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Review Article

Use of modified tapioca starches as pharmaceutical excipients

Nattawut Charoenthai, Thiraphong Sanga-ngam, Satit Puttipipatkhachorn*

Department of Manufacturing Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand

*Corresponding author:
Satit Puttipipatkhachorn
Satit.put@mahidol.ac.th

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ABSTRACT

Tapioca starch is derived from the roots of cassava which is abundantly available in the world. During a past few decades, many attempts have been made to modify tapioca starch by physical and chemical processes. This review summarizes the current knowledge of modified tapioca starch and their applications as pharmaceutical excipients. These modified tapioca starches are carboxymethyl tapioca starch, acid-modified tapioca starch, cross-linked tapioca starch, grafted tapioca starch, enzyme-catalyzed tapioca starch, pregelatinized tapioca starch and hydroxypropyl tapioca starch. Wide ranges of application as a carrier for solid dispersion, a suspending agent, a direct compression filler, a matrix forming agent for controlled release tablet, a film coating agent and a carrier for mucoadhesive microsphere are reported. Thus, modified tapioca starches have a potential to be used as pharmaceutical excipients. Nevertheless, systematic studies on their properties and excipient functionalities are still be needed.

1. INTRODUCTION

Tapioca starch is derived from the roots of cassava (*Manihot esculenta* Crantz). The cassava plant was named varying on the region, for example yucca, mandioca, manioc, tapioca and cassava. It belongs to the spurge family (Euphoriaceae) which is perennial woody shrub with tuberous roots. This plant is widely cultivated in Asia, Africa and Latin America. The world production of cassava in 2016 was estimated as 277,102,564 tonnes with the top producers being Nigeria, Thailand, Brazil, and Indonesia[1]. Cassava is generally considered as a source of carbohydrate which is used as food and feed consumption. Starch is the major components of cassava root and exists up to 80% of dried weight of the root[2]. Cassava is abundantly available in the world, thus the supply of tapioca starch is sustainable and cheap. Apart from food and feed products, tapioca starch is extensively used for various industrial applications.

In pharmaceutical industry, starch is used as a common excipient in pharmaceutical products. Starches used in pharmaceutical industry are obtained from various botanical sources, for example, corn, potato, cassava or tapioca, rice and wheat. Corn starch is mostly used when compared with other starches because of its well-known properties and availability of pharmaceutical grade raw materials in the market. Compared with corn starch, the studies of tapioca starch as pharmaceutical excipient were not extensively done although it appears in British

Pharmacopoeia[3]. Most of studies are done in developing countries where cassava is cultivated.

Conventionally, native tapioca starch can be used as diluent, binder and disintegrant in tablet and capsule formulations. During a past few decades, many researchers have made modification of tapioca starches by physical and chemical methods to obtain modified tapioca starches with various functionalities. The chemical and functional properties of modified starch are dependent on many factors including reaction conditions, type of substituent, and molar substitution, but may also be affected by the distribution of substituents. This review summarizes the current knowledge of modified tapioca starch and their applications as pharmaceutical excipients.

2. NATIVE TAPIOCA STARCH

2.1. Chemical composition and physical properties

Cassava root contains starch more than 80% and is rich in vitamin C, carotenoids and minerals[2]. The very low protein and lipid content is an important factor which differentiates tapioca starch from cereal starches. The small amount of phosphorus in tapioca starch is partially removable and therefore, not bound as the phosphate ester as in potato starch. The morphology of starch granules is oval, truncated, and rounded with a size range of 2–32 μm as shown in Figure 1. The crystallinity of starch granules is A- or C_a-type polymorph[4], where C_a-type denotes the portion of A-type is dominant over B-type in the polymorphic composition [5]. In general, starch is composed of amylose and amylopectin (Figure 2). Amylose is a liner polysaccharide with α-(1–4) -linked D-glucose whereas amylopectin is a branch chain glucose polymer. Amylopectin, is a highly branched polysaccharide with α-(1–4)-linked D-glucose backbones and exhibits about 5% of α-(1–6)-linked branches[5]. The ratio of amylose and amylopectin is normally constant for a given species of starch. The content of amylose in tapioca starch varies between 18 and 24%[6] whereas corn starch and wheat starch have a much higher amylose content[7].

