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Structure-Functions Relationship of Modified Starches for Pharmaceutical and Biomedical Applications

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Modified starch is widely used in pharmaceutical and biomedical sciences. Various modifications such as functionalization, reorganization of the structure, or depolymerization may be used to tune ionicity, hydrophilicity, mucoadhesion, susceptibility to amylolysis by α-amylase, or porosity. These chemical, physical, or enzymatic modifications modulate and adapt the properties of starches to different usages as tablet excipients, drug carriers, transdermal patches, injectables, wound dressing materials, transient embolizants, scaffolds, and stents. Through an understanding of the starch structure, this Review aims to aid the design of new starch materials for biomedical and pharmaceutical applications. The correlation between structure and properties is analyzed and various phenomena are discussed from this perspective, with particular eye toward the envisaged functionality of new starch-based materials.

1. Introduction

There is a rising interest in pharmaceutical and biomedical sciences for biocompatible and biodegradable materials. In the human body, starch is degraded due to its susceptibility to amylolysis by α-amylase. There are large amounts of pancreatic α-amylase liberated in the intestinal lumen and limited amounts of circulatory α-amylase liberated by salivary glands. Certain biomedical applications of starch biomaterials (i.e., transient embolizing agents, temporary occludants, degradable implants) are based on this limited susceptibility to α-amylase, a parameter that may be modulated by various physical, chemical, and enzymatic processes.[1]

The multiple applications of starch are interrelated to its structural features. Starch organization and composition (amylose content, degree of polymerization) vary with the sources and impact its physical properties and its behavior in various processes (i.e., gelatinization and retrogradation). The various structural organizations of starch are the result of self-assembly phenomena at macromolecular level. The driving forces of the self-assembly are weak physical interactions including hydrogen bonding, electrostatic interactions, hydrophobic associations, and van der Waals forces. The hydrophilicity/hydrophobicity ratio and the presence of ionic charges on polymeric chains have a major influence on starch stabilization under different geometry.[2] Certain modifications operated on starch are aimed to change the hydrophilic/hydrophobic pattern and/or the ionic character of the chains that will impact properties such as their self-organization under external interactions. Intramolecular interactions are responsible for the conformation of the molecular conformation conducting to a specific secondary structure (helix, random coil) while the types of starch crystals are related to organization at nanoscale level (i.e., square-like nanocrystals). The intermolecular non-covalent interactions are responsible of self-assembled nano-structures (i.e., micelles, spherulites, cyclodextrins, quantum dots).[3,4] Certain modifications of starch may diminish crystallinity and induce structural reorganization leading to desired properties, that is, increased swelling or higher porosity. The new obtained characteristics allow, for example, encapsulation of bioactive agents, modulation of drug release rate from pharmaceutical dosages and preparation of biodegradable biomedical devices.

To better correlate starch structure and its functions, in this review the modifications leading to various applications are presented in four categories: 1) physical, 2) chemical, 3) enzymatical, and 4) combined modifications, and the vast usage of starch in pharmaceutical and biomedical fields is revisited from this perspective.

2. Physical Modifications

Gelatinization is a key process in starch modification consisting in disorganization of compacted crystalline structures with the aim to eventually introduce a new order in the system. When the H-bonds in the helical forms are disrupted, the chains can adopt a random coil conformation, allowing the structure to swell and amylose to leach out (**Figure** 1A). In high amylose starch (HAS), with 70% or more amylose content, the amylose acts like an armature. The structure is less crystalline and more entangled which translates in increased gelatinization temperature, lower solubility, and susceptibility to amylolysis by α-amylase.[5] Regular starches may be gelatinized by hydrothermal treatment

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but HAS requires a higher gelatinization temperature and/or alkaline treatment to disrupt the hydrogen bonding.[6] The impact of hydrothermal and alkaline gelatinization methods is evident on the behavior of pharmaceutical starch excipients: the hydrothermal treatment of starch gave erodible and soluble pills whereas the alkaline-treated starch could form a network, generating hydrogels.[7] Hydrothermal treatment of starch at temperature above the glassy temperature but below the gelatinization temperature (annealing) resulted in reorganization of the structure with increased crystallinity.[8] This phenomenon happens due to hydration of the amorphous layers, seen by expansion of the structure, allowing reorganization of the chains.[9] The structural reorganization is influenced by the flexibility of the amylopectin, related to the starch type.[10]

Pre-gelatinized corn starches such as Starch1500 (Colorcon) are good binders and fillers.[11] The structurally disorganized starch exhibits better compressibility and forms hard tablets by direct compression. On the other hand, cast films of gelatinized, unmodified HAS presented cracks (explained by remaining crystallinity of amylose whereas amylopectin cast films were amorphous).[12,13] To obtain a more rubber-like behavior, most starches are modified or associated with other compounds as plasticizers.

Association with other materials. Once the structure is altered, gelatinized starch may be associated with other polymers to add new functional features to composites. Shape memory materials were created modulating starch capacity to swell and its degradability by α-amylase.[14,15] Its morphological changes were used in applications ranging from fast disintegrating films to fibers, scaffolds, and stents.[16–23]

The erosion rate of the pharmaceutical dosage forms can be tuned by association with other polymers.[24,25] Sodium alginate interacted with gelatinized starch gel via hydrogen bonding enhancing the system viscosity and allowing a higher entrapment of sodium diclofenac into the beads compared to ungelatinized starch.[24]

Various commercial pre-gelatinized starches were formulated as oral fast disintegrating films. The AMIDOMAX3600 (Cargill Ltd., Brazil) was used with gelatin (to lower solubility) to formulate fast disintegrating films for vitamin C administration.[16] Daktarin oral gel is a quick-dissolving orodispersible film of miconazole containing pre-gelatinized potato starch.[26]

Starch may be associated with nanomaterials as graphene to enhance its conductivity. With a high surface area, the starch-graphene material was used to build a molecular imprinting probe to estimate transferrin in blood.[27] Such reusable probe with a detection limit of 20 ppb represents a great improvement in terms of sensitivity and selectivity.

In presence of plasticizers, the behavior of starch passes from glassy to rubbery state and the changes are reflected in glass transition temperature (T_g). The structure can be modulated and shape-memory resorbable materials designed. The molecular structure responsible for shape-memory properties combines a permanent and a temporary network. The amylopectin holds the structure together while the addition of plasticizer lowers the T_g, allowing chain-chain reorganization and shape memory behavior in presence of moisture.[19] Combination of gelatinized potato starch, waxy starch nanocrystals, glycerol, and catechin (as antioxidant) generated multifunctional hydrophilic films exhibiting shape memory upon rehydration.[14] Extruded potato starch/glycerol biomaterials exhibiting shape-memory could be resorbed after up to 21 days following their immersion in aqueous media presenting also a low inflammatory response.[15] Salivary duct stents were used after sialendoscopic surgery to

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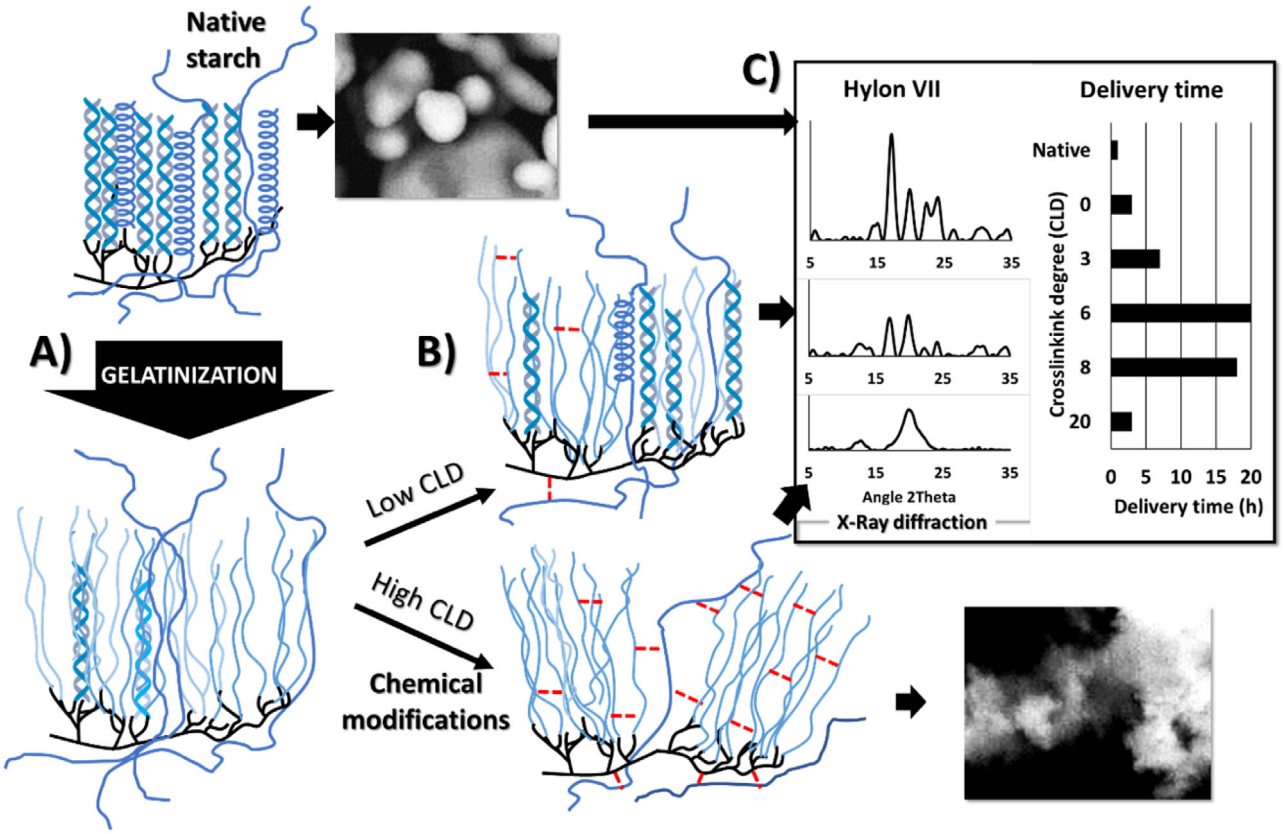

