# Chapter 10
# Gelatin Nanocomposites (GNCs): An Efficient Drug Delivery System

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**Abstract** The literature reported that natural proteins are being widely used as potential carriers for site-specific drug delivery as they bear nontoxic and biocompatible behavior. Modified proteins have shown also their potent role in gene delivery, cell culture, and tissue engineering. Gelatin is one of the most versatile widely used proteins in pharmaceutics because of biocompatibility, biodegradability, low cost, and other applications. These advantages led to its application in the synthesis of nanoparticles to deliver drugs and genes in the last few decades. Impact of gelatin binding to various drugs has been investigated for controlled release applications by various research groups. Various parameters like cross-linking density and isoelectric point can be used to tune the optimization of gelatin degradation and drug delivery kinetics. At present, gelatin nanocomposites play a crucial role in various aspects of biology and medical sciences. Various cross-linkers used to improve the physicochemical behavior of gelatin nanocomposites (GNCs) have been reported. Further, physicochemical behaviors of GNCs

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including drug loading, release, particle size, zeta-potential, cytotoxicity, cellular uptake, and stability are explained. Various groups explained the applications of GNCs in delivery of drugs and genes as well as their in vivo pharmacological performances. Our emphasis is to study the interaction of various factors of biological macromolecules in the extracellular matrix which regulate the function of bioactive molecules. In light of the importance of GNCs, gelatin has proven to be a good biomaterial for the controlled release of several biologically active molecules. Although, research is still continued to improve the role of gelatin to release drugs/genes through the use of composite scaffolds and gelatin modification.

**Keywords** Gelatin · Modified biopolymers · Biodegradation · Drug delivery

## 10.1 Introduction

Gelatin is a well-known structural natural protein used in the daily life in the scientific and technological areas for the preparation of a great variety of composite materials. In spite of its abundance and common applications, gelatin presents itself with a mixed character between a protein as it is derived from collagen, and a synthetic linear polymer with random spatial arrangement above certain temperature [1–4]. Gelatin has numerous applications like biomedicine, biocompatibility, and biodegradability are decisive and the reinforcement of gelatin matrix by assembling to inorganic or hybrid nanoparticles (NPs) is also required to improve its mechanical stability. Alternative treatments such as chemical crosslinking may also contribute to reduce water swelling and enhance the mechanical properties as well as thermal stability [5–10]. Incorporation of inorganic solids into the proteinous matrix allows the tailoring in terms of the mechanical and functional properties of the resulting gelatin-based composites. Different strategies have been proposed by various groups to tune the functional properties of gelatin like selection of inorganic solids, grafting of suitable functional groups to the gelatin hybrids, and combination of additional polymers or fillers in ternary composites. Using these approaches, advanced functional materials of increasing complexity were developed and opening the way for a wide range of applications of the gelatin-based nanocomposites [11–15].

## 10.2 Properties of Gelatin and Its Composites

### *10.2.1 Composition*

Gelatin is a mixture of peptides and proteins produced by partial hydrolysis of collagen extracted from the skin, bones, and connective tissues of domestic animals. Pharma grades of gelatin are usually obtained from beef bones, although some beef bone gelatin is used by the food industry [6–10].

### *10.2.2 Properties*

Natural molecular bonds between individual collagen strands are broken down to a form that rearranges more easily. Gelatin melts when heated and solidifies when cooled again. In the presence of water, it forms a semi-solid gel.

### *10.2.3 Salvation Properties*

Gelatin forms a viscous solution in water, and sets to a gel on cooling. Further, its chemical composition resembles to that of its parent collagen. Gelatin is soluble in many polar solvents and shows viscoelastic flow and streaming birefringence.

### *10.2.4 Thermal Properties*

Gelatin gels exist over a small temperature range, wherein the upper limit being the melting point of the gel depends on gelatin grade and the lower limit is the freezing point at which ice crystallizes [16–21].

### *10.2.5 Mechanical Properties*

The literature revealed that gelatin gels are sensitive to temperature and time. The viscosity of the aqueous gelatin increases with concentration and when kept on cooling (≈4 °C). Further, viscosity and other mechanical properties can also be tuned by mixing other inorganic/organic material to it.