Gelatinization properties are the important properties of starches. Gelatinization is a process of heating starch in excess water (>1:2 starch:water) above the temperature that disrupts the starch granules and melts the crystallites. Differential scanning calorimetry (DSC) and Kofler hot stage microscopy (KHSM) are usually used to measure gelatinization parameters i.e., gelatinization onset temperature (To), gelatinization peak temperature (Tp), gelatinization conclusion temperature (Tc) and gelatinization enthalpy (ΔH). The ratios of starch

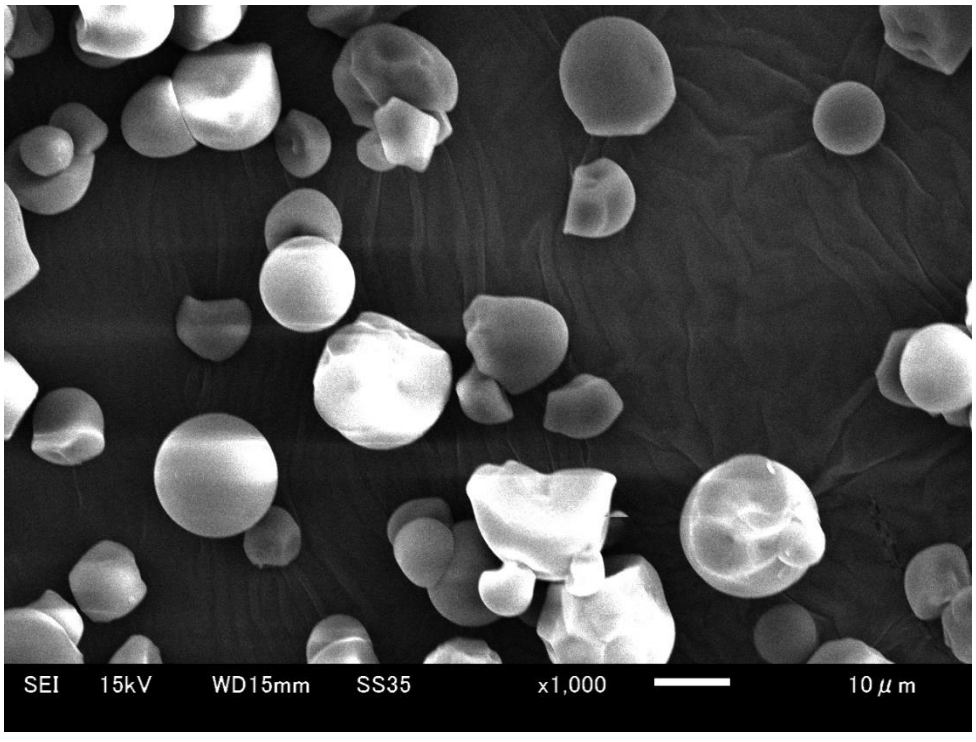

Figure 1. Scanning electron micrograph (SEM) of native tapioca starch.