Figure 1. Schematic representation: A) gelatinization of high amylose starch; B) cross-linking at different degree generates new organizations by self-assembling; C) the crystallinity at different cross-linking degree was related to the drug release time from monolithic tablets. The native starch (i.e., Hylon VII) has many crystalline peaks but after modification, the structure is mainly amorphous. (C) Adapted with permission.[42] Copyright 1999, Elsevier.

maintain the salivary duct open. The plasticized starch stent showed shape-memory properties and was proposed as a self-deploying stent.[19]

By electrospinning, the starch macromolecules are allowed to dry as narrow filaments. Interlacing of these filaments creates a spaced network with high porosity and increased surface area. By tuning the size of nanofibers, it is possible to fabricate at larger scale tissues and 3D materials for wound dressing. The electrospinning gave brittle, weak starch fibers. This may be corrected by addition of other polymers such as polyvinyl alcohol (PVA) and chitosan. Electrospun PVA/chitosan/starch fibers were more flexible with enhanced antibacterial activity and water absorption capacity.[28]

Mucoadhesive composite fibers based on starch (i.e., starch-gelatin, starch/PVA, and starch/polycaprolactone) offer a biocompatible, biodegradable, flexible support with increased surface area for cell proliferation and attachment showing good blood clotting rates.[17,18] Due to their hydrophilicity and high absorption capacity, the liquid is absorbed and the blood solids aggregate on surface. Using starch/ gelatin/ herbal extract composite fibers, the healing was fast in vivo and with lower inflammatory response than gauze.[29] Electrospun HAS fibers, with linear structure, were stronger, and proposed for tissue engineering whereas ramified amylopectin-rich fibers were weak and brittle and convenient for drug release.[30] Forming a network between starch and other polymers reduces the retrogradation and the brittleness. Thus, the amorphous chains expose their hydroxyls on the surface, which is beneficial for mucoadhesion.

Tissue engineering helps the regeneration of damaged tissues by using scaffold-shaped biological substitutes.[23] These materials require biodegradability, porosity (for cell proliferation), and cytocompatibility. Natural polymers as starch are similar (but not identical) as texture to the extracellular matrix, offering good interactions and compatibility. Silver-embedded potato starch-PVA antibacterial materials were developed for soft tissue engineering and showed good cell proliferation and degradability over one month.[31] Bone scaffolds require also good mechanical strength and therefore, starch was associated with other polymers, generating composites of starch blended with polycaprolactone, polylactic acid, chitosan, and/or silk fibroin, all with good cell attachment.[20–23] The surface of starch-based biomaterials is easily sterilized by UV irradiation or plasma cleaning ("etching"), two cost-effective methods.[32] Association of starch with PVA resulted in a nontoxic and cytocompatible material with good elastic behavior and with only 40% degradation by α-amylase over 3 months.[33] Blends of starch and polyethylene glycol (PEG) processed into a repairing bone wax had better adhesion

than other commercial waxes. The presence of pre-gelatinized starch enhanced the molding texture.[34] The starch-PEG was degraded and did not inhibit osteogenesis. A mixture of silicone and corn starch was used for creation of auricular frameworks. Using 3D imaging from computed tomography, a simulated cartilage was produced, with texture and firmness similar to human cartilage.[35] Such resorbable materials with modulable biodegradability may remain functional for a determined time laps and can degrade gradually. Starch-hydroxyapatite bone scaffolds with improved mechanical strength showed an increase in proliferation of osteoblast cells in vitro.[36,37]

In conclusion, physical modifications of starch can be used to generate at supramolecular level a new organization of polyglucosidic chains without operating any change of starch chemistry. New properties were obtained only from remodeling the way how starch-based systems stabilize themselves intramolecularly and/or intermolecularly (themselves or with other molecules). The gelatinized starch is a metastable system where the polyglucosidic chains are self-assembled spontaneously and stabilized under new forms (random coils, double or single helices). This physical process known as starch gelation consists in creation of an extended and stable polymeric network obtained by simple self-assembling phenomena. Addition of other entities (i.e., polymers, plasticizers) offers an expanded panel of structures and implicitly new applications.

3. Chemical Modifications

Chemical modifications operated on starch chains can greatly impact their capacity of organization under various conformations (i.e., helices, random coils) and offer additional tools to modulate their self-assembling. Various products for pharmaceutical or biomedical applications were obtained by cross-linking, grafting of new functional groups or complexation reactions (**Table 2**). Interesting to note is the fact that the capacity of starch to self-assembly in helical forms differentiates completely its behavior compared to synthetic polymers. More generally, the ratio between order (expressed under various forms, i.e., presence of helices and crystals) and disorder (i.e., amorphous structures) of the system is a key element to obtain specific properties.[38]

3.1. Cross-Linking

Several years ago, the concept of minor alterations may trigger major modifications in self-assembling starch excipient opened the way to produce, with the same chemistry, totally different starch excipient materials.[39,40] For instance, Contramid excipient for sustained drug release was obtained at low cross-linking degree (CLD) whereas a binder-disintegrant was obtained at slightly higher CLD.[39,41–44] The only difference was a minor variation in cross-linking level, but the structural and functional impact was major: low CLD allows enough flexibility of chains to establish hydrogen associations in addition to cross-linking bridges, stabilizing the matrix, limiting hydration, and enhancing the release time (Figure 1B). It was shown that starch crystallinity is related to the CLD and impacted significantly the drug release time (Figure 1C).[42] Differently, a higher CLD hinders the hydrogen associations for steric reasons: thus, the hydroxyl groups are free to hydrate, favoring the tablet disintegration. Contramid was patented as a good matrix-forming for drug slow-release.[39,45] With quasi-zero order drug release pattern over 12–24h, it is still used for once-a-day sustained release Tramadol commercial tablets. Contramid was also used to generate subcutaneous and intramuscular implants for local antibacterial therapy.[46] They were obtained by direct compression of powder blends. As example, the implants containing ciprofloxacin could prevent and treat osteomyelitis with conclusive in vivo trials. No local adverse reaction occurred, the drug level was above the minimum inhibitory concentration for at least 28 days and a time-dependent resorption was observed.[46]

Transarterial chemoembolization may contribute to inhibition of tumor growth by producing transient ischemia, favoring local delivery of chemotherapeutics to prompt tumor necrosis.[47] Permanent embolization agents may induce foreign body reactions, inflammation, or ischemia-triggered neoangiogenesis.[48] Differently, starch degradable microspheres, being susceptible to slow hydrolysis by circulatory α-amylase, allowed the same treatment without permanent embolization. Although the level of α-amylase in blood is low, it is enough to clear the CL-Starch microspheres, re-establishing the blood flow. For several years, injectable CL-starch microspheres have been commercialized under the trademark Spherex (Pharmacia Uppsala) and EmboCeptS (Pharmacept) aiming to limit side effects of radiotherapy and prevent heat dissipation during hyperthermia treatments of tumors.[49] EmboCeptS showed a higher efficiency to inhibit metastatic growth than another embolization agent (Lipiodol) and a reduction of tumor size, comparable to PVA-based DC Beads.[50]

3.2. Substitution

3.2.1. Starch Ionic Derivatives

The self-assembling capacity can be reinforced or weakened by the presence of electrostatic charges. Stimuli-responsive hydrogels (i.e., pH-sensitive) were considered with particular focus on pharmaceutical applications. Depending of the type of charge (anionic, cationic) and of its location (on the same or different chains) the attractive /repulsive electrostatic forces may impact the conformation of the chains and consequently their geometry and stabilization.

