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Review

A review of polyvinyl alcohol derivatives: Promising materials for pharmaceutical and biomedical applications

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In recent years, a technological breakthrough in the pharmaceutical and biomedical fields have been reflected in the development of more complex, safe and effective dosage forms to improve the administration, delivery, disposition and stability of drugs, as well as at creating more biocompatible and biodegradable materials. As a result, modified release devices and functional coatings which improve the effectiveness and efficacy of drugs have been generated. This advancement has been achieved by physical or chemical modification of natural or semisynthetic polymers which stabilize and protect drugs against harsh environmental factors. Therefore, the development of novel excipients with a high functionality and robustness has become an important quest. Among these materials, polyvinyl alcohol is one of the most versatile and biocompatible, since by chemical or physical modification its properties are modulated, improving drug stability, drug targeting, and ensures patient compliance. Freezing-thawing cycles, heat treatment and formation of composites are the most significant physical modifications to improve the performance of polyvinyl alcohol. On the other hand, the chemical modifications by cross-linking with aldehydes, carboxylic acids, sodium tetraborate, epichlorohydrin have enhanced the physical and mechanical properties, such as the oil sorption ability, oxygen and waterproof characteristics, mechanical strength, drug diffusion and rate of swelling.

Key words: Polyvinyl alcohol, composites, crosslinking, pharmaceutical and biomedical applications.

INTRODUCTION

Polyvinyl alcohol (PVA) is a semicrystalline synthetic polymer (Figure 1), which is soluble in water, slightly soluble in ethanol and insoluble in other organic solvents (Saxena, 2004; Kadajji and Betagari, 2011; Song and Kim, 2004). It is tasteless, odorless, has good mechanical properties (that is, tensile strength), a high ability to form films and a good compatibility and biodegradability in human tissues and fluids (Tsujiyama et al., 2011; Moore et al., 1998;

Chandra and Rustgi, 1998; Chiellini et al., 2002). PVA is commercially available in grades according to the degree of hydrolysis and viscosity (Goodship and Jacops, 2005). It is also available in combination with other materials for specific applications (Chen et al., 2007; Rahman et al., 2010; Murphy et al., 2012; Muñoz et al., 2011; Briscoe et al., 2000; Jagur and Grodzinski, 2010).

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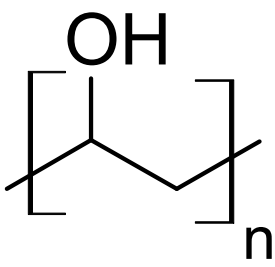

Figure 1. Monomeric structure of polyvinyl alcohol.

Partially hydrolyzed grades range from 84.2 to 89.0% (viscosity, 3.4 to 52.0 mPa.s), the moderately hydrolyzed grade ranges from 92.5 to 96.5% (viscosity, 14.5 to 30.0 mPa.s), and the completely hydrolyzed grade ranges from 98.0 to 99.0% (viscosity, 4.0 to 60.0 mPa.s) (Goodship and Jacops, 2005). Due to its poor gastrointestinal absorption and high LD_{50} (15 to 20 g/kg), it is considered as non-toxic by oral administration. Therefore, it does not accumulate in the body after oral administration, presents no adverse effects, it is not mutagenic, making it suitable for pharmaceutical and biomedical applications (DeMerlis and Schoneker, 2003; Food and Agriculture Organization (FAO), 2004).

Since its discovery, this material has been used for many applications. For instance, in the production of composites reinforced with polyester or cellulose to give mechanical strength to carbon nanotubes (Zuber et al., 2012; Zia et al., 2012; Guanghua et al., 2008). In the biomedical field (Baker et al., 2012; Jiang et al., 2011; Pal et al., 2009), it has been employed to develop a cross-linked PVA tubular graft with sodium trimetaphosphate (STMP) as a crosslinker. Vascular grafts were implanted in rats for one month and showed excellent performance. The PVA film showed a wall thickness comparable to that of human artery (344 ± 13 µm vs. 350 to 710 mm, respectively). Further, it showed a higher compliance than saphenous vein (3.0 vs. 0.7 mm). Likewise, suture retention (140 g) and burst pressure (507 mm Hg) were better than saphenous vein (1680 to 2273 mm Hg) (Chaouat et al., 2008).

Other studies suggest the use of a PVA hydrogel as an alternative synthetic articular cartilage to alleviate pain and/or correct joint deformity due to the high water content and high-creep resistance. In this case, the PVA (average molecular weight of 115,000 g/mol) annealing rendered a material with decreased water content, high crystallinity, strength and toughness, but a decreased lubricity due to a pore size reduction. In these studies, freezing-thawing cycles along with the addition of poly(ethylene glycol) and poly(acrylamide) minimized water loss and increased the lubricity of the hydrogel (Bodugoz et al., 2008, 2009). Further, cartilage regeneration has been achieved using the freeze-thawing technique, rendering mechanical and water loss properties similar to the reference cartilage (Chaouat et al., 2008; Baker et al., 2012). In other studies, the insulin-like growth factor-1 (IGF-1) was encapsulated in poly(lactic-co-glycolic) acid (PLGA) microparticles and dispersed in PVA (99% hydrolyzed, 99 kDa) hydrogels followed by two freezing-thawing cycles. The *in vitro* bioactivity was tested in Chondrocytes isolated from knee joints of a 2 week-old piglet. The IGF-1 release was sustained over 6 weeks *in vitro*. This controlled release enhanced cartilage formation and cartilage-hydrogel integration (Spiller et al., 2012).

