

CHAPTER 5

STARCH – A POTENTIAL BIOMATERIAL FOR BIOMEDICAL APPLICATIONS

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Abstract: The unique physicochemical and functional characteristics of starches isolated from different botanical sources such as corn, potato, rice and wheat make them useful for a wide variety of biomedical and pharmaceutical applications. Starch properties such as swelling power, solubility, gelatinization, rheological characteristics, mechanical behaviour and enzymatic digestibility are of utmost importance while selecting starch source for distinctive applications such as bone fixation and replacement. Starches can also be used as carriers for the controlled release of drugs and other bioactive agents. The chemically modified starches with more reactive sites to carry biologically active compounds are useful biocompatible carriers, which can easily be metabolized in the human body. This chapter reviews the physico-chemical, morphological and thermal characteristics of different starches that may be of importance during their use in specific biomedical and pharmaceutical applications

Keywords: starch; biomaterial; biomedical; pharmaceutical; rheological; digestibility; chemical modification

1. INTRODUCTION

The physico-chemical and functional characteristics of starch systems and their uniqueness in various products vary with starch biological origin (Svegmark & Hermansson, 1993). Starches from various plant sources, such as wheat, corn, rice and potato have received extensive attention in relation to structural and physico-chemical properties. Starch is widely used in food, pharmaceutical and biomedical applications because of its biocompatibility, biodegradability, non-toxicity, and abundant sources. The role of starch for tissue engineering of bone, bone fixation, carrier for the controlled release of drugs and hormones; and as hydrogels has already been recognized (Mano & Reis, 2004; Won et al, 1997; Lenaerts et al., 1998; Pal et al., 2006; Pereira et al., 1998; Chakraborty et al., 2005). Starch-based

biodegradable bone cements are highly advantageous because they can provide for immediate structural support and, as they degrade from the site of application, allow the ingrowth of new bone for complete healing of bone fracture (Domb et al, 1996; Pereira et al, 1998). Starch nanoparticles, nanospheres, and nanogels have also been used as base materials for nanoscale construction of sensors, tissues, mechanical devices, and drug delivery systems (Chakraborty et al., 2005). Starches of different sources have been studied extensively in relation to their structural, physico-chemical and functional properties, and it has been suggested that the extent of variation in these properties depends on the source of starch (Tester & Karkalas, 2002; Singh et al, 2002, 2003, 2004; Kaur et al, 2002; Yusuph et al, 2003).

Native starch characteristics, their correlation with different properties of starch based products and their interactions with different ingredients during product development have been studied (Singh et al, 2002a, 2002b; Kaur et al, 2005; Azizi & Rao, 2005). Many techniques and methods for the characterization of starch have been developed that are suitable for screening of starches from different sources (Singh & Singh, 2001, 2003; Kim et al, 1995). Industrial interest in new value-added products has resulted in many studies being carried out on the characterization of starches isolated from different genotypes and novel sources (Singh et al, 2006, 2007a; Kim et al, 1995; Romero-Bastida et al, 2005; Taveres et al, 2005; Wang et al, 2005). The native starch isolated from different sources has limitations such as low shear resistance, thermal resistance, thermal decomposition and high tendency towards retrogradation which limits its use in some industrial applications. Starch modification, which involves the alteration of the physical and chemical characteristics of the native starch to improve its functional characteristics, can be used to tailor starch to specific applications (Singh et al, 2007b; Kaur et al, 2006; Hermansson & Svegmarm, 1996). Starch modification is generally achieved through derivatization such as etherification, esterification, cross-linking and grafting of starch; decomposition (acid or enzymatic hydrolysis and oxidization of starch) or physical treatment of starch using heat or moisture etc. Chemical modification involves the introduction of functional groups into the starch molecule, resulting in markedly altered physico-chemical properties. Such modification of native granular starches profoundly alters their swelling, gelatinization, retrogradation, pasting, and digestibility properties.

The physico-chemical, morphological and thermal properties; as well as the enzymatic digestibility of the starches from different sources have been discussed in detail in this chapter. An account of the different types of chemical modifications, which are important to tailor the starch characteristics for a particular biomedical or pharmaceutical use, is given in the final section of this chapter.

