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REVIEW

Burgeoning Polymer Nano Blends for Improved Controlled Drug Release: A Review

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Abstract: With continual rapid developments in the biomedical field and understanding of the important mechanisms and pharmacokinetics of biological molecules, controlled drug delivery systems (CDDSs) have been at the forefront over conventional drug delivery systems. Over the past several years, scientists have placed boundless energy and time into exploiting a wide variety of excipients, particularly diverse polymers, both natural and synthetic. More recently, the development of nano polymer blends has achieved noteworthy attention due to their amazing properties, such as biocompatibility, biodegradability and more importantly, their pivotal role in controlled and sustained drug release in vitro and in vivo. These compounds come with a number of effective benefits for improving problems of targeted or controlled drug and gene delivery systems; thus, they have been extensively used in medical and pharmaceutical applications. Additionally, they are quite attractive for wound dressings, textiles, tissue engineering, and biomedical prostheses. In this sense, some important and workable natural polymers (namely, chitosan (CS), starch and cellulose) and some applicable synthetic ones (such as poly-lactic-co-glycolic acid (PLGA), poly(lactic acid) (PLA) and poly-glycolic acid (PGA)) have played an indispensable role over the last two decades for their therapeutic effects owing to their appealing and renewable biological properties. According to our data, this is the first review article highlighting CDDSs composed of diverse natural and synthetic nano biopolymers, blended for biological purposes, mostly over the past five years; other reviews have just briefly mentioned the use of such blended polymers. We, additionally, try to make comparisons between various nano blending systems in terms of improved sustained and controlled drug release behavior.

Keywords: polymer blends, drug delivery, wound dressing, PLGA, chitosan, starch

Introduction

The past two decades have seen widespread progress in the development of drug delivery vehicles. However, over the past several years, despite the significant advances in developing novel excipients for releasing specific drugs in a sustainable and controllable way, limitations on experimental achievements have remained a major concern. Thus, there is an urgent need for proposing new drug delivery approaches to ameliorate this pressing issue.

Drug delivery systems (DDSs) consisting of biocompatible and biodegradable materials that take into account distinct physiological and physiochemical changes, are of special interest because they can significantly release biological agents at the right place and/or at a rate adjusted to disease progression.[1] DDSs can be categorized either as diffusion-controlled, chemically-controlled, swelling-controlled or modulated-release systems.[2] Novel DDSs which release drugs at a controlled rate, slowly,

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and in a targeted manner have been promising.[3] For more than ten years, numerous articles of various concentrated topics have been devoted to the field of DDSs and several advancements have been made. Nevertheless, it should be kept in mind that many therapeutic agents may cause severe side effects as they need to be delivered at a prolonged exposure time which results in reducing their toxicity by releasing smaller concentrations over longer drug exposure, particularly, as antitumor and antibacterial agents.[4,5]

Polymers in Controlled Nano Drug Delivery Systems

Controlled drug delivery systems (CDDSs) bring about a variety of positive points, including improved drug administration, efficacy and patient compliance, tailored therapeutic activity, reduced side effects, toxicity and drug administration frequency, as well as improved premature degradation.[1,6,7] In all circumstances, the main purpose of CDDSs is a sensible combination between biocompatible, soft and biodegradable polymers and drugs such that drugs can be released in a sustained or controlled manner over a long time span (Figure 1).[8] In order to acquire novel and beneficial controlled drug release, different approaches among polymers have emerged—such as injectable hydrogels,[9] direct implantation,[10] crosslinked micelles,[11] injectable suspension[12] and depots.[13]

As time goes by, biopolymers of various nanometer sizes, shapes, and surface properties have played a crucial role as CDDSs[14] and their synergic effects have ameliorated drug entrapment and mechanical property concerns.[15] It is an indisputable fact that polymers—either natural or synthetic—have become predominantly important materials as CDDSs, providing the weight, consistency and volume for the beneficial administration of drugs.[16] Stimuli-responsive polymers could mitigate the many dilemmas with biological systems, demonstrating a significant response to modifications in chemical and physical stimuli such as pH, temperature, concentration, pressure, ionic strength, light and redox potential.[17] Hence, these responses can lead to swelling, precipitation and dissolution, along with a change in hydrophilicity and hydrophobicity.[18] As our body is influenced by external stimuli by adjusting to changing external conditions, rationally designed new responsive polymers are of particular importance to meet such criteria. For CDDs applications, devices must be able to deliver agents at the right place in response to a stimulus and be easily administered aside from possessing non-toxic, biocompatible and biodegradable materials.[19] Here, we attempt to include the most recent publications of stimuli-responsive polymers in CDDSs by introducing one of the most notable types of these materials used for CDDSs, namely crosslinked polymer networks termed hydrogels.

Over the past years, nanotechnology-based devices have been attractive tools for discovering optimally safe and beneficial drug candidates. Scientists have taken advantages from various nanoscale delivery vehicles for targeted and controlled drug release applications since

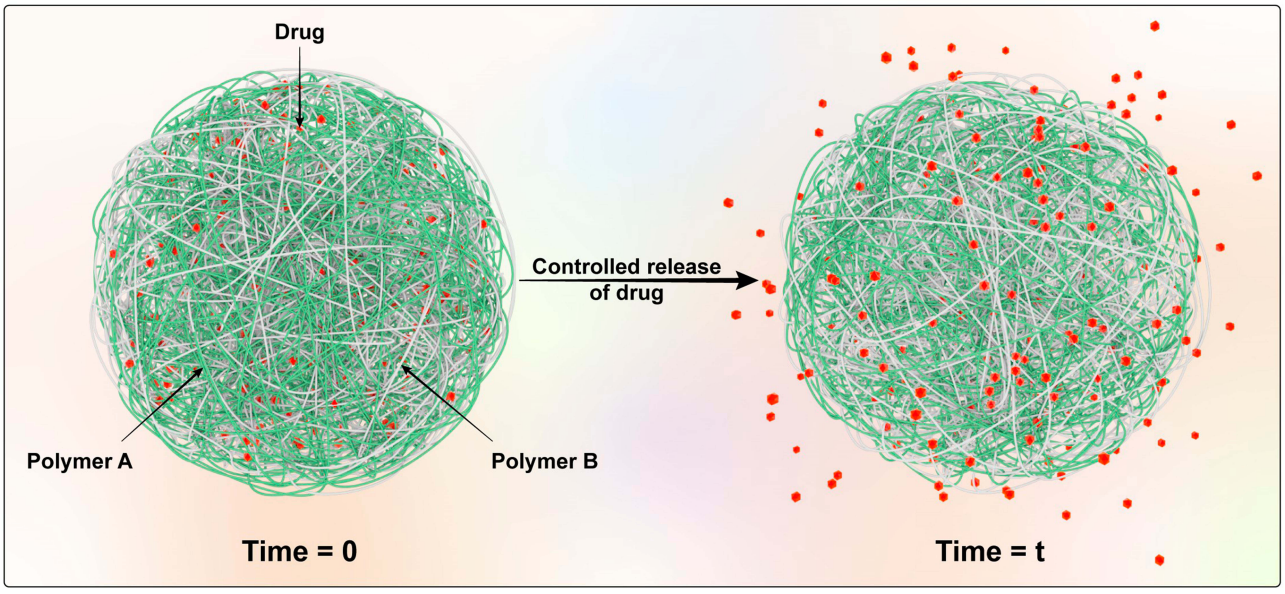

Figure 1 A simple depiction of CDDSs at different time points.
Abbreviation: CDDSs, controlled drug delivery systems.

nanoparticles can avoid immune system clearance and penetrate cells and tissues where conventional delivery systems cannot. Recently, many organic and inorganic nanomaterials and devices have been utilized as delivery systems to develop potential therapeutic modalities. Additional advantages of these vehicles can be improving drug therapeutic activity through prolonging drug half-life, enhancing hydrophobicity of drugs, reducing potential immunogenicity and more importantly, releasing drugs in a controllable and limited manner.[20,21]

Polymeric nanofibers ranging from 50 to 1000 nm, in particular, due to their unique properties (including specific surface area per unit mass, greater porosity with small pore sizes, significant mechanical properties based on architectural arrangement and magnificent flexibility) are of great interest to release drugs locally and slowly for numerous biomedical applications, such as wound dressings.[22,23] Nanofibrous mats are also very good candidates for sustained release applications for antibiotic, antibacterial, antifungal or anticancer agents as they can beneficially encapsulate drugs in dressings and/or scaffolds.[24]

Polymer nanoparticles (NPs) have also revolutionized the field of CDDSs due to their larger surface areas per volume compared to conventional particles leading to enhanced drug encapsulation, better loading capacity, stability, local release and can be easily attached to a variety of compounds.[25] It is interesting to mention that drug delivery is directly affected by the morphology and shape factors of the nanoparticle systems. Moreover, it is a proven fact that particles of nanometer to sub-micron size significantly outperform microparticles in DDSs. While larger particles possess large cores contributing to faster polymer degradation permitting drugs to be better encapsulated and slowly diffuse out, smaller particles with their greater surface areas allow the drug to be at or near the particle surface, causing even faster drug release. Furthermore, the geometry of the nanoparticle can influence drug release. For instance, discs and rod-shaped nanocarriers have superior blood circulation properties over spherical particles, enabling longer circulation times and better targeting.[26]

In the majority of these situations, drug loaded nanofibers have emerged remarkably in favor of a blended polymeric solution, resulting in sustained and burst release.[27] Biocompatible and biodegradable synthetic polymers (such as PLGA, PLA, PGA, poly (vinyl alcohol) PVA, poly (ε-caprolactone) (PCL), poly (ethylene glycol) (PEG), poly (L-lysine) (PLL) and polyphosphoesters (PPEs)) and natural ones (namely cellulose, CS, starch and gelatin) have opened many avenues for improving medical and pharmaceutical applications, and when fabricating them at the nanoscale, they have revolutionized controlled drug delivery research.[28,29]

Polymeric Hydrogels and Micelles as Drug Delivery Vehicles

Hydrophilic gels, so-called hydrogels, are a crosslinked network of polymers of considerable absorbent compositions, produced by both natural and synthetic polymers. The distinctive characteristic of hydrogels include their soft material environment due to their high degree of hydrophilicity, which promotes the uptake of water.[30,31] This high water content makes hydrogels very promising for the significant loading of hydrophilic drugs for CDDS applications which mimics biological tissues (Figure 2).[32] Furthermore, their porous configuration allow drugs to be loaded into the gel matrix giving rise to drug release gradually based on the diffusion coefficient of the small and/or macro molecule in the gel network.[19] For more information on hydrogels, we refer the reader to a comprehensive review by Li et al,[9] as here we emphasize only their nano aspects.

Three-dimensional hydrogels—such as copolymeric hydrogels—bring a number of exceptional applications in CDDSs.[33–35] For instance, enzyme-mediated redox chain initiation including glucose oxidase (GOX) was used to build three-dimensional hydrogels through stable aqueous conditions under ambient temperature and atmospheric circumstances. This process was completed via an easy interfacial polymerization approach for producing nanometer-scale constructs and consistent PEG-based hydrogel layers safe for use after incubation in water for 16 weeks. Moreover, such three-dimensional hydrogel layers were able to load both biological agents and fluorescent nanoparticles predicted to be a suitable technique for CDDSs.[36] This study revealed that three-dimensional hydrogels could be a remarkable approach for evaluating controlled drug release profiles owing to the fact that they possess a uniform, conformal coating and multilayer nano structure. Besides, in order to obtain a high degree of swelling for the beneficial release of drugs in a controlled manner, it is highly recommended to use synthetic nanostructured polymers over natural ones, as they possess much better water-soluble properties and their nanoscale properties provide for increased surface area which leads to greater control.[37]

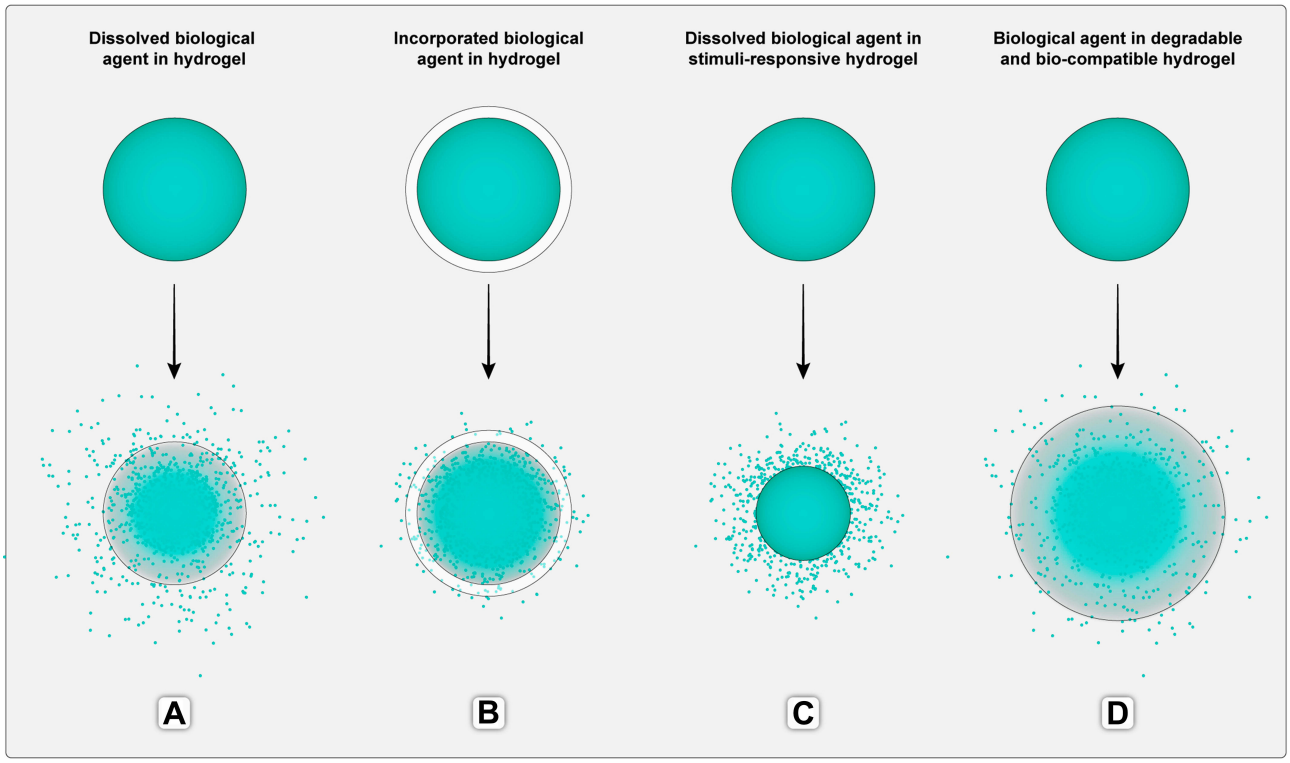

Figure 2 Drug release from hydrogels: (**A**) drug is released by dissolving from the hydrogel, (**B**) drug is incorporated into the hydrogel to maintain its native structural integrity and function, (**C**) stimuli-responsive hydrogels loaded with a drug as a drug carrier, and (**D**) entrapment of a drug in a degradable hydrogel allowing the drug to diffuse out of the hydrogel.