Anionic carboxymethyl starch (CMS) was largely used as pH-responsive pharmaceutical excipient. The aqueous carboxymethylation of HAS with low DS (degree of substitution) produced a semi-amorphous starch excipient. By protonation of carboxylic groups in gastric acidity, an outer compact layer is formed, preventing the acidic medium to penetrate the tablet (**Figure 2**), offering thus protection against gastric acidity. In the intestinal fluid, the outer CM groups are deprotonated, ionized, and hydrated. The tablet swells, and by erosion or disintegration, releases the drug. These structural changes phenomenon (schematically presented in Figure 2) was valorized in formulation of gastro-resistant tablets for oral delivery of various drugs

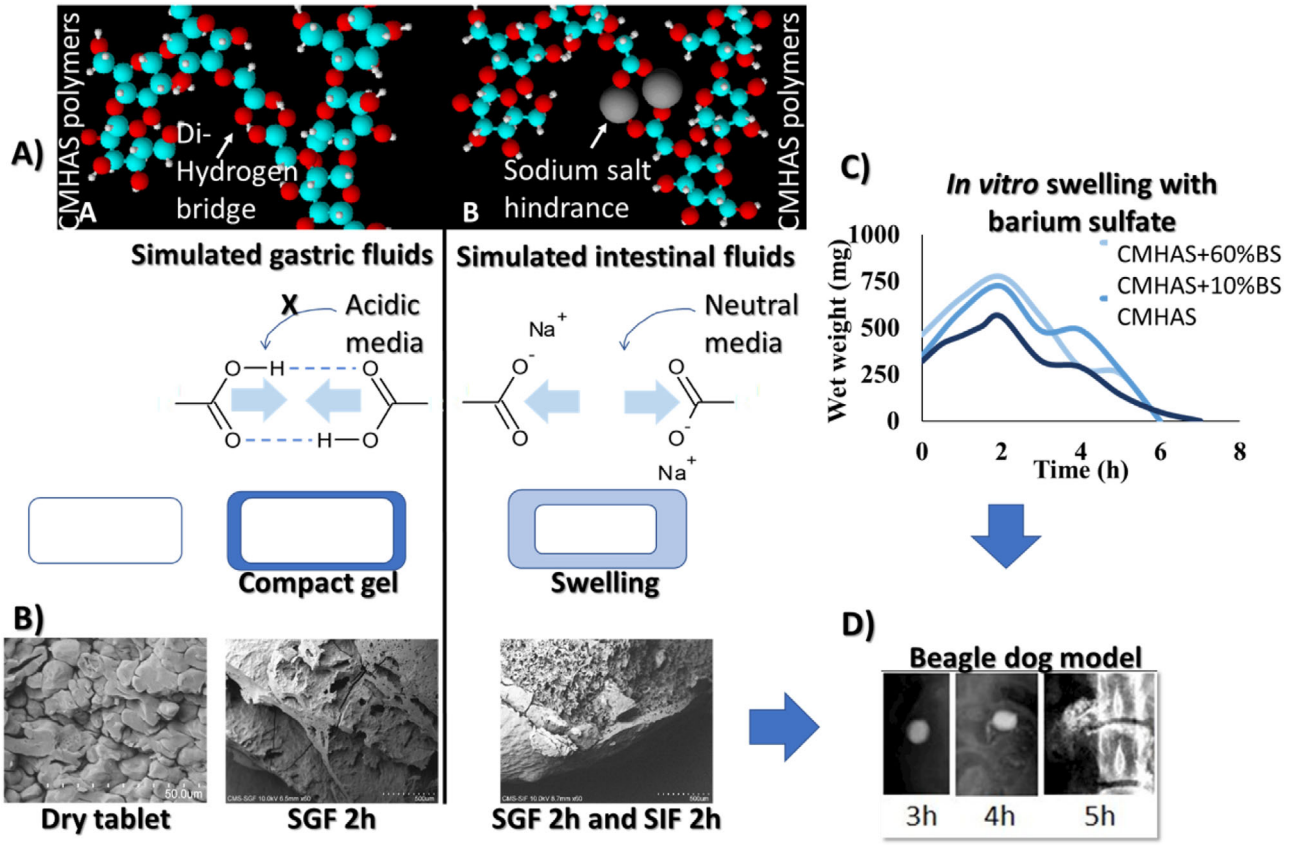

Figure 2. A) In simulated gastric fluid (SGF), the CMS is protonated and the CM- groups form dimers; in simulated intestinal fluid (SIF) they are deprotonated and ionized. The sodium of the carboxylate causes a hindrance, allowing penetration of the fluid. B) The scanning electron microscopy of the lyophilized tablets revealed the compact grains on the surface of dry tablet. After 2h in SGF, a gelatinized network is observed. After 2h in SGF and 2h in SIF, a smooth hydrophilic gel begins to form on surface; C) In vitro, the tablet CMS-barium sulfate (BS) swells a little in SGF and begins to solubilize in SIF; D) In vivo tracing of the same tablets CMS-BS. (B,D) Adapted with permission.[56] Copyright 2019, Elsevier.

including macromolecular bioactive agents such as pancreatic enzymes, diamine oxidase, F4 fimbriae oral vaccine, *Escherichia coli* and probiotics (*Lactobacillus rhamnosus*).[51–55] These bioactive agents were well protected, the presence of CM groups offering additional stability against gastric acidity and counter to the intestinal α-amylase. In the last decades, challenging colon-targeting formulations were successfully designed using CMHAS (**Table 1**). A CMHAS tablet containing 30% of a protein model and a radio-opacifier was followed in vivo, during its intestinal transit by X-ray.[56] The CMHAS-based formulation had similar disintegration times (4h30) in vitro and in vivo (Figure 2C). The carboxylic functions also increased the starch bioadhesion. The CMS was processed into microspheres and cross-linked for gastric and colonic delivery.[57] These microspheres were retained on gastric mucosa in acidic conditions and allowed a sustained delivery of active agents (furosemide), increasing its bioavailability.[57,58]

Formulation of low soluble drugs remains highly challenging. A recent controlled release form of ibuprofen was formulated with ionically stabilized CMHAS excipients. An in vivo equivalence study with "Two Release Rates"/TwoRR showed that ibuprofen formulated with CMHAS stabilized with Ca^{2+} ions presented over 24 h an equivalent bioavailability (on a beagle dog model) with three classical dosage forms of Motrin.[59]

Octenyl-succinate starch has steric hindrance and amphiphilic features due to polar character of the anionic carboxylate and to its hydrophobic lateral chain. It can stabilize emulsions and is less affected by pH than other stabilizers as proteins.[60] CapsulTA (octenyl-succinate tapioca starch, Ingredion) and N-Lok (octenyl-succinate waxy corn starch, Ingredion) were used to encapsulate an antifungal agent in alginate films for buccal delivery and are suitable for encapsulation of probiotics by spray-drying.[61,62]

Cationic starch exhibiting amino groups had higher macrophage response but weaker electrostatic interactions than anionic and zwitterionic starch.[63] Histidine or arginine cationic starch gold nanoparticles are good carriers for gene delivery and showed high cell viability but low transfection. Their efficiency was increased when modified with L-arginine.[64]

Cationic starch-siRNA nanocomplexes for gene silencing were protected from enzymatic degradation and showed high cellular uptake and successfully prevented specific gene expression in human ovarian adenocarcinoma cells.[65] Gene transfection with plasmids alone is difficult. However, plasmids after complexation with cationic starch, were found in the cells. The spermine

Table 1. Pharmaceutical applications of high amylose starch derivatives in monolithic tablets.

Derivative	Application	Ref.
HAS-CL	Controlled drug release	[42]
AE-HAS-CL CM-HAS-CL Ac-HAS-CL	High loadings and controlled release	[120]
HAS-CL	Structure-property relationships in films	[121]
CMHAS	Anti E. coli agent	[51]
CMHAS	F4 Fimbriae as swine vaccines	[52]
CMHAS	Swine vaccines clinical trials	[122]
CMHAS	Pancreatic enzymes	[54]
CMHAS/chitosan	Probiotic colon delivery	[53]
CMHAS/chitosan	Diamine oxidase	[55]
CMHAS	Impact of drying method on drug release	[123]
CMHAS	Impact of protonation ratio on drug release	[124]
CMHAS/chitosan	NMR monitoring of tablet hydration	[125]
CMHAS/chitosan	Polyelectrolytic complex (PEC)	[106]
CMHAS	Complex with lecithin	[126]
TMA-CM-HAS[a)]	Ampholytic starch for controlled release	[69]
AE-CM-HAS[b)]	Ampholytic starch for high drug loadings	[68]
CMHAS	In vivo following with barium sulfate	[56]

[a)] TMA-CM-HAS: trimethylammonium-carboxymethyl-starch; [b)] AE-CM-HAS: aminoethyl-carboxymethyl-starch

grafting generated a type of cationic starch and was also used to complex plasmids.[66] A higher modification of starch led to better transfection (≈40%).

A new ampholytic starch, CM-AE-HAS, carrying both anionic carboxymethyl (CM) and cationic aminoethyl (AE) groups was proposed as an excipient for targeted drug delivery (lower intestine or colon).[67,68] This ampholytic excipient provides an extensive self-stabilization by hydrogen bonding combined with ionic interactions. It was used to formulate highly soluble drugs such as metformin, even at high loading (60%) and other model drugs from all classes of BCS (biopharmaceutical classification system). Carrying anionic and cationic groups, the ampholytic starch generates a network structure having the capacity to control the drug release irrespective of the pH.[67–69] Zwitterionic starch was obtained by modification with sulfobetaine. It showed lower macrophage activation and was more effective in vivo to prolong circulation time than starch micelles without sulfobetaine.[70]

3.2.2. Nonionic Starch Derivatives

The hydrophilicity of starch can be decreased by grafting acetyl or hydroxyethyl groups on carbohydrate chains. Their hydrophobicity and the vicinity with amylose molecules generate a different organization of hydrogen bonds and allowed less water in the gel system. Acetate HAS is a filler-binder or matrix-forming material for controlled release having also film-forming properties. It was used to formulate colon-targeting coatings.[71–73] Hydroxyethyl starch (HES), formulated as colloidal suspensions (i.e., Voluven, Pfizer), is used as plasma expander to increase the blood volume (in case of hypovolemia). It generated less post-surgery infections compared to conventional sodium lactate solution.[74] The molecular weight of HES is much greater than that of albumin, facilitating the obstruction of pericellular space, reducing the endothelial permeability.[75] Approved for intravenous infusion, it was also used for tumor targeting. Plasma expanders were tested for tumor targeting and the in vivo biodistribution was followed by NIR imaging using a fluorescent dye conjugated to starch.[76] A higher tumor specific accumulation was found for HES of 450 kDa, compared to HES 200 kDa and to dextran 500 kDa. Dextran was mostly accumulated in the liver, whereas both HES were distributed homogeneously in organs. It was hypothesized that the more hydrophilic surface of starch prevents its recognition (by the opsonins—serum proteins) in the blood stream. HES of 450 kDa was degraded more slowly and showed a certain accumulation in mice tumor. These products require biocompatibility, degradability, and functionality. HES, with over 60 registered products in Europe, is currently under rigorous evaluation.[77]

