Cellulose-Based Materials Crosslinked with Epichlorohydrin: A Mini Review

Materiais à Base de Celulose Reticulados com Epicloridrina: Uma Mini Revisão

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Cellulose, the most abundant biopolymer worldwide, has received a great deal of attention by researchers in several different fields. Hydroxyl groups on cellulose chains can be chemically modified in order to improve physico-chemical properties enabling applications in different areas such as biomaterials for implants, removal of chemical components from water and hydrogels for the delivery of drugs and fertilizers. In this context, chemical crosslinkers may also bring advantages to cellulose-based materials and derivatives improving their thermal stability, surface area and swelling degree of hydrogels. Among many chemical crosslinkers, epichlorohydrin has been used in recent years to prepare materials based on cellulose and other biopolymers. Thus, here we aim to review recent works reporting cellulose-based materials crosslinked with epichlorohydrin in a comparative approach with other common agents such as glutaraldehyde and citric acid, their advantages and disadvantages as well as future prospects.

Keywords: Cellulose; cellulose derivatives; epichlorohydrin; crosslinking.

1. Introduction

In the search for new materials exhibiting simultaneous efficiency, low environmental impact and favorable costs, researchers always rely on nature as a source of raw materials and bioinspiration to preparation and application strategies.[1] In contrast to engineering materials, biological structures show hierarchically built anatomies, designed and optimized during a long process of genetic evolution. In this context, the comprehension of biological structures as well as the development of strategies for their manipulation has motivated a large volume of studies.[2] The use of natural polymers in different areas has increased in recent years, including systems such as cyclodextrins, starch, alginic acid, chitosan and cellulose -the most abundant biopolymer on earth. Cellulose exhibit advantages in comparison to other polymers, including abundance, non-toxicity, biodegradability, biocompatibility, environmental friendliness and low cost, favoring its use in many industrial activities.[3]

However, native cellulose in insoluble in water and only slightly soluble in organic solvents due to the complex structure of crystalline and amorphous regions as well as the strong intra- and intermolecular hydrogen bonds.[3] Thus, several solvent systems have been evaluated in order to dissolve cellulose and to increase its applicability. [4] In addition to methods to dissolve cellulose chains, breaking up the intermolecular interactions that make those chains strongly packed and allowing for chain separation, the methods and procedures shown here aim also to reconstruct the macromolecular structure, forming lightweight materials such as hydrogels, aerogels, xerogels, foams and sponges.[5] Figure 1 illustrates some of the general pathways from the natural cellulose sources to a crosslinked cellulose hydrogel, showing the distribution of native cellulose in the natural architecture followed by separation, dissolution and hydrogel assembly.

