18

Starch: From Food to Medicine

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1. Introduction

Starch is a natural, cheap, available, renewable, and biodegradable polymer produced by many plants as a source of stored energy. It is the second most abundant biomass material in nature. It is found in plant leaves, stems, roots, bulbs, nuts, stalks, crop seeds, and staple crops such as rice, corn, wheat, cassava, and potato. It has found wide use in the food, textiles, cosmetics, plastics, adhesives, paper, and pharmaceutical industries. In the food industry, starch has a wide range of applications ranging from being a thickener, gelling agent, to being a stabilizer for making snacks, meat products, fruit juices (Manek, et al., 2005). It is either used as extracted from the plant and is called "native starch", or it undergoes one or more modifications to reach specific properties and is called "modified starch". Worldwide, the main sources of starch are maize (82%), wheat (8%), potatoes (5%), and cassava (5%). In 2000, the world starch market was estimated to be 48.5 million tons, including native and modified starches. The value of the output is worth €15 billion per year (Le Corre, et al., 2010). As noted by Mason (2009), as far back as the first century, Celsus, a Greek physician, had described starch as a wholesome food. Starch was added to rye and wheat breads during the 1890s in Germany and to beer in 1918 in England. Also, Moffett, writing in 1928, had described the use of corn starch in baking powders, pie fillings, sauces, jellies and puddings. The 1930s saw the use of starch as components of salad dressings in mayonnaise. Subsequently, combinations of corn and tapioca starches were used by salad dressing manufacturers. *(Mason, 2009).* Starch has also find use as sweetners; sweeteners produced by acid-catalyzed hydrolysis of starch were used in the improvement of wines in Germany in the 1830s. Between 1940 and 1995, the use of starch by the US food industry was reported to have increased from roughly 30 000 to 950 000 metric tons. The leading users of starch were believed to be the brewing, baking powder and confectionery industries. Similar survey in Europe in 1992, showed that, 2.8 million metric tons of starch was used in food. Several uses of starch abound in literature and the reader is advised to refer to more comprehensive reviews on the application of starch in the food industry. In fact, the versatility of starch applications is unparalleled as compared to other biomaterials.

It is obvious that, the need for starch will continue to increase especially as this biopolymer finds application in other industries including medicine and Pharmacy. From serving as food for man, starch has been found to be effective in drying up skin lesions (dermatitis), especially where there are watery exudates. Consequently, starch is a major component of dusting powders, pastes and ointments meant to provide protective and healing effect on skins. Starch mucilage has also performed well as emollient and major base in enemas. Because of its ability to form complex with iodine, starch has been used in treating iodine poisoning. Acute diarrhea has also been effectively prevented or treated with starch based solutions due to the excellent ability of starch to take up water. In Pharmacy, starch appears indispensable; It is used as excipients in several medicines. Its traditional role as a disintegrant or diluent is giving way to the more modern role as drug carrier; the therapeutic effect of the starch-adsorbed or starch-encapsulated or starch-conjugated drug largely depends on the type of starch.

2. The role of excipients in drug delivery

The International Pharmaceutical Excipient Council (IPEC) defines excipients as substances, other than the active pharmaceutical ingredient (API) in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance other attributes of the overall safety and effectiveness of the drug delivery system during storage or use (Robertson, 1999). They can also be defined as additives used to convert active pharmaceutical ingredients into pharmaceutical dosage forms suitable for administration to patients. Excipients no longer maintain the initial concept of ―Inactive support; because of the influence they have over both biopharmaceutical aspects and technological factors (Jansook and Loftsson, 2009; Killen and Corrigan, 2006; Langoth, et al., 2003; Lemieux, et al., 2009; Li, et al., 2003; Massicotte, et al., 2008; Munday and Cox, 2000; Nykänen, et al., 2001; Williams, et al.) The desired activity, the excipient's equivalent of the active ingredients efficacy, is called its functionality. The inherent property of an excipient is its functionality in the dosage form. In order to deliver a stable, uniform and effective drug product, it is essential to know the properties of the active pharmaceutical ingredient alone and in combination with all other ingredients based on the requirements of the dosage form and process applied. This underscores the importance of excipients in dosage form development.

The ultimate application goal of any drug delivery system including nano drug delivery, is to develop clinically useful formulations for treating diseases in patients (Park, 2007). Clinical applications require approval from FDA. The pharmaceutical industry has been slow to utilize the new drug delivery systems if they include excipients that are not generally regarded as safe. This is because, going through clinical studies for FDA approval of a new chemical entity is a long and costly process; there is therefore, a very strong resistance in the industry to adding any untested materials that may require seeking approval. To overcome this reluctant attitude by the industry, scientists need to develop not only new delivery systems that are substantially better than the existing delivery systems (Park, 2007), but also seek for new ways of using old biomaterials. The use of starch (native

or modified) is an important strategy towards the attainment of this objective. This is because starch unlike synthetic products is biocompatible, non toxic, biodegradable, eco-friendly and of low prices. It is generally a non-polluting renewable source for sustainable supply of cheaper pharmaceutical products.