On the other hand, the pharmaceutical applications of PVA include the inhibition of crystal transformation of drugs such as carbamazepine and caffeine and which takes place during wet granulation. If it is used as granulating liquid, it prevents nucleation, slow crystal growth and removes water excess by absorption (Mansour et al., 2010; Gift et al., 2009). Further, PVA has been used to prepare solid dispersions to improve the solubility of drugs such as escitalopram oxalate. This technique implies the dispersion of a drug in aqueous medium followed by drying. The best results were obtained for a 1:4 PVA:urea ratio (Purohit and Patel, 2012). Other studies suggest PVA as a suitable coating agent for tablets at a 2% level. As a result, compacts showed better mechanical properties and increased disintegration time (180 s) (Qiao et al., 2010; Zhang et al., 2007; Hernández et al., 2007; Fujii et al., 2008).

PVA is not prepared by polymerization of the corresponding monomer, but by indirect methods. This is due to the unstable nature of vinyl alcohol becoming acetaldehyde and thus, it does not exist in a free form. PVA is produced by various methods (Haweel et al., 2008), but the most widely used is that developed in 1924 by the German scientists WO Herrmann and Haehnel (Herrmann and Haehnel, 1924) who obtained PVA by free radical polymerization of vinyl acetate forming an intermediate product called polyvinyl acetate followed by hydrolysis of the acetate group with a strong base in presence of methanol (Figure 2). In this case, vinyl acetate is polymerized to polyvinyl acetate under reflux followed by addition of a free radical initiator such as potassium persulfate at 80°C for 40 min. The hydrolysis of the acetate group involves a partial or total replacement of the ester group of vinyl acetate by hydroxyl groups, under alkaline methanolic conditions. Polyvinyl alcohol is then precipitated, washed and dried (Scott and Bristol, 1941). The physicochemical properties of the resulting PVA depend on the length of the polymer chain (polymerization degree) and the hydrolysis rate of the parent material (polyvinyl acetate) (Rahman et al., 2010).

The physical and functional properties of the polyvinyl alcohol are affected by the reaction conditions and degree of hydrolysis of polyvinyl acetate (Goodship and Jacops, 2005). Depending on the degree of hydrolysis,

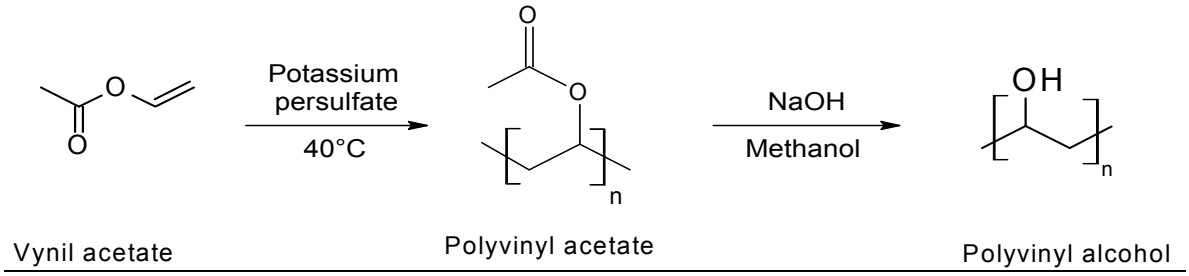

Figure 2. Conventional method for the synthesis of PVA.

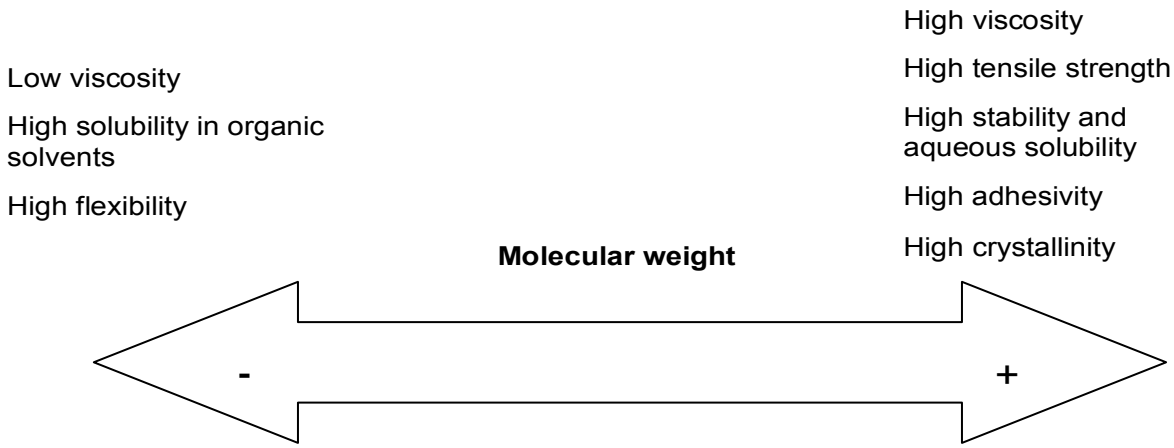

Figure 3. Effect of molecular weight on the physical properties of PVA.

