Review Article

Modified Starch as a Versatile Pharmaceutical Excipient: A Comprehensive Review

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ABSTRACT

Starch is a naturally occurring, most abundant carbohydrate with unique physicochemical properties. Since years it has been utilized as popular pharmaceutical excipients as binder, diluents, disintegrant etc. Current trends in the path of technologies and developments enhances the application of starch and its derivatives an important substitute in multiple applications due to its versatility, low cost and ease of use when its physicochemical properties are altered. Starch can be modified to improve its positive attributes and eliminate deficiencies in its natural characteristics. By employing modified excipients quality and efficacy of the formulation is improved. This review aims to summarize the latest developments of different techniques concerning to modification of starches.

Keywords: Starch, physical modification, chemical modification, microwave modification.

INTRODUCTION

Starch is a relatively inexpensive raw material with physical and chemical properties that convey various uses in pharmaceutical industry. Starch can be extracted using different processes, depending on the plant source and end use of the starch. It is one of the most widely used excipient as filler, binder, and disintegrant in the production of solid dosage forms. Starches are inherently unsuitable for most applications and must be modified chemically or physically to enhance their positive attributes and to minimize their defects. Starch modification, mainly involves the alteration of the physical and chemical characteristics of native starch to improve its functional characteristics. This will enhance its application in formulation of solid dosage form and cosmetic formulations. Some starch is included into plastics to enhance environmental fragmentation and decay. Thermoplastic starch and starch–polymer composites can substitute petroleum-based plastics in some applications. The modification technology consists of oxidation or chemical substitution, annealing or heat with moisture content within granule to change native starches properties for better functionality. The requirement of native starch modification is due to the inbuilt deficiencies in its properties. Native starches are easily retrograde, insoluble in water with associated syneresis and most significantly pastes and gels produced by native starches are unstable at mechanical stress, pH and high temperature. Due to these inbuilt native starch deficiencies, there is need for modification. [1-2] These can be found applicable practices in: textile, pulp and paper, foods, feedstuff, foundry, pharmacy and oil drilling. Various attempts have been made for modification of starch based on application. These are summarized in Figure 1.

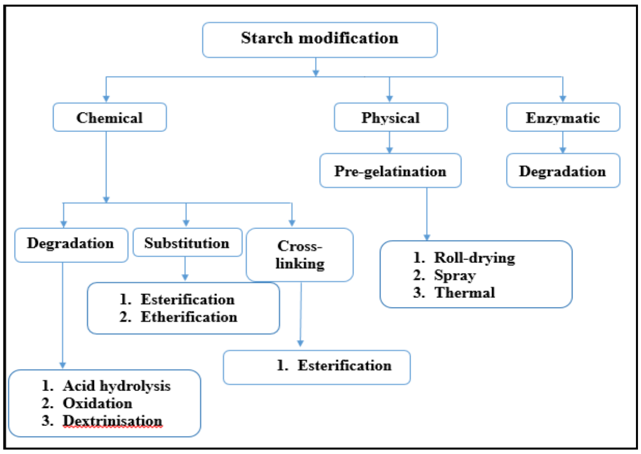

Figure 1: Methods of modification of starch

Chemical Modifications of Starch

Native starch modified so as to introduce new functional group in inherent structure. To achieve this native starch is treated with precise chemical at definite concentration which results in reaction with hydroxyl group.[3] The susceptibility of starch to modification is determined by the presence of certain functional groups and macroscopic granular structure. Depending on the location of the hydroxyl group and the bond type $\alpha(1\rightarrow4)$–glycosidic versus $\alpha(1\rightarrow6)$–glycosidic) starch shows different properties when chemical modification is done. Hydroxyl group at carbon C6, C_2 and C_3 carbons forms alcohol. When –CHOH–CHOH– is present in place of carbon atoms C_2 and C_3 it forms triol. Due to the presence of the three hydroxyl groups starch is susceptible to substitution reactions that enables the number of possible modifications of starch. The grain size of the starch also affects its reactivity. Susceptibility increased with increasing grain size. Basic mechanism involved in production of starch is derivatization via ether or ester formation, oxidation of hydroxyl groups to carbonyl or carboxylic groups and hydrolysis of glycosidic bonds. There are different forms of chemical modification depending on the modifying agent used. There are three major methods of chemical modification as listed below.[4]