3. What is starch?

Starch, which is the major dietary source of carbohydrates, is the most abundant storage polysaccharide in plants, and occurs as granules in the chloroplast of green leaves and the amyloplast of seeds, pulses, and tubers (Sajilata, et al., 2006). Chemically, starches are polysaccharides, composed of a number of monosaccharides or sugar (glucose) molecules linked together with α-D-(1-4) and/or α-D-(1-6) linkages. The starch consists of 2 main structural components, the amylose, which is essentially a linear polymer in which glucose residues are α-D-(1-4) linked typically constituting 15% to 20% of starch, and amylopectin, which is a larger branched molecule with α-D-(1-4) and α-D-(1-6) linkages and is a major component of starch. Amylose is linear or slightly branched, has a degree of polymerization up to 6000, and has a molecular mass of 105 to 106 g/mol. The chains can easily form single or double helices. Amylopectin on the other hand has a molecular mass of 107 to 109 g/mol. It is highly branched and has an average degree of polymerization of 2 million, making it one of the largest molecules in nature. Chain lengths of 20 to 25 glucose units between branch points are typical. About 70% of the mass of starch granule is regarded as amorphous and about 30% as crystalline. The amorphous regions contain the main amount of amylose but also a considerable part of the amylopectin. The crystalline region consists primarily of the amylopectin (Sajilata, et al., 2006).

Starch in the pharmaceutical industry

During recent years, starch has been taken as a new potential biomaterial for pharmaceutical applications because of the unique physicochemical and functional characteristics (Cristina Freire, et al., 2009; Freire, et al., 2009; Serrero, et al.).

3.1 Starch as pharmaceutical excipient

Native starches were well explored as binder and disintegrant in solid dosage form, but due to poor flowability their utilization is restricted. Most common form of modified starch i.e. Pre-gelatinized starch marketed under the name of starch 1500 is now a day's most preferred directly compressible excipients in pharmaceutical industry. Recently modified rice starch, starch acetate and acid hydrolyzed dioscorea starch were established as multifunctional excipient in the pharmaceutical industry. The International Joint Conference on Excipients rated starch among the top ten pharmaceutical ingredients (Shangraw, 1992).

3.2 Starch as tablet disintegrant

They are generally employed for immediate release tablet formulations, where drug should be available within short span of time to the absorptive area. Sodium carboxymethyl starch, which is well established and marketed as sodium starch glycolate is generally used for immediate release formulation. Some newer sources of starch have been modified and evaluated for the same.

3.3 Starch as controlled/sustained release polymer for drugs and hormones

Modified starches in different forms such as Grafted, acetylated and phosphate ester derivative have been extensively evaluated for sustaining the release of drug for better patient compliances. Starch-based biodegradable polymers, in the form of microsphere or hydrogel, are suitable for drug delivery (Balmayor, et al., 2008), (Reis, et al., 2008). For example, high amylose corn starch has been reported to have good sustained release properties and this has been attributed to its excellent gel-forming capacity (Rahmouni, et al., 2003; Te Wierik, et al., 1997). Some authors (Efentakis, et al., 2007; Herman and Remon, 1989; Michailova, et al., 2001) have explained the mechanism of drug release from such gel-forming matrices to be a result of the controlled passage of drug molecules through the obstructive gel layer, gel structure and matrix.

3.4 Starch as plasma volume expander

Acetylated and hydroxyethyl starch are now mainly used as plasma volume expanders. They are mainly used for the treatment of patients suffering from trauma, heavy blood loss and cancer.

3.5 Starch in bone tissue engineering

Starch-based biodegradable bone cements can provide immediate structural support and degrade from the site of application. Moreover, they can be combined with bioactive particles, which allow new bone growth to be induced in both the interface of cement-bone and the volume left by polymer degradation (Boesel, et al., 2004). In addition, starch-based biodegradeable polymer can also be used as bone tissue engineering scaffold (Gomes, et al., 2003).

3.6 Starch in artificial red cells

Starch has also been used to produce a novel and satisfactory artificial RBCs with good oxygen carrying capacity. It was prepared by encapsulating hemoglobin (Hb) with long-chain fatty-acids-grafted potato starch in a self-assembly way (Xu, et al., 2011).

3.7 Starch in nanotechnology

Starch nanoparticles, nanospheres, and nanogels have also been applied in the construction of nanoscale sensors, tissues, mechanical devices, and drug delivery system. (Le Corre, et al., 2010).

3.7.1 Starch microparticles

The use of biodegradable microparticles as a dosage form for the administration of active substances is attracting increasing interest, especially as a means of delivering proteins. Starch is one of the polymers that is suitable for the production of microparticles. It is biodegradable and has a long tradition as an excipient in drug formulations. Starch microparticles have been used for the nasal delivery of drugs and for the delivery of vaccines administered orally and intramuscularly. Bioadhesive systems based on polysaccharide microparticles have been reported to significantly enhance the systemic absorption of conventional drugs and polypeptides across the nasal mucosa, even when devoid of absorption enhancing agents. A major area of application of microparticles is as dry powder inhalations formulations for asthma and for deep-lung delivery of various

agents. It has also been reported that, particles reaching the lungs are phagocytosed rapidly by alveolar Macrophages. Although phagocytosis and sequestration of inhaled powders may be a problem for drug delivery to other cells comprising lung tissue, it is an advantage for chemotherapy of tuberculosis. Phagocytosed microparticles potentially can deliver larger amounts of drug to the cytosol than oral doses. It is also opined strongly that, microparticles have the potential for lowering dose frequency and magnitude, which is especially advantageous for maintaining drug concentrations and improving patient compliance. This is the main reason this dosage form is an attractive pulmonary drug delivery system. (Le Corre, et al., 2010).

3.7.2 Starch microcapsules

Microencapsulation is the process of enclosing a substance inside a membrane to form a microcapsule. it provides a simple and cost-effective way to enclose bioactive materials within a semi-permeable polymeric membrane. Both synthetic/semi-synthetic polymers and natural polymers have been extensively utilized and investigated as the preparation materials of microcapsules. Although the synthetic polymers display chemical stability, their unsatisfactory biocompatibility still limits their potential clinical applications. Because the natural polymers always show low/non toxicity, low immunogenicity and thereafter good biocompatibility, they have been the preferred polymers used in microencapsulation systems. Among the natural polymers, alginate is one of the most common materials used to form microcapsules, however, starch derivatives are now gaining attention. For instance starch nasal bioadhesive microspheres with significantly extended half-life have been reported for several therapeutic agents including insulin. Improved bioavailability of Gentamycin-encapsulated starch microspheres as well as magnetic starch microspheres for parenteral administration of magnetic iron oxides to enhance contrast in magnetic resonance imaging has been reported. (Le Corre, et al., 2010).

