Dextrin

Catarina Gonçalves
Center of Biological Engineering (CBE), University of Minho, Braga, Portugal

Susana M. Moreira
Vera Carvalho
Dina M. Silva
Institute for Biotechnology and Bioengineering (IBB), Center for Biological Engineering, University of Minho, Braga, Portugal

Miguel Gama
Center of Biological Engineering (CBE), University of Minho, Braga, Portugal

Abstract
Dextrins are low-molecular-weight carbohydrates produced by partial hydrolysis of glycogen or starch achieved by applying dry heat under acidic conditions (pyrolysis or roasting) and/or using enzymes (amylases), malting or mashing. Dextrin is thus a glucose-containing saccharide polymer having the same general formula of starch, but smaller and less complex. Depending on the source and on how it is digested, it can exhibit different structural features (linear, branched, or cyclic) and properties such as hygroscopicity, fermentability, sweetness, stability, gelation, solubility, bioavailability, and molecular compositions. Among starch-derived materials, dextrin is widely used in a variety of applications, namely, adhesives in the manufacture of gummed tapes, textiles and paper, as moisturizing component in cosmetics, or in the food industry. However, its biocompatibility and biodegradability combined with its low cost, abundance, and availability in medical grade make dextrin an excellent polymer for biomedical applications. In this entry, we present an overview of biomedical applications of linear dextrins. The potential of dextrin as tissue engineering scaffolds, hydrogels, drug delivery systems, excipient in tablets, or nanomedicines are thoroughly discussed in this entry.

INTRODUCTION

The selection of a polymer for biomedical applications is a demanding task, given the large variety of available natural and synthetic polymers, often associated with structural and size heterogeneity. The choice is dependent not only on the physicochemical and biochemical properties, but also on mandatory preclinical tests to insure safety.[1] In spite of the large availability of biodegradable polymers, the increasing demand continues to feed interest not only in the development of new materials, but also in improving the performance of the existing ones.

Natural polymers are usually biodegradable and many of them offer excellent biocompatibility. These polymers can be manipulated to produce different formulations such as capsules, hydrogels, or nanogels (hydrogel nanoparticles), meeting specific requirements such as—in the latest case—loading capacity, circulation time, and ability to accumulate in targeted pathological sites.[2,3]

Starch is the most widespread and abundant storage carbohydrate in plants, cereal seeds (rice, maize, wheat, barley, sorghum, and others) representing the most important source, followed by tubers (e.g., potato, sweet potato, yam), roots (e.g., cassava, taro), and seeds of beans and peas.[4]

Most native starches consist of two polymers of glucose, called amylose and amylopectin. Amylose is mainly a linear chain composed of α-D-glycopyranose residues linked by α-1,4 glycosidic linkages. Amylopectin molecule has the same structure as amylose but, in addition, contains α-1,6 glycosidic linkages at branching points.[5] Amylopectin is chemically similar to glycogen (the soluble polyglucan accumulated as a storage compound in animals, fungi, and bacteria) also a glucose polymer composed of α-1,4 linked and α-1,6 branched chains. However, glycogen is more ramified than amylopectin.[4] Starches from various botanical origins differ slightly in amylose content, chain-length distribution, molecular weight, and number of chains per cluster, among others. The overall molecular features of starches, however, are more or less the same, all containing 10–20% amylose and 80–90% amylopectin.[6] Recently, several reviews reported the utilization of starch for biomedical purposes;[7,8] therefore, in this entry we will not address this subject. This entry will instead be focused on the biomedical applications of a starch derivative: dextrin.

Dextrins are low-molecular-weight carbohydrates produced by partial hydrolysis of glycogen or starch. Dextrin is thus a glucose-containing saccharide polymer having the same general formula of starch, but smaller and less

complex.[9] Dextrin exhibits different structural features and properties, including hygroscopicity, fermentability, sweetness, stability, gelation, solubility, bioavailability, and molecular compositions, depending on the source and on how it is digested.[10] Dextrins can be linear, branched, or cyclic. Cyclodextrins, obtained through enzymatic degradation of starch, by certain bacteria such as *Bacillus macerans* are of interest due to their ability to improve drug bioavailability.[5] Cyclodextrins will not be discussed in this entry, fully dedicated to linear dextrins. As mentioned, dextrin is produced by partial hydrolysis of starch, accomplished by 1) applying dry heat under acidic conditions (pyrolysis or roasting); 2) using enzymes (amylases), malting, or mashing; or 3) a combination of both.[11] The first process is used industrially and also occurs on the surface of bread during the baking process, contributing to flavor, color, and crispiness. Dextrin produced by heat is also known as pyrodextrins. Under acid conditions, the starch hydrolyses and short-chained molecules partially rebranch through α-1,6 linkages.[10]

The enzyme α-amylase efficiently hydrolyzes α-1,4, but not α-1,6 linkages, leaving behind a small amount of high-molecular-mass residues[11] although the rate of biodegradation of the late linkages is typically lower. For many applications, a content of α-1,6 linkages below 10% or 5% is preferred.[12] On the other hand, hydrolysis with a α-1,6-specific enzyme (e.g., pullulanase) will render a higher proportion of linear α-1,4 oligosaccharides, which are more susceptible to retrogradation and gelling.[13] Generally, acid hydrolyzates contain larger amounts of residual high molar mass oligomers than their enzymatic counterparts. In summary, any dextrin is a mixture of polyglucose molecules of different chain lengths, containing an assortment of branched and linear oligosaccharides.[6,11] The extent of hydrolysis is usually expressed in terms of "dextrose equivalent" (DE), the total sugar reducing power, normally determined by titration using dextrose (D-glucose) as the standard and expressed as a percentage on a dry mass basis. A higher DE reflects a superior degree of hydrolysis and thus a smaller average molecular mass of the resulting oligomers.[6] Those materials generally exhibit higher browning, hygroscopicity, sweetness, and solubility, while lower DE materials, such as maltodextrin (malt-dex), are preferred when viscosity control, cohesiveness, or film-forming properties are required. Thus, dextrins with similar DE can have different properties, hence different functionality appropriate for specific applications.[11]

Maltodextrin is defined by the United States Food and Drug Administration (FDA) as nonsweet, soluble, and nutritive saccharide polymer, which consists of D-glucose units linked primarily by α-1,4 linkages, having a DE of less than 20.[6] It is efficiently digested and assimilated in the body. As referred above, the properties of dextrins rely to some extent on the starch from which they are derived. All dextrins are soluble in water, being precipitated by ethanol. They are classified according to their ethanol solubility as: 1) amylodextrin, which is soluble in 25% ethanol and gives a blue color upon reaction with iodine; 2) erythrodextrin, soluble in 55% ethanol, turns iodine to a reddish-brown color; and 3) achrodextrin, which is soluble in 70% ethanol, yields no color at all with iodine.[14]

Among starch-derived materials, dextrin is widely used in a variety of applications. Dextrin forms a strongly adherent paste mixed with water, being used as adhesive in the manufacture of gummed tapes, textiles, and paper[15] and also as moisturizing component in cosmetics.[16] In addition, dextrin has been described as a biocompatible material and, besides its utilization in the production of nutritional products,[10] several studies also refer its biomedical/pharmaceutical applications. For instance, icodextrin is used clinically as a peritoneal dialysis solution.[17–19] Other biomedical applications have been explored, such as tissue engineering scaffolds, hydrogels as drug delivery systems, excipient in tablets to facilitate packaging and/or drug delivery, or nanomedicines. These applications will be reviewed along this entry.

