and nonimmunogenic character, calcium-alginate hydrogels are used in a variety of biomedical applications including scaffolding for cell cultures, drug release, and tissue engineering (including wound dressing) [52]. The alginate backbone can be modified with cell-interactive peptides binding integrin receptors (such as RGD) or other cellular receptors (e.g., VEGF) in order to increase cell adhesion.

Finally, crystallization crosslinking is exploited in the formation of poly(vinyl alcohol)- (PVA) based gels. In this case, the gel formation is attributed to the arrangement crystallites which acts like a physical crosslinking site in the network, through the repeated freezing/thawing method [52].

Polymeric nanogels represent a new generation of drug delivery systems due to their high drug encapsulation capacity, tuneable size, ease of preparation, minimal toxicity, stability in the presence of serum, and stimulus responsiveness. For those reasons, biomedical nanoplatforms based on responsive hydrogels have found applications in biosensors, drug delivery, tissue engineering, and biomimetic materials development [48–50].

3.3. Liposome Nanocarriers. Although the polymer-based nanocarriers have many attractive properties for in vitro/in vivo applications, lipid-based drug delivery systems are still prevalent in the market and still maintain the supremacy in clinical applications. Vesicles composed of natural or synthetic lipids (so called *liposomes*) represent a versatile nanomaterial platform for the development of enhanced drug delivery systems in a wide range of applications in the field of biotechnology and nanomedicine [56, 57]. Liposome nanocarriers offer many benefits connected with their ability for a versatile self-assembly [58–60] and governed by specific soft interactions that control the colloidal stability of therapeutic drugs in a harsh bioenvironment of diseased tissues [61–64].

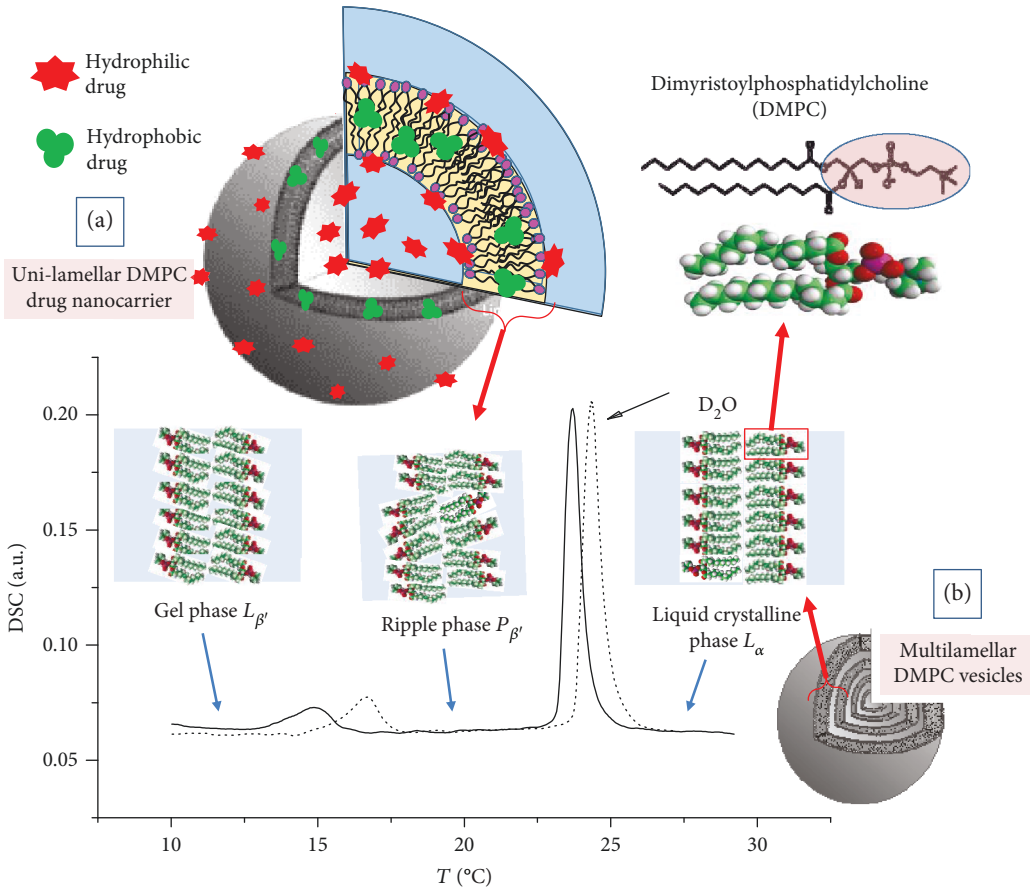

FIGURE 7: Schematic representation of the encapsulation of hydrophobic/hydrophilic drugs into unilamellar dimyristoyl-phosphatidylcholine DMPC liposome (a). Characteristic phases (*gel* L_{β}, *ripple* $P_{\beta'}$, and *liquid crystalline* L_{α} phases) and main transitions of a multilamellar DMPC lipid in H_2O (and D_2O) solution, obtained by DSC experiments (b).

Lipid–based systems are easy to manufacture than biopolymers, due to the large availability of the base (phospho-)lipid compounds. They also have better control over drug release kinetics.

Synthetic or natural (phospho-)lipids consist of a hydrophilic head and (one or more) hydrophobic tails. In water solution, they self-assemble into a highly flexible bilayer vesicles (Figure 7(a)), with the hydrophilic heads facing the water, and are able to undergo various conformational and dynamic transitions which are essential for many biological functions.

From the structural point of view, the lipid bilayer vesicle (liposomes) in aqueous solution strongly depends on the conditions of preparation (i.e., stirring, sonication, extrusion, microfluidification, or electroformation), while their sizes range mainly between 50 and 500 nm and may be composed of small unilamellar vesicles (SUVs < 100 nm), large unilamellar vesicles (LUVs 100–1000 nm), or giant unilamellar vesicles (GUVs > 1 μm). Finally, multilamellar vesicles (MLVs) are composed of concentric bilayer surfaces in an onion-like structure (hydrated multilayers) [58, 59]. Finally, novel promising lipid-based nanocarriers (especially for lipophilic drugs) are given by the *solid lipid nanoparticles* (SLN), consisting of a solid hydrophobic core that contains the drug (dissolved in a solid high melting fat matrix), surrounded by a monolayer of phospholipid coating that ensures the colloidal stability in the aqueous environment [60].

Fluidity of a lipid bilayer, which depends on both its composition and temperature, has been shown to have a large impact on uptake and release functions of cellular systems [65–67]. With increasing temperature, a bilayer made of phospholipids passes from a highly ordered, rigid crystalline (or gel) state to a more mobile fluid state [68, 69]. An example is given by structural changes in the dimyristoylphosphatidylcholine (DMPC) phospholipid bilayer in water at excess during temperature-dependent phase transitions (Figure 7) [68]. In Figure 7(b), the structural changes on multilamellar vesicles (MLVs) of dimyristoyl phosphatidylcholine (DMPC) lipids in H_2O and D_2O are investigated by differential scanning calorimetry (DSC) experiments as a function of temperature. The first endothermic peak at $T = 15^{\circ}C$ (pre-transition) and the second endothermic peak at $T = 23.4^{\circ}C$ (main phase transition) identify the border between the three different characteristic phases (passing from the *gel*L_{β} to the *ripple*$P_{\beta'}$ and finally to the *liquid crystalline*L_{α} phases). It is worth noticing how the substitution of the solvent from H_2O to D_2O produces a sensitive shift of the main transition peaks [68].

The presence of inclusion of macromolecular compounds (such as drugs) may strongly influence the structure

of the lipid bilayer nanocarriers while the final morphology is strongly determined by the size, charge, and composition of the interacting components [70–72]. Often, the inclusion of macromolecular compounds may induce structural perturbations against the long-range cohesive tendency of the lipid bilayer vesicles [73–76]. The encapsulation of active compounds into the bilayer of the liposomes, while facilitating drug solubilisation in aqueous media, also provides additional protection and control against drug degradation. These characteristics cause a sensitive amelioration in the toxicity profiles with a correlated improvement of therapeutic efficacy. While hydrophilic drugs are localized nearby the hydrophilic head groups or in the aqueous core region, the hydrophobic drugs are hosted within the liposome acyl chain region. As many anticancer drugs are of intermediate solubility, they undergo then a partition between the exterior (or interior) liposome aqueous phase and the hydrophobic interior of the bilayer.

