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Chapter

Starch Source and Its Impact on Pharmaceutical Applications

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Abstract

Starch can be obtained from a variety of plant sources. The specific source of starch, the environmental conditions during starch maturation, and the age of the plant affect the physicochemical composition of the starch. This is because of the effect they have on critical factors especially the amylose amylopectin content of the starch as well as their relative quantities. These factors also affect the starch granule size and size distribution and the levels of minor components such as phosphates, lipids, and the nature of these interactions with amylose and amylopectin. In its wide use as a pharmaceutical excipient especially as binder and disintegrant, unmodified starch is affected in its functionality by the physicochemical properties of the starch. These factors especially by their influence on the swelling power and gelatinization as well as granule size and shape determine the properties of dosage forms in which the starches are used. This results in dosage forms that, although meeting compendial standards, differ in specific properties. The source of starches therefore affects the properties of pharmaceutical dosage forms. This should be taken into consideration in the choice of excipients in drug formulation and before the substitution of one starch for another in a formulation.

Keywords: starch, source, amylose, amylopectin, swelling, viscosity, pharmaceutical excipients

1. Introduction

In its native form, pure starch is a white, amorphous relatively tasteless powder which is odorless and is insoluble in water and other common organic solvents. It is one of the most widely distributed chemical substances in nature being the energy storage form of plant materials.

Microscopically, starch consists of colorless, highly refractive particles whose size and shape depend on various factors most important of which is the source of the starch. A starch granule involves alternating regions of amorphous and crystalline lamellae seen as rings which are essentially the crystalline portion.

Starch is chemically a carbohydrate composed of two similar carbohydrate molecules—amylose and amylopectin. Amylose is a straight chain α-1,4-glycosidic bonds, while amylopectin is a branched polymer also made of α-1,4-glycosodic with branched chain linked by α-1,6-glycosidic bonds. This conformational difference confers different properties on each of these polymers. For example the short branching of amylopectin at the α-1,6-glycosidic bonds is responsible for the crystalline region of the granules [1–3]. In the natural state, starch is approximately 20–30% amylose and 70–80% amylopectin.

Amylose which is rigid due to packing resulting from its straight chain is insoluble in water but soluble in hot water without gel formation. Amylopectin is, however, nonrigid in structure and soluble in water and forms a gel in hot water.

Starch which is largely synthesized in the amyloplast of the storage organs of plants and/or the chloroplast of plant leaves also contains traces of lipids and phosphate groups.

2. Pharmaceutical applications of starch

Starch is one of the most widely used pharmaceutical excipients because it is one of the few natural products that, with minimal processing, meet most of the requirements for excipients. It is nontoxic, odorless, inexpensive, widely available, and biocompatible.

In its native form, starch is used in the formulation of a number of dosage forms where its particular functions depend on the specific dosage form. This section discusses the most commonly utilized functions of starches as an excipient.

2.1 Binder

Starch is widely used as a binder in the wet granulation process of massing and screening which is an important step in the production of tablets, capsules, and other solid dosage forms. The granulation process is used to improve the flow of APIs which tend to be very cohesive. Flow is critical to the maintenance of dosage form weight consistency in high-speed manufacturing equipment, to avoid the dose variation that can result from irregular flow and powder segregation. In this process, starch is used as a liquid binder to create agglomerates with good flow properties. The paste produced on heating a suspension of starch is used to cause the "sticking together" of the particles in the formulation to create larger sized agglomerates that will reduce cohesiveness and encourage flow. This is achieved by the creation of bonding between particles in the powder bed which become solid bridges on drying. The more viscous the paste, the stronger the bridges formed, and the larger the size of the particles formed up to a limit [4]. It would therefore imply that any factors that affect the viscosity of the starch paste would affect the functionality of the starch as a binder. Studies have shown that the source and by implication the chemical composition and nature of starches influence their viscosity [5].