The presence of three distinct hydroxyl groups in each anhydroglucose moiety in cellulose chains makes many chemical modifications possible including esterification, etherification, oxidation by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), polymer grafting, crosslinking among others.[6] In this mini-review we will focus on crosslinking, which takes place through physical as well as chemical interactions between different polymer molecules or different parts of the same molecule. The possible interactions include ionic or hydrogen bonding as well as the use of bi- or trifunctional chemical agents able to react with functional groups creating interchain bridges.[7] Distinct crosslinking techniques have been developed and can be classified as physical, chemical and enzymatic crosslinking. Within the physical crosslinking, there
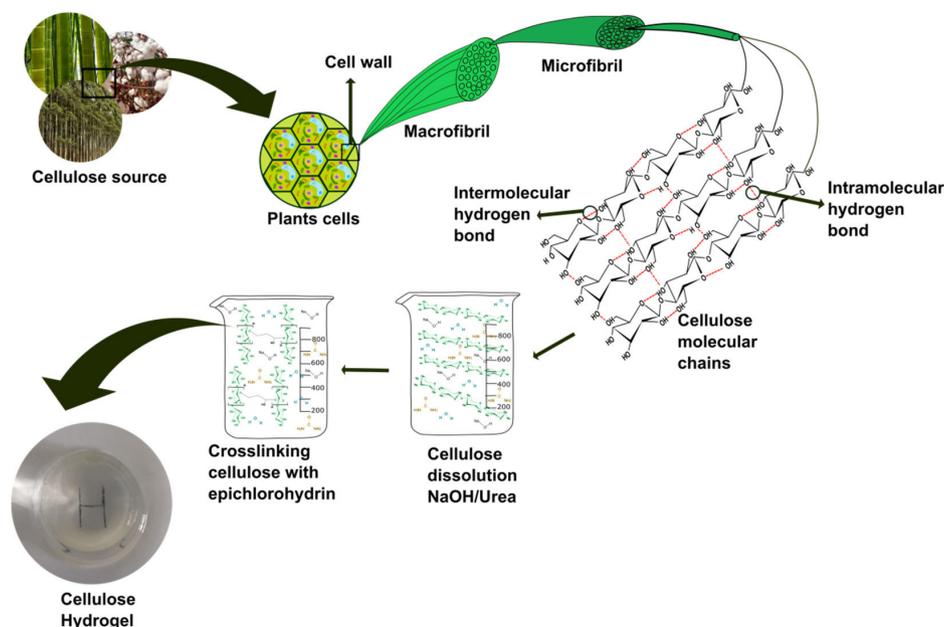
Figure 1. Representation of the pathways along which cellulose is formed in natural sources, provide the plant the necessary structural properties, can be extracted, dissolved and transformed in material architectures with desired properties

are the freeze/thaw, photoinitiator and radiation-induced mechanisms,[4] for example. While in chemical crosslinking, crosslinking agents such as citric acid, epichlorohydrin and glutaraldehyde are generally used,[4] different mechanisms can be application, such as free radical polymerization, Michael addition reaction, schiff base reaction, enzymatic reaction and click reaction.[8] As it will be detailed later in this mini-review, all techniques have advantages and disadvantages and, among them, chemical crosslinking is the most widely used although it may involve several reaction steps, reactants and generate wastes.[7]

Here we review studies on epichlorohydrin (ECH) (1-chloro-2,3-epoxypropane) which, in addition to glutaraldehyde and citric acid, is widely used as crosslinker of biopolymers such as cellulose, chitosan and starch. Nevertheless, other chemical crosslinkers are often reported in the literature, such as polyethylene glycol,[9] genipin[10] and vinylsulphone,[11] in order to yield rationally designed materials as well as to overcome limitations of the most commonly used crosslinkers. The choice of the crosslinker lies on factors including the nature of the aimed application, the material architecture, hydrophilicity/hydrophobicity, porosity, swelling degree, mechanical properties and biocompatibility. Among the three crosslinkers cited, ECH has the shortest chain and provides an intermediate hydrophilicity in comparison with the other ones, in addition to give higher chemical durability against hydrolysis. ECH is known for more than 50 years and is the most common crosslinker used in cyclodextrin chemistry to yield nanosponges for water treatment and drug delivery.[12-13] Another attractive of this crosslinker is that it allows to obtain polymers free from crosslinker residues due to the high efficiency of the washing process. On the other hand, glutaraldehyde is a more versatile crosslinker for

different biopolymers such as proteins and polysaccharides and as a result is has long been applied for medical implants. Finally citric acid-crosslinked materials are in an earlier stage of development but are extremely promising on the basis of the non-toxic nature.

There are excellent review articles in the literature focusing the crosslinking of biopolymers in general,[14] the crosslink of cellulose and its derivatives[15] and cellulose-based hydrogels.[16-17] However, there is currently a lack of review articles treating specifically the role of ECH in cellulose crosslinking, which would be helpful for a more rational choice among the common crosslinkers in order to obtain materials addressing specific demands. Thus, this mini-review is aimed at summarizing the main chemical and toxicity differences between ECH and other common crosslinkers as well as showing the effect of crosslinking cellulose-based materials with ECH on relevant properties of the resulting materials.

