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Review Article

Advances in Hybrid Polymer-Based Materials for Sustained Drug Release

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The use of biomaterials composed of organic pristine components has been successfully described in several purposes, such as tissue engineering and drug delivery. Drug delivery systems (DDS) have shown several advantages over traditional drug therapy, such as greater therapeutic efficacy, prolonged delivery profile, and reduced drug toxicity, as evidenced by *in vitro* and *in vivo* studies as well as clinical trials. Despite that, there is no perfect delivery carrier, and issues such as undesirable viscosity and physicochemical stability or inability to efficiently encapsulate hydrophilic/hydrophobic molecules still persist, limiting DDS applications. To overcome that, biohybrid systems, originating from the synergistic assembly of polymers and other organic materials such as proteins and lipids, have recently been described, yielding molecularly planned biohybrid systems that are able to optimize structures to easily interact with the targets. This work revised the biohybrid DDS clarifying their advantages, limitations, and future perspectives in an attempt to contribute to further research of innovative and safe biohybrid polymer-based system as biomaterials for the sustained release of active molecules.

1. Introduction

This work demonstrates the wide possibility of advanced materials developments in the drug delivery/release field based on a molecular approach. It draws a parallel line between the nanostructured drug delivery systems (DDS) or drug release systems studied in recent years and their hybridization processes from an assembly with polymeric materials able to bypass many of the intrinsic limitations to each system. These versatile polymer-based hybrid nanostructures combine the advantages of each excipient, resulting in formulations or pharmaceutical forms designed to specifically interact with the targets, acting as smart drug delivery systems. The current literature revision aims to show the mainly polymeric materials used as DDS, as well as those organic hybrid nanocarriers based on polymer molecules. We have also moved efforts to inspire novel hybrid DDS in the search of a perfect DDS design, which is still a challenge.

The pioneering use of biomaterials dates back to early civilizations, such as Ancient Egypt, since artificial ears, noses, and teeth were found in many mummified bodies [1]. In the last 50 years, much effort has been focused on understanding the interactions between biomaterials and targets, contributing to the creation of advanced products with different biomedical applications [1]. Polymeric blends as well as the combination of different types of biomaterials

have been tried for the development of biosensors, scaffolds, implants, tissue engineering, wound healing, and sustained drug delivery [2].

The so-called DDS are technological devices that have been studied since 1959 to overcome the limitations of the traditional drug therapy [3]. DDS are composed of excipients such as inorganic, lipid, or polymeric origin (or their combination), used in the preparation of nanosystems (e.g., vesicles, micelles, nanocapsules, and nanospheres), microparticulates (e.g., microspheres and microemulsions), or dosage forms, such as films and hydrogels. Each carrier system has specific properties and can bind, encapsulate, adhere to, or adsorb active compounds such as genes or drugs [4]. Among the desirable features of DDS are nontoxicity, high drug upload, and targeting, thus reducing side effects in nontarget tissues, sustained delivery of therapeutic molecules, physicochemical stability, ability to protect drugs from degradation, sterilization, and large-scale production [3–5].

One of the first lipid-based DDS described in the literature were liposomes, in 1963, being to this day one of the most studied nanocarriers. The evolution and technological improvement led almost 30 years later to the development of solid lipid nanoparticles (SLN, in 1990) and nanostructured lipid carriers (NLC, in 2000), with greater stability and ability to efficiently encapsulate hydrophobic drugs than liposomes [6].

Among polymeric carriers, cyclodextrins (CD) have unique inclusion complex formation properties, even though their use as carriers (1997) was only described 100 years after their isolation [7]. In addition to CD, other polymeric carriers were later described, capable of forming micro- or nanoparticles (nanocapsules and nanospheres) that require the use of high amount of organic solvents in the preparation method [8]. However, many of these above-mentioned DDS systems may not provide specific properties such as adhesion, fixation, proper consistency, and viscosity; these properties are required for several administration routes, where preservation of the dosage form at the target site, permeation, and suitable mechanical properties are essential for the efficient delivery of active molecules. In this context, the use of nanocarriers systems combined with (bio)polymeric materials may overcome such limitations.

Thus, organic-organic biohybrid systems for sustained drug release emerged as a versatile strategy for the development of optimized formulations and dosage forms. Biohybrid materials are advanced systems that combine the properties of organic nanocarriers with the adhesiveness and biodegradability of (bio)polymers [9]. Within this context, this minireview aims to examine the main advances in biohybrid materials based on organic compounds for sustained drug release and provides a perspective to inspire their future developments.

2. Polymeric Matrices for Sustained Release of Active Molecules

When choosing the matrix in the development of a pharmaceutical form, properties such as versatility, biocompatibility, biodegradability, high drug retention capacity, and low cost should be considered. In this sense, for over 50 years, several types of polymeric materials have been used in biomedical applications [10]. The flexibility to design and select polymers with desirable characteristics ensures their use in a wide variety of applications. Compared to other types of biomaterials, polymers offer wide structural diversity and distinct properties [11]. Polymers used as matrices for sustained drug delivery may be synthetic, natural, or a combination of both. Synthetic polymers include aliphatic polyesters of hydroxy acids, such as polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), or polyvinyl acid (PVA). Among polymers of natural origin (biopolymers) are polypeptides, proteins (e.g., albumin, zein, fibrinogen, gelatin, and collagen), and polysaccharides (e.g., hyaluronic acid, alginate, pectin, and chitosan) [12–14].

In any case, and regardless of origin and chemical nature, the essential feature for a polymer to be used as a matrix in sustained drug release is its biocompatibility. This means that the polymer should not stimulate or cause any kind of allergic reaction or inflammatory response when in contact with living tissues or organic fluids [15]. In this sense, biodegradable polymeric matrices, known as biopolymers, are one of the most promising alternatives in the design of new sustained DDS. As they are biocompatible and biodegradable, the body through usual metabolic processes can excrete them. In addition, they are extremely versatile and can be processed in the most varied forms, such as films, beads, and foams [16, 17].

Among the most commonly used biopolymers in DDS, polysaccharides stand out for their abundance, structural diversity, versatility, desirable physicochemical properties, easy handling, and low cost. From the chemical point of view, polysaccharides combine large and distinct carbohydrates, which may be composed of a single kind of monosaccharide or two or more different monomeric units. The ability of polysaccharides to respond to different stimuli such as pH, temperature, ionic strength, and concentration makes them particularly attractive for the development of innovative delivery matrices. Additionally, polysaccharides can be functionalized, which gives them an overall positive or negative charge. The presence of such positively or negatively charged groups is extremely useful in preparing networks of stable gels through cross-linking reactions. Thus, polysaccharide networks can be obtained by cross-linking assisted by interactions of diverse forces (from weak physical forces to irreversible covalent bonds) [18].