3.7.3 Starch nanoparticles

Nanoparticles are solid or colloidal particles consisting of macromolecular substances that vary in size from 10-1000 nm. The drug may be dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. The matrix may be biodegradable materials such as polymers or proteins or biodegradable/biocompatible/bioasborbable materials such as starch. Depending on the method of preparation, nanoparticles can be obtained with different physicochemical, technical or mechanical properties as well as modulated release characteristics for the immobilized bioactive or therapeutic agents. (Le Corre, et al., 2010).

4. Application of modified starches in drug delivery

Native starch irrespective of their source are undesirable for many applications, because of their inability to withstand processing conditions such as extreme temperature, diverse pH, high shear rate, and freeze thaw variation. To overcome this, modifications are usually done to enhance or repress the inherent property of these native starches or to impact new properties to meet the requirements for specific applications. The process of starch modification involves the destructurisation of the semi-crystalline starch granules and the effective dispersion of the component polymers. In this way, the reactive sites (hydroxyl groups) of the amylopectin polymers become accessible to electrophilic reactants (Rajan, et al., 2008). Common modes of modifications useful in pharmaceuticals are chemical, physical

and enzymatic with, a much development already seen in chemical modification. Starch modification through chemical derivation such as etherification, esterification, cross-linking, and grafting when used as carrier for controlled release of drugs and other bioactive agents. It has been shown that, chemically modified starches have more reactive sites to carry biologically active compounds, they become more effective biocompatible carriers and can easily be metabolized in the human body (Prochaska, et al., 2009; Simi and Emilia Abraham, 2007).

4.1 Chemical modification of starch

There are a number of chemical modifications made to starch to produce many different functional characteristics. The chemical reactivity of starch is controlled by the reactivity of its glucose residues. Modification is generally achieved through etherification, esterification, crosslinking, oxidation, cationization and grafting of starch. However, because of the dearth of new methods in chemical modifications, there has been a trend to combine different kinds of chemical treatments to create new kinds of modifications. The chemical and functional properties achieved following chemical modification of starch, depends largely on the botanical or biological source of the starch,, reaction conditions (reactant concentration, reaction time, pH and the presence of catalyst), type of substituent, extent of substitution (degree of substitution, or molar substitution), and the distribution of the substituent in the starch molecule (Singh, et al., 2007). Chemical modification involves the introduction of functional groups into the starch molecule, resulting in markedly altered physico-chemical properties. Such modification of native granular starches profoundly alters their gelatinization, pasting and retrogradation behavior (Choi and Kerr, 2003; Kim, et al., 1993) (Perera, et al.) and (Liu, et al., 1999) (Seow and Thevamalar, 1993). The rate and efficiency of the chemical modification process depends on the reagent type, botanical origin of the starch and on the size and structure of its granules (Huber and BeMiller, 2001).This also includes the surface structure of the starch granules, which encompasses the outer and inner surface, depending on the pores and channels (Juszczak, 2003).

4.1.1 Carboxymethylated starch

Starches can have a hydrogen replaced by something else, such as a carboxymethyl group, making carboxymethyl starch (CMS). Adding bulky functional groups like carboxymethyl and carboxyethyl groups reduces the tendency of the starch to recrystallize and makes the starch less prone to damage by heat and bacteria. Carboxymethyl starch is synthesized by reacting starch with monochloroacetic acid or its sodium salt after activation of the polymer with aqueous NaOH in a slurry of an aqueous organic solvent, mostly an alcohol. The total degree of substitution (DS), that is the average number of functional groups introduced in the polymer, mainly determines the properties of the carboxymethylated products (Heinze, 2005). The functionalization influences the properties of the starch. For example, CMS have been shown to absorb an amount of water 23 times its initial weight. This high swelling capacity combined with a high rate of water permeation is said to be responsible for a high rate of tablet disintegration and drug release from CMS based tablets. CMS has also been reported to be capable of preventing the detrimental influence of hydrophobic lubricants (such as magnesium stearate) on the disintegration time of tablets or capsules.. Some of the recent use of carboxymethylated starch in pharmaceuticals are summarised in Table 1.