2. Cellulose

Cellulose is the most abundant renewable polymer on Earth and can be found in plant cell walls, marine organisms and can also be synthesized by certain algae, fungi and bacteria.[18] However, the cellulose structure contains the same polymeric chains consisting of repeated glucopyranose units connected by β-1,4-glycosidic bonds, irrespective of the origin. Each glucose moiety has hydroxyl groups at C2, C3 and C6 positions able to form intra- and interchain hydrogen bonds.[19]

Cellulose is a suitable candidate for biomaterial applications as it has advantages as biodegradability, biocompatibility

and environmental benignity.[20] Thus, it has been used in the development of composites,[21-23] nanocomposites,[24-26] hybridization with carbon nanomaterials,[27-29] nanospheres,[30-32] hydrogels[33-35] and ionogels[36-38] being applied in different areas such as in the adsorption of heavy metals,[39] controlled delivery of drugs,[40] wound dressing[41] and delivery of fertilizers,[42] among other applications. Important drawbacks for cellulose application are brought by its difficult solubility[4] which results from the strong intra- and intermolecular hydrogen bonding in the structure. As a consequence, cellulose in insoluble in water and only slightly soluble on some organic solvents.[3,19] The use of alkaline solutions has been employed since Mercer proposed the so-called mercerization process, based on the use of NaOH or LiOH to solubilize cellulose and overcome this limitation. The solubility and stability of cellulose can also be improved by the addition of urea and thiourea in solution medium.[43] Efficient cellulose dissolution was observed using pre-cooled solutions containing 7% NaOH and 12% urea,[44] 4.6% LiOH and 15% urea[45] and 9.5% NaOH and 4.5% thiourea[46]. The mechanism of cellulose solubilization by NaOH and urea is not fully understood, but some hypotheses were raised such as that the hydrogen bonds are broken apart by aqueous OH^- species while hydroxyl groups in cellulose molecules are stabilized by hydrated Na^+ ions and urea stabilize the hydrophobic regions in the chains.[43]

Other types of chemical modifications including etherification, esterification, surface polymerization,[19] and TEMPO mediated oxidation[47-48] contribute to a higher availability of cellulose derivatives with favorable properties. Among the most studied cellulose derivatives, microcrystalline cellulose is a white crystalline powder obtained through hydrolysis with strong acids and is widely studied.[49] Carboxymethylcellulose is obtained via partial substitution of 2, 3 and 6 hydroxyl groups in the cellulose structure by carboxymethyl group in nonaqueous medium.[4] Finally, it is worth to mention TEMPO oxidized cellulose which can be obtained through carboxyl conversion of the C6 hydroxyl group.[48]

A modification strategy capable of changing dramatically both the chemical and architectural characteristics of polymers is the physical and chemical crosslinking. As mentioned, crosslinking involves the generation of innumerous interaction points between different polymer molecules or along the same molecule. Crosslinking affects important properties including swelling, solubility, response to stimulus, mechanical properties, turbidity, elasticity among others.[50]

Physical crosslinking usually takes place through reversible intermolecular interactions such as ionic, electrostatic, and hydrogen bonds leading to chain entanglement and high structural cohesion.[51] The main advantage of physical crosslinking is the absence of chemical crosslinkers avoiding their potential cytotoxicity.[51] One class of physical hydrogels are the cryogels obtained by freeze-thawing cycles.[52] In this process, the polymer concentration in the remaining liquid phase increases during the freezing step, favoring interactions between polymer molecules as well as their alignment. The resultant interchain connections remain intact after thawing, making the hydrogel structure stable.