In this perspective, chitosan, the second most abundant polysaccharide on the planet (after cellulose), is the only natural polysaccharide positively charged, obtained from the partial alkaline deacetylation of chitin. The level of chitosan deacetylation is a critical parameter in its ability to respond to stimuli. Chitosan-free amine groups are responsible for its sensitiveness to pH and for high affinity to mammalian cell components and bactericidal activity [15]. Such amine groups may interact with opposite charges of drugs, polymers, or cross-linking agents, such as glutaraldehyde, formaldehyde, genipin, or oxalic acid, used to prepare covalently cross-linked networks, or to either calcium phosphate, β-glycerophosphate, citrate, or tripolyphosphate, which are employed to generate ionically cross-linked

hydrogels [19–21]. Thus, studies simulating the gastrointestinal tract showed that chitosan networks present a typical swelling, which is related to the pH of the medium: high sensitivity in acid medium (high degree of swelling) and low sensitivity in neutral and alkaline medium (low degree of swelling). Such behavior is strategic in the development of dosage forms in which the drug of interest must be absorbed in acidic pH milieu, being quickly dispersed in the medium. This is the case, for example, of chitosan systems processed as films and cross-linked with different multivalent phosphates for the sustained delivery of riboflavin [22] or of chitosan microspheres cross-linked with glutaraldehyde or epichlorohydrin for release of sodium diclofenac [23]. Some studies have been reported for microspheres prepared from chitosan derivatives, such as malonylchitosan cross-linked with glutaraldehyde for the delivery of acyclovir in the treatment of infections caused by *Herpes zoster* virus strains [24].

However, in order to increase the resistance of chitosan-based systems to acidic pH, allowing the sustained drug delivery of interest into the digestive system, a commonly employed strategy is the combination of chitosan with other biopolymers that act as macromolecular cross-linking agents. Among them, the polysaccharide alginate was one of the first used in chitosan-based dosage blends. The alginate-chitosan blend is widely used as a drug carrier in the most varied designs and purposes [16]. In this sense, nitrofurantoin encapsulated in chitosan-calcium alginate microcapsules proved to have a better-sustained release profile than the antibiotic in pure chitosan particles [25]. The success of the association between these two polysaccharides is the result of a highly synergistic effect of polyelectrolyte-type interactions generated between the protonated amine groups of chitosan and the carboxyl groups of alginate. The combination of chitosan and alginate served as the inspiration for the development of new blends employing other biopolymers, such as glucomannan [26] or silk fibroin [27]. In the latter case, the carrier properties of the chitosan-silk fibroin systems as carriers of four model drugs (theophylline, sodium diclofenac, amoxicillin, and salicylic acid) were evaluated. *In vitro* delivery studies, performed at 37°C in buffer solutions at pH 2.0, 5.5, and 7.2, revealed that systems processed as films containing 80% chitosan delivered at pH 2.0 the maximum amount of all model drugs studied (~90%). For the pH that simulated the intestinal region (7.2), a sustained release profile was evidenced due to the amount of silk fibroin in the system's composition [27].

The combination of chitosan with synthetic polymeric matrices can be employed to increase the biocompatibility of these systems. Thus, drug delivery devices for gingival treatments were developed from the combination of chitosan with polyvinyl acid (PVA), polyethylene glycol (PEG), and polyvinylpyrrolidone (PVP) [28]. FTIR analyses and stress tests in materials processed as films indicated that chitosan-PEG and chitosan-PVP blends presented miscibility in all the studied proportions, while the chitosan-PVA blend only showed interaction at 50 : 50 and 80 : 20 ratios (chitosan : PVA). This study also suggested that chitosan blends possessed improved properties when compared to pure chitosan, being a promising alternative for oral mucosal DDS.

Another polysaccharide widely used as matrix in drug delivery systems is alginate, extracted from brown marine algae [29]. Unlike chitosan, this biomacromolecule has carboxylic functional groups, resulting in an overall negative charge. In this case, the usual method of forming alginate networks is to cross-link the gel with bivalent cations, such as Ca^{2+}, forming a three-dimensional structure known as egg box, which allows the processing of hydrogels as spun or microspheres, for example. However, for dosage forms to be administered orally, such calcium alginate cross-linked systems become sensitive in basic pH fluids, such as intestinal regions, where the alginate matrix tends to exhibit high swell ability, delivering the drug encapsulated in its matrix abruptly [30]. To overcome this drawback, different approaches have been employed to improve the properties of the alginate matrices in an attempt to prolong the rates of release profile, such as the use of other hydrophilic macromolecules able to establish ionic interactions with carboxyl groups, such as pectin, in order to create a coating that renders the alginate system more resistant for oral administration [31].

On the other hand, studies revealed that such matrices may present certain drawbacks such as high degree of swelling, low encapsulation efficiency, and high hydrophilicity [30]. An alternative proposed was the use of other biomacromolecules with reduced hydrophilicity or even insoluble in water. In such biopolymeric associations, the second biopolymer is incorporated into the alginate gel, forming a homogeneous blend with improved physicochemical properties compared to those of pure alginate matrix. In this sense, i*n vitro* studies have shown that the formation of a complex between alginate carboxyl groups and amine groups from zein (a hydrophobic protein) [32] made it possible to develop a prolonged release system of drugs in solutions that simulate intestinal fluid (pH 6.8 and 7.4) [33].

Less studied as DDS than polysaccharides, proteins are promising candidates for the development of innovative pharmaceutical systems. The literature reported that gelatin microparticles can serve as vehicles for the delivery of large bioactive molecules, while nanoparticles are more suitable for intravenous administration or drug delivery to the brain [34]. Gelatin hydrogels can encapsulate drugs of interest between the empty spaces formed by the biopolymer cross-linking, allowing these active molecules to diffuse into the bloodstream, such as the creation of bioinspired gelatin-based films, which incorporated antibiotic and analgesic drugs [34–36].

As exposed, the application of biopolymers in dosage forms is highly innovative, versatile, and extensive, since various polymeric combinations can be developed using the most distinct synthesis strategies. It is important to note that these systems may have limitations such as great affinity between the drug and the matrix, hindering the latter's delivery into the medium of interest, poor miscibility between biopolymers of distinct hydrophilicity, rendering the system heterogeneous and creating drug domains in the prepared device, and structural similarity, for example, in a polysaccharide blend, which makes it difficult to elucidate

Table 1: Blended polymers as pharmaceutical forms for DDS discussed here.

Polymeric blend	Form	Drug	Ref.
PLGA-PEG	Micelle	Doxorubicin	[4]
Chitosan-alginate	Beads	BSA	[16]
Chitin-Pluronic F108	Microparticles	Paclitaxel	[20]
Chitosan-gelatin	Hydrogel	Chloramphenicol	[22]
Chitosan-alginate	Microcapsules	Nitrofurantoin	[25]
Chitosan-glucomannan	Hydrogel	Ofloxacin	[26]
Chitosan-silk fibroin	Film	Theophylline	[27]
Chitosan-silk fibroin	Film	Sodium diclofenac	[27]
Chitosan-silk fibroin	Film	Amoxicillin	[27]
Chitosan-silk fibroin	Film	Salicylic acid	[27]
Alginate-gelatin	Film	Ciproflaxin	[29]
Alginate-zein	Beads	Ibuprofen	[32]
Chitosan-pectin	Beads	5-Aminosalicylate	[33]
PEG-gelatin	Nanoparticles	Ibuprofen	[34]
PEG-gelatin	Hydrogel	Ciproflaxin	[34]
PLGA-gelatin	Nanofiber	Fenbufen	[34]

details on the molecular interactions between them. Therefore, biopolymers can be applied as drug delivery matrices, conferring important physical and mechanical properties to the systems, and their major limitations may be circumvented when combined with other materials. Table 1 summarized the above-mentioned DDS based on blended polymers.