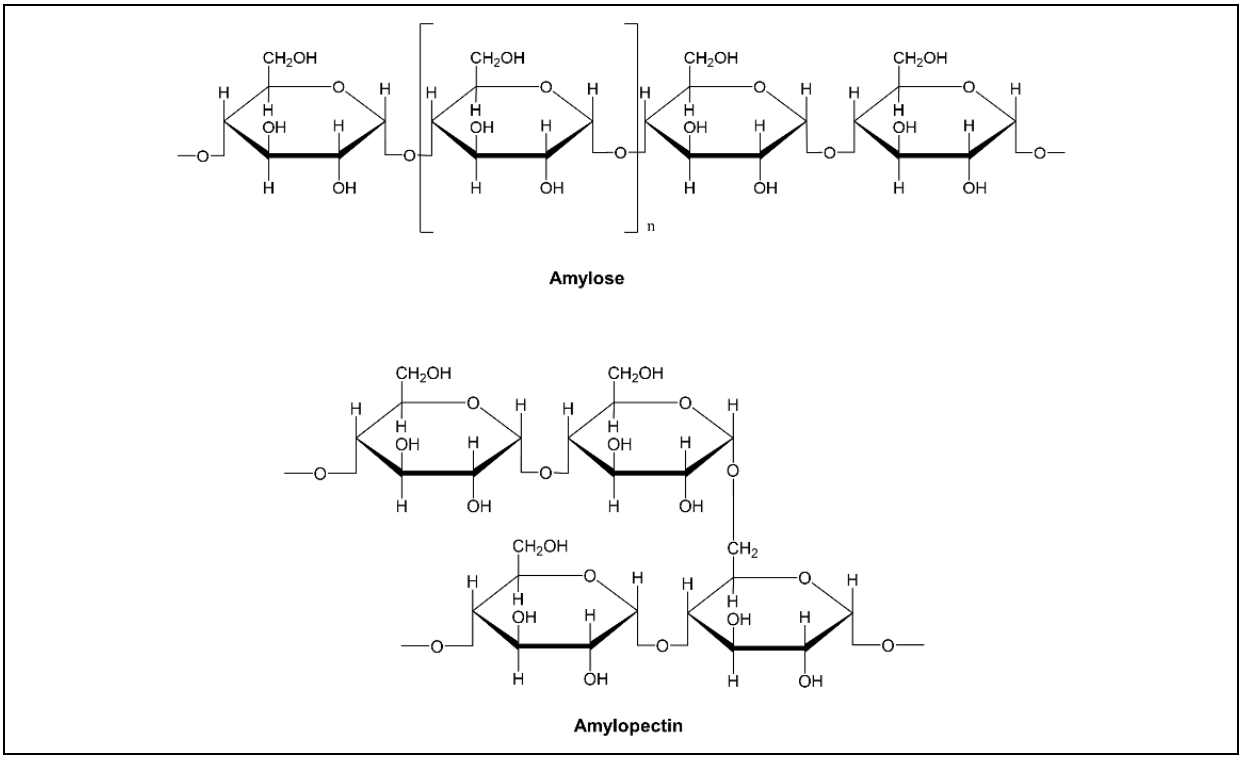

Figure 2. Starch structure of amylose and amylopectin.

to water have an effect on gelatinization temperature as presented in Table 1. Tapioca starch shows higher swelling power than the cereal starches[8]. Tapioca starches give relatively stable, clear sols on cooling, despite their amylose and may be more branched – both factors interfering with retrogradation and gelation.

2.2. Use of native tapioca starch as pharmaceutical excipients

Tapioca starch appeared as a pharmaceutical excipient in BP 2018[3]. Native tapioca starch has been widely studied by many researchers to investigate its suitability as an excipient in tablets and capsules. Due to good flowability, tapioca starch was used as diluent for capsule and tablet formulations.

Ruangchayajatuporn et al.[12] evaluated native tapioca starch as tablet disintegrant in direct compression process. The results indicated that disintegrating property of tapioca starch was less than potato starch and corn starch. Alebiowu and Adeyemi[13] extracted tapioca starch from root tubes of cassava using different steeping periods and evaluated the obtained tapioca starches as tablet disintegrant in wet granulation process. The disintegration time of tablets produced was dependent on concentration of tapioca starch and steeping period.

Native tapioca starch is mostly used as a binder in the form of starch paste in wet granulation process. Generally, higher amount of tapioca starch produced the tablets with higher tensile strength, less friability, longer disintegration time and slower drug dissolution rate. Some of studies on tapioca starch as binder are presented as follows. Tapioca starch could produce paracetamol tablets with the highest hardness and the least tendency to brittle fracture

Table 1. Gelatinization properties of tapioca starch in excess water measured by differential scanning calorimetry (DSC)

Starch : Water (w/w)	To (˚C)	Tp (˚C)	Tc (˚C)	Tc-To (˚C)	References
1:3	55–64	61–68	71–74	10–16	Jane et al., 1999[7]; Gomand et al., 2010[9]
3:7	60	65	75	15	Teng et al., 2013[10]
1:4	64–66	68–70	–	–	Anggraini et al, 2009[8]
1:9	65	71	–	–	Li and Yeh, 2001[11]

Note: To = Gelatinization onset temperature, Tp = Gelatinization peak temperature, and Tc = Gelatinization conclusion temperature.

when compared with cocoyam or maize starch[14]. Diclofenac sodium tablets using tapioca starch as a binder showed good dissolution characteristics when compared to potato and maize starch[15]. Ibuprofen 400 mg tablets with less friability and fast disintegration time could be obtained when 2% w/w tapioca starch was used[16].