While natural polymers [e.g., dextran and poly(amino acids)] are biodegradable, even low levels of chemical modification—for example to promote drug attachment—can lead to the generation of nonbiodegradable derivatives. Dextran (α-1,6 poly(glucose) used as plasma expander) is slowly degraded by mammalian enzymes, but modification with pendant group (>5%) has been shown to render the polymer nonbiodegradable within the experimental time frame explored.[20]

In contrast, dextrin [α-1,4 poly(glucose)], is readily degraded within minutes on exposure to α-amylase present in extracellular fluids and plasma. The rate of dextrin degradation was studied using two dextrin samples with different molecular weights (MW 15.5 and 51.0 KDa), incubated (pH 7.4 and 5.5) with α-amylase or isolated rat liver lysosomal enzymes. Dextrin was degraded rapidly (within 20 minutes) by rat plasma and porcine pancreatic α-amylases. In contrast, over 48 hours no degradation was observed in the presence of tritosomes.[21]

The polymer backbone modification can be determinant on the degradability of polymeric carriers. Figure 1 shows some dextrin modifications.

Succinoylation is a method that can be used to reproducibly introduce various pendant groups into dextrin chains. This kind of dextrin derivative has been used to conjugate drugs or probes selected to monitor pharmacokinetics (doxorubicin, tyrosinamide, and biotin).[22] The rate of α-amylase degradation of succinoylated dextrins (MW 51 KDa) was reduced with increasing succinoylation degree. Dextrin–doxorubicin conjugates, synthesized from succinoylated dextrin, were used to follow the rate of degradation. The conjugates (doxorubicin loading of 8 and 12 wt.%) were slowly degraded over 7 days to release oligosaccharide–doxorubicin species.[21] Other dextrin modifications will be further discussed.

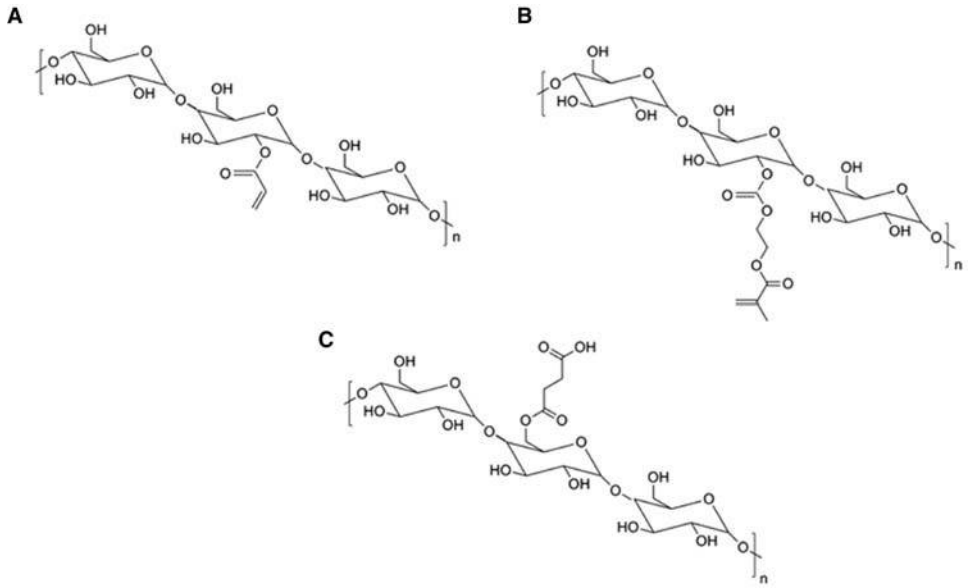

Fig. 1 Modified-dextrin: (**A**) dextrin–acrylate, (**B**) dextrin–hydroxyethylmethacrylate, and (**C**) succinoylated dextrin.

PRODUCTS AND APPLICATIONS

Icodextrin

Icodextrin, derived from malt-dexs, is approved for clinical use as a peritoneal dialysis solution. It is a polymer with less than 10% of α-1,6 bonds and an average molecular weight between 13 and 19 kDa. The substance is a white to off-white solid, and the solution is clear and colorless to pale yellow (Extraneal, Baxter International Inc.).

Conventional peritoneal dialysis solutions, based on dextrose as an osmotic agent, are strongly hypertonic to blood plasma, exerting stress on the peritoneal membrane, which can result in membrane damage. Furthermore, this hypertonicity also appears to destroy peritoneal macrophages, thereby compromising the host defense system. Also, peritoneal dialysis with glucose solutions causes the patient to receive a massive influx of glucose, which can cause obesity among other problems.[23,24]

Since the 1980s, there has been increasing interest in the use of icodextrin-containing peritoneal dialysis solutions because of their demonstrated ability to induce sustained peritoneal ultrafiltration. Although some cases of cutaneous reactions to icodextrin have been reported in the literature, they are rare, and some eruptions are psoriasiform, limited to the palms and soles. A few cases of peritonitis, an inflammation of the membrane that lines part of the abdominal cavity and viscera, called peritoneum, were also reported.[18,25–27] Thus, its clinical safety is well documented and several in vitro and ex vivo studies suggest that icodextrin may offer improved peritoneal membrane biocompatibility compared with conventional glucose-based dialysates, especially in patients with diabetes and individuals with low net daily ultrafiltration volumes or high peritoneal transport status, by virtue of decreased glucose exposure, isoosmolarity, and reduced carbonyl stress (which have been implicated in the formation of advanced glycation end products).[28–31]

Johnson et al.[28] suggested that icodextrin might play a useful role in alleviating symptomatic fluid overload and extending technique survival in patients who have failed peritoneal dialysis because of intractable hypervolemia. Their results showed that icodextrin can significantly augment peritoneal ultrafiltration, alleviate fluid overload, improve diabetic glycemic control, and extend technique survival in peritoneal dialysis patients with refractory, symptomatic fluid overload. In recent long-term clinical trial, Takatori et al.[17] showed that for diabetic nephropathy, the use of icodextrin-containing solutions has a beneficial effect on technique survival in peritoneal dialysis therapy compared with conventional glucose peritoneal dialysis solution.

Although peritoneal dialysis is not intended to be a drug delivery system, it has been used as such in some particular cases. For instance, when the patient suffers from diabetes or renal failure, insulin may be added to the dialysis solution, being administrated from the peritoneum instead of intravenously. Since dextrin overcomes the side effects caused by peritoneal dialysis based on glucose, it has been proposed as an effective medium for drug delivery via the peritoneum.

A dextrin-based solution was proposed for the intraperitoneal administration of therapeutic proteins for which the enteral route is unsatisfactory; the particular case of erythropoietin and growth hormones was described and patented.[12,32] Dextrin solutions have also been described

for the administration of chemotherapeutic agents in the treatment of ovarian cancers. The use of icodextrin formulations (Icodextrin 20) to increase the efficacy of chemotherapeutics, especially of the cytotoxic drug 5-fluorouracil, by increasing their dwell time in the peritoneal space is well described.[33,34] Reference is also made to antibiotics, such as cefepime[35] and vancomycin (antibiotic with Gram-positive bacterial coverage), that are stable in the icodextrin solutions, depending essentially on the storage temperature.[36] However, other antibiotics, such as tobramycin (an aminoglycoside antibiotic that provides excellent Gram-negative bacterial coverage) and ceftazidime (a semisynthetic third-generation cephalosporin antibiotic, with coverage for both Gram-negative and Gram-positive organisms) have showed instability in icodextrin solutions.[37]

Dextrin as Excipient in Tablets

Tablets are widely used as a convenient solid dosage form of medicines. Usually tablet formulations contain drugs and excipients. Excipients can be binders, desintegrants, diluents, lubricants, glidants, surfactants, dyes, and flavoring agents.

