Review Article

FUNCTIONALIZATION AND CROSSLINKING OF MICROCRYSTALLINE CELLULOSE IN AQUEOUS MEDIA: A SAFE AND ECONOMIC APPROACH

John Rojas[1*], Eduardo Azevedo[2]
[1]Department of Pharmacy, School of Pharmaceutical Chemistry, The University of Antioquia, Medellín, Columbia.
[2]Department of Pharmacy, College of Pharmacy, The University of Iowa, Iowa City, IA, USA.
*Corresponding author's E-mail: jrojasca@gmail.com

Accepted on: 19-02-2011; **Finalized on:** 28-04-2011.

ABSTRACT

Cellulose is the most abundant biopolymer in nature and has a broad range of applications in the pharmaceutical, food and biomedical fields. This review article describes the functionalization conditions, crosslinking agents, reaction pathways and the resulting physicochemical and mechanical properties of functionalized cellulose derivatives. The discussion is focused on aqueous reactions and crosslinking agents that render a material of low toxicity and better biodegradability with a broad range of applications. Crosslinking agents such as dialdehydes (glyoxal and glutaraldehyde), acetals (1,1,4,4-tetramethoxybutane and 1,1,5,5-tetramethoxybutane), polycarboxylic acids (acrylic, maleic, polymaleic, succinic polyitaconic and citric acids), phosphorus derivatives (phosphoric acid and triethyl phosphate), silica derivatives (tetraethoxysilane), epichlorohydrin and polyepichlorohydrin were selected for the discussion since they present a low toxicity risk and are able to react efficiently with cellulose rendering products with unique properties.

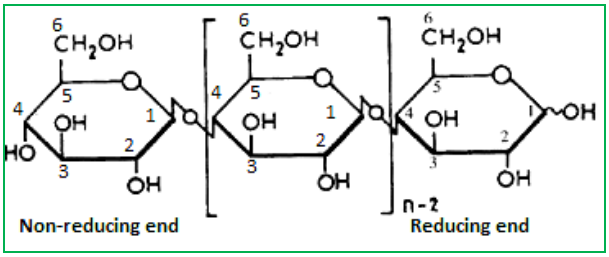
Keywords: Microcrystalline cellulose, functionalization, crosslinking agents, toxicity.

INTRODUCTION

Cellulose is the most abundant, renewable and biodegradable polymer in nature and along with its derivatives has been widely used in textiles (cotton, linen, viscose, and acetate), plastics (cellophane and celluloid), paper, food (thickener agent, enhancer of organoleptic properties, texture modifier, etc) and as a pharmaceutical additive (filler, binder, disintegrant, film maker adhesive, etc). Cellulose is made of poly (β-1,4-D-anhydroglucopyranose) units. The reactivity of the hydroxyl groups at positions 2, 3 and 6 of the glucosyl units offers a variety of possibilities for making useful derivatives from this raw material (Figure 1). The C-6 OH group is the most reactive (linked to a primary carbon), the C-2 OH is the less reactive and the C-3 OH is the weakest for bending due to the formation of hydrogen bond with the neighboring oxygen molecule[1]. This particular chemistry allows for derivation resulting on a wide range of chemical entities with a high variety of water solubility, porosity, mechanical strength, swelling ability and stability according to temperature and pH of the reaction [2].

Functionalization of cellulose is of a great scientific significance and proceeds mainly through esterification and etherification reactions involving the above mentioned hydroxyl groups. The ester type derivatives include cellulose acetate (by reaction of cellulose with acetic acid and anhydride in the presence of sulfuric acid), which has the ability to form films, and cellulose nitrate (by reaction of cellulose with nitric acid), which is mainly used to produce lacquers. Similarly, cellulose ethers have been successfully produced, where ethylcellulose (produced by the reaction of alkali cellulose and ethyl chloride) has been used mainly as a thermoplastic material for compact coating and controlled release of drugs, which makes it the most important cellulose ether derivative. Other cellulosic ethers are methylcellulose (produced by heating alkali cellulose with methyl chloride), hydroxypropylcellulose (produced by reaction of alkali cellulose with propylene oxide) and carboxymethyl cellulose (produce by alkali-catalyzed reaction of cellulose with chloroacetic acid)[3]. Compared to the parent microcrystalline cellulose material, most of these ether derivatives are more reactive, water soluble, biodegradable and perhaps, as safe as cellulose. In general, these cellulose ethers are very important because they can be used for pharmaceutical applications and in the food industry as gelling, foaming and binding agents. The goal of this paper is to review and and describe the different crosslinking agents and reactions for cellulose functionalization which render non-toxic products with possible pharmaceutical and food applications

Figure 1: Schematic of a cellulose chain.



Traditionally, most of the functionalization reactions of cellulose are carried out using harmful solvents such as dimethyl sulfoxide (DMSO), formaldehyde, dimethyl formide (DMF), tetrahydrofuran (THF), ethylamine, etc.

Likewise, toxic agents such as organic halides, dimethyloldyloldyhydroxyethylenenurea (DMDHEU), 1,2,3,4-butanetetratcarboxylic acids, polyacrylates, acrylamide, maleic acid, formaldehyde, dimethylurea, etc, limit their applications in the pharmaceutical field since elimination of by-products has always been a concern[4]. Another reported unsafe method for cellulose functionalization involves methyl metacrylate (MMA), LiCl, and o-xylene[5]. The eventual toxicity due to the presence of the residual crosslinking agent, or to the unwanted reaction between the tissue and the crosslinking agent once the product is ingested and degraded is also a concern[6]. For instance, alkyl halides are proved to be toxic and carcinogenic to humans, and can potentially cause reproductive and developmental neurotoxicity. Even if the cellulose derivative is not intended for clinical applications, possible residual crosslinking agents present in fabrics and absorbent papers might lead to allergies and contact dermatitis[7]. However, for cellulose derivatives, traces of toxic precursors or solvents might hinder and fringe the broad range of possible applications. For this reason, it is important to develop a series of alternative, less toxic and safer crosslinking agents. These include dialdehydes (except for formaldehyde), epichlorohydrin, adipic anhydride and citric acid, which replace the traditional toxic and non biodegradable crosslinking materials and at the same time, render the expected functional properties.