Study Title	Methodology	Drug used	Summary	References
Synthesis and in vitro evaluation of carboxymethyl starch-chitosan nanoparticles as drug delivery system to the colon.	Complex coacervation process.	5-aminosalicylic acid	Chitosan-carboxymethyl starch nanoparticles developed based on the modulation of ratio show promise as a system for controlled delivery of drugs to the colon.	(Saboktakin, et al., 2010)
Carboxymethyl-Starch Excipients for Gastrointestinal Stable Oral Protein Formulations Containing Protease Inhibitors.	Monochloroacetic acid Semisynthesis	Protease inhibitors	The feasibility to deliver stable bioactive proteins into intestinal environment using CMS was demonsttrated. In addition to its protective role, the CMS allows the release of the bioactive agents in less than 6 h, fitting well with the upper intestinal transit. Such stability is needed for formulation of oral vaccines with specific antigens.	(Patrick De Koninck, 2010)
Novel Polymeric Biomaterial Based on Carboxymethyl starch and its Application in Controlled Drug Release.	Blender, mixing and sieving	Acetylsalicylic acid	Matrix (CMS) releases the enclosed drug at a much faster rate in neutral and alkaline pH than in acidic pH, thus holding the promise of being developed into a vehicle for targeted drug delivery (oral route) to the lower gastrointestinal tract.	(Sen and Pal, 2009b)
Carboxymethyl high amylose starch as excipient for controlled drug release: Mechanistic study and the influence of degree of substitution.	Non aqueous medium synthesis, protanated using acid treatment.	Acetaminophen	The results showed that, CMHAS(Na) with DS between 0.1 and 0.2 can be used as sustained release excipients, while those with high DS, between 0.9 and 1.2, are better as delayed release excipient.	(Lemieux, et al., 2009)
High-amylose sodium carboxymethyl starch matrices for oral, sustained drug-release: Formulation aspects and in vitro drug-release evaluation.	Spray Drying	Acetaminophen	The results proved that the new Spray Drying process developed for High-amylose sodium carboxymethyl starch (HASCA) manufacture is suitable for obtaining similar-quality (HASCA) in terms of drug release and compression performances.	(Brouillet, et al., 2008)
Carboxylated high amylose starch as pharmaceutical excipients and formulation Structural insights of pancreatic enzymes.	Carboxylation and protonation	Pancreatic enzymes	High loading capacity (up to 70–80% enzymes) was obtained. An advantage of these formulations is that gastroprotection is afforded by the carboxylated matrices (carboxylic groups), without enteric coating.	(Massicotte, et al., 2008)

High-amylose carboxymethyl starch matrices for oral sustained drug-release: In vitro and in vivo evaluation.	Blending of HASCA with NaCl	Acetaminophen	In vitro drug-release from an optimized HASCA formulation was not affected by either acidic pH value or acidic medium residence time. Compressed blend of HASCA with an optimized quantity of sodium chloride provided a pharmaceutical sustained-release tablet with improved integrity for oral administration. In vivo studies demonstrated extended drug absorption.	(Nabais, et al., 2007)
Physicochemical and Pharmaceutical Properties of Carboxymethyl Rice Starches Modified from Native Starches with Different Amylose Content.	Monochloroacetic acid Reaction	Material science	Carboxymethyl rice starches (CMRS) can function as tablet binder in the wet granulation of both water-soluble and water-insoluble diluents. The tablets compressed from these granules showed good hardness with fewer capping problems compared with those prepared using the pregelatinized native rice starch as a binder.	(Kittipongpatana, et al., 2007)
An Aqueous Film-coating Formulation based on Sodium Carboxymethyl Mungbean Starch	Petri dish method	Material scienc	Carboxymethyl mungbean starch (SCMMSs) exhibited the ability to form a clear, thin film with greater flexibility and strength than that of the native starch. This study reports the potential of SCMMS as tablet film coating agent	(Kittipongpatana, et al., 2006)

Table 1. Use of carboxymethylated starch in drug delivery

4.1.2 Acetylated starch

Acetylated starch has also been known for more than a century. Starches can be esterified by modifications with an acid. When starch reacts with an acid, it loses a hydroxyl group, and the acid loses hydrogen. An ester is the result of this reaction. Acetylation of cassava starch has been reported to impart two very important pharmaceutical characters to it; increased swelling power (Rutenberg, 1984) and enhanced water solubility of the starch granules (Aziz, 2004). Starch acetates and other esters can be made very efficiently on a micro scale without addition of catalyst or water simply by heating dry starch with acetic acid and anhydride at 180°C for 2-10 min (Shogren, 2003). At this temperature, starch will melt in acetic acid (Shogren, 2000)and thus, a homogeneous acetylation would be expected to occur. Using acetic acid, starch acetates are formed, which are used as film-forming polymers for pharmaceutical products. A much recent Scandium triflate catalyzed acetylation of starch at low to moderate temperatures is reported by (Shogren, 2008). Generally, starch acetates have a lower tendency to create gels than unmodified starch. Acetylated starches are distinguishable through high levels of shear strength. They are particularly stable against heat and acids and are equally reported to form flexible, water-soluble films. Some of the recent uses of acetylated starch in pharmaceuticals are summarized in Table 2.

Study Title	Methodology	Drug used	Summary	References
An Oral Colon-Targeting Controlled Release System Based on Resistant Starch Acetate: Synthetization, Characterization, and Preparation of Film-Coating Pellets.	Acetic anhydride synthesis	5-ASA, BSA, HGF, and insulin	The study suggests that an oral colon-targeting controlled release system based on resistant starch acetate (RSA) as a film-coating material has an excellent colon-targeting release performance and the universality for a wide range of bioactive components.	(Pu, 2011)
Preparation and Properties of Starch Acetate Fibers for Potential Tissue Engineering Applications	Extruded as fibers onto a rotating drum with variable speed using a syringe and needle	Tissue engineering scaffolds	The starch acetate fibers support the adhesion of fibroblasts demonstrating that the fibers would be suitable for tissue engineering and other medical applications. They possess better mechanical properties and water stability than most polysaccharide-based biomaterials and protein fibers used in tissue engineering.	(Narendra Reddy, 2009)
Acetylated starch-based biodegradable materials with potential biomedical applications as drug delivery systems.	Acetyl esterification	Bovine serum albumin	Drug release studies show that the starch acetate coated tablets could deliver the drug to the colon suggesting that it can be a potential drug delivery carrier for colon-targeting.	(Chen, et al., 2007)
Optimization and characterization of controlled release multi-particulate beads coated with starch acetate	Organic synthesis	Dyphylline	Starch acetate-coated beads provided controlled release of dyphylline.	(Nutan, et al., 2005)
Drug release from starch-acetate microparticles and films with and without incorporated alpha-amylose.	Acetyl Esterification /aqueous synthesis	Timolol calcein and bovine serum albumin	This study demonstrates the achievement of slow release of different molecular weight model drugs from the starch acetate microparticles and films as compared to fast release from the native starch preparations.	(Tuovinen, et al., 2004a)
Starch acetate microparticles for drug delivery into retinal pigment epithelium-in vitro study.	Modified water-in-oil-in-water double-emulsion technique.	Calcein	The study indicates that the natural enzyme-sensitive starch acetate is suitable for drug delivery into retinal pigment epithelium (RPE). The starch acetate microparticles were easily taken up by cultured human RPE cells without significant toxicity.	(Tuovinen, et al., 2004b)