## 10.3 Applications of Various Organic, Inorganic, and Polymeric Systems for Drug Delivery (Fig. 10.1)

### *10.3.1 Metal Nanoparticles (NPs) Containing Biomolecules*

Applications of metal nanoparticles (NPs) have been liberated by the use of nanobioconjugates after the discovery of immune gold labeling. Metal NPs have been used in various biomedical applications including drug delivery (vehicle for delivering drugs, proteins, peptides, plasmids, DNAs, etc.), detection, diagnosis, and therapy. Metal NPs (gold or silver) have optical and electronic properties derived based on size and composition. These nanomaterials have found important

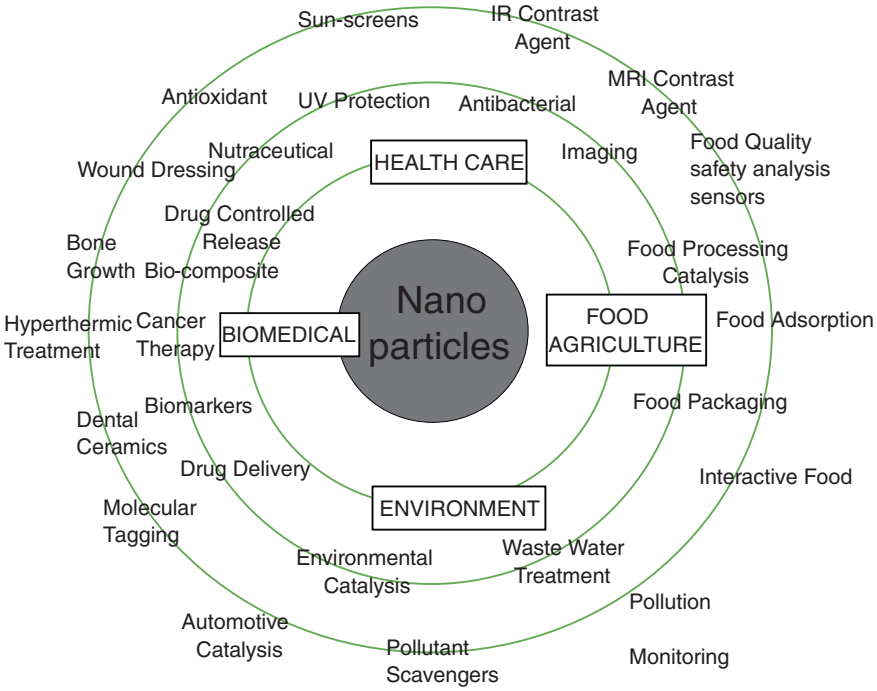


**Fig. 10.1** Various applications of nanoparticles in various fields of sciences

applications as chemical sensors, when coupled to affinity ligands. Au NPs conjugated with specific oligonucleotides can sense complementary DNA strands, detectable by color changes [22–25].

### *10.3.2 Core Metal Nanoparticle*

Au nanoparticles can be readily functionalized with probe molecules such as antibodies, enzymes, nucleotides, etc. These hybrid nanostructures are the active elements of a number of biosensor assays, drug and gene delivery systems, laser confocal microscopy diagnostic tools, and other biomaterial-based imaging systems. Silver (Ag) has been known since ancient times as a very effective antimicrobial agent. Ag NPs have been routinely used to prevent the attack of a broad spectrum of microorganisms on prostheses, catheters, vascular grafts, and human skin, reduce infection in burn treatment, arthroplasty, etc. [22–25].

### *10.3.3 Magnetic Metal Nanoparticles (NPs)*

Currently, magnetic nanoparticles (MNPs) have attracted the researchers due to their unique magnetic property. They have the ability to function at the cellular and molecular level of biological interactions making them an attractive platform as contrast agents for magnetic resonance imaging (MRI) and for drug delivery. Recent advances in the field of nanotechnology, the ability to specifically tailor the features and properties of magnetic NPs for these biomedical applications has been improved. However, the safety and efficacy of using magnetic nanoparticles is debatable among scientists. Various researchers worked on the relationship between biocompatibility and surface chemistry of gelatin and magnetic NPs-based composites. The results show that the biocompatibility of gelatin nanocomposites is dependent on both the cell type and the nanoparticles' surface chemistry [26–30].

### *10.3.4 Metal-Oxide Nanoparticles*

Metal-oxide nanoparticles such as titanium oxide ($TiO_2$) and zinc oxide (ZnO) serve many functions in various polymeric materials. Traditionally, they have been used as pigments to enhance the appearance and improve the durability of polymeric products and usually they have been considered to be inert. Magnetic NPs exhibit unique physical and chemical properties due to their limited size and high density of corner or edge surface sites [31–33].

### *10.3.5 Effect of Size of NPs*

The size and shape of metal nanoparticles influence the properties of gelatin. It comprises the structural characteristics like the lattice symmetry and cell parameters. Metal oxides are usually robust and stable systems with well-defined crystallographic structures. However, the growing importance of surface free energy and stress with decreasing particle size must be considered. Changes in thermodynamic stability associated with size can induce modification of structural transformations and sometimes cause the nanoparticle to disappear due to interactions with its surrounding environment and high surface free energy. In order to display mechanical or structural stability, a nanoparticle must have a low surface free energy. As a consequence of this requirement, phases that have low stability in bulk materials can become very stable in nanostructures. This structural phenomenon has been detected in $TiO_2$, $VO_x$, $Al_2O_3$, or $MoO_x$ oxides [29, 30, 34, 35].