DIALDEHYDES AS CROSSLINKING AGENTS

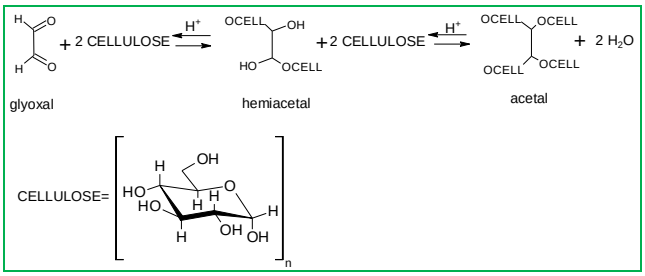
Traditionally, formaldehyde and dimethylol methyl carbamate (DMMC) dissolved in either phosphoric or sulfuric acid have been used as a model crosslinking agents for cellulose, rendering a product with excellent applications in the textile industry since the resulting fibers possess higher wrinkle recovery than the parent material[8]. Formaldehyde is absorbed in the cellulose fibers without the presence of catalyst because of the ease of formation of the hemiformal product. However, according to Ballantyne and Jordan (2001), formaldehyde is slowly released from the fibers making it non-suitable for pharmaceutical applications.

Recent efforts to develop formaldehyde-free agents have led to the use of less toxic dialdehydes such as glutaraldehyde and glyoxal, which can be used in materials which are not intended for human implants. In general, dialdehydes impart resilience, thermal stability and improve the mechanical properties of cellulose fibers[9]. A major consequence of this crosslinking reaction is a reduction of the water absorption capacity of the crosslinked product compared to the parent cellulose. Briefly, cellulose is soaked in the dialdehyde solution at pHs between 3 and 5 in the presence of a catalyst, followed by curing, washing and drying. Hurwitz suggested in 1958 that the degree of cellulose crosslinking is independent of the curing time and curing temperature. Hurwitz also claimed that treatment either at 70°C for 7 min or at 160°C for 3 min at a pH of 5, using $MgCl_2.6H_2O$ as a catalyst, gave comparable results. The curing step guarantees the absorption of the dialdehyde onto the structure of cellulose improving the crosslinking efficiency. However, if the curing step is not employed, the crosslinking efficiency is too low or negligible[10]. It is well known that the dialdehyde reacts with the hydroxyl groups of cellulose to form an acetal under a catalyst of Lewis acid. The acetal formed is stable under neutral and alkaline conditions. The work of Guozhong et al. (2001) shows that the aldehyde absorption might happen by the formation of the cellulose hemiacetal preventing the aldehyde volatilization from the fibers before the crosslinking reaction happens, and at the same time, keeping the aldehyde in the reactive sites of cellulose. Since crosslinking occurs in the amorphous regions, the aldehyde treatment produces little change in the crystallinity and no change in the cellulose crystal lattice. According to Fujimura and Okamoto (2003), the drawback of this reaction is the stability of these cellulose derivatives because the reaction of dialdehydes with the hydroxyl groups of cellulose forms acetals which in turn, have different degrees of hydrolysis rate. The reaction efficiency increases steadily as the concentration of dialdehyde increases and is favored by high curing temperatures, probably due to the more available aldehyde groups for crosslinking[11].

Glyoxal

Glyoxal does not offer a toxicity issue since it is endogenously produced during the normal cellular metabolism by a multitude of enzyme-independent pathways, and it is metabolized by the glyoxalates enzymatic group. Kielhorn et al. (1992) reported that high concentrations of glyoxal, favors the acetylation of cellulose, which is reflected in a lower fiber strength and water sorption[12]. According to these authors, the curing conditions also contributed to acetylation as water and part of the glyoxal are evaporated during this step, which concentrates the glyoxal in the fibers and increases the acetylation degree. Higher curing temperatures favor acetylation. Thus, if different curing times are used, the one which gives the highest concentration of glyoxal determines the degree of acetylation. A typical reaction condition comprises a soaking time from 5 to 15 min, a glyoxal concentration between 6 to 12%, a curing temperature between 50 and 140 °C, a curing time from 5 to 60 minutes and the presence of 1% boric acid (catalyst). Since the acetal formation is reversible, the presence of an acid catalyst is a prerequisite for the reaction (Figure 2). However, Choi et al. (1999) claimed that the reaction mechanism between cellulose and glyoxal is more complex than the simple acetal development[13].

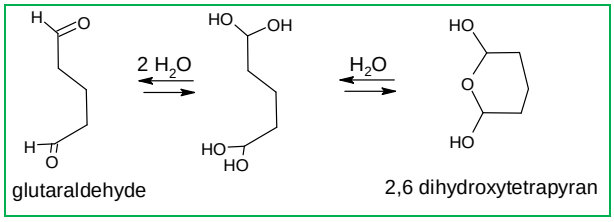
Figure 2: Mechanism of crosslinking of cellulose with glyoxal.



Glutaraldehyde

The main concern about the use of glutaraldehyde is the possible sensitization[14-16]. This material has been found appropriate to crosslink starch, dextran, chitosan, polyvinyl alcohol and cellulose[17]. Glutaraldehyde is present as a hydrate in water solution, improving the ability to crosslink cellulose. For instance, acetals of glutaraldehyde and cellulose could have a high resistance to hydrolysis because of its cyclic structure. Glutaraldehyde forms a cyclic monohydrate of a six membered ring (2,6-dihydroxytetrahydropyran), which forms a hydrate more easily than the inactive aliphatic aldehydes (Figure 3)[18]. These authors also stated that the cyclic structure seems to be able to bind two aldehydes or potential vicinal aldehyde groups.

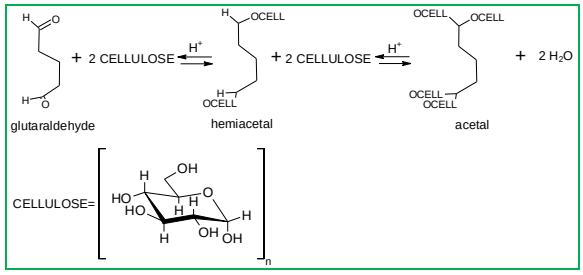
Figure 3: Cyclic structure of glutaraldehyde in water.



Glutaraldehyde could easily condensate or polymerize in aqueous solutions forming polygluratdehydes which can be acetylated and form products with high thermal stability (Figure 4). Wang and Hsiegh (2001) reported that the free aldehyde groups account for only a small fraction in the glutaraldehyde solution leading to several crosslinking reactions operating simultaneously giving different products. In the most common approach, cellulose is immersed in the glutaraldehyde solution between 3 and 16 hours and the curing time is varied between 2 and 6 minutes, at a temperature range from 80 to 150°C. $Al_2(SO_4)_3$ is commonly used as catalyst from 0.01 to 0.03 g/g of cellulose[17]. The glutaraldehyde concentration is also important for the efficiency of crosslinking. Thus, only concentrations higher than 8% show the aldehyde peak in the FT-IR spectrum. The main concern is the final washing step to eliminate by-products and traces of glutaraldehyde in the cellulose particles [17].