Oxidation

This process includes oxidation of primary or secondary hydroxyl groups of the glucose units with formation of aldehyde or carboxyl groups. Obtained starch has altered viscosity, stability at lower temperature and better water solubility. Oxidation causes depolymerisation, which results in an altered dispersion viscosity, adds carboxyl and carbonyl groups that increases hydrophilic nature. Increased hydrophilic nature of carbonyl-starch has major application in matrix drug delivery systems which are required to swell and control the release of active agents in oral systems and the increased the delivery of poorly water soluble drugs. Oxidized starch also shows film formation and adhesiveness in few formulation as a result of modification of surface morphology, thus these can be applied in controlled release system. Modified viscosity and transformed thermal properties due to oxidation has impact on the swellability that affects the water uptake potential, that made it suitable for applications in most oral formulations such as tablets and hydrogels.[5-8] Efficacy of oxidation depends on the botanical origin of starch, type of oxidant used and the process conditions. Oxidizing agents mainly include air or oxygens in the presence of catalyst, permanganates, nitrogen dioxide, sodium hypochlorite, inorganic peroxides, organic oxidants, nitrogen and metal compounds are used to modify starch. Oxidation reaction may cause breaking of intermolecular bonds or partial depolymerisation of the polymer chains. During the process of oxidation toxic products are generated which discourages this process to be applied widely.

Oxidation with Hydrogen peroxide

Hydrogen peroxide contains high content of active oxygen and possess high oxidation potential, production of nontoxic wastes and lower cost which makes it effective and cheap oxidant. However it has lower reactivity towards certain organic functional groups this can be overcome by use of metal catalyst. Though, this type of oxidation cannot be utilized for the modification starch for pharmaceutical, cosmetic and food as the end product may be contaminated with heavy metals. Oxidation of starch with hydrogen peroxide adds aldehyde groups in starch that can oxidized to carboxylic acids. Polysaccharide chain polymerization chain occurs during oxidation process that diminishes the crystallinity. Thermoplastic properties are enhanced due to reduction of the hydrogen bonds.

Substitution

The purpose of substitution is to reduce or avoid retrogradation by adding mono-functional groups such as hydroxypropyl or acetyl groups along the polymer backbone. This practice drops the gelatinization temperature and stabilizes the starch to prevent re-association. Degree of substitution is level of substituents of the hydroxyl groups along the starch chain. As maximum three groups are available in each glucose unit maximum degree of substitution will be three. Various substitution techniques are used as listed below:

Esterification

Esterification of starch includes the translation of the available three hydroxyl groups to alkyl or aryl derivatives. This modification translates to limited intra-amylase chain interactions, along with interactions with the outer amylopectin chains. Acetyl group is larger in size as compared to hydroxyl group, as a result individual chain repel each other. Repulsion between two chains leads to enlarged granular size, swelling power, solubility, and water absorption capacity.[9-10] Numerous approaches have been used to achieve esterification, the most frequently used process is acetylation, which leads to formation of starch acetate. Acetylated starch may be obtained by reacting starch with acetic anhydride or vinyl acetate at basic pH and at a temperature of between 25 and 30°C. The product is neutralized and washed and acetylated starch powder is prepared by drying. The interruption of the granular hydrogen bonds moreover prevents re-association, which makes acetylated starch resistant to retrogradation and gelatinization temperature. Based on degree of substitution acetylation can be effectively utilized for sustained release of tablet with increasing degree of substitution. Paracetamol and theophylline was studied in tablet formulation containing acetylated starch and results indicate that strength and compactability of tablet in increased with increasing degree of substitution thus sustained release effect is enhanced. Strength of the tablet is enhanced as result of deformed plasticity.[11-12]

Etherification

Etherification is a process in which the hydroxyl groups are substituted with hydroxypropyl, carboxymethyl or hydroxyethyl group that forms an ether linkage.