## 10.4 C-Based Giant Like Molecules (Fullerenes, CNT, Graphene) (Fig. 10.2)

Carbon nanotubes and buckyball clusters belong to the fullerenes (composed of carbon). Carbon nanotubes (CNTs) are carbon coaxial graphite sheets of < 100 nm rolled up into cylinders. They can be classified in two categories based on their structure (i) single-walled carbon nanotubes (SWNT) and (ii) multi-walled carbon nanotubes (MWNT). They have been applied in biology as biosensors for detecting protein, DNA, diagnostics, and carriers. These types of NPs are insoluble in several solvents, provoking toxicity problems and some health concerns. However, they can be chemically modified to make them water soluble and can be functionalized so that they can be linked to active molecules such as nucleic acids, proteins, and therapeutic agents. They have unique electronic, structural, and thermal characteristics that make them appropriate vehicles for drug delivery systems [36–40] (Fig. 10.3).

Liu et al. used single-walled carbon nanotubes (SWNT) chemically functionalized with PEG-paclitaxel (SWNT-PEG-PTX) in a xenograft breast cancer mouse model. They also observed that higher tumor uptake of PTX and higher ratios of tumor to normal-organ PTX uptake for SWNT-PEG-PTX compared to taxol and PEG-PTX. They also showed effective in vivo delivery of SWNT-PEG-PTX with higher tumor suppression efficacy and minimum side effects than taxol. Due to their physicochemical properties, carbon nanotubes have additional applications in computer, aerospace, electronics, and other industries [41–44].

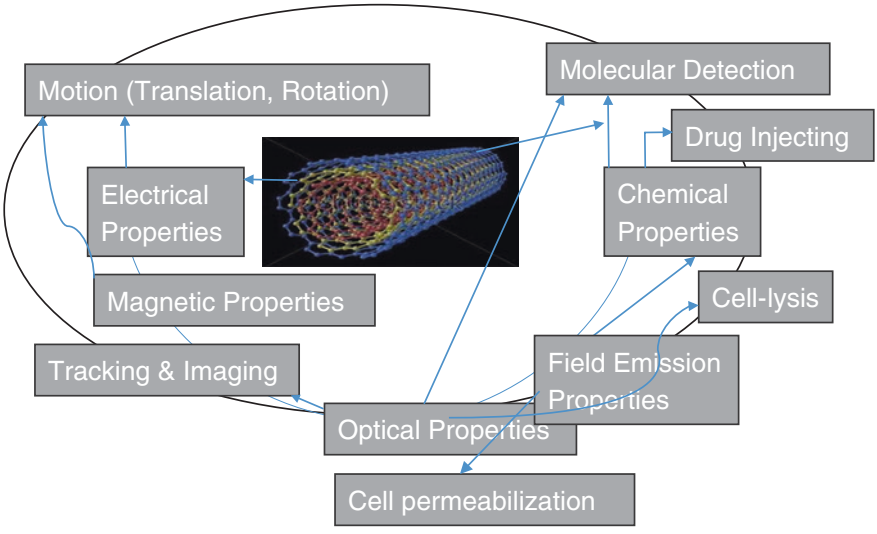


**Fig. 10.2** Use of CNT in various fields along with their properties

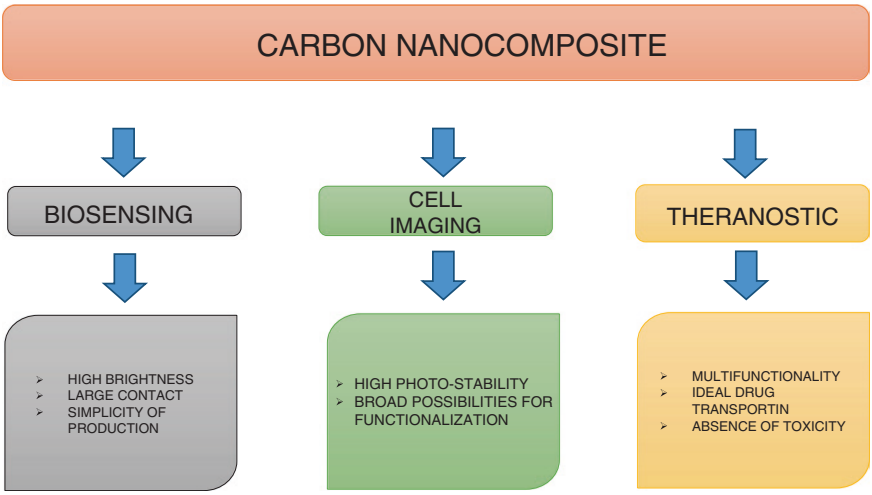


**Fig. 10.3** Organic particles in various fields

Buckyball fullerenes have been tested in vitro as carriers for conventional anticancer agents (i.e., fullerene-paclitaxel conjugates) and nucleic acids. However, there is striking evidence that fullerenes can cause oxidative damage to cellular membranes, and cause toxicity. The in vivo efficacy and safety of fullerenes require further studies [42–45].