Chemical crosslinking employs bi- or trifunctional reactants forming bridges between sites in different or within the same polymer chain, usually by covalent bonds.[14] In general those bonds are strong and permanent providing higher mechanical stability in comparison to physical crosslinking.[53] However, chemical crosslinking may affect negatively the biodegradability and also some of the mechanical properties owing to the less compact network and relative chain motion. It also reduces the availability of functional groups for further interactions in the crosslinked polymer.[14] In spite of the disadvantages, chemical crosslinking is the predominant approach due to the higher possibility of control as well as the permanent nature of the modification.[14]

3. Crosslink and Crosslinkers for Cellulose and its Derivatives

Integrated polymer chains including hydrogels, aerogels and foams can be obtained via the reversible or permanent crosslinking depending on specific demands.[54,55,56] In cellulose the hydroxyl and carboxyl groups, the carboxyl group being present in carboxymethylcellulose, for example, are covalently linked to the reactive groups of the crosslinking agents through different mechanisms such as free radial polymerization, esterification and Michael addition.[57] Regarding the chemical approach, two distinct strategies can be used: the simultaneous radical polymerization of the monomer with the crosslinker and the crosslinking of pre-formed polymers.[50] Here the scope of the review is the second strategy, which takes into account that many polymers contain functional groups available to react with crosslinking agents via condensation reactions, commonly aldehydes, polycarboxylic acids and epoxides. In this context, glutaraldehyde, citric acid and ECH are widely employed in the preparation of biocompatible materials.[58] The crosslinkers cited can be compared with each other in terms of chemical nature, durability of the connections and biocompatibility/cytotoxicity.

Regarding the chemical properties, polyfunctional carboxylic acids such as citric acid can form ester bonds with hydroxyl groups of cellulose. As described by Yang,[15] esterification mechanism involves a cyclic anhydride intermediate and thus requires the crosslinker to have at least three carboxyl groups. Additionally, the resulting ester crosslinks may be hydrolyzed as well as open and rebound via heat induced transesterification.[59] In addition to the undesirable reversibility, unreacted hydroxyl groups in cellulose structure may take part in ion exchange processes leading to adsorption of proteins or cationic species. A very positive aspect of citric acid as

crosslinker is the potential lack of toxicity.[4] In this context, Raucci *et al*., 2015,[60] evaluated the effect of crosslinking carboxymethylcellulose and hydroxymethylcellulose with citric acid to form hydrogels with higher hydrophilicity and surface roughness. Additionally, biological assays with human mesenchymal stem cells evidenced the absence of toxic effects.[60] Hassan *et al*., 2020,[61] observed that mixed microcrystalline cellulose and starch foams crosslinked with citric acid showed improved thermal stability, stiffness and lower water absorption compared with the non-crosslinked foams. The use of citric acid as crosslinker is very promising but some challenges must be overcome such as the limited *in vivo* biodegradability and immune reactions triggered by the presence of the biopolymers in live organisms.[62]

After reacting with cellulose hydroxyl groups, glutaraldehyde and other mono- and bifunctional aldehydes form acetal and hemiacetal groups in the chemical bridges connecting polymer chains. As it is well known, acetal groups are susceptible to hydrolysis reactions under certain conditions such as acidic medium, thus requiring special storage conditions. Nevertheless, this didn't stopped glutaraldehyde from being widely used due to the excellent ability to create tridimensional networks from linear structures,[48] providing suitable hydrophobicity when required Hou *et al*., 2019,[63] and modulating biodegradable and thermal properties of methylcellulose films.[64] Although crosslinking with glutaraldehyde improves several properties, it must be emphasizes that the pure crosslinker is a toxic compound which often raises concerns about its use in biomedical applications.[55] In this context new synthetic dialdehydes for use as specially designed crosslinkers have been reported such as a carboxymethylcellulose dialdehyde derivative ,[65] based on the hypothesis that short-chain dialdehydes are more cytotoxic due to their release from crosslinked polymers.[66] Considering that these effects are observed only after medium and long terms, glutaraldehyde is the most common crosslinker used in heart valve prosthesis as it has been used for more than 50 years. Problems such as extensive degradation and calcification in valve implants reduce the lifespan of those prosthesis to 10-15 years, in addition to the need to storage in glutaraldehyde solution prior to use and washing it immediately before surgery, which creates the risk of presence of glutaraldehyde residue.[67]

