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Application of Starch and Starch Derivatives in Pharmaceutical Formulation

Christian Chibuogwu, Ben Amadi, Zikora Anyaegbunam, Benjamin Emesiani and Sabinus Ofoefule

Abstract

Starch is a homo-glucose unit connected with glycosidic linkage. It is well known for its biodegradability, renewability, low cost, flexibility, and availability. However, to reach its potential in the pharmaceutical application, modification is necessary to solve the problem of solubility, retrogradation, and loss of viscosity. In this chapter, we discuss the different physical, chemical, enzymatic, and biotechnological modifications and their subsequent pharmaceutical application both as an excipient and directly as drug delivery vehicles. Overall, there were different characteristics conferred in a modification which were exploited in pharmaceuticals, drug delivery, and antimicrobial preparation. We, however, believe that collation of the data on modification would go a long way toward standardizing the application of the modified products.

Keywords: starch, modification, pharmaceutical, drug, delivery

1. Introduction

Starch is the most abundant reservoir of carbohydrate in plants and a naturally occurring polysaccharide whose wide distribution makes it the second most abundant biomass material found in nature, only second to cellulose [1]. It is a product of the photosynthetic process in plants, storing the chemical energy of the sun in different parts of plants including the leaves of green plants, seeds, fruits, stems, roots, and tubers of most plants and making it available to non-photosynthetic organisms with humans being the most significant beneficiaries. Starch is a polymeric molecule consisting of the six-carbon-ring glucose molecules with molecular weight varying from 10^4 to 10^7 Daltons and produced as discrete granules with distinct morphology in different plants [2–4]. Starch is formed in the chloroplasts of green leaves and amyloplasts of seeds, fruits, and tubers. Sources of starch include cereal grains such as corn, wheat, sorghum, rice, and tubers and roots such as cassava, potato, tapioca, yam, etc., which are all sources of dietary carbohydrates [5]. Beyond its natural usefulness as food, this polysaccharide has obtained wide acceptance in various industries such as in textile for stiffening fabrics, in the food industry as additives and thickeners among other uses, in the pharmaceutical industry as an excipient and more recently used as a drug carrier, and also in cosmetics and paper industries [1].

Starch is utilized either in its native form or in the modified form. Native starch refers to starch in its natural, unmodified state, as extracted from its plant source, while modified starch is one in which certain properties have been modified or altered to meet the desired specifications. In its native state, starch is unsuitable for many industrial processes mainly due to its poor solubility and also its inability to withstand industrial conditions such as high temperatures. Therefore, modifications are done not only to alter the physicochemical properties of starch and improve its technological value but also to exhibit desired qualities in finished products [5].

2. Starch composition

Structurally, starch is a polysaccharide composed of glucose (monosaccharide) units connected by α -D-(1-4) and α -D-(1-6) linkages. The starch molecule consists of two major types of polymers, namely amylose and amylopectin. Amylopectin consists of linear chains of glucose units linked by α -1,4 glycosidic bonds and is highly branched at the α -1,6 positions by small glucose chains at intervals of 10 nm along the molecule's axis, constituting about 70–85% of common starch. Amylose, on the other hand, is a linear chain of α -1,4 glucans with limited branching points at the α -1,6 positions and constitutes between 15 and 30% of common starch [2]. There are, however, exceptions to the rule in terms of glucan compositions (amylose/amylopectin ratio) of starches. This is because modifications have been introduced to starch molecules recently to alter the glucan composition to meet specific requirements with some starches genetically modified to have almost a 100% amylose content while some are designed to be amylose-free [3]. Irrespective of the source, the starch molecule is usually present as granules. However, the size and shape of starch granules depend on their botanical origin. For example, the granule size for rice starch is about 3–8 μm , while potato starch ranges from 15 to about 100 μm [4].

Starch granules have very complex structures, resulting from variations in their components. They also exhibit variations between amorphous and crystalline regions. The amorphous region of the granules consists of amylose associated with large branches of amylopectin molecules. On the other hand, the crystalline region consists of amylopectin molecules with short branches; therefore, the higher the amylopectin proportion in starch granules, the greater the crystallinity [5]. Starch granules have also been found to exist in varying shapes, including oval, round, elliptical, flattened ovoid, polygonal, lenticular, and disc shapes [4].