## 10.5 Organic Nanoparticles

### *10.5.1 Polymeric Nanoparticles (PNPs) (Fig. 10.4)*

PNPs are colloidal solid particles prepared from biodegradable polymers such as chitosan and collagen or nonbiodegradable polymers such as poly(lactic acid) (PLA) and poly(lactic co-glycolic acid) (PLGA). Their small size (50–300 nm) allows them to penetrate capillaries and to be taken up by the cells and increases the accumulation of the drug at the target site. Majority of these compounds are formulated through a spontaneous self-assembly process using block polymers of two or more polymeric chains with different hydrophilicity. They are considered promising nanocarriers for drug delivery because they can improve the specificity to the target site of action by changing their physicochemical properties and pharmacokinetics. The stability of PLGA NPs can be further improved by coating them with PEG [3, 46–48].

Danhier et al. used paclitaxel-loaded PEG-PLGA-based NPs grafted with RGD peptide and found that the target NPs reduced tumor growth more efficiently, and prolonged survival times of mice, compared with nontargeted nanoparticles [3, 46–48].

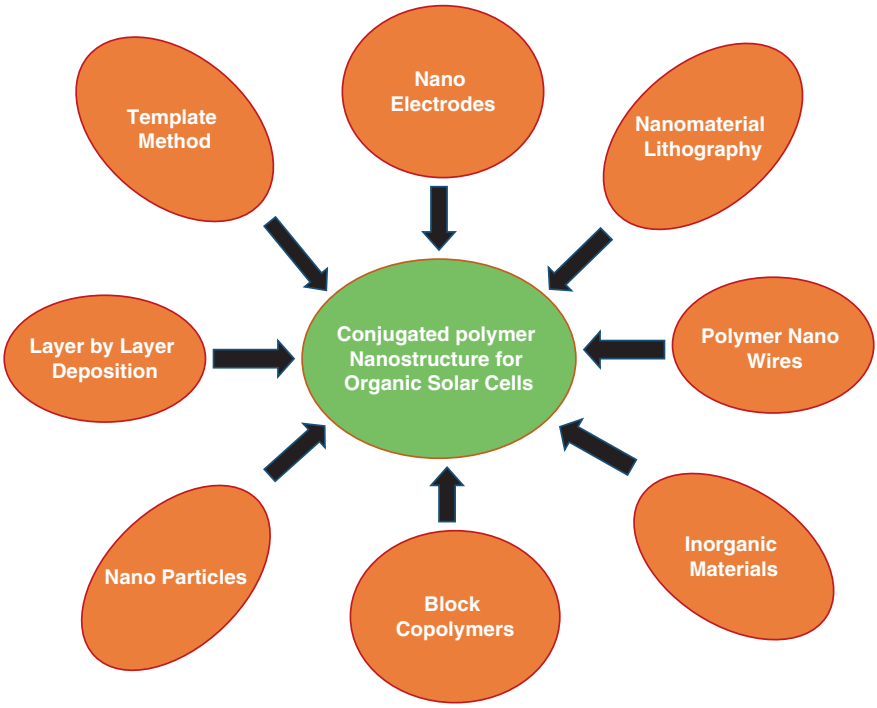


**Fig. 10.4** Polymeric nanoparticles in various fields

A very promising polymeric nanoparticle is the chitosan-based nanoparticles. Chitosan is a natural polymer and it is obtained by the partial N-deacetylation of chitin. It is the second most abundant polysaccharide in nature. Doxorubicin (DOX)-loaded chitosan nanoparticles, and DOX-loaded anti-human growth factor receptor 2 (Her2)-surface modified chitosan nanoparticles have been reported. A modified PLGA nanoparticle containing chitosan through physical adsorption and chemical binding methods has been described. However, more in vivo studies are needed to demonstrate the efficacy and safety of PLGA and chitosan nanoparticles as drug carriers [3, 47, 48].

### *10.5.2 Polymeric Micelles*

Polymeric micelles are made up by amphiphilic block copolymers such as poly (ethylene oxide)-poly(β-benzyl-L-aspartate) and poly(*N*-isopropylacrylamide)-polystyrene. Micelles of less than 100 nm assembled with a hydrophobic core and hydrophilic shell are used as drug carriers. The small size of micelles, allows the specific accumulation in the pathologic tissue. Their hydrophobic core and

hydrophilic shell make micelles potent nanocarriers for poorly water soluble anticancer drugs, including paclitaxel and docetaxel. One particular feature of micelles is that the amount of drug released can be controlled by an external stimulus like pH, temperature, ultrasound, or certain enzymes.