Desintegrants are an important component of the tablet excipients, usually added to facilitate the rupture of bonds and subsequent disintegration of the tablets, resulting in the increase of the surface area of the drug exposed to the gastrointestinal fluid; incomplete disintegration can result in incomplete absorption or a delay in the onset of the drug action.[38] Typical disintegrates are maize, potato starch, gelatinized starches, alginic acid crosscarmellose, crosspovidone, sodium starch glycolate, etc. Dextrin is commercially available in abundant quantities quite economically, which make its utilization for tablet formulations appealing. The preparation of cross-linked dextrin and its use as tablet disintegrant was described and patented. Treating dextrin with epichlorohydrin yields a polymer cross-linked through the hydroxyl groups, bearing improved water swelling. Several cross-linked dextrin formulations were evaluated regarding disintegration, using paracetamol and folic acid tablets prepared by wet granulation or direct compression technique, respectively. The rate of tablet disintegration varied between one to four minutes, depending on the techniques and the degree of cross-linker used, thus making dextrin a potential new member of the superdisintegrants class. At present there are—three or four superdisintegrants available in the market; as these are expensive, dextrin-based desintegrants could be a competitive alternative.[39]

Paracetamol was also used as a drug model in tablet formulations to study, both in vitro and in vivo, the utilization of amylodextrin (linear dextrin produced by enzymatic hydrolysis of the amylopectin α-1,6 linkages) as excipient for the design of drug-controlled release systems. In vitro dissolution profiles showed almost-constant drug release rates during 8 hours. Peroral administration of the tablets to humans showed almost-constant paracetamol plasma levels up to 14 hours, as compared to fast absorption and elimination using a paracetamol solution. Thus, tablets compacted from pure amylodextrin showed good binding properties and did not disintegrate in aqueous media. The authors showed that the release rate could be adjusted by selecting tablet thickness and through the incorporation of either lactose as a highly water-soluble excipient or talc as a hydrophobic one.[40]

More recently, Salunkhe and Kulkarni[42] developed a colon-targeted carrier system based on dextrin and ethyl cellulose. Targeting pharmaceutical drugs to the colon—ibuprofen was used in that study—makes it possible to achieve local or systemic drug delivery. Such a smart formulation should first of all pass through the stomach and the upper part of the intestine, finally delivering its cargo, by reacting to specific physiological environment, at the lower part of the digestive tract.[41] The matrices made of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach the colon, they are acted upon by bacterial polysaccharidases, resulting in the degradation of the matrices. Formulations containing dextrin and ethyl cellulose as binder released 95–98% of ibuprofen in simulated colonic fluid with 4% human fecal matter solution, after 20 hours of incubation. Further, tablets containing dextrin showed no change in physical appearance and dissolution profile upon storage at 40°C with 75% relative humidity for 3 months.[42]

Shendge et al.[43] showed that dextrin tablets are also good carriers for aceclofenac (a novel nonsteroidal anti-inflammatory drug known to exhibit multifactor mechanism of action) colonic delivery, using ethyl cellulose as binder. Furthermore, stability studies confirmed the tablet's stability, showing no significant change in hardness, friability, drug content, and dissolution profile.

Dextrin-based solid dispersions for enhancing the oral absorption of amlodipine free base were developed by Jang, Sim, and Oh[44] Amlodipine is an antihypertensive drug that has a low aqueous solubility and slow dissolution, which impaired its oral absorption. In this work, a dextrin-based solid dispersion containing sodium lauryl sulfate (absorption enhancer) and amlodipine-free base was developed. This kind of formulation improved the oral absorption of the drug due to the increased dissolution rates by the dextrin dispersion and the absorption enhancement by sodium lauryl sulfate. The formulation remains stable at least after 6 months in terms of appearance, particle size distribution, crystal structure, and drug content. The pharmacokinetics of the formulation in rats was comparable to the correspondent commercial product.

β-Limit

The β-limit dextrin is found in nature, where it is generated from starch in germinating plants (commonly identified in malting barley). In vitro, β-limit dextrin is obtained by

treating solubilized starches with pure β-amylase, which catalyses the hydrolysis of α-1,4 linkages of amylose/amylopectin, by the successive liberation of maltose from the nonreducing ends. However, when a branch point (α-1,6 glucosidic linkage) or a modified glucose unit (e.g., phosphorylated or oxidized) is approached, the β-amylase cannot further act and the hydrolysis ends. As a result, linear amylose is completely hydrolyzed to maltose, whereas about 50–60% of amylopectin is converted into maltose, with the remaining material being known as β-limit dextrin.[45,46] Since the β-amylase is highly specific, it has been studied for many years as a means to investigate the internal structures of amylose and amylopectin.

β-limit dextrin is a large highly branched molecule, resulting in high-viscosity dispersions, which together with its hydrophilic nature makes it a suitable candidate for bioadhesive applications.[45] In addition, due to its high molecular weight, β-limit dextrin provides a low osmotic pressure in solution while providing a readily available source of calories, which are especially desirable in clinical nutrition (e.g., infant and geriatric nutrition, intervention feeds for diarrhea management) where individuals are particularly vulnerable to osmotic dehydration.[46]

Recently, Qi and Tester[45] described the role of β-limit dextrin as an excipient for pharmaceutical industry applications. They explored its potential as an excipient to aid drug delivery in comparison with well-known bioadhesive polymers. The β-limit dextrin showed significant mucoadhesive properties, similar to carbopol but superior to chitosan. It may thus represent a safe and natural alternative to synthetic polymers; as it is digested by salivary amylase, it provides a clean mouth feel. In a more recent work, Qi et al.[47] compared the properties of oral fast disintegrating tablets (wafers) constituted by dextrin, β-limit dextrin and pregelatinized starch. In this study, β-limit dextrin wafers demonstrated better properties for buccal delivery than the ones of dextrin and gelatinized starch. In terms of break strength, dextrin formulations were the most fragile ones whereas β-limit and gelatinized starch wafers were more robust, the last being very hard. β-Limit dextrin wafers were the most mucoadhesive probably due to being a highly branched molecule with a high molecular weight that favors the interaction with the oral mucosa; also, the dissolution profile of these tablets (about 20 seconds maintaining some of the structure) is the desired behavior for this kind of applications.

