Chapter

Chemically Modified Starches as Excipients in Pharmaceutical Dosage Forms

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Abstract

Excipients play a great role in ensuring that pharmaceutical dosage form meets the required specifications of quality approved by the relevant authorities. Starches are the most widely used excipients in dosage form development, but their use is enhanced by several modification methods (such as chemical degradation, physical alteration, enzymatic modifications or crystalline-genetic transformation), all aimed at restructuring the starch granules, thus ensuring that the reactive polymers are accessible to reactants. Chemical modification of starch usually follows the pathway of substitution, degradation or cross-linking. The most common approaches to chemical modification of starches for pharmaceutical use include oxidation, esterification and etherification, which are employed to optimize the structural and nutritional properties for targeted applications. The oxidant type, botanical origin of starch, and process conditions are all determinants of how effective the oxidation is. Esterification improves the hydrophobicity of starch usually via acetylation and phosphorylation, while etherification is a derivatization technique that involves the use of various alkylation agents such as dimethyl sulphate, diethyl sulphate, alkylene oxides (epoxides) and alkyl halides. Chemically modified starch enhances thermoplasticity, solubility and flow properties. In conclusion, chemically modified starches have shown excellent potentials and are, thus, incorporated as core excipients in several pharmaceutical drug formulations.

Keywords: excipients, modified starches, chemical modification, formulations, polymers

1. Introduction

The goal of an ideal oral solid-dosage drug delivery system is to achieve a situation where the desired therapeutic effect is obtained in conformity with official standards. Excipients play a great role in ensuring that the dosage form meets the required specifications of quality by modifying the release, absorption, distribution and elimination profiles of the drug. This assures product efficacy, safety, patient compliance and acceptance. Compressed tablets still account for the most widely used oral solid dosage form due to their compactness, precision of doses and ease of administration and production. The process of tableting requires that all the ingredients are fairly dried, powdered (or granulated) to form uniform particle sizes, with good content uniformity to ensure delivery of the right dose of the active

pharmaceutical ingredient. Excipients form a larger bulk of the constituent of tablets and the presence of the excipients ensures, amongst other goals, that acceptable physical and mechanical properties of tablets are achieved.

Based on their primary functions, excipients are classified into two categories as follows:

i. Those which principally affect the compressional characteristics of the tablets: diluents (fillers), binders (adhesives), lubricants, glidants, anti-adherents.

ii. Those which principally affect the bio-pharmaceutics, chemical and physical stability: disintegrants, flavourants, sweeteners and colourants.

Ideally, pharmaceutical excipients are expected to be non-toxic, physically and chemically stable, commercially available, pleasant organoleptic properties and economically feasible [1].

This chapter will discuss the different chemical modifications of starch and give documented examples of starches that have been modified and used as excipients in pharmaceutical dosage forms.

2. Starch

Starch is one of the most abundant organic chemicals on earth and it is synthesized in the amyloplasts of seeds, grain, roots and tubers of many plants where it serves as the chemical storage form of energy from the sun [2]. It is a carbohydrate consisting of a large number of glucose units joined by glycosidic bonds. It is the most common carbohydrate in the human diet and is contained in large amounts in such staple foods as potatoes, wheat, maize (corn), rice, and cassava [3]. Pure starch is a white, tasteless and odourless powder that is, insoluble in cold water or alcohol. It consists of two types of molecules: the linear helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 20–25% amylose and 75–80% amylopectin by weight [4]. The amylose portion is a macromolecule that is, linear in nature, while the amylopectin is the highly branched portion of the starch. Glycogen, the glucose store of animals, is a more branched version of amylopectin.

Starch is the most commonly used excipient in the pharmaceutical industry and this wide application is premised on its availability, low cost, high caloric value, inherent excellent physicochemical properties and the ease of its modification to other derivatives. The versatility of starch in industrial applications is clearly defined by its physicochemical properties; therefore a thorough evaluation of the necessary parameter is important in elucidating its industrial use. The morphology and physicochemical characteristics of starch are typical of its biological origin; hence starch from each plant source will vary somewhat in appearance, composition and properties [2].

The preclusion of the application of starch in its native form in the pharmaceutical industry is based on certain setbacks that have necessitated the need to modify starches to achieve the objective of the formulation scientist in ensuring the production of standard tablets, thereby circumventing the limitations inherent in the use of native starch as pharmaceutical ingredients. Such setbacks that have been linked to the unfavourable properties of native starch include poor solubility, poor flow properties and high hydrophilicity.

Starch has been extensively modified to stabilize the granules during processing. This involves restructuring the starch granules and dispersion of the amylopectin

polymers within the granules, thus ensuring that the reactive polymers are accessible to the reactants. Consequently, the profile of starch (after modification) is enhanced as an excipient in the drug manufacturing industry. Starch can be modified through chemical degradation, physical alteration, enzymatic modifications or genetic transformation.