2.2 Disintegrant

A disintegrant is an excipient included in a pharmaceutical formulation to achieve the breakup of solid dosage forms such as tablets or granules into smaller discrete particles. Disintegration is a critical step in the process of drug release and absorption as it exposes a larger surface area for the drug to more easily and quickly go into solution. This accelerates the dissolution process, drug release, and absorption to achieve the desired therapeutic activity of the drug. Starch is a cheap and convenient disintegrant which is thought to exert this action as a result of the swelling properties of its particles in the presence of water leading to the disruption of the solid bridges and other binding forces in the dosage form. The extent of swelling is a function of the source or type of the starch which is reflective of the relative proportion and conformation of the amylose and amylopectin in the particular starch [6, 7]. Weak associative forces in a starch could be an indication of its potential as a disintegrant [1]. Disintegrant action could also be due to the formation of channels through which fluids are able to penetrate the solid dosage form allowing the dissolution of the drug.

2.3 Diluent

Some drugs are used at very low doses thus making it very difficult to process them and eventually compress them into tablets and other required dosage forms. In such cases, inert materials that do not exert the pharmacological effect of the drug can be included in the formulation to bulk it up to allow for the normal formulation processes. Because it is bland, odorless, and digestible, starch is used for this purpose.

2.4 Absorbents

Starch is hygroscopic and can absorb moisture up to 10–17% when equilibrated at normal atmospheric conditions [8]. It therefore finds use as an absorbent in drug formulations to keep powders dry and ensure the stability of drugs that are liable to deteriorate by hydrolysis and other similar chemical reactions.

2.5 Glidant/lubricant

Starches have been studied for use as lubricants and glidants [9] because of their slippery nature and ability to adhere to surfaces.

2.6 Modified starches

In its native form, the uses of starch are limited by its inability to withstand some processing conditions such as high temperatures, varying pH, freeze-thaw cycles, its tendency for retrogradation and decomposition, and brittleness.

When modified, starch becomes even more versatile in its pharmaceutical applications. For example, acetylation results in improved paste clarity and flow, as well as increased swelling capacity [10, 11], while with carboxylmethylation there is increased water solubility, lowered gelatinization temperature, and paste stability [12, 13]. An important factor in the modification processes and the specific properties of the modified products is the physicochemical characteristics of the particular starch used. Modifications could be physical using heat and moisture, gelatinization, extrusion, spray drying, granulation, or agglomeration. Starch can also be modified chemically by the introduction of functional groups using derivatization techniques such as esterification, cationization, cross-linking, or hydrolysis and oxidation which are usually achieved by the replacement of all or some of the hydroxyl groups.

3. Starch source and its pharmaceutically relevant properties

Starch is one of the most widely distributed substances in nature and can therefore be obtained from several different plant sources. Starch for use as an excipient is one that meets the official compendial standards of quality in the relevant official books (pharmacopeias) and is generally referred to as official starch. Examples of such are potato, corn, rice, and tapioca starches. Pharmaceutical grade starch can be obtained from several plant sources but generally meet the standards shown in **Table 1**.

In addition to the compendial starches, several other plant sources have been investigated by various workers and reported as suitable sources of pharmaceutical grade starch in studies using the pharmacopeial starches as standards [9, 14, 15].

Description	Starch grains, size, shape and distribution, presence/absence of hilum, and striations depend on the plant material from which the starch is obtained
Characteristics	Fine to very fine powder, white to slightly yellowish, tasteless, insoluble in cold water and alcohol
Identification	A translucent whitish jelly is produced on cooling 1 g of the starch mixed with 2 ml of cold water, stirred into 15 ml of boiling water, and boiled gently for 2 min. A reddish violet to deep blue color is obtained on adding iodine to water slurry of the starch
Foreign matter	Not more than traces of cell membranes and protoplasm should be present
Acidity	Not >2.0 ml of 0.1 M NaOH should be required to change the color of 50 ml of a solution obtained from shaking suspension of 10 g starch in 100 ml ethanol (70% v/v), previously neutralized to 0.5 ml of phenolphthalein solution, for 1 h and filtered
Loss on drying	≤15% determined by drying1g in an oven at 100–105°C
Sulfated ash	≤0.6% determined on 1 g of starch
Microbial limits	Total viable aerobic count <103 bacteria/g (determined by plate count)
	Absence of *E. coli*

Table 1.
Pharmacopoeial requirements of pharmaceutical grade starch [14].