3. Biohybrid Sustained Release Systems

A challenging strategy is the development of complex systems able to combine the properties of different materials into a single formulation with optimized properties. Such systems self-organize synergistically and can be used for the most varied applications. Although the use of the synergism among materials may suggest an innovative field of research, such approach was already employed since Ancient Greece [1, 2]. An example of a hybrid system with synergistic properties is adobe, a building material composed of a mixture of clay and straw, used as an effective hybrid system in the manufacture of bricks and walls in arid regions throughout history. The addition of straw contributed significantly to preventing the formation of cracks in building structures, generating a system with superior properties by the synergism between the components [37]. There are also biohybrid systems perfectly engendered in nature, such as mother-of-pearl, formed by the interaction of calcium carbonate (aragonite) crystals strictly oriented with fibrous proteins (Lustrin A), which provides exceptional mechanical properties to the mineral. Mother-of-pearl is an inspiration for several hybrid devices of biomedical interest [9].

Organic-organic biohybrid systems have combined properties that offer many advantages compared to current DDS systems [38]. Different types of interactions such as hydrophobic, electrostatic, hydrogen bonds, donor-receptor, coordinating, and, less commonly, covalent interactions govern the molecular organization of these systems [39]. In all cases, the resulting materials must present biocompatibility and the ability to self-organize, maintaining a state of thermodynamic equilibrium [40].

3.1. Emulsions. An emulsion is a colloidal system consisting of two immiscible liquids that form small and dispersed droplets, mainly used as a strategy for the delivery of lipophilic molecules in the pharmaceutical and food industries [41]. They can be either oil-in-water (O/W) or water-in-oil (W/O) and are classified into five types: O/W or W/O microemulsions, with droplet size between 0.1 and 5 μm; nanoemulsions, with droplet size generally around 20–100 nm; micellar emulsions, with droplet size ranging from 5 to 50 nm; and double or multiple emulsions of the water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) types [41]. Despite these differences, a limitation of emulsions is the thermodynamic instability, which can result in cream formation, flocculation, coalescence, phase inversion, and "Ostwald ripening" [42]. The preparation of stable formulations requires the incorporation of emulsifiers, thickeners, gelling agents, and/or ripening inhibitors [43]. These agents stabilize the system and also confer other interesting features such as improved mechanical property. They are able to change in the final pharmaceutical form, as a biphasic gel, known as "emulgel," which is widely explored. Emulgel has an internal nonpolar liquid phase and a viscous matrix composing the continuous phase [43].

The emulgel development contributed to the preparation of novel biohybrid emulsions composed of organic excipients, combining suitable properties of all compounds. In the development of biohybrid emulsions, it is important to analyze the rheology properties and, consequently, the delivery kinetics of the compound of interest, which would be modified [44]. In general, an increase in viscosity causes a decrease in the rate of drug delivery [45]; it also affects the structural excipients organization in the final pharmaceutical form [46].

Jacobs et al. formulated emulsions modified of different concentrations of xanthan gum aiming at the delivery of acyclovir and ketoconazole for the treatment of epidermal fungal disorders [47]. Two different forms were produced from the same matrix: a cream with 0.5% (w/w) xanthan gum and emulgel with 1.5% (w/w) xanthan gum. The authors evaluated the physicochemical properties (viscosity, pH, mass loss, and particle size) for 6 months. In all the analyzed parameters, the formulations had better results than those shown by the commercial form analyzed, as in the viscosity measures over time, showing the advantages of the xanthan gum use in the biohybrid system. In addition, for such systems, the *in vitro* permeation through human skin (obtained from abdominal plastic surgery) was sustained up to 12 h, reaching deeper layers of the skin compared to the commercially available formulations. Wakhet et al. [48] studied the structural elucidation of hydrogel and emulgel formulations composed of agar and gelatin as the biopolymeric counterpart. X-ray diffraction (XRD) measurements confirmed the incorporation of the oil phase in the gel through the relative increase in its crystallinity, corroborated by Fourier Transform Infrared spectroscopy (FTIR-ATR) analysis, followed by the electrical

impedance and mechanical measurements, which were superior to those of the conventional hydrogel.

Thus, the development of biohybrid emulsions can be an interesting alternative to improve the delivery of drugs, with several options of composition, and may even improve some properties of the commercially available formulations. The great advantage of these systems is the ability to solubilize hydrophobic molecules with efficiency, improving the physicochemical stability with a sustained release profile of the therapeutic molecules.

3.2. Polymer-Protein Nanoparticles Formulations. The conjugation of a polymer with a protein results in a new biomacromolecule with different physicochemical properties. These changes are usually reflected in solubility, stability, *in vitro* activity, biodistribution, and pharmacokinetic and pharmacodynamic profiles, as well as immunogenicity and toxicity [49]. As therapeutic agents, peptides and proteins are generally covalently bound to polymers to form peptide/protein-polymer conjugates. Such systems have been widely studied as possible devices for drug delivery over the last decades [50].

The first polymer-protein complex was reported in 1970 when polyethylene glycol (PEG) was conjugated with bovine serum albumin (BSA) [51], opening way for a new field of study for proteins. US Food and Drug Administration (FDA) approved the first PEG-protein conjugate for routine clinical use in the early 1980s. PEG-adenosine deaminase (Adagen®) [52] is currently used for the treatment of the severe immunodeficiency associated diseases and PEG-asparaginase (Oncaspar®) [53] is applied in the treatment of acute lymphoblastic leukemia [54]. Conventionally, polymers are conjugated with proteins in the lysine or cysteine domains. Normally, the protein acts as an active component, while the polymer plays the role of carrier, targeting moiety or having cofunctional groups [49]. As mentioned, proteins are versatile biopolymers and their functional properties depend on their amino acid composition, besides several functional groups (-NH_2, -COOH, and -SH), which may be used for covalent and noncovalent bonds with other molecules of interest. So far, only linear polymers such as PEG, polysaccharides (e.g., dextran), polyglutamic acid, N-(2-hydroxypropyl) methacrylamide acid, and their copolymers have been clinically explored [50]. Covalent conjugation strategies are often used in reactions of amine groups with carboxylic acid, via carbodiimide, or amine-aldehyde addition-elimination reactions, leading to nonselective conjugations and thiol-ene and azide-alkyne click reactions, which cause stereospecific conjugations. Noncovalent conjugations have been used as a "layer-by-layer" strategy, usually through electrostatic interactions, hydrophobic attractions, or highly selective bioaffinity bonds. Although it is common for conjugated proteins to lose their biological activity after nonspecific covalent conjugation with polymer particles, noncovalent conjugation strategies using electrostatic interactions can be adopted, which do not affect the biological activity of the native protein [55].