Reus and Kumar have crosslinked cellulose II with glutaraldehyde in dilute HCl at 100° C for 8 h followed by washing with acetone and drying. The resulting product had a lower degree of polymerizacion and crystallinity than cellulose II. This product was also denser, had more water affinity and flow than Avicel PH-102. It also showed higher yield pressure and formed stronger compacts than cellulose II with disintegration times less than 200 sec[19].

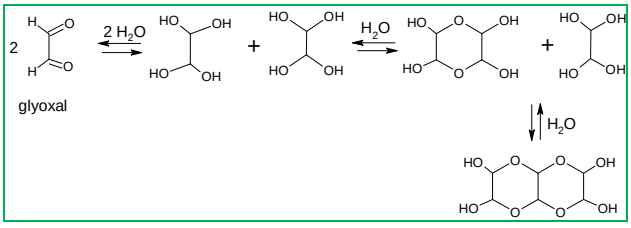
Figure 4: Mechanism of crosslinking of cellulose with glutaraldehyde.



Glutaraldehyde vs. glyoxal

The ability of these two dialdehydes to hydrate is an important factor to determine their reactivity with cellulose. If both agents are compared, a higher degree of crosslinking is achieved for glutaraldehyde treated samples than the glyoxal ones in the presence of $Al_2(SO_4)_3$ as catalyst[13]. Researchers showed that in aqueous solutions, glyoxal forms an olygomeric structure hindering its absorption by cellulose fibers (Figure 5). On the other hand, glutaraldehyde retains its monomeric form without having a steric hindrace to bind cellulose. Similarly, the acetal formation is strongly affected by steric and conformational factors. Glutaraldehyde may react with all four cellulose hydroxyl groups by acetylation. However, for glyoxal the two aldehyde groups are too close to each other leading to brittleness in the glyoxal crosslinked product because its short crosslinking length restricts the mobility of cellulose chains. Glutaraldehyde gives more yield of acetal than glyoxal because of its greater length and flexible chain between two aldehyde groups resulting in a less steric hindrance for the crosslinking reaction. Scientists concluded that structural features in these two aldehydes alone cannot explain their reactivity toward cellulose [13].

Figure 5: Cyclic formation of glyoxal in aqueous solutions.



In addition, those authors also concluded that low dialdehyde concentrations are not recommended for the reaction with cellulose since acid degradation seems to counteract the crosslinking effect resulting in a low product yield. On the contrary, high curing temperatures favor product yield. Opposite to glutaraldehyde-treated products, the glyoxal-treated samples usually do not show aldehyde carbonyl peaks in the IR spectrum since glyoxal tends to be in hydrated form in the cellulose particles. Further, opposed to glutaraldehyde, glyoxal need to be non-ionized to react, so low pHs and high

glyoxal concentrations are desirable to favor the reaction[13]. Glyoxal treatment without catalyst imparts temporary strength, because hemiacetal bonds can be replaced by hydrogen bonding when the cellulose derivative is soaked in water. On the contrary, glutaraldehyde has some reactivity towards cellulose, even if no catalyst is present. At the same reaction conditions, glutaraldehyde is much more efficient for acetylation than glyoxal rendering higher strength in the cellulose particles.

Dialdehyde/polyvinyl alcohol (PVA)

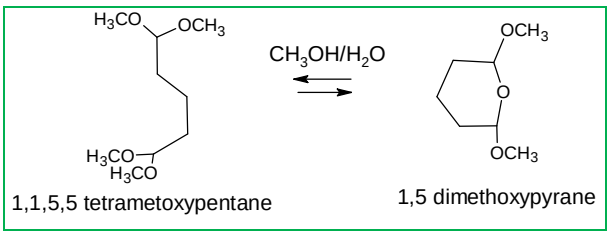
When cellulose is treated with either glyoxal (0.2 mol/l) or glutaraldehyde (0.2 mol/l) in combination with 2% PVA at pHs between 3.0 and 5.4, in the absence of catalyst, a temporary increase in the particle strength is observed due to the hydrolysis of acetal, as reported by Gordon et al. (2004). According to these scientists, if $Zn(NO_3)_2$ is used as catalysts, the crosslinking reaction rate increases with increasing curing temperature, but this rate is independent of the medium pH. The glutaraldehyde-PVA product is more resistant to hydrolysis than the glyoxal-PVA product[20]. They also show that different curing temperatures do not have any significant effect on the wet strength of the fibers. The reaction mechanism goes first through a hemiacetal formation and then to a more stable acetal (in neutral and alkaline conditions). Aluminum chloride and magnesium chloride if used as catalysts decrease notably the degree of crosslinking at pHs higher than 4.0[20].

ACETALS

Acetals provide an interesting crosslinking approach, since the reactions do not go through the hemiacetal intermediate. Acetals, which react with cellulose, come from the dialdehyde that can form a five (tetrahydrofuran) or six membered (tetrahydropyran) rings, such as succinaldehyde and glutaraldehyde. The work of Frick and Robert (1984) show that the intrinsic reactivity of acetals increases with the increased branching of the alcoxy group, but the increase is often hindered by the effect of solvents[18]. However, the loss of cellulose fibers with crosslinking agents is greater for acetals than when conventional crosslinkers such as formaldehyde are used because even the most reactive acetals are less reactive than the more rigorous reactions with conventional agents[18].

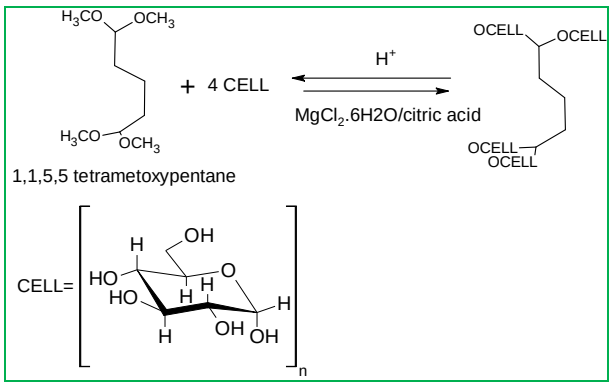
One of the most promising crosslinking acetals is the 2,5-dimethoxytetrahydrofuran. It is used with $MgCl.6H_2O$ (2 - 5%) in 0.5% citric acid at pH of 5 and at a curing temperature from 100 to 160°C. Interestingly, highly reactive acetals come from reactive aldehydes that are themselves reactive with cellulose. Thus, the highest fiber durable press and cellulose elasticity is achieved with 1,1,4,4- tetramethoxybutane (derived from succinaldehyde) and 1,1,5,5-tetramethoxypentane (derived from glutaraldehyde). They form a five and a six membered ring by forming an internal ether linkage (Figure 6).