PVA is classified into fully hydrolyzed and partially hydrolyzed grades. The partially hydrolyzed grade (87 to 89%) contains residual acetate groups which reduces the degree of crystallinity, lowers the melting point, gives a greater aqueous solubility, increases flexibility and increases its ability to adhere to hydrophobic surfaces. Conversely, highly hydrolyzed grades (91 to 99%) have a high degree of crystallinity (40 to 50%), a low aqueous solubility (require 91 to 96°C for 30 min for a complete dissolution), improve stability in presence of organic solvents and increase tensile strength and adhesion onto hydrophilic surfaces (Tang and Alavi, 2011). There is also an inverse relationship between the molecular weight and degree of hydrolysis of this polymer (Figure 3). Another important property is the polydispersity index. This index, measures the distribution of molecular mass in a sample. The PVA synthesis pathway plays a major role on its molecular weight distribution. For instance, a polydispersity index from 2 to 2.5 is common for commercial grades. Deviations from this range might affect its properties including crystallinity, adhesion, mechanical strength and diffusivity (Hassan and Peppas, 2000).

The high reactivity of PVA allowed for an expansion of its applications in several scientific fields, including the biomedical and pharmaceutical. In order to improve the performance of PVA, a chemical functionalization and formation of composites have been developed.

PHYSICAL MODIFICATIONS

The physical modification is the preferred way to obtain a PVA intended for pharmaceutical and biomedical applications since the chance to find toxic residual crosslinking agents is avoided (Kenawy et al., 2010; Hassan and Peppas, 2000; Guanghua et al., 2008). These modifications cause a molecular rearrangement, forming more crystalline regions. The main physical modifications reported are as follows:

Freeze-thawing

In this technique PVA is submitted to freezing and thawing cycles forming new crystalline regions (Bolto et al., 2009; Hickey et al., 1995). Further, this technique has been used to form hydrogels in combination with polyacrylic acid (PAA) (Figure 4) to achieve a pH-dependent aspirin (ASA) release. At pH of 4.0 the polymer has the largest swelling, whereas at pH of 9.0 it shows a minimal swelling. This hydrogel is prepared by

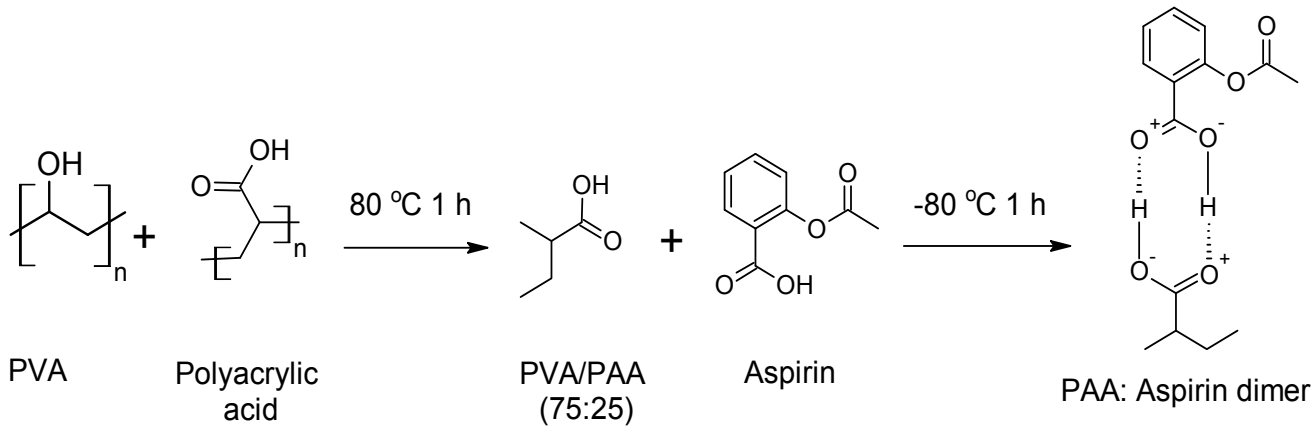

Figure 4. Reaction between PVA, PAA and ASA.

dissolving PVA (MW, 146 to 186 kDa and saponification degree, 98 to 99%) and PAA in water under constant stirring for 1 h and 80°C. The optimal PVA to PAA ratio is 75:25% (Gann et al., 2009). In this case, a physical blend is produced and then added to an aqueous solution of ASA (0.5 to 1% w/v). This solution is then submitted to freeze-thawing cycles to form a hydrogel. Thus, freezing is conducted at -80°C followed by thawing at room temperature. These cycles can be repeated up to 10 times avoiding the hydrolysis of the drug since a dimer between PAA and aspirin is formed.

Annealing

As stated earlier, this process involves heating of an aqueous dispersion of polymer followed by a slow cooling until a complete removal of solvent is achieved. Usually, this treatment renders semipermeable membranes with many chain scissions. Usually, if this process is conducted alone, it is not reproducible due to the heterogeneous nature of the semicrystalline regions of the polymer produced leading to a membrane with diverse properties (Reid et al., 1959).

Irradiation

If an aqueous solution of PVA (100% hydrolyzed, 86000 MW) is irradiated, a semipermeable membrane is obtained. This membrane is capable of selectively retaining salt independent of the media temperature. Irradiation is performed with cobalt-60 at room temperature with doses in the range 0.5 to 40 Mrad and at a rate of 153 krad/h. The ability to retain salt of this modified material is higher compared to the unmodified PVA. On the contrary, water permeability is higher for the unmodified material (Katz and Wydeven, 1981).