The work by Ge et al. [56] reported a new DDS based on self-assembled nanoparticles of BSA conjugated with polymethyl methacrylate (PMMA). PMMA is a thermoplastic material approved by FDA for medical applications. Uniform spherical nanoparticles with BSA-PMMA core and layers were prepared by precipitation to encapsulate camptothecin. The camptothecin-loaded BSA-PMMA nanoparticles showed antitumor activity improvement in both *in vitro* and *in vivo* studies, reducing the tumor growth around 79%, being more effective than free drug. Zhang et al. described another biohybrid polymer-protein system as a delivery vector for nonviral genes [57]. Nanoparticles of BSA-poly(dimethylamino)ethyl methacrylate (nBSA) were synthesized by *in situ* polymerization, with BSA as the macroinitiator. The size and surface charge of the hybrid nanoparticles (polyplexes) were controlled by modulation of the polymerization time. It was postulated that the delivery of these complexes to the cells would be facilitated by the positive charge on the surface of the polyplexes. The ability of nBSA to mediate nonviral gene delivery to cells was studied and compared to that of traditional cationic polymers, that is, polyethylenimine (PEI) and poly(2-(dimethylamino)ethyl methacrylate) (PDMA), linear and branched. The nBSA/pDNA conjugates were able to transfer genes to cells with similar or improved efficiency compared to the PEI and PDMA polymers. It is believed that the use of polymer-protein conjugates for gene delivery provides additional biofunctionality to the systems [57].

Saarai et al. [58] tested a polymer-protein nanoparticles system consisting of diblock copolymers composed of elastin-like polypeptides (ELP) bonded to FKBP12 (intracellular protein) to deliver a potent immunosuppressant, rapamycin (Rapa), and evaluated its effects on lacrimal gland inflammation in nonobese diabetic (NOD) rats. The formulations were characterized regarding purity, hydrodynamic diameter, encapsulation, and drug delivery. The dosage form associated with Rapa was successful, with a half-life five times longer (62.5 h) than the free drug. When administered by injection in NOD, the formulations significantly suppressed lymphocytic infiltration in the lacrimal gland compared to the control group, while reducing toxicity, proving to be a promising tool for the delivery of Rapa in the treatment of Sjögren's syndrome.

3.3. Cyclodextrins. Since 1970, biotechnological advances allowed the purification and production of cyclodextrins to be applied as pharmaceutical excipients [59]. Cyclodextrins (CD) are cyclic oligosaccharides composed of glucopyranose units, joined by 1.4 alpha linkages [60]. CD are capable of interacting noncovalently with a wide variety of lipophilic and hydrophilic molecules by forming molecular inclusion complexes in the inner (nonpolar) cavity of their macrocyclic ring or through hydrogen interactions with the hydroxyls of their outer (polar) surface [61]. Natural CD (α, β, γ, with six, seven, and eight units of glucopyranose, resp.) underwent chemical modifications, producing even more soluble and less toxic derivatives, such as hydroxypropyl-β-CD, sulfobutyl ether-β-CD, and methyl-β-CD, the first two cited as inactive pharmaceutical ingredients by the FDA. There are currently more than 35 CD-based products commercially available [62].

CD/polymer biohybrid systems were synthesized to obtain more biocompatible and multifunctional formulations. The CD are covalently linked to the backbone chain or conjugated with the side groups of polymers. When CD are synthesized by charged functional monomers, electrostatic interactions may occur, allowing the spontaneous formation of nanospheres, nanogels, and nanocapsules [63]. El Fagui et al. described the development of CD (hydrophilic)-PLA (hydrophobic) nanoparticulated biohybrid systems. Structural characterization by NMR (nuclear magnetic resonance) and small-angle X-ray scattering (SAXS) demonstrated that the CD coated the PLA nanoparticles by absorption, protecting their hydrophobic core which modified the physicochemical properties of the PLA nanoparticles, opening the possibility for future conjugations [64]. Another interesting possibility is the incorporation of CD in hydrogels matrices, stabilizing the inclusion complexes formed by CD in their hydrophilic network. In addition, the presence of CD optimizes mechanical properties, makes the system sensitive to physiological stimuli, and allows the sustained delivery of drugs [65].

Zhou et al. described the creation of an injectable thermosensitive gel composed of chitosan and β-CD, which presented a lamellar structure with fractal characteristics and showed a prolonged release profile for Aspirin®. It was evidenced that the presence of CD in the system modulated the drug release profile, delivering around 50% after 24 h [66]. McCormack and Gregoriadis were the first to propose the encapsulation of drug-CD inclusion complex by liposomes, improving its ability to encapsulate hydrophobic drugs with success. Thus, the complex formed was encapsulated in the internal aqueous medium of the liposomes, which maintained the integrity of the lipid bilayer after inclusion of CD. Therefore, this approach has been widely explored as DDS [67]. Recently, Sharma et al. developed a CD-liposome inclusion complex with improved physicochemical stability for the transdermal delivery of aceclofenac (ACE), an anti-inflammatory drug indicated for the osteoarthritis treatment. The drug was previously conjugated with a β-CD and the resulting compound was encapsulated by multivesicular liposomes. FTIR analysis suggested that Van der Waals interactions governed the ACE-β-CD system, as well as this complex conjugated to liposomes. The resulting material was further incorporated in a polymeric matrix and processed as a gel, which presented better *in vitro* permeation (through mouse skin) compared to the control group, being a promising candidate for the treatment of osteoarthritis [68].

3.4. Liposomes. Liposomes are composed of lipid bilayers, in which amphiphilic phospholipids carry a hydrophilic group (head) and two hydrophobic acyl chains (tail) [69]. In these lipid vesicles, formed by the hydrophobic effect to maximize the interaction between the acyl chains, protecting them from the contact with the aqueous medium, the hydrophobic tails turn towards the inside of the lamella and the polar heads are exposed outward, in contact with water [69]. Due to the presence of an aqueous compartment and lipid bilayers, liposomes can incorporate hydrophilic and hydrophobic molecules, which is quite interesting for a drug carrier [70]. Several advances are required for liposomes to be clinically applied, given their short half-life and low physicochemical stability [71]. One of the strategies to improve these limitations is the association of liposomes with other drug delivery systems, usually polymers, forming the liposome-based biohybrid systems.

To improve the stability and half-life of liposomes in the bloodstream, a hydrophilic polymer is commonly used, usually PEG, covalently bound to a phospholipid, for example, phosphatidylethanolamine (PE). In these so-called stealth liposomes, even containing a low molar fraction of PEG-PE (usually 5%), the surface of the liposomes is coated by PEG, creating a steric hindrance that reduces the absorption of plasma protein and, consequently, the metabolism [72]. This strategy has been widely used to produce stealth liposome with the particle size in the range of 100 nm. Abe et al. evaluated, by NMR, the molecular state of PEG on the surface of liposomes composed of DSPC (distearoyl-3-phosphatidylcholine), finding that the PEG chain's flexibility depends on its molecular weight and lipid composition [73]. However, extensive PEGylation can also cause inhibition of cellular uptake, which is not desired for the cancer treatment. Pozzi et al. reported by SAXS that phase separation on liposome can occur due to PEG. Thus, they developed a moderated PEGylated (size 2 K) multicomponent liposome that hindered protein adsorption but still presented high cellular uptake in cancer cells [74]. Therefore, all of these studies were relevant for the development of efficient biohybrid liposomal pharmaceutical forms, contributing to the elucidation of their performance in the bloodstream [75, 76].