2. PHYSICO-CHEMICAL CHARACTERISTICS OF STARCHES

Starch is the major reserve polysaccharide of plants and is present in the form of discrete granules comprised of amylose and amylopectin. Amylose is a linear polymer composed of glucopyranose units linked through α -D-(1 \rightarrow 4) glycosidic linkages while the amylopectin is a branched polymer with one of the highest

molecular weights known among naturally occurring polymers (Karim et al, 2000). Amylopectin is the major component with an average molecular weight of the order 10^7 – 10^9 (Aberle et al, 1994). It is composed of linear chains of (1→4)- α -D-glucose residues connected through (1→6)- α -linkages. A slight degree of branching (9–20 branch [α -(1→6)] points per molecule) has been reported for amylose (Hoover, 2001). The extent of branching has been shown to increase with the molecular size of amylose (Greenwood & Thomson, 1959). The characterization of starch/starch based biomaterials for use in biomedical applications is important due to their different swelling, solubility and surface characteristics. The conversion of starch from powder to gel form is required for their use in pharmaceutical applications and this transformation is achieved through gelatinization (gelatinization is discussed in detail in the gelatinization and retrogradation section). During and after gelatinization, the amylopectin has stabilizing effects, whereas amylose forms gels and has a strong tendency to form complexes with lipids and other components (Singh et al, 2003).

Amylopectin and amylose are therefore preferred for many food and pharmaceutical applications, respectively. By genetic engineering, using, antisense technique, it has been possible to modify the botanical source so that it produces granular starch practically without amylose/amylopectin (Hofvander et al, 1992; Talberg et al, 1998). Starch properties depend on the physical and chemical characteristics such as granule size and size distribution, amylose/amylopectin ratio and mineral content (Madsen & Christensen, 1996). The amylose content of the starch granule varies with the botanical source of starch and is affected by climatic conditions and soil type during growth (Juliano et al, 1964; Morrison et al, 1984; Asaoka et al, 1985; Morrison & Azudin, 1987). Amylose content of potato starch varies from 23% to 31% for different genotypes (Kim et al., 1995; Wiesenborn et al., 1994). Amylose content of rice is specified as waxy, 0–2%; very low, 5–12%; low, 12–20%; intermediate, 20–25%; and high 25–33% (Juliano, 1992).

The amylose content of wheat starch varies from 18 to 30% (Deatherage et al, 1955; Medcalf & Gilles, 1965; Soulaka & Morrison, 1985). Phosphorus is one of the important non-carbohydrate constituents present in the starches, which vary from 0.003% in waxy corn starch to 0.09% in potato starch (Schoch, 1942a). Phosphorus at such a low concentration has been reported to significantly affect the functional properties of starches. Phosphate is present as phosphate monoesters and phospholipids in starches. The phosphate monoesters affect starch paste clarity and viscosity while the presence of phospholipids results into opaque and lower viscosity pastes (Schoch, 1942a,b; Craig et al, 1989). Phosphate groups esterified to the amylopectin fraction of potato starch contribute to the high viscosity and also to a high transparency, water binding capacity and freeze thaw stability (Craig et al., 1989; Swinkels, 1985). Phospholipids present in starch have a tendency to form complex with amylose and long branched chains of amylopectin, which results in limited swelling. Wheat and rice starches have higher phospholipids content and produce starch pastes with lower transmittance as compared to the corn and potato starches with lower phospholipids content. Free fatty acids in rice and maize starches

contribute to their higher transition temperatures and retrogradation (Davies et al., 1980), which is due to amylose-lipid complex formation.