Kagaya et al. reported the determination of gene delivery efficacy to vascular lesions using cyclic RGD (cRGD)-PEG-polyplex micelles. They found that cRGD-PEG-polyplex micelles achieved significantly more efficient gene expression and cellular uptake compared with ligand-free PEG-micelles in vitro. Micelles are normally formulated with biocompatible and biodegradable materials which makes them excellent nanocarrier systems. The targeting ability of polymeric micelles is limited due to their low drug incorporation stability and low drug loading [49, 50].

### *10.5.3 Dendrimers*

Dendrimers differ from traditional polymers in the sense that they are highly branched synthetic polymers made of macromolecules such as poly (*N*-isopropylacrylamide)-polystyrene and poly(ethylene oxide)-poly(β-benzyl-L-aspartate) with an inner core diameter of less than 15 nm. Dendrimers possess perfect nanoarchitecture composed of three different parts: (i) focal core, (ii) repetitive units of several interior layers, and (iii) multiple peripheral functional groups. Dendrimers are synthesized from branched monomers in a stepwise manner. It is possible to control several molecular properties including shape, size, dimension, and polarity. Dendrimers offer enormous capacity for solubilization of hydrophobic compounds and can be modified with guest molecules. Therefore, dendrimers have shown enormous potential as anticancer drug delivery systems [44, 51, 52].

Choi et al. reported the synthesis of dendrimers conjugated with fluorescein (FITC) and folic acid (FA) for biomedical application like imaging and therapeutic purposes. They linked dendrimers with complementary DNA oligonucleotides to produce clusters to target cancer cells overexpressing high-affinity folate receptors. Few preclinical or clinical studies of dendrimers as drug carriers is currently available. Thus, it is not possible to make any conclusion about the safety efficacy of dendrimers for human use [53, 54].

### *10.5.4 Polymeric Nanofibers*

Polymeric nanofiber explains fibers with diameters from 1 to 100 nm closely matching the size scale of extracellular matrix (ECM) fibers. Polymeric fibers are derived from inorganic (titanium, silicon or aluminum oxides) or organic

(polyvinyl alcohol, gelatin, poly(N-isopropylacrylamide, polycaprolactone, or polyurethane) materials. There are three techniques for the synthesis of nanofibers, electrospinning, phase separation, and self-assembly; however, the most commonly used is electrospinning. Due to large surface area, low density, high pore volume, and tight pore size of nanofibres, various properties like voltage, capillary collector distance, and polymer flow rate can be tuned. Further, the surface tension and viscoelasticity of nanofibers in solution can also be modified. Nanofibers are being used in medical (tissue engineering), filtration, barriers, wipes, personal care, composite, insulation, garments, and energy storage. They have also been used as drug delivery systems [2, 47, 48, 55].

Tseng and coworkers used biodegradable nanofibers to successfully deliver vancomycin, an antibiotic, to the brain tissue of rats and reduce the toxicity associated with parenteral antibiotic treatment. However, there are very few examples using polymeric nanofibers as cancer drug carriers [2, 47, 48, 55].

## 10.6 Quantum Dots (Fig. 10.5)

Quantum dots (QD) are small in size (2–10 nm) and colloidal fluorescent semiconductor nanocrystals composed from 10 to 50 atoms of groups II–IV or III–V. They usually consist of a metalloid crystalline core and a shell, which is used to protect the core and renders the QD available for in vivo applications.

The size and shape of QD can be controlled precisely. One of the most valuable properties of QD is their fluorescent behavior, which make them optimal fluorophores for biomedical imaging. Fluorescent QD can be conjugated with bioactive

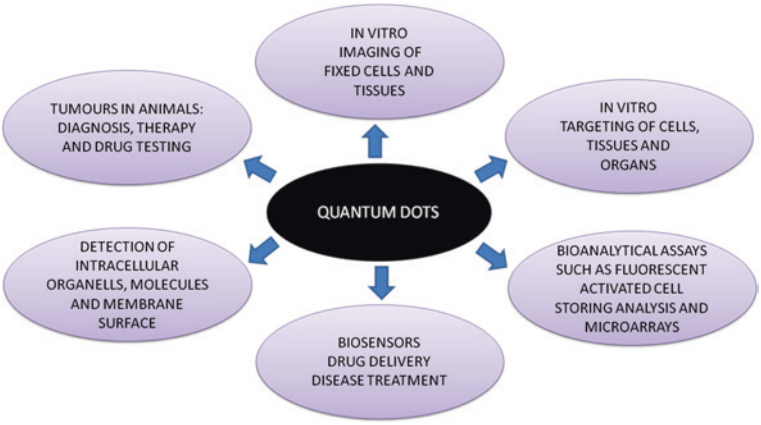


**Fig. 10.5** Various applications of quantum dots

moieties or specific ligands (e.g., receptor ligands and antibodies). QD are stable for months without degradation or alteration. QD are mostly used as highly sensitive and multicontrast imaging agents for detection and diagnosis of cancer in vivo. QD are also used in transistors, solar cells, and quantum computing. Nevertheless, because they are composed of hazardous heavy metals, it is important to be cautious about their toxicity [5, 56].