Owing to a facile modulation of their size, hydrophobic/hydrophilic character, low toxicity, and biocompatibility, liposomal nanocarriers still represent the largest group of clinically approved anticancer drug formulations [77, 78]. Liposome formulations are devoted mainly to cancer treatment and are mainly administrated intravenously, due to the high degradation of lipids in the gastrointestinal tract [65–67]. Anticancer drugs doxorubicin, daunorubicin, cisplatin, paclitaxel, and vincristine are among the most extensively investigated agents for the liposome-based drug formulations, and several liposomal formulations of these agents are currently in clinical use in cancer therapy [77–79].

An important approach for the improvement of circulation times of lipid nanocarriers consists in conjugation of suitable polymers on their surface, such as natural (e.g., dextran, alginate, and chitosan) or synthetic (e.g., poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), and poly (vinyl pyrrolidone) (PVP)) hydrophilic polymers [80]. This approach allows overcoming the interception by the immune system, the low blood circulation half-life, toxicity, and biocompatibility issues. PEGylation of the liposome surface, the most widely used polymer conjugation process, creates a local surface concentration of highly hydrated polymer brushes that sterically inhibit both hydrophobic and electrostatic interactions with plasma proteins or cells, thus reducing the liposomal uptake process by the RES [81]. As a result, PEGylated liposomes are not opsonized and are able to escape the capture by the cells' phagocytic systems by rendering the nanocarriers invisible to macrophages ("stealth liposomes") [57]. The interaction between a nanomaterial and biological tissue initiates, in fact, with the nonspecific adsorption of proteins (such as albumin, globulin, and fibrinogen) at the nanomaterial surface and could have a negative impact on the availability of the nanocarriers' activity and functionality. Moreover, the layer of adsorbed protein on surfaces may favour cell attachment and subsequent bacterial colonization which leads to the formation of bacterial films. The inhibition of protein adsorption, by surface functionalization based on PEG polymers, represents therefore a crucial step not only in order to prevent biomaterial failure but also to inhibit biofouling (i.e., the contamination of surfaces by microbes including bacteria, fungi, and viruses) [82]. Many studies demonstrated that PEGylated liposomes were able to improve the stability and blood-circulation time, together with low plasma clearance and low volume of distribution (with minimal interaction with nontumoral tissues) [57, 83, 84]. However, phase separation transition on liposome can be induced due to liposome PEGylation, while excessive PEGylation can also cause inhibition of cellular uptake, which is undesired for cancer treatment [85]. Thus, a moderated PEGylated multicomponent liposome may represent the best compromise to hinder the protein adsorption but still present a high cellular uptake in cancer cells [85]. In Figure 8, we report a representation of the PEGylated phospholipid 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000] (DSPE-PEG2000) ammonium salt (a), together with a sketch of steric repulsion between PEGylated liposomes (b).

Liposomes can also be used to target active drug molecules to specific sites within the biological systems, such as diseased tissues or tumors. The incorporation of different ligands, such as peptides, monoclonal antibodies, aptamers, and growth factors, improves the specificity of the liposome interaction during the drug release process [86, 87]. Cationic liposomes containing small interfering RNA (siRNA) were developed to target EGFR (a surface receptors overexpressed in many solid tumors) by conjugation of thiolated antibody with the maleimide (MAL) group at the distal end of DSPE-PEG-MAL chains of preformed liposomes. The liposomes showed an efficient transfer of siRNA to mouse (transfection) compared to nontargeted liposomes, while the suppression of lung cancer metastasis was observed [88]. Recently, dual functional paclitaxel liposomes with pH response and mitochondrial targeting were proposed as a new approach for treating multidrug-resistant cancer. The liposomes were effective in treating A549 (drug-resistant) cancer cells [89]. Antibody molecules have groups (e.g., carboxyl, amine, and thiol groups) which can be easily modified for active targeting. By using various surface engineering techniques, antibodies or their fragments can be conjugated to the liposome's surface to obtain immunoliposomes [90]. Recently, liposomes containing triptolide were functionalized with the anti-CA-IX antibody and showed higher efficacy in lung cancer therapy in mice bearing lung cancer [91]. Recently, a number of studies have focused on modifying liposome drug-releasing mechanisms by using functionalized *stimulus-responsive liposomes*. Drug release processes from liposome nanocarriers can be triggered by *external stimuli*, such as heat (hyperthermia) [92], light [93], magnetic field [94], ultrasound [95], or *internal stimuli*, such as pH [96], enzymes [97], and redox [98]. Moreover, liposomes have the ability to simultaneously conjugate cancer-targeting molecules (active targeting) for therapy treatment and diagnostic tasks (theranostics) [87]. Recently, Li and coworkers reported the development of a thermosensitive liposome formed by a mixture of 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC), 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC), and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine- (DSPE-) PEG and loaded with the MRI contrast agent Gd-DTPA as well

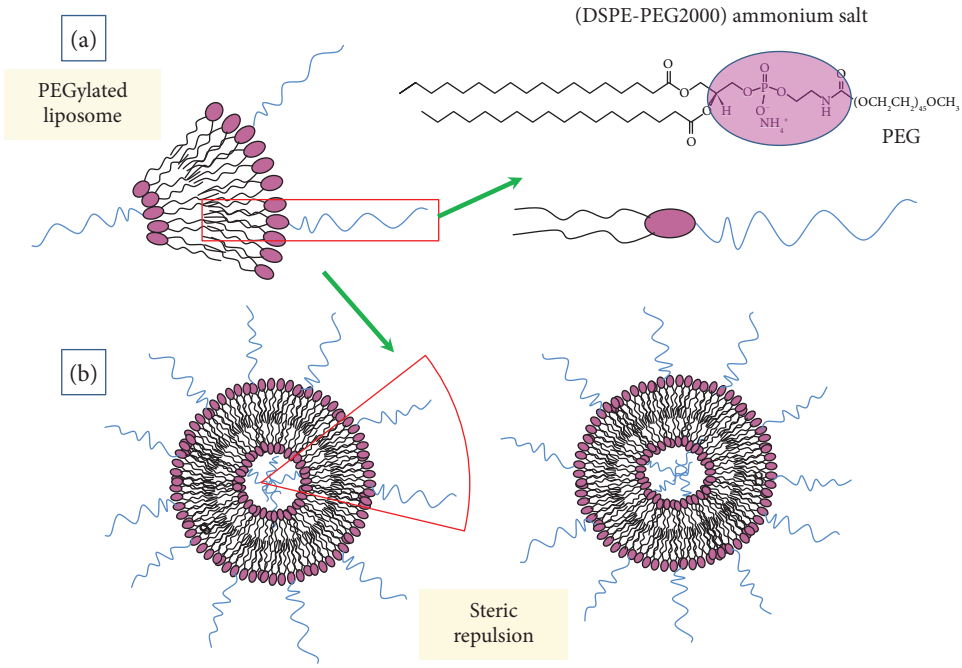

Figure 8: Schematic representation of the PEGylated nanocarrier composed of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000] (DSPE-PEG2000) ammonium salt (a). View of sterically stabilised lipid bilayer nanocarriers (b).

as doxorubicin (DOX) [99]. The simultaneous delivery of both Gd-DTPA and DOX allows drug release to be simultaneously carried out and monitored, with triggerable release in the environment of a tumor by localized heating. Theranostic carboxymethyl dextran- (CMD-) coated magnetoliposomes (CMD-MLs) for controlled drug release under a low-frequency alternating magnetic field has been recently developed [94]. This theranostic nanoplatform also acted as an efficient T2-weighted contrast agent during in vitro MRI measurements, evidencing the in vivo diagnostic/therapeutic efficacy of DOX-loaded CMD-MLs for some cancers, such as brain cancers [94].

Although the modification of the physicochemical properties strongly influences the structure and secondary properties of functionalized liposome nanocarriers [76], the lipid-based vesicle nanocarriers (liposomes) containing therapeutic drugs produce fewer side effects than do non-liposomal anticancer formulations and still represent the best approach to effectively target the diseased tissues (including tumors).