Proniosomes

Maltodextrin was described as a suitable material for the preparation of proniosomes.[48] Proniosomes are dry formulations of carriers coated with nonionic surfactants, which can be further converted into niosomes (a nonionic surfactant-based liposome) immediately before use, by hydration (Fig. 2).[49] Niosomes represent an emerging class of novel vesicular systems that were developed as stable and inexpensive alternatives to liposomes. Some of the niosomes's limitations related to physical stability such as fusion, aggregation, sedimentation, and leakage during storage were overcome with the proniosome formulations.[50] Since their early introduction to cosmetic industry, their role has diversified to other applications, such as potential carriers for sustained and targeted drug delivery. In addition to conventional oral and parenteral routes, they are amenable to administration by ocular, transdermal, vaginal, and inhalation routes. Blazek-Welsh and Rhodes[48] developed a method to produce niosomes able to carry amphiphilic drugs using two types of malt-dex (Maltrin M500 and Maltrin M700). The utilization of malt-dex, replacing sorbitol, overcame the problems related with the sorbitol solubilization, which in turn interfered with drug encapsulation. Moreover, the malt-dex utilization allowed rapid preparation of proniosomes with a wide range of surfactant and other components loading.[50]

Hydrogels

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers swollen with a large amount of water, which normally represents more than 50% of the

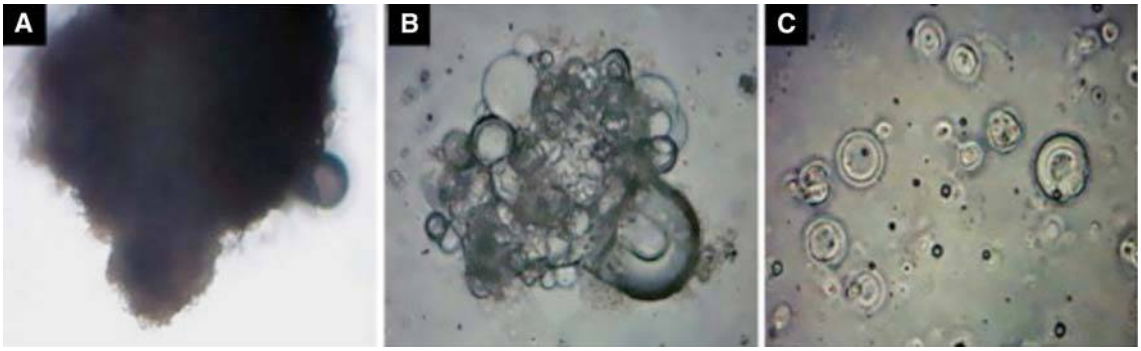

Fig. 2 Optical microphotographs showing (**A**) proniosome powder, (**B**) formation of vesicles on maltodextrin after hydration, (**C**) niosome dispersion from proniosome powder upon gentle agitation.
Source: From Gurrapu et al.[122] © 2011, with permission from Elsevier.

total weight. On the macroscopic scale, hydrogels are solids: they have definite shapes and do not flow; nevertheless, they also behave like solutions on the molecular scale: the transport of water-soluble molecules is characterized by diffusion constants, reflecting the size and shape of the diffusing molecules as well as the porosity and tortuosity of the hydrogel.[51] Hydrogels can be achieved through chemical or physical cross-linking of polymers, its properties depending on the chemical composition, cross-linking density, and hydrophobicity.[52,53]

The polymer's bulk properties, such as molecular weight and solubility, influence the mechanical and physical properties, thus microstructural design and chemical composition can be used to customize the biomaterial to its applications. Structural features of the matrix, namely micromorphology and pore size, determine the mass transport properties. For nonbiodegradable matrices, drug release is in most cases diffusion-controlled and occur only through the pores and channels created by the dissolved drug phase.[1]

Surface properties, such as hydrophilicity, lubricity, smoothness, and surface energy, influence the biocompatibility, including hemocompatibility, also affecting the physical properties, hence the durability, permeability, water sorption, and degradability.[1,54] The surface properties can be modified by a variety of methods, e.g., oxidation, hydrolysis, polymerization, or grafting of water-soluble polymers, incorporation of biologically active molecules, in order to improve biocompatibility.

Hydrogels can be formulated in a wide range of physical forms, such as slabs, microparticles, coatings, films, and nanoparticles (nanogels). They are usually used in clinical practice and experimental medicine in diverse applications,[55] including tissue engineering and regenerative medicine,[56] diagnostics,[57] cellular immobilization,[58] and as barrier materials to regulate biological adhesions.[59]

Tissue engineering is an interdisciplinary field that aims at regenerating new biological tissues for replacing diseased or destroyed tissues. Tissues or organs can theoretically be engineered using different strategies, but the most common approach is the combination of the patient's cells with polymer scaffolds. The ideal scaffold is a three-dimensional, highly porous structure with interconnected porosity. It must serve as template for the tissue growth, as a delivery vehicle for transplanted cells, and as drug carrier, activating specific cellular functions resulting in the regeneration of tissues.[60–62] Hydrogels are considered good scaffolds due to their high biocompatibility[52,55,56,63] owing to their high water content, and also to the physicochemical similarity with the native extracellular matrix (ECM).

The hydrogel distinctive physical properties have generated particular interest concerning its potential for drug delivery applications. Their highly porous structure can easily be adjusted by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment.[55] Drugs can be loaded into the highly porous gel matrix and subsequently released at a rate dependent on the diffusion coefficient of the small molecule or macromolecules through the gel network.

The degradation of hydrogels, and therefore the time scale and the drug release kinetics, can be altered via enzymatic or hydrolytic pathways, or through environmental switches, such as pH and temperature. Hydrogels are also relatively deformable and can match the shape of the surface to which they are applied. Also, the muco- or bioadhesive properties of some hydrogels can be favorable to promote their immobilization to the site of application.

Carvalho et al.[64] presented a dextrin hydrogel as scaffold for biomedical applications. Soluble dextrin was modified by transesterification with vinyl acrylate (VA) in anhydrous dimethylsulfoxide. Hydrogels were obtained by free radical polymerization of dextrin–VA with ammonium persulfate (APS) and *N*,*N*,*N*′,*N*′-tetramethylenethylenediamine in water. This method allowed the production of dextrin with varying amounts of grafted acrylate groups by varying the VA concentration. Subsequently,[65] the potential of the dextrin–VA hydrogels as a controlled release system was evaluated by accessing the diffusion of two different molecules (glucose and bovine serum albumin) from the hydrogel matrixes, in the presence and absence of amyloglucosidase. The enzyme was used to modulate the release of proteins entrapped in the hydrogel by accelerating the hydrolysis of the dextrin–VA hydrogel. This study showed that by regulating the degree of substitution (DS) with the acrylate groups and the enzyme concentration it was possible to control the release rate, from days (low DS, higher enzyme) to months (higher DS, no enzyme). To further evaluate the dextrin hydrogels potential as biomedical devices, Carvalho et al.[66] and Moreira et al.[67] accessed the in vitro and in vivo biocompatibility and degradation of the dextrin–VA hydrogel. They also developed a new class of degradable dextrin-based hydrogels by derivatizing dextrin with hydroxyethyl methacrylate ester (HEMA) followed by radical polymerization in water. In vitro, the comparative study of both dextrin hydrogels revealed that only the dextrin–HEMA hydrogels were effectively hydrolyzed under physiologic conditions. In terms of biocompatibility, both dextrin hydrogels revealed negligible cell toxicity, allowing cell adhesion and proliferation. The in vivo studies confirmed the results obtained in vitro: the dextrin–VA hydrogels are nondegradable (irrespective of the DS of polymer used) while the dextrin–HEMA ones are degradable (the degradation rate depending on the polymer DS); both were biocompatible, as none of them induced necrosis, immunotoxicity, nor damage to muscle tissue.