In addition to amylose and amylopectin, starch also contains other noncarbohydrate components such as lipids (up to 1%), residues of protein (0.4%), and a relatively small amount (<0.4%) of minerals (calcium, magnesium, phosphorus, potassium, and sodium) of which phosphorus occupies an important position [6, 7] (**Figures 1** and **2**).

Figure 1.
Structure of amylose [8].

Figure 2.
 Structure of amylopectin [8].

Lipids in starch are present in the form of phospholipids and free fatty acids and are usually associated with the amylose fraction. Lipids, particularly phospholipids, have great tendencies to form helical complexes with starch (mainly with amylose). The lipid complexes in starch granules are present as a hydrophobic nucleus situated within helices formed by amylose chains [9], and, although representing a small fraction of the starch granules, lipid complexes can significantly reduce not just the solubility of the granules but also the swelling capacity of the starch paste [7].

Phosphorus is a noncarbohydrate component of starch whose presence has been found to exert significant influence on functional characteristics such as clarity and viscosity of starch pastes. It is present either as monoester phosphates (proportionally associated with the amylopectin fraction by covalent bonds) or as phospholipids (proportionally associated with the amylose content of starch), with the latter significantly lowering these characteristics [10]. Properties such as solubility and transmittance of starch granules are also affected by the nature of the phosphorus present in the starch. It is reported that the presence of phosphorus in the form of monoester phosphates enhances these properties in starch granules [11].

3. Properties of starch

3.1 Structure of starch granules

X-ray analyses of starch granules reveal varying degrees of crystallinity of the granules. Three distinct X-ray patterns (A-, B-, and C-patterns) have been observed with the A-pattern's characteristic of cereal grain starches, such as maize, waxy maize, wheat, and rice, while the B-patterns are characteristics of tuber, fruit, and stem starches, such as canna, potato, sago, banana starches, and some mutant maize starches such as amylomaize-5 and amylomaize-7. C-type patterns are found in roots such as tapioca starch, beans, and peas and are an intermediate between A- and B-types [11]. Also B- and C-type native starches can be converted to the A-type by heat-moisture treatment (30°C for B-type and approximately 50°C for C-type). However, the original structure of the A-type starches needs to be destroyed and allowed to recrystallize for conversion into other crystalline forms to occur [12].

3.2 Swelling capacity and solubility

One of the characteristics of starch is the ability of its granules to absorb water. Water absorption results in swelling of the starch granule contributing to amylopectin-amylose phase separation and loss of crystallinity, which in turn promotes the leaching of amylose to the intergranular space [13]. Heating of starch molecules in excess water causes the breaking of its semicrystalline structure, allowing water molecules to interact (via hydrogen bonding) with the hydroxyl groups exposed on the amylose and amylopectin molecules. This association causes swelling and increases granule size and solubility. The extent of this interaction is influenced by the amylose-amylopectin proportion as the swelling capacity of the starch granule is a function of its amylopectin content. The high tendency of the amylose component of starch granules to complex with phospholipids (forming amylose-lipid complexes) greatly inhibits the solubility and, consequently, the swelling capacity of starch granules [11].

3.3 Gelatinization of starch

Starch, when heated in excess water, undergoes a transition phase known as gelatinization. Gelatinization of starch is useful in particular industries, especially the textile and hydrolyzed starch industries. Generally, starch gelatinization can be defined as the conversion of starch from the crystalline, granular form to the dispersed and amorphous state [6]. Gelatinization occurs when water diffuses into the granule, which then swells substantially due to hydration of the amorphous phase causing loss of crystallinity and molecular order [14]. The gelatinization temperature of the starch granules varies depending on the source of starch. This is due to the influence of the organization (packing of the double helices) of the glucan chains in the crystalline lamellae of the granules. This includes the nature of the branching pattern (distance between the branching points and numbers of chains in the building blocks) and the length of external chains. Other factors include the concentration of amylose and the lipid content of the starch. Chemical methods of starch gelatinization and consequent solubilization are also available such as the use of alkali (NaOH) and dimethyl sulfoxide (DMSO). However, the conditions and pathways of gelatinization are different from the process of boiling water. For instance, apart from occurring at a low temperature (20°C), starch granules do not swell in DMSO as they do in hot water but dissolve slowly by fragmentation of the interior of the granule into smaller pieces [15].