Polymeric micelles have been a superior strategy in tackling the delivery of poorly water-soluble drugs in a controlled manner at target sites. They are formulated by the spontaneous self-assembly of amphiphilic block copolymers in an aqueous solution.[38] Polymeric micelles are naturally nanostructured and provide for much better stability, tailorability and no toxicity. Because of their special core-shell structure, the hydrophobic part paves the way for the encapsulation of hydrophobic drugs. The hydrophilic part, however, could protect the hydrophobic section from the biological invasion owing to its brush-like nanostructure. With respect to the hydrophobic nature of the micelle core, water-insoluble drugs can be encapsulated and solubilized in the micellar core by either chemical conjugation or physical entrapment to reach their desired target (Figure 3).[39] Several studies have reported the progression of polymeric micelles in CDDSs.[40,41]

The State of the Art of Nano Polymer Blends in CDDSs

Polymer blends are simple and successful combinations of at least two polymers to provide a new and economical excipient with different physical properties without the preparation of particular copolymers.[42,43] They provide new products with various applications in the pharmaceutical and biomedical fields. This straightforward and time-saving approach can combine the flavor of different polymers and benefit not only drug and gene delivery, but also many technological advancements such as organic solar cells, thick plastics and membrane separation.[44,45] The blending of polymers can reduce the undesired side effects of many drugs, particularly, those biological agents in which drug release is very important. In that way, the timing of drug release and drug dosage should be regulated and improved. However, in terms of drug delivery, some key factors should be taken into consideration, including intrinsic miscibility among two polymers, the interaction between the active pharmaceutical ingredients (API) with polymers and the critical situation of the environment during storage.[46] Fundamentally, drug delivery in the presence of blended polymers is a complicated process suggested by three mechanisms: polymer relaxation, degradation, and diffusion (Figure 4).[47]

Different classifications of biological products, ranging from proteins to antibodies, can be incorporated into copolymers based on their properties either indirectly or physically

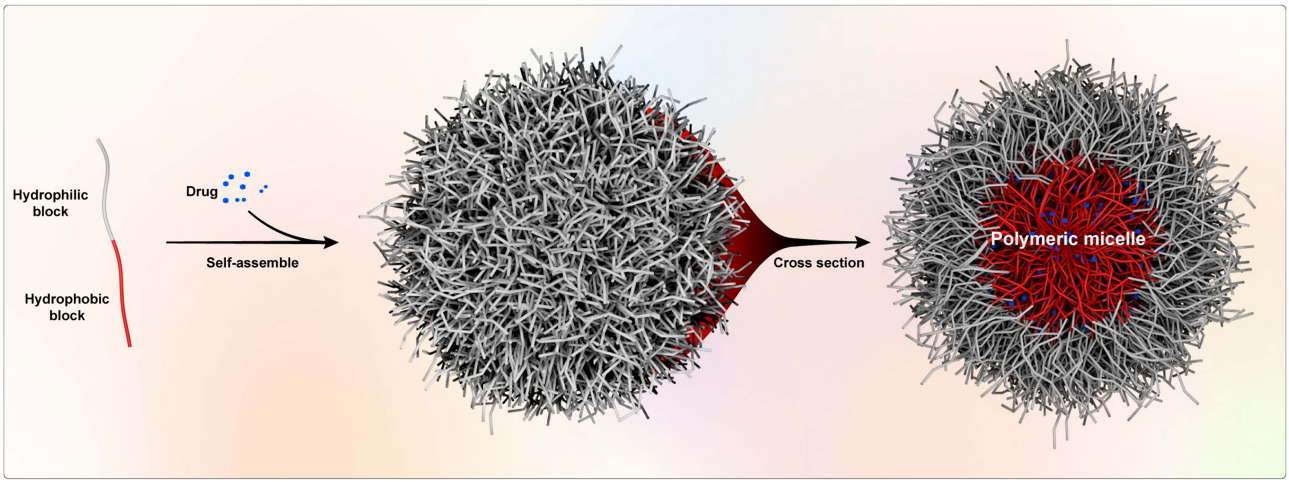

Figure 3 Polymeric micelles in CDDSs. Hydrophilic block copolymers can establish micelles in an aqueous solvent with a hydrophobic core sterically stabilized by a hydrophilic shell. The drug is localized in the hydrophobic core separated from the outside environment by a hydrophilic shell.
Abbreviation: CDDSs, controlled drug delivery systems.

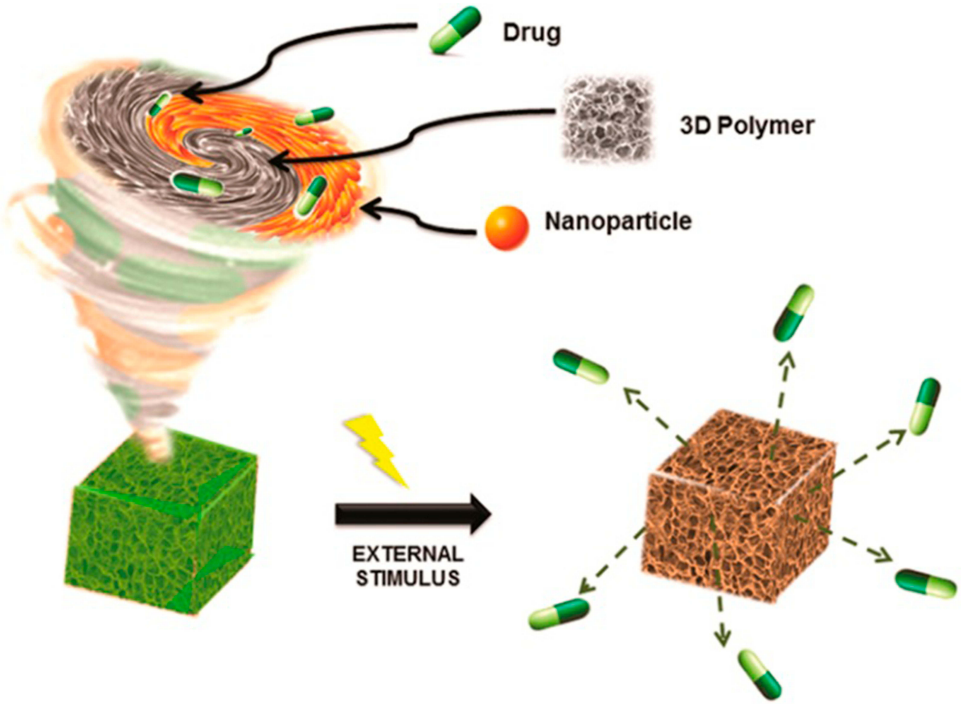

Figure 4 Schematic illustration of drug release from a typical nanoparticle/nanocomposite/polymeric based material. **Notes:** Reprinted with permission Merino S, Martin C, Kostarelos K, Prato M, Vazquez E. Nancsite hydrogels: 3D polymer–nanoparticle synergies for on-demand drug delivery. *ACS Nano*. 2015;9(5);4686-4697. Copyright 2015 American Chemical Society.[211]

and even be chemically surface-immobilized.[49] Even though the properties of natural polymers are less similar to synthetic polymers, there has been some evidence of the interaction between them, most of which have led to polymer hydrogel compounds as three-dimensional heavy networks formed by a polymer backbone, water and crosslinking agents in CDDSs.[50] Indeed, hydrogels are produced by hydrophilic monomers with crosslinkers used for a wide variety of medical applications, particularly for controlled drug release in vivo and in vitro.[51] Polymer combinations are usually used for enhancing the poorly water-soluble delivery of pharmaceutical ingredients.

The Aim of Using Nano Polymer Blends in CDDSs

The reasons why polymer blending outclass single polymers could be the reduction or even removing of long and costly procedures necessary for producing new polymers that not merely lead to new and great properties, but also improve material processability and polymerization steps.[52] Besides, polymer blending has made a breakthrough in tailoring the important disadvantages of polymers such as biodegradability, physico-mechanical, poor mechanical and thermal properties. For instance, the biodegradability of polymer matrices can be improved through blending of biodegradable and non-biodegradable polymers and changing their composition.[53,54]

Generally, polymer blends can be categorized as (i) miscible, (ii) compatible and (iii) immiscible. As miscible blends do not provide preferred properties, their applications in industry is not favorable. The significant feature of polymer blends is their phase behavior in which polymers mostly produce immiscible and incompatible blends resulting in a coarse phase morphology with a particulate minority phase dispersed in a matrix and poorly distributed. Moreover, polymer mixtures are more likely to be in two separate layers, like oil and water, owing to the unfavorably low value of entropy. Therefore, morphologies of polymer blends are determined by their processing and thermal history. After blending of two polymers, they are prone to obtain a small-scale arrangement of the phases, called the "microstructure". The blend properties, eventually, are greatly affected by the size scale of the microstructure, giving rise to a pressing issue between processing flow conditions and microstructure. As a consequence, the compatibilization of polymer blends plays a crucial role in altering the interfacial properties in an immiscible polymer blend. The major advantage of this approach can be a decrease in the interfacial tension coefficient and the generation and stabilization of the satisfactory morphology.[52,55–57] Among different compatibilizers, the role of nanoparticles to improve the final morphology of the polymer blend has gained popularity. Nanostructured blends achieved by cross-linking the major phase and/or minor phase are of ideal interest in producing materials with smart properties. The myriad of benefits of nanostructured polymeric blends in CDDSs may be better device fabrication, modification of device characteristics, enhanced drug loading and the use of the dispersed phase domains for improved drug release properties.[58] Among nanostructured materials, nanostructured hydrogels have received much attention in the field of nanotechnology.[59] The rate of drug release from nanostructured hydrogels can be controlled through various approaches, such as modifying the cross-linking density or controlling the ratio of hydrophilic to hydrophobic monomers.[60]

The compositions of different types of polymers—such as PLGA, PLA, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), surfactants, etc.—can increase the rate of drug water solubility and their release.[61,62] Further, creating such polymers to be nanostructured can increase surface area and increase water solubility. For instance, Liu et al utilized an ethylene-vinyl acetate copolymer (EVA) blended with PLA and PEG as a stent coating drug carrier for delivering paclitaxel (PTX), and as a result, they demonstrated that these blends released PTX in a highly tunable and controlled way.[63] In another example, hydroxypropyl methylcellulose acetate succinate (HPMCAS) was blended with dodecyl (C12)-tailed poly (N-isopropylacrylamide) (PNIPAm) for improving low water-soluble drugs, such as phenytoin.[45] It should be noted that among synthetic and natural polymers used in drug delivery, synthetic–natural polymer blends have attracted more attention than either synthetic–synthetic or natural–natural polymer blends providing a satisfying platform to combine mechanical and bioactive properties.[48]

With all of these considerations, the potential applications of polymer blends as carrier materials in CDDSs has been inextricably bound with several difficulties in the design and development of devices in comparison to forms coated with just one group of polymers. However, owing to advancements in CDDSs in the last two decades, the optimal architecture and application of CDDSs with tunable drug release profiles have been achieved.

The main aim of this review is to provide recent developments in nano polymer blends with an emphasis on controlled and sustained delivery, carrier fabrication, drug loading efficacy, and physicochemical properties. Here, we make comparisons between the role of natural and synthetic polymers in CDDSs. In particular, the manner of controlled release from CS, cellulose, and starch, as well as PLGA, PLA, and PGA will be discussed from research over the last five years in the sections that follow. In most sections, we bring additional applications of different nano polymer blends to a diversity of drug delivery systems and medical devices through succinct tables. We give particular attention to approaches for CDDSs for hydrophilic drugs that are highly loaded in their fiber

forms. Furthermore, future potentials and challenges of nano polymer blends are also discussed.

In Table 1, we provide advantages and disadvantages of the above natural and synthetic polymers.

Types of Polymers Used in CDDSs

Natural Polymers

Natural polymers—which are fundamentally polysaccharides—play a versatile role in medical applications, including CDDSs, regarding the regulation of the dosage form and improvements in physicochemical parameters. They serve as excipients in pharmaceutical companies due to their low cost, biodegradability, biocompatible structures, availability and having safe properties.[64,65] These polymers are water-soluble, biogenic, enzymatically degradable, chemically flexible and consist of large molecules which originate from nature—namely plants, microorganisms, and animals.[16] Furthermore, these polymers can be classified into two major groups: (1) protein polymers, such as collagen and gelatin, and (2) polysaccharides, like CS, glycogen, cellulose, and starch.[66] During recent years, there has been a great deal of interest in biodegradable polysaccharides for CDDSs exploited as drug carriers or enhancers of the viscosity in liquids or emulsions.[8]

Current studies on biocompatible and biodegradable natural polymers have led to a considerable evolution of more novel types of wound dressings and applications in the biomedical area. Among them, natural polysaccharides—such as CS, cellulose, and starch—have garnered attention because of their organized structures, and thus, they are preferable for producing polymer-based composites and biopolymers. This section aims to demonstrate recent progress in CS, cellulose and starch blends and their application in CDDSs.