ECH, as other epoxide crosslinkers, provides a particularly high hydrolytic stability for the crosslinked materials, owing to the chemically stable ether bonds responsible for the crosslinking. Each bridge formed in crosslinking with ECH also contains a hydroxyl group, which compensates partially the consumption of hydroxyl groups originally in cellulose.[12,68,69] Thus, ECH has been widely applied as crosslinker yielding materials for drug immobilization and delivery,[70-71] prosthesis and tissue regeneration.[72] However, it has poor mechanical properties and sensitive to enzymatic biodegradation that limits its application in 3D scaffold fabrication. Cellulose nanofibrous

(CNF However, careful safety evaluation must be carried out since there is evidence that pure ECH is cytotoxic.[73] Regarding the safety of polymeric materials crosslinked with ECH in biomedical applications, promising results have been reported such the evaluation of long term of porcine valve implants containing ECH (15 years), revealing excellent performance and durability.[74]

Other important crosslinkers have been used to prepare cellulose-based materials such as glycerol diglycidyl ether,[75] zinc nitrate[76] and 1,2,3,4-butanetetracarboxylic acid,[77] in addition to ionizing radiation which uses radiation for initiation of the polymerization. This approach has some advantages in comparison with chemical initiation including purity and better control,[78] but here our emphasis will be specifically on chemical crosslinking of cellulose and its derivatives with ECH.

4. Epichlorohydrin as Crosslinking Agent

The reaction of ECH and cellulose is usually catalyzed by bases (NaOH, LiOH) and the process is controlled by the synergy between physical and chemical interactions, as both the formation of ether bonds and chain entanglement take place simultaneously.[42] This type of crosslinking improves pore size distribution, chemical stability, mechanical properties and adsorption capacity, in addition to versatility in terms of the shape of the final material.[4] For instance, Garnica-Palafox *et al*., 2014,[79] showed that ECH-crosslinked mixed polyvinyl alcohol and cellulose hydrogels were found to be more stable against dissolution in the presence of solvents than non-crosslinked samples. Guo *et al*., 2013,[80] showed that it is possible to prepare transparent cellulose films with improved thermal properties. The preparation of beads is also possible,[81] along with microspheres,[82-83] hydrogels,[42-84] membranes[85] and film. Versatile applications are possible including adsorbent for dyes,[82] heavy metals,[86] selective adsorption,[87] medium for seed germination,[88] delivery of fertilizers,[42] and delivery of drugs,[89] in addition to applications in the food area[90-91] and oil-water separation.[92]

Other works reporting the use of ECH to crosslink cellulose and its derivatives are summarized in Table 1. Those works did not particularly address the effects of the crosslinker on the resulting properties.

The crosslinking efficiency of epichlorohydrin, as well as other crosslinking agents such as glutaraldehyde and citric acid, is dependent on reaction temperature and crosslinker concentration. In the case of glutaraldehyde, with increasing concentration, the concern with the elimination of possible residues after reaction arises, due to its degree of toxicity.[96] This has led to strategies to reduce cytotoxic effects, such as lowering the concentration, which can lead to reduced crosslinking efficiency, extensive rinsing with water, or adding molecules capable of binding to unreacted glutaraldehyde molecules. In addition, the many equilibrium structures of glutaraldehyde in aqueous solution generate complexity in

Table 1. Works reporting epichlorohydrin as crosslinker of cellulose and its derivatives