Carboxymethylation

It is most common method of etherification due to its rapidity and simplicity. In this process hydroxyl group is replaced by anionic carboxymethyl groups. This group is bulkier than hydroxyl group hence reduces the recrystallization property. It furthermore introduces the chances of increased pH responsiveness which renders the modified starch suitable for controlled drug delivery application. Carboxymethylation enhances hydrophilicity, thus facilitating water absorbance through the mechanism of osmosis, thus it can be applied as superdisintegrant in tablet.[13-14] A routine example of carboxymethylation is a superdisintegrant sodium starch glycolate. It is commercially used as a directly compressible excipient.

Synthesis of carboxymethyl starch may be processed by dissolving aqueous sodium hydroxide in an aqueous organic solvent, such as dimethyl sulphoxide. A slurry of the starch (2% w/v) is prepared by dispersing in the alkali-containing solvent. The mixture is heated to reach the reaction temperature and this is maintained to ensure the activation of the starch. This mixture is then reacted with the modifying agent such as monochloroacetic acid or its sodium salt.[15]

Hydroxypropylation

This method is derived from treatment of native starch with propylene oxide in the presence of a strong alkaline catalyst. Starch slurry is prepared and treated with propylene oxide at temperatures of 40°C. The hydroxyl groups are substituted, through a nucleophilic substitution reaction mechanism with hydroxypropyl groups. The resulting product are physicochemically resembles to carboxymethylation process but the hydroxypropyl group is bulkier and can interrupt the inter- and intra-molecular forces in starch. As a result, the hydrogen bonds are broken and weakening the starch granules, allowing in an increased water uptake and thus an increase in the swellability and viscosity. It also reduces the retrogradation property of starch, yielding a product that is stable at high temperature. This renders these starch derivatives applicable as excipients in formulations that require long-term freeze-thaw, cold storage stability or improved general shelf-life.[16-17]

Starch citrate

Starch citrate had application in directly compressible tablet as it has good flow properties and swellability. Swellability is linked with faster disintegration and dissolution rate. The direct compressed tablets of gliclazide and pioglitazone prepared with potato starch citrate indicates faster dissolution rate. Detailed description of preparation of starch citrate is given below:

Citric acid (20g) was dissolved in 20 ml of water, the pH of the solution was adjusted to 3.5 with 10 M sodium hydroxide and finally the volume was made up to 50 ml by adding water. This solution was mixed with 50g of potato starch in a stainless steel tray and conditioned for 16 h at room temperature (28°C). The tray was then placed in hot air oven and dried at60°C for 6 h. The mixture obtained was ground and further dried in a hot air oven at 130°C for 2 h. The dry mixture was frequently washed with water to remove unreacted citric acid. The washed starch citrate was further dried at 50°C to eradicate the moisture totally.[18]

Conversion

This technique is aimed at reducing the viscosity of solubilized starches by producing lower molecular weight compound. Most routine methods of conversion are acid oxidation, hydrolysis, pyroconversion (dextrinization), and enzyme conversion. This process drastically alters the molecular weight of the starch molecule. Acid hydrolyzed starches are more probably used as excipients for tablets, pyroconversion and enzyme conversion are used in formation of dextrins.

Acid Hydrolysis

This includes acid catalyzed hydrolysis of the α-1, 4 and α-1, 6 glycosidic linkages of the starch molecule. Acid hydrolysis prominently affects the amorphous regions of the starch granule and the crystalline region remains protected, in that way starch with a more crystalline structure is generated.[19] The resultant starch maintains its granular structure but shows reduced viscosity, swelling capacity and increased solubility and gel strength.[20-21]

The process of acid hydrolysis may be proceeding by adding hydrochloric or sulfuric acid to a starch slurry under agitation at a temperature ranging from 25°C to a certain degree below the typical starch gelatinization temperature until the sufficient degree of hydrolysis is obtained. The acid is then neutralized before recovering the converted starch granules by filtration, washing, and drying. When applied as a filler-binder, this derivative possesses better flow and compressibility properties than microcrystalline cellulose in the formulations. The compacts of the modified starch had considerably higher crushing strength and lower friability specifying its good capabilities as a directly compressible excipient.

Physical modification of starch

Physical modifications of starch can enhances its water solubility and reduce the size of the starch granules. Physical methods to treat the native granules include: different combinations of temperature, moisture, pressure, shear and irradiation. Physical modification of starch granules is cheap, simple and safe. These techniques do not require chemical or biological agents and are favoured when the product is intended for human use.[1] Various methods have been adopted to modify starch physically, these are described as follows:

Thermal methods:

These methods involve heating or cooling as a for modification of starch. Viscosity of the starch is increases when it is heated along with improved stability.