Another interesting approach was the combination of liposomes with (bio)polymers as matrices for hydrogels preparation. The association of liposomes of different charges (negative, neutral, and positive) with a chitosan hydrogel was evaluated. Using rhodamine as a model molecule, fluorescence experiments revealed its *in vitro* delivery profile from the hybrid system. The hydrogel containing anionic liposomes showed a burst release of rhodamine, probably because the positive charges of chitosan destabilized the anionic liposomal membrane, which was able to increase the rhodamine delivery. The neutral liposomes/chitosan preparation presented a more sustained delivery profile than the anionic liposomes. On the other hand, the cationic liposomes/chitosan preparation, in turn, presented the most sustained rhodamine profile of all liposomal hydrogels tested. The positive charges of the phospholipids and chitosan chains probably were repelled, preserving the integrity of the lipid bilayer [77]. Another study developed a liposomal thermosensitive hydrogel for the delivery of doxorubicin. In these forms, besides the *in vitro* sustained delivery profile, a decrease in *in vivo* toxicity was observed [78]. On the other hand, Caddeo et al. showed the use of chitosan as coating for liposomes containing quercetin. The formulation was able to modulate the quercetin release profile according to the pH, increasing the bioavailability of the encapsulated drug. Chitosan was able to protect quercetin-loaded liposomes and provide special resistance to acidic environments, such as that found in gastric environment [79].

Liposomes can also be used to target active molecules to specific sites, such as tumors. The incorporation of different ligands, such as monoclonal antibodies, peptides, growth factors, or integrin, improves the specificity in the drug release. Protein-coated liposomes are considered promising in comparison to conventional liposomes. Different forces such as electrostatic interactions, or even more specific such as receptor-ligand interactions, will determine the biohybrid system interaction with the plasma membrane of cells. A biohybrid system composed of liposomes and specific proteins (MCF-7) for the transport of DOX through the blood-brain barrier (BBB) was recently described. Through covalent interactions between the liposomal lipid and protein, the system was proven to be effective in overcoming BBB, showed a sustained delivery profile, and was able to kill tumor cells *in vitro* [80].

3.5. Innovative Hybrid Lipid Nanoparticles: Solid Lipid Nanoparticles (SLN), Nanostructured Lipid Carriers (NLC), Lipospheres, and Lipid Nanocapsules. Lipid nanoparticles are innovative nanocarriers that have been studied since 1990, representing a progress in the physicochemical stability of the lipid-based formulations and the encapsulation of hydrophobic molecules. Solid lipid nanoparticles (SLN), the first generation of these systems, are composed of solid lipids (core) at room temperature, surfactant, and water. Nanostructured lipid carriers (NLC) are the second generation, having as the lipid phase a blend of one or more solid and liquid lipids at room temperature [81]. Both systems still present some disadvantages, such as a possible expulsion of the drug over time (SLN) and low capacity to encapsulate hydrophilic molecules [82] due to limited thermodynamic interactions between the hydrophilic and hydrophobic interfaces of the drug and the lipid nanoparticle, respectively [83].

An important strategy employed to minimize such limitations of SLN and NLC is their hybridization with other classes of biomaterials, mainly polymers. The electrostatic and hydrogen interactions among the excipients thus provide biohybrid systems with improved properties, such as the delivery profile of active molecules increasing plasma half-life [83], permeation [84], and efficacy [85]. Furthermore, this combination of materials can be used to modulate viscosity, consistency, and mucoadhesion of lipid nanoparticles [86] or to add thermoreversible properties to the systems [87, 88].

Pandit and Dash [88] modified the surface of SLN systems in order to improve the encapsulation of the hydrophilic antineoplastic ifosfamide (IFO), indicated for the treatment of soft tissue sarcoma, for oral administration. The formulations were composed of glycerol monooleate, oleic acid (surfactant), and cross-linked chitosan. Despite the low encapsulation efficiency of IFO (~10%), the biohybrid SLN showed an *in vitro* sustained drug delivery profile up to 60 h. The system was able to protect drug against degradation in acidic environments, demonstrating the benefits of using hybrid systems in a single dosage form.

Biohybrid hydrogels (Figure 1) have been widely employed in association with SLN for topical applications. Among the most commonly used polymeric matrices are

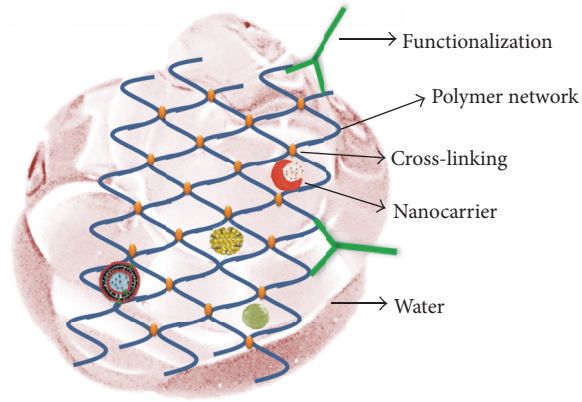

Figure 1: Hydrogels are semisolid pharmaceutical forms composed mostly of water, tridimensional polymeric network, and cross-linked chains. Their hybridization process allows incorporating other functional groups, drug-loaded nanocarriers, and triggers, improving the DDS performance.

Carbopol [89, 90], alginate [91], and dextran [92]. Hao et al. [93] developed a thermosensitive biohybrid hydrogel composed of poloxamer to improve the ophthalmic drug delivery. The hydrogel gelled only in contact with the ocular mucosa, improving adhesion and permeation of the Chinese phytochemical resin, known as "Dragon's blood." The SLN with particle size around 150 nm showed an abrupt increase when incorporated in the hydrogel (~450 nm) due to the adsorption of poloxamer portions on the surface of the nanoparticles. The biohybrid hydrogels improved the stability of the drug and increased mucoadhesion and penetration capacity in the cornea when *in vitro* evaluated. The evaluation of transcorneal mechanism across the cornea was performed in rabbits, showing that the system allowed a prolonged residence time and reduced the systemic side effect. On the other hand, Hazzah et al. [86] developed biohybrid sponges based on hydroxypropyl methylcellulose (HPMC) and polycarbophil as polymeric matrices, incorporating curcumin-loaded SLN for oral mucosal administration. The resulting materials showed a sustained delivery profile of curcumin and excellent mucoadhesion properties evaluated in five adult healthy volunteers.