3.4. Dendrimers. Dendrimers are three-dimensional, hyperbranched nanoparticles, consisting of polymeric branching units covalently attached to a central core, organized in concentric layers (named generations) and that terminate with a number of external surface functional groups [100, 101] (Figure 9(a)). Unlike the self-assembly systems illustrated so far, they are obtained by specific *synthesis methods*, based on an iterative stepwise reaction sequence that allows a precise control over molecular design parameters (such as size, shape, and internal/surface chemistry) which results in highly monodisperse nanostructures. One of the most important applications of dendrimers consists in the conjugation of suitable chemical species into their surface. This approach stimulates the development of new prototypes that can function as detecting affinity ligands and targeting components, or imaging agents, while drug delivery applications indicated an efficient use of dendrimers for (in vitro) transfer of genetic material into cells [102–104]. The structure of dendrimers in solution can be influenced by many factors, such as the generation, spacer length, surface modification, ionic strength, pH, and temperature [105, 106]. On the other hand, the charge effects and electrostatic forces seem to play the main role in drug delivery processes.

Dendrimers have the ability to increase the solubility and bioavailability of hydrophobic drugs that can be entrapped in their intramolecular cavity or conjugated to their surface functional groups (see Figures 9(b) and 9(c)). A quantitative analysis of the physical interactions between dendrimers and inclusion components is a crucial step for the development of novel technology. In this respect, the small-angle scattering techniques represent powerful approaches to study the structure and interaction properties of dendrimers in a solution environment [106–108]. The modelling of the inter-dendrimer interaction provides substantial insight into the fundamental mechanisms of dendrimer-drug interaction in solution. Notably, the solution conditions (including solvent pH, counterion distribution, and ionic strength) have been shown to play a key role in the control of the charge interaction and can be exploited in the rational design of dendrimer properties for suitable applications in biotechnology [109–112].

A new emerging field of clinical application concerns the combination of dendrimers and bioactive ligands. Dendrimer conjugates containing saccharides or peptides

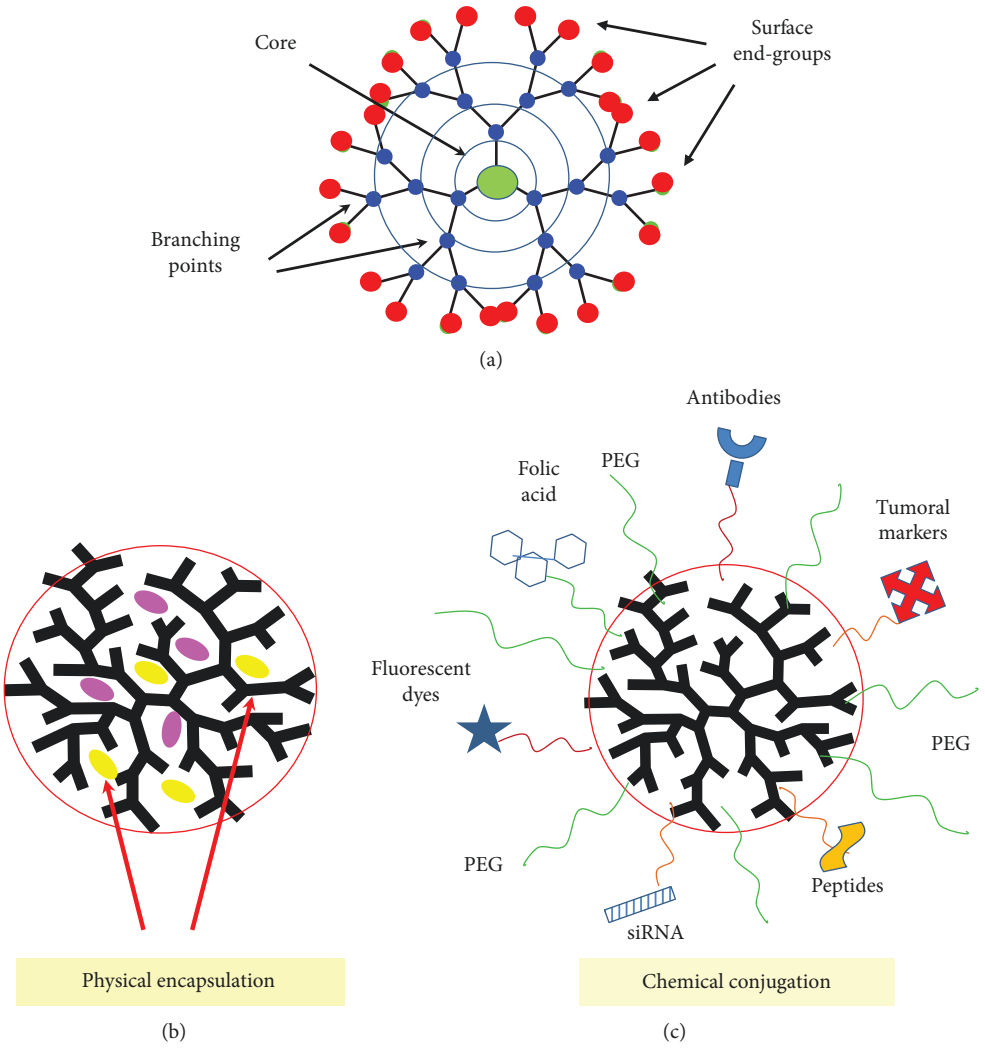

Figure 9: Main structural features of dendrimers (a). Dendrimer nanocarriers. Active components (and drugs) are entrapped in the internal cavity of the dendrimers (b) or conjugated to their surface functional groups (c).

may exhibit therapeutic application for the development of antimicrobial, antiprion, and antiviral agents. Moreover, they offer additional advantages for their versatile capabilities to enhance solubility and stability upon absorption of various types of therapeutics. This approach has been used for nucleic acid-based therapeutics and other charged therapeutics [113]. Another relevant aspect of charge-mediated self-assembly processes involving dendrimers regards the study of the formation of dendrimer-surfactant (lipids) complexes, as it has important implications for the understanding of the translocation mechanism of dendrimers and biomacromolecules in living cells. In this respect, several model systems that mimic the structure of biomembranes were developed during the last decades [109–111]. Depending on the dendrimer chemical composition, size, and surface charge, different mechanisms can be identified, that depend on the main interactions between dendrimers and lipid bilayers, including adsorption on membrane, hole formation, and vesicle disruption. The different mechanisms of interaction strongly depend on the force balance between charged dendrimers and the zwitterionic lipids (that have a net dipolar charge) and on the hydrophobic interaction between the arms of the dendrimers and the lipid hydrocarbon chains [111–113]. The presence of functional groups in the dendrimer's exterior also permits the addition of other moieties that can actively target certain diseases and improve the drug delivery process, such as folate and antibodies, now widely used as tumor targeting strategies [114].

Finally, dendrimers are promising nanocarriers of gene therapy [114]. Nucleic acids usually form complexes with the positively charged surface of most cationic dendrimers. Under physiological conditions, polyamidoamine (PAMAM) dendrimer-DNA complexes (called dendriplexes) maintain a positive net charge and bind to negatively charged surface molecules on the cell membranes. Dendrimers are taken up into cells by nonspecific endocytosis and are then degraded by lysosomes. The targeting genes are then released and enter the nucleus to play a role in gene therapy [115, 116]. Transfection efficiency, mediated by PAMAM dendrimers, appears to be dependent on dendrimer generation (with larger-size dendrimers providing higher efficiency) as well as on the charge ratio of the complexes.

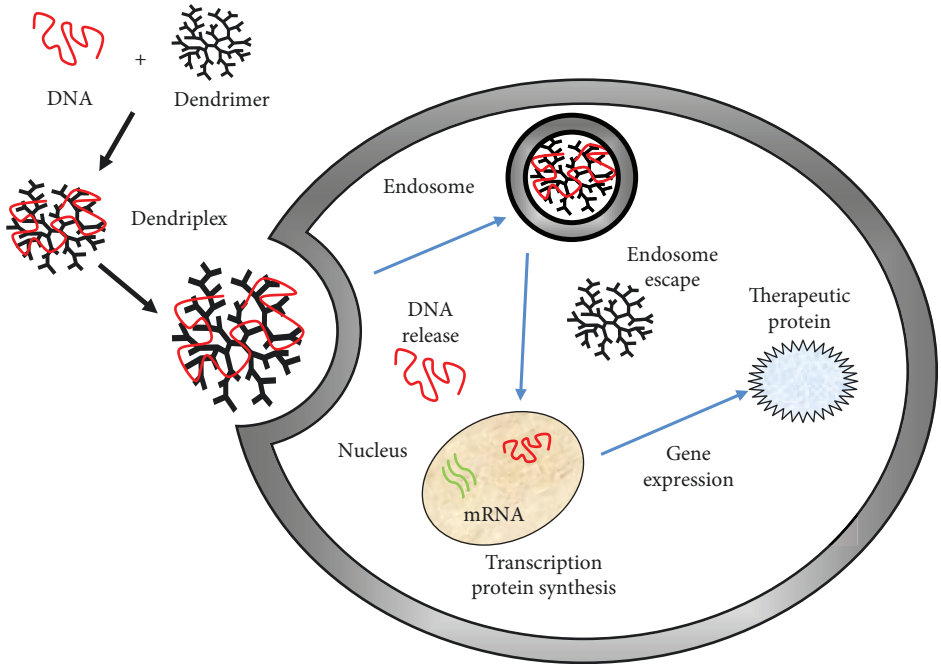

Figure 10: Schematic diagram for a possible route in the use of dendrimers as gene delivery vectors.