Pre-gelatinized starch

This method involves heating the native starch and convert into gelatinized mass with subsequent drying. Heating process results in gelation which results in disruption of molecular order within the starch which causes certain reversible changes in the solubility, crystalline melting and swelling of the granules.[22] Pregelatinized starch prepared by mechanically and chemically rupturing all the parts of starch granules to convert it into a soluble product that can be used as an directly compressible excipients. Due to disruption in granular structure of starch large aggregated particles with relative densities are formed which results in cold water swellability and improved solubility. These morphological changes significantly impact on the functional properties of pregelatinized starch, as they enhance the flowability and compressibility characteristics of starch, making it very suitable for directly compressible applications.[23] Pregelatinization methods include drum drying, spray drying and extrusion. The principal properties of pregelatinized are an increase in swelling capacity, solubility and cold water dispersion. [24-25]

Pregelatinized starch may be synthesized by dispersing 100 g of native starch powder in 100mL of distilled water and heating the slurry while continuously stirring for about 10 min until a thick, homogenous gel is formed. The temperature is typically maintained at 55^0C. The paste like pregels may then be dried in an oven. The dried product which is flaky in texture should be ground and screened to the desired particle size.[26] Enhanced the compressional properties of corn, cassava, and sweet potato starches used as directly compressible excipients have been studied for paracetamol tablet and results are found satisfactory. This modification improved the mechanical and release properties of the directly compressed tablets as they manifested better strength and reduced friability and permitted timely release of paracetamol in the same formulations.[27]

Hydrothermal modification

This physical modification includes changes in the physical and chemical properties of the starch without destroying the granule structure.[28] Essentially, hydrothermal modification can only occur when starch polymers conversion from the amorphous region to the semi crystalline region. Starch in its native form revelations amylopectin ramifications by forming a double helix chain, and this behaviour imparts a crystalline structure to the starch molecule. Heat treatment involving temperatures between the T_{gel} and melting temperature (Tm) may not alter the double helix conformation or degree of starch crystallinity; these conditions are present when starch pastes are drying. Physical modification of starch performance improves starch paste characteristics such as texture and plasticity by reducing T_{gel} and subsequently relaxing the hydrogen bonds and polymer-polymer interactions. The presence of water reduces the Tm.[29] Hydrothermal modification is differentiated into annealing and hydrothermal treatments.[30] The major difference between these process is temperature and water content associated to these processes. Certain physicochemical properties are affected hydrothermal processes such as crystallinity and morphology of starch granule, amount of amylose-lipid complexes, double helix content, gelatinization and pasting, gel properties and susceptibility to acid and enzymatic hydrolysis swelling power and solubility.[31]

Annealing

It refers to treatment of starch in excess water (<65% w/w) or at intermediate water contents (40–50% w/w) at temperatures below the onset temperature of gelatinization. Basic purpose of annealing is to attain near by the glass transition temperature, which increases molecular mobility without activating gelatinization. Starch granule hydration causes a transition from a glossy to a static state, increasing the ability of the amorphous regions to a crystalline state. These changes generate tangential and radial movements in the crystalline and amorphous regions, and physicochemical modifications increase chain interaction in the crystallinity region.[32] Many researchers studied that annealing tends to modifications to starch structure like starch chain interactions, perfection of starch crystallites, increase in granular stability, formation of double helices and compartmentalization of amylopectin-amylopectin, amylose-amylopectin and properties sch as elevation of starch gelation temperature, narrowing of gelation temperature range and decrease in swelling ability. [33]

Heat moisture treatment

This treatment includes a thermal application in the presence of a limited amount of water (typically less than 35% w/w) and a process time between 15 min to 16 h.[34] The physical properties of heat moisture treated starches depend on the botanical origin of the starch, organization of amylose and amylopectin and treatment conditions. The effects of this treatment on the morphological and physicochemical properties of starch granules include important changes in crystalline structure, swelling capacity, gelatinization, paste properties and retro gradation. [35] It is also used as a pre-treatment because of the organizational modification into amorphous and crystalline regions on the granules. These variations make the granule susceptible to chemical and enzymatic modifications and acid hydrolysis.[36]