The incorporation of polyelectrolytes on the surface of nanoparticles is also a strategy to improve stability and optimize targeting. Doktorovová et al. [94] developed PEGylated-based NLC through the blend between Precirol (solid lipid) and a PEGylated liquid lipid (Labrasol) for the sustained delivery of fluticasone propionate in dermatology. The nanoparticles showed excellent encapsulation efficiency (95%) and physicochemical stability (60 days), stored at room temperature. The crystallinity and polymorphism of the compounds were analyzed by wide-angle X-ray scattering (WAXS) and DSC, which showed that although the formulations presented a lower melting point than pure Precirol (63°C), the nanoparticles were in solid state at room temperature, with a melting point above 50°C, as required for biological applications.

Devkar et al. [95] developed a biohybrid NLC based on glycerol monostearate and Capryol 90 as the lipid matrix,

stabilized with soy lecithin and poloxamer and superficially modified by the natural *Delonix regia* gum, combining mucoadhesive properties to the system. The hybrid system was intended for intranasal delivery of ondansetron and showed *ca.* 44% encapsulation efficiency. Mucoadhesive properties were achieved and the drug efficiently reached the target site (brain) with a sustained release profile, as observed by *in vivo* biodistribution assay, showing higher drug concentration in the brain than the plasma compared to intravenous route. Wong et al. described polymer-lipid hybrid nanoparticle systems composed of SLN and soybean-based anionic polymer, which efficiently loaded doxorubicin (~50%) and improved the toxicity against human breast cancer cells [96]. Li and coworkers designed polymer-lipid hybrid nanoparticles based on SLN and dextran sulfate sodium as a polymeric counterpart to complex the ionized verapamil. The structural characterization suggested that verapamil was in the amorphous form into SLN, further corroborated by the high encapsulation efficiency (~88%), when the lipid : drug ratio in the hybrid was 1 : 1 (w/w) [97].

Rose et al. [87] developed optimized lipid-polymer nanoparticles composed of PLGA electrostatically modified with dimethyl octadecyl ammonium as cationic surfactant and conjugated with a complex formed between the glycolipid trehalose dibehenate and PVA. This formulation aimed to act as an immunopotentiator to modify cellular and humoral immunity by antibodies and Th1/Th17 responses, proposed as adjuvant in topical vaccine, improving the specificity of the system against many bacterial pathogens of the oral mucosa. The main force that governed its molecular arrangement was the electrostatic interaction between the quaternary ammonium group of dimethyl octadecyl ammonium and the negatively charged PLGA-PVA polymer conjugate. The lipid polymer nanoparticles were able to stimulate immune response, acting as efficient adjuvants, as demonstrated by *in vivo* mice immunization model.

On the other hand, lipospheres are drug upload systems composed of an oily solid core (triglycerides) [98], in which a hydrophobic drug may be dissolved or dispersed, stabilized by a monolayer of phospholipid molecules that cover its surface [99]. These systems were developed for the delivery of bioactive compounds by parenteral and topical routes, exhibiting a great *in vivo* anti-inflammatory effect by piroxicam-loaded lipospheres [100]. They consist of solid microparticles with sizes between 0.2 and 100 μm [101]. Their advantages over other DDS (emulsions, liposomes, and polymer nanoparticles) include physical stability, being easy to disperse in aqueous medium, simple preparation, high retention of hydrophobic drugs in the core, and prolonged delivery [102]. Lipospheres have been used for the delivery of several classes of drugs, such as local anesthetics [99], anti-inflammatories [100], antineoplastic [101], immunosuppressant [102], hypoglycemic agents [103], antimalarial agents [104], and antihypertensive agents [105].

Lipospheres are usually associated with other types of carrier systems, such as cyclodextrins or polymeric matrices. These biohybrid systems aim to potentiate the lipospheres' properties and/or modulate drug delivery. An example is the incorporation of butyl methoxydibenzoylmethane (BMDBM)/hydroxypropyl-β-cyclodextrin (HP-β-CD) complex into lipospheres, aiming to increase the effect and photostability of the sunscreen agent. DSC analysis revealed that the endothermic peak of the pure drug disappeared in the liposphere-BMDBM/HP-β-CD sample. Such thermal behavior suggested that the drug was dispersed in the liposphere core, in an amorphous state, which explained the sustained drug release, as well as the increase in photostability achieved [106]. In another study, Ma et al. [107] developed a biohybrid system based on PLGA copolymer conjugated with the liposphere core for the delivery BSA for oral administration. The lipospheres exhibited spherical morphology with PLGA hydrophobic core delimited by a weak ring, suggesting that the lipid layer was on its surface, as shown by scanning electron microscopy. This system, compared to conventional PLGA microspheres, showed better uploading of BSA (~ 91%) and a sustained delivery profile. The biohybrid system improved the protein delivery capacity as well as its bioavailability, being potentially useful for oral administration.

Lastly, lipid nanocapsules are further bioinspired hybrid nanocarriers, composed of a triglycerides core delimited by a polymeric shell, stabilized by surfactants and/or cosurfactants, and obtained by thermal inversion [108]. Recently, Jones et al. developed lipid nanocapsules functionalized with cytotoxic T-cells (CTLs) as mediator of antigen recognition-triggered drug release. In an *in vivo* model of HIV infection (mice), the nanocapsules were able to detect immunosuppressed cells with a sustained interleukin-15 (IL-15) release at the HIV-specific site [109]. Kim et al. proposed a treatment for non-small cell lung cancer, based on the release of erlotinib encapsulated by PEGylated polypeptide-lipid nanocapsules. The nanocapsules were biocompatible with particle size lower than 200 nm and a monodisperse distribution. The PEG covering exerted a protective role, acting as a molecular barrier that prolonged the erlotinib release in the acidic target medium. The lipid nanocapsules were found cytotoxic for NCI-H358 and HCC-827 lung cancer cells. The efficacy was evaluated in mice by a tumor regression profile model, showing an improved therapeutic action for the hybrid lipid nanocapsules in comparison with free drug, being a promise for the treatment of lung cancer [110]. Antonow et al. described lipid nanocapsules loaded doxorubicin to study the *in vitro* antiproliferative property and determine the nanocapsules uptake by MCF-7 cells. The nanocapsules' particle size was *ca.* 200 nm and a high antiproliferative capacity (>90%) was observed. These systems were cytotoxic for MCF-7 cell exhibiting a sustained effect evaluated for 72 h [111]. Quercetin lipid nanocapsules for dermatological uses were prepared by phase inversion method. The formulations presented particle size around 50 nm, high encapsulation efficiency, and antioxidant activity (92%) *in vitro*, with a sustained release profile over 24 h, being stable for 28 days at room temperature [112]. While lipid nanocapsules appear as a novel hybrid-based approach with great potential as DDS, allowing for small-sized (<100 nm) nanoparticles' preparation, cytotoxic issues related to their high surfactant content are still pending. Figure 2 compares the structure of some types of traditional DDS and the respective hybrid systems. Table 2 shows relevant information of main published works

Table 2: Main published works regarding biohybrid systems for sustained drug delivery, listed in terms of kind, activity, and encapsulation efficiency (EE%).