Figure 6: Cyclic formation of 1,1,5,5-tetrametoxypentane in aqueous solutions.



Although the two acetal groups need to be in proximity for the reaction with cellulose, the reaction does not go through the ring structure as happens for the dialdehydes. On the contrary, a linear polymethylene structure is suggested for the crosslinking, which forms an acetal in contrast to the substituted monomethylene structure proposed for the aldehydes (Figure 7).

Figure 7: Reaction of cellulose with 1,1,5,5 tetrametoxypentane.



The reactivity of the alcoxy groups is hindered by the effect of solvent. In this case, the reactivity depends mainly on the steric factors since it varies as metoxy>isopropoxy>tert-butoxy. Likewise, reactivity decreases as viscosity of the solvent increases because penetration of acetal into the particles is hindered by increasing the viscosity of the solvent. Interestingly, the particle strength loss resulted from treatment with acetals is closer to that experienced after treatment with aldehydes, such as formaldehyde and glutaraldehyde, because of the acid degradation of cellulose caused by treatment with aldehydes. For this reason, these reactive acetals require low curing temperatures to avoid cellulose degradation. In general, these acetals have a low efficiency as crosslinkers compared to the conventional toxic crosslinking agents, such as dimethyloldihydroxyethyleneurea (DMDHEU) which is the typical crosslinker for cellulose employed commercially to improve the elasticity in cotton fibers. Thus, the crosslinked materials produced with 1,1,5,5 tetrametoxypentane are more sensitive to hydrolysis than the commercial crosslinked product with DMDHEU [18].

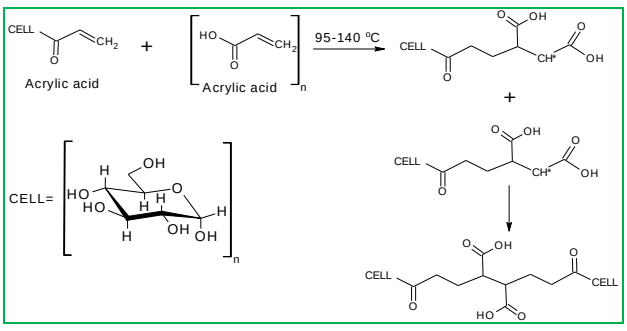
POLYCARBOXYLIC ACIDS

Polycarboxylic acids esterify cellulose through the formation of a five member cyclic anhydride (reactive intermediate) by dehydration of the carboxylic groups bound to the adjacent carbons in the backbone of the molecule[21]. For this reason, polycarboxylic acids having their carboxyl groups linked to adjacent carbons of their molecular backbone are capable of forming a five member cyclic anhydride, being more effective for esterifying cellulose than those polycarboxylic acids having their carboxyl groups linked to their alternate carbons[22, 23]. Zhou and collaborators (1995) reported that an effective crosslinking agent should possess three or more carboxyl groups bounded to the adjacent carbons of their molecular backbones and that the reaction mechanism involves the formation of a cyclic anhydride intermediate to form an ester[24]. According to Yang and Wang (1997), the ester formation increases as the temperature increases from 110 to 200°C. The anhydride formation first increases and then starts to level off at 160°C once the product is formed. In the absence of catalyst, the ester formation is negligible. In addition, Yang and collaborators (2003) reported that the steric hindrance of the polycarboxylic acid on the other hand, reduces accessibility of cellulosic hydroxyl groups, reducing the amount of crosslinked product, but at the same time increasing the untreated anhydride intermediate on the cellulose particles[25].

Acrylic acid (AC)

Polycarboxylic acids, such as 1,2,3,4-butanetetracaboxylic acid (BTCA), has been used to increase the wet tensile strength and brittleness of cellulose fibers. The BTCA is expensive, requiring high curing temperatures (between 170 to180°C) and it is very toxic, which limits its application in the pharmaceutical, food and even in the textile field[26]. These authors showed that acrylic acid can be used with $K_2S_2O_8$, Na_3PO_4 and NaH_2PO_4 as catalysts at a typical curing temperature of 140°C for 5 min and neutral pH. The reaction mechanism is shown in Figure 8. The resulting crosslinked fibers have improved texture, flexibility, tenacity, wrinkle resistance and water uptake. Nevertheless, Mao and Yang (2000) demonstrated that the particles can lose part of the original tensile strength as a direct consequence of the rigidity conferred to cellulose particles[27].

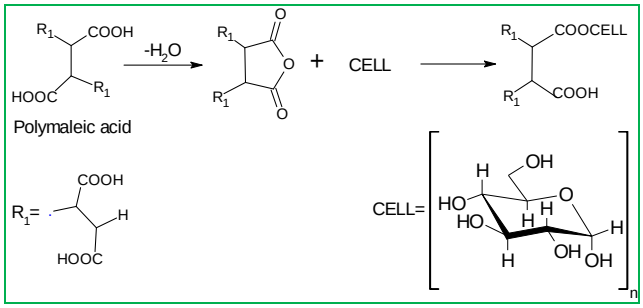
Figure 8: Mechanism of reaction of cellulose with acrylic acid.



Maleic (MA), Polymaleic (PMA) and Succinic (SA) acids

The study of Mao and Yang (2000) suggest that crosslinking of cellulose with polycarboxylic acids such as MA and the use of catalysts such as sodium phosphate and sodium hypophosphate can give cellulose fibers a flame resistant properties, and at the same time increases resilience and elasticity in the fibers. The reaction mechanism is shown in Figure 9. They reported a typical curing condition of 150°C for 10 min. The use of PMA reduces acidity of the polymerization mixture and hence, reduces the loss of fabric strength caused by acid degradation as the polymerization time increases. An interesting crosslinking approach reported by Chen at al. (2005), involves SA and titanium dioxide in presence of UV radiation at 254 nm using water as solvent at 25°C. The resulting product possesses higher elasticity without decrement of tensile strength. The highest crosslinking yield is achieved after 45 minutes of radiation treatment. The carboxylic group of SA is photoreduced to an aldehyde group to provide a crosslinking ability to SA. This aldehyde can then react with the hydroxyl groups of cellulose[21].