Ramos, Carvalho, and Gama[68] developed a hydrogel by reticulation of chitosan with modified dextrin (dextrin-VA), without cross-linking agents. It was possible to obtain hydrogels with different properties (charge, porosity, mechanical strength) by varying the proportion of chitosan to dextrin–VA, and the dextrin–VA degree of substitution.

These hydrogels were simple to produce and presented interconnected micro and macropores that made them suitable for cell and tissue culture.

Gelatin-malt-dex hydrogels, cross-linked with genipin, were described recently.[69–71] These hydrogels consist of continuous or bicontinuous microstructures whose morphologies and physical properties could be tailored by controlling composition, pH, and cross-linker. Studies using four fluorescent markers with different molecular weights corroborated that, with the proper combination of cross-linker density, solvent pH and microstructure, hydrogels with specific swelling behavior could be obtained, leading to controllable rates of drug release. The authors stated that the cross-linked gelatin–malt–dex hydrogels could be a valid option for controlled release systems.[69]

Molinos et al.[72] described a fully resorbable dextrin hydrogel, produced without using chemical initiators. Dextrin was first oxidized with sodium periodate and then cross-linked with adipic acid dihydrazide (a nontoxic cross-linking molecule). These oxidized dextrin (oDex) hydrogels showed good mechanical properties and biocompatibility, allowing the proliferation of mouse fibroblasts 3T3 cells on top of the gel. They were biodegradable and presented a three-dimensional network with continuous porous structure. Due to their properties, these oDex hydrogels showed potential as a controlled drug delivery system.

Although generally considered biocompatible, hydrogel surfaces are often resistant to cell adhesion and differentiation; this may be a key limitation to their successful application for tissue engineering applications. Several strategies can be employed to improve cell adhesion, proliferation and differentiation on the hydrogel surfaces, such as the reduction of unspecific protein adsorption or the immobilization of adhesion molecules to ensure controlled interaction with cells.[63,73–76] Various molecules, namely proteins of ECM, have been used to promote cell adhesion and proliferation.[77–81] Moreira et al.,[82] successfully functionalized a dextrin-VA hydrogel, using a recombinant fusion protein containing a C-terminal starch binding module (SBM) and a N-terminal Arg-Gly-Asp (RGD) sequence. The RGD sequence, present in several proteins of the ECM, was already described as the major functional group responsible for cellular adhesion.[78,83,84] The recombinant RGD–SBM protein improved by more than 30% the adhesion and spreading of fibroblasts on the dextrin–VA hydrogel surface enhancing its biocompatibility and consequently widening its potential for biomedical application.

In spite of their many favorable properties, hydrogels also have some limitations. The low tensile strength limits their use in load-bearing applications and, as a consequence, the premature dissolution or flow away of the hydrogel from the targeted local site can occur. Regarding drug delivery, the most important disadvantage of hydrogels relates to the quantity and homogeneity of drug loading, which may be limited, especially in the case of hydrophobic drugs; on the other hand, the high water content and large pores frequently result in relatively rapid drug release. Although some hydrogels are sufficiently deformable to be injectable, many are not, requiring surgical implantation.

It is known that increasing the cross-linker concentration can enhance the mechanical strength of hydrogels. Nevertheless, a large amount of cross-linker agent can result in the reduction of swelling capability and mechanical toughness. To surmount the physical and mechanical hydrogel limitations and to make them strong and elastic, small-scale inorganic particles are commonly used as reinforcing agents.[85–88] These new nanocomposite hydrogels have improved properties, such as mechanical strength, large deformability, high swelling/deswelling rates, over the unmodified counterparts. Recently, Guilherme et al.[89] developed a nanocomposite hydrogel comprising a dispersed montmorillonite-cross-linked malt-dex-*co*-dimethylacrylamide. The malt-dex and montmorillonite (MMT) were modified as to incorporate carbon–carbon π-bonds (malt-dex-π and MMT-π, respectively): then, the nanocomposite copolymer hydrogel was obtained via radical cross-linking reaction of malt-dex-π with MMT-π in the presence of dimethylacrylamide. The dispersion and stability of MMT-π inside the matrix were excellent. It was established that the nanocomposite hydrogel was a stable device suitable for pharmaceutical formulations where the release of solutes is dependent on a diffusional process.

Additionally, in the last decade, composite systems where micro or nano hydrogels are incorporated in a bulk hydrogel matrix appeared as a platform for drug delivery.[90–93] The micro or nano hydrogel particles can act as drug reservoirs from which release can be triggered by a suitable stimulus, or simply in a diffusion-controlled manner. Simultaneous diffusion of different molecules at different rates can be obtained from the same platform, by adding two (or more) populations of micro or nanogels, each loaded with one kind of drug, in the same hydrogel matrix.[90,93] The major advantage relies on the improvement of the drug release profile, as the nanogel phase provides an additional diffusion barrier moderating or eliminating the initial burst release typically observed in hydrogel or nanogel drug delivery systems.

Simultaneously with the oDex hydrogel previously mentioned, Molinos et al.[72] also described a new bidimensional composite hydrogel made of oDex incorporating dextrin nanogels (oDex–nanogel hydrogels) (Fig. 3). These hybrid hydrogels were also biodegradable and had a porous structure similar to the oDex hydrogel. The new hybrid hydrogel enabled the release of the dextrin nanogels over an extended period of time; the nanogels allowed the efficient incorporation of interleukin-10 and insulin, offering a sophisticated system of controlled release. Due to the straightforward preparation and the controllable release properties of oDex hydrogels, the authors concluded that these hybrid hydrogels were interesting for the design of

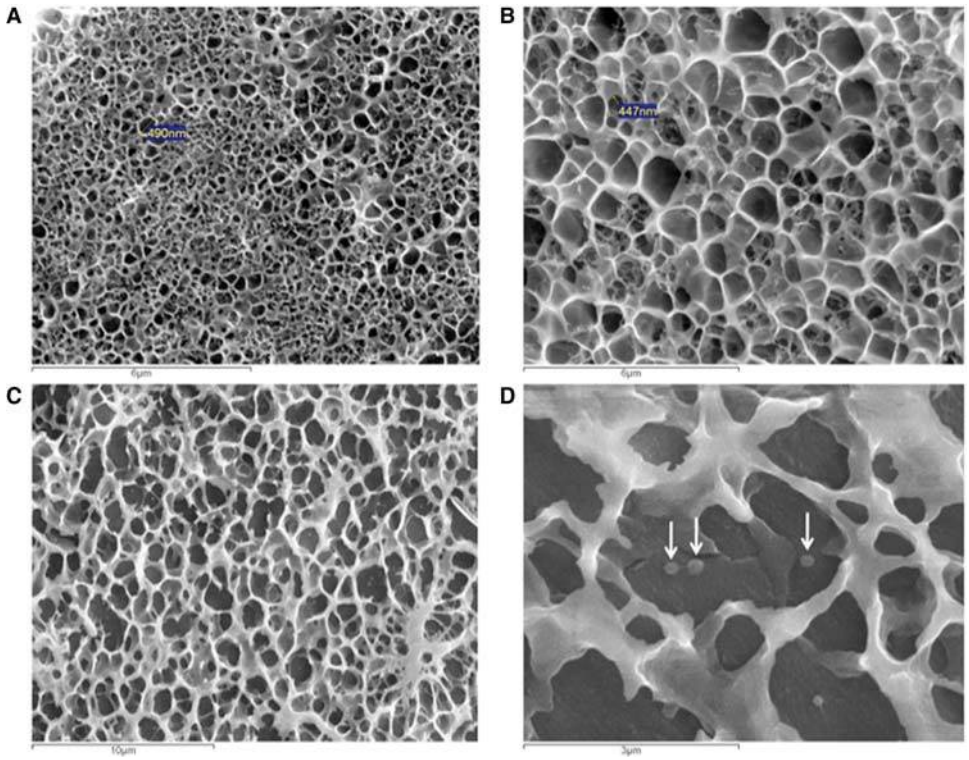

Fig. 3 Cryo-SEM images from cross-section of oDex hydrogel (**A**) before and (**B**) after immersion on PBS buffer for 24 hours and (**C**, **D**) oDex-nanogel hydrogel. Arrows show the dextrin nanogels.
Source: From Molinos et al.[72] © 2012, with permission from American Chemical Society.

injectable protein delivery systems and that the inclusion of a dispersed hydrophobic phase (dextrin nanogels) in the hydrogel was an important improvement of the newly developed material.