Cellulose type	Material	Application	Reference
Cellulose	Hydrogel		93
Cellulose Quaternized/carboxymethylcellulose	Hydrogel		94
Carboxymethylcellulose	Microspheres	Methylene blue adsorption	95
Carboxymethylcellulose	Microspheres	Methylene blue adsorption	82
Cellulose from pulp and cotton linters	Hydrogel	Heavy metal adsorption	39
Cellulose from cotton pulp	Doubly crosslinked hydrogels		69
Sodium carboxymethylcellulose	Ion-imprinted polymer	Selective chromium adsorption	87
Microcrystalline cellulose	Adsorbent	Heavy metal adsorption	86
TEMPO-oxidized cellulose	Hydrogel	Seed germination medium	88
Cellulose		2-naftoxyacetic acid adsorption	56
Cellulose kraft	Hydrogel	Orange juice dehydration	90
Cellulose from corncobs	Hydrogel	Fertilizer carrier	42
Cellulose	Hydrogel	Oil/water separation	92
Microcrystalline cellulose	Microspheres	Adsorption of 2-diethylethylamine chlorhydrate	83

the reaction mechanisms with proteins and polysaccharides.[97] The dependence of the concentration and temperature of the reaction was also observed for citric acid by Ma *et al*., 2021,[98] who for the concentration of 100 g/L of citric acid and a temperature of 180 ℃ obtained better crosslinking efficiency of cellulose fibers. But unlike glutaraldehyde, citric acid does not show cytotoxicity, being a crosslinking agent considered non-toxic. However, high temperatures can lead to cellulose degradation forming a brown product.[96] On the other hand, despite the toxicity of epichlorohydrin, with the washing process after crosslinking to remove traces of reagents, a decrease in toxicity was observed.[99] Assays with cell cultures were also carried out showing that the materials were innocuous and NMR data revealed the absence of crosslinker residues.[79] Safety evaluation was also reported by Islam *et al*., 2020,[90] for ECH-crosslinked carboxymethylcellulose hydrogels prior to application in the dehydration of orange juice. In terms of cost, epichlorohydrin and citric acid have similar costs, with glutaraldehyde being the most expensive agent compared to epichlorohydrin. Although the whole process has inherent costs, considering only the price of 1g of crosslinker, the cost of epichlorohydrin corresponds to approximately $0.05, while citric acid and glutaraldehyde cost respectively $0.07 and $0.12.

Changes in properties such as viscosity, surface area, thermal stability, swelling degree, crystallinity, mechanical properties evidence the main effects of cellulose crosslinking. The following sections describe recent studies reporting effects of crosslinking with ECH on the properties of cellulose-based materials.

5. Viscosity

The evolution of the viscosity of cellulose solutions during crosslinking with ECH was studied by Salleh *et al*., 2020[100] revealing that this is a useful parameter to monitor the occurrence of crosslinking. The amount of ECH is also an important factor influencing the reaction medium

viscosity during crosslinking as shown by Salleh *et al*., 2018.[99] Authors studied different crosslinker amounts of (2.5% to 10%) on the gelification of cellulose, observing that 2.5% is insufficient to promote crosslinking, although a continuous increase in viscosity can be observed in the range of amounts. It is well known that the higher the resistance of molecules to motion, the higher the viscosity observed, evidencing a correlation between viscosity and the number of crosslinkings in the network.

6. Surface Area

Intermolecular bonds between biopolymer units formed by crosslinking agents can influence the surface chemistry of the materials.[101] This aspect has been studied by Bai & Li, 2006,[81] through the evaluation of the effect of ECH concentration on the formation of cellulose diacetate porous beads, showing that porosity as well as pore diameter and volume depended on the crosslinking density. A low crosslinking density led to relatively large pore volumes along with high porosity and high swelling degree, when compared to higher ECH concentrations.

Udoetok *et al*., 2016,[84] also studied the effect of different cellulose:ECH ratios on the textural properties, observing that ratios close to the stoichiometric proportion led to the higher surface areas as well as the best adsorption capacity of p-nitrophenol. It is worth to mention that crosslinked materials irrespective of the ECH amount improved the adsorption capacity in comparison with non-crosslinked cellulose, which was also confirmed through adsorption of phenolphthalein.