Composites

A composite is a homogeneous blend where interaction forces are generated between two or more materials at the particle level rendering improved physicochemical properties. PVA in composites with other polymers such as starch, gelatin, polylactic acid and caprolactone showed better biodegradability and other physical properties such as tensile strength and adhesiveness (Yu et al., 2008; Goodship and Jacops, 2005; Chen et al., 1997; Zhao et al., 2010).

CHEMICAL MODIFICATIONS

Crosslinking is a multidirectional chain extension of polymers leading to the formation of network or branched structures. PVA functionalization by chemical modifications has become the preferred choice because of the similarity with the reactions of most organic polymers (Misha et al., 2011). Under this approach, PVA properties can be modified depending on the intended application. The great accessibility and reactivity of PVA is attributed to its geometric conformation and its interaction with the solvent used. In theory, all compounds capable of reacting with hydroxyl groups could be used as potential crosslinking agents for PVA (Gohil et al., 2006). If chemical agents are used to crosslink PVA, toxic residues could be present in the final product. These residues could have undesirable effects. Therefore, traces of these agents should not be present in a crosslinked product intended for biomedical and pharmaceutics applications (Hassan and Peppas, 2000).

Radical formation

This reaction involves a free radical generator to initiate the polymerization reaction. The free radicals are bonded to PVA, causing an internal polymerization, leading to an

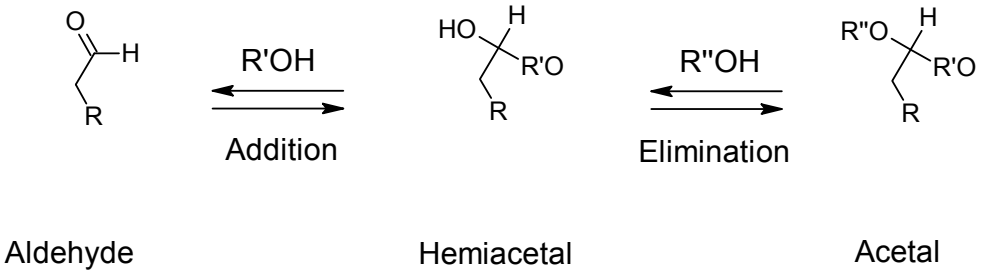

Figure 5. General mechanism for the reaction between aldehydes and alcohols.

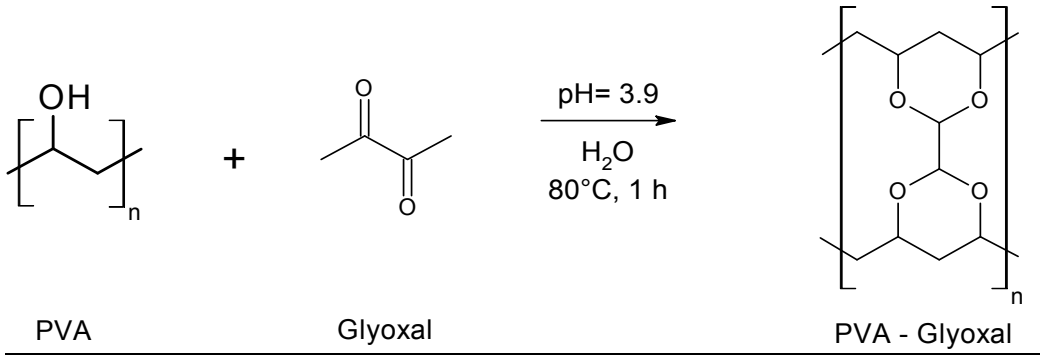

Figure 6. Crosslinking reaction between PVA and glyoxal.

increase in the molecular weight and consequently, an increase of its hydrophobicity (Lank et al., 1996; Bolton et al., 2009). This reaction is not suggested due to its complex nature and the latent presence of radicals in the final product which could have toxic effects.

Reaction with aldehydes

In general, the reaction between an aldehyde and an alcohol is carried out in acid media, producing a hemiacetal (obtained by nucleophilic addition). This is produced by an addition-elimination mechanism where a carbonyl group is formed followed by addition of alcohol developing intermediate specie (hemiacetal) which then becomes an acetal (Figure 5).

Reaction with dialdehydes

In general, the hydroxyl groups of PVA react with the aldehyde groups via acetal bond formation. This reaction happens twice for each aldehyde group present. The simplest case is the reaction with glyoxal (Figure 6). In this reaction, a solution of glyoxal and PVA (98 to 98.8% hydrolyzed, 61000 MW) is adjusted to a pH of 3.9 with a 1 M hydrochloric acid. The solution is then heated at 80°C for 1 h. The solution is allowed to cool down to room temperature, adjusting the pH to ~7.0 with sodium hydroxide. The final product is filtered, washed with acetone three times and dried in an oven at 60°C for 15 h. Characterization by infrared spectrophotometry shows typical bands of hydroxyl group of PVA at 3326 cm^{-1} and bands at 2941 and 2907, corresponding to asymmetric and symmetric stretching of the CH, respectively. The peaks at 1426 and 1330 cm^{-1} correspond to the bending vibration of CH and the band at 1094 cm^{-1} corresponds to the C-O stretching band (Zhang et al., 2010; Mansur et al., 2008).