Bioadhesives

Adhesion to biological tissues is a challenge because the adhesive, which is in contact with physiological fluids, has to be both efficient and biocompatible. Tissue adhesives can be used for a wide range of applications such as hemostasis and sealing or adhesion between different biological tissues or between an implanted device and biological tissues.[94]

Among the malt-dex applications, its use as a biomedical coating agent has been described. Thus, a hydrophilic wound dressing based on malt-dex (Multidex® Maltodextrin Wound Dressing) was clinically proven to promote the growth of granulation tissue and epithelial proliferation. This product is available commercially as a powder for moist and wet wounds application and as a gel for applications on dry and minimally draining wounds. These formulations present some appealing characteristics, namely, they are able to quickly fill a wound site, mixing with exudate in order to produce a protective coating, which maintains an ideal moisture balance protecting against dehydration. They were specifically formulated to provide topical nutrients to wound sites in order to create a natural healing environment.[95]

Bioadhesive formulations containing malt-dex (Glucidex1, potato-based malt-dex) were also described by Serrero et al.[94] They have developed a versatile bioadhesive system based on solutions of chitosan and modified starch (oxidized malt-dex). Their work shows that chitosan alone did not provide any significant adhesion, however, a system comprising chitosan and oxidized starch promoted the adhesion. Moreover, they have shown that depending on the experimental parameters (chitosan concentration, starch degree of oxidation, molar ratio between amine and aldehyde functions, pH, etc.), the mixtures of these polysaccharides form either viscoelastic solutions or hydrogels, suggesting that multipolysaccharide systems composed of chitosan and oxidized starch are relevant for the design of bioadhesives for tailor-made biological applications.[94]

A malt-dex-based, biodegradable, nontoxic bioadhesive formulation was recently patented to protect and/or promote smooth tissue regeneration. This dextrin-based adhesive was envisioned to prevent anastomosis failure during the initial critical recovery time, to improve the fixation of inguinal prosthesis in hernia surgery and to occlude certain types of fistulas. The formulation is composed by malt-dex, an adhesiveness modifier agent (zinc oxide), which improves the polymer adhesiveness to biological tissues

and its drying time, and an antibiotic (kanamycin). Depending on the malt-dex viscosity the tack time can be modulated to better suited for application.[96]

Nanomedicines

Both synthetic and natural polymers have been explored as drug carriers; several polymers used clinically are still nonbiodegradable synthetic polymers. Poly(ethyleneglycol) (PEG) is the most commonly used polymer in first generation marketed nanomedicines, essentially within the polymer therapeutics category.[97] PEG is also often proposed as coating polymer to improve "stealth" properties or prevent aggregation of nanosystems. Although well tolerated in humans, such polymer is not biodegradable.[98] Thus, in order to ensure renal elimination and to exclude the threat of progressive accumulation after repeated administration, only PEG chains with a molecular weight below the renal threshold (40,000 Da) should be used. Even if lower molecular weights are used, their lack of biodegradability remains a threat. There is a particular danger of accumulation within lysosomes after high dose and/or repeated administrations. The pathophysiological consequences of macromolecular accumulation in lysosomes are well documented in the context of the lysosomal storage diseases. Even if the material is excreted through the kidney, renal tubular reabsorption can be an issue for certain PEGylated proteins inducing intracellular vacuolation in animal models.[99]

Nanomedicines should preferably be biodegradable (to safe metabolites) if proposed for use at high dose or for long-term administration. If they are nonbiodegradable, renal, and/or hepatobiliary elimination should be verified, at an early research stage.

Self-assembled nanogels

Dextrin allows preparation of amphiphilic derivatives, through conjugation with hydrophobic chains. Hydrophobized dextrins, in aqueous environment, self-assemble originating hydrophobic domains able to solubilize by complexation, different type of hydrophobic molecules. Moreover, to obtain stability of the complex upon dilution in the body fluids, the amphiphilic domains must bear multiple intermolecular interactions (hydrophobic interactions), stabilizing the self-assembled structure toward dilution.

Orienti et al.[100] have reported the preparation of several amphiphilic dextrins and their evaluation as complexing agents for antitumor hydrophobic drugs such as fenretinide, paclitaxel, etoposide, and camptothecin. Low-molecular-weight dextrin (MW 1670 Da) was linked to different acyl hydrocarbon chains (substitution degree of about 0.1 mole hydrocarbon chain per mole of glucose monomer) by direct ester bond formation. Briefly, dextrin was dissolved in *N*-methylpyrrolidone (NMP) and the acyl chloride (lauroyl, miristoyl, palmitoyl, stearoyl, or oleoyl chloride) was added in the presence of polyvinylpyridine 2% cross-linked, used as a proton scavenger. The aqueous solubility of amphiphilic dextrins, containing saturated hydrocarbon chains, decreased with increasing molecular weight of the chain. Dissolution process of modified dextrin induces formation of nano-aggregates endowed with hydrophobic inner cores able to host hydrophobic drugs by complexation (physical interaction). Complexation raised hydrophobic drugs aqueous solubility; the best results were obtained with fenretinide. Solid complexes with fenretinide were prepared by using three different approaches: the kneading method, the co-solubilization method, and the co-precipitation method.

In the kneading method, the amphiphilic dextrin was dissolved in the minimum volume of NMP to obtain a viscous solution (250 mg/mL). The hydrophobic drug was added and the viscous suspension obtained was kneaded to homogeneity and subsequently diluted with an excess of water (100 mL) under stirring at room temperature until a fluid suspension was obtained. The suspension was dialyzed against water to completely remove the organic solvent. The undissolved drug was removed by filtration and the aqueous solution obtained was freeze-dried.

In the co-solubilization method, the amphiphilic dextrin was dissolved in water (50 mg/mL) and then the hydrophobic drug was added. The suspension was stirred at room temperature for 24 hours, then the uncomplexed drug was removed by filtration, and the aqueous solution obtained was freeze-dried.

In the co-precipitation method, the amphiphilic dextrin was dissolved in NMP (50 mg/mL) together with the hydrophobic drug. Diethyl ether was subsequently added in excess to the solution to induce coprecipitation of drug and amphiphilic dextrin. The solid obtained was separated by centrifugation, resuspended in water, and dialyzed against water to completely remove the organic solvents. The undissolved drug was removed by filtration and the aqueous solution obtained was freeze-dried.