Biohybrid system	Therapeutic molecule	EE%	Ref.
NE-alginate/chitosan	Capsaicin	68.0%	[44]
Emulgel-jojoba oil/HPMC	Clotrimazole	—	[46]
Emulgel-xanthan gum	Acyclovir and ketoconazole	—	[47]
Emulgel-lecithin soy	Ketoprofen	—	[113]
Nanogel-agar	Sodium diclofenac	—	[48]
Emulgel-CMC	Sodium diclofenac	—	[114]
Emulgel-gelatin	Metronidazole	—	[45]
Poly(SMA)-neocarzinostatin	Neocarzinostatin	—	[115]
PEG-DNA	DNA	—	[52]
PEG-streptavidin	Streptavidin	—	[116]
PEG-L-asparaginase	L-Asparaginase	—	[53]
PEG-streptavidin	Streptavidin	—	[117]
PDMA-BSA	DNA	—	[57]
PMMA-BSA	Camptothecin	11.0%	[56]
ELP-FKBP	Rapamycin	—	[58]
Liposome-chitosan	Doxorubicin	98.0 %	[78]
Liposome-cellulose	Quercetin	40.0%	[77]
Liposome-cellulose	Rutin	58.0%	[77]
Liposome-gel	Lidocaine	21.6%	[118]
Liposome-gel	Bupivacaine	98.8%	[119]
Liposome-alginate	Benzocaine	63.2%	[120]
Liposome-PEG	Lidocaine	98.8%	[73]
Cyclodextrin/liposome	Quercetin	91.0%	[121]
Cyclodextrin/liposome	Tretinoin	88.7%	[122]
Cyclodextrin/liposome	Curcumin	50.0%	[123]
Cyclodextrin/PLGA	Oxaprozin	62.0%	[124]
SLN-PLGA-PEG-PLGA	2-Methoxyestradiol	91.3%	[125]
SLN-hydrogel	Natural resin	—	[93]
SLN-polycarbophil	Curcumin	88.1%	[86]
SLN-B_{12} vitamin	Insulin	55.9%	[85]
SLN-chitosan	Amphotericin B	88.5%	[126]
SLN-PLGA	Flurbiprofen	91.7%	[127]
SLN-dicetyl phosphate	Retinyl palmitate	99.1%	[128]
SLN-PEG	EGFP Plasmid	89.0%	[129]
SLN-PEG	Paclitaxel	11.0%	[130]
SLN-PEG	Salbutamol sulphate	30.0%	[131]
SLN-PEG	Noscapine	83.6%	[84]
SLN-chitosan	Carbamazepine	66.7%	[132]
SLN-chitosan	Ifosfamide	—	[89]
SLN-dextran	Ibuprofen	99.1%	[133]
SLN-chitosan	Tretinoin	99.6%	[134]
SLN-PLGA	DNA	93.1%	[135]
NLC-natural gum *(D. regia)*	Ondansetron	29.9%	[95]
NLC-PEG	Fluticasone propionate	97.0%	[94]
NLC-peptides	Docetaxel	77.5%	[136]
NLC-PEG	Biochanin A	99.0%	[137]
NLC-chitosan	Curcumin	96.6%	[138]
NLC-chitosan	Fubiprofen	97.5%	[139]
Lipospheres-β-CD	Butyl methoxydibenzoylmethane	85.0%	[106]
Lipospheres-β-CD	Rifampicin	—	[140]
Lipospheres-PLGA	Albumin	90.8%	[107]
Lipospheres-PLGA	Donepezil hydrochloride	—	[141]
Lipospheres-PEG	Ceftriaxone	60.1%	[142]
Lipospheres-PEG	Gentamicin	85.0%	[143]
Lipid nanocapsules	Interleukin-15 (IL-15)	—	[109]
Lipid nanocapsules	Erlotinib	90.0%	[110]
Lipid nanocapsules	Doxorubicin	90.0%	[111]
Lipid nanocapsules	Quercetin	92.0%	[112]

related to biohybrid systems for sustained delivery of therapeutic molecules.

4. *In Vivo* Performance of Biohybrid Polymer-Based Hybrid DDS

The polymer-based hybrid systems' development has been exponentially increased in the last years. However, most of the publications noticed the *in vitro* performance of such materials in addition to their structural elucidation. This theoretical approach is fundamental to guarantee their success and physicochemical stability. Therefore, multidisciplinary efforts are necessary to precisely evaluate the efficacy, bioavailability, and pharmacokinetics of these multipurpose systems, considering that there is a lack of animal models for testing different DDS for specific applications [144].

In general, we observed advantages of such hybrid systems over their respective traditional DDS, which significantly improved the *in vivo* pharmacokinetics and the activity of several classes of drugs [67, 72, 100, 104, 118, 119, 128]. As in the case of protein nanoparticles, where polymer-protein conjugates for gene delivery provided biofunctionality to the systems [57], other formulations reduced *in vivo* tumor growth [56]; and the anti-inflammatory activity five times higher than the traditional protein nanoparticle was noticed [58]. Regarding the hybrid lipid-based DDS, the outlook is exciting. The well-known stealth liposomes commonly hybridized with PEG were able to improve the *in vivo* short half-life [71] and the low bloodstream stability [72] of pure liposomes in mice. The decrease of *in vivo* chemotherapeutics toxicity was noticed for liposomes in gel [78]. With respect to hybrid lipid nanocapsules, a sustained interleukin-15 (IL-15) release at the HIV-specific site in an HIV infection