Potato starch with higher phosphate monoester content resulted into paste with higher light transmittance. More than 90% of the lipids inside wheat starch granules are lysophospholipids and have been thought to occur in the form of inclusion complexes with amylose (Morgan et al, 1993). ³¹P-nuclear magnetic resonance has been used to locate the phosphorylations in modified wheat and corn starches and in native potato and taro starches (Muhrbeck & Tellier, 1991; Jane et al, 1992). This technique has also been used to determine the locations of phosphodiester cross-linkages in corn starch (Kasemsuwan & Jane, 1994). Starch phosphate-monoesters in native potato starch are mainly found on amylopectin which contains one phosphate-monoester group per 317 glucosyl residues. The phosphorus in potato starch is located densely in the granule core together with amylopectin. Wheat starch lipids constitute 1% of the granular weight, having surface lipids to the extent of 0.05% (Eliasson et al, 1981). The lipids are present at lower levels and significantly affect the swelling of wheat starch (Morrison et al, 1993). It has also been reported that surface lipids oxidize and contribute to the so-called cereal odor of wheat starch.

Swelling power and solubility provide evidence of the magnitude of interaction between starch chains within the amorphous and crystalline domains. The extent of this interaction is influenced by the amylose/amylopectin ratio, and by the characteristics of amylose and amylopectin in terms of molecular weight/distribution, degree and length of branching, and conformation (Hoover, 2001). Swelling/water absorption capacity of starches is very important in biomedical and pharmaceutical applications such as implants and drug-delivery systems because the equilibrium degree of swelling influences: (a) the solute diffusion coefficient through the starch based hydrogels, (b) the surface properties and surface mobility, and (c) its mechanical properties (Peppas, 1996; Pereira et al, 1998). Swelling power and solubility of the starches from different sources differ significantly. Potato starch has much higher swelling power and solubility than other starches (Singh et al, 2002). Corn starch exhibits higher swelling power than wheat starch but lower than potato starch (Singh et al., 2002). The high swelling powers and solubility of potato starches might be due to higher content of phosphate groups on amylopectin-repulsion between phosphate groups on adjacent chains will increase hydration by weakening the extent of bonding within the crystalline domain (Galliard & Bowler, 1987). The presence of lipids in starch may have a reducing effect on the swelling of the individual granules (Galliard & Bowler, 1987). Since corn, rice and wheat starch granules contain lipids contrary to potato starch granules; this may possibly explain the difference in the swelling power of these starches. The differences in swelling power and solubility of starches from different sources may also be due to the difference in morphological structure of starch granules. Water Binding and solubility of starch depend on damage starch content (Evers & Stevens, 1985). The damage starch content in rice starch has been reported to depend on starch isolation method. The damage starch was observed to be lower in the starch isolated by the

protease digestion as compared to alkaline steeping method (Wang & Wang, 2001). Starch isolated with alkaline steeping method with 0.1–0.2% sodium hydroxide had 73–85% yield (on dry starch basis, dsb), 0.07–0.42% residual protein, and 0.07–2.6% damaged starch (Yang et al, 1984; Lumdubwong & Seib, 2000). Granules continue to swell as the temperatures of the suspension are increased above the gelatinization range. According to Hermansson and Svegmarm (1996) corn and wheat granules may swell up to thirty times their original volume and potato starch granules up to hundred times their original volume, without disintegration. It has been suggested that amylose plays a role in restricting initial swelling because this form of swelling proceeds more rapidly after amylose has been exuded. The increase in starch solubility, with the concomitant increase in suspension clarity is seen mainly as the result of the granule swelling permitting the exudation of the amylose. The granules become increasingly susceptible to shear disintegration as they swell, and they release soluble material as they disintegrate. The hot starch paste is a mixture of swollen granules and granule fragments, together with colloidal and molecularly dispersed starch granules. The mixture of the swollen and fragmented granules varies with the botanical source of the starch.