A very common dialdehyde used as the crosslinking agent is glutaraldehyde (Figure 7). These reactions generate intra and intermolecular bonds. A PVA solution (87 to 89% hydrolyzed, 124000 to 186000 Dalton) from 5 to 15% is prepared and heated at 80 to 90°C to dissolve the polymer. The resulting product is water insoluble but disintegrates in aqueous media. This material is useful to prepare fibrous membranes (Wang and Hsiesh, 2009). Therefore, crosslinking of PVA with glutaraldehyde under acidic conditions results in a compound with excellent disintegrating properties of tablets as compared to commercial products such as Ac-Di-Sol®. The latter product is used as a superdisintegrant for the preparation of solid dosage forms (Patel and Vavia, 2010; Mansour et al., 2008).

Another case involves crosslinking of PVA with glutaraldehyde and chitosan to form hydrogels of N-(2-hydroxy) propyl-3-trimethylammonia-chitosan (HTCC) (Figure 8). This product has better swelling properties,

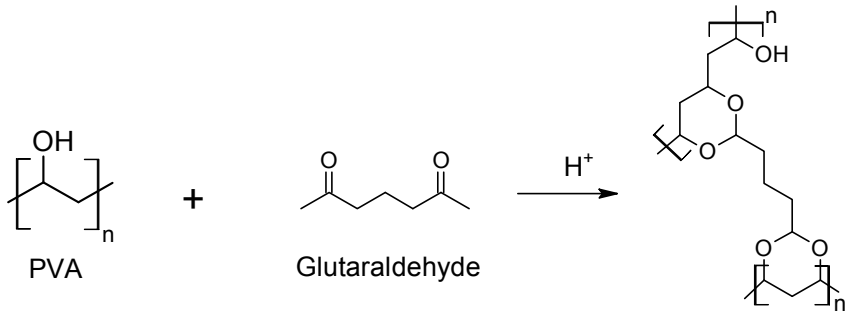

Figure 7. Crosslinking reaction of PVA with glutaraldehyde.

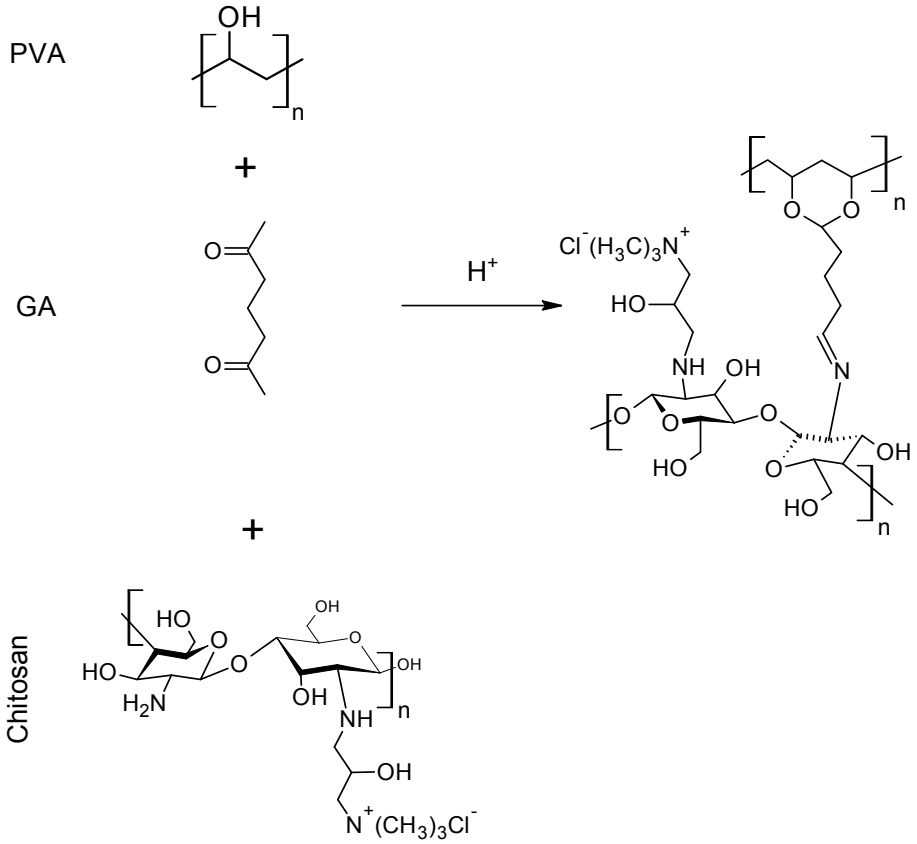

Figure 8. Crosslinking reaction among PVA, glutaraldehyde and chitosan.

degree of crosslinking and antibacterial properties as compared to the parent compounds. This makes it suitable for the production of bandages and modified release systems of drugs (Yu et al., 2011).

Reaction with polycarboxylic acids

The chemical reaction that occurs between a carboxylic acid and an alcohol leads to the formation of an ester and this reaction is known as esterification. The reaction is catalyzed in an acidic media and generates water as a by-product (Figure 9). A typical example of PVA esterification with lactic acid occurs in an aqueous media of a low viscosity. In this case, an intermediate if formed which upon further water addition forms the PVA-lactate ester. The excess water is then removed by heating between 75 to 175°C with subsequent curing (Figure 10). Further, the presence of oxygen in the reaction is not desirable since it could induce degradation. The material thus obtained is useful for the manufacture of resins, membranes, fibers and hot-melt (Han et al., 2003) adhesives (Spinu, 1994).