Use of tapioca starch as film former was also investigated. Tapioca starch film had low mechanical properties, cellulose fiber and nanoclay were introduced to reinforce the strength of the film[17]. The tapioca starch film reinforced with cellulose fiber and/or nanoclay exhibited an increased tensile strength, but a decreased elongation at break. The water vapor permeability of the tapioca film with cellulose fiber or nanoclay did not change. Tapioca starch was also used to prepare bionanocomposites with gelatin and nanorod zinc oxide[18]. The bionanocomposites provided the film with reduced mechanical properties. In addition, oxygen permeation through the tapioca starch film with gelatin and nanorod zinc oxide are comparable to tapioca starch/gelatin film.

3. MODIFIED TAPIOCA STARCHES

Common limitations associated with native normal starches are excessive viscosity at low solids content (difficulty in handling, lack of body), high susceptibility to retrogradation (gel opacity, syneresis and lack of freeze-thaw stability) and lack of process tolerance. Therefore, proper modification has been made to obtain modified starch with desired functionality. Both physical and chemical processes were used. The chemical modifications are performed by using various reactions such as oxidization, esterification, etherification and treatment with enzyme. The physical modifications include pregelatinization and mechanical treatment (e.g. ball milling, annealing and spray drying). The studies on modification of tapioca starch are summarized as followings.

3.1. Carboxymethyl tapioca starch

The carboxymethyl starches were generally prepared through the reaction of starch with monochloroacetic acid or sodium monochloroacetate using various methods such as dry method, semi-dry method, solvent method, water solvent method[19,20] and ultrasonic irradiation method[21]. This etherification process substituted hydroxyl groups of glucose subunit with anionic carboxymethyl groups as shown in Figure 3. It improves hydrophilicity and increases water absorption[22]. In addition, the carboxy-methylation reduces the tendency of retrogradation, lowers the gelatinization temperature, increases solubility in cold water with clear gel and leads to higher storage stability[23]. The viscosity property is varied with the degree of molar substitution. Carboxymethyl starches are generally used in medicine, pharmaceuticals, cosmetics and food[23]. Lin et al.[24] prepared and evaluated nano-sized carboxymethyl tapioca starch as a carrier in solid dispersions to improve the solubility of a poorly water-soluble drug, acetylsalicylic acid. Sodium carboxymethyl tapioca starch was used as suspending agent in ibuprofen suspension at concentration of 0.5 – 2.0% w/v in comparison with sodium carboxymethyl mungbean starches, sodium carboxymethyl cellulose and xanthan gum[25].