7. Thermal Stability

Improvements in thermal stability were observed by Guo *et al*., 2013,[80] through crosslinking of microcrystalline cellulose with ECH after dissolution of samples in NaOH/

urea medium. This enabled the preparation of transparent films which were thermally stable up to 345 ºC, while the non-crosslinked material was stable up to 304 ºC. Similar results were reported by Udoetok et al., 2016,[84] and Udoetok et al., 2018a,[102] with different ECH amounts as crosslinker. Some works report opposite effects regarding thermal stability, such as the work by George et al., 2020.[89] Authors observed a decrease in thermal stability of ECH-crosslinked cellulose hydrogels in comparison to non-crosslinked material. However, it must be emphasized that this observation has been based on evidences related to a limited temperature range (30 ºC to 150 ºC). Shi et al., 2019,[85] reported no effect at all on thermal stability of cellulose membranes upon crosslinking with ECH in the range up to nearly 350 ºC. Thus, probably the preparation conditions and origin of each specific cellulose derivative are also important in the evaluation of thermal stability.

8. Swelling Degree

Based on the construction of a tridimensional network, it is expected that the chemical crosslinking improves the swelling degree in comparison to non-crosslinked samples. This has been evidenced by Chang et al., 2008,[103] showing also that chemical crosslinking was better than physical crosslinking by freeze-thawing for hydrogels based on cellulose and polyvinyl alcohol, since the covalent crosslinks led to a higher structural resistance against rupture. This trend has been confirmed also by Udoetok et al., 2016,[84] as crosslinked cellulose showed a swelling degree of 297% while the degree was 161% for the non-crosslinked sample. The swelling degree was found to depend continuously on the ECH concentration according to Salleh et al., 2018,[99] being also observed by Yang et al., 2019.[104] Alam et al., 2019,[105] evaluated the swelling behavior of ECH-crosslinked carboxymethylcellulose hydrogels in water and saline aqueous solutions. Authors observed that the swelling degree is clearly affected by the crosslinker amount. They also compared the obtained samples with commercial superabsorbent hydrogels, verifying that the prepared samples were poorer than commercial ones in the case of water, being better for saline solutions though. Regarding the swelling response of doubly crosslinked hydrogels (both ionically with ions and covalently with ECH), it has been observed that samples crosslinked only covalently showed higher swelling degree than the doubly crosslinked ones, Xu et al., 2019.[106] This suggests that the predominance of covalent bridges favors structural resistance against rupture as a large amount of water is accommodated.

9. Crystallinity

Medium to long range structural order or crystallinity is an important characteristic of any material as it can influence

mechanical properties, as we shall see in this section. Chang et al., 2008[103] showed that the crosslinking with ECH led to a lower crystallinity of cellulose hydrogels in comparison to physical hydrogels, indicating an increase of the amorphous region. This also suggested that the compact packing of the original cellulose structure has been broken apart during crosslinking. Several other works also reported the crystallinity decrease upon crosslinking of cellulose, such as the works by Guo et al., 2013,[80] Chang et al., 2009,[107] Kadry et al., 2019,[11] and Gan et al., 2017.[108] In general, native cellulose exhibits a higher tendency to aggregate in highly organized structures as result of the hydrogen bonds, while crosslinking consumes large fractions of the functional groups responsible for those interactions, also keeping the chains permanently separated.

The decrease of crystallinity may also influence other properties such as visible region transmittance, as shown by Shi et al., 2019[85] for cellulose membranes, as result of the decrease in the amount of crystallites acting as scattering clusters. In contrast to the predominant trend reported in many works, Udoetok et al., 2018a[102] did not observe evidence of disordering of the crystalline cellulose domains upon crosslinking with ECH, suggesting that in their case crosslink was limited to the amorphous regions.