These reports show that although starches from a variety of sources can be used as excipients, the specific effects (especially quantitative) on the formulation properties are dependent on the source. For example, the disintegrant effect of yam starch was higher than that of cocoyam starch. This is attributed to the difference in the fundamental properties of the starches such as particle size and the amylose/amylopectin ratio which affect functional properties such as swelling, water sorption, and viscosity [16].

Pharmaceutical grade starches can come from either underground plant storage organs such as tubers, rhizomes, or roots or from grains and cereals. The choice of starch source is largely dependent on the availability, ease of extraction, and the yield. The underground storage organs tend to be more easily processed as they are less associated extraneous materials.

While the general physical and chemical properties of starches are the same, their specific functional properties are dependent on the particular plant source which determines their physicochemical properties. The biological origin of starch serves as a determining factor in the granule shape, size, and morphology [17]. This section will examine the effect that the specific plant sources have on some physicochemical properties of starch that are relevant to their use in pharmaceutical formulations.

3.1 Swelling and gelatinization properties

3.1.1 Gelatinization

The most common use of starch as a pharmaceutical excipient is as binder and disintegrant in the formulation of tablets and other solid dosage forms. Its behavior in the presence of water is therefore its most important property from the perspective of the pharmaceutical industry. While the disintegrant action of starch is substantially determined by the response of the starch particle to water uptake leading to a ballooning before the leakage of its contents and complete rupture, its use as a binder will depend on the cohesiveness resulting from the series of events that result in increased viscosity of the starch paste. The extent of changes induced

in the starch particle by heating depends on the temperature and duration [18] and has been reported to be greatly influenced by the starch species [1].

Gelatinization is the disruption of the granular structure of starch by heating with an excess of water. This is because as the suspension is heated gradually, the starch particles begin to swell tangentially [19], and particle content begins to leak with the leakage of amylose, until the eventual rupture of the granule which results in further increase in viscosity and solubility. Initially some amylose is retained in the interior cavity, but rupture and collapse and dissolution of the swollen granule occur during prolonged heating. This process results in a gradual increase in viscosity of the suspension until the complete rupture of the starch granules until the peak viscosity is attained [20].

It essentially involves the weakening of the micellar network within the particle subjected to heat in a suspension by disrupting the hydrogen bonds which permits further hydration and irreversible starch particle swelling. This conversion has been related to various irreversible changes such as granule swelling, loss of birefringence, leaching of amylose, and increased viscosity and solubility and tangential swelling of the particle [19]. From a thermodynamic standpoint, gelatinization refers to the enthalpic transitions involving the starch granule treated as a semicrystalline entity (spherulite). Collapse of the crystalline structure leads to a gain in entropy. This tends to dislodge the hydrogen bonding network occurring in the spherulite.

The apparent viscosity of a starch paste is essentially the result of properties of the individual swollen entities, their fragments, presence of starch soluble, and the interaction or cohesiveness between swollen particles.

Gelatinization begins from portions of the granule where bonding is weakest, and so since the degree of association in individual particles differs and is influenced by factors such as plant source and some environmental conditions of growth, gelatinization temperature and pattern would differ from one starch source to another [14].

3.1.2 Retrogradation

Retrogradation is a slow recrystallization of starch components (amylose and amylopectin) upon cooling or dehydration [21]. It is as a result of the long molecular chains and the numerous hydroxyl groups present causing a great tendency for bonding between chains, thus producing bundles of amylase molecules which are rigid resulting in rigid gels and insoluble precipitates. The rate of retrogradation in a starch paste depends on the amount of amylose, the size of the amylose molecule, and the method of preparation of the paste [22, 23].