Starch acetate as a tablet matrix for sustained drug release	Monolithic matrix system	Propranolol hydrochloride	The drug release was considerably slower from sodium acetate tablet matrices. Also, a decrease in starch acetate concentration increased the drug release rate. Crack formation increased area available for Fickian diffusion, which caused slow attenuation of drug release rate.	(Pohja, et al., 2004)
Drug release from starch-acetate films.	Monolithic matrix system	BSA, FITC-dextran timolol and sotalol–HCl	The results showed that acetylation of potato starch can substantially retard drug release thus allowing sustained drug delivery. The drug release profiles may be controlled by the degree of substitution.	(Tuovinen, et al., 2003)
Acetylation enhances the tabletting properties of starch	Acetic Anhydride synthesis	materials science	The acetate moiety, perhaps in combination with existing hydroxyl groups, was a very effective bond-forming substituent. The formation of strong molecular bonds increased, leading to a very firm and intact tablet structure.	(Raatikainen, et al., 2002)

Table 2. Some acetylated starches and their application in drug delivery.

4.1.3 Hydroxypropylated starch

Hydroxypropyl groups introduced into starch chains are said to be capable of disrupting inter- and intra-molecular hydrogen bonds, thereby weakening the granular structure of starch leading to an increase in motional freedom of starch chains in amorphous regions (Choi and Kerr, 2003; Seow and Thevamalar, 1993; Wootton and Manatsathit, 1983). Such chemical modification involving the introduction of hydrophilic groups into starch molecules improves the solubility of starch and the functional properties of starch pastes, such as its shelf life, freeze/thaw stability, cold storage stability, cold water swelling, and yields reduced gelatinization temperature, as well as retarded retrogradation. Owing to these properties, hydroxypropylated starches is gaining interest in medicine.

Study Title	Methodology	Drug used	Summary	References
Hydroxypropylated starches of varying amylose contents as sustained release matrices in tablets	Monolithic matrix tablet formulation	Propranolol hydrochloride	Hydroxypropylation improved the sustained release ability of amylose-containing starch matrices, and conferred additional resistance to the hydrolytic action of pancreatin under simulated gastrointestinal conditions.	(Onofre and Wang, 2010)

Table 3. Hydroxyl-propylated starch in drug delivery.

4.1.4 Succinylated starch

Modification of starch by Succinylation has also been found to modify its physicochemical properties, thereby widening its applications in food and non-food industries like pharmaceuticals, paper and textile industries. Modification of native starch to its succinate derivatives reduces its gelatinisation temperature and the retrogradation, improves the freeze-thaw stability as well as the stability in acidic and salt containing medium (Trubiano Paolo, 1997; Trubiano, 1987; Tukomane and Varavinit, 2008). Generally, succinylated starch can be prepared by treating starches with different alkenyl succinic anhydride, for example, dodecenyl succinic anhydride, octadecenyl succinic anhydride or octenyl succinic anhydride. The incorporation of bulky octadecenyl succinic anhydride grouping to hydrophilic starch molecules has been found to confer surface active properties to the modified starch (Trubiano Paolo, 1997). Unlike typical surfactants, octadecenyl succinic anhydride starch, forms strong films at the oil–water interface giving emulsions that are resistant to reagglomeration. A recent application of succinylated starch in pharmaceuticals are summarized in Table 4.

Study Title	Methodology	Drug used	Summary	References
Preparation and characterisation of octenyl succinate starch as a delivery carrier for bioactive food components	Pyridine-catalyzed esterification	Bovine serum albumin/ASA	Ocetyl succcinate starch was found to be a potential carrier for colon-targeted drug delivery	(Wang, et al., 2011)

Table 4. A recent application of succinylated starch in drug delivery

4.1.5 Phosphorylated starch

Phosphorylation was the earliest method of starch modification. The reaction gives rise to either monostarch phosphate or distarch phosphate (cross-linked derivative), depending upon the reactants and subsequent reaction conditions. Phosphate cross-linked starches show resistance to high temperature, low pH, high shear, and leads to increased stability of the swollen starch granule. The presence of a phosphate group in starch increases the hydration capacity of starch pastes after gelatinization and results in the correlation of the starch phosphate content to starch paste peak viscosity , prevents crystallization and gel-forming capacity (Nutan, et al., 2005). These new properties conferred on starch by phosphorylation, makes them useful as disintegrants in solid dosage formulations and as matrixing agents. Interestingly, it has been documented that, the only naturally occurring covalent modification of starch is phosphorylation. Traditionally, starch phosphorylation is carried out by the reaction of starch dispersion in water with reagents like mono- or di sodium orthophosphates, sodium hexametaphosphate, sodium tripolyphosphate (STPP), sodium trimetaphosphate (STMP) or phosphorus oxychloride. Alternative synthetic methods such as extrusion cooking, microwave irradiation and vacuum heating have been

reported (A. N. Jyothi, 2008; Sitohy and Ramadan, 2001). Some of the recent uses of phosphorylated starch in pharmaceuticals are summarized in Table 5.