Applications of Chitosan (CS) and Its Blend Derivatives in CDDSs

CS is the second most plentiful polysaccharide with abundant bio-applications. It can be produced from the alkaline N-deacetylation of chitin but it is also a biopolymer found in insects, fungi and more greatly, in the shells of crustaceans.[67,68] With respect to medical applications, CS has gained popularity because of its great properties, specifically in its ability to blend with polymers. Therefore, CS can blend with numerous natural and synthetic polymers, displaying a diversity of features that enhance its utility as a drug delivery vehicle based on its mucoadhesive nature.[69] Recently, CS blends have been successfully utilized for drug

Table 1 Advantages and Disadvantages of the Mentioned Natural and Synthetic Polymers

Polymer	Advantages	Disadvantages	Ref.
Natural (CS, Cellulose, and Starch)	• Water solubility enhancer • Less/non-toxic • Good transparency and swelling • Biocompatible and biodegradable • Capable of incorporating with drugs • Readily available • Low immunogenicity • Inertness • Less side effects • Cheaper • Easily chemical modifiable • Abundance naturally	• Microbial and heavy metal contamination • Hydration uncontrolled rate • Batch to batch variation • Slow rate of production • Complicated extraction procedure • Variable in natural materials derived from animal sources	26,64–66
Synthetic (PLGA, PLA, and PGA)	• Easy tailoring • Better mechanical and chemical stability • Higher reproducibility • Tunable • Specificity and selectivity • Easily degradable • Better conjugation properties • Clinically applicable	• Lack of intrinsic biocompatibility and bioactivity • Possible to cause toxicity, inflammation, and immune response • Difficult and expensive synthesis procedure • Water solubility problems	67–70

Abbreviations: CS, chitosan; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PLA, polylactic acid; PGA, poly(glycolic acid).

and vaccine delivery,[70,71] cranial defects,[72] anti-cancer activity,[73,74] anti-adhesion therapy,[75] antibacterial activity,[76] anti-aging therapy[77] and anti-inflammatory wound dressing activity.[78] As with the aforementioned polymers, nano CS possesses increased surface area per volume compared to conventional CS, and thus has even greater biological properties.

For wound healing applications, stimuli-responsive CS and poly (N-vinyl-2- pyrrolidone) (PVP) were blended with 74% neutralized poly ascorbic acid (PAA). The obtained hydrogels showed not only antimicrobial properties against *E. coli* but also demonstrated significant behavior for delivering silver sulfadiazine with approximately 90% of release in a controlled manner within 80 min.[79] Texier et al showed intermolecular interactions between CS and PEG sponges as a chemical crosslinking of the PEG network in the CS matrix via nucleophilic thiolyne addition. The morphology of the composite demonstrated that these novel crosslinked-sponges possess high stability with a porous structure for topical drug delivery at physiological conditions.[80] In a recent study, CS and PVP were combined to effectively deliver betamethasone-17-valerate (BMV) for treating recurrent aphthous stomatitis (RAS). The existence of PVP with CS can enhance both thermal stability and swelling ratio for the release of BMV at roughly 80%.[81] Polymer blending here enabled PVP with a higher swelling ability to increase tensile strength leading to an efficient mucoadhesive drug delivery system.

In another study, Jesus and colleagues developed a blended material produced by CS and PCL NPs in order to improve the controlled release of vaccine, protein, and antigen, as well as reduce their cytotoxicity. Notably, over a span of 6 months, ovalbumin (OVA) adsorption on PCL/CS NPs led to an expected loss of protein ellipticity along with an alteration to a marked β-sheet content, but it did not induce protein-unordered conformation. The release of the drug was reported over 6 h.[70] Carboxymethyl CS (CMCS) was blended with gelatin, a biodegradable and biocompatible polypeptide, as a controlled release polymeric hydrogel, in order to analyze the release of 5-Fluorouracil (5-FU). The blended microspheres were examined with different analytical techniques to understand the interaction of the polymer and 5-FU. As a result, the in vitro release of 5-FU increased to 12 h at a physiological pH,[82] with an expected enhancement for nanospheres.

To tackle problems of infection and traumatic musculoskeletal injuries, Berretta et al developed a blend of CS and PEG pastes to provide biocompatibility, biodegradability and the local delivery of vancomycin and amikacin to a larger distribution of eluted antibiotics to prevent or even treat musculoskeletal wounds and bone infections. Therefore, preliminary studies showed satisfying results for the CS/PEG copolymers with the mentioned antibiotic drugs, which resulted in degradability, biocompatibility, injectability and prevention of infection for musculoskeletal-type wounds.[83] The injectable, cytocompatible and biodegradable gels based on an easy blending of 4.0% carboxymethyl hexanoyl CS (CHC) with 4.0% hyaluronic acid (HA) was described. These injectable in situ gels were not made by high temperature nor crosslinking reagents and förster resonance energy transfer (FRET) controlled the mechanism of gel formation. With this blend, a turbid colloidal suspension and subsequently supermolecular hydrogels were obtained immediately to sustain and provide pH-dependent delivery of berberine as an anti-apoptotic and anti-arthritis herbal medicine. In vitro degradation was evaluated through dipping of the gels in various buffer solutions at 37 °C of hyaluronidase and lysozyme. The weight loss ratio of the gels in pH 6.0 buffer was 7.8%, 40.5%, 45.1% and 62.1% in the buffer and lysozyme, hyaluronidase and both enzymes, respectively. Sustained drug delivery was achieved at pH 6.0 showing that the gel was more stable at pH 6.0. Moreover, the gels greatly swelled within a day, preceded by a sharp reduction in mass in a pH 7.4 buffer. Besides, the drug-loaded blends kept chondrocytes safe against sodium nitroprusside-induced apoptosis and arthritis resulting in an improvement of the anti-apoptotic efficiency of berberine. From another perspective, another research group focused on preparing LbL assembled multilayer films using the above mentioned feature of CMC and chitosan, which helped them study the chemistry of those biocompatible polysaccharides by investigating both cross-linked and non-cross-linked nanostructures (Figure 5).[84]

Moreover, Rokhdadeh et al formulated pluronic F127/CS blend microspheres and glutaraldehyde as a crosslinker. These blended compounds showed high physical activity and drug-polymer harmony in comparison to CS microspheres with excellent mucosal DDSs. It is noteworthy to indicate that the release profile of the 5-FU as a model drug improved to 1 day.[85] More recently, a novel composite developed by Anirudhan et al consisted of blends of biodegradable thiolated CS-PEG contained with medical clay (MMT), named TCS-PEG/MMT, and was used for the oral drug delivery of insulin. Consequently, after 8 h, almost 70% of insulin was

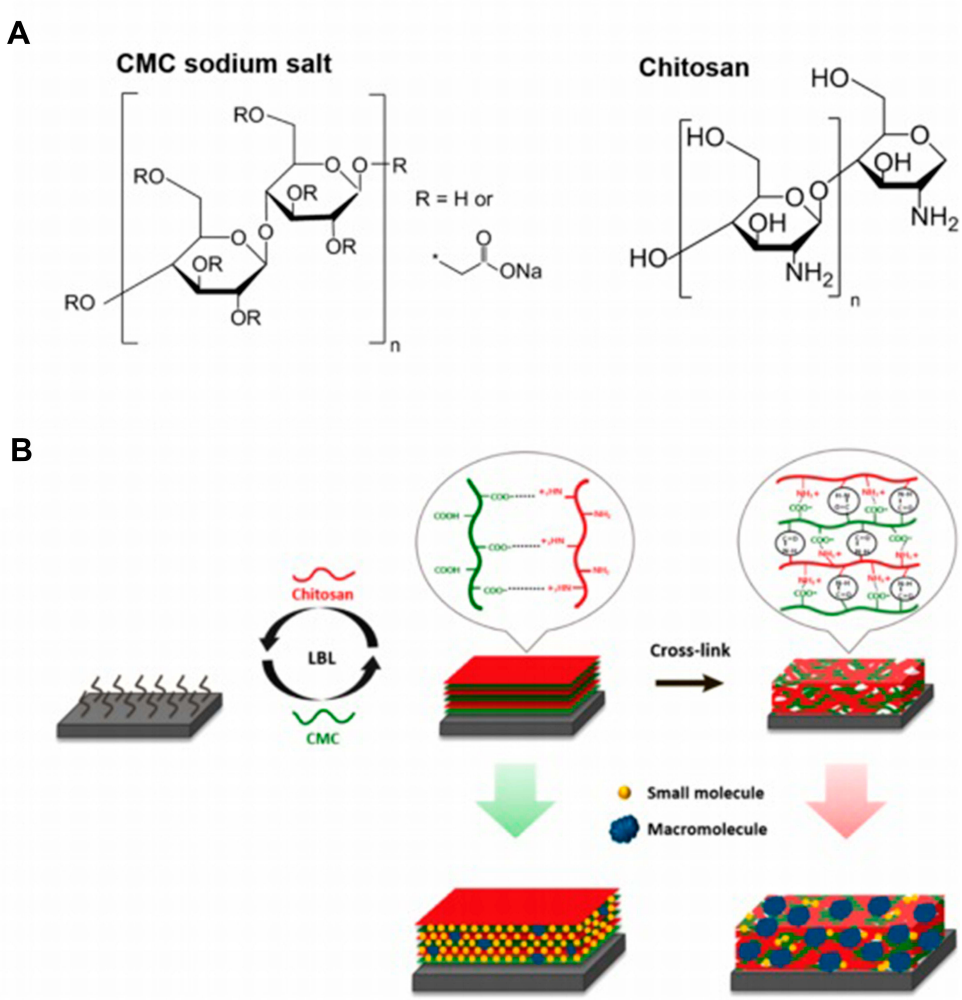

Figure 5 (A) Chemical structures of chitosan and carboxymethyl cellulose sodium salt. **(B)** Schematic illustration of the cross-linking-induced structural change of the LbL-assembled CMC/CHI multilayer film and its effect on the loading of drugs with different molecular weights.
Notes: Reprinted with permission Park S, Choi D, Jeong H, Heo J, Hong J. Drug loading and release behavior depending on the induced porosity of chitosan/cellulose multilayer Nanofilms. *Mole Pharm*. 2017;14(10):3322-3330. Copyright 2017 American Chemical Society. [84]
Abbreviations: CMC,carboxymethyl hexanoyl chitosan; LbL, Layer-by-Layer.

released at a basic pH of 7.4, which revealed the controlled release of the drug.[86] Tolbutamide (TOL), a significant hypoglycemic drug, was released in a controlled manner loaded with CS/PLGA NPs with the solvent evaporation method. Thermal gravity analysis (TGA) and transmission electron microscope (TEM) proved that not only did this copolymer enhance the bioavailability of the drug, but it decreased TOL dosage. Additionally, TOL was released by CS/PLGA-TOL NPs at a pH of 7.4 and in a phosphate buffer solution (PBS) in a sustained manner.[87]

Arya et al utilized curcumin (Cur), a herbal anti-cancer drug, loaded PLGA NP surfaces coated with a blend of CS/PEG in order to increase bioavailability and reduce limitations in conventional chemotherapy. These Cur nanoparticles showed a controlled release rate of Cur after 6 days, followed by a biphasic phenomena, together with higher cytotoxicity, improved anti-migratory, as well as anti-invasive and apoptosis-inducing ability of the CS/PEG blend in various pancreatic cancer cell lines in comparison with the native counterpart.[73] In another study, the controlled release behavior of Metformin (Met) was reported by Shariatinia et al. This group developed a highly efficient film from a blend of CS and poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene) consisting of mesoporous MCM-41 or MCM-41-APS (APS=aminopropylsilane) nanoparticles for the controlled release of Met. The release of the drug increased considerably within 22–24 h (burst release), after which the release of the drug was slowed to release over

15 days (controlled release). Moreover, the film including 4% MCM-41-APS and 10% Met revealed improved tensile strength, hydrophilicity, biocompatibility, and drug release.[88] In Table 2, additional applications of CS blends are summarized for the controlled release of various drugs.