Kneading method provided the complexes endowed with the best functional properties. Particle size analysis confirmed the dimensional suitability of the complexes for parenteral administration. Moreover, sustained drug release, in vitro, has been observed from all the complexes analyzed. Regarding the biological effects, the cytotoxicity of complexed fenretinide toward HTLA-230, a neuroblastoma (NB) cell line, was always higher than the free drug, suggesting that complexation increased drug bioavailability.[101]

Recently, fenretinide-loaded amphipilic dextrin, in comparison with fenretinide alone, was studied both in vitro (human NB cells) and in vivo (pseudometastatic NB models). Fenretinide-loaded amphipilic dextrin exerted a more potent cytotoxic activity on NB cells and significantly increased the proportion of sub-G1 cells, with respect to free drug. Dextrin derivatives showed no hemolytic activity, indicating their suitability for parenteral

administration. Conjugates increased the life span and the long-term survival of treated mice over controls. The analysis of drug plasma levels indicates that the complexed drug has a higher area under the concentration–time curve due to a reduced clearance from the blood. Thus, the dextrin injectable formulation seems to be a good carrier for fenretinide, able to improve drug aqueous solubility and bioavailability.[102]

Dextrin modification may be achieved in another strategy through transesterification, producing an acrylate ester functionalized dextrin: dextrin–VA (mentioned above in the Hydrogels section). The acrylate group in the dextrin chain allows Michael addition reaction, with thiol or amine groups acting as nucleophile agents. A versatile synthetic method was developed allowing control of the dextrin degree of substitution with thyolated alkyl chains (hexadecanethiol). Amphiphilic dextrin, dexC_{16}, self-assembles into well-defined spherical nanoparticles (nanogel) with high colloidal stability. The critical micelle concentration is around 0.001 g/dL.[103] Size distribution obtained by dynamic light scattering showed two distinct populations, with 25 and 150 nm, the former being the predominant one.[104]

To evaluate the potential of the dextrin nanogel for drug delivery purposes, the nanogel was labelled with a thiol-functionalized fluorescent probe and its blood clearance was studied in BALB/c mice.[105] It is widely accepted that the physical and chemical properties of the nanoparticles, including particle size, surface charge, and surface hydrophilicity, are important parameters determining their biological fate after intravenous administration.[106] To obtain the biodistribution profile of the nanogel in experimental animals, a new ω-thiol-functionalized DOTA-monoamide type metal chelator (DOTA = 1,4,7,10-tetraazacyclododecanetetraacetic acid) was synthesized for covalent functionalization of nanogel and labeling with a suitable Ln^{3+} (e.g., $^{153}Sm^{3+}$) radioisotope. The labeling process had no significant effect on the nanogel size and surface charge; hence the biodistribution profile obtained in Wistar rats following intravenous administration was considered representative of the unmodified nanogel. The nanogel displayed a characteristic biodistribution profile, being mainly taken up by the organs of the Mononuclear Phagocytic System—liver and spleen. The blood circulation time extends for several hours, although the concentration is halved in about 1 hour. The nanogel surface decoration with PEG 5,000 improves circulation time in the bloodstream and reduces the accumulation in the liver and spleen.[107]

The suitability of the hydrophobically modified dextrin (0.1 and 0.25 mg/mL) to perform as a nanocarrier was studied using curcumin, as a model of hydrophobic molecule. The stability and loading efficiency of curcumin-loaded nanogel depend on the nanogel/curcumin ratio. The release profile, using sink conditions, indicates that dextrin nanogel may perform as a suitable carrier for the controlled release of curcumin, overcoming the limited bioavailability of curcumin after in vivo administration, without using organic solvents.[108]

Another kind of nanoformulations using amphiphilic dextrin were described by Senanayake, Warren, and Vinogradov[109] for the delivery of novel anticancer drugs. Their work reports the use of activated nucleoside analogs (NA) through the conjugation with a modified dextrin nanogel. NA are a class of therapeutics drugs that are used in the treatment of hematological disorders, solid tumors, and antiviral infections. The major limitation of NA cancer treatment is the development of resistance for these drugs that is associated with deactivation of the molecules, limited amount of drug that actually enters the cell, or resistance to apoptosis. Clinically, the resistance development leads to an increasing in therapy sessions, which results in adverse side effects in the patients. Dextrin (MW 9000 Da), a hydrophilic polymer, was first modified with cholesterol, a hydrophobic molecule, which, in an aqueous environment, promotes the formation of a nanogel with a hydrophobic core. The cholesterol moieties allow the nanogel formation, which confers protection to the NA and also will facilitate the transport of these molecules across cellular membranes, two major issues in NAs resistance. The conjugation of floxuridine (FdU), the active metabolite of the chemotherapeutic drug 5-fluorouracyl, was achieved by grafting in the hydroxyl groups of modified dextrin through a biodegradable tetraphosphate linker. The cytotoxic effect of polymeric–FdU conjugate was accessed in human prostate adenocarcinoma, breast carcinoma, hepatic carcinoma, gemcitabin-resistant follicular lymphoma, and cytarabin-resistant T-lymphoma cell lines. The conjugate potentiated an increased toxicity and a lower IC_{50} value when compared to free FdU in all the cell lines, including the resistant ones. The modified dextrin nanogel alone does not induce toxicity in all the cell lines.[109] More recently, the same group tested the conjugation of an acylated gemcitabine in dextrin–cholesterol nanogel for the treatment of resistant tumor by oral delivery. The acylation of the drug prevents the deamination toward an inactive form and improves its stability in the gastrointestinal (GI) tract. Gemcitabine–dextrin conjugate lowered the IC_{50} values for NA-resistant cell lines when compared with the free drug. Furthermore, the conjugate were able to permeate Caco-2 cell line monolayers that mimic the GI tract. This dextrin-modified nanogel appear to be a suitable carrier to NA drugs in order to overcome the resistance issues associated with chemotherapy.[110]

Polymer therapeutics

Polymer therapeutics, including polymeric drugs in the form of polymer–drug and polymer–protein conjugates, are finding increasing clinical use.[97] For several bioactive molecules, therapeutic efficacy is greatly limited by poor water solubility and/or instability in physiologic conditions,

limiting bioavailability, and clinical efficacy. Interest in the development of nanocarriers for bioactive molecules is emerging. Polysaccharides appear to be particularly suitable to this aim. A successful nanodelivery system should have a high drug-loading capacity, thereby reducing the required amount of carrier. Therapeutic agents can either be physically entrapped into the polymeric matrix or covalently bound to the polymer backbone.

Polymer–drugs dextrin was used in polymer–drug conjugates as a platform to covalently bind drugs via a spacer that is designed to allow drug release. Its chemical structure is suitable for conjugation through the hydroxyl groups, providing reaction sites that can be used to attach bioactive molecules.

Dextrin–zidovudine (AZT) conjugate was designed as a sustained release prodrug of AZT for parenteral administration. AZT was first reacted with succinic anhydride to form a succinoylated AZT, which was subsequently coupled with dextrin to yield the dextrin–AZT conjugate. The drug content of the conjugate was 18.9 wt.%. AZT and succinoylated AZT release from the conjugate was 1.4% (pH 5.5), 41.7% (pH 7.4), and 78.4% in human plasma after 24 hours. Release was complete in human plasma after 48 hours.