## 10.7 Gelatin Nanoparticles (Fig. 10.6)

In the last decade, gelatin is extensively used in food and medical products. It is attractive for controlled drugs release due to its nontoxic, biodegradable, bioactive, and inexpensive properties. It is a polyampholyte and bears both cationic and anionic parts along with the hydrophilic group. Various biological applications of gelatin NPs including drug delivery were reported. It is known that mechanical properties, swelling behavior, and thermal properties depend significantly on the crosslinking degree of gelatin. Gelatin NPs can be prepared by desolvation/coacervation or emulsion method. Desolvation/coacervation processes wherein a homogeneous solution of charged macromolecules undergoes liquid–liquid phase separation and results in a polymer-rich dense phase at the bottom and a clear supernatant. The addition of natural salt or alcohol normally promotes coacervation and the control of turbidity that resulted in desired nanoparticles. Many encapsulants have been successfully encapsulated into gelatin nanoparticles (Table 10.1), [16, 18, 36, 39, 57–59].

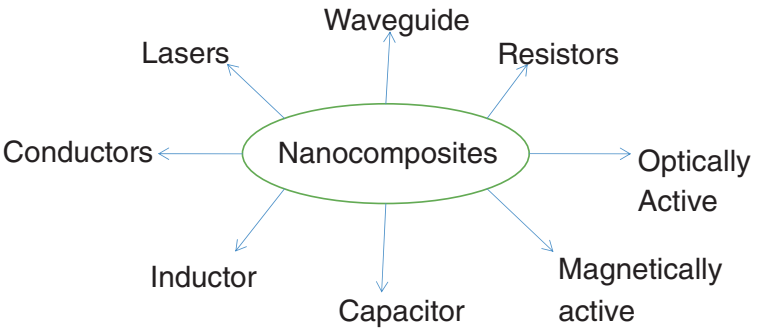


**Fig. 10.6** Nanocomposites and their applications

**Table 10.1** Encapsulation, synthesis and therapeutics, and mechanism of gelatin diffusion

| Encapsulant | Encapsulation efficiency (%) | Synthesis method | Therapeutic improvement | In vitro |
|---|---|---|---|---|
| Paclitaxel | 33–78 | Desolvation | Biological activity of Paclitaxel is retained | Paclitaxel-loaded NPs were active against human RT4 bladder transitional cancerous cell |
| Didanosine | 72.5 | Double desolvation technique | Slow drug release up to 24 h | Higher accumulation of didanosine in brain |
| Chloroquine phosphate | 15–19 | Solvent evaporation method | Reduced side effect | |
| Insulin | 72.8 | Ionotropic gelation method | Oral absorption and oral bioactivity was increased | Nanoparticle adhere to intestinal epithelium and internalized by intestinal mucosa |
| Sulfamethoxazole | 39 | Solvent evaporation | Slow release up to 10 h | |

## 10.8 Superiority of Gelatin Over Other Polymeric Materials

In last few years, researchers have focused on the various aspects of gelatin within composite materials for the controlled delivery of therapeutics and genes. Composites synergistically combine two or more materials in order to produce a new system with new properties unique to either material alone, like release kinetics, mechanical properties etc. As a mark of its versatility, gelatin has been demonstrated to be a useful component in composites featuring materials ranging from ceramics to natural and synthetic polymers [16, 18, 36, 39, 57–59].

Composites of gelatin and ceramics are used in order to deliver drugs and promote bone regeneration. Most challenging clinical complications occurring due to bone defects are wound infection and nonunion. Two most explored types of drugs can be delivered by ceramic/gelatin composite systems. Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA) is a naturally-occurring mineral and comprises the inorganic component of bone matrix. A simple two-phase composite, porous HA can be coated with gelatin in order to increase mechanical properties. Increase in mechanical properties is proportional to the concentration of gelatin and it was to hypothesize that gelatin increases HA toughness by bridging material cracks. More advanced fabrication techniques have been employed, so HA NPs can be precipitated within gelatin networks to form scaffolds capable of drug delivery. Compared with HA microparticles without gelatin, cells seeded on composite microparticles experienced greater proliferation. It proves that gelatin–HA composite could potentially be used as an carrier to deliver cell [8, 16, 60–62].

Calcium phosphate cements (CPCs) are mixtures of calcium orthophosphates and can be injected to fill craniofacial and orthopedic defects. CPCs have also been used as carriers for the delivery of drug via incorporating in the liquid or solid phase. CPCs have had great success in biomedicine due to inherent osteoconductivity and ease of material delivery, lack of biodegradation, and drug release. Habraken et al. developed degradable gelatin microparticles into CPCs in order to generate porosity degradation to tissue integration. Subsequently, the embedded gelatin microparticles within this composite system were used not only as paragons but also to deliver drug [63, 64].