Aggregation of foreign materials with antibodies (for further phagocytosis) is a first-line defensive mechanism that may greatly reduce circulation time of drug and gene carriers. Highly PEGylated HES nanocarriers showed less interaction with human serum proteins (i.e., opsonins) in vitro and longer circulation time in plasma.[78] PEGylation may slow aggregation but greatly reduces transfection. Using HES, it was possible to obtain a "shreddable" shield, preventing rapid aggregation in the blood stream and deshielded in presence of circulating α-amylase (passive targeting).[79] As example, a DNA plasmid-expressing luciferase shielded with HES-polyethyleneimine showed low aggregation in vitro, and upon exposition to α-amylase, twofold higher transfection and increased DNA delivery per cell were found. The system ensured better protection at higher molecular weight HES and a slower degradation by α-amylase with increased DS of HE groups. Paclitaxel was conjugated to HES to improve its half-life and showed higher in vivo accumulation in the tumor, compared to the commercial formulation Taxol.[80]

3.3. Complexation

Preparation of inclusion complexes by "inserting" guest molecules into preformed "empty" V-type amylose helices was largely studied as an easy encapsulation procedure providing protection of guest compounds. The capacity of starch to bind iodine is used as test for diagnosis of hypo and hyperhidrosis (i.e., after burns or surgery or in Horner's syndrome).[81–83] An iodine solution is applied, allowed to dry and covered with soluble starch powder. Upon hydration, the starch is rapidly swollen and the starch-iodine complex shows a marked dark-blue color change (the Minor test).[81] The test was developed as a soluble starch treated with iodine or as pre-treated bands covered with iodine and starch, offering simpler one-step methods.[81,82] Cadexomer (Iodosorb) is a starch cross-linked with epichlorohydrin and containing iodine for wound healing.[84] It absorbs exudates and upon hydration, the material swells, and releases iodine as an antimicrobial agent.

Table 2. Main applications of modified starches and their commercial products.

Starch modification	Main characteristics	Applications	Commercial product/Reference
PHYSICAL			
Gelatinization	Forming strong gels	Binder	Starch 1500
Co-processing			
-with graphene	Increased conductivity, biodegradability	Molecular imprinted probe	[27]
	Improving compatibility of graphene nanosheets and preventing their aggregation	Tumor targeting	[116]
-with hydroxyapatite	Mechanical strength, enzymatic susceptibility	Bone scaffolds	[36,37]
-with polyacrylic acid	Bioadhesion	Drug transdermal delivery	Proloc[127,128]
-with plasticizers	Shape memory	Resorbable stents	[19]
		Hydrophilic films	[14]
-with PVA/chitosan	Degradability, porosity	Fibers for wound dressing	[28]
-with PVA		Tissue engineering	[31,33]
		Fibers for wound dressing	[18]
-with polycaprolactone		Wound dressing materials	[17]
		Bone scaffolds	
-with silicone		Tissue engineering	[35]
CHEMICAL			
Cross-linking	Gel-forming	Matrices for controlled release	Contramid[39,40,42]
	Slow degradation by α-amylase	Embolization microspheres	Spherex[49,50]
		Encapsulation of probiotics	[129]
	Biodegradability and limited swelling	Implants	Contramid[46]
Substitution with ionic groups			
-Carboxymethyl starch	Gastro-protection	Monolithic matrices for pH-sensitive formulations	[51–55]
-Octenylsuccinate	Porosity, emulsifier	Encapsulation of probiotics	CapsulTA, N-Lok[62]
-Folic acid	Increase tumor specificity	Tumor targeting	[111]
-Ampholytic starch	pH-independent ionic hydrogels	High drug loading matrices	[67–69]
-Aminated starch	Increased transfection	Gene delivery	[65,70,64,66]
-Cystein	Enhanced mucoadhesion	Transdermal delivery	[119]
Substitution with neutral groups			
Hydroxyethyl starch	Slow degradation by α-amylase, biocompatibility	Plasma expander	Voluven[79]
		Injectable drug delivery	[74,76–78,80]
Starch complexes			
-Calcium	Increased hemostatic properties	Hemostats	[93,94]
-Iodine	Releasing iodine upon degradation/hydration	Wound-dressing	Cadexomer[81–84]
		Diagnosis of hyperhidrosis	
-Iron oxide and itaconate starch	Magnetic targeting	Tumor targeting	[90]
Grafting			
Methacrylates	Thermal sensitivity	Tumor targeting	[117]
Drug Conjugated with HES	Enzyme-triggered release	Increase half-life	[80]
ENZYMATIC			
Debranched	Gel-forming; film-forming, porosity	Excipient (films, tablets, granules) for transmucosal delivery	VeloxMCS[87]

In conclusion, chemical modifications represent additional tools that can be used to create new starch structures and implicitly envisage new applications, avoiding the use of other materials (as expensive polymers). In the case of physical modifications, the changes resided mainly in alteration of crystalline versus amorphous organization and the systems were stabilized by formation of hydrogens bonding. By introduction of new chemical entities on the starch chains, more intricate structures were generated. The supramolecular organization of such systems involved stabilization where the self-assembly was generated by a combination of electrostatic, van der Waals and hydrogen bonding. The understanding of structural aspects of such modified materials opened new perspectives allowing the expansion of starch applications.

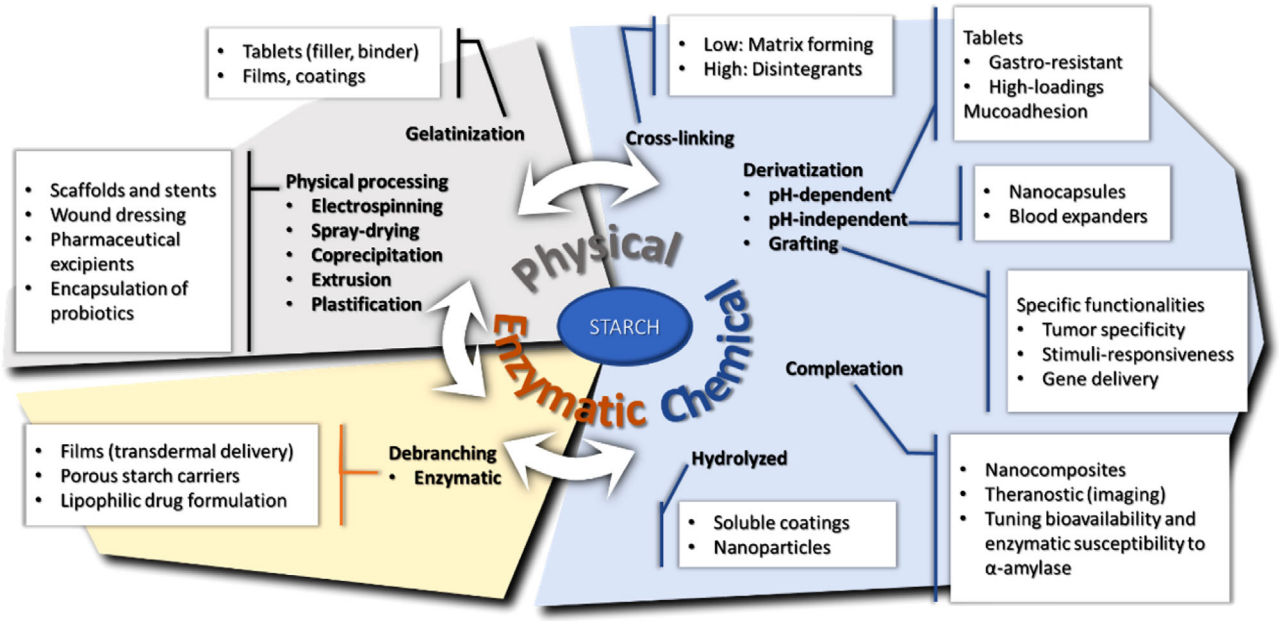

Figure 3. Relationship between starch modifications and its pharmaceutical and biomedical applications.