In Figure 10, a possible route for the use of dendrimers as gene delivery vectors is reported [94, 95]. As plasmid DNA by itself is unable to penetrate the cell membrane, the first stage is then to form (in vitro) a complex between dendrimer and DNA (called *dendriplex*). The dendriplex is then added to cells in vitro (or is introduced into animals in vivo or ex vivo), where it will be transported to the specific cell via the blood system. The dendriplex will bind to the cell membrane and wait for the cellular uptake (endosome uptake), thus allowing its internalization inside the cytoplasm. When the pH changes from 7.4 (extracellular value) to 5.5 (intracellular value), the deprotonation of dendrimer surface groups causes the dendriplex destruction and the release of nucleic acid. This causes the endosome escape; otherwise, the dendriplex will be degraded after the fusion of the endosome with lysosomes. Simultaneously, the endosomes undergo lysis and the free nucleic acid (DNA) is released into the cytoplasm. Finally, the DNA travels through the cytoplasm to enter the nucleus for successive gene expression [115, 116].

In conclusion, more studies are necessary to elucidate the complex structure–function relationship of ligand–dendrimer conjugates in drug delivery processes. Dendrimer nanocarriers hold promise to facilitate targeted delivery and improve drug efficacy for the smart application of modern pharmaceutics and nanomedicine.

4. Inorganic Nanoparticles

The employment of inorganic nanostructured materials has been recently used for the construction of efficient nanocarriers for drug delivery application [117]. The inorganic nanocarriers are generally composed of two regions: a *core* containing the inorganic component (such as gold, quantum dots, silica, or iron oxide) and a *shell* region composed mainly of organic polymers (or metals) that provide a suitable substrate for the conjugation of biomacromolecules or protect the core region from unwanted physicochemical interactions with the external biological microenvironment [117, 118]. Due to the unique magnetic and plasmonic properties, inorganic nanomaterials may generate imaging contrast by magnetic resonance (MR), computed tomography (CT), or positron emission tomography (PET) [117, 118].

This characteristic is employed and exploited for a diagnostic imaging of the diseased region. However, in spite of such advantages, inorganic nanoparticles have shown only limited success in the treatment of disease tissues due to the critical issues connected with limited amounts of active drug carried and to the high degree of toxicity of the nanoparticle [119]. In Figure 11, we report a list of some of the most employed inorganic nanocarriers for drug delivery applications.

4.1. Carbon Nanotubes. CNTs belong to the family of fullerenes (a third allotropic form of carbon) and are composed of one or more graphene sheets rolled up into a cylindrical tube-like single-walled carbon nanotube (SW-CNT) or multiwalled (MW-CNT) structure [120, 121]. CNTs possess some distinctive physicochemical and biological characteristics and high ability for surface modifications that make them a promising carrier for drug delivery. CNTs may assume the shape of a hollow sphere, ellipsoid, and many other forms, while the outer diameters are typically in the range of 0.4–2 nm for the SWCNTs (and 2–100 nm for the MWCNTs). They present peculiar structural properties characterised by a high aspect ratio (length : diameter > 200 : 1), and surface area, ultralight weight, high mechanical strength, and electrical and thermal conductivities [120, 121].

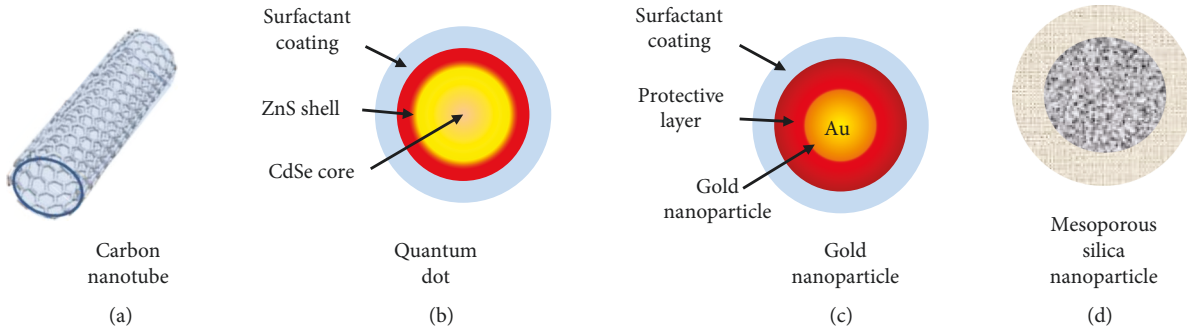

Figure 11: Example of the most employed inorganic nanocarriers: carbon nanotube (a), quantum dot (b), gold nanoparticle (c), and mesoporous silica nanoparticles (d).

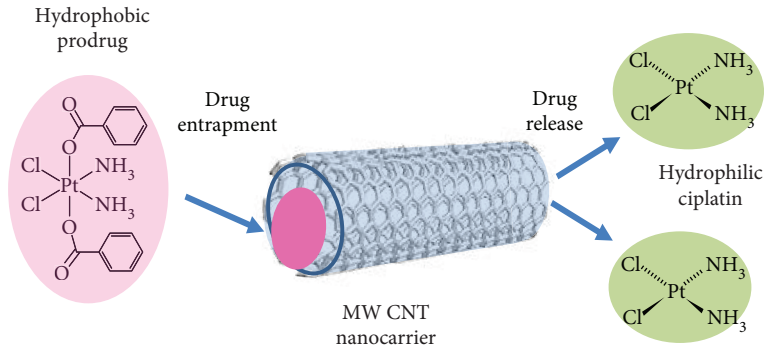

Figure 12: Entrapment of hydrophobic platinum(IV) prodrug within the cavities of multiwalled carbon nanotubes. Release from the CNT carrier of hydrophilic anticancer drugs (cisplatin) upon chemical reduction and hydrophobicity reversal. Adapted from ref. [125].

The characteristic *nano-needle shape* is particularly interesting, as it allows crossing the cell membrane via endocytosis (so-called *needle-like penetration* ability), while CNTs with sizes in the range from 50 to 100 nm are easy to be engulfed. The (aggregation) structure, purity, and size distribution, as well as area, surface charge, and chemistry, represent crucial properties that regulate the reactivity of carbon nanotubes with biological systems [121, 122]. Owing to their cell penetration abilities, unique physicochemical characteristics, high drug payload, intrinsic stability, structural flexibility, and appropriate surface functionalization, CNTs representone of the most investigated family of nanocarriers for cancer therapy [122, 123]. Anticancer drugs can either be encapsulated in the inner cavity or be attached (with covalent or noncovalent functionalization) to the surface of CNTs [119]. Furthermore, the attachment of different targeting agents to the surface-functionalized CNTs allows targeted *delivery of anticancer* including doxorubicin, methotrexate, paclitaxel, and cisplatin [122, 123]. An approach was conceived for the entrapment (via hydrophobic–hydrophobic interactions) within the protective inner cavities of a multiwalled carbon nanotube of an inert and strongly hydrophobic platinum(IV) complex (Figure 12). Upon chemical reduction, the drug was converted to its cytotoxic and hydrophilic form and released from the carrier [124],

CNTs have shown promise in carrying plasmid DNA, small-interfering ribonucleic acid (siRNA), antisense oligonucleotides, and aptamers [121]. In addition to gene delivery, functionalized CNTs can be used as diagnostic tools for the early detection of cancer, while the strong optical absorption in the near-infrared region makes CNTs an interesting tool for photothermal ablation of a cancer site (*photothermal therapy*) [122]. The major problems with CNT nanocarriers are their poor water solubility, their nonbiodegradable nature, and their cytotoxicity. However, CNTs have the ability to be surface-functionalized (either chemically or physically), which render them water-soluble, biocompatible, and non (or less) toxic. While PEGylation is employed to increase solubility, to avoid the RES, and to lower the toxicity, their surface functionalization with the PNIPAM polymer could be used to modify CNTs for (temperature) stimulus-responsive nanocarriers. Due to those characteristics, CNTs are considered a good candidate for the treatment of cancer.