3.1.3 Factors that affect gelatinization/swelling properties

The strength of the starch granular structure would depend on the specific nature of the component molecules, their association, and spatial arrangement as well as their interaction with water molecules. Since the crystalline region of starch is largely composed of amylose, the exact amount will have a bearing on the gelatinization process. There is significant correlation between apparent amylose content and viscosity parameters such as peak viscosity (PV), minimum viscosity (MV), final viscosity (FV), breakdown (BD), total setback viscosity (TSV), and setback viscosity (SV) [24]. Phosphate monoester derivatives increase the paste viscosity; potato starch which contains a large amount of phosphate monoesters is more resistant to heat and shearing than cereal starches, but hot paste stability is lost when potassium bound to phosphate monoester is displaced by other cations [25].

Amylopectin is primarily responsible for granule swelling and viscosity [26], and starch pasting properties are affected by amylose and lipid contents [27, 28]. Increased gelatinization temperatures have been associated with higher levels of amylopectin double helices resulting in enhanced rigidity of the amorphous region [29].

The lipids contained in starches in the form of phospholipids and free fatty acids [30] tend to form complexes with amylose and the long branches of amylopectin resulting in starch granules with limited solubility [28]. They result in opaque and low-viscosity pastes [31] significantly reducing the swelling capacity of starch particles [32]. The phosphorylation level, which appears to be confined to the amylopectin fraction and is enriched in the amorphous regions, is lower in cereal than in tuber starches [33]. It is associated with increased granular hydration and lowered crystallinity, yielding pastes with higher transparency, viscosity, and freeze-thaw stability [34].

The swelling power of starch is associated more with granule structure and chemical composition especially amylose and lipid component than with granule size. Higher amounts of lipid-complexed amylose would inhibit swelling and gelatinization [26].

3.1.4 Moisture sorption

Moisture sorption by starch which leads to particle swelling has been attributed to the interaction between the hydroxyl groups of the hexose moiety and water molecules. Although water molecules form hydrogen bonds with both amylose and amylopectin, the amylopectin structure has been shown to physically trap water molecules. Based on this, it has been hypothesized that starch particles high in amylopectin would have a higher moisture sorption potential. Crystalline polymers have been proposed to have extensive secondary intermolecular bonding. This secondary bonding causes the hydroxyl groups on adjacent glucose units to interact with each other and hence reduces the available sites for absorption of water molecules. As a result, the higher degree of crystallinity could reduce the moisture sorption [1].

3.1.5 Effect of growth conditions

The conditions of growth of starch-containing plants especially during starch maturation affect the content and gelatinization behavior of the starch [35]. Gelatinization peak temperature has been reported to be lower for barley cultivar grown at low temperatures [36].

Higher growing temperature and abundant moisture during the development of starch granules could cause annealing of starch and result in higher onset and narrower gelatinization temperatures of the starch [37]. The swelling properties of starch particles are significantly affected by the growing temperatures of the plant during its development.

3.2 Amylose/amylopectin content

Amylose/amylopectin ratio, molecular weight, and molecular fine structure influence the physicochemical properties of starch and are therefore major determinants of its functional properties such as flow and swelling properties [38]. This is especially because of its swelling and pasting characteristics which have been earlier mentioned and are critical to the pharmaceutical uses of starch. Physicochemical properties of starch in solution are likely direct functions of the molecular constitution of the polymer including the molecular size, unit chain length distribution, branching pattern, degree of phosphate substitution, and granule size and

distribution [39]. Thermal properties are largely influenced by the branch chain length of amylopectin [40, 41].

A number of factors including environmental and genetic [42] factors influence the amylose amylopectin content and their relative content in a particular starch.

It can occur within the range 65–85:15–20. This difference in composition has been reported to result in some of the peculiar physical and functional properties seen in some starches, such as a difference in crystallinity, starch granule size, gelling, pasting, and flow properties. The membranous structures and physical characteristics of plastids can affect the arrangement and association of the amylose and the amylopectin molecules within the granules [43] with amylose content increasing with granule maturity [44].

The effect of growth conditions on the gelatinization behavior of starches is essentially through their effects on their amylose content. For example, studies have shown that matured at 15 degrees had higher peak viscosity temperatures. FV, TSV, and shorter time maintained at greater than 80% of peak viscosity than starch from plants grown at ambient temperature in the field due to the difference in amylose content [35].