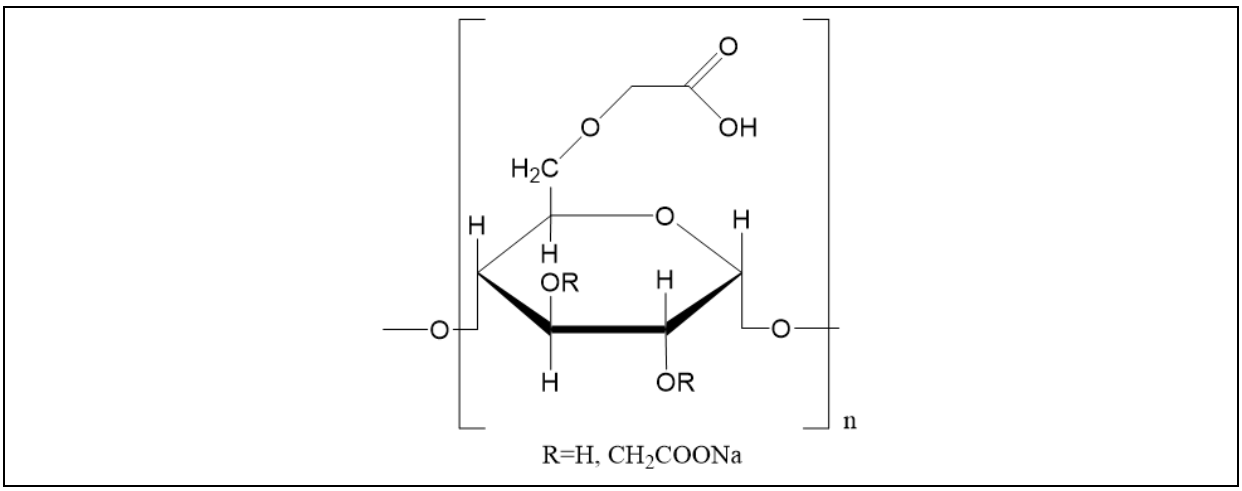

Figure 3. Structure of carboxymethyl starch.

3.2. Acid-modified tapioca starch

The acid-modified or acid treated starches are normally prepared by treatment concentrated starch slurry with diluted mineral acid below the gelatinization temperature of the starch for a period of time. When the desired degree of hydrolysis is reached, the starch is neutralized and the starch granules are filtered and dried at a temperature below the gelatinization temperature[26,27]. During acid hydrolysis, amorphous regions are preferentially hydrolyzed, leading to enhance the crystallinity and double helical content of acid hydrolyzed starch[26]. Therefore, the high crystalline starches were obtained. The resulting starch is milled to provide the free-flowing starch powder[27].

In the pharmaceutical applications, Achor et. al.[28] investigated the acid-modified tapioca starch as a filler or binder in direct compression. The tablet containing acid-modified starch showed higher tensile strength, lower friability, faster dissolution than the native tapioca starch. Intarapanich et al.[29] found that increasing acid hydrolysis time and concentration of acid provides the acid-modified starch with improved compactability. However, the disintegration time of tablet was impaired when compared with the tablet containing native tapioca starch. Atichokudomchai et al.[30] also investigated the acid modified tapioca starch as a direct compression filler and reported that the crushing strength of the tablets increased in line with the crystallinity. The spray-dried powder of acid-modified tapioca starch had good flow characteristic and higher compressibility when compared to some commercial fillers, indicating that it was a good direct compression filler,

Currently, the nanosized acid-modified starch is called starch nanocrystals. Starch nanocrystals are crystalline platelets prepared by the disruption of the semi-crystalline structure of starch granules through the acid hydrolysis of amorphous parts[31]. Although starch nanocrystals have been extensive reported as a reinforcement filler in various polymeric composites[32], there was a few reports on cassava starch nanocrystals[33]. Charoenthai et al.[34] used cassava starch nanocrystals to modify ethylcellulose film in rupturable pulsatile drug delivery system. Cassava starch nanocrystals reduced the mechanical properties of the rupturable film and increased water vapor permeability rate of the ethylcellulose film.

3.3. Cross-linked tapioca starch

This cross-linking treatment is used to reinforce the strength of the starch granule. When starch aqueous suspension is heated, the hydrogen bonds holding the segment of condensed chain of glucose unit together are weaken, which cause the water to penetrate into the molecules and subsequently make the starch granules swell. The cross-linked bonds react as bridges to the molecules and cause the starch granule swell improperly inversely with the increasing degree of reaction. Consequently, the cross-linking reaction uses the specific chemical containing two or more moieties capable of reacting with hydroxyl groups on the same or different molecules. The marketed cross-linked starches are starches that are modified by cross-linking treatment in combination with other treatments such as derivatization with monosubstituents such as acetyl or hydroxypropyl groups[35,36]

When a crosslinked starch is cooked above the gelatinization temperature, the hydrogen bonds in the crystalline domains weaken and break. The cross-links, however, do not rupture and help maintain the integrity of the swollen granule. The increased integrity helps in minimizing both viscosity breakdown and limits the development of cohesive, rubbery texture in the gel. Cross-linking also provides greater resistance to thermo-mechanical shearing, improves paste stability in acidic media, and changes the typical viscoelastic structure of some starch gels to give them a short texture[37].