Glow Discharge Plasma Treatment

Glow discharge plasma can generate high energy electrons and other highly active species at room temperature. When applied to starch, the highly active species can excite chemical groups in starch, encouraging modification process without the use any other chemicals. Thermal degradation is minimized.[37]

Non-thermal physical modification of starches

Some developments in food production are useful to extend the life of a product using thermic treatments at boiling temperatures (or even higher) for seconds or minutes. Traditional treatments cause a loss of some vitamins and nutrients and alter their organoleptic properties. Non-thermal modification is an alternative to traditional processes that also eliminates pathogenic microorganisms and spores. Few non-thermal are discussed below:

High hydrostatic pressure

High pressure includes using a uniform pressure throughout a product. The high pressure technology in industry uses pressure from 400 to 900 MPa. High pressure generally limits the swelling capacity and consequently reduces paste viscosity.[38] For this treatment, the gases used include ethylene, hydrogen, oxygen, ammonia, air, methane or argon in a plasma state. This treatment modifies the starch in different ways, including its hygroscopicity, degree of polymerization and oxidation.[39]

Ultrasound

Ultrasound is the sound that is above the threshold of the human ear (>18 KHz). It is produced with either piezoelectric or magnetostrictive tranducers that generate high energy vibrations. These vibrations are amplified and transferred to a sonotrode or probe, which is in direct contact with the fluid. [40-41] Some advantages of ultrasound are reduction in processing time, energy efficiency and eco-friendly process, reduction of processing temperature, batch or continuous process can be utilized, increased heat transfer, deactivation of enzymes and possible modification of food structure and texture. [42] An increase in solubility and disruption of crystallinity of starch granules as observed by X-ray diffractometry when these are treated with ultrasound.[43] Molecular weight os starch can be reduced by treating aqueous solution with 360 KHz ultrasound. Ultrasound primarily affects the amorphous region, while maintaining the granule's shape and size. The starch surface becomes porous, and properties such as the swelling capacity, solubility and viscosity of the paste are modified.[44] Ultrasonic modification depends on the sound, frequency, temperature, process time and the starch suspension properties (i.e., concentration and botanical source of starch).[45]

Pulsed electric field

It is non-thermal food preservation methods which kills pathogens and inactivate enzymes and minimize the loss of taste, color, texture, nutrients and heat labile functional components of foods. Recent studies observed by Hans et al. shows that various treatments affect the physicochemical properties of starches in a different way. When corn starch –water suspension were processed in pulsed electric field with electric field strength of 50 KV/cm certain observations are noted. The gelation temperature and enthalpy of the altered corn starch decrease with an increase of electric field strength. Starch also lost granule shape and the crystallinity, viscosities of the modified corn starch were decreased with increasing electric field.[46]

Microwave-Assisted Modification of Starch

Microwave radiation is the electromagnetic radiation in range from 3000 MHz to 30 GHz. It is a non-ionizing radiation that produces heat in the penetrated medium by "molecular friction" in an alternating electromagnetic field.[47] It is a very good source of energy and allows rapid transmission of the energy into internal of the material where the energy is converted into heat, along with noteworthy decrease of processing time when compared to conventional processes. Microwave field also has impact on the properties of the finished product. Research is piloted also on the influence of microwave radiation on the physicochemical properties of starch. Microwave technique is having potential to alter gelatinization mechanism and affects the rheological characteristics of the starch. Microwave irradiation on the starch causes an enhancement of gelation temperature and reducing the process enthalpy.[48] Microwave treated starch may be processed by irradiation of a slurry of native starch in a microwave oven at a range of about 20 s to 30 min. If required, the product may be further air dried or dried in a conventional oven at a temperature of about 60 ^{0} C for 24 h. The dried paste may be ground with a mortar and pestle or laboratory blender and screened to the desired size.[49]

Microwave technique is getting significant importance as a processing method in the production of modified starch, particularly including chemical modification. It could be valuable for manufacturing modified starches with characteristic properties. Examples comprise of microwave-assisted succinylation and acetylation or methylation of starches. It has been postulated that microwave-assisted transformation of starches manufactured better products as it releases higher energy to break the covalent bonds in glucose units, than by conventional techniques Benefits of microwave irradiation includes cost-effectiveness, speed, selectivity of heating, and environmental safety. However, microwave treatment also has few drawbacks like of producing thermally unstable or degraded materials arising from uneven distribution of heat.[50]