The elevation of growth temperature increases the gelatinization temperature of wheat starch due primarily to the enhanced presence of amylopectin double helices and probably enhanced rigidity of the amorphous region [29]. The effect of environmental temperature on amylose content is dependent on the specific plant with the possibility of both increase and decrease.

The amylose content of rice and maize were reduced at elevated growth temperatures [38, 45], while with wheat the amylose content increased slightly as a function of temperature [29] indicating that the specific plant is also important. Further illustrating the effect of temperature on the amylose content, it was found to differ significantly in plants grown at 15° from those grown at 20° and that the longer rice plants were exposed to cool temperatures, the greater the accumulation of amylose [46]. Additionally, starch granule size is a factor in amylose content of a starch, with the level increasing with granule size [40, 41].

3.3 Starch granule size

Granule size influences the physicochemical characteristics of starch, and since starches from different botanical origins differ in morphology [47], it is one of the important physicochemical parameters that could affect the functional properties of different starches. Characteristics affected include starch composition, gelatinization and pasting properties, enzyme susceptibility, crystallinity, swelling, and solubility. The membranous structures and physical characteristics of plastids can impart a particular shape or morphology to the starch granules [43]. Granules of tuber and root starches, for example, are generally oval [17] while granules from fruits and nuts vary in shape. Granules of small granule starches are characterized by their very irregular, polygonal shape [43].

At similar amylose contents, small granule starches tend to have a lower pasting temperature and more amylose leakage out of the intact granule than do their larger granules at 55 degrees and above [48]; they (small granules) are associated with a higher rate of water absorption, earlier hydration, and more swelling than larger granules [49]. This is due to the less crystallized arrangement of the polysaccharide chains in the smaller starch particles thus providing a higher proportion of amorphous zones which are more accessible to water. Other factors such as amylose/amylopectin ratio and molecular weight and molecular fine structure also contribute [47] with amylose content increasing with granule size [44]. The branch chain length of amylopectin is also correlated with granule size and granule size

distribution. Decreasing granule size has been associated with reduced degree of polymerization of amylopectin, and smaller less branched amylose polymers are seen in large size starch granules [49, 50].

However the dissociation enthalpy of the amylose-lipid complexes of small granules is higher than that of large granules [51, 52]. The pattern is similar for acid or enzyme hydrolysis with small granules hydrolyzing faster than do large granules [53, 54]. The pattern of enzyme digestion also differs between small and large granules [55].

Starch particle size distribution is affected by the environment with the elevation of growth temperature tending to decrease the number and size of starch granules [41].

4. Effect of source on the pharmaceutical applications of starch

Starches that have been investigated for their potential as pharmaceutical excipients differ in their granule morphology, amylose/amylopectin ratios, water sorption, swelling power, and gelatinization characteristics. A number of workers have found that the physicochemical properties of starches affect the pharmaceutico-technical properties of the dosage forms produced using the various starches [9, 14, 15]. This is the case irrespective of the particular use to which the starch was put in the formulation.

While, in most cases, formulations containing novel starches meet the compendial quality standards, they differed from those containing the official starches. These differences can be attributed to the differences in the physicochemical properties of the starches.

As earlier stated the pharmaceutical uses of starch, especially in drug formulation, are largely based on its water sorption, swelling, and gelatinization properties. While these properties are generally applicable and qualitatively similar whatever the source of the starch, the previous section has shown that the specific or quantitative values of these properties differ from one starch source to another and even among starches from the same source if growth conditions differ. A few cases are mentioned below to illustrate the effect of these differing properties on dosage form characteristics.

A comparative study indicated that cocoyam starch has a higher viscosity than yam and cassava starches, when used as binder resulted in more fragile tablets relative to the other starches as indicated by the high tablet friability values obtained for such tablets [16].