4. Enzymatic Modifications

Porous starch may be obtained as result of amylases action.[25] Selection of specific enzymes for processing allows modulating either starch chains length or size of the pores. Porous starch obtained from in situ enzymatic hydrolysis process on starch material has the particularity of keeping the granule shape by the use of α-amylase (endoamylase, alone or in association with the exoamylase amyloglucosidase), offering good release of the adsorbed content.[25] Porous starch is convenient for delivery of lipophilic drugs or probiotics by incorporation into its porous structure.[85]

Debranched starch is obtained by modification with pullulanase or isoamylase that selectively act on α-1,6 bonds. With a reduced level of 1,6 linkages, it can hold more water, forming a soft, non-sticky gel that can last longer.[86]VeloxMCS (Henkel Co.) is a crystalline, debranched, amylase-resistant starch, and multipurpose excipient. It can be extruded into pellets comprising the active agents and further be formulated to a convenient form, that is, tablets, capsules, pessaries, or creams and is suitable for application on vaginal, urogenital, or rectal surfaces.[87]

Cyclodextrins have extremely attractive pharmaceutical applications and they can be obtained from starch using cyclodextrin glucosyl transferase. This enzyme normally produces a mixture of α-, β-, and γ-cyclodextrins requiring further separation and purification.[88] Cyclodextrins are supramolecular oligosaccharides having toroid cone structures with a hydrophobic core and hydrophilic exterior. Hydrophobic drug molecules can easily get assembled in their cavity via non-covalent interactions resulting in increased solubility and bioavailability.[89] Due to their low toxicity and low immunogenicity, cyclodextrins were used for oral, ocular, nasal, rectal, and dermal delivery. In nanodelivery they facilitate cellular uptake and reduce cytotoxicity.

5. Combined Modifications to Design "Smart" Starches

Previously mentioned modifications (**Figure 3**) may be combined as complementary methods to obtain starches responding to precise functions (**Table 3**). By association of physical, chemical, and/or enzymatic methods, the starch structure could be modulated in order to respond to required applications. After first step of grafting ionic groups, starch may be further complexed with magnetic particles by co-precipitation with ferrous and ferric chloride. A starch-based temperature-responsive magnetic nanohydrogel was reported for theranostic applications.[90] Starch was modified with itaconic anhydride, complexed with iron(II, III) oxide (Fe_3O_4), grafted with the thermosensitive *N*-isopropylacrylamide and loaded with methotrexate. The release was about 15% at 37 °C and greatly increased to ≈80% at 41°C. The tumor environment is slightly warmer and such new systems provide new tools for tumor treatment.

The biodegradability and hemostatic properties of porous starch were markedly increased by amination, cross-linking with chitosan or complexation with calcium.[91–94] Other modifications could add new properties as grafting of antioxidants to reduce risks of oxidative stress or of ellagic acid for a rapid coagulation.[95,96] Starch oxidation with periodate or hydrogen peroxide produces dialdehydes, an efficient way to increase its functionality. Complex matrices were obtained by direct cross-linking of gelatin with oxidized starch during the spray-drying co-processing.[97] This resistant composite was used as microcapsules to control the release of the highly soluble citric acid.

Spray-drying and electrospinning are efficient methods for encapsulation of *Lactobacillus,* ensuring encapsulation efficiency, good protection, and stability.[61,98,99] Wall materials are used for entrapping active agents by spray-drying. They must be able

Table 3. Smart starches obtained from dual or multiple modifications.

Starch modification	Main characteristics	Applications	Commercial product/Reference
Smart starch obtained from combined modifications			
Gelatinization/lyophilization	Porosity, hydrophilicity, biodegradability	Foams for low-soluble drugs	[130]
Chemically modified porous starch	Ionicity and faster coagulation rate	Hemostats	[91–96]
Oxidized starch cross-linked with gelatin	Lower solubility, film-forming	Long lasting oral films	[97]
Co-processed CMS with chitosan	Polyelectrolytic complex	Colon-targeting monolithic tablets Microspheres Nanoparticles	[53,55,105,106] [25,107] [110]
CMS/quaternary ammonium starch	Cationic, anionic or ampholytic features	Encapsulation of proteins High loading tablets	[108] [68,69]
Hydrolyzed hydroxypropyl starch	Film-forming, solubility	Oral fast-disintegrating films Tablet coating	(Lycoat)[102,131]
Hydrolyzed and cross-linked starch	Slow degradation by α-amylase	Transient embolizing agent	(Pharmacept)[50]
Uncommon associations			
Modified starch and clay	Tunable porosity, mucoadhesion	Transmucosal delivery	[103,104]
Isotopes/ iron particles	Radiolabeling	Imaging	[112,113]
3-aminophenylboronic acid	Glucose-responsive	Controlled insulin delivery	[114]
Cross-linked and substituted			
-Potato starch	Soluble	Disintegrant, soluble films	(Vivastar)[100,101]
-High amylose starch (HAS)	Matrix-forming	Monolithic matrices for sustained release	Contramid (Labopharm)[45]

to form emulsion, with acceptable viscosity at high solid content and protect the active content through the process. Octenylsuccinate waxy starch (N-Lok, Ingredion) and HAS-formate could fulfill these requirements, resulting in stable fibers loaded with *Lactobacillus* for probiotic formulation.[61,98]

After chemical and physical modifications, starch may be sufficiently amorphous to be solubilized and cast as films. Precise modifications will increase the solubility, giving films for quick release. Due to its hydrophilic nature, starch shows strong adhesive properties, making it an excellent film matrix for buccal delivery. The hydrophilicity of starch is increased by acid hydrolysis and substitution with hydroxypropyl starch as Lycoat, (Roquette America Inc.) or with carboxymethyl groups and cross-linking of potato starch (sodium starch glycolate (SSG), as Vivastar, JRS Pharma). SSG was used for buccal formulation of metformin or of the poorly soluble drugs, that is, fenofibrate.[100,101] LycoatRS780 is a pre-gelatinized, hydrolyzed hydroxypropyl pea starch commercialized as tablet coating for fast release forms. Pediatric-focused, solvent-free oral fast disintegrating films based on Lycoat were formulated with chlorpheniramine maleate, an antiallergic agent.[102] The films were easy to handle, with disintegration time of 6–11 s and subject to in vivo taste masking trials. Many starch derivatives have suitable film forming capacity. They gelatinize and form networks, easily forming strong films upon drying. The physical and chemical modifications increased the solubility and decreased retrogradation of starch, forming homogeneous films.

Control of hemorrhagic bleeding may be obtained by adhesion (passive) or by inducing coagulation (active intervention). Some commercial materials offer both cell adhesion and coagulation enhanced capacity but with certain concerns (i.e., flexibility and degradability).[91] Porous starch and CMS, complexed with calcium ions, showed enhanced dual action (passive/active) hemostatic capacity.[93,94] The starch microspheres had a better hemostatic activity in vivo than commercial hemostatic agents due to active action of calcium ions.[94] The material is biodegradable and gel-forming, with increased blood-clotting efficiency and fibril formation.[93]

The grafting of polymethacrylic acid (PMA) groups on starch increased its pH-sensitivity while maintaining biodegradability.[103] Further addition of calcium montmorillonite was found to increase the mechanical properties of cast films of CMS and they were proposed for drug delivery. For vaginal delivery, the tablets of gelatinized wheat starch-PMA with fast swelling exhibit low adhesion and low water absorption from the mucus. Addition of calcium montmorillonite acting like a nano-filler increased the mucoadhesion by reducing porosity and limiting water absorption.[104]

New structures and properties can be obtained by co-processing. When chitosan was spray-dried with CMHAS, a new compound was obtained by ionic self-stabilization between the amine and carboxylate groups. This pH-responsive polyelectrolytic complex (PEC) excipient offered good matrix-forming properties. These matrices have been used as carriers for various drugs (anti-inflammatory, enzymes, and probiotics for intestinal or colonic delivery).[53,55,105,106] Alginate, CMHAS and the enzymes (as diamineoxidase) were dissolved and co-precipitated (under stirring) by ionotropic gelation to obtain enzyme-containing microspheres with 92–95% entrapment yield.[107] This process generated compact, less porous structures, reducing the fluid penetration. The enzymatic activity was maintained (70%) after immersion of the microspheres in simulated gastric fluid (SGF), acidic medium (pH 1.2) and in simulated intestinal fluid (SIF) with pancreatin (65% over 24 h). In similar

conditions, the free enzyme was totally inactivated. Furosemide has a low solubility, especially in acidic media. To increase residence time and permeability, it was co-processed with CMS by forming a w/o emulsion, precipitated under thorough stirring to form microspheres and dried.[57] A higher DS (0.1–1.5) of CMS increased the swelling, mucosal adhesion and furosemide permeability through epithelial Caco-2 cells. The transepithelial electric resistance, used to investigate mucoadhesive properties, was not greatly changed on gastric cells using CMS of different DS but changed for intestinal cells (Caco-2). This phenomenon may involve the tight junctions enhancing the intestinal absorption. It was more accentuated for CMS microspheres with higher DS (more ionic groups).

Bovine serum albumin (BSA) was encapsulated by emulsion with anionic CMS and cationic quaternary ammonium starch.[108] The nanocapsules with CMS of higher DS showed better encapsulation but those of low DS were more compact and had better colon-targeting profiles. The CMS/CHI PEC microparticles had better entrapment efficiency of BSA than CHI alone, possibly due to a higher solubility of CHI during the processing as PEC and also due to interaction of the CM groups with CHI and the protein.[109] A controlled release of mesalamine was obtained from nanoparticles based on CMS-CHI mixture, the system being modulated by an ion-exchange mechanism.[110]

Theranostics—lately, the concept of dual diagnostic/therapeutic agents is emerging as theranostic systems. Diagnostic is achieved by using ligands with affinity for receptors that are common or specific to the target (i.e., folate receptors in tumors) and may be monitored with a marker (i.e., isotopes), followed by therapeutic treatment with bioactive agents.[111] Starch is easily functionalized with markers as Gadolinium-HES for magnetic resonance imaging.[112] To be used as a carrier, starch was functionalized to increase tumor-targeted specificity and transport of therapeutic agents, respectively. For instance, to treat hepatic carcinoma, the starch microparticles were radiolabeled before intra-arterial injection to irradiate liver tumors.[113] In vivo, 95% of radioactivity was accumulated in the liver, mostly in the tumoral part of affected liver. Such starch-based carriers are promising platforms for the selective internal radiation therapy in the frame of various antitumor treatments.