3. Degradation of starch

Starch degradation proceeds under basic conditions and the extent of degradation depends on the several factors such as the presence or absence of oxygen, concentration of the base used, duration of the reaction and the temperature at which it occurs. Matsunaga and Seib reported the liberation of the proteins and lipids present in wheat starch when exposed to 0.4%w/w dilute aqueous alkali solution at 25°C. It was documented that the process of degradation was slowed down by the presence of hydroxyl ions [5]. In the presence of oxygen, starch degradation is a slow process that has a direct relationship with the concentration of alkali. However, it is not all parts of starch that undergoes degradation when exposed to alkali conditions. Those parts that are alkali resistant to degradation are sensitive to the presence of acids, thus suggesting that starch has selective degradation, depending on the chemical used.

The reducing end of the macromolecular chain of starch has been suggested to be the point where starch degradation progresses from; hence, the reducing-terminal glucose units, even in branched structures, are split off, indicating that, not only amylose but also amylopectin is alkali labile [6].

Starch can be degraded by pregelatinization. Gelatinization involves the disruption of the crystalline and granular structures of starch when heat and water are applied. The presence of excess water (not less than 90%w/w) causes the starch granules to swell due to preferential solubility of the amylose molecules in water. When heat is applied and the gelatinization temperature is exceeded, the crystalline region of the starch becomes irreversibly disoriented, eventually leading to lattice disruption. Alabi et al. pregelatinized millet, sorghum and cocoyam starches and the process resulted in better flowability and compressibility than the natural starches. Tramadol tablets prepared with freeze-dried pregelatinized starches generally exhibited higher crushing strength but lower friability than those prepared with the natural starches [7].

4. Chemical modification of starch in drug formulations

The biodegradable nature of starch, presence of certain functional groups and the granular structure (macroscopic) have contributed significantly to the chemical modifications that starch is susceptible to. Moreover, the presence and location of hydroxyl groups at C2, C3 and C6 increases this susceptibility to substitution reactions [8]. **Figure 1** shows a representation of the different methods of chemical modifications of starch in the pharmaceutical industry.

Chemical modification of starch usually follows the pathway of substitution, degradation or cross-linking, and these methods are employed to optimize the structural and nutritional properties for targeted applications. Enhancement of the thermoplasticity of starch is achieved by chemical modification of starch, thus causing a disorientation of the hydrogen bonds between the hydroxyl groups of the native starch, and disruption of the crystalline nature. Subsequently, the starch is becomes *more fluid* and the temperature at which it melts become lowered.

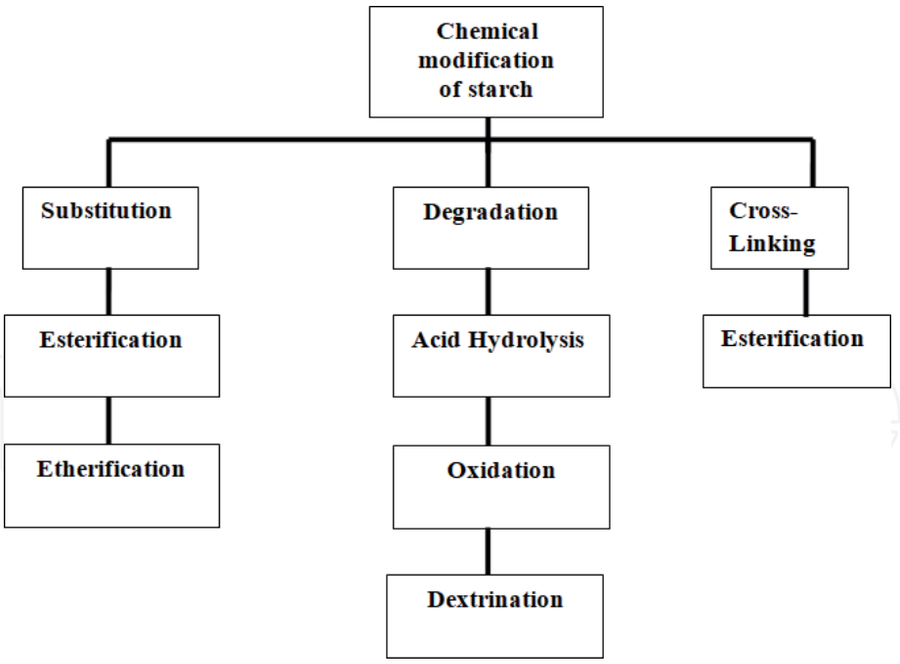

Figure 1.
Methods of chemical modification of starch.