4.2. Gold Nanoparticles (Au NPs). Due to their special electronic, optical, sensing, and biochemical properties, gold nanoparticles (Au NPs) have been intensively investigated for potential applications in medical imaging (early detection and diagnosis) and treatment of diseases (including tumor therapy) and drug delivery processes [125, 126]. Gold NPs are composed of a gold atom core surrounded by negative reactive groups on the surface that can be easily functionalized by adding a monolayer of surface moieties (ligands for active targeting). Although they can be assembled by means of different chemical and physical routes, Au NPs for biomedical applications are mainly prepared using the colloidal synthesis method (utilizing a

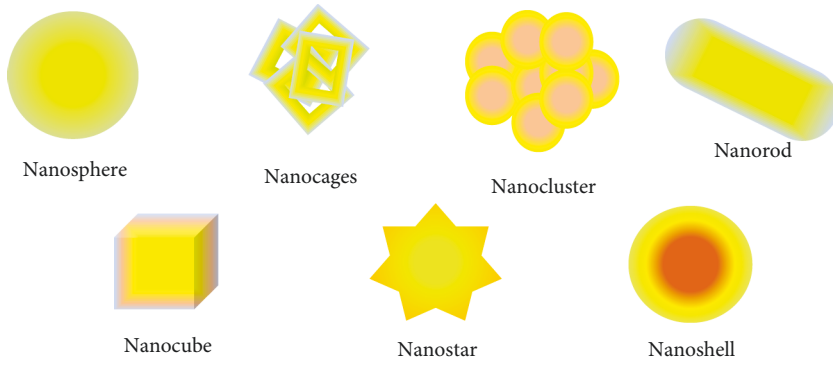

Figure 13: Example of the morphology of gold nanoparticle synthesized nanostructures.

metal precursor, a reductant, and a stabilizer). This approach allows a precise control of the optical and electrical properties that strongly depend on the shapes (as nanosphere, nanorod, nanocage, and nanoshell) and sizes (ranging from 1 nm to more than 100 nm) of the generated Au NP nanostructures [125, 126]. A schematic representation of the variety of shapes for the gold nanoparticle-based nanocarriers is reported in Figure 13.

Due to the presence of a negative charge on Au NPs, they can be easily (bio)functionalized (via ionic or covalent bonding or by physical absorption) by a wide range of different biomolecules, including drug molecules, or large biomolecules, such as antibiotics, proteins, genes (DNA and RNA), and a variety of targeting ligands, while recent investigations evidenced their nontoxicity for some human cell lines and their biocompatibility and biodegradability in vivo [125–128]. Au NPs are particularly attractive due to the presence of the *surface plasmon resonance* (SPR) bands [129, 130], which enable them to convert light to heat and scatter the produced heat to kill the cancer cells. The interaction of light with electrons on the Au NP surface at a given wavelength (frequency) of light induces a collective oscillation of electrons on the Au NP surface that causes the *surface plasmon resonance effect*. This phenomenon generates a strong extinction of light (absorption and scattering) at a given wavelength (or frequency) of light which strongly depends on AU NP size, shape, surface, and aggregation state. By synthesizing gold nanoparticles of different shapes, the surface plasmon resonance can be easily tuned to give absorption maxima from around 500 nm into the near-infrared part of the spectrum, thus allowing an efficient monitoring of the Au NPs' colloidal stability over time [128, 129].

Generally, Au NPs without surface modification present a reduced colloidal stability in blood flow. To overcome these limitations, the surface of Au NPs can be modified by using polyethylene glycol (PEG) which ensures an increased colloidal stability in the harsh physiological conditions of diseased tissues [125]. Because of their ease in synthesis and surface functionalization (with a large variety of organic and biological molecules), the high biocompatibility and low toxicity (which is related to their high physicochemical and colloidal stability), and the variety of optical properties related to surface plasmons, Au NPs have been employed in the synthesis of various biomedical nanoplatforms and for a wide range of applications, including biosensing, tumor imaging, and targeting (multimodal) drug delivery systems [126, 127]. A recent investigation of del Pino et al. [131] evidenced that thinner, more hydrophilic coatings, combined with functionalization with positively charged groups (such as quaternary ammonium cations), result in a more efficient cellular uptake [132], attributed to the favourable electrostatic interactions with the negatively charged cellular membrane [131, 132]. Mosquera et al. evidenced that cellular uptake of gold nanoparticle functionalised with negatively charged pyranines can be activated in situ through the addition of cationic covalent cages that specifically recognize the fluorescent pyranine dyes and counterbalance the negative charges. This highly selective and reversible host-guest recognition process is able to activate the cellular uptake, even in protein-rich biological media, as well as its regulation by rational addition of either cage or pyranine [131]. Many investigated Au NP nanoplatforms incorporate cellular affinity ligands into their surface in aims for specific cellular targeting. Doxorubicin (DOX) was attached to Au NPs, through a pH-sensitive linker, in order to provide an efficient intracellular triggered DOX release (inside acidic organelles), thereby enhancing therapeutic effects in drug-resistant tumor cells [133]. Based on the conjugation of a fluorescent DNAzyme onto Au NPs, Wu et al. [134] developed the first DNAzyme-based metal sensors for intracellular metal ion detection. Finally, the Au NPs have been successfully used in the development of novel approaches for the control of the delivery and release of drugs by means of external stimuli (such as light) or internal stimuli (such as pH or glutathione) [127, 128].

4.3. Quantum Dots (QDs). Quantum dots are fluorescent semiconducting inorganic nanocarriers that have shown potential use for many biomedical applications, such as drug delivery and cellular imaging [135]. They are composed of atoms of group II and group VI of the periodic table (i.e., molecules such as CdS, CdTe, and ZnS). They are synthesized either by means of a *bottom-up* approach (by self-assembly processes in solution following chemical reduction) or by a *top-down* method (by means of molecular beam epitaxy, ion implantation, e-beam, or X-ray lithography) [135, 136].

Most QDs consist of three parts: an extremely small core (2–10 nm in diameter) of a semiconductor material (e.g.,

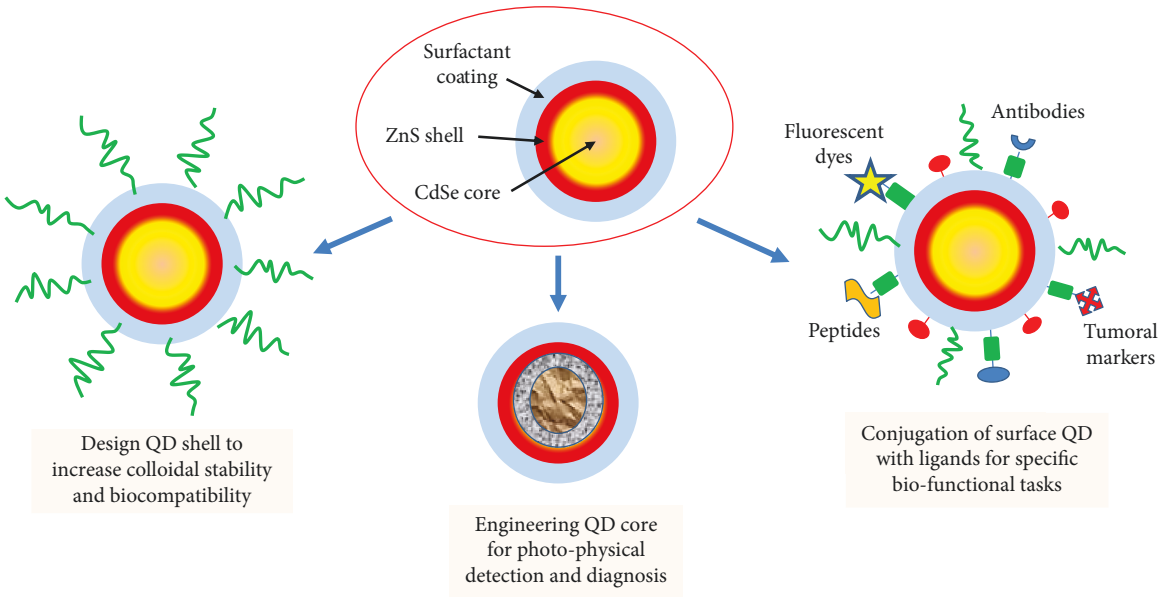

Figure 14: Design strategies of QD nanocarriers for biomedical and nanomedicine applications.