Maleic acid also crosslinks PVA at a high concentration

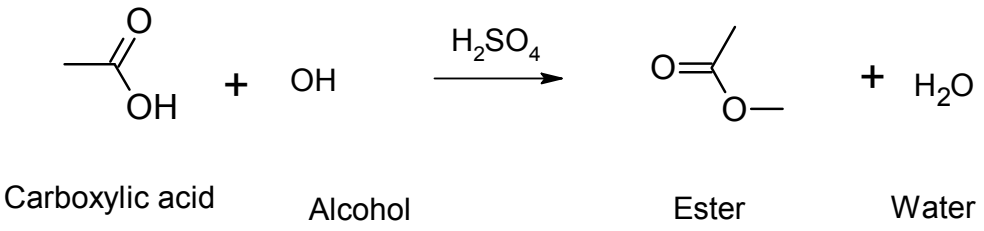

Figure 9. General reaction between a carboxylic acid and alcohol.

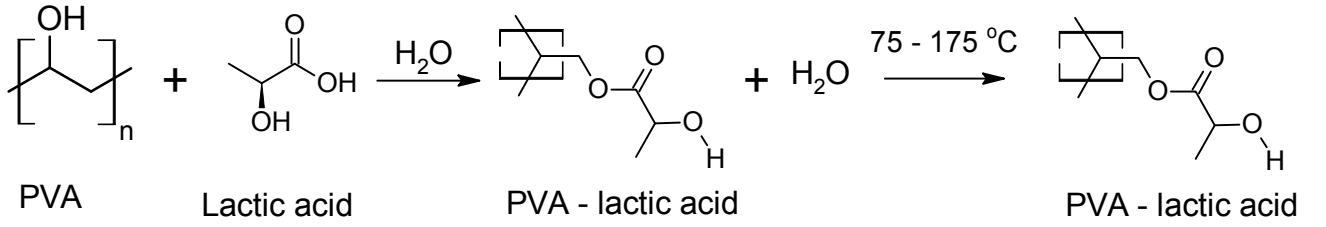

Figure 10. Esterification reaction between PVA and lactic acid.

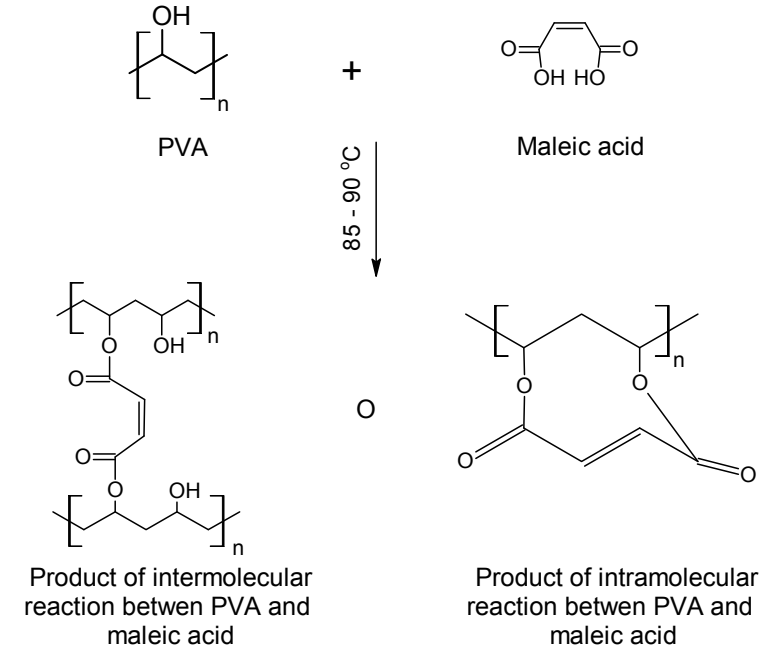

Figure 11. Reaction between PVA and maleic acid.

(30 to 40%) and high temperature (140°C), using a curing time of 90 min (Figure 11). Films thus formed have a higher swelling index and chemical stability than the original material (Gohil et al.; 2006; Riyajan et al., 2009). Sulfosuccinic acid (SSA) also reacts with PVA to form a material useful for the preparation of electrolytic membranes. Sulfosuccinic acid acts as intermolecular crosslinking agent enhancing proton conductivity and reducing methanol permeability. The reaction consists of two steps. The first step is performed at 70°C under a continuous stirring for 6 h (Figure 12), followed by casting the solution into molds and drying to obtain thin membranes (PVA/SSA). In a second step, these membranes are treated with a solution of glutaraldehyde (GA) in acetone where aldehyde groups of GA react with the hydroxyl groups of PVA in the presence of sulfosuccinic