Moreover, the reduction in the number of hydroxyl groups due to the chemical modification increases the hydrophobicity of the starch. The most common approaches to chemical modification of starches for pharmaceutical use include oxidation, hydrolysis, esterification and etherification. However, several approaches that involve a combination of the aforementioned chemical modification methods are also applicable.

Starches can be chemically modified following different pathways:

i. **Liquid pathway:** here, the chemical modification is carried out in a water medium. The starch is formulated as a suspension (with water as the vehicle) and the chemical modification is carried out until the desired property of the starch is achieved.

ii. **Semi-solid pathway:** this involves the chemical modification of native starch in form of a paste or gel. The resultant modified starch is usually dried by lyophilisation.

iii. **Solid pathway:** dry native starch is modified using the liquid form of the derivatization chemical as the medium, usually at a high temperature (≥1000°C).

Generally, the biodegradable nature of starch due to its macroscopic granular structure and presence of several functional groups makes it easily susceptible to modification. The glucose residues of starch are responsible for its chemical reactivity, and as mentioned earlier, the presence of the hydroxyl on the amylose and amylopectin are prone to the oxidation, reduction and hydrogen bond formation that starch undergoes in the process of chemical modification. The occurrence of large-sized grains in the granular structure exposes starch to external factors, thereby enhancing modification. The penetrating ability of the chemical involved in the modification process, into the starch granular surface or the interior also influences the chemical modification of starch.

5. Starch modification by oxidation

Starch modification by oxidation, which is one of the most common modification methods, involves oxidation of primary or secondary hydroxyl groups of the glucose units with formation of aldehyde or carboxyl groups. The oxidized starch has better water solubility and lower viscosity tendency in comparison to the native one [9]. The type of oxidant used, the botanical origin of starch, and the process conditions are all determinants of how effective the oxidation is. Moreover, the oxidation reaction may cause loosening of intermolecular bonds and/or partial depolymerization of the polymer chains [10]. It is worthy of mention that not all methods of oxidation are applicable for use in the pharmaceutical industry. Aerobic oxidation methods are not applicable for use in the pharmaceutical industry, simply due to the unique category of reactions that simply cannot be performed in batches as applicable in most starch oxidation techniques.

Oxidation with hydrogen peroxide appears very promising, especially because of the production of non-toxic residues such as water. However, a limitation of the use of hydrogen peroxide is its low reactivity towards most organic functional groups and the fact that in the presence of the compounds with electrophilic character it behaves as a nucleophile, not exhibiting oxidizing properties [11]. This limitation of hydrogen peroxide can be improved by the use of metal ions as catalysts, subsequently leading to heavy metal contamination of the modified starch.

Oxidation of starch with sodium hypochlorite involves the oxidation of the primary hydroxyl groups to either aldehyde or carboxyl groups. High concentration of the oxidant in an acidic medium has a direct relationship with the progression of oxidation as more of starch is oxidized in the aforementioned conditions. The modification of the hydroxyl group is affected by the protein content of the starting material considering the fact that any reaction on the starch is preceded by oxidation of the proteins. The starch oxidized by sodium hypochlorite is characterized by higher resistance to amylase activity and better stability at higher temperature and is capable of complexing calcium ions while exhibiting the polyelectrolyte properties [8]. Chemical oxidation of starch can also be carried out using sodium periodate. The bonds of the carbon atoms on the second and third positions are cleaved and dialdehyde groups are formed within the starch structure.

Garrido et al. successfully demonstrated the increase in the crystallinity, better water solubility and lower viscosity of cassava starch when modified by oxidation using sodium hypochlorite [12].

6. Starch modification by esterification

The hydrophobicity of starch is improved by the process of esterification, subsequently leading to improved thermoplasticity of the starch. Starch forms esters with reagents (organic and inorganic acids, and their derivatives such as chlorides, oxychlorides and acid anhydrides) due to the presence of the hydroxyl groups on each glucose residue, been converted to hydrophobic ester groups.

6.1 Esterification by acetylation

This is carried out with the aid of acetic acid or acetic anhydride. The esterification can be carried out in the presence of acetic acid as an activator or with acetic anhydride in the presence of sodium hydroxide as the activator [13]. A high degree of substitution was obtained when potassium carbonate was applied as the activator in the reaction of starch with acetic anhydride [14]. Starch acetates have been

used extensively in the pharmaceutical industry as binders. In 2011, Singh and Nath demonstrated the potential of acetylated moth bean starch as a carrier for controlled drug delivery of lamivudine tablets [15]. On a micro scale, starches can be acetylated without the presence of a catalyst. The process involves heating the native starch with acetic acid at a temperature between 179 and 181°C for a period of 2–4 min, resulting in a homogenous mixture. Tuovinen et al. documented the potential of natural sensitive starch acetate as an excipient in the retinal delivery of calcein; the *in-vivo* studies revealed that starch acetate nanoparticles, when compared with native starch, were taken up faster by reticuloendothelial cells without significant toxicity [16]. Akin-Ajani et al. also demonstrated the increase in crushing strength and disintegration time but lower friability of acid modified white fonio (*Digitaria exilis*) and sweet potatoe (*Ipomea batatas*) starches when incorporated as exo-disintegrants in paracetamol tablet formulations [17].