CdSe) surrounded by another semiconductor (such as ZnS). Finally, a cap made of different materials encapsulates the double-layer structures of the QDs (Figure 14). QDs with the inner semiconductor core of CdSe coated with the outer shell of ZnS represent the most commonly investigated nanoplatform. Due to their size and quantum effects, they show unique optical (*photophysical*) properties that allow visualizing the tumor, in real-time monitoring, during the drug-carrying and drug release processes at the targeted site [135, 136]. Cells labeled with QDs were intravenously injected into a living animal (mice) and followed during *tumor cell extravasation* into the lung tissue, by detecting the emission spectrum by scanning multiphoton microscopy [129].

Since most of the conventional organic label dyes do not offer the near-infrared (>650 nm) emission possibility, QDs with their tunable optical properties offer considerable advantages over organic fluorophores for this purpose. Due to their fluorescence properties (which is intense and stable for a longer time), highly sensitive detection (high quantum yield and resistance to photobleaching), and size-tunable light emission, QDs are particularly suited for the development of a new class of biosensors used for cancer imaging and diagnosis [135, 136].

As reported for other nanocarriers, QDs also experience nonspecific uptake by the RES. Moreover, some critical issues connected with their biomedical employment regard their toxicity, especially with the use of QD containing heavy metal ions (such as Cd and Hg). However, their toxicity can be reduced by functionalizing the QD surface with biocompatible molecules. In this respect, PEGylation allows the QDs to accumulate in tumor sites by an enhanced permeability and retention (EPR) effect without the employment of a targeting ligand [130]. This effect has been demonstrated recently by coating ITK705-amino QDs with methoxy-terminated poly(ethylene glycol) (PEG) of different chain lengths [130].

In order to passivate QDs for biological applications, several advantages have been demonstrated by encapsulating QDs in phospholipid micelles [137]. Finally, to actively target a tumor site, various ligands, such as peptides, folate, and large proteins (monoclonal antibodies), can be grafted on the QD surface (Figure 12). This possibility stimulates an increasing interest in the development of nanotheranostic platforms for simultaneous sensing, imaging, and therapy [138].

4.4. Superparamagnetic Iron-Oxide Nanoparticles (SPIONs). Superparamagnetic iron-oxide nanoparticles (SPIONs), such as magnetite (Fe_3O_4) and maghemite (Fe_2O_3), have been successfully proposed for target drug delivery by using a magnetic force [139–141]. When magnetic particles are reduced to 10–20 nm, they show a *super para-magnetism effect*, consisting of the magnetization of the nanoparticles up to their saturation, but they show no residual magnetism upon extinction of the magnetic field. Functionalization of SPIONs prevents the aggregation and protects their surfaces from oxidation and also provides a surface to conjugate drugs and targeting ligands, thus increasing the blood circulation by avoiding the RES and reducing nonspecific targets [141]. Superparamagnetic nanohybrids may be concentrated at a specific target site within the diseased tissues by an external, high-gradient magnetic field [140–142]. Modification of the SPION surface allows the bind with various proteins, antibodies, peptides, and anticancer drugs which can bind specifically to their target receptors that are expressed on cancer cells [116]. Surface-modified SPIONs with the anticancer drug methotrexate, which tags to the tumor cells expressing folate receptors, showed an increased uptake of SPIONs in tumor cells [142]. Despite their potential biomedical application, the possible alteration in gene expression profiles, disturbance in iron homeostasis, oxidative stress, and altered cellular responses are some of the main critical issues of SPION-related nanocarriers that limit their application in the clinic [141].

4.5. Mesoporous Silica Nanoparticles. Silica (SiO_2) materials have increased biomedical and nanomedicine applications owing to their simple synthesis procedures and their characteristic porous architecture [143–145]. Mesoporous silica nanocarriers (MSNs) allow loading a large amount of (anticancer) drugs, thus facilitating their accumulation in tumor tissues via passive targeting. PEGylation processes promote escape from the RES, thus prolonging the circulation time, drug availability, and biodistribution of therapeutic drugs [145–148]. MSNs possess several attractive features such as good biocompatibility, large specific surface area, high loading (of hydrophilic/lipophilic drugs) capacity, controllable pore diameters ranging from 2 to 50 nm (with narrow pore size distribution), and good thermal and chemical stability, which make them promising nanoscale drug carriers. Moreover, the convenient surface functionalization of MSNs (through the chemical modification of the active silanol surface group) with different site-specific targeting agents enables them to target tumor tissues via an active targeting mechanism [147–150]. Many different anticancer drugs, including paclitaxel, doxorubicin, and methotrexate, have been effectively delivered via MSNs. A variety of stimuli responsive systems have been developed to induce the controlled drug release triggered by temperature, light, pH, magnetic, electric and mechanical stimuli, as well as enzyme and chemical reactions [151, 152]. MSNs are particularly suited for diagnosis, targeted drug delivery, biosensing, and cellular uptake, in the biomedical application field.

Recently, monodisperse spherical silica nanoparticles (SNPs) with diameters of 20–200 nm were employed to study size, dose, and cell type-dependent cytotoxicity in A549 and HepG2 epithelial cells and NIH/3T3 fibroblasts. The extent and mechanism of SNP cytotoxicity (such as cell viability, membrane disruption, oxidative stress, and cellular uptake) were found to be not only size- and dose-dependent but also highly cell type-dependent. Specifically, the 60 nm SNPs were preferentially endocytosed by cells and, at high doses, caused a disproportionate decrease in cell viability [151]. Recently, Hu et al. [152] synthetized a multifunctional theranostic nanoplatform (designated as MMTNP) for tumor imaging and controlled drug release, consisting of MCM-41 mesoporous silica nanoparticles (MSNs), functionalized with a diagnostic probe of metalloprotease-2- (MMP-2-) activated fluorescence imaging peptides and an enzyme-responsive nanovalve blocking the pores, with the cRGD peptides further functionalized on the surface of MSNs for tumor targeting. Endocytosis experiments evidenced that MMTNP enhances the tumor targeting *in vitro* through receptor-mediated endocytosis. In addition, the antitumor drug CPT could be efficiently loaded in MMTNP and released rapidly in tumor cells, thus leading to enhanced inhibition of tumor cell growth [152].

Although clinical translation of mesoporous silica nanoparticles still remains a challenge, their unique properties evidence their efficient performances and a promising tool for innovative biomedical application.

4.6. Organic/Inorganic Hybrid Nanocarriers. Organic/inorganic hybrid nanocarriers combine the advantages of organic and inorganic materials and can be obtained by specific functionalization of the surface of inorganic nanocarriers with organic materials or by employing an organic colloidal macromolecular species as template for the controlled growth of inorganic materials [153–160]. For instance, surface coating with polyethyleneimine of mesoporous silica nanoparticles enhances the cellular uptake and allows safe delivery of siRNA and DNA constructs [156]. Systems composed of lipid bilayers supported on solid material have attracted significant interest owing to their biomaterial and nanomedicine applications. In MSNs/lipid bilayer hybrid nanocarriers, lipid bilayers are used to cap the MSN channels to prevent premature release of loaded drug, circumvent multidrug resistance, prolong retention of hydrophilic drug cargo, and achieve stimulus-responsive drug release [154, 155]. Recently, lipid-coated mesoporous silica nanoparticles (LC-MSNs) were employed to overcome the critical issues connected with limited solubility and stability during delivery of antiviral molecule ML336 [161]. The large surface area of the MSN core promotes hydrophobic drug loading while the liposome coating retains the drug (ML336) and enables enhanced circulation time and biocompatibility. In vivo safety studies conducted in mice evidenced that LC-MSNs were not toxic when dosed at 0.11 g LC-MSNs/kg/day (for four days). ML336-loaded LC-MSNs showed significant reduction in brain viral titer in VEEV-infected mice compared to PBS controls [161]. Choi et al. developed a model PEGylated lipid bilayer-supported mesoporous silica nanoparticle (MSN) composite for synergistic codelivery of axitinib (AXT) and celastrol (CST) in targeting angiogenesis and mitochondrial-based apoptosis in cancer [162]. This hybrid nanoplatform inhibited cell proliferation and induced an apoptosis effect against cancer cells by blocking mitochondrial function, thus leading to enhanced antitumor efficacy [162]. In Figure 15 we report a schematic description of the design strategies of PEGylated lipid bilayer supported MSNs composite for dual drug synergistic co-delivery.