2.1. Morphological Characteristics and Granular Structure

Starch is laid down in the form of granules that function as an energy reserve. The granules vary in size and shape based on their botanical origin. Tuber starch granules are generally voluminous and oval shaped with an eccentric hilum. Cereal starch granules such as maize, oats, and rice have polygonal or round shapes. High amylose maize starch exhibits filamentous granules (budlike protrusions). Legume seed starch granules are bean-like with a central elongated or starred hilum. The hilum is not always distinguishable, especially in very small granules. The semi-crystalline structure of a starch granule can be identified at the light microscope level and through characteristic X-ray diffraction patterns. Microscopy (predominantly optical and scanning electron microscopy) is mainly used for looking at the whole granule. Under polarized light in a microscope, a typical birefringence cross is observed as two intersecting bands (the “Maltese cross”). It indicates that the starch granule has a radial orientation of crystallites or there exists a high degree of molecular order within the granule. An examination of these granules under optical or electron microscopy reveals pronounced concentric rings (French, 1984). At higher levels of organization, the semi-crystalline rings are composed of stacks of alternating crystalline lamellae (Yamaguchi et al, 1979; Kassenbeck, 1978). The combined repeat distance of crystalline and amorphous lamellae accounts for the peak observed in small angle X-ray and neutron scattering experiments (Oostergetel & Van Bruggen, 1989). The currently accepted crystalline structure consists of a radial arrangement of clusters of amylopectin. Cameron and Donald (1992) have developed a model, which allows quantification of the various parameters needed to describe this complex model. The starch granule structure is modeled as a finite number of lamellae of alternating electron density

embedded in a background region of a third electron density, assumed to correspond to the amorphous growth ring. X-ray scattering is another approach that has been frequently used in starch granule structure investigation. Wide-angle X-ray diffraction (WAXD) has revealed the packing within the crystals of the granule, enabling a detailed analysis of the different polymorphs (Imberty & Perez, 1988). Cereal starches typically exhibit the A polymorph, where as tubers show the B form and legumes exhibit the mixed state polymorph C. The V type can only be found in amylose helical complex starches after starch gelatinization and complexing with lipid or related compounds. The X-ray diffraction pattern of starch could be altered by heat-moisture treatment. For example, B-type of potato starch can be converted to A or C type using heat/moisture treatment. WAXD essentially deals with the interatomic distances. Less extensively used is small-angle X-ray scattering (SAXS) which, due to the reciprocal relationship between spacings in real space and in the scattering pattern, probes larger length scales than WAXS (Donald, 2001). Lenaerts et al. (1998) carried out the solid-state ^{13}C NMR on cross-linked high amylose starch powders, tablets and hydrated tablets with different cross-linking degrees. They reported the predominance of V type of single helix arrangement of amylose in the dry state, which changed to B type double helix arrangement upon hydration, in low cross-linking degree homologues. They therefore hypothesized that the tendency of amylose to undergo the V to B transition is an important factor in controlling water transport and drug release rate.

Morphological characteristics of starches from different plant sources vary with the genotype and cultural practices. The variation in the size and shape of starch granules may be due to the biological origin (Svegmark & Hermansson, 1993). The morphology of starch granules depends on the biochemistry of the chloroplast or amyloplast, as well as physiology of the plant (Badenhuizen, 1969). The granular structure of potato, corn, rice and wheat starches show significant variation in size and shape when viewed by scanning electron microscope (SEM). The average granule size ranges between 10 and 100 μm for potato starch granules. The average size of individual corn and wheat starch granules ranges between 5 and 25 μm . The rice starch granules are smaller in size and ranges between 3–5 μm . Potato starch granules have been observed to be oval and irregular or cuboidal in shape. The starch granules are angular shaped for corn, and pentagonal and angular shaped for rice. At maturity, wheat endosperm contains two types of starch granules: large (A-granules) and small (B-granules). A-granules are disk like or lenticular in shape with diameter range between 10–35 μm . On the other hand, B-starch granules are roughly spherical or polygonal in shape, ranging between 1–10 μm in diameter. Each amyloplast of wheat contains one large A-granule and a variable number of B-granules (Parker, 1985). The A-granule forms soon after anthesis and may continue to grow throughout grain filling, while the B-granules are initiated some days after anthesis and remain considerably smaller (MacLeod & Duffus, 1988). There have been reports of a third class of very small C-granules that are initiated at very late stage of grain filling (Bechtel et al, 1990). The small B-granules have a particular impact on the processing quality of the wheat (Stoddard, 1999). The higher