6.2 Esterification by phosphorylation

Phosphorylation of starch enhances the rheological and pasting properties of starch, which improves the flowability of starch when used in tablet formulation as documented by Adetunji and Kolawole [18]. This is as a result of addition of phosphate groups to the C6 position of the glucose residue [19].

Starch phosphate esters containing magnesium, calcium, or aluminum ions are used extensively as disintegrants in the pharmaceutical industry. Monostarch phosphate is obtained by treating starch with potassium or sodium phosphates, while distarch phosphates can be obtained by treating starch with phosphorus oxychloride or sodium trimetaphosphate. The degree of cross-linking of phosphorylated starch determines the swelling ability of the modified starch. At a low degree of cross-linking, starch has high swelling ability but with increasing degree of cross-linking; swelling ability in water decreases, until complete loss of this ability [20].

Zuo et al. documented the use of maleic anhydride in the esterification of corn starch. The esterification led to roughness on the surface of the starch particle with a subsequent increase in particles size. Crystal lattice destruction of the starch during the maleic anhydride esterification also led to improved thermoplasticity and reduction in gelatinization temperature [21]. Phosphorylated starch yielded a better result than native starch when Prosanthi and Rama incorporated it a disintegrant in Ziprasidone tablet formulations [22], while starches from various botanical sources with different amylose contents (way corn, common corn, Hylon V, Hylon VII and potatoe) were phosphorylated at pH 9.0 and 11.0 using reactive extrusion method prior to their use in the formulation of sustained release metoprolol tartrate tablets; these phosphorylated starches produced stronger hydrogels than the corresponding native starch [23]. Chowdary et al. used phosphorylated potatoe starch prepared by the reaction of the native starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures as a carrier in solid dispersions for enhancing the dissolution rate of aceclofenac; better results were achieved from the formulations containing the phosphorylated starches [24].

7. Starch modification by etherification

Etherification of starch is a derivatization technique that involves the use of various alkylation agents such as dimethyl sulphate, diethyl sulphate, alkylene oxides (epoxides) and alkyl halides. The use of diethyl (or dimethyl) sulphates in starch etherification was documented to have taken place in dimethyl sulfoxide with the addition of aqueous sodium chloride [25]. Starch ethers with branched chains are usually produced through reactions with alkyl halides.

The use of epoxides in starch etherification can proceed in the absence of sodium hydroxide. According to Cui, the high reactivity of the asymmetrical epoxide group is due to the highly strained three-membered ring with bond angles of 60° [25]. Etherification of macrogranular starch (containing ≤10%w/w moisture) by pressurized hot air can also be carried out using ethylene oxide [26].

Starch etherification involving the introduction of ammonium, amino or imino group yields important industrial derivatives. The use of different amino-alkyl agents, such as 2-diethylaminoethyl chloride, 2,3-(epoxypropyl), trimethylammonuim chloride, (4-chlorobutene-2)-trimethylammonium chloride, etc., in etherification is a major way of producing cationic starches with enhanced gelatinization behavior, pasting properties and solubility [6].

Carboxymethylated starches are derivatives of etherification of starch that are formed when hydrogen atoms are replaced by carboxymethyl functional groups. Carboxymethylated starches have been documented to show low gelatinization temperature and swelling properties and, solubility in cold water than most interesting native starches [27]. Synthesis of carboxymethyled starch involves initial activation of the native starch with aqueous sodium hydroxide in an organic slurry, followed by the reaction with monochloroacetic acid or its sodium salt. The tablet film-coating potential of carboxymethylated mungbean starch was reported by Kittipongpatana et al. as due to the formation of clear, thin film with greater flexibility and strength than that of the native starch [28]. Drug release was better sustained when high amylose sodium carboxymethylated starch matrices were used in the formulation of oral acetaminophen tablets [29].

8. Conclusion

The modification of starch using different approaches such as oxidation, esterification and esterification is well documented in literature. While small scale researches have substantiated the usefulness of modified starches as excellent excipients in the manufacture of different dosage forms due to enhancement of characters such as flow properties of starch, favorable particle size, robust crystallinity etc., it is pertinent to develop more methods of chemically modifying starch that can be scaled-up in the pharmaceutical industry to increase the options that drug formulation scientists can exploit when choosing excipients for drug dosage form designs.

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