3.4 Retrogradation

Retrogradation refers to the molecular interaction produced after gelatinization and cooling of the starch paste, that is, the recrystallization of glucan chains in gelatinized starch. It can be described as the tendency for solvated, amorphous starch to return to an insoluble, aggregated, or crystalline state when stored at a temperature above its glass transition temperature. This characteristic of starch is favored both by low temperature (0–5°C) and high starch concentration [6]. This property is one of the causes of staleness of baked products during storage and is generally considered unfavorable in terms of food quality. The glucan composition (amylose/amylopectin ratio of starch), as well as the presence of other noncarbohydrate components, has a significant influence on the retrogradation potentials of starch. For instance, high amylose content increases retrogradation potentials of starch, whereas amylose-free starches have less tendency towards this behavior. This is because, during retrogradation, amylose molecules associate with other

glucose units to form a double helix, while amylopectin molecules recrystallize through the association of its small chains [11]. The presence of other components such as proteins, lipids, other carbohydrates, salts, and polyphenols significantly affects retrogradation. For example, proteins can complex with starch to retard the retrogradation process during refrigerated storage [16].

4. Starch modification and pharmaceutical application

The abundance, biodegradability, and cost-friendly characteristics of starch make it an important raw material for many industrial processes. However, certain properties of starch make it undesirable for all applications. Most native starches are limited in their direct application due to poor solubility in water and a strong tendency for decomposition and retrogradation. They also display high instability with respect to changes in temperature, pH, and shear forces [15]. Therefore, starches are often subjected to either physical, chemical, or enzymatic modifications. These modifications are done to develop specific properties such as solubility, hydrophobicity, thermal stability, amphiphilicity, paste clarity, mechanical strength, freeze-thaw stability retrogradation resistance texture, adhesion, and tolerance to high temperatures used in industrial [6, 17].

Several factors affect the digestibility of native starch and, hence, possible pharmaceutical application. These include amylopectin: amylose ratio, amylopectin chain length, degree of crystallinity, and intermolecular association in granules [17]. Modification typically affects all these properties, and the choice of modification can lead to customization and flexibility in starch use.

Summarily, these are modification methods currently in use:

4.1 Physical modification

Physical treatments are generally divided into thermal and nonthermal treatments. Thermal treatments involve the use of heat to rearrange the amylopectin: amylose ratio and length of chain. This typically leads to highly soluble excipients, and when exposed to such temperature conditions, gelatinization occurs, improving the swellability and solubility. Thus starch produced in this manner is easily plasticized and can be used in the production of antimicrobial films and also as superdisintegrants.

Thermal treatments include pregelatinization, heat-moisture treatment, annealing, dry heating, and osmotic pressure treatment.

Pregelatinization involves the starches to be cooked at a specified temperature and dried to allow little or no molecular reassociation.

Heat moisture treatment consists of heating starch granules at a temperature above the starch's glass transition temperature at the adiabatic condition with a relative humidity of 10–40% for 1–24 h [17]. The changes observed show no crystallinity in A-type; however, B-type starch granules change to C-type. Increase in crystallinity, however, is only a desired trait in sustained release formulation [17].

The nonthermal treatment includes ultrasonic treatment, milling, high-pressure treatment, pulsed electric field, freezing/thawing, and freeze-drying treatment.

4.2 Chemical modification

This involves the insertion of a new functional group on the starch backbone to give unique properties to the starch. There are numerous methods of chemical modification, but the most relevant are acid hydrolysis, cross-linking, acetylation, dual modification, oxidation, and grafting.