surface-to-volume ratio of the B-granules has been associated with a higher rate of water absorption than that of A-granules, affecting the mixing of the dough and the baking properties of the final products (Bechtel et al, 1990). The surfaces of the granules from corn, rice and wheat appear to be less smooth than potato starch granules. The individual granules in case of rice starch develop in compact spherical bundles or clusters, known as compound granules, which fill most of the central space within the endosperm cells. Physico-chemical properties like percent light transmittance, amylose content, swelling power and water binding capacity were significantly correlated with the average granule size of the starches separated from different plant sources (Singh & Singh, 2001; Zhou et al, 1998). Recent research has illustrated the potential of microscopy for elucidating the phenomena underlying starch functionality. Light microscopes and confocal scanning laser microscopes can be used to obtain information about features such as distribution of granules, degree of swelling of granules, and the general distribution of amylose rich and amylopectin rich phases, where as electron microscopes are required to reveal fine details of the granules and for the studies of the supramolecular structures of macromolecular dispersions (Hermansson & Svegmak, 1996).

3. GELATINIZATION AND RETROGRADATION CHARACTERISTICS

The gelatinization of the native starch granule is required in almost all culinary and industrial uses of starch (Blanshard, 1987). Gelatinization leads to a change in the organization of granules. The phase transitions involved are only slowly being discovered, in a large part hampered by the lack of understanding of the native granule structure (Waigh et al, 1997). The crystalline order in starch granules is often the basic underlying factor influencing its functional properties. Collapse of crystalline order within the starch granules manifests itself as irreversible changes in properties such as granule swelling, pasting, loss of birefringence, and starch solubility (Atwell et al., 1988). Many techniques, including differential scanning calorimetry (DSC), X-ray scattering, light scattering, optical microscopy, thermo-mechanical analysis (TMA) and NMR spectroscopy have been employed to study these events in an attempt to understand the precise structural changes underlying gelatinization (Jenkins & Donald, 1998).

The starch granule is a semicrystalline, and gives rise to birefringence when viewed under polar light in the microscope. As the starch granule gelatinizes and its structure is disrupted, this birefringence is lost. Many studies have attempted to characterize the point at which all birefringence is lost for a sample studied under an optical microscope. This point is termed the birefringence end point temperature. The order-disorder transitions that occur on heating an aqueous suspension of starch granules have been extensively investigated using DSC. This technique has been widely used to study the thermal behavior of starches, including gelatinization, glass transition temperature and crystallization. Stevens and Elton (1971) first reported the application of DSC to measure the heat of gelatinization of starch. Donovan

(1979) reported that there are two endothermic peaks when heating wheat and potato starches with 27% water to 150°C, and suggested that two kinds of structures or two different environments may be present. Eliasson (1980) observed three peaks when a wheat starch/water mixture with water content in the interval 35–80% was heated to 140°C and concluded that DSC could not explain the second peak. Shorgen (1992) studied the gelatinization of corn starch with 11–50% water and reported that the starch gelatinized (melted) at 190–200°C in the range of water content of 11–30%. Starch transition temperatures and gelatinization enthalpies by DSC may be related to characteristics of the starch granule, such as degree of crystallinity (Kruger et al, 1987). This is influenced by chemical composition of starch and helps to determine the thermal and other physical characteristics. Starches from different botanical sources, differing in composition exhibited different transition temperatures and enthalpies of gelatinization.