Figure 9: Mechanism of reaction of polymaleic acid with cellulose.

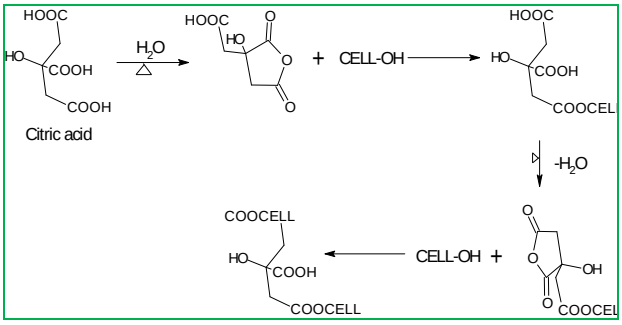


Citric acid (CA)

The reaction of cellulose with CA goes through the esterification of the monoanhydride intermediate which reacts with the cellulose hydroxyl groups (Figure 10). Then, a second adjacent carboxylic group becomes available for the needed anhydride moiety to finish the crosslinking process[28]. Teramoto et al. (2003) show that the reaction of cellulose with CA has a pH-dependency, being the best condition at pH of 2 and the typical curing temperatures employed are between 120 and 160°C. These authors also reported that particle size does not affect the reaction efficiency. In addition, temperature and time of exposure during curing decrease the tensile strength and make particles brittle. Minor factors such as concentration of the acid, pKa and pH of the solution medium need to be considered[29]. The strength loss is caused by irreversible cellulose acid degradation and reversible cellulose crosslinking. As expected, without catalyst, the esterification reaction does not occur. If the pKa and pH increases, the tensile strength retention ability increases. A yellowing color might result in the

product from the formation of unsaturated polycarboxylic acid at elevated temperatures[24, 30].

Figure 10: Mechanism of reaction of citric acid with cellulose.



Itaconic acid (IA) and Poly(itaconic) acid (PIA)

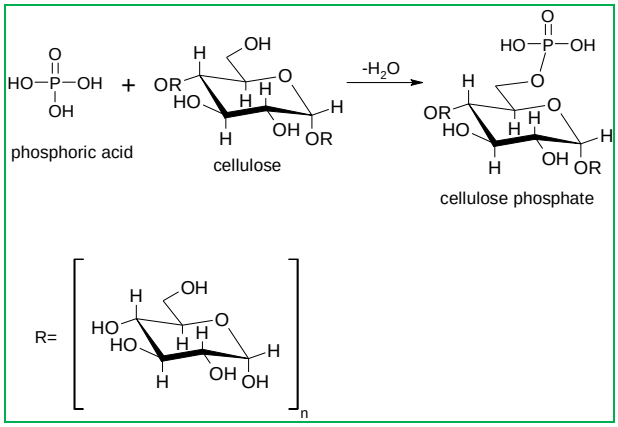
PIA exhibits the same crosslinking mechanism with cellulose as the one shown by the carboxylic acids. Yang et al. (2003) reported the use of $K_2S_2O_8$ and NaH_2PO_2 as catalysts. They showed that the highest crosslinking yield is obtained at curing temperatures between 140°C and 160°C and when compared with PIA, itaconic acid (IA) it has a higher ability to crosslink cellulose. According to those authors, the small molecules of IA possess a better penetration into the amorphous regions of cellulose forming a more homogeneous crosslinking material than the one produced by PIA. Since the mechanical strength is also affected by the size of crosslinking agent, IA treated samples show higher tensile strength loss compared to the PIA treated ones. However, tensile strength decreased up to almost 50% when cellulose samples are treated with both acids. The strength loss is attributed to the irreversible cellulose degradation due to the polycarboxylic acid and the oxidative effect of $K_2S_2O_8$. The effect of $NaHPO_4$ on tensile strength is negligible [25].

PHOSPHORUS DERIVATIVES

Phosphoric acid (PA)

The reaction of PA and cellulose leads to swelling and crosslinking, producing a material with flame retardant properties as reported by Blanchard et al. (2000) (Figure 11). The typical process involves soaking the fibers in a 4% w/v PA followed by curing at 80°C for 10 min and a final drying step at 21°C for 24 h. The PA treated samples present a higher activation energy for decomposition and lower heat of combustion than the untreated cellulose[31]. This implies that a lower amount of heat is liberated during the actual combustion process due to the catalytic dehydration effect of PA. The flame retardant properties of fibers can be improved by using polycarboxylic acids and sodium hypophosphite as efficient catalysts. In this case, the mechanism involves the formation of a five member cyclic anhydride when the temperature reaches the vicinity of their melting point and the formation of anhydride which is accelerated when the temperature increases above their melting point[32].

Figure 11: Mechanism of reaction of phosphoric acid with cellulose.



Organophosphates

Cellulose phosphates have been widely used to treat calcium related diseases since they have a great ability for binding to calcium ions[33]. Similarly, organophosphates have been used as a flame retardant agent for cellulose. Using a simple methodology, Gaan and Sun (2007) soaked cellulose in hexanol and then phosphorous pentoxide, triethyl phosphate and orthophosphoric acid were added altogether. The mixture was stirred at 30°C for 72h and finally filtered and washed with hexanol, ethanol and water. The residual phosphates are then eliminated by conducting a Soxhlet extraction for 24 h. The gel obtained is then freeze-dried. Temperatures higher than 50°C promote hydrolysis instead of phosphorilization. Solvents like dimethyl-formamide and phosphoric acid are undesirable because they produce many types of degradation products. After phosphorilization, the degree of crystallinity decreases and as a result, water sorption increased including the standard amorphous cellulose. As expected, ^{13}C and $^{H}CP/MAS$ NMR analyses showed that phosphorilization happened in the hydroxy groups of C2, C3 and C6 of cellulose, being more prevalent in the C6 hydroxy groups. The final product is able to form a homogeneous gel in presence of water [34]. The resulting hydrogels have a potential for use in medical applications such as wound dressing.