Microwave-Assisted Modifications

Microwave-Assisted Oxidation

Oxidation of starch paste produced substantial variations in its rheological behaviour as compared to starting material. Viscosity is lowered 10–100 times of modified starch pastes. Yield stress was not detected and there were no changes in the uniformity coefficient. Microwave irradiation responsible for greater degradation of starch, the resultant products were characterized by a high degree of oxidation and wide range of possibilities of application.[51]

Microwave-Assisted Esterification

Lewandowicz et al. studied the microwave assisted esterification on tapioca starch with succinic anhydride and the succinates resulted had higher viscosity and higher water absorption capacity as accompanying to native starch.[52] Biswas et al. developed microwave heating in the reaction of starch with acetic anhydride by using iodine as catalyst. Within the duration of 2 minutes at a temperature of 100°C with catalyst concentration of 0.16–2.5 mol%, starch acetates with a degree of substitution equal to 3 were produced.[53]

Application of Modified starch in Pharmaceuticals

Various application of modified starch as compared to native starch has been identified. These are summarized below:

Controlled/ Sustained release polymer

Modified starch was evaluated as sustained release polymer, especially oxidized starch and starch prepared by esterification reaction. Drug can be entrapped in matrix assisted system which is swellable or non swellable and release in response to stimuli.[54] Acetylation has proved sustained release of drug in some polymeric systems as a result of enhanced swellability and reduced enzyme sensitivity during gastrointestinal digestion.[55] Carboxymethylstarch has widely used in various hydrogel applications as it established an additional advantage for sustained release due to poly-anionic behaviour that imparts swellability characteristics.[56] Hydroxypropylated could be effectively used in targeted drug delivey system as its dissolution is dependent on pH due to high hydrogen content. Zhang et al. developed particles for colon specific drug delivery.[57]

Directly compressible Excipient

Acid hydrolysed starch has been explored as directly compressible excipient and results are found promising as compared to microcrystalline cellulose. It also possess better flow and compressibility properties, higher crushing strength along with less friability.[58] Pregelatinized starch also studied as directly compressible excipient for paracetamol tablet formulation. Heat moisture treatment starch could be applied in directly compressible formulations when very strong compacts are undesirable, sch as chewable and fast disintegrating tablets. Starch citrate was established to have good flow and swelling properties, making it beneficial as a directly compressible excipient. The direct compressed tablets of gliclazide and pioglitazone prepared with potato starch citrate showed fast and high dissolution rates within acceptable good manufacturing standards.[59]

Tablet Disintegrant

Carboxymethylstarch has been widely applied as a disintegrant due to the pH responsiveness imparted by the carboxymethyl group.

Carrier of poorly water soluble drug

One possible approach of modification by oxidation is formation of carbonyl group which enhances hydrophilic nature of the starch. This may be linked with applications in matrix drug delivery systems that are necessary to swell and enhances delivery of poorly water soluble drugs.[60-61] Acetylated starch improves the bioavailability of macromolecules such as insulin.[62]

Transdermal drug delivery system

Nanoparticle prepared from maize starch has been used to bypass the the skin structure without interference to skin integrity.[63-64]

CONCLUSIONS

Formulation and development of oral delivery system has been always popular since so many years as it is most convenient rote of administration. Various new excipients are being evolved so as to get better advantage of this rote. Modification of starch obtained from different botanical sources has been studied for different formulations. In detail chemical and physical methods of modification of starch with the view of pharmaceutical application is discussed in this review. It can be concluded that modification of starch surely have specific advantages than native starch. Among various modification discussed physical methods such as annealing, heat moisture treatment, Ultrasonication etc. may be used to processing by direct compression techniques. Chemical methods such as oxidation, esterification, etherification, acid hydrolysis, carboxymethylation etc. possesses sustain release as well as fast disintegration potential. Microwave irradiation has proved to be rapid and cost-effective method of modification of starch. Depending upon source used, method employed for modification starch may explore wide range of application in pharmaceuticals.

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