Kim et al (1995) have studied the thermal properties of starches from 42 potato cultivars and correlated these properties with the physicochemical characteristics. Gelatinization occurs initially in the amorphous regions as opposed to the crystalline regions of the granule, because hydrogen bonding is weakened in these areas. Gelatinization temperatures and enthalpies (ΔH_{gel}) associated with gelatinization endotherm varied between the starches from different sources. In wheat starch, onset (T_o), peak (T_p) and final (T_c) temperature values have been found to range between 46–52°C, 52–57°C and 58–66°C, respectively. T_o , T_p and T_c for potato starches range between 59–60°C, 63–64°C and 67–69°C, respectively. T_p gives a measure of crystallite quality (double helix length). Enthalpy gives an overall measure of crystallinity (quality and quantity) and is an indicator of the loss of molecular order within the granule (Tester & Morrison, 1990; Cooke & Gidley, 1992). ΔH_{gel} value for wheat and potato starches range between 14–17 J/g and 12–13 J/g, respectively. DSC endothermic peaks appear between 69 to 78°C, for corn and rice starches, while ΔH_{gel} values range between 9–11 J/g (Singh et al, 2003). The higher transition temperatures for corn and rice starch may be due to the more rigid granular structure and the presence of lipids. Because amylopectin plays a major role in starch granule crystallinity, the presence of amylose lowers the melting point of crystalline regions and the energy for starting gelatinization (Flipse et al., 1996). More energy is needed to initiate melting in the absence of amylose-rich amorphous regions (Kreuger et al, 1987). This correlation indicates that the starch with higher amylose content has more amorphous region and less crystalline, lowering gelatinization temperature and endothermic enthalpy (Sasaki et al., 2000). The gelatinization characteristics of intact A and B type starch granules in mature wheat endosperm have different temperature regimes (Eliasson & Karlsson, 1983; Soulaka & Morrison, 1985). Compared with the A-starch granules, B-granules started gelatinization at a lower T_o , but had higher T_p and T_c (Seib, 1994). A-granules have higher ΔH_{gel} value than B-granules.

Endothermic peak of starches after gelatinization and storage at 4°C appears at lower transition temperatures. Recrystallization of amylopectin branch chains has been reported to occur in less ordered manner in stored starch gels as it is

present in native starches. This explains the observation of amylopectin retrogradation endotherms at a temperature range below that for gelatinization (Ward et al, 1994). The variation in thermal properties of starches after gelatinization and during refrigerated storage may be attributed to the variation in amylose to amylopectin ratio, size and shape of the granules and presence/absence of lipids. The amylose content has been reported to be one of the influential factors on starch retrogradation (Gudmundsson & Eliasson 1990; Chang & Liu 1991; Baik et al 1997; Fan & Marks, 1998). Pan and Jane (2000) reported the presence of higher amount of amylose in large size maize starch granules. A greater amount of amylose has traditionally been linked to a greater retrogradation tendency in starches (Whistler & Bemiller, 1996), but amylopectin and intermediate materials also play an important role in starch retrogradation during refrigerated storage. The intermediate materials with longer chains than amylopectin may also form longer double helices during reassociation under refrigerated storage conditions. The retrogradation has been reported to be accelerated by the amylopectin with longer amylose chain length (Kalichevsky et al 1990; Yuan et al 1993). Shi and Seib (1992) indicated the retrogradation of waxy starches was directly proportional to the mole fraction of branches with degree of polymerisation (DP) 14–24, and inversely proportional to the mole fraction of branches with DP 6–9. The high rate of branches with DP-20–30 or DP \geq 35 has been requested to uncleave the retrogradation enthalpy (Sasaki & Matsuki, 1998). The low degree of retrogradation for waxy starches has been attributed to the high proportion of short chain branches of DP 6–9 (Lu et al., 1997). Using SAXS and WAXD simultaneously during gelatinization in water, together with small angle neutron scattering (SANS), it has been possible to probe the processes that occur at both the molecular and supramolecular length scales (Donald, 2001).

4. ENZYMATIC DIGESTIBILITY OF STARCHES

Starch is hydrolyzed to glucose, maltose and malto-oligosaccharides by α - and β -amylase and related enzymes. Glucoamylase, an exo-acting hydrolase, hydrolyses α -(1 \rightarrow 6) branching points, converting starch completely to glucose (Tester et al, 2004). Enzymatic hydrolysis of native starches at low temperature leads to the formation of pitted or porous granules, which could find useful applications in the food, cosmetic and pharmaceutical industries (Morelon et al, 2005). High amylose maize and legume starch granules have unique properties imparting resistance to digestive enzymes. Resistance is probably related to the crystalline order or packing of the glucan chains of amylose and amylopectin. Raw potato starch is an enzyme-resistant starch which is associated with the large granule size, higher phosphate content, B-type crystalline, different chain length and chain length distribution, as well as different molecular weight and weight distribution, as compared to normal cereal and other starches (Jane et al, 1997). However, when the potatoes are cooked for consumption, the starch is gelatinized and becomes susceptible to hydrolysis by α -amylase (Englyst & Cummings, 1987).