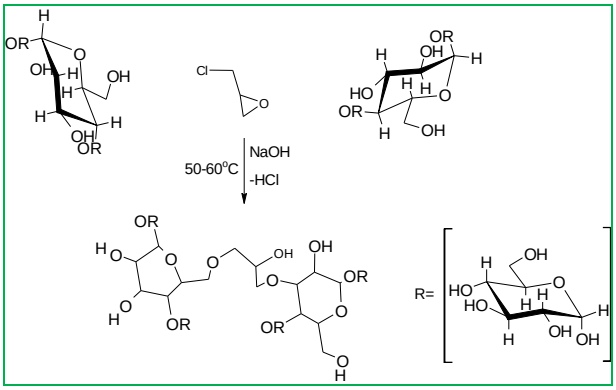
EPICHLOROHYDRIN (EPC)

The simple method

EPC reacts with cellulose through a formation of two ether bonds between two cellulose chains, usually between the hydroxyl groups at C3 and C6 (Figure 12), as suggested by Ishimura and collaborators[35]. According to these authors, the best crosslinking performance is achieved between 1 to 2 hours at 50°C at a CEL:NaOH:EPC molar ratio of 1:1.5:0.5-1. Interestingly, there is only a narrow range of temperatures for the optimum crosslinking reaction. Temperatures below 50°C decrease the crosslinking efficiency (Figure 13), whereas at temperatures above 60°C cellulose degrades to polysaccharides forming a brown color product[35]. Likewise, a low NaOH concentration is beneficial, where

the optimal concentration of NaOH is 25%. Other researchers suggested that decreasing the NaOH concentration, as well as increasing the EPC content and temperature could improve crosslinking efficiency[36, 37]. This approach probably leads to a lower yield and high degradation or by-products. Another interesting approach involves alcoholic solvents to shorten the reaction time. For instance, CEL:EPC (1:1) dissolved in a mixture of 25 ml of 18% NaOH and 25 ml of isopropanol, heated at 60°C for 1 h, could also be used to enhance crosslinking efficiency[38].

Figure 12: Optimal crosslinking reaction of cellulose with epichlorohydrin.



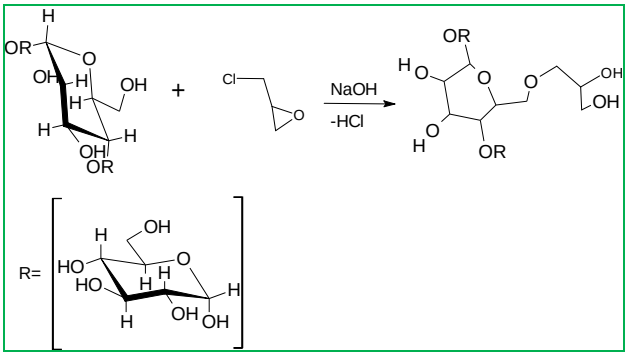
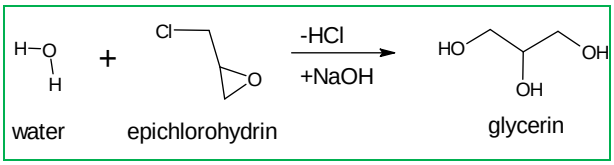


Figure 13: Partial crosslinking reaction of cellulose with epichlorohydrin

In general, the crosslinked product is more stable than the parent cellulose, which is reflected by the lower mass loss shown by the TGA[36]. It is suggested that these crosslinked materials are able to absorb drugs in which the rate of absorption is pH-dependant. Furthermore, release of dies resulted on a biphasic behavior. Thus, there is an initial burst release of the dye located on the surface followed by a linear release of the molecules occluded into the pores or bound to the material. Interestingly, if the amount of EPC is doubled, the swelling ability of the product has a 5-fold increase, while porosity has almost a 2-fold increase. Swelling can be explained by the formation of side reactions such as a polymer branching, as suggested by Bragina and collaborators[39]. Thus, excess of EPC induces substitution of the cellulose hydroxy groups by the hydroxypropylether groups and hydrolysis of EPC to glycerol by NaOH in the reaction medium (Figure 14).

Figure 14: Epichlorohydrin hydrolysis.



Bai and Li (2006) reported that under low concentrations of EPC, the degree of swelling is low and the resulting crosslinked material presents an increase in the tensile strength compared to the parent cellulose. Thus, the chains cannot realign when crosslinked, so they are brought closer to each other in a parallel way. This results in a tightening of the network by covalent crosslinks and a spacer action caused by the hydrophilic dihydroxypropylether side chains[40]. Since the crystallinity of the product does not change, crosslinking occurs in the amorphous regions of cellulose. Interestingly, drying prior the alkaline crosslinkling has no effect on the swelling and degradability of the crosslinked materials because alkalinization only affects the supramolecular and morphological structure of cellulose[41].

The solvent exchange method

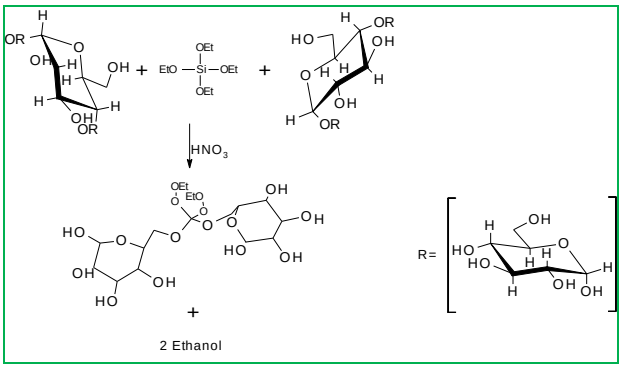
In this approach, Loth and Phillipp (1989) coagulated a cellulose-NaOH dispersion in chlorobenzene under heating, then washed it with water, followed by water exchange by ethanol, and finally this solvent is exchanged by diethyl ether and then dried. DMSO and 2-propanol are also used as solvents for the crosslinking reaction which commonly takes place for 1 h at 80°C. These organic solvents lead to a product of low crystallinity, indicating extensive crosslinking even in the crystalline regions of the cellulose matrix. If water is used as solvent, the resulting material shows a high water retention compared to that of cellulose treated with DMSO and 2-propanol. The concentration of NaOH in the medium also influences the degree of crosslinking. Thus, a high NaOH concentration favors the formation of degradation reactions instead of the crosslinking of cellulose. The presence of degradation products increases the water retention ability. Crosslinking of these cellulose gels reduce their swelling and water solubility[42].