Tablets produced by dry granulation with yam (a large granule) starch as disintegrant were more friable than those formulated with cocoyam (a small granule) starch which also had the highest hardness. There was also an inverse relationship between the starch swelling power and the rate and extent of disintegration and dissolution of the tablets. This is an indication that one of the mechanisms of tablet disintegration by starches is by swell rupture [56].

Starch size and shape affect the compaction characteristics of granulations for tableting. Yam starch which is ovoid in shape with a high mean diameter has high densification as a result of die filling and less densification from subsequent rearrangement of particles at low pressures, while potato and cassava starches with smaller diameters and more rounded shape were the reverse. While yam starch had the highest yield pressure, it had the lowest tensile strength and brittle fracture index [57].

The gelatinization characteristics of *Tacca* starch as determined by onset, peak, and conclusion temperatures of gelatinization, crystallinity, and enthalpy of gelatinization were lower than for maize starch. This implies that it has more crystalline

regions that are thermally and structurally less stable than maize starch [1]. These differences in properties resulted in the starches having different compaction properties. While they both underwent plastic deformation, the deformation for maize was more extensive than for *Tacca* which was more resistant to deformation. Maize starch also produced harder compacts. There was a correlation between these formulation characteristics and the starch properties [58].

Other workers have reported similar co relationship between fundamental properties and formulation properties [59, 60].

The functionality of the modified starches used in modified drug formulations has also been reported to be dependent on the source of the native starch. Studies using starches obtained from diverse sources have shown that the source of a starch will affect its function as a sustained release excipient [61–63].

5. Conclusion

Starch is a widely available natural material. It is versatile and has found use in many industries due to its different physical and functional properties. A number of modifications or derivatives can be produced because of the presence of a high number of hydroxyl groups on the surface. In the pharmaceutical industry, it finds extensive use as an excipient especially as a disintegrant and binder in the formulation of solid dosage forms. This use is dependent on its behavior in the presence of moisture, essentially the way it interacts and behaves in the presence of water.

Its use as a disintegrant is largely dependent on its insolubility which creates channels in the compact that allow for water to penetrate the compact to dissolve the active drug component. It also depends on the swelling of starch particles which results in the disruption of the solid bridges formed in the compact. The swelling behavior of any particular starch is dependent on a number of factors which are closely related to the exact chemical composition (amylose, amylopectin, lipids, and phosphates) of the starch. The relative quantities of the two carbohydrate moieties—the straight chained amylose and the branched chained amylopectin—is critical to the pattern and extent of interaction between starch and water since it determines the extent of interaction as well as the speed of interaction between water and the OH group on the chain. The conformation and the extent of branching of the molecules also determine the speed with which water can access and eventually disrupt the bonds within the molecule.

The use of starch as binder is dependent on its behavior when a suspension of starch powder is subjected to increased temperatures which cause the gradual weakening of the intermolecular bonding in the starch granule. The continued supply of energy in the form of heat eventually results in the breakdown of the granules, the outflow of the amylose, and eventually the breakdown of amylopectin. All these processes result in increased viscosity. It is the viscous gel produced that provides the gluing property exploited for the binding of powder particles to obtain granules in drug formulation. On drying, the wet bridges formed dry into solid stable bridges that create the granules for improved flow. This process is also dependent on the amylose amylopectin ratio as well as the moisture content of the starch and the conditions during the production of the starch in the plants.

The relative quantities of amylose and amylopectin, the extent of branching, the conformation of the moieties, the presence of phospholipids, the interaction between the carbohydrates and lipid, the particle size, and the extent of phosphorylation, all of which are affected by environmental and genetic factors, influence starch fundamental (physicochemical) properties that relate to its functional properties as a pharmaceutical excipient.

In general it can be concluded that although starches from different sources can be used as pharmaceutical excipients, as long as they meet compendial standards, consideration should always be given to the fact that their performance in formulation is dependent on their source. Since they affect functional properties especially the key properties of swelling and pasting, it is necessary to collect as much information on the growth conditions and physicochemical properties of starches to be used as pharmaceutical excipients to ensure batch-to-batch consistency in drug production. These considerations are particularly important when considering changing from one type of starch to another as excipients and in formulary development.

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