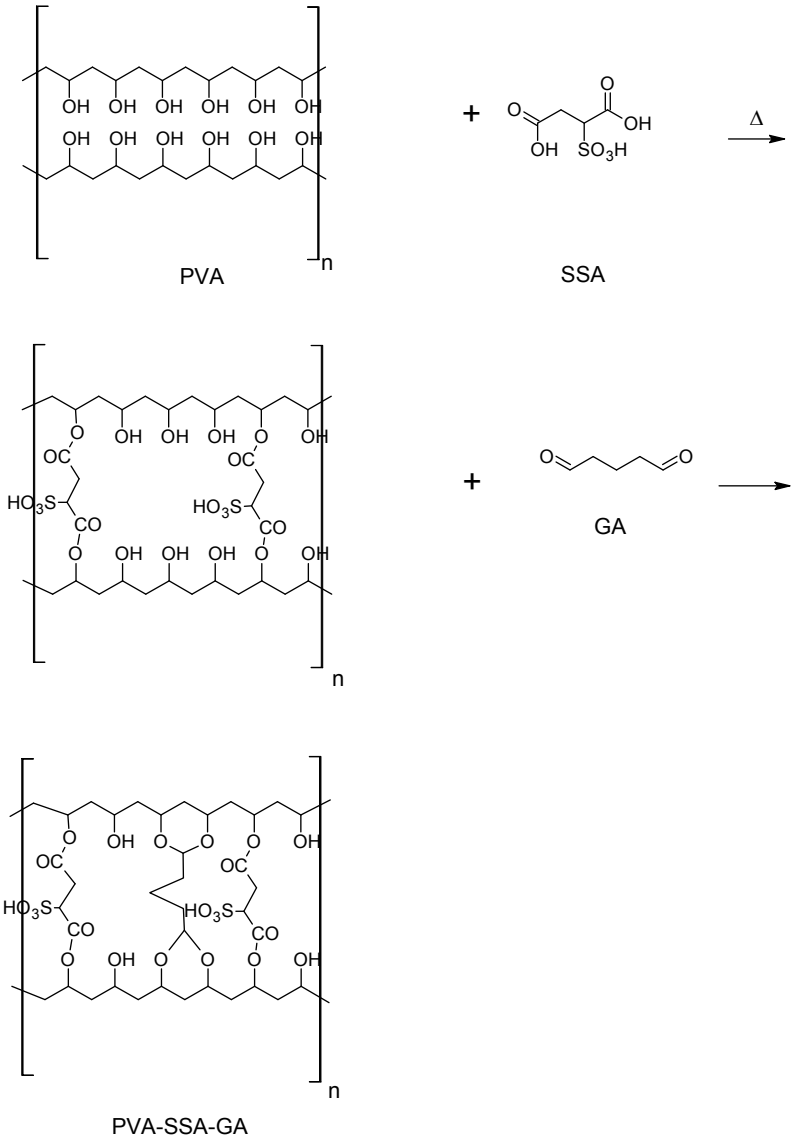

Figure 12. Reaction of PVA with SSA and GA.

acid (Tsai et al., 2010).

PVA is also esterified with acrylic acid and methacrylic acid in the presence of acetic acid for 24 h at 40°C. Ultraviolet radiation can also be used as a catalyzer to improve the reaction yield. Furthermore, small variations in the amount of acetic acid, acrylic or methacrylic acid, water and PVA can be varied to change the composition of the x, y, z segments of the resulting polymer (Figure 13). The material thus obtained is used for the production of implants, hydrogels and the manufacture of contact lenses (Muhlebach et al., 1997).

Acid-catalyzed dehydration

A typical dehydration reaction occurs when coating a membrane of polyethersulfone (PES) or polytetrafluoroethylene with a solution of PVA in the presence of sulfuric acid at high temperatures (150°C). The wafer thus obtained is then coated with a solution of polyacrylic and sulfuric acids (50:50 ratio) followed by heating at 160°C. As a result, a multilayer composite membrane is obtained, which is useful to retain a high salt concentration at low flow rates (Bolto et al., 2009).

Reaction with sodium tetraborate

Sodium tetraborate reacts with PVA forming a cyclic compound (Figure 14). The reaction is very sensitive to the media pH and the concentration of sodium tetraborate (Loughlin et al., 2009).

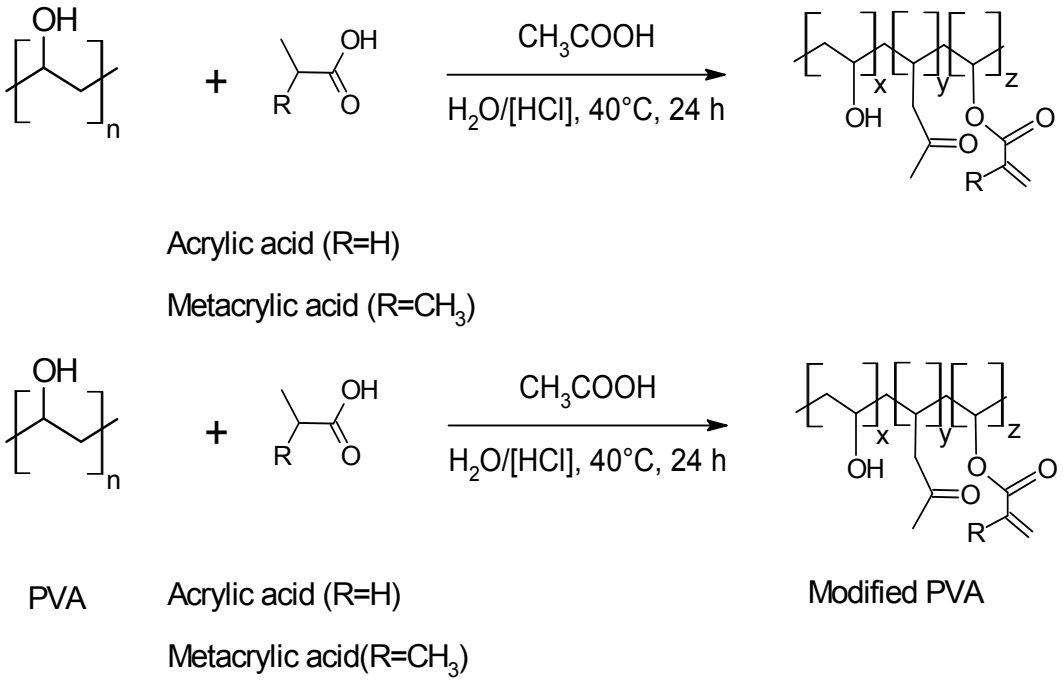

Figure 13. PVA esterification with acrylic acid or methacrylic acid.