Differently charged starch hydrogels were compared for their protein absorption to evaluate their behavior in the formation of a protein layer in plasma.[63] The anionic and zwitterionic starch had low cell adhesion and better hydration, being good candidate as carriers. Indeed, zwitterionic sulfobetaine-starch showed lower macrophage activation and was more effective in vivo to prolong circulating time than micelles without sulfobetaine.[70]

Stimuli-responsive systems are very useful for multiple applications. Modified starch was also used as carrier for controlled release of insulin.[114] A glucose-responsive insulin release was achieved by grafting 3-aminophenylboronic acid on starch as glucose-responsive groups. By specific binding to 3-aminophenylboronic acid, glucose induces starch expansion, releasing the insulin. The self-assembled zwitterionic starch-based micelles release of 22% insulin in 48 h in glucose-free media. The release was increased to 67% in glucose solution. Such system could control the plasma glucose level in diabetes-induced rats for 14–22h with different oral dosages, without glycemic fluctuation. As a stimulus-responsive system for chemotherapy, a starch microcapsule carrier, functionalized with folic acid and cysteine, could increase tumor-targeted release of a model drug (coumarin 6).[111] Folic acid, as ligand for the folate receptors, serves as tumor marker. Cysteine, forming di-sulfide bonds by ultrasonication, was used as a reductive-responsive cross-linking agent to bind the drug. Glutathione, with higher concentrations in tumoral environments, may break disulfide bonds by thiol-disulfide exchange.[115] These microcapsules showed high selectivity to human cervical cancer cells and a triggered release in vitro in presence of glutathione, successfully reaching the cytoplasm of cancer cells.[116]

A thermo-responsive carrier was designed by starch association with PEG and polymethacrylate derivatives; it was loaded with doxorubicin and could form micelles by self-assembly in tumor environment (pH 7.4).[117]

Adhesive vaginal tablets made of various modified starches could extend progesterone release with better in vivo performances than commercial CIDR dosage (a progesterone gelatine capsule insert for veterinary use from EAZI-BREED, Pfizer, Turkey).[118] Gelatinized and cross-linked starches (maize, rice, wheat, and potato) resisted more than 24 h. At higher swelling, the adhesion was lower. The progesterone blood level for the 75 mg wheat starch-based dosage was similar to the 330 mg dosage CIDR, but with a longer release, over 16 days. Mucoadhesion was higher for starch modified with thioglycolic acid, forming thioesters and thioethers, than with cysteine, having less-polarizable S-H groups.[119]

6. Conclusions and Perspectives

Accumulated knowledge on starch structural aspects allowed the expansion of its application fields. Decades ago, starch served in tableting as disintegrant or binder but more recently its uses range from drug targeting to biodevices and design of theranostic agents. Various physical and chemical modifications represent keys in modulation of self-assembling phenomena and allow the design of complex structures (i.e., micelles, nanoparticles, fibers) used for gene delivery, injectable anticancer forms, transdermal products or wound dressing. New applications emerged, that is, degradable stents, agents for non-permanent embolization, cell-permeation enhancers, prebiotics. Due to its high versatility, several forms of starch can be called multifunctional smart excipients. The numerous hydroxyl groups, the complex structure of amylopectin, the helix-forming properties of amylose and the enzymatic susceptibility as combined features are making starch a unique and highly valuable material for pharmaceutical and biomedical applications.

Considering the huge variability of the starch types, sources, and derivatives, there is a continuous need to better understand the impact of their structure on the expected applications. None of other biopolymers combine as much features as starch. It is biodegradable and majority of the modifications are green chemistry in aqueous media. In a near future, usage of modified starch for pharmaceutical and biomedical applications is very likely to increase, owing to its versatility, biodegradability, biocompatibility, low-cost and availability. Many reports on pharmaceutical and biomedical applications limited their study to commercial food-grade starch. Reglementary acceptation of more starch

derivatives and new starch sources would be a great opportunity to increase the number of starch products integrated on the market for pharmaceutical and biomedical applications.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] M. D. O'Donnell, K. F. McGeeney, *Clin. Chem.* **1983**, *29*, 510.
[2] P. Ispas-Szabo, M.-A. Labelle, M. A. Mateescu, *J. Chem. Allied Res.* **2017**, *1*, 28.
[3] D. LeCorre, J. Bras, A. Dufresne, *J. Nanopart. Res.* **2011**, *13*, 7193.
[4] C. Liu, Y. Liu, H. Deng, S. Tang, Y. C. Cao, *Luminescence* **2019**, *34*, 200.
[5] H. Patel, P. G. Royall, S. Gaisford, G. R. Williams, C. H. Edwards, F. J. Warren, B. M. Flanagan, P. R. Ellis, P. J. Butterworth, *Carbohydr. Polym.* **2017**, *164*, 154.
[6] J. Jane, Y. Y. Chen, L. F. Lee, A. E. McPherson, K. S. Wong, M. Radosavljevic, T. Kasemsuwan, *Cereal Chem. J.* **1999**, *76*, 629.
[7] B. Biduski, W. M. F. d. Silva, R. Colussi, S. L. d. M. E. Halal, L. T. Lim, Á. R. G. Dias, E. d. R. Zavareze, *Int. J. Biol. Macromol.* **2018**, *113*, 443.
[8] R. F. Tester, S. J. J. Debon, *Int. J. Biol. Macromol.* **2000**, *27*, 1.
[9] M. Xu, A. S. M. Saleh, B. Gong, B. Li, L. Jing, M. Gou, H. Jiang, W. Li, *Food Res. Int.* **2018**, *111*, 324.
[10] T. A. Waigh, M. J. Gidley, B. U. Komanshek, A. M. Donald, *Carbohydr. Res.* **2000**, *328*, 165.
[11] J. Rojas, Y. Uribe, A. Zuluaga, *Pharm. Int. J. Pharm. Sci.* **2012**, *67*, 513.
[12] A. Dimantov, M. Greenberg, E. Kesselman, E. Shimoni, *Innovative Food Sci. Emerging Technol.* **2004**, *5*, 93.
[13] Å. Rindlav-Westling, M. Stading, P. Gatenholm, *Biomacromolecules* **2002**, *3*, 84.
[14] V. Sessini, M. P. Arrieta, A. Fernández-Torres, L. Peponi, *Carbohydr. Polym.* **2018**, *179*, 93.
[15] A. Beilvert, F. Chaubet, L. Chaunier, S. Guilois, G. Pavon-Djavid, D. Letourneur, A. Meddahi-Pellé, D. Lourdin, *Carbohydr. Polym.* **2014**, *99*, 242.
[16] V. A. d. S. Garcia, J. G. Borges, V. B. V. Maciel, M. R. Mazalli, J. d. G. Lapa-Guimaraes, F. M. Vanin, R. A. de Carvalho, *Food Hydrocolloids* **2018**, *79*, 127.
[17] V. R. G. Dev, T. Hemamalini, *Int. J. Biol. Macromol.* **2018**, *118*, 1276.
[18] V. S. Waghmare, P. R. Wadke, S. Dyawanapelly, A. Deshpande, R. Jain, P. Dandekar, *Bioact. Mater.* **2018**, *3*, 255.
[19] A. Beilvert, F. Faure, A. Meddahi-Pelle, L. Chaunier, S. Guilois, F. Chaubet, D. Lourdin, A. Bizeau, *Laryngoscope* **2014**, *124*, 875.
[20] L. Goimil, M. E. M. Braga, A. M. A. Dias, J. L. Gómez-Amoza, A. Concheiro, C. Alvarez-Lorenzo, H. C. de Sousa, C. A. García-González, *J. CO2 Util.* **2017**, *18*, 237.
[21] S. M. Davachi, B. S. Heidari, I. Hejazi, J. Seyfi, E. Oliaei, A. Farzaneh, H. Rashedi, *Carbohydr. Polym.* **2017**, *155*, 336.
[22] J. Nourmohammadi, A. Ghaee, S. H. Liavali, *Carbohydr. Polym.* **2016**, *138*, 172.
[23] Z. Hadisi, J. Nourmohammadi, J. Mohammadi, *Ceram. Int.* **2015**, *41*, 10745.
[24] R. Khlibsuwan, W. Tansena, T. Pongjanyakul, *Int. J. Biol. Macromol.* **2018**, *118*, 683.
[25] J. Zhu, L. Zhong, W. Chen, Y. Song, Z. Qian, X. Cao, Q. Huang, B. Zhang, H. Chen, W. Chen, *Food Hydrocolloids* **2019**, *95*, 562.
[26] S. Lefnaoui, N. Moulai-Mostefa, *Colloids Surf. A* **2014**, *458*, 117.
[27] J. Srivastava, A. Kushwaha, M. Srivastava, A. Srivastava, M. Singh, *J. Electroanal. Chem.* **2019**, *835*, 169.
[28] H. Adeli, M. T. Khorasani, M. Parvazinia, *Int. J. Biol. Macromol.* **2019**, *122*, 238.
[29] Z. Hadisi, J. Nourmohammadi, S. M. Nassiri, *Int. J. Biol. Macromol.* **2018**, *107*, 2008.
[30] G. Vasilyev, R. Vilensky, E. Zussman, *Carbohydr. Polym.* **2019**, *214*, 186.
[31] P. Wadke, R. Chhabra, R. Jain, P. Dandekar, *Surf. Interfaces* **2017**, *8*, 137.
[32] I. Pashkuleva, A. P. Marques, F. Vaz, R. L. Reis, *J. Mater. Sci.: Mater. Med.* **2010**, *21*, 21.
[33] M. A. Susano, I. B. Leonor, R. L. Reis, H. S. Azevedo, *J. Appl. Polym. Sci.* **2014**, *131*, 40504.
[34] J. Suwanprateeb, S. Kiertkrittikhoon, J. Kintarak, W. Suvannapruk, F. Thammarakcharoen, P. Rukskul, *J. Mater. Sci.: Mater. Med.* **2014**, *25*, 2131.
[35] A. M. Berens, S. Newman, A. D. Bhrany, C. Murakami, K. C. Y. Sie, D. A. Zopf, *Otolaryng. Head Neck* **2016**, *155*, 356.
[36] C. Koski, B. Onuike, A. Bandyopadhyay, S. Bose, *Addit. Manuf.* **2018**, *24*, 47.
[37] J. C. Flores-Arriaga, A. de J. Pozos-Guillen, D. M. Escobar-Garcia, C. Grandfils, B. I. Cerda-Cristerna, *Odontology* **2017**, *105*, 398.
[38] M. A. Mateescu, P. Ispas-Szabo, J. Mulhbacher, in *Polysaccharides for Drug Delivery and Pharmaceutical Applications* (Eds: R. Marchessault, F. Ravenelle, X. X. Zhu), ACS Symposium Series, Washington, D.C., USA **2006**, *6*, 121.
[39] M. A. Mateescu, V. Lenaerts, Y. Dumoulin, *US5456921*, **1995**.
[40] M. A. Mateescu, P. Ispas-Szabo, E. Assaad, *Controlled Drug Delivery: The Role of Self-Assembling Multi-Task Excipients*, Elsevier, New York, USA **2014**.
[41] V. Lenaerts, I. Moussa, Y. Dumoulin, F. Mebsout, F. Chouinard, P. Szabo, M. A. Mateescu, L. Cartilier, R. Marchessault, *J. Controlled Release* **1998**, *53*, 225.
[42] P. Ispas-Szabo, F. Ravenelle, I. Hassan, M. Preda, M. A. Mateescu, *Carbohydr. Res.* **1999**, *323*, 163.
[43] L. Cartilier, M. A. Mateescu, Y. Dumoulin, V. Lenaerts, *US5616343*, **1997**.
[44] Y. Dumoulin, P. Clement, M. A. Mateescu, L. Cartilier, *S.T.P. Pharma Sci.* **1994**, *4*, 329.
[45] F. Ravenelle, M. Rahmouni, in *Polysaccharides for Drug Delivery and Pharmaceutical Applications* (Eds: R. Marchessault, F. Ravenelle, X. X. Zhu), ACS Symposium Series, Washington, D.C., USA **2006**, *4*, 79.