Collagen is the building block of the extracellular matrix and therefore are the attractive materials for drug delivery and tissue engineering. These materials have been polymers synthesized by human cells like collagen, hyaluronan, and naturally-derived polymers obtained by other organisms like chitin and silk. Composites of gelatin and other naturally-occurring polymers offer good biocompatibility and enable biomimetic strategies for drug delivery [64, 65].

Hyaluronan has the ability to act as a binding agent for molecules and create interest in making it an attractive biomaterial for drug delivery and tissue engineering. However, the hydrophilicity of hyaluronan can inhibit protein adsorption and prevent cell attachment. Therefore, gelatin–hyaluronan composites have been explored in order to take advantage of the strengths of both materials. Gelatin and hyaluronan have been blended simply by electrospinning to prepare biodegradable sheets with tunable surface tensions that may be used as drug delivery carrier [14, 15, 43, 66].

Literature revealed that chitosan has a high charge density and good biocompatibility like hyaluronan. Gelatin and chitosan are used to prepare polyionic complexes and therefore composite preparation drug release kinetics and degradation can be altered by the amount of gelatin incorporation. The release kinetics can be controlled by varying the Ph. It was observed that on decreasing pH, release of drug increases. Gelatin chitosan sponges have been reported as carriers for drug release to cure wound. Silk is a popular protein obtained from insects and spiders. In recent years, silks and silk-derivatives were used in tissue engineering due to their light weight and tough behavior. Silk was also exposed to reinforce gelatin scaffolds, tensile, and bending strength [14, 15, 43, 66].

Mandal et al. synthesized gelatin–silk nanocomposites which can be used to load and deliver water soluble drugs. Gelatin–silk composites were prepared to enhance the strength of silk and favor the biodegradation profile and drug-loading capability of gelatin. One of the major advantages of synthetic polymers in drug delivery is their modification to prepare suitable material. However, without considering the specific design, many synthetic polymers inherently have demerits like cell-recognition sequences, binding sites, eliciting inflammatory response, and foreign body reaction. Therefore, modification of gelatin in combination with synthetic polymers has been used to prepare highly customizable platforms for drug delivery [20, 67].

Poly(lactic *co*-glycolic acid) (PLGA) is one of the most potent synthetic polymers, which has applications in the field of drug delivery and tissue engineering.

Composite of PLGA and gelatin have been used for controlled delivery and can be prepared via electrospinning techniques. Drug delivery through encapsulation took place within electrospun fibers and it sounds interesting due to the high surface-to-volume ratio. In general, incorporation of gelatin into PLGA composite makes it available for further mechanisms to control the release kinetics and also used to enhance the cell biocompatibility. Cross-linked oligo(poly(ethylene glycol) fumarate) (OPF) is a PEG-based hydrogel with cleavable fumarate groups allowing for biodegradation. OPF has been proven to support controlled drug release, cell encapsulation, and tissue regeneration. However, a great enhancement in the field of drug delivery has been achieved on using OPF hydrogels on the inclusion upon embedded gelatin microparticles. Such composite systems were used for the controlled delivery of biomolecules and others as like DNA, minerals such as HA, for in vitro and in vivo models. A huge research in the area of gelatin–OPF composite system used for controlled drug delivery is still ongoing and has great promises for the generation of complex tissues [46, 54, 68].

Poly(propylene fumarate) (PPF) is one of the synthetic polymer that carries fumarate anion and biodegradable ester bonds which makes it interesting. However, PPF has greater hydrophobicity, stiffness, and strength. The positive aspects of PPF as a substrate alone and when combined with the gelatin microparticles for delivery of drug have been synergized. Gelatin–PPF composites can be tuned and modified to release multiple growth factors at different kinetics which makes them for temporal control over drug delivery. It results in successful bone regeneration in chosen animal models [69–72].

## 10.9 Gelatin Nanocomposites

Nanocomposite (NC) is a multiphase solid material system, formed by the combination of two or more components that includes polymers as matrices and nanostructured materials in one dimension. In the last few decades, interests in biopolymer-based nanocomposites have been increased due to their biodegradability, biocompatibility, and improved physical and mechanical properties. Further, remarkable antimicrobial functions obtained in certain nanocomposites have a gray area in the application of nanocomposite films in various academic and research applications like biomedical and food packaging areas. Combination of nanostructures and biomaterials provide a platform to academician and researchers to find new nanobiotechnology areas. Metal oxides, such as ZnO, MgO, and $TiO_2$ are used extensively to construct functional coatings and bionanocomposites because of their stability under harsh processing conditions. Further, these materials also show the antimicrobial, antifungal, antistatic, and UV-blocking properties [1, 25, 73–79].

Use of gelatin as an organic additive in composites with inorganic nanohybrids has gained interest tremendously because of the bioadhesive and biodegradable properties. Thus, several experts have concentrated their research on gelatin films.