Study Title	Methodology	Drug used	Summary	References
Starch Phosphate: A Novel Pharmaceutical Excipient For Tablet Formulation.	Phosphorylation using mono sodium phosphate dehydrate	Ziprasidone	At low concentration, starch phosphate proved to be a better disintegrant than native starch in tablet formulation.	(N.L Prasanthi, 2010)
Starch phosphates prepared by reactive extrusion as a sustained release agent.	Reactive extrusion	Metoprolol tartrate	Starch phosphate prepared by reactive extrusion produced stronger hydrogels with sustained release properties as compared with native starch.	(O'Brien, et al., 2009)

Table 5. Use of phosphorylated starch in Pharmaceuticals.

4.1.6 Co-polymerized starch

Chemical modification of natural polymers by grafting has received considerable attention in recent years because of the wide variety of monomers available. Graft copolymerization is considered to be one of the routes used to gain combinatorial and new properties of natural and synthetic polymers. In graft copolymerization the guest monomer benefits the host polymer with some novel and desired properties in which the resultant copolymer gains characteristic properties and applications (Fares, et al., 2003). As a rule, graft copolymerization produces derivatives of significantly increased molecular weight. Starch grafting usually entails etherification, acetylation, or esterification of the starch with vinyl monomers to introduce a reaction site for further formation of a copolymeric chain. Such a chain would typically consist of either identical or different vinyl monomers (block polymers), or it may be grafted onto another polymer altogether. Graft copolymers find application in the design of various stimuli-responsive controlled release systems such as transdermal films, buccal tablets, matrix tablets, microsphers/hydrogel bead system and nanoparticulate system (Sabyasachi Maiti, 2010). Some of the recent uses of graft co-polymerized starch in pharmaceuticals is summarized in Table 6.

Study Title	Methodology	Drug used	Summary	References
Grafted Starch-Encapsulated Hemoglobin (GSEHb) Artificial Red Blood Cells Substitutes.	Self –assembly	Artificial RBCs	Satisfactory artificial RBCs with good oxygen carrying capacity obtained.	(Xu, et al., 2011)
Preparation and using of acrylamide grafted starch as polymer drug carrier.	Chemical grafting of acrylamide on the starch polymer	Ceftriaxone Sodium	Acrylamide grafted starch showed higher uptake of water compared with native starch. The starch exhibited good controlled release properties.	(Al-Karawi and Al-Daraji, 2010)
Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: Physicochemical and technological characterisation	Free radical polymerization and alternatively dried in a vacuum oven (OD) or freeze-dried (FD)	Material science	The copolymers could be used as excipients in matrix tablets and have potentials for use as controlled release materials.	(Marinich, et al., 2009)
Physical blends of starch graft copolymers as matrices for colon targeting drug delivery systems.	Synthesis by Cerium iv ion method	Theophylline, procaine and bovineserum	The physical blend offered good controlled release of drugs, as well as of proteins and presented suitable properties for use as hydrophilic matrices for colon-specific drug delivery.	(Silva, et al., 2009)
Microwave initiated synthesis of polyacrylamide grafted carboxymethylstarch (CMS-g-PAM): application as a novel matrix for sustained drug release.	Microwave initiated synthesis	5-amino salicylic acid	'In vitro' release of a model drug (5-amino salicylic acid) from CMS-g-PAM matrix showed a sustained drug release. In this matrix, the rate of release of the enclosed drug could be precisely programmed simply by adjustment of percentage grafting during synthesis.	(Sen and Pal, 2009a)
Starch–Acrylics Graft Copolymers and Blends: Synthesis, Characterization, and Applications as Matrix for Drug Delivery	Polymerization reaction	Paracetamol	The graft copolymers, provided a pH sensitive matrix system for site-specific drug delivery. The authors concluded that graft copolymers may be a useful tool to overcome the harsh environment of the stomach and can possibly be used in future as excipient for colon-targeted drug delivery.	(Shaikh and Lonikar, 2009)

Characterization and in vitro evaluation of starch based hydrogels as carriers for colon specific drug delivery systems	γ-rays induced polymerization and crosslinking	Ketoprofen	Hydrogels prepared showed pH responsive property; preventing drug release pH 1, but released it at pH 7.	(El-Hag Ali and AlArifi, 2009)
Hydrophobic grafted and crosslinked starch nano particles for drug delivery.	Grafted using potassium persulphate as catalyst	Indomethacin	Fatty acid grafted starch nano particle with high swelling power was obtained and was found to be a good vehicle for oral controlled drug delivery	(Simi and Emilia Abraham, 2007)
Bioadhesive grafted starch copolymers as platforms for peroral drug delivery: a study of theophylline release.	Radiation of starch and acrylic acid mixtures with ^{60}Co	Theophylline	Results show that,the release of theophylline from the graft copolymer tablets was practically independent of the pH of the dissolution medium and the type of starch used for grafting. Incorporation of divalent cations into the graft copolymers led to a significant decrease in swelling and retardation of drug release.	(Geresh, et al., 2004)
Ethyl Methacrylate grafted on two starches as polymeric matrices for drug delivery	Ceric ion redox initiation method	Theophylline and procaine hydrochloride	The HS-EMA and S-EMA were found to be efficient matrices for insoluble drugs	(Echeverria, et al., 2005)

Table 6. Use of graft co-polymerized starch in Pharmaceuticals.

4.2 Physical modification of starch

Physical modification of starch is mainly applied to change the granular structure and convert native starch into cold water-soluble starch or small-crystallite starch. The major methods used in the preparation of cold water-soluble starches involve instantaneous cooking–drying of starch suspensions on heated rolls (drum-drying), puffing, continuous cooking–puffing–extruding, and spray-drying (Jarowrenko, 1986). A method for preparing granular cold water-soluble starches by injection and nozzle-spray drying was described by (Pitchon & Joseph 1981). Among the physical processes applied to starch modification, high pressure treatment of starch is considered an example of 'minimal processing'(Stute, et al., 1996). A process of iterated syneresis applied to the modification of potato, tapioca, corn and wheat starches resulted in a new type of physically modified starches (Lewandowicz and Soral-Smietana, 2004). Some of the recent uses of physically modified starch in pharmaceuticals are summarized in Table 7.