Applications of Cellulose and Its Blend Derivative in CDDSs

Cellulose is a fibrous and water-soluble organic material with a linear homopolymer of β-1,4-linked anhydro-D-glucose units having abundant hydroxyl groups, which possess a high ability to blend with different kinds of materials.[89] Cellulose and its derivatives (such as microcrystalline cellulose (MCC), ethyl cellulose (EC), methylcellulose (MC), HPMC, HPC, carboxymethyl cellulose (CMC), and several other forms) have been widely used in CDDSs as significant carriers.[90–92] Blends of different cellulose derivatives with other excipients participate in coating and enteric coating roles in pharmaceutical industries by releasing biological molecules in a controlled manner.[93]

The effect of blending cellulose and PEG for loading vitamin C as a typical drug was reported by Shen and colleagues. In this experiment, pH and temperature responses were conducted and an effective controlled drug release was reported. An interesting point in this report is that it used cellulose and showed pH responsive-based drug release in multi-pulses, which means that according to the Grayson et al experiment,[94] this blend could be regarded as a valuable device for CDDSs.[95] β-cyclodextrin (β-CD) and CMC hydrogels were blended for the controlled release of the antiviral drug, acyclovir. The degree of swelling and crystallinity, which are two remarkable factors for drug release,[96] demonstrated improved drug loading and sustained release capability.[97]

Here, nanomedicine has also provided significant improvements. Specifically, electrospun nanofibers have extensively been used in CDDSs due to their particular advantages as highly effective nanofibers.[98,99] Electrospinning is a fiber production process that makes micro/nanometer-sized polymeric fibers. Their applications in sustained drug release can be achieved if surface modification is performed on blends of electrospun fibers.[100] It needs uncomplicated equipment compared to other fiber fabrication methods, such as wet chemistry methods and molecular beam lithography. Because the process can create diverse polymer construct properties such as compatibility, high surface to volume ratio, high porosity, and straightforward encapsulation of therapeutic molecules, it has been widely used in CDDSs specifically in regenerative medicine and wound dressings. The electric force in electrospinning is used to control the surface tension and polymer solution viscosity to make electrospun fibers.[101,102]

Recently, El-Newehy et al developed a polymer blend made of HPC with PVA and PVP to release diclofenac

Table 2 Other Applications of CS Blends in CDDSs

Loaded Active Component	Blend Composition	Duration of Release (Days)	Therapeutic Effect	Ref.
ASCs	CS/Gelatin	5	Promotion of angiogenesis in ischemic disease	89
BFGF & BSA	CS/PVA/Gelatin	4 & 25	Wound healing	90
Deferoxamine	CS/HA	10	Promotion of angiogenesis	91
Dopamine and metronidazole	CS/Gelatin	>20 & >12	Treatment of Parkinson's disease	92
Potassium nitrate	CS/Starch	14	Modulate fertilizer release	93
Naproxen	CS/PEG	1	Wound healing	94
TCH	CS/SA	14	Wound healing	95
Lupeol	CS/Gelatin	1	Wound healing	96
Methyl Orange	CS/Cyclodextrin	1	Favorable for drug carriers	97
TCH	CS/PEG/PVP	2	Wound healing	98
Levofloxacin	CS/PVA	3	Effective for sustained drug release	99
Gentamicin	CS/PVA	2	Wound healing	100
BMP-2	CS/HA	>30	Potential for bone and soft tissue engineering	101
Deferoxamine	CS/SA	10	Treatment of iron dysregulation diseases	102
Ofloxacin	CS/PAM	1	Favorable for antibacterial activity	103
BSA	CS/SA	17	Potential for soft tissue engineering	104

Abbreviations: CS, chitosan; PEG, polyethylene glycol; ASCs, adipose-derived stem cells; Bfgf, basic fibroblast growth factor; HA, hyaluronic acid; TCH, tetracycline hydrochloride; BMP-2, bone morphogenetic protein-2; BSA, bovine serum albumin; PAM, polyacrylamide; SA, sodium alginate; PVA, polyvinyl alcohol; SA, salicylic acid; CDDS, controlled drug delivery system; PVP, polyvinyl propyl.

sodium (DS) as a model drug based on electrospun nanofibers. In this study, in vitro entrapment efficiency and the sustained release of DS were controlled by UV spectroscopy when loaded into electrospun nanofibers of HPC with PVA and PVP, at a pH of 7.4 and at body temperature; in the first two hours, the amount of the DS released from the electrospun fiber was 63, 61, 58, and 46% of its DS content from HPC/PVA 100/0, 75/25, 50/50 and 25/75, respectively, whereas it released 85, 69, 63, and 57% of its DS content after three hours, respectively. However, the rate of release was diminished by increasing the PVA concentration because PVA in the nanofiber mats controls the DS release by forming hydrogen bonds with DS. Therefore, the blends of PVA and PVP with HPC enhanced the mechanical properties of the HPC nanofibers mats which could clearly be fruitful for biomedical therapy.[103]

In terms of a nanomedicine approach, CMC and PVA were blended and loaded with ZnO nanoparticles and erythromycin (EM), the selected antibacterial drug (both alone and in combination), for achieving a more beneficial antibiotic activity with regards to a synergistic effect. Electrospinning procedures and crosslinking with 2% glutaraldehyde vapor and a 3% $AlCl_3$ alcoholic solution were used for fabrication. Therefore, EM-loaded PVA-CMC/ZnO nanocomposite mats demonstrated a good ability for not only sustained drug release but also for wound dressings owing to their satisfactory antibiotic efficacy. It should be noted that the release of EM was completed after three days (another CMC delivery system is presented in Figure 6).[22]

Moreover, the controlled release of donepezil hydrochloride was investigated by Gencturk et al. They developed potential and non-toxic electrospun polyurethane/HPC (PU/

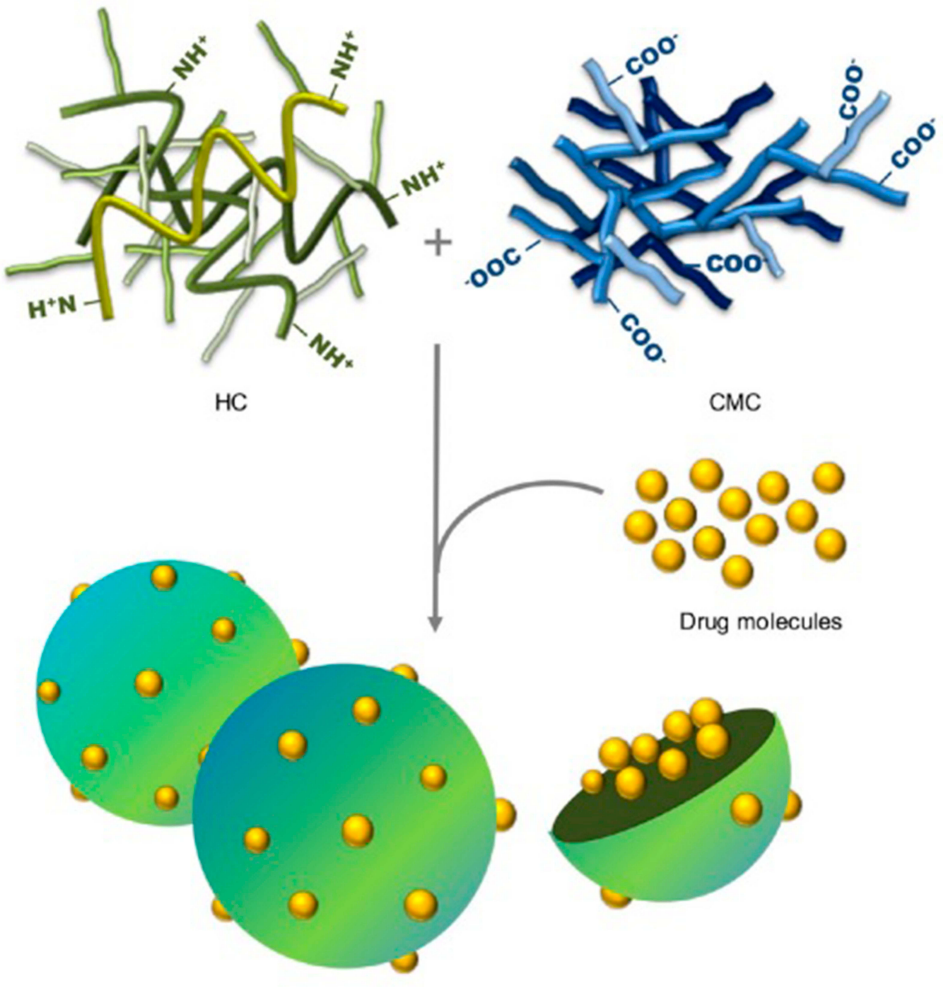

Figure 6 Schematic representation of the preparation of a carboxymethyl cellulose (CMC) based drug delivery system.
Notes: Reprinted with permission Lai, WF, Shum HC. Hypromellose-graft-chitosan and its polyelectrolyte complex as novel systems for sustained drug delivery. ACS Applied Materials & Interfaces. 2015;7(19):10501-10510. Copyright 2015 American Chemical Society.[108]
Abbreviation: CMC, carboxymethyl cellulose.

HPC) nanofibers for transdermal CDDSs according to in vitro preliminary permeation data. Approximately 90% of donepezil hydrochloride in the nanofibers released slowly over 6h.[104] Zhu et al developed smooth and cylindrical nanoscale fibers of poly (N-isopropylacrylamide) (PNIPAAm) and EC blends loaded with ketoprofen (KET) with considerable intermolecular interactions between them. The intermolecular interactions between the drug and blend were very good and KET release was reported at different ratios. Heating changed unexpectedly as observed from the water contact angle on the PNIPAAm and blend nanofibers, and the fibers underwent a fast hydrophilic/hydrophobic transition. At a 1:2 weight ratio of PNIPAAm/EC in the fibers, KET release at 25 °C was much faster than at 37 °C owing to this drastic change in properties. For the 1:1 ratio, the release rate from the fibers was relatively low at 37 °C. Finally, for the 1:4 weight ratio of PNIPAAm/EC, the materials lost most of their thermoresponsive properties. But not only were these blended fibers safe and appropriate for cell growth, but more importantly, the electrospun-blends of PNIPAAm/EC fibers played a beneficial role in the controlled release of poorly water-soluble drugs for tissue engineering applications.[105]

Core-shell nanofiber drug carriers were reported via a graft blending of NaCMC, poly (ethylene oxide) (PEO) and methyl acrylate (TCMC) loaded with TCH to build TCMC/PEO/TCH(CS) core-shell polymeric nanofibers, which were fabricated by coaxial electrospinning as a novel controlled drug delivery system. Spectroscopy analyses demonstrated that the release of TCH was slow and at a controllable rate within 72 h. Additionally, core-shell TCMC4/PEO(CS) electrospun nanofibers exhibited outstanding antibacterial effects against both gram-positive and gram-negative bacteria, as well as good cell viability. For toxicity and biocompatibility of the TCMC4/PEO/TCH(CS) and TCMC4/PEO(CS) core-shell electrospun nanofibrous mats, an MTT assay was used and showed that cell viability on the nanofibrous reached 100% after a day. While after two days, the TCMC4/PEO(CS) revealed no cytotoxicity and the TCMC4/PEO/TCH(CS) nanofibers demonstrated a decrease in the viability of human fibroblasts (HDF) reporting that the released TCH at 24 h and 48 h affected cell viability.[106]

Further, different quantities of cellulose nanocrystals (CNCs) were blended with gelatin hydrogels with glutaraldehyde used as a crosslinker, due to its high reactivity toward the -NH_2 group of gelatin, and on account of the weak mechanical properties of gelatin. Figure 6 shows a schematic of a typical preparation process of a nanocarrier based on carboxymethyl cellulose (CMC) based on the reaction between different functional groups as well as loading of the drug into the main core of the nanocarrier along with conjugation to the surface. In another study, different proportions of CNCs (0.5, 5, 15, 20 and 25%) were selected to investigate the effects of CNCs on the swelling ratio, as well as dynamic mechanical properties of gelatin-based hydrogels to make semi-interpenetrating polymer networks (semi-IPNs). Semi-IPNs ameliorated not only the mechanical properties of the hydrogel and drug release, but it also controlled swelling ratio. Theophylline was incorporated as a drug model in this study. As a consequence, the highest swelling ratio and drug release and efficacy were related to 5% CNC at pH 3. Nevertheless, the best drug loading for sustained and controlled drug release was associated with 15% CNC. Drug release rates continuously decreased with time owing to the thickness of the hydrogel that acted as a diffusion barrier. It should be noted that the hydrogel with the higher swelling ratio resulted in higher drug release percentages, and as a result, the 5% CNC-gelatin hydrogel showed the highest drug release percentage while the 25% CNC-gelatin hydrogel showed the lowest drug release percentage.[107]

HPMC of diverse viscosities has been thoroughly used in the pharmaceutical industry for the controlled release of drugs. Its considerable swellability, hydrophilicity and non-ionic nature has paved the way for blending with various excipients, in the form of hydrogels, to achieve the controlled release of biological products.[109–111] In this case, HPMC was blended with different kinds of polymers, such as PVP,[112] CS,[113] EC,[114] gelatin, and xanthan gum[115] and in most cases, these blends showed remarkable controlled release activity.[116–119]

Dharmalingam et al designed a combination of HPMC and NaCMC in the presence of citric acid (CA) as a crosslinking agent (citric acid crosslinked HPMC-NaCMC hydrogel films) in order to evaluate the controlled release of methylene blue and TCH for wound healing applications. The loading efficacy for the drugs reversed for different ratios of CA at a pH 7.4 and 37 °C. Specifically, when the concentration of CA in the hydrogel increased from 5 to 10 to 20%, the loading efficacy of methylene blue increased (approximately 35, 45 and 55%, respectively), whereas the pattern for TCH was the complete reverse (approximately 10, 8 and 6 %, respectively). Moreover, this increase led to a reduction of the swelling ratio, the water contact angle (surface hydrophilicity) and tensile strength of the hydrogel films, while the elongation at break (%) increased. Additionally, both drugs released in a controlled manner for more than 3 days, demonstrating that the HPMC/NaCMC hydrogels were highly satisfactory not only for controlled

drug release but for effective wound healing as an excellent antibacterial agent.[120]

Similarly, atenolol-controlled release was investigated by Lotfipour et al in an experiment with different concentrations of soluble and insoluble binary blended polymers, including Eudragit RSPO, EC, and NaCMC with HPMC. The controlled release profile of atenolol from different weight ratios of matrices containing the blends of HPMC and other excipients was confirmed with diffusion and erosion processes, depending on the type of polymer and concentration.[121] Blends of HPMC with SA were also investigated for the release profile of three drugs: BSA, Met, and indomethacin (IDM), with different molecular weights and solubility properties. Due to the large pores in the HPMC-SA hydrogels, small and water-soluble Met, had a burst release within just 2.5 h. Nevertheless, other drugs and BSA and IDM as two water-insoluble compounds had better-controlled release profiles in which the macromolecular drug BSA had the best-sustained release profile for blockage by a semi-interpenetrating polymeric network and IDM showed controlled release after 12 h.[122] In Table 3, additional applications of cellulose blends are summarized for their controlled release of various drugs.