The cross-linked tapioca starch-borate-urea was synthesized using urea as monomer[38]. It was evaluated as a matrix forming agent in controlled release tablets. The results indicated that the matrix system with higher urea content exhibited a slower release of the active ingredient, whereas that with higher sodium borate content showed a faster drug release[38]. Atichokudomchai and Varavinit[30] prepared the cross-linked tapioca starch in the presence of alkaline sodium trimetaphosphate solution and was further hydrolyzed by 6% w/v HCl solution at room temperature for 192 h. It was found that the acid-modified cross-linked tapioca starch gave better tablets than the acid-modified tapioca starch.

Mitrevej et al.[39] investigated the crosslinked tapioca starch phosphate as a tablet disintegrant. The crosslinked tapioca starches were esterified using sodium trimetaphosphate at

different concentrations and reaction times to produce cold water swelling ability. The results showed that the increase in crosslinking degree improved the disintegration time by reducing the viscosity of the swollen starch granules.

3.4. Grafted tapioca starch

Graft copolymers are prepared by generating free radicals on starch molecule and then allowing these free radical initiated graft copolymers to have high molecular weight branches that are infrequently spaced along the starch backbone. A number of free radical initiating systems have been used to prepare graft copolymers. These may be divided into two broad categories of chemical initiation and initiation by irradiation. The copolymerizations can also be initiated anionically by allowing monomer to react with an alkali metal alkoxide derivative of starch. The grafting efficiency is a term often used to describe graft polymerization reactions and is defined as the percentage of the total synthetic polymer formed that has been grafted to starch[35]. In free radical graft polymerizations, the average number of anhydroglucose units (AGUs) per high molecular weight graft (grafting frequency) ranges from several hundred to several thousand. Therefore, each starch molecule will have only a very few grafted branches. Grafting frequency, expressed in AGUs per graft, can be calculated from the weight percent synthetic polymer in the graft copolymer (percent add-on) and the average molecular weight of the grafted branches[40].

The copolymers of methyl methacrylate grated hydroxypropyl starch[41], ethyl methacrylate grafted on tapioca starch (TSEMA), and hydroypropyl tapioca starch (THSEMA) were synthesized by free radical copolymerisation[41-45]. All of the grafted tapioca starch copolymers showed a potential as direct compression filler for controlled release tablets[41,42]. The TSEMA matrices had better binding properties with slower release than the THSEMA tablets[43]. In addition, TSEMA and THSEMA grafted copolymers were used to develop the assembled modules for the controlled release gastro-retentive dosage forms by Dome Matrix® technology[44,45]. The assembled modules with grafted tapioca starch copolymers exhibited good floatation capability and prolonged riboflavin release.

3.5. Enzyme-catalyzed tapioca starch

Amylases are used to modify starch[46]. The enzymes involved in the breakdown of starch chains are primary of four types, e.g. hydrolyze (1→4) α-D-glucosidic bonds (amylases), hydrolyze (1→6) α-D-glucosidic bonds (isoamylases), transfer (1→4) α-D-glucosidic bonds (glucanosyltransferases) and branching enzymes [α-(1→4) α-(1→6) transferases]. Le et al.,[47] modified tapioca starch by using branching enzyme (BE) isolated from *Bacillus subtilis* 168 and *Bacillus stearothermophilus* maltogenic amylase (BSMA). The hydrolysis by BE is known to catalyze the formation of a-1,6-glucosidic linkages by transglycosylation in amylopectin, thereby creating branched glucan molecules. Furthermore, BE cleaves the a-1,4 glucosidic bond of the segment between clusters to produce amylopectin cluster from amylopectin. On the other hand, maltogenic amylase (MAase), a glycoside hydrolase cloned from various gram-positive bacteria, hydrolyzes cyclomaltodextrins and starch mainly to maltose, and pullulan to panose, by cleavage of a-1,4 glycosidic bonds. The result showed that the product was further modified with BSMA to produce highly-branched tapioca starch with 9.7% of extra branch points.