5. Nanomedicine Formulations: Clinical Development and Approved Materials

In recent years, both the broadening in nanocarrier typology and the increase in the complexity of particles and materials employed have inspired explorations for new nanodelivery systems and brought about various products as well as numerous clinical trials for biotechnology and nanomedicine applications. However, before the premarket authorization, nanocarriers are subject to a range of preclinical and clinical validation by regulatory agencies, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the USA. Recent review articles provide a summary of the range of approved therapeutic nanomedicines and a description of novel nanoplatforms that are emerging through the clinical trial pipeline [163–165].

In Table 1, we report the main organic and inorganic nanomedicines approved by FDA [163, 164]. Among the organic nanomedicines approved for use on the market, it is useful to distinguish between the two main categories of polymer-based and lipid-based nanoparticles. Despite the

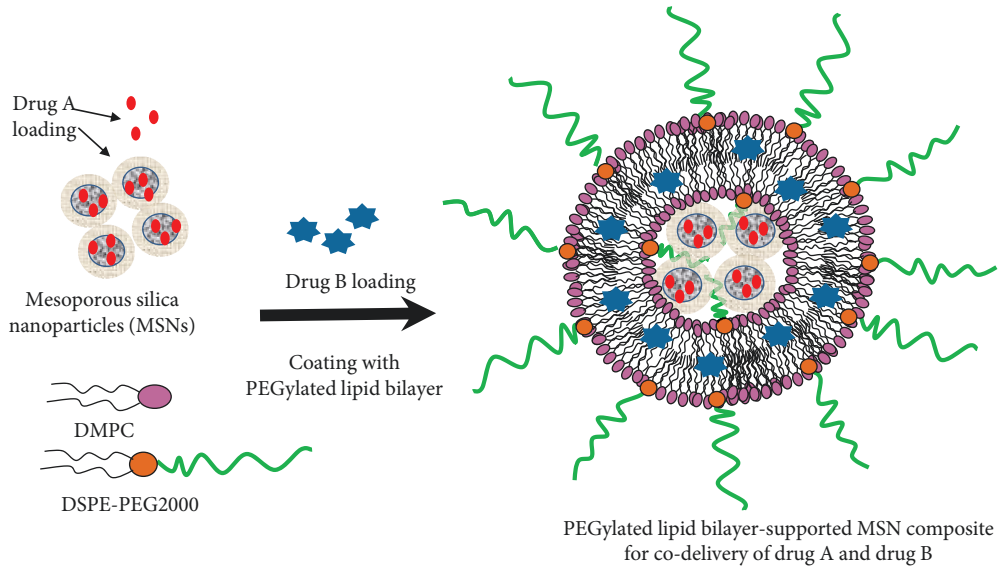

Figure 15: Design strategies of a PEGylated lipid bilayer-supported mesoporous silica nanoparticle (MSN) composite for dual drug synergistic codelivery.

intensive (preclinical) research involving block copolymer micelle nanocarriers, only a few of them have reached clinical evaluation or have been approved for the employment in the market [165]. The degradable hydrophobic polymers PLA, PLGA, and PDLLA are the most promising polymer systems for the development of nanoformulation, as they slowly decompose into constituent monomeric units over well-defined time courses. For example, *Eligard* formulation, obtained from the incorporation of leuprolide (a testosterone-inhibiting drug) into a polylactide-co-glycolic acid (PLGA) nanoparticle, represents a long-established polymer nanoparticle for the treatment of the prostate cancer symptoms. As evidenced in previous sections, the employment of PEG ensures the shield action against the recognition and degradation by the immune system and can ameliorate the biodistribution of the drug by increasing the circulation half-life. This effect is exploited in the *Adynovate* formulation (obtained by the PEGylation of the antihemophilic factor VIII), which is employed for the treatment of hemophilia A, and in the *Cimzia* formulation (obtained by the PEGylation of the antibody fragment Certolizumab) which is employed for the treatment of Crohn's disease, rheumatoid/psoriatic arthritis, and ankylosing spondylitis [163–165]. Over the last decade, a number of promising block copolymer micelle formulations entered the clinical development, with two receiving regulatory approval: namely, the *Cynviloq* (paclitaxel-loaded PEG-PDLLA block copolymers) and *Nanoxel* (docetaxel-loaded PEG-PDLLA block copolymers) [165]. Finally, *Genexol-PM* is a poly(ethylene glycol)-block-poly(D,L-lactide) (PEG-PDLLA) diblock copolymer micelle loaded with paclitaxel (developed by Samyang Corporation) which was first introduced in the Korean market and is actually approved by FDA in clinical trials for the treatment of metastatic breast cancer.

Liposomal formulations represent the most successful category of nanocarriers employed for drug delivery purposes [163, 164]. Two largely employed PEGylated liposome-based doxorubicin formulations for the treatment of epithelial ovarian Kaposi's sarcoma are *Doxil*, composed of hydrogenated soy L-α-phosphatidylcholine (HSPC) : cholesterol : PEG 2000-DSPE (56 : 39 : 5 molar ratio), and *Lipo-Dox*, composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) : cholesterol : PEG 2000-DSPE (56 : 39 : 5 molar ratio). A non-PEGylated version of liposomal doxorubicin formulation employed for breast cancer treatment is provided by *Myocet*, composed of egg PC (EPC) : cholesterol (55 : 45 molar ratio). Other anticancer drugs formulated with liposomes are approved for (different stages) clinical studies. Finally, *Thermodox* (produced by Celsion Corporation), composed of DPPC, mono steroyl PC (MSPC), and PEG 2000-DSPE, is a temperature-responsive version of the PEGylated formulation of liposomal doxorubicin, actually in phase III clinical trials, which is able to release its drug content inside the tumor upon heat transfer, using a radiofrequency ablation (RFA) process.

In Figure 16, we report a sketch of the main characteristic of PEGylated liposomal formulations employed for intravenous administration of anticancer drugs (inset A), together with the main components of Doxil (inset B), the first FDA-approved nanodrug formulation, developed by Barenholz [166]. Anticancer drugs doxorubicin, daunorubicin, paclitaxel, and vincristine (Figure 16(a)) are among the most extensively investigated agents for the liposome-based drug formulations, and several liposomal formulations of these agents are currently in clinical use in cancer therapy.

Inorganic nanoparticles represent the category of nanocarriers which received the approval of the minor number of nanomedicines for their use in the market. A number of metallic nanoparticles with applications in both therapeutic and imaging processes (theranostics) are under the different phases of clinical trials. In particular, some of the inorganic nanomaterials, such as gold nanoparticles and

Table 1: List of relevant (polymer-based and lipid-based) organic and inorganic (and metallic) nanomedicines approved by the FDA.