Applications of Starch and Its Blend Derivatives in CDDSs

Starch is a natural polymeric carbohydrate and is the most abundant storage polymer used extensively in the pharmaceutical industry because of its high availability, affordability, and biodegradability.[123,124] It is constituted by amylose (typically 18–33%) and amylopectin (typically 67–82%), which are highly applicable for many pharmaceutical and food applications.[125,126] Scientists have a positive attitude towards developing starch-related compounds as magnificent materials with advantages of greater biocompatibility and non-toxicity.[127]

Importantly, however, native starch separated from various sources has some significant drawbacks such as narrow shear and thermal resistance, thermal decomposition and a high proclivity for retrogradation.[128] Therefore, the combination between starch and other biodegradable and biocompatible polymers has addressed these problems, making it enormously beneficial in tissue engineering, drug delivery and for the effective release of biologically active compounds.[129] Different starch-based DDSs have been projected for therapeutic effects and these DDSs can be associated with various drug carrier strategies.[130]

Blending starch and its derivatives (such as sodium starch glycolate and pregelatinized starch) with both compatible and non-compatible polymers can be an advantageous strategy in order to improve the properties and stability of starch-based films.[131] Many studies have reported the ability of starch to blend with a variety of materials to advance ionotropically gelled multiple-unit systems for the enhancement of drug encapsulation, swelling, stability and controlled release of biological agents.[132–136] Ayorinde et al reported blends of natural starches with HPMC for orally dissolving films of amlodipine besylate (AB). They utilized Bambara nut (BAM) and the African yam bean (AYB) starches separately blended with HPMC. AB was included by dispersion and films were made by solvent evaporation. The AYB/

Table 3 Other Applications of Cellulose Blends in CDDSs

Loaded Active Component	Blend Composition	Duration of Release (Days)	Therapeutic Effect	Ref.
BSA	MC/HA	>2	Wound healing	123
Ibuprofen	HPMC/Eudragit	1/2	Improve patient compliance	124
DS	HPMC/Cedrela gum	1/2	Highly suitable for sustained drug release	125
Furosemide	HPMC/EC	>1/2	Remarkable drug entrapment efficiency	126
Theophylline	HPMC/Psyllium	1/2	Suitable for sustained drug release	127
Cilostazol	HPMC/Carbomer	1	Improved plasma concentration and better bioavailability	128
Naproxen	EC/PVP	>3	Wound healing	129
Isoliquiritigenin	HEC/HA	1	Enhanced skin permeation of the drug	130
FDZ and Bismuth(III)	CMC/SA	1	Treatment of gastrointestinal disorders	131
BSA	CMC/HA	30	Potential for cell encapsulation, regenerative medicine, and tissue engineering	132
BSA	CNCs/SA	8	Potential as drug carriers and wound dressing	133
Soil Nutrients	Cellulose/CS	30	Beneficial for agriculture and horticultural applications	134

Abbreviations: FDZ, furazolidone; CS, chitosan; PEG, polyethylene glycol; ASCs, adipose-derived stem cells; Bfgf, basic fibroblast growth factor; HA, hyaluronic acid; TCH, tetracycline hydrochloride; BMP-2, bone morphogenetic protein-2; BSA, bovine serum albumin; PAM, polyacrylamide; SA, sodium alginate; PVA, polyvinyl alcohol; SA, salicylic acid; CDDS, controlled drug delivery system; PVP, polyvinyl propyl; HPMS, hydroxyl-terminated polydimethylsiloxane.

HPMC, BAM/HPMC demonstrated high viscosity, and among all ratios, it was the BAM/HPMC (1: 1) and AYB// HPMC (2: 1) that most effectively released all of the AB content within 30 h. This activity can be traced back to the individual physicochemical properties of BAM and AYB (such as thickness, variation of mass, disintegration time, folding endurance, and surface pH) influencing the dissolution of the drug from films and, thus, increasing AYB concentration for a better sustained drug release while drug release was reduced with increasing BAM concentrations.[137]

Dual crosslinking (DC) has been exploited as a beneficial strategy for tailoring drug delivery approaches.[138] The ionic crosslinking and DC were evaluated as a novel mucoadhesive DDS by de Oliveira Cardoso et al. In this experiment, blends of natural polysaccharides, gellan gum and retrograded starch hydrogels loaded with KET were proposed resulting in hydrogels with various rheological and mechanical properties and improvements in texture, as well as sustained drug release rate.[139] The blending of starch and gelatin and their predominant effect on controlled drug release—for methylthioninium,[140] ascorbic acid[141] and vancomycin hydrochloride[142]—have been reported.

High amylose has a chemical reaction affinity due to its hydroxyl groups (esterification, etherification, and oxidation) that can modulate their solubility, swelling, film and gel formation and biodegradability rates.[143] In this sense, a crosslinked interaction between high amylose starch and pectin incorporated by DS for additional applications in CDDSs was reported by Soares et al. The analytical results, including thermal analysis and X-ray diffraction, showed that while both thermal stability and crystallinity increased, the mechanical strength of the structures reduced due to drug loading. If we consider the suffix WD and CD as the samples without a crosslinker and the samples containing DS respectively, the greatest recovery (R %) indicated that the larger the amount of pectin in WD and CD samples they had (1:4 samples), the stronger and more elastic gels that were achieved. Moreover, drug loading did not qualitatively influence the rheological behavior which remained as gels, contributing that the extra drug can weaken the polymer network, and further interactions between the DS and carboxyl groups of the polymers could prevent hydrogen bonding.[144]

In another novel study, starch grafted with PEG (starch-g-PEG) and disulfide crosslinked micelles through lipoic acid (LA) loaded with the anti-cancer drug doxorubicin (DOX) were used for stimuli-responsive intracellular drug delivery. Another study, as is illustrated in Figure 7, used H40-star-PLA-SS-PEP as the main self-assembly polymeric structure for the preparation of the nanocarrier with the ability of loading DOX on its structure, and also on the surface. By comparing this study with the previous one, it can be concluded that in the absence of reductive glutathione (GSH), only a small amount of DOX could release, whereas, for the 10.0 mM of GSH, roughly 90% of DOX was efficiently released. Furthermore, the disulfide crosslinked micelles demonstrated a quicker DOX release in glutathione monoester (GSH-OEt) pretreated HeLa cells compared to non-pretreated and buthionine sulfoximine (BSO) pretreated cells, and as a result, disulfide crosslinked starch-g-PEG micelles paved the way for drug release.[145,146]

In a significant study, Setti et al developed a stable emulsion comprised of MaterBi® (a blend of thermoplastic starch and PCL) as the hydrophobic phase and SA as the hydrophilic phase for the controlled delivery of two commercial drugs: Neomercurocromo® and Cur. Homogenous polymer films were achieved by an ultrasonic processor without using any surfactants. Different MaterBi®/alginate fractions were tested, and finally, in vitro studies showed that these films were able to release both drugs separately and simultaneously in controllable rates compared to a pure PCL polymer. They made three sample films from the matrix of MaterBi®: (1) uncrosslinked and (2) crosslinked 50 wt% alginate 50 wt% MaterBi® films as well as (3) 30 wt% alginate 70 wt% MaterBi®. Over a span of 3 hours, the sample (1) released more hydrophilic drugs (Neomercurocromo®) while for (2), both drugs were released in lower amounts than their particular counterpart and finally for (3), Cur release was lower whereas for the Neomercurocromo®, release increased. Moreover, cell viability assays confirmed the biocompatibility of the films and suitability for superficial cell proliferation against human dermal fibroblasts in adult cells, and even for applications in wound healing and in the field of hygienic packaging of special pharmaceutical products.[147]

The superior advantages of starch nanocomposites — in comparison to conventional composites — include their optimal thermal, renewability, biodegradability, and mechanical and barrier properties, which have been widely used in the pharmaceutical industry as coating materials for CDDSs. However, our strongly held belief is that more research should be conducted for improving their controlled and local release area focussed on the physicochemical properties of starch and how to manufacture and make starch nanoparticles.

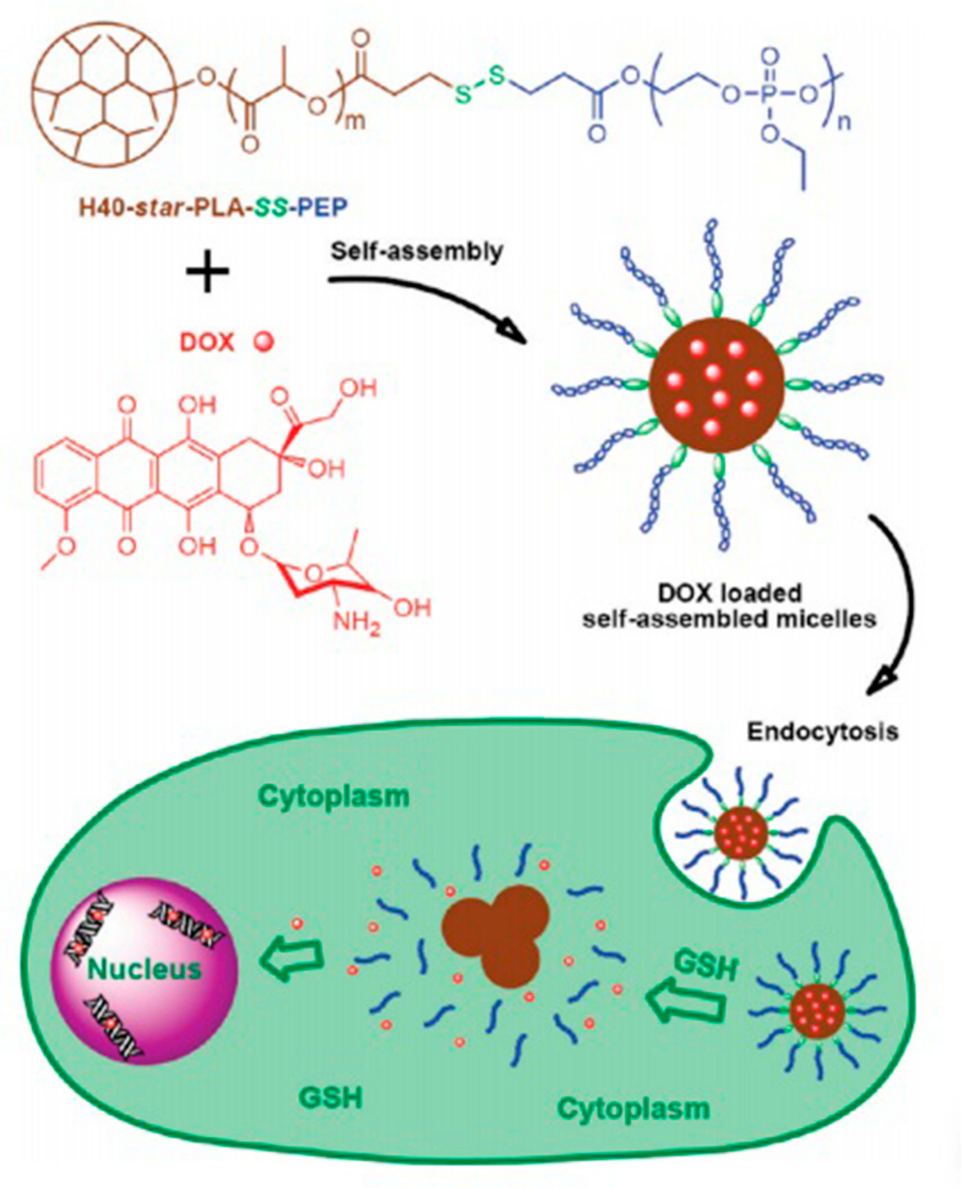

Figure 7 Illustration of Reduction-Stimulus Micelles Based on H40-star-PLA-SS-PEP for Intracellular DOX Release Triggered by Glutathione (GSH) Tripeptide.
Notes: Reprinted with permission Liu J, Pang Y, Huang W, et al. Bioreducible micelles self-assembled from amphiphilic hyperbranched multiarm copolymer for glutathione-mediated intracellular drug delivery. *Biomacromolecules*. 2011;12(5):1567-1577. Copyright 2011 American Chemical Society.[146]
Abbreviations: DOX, doxorubicin; GSH, glutathione

Synthetic Polymers Used in CDDSs

The role of synthetic polymers is of greatest importance in CDDSs as both a polymeric drug itself or as a carrier for small molecule drugs/bio-macromolecules, as such proteins embrace a significant function in releasing a drug, peptide or oligo or poly (nucleic acid) and can be regarded as stimuli-responsive polymers.[17] Several studies have focused on using synthetic polymeric matrices in many biomedical industries due to their remarkable physical, resistance and mechanical properties.[127,148] It is worth noticing that in the case of polymer blending, natural polymers often do not show gratifying results because of their preparation problems; thus, synthetic polymers are more favorable than natural polymers in many cases.[149] Among those used for the sustained release and CDDSs, PLGA, PLA, and PGA have been emphasized more, owing to their approval by the US Food and Drug Administration (FDA) and the European Medicines Authorities (EMA) for human use.[150] It should be mentioned that among all synthetic polymers, PEG has been blended more with the above compounds because it can

increase hydrophilicity, avoid immune system clearance and provide a controlled release time, and in this way, much work has been published.[151]

The aforementioned polymers are usually blended with natural polymers to produce new hybrid products with suitable physicochemical and thermo-mechanical properties for promoting their fabrication into biomedical devices for prolonged release systems,[152,153] which prevent fabrication and handling issues for medical applications.[48] Novel synthetic polymers are being increasingly used in pharmaceutical sections as coating materials that provide for adequate mechanical properties and better polymeric electrospinnability. Over the past years, modified synthetic polymeric hydrogels have been blended with some natural polymers to achieve advanced biopolymers, which have paved the way for CDDSs. In this section, we illustrate the recent applications of PLGA, PLA and PGA and their blends with different excipients in numerous biomedical devices.