Mammalian gelatin films showed excellent mechanical properties in comparison with other types of gelatin films. At present, researchers have focused on the use of marine gelatin sources as alternatives to mammalian gelatins, such as those from fish. Marine gelatin sources are not related to the risk of bovine spongiform encephalopathy [1, 25, 73–79].

## 10.10 Gelatin Nanocomposites in Drug Delivery

Gelatin when used as a matrix in mineralization has shown a lot of interest in the field of tissue engineering. Composite of gelatin with poly(ethylene glycol), chitosan, and poly(d,l-lactide) have proven for potential pharmaceutical applications.

Rouhi et al. has reported the nanocomposite fish prepared by adding ZnO nanorods (NRs) as fillers and the nanocomposites can be used in drug delivery. The impact of ZnO NR fillers has been investigated to study the mechanical, optical, and electrical properties of fish gelatin bionanocomposite films. It was observed that an increase in Young's modulus and tensile strength of nanocomposites incorporated with 5 % ZnO NRs compared with unfilled gelatin-based films [15, 51, 66, 80]. Gaihre et al. reported gelatin-coated magnetic iron oxide nanoparticles as carrier systems for loading and release of drugs. Magnetic iron oxide nanoparticles (IOPs) were coated with gelatin A and B and the drug-loading efficiency was investigated using doxorubicin (DXR) via various techniques. The DXR-loaded particles are sensitive to pH and showed response to drug release at pH 4 which was high as compared to pH 7.4. Han et al. reported the synthesis of amphiphilic copolymer nanoparticles based on gelatin as drug carriers for the delivery of doxorubicin. Doxorubicin was incorporated into polymeric nanoparticles by double emulsion or nanoprecipitation method. DOX-loaded nanoparticles showed rapid and frequent release at pH 5.0 than at pH 7.4 buffer. They also demonstrated that DOX-loaded copolymer nanoparticles showed comparable anticancer efficacy with the free drug in vitro and in vivo [1, 7, 64]. Cheng et al. reported gelatin-encapsulated iron oxide nanoparticles for platinum (IV) prodrug delivery, enzyme-stimulated release, and also in MRI. They encapsulated $Fe_3O_4$ nanoparticles in gelatin and demonstrated applications in multifunctional drug delivery system for disease therapy, MR imaging, and fluorescence sensors [17, 81].

Lee et al. reported biocompatible gelatin nanoparticles for tumor-targeted delivery of polymerized siRNA in tumor-bearing mice. The prepared composite presented efficient siRNA delivery in red fluorescence protein expressing melanoma cells (RFP/B16F10) to downregulate target gene expression. The psi-tGel NPs have great potential for systemic siRNA delivery system for cancer therapy, based on their characteristics of low toxicity, tumor accumulation, and effective siRNA delivery [82].

Xiaoyan et al. reported the preparation of chitosan–gelatin scaffold containing tetrandrine-loaded nanoaggregates and its controlled release behavior. They showed that the Ted-loaded nanospheres could be embedded within Cs–Gel

scaffolds and no initial burst release could be observed in the release patterns [5, 10, 13, 63].

Patel et al. reported hyaluronidase enzyme core-5-fluorouracil-loaded chitosan-PEG-gelatin polymeric nanocomposites for controlled drug delivery. These nanoparticles were proven to be potential carriers for targeted and controlled drug delivery to cancer cells [10, 13]. Tran et al. reported enhanced solubility and modified release of poorly water soluble drugs via self-assembled gelatin–oleic acid (GO) nanoparticles. They have compared the drug and drug-loaded nanoparticles in terms of solubility and found drug-loaded NPs more efficient. Furthermore, the release profiles of the model drugs were modified in a controlled manner and the current self-assembled GO nanoparticles can provide a versatile potential in drug delivery and tumor targeting [2, 55, 65, 83]. An et al. reported the synthesis of a biocompatible gelatin-functionalized graphene nanosheets (CNs) and its application for drug delivery. They showed that the prepared nanohybrids system offers a novel formulation that combines gelatin and graphene for biomedical applications. Therefore, the gelatin-GNS with good stability and biocompatibility can be selected as an ideal drug carrier to be applied in biomedicine studies [24, 39].

## 10.11 Conclusion

Gelatin is a natural biodegradable polymer which exhibits excellent biocompatibility, plasticity, and adhesiveness and is widely applied in tissue engineering. Gelatin NP–composite system often used for various biomedical applications revealed the combined benefits of activity, bioactivity of system, and the morphological features of gelatin. The combination of nanostructures and biomaterials provide gray area for researchers to find new nanobiotechnology areas. Nanorods (NRs) and nanoparticles combined with biomolecules are used for various applications in biomolecular sensors, bioactuators, drug delivery and medicines, such as in photodynamic anticancer therapy. Biodegradable nature of composite containing gelatin may also lead to various specific applications in biomedical.

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