Clinical products	Formulation	Indication	Company	Year
		Polymer-based nanoparticles		
Renagel	Poly(allylamine hydrochloride)	Chronic kidney disease	Sanofi	2000
Eligard	Leuprolide acetate and polymer PLGA (poly (DL-lactide-co-glycolide))	Prostate cancer	Tolmar	2002
Estrasorb	Micellar estradiol	Menopausal therapy	Novavax	2003
Cimzia/certolizumab pegol	PEGylated antibody fragment (certolizumab)	Crohn's disease Rheumatoid/psoriatic arthritis Ankylosing spondylitis	UCB	2008-2013
Genexol-PM	mPEG-PLA micelle loaded with paclitaxel	Metastatic breast cancer	Samyang Corporation	2007 South Korea
Adynovate	Polymer-protein conjugate (PEGylated factor VIII)	Hemophilia	Baxalta	2015
		Lipid-based nanoparticles		
Doxil/Caelyx	Liposomal doxorubicin	Ovarian, breast cancer, Kaposi's sarcoma, and multiple myeloma	Janssen	1995-2008
DaunoXome	Liposomal daunorubicin	AIDS-related Kaposi's sarcoma	Galen	1996
Myocet	Liposomal doxorubicin	Combination therapy with cyclophosphamide in metastatic breast cancer	Elan Pharmaceuticals	2000
Marqibo	Liposomal vincristine	Acute lymphoblastic leukemia	Talon Therapeutics Inc.	2012
AmBisome	Liposomal amphotericin B	Fungal/protozoal infections	Gilead Sciences	
Visudyne	Liposomal verteporfin	Choroidal neovascularisation, macular degeneration, wet age-related, myopia, and ocular histoplasmosis	Bausch and Lomb	2000
Onivyde	Liposomal irinotecan	Pancreatic cancer	Merrimack	2015
		Inorganic and metallic nanoparticles		
INFed	Iron dextran (low MW)	Iron deficiency in chronic kidney disease (CKD)	Sanofi Aventis	1957
Feridex/Endorem	SPION coated with dextran	Imaging agent	AMAG Pharmaceuticals	1996-2008
Venofer	Iron sucrose	Iron deficiency in chronic kidney disease (CKD)	Luitpold Pharmaceuticals	2000
GastroMARK; umirem	SPION coated with silicone	Imaging agent	AMAG Pharmaceuticals	2001-2009
NanoTherm	Iron oxide	Glioblastoma	MagForce	2010

silica nanoparticles, have encountered obstacles in early-stage clinical trials, due to toxicity and a lack of stability critical issues. To date, only three iron oxide nanoparticles have completed FDA approval (*Feraheme*, *Feridex*, and *Gastro-MARK*), two of which have been later withdrawn from the market [163]. Although the iron oxide nanoparticles present an increasing research interest as contrast enhancement reagents for magnetic resonance imaging, the majority of FDA-approved nanoplatforms (such as *INFeD* and *Venofer*) are indicated as iron replacement therapies. *NanoTherm* is the only one that has obtained approval for clinical use for the treatment of glioblastoma, whereby tumors are thermally ablated by magnetic hyperthermia induced by entrapped superparamagnetic iron oxides.

Finally, significant research is still required to understand and predict how these materials will behave in biological systems, while further preclinical and clinical studies are required in order to offer the best performance into the (in vivo) environment where the actual release will take place.

6. Conclusions and Future Perspectives

We highlight recent advances of smart nanocarriers in the development of novel platforms for the efficient transport and controlled release of drug molecules. The main aim of efficient nanostructured delivery systems is to reduce the drug dose needed to achieve a specific therapeutic effect, thus lowering the costs and reducing the side effects associated

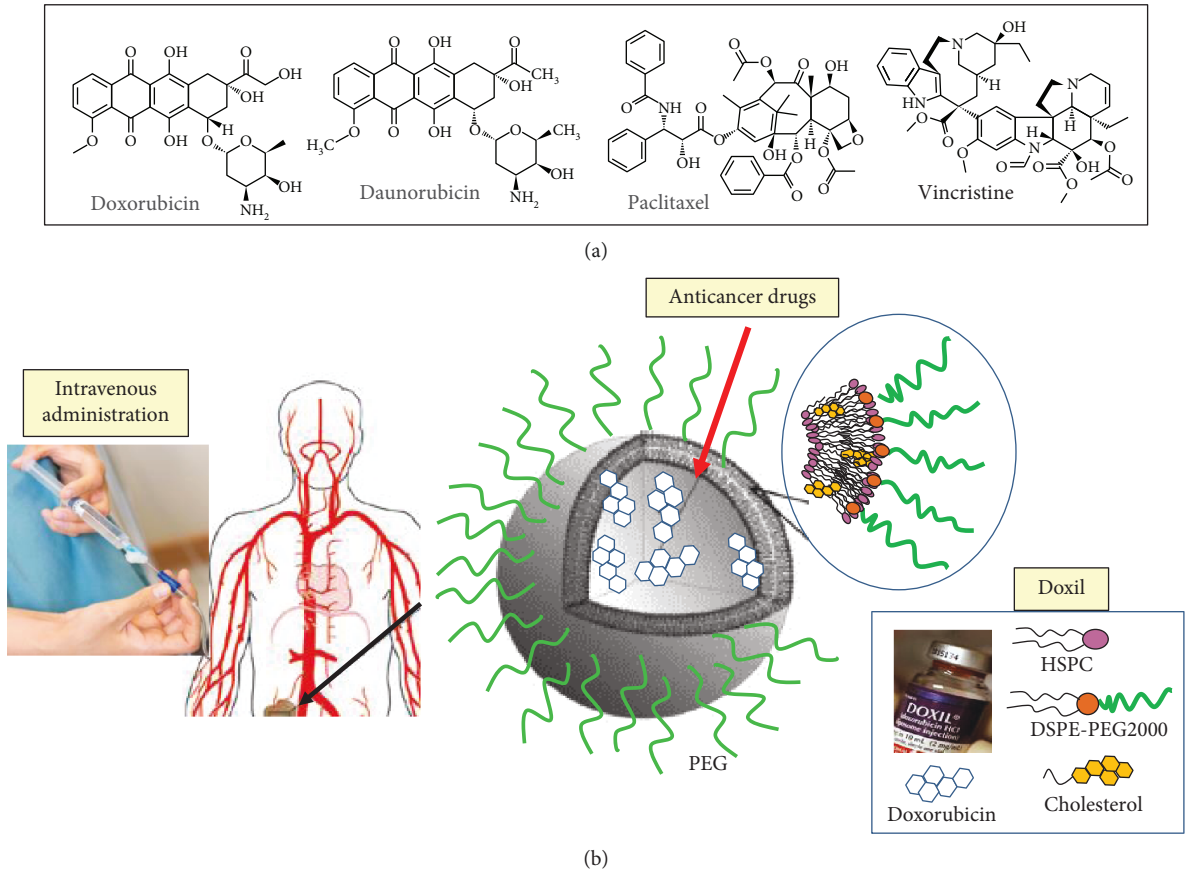

Figure 16: Main characteristic of PEGylated liposomal formulations employed for (intravenous administration) of anticancer drugs (a). We also reported the main components of the *Doxil* formulation, a PEGylated liposome-based doxorubicin formulation for the treatment of epithelial ovarian Kaposi's sarcoma.

with their use. The two main categories of organic and inorganic nanostructured materials widely employed in drug delivery processes present a variety of complementary and synergistic properties that can be profitably exploited. On the one hand, the organic *soft nanocarriers* (such as amphiphilic polymers and liposomes) present better properties to match the physicochemical condition encountered in biological (and pathological) tissues, thus furnishing the best examples of biocompatible nanostructures. On the other hand, the *hard nanoparticles* composed of inorganic materials (such as quantum dots and gold and mesoporous silica nanoparticles) propose the complementary functions for the diagnosis and detection of the pathological conditions within the diseased tissues. As the microenvironment conditions within the diseased tissues have a great impact on delivery efficiency of nanocarrier systems, the choice of nanocarrier properties (such as the size, shape, material substrate, and surface chemistry) plays a crucial role in the design of efficient nanocarriers for specific functions.

Despite that a large variety of smart nanocarriers have been developed in recent years, the intrinsic complexity of biological environments strongly influences the functionality of the nanomaterial and often complicates their effective use for therapeutic treatments. Although these nanomedicines show good performance against specific diseases, their inherent drawbacks, mainly connected with the limited absorption and request of frequent injection for patients, cannot be ignored [167]. Therefore, a deeper knowledge and understanding of the real interactions involved in the diseased tissues is fundamental for the development of novel therapeutic protocols based on the employment of smart nanocarriers. The difficulty to predict the behavior (and responses) of nanocarriers during the drug delivery processes is connected with the difficulty to fully describe (and model) the complex structural and dynamic processes involved in biological systems. In this respect, the investigation of a multiplicity of simultaneous factors and biological functionality may be replaced with the systematic study of the effect of a few parameters at a time (such as surface charge density and/or nanoparticle size/topology). The identification of the key factors for the design of efficient nanocarriers represents then the fundamental (initial) step to decipher the complexity involved in complex biological processes. Therefore, a deeper knowledge and understanding of the real interactions involved in the diseased tissues is fundamental for the development of novel therapeutic approaches and protocols based on the employment of smart nanocarriers.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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