Applications of PLGA Blends in CDDSs

PLGA, a polyester of hydroxy acids, is one the most biocompatible, biodegradable and injectable polymers approved by the FDA for many biomedical and therapeutic applications, ranging from DDSs to tissue engineering.[154–156] Although PLGA is a glassy synthetic polymer, it has a quite rigid structure along with remarkable mechanical strength, permitting its use as CDDSs. Besides, PLGA copolymers possess high ratios of lactic acid which are less hydrophilic than functional groups in PGA, absorbing less water and consequently are more slowly degradable. Most importantly, PLGA hydrogels degrade in a dynamic process through hydrolytic cleavage of its poly (ester) backbone.[157] To enhance the efficacy of PLGA in CDDSs, many modifications have emerged, such as PLGA copolymers containing blocks and alternating polymers through different hydrophilic moieties—namely PEG or PEO.[158]

However, PLGA has brittle and low elongation characteristics, so the blending of PCL with PLGA has emerged for developing nanofibers with sufficient flexibility, good porosity, slow degradability and a better biological nature.[159] Individually controlled release of some hydrophilic antiretroviral drugs—including Tenofovir (TFV), Raltegravir (RAL), Maraviroc (MVC) and Azidothymidine (AZT)—was accomplished in vitro through uniaxial electrospun PLGA/PCL nanofibers. By utilizing representative scanning electron micrographs (SEM), different ratios of compositions demonstrated a shift in drug release from a burst to sustained release, as fibers with a high PCL concentration showed fast release (24 h), while fibers with high PLGA content could ameliorate limitations for the sustained release of TFV (30 days). In another study, scientists showed that different preparation procedures could lead to different surface morphologies, and in the following, different properties and biomedical applications. For instance, the addition of metal nanoparticles (such as Ag) or even metal salts into a polymeric structure as a dopant in the first phase of synthesis and in the last phase of synthesis can create two different surface morphologies of an obtained scaffold (Figure 8).[160,161]

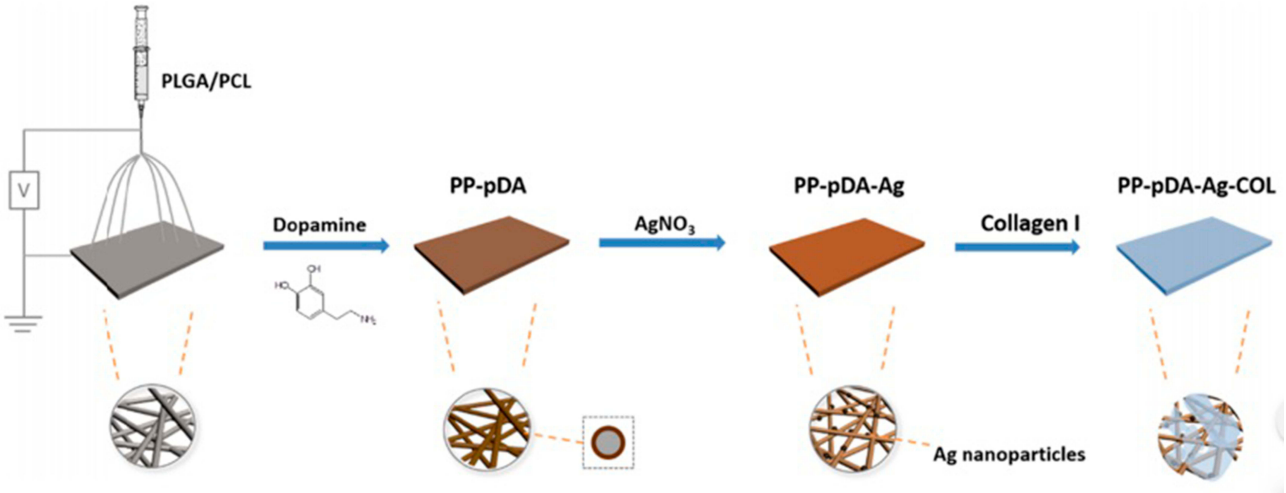

Figure 8 Schematic illustration of the preparation procedure of PP-pDA-Ag-COL scaffolds. PLGA/PCL scaffolds were prepared by electrospun technology. Ag nanoparticles were in situ reduced by polydopamine and then coated by collagen I.

Notes: Reprinted with permission Qian Y, Zhou X, Zhang F, Diekwisch TGH, Luan X, Yang J. Triple PLGA/PCL Scaffold Modification Including Silver Impregnation, Collagen Coating, and Electrospinning Significantly Improve Biocompatibility, Antimicrobial, and Osteogenic Properties for Orofacial Tissue Regeneration. ACS Appl Mater Interfaces. 2019;11(41):37381-37396. Copyright 2011 American Chemical Society.[161]

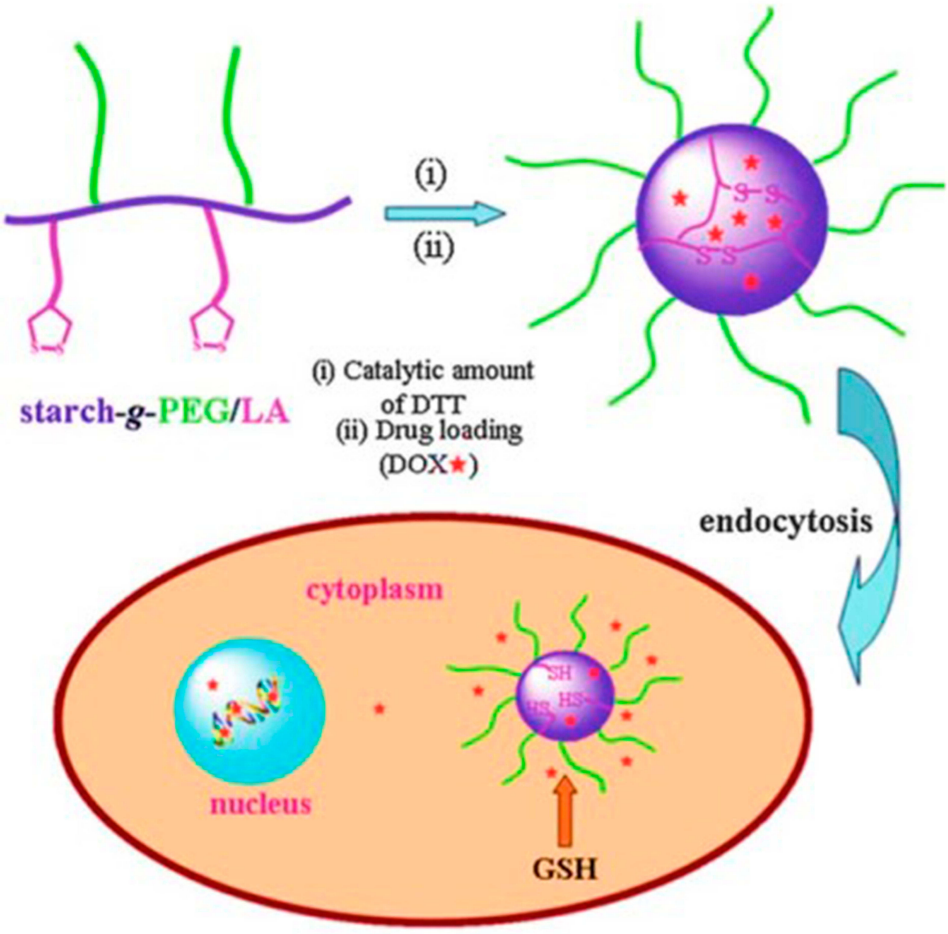

Figure 9 In vitro sustained cumulative release of DOX from starch-g-PEG/LA.
Notes: Reprinted with permission from Jin F, Liu D, Yu H, et al. Sialic acid-functionalized PEG–PLGA microspheres loading mitochondrial-targeting-modified curcumin for acute lung injury therapy. *Mol Pharm*. 2018;16(1):71–85. Copyright 2018 American Chemical Society.[165]
Abbreviation: PEG, polyethylene glycol;

To overcome the drawbacks of PLGA hydrogels, such as short blood circulation and quick uptake by the reticuloendothelial system (RES), PEG-MS and PL/PEG compositions have been developed.[162] These copolymers have largely been utilized in medicine, notably, for CDDSs for proteins and drugs. Their suitable interaction with drugs has alleviated drug loading content (DLC) problems even though producing surface-modified PEG-MS and PL/PEG loaded with drugs is a highly complicated issue because there are a few surface attachments of PEG in the production of PLGA/PEG.[163,164] Jin et al developed sialic acid (SA) modified lung-targeted microspheres (MS) conjugated with PLGA/PEG (SA-PLGA/PEG-MS) to achieve the controlled release of triphenylphosphonium cation (TPP) coated with Cur (Cur-TPP) for treating acute lung injury (ALI) through emulsion solvent evaporation techniques. In vitro drug release studies indicated that 63 and 20% TPP- Cur had a prolonged (72 h) and burst (3 h) release, respectively, from both SA-PEG-MS and PL/PEG-MS and PLGA/PEG-MS. In another study, the sustained cumulative release of a typical drug from a starch-g-PEG/LA-based nanocarrier was investigated in typical biological conditions showing highly-dependant behavior to the structure of the polymer-based nanocarrier and also the drug loading ability (Figure 9).[165]

Recently, Sánchez-López et al designed Memantine-PEG-PLGA (MEM-PEG-PLGA) with the expectation of targeting the blood-brain barrier (BBB) for Alzheimer's treatment. In this experiment, the MEM was well distributed in the matrix of PLGA. DLC results were promising due to the growth of the thermogravimetric (T_g) parameter of the polymeric solution, although there was not a clear result concerning the strength of the interaction between the drug and hydrogels. Both in vivo and in vitro studies showed that the PLGA/PEG hydrogels delivered MEM in

a controlled release manner to the target tissue, and the improvement in the drug therapeutic effect demonstrated a stable drug amount into the target organ.[166]

Likewise, in vitro, DOX release was controlled when loaded with a high affinity single-stranded EpCAM RNA aptamer conjugated to PLGA-PEG copolymers. In favor of PLGA-PEG nanopolymersomes, the cytotoxicity ($P < 0.01$) toward MCF-7 was greater than non-targeted nanopolymersomes, and the drug was released in a controlled and sustained manner.[167] Farajzadeh and colleagues conducted a study to evaluate the synergistic inhibitory effect of Met and Cur loaded PLGA/PEG against T47D breast cancer cells. The morphology and dynamic light scattering (DLS) results were utilized to improve the nanoformulations. The drugs were encapsulated into the PLGA/PEG at a 1000:1 molar ratio, and the release profile of free drugs with the drug-NPs (Met-NP and Cur-NP) were compared. Impressively, the drugs were released in a sustained manner for more than 120 h without any initial burst release. This combination not only killed the T47D breast cancer cells more quickly than free drugs, but it also decreased cytotoxicity and side effects to patients.[168]

Novel PEG-PLGA/PLGA nanofibers were prepared and then loaded with gentamycin through a solid-oil-in water method to investigate the role of hydrogels in CDDSs. Drug release kinetics from the polymeric nanofibers were investigated by fitting the drug release data within four kinetic equations: zero order, first order, Higuchi and Korsmeyer-Peppas models. As a result, gentamycin content increased to 10.5 w/w% resulting in enhanced antibacterial activity as well as complete sustained release after 10 h.[169] The anticancer activity of 9-cis-retinoic acid incorporated PEG-coated PLGA NPs was reported by Cosco et al. The dynamic Franz-type diffusion cell (comprised of a donor and a receptor) separated by a cellulose acetate membrane was evaluated for drug release. Therefore, the rapid and prolonged release of 9-cis-retinoic acid after 10 h and 48 h, respectively, were reported.[170]

It should be noted that blending has not always come with sustained release. For instance, electrospun nanofibers of PEGylated PLGA (PEG-PLGA) were selected to evaluate the release kinetics of amoxicillin (AMX). When recording the absorbance of the drug at 228 nm through a Lambda 25 UV–vis spectrophotometer, the release profiles of AMX from PLGA/AMX and PLGA-PEG/AMX nanofibers were obtained. This study showed that PLGA-PEG could release the drug in a faster manner than PLGA nanofibers. The reason is interesting: on account of the hydrophilicity of both AMX and PEG, and on the other hand, the hydrophobicity of PLGA in that its hydrophilicity was improved by PEG, AMX is more likely to disperse uniformly in the PLGA-PEG/AMX nanofibers than in the PLGA/AMX nanofibers. The greater surface area of the nanofibers also played a critical role. Furthermore, 3% PLGA/AMX exhibited a smaller release of AMX than 5% AMX/PLGA fibers (2 days) while the release profile for AMX for 3% PLGA-PEG/AMX was higher than for 5% PLGA-PEG/AMX nanofibers because of the low quantity of incorporation which was dispersed much more uniformly in the 3% PLGA-PEG/AMX than in the 5% PLGA-PEG/AMX nanofibers.[171] In Table 4, additional applications of PLGA blends are summarized for the controlled release of various drugs.

Applications of PLA Blends in CDDSs

Undoubtedly, PLA— as a tremendously versatile and aliphatic polyester discovered by Carothers in 1932[172]—is a biopolymer with much potential for biomedical applications. It can be produced by lactic acid (obtained by the fermentation of sugars originating from renewable resources) polymerization or through the ROP of lactic acid. Therefore, it is astonishingly biocompatible, biodegradable, eco-friendly and sustainable.[173,174] PLA, additionally, has been extensively used in producing tissue scaffolds and drug carriers because of its degradability in carbon dioxide and water in vivo.[175] PLA possesses three stereoisomers: semi-crystallized poly (D-lactide acid) (PDLA), poly(L-lactide acid) (PLLA) and amorphous poly(DL-lactide acid) (PDLLA), each with different structures as carriers for drug delivery.[176] During recent years, various PLA blends have been introduced for CDDSs as beneficial copolymers for a wide range of medical and pharmaceutical applications.[173,177,178] In the last years, many PEGylated PLA hydrogels have been synthesized and investigated for their application in CDDSs.[151] Sirc et al have demonstrated the controlled release of some drugs based on PLA/PEG hydrogels. They reported not only the sustained release for Cyclosporine A (controlled release for a day)[179] but more recently for PTX. The compositions of PLA/PEG-PTX were architected by a needleless electrospinning technique. HPLC-UV analysis ensured the advantages of this hydrogel on the prolonged and efficient release of PTX, including the sustained release of PTX in favor of additional ratios of PEG (15 wt %), remarkable cytotoxicity of PLA/PEG-PTX fibers against a human fibrosarcoma HT1080 cell line, as well as an increased antiangiogenic effect.