Significant differences exist among the hydrolysis rate values for different starches. These differences could be attributed to the interplay of many factors such as starch source, granule size, amylose/amylopectin ratio, extent of molecular association between starch components, degree of crystallinity and amylose chain length (Tester et al, 2004; Hoover & Sosulski, 1985; Ring et al, 1988; Jood et al, 1988; Dreher et al, 1984). The presence of pores on the granule surface may affect the digestibility of starches. Starch granule size has been reported to affect the digestibility of starches (Svihus et al, 2005; Chiotelli & Meste, 2002). The susceptibility of starches towards enzymatic hydrolysis has also been suggested to be affected by the starch granule specific surface area, which may decrease the extent of enzyme binding; and ultimately result in less hydrolysis in large granules than that in small granules (Tester et al, 2004; Cottrell et al, 1995).

5. CHEMICAL MODIFICATION OF STARCHES

Starches from various plant sources, such as wheat, maize and rice, have received extensive attention in relation to structural and physico-chemical properties (Takeda & Preiss, 1993). Limitations like low shear stress resistance, thermal resistance, thermal decomposition and high retrogradation of native starches limit their industrial applications. These shortcomings can be overcome by chemical and physical modification of starches (Fleche, 1985). There are several literature reports describing the use of chemically modified starches for drug delivery systems (Chakraborty et al, 2005). Epichlorohydrin cross linked high amylose has been used for the controlled release of con-tramid (Lenaerts et al, 1998). A complex of amylose, butan-1-ol, and an aqueous dispersion of ethylcellulose has been used to coat pellets containing salicylic acid to treat colon disorders (Vandamme et al 2002). The modified starches generally exhibit better paste clarity, stability and increased resistance to retrogradation (Agboola et al, 1991). In chemical starch modification, cross-linking and substitution are used to produce modified starches with desired applications. For example, acetylation of starches is an important substitution method that has been applied to the starches that impart the thickening during many food and non food applications. Cross-linked starches have been used as food additives for a long time because of their non-toxicity and low cost. Cross-linking is generally carried out by treating the granular starch with multi-functional reagents that form either ether or ester inter-molecular linkages between hydroxyl groups on the starch molecules (Rutenberg & Solarek, 1984; Wurzburg, 1986). Sodium trimetaphosphate (STMP), monosodium phosphate (SOP), sodium tripolyphosphate (STPP), epichlorohydrin (EPI), phosphoryl chloride (POCl_3), a mixture of adipic acid and acetic anhydride, and vinyl chloride are the important food grade cross-linking agents (Wu & Seib, 1990; Yeh & Yeh, 1993; Yook et al., 1993; Woo & Seib, 1997). STMP has been reported to be an effective cross-linking agent at high temperature with semi-dry starch and at warm temperature with hydrated starch in aqueous slurry (Kerr & Cleveland, 1962). EPI is poorly soluble in water and partly decomposes to glycerol, and also EPI cross-links are