SILICA DERIVATIVES

Recent attempts have been made to create organic-inorganic hybrid materials (OIHs) where cellulose and silica represent the organic and the inorganic components, respectively. The inorganic particles govern the properties of density, free volume and thermal stability, whereas hardness, brittleness and transparency depend on the organic host polymer. Sequeira and collaborators (2007) prepared OIHs by using the inorganic precursor tetraetoxysilane (TEOS), which hydrolyzed and polycondensated with cellulose in ethanol at 24°C for 24h in the presence of nitric acid as catalyst (Figure 15). These authors claim that the properties of OIHs depend on the synthesis conditions, especially the mineral acid catalyst, which might damage the fragile polymer matrix during

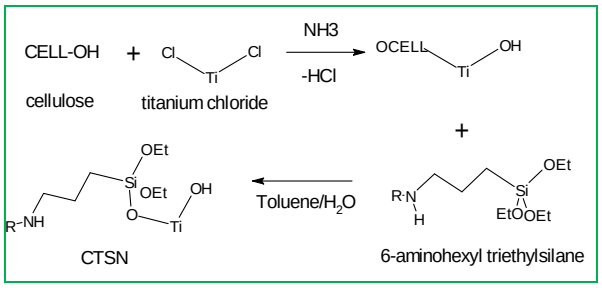
the aging and drying steps. Nonetheless, if the catalyst concentration is increased, the amount of amorphous material also increases. Thus, a high concentration of the catalyst might favor hydrolysis rather than condensation. An excess of water promotes the condensation reactions to form a gel. In the resulting material, silicon dioxide particles cover interruptedly the cellulose particles. The hydrophobic character of SiO_2 decreases the water retention capacity of cellulose, but at the same time improves the thermal stability[43].

Figure 15: Crosslinking reaction of tetraetoxysilane with cellulose.



Silica is of special interest since it improves the thermal properties of the parent polymer matrix (cellulose) and improves the lipophylic behavior towards specific substrates like human protein. Meng and collaborators prepared a cellulose-titanium (IV) oxide modified organosilicon (CTSN), which was produced by reaction of cellulose with titanium chloride (Figure 16), followed by reaction with 6-aminohexyl triethylsilane[44]. This derivative had a homogeneous dispersion of Ti and Si atoms on the surface and had a high adsorption capacity for human serum protein comparable to commercial silica absorbents. Likewise, Kulpinski and collaborators produced cellulose-silicon dioxide modified nanoparticles using the environmentally friendly NMMO (N-methyl morpholine-N-oxide) as solvent, rendering a transparent material of high thermal stability[45]. Interestingly, this material is more amorphous and has lower tensile strength, but higher elongation (more plasticization) than the original cellulose, due to the added amorphous silicon dioxide.

Figure 16: Crosslinking reaction of titanium oxide and 6-aminohexyl triethylsilane with cellulose



A special type of cellulose obtained from microbial sources is called bacterial cellulose (BC), which is produced by Glucunonacetobacter xylinus. This material has been used to produce a hydrogel, which is a polymer capable to absorb a large amount of water or saline solutions from 10 to 1000 times its own weight[46]. Maeda et al. (2006) reported the preparation of gels and films based on BC in which this material was immersed for 72h in an aqueous solution of the silanol derived from the TEOS. Silanol was then converted in-situ into silica in the hydrogel matrix or condensated with hydroxyl groups of cellulose. The resulting gel is then converted into films by drying the gel at 120°C and pressing at 2 MPa. The resulting product exhibits a higher elastic modulus and tensile strength than the parent BC. The temperature dependence of the viscous modulus from 145 to 280°C is negligible because the thermal stability is enhanced by the TEOS. Deformation of BC/gel/silica hybrids decreases with increasing the TEOS content, since large amounts of silica lead to a very brittle hybrid. Therefore, a large amount of deposited silica in-situ in the BC gels is able to reinforce the BC gel hybrids and suppress the formation of the BC gels[47].

REFERENCES

1. Kuniak L, Luby P, Crosslinking statistics, relation between relative reactivity and accessibility of cellulose hydroxyl groups, Makromol Chem, 18(1), 1979, 2379-86.
2. Pinto BM, Cellulose: In Comprehensive Natural Products Chemistry, Elsevier science B, Amsterdam, 1999, 939.
3. Krassig H, Cellulose, Structure, Accessibility and Reactivity, Gordon and Breach science publishers, Asterdam, 1996, 376.
4. Klemm D, Philipp B, Heinze T, Heinze U, Comprehensive Cellulose Chemistry: Functionalization of Cellulose, John Wiley & sons, New York,1998, 249.
5. Heinze T, Liebert T, Unconventional methods in cellulose functionalization, Prog Polym Sci, 26(1), 2001, 1689-762.
6. Cortesi R, Natruzzi C, Davis SS, Sugar cross-linked gelatin for controlled release: Microspheres and disks, Biomaterial, 19(18), 1998, 1641-9.
7. Hatch K, Maibach H, Textile fiber dermatitis, Contact Dermatitis, 12(1), 1985, 1-11.
8. Pierce AG, Frick JG, Crosslinking cotton with formaldehyde in phosphoric acid, J Appl Polym Sci, 11(12),1967, 2257-585.
9. Xu GG, Young C, Deng Y, Combination of bifunctional aldehydes and poly(vinyl alcohol) as the crosslinking systems to improve paper wet strength. J Appl Polym Sci, 93(4), 2004, 1673-80.
10. Hurwitz MD, Dialdehydes as cotton cellulose cross-linkers, Tex Res J, 28(3), 1958, 257-62.
11. Fujimura T, Okamoto S, On the acetalization of regenerated cellulose with dialdehydes, J. Appl Polym Sci, 51(1), 2003, 173-83.
12. Kielhorn C, Pohlenz M, Schmidt S, Fraunhofer M, Concise international chemical assessment document 57, Glyoxal, Wld Hlth Org Techn Rep Ser, 1992, 1-49.
13. Choi H, Kim JH, Shin S, Characterization of cotton fabrics treated with glyoxal and glutaraldehyde, J Appl Polym Sci, 73(13), 1999, 2691-9.
14. Leung HW, Ecotoxicology of glutaraldehyde: Review of environmental fate and effects studies, Ecotoxicol Environ Saf, 49(1), 2002, 26-9.