Table 4 Other Applications of PLGA-Based Hydrogels in CDDSs

Loaded Active Component	Blend Composition	Duration of Release (Days)	Therapeutic Effect	Ref.
TCH	PLGA/Gum tragacanth	75	Potential for periodontal diseases	172
Neuregulin-1	PLGA/NCO-sP(EO-stat-PO)	7	Potential for myocardial ischemic	173
Caffeine	PLGA/PLA	30	Suitable for sustained drug release	174
Cur	PLGA/Poloxamer	4	Protecting the drug from rapid CURC hydrolytic degradation	175
Teriparatide	PLGA/PHBV	50	Enhance serum calcium concentration	176
Ibuprofen	PLGA/PCL	17	Effective for drug encapsulation & sustained release	177
Fenbufen	PLGA/CS	1	Treatment of acute & chronic pain	178
SDF-1α	PLGA/PEG-PLGA	3	Trapping of glioblastoma cells	179
Amphotericin B	PLGA/PLGA-PEG	7	Potential for antifungal therapy	180
Naringin	PLGA/PLLA/PDLLA	20	Potential for bone regeneration therapy	181
Triamcinolone acetonide	PLGA/mPEG	45	Treatment of chronic & recurrent uveitis	182
Vancomycin, gentamicin, and lidocaine	PLGA/Collagen	14	Wound healing	183
Tenofovir	PLGA/PCL	10	Potential as drug carriers and sustained release	184
Sorafenib and DOX	PLGA/PEG	6 & 1	Improved cellular uptake in cancer cells	185
Cathelicidin-BF (BF30)	PLGA/4-arm-PEG	15	Enhanced antibacterial therapy	186
Cur	PLGA/PEG-B6	3	Potential for Alzheimer's disease	187
Bevacizumab	PLGA/PCADK	50	Potential for ocular diseases	188
Simvastatin	PLGA/PEG	3	Treatment of osteoporosis	189
DOX	PLGA/PEG	5	Potential for cancer treatment	190
Rutin and Benzamide	PLGA/PEG	5	Potential for anti-biofilm therapy	191
5-FU	PEG/PLGA-PCL	3	Induces apoptosis in HT-29 human colon cancer cells	192
Insulin	PPP/CS	60	Potential for subconjunctival injection & ocular drug delivery	193
Dactolisib	PLGA/PEG	10	Potential for anti-inflammatory therapy	194
Acyclovir	PLGA/PEG	18	Potential as drug carriers and sustained release	195

Abbreviations: CURC, The pharmacological potential of curcumin; SDF-1α, stromal cell-derived factor-1 alpha; PPP, PLGA-PEG-PLGA triblock; FDZ, furazolidone; CS, chitosan; PEG, polyethylene glycol; ASCs, adipose-derived stem cells; Bfgf, basic fibroblast growth factor; HA, hyaluronic acid; TCH, tetracycline hydrochloride; BMP-2, bone morphogenetic protein-2; BSA, bovine serum albumin; PAM, polyacrylamide; SA, sodium alginate; PVA, polyvinyl alcohol; SA, salicylic acid; CDDS, controlled drug delivery system; PVP, polyvinyl propyl; HPMS, hydroxyl-terminated polydimethylsiloxane; PCL, polycaprolactone; NCO-SP, star shaped polyethylene oxide based prepolymers; DOX, doxorubicin; EO, electro-optic; PO, polyolefin; 5-FU, 5-fluorouracil.

Most significantly, an in vivo study illustrated that PTX (at a concentration of PTX 0.1mg/cm^2) loaded PLA-PEG(20) (PLA-PTX(10)-PEG(20)) prevented tumor recurrence, which paved the way for beneficial and safe local recurrence of tumor treatment.[180] PEG-b-PLA NPs were designed through an organocatalyzed ring-opening polymerization process for assessing the in vitro drug release kinetics of Rhodamine B base (RhB), by utilizing two various surfactants to achieve diversely charged NPs: (i) choline chloride (CC) for positive charges and (ii) sodium dodecyl sulphate (SDS) for negative charges. With respect to the previously synthesized hydrogel, AC6, RhB loaded within AC6-NPs_SDS showed a prolonged release time of over a day (Figure 10).[181]

The controlled release of an important cephalosporin antibiotic drug, cefixime (Cfx), was assessed by Sherif et al who developed an effective composition prepared from PLA/PCL blends, including nano-hydroxyapatite (n-HA)—a prime mineral material of bone tissue in mammals—loaded with β-cyclodextrin (β-CD) and Cfx (PLA/PCL-βCD-Cfx) in the electrospun membranes. To evaluate the controlled release profile, PLA/PCL-nHA membranes were placed into 30 mL of a PBS solution. In the presence of βCD, the release of the drug was controlled to about half after 24 h, which exhibited a promising delivery approach of Cfx over a proper time period.[182] Correspondingly, the Herrero group reported effective controlled BSA release from electrospun membranes of PLA/PCL blends possessing micron fiber diameters. Electrospinning parameters—such as flow rate, voltage, distance to the collector and solvents—played a crucial role in determining drug loading and release. As a consequence, PLA/PCL was able to cumulatively release BSA for up to three weeks.[172] This study also highlights the additional significant improvement that could be obtained through the use of nanometer fibers, rather than the afore-mentioned studied micron fibers, due to their significantly greater surface area.

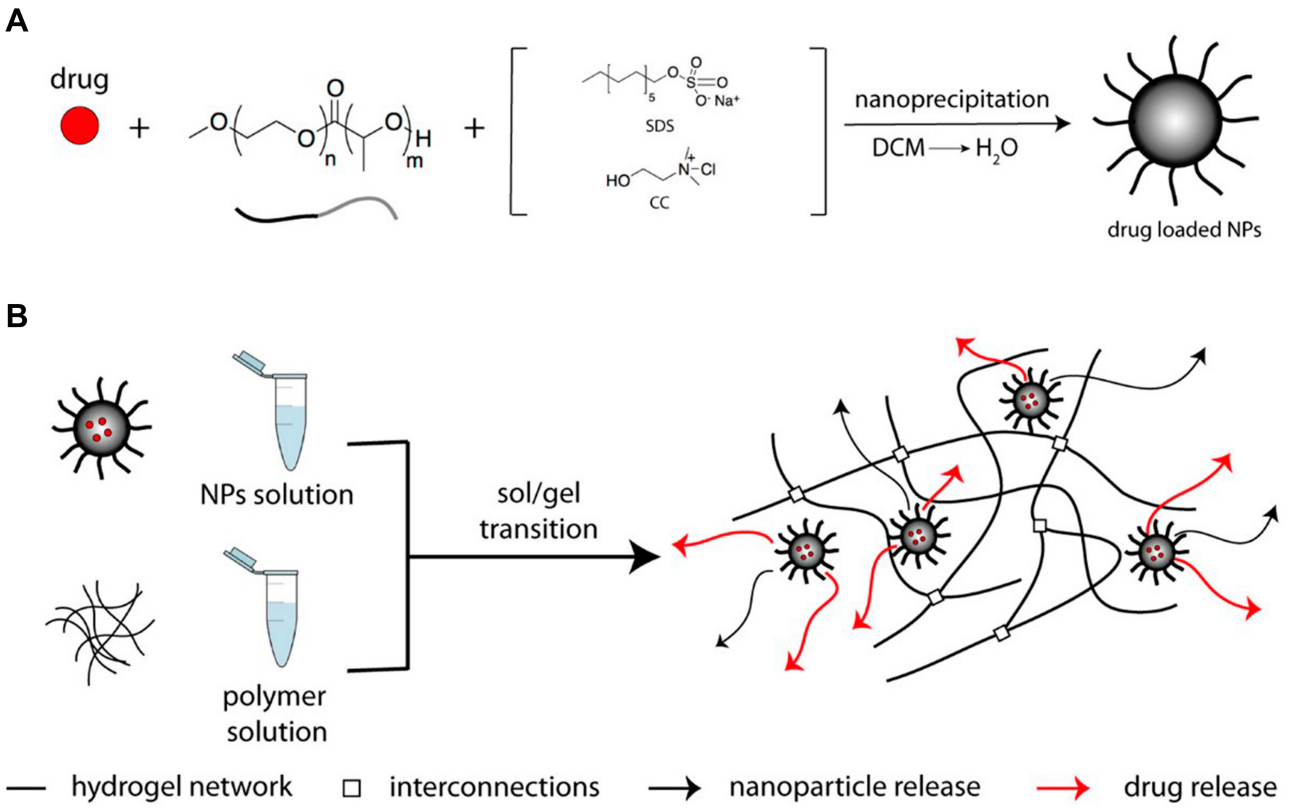

Figure 10 (**A**) Preparation of the drug loaded carrier and (**B**) the sustained release of RhB in AC6-NPs. Reproduced from Mauri E, Negri A, Rebellato E, Masi M, Perale G, Rossi F. Hydrogel-nanoparticles composite system for controlled drug delivery. *Gels*. 2018;4(3):74. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[181]
Abbreviations: DCM, dichloromethane; NPs, nanoparticles; SDS, sodium dodecyl sulfate.

Several publications have reported the promising benefits of biodegradable copolymer use for CDDSs of pesticides and fertilizers, such as reducing environmental hazards, improving agricultural product yields, decreasing environmental contamination and reducing phytotoxicity.[183–186] Under these advantages, Wang et al reported CDDSs for pesticides, azoxystrobin, and difenoconazole, by exploiting the solvent evaporation method to obtain low toxicity and synergetic effects by utilizing microsphere poly (butylene succinate) (PBS) blended with PLA (70/30 w/w) as shells. Compared to the difenoconazole-ascomycete (5:8) 32.5% w/v suspension concentrate (SC) with 17 days of release, it was the PLA/PBS microsphere which helped the cumulative release of the drugs for up to 25 days at a concentration ratio of about 85%.[187]

Numerous studies have researched the advantages of PLA/PLGA copolymers, including their biodegradability and mechanical properties as well as their effective role in CDDSs of opioid antagonists, anti-cancer, anti-diarrheal, anti-bacterial, anti-psychotic, anti-inflammatory and anti-diabetic drugs for intramuscular, subcutaneous, periodontal and oral administration.[188–192] Milovanovic et al used a PLA/PLGA matrix with supercritical carbon dioxide ($scCO_2$) as an effective solvent to proceed with the production of PLA/PLGA foams for the controlled delivery of thymol (a model drug) in a single-step procedure according to supercritical impregnation and foaming. The tested foams could release thymol in a controlled manner based on DSC and FTIR analyses between 3 to 6 weeks in PBS at 37 °C. Furthermore, the maximum thymol release rate (6.62%) of this foam demonstrated controlled release of the drug (3 days) at a pH value of 1.1.[193] Hence, high surface area, tunable pore size and pore interconnectivity of pores could lead to remarkable controlled release carriers.

PLA would be an excellent candidate for polymer blending for a diverse number of medical applications. However, the commercial use of PLA blends has been restricted and is a long way from scale-up to date. Stable and effective formulations of PLA blends need to be more of a focus. In Table 5, additional applications of PLA-based NPs are summarized for the controlled release of various drugs.

Table 5 Other Applications of PLA-Based Hydrogels in CDDSs

Loaded Active Component	Blend Composition	Duration of Release (Days)	Therapeutic Effect	Ref.
5-FU	PLA/PEG	>13	Improve drug pharmacokinetics & potential for solid tumors	194
TCH	PLA/PCL	10	Wound healing and quick surgery infective protection	195
Methylene Blue	PLA/PEG	120	Potential as drug carriers & sustained release	196
Minocycline	PLA/PEG	12	Treatment of periodontitis in dogs	197
Cur	PLA/HPG	3	Wound dressing	198
Teriflunomide	PLA/PBAd	>5	Treatment of rheumatoid arthritis	199
Anastrozole	PLA/PEG-PLA	6	Treatment of breast cancer cell lines	200
Naltrexone	PLA/PVA	>30	Conventional treatment of medical conditions and sustained release	201
Risperidone	PLA/PPAd	6	Increase the short-term drug activity	202
Salicylic acid	PLA/CS	5	Potential as drug carriers & sustained release	177
Voriconazole	PLA/PESu	>3	Treatment of skin infection	203
DOX	PLA/PVP	6	Improve drug loading efficiency and incorporation	204
Cfx	PLA/PEG	>1	Potential as drug carriers & sustained release	24
Celecoxib	PLA/PEtG	1	Potential for anticancer therapy	205

Abbreviations: PBAd, poly(butylene adipate); HPG, hyperbranched polyglycerol; PPAd, poly(propylene adipate); PESu, poly(ethylene succinate); PEtG, poly(ethylglyoxylate) CS, Chitosan; PEG, polyethylene glycol; PAM, polyacrylamide; PVA, polyvinyl alcohol; CDDS, controlled drug delivery system; PVP, polyvinyl propyl; DOX, doxorubicin; PLA, Polylactic acid; Cfx, Ciprofloxacin; 5-FU, 5-Fluorouracil; PCL, polycaprolactone; TCH, Tetracycline hydrochloride; Cur, curcumin.

Applications of PGA Blends for CDDSs

PGA is a safe and non-immunogenic polymer that was initially explored for the delivery of small products and antitumor agents in Phase III trials. PGA nanoparticles have been widely used as polymer-carriers for CDDSs due to their superb biodegradability and biocompatibility properties, which are being utilized for the targeted delivery of poorly soluble or unstable bioactive compounds bringing about low side effects and high drug loading efficacy.[194–196] Nevertheless, PGA has some limitations in CDDSs, such as insolubility in common solvents, problems in fabrication, high melting temperature (220 °C) and high crystallinity of approximately 50%.[197,198]

Accordingly, a naturally occurring anionic polypeptide γ-PGA—linked by the peptide bond among the α-amino and the abundant γ-carboxyl groups[30]—produced mostly using *Bacillus subtilis* bacteria[199], has gained popularity on account of its satisfactory water solubility, favorable fiber-formation, film-forming ability, plasticity, and most greatly, for its activity in controlled drug release.[175] Notably, γ-PGA with a negatively charged structure can blend with a positively charged polymer, providing electrostatic interactions to make biocompatible and biodegradable compositions, see Figure 11.[200]

Novel injectable and stimuli-responsive γ-PGA/collagen hydrogels loaded with DOX and granulocyte-macrophage colony-stimulating factor (GM-CSF) were developed by Cho et al. The γ-PGA ameliorated the innate temperature-based phase transition nature of collagen to a limited viscous sol and non-flowing gel states at room and body temperatures, respectively.