likely to be less uniformly distributed than STMP ones (Shiftan et al., 2000). POCl_3 is efficient in aqueous slurry at $\text{pH} > 11$ in the presence of a neutral salt (Felton & Schopmeyer, 1943). Therefore, the cross-linking agent greatly determines the change in functional behaviour of the modified starches. Starch phosphates have been reported to give clear pastes of high consistency, and are classified into two groups: monostarch phosphates and distarch phosphates (cross-linked starches). Monostarch phosphates (monoesters) can have a higher DS than distarch phosphates (diesters) as even a very few cross-links (in the case of diesters) can drastically change the paste and gel properties of the starch. Starch phosphates are prepared by reacting starch with salts of ortho-, meta-, pyro-, and tripolyphosphoric acids and phosphorus oxychloride (Paschall, 1964; Nierle, 1969). Lenaerts et al (1991) suggested the use of cross-linked starches as an excipient for the production of controlled release solid oral dosage forms of drugs. Drug release rate of the high amylose starch excipients crosslinked using epichlorohydrin has been reported to increase with increasing cross-linking degree of the polymer (Lenaerts et al, 1992). The benefits of high amylose corn starch, gelatinized and treated with between 1 and 10% short chain cross-linking agents are: high active ingredient core loading, possibility to obtain quasi zero-order release profiles, and very low sensitivity of release profiles to manufacturing conditions such as i.e. tableting pressure (Lenaerts et al, 1992; Lenaerts et al, 1998; Mateescu et al, 1995). Pal et al (2006) prepared a starch based hydrogel membrane by crosslinking of polyvinyl alcohol with starch suspension using glutaraldehyde as a crosslinking agent, and proposed that the membrane had sufficient strength to be used as artificial skin.

Acetylated starches are produced with acetic anhydride in the presence of an alkaline agent like sodium hydroxide (Wurzberg 1978). The acetylation of starches depends upon factors such as starch source, reactant concentration, reaction time and pH. The extent of physicochemical property changes in the acetylated starch compared to the native starch is proportional to the degree of acetylation or degree of C=O substitution incorporated into the starch molecules (Phillips et al, 1999). The degree of acetylation in chemically modified starches is calculated by wet chemistry methods that involve separation and titration methods. The wet chemistry methods assume that the modified starch samples have been purified and are free of any residual compounds that could interfere with the titration used to measure the degree of acetylation (Phillips et al, 1999). Infrared and Raman spectroscopy have been recognized as powerful analytical techniques in the industry for many years (Phillips et al, 1999) and can be used to study the level of acetylation in different starches. The methods involve the calibration of a curve for the level of acetylation versus the intensity ratio of the C=O stretch Raman band to a C-C stretch Raman band. The intensity of the Raman peaks increases linearly with the amount of compound present in the sample (Hendra et al, 1991). Betancur et al (1997) studied the physico-chemical, rheological and functional properties of acetylated *Canavalia ensiformis* starch and reported that starch acetylated with 10% acetic anhydride at pH 8.0–8.5 for 30 minutes reached 2.34% acetyl value and compared to native starch these acetylated starches showed lower gelatinization

temperatures, an increased paste and gel clarity, solubility, swelling power and viscosity. Starch has also been used as a carrier for phenethylamines (Weiner et al, 1972), estrone (Won et al, 1997), and acetylsalicylic acid (Laakso et al, 1987). Won et al (1997) prepared bromoacetylated starch using bromoacetyl bromide to provide more reactive sites for coupling of bioactive estrone and a suitable spacer between the drug carrier and the hormone. The starch-estrone conjugate was then prepared by reacting the modified starch with the sodium salt of estrone. The structures of the modified starch and the conjugate were predicted using FTIR, ^1H NMR, ^{13}C NMR, and UV. It would be beneficial if starch esters used as matrices for drug delivery could be prepared so that they are modified at selected positions of the glucose residues (i.e., at only the primary or secondary positions). This is difficult because of the presence of three hydroxyl groups per glucose residue each in different chemical environments. Also, starch should be solubilized in polar aprotic solvents to achieve homogeneous modification (Chakraborty et al, 2005). Chakraborty et al. (2005) carried out the selected esterification of starch nanoparticles using *Candida antarctica* Lipase B (Cal-B) as a catalyst. Starch nanoparticles were treated with vinyl stearate, ϵ -caprolactone and maleic anhydride at 40°C to form starch esters with varying degrees of substitution.

6. CONCLUSIONS

Progress in understanding the factors affecting starch functionality, and the results of chemical modification, has enabled the starch industry to produce starches with desired and improved functional characteristics. The physico-chemical characteristics of starches such as granule size distribution, amylose to amylopectin ratio and lipids content provide a crucial basis for understanding the underlying mechanisms of starch functionality in different systems. Recent advances in the field of starch chemistry and technology reflect the potential of starches isolated from various botanical sources for use in biomedical and pharmaceutical applications.

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