Study Title	Methodology	Drug used	Summary	References
Microwave Assisted Modification of Arrowroot Starch for Pharmaceutical Matrix Tablets	Microwave Assisted Modification	Theophylline	The modified arrowroot starch, demonstrated promising properties as hydrophilic matrix excipients for sustained release tablets	(Pornsak Sriamornsak 2010)
Effect of heat moisture treatment on the functional and tabletting properties of corn starch Gelatinized/freeze-dried starch as excipient in sustained release tablets.	Heat moisture treatment	Material science	Heat moisture treatment (HMT) of corn starch could be useful when fast disintegration, lower swelling power, and lower crushing strength are desired in tablet.	(Iromidayo Olu-Owolabi.B, 2010)
Pregelatinized glutinous rice starch as a sustained release agent for tablet preparations	Heat treatment and spray drying	Propranolol HCl	In this study glutinous rice starch slurry was physically modified by heat and then dried by spray drying. The tablet containing pregelatinized glutinous starch and propranolol HCl were prepared by wet granulation method. The mechanisms of drug release from the matrices were anomalous (non-Fickian) diffusion in both hydrochloric buffer (pH 1.2) and phosphate buffer media (pH 6.8).	(Peerapattana, et al.)
A Novel Pregelatinized Starch as a Sustained-Release Matrix Excipient.	Controlled thermal pregelatinization And spray-drying	Ethenzamide acetaminophen and sodium salicylic acid	The study shows that highly functional pregelatinized starch is a new matrix excipient that can control drug-release profiles from first- to zero-order sustained release and enables drug release independent of drug solubility and external conditions.	(Masaaki Endo, 2009)
Effects of Drying Process for Amorphous Waxy Maize Starch on Theophylline Release from Starch-Based Tablets.	Oven drying and freeze drying procedure	Theophylline	The drying method was found to affect the morphology and drug release profiles of the compressed tablets.	(Yoon, et al., 2007)

Gelatinized/freeze-dried starch as excipient in sustained release tablets.	Gelatinization and freeze-drying	Material science	A new technique for the production of cold water-swellable starch using gelatinization and freeze-drying processes was obtained and the matrices containing different modified starch -hydroxypropyl methylcellulose mixtures possess good sustained release properties.	(Sánchez, et al., 1995)
Modified starches as hydrophilic matrices for controlled oral delivery III. Evaluation of sustained-release theophylline formulations based on thermal modified starch matrices in dogs	Thermal Modification	Theophylline	Several thermally modified starch matrices evaluated in dogs demonstrated good sustained-release performance	(Herman and Remon, 1990)
Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches.	Thermal Modification	Theophylline	Thermally modified starches containing a low amount of amylose (25% and lower) revealed promising properties as directly compressible tabletting excipients for sustained release purposes.	(Herman and Remon, 1989)

Table 7. Some of the recent uses of physically modified starch in medicine.

Study Title	Methodology	Drug used	Summary	References
Enzymatic modification of cassava starch by fungal lipase.	Esterification using fungal lipase	Material science	Esterification of starch using fungal lipase with long chain fatty acids like palmitic acid gives thermoplastic starch which has got wide use in plastic industry, pharmaceutical industries, and in biomedical applications such as materials for bone fixation and replacements, carriers for controlled release of drugs and other bioactive agents. Unlike chemical esterification, enzymatic esterification is ecofriendly and avoids the use of nasty solvents.	(Rajan, et al., 2008)
Enzyme-Catalyzed Regioselective Modification of Starch Nanoparticles	Etherification of starch nanoparticles catalyzed by Candida antartica Lipase B	Material science	Selective etherification of starch nanoparticles catalyzed by Candida antartica Lipase B (CAL-B) in its immobilized (Novozyme 435) and frees (SP-525) forms. The starch nanoparticles were made accessible for acylation reactions by formation of Aerosol-OT (AOT, bis[2-ethylhexyl]sodium sulfosuccinate) stabilized microemulsions. The close proximity of the lipase and substrates promotes the modification reactions.	(Chakraborty, et al., 2005)

Table 8. Some enzymatically modified starches and potential medical/pharmaceutical applications

4.3 Enzymatic modification of starch

An alternative to obtaining modified starch is by using various enzymes. These include enzymes occurring in plants, e.g pullulanase and isoamylase groups. Pullulanase is a 1,6-α-glucosidase, which statistically impacts the linear α-glucan, a pullulan which releases maltotriose oligomers. This enzyme also hydrolyses α-1,6-glycoside bonds in amylopectin and dextrines when their side-chains include at least two α-1,4-glycoside bonds. Isoamylase is an enzyme which totally hydrolises α-1,6-glycoside bonds in amylopectin, glycogen, and some branched maltodextrins and oligosaccharides, but is characterised by low activity in relation to pullulan (Norman 1981). In a study (Kim and Robyt, 1999) starch granules was modified in situ by using a reaction system in which glucoamylase reacts inside starch granules to give conversions of 10–50% D-glucose inside the granule. Enzymatic modification of starch still needs to be explored and studied. Some of the recent uses of enzymatically modified starch in pharmaceuticals is summarized in Table 8.