Chung et al exploited a spin-coating technique for the controlled release of bone morphogenetic protein 2 (BMP-2) incorporated with polyelectrolyte multilayers of CS/γ-PGA coated on a Ti6Al4V substrate. To fully decompose ex vivo, the prepared film required a 5–8 μm thickness and more than 45 days. Consequently, a 50% release of BMP-2 was observed to have an initial burst release within 3 h, while after that, the controlled release of BMP-2 over a span of 5 days was reported.[202]

In a recent study, aldehyde hyaluronic acid (HA-CHO) hydrazide-modified γ-PGA (γ-PGA-ADH) was synthesized to form HA/γ-PGA hydrogels through a Shiff base reaction. The controlled release of BSA as a biological compound with a variety of composition ratios was confirmed after 30 h during either diffusion or case-II relaxation mechanisms.[203] Temperature and pH-responsive hydrogels based on poly (NIPAAm-co-poly (γ-glutamic acid) - Allyl glycidyl ether) (poly (NIPAAm-co- γ-PGA -AGE)) were synthesized by crosslinking polymerization to evaluate the controlled release of naproxen. In this study, γ-PGA-Allyl glycidyl ether (γ-PGA-AGE), which was obtained by the reaction of γ-PGA and AGE through ring-opening grafting, played an indispensable role in preparing the thermo/pH-sensitive

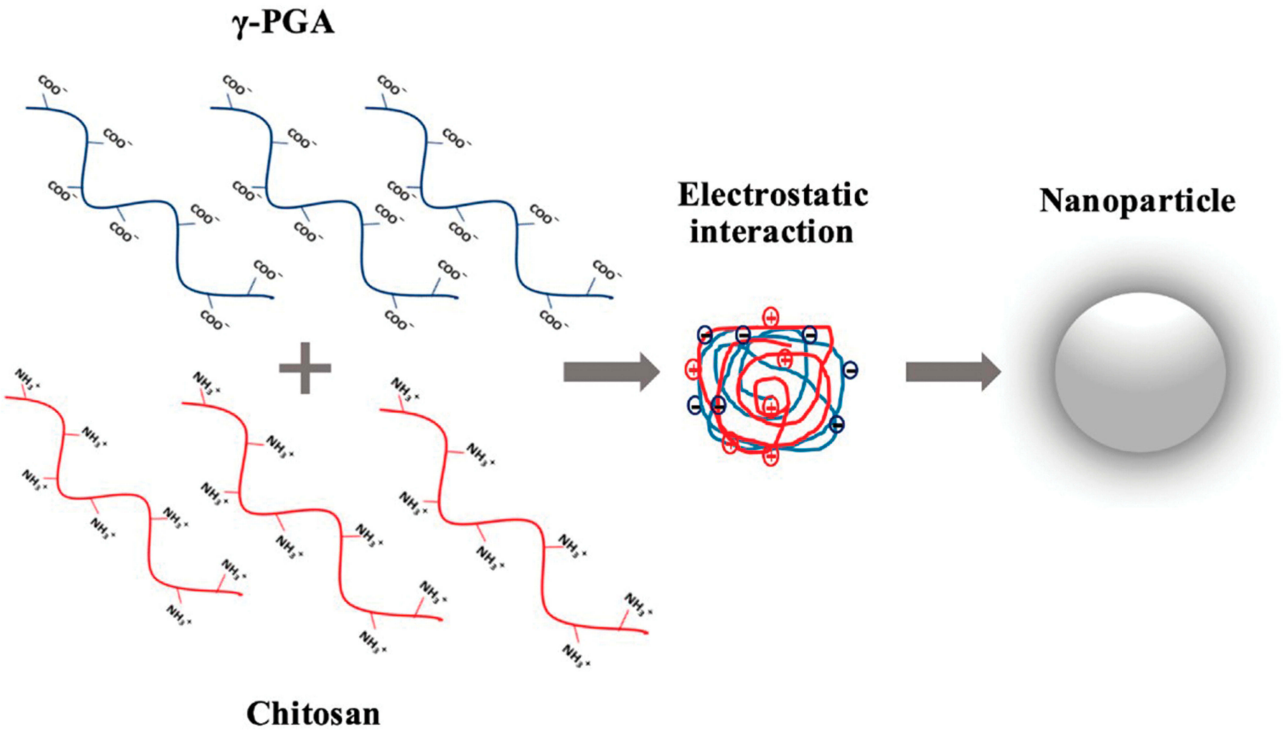

Figure 11 The composition between γ-PGA as the negatively charged polymer and the positively charged polymer CS. Reproduced from Khalil I, Burns A, Radecka I, et al. Bacterial-derived polymer poly-γ-glutamic acid (γ-PGA)-based micro/nanoparticles as a delivery system for antimicrobials and other biomedical applications. *Int J Mol Sci*. 2017;18(2):313. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[200]
Abbreviation: γ-PGA, poly-γ-glutamic acid.

NIPAAm-co- γ-PGA -AGE hydrogels. The cytocompatibility of the hydrogels was enhanced by increasing the ratio of γ-PGA-AGE. After 36 h, naproxen was released at 88 and 81% according to r= 0.20 and r= 0.15 hydrogels, respectively, while for r= 0.05 and r= 0.10, up to 12 h was required to reach the maximum release rate. As a result, the poly (NIPAAm-co-γ-PGA-AGE) hydrogels can be considered as a controlled drug release carrier.[30]

A novel diblock copolymer d-α-tocopheryl polyethylene glycol 1000 succinate-b-poly(e-caprolactone-ran-glycolide) (TPGSb-(PCL-ran-PGA) (TPP) was synthesized by ring-opening polymerization incorporated with potential antifungal drug itraconazole (ITZ) to form ITZ-TPP NPs by a modified double emulsion technique. Not only did this composition enhance antifungal activity of ITZ with no clear cytotoxicity on HeLa cells and fibroblasts nor any obvious inhibitory activity against fungal growth, more importantly, it showed a controlled release from 23.75 and 56% of the encapsulated drug during the first 3 days and more than 12 days, respectively.[197] Liu et al developed polymersomes of folic acid (FA), which were effective for the controlled and targeted release of DOX, and the diblock PGA/PCL (FA-PGA-b-PCL) for ultrasensitive transverse (T2) MRI. Afterward, ultra-small superparamagnetic iron oxide NPs (SPIONs) were explored in situ as hydrophilic PGA coronas of FA-PGA-b-PCL to obtain magnetic polymersomes. Thus, a lower water diffusion coefficient and higher fruitful diameter were achieved, which could be a potential advantage resulting in greater T2 relaxivity of the FA-PGA-b-PCL. Besides, in terms of controlled release, DOX loaded FA-PGA-b-PCL released in a controlled manner for about 15 days. Both in vitro and in vivo tests reported that DOX was delivered and released significantly into the nucleus of HeLa cells with great efficiency (ie, tumor volume decreased gradually after two weeks) owing to the certain recognition and binding between FA on the surface of the polymersomes and the FA receptors on cancer cell membranes, indicating that these DOX-loaded magnetic polymersomes are favorable for numerous biomedical applications.[204]

Many studies have highlighted the different strategies of modern drug delivery to overcome the serious dilemma of platinum (II) drugs for cancer therapy, such as drug resistance, detoxification and side effects.[205–208] Recently, Yang et al developed a novel micelle of methoxy PEG-PGA and

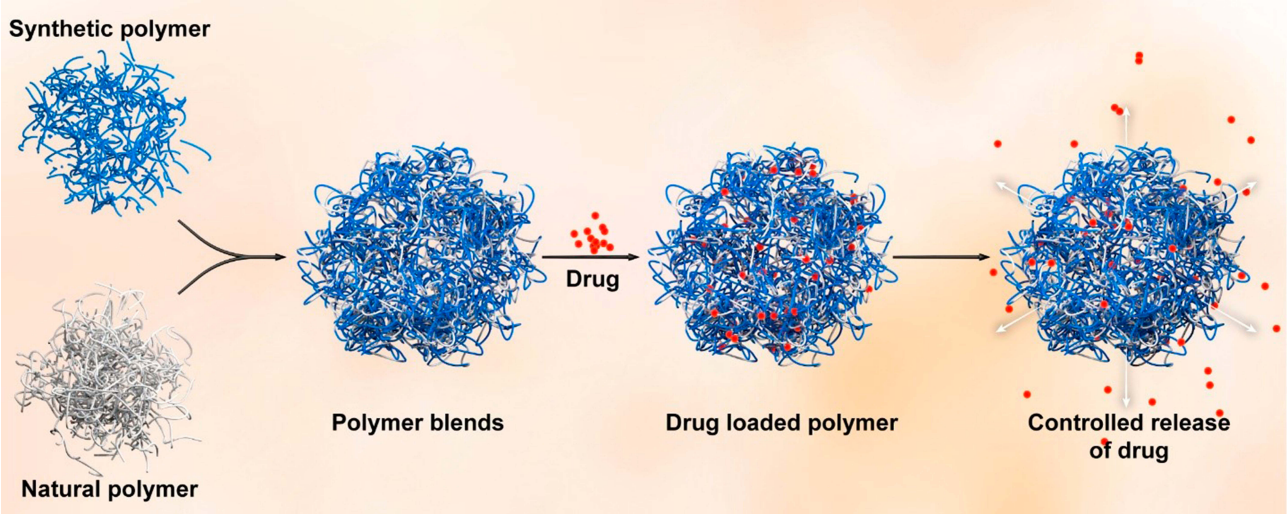

Figure 12 Schematic illustration of the preparation of a typical polymer nano blend system.

newly synthesized cisplatin derivative PyPt M (PyPt) as PyPt drugs in the polymeric core and PEG as the shell. PyPt is a poorly water-soluble drug, however, its aquated species can interact with mPEG-b-PLG—with the protection of PyPt from glutathione (GSH) detoxification—to enhance solubility in order to increase cellular uptake and the cytotoxicity of M (PyPt) compared to free cisplatin and PyPt. Consequently, the benefits of M (PyPt) include less detoxification of GSH in PyPt, resulting in a high affinity to bind DNA, higher apoptosis, improved cisplatin efficacy and resistance. Moreover, the M (PyPt) demonstrated the potential controlled release of Pt in tumor micro-environments, which prohibited the division of cancer cells. However, basically, the preparation of a nano polymer blend system is the same for any study and investigation, and follows basic rules in this matter (Figure 12).[209]

The controlled release necessary for overcoming biological barriers related to the oral administration of peptides was reported by Niu and co-workers. In this scenario, they created core-shell nanoparticles in which the core was a hydrophobically-modified cell-penetrating peptide (CPP) and insulin and the shell was a selected model peptide along with the copolymer PGA-PEG in order to preserve the drug and carrier from the inclement conditions of the intestine. Moreover, they chose octaarginine (r8) as the CPP, which can interact with insulin through electrostatic and hydrophobic forces. One way to design PGA-PEG enveloped r8-insulin nano-complexes (ENCPs) is to dissolve PGA-PEG in water, followed by evaporating water in a round flask under reduced pressure at 37 °C, then adding r8-insulin nano-complexes (NCPs) to the flask for about a 10 min rotation until the NCPs were enveloped with the film, followed by the adjustment of ENCPs at a pH of 7. ENCPs had such fascinating advantages, such as the potential controlled release of insulin in vivo (release from the ENCPs was slower than the NCPs alone), better protection of insulin from enzymatic degradation and to solidify in simulated intestinal fluid (SIF).[210]

Conclusions and Future Prospects

This review scrutinized recent developments and the characterization of nano polymeric blends for CDDSs. Recently, CDDSs have attracted much attention due to their massive advantages over conventional drug therapy. They are distinguished by a variety of categories, such as diffusion-controlled, chemically controlled, solvent activated and modulated release systems.[50] CDDSs have been additionally reported in which drugs can be dissolved or dispersed in the films. The effective delivery of a drug at a controlled rate over an accurate time frame to a selected target organ has been the absolute necessity in drug delivery technology and pharmacokinetics.

Polymer blends have demonstrated a good response to external stimuli—such as pH, temperature, ionic factor, electric field and magnetic field—which can be regarded as a novel class of carriers or coating materials for sustained drug release and for CDDSs. Synthetic as well as naturally occurring polymers can blend to generate a hybrid polymer with new physical and chemical properties. Examples of naturally occurring polymers include CS, cellulose, and starch, while

on the other hand, PLGA, PLA and PGA are salient examples of synthetic polymers.

Different types of drugs can be fabricated into biocompatible and biodegradable polymers with various strategies. During past years, there has been a promising need for the development of polymer blends, and these necessities will continue to steadily increase in the future. Moreover, polymer blends loaded with a drug could release a drug over a prolonged time by reducing the drug dosage and unwanted toxic effects. Consequently, these compositions are ideal candidates for CDDSs. However, functionality and drug release mechanisms of these systems are highly complicated, more than that of just one polymer. Thus, it is worth implementing a practical decision to reduce time and a cost-intensive series of trial and error experiments in order to accurately assess therapeutic efficacy and ameliorate the clinical practice of polymer blends. It is of critical importance to evaluate such systems more clinically and pathologically in animal models.

Therefore, in summary, even though improvements and enhancements have been reported by numerous researchers worldwide, there are still too many challenges that must be solved before the widespread use of nano polymer blends are realized in medicine. In addition, the field of CDDSs suggests a large variety in scope and prospect to develop novel technologies with high performance and potential economically viable solutions, issues commonly ignored in today's published papers.

Disclosure

The authors report no conflicts of interest in this work.

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