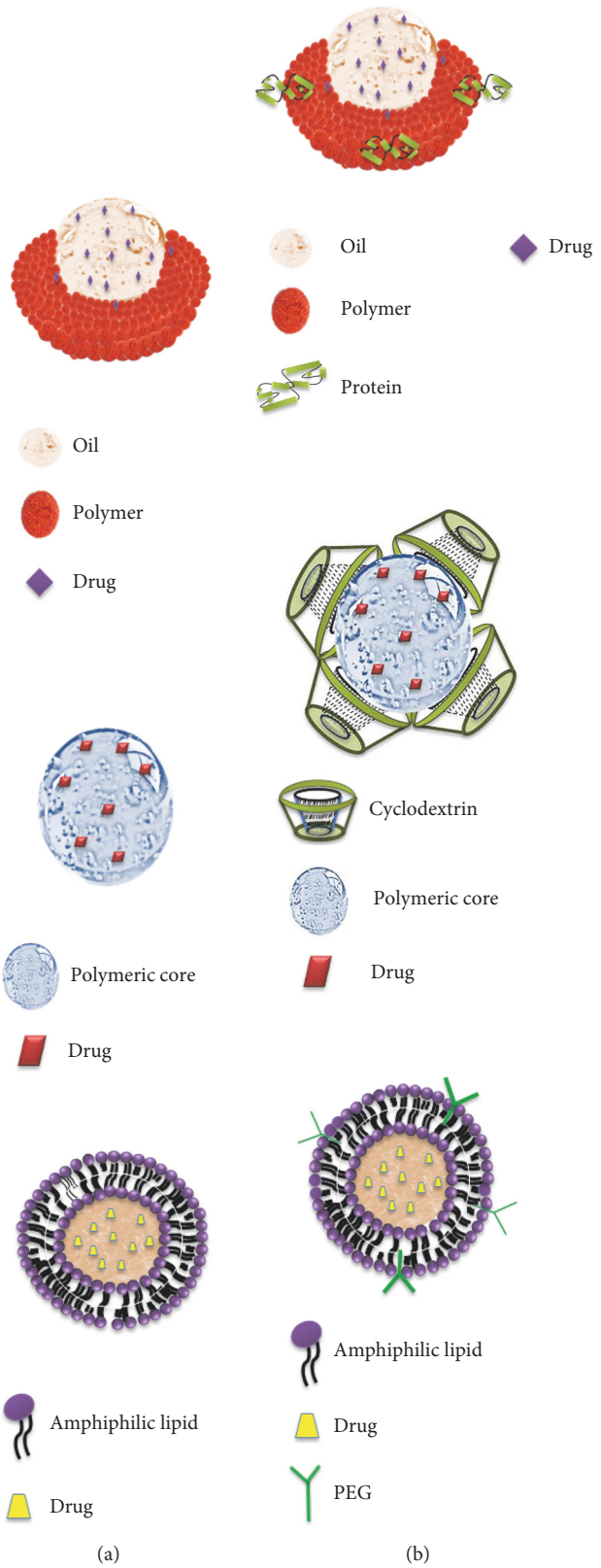

Figure 2: Schematic representation of some traditional nanocarriers' structures (a) and their respective organic biohybrid systems (b).

model in mice was provided [109]. A promising hybrid-based lipid nanocapsule was described for the treatment of lung cancer, which described the *in vivo* (mice) tumor regression profile [110]. *In vivo* pharmacokinetics studies in rats demonstrated higher bioavailability of hybrid artesunate-loaded lipospheres when compared to the commercial tablet for malaria treatment [104]. Different *in vivo* studies were described for SLN- and NLC-based hybrid systems for topical and parenteral applications, using mice, rat, and rabbit, as well as in human clinical trial, which demonstrated the effectiveness, nontoxicity, and bioavailability of these biodevices compared to their respective traditional DDS or free drug [86, 88, 94, 96].

5. Perspectives

It is utopian to expect that a single nanosystem will accomplish all drug delivery demands. Despite the progress in pharmaceutical nanotechnology, all current DDS present advantages and limitations for its clinical use. The DDS composed of biopolymers as single component can exhibit undesirable mechanical properties and do not have the advantages of drug encapsulation. On the other hand, despite the capability of encapsulation of hydrophilic molecules, protein nanoparticles and liposomes can present low physicochemical stability, as also occurs in the emulsions, affecting their therapeutic properties. SLN and NLC present long-term stability and low encapsulation efficiency of hydrophilic molecules. CD and all the colloidal formulations cannot be applied for topical routes with success, due to undesirable adhesion, spreadability, and viscosity, which are advantages of the emulsions and polymeric systems. Finally, CD and liposomal systems are able to incorporate both hydrophilic and hydrophobic molecules in their structure. Considering that there is no perfect DDS system, a deep understanding of the structural, physicochemical, and biological properties of the route and drug is necessary, making the choice of the appropriate device possible.

Therefore, the strategic association of different organic biomaterials combines suitable intrinsic properties of each component in a single DDS. The organic-organic biohybrid systems represent important advances in drug delivery field, such as efficient encapsulation of hydrophilic molecules by SLN and NLC formulations; improved mechanical (emulsions), adhesion (colloidal formulations and CD), and physicochemical properties (emulsions, liposomes, and protein nanoparticles); functionalization of protein and lipid nanocarriers enhancing target specificity and cancer cells cytotoxicity; improved protein bioavailability for oral administration; multiple therapeutic properties in a single system; and better *in vivo* performance than the most of conventional DDS.

The use of (bio)polymeric excipients in biohybrid systems development is especially relevant due to its diversity, abundance, low cost, and biocompatibility. These versatile materials have several uses, such as surface modifiers, complexing agents, stimulus-response dependence, and matrices for solid pharmaceutical forms that improve mechanical, adhesion, and permeation properties of the nanocarriers. This class of biohybrid systems (organic-organic) deserves attention, considering the ability to interact with ability to interact with site of interest, predicting and controlling the DDS performance when in contact with the target, solving several limitations of traditional DDS.

There are several hybridization processes of DDS currently employed to improve the nanocarrier specificity to the targets. Changes in the global charge of the traditional nanocarriers by superficial functionalization or thiomerization provide hybrid smart drug delivery systems, which are able to electrostatically interact with the different mucosal tissues, fixing them at the desired site. Moreover, molecular designed polymer-based hybrid DDS can combine several stimuli-dependent effects in a single biodevice, such as pH and temperature, which should be specific to the action site, as a tumor tissue. Therefore, a multidisciplinary point of view is mandatory to understand the particularities of the target, carrier, and therapeutic molecules, linking physical, chemical, and biological aspects to design creative and efficient systems to improve the efficacy and stability of delivered drugs.

However, despite the excellent performance in the *in vitro* and *in vivo* assays, the human trials of these creative DDS are still scarce, which hinders the market arrival of the biohybrid nanocarriers systems. Along with that, the regulatory issues of the excipients safety as well as their conjugation in a single nanostructured biodevice are not fully established, contributing to the delay in commercial availability of these promising DDS. Moreover, the long-term consequences of nanostructured systems as DDS in the environment have not been fully elucidated yet.

6. Conclusions

The development of biohybrid advanced materials for sustained release has been widely described over the last years. However, a thorough review of these findings is not yet available in the literature. Characteristically, a synergistic interaction among the components, combining the advantages of each raw material, governed the molecular organization of these systems. Different systems have been efficiently prepared, which combine different classes of organic excipients, such as polymer, protein, and lipid, yielding formulations or pharmaceutical forms with several advantages, such as dynamic interaction with targets, enhancing their performance. This work revised the biohybrid DDS, elucidating their advantages and limitations, contributing to further study of creative, molecularly planned, and safe biohybrid systems as advanced materials for the sustained release of active molecules. These systems showed exciting *in vitro* and *in vivo* results, being a promise for the delivery of many drugs for different routes. This work also directed efforts to inspire new research with this innovator multidisciplinary approach.

Abbreviations

BMDBM: Butyl methoxydibenzoylmethane
BSA: Bovine serum albumin
CD: Cyclodextrin

CMC: Carboxymethyl cellulose
DDS: Drug delivery systems
DOX: Doxorubicin
DSC: Differential scanning calorimetry
ELP: Elastomer-like proteins/polypeptides
FKBP12: Protein receptor for rapamycin
FTIR: Fourier Transform Infrared spectroscopy
HA: Hyaluronic acid
NLC: Nanostructured lipid carriers
NMR: Nuclear magnetic resonance
PEG: Polyethylene glycol
PEI: Polyethylenimine
PLA: Polylactide
PLGA: Polylactide-co-glycolide
PDMA: Poly(dimethylamino)ethyl methacrylate
PMMA: Polymethyl methacrylate
PVA: Polyvinyl acid
PVP: Polyvinylpyrrolidone
Ref.: References
SLN: Solid lipid nanoparticles
XRD: X-ray diffraction.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

All the authors contributed equally to this work.

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