Tokumane et al.[48] prepared the enzyme-catalyzed starches by heating the native tapioca starch and subsequent treatment with thermostable alpha-amylase to obtain high crystalline starches. The reaction products were spray-dried to obtain annealed-enzymatically hydrolyzed tapioca starch (SANET) in the form of spherical agglomerate granules. It was evaluated as tablet filler in direct compression process. The increased relative crystallinity of this enzyme-catalyzed tapioca starch, SANET, resulted in increased crushing strength and decreased tablet friability, but prolonged disintegration time.

3.6. Pregelatinized tapioca starch

Pregelatinized starch is a common type of physically modified starch widely used in food and pharmaceutical industries. It is also referred to as "pre-gel" or "instant starch" and is generally produced by spray dryer, drum dryer and extruder[49,50]. Gelatinization is the process involving the transformation of an aqueous starch suspension into a starch paste. In water, starch

granules start to swell irreversibly with increasing temperature. When temperature reaches 60-70 °C, insoluble starch granules are disrupted by the heat supplied, resulting in a loss of molecular organization and consequently, loss of its crystallinity. The process of gelatinization causes substantial changes in both chemical and physical nature of granular starch due to the rearrangement of intra- and inter-molecular hydrogen bonding between water and starch molecules resulting from the collapse or disruption of molecular orders within the starch granules. This causes irreversible changes in the starch properties including loss of organized structure of starch, granule swelling, loss of birefringence and crystallinity[50,51]. This process leads to increasing viscosity and starch solubilisation as a result of such irreversible changes[52]. On cooling, the starch chains (amylose and amylopectin) in the gelatinized paste associate, leading to the formation of a more ordered structure. These molecular interactions are termed collectively "retrogradation" and have important textural and dietary[50-52].

Pregelatinized tapioca starches were prepared by cooking starch slurry at different temperatures and cooking times[53]. The direct compressed tablets with 2% of pregelatinized tapioca starch exhibited good disintegration and dissolution. In addition, pregelatinized tapioca starch paste was used as binder in wet granulation. The results indicated that more pronounced effect of pregelatinized tapioca starch was found in wet granulation when compared with direct compression method.

Anwar et al.[54] used pregelatinized tapioca starch phosphate as hydrophilic matrix forming agent in controlled release tablet. There are two classes of starch phosphate esters, substituted starch phosphate esters and cross linked starch esters. First, pregelatinized tapioca starch was phosphorylated by adding phosphorous oxychloride for making cross-linked reaction. Secondly, pregelatinized tapioca starch was phosphorylated by adding sodium mono-hydrogen phosphate for making substituted reaction. The obtained hydrophilic matrix tablets showed the controlled release profile of theophylline with zero-order kinetics. The drug release rate could be modified with varying concentrations of pregelatinized cassava starch phosphate, which the slowest drug release rate was obtained at polymeric concentration of 50% w/w. Mucoadhesive microspheres were prepared using pregelatinized tapioca starch succinate[55]. The findings revealed that the microspheres with pregelatinized tapioca starch succinate had good mucoadhesive property on both of gastric and intestinal mucosa. Furthermore, the pH-dependent extended release of drug from the microspheres was achieved.

3.7. Hydroxypropyl tapioca starch

Hydroxypropyl starch is prepared by using propylene oxide under alkali condition where hydroxypropyl substitutes are added at the OH positions of anhydroglucose unit of native starch by an ether linkage (Figure 4). When introduced into starch granules, hydrophilic hydroxypropyl groups weaken or strain the internal bond structure holding the granule together and also prevent water in the starch paste from separating through syneresis when subjected to freeze–thaw cycling[56]. Hydroxypropyl groups also prevent retrogradation providing more fluid paste with improved clarity[56,57].

Studies on use of hydroxypropyl tapioca starch as common tablet excipients are not found. A report on evaluation of hydroxypropyl starch from waxy corn starch as tablet binder and disintegrant showed that there is no advantages in use of hydroxypropyl starch as a binder or disintegrant over corn starch[58]. However, its pregelatinized hydroxypropyl starch exhibited good disintegrating properties in direct compressed tablets and could be used as a binder in wet granulation.