Study Title	Methodology	Drug used	Summary	References
Evaluation of glutinous rice starch based matrix microbeads using scanning electron microscopy	Micro orifice ionotropic-getation method	Material science	Microbeads were prepared by ionotropic-getation method using glutinous rice starch from Assam Bora rice, and sodium alginate backbone with different crosslinking agents. Photomicrographs provides information on the surface texture, size, mechanistic properties, suitability of drying condition and mechanism of drug release from the prepared micro devices.	(Nikhil K Sachan, 2010)
Development of porous HAp and β-TCP scaffolds by starch consolidation with foaming method and drug-chitosan bilayered scaffold based drug delivery system.	Starch consolidation with foaming method	Ceftriaxone	This study confirmed the ability of starch consolidation scaffolds to release drugs suitable for treating osteomyelitis.	(Kundu, et al.)
Preparation of starch-based scaffolds for tissue engineering by supercritical immersion precipitation.	Supercritical immersion precipitation	Scaffolds	Highly porous and interconnected scaffolds were obtained in this report which made use of polymeric blend of starch and poly (L-lactic acid) for tissue engineering purposes. Good porosity is critical in scaffolds technology	(Duarte, et al., 2009)
Porous scaffold of gelatin-starch with nanohydroxyapatite composite processed via novel microwave vaccum drying.	Microwave vaccum drying	Hydroxyapatite	Gelatin blended with starch results in scaffold composites with enhanced mechanical properties. A gelatin–starch blend reinforced with HA nanocrystals (nHA) gave biocompatible composites with enhanced mechanical properties.	(Sundaram, et al., 2008)

Novel Starch-Based Scaffolds for Bone Tissue Engineering: Cytotoxicity, Cell Culture, and Protein Expression	Melt-based technology	Scaffolds	A study on 50/50 (wt%) blend of corn starch/ethylene-vinyl alcohol (SEVA-C) led these authors to conclude that, starch-based scaffolds should be considered as an alternative for bone tissue-engineering applications in the near future.	(Salgado, et al., 2004)
Microwave Processing of Starch-Based Porous Structures for Tissue Engineering Scaffolds	Microwave Processing	Scaffolds	This study reports the suitability of different types of starch-based polymers; Potato, sweet potato, corn starch, and nonisolated amaranth and quinoa starch in preparing porous structures.	(Torres, et al., 2007)
Scaffold development using 3D printing with a starch- based polymer.	Rapid prototyping	Scaffolds	In this study, a unique blend of starch-based polymer powders (corn starch, dextran and gelatin) was developed for the 3DP process. Cylindrical scaffolds of five different designs were fabricated and found to possess enhanced mechanical and chemical properties.	(Lam, et al., 2002)
New partially degradable and bioactive acrylic bone cements based on starch blends and ceramic fillers	Free radical polymerization of methyl methacrylate and acrylic acid	Acrylic bone cements	This work reports the development of new partially biodegradable acrylic bone cements based on corn starch/cellulose acetate blends (SCA).	(Espigares, et al., 2002)
Porous starch-based drug delivery systems processed by a microwave route	Microwave baking method	Non-steroid anti-inflammatory agent	A new simple processing route to produce starch-based porous materials was developed for the delivery of non-steroid anti-inflammatory agents.	(Malafaya, 2001)

Table 9. Other starch derivatives and starch scaffolds with potential medical/pharmaceutical applications

5. Conclusions

It is obvious that starch has moved from its traditional role as food to being an indispensable medicine. The wide use of starch in the medicine is based on its adhesive, thickening, gelling, swelling and film-forming properties as well as its ready availability, low cost and controlled quality. From the foregoing, to think that starch is still ordinary inert excipients is to be oblivious of the influence this important biopolymer plays in therapeutic outcome of bioactive moieties. Starch has proven to be the formulator's "friend" in that, it can be utilized in the preparation of various drug delivery systems with the potential to achieve the formulator's desire for target or protected delivery of bioactive agents. It is

important to note that apart from the low cost of starch, it is also relatively pure and does not need intensive purification procedures like other naturally occurring biopolymers, such as celluloses and gums. A major limitation to starch use appears to be its higher sensitivity to the acid attack; however, modification has been proved to impart acid-resistance to the product. It is important to optimize the process of transition of starch granules from its native micro- to the artificial submicron levels in greater detail and also pay greater attention to its toxicological profiles especially when it is desired to be used at nanoscale. Although starch is generally regarded as safe, its derivatives and in fact at submicron levels it may pose some safety challenges especially as carriers in drug delivery systems. It is possible to conclude that, although starch is food, it is also medicine.

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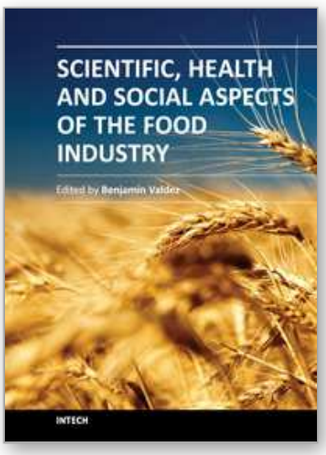

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This book presents the wisdom, knowledge and expertise of the food industry that ensures the supply of food to maintain the health, comfort, and wellbeing of humankind. The global food industry has the largest market: the world population of seven billion people. The book pioneers life-saving innovations and assists in the fight against world hunger and food shortages that threaten human essentials such as water and energy supply. Floods, droughts, fires, storms, climate change, global warming and greenhouse gas emissions can be devastating, altering the environment and, ultimately, the production of foods. Experts from industry and academia, as well as food producers, designers of food processing equipment, and corrosion practitioners have written special chapters for this rich compendium based on their encyclopedic knowledge and practical experience. This is a multi-authored book. The writers, who come from diverse areas of food science and technology, enrich this volume by presenting different approaches and orientations.

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