4.3 Enzymatic modification

The enzymatic modification of starch targets the amylopectin: amylose chain length and content and also the molecular weight. Typically, when the mentioned variables are reduced, the modified starch can be used to formulate fast-releasing micro and nano-particles. Alternatively, used in immediate release tablet formulation. The modification, however, does not improve the swellability of the starch granules, and as such, it cannot be used as a disintegrant.

5. Advances of modified starch in some drug delivery application

The modification of starch has given it some controlled delivery in drug delivery system, and depending on the modification carried out in the starch, such as acid modified, pre-gelatinized, freeze-dried, cross-linked, and hydroxypropylation, the disintegration and binding properties are affected. This can subsequently affect the rate of release.

A study was done by Alexiou et al. [18] to study the biocompatibility of starch as a carrier to targeting cancer cells. Phosphate-modified starch was used to prepare iron oxide nanoparticle, which was then mixed with mitoxantrone. The iron oxide nanoparticles improved drug concentration and targeting using a magnetic field. This improved the in vivo effect.

Rice starch modified with carboxylation and oxidation [20] was used in the tablet preparation of metronidazole. It was found out that the starch conferred a controlled release mechanism owing to its enzymatic and pH resistance leading to a slow-release with prolonged effect.

Thermosensitivity of starch derivative was recently tested in the drug delivery system. Acid-hydrolyzed starch treated with butyl glycidyl ether to yield 2-hydroxy-3-butoxypropyl starch polymer micelles was loaded with prednisolone and the in vitro dissolution profile investigated in distilled water at 20 and 40°C. It was discovered that 38% of the drug was released at 20°C, while 90% was released at 40°C. The effect of molar substitution (MS) and lower critical solution temperature (LCST) of the modified starch offered a mechanism to this release. The above factors were investigated and discovered to be inversely proportional, thus, when MS was doubled from 0.32 to 0.67, the LCST decreased from 32.5 to 4°C. This increase in molar substitution affects the micelles leading to swelling and controlled release at different temperature [20].

Antimicrobial agents have low molecular weight and can display poor retention, and easily leaking out without attaining stability in the formulation. This has provided the rationale for conjugating the antimicrobials with high-molecular-weight starches which prevent leaching and improve the encapsulation efficiency. A work done by Guan et al. [20] showed the microbicidal effect of covalently bonded polyhexamethylene guanidine hydrochloride (PHGH) and potato starch on the activity of nonresistant *Escherichia coli* and *Staphylococcus aureus*. The microbial growth was inhibited to almost 100% when 1% of the PHGH was used in the modification [28].

There is no direct compilation of how the different modifications affect the inherent properties of native starch to the point of predictive usage, but the effect is always felt in the modification technique used and the observed pharmaceutical function. Below is a tabulated list of some of the current usages of modified starches in drug delivery systems (Tables 1 and 2).

Starch	Antimicrobial agent	Concentration	Micro-organism	Observation	References
Potato	PHGH	1%	<i>E. coli</i>	100%	[19]
			<i>S. aureus</i>		
		12%	<i>E. coli</i>	Excellent antimicrobial activities	
Cassava	Chitosan-oregano	0.1, 0.5, 1.0%	<i>E. coli</i> , <i>S. aureus</i>	Increased biocidal activity against gram-positive than gram-negative bacteria	[20]
Sweet potato	Potassium sorbate	5, 10, 15%	<i>E. coli</i>	Inhibition at 5% only	[21]
			<i>S. aureus</i>	No inhibition zones	
	Chitosan	5, 10, 15%	<i>E. coli</i>	Excellent antimicrobial activities	
Wheat	Chitosan		<i>Bacillus subtilis</i> , <i>E. coli</i>	Low inhibition	
	Chitosan-lauric acid	8%	<i>B. subtilis</i> , <i>E. coli</i>	Efficient inhibitory effect	[22]
Potato	Guanidine hydrochloride	4, 8, 12, 16 mol	<i>E. coli</i> , <i>S. aureus</i>	Excellent antimicrobial properties	

Key PHGH-polyhexamethylene guanidine hydrochloride.