15. Takigawa T, Young E, Effects of glutaraldehyde exposure on human health, J Occup Health, 48(2), 2006, 75-87.
16. Zeiger E, Gollapudi B, Spencer P, Genetic toxicity and carcinogenicity studies of glutaraldehyde—a review, Mutat Res, 589(2), 2005, 136-51.
17. Wang Y, Hsiegh YL, Cellulose functionalization by glutaraldehyde, 42(1), 2001, 520-1.
18. Frick JG, Robert JH, Acetals as crosslinking reagents for cotton, J Appl Polym Sci, 29(4), 1984, 1433-47.
19. Reus M. Preparation, characterization and tableting properties of cellulose II powders [dissertation]. Iowa City, The University of Iowa (2005) 358.
20. Gordon GX, Yang CQ, Deng Y, Combination of bifunctional aldehydes and poly(vinyl alcohol) as the crosslinking systems to improve paper wet strength, J Appl Polym Sci, 93(40), 2004, 1673-80.
21. Chen D, Yang C, Qui X, Aqueous polymerization of maleic acid and cross-linking of cotton cellulose by poly(maleic acid), Ind Eng Chem Res, 44(21), 2005, 7921-7.
22. Yang C, Xu Y, Wang D, FT-IR spectroscopy study of the polycarboxilic acids used for paper wet strength improvement, Ind Eng Chem Res, 35(11), 1996a, 4037-42.
23. Yang C, Wang X, FT-IR infrared spectroscopy studies of the cyclic anhydride as the intermediate for the ester crosslinking of cotton cellulose by polycarboxylic acids, J Appl Polym Sci, 81(9), 1996b, 2142-50.
24. Zhou Y, Luner P, Caluwe P, Mechanism of crosslinking of papers with polyfunctional carboxylic acids, J Appl Polym Sci, 58(9), 1995, 1523-34.
25. Yang CQ, Hu C, Lickfiel G, Crosslinking cotton with poly(itaconic acid) and is situ polymerization of itaconic acid: Fabric mechanical strength retention, J Appl Polym Sci, 87(12), 2003, 2023-30.
26. Ghosh P, Das D, Modification of cotton by acrylic acid (AA) in the presence of NaH2PO4 and K2S2O8 as catalyst under thermal treatment, Eur Polym J, 36(11), 2000, 2505-11.
27. Mao Z, Yang C, Infrared spectroscopy study of cyclic anhydride as intermediate for ester croslinking of cotton cellulose by polycarboxilic acids. II. comparison of 1,2,3,4-butanetricarboxilic acid and 1,2,3-propanetricarboxilic acid, J Appl Polym Sci, 81(1), 2000, 2142-50.
28. Wing RE, Cellulose citrates: Preparation and ion exchange properties, J Polym Mater, 1997, 303-9.
29. Teramoto N, Saitoh M, Kuroiwa J, Shibata M, Yosomiya R, Dependence of the mechanical properties of a pullulan film on the preparation temperature, Biosc Biotech Biochem, 67(4), 2003, 893-5.
30. Coma V, Sebti I, Pardon, Pichavant FH, Deschamps A, Film properties from crosslinking of cellulosic derivatives with a polyfunctional carboxilic acid, Carbohydr Polym, 51(3), 2003, 265-71.
31. Blanchard EJ, Graves EE, Salame PA, Flame resistant cotton/polyester carpet materials, J Fire Sci, 18(151), 2000, 151-64.
32. Yang C, Wu W, Combination of a hydroxyl-functional organophosphorus oligomer and a multifunctional carboxylic acid as a flame retardant finishing system for cotton, part I. the chemical reactions, Fire Mater, 27(1), 2003, 223-37.
33. Granja PL, Pouysegu L, Petrau M, De jeso B, Baquey C, Barbosa MA, Cellulose phosphates as biomaterials, I. synthesis and characterization of highly phosphorylated cellulose gels, J Appl Polym Sci, 82(13), 2001, 3341-53.
34. Gaan S, Sun S, Effect of phosphorus flame retardant on the thermo-oxidative decomposition of cotton, Polym Degrad Stab, 92(6), 2007, 968-74.
35. Ishimura D, Morimoto Y, Saito H, Influences of chemical modifications on the mechanical strength of cellulose beads, Cellulose, 5(2), 1998, 135-51.
36. Constantinescu G, Cazacu G, and Popa VI, Contributions to the modification of lignocellulosic by epoxidation and esterification, Cellul Chem Technol, 39(3), 2005a, 201-3.
37. Constantinescu G, Cazacu G, Popa VI, Contributions to the modification of lignocellulosics by epoxidation and esterification, Cellul Chem Technol, 39(3-4), 2005b, 201-10.
38. Morales A, Bordallo E, Leon V, Adsorption and releasing properties of bead cellulose, Chin J Polym Sci, 22(5), 2004, 417-23.
39. Bragina OA, Dorokhova VV, Kazankii GA, Kabalin V, Nizovtsev VP, Rokhin AV, Sukmankii OB, Reaction of CMC with epichlorohydrin, Russ. J. Appl Chem, 70(4), 1996, 679-82.
40. Bai Y, Li Y, Preparation and characterization of crosslinked porous cellulose beads, Carbohydr Polym, 64(3), 2006, 402-7.
41. Chebli C, Cartilier L, Cross-linked cellulose as a tablet excipient: A binding/disintegrating agent, Int J Pharm, 171(1), 1998, 101-10.
42. Loth F, and Phillipp B, The macroporous network of bead cellulose and its response to crosslinking with epichlorohydrin, Makromol Chem –Macromolecular Symposia, 30(1), 1989, 287.
43. Sequeira S, Evtuguin D Portugal I, and Esculcas A, Synthesis and characterization of cellulose/silica hybrids obtained by heteropoly acid catalyzed sol-gel process, Mater Sci Eng, A, 27(1), 2007, 172-9.
44. Meng LZ, Du CQ, Chen YY, He YB, Preparation, characterization and behavior of cellulose-titanium (IV) oxide modified with organosilicone, J Appl Polym Sci, 84(1), 2002, 61-6.
45. Kulpinski P, Cellulose fibers modified by silicon dioxide nanoparticles, J Appl Polym Sci, 98(4), 2005, 1793-8.
46. Sannino A, Nicolais L, Concurrent effect of microporosity and chemical structure on the equilibrium sorption properties of cellulose based hydrogels, Polymer, 46(13), 2005, 4676-85.
47. Maeda H, Nakajima M, Hachiwara T, Sawaguchi T, Yano S, Bacterial cellulose/silica hybrid fabricated by mimicking biocomposites, J Mater Sci, 41(17), 2006, 5646-56.

About Corresponding Author: Mr. John Rojas

Mr. Rojas got his Bs. In Pharmaceutical Chemistry at the University of Antioquia and earned his PhD in Pharmacy (Physical Pharmacy) at the University of Iowa (USA) the title of his dissertation was: “Preparation, characterization and evaluation of cellulose II powders and cellulose II:silicon dioxide composites as direct compression excipients”. Currently working as an assistant professor at the University of Antioquia, Columbia.