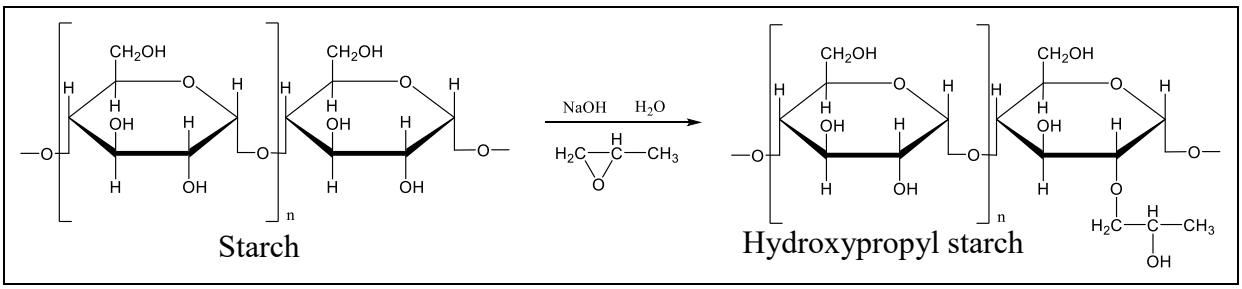

Figure 4. Preparation of 2-hydroxypropyl tapioca starch.

Hydroxypropyl tapioca starch was used to prepare grafted copolymers with methyl methacrylate[41] and ethyl methacrylate[42-45] to modify its functional properties. As presented in previous section, ethyl methacrylate grafted hydroypropyl tapioca starch copolymers showed potential use as direct compression filler for controlled release tablets[41-43] and to fabricate the assembled modules for the controlled release gastro-retentive dosage forms[44, 45].

Cross-linked hydroxypropyl tapioca starch was prepared and evaluated a suspending agent in ibuprofen formulation in comparison with xanthan gum and tragacanth[59]. The results showed that the cross-linked hydroxypropyl tapioca starch gave the suspension with good physical appearance, redispersibility, and no caking. The cross-linked hydroxypropyl tapioca starch was pregelatinized and used as hydrophilic matrix former[60]. The pregelatinized hydroxypropyl tapioca starch with the highest degree of substitution of 0.106 exhibited the highest viscosity and swelling power. The hydrophilic matrix tablets using pregelatinized hydroxypropyl tapioca starch showed similar behavior to the formulation containing only HPMC E4M.

Carboxymethyl hydroxypropyl starch (CMHPS) and hydroxypropyl carboxymethyl starch (HPCMS) were prepared and evaluated as film-forming agent incomparison with carboxymethyl tapioca starch (CMS), hydroxypropyl tapioca starch (HPS) and native tapioca starch[61]. The CMHPS and HPCMS formed clear films with good strength and fair flexibility. Moreover, CMHPS film showed a significant improvement on the water vapor transmission rate (WVTR) compared to CMS and HPCMS and can be developed as new aqueous-based film-coating agents for pharmaceutical tablets.

4. CONCLUSION

Native tapioca starch can be used as diluent, binder and disintegrant in capsule and tablet formulations. Physical and chemical modifications have been made to prepare modified tapioca starches with different functionalities. The modified tapioca starches that were investigated as pharmaceutical excipients include carboxymethyl tapioca starch, acid-modified tapioca starch, cross-linked tapioca starch, grafted tapioca starch, enzyme-catalyzed tapioca starch, pregelatinized tapioca starch and hydroxypropyl tapioca starch. Systematic review of many literatures indicated that the modified tapioca starches can be used as a carrier for solid dispersion, a suspending agent, direct compression filler, a binder, a disintegrant, a matrix forming agent for controlled release tablet, a film coating agent and a carrier for mucoadhesive microsphere. Thus, modified tapioca starches have a potential as pharmaceutical excipients in wide application. Nevertheless, systematic studies on modified tapioca starches are suggested to obtain more understanding of their properties which will be helpful in their application as pharmaceutical excipients.

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