Table 1.
Antimicrobial modified starch and its activities.

Material	Delivery method	Preparation technique	<i>In vitro</i> result	References
Corn starch-polycaprolactone blend	Porous microparticles	Emulsion solvent extraction/evaporation	There was a steady release of the drug over 30 days	[23]
Sweet potato starch	Microparticle	Spray drying of gelatinized starch	There was a sustained release for up to 6 h. the concentration of starch used also affected the release model	[24, 28]
Corn and potato starch	Hydrogel	Isostatic ultra-high pressure	Corn starch showed sustained release while potato starch hydrogel showed fast drug release	[25]
Hydrolyzed potato starch	Microsphere	Single emulsion cross-linking	The release was rapid within the first 2 h	[26]
Cross-linked starch	Mucoadhesive nanoparticle		The nanoparticles led to rapid drug delivery and were also directly depend on the extent of cross-linking	[27, 29]

Table 2.
Modified starch and their application towards drug delivery systems.

6. Conclusion

The role of starch keeps diversifying. The pharmaceutical potential of modification of starch in drug delivery systems has been shown in this report to vary and is not easily predictable until the final outcome. It is our recommendation that documenting the observable physical and molecular change in the starch modification alongside with the observable drug delivery effect would improve the predictional use of this versatile material.

Author details

Christian Chibuogwu*, Ben Amadi, Zikora Anyaegbunam, Benjamin Emesiani and Sabinus Ofoefule
Institute for Drug-Herbal Medicine-Excipient Research and Development,
University of Nigeria, Nsukka, Nigeria

*Address all correspondence to: christian.chibuogwu@unn.edu.ng

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References

- [1] Emeje MO, Rodrigues A. In: Valdez B, editor. *Starch: From Food to Medicine, Scientific, Health and Social Aspects of the Food Industry*. InTech; 2012. ISBN: 978-953-307-916-5. Available from: <http://www.intechopen.com/books/scientific-health-and-social-aspects-of-the-food-industry/starch-fromfood-to-medicine>
- [2] Durrani CM, Donald AM. Physical characterization of amylopectin gels. *Polymer Gels and Networks*. 1995;**3**(1):1-27
- [3] Bertoft E. Understanding starch structure: Recent progress. *Agronomy*. 2017;**7**:56. DOI: 10.3390/agronomy7030056
- [4] Waterschoot J, Gomand SV, Fierens E, Delcour JA. Production, structure, physicochemical and functional properties of maize, cassava, wheat, potato and rice starches. *Starch/Staerke*. 2015;**67**(1-2):14-29
- [5] Cheetham NWH, Tao L. Variation in crystalline type with amylose content in maize starch granules: An X-ray powder diffraction study. *Carbohydrate Polymers*. 1998;**36**(4):277-284
- [6] Jane J. Starch properties, modifications, and applications. *Journal of Macromolecular Science, Part A: Pure and Applied Chemistry*. 1995;**32**(4):751-757
- [7] Alcázar-Alay SC, Meireles MAA. Physicochemical properties, modifications, and applications of starches from different botanical sources. *Food Science and Technology*. 2015;**35**(2):215-236
- [8] Lewicka K, Siemion P, Kurcok P. Chemical modifications of starch: Microwave effect. *International Journal of Polymer Science*. 2015;**2015**:867697
- [9] Tester RF, Karkalas J, Qi X. Starch—Composition, fine structure and architecture. *Journal of Cereal Science*. 2004;**39**(2):151-165
- [10] Craig SAS, Maningat CC, Seib PA, Hoseney RC. Starch paste clarity. *Cereal Chemistry*. 1989;**66**(3):173-182
- [11] Singh N, Singh J, Kaur L, Sodhi NS, Gill BS. Morphological, thermal and rheological properties of starches from different botanical sources. *Food Chemistry*. 2003;**81**(2):219-231
- [12] Robyt JF. Starch: Structure, properties, chemistry, and enzymology. In: Fraser-Reid B, Tatsuta K, Thiem J, editors. *Glycoscience*. Heidelberg, Berlin: Springer-Verlag; 2008. pp. 1437-1472
- [13] Conde-Petit B, Nuessli J, Arrigoni E, Escher F, Amadò R. Perspectives of starch in food science. *Chimia*. 2001;**55**(3):201-205
- [14] Jiménez A, Fabra MJ, Talens P, Chiralt A. Edible and biodegradable starch films: A review. *Food and Bioprocess Technology*. 2012;**5**(6):2058-2076
- [15] Wu Y, Chen Z, Li X, Wang Z. Retrogradation properties of high amylose rice flour and rice starch by physical modification. *LWT- Food Science and Technology*. 2010;**43**(3):492-497
- [16] Berski W, Ptaszek A, Ptaszek P, Ziobro R, Kowalski G, Grzesik M, et al. Pasting and rheological properties of oat starch and its derivatives. *Carbohydrate Polymers*. 2011;**83**(2):665-671
- [17] Hoover R. Composition, molecular structure, and physicochemical properties of tuber and root starches: A review. *Carbohydrate Polymers*. 2001;**45**(3):253-267