[46] L. Huneault, B. Lussier, P. Dubreuil, L. Chouinard, C. Désévaux, *J. Orthop. Res.* **2004**, *22*, 1351.
[47] A. Poursaid, M. M. Jensen, E. Huo, H. Ghandehari, *J. Controlled Release* **2016**, *240*, 414.
[48] C. M. Sommer, T. D. Do, C. L. Schlett, P. Flechsig, T. L. Gockner, A. Kuthning, D. F. Vollherbst, P. L. Pereira, H. U. Kauczor, S. Macher-Goppinger, *J. Biomater. Appl.* **2018**, *32*, 932.
[49] L. Hakansson, A. Hakansson, O. Morales, L. Thorelius, T. Warfving, *Semin. Oncol.* **1997**, *24*, S6.
[50] C. Ziemann, J. Roller, M. M. Malter, K. Keller, O. Kollmar, M. Glanemann, M. D. Menger, J. Sperling, *BMC Cancer* **2019**, *19*, 938.
[51] C. Calinescu, J. Mulhbacher, E. Nadeau, J. M. Fairbrother, M. A. Mateescu, *Eur. J. Pharm. Biopharm.* **2005**, *60*, 53.
[52] C. Calinescu, E. Nadeau, J. Mulhbacher, J. M. Fairbrother, M. A. Mateescu, *Int. J. Pharm.* **2007**, *343*, 18.
[53] C. Calinescu, M. A. Mateescu, *Eur. J. Pharm. Biopharm.* **2008**, *70*, 582.
[54] L. P. Massicotte, W. E. Baille, M. A. Mateescu, *Int. J. Pharm.* **2008**, *356*, 212.
[55] C. Calinescu, B. Mondovi, R. Federico, P. Ispas-Szabo, M. A. Mateescu, *Int. J. Pharm.* **2012**, *428*, 48.
[56] M. A. Labelle, P. Ispas-Szabo, I. Masseau, Y. Chorfi, M. A. Mateescu, *Int. J. Pharm.* **2019**, *572*, 118801.
[57] M. Lemieux, P. Gosselin, M. A. Mateescu, *Int. J. Pharm.* **2015**, *496*, 497.
[58] M. Lemieux, F. Bouchard, P. Gosselin, J. Paquin, M. A. Mateescu, *Biochem. Biophys. Res. Commun.* **2011**, *412*, 429.
[59] T. C. Le, M. A. Mateescu, *Drug Delivery Transl. Res.* **2017**, *7*, 516.
[60] S. Tesch, C. Gerhards, H. Schubert, *J. Food Eng.* **2002**, *54*, 167.
[61] Z. Hernández-López, E. Rangel-Vargas, J. Castro-Rosas, C. A. Gómez-Aldapa, A. Cadena-Ramírez, O. A. Acevedo-Sandoval, A. J. Gordillo-Martínez, R. N. Falfán-Cortés, *LWT* **2018**, *95*, 216.
[62] A. Cossu, M. S. Wang, A. Chaudhari, N. Nitin, *Int. J. Pharm.* **2015**, *493*, 233.
[63] J. Wang, H. Sun, J. Li, D. Dong, Y. Zhang, F. Yao, *Carbohydr. Polym.* **2015**, *117*, 384.
[64] G. R. Dhanya, D. S. Caroline, M. R. Rekha, K. Sreenivasan, *Int. J. Biol. Macromol.* **2018**, *120*, 999.
[65] E. Amar-Lewis, A. Azagury, R. Chintakunta, R. Goldbart, T. Traitel, J. Prestwood, D. Landesman-Milo, D. Peer, J. Kost, *J. Controlled Release* **2014**, *185*, 109.
[66] X. Huang, X. Li, L. Chen, L. Li, *Carbohydr. Polym.* **2017**, *173*, 690.
[67] K. Sakeer, P. Ispas-Szabo, M. A. Mateescu, *AAPS PharmSciTech* **2017**, *18*, 2658.
[68] N. Benyerbah, P. Ispas-Szabo, K. Sakeer, D. Chapdelaine, M. A. Mateescu, *Pharmaceutics* **2019**, *11*, 253.
[69] K. Sakeer, P. Ispas-Szabo, N. Benyerbah, M. A. Mateescu, *Int. J. Pharm.* **2018**, *535*, 201.
[70] L. Ye, Y. Zhang, B. Yang, X. Zhou, J. Li, Z. Qin, D. Dong, Y. Cui, F. Yao, *ACS Appl. Mater. Interfaces* **2016**, *8*, 4385.
[71] L. Bisharat, S. A. Barker, A. Narbad, D. Q. M. Craig, *Int. J. Pharm.* **2019**, *556*, 311.
[72] K. J. Kumar, C. A. K. Varma, S. G. Panpalia, *Int. J. Biol. Macromol.* **2014**, *69*, 108.
[73] P. Seenivasan, K. P. R. Chowdary, C. U. M. Reddy, J. S. N. Murthy, *J. Pharm. Res.* **2013**, *6*, 653.
[74] A. Hamaji, L. Hajjar, M. Caiero, J. Almeida, R. E. Nakamura, E. A. Osawa, J. Fukushima, F. R. Galas, J. O. A. Junior, *Rev. Bras. Anestesiol.* **2013**, *63*, 27.
[75] P. D. Constable, K. W. Hinchcliff, S. H. Done, W. Gruenberg, in *Veterinary Medicine: A textbook of the diseases of cattle, horses, sheep, pigs and goats*, 11th ed., Elsevier, New York, USA **2016**, Ch. 5.
[76] S. Hoffmann, H. Caysa, J. Kuntsche, P. Kreideweiß, A. Leimert, T. Mueller, K. Mäder, *Carbohydr. Polym.* **2013**, *95*, 404.
[77] K. N. Adamik, I. D. Yozova, *Front. Vet. Sci.* **2019**, *5*, 336.
[78] B. Kang, P. Okwieka, S. Schöttler, O. Seifert, R. E. Kontermann, K. Pfizenmaier, A. Musyanovych, R. Meyer, M. Diken, U. Sahin, V. Mailänder, F. R. Wurm, K. Landfester, *Biomaterials* **2015**, *49*, 125.
[79] M. Noga, D. Edinger, W. Rödl, E. Wagner, G. Winter, A. Besheer, *J. Controlled Release* **2012**, *159*, 92.
[80] L. Yihui, H. Hang, Z. Qing, W. Jiangling, W. Ying, L. Zifu, Y. Xiangliang, *Nanomed.: Nanotechnol., Biol. Med.* **2018**, *14*, 1798.
[81] K. T. Sato, A. Richardson, D. E. Timm, K. Sato, *Am. J. Med. Sci.* **1988**, *295*, 528.
[82] N. Shoji, T. Sasano, K. Inukai, S. Satoh-Kuriwada, M. Iikubo, T. Furuuchi, M. Sakamoto, *Arch. Oral Biol.* **2003**, *48*, 761.
[83] J. Bürmann, A. Devlioti, M. Manitz, P. Bialas, K. Faßbender, U. Dillmann, *Clin. Neurophysiol.* **2015**, *126*, e168.
[84] M. N. Khan, A. H. Naqvi, *J. Tissue Viability* **2006**, *16*, 6.
[85] H. Li, V. T. T. Ho, M. S. Turner, S. Dhital, *LWT* **2016**, *74*, 542.
[86] G. Liu, Z. Gu, Y. Hong, L. Cheng, C. Li, *Trends Food Sci. Technol.* **2017**, *63*, 70.
[87] J. P. Remon, C. Verva, P. Foreman, *US20120207823A1*, **2012**.
[88] N. Ahmad, S. Mehboob, N. Rashid, *Biologia* **2015**, *70*, 709.
[89] M. D. Moya-Ortega, C. Alvarez-Lorenzo, A. Concheiro, T. Loftsson, *Int. J. Pharm.* **2012**, *428*, 152.
[90] N. Poorgholy, B. Massoumi, M. Jaymand, *Int. J. Biol. Macromol.* **2017**, *97*, 654.
[91] F. Chen, X. Cao, J. Yu, H. Su, S. Wei, H. Hong, C. Liu, *Colloids Surf., B* **2017**, *159*, 937.
[92] Y. Chen, J. Qian, C. Zhao, L. Yang, J. Ding, H. Guo, *Eur. Polym. J.* **2019**, *118*, 17.
[93] V. Panwar, A. Sharma, J. Thomas, V. Chopra, S. Kaushik, A. Kumar, D. Ghosh, *Materialia* **2019**, *7*, 100373.
[94] J. Zhu, Y. Sun, W. Sun, Z. Meng, Q. Shi, X. Zhu, H. Gan, R. Gu, Z. Wu, G. Dou, *Int. J. Biol. Macromol.* **2019**, *134*, 435.
[95] S. K. Filippov, O. Y. Sergeeva, P. S. Vlasov, M. S. Zavyalova, G. B. Belostotskaya, V. M. Garamus, R. S. Khrustaleva, P. Stepanek, N. S. Domnina, *Carbohydr. Polym.* **2015**, *134*, 314.
[96] K. Björses, L. Faxälv, C. Montan, K. Wildt-Persson, P. Fyhr, J. Holst, T. L. Lindahl, *Acta Biomater.* **2011**, *7*, 2558.
[97] X. Dang, M. Yang, Z. Shan, S. Mansouri, B. K. May, X. Chen, H. Chen, M. W. Woo, *Mater. Sci. Eng., C* **2017**, *74*, 493.
[98] A. Lancuški, A. A. Ammar, R. Avrahami, R. Vilensky, G. Vasilyev, E. Zussman, *Carbohydr. Polym.* **2017**, *158*, 68.
[99] M. M. Cruz-Benítez, C. A. Gómez-Aldapa, J. Castro-Rosas, E. Hernández-Hernández, E. Gómez-Hernández, H. A. Fonseca-Florido, *LWT* **2019**, *105*, 110.
[100] L. Zhang, M. Aloia, B. Pielecha-Safira, H. Lin, P. M. Rajai, K. Kunnath, R. N. Davé, *J. Pharm. Sci.* **2018**, *107*, 2107.
[101] S. E. Haque, A. Sheela, *Int. J. Nanomed.* **2015**, *10*, 199.
[102] M. B. Pimparade, A. Vo, A. S. Maurya, J. Bae, J. T. Morott, X. Feng, D. W. Kim, V. I. Kulkarni, R. Tiwari, K. Vanaja, R. Murthy, H. N. Shivakumar, D. Neupane, S. R. Mishra, S. N. Murthy, M. A. Repka, *Eur. J. Pharm. Biopharm.* **2017**, *119*, 81.
[103] K. Wilpiszewska, A. K. Antosik, T. Spychaj, *Carbohydr. Polym.* **2015**, *128*, 82.
[104] M. A. Güler, M. K. Gök, A. K. Figen, S. Özgümüş, *Appl. Clay Sci.* **2015**, *112-113*, 44.
[105] E. Assaad, Y. J. Wang, X. X. Zhu, M. A. Mateescu, *Carbohydr. Polym.* **2011**, *84*, 1399.
[106] E. Assaad, L. Blemur, M. Lessard, M. A. Mateescu, *J. Biomater. Sci., Polym. Ed.* **2012**, *23*, 1713.
[107] L. Blemur, T. C. Le, L. Marcocci, P. Pietrangeli, M. A. Mateescu, *Biotechnol. Appl. Biochem.* **2016**, *63*, 344.