In plasma, the rate of the release of AZT and succinoylated AZT from the conjugate was faster than in buffer at pH 7.4, indicating that the succinic spacer allows the release of drug through both hydrolytic and enzymatic mechanisms. Due to the ester type of the succinic spacer, succinoylated AZT would be cleaved by esterases in the blood resulting in free AZT that exerts its anti-HIV activity. Free succinate (spacer) will be metabolized to fumarate by succinate dehydrogenase, hence the free spacer would not accumulate and would thus be safe for long-term use of the dextrin–AZT conjugate.[111]

The degree of hemolysis obtained for the dextrin–AZT conjugate was compared with that of the parent polymer (dextrin), dextran, and poly(ethyleneimine) (PEI) as reference controls. Dextran is used as a plasma volume expander in the form of i.v. infusion solutions.[112] PEI was used as positive control because it has high hemolytic activity. The dextrin–AZT conjugate showed a low hemolytic activity that was equivalent to dextrin, dextran, and to AZT. The hemolytic activity of AZT did not increase when it was covalently linked to dextrin or physically mixed with dextrin. A pharmacokinetic study in rats following intravenous administration of the conjugate showed prolonged plasma levels of AZT compared to free AZT. The conjugate extended the plasma half-life of AZT from 1.3 to 19.3 hours and the mean residence time from 0.4 to 23.6 hours. Furthermore, the conjugate provided a significant greater area under the plasma concentration–time curve and reduced the systemic clearance of AZT. This study suggested the potential of this novel dextrin–AZT conjugate as a new intravenous preparation of AZT.[113]

Polymer–proteins polymer–protein conjugation, particularly PEGylation, is well-established as a means of increasing circulation time, reducing antigenicity, and improving the stability of protein therapeutics. However, PEG has limitations including lack of polymer biodegradability, and conjugation can diminish or modify protein activity.

A new concept for polymer–protein modification, called polymer masking–unmasking protein therapy (PUMPT), was presented by Duncan et al.[114] It was hypothesized that coupling a biodegradable polymer to a protein would create a conjugate that would be inactivate in transit due to protein masking but, by triggered degradation of the polymer, would reinstate protein activity at a rate tailored to suit its mode of action. To test the feasibility of PUMPT, succinoylated dextrin was conjugated to trypsin, as a model enzyme or to melanocyte-stimulating hormone (MSH), as a model receptor-binding ligand. The coupling was promoted by 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide and *N*-hydroxysuccinimide.

Dextrin conjugation reduced enzyme activity by 34–69% depending on the molecular weight and degree of succinoylation of dextrin. However, incubation with α-amylase led to reinstatement of activity to a maximum of 92–115%. The highest molecular dextrin (MW 47,200 g/mol) tested gave optimum trypsin masking–unmasking.

Dextrin–MSH conjugate reduced melanin production by murine melanoma (B16F10) cells, to 11%, but addition of α-amylase was able to restore activity to 33% of the control value.[114] The novel PUMPT concept was applied with phospholipase A2 (PLA2) crotoxin, an antitumor protein that acts by interaction with epidermal growth factor receptors (EGFR). The referred protein showed activity in breast cancer, in phase I clinical trials, but it also displayed nonspecific neurotoxicity. A PLA2–dextrin conjugate was produced to promote tumor targeting by the enhanced permeability and retention effect, decrease systemic toxicity of PLA2, and allow reinstatement of antitumor activity at the target site, after α-amylase triggered degradation of dextrin. It was reported that the levels of α-amylase are higher in the tumor environment providing an opportunity to activate the conjugate within the tumor interstitium.[115] The conjugate showed decreased enzyme activity compared to native PLA2, but activity was restored to ~100% following incubation with α-amylase. Whereas dextrin conjugation caused a marked reduction in PLA2's hemolytic activity, the conjugate was cytotoxic toward MCF-7, HT29, and B16F10 cells at a level that was comparable to, or greater than, that seen for free PLA2. In these cell lines, cytotoxicity showed partial correlation with the level of EGFR expression.[116]

These encouraging results lead to the further exploitation of the PUMPT concept with growth factors, to promote wound repair. Growth factor topical application rarely leads to a significant clinical improvement of chronic wounds due to premature inactivation in wound environment. Succinoylated dextrin and recombinant human epidermal growth factor (rhEGF) were conjugated. rhEGF has two lysine residues with one being conveniently located peripherally, allowing easy access for conjugation. It was

demonstrated that dextrin conjugation could protect rhEGF against degradation by proteinases (including the clinically important wound protease neutrophil elastase). Proliferation assays, involving the high EGFR-expressing epidermoid carcinoma cell line (HEp2) and HaCaT keratinocytes as models, showed that whereas polymer conjugation reduced activity, exposure to physiological concentrations of α-amylase led to time-dependent restoration of bioactivity that was prolonged over 8 days with HEp2 cells. Moreover, the enzyme-activated conjugate induced phosphorylation of EGFR in HEp2 cells, suggesting that, like rhEGF, it acts by stimulation of signal transduction pathways.[117]

Further studies were developed with dextrin–rhEGF using patient-derived acute and chronic wound fluids to quantify levels of EGF, elastase, and α-amylase. Dextrin–rhEGF incubation in chronic wound fluid led to endogenous α-amylase-mediated release of rhEGF that was maximal at 48 hours. In wound repair, a key step is the induction of local cellular responses in keratinocyte and fibroblast cellular populations. Enhanced cell migration of HaCaT keratinocytes and of human fibroblasts (isolated from patient-matched, normal skin, and chronic dermal wounds) was observed, in vitro, in response to both free rhEGF and α-amylase-activated dextrin–rhEGF conjugate compared to controls. In addition, fibroblasts displayed increased proliferation following incubation (72 hours) with dextrin–rhEGF that had been exposed to physiological levels of α-amylase.[118]

In order to extend these findings, the effects of dextrin–rhEGF on wound healing in the (db/db) diabetic mouse, a widely used in vivo model of delayed wound healing, were studied. Standardized, full-thickness excisional wounds, created in the dorsal flank skin, were treated topically with succinoylated dextrin, rhEGF, or dextrin–rhEGF. Treatments were applied immediately after injury and subsequently on postwounding, days 3 and 8. In this wound healing model, the topically applied dextrin–rhEGF significantly accelerated wound closure and neodermal tissue formation at the macroscopic level; and significantly increased granulation tissue deposition and angiogenesis at the histological level, relative to untreated, succinoylated dextrin and rhEGF alone controls.[119]

An ex vivo whole-eye organ model was also to demonstrate that dextrin–rhEGF conjugate stimulates corneal re-epithelialization, post-wounding.[120]

These studies on dextrin conjugation with growth factor underline the general potential of dextrin as bioresponsive polymer integrating a novel nanomedicine for tissue regeneration and repair. Actually, Regranex® (Becaplermin), a carboxymethylcellulose gel containing recombinant human platelet-derived growth factor, is the only FDA-approved growth factor therapy for chronic wounds,[121] with its use limited to the treatment of deep, neuropathic diabetic foot ulcers.

CONCLUSIONS

Dextrin is an abundant resource, cheap, available in medical grade, and with well-established safety for biomedical applications. Its potential for different biomedical applications has been confirmed in a variety of examples, including dextrin–protein and dextrin–drug conjugates, tablet formulations, peritoneal dialysis solutions, etc. There is a huge potential for the development of new applications, given the low molecular weight of the material and its metabolization in vivo, which makes full resorption possible, and the feasibility of modification and production of different materials, including nanogels and hydrogels.

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