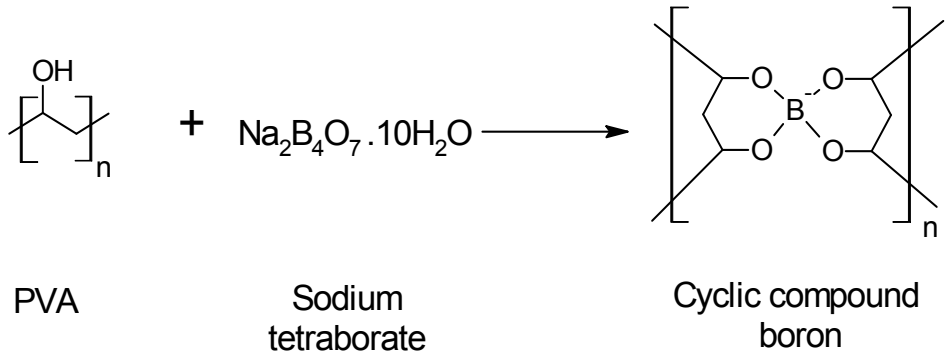

Figure 14. PVA reaction with sodium tetraborate.

Complexation reaction

Another crosslinking reaction involves the interpolymer complexation between the poly (methyl vinyl ether-co-maleic acid) and PVA. The resulting material has a reduced volume so it could serve as a coating material providing a better oxygen barrier than the individual components (Labuschagne et al., 2008).

Reaction with epichlorohydrin (EPC)

The crosslinking reaction between Xanthan (Xan) and PVA in presence of EPC occurs under basic conditions. As a result, a superabsorbent hydrogel with more than 95% swelling is formed (Gulrez and Al-Assaf, 2011). The increase of temperature, reaction time and PVA level also increase the hydrogel swelling degree. The process is performed by mixing ~14% w/v of each polymer (88% hydrolysis grade for PVA or Xan) with a known amount of sodium hydroxide and EPC. The resulting slurry is treated at different temperatures (40 to 80°C) and reaction times (9 to 24 h) to obtain a thin film. In order to remove the excess of sodium hydroxide, the sodium chloride formed and the unreacted polymer, the membrane is washed several times with distilled water at a temperature of 60°C. Finally, the membranes are washed with acetone to remove traces of EPC and dried at 50°C (Figure 15). The resulting hydrogel shows important drug release properties (Alupei et al., 2002).

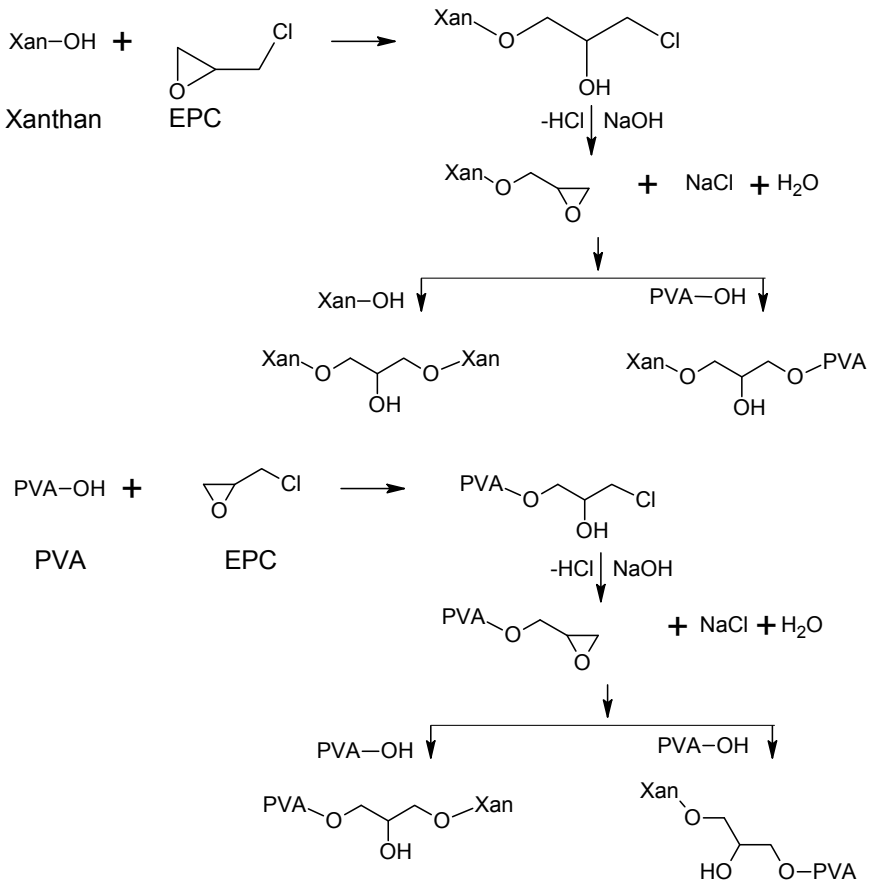

Figure 15. Reaction of PVA with Xanthan and EPC.
Source: Alupei et al., (2002).

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