[108] Y. Zhang, C. Chi, X. Huang, Q. Zou, X. Li, L. Chen, *Carbohydr. Polym.* **2017**, *171*, 242.
[109] R. F. N. Quadrado, A. R. Fajardo, *Arabian J. Chem.* **2020**, *13*, 2183.
[110] M. R. Saboktakin, R. M. Tabatabaie, A. Maharramov, M. A. Ramazanov, *Int. J. Biol. Macromol.* **2011**, *48*, 381.
[111] Y. Sun, C. Shi, J. Yang, S. Zhong, Z. Li, L. Xu, S. Zhao, Y. Gao, X. Cui, *Carbohydr. Polym.* **2018**, *200*, 508.
[112] A. Besheer, H. Caysa, H. Metz, T. Mueller, J. Kressler, K. Mäder, *Int. J. Pharm.* **2011**, *417*, 196.
[113] E. Verger, P. Drion, G. Meffre, C. Bernard, L. Duwez, N. Lepareur, O. Couturier, F. Hindré, R. Hustinx, F. Lacoeuille, *PLoS One* **2016**, *11*, e0164626.
[114] N. Wen, S. Lü, C. Gao, X. Xu, X. Bai, C. Wu, P. Ning, M. Liu, *Chem. Eng. J.* **2018**, *335*, 52.
[115] S. L. Blair, P. Heerdt, S. Sachar, A. Abolhoda, S. Hochwald, H. Cheng, M. Burt, *Cancer Res.* **1997**, *57*, 152.
[116] K. Liu, Y. Wang, H. Li, Y. Duan, *Colloids Surf., B* **2015**, *128*, 86.
[117] X. Wang, Z. Liu, L. Huang, *React. Funct. Polym.* **2019**, *141*, 165.
[118] M. K. Gök, S. Özgümüş, K. Demir, Ü. Cirit, S. Pabuccuoğlu, E. Cevher, Y. Özsoy, S. Bacınoğlu, *Carbohydr. Polym.* **2016**, *136*, 63.
[119] M. K. Gök, K. Demir, E. Cevher, Y. Özsoy, Ü. Cirit, S. Bacınoğlu, S. Özgümüş, S. Pabuccuoğlu, *Carbohydr. Polym.* **2017**, *163*, 129.
[120] J. Mulhbacher, P. Ispas-Szabo, V. Lenaerts, M. A. Mateescu, *J. Controlled Release* **2001**, *76*, 51.
[121] B. Rioux, P. Ispas-Szabo, A. Aït-Kadi, M. A. Mateescu, J. Juhász, *Carbohydr. Polym.* **2002**, *50*, 371.
[122] B. Delisle, C. Calinescu, M. A. Mateescu, J. M. Fairbrother, E. Nadeau, *J. Pharm. Pharm. Sci.* **2012**, *15*, 642.
[123] M. Lemieux, P. Gosselin, M. A. Mateescu, *AAPS PharmSciTech* **2010**, *11*, 775.
[124] E. Assaad, M. A. Mateescu, *Int. J. Pharm.* **2010**, *394*, 75.
[125] Y. J. Wang, E. Assaad, P. Ispas-Szabo, M. A. Mateescu, X. X. Zhu, *Int. J. Pharm.* **2011**, *419*, 215.
[126] M. Friciu, C. Le Tien, P. Ispas-Szabo, M. A. Mateescu, *Eur. J. Pharm. Biopharm.* **2013**, *85*, 521.
[127] U. Geister, S. Schweizer, M. Buerger, R. Stefan, G. Huber, T. Pries, *US20150328277A1*, **2015**.
[128] A. B. Nair, B. E. Al-Dhubiab, J. Shah, P. Vimal, M. Attimarad, S. Harsha, *J. Drug Delivery Sci. Technol.* **2018**, *47*, 351.
[129] B. A. Ashwar, A. Gani, A. Gani, A. Shah, F. A. Masoodi, *Food Chem.* **2018**, *239*, 287.
[130] C. Wu, Z. Wang, Z. Zhi, T. Jiang, J. Zhang, S. Wang, *Int. J. Pharm.* **2011**, *403*, 162.
[131] D. A. El-Setouhy, N. S. A. El-Malak, *AAPS PharmSciTech* **2010**, *11*, 1018.