- [18] Alexiou C, Schmid RJ, Jurgons R, Kremer M, Wanner G, Bergemann C, et al. Targeting cancer cells: Magnetic nanoparticles as drug carriers. *European Biophysics Journal*. 2006;**35**:446-450
- [19] Ziaee Z, Qian L, Guan Y, Fatehi P, Xiao H. Antimicrobial/antimold polymer-grafted starches for recycled cellulose fibers. *Journal of Biomaterials Science. Polymer Edition*. 2010;**21**(10):1359-1370
- [20] Guan Y, Qian L, Xiao H, Zheng A. Preparation of novel antimicrobial-modified starch and its adsorption on cellulose fibers: Part I. Optimization of synthetic conditions and antimicrobial activities. *Cellulose*. 2008;**15**:609-618
- [21] Pelissari FM, Grossmann MVE, Yamashita F, Alfonso E, Pineda G. Antimicrobial, mechanical, and barrier properties of cassava starch-chitosan films incorporated with oregano essential oil. *Journal of Agricultural and Food Chemistry*. 2009;**57**:7499-7504
- [22] Shen XL, Wu JM, Chen Y, Zhao G. Antimicrobial and physical properties of sweet potato starch films incorporated with potassium sorbate or chitosan. *Food Hydrocolloids*. 2010;**24**:285-290
- [23] Balmayor ER, Tuzlakoglu K, Azevedo HS, Reis RL. Preparation and characterization of starch-poly- ϵ -caprolactone microparticles incorporating bioactive agents for drug delivery and tissue engineering applications. *Acta Biomaterialia*. 2009;**5**:1035-1045
- [24] Liu C-S, Desai KGH, Meng X-H, Chen X-G. Sweet potato starch microparticles as controlled drug release carriers: Preparation and in vitro drug release. *Drying Technology*. 2007;**25**:689-693
- [25] Szepes A, Makai Z, Blümer C, Mäder K, Kása P, Szabó-Révész P. Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure. *Carbohydrate Polymers*. 2008;**72**:571-578
- [26] Malafaya PB, Stappers F, Reis RL. Starch-based microspheres produced by emulsion crosslinking with a potential media dependent responsive behavior to be used as drug delivery carriers. *Journal of Materials Science. Materials in Medicine*. 2006;**17**:371-377
- [27] Jain AK, Khar RK, Ahmed FJ, Diwan PV. Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier. *European Journal of Pharmaceutics and Biopharmaceutics*. 2008;**69**:426-435
- [28] Zaki Ahmad M, Akhter S, Ahmad I, Rahman M, Anwar M, Jain GK, et al. Development of polysaccharide-based colon targeted drug delivery system: Design and evaluation of Assam bora rice starch-based matrix tablet. *Current Drug Delivery*. 2011;**8**:575-581
- [29] French D. Organization of starch granules. In: Whistler RJ, BeMiller JN, Paschall EF, editors. *Starch: Chemistry and Technology*. 2nd ed. New York: Academic Press; 1984. pp. 200-210