A distinctive effect of the subsequent formation of carboxymethylcellulose and crosslinking with ECH on the crystalline structure of cellulose was described by Alam et al., 2019,[105] that reported a partial conversion of cellulose I to cellulose II polymorph, on the basis of a shift in the diffraction peak position. Also, the crystallinity degree decreased from 73% in cellulose to 52% in crosslinked carboxymethylcellulose, suggesting that originally crystalline regions were also modified.

10. Mechanical Properties

Crosslinking of polymers strongly affects several mechanical properties. In this context, Chang et al., 2008,[103] reported that hydrogels crosslinked with ECH exhibited lower strength and storage modulus than physical gels due to the disintegration of crystalline regions upon the formation of covalent bonds in chemical crosslinking, resulting in higher mobility of chains. Moreover, the consumption of hydroxyl groups in chemical crosslinking led to a decrease in PVA-cellulose interactions making the water permeation easier and contributing to increase the swelling degree. The role of hydrogen bonds in physical gels, on the other hand, is determinant of the properties making the arrangement more compact with high entanglement between chains. This increases the mechanical properties while decreasing the swelling degree. The role of amorphous and crystalline regions on the mechanical properties may depend on the specific property as shown in the work by Shi et al., 2019.[85] Authors prepared membranes with both broken strength and broken elongation improved after crosslinking with ECH mainly due to the crystallinity decrease, as the amorphous

component increases the elongation capacity while the crosslinkings are able to dissipate the mechanical energy.

The effect of increasing amounts of ECH was reported by Qin *et al.*, 2013,[109] observing an increase in the compressive modulus as the crosslinker amount increased from 5 to 10 and 15%, while in the work by Huber *et al.*, 2019,[110] the concentration of ECH did not produce a statistically significant change in mechanical properties in the range of 5–15%. Direct comparison of results from different works can be difficult owing to lack of details in sample description by Qin *et al.*, 2013.[109] Huber *et al.*, 2019[110] discussed their results considering that cellulose concentration was insufficient to effective interchain crosslinking to occur in their samples, as the samples suffered mainly intrachain crosslinking. Those crosslinked chains will form gels with less crystalline configurations, consequently with poor mechanical properties. In order to overcome this limitation, additional cellulose was used as reinforcing agent, proving to be a successful approach due to the higher availability of hydroxyl groups.[110] The higher crosslinking density obtained led to better stiffness and strength values.

The addition of a second polymer or providing alternatives to additional interchain interactions were proposed in some works in order to simultaneously obtain high swelling degrees and good mechanical properties. In this context, Yang *et al.*, 2019,[104] prepared mixed hydrogels by adding polyacrylamide to cellulose with promising results, as a 4-fold increase in the compressive strength in comparison with the unmixed hydrogel was observed.

Xu *et al.*, 2019[106] prepared hydrogels with both covalent crosslinking with ECH and ionic crosslinking and observed that the mechanical properties increased, which was attributed to the higher crosslinking density. In contrast to tridimensional hydrogels monoliths, crosslinking with ECH in films and membranes was found to have positive effects on mechanical properties as reported by Guo *et al.*, 2013,[80] in a study of cellulose films crosslinked with different ECH concentrations. However, it must be emphasized that the cellulose:ECH must be optimized in each case, in order to improve the mechanical performance. Xie *et al.*, 2022,[91] showed that the mechanical properties of cellulose:ZnO films for use in packages can be considerably improved upon crosslinking with ECH making the application feasible, which otherwise is not be possible in the absence of crosslinking. Double crosslinking strategy can further improve the mechanical properties of films and membranes as demonstrated by Lee *et al.*, 2021.[111] Authors evaluated the properties of TEMPO oxidized cellulose films crosslinked chemically with ECH and physically with Ca^{2+} ions. The Young modulus and tensile strength were both improved in the order non-crosslinked cellulose < singly crosslinked film < doubly crosslinked films.

Figure 2 illustrates a simple pictorial idea of some general correlations between the type of crosslinking with changes in the ordered/disordered regions in cellulose-based materials and mechanical properties suggested by works in the field, not to be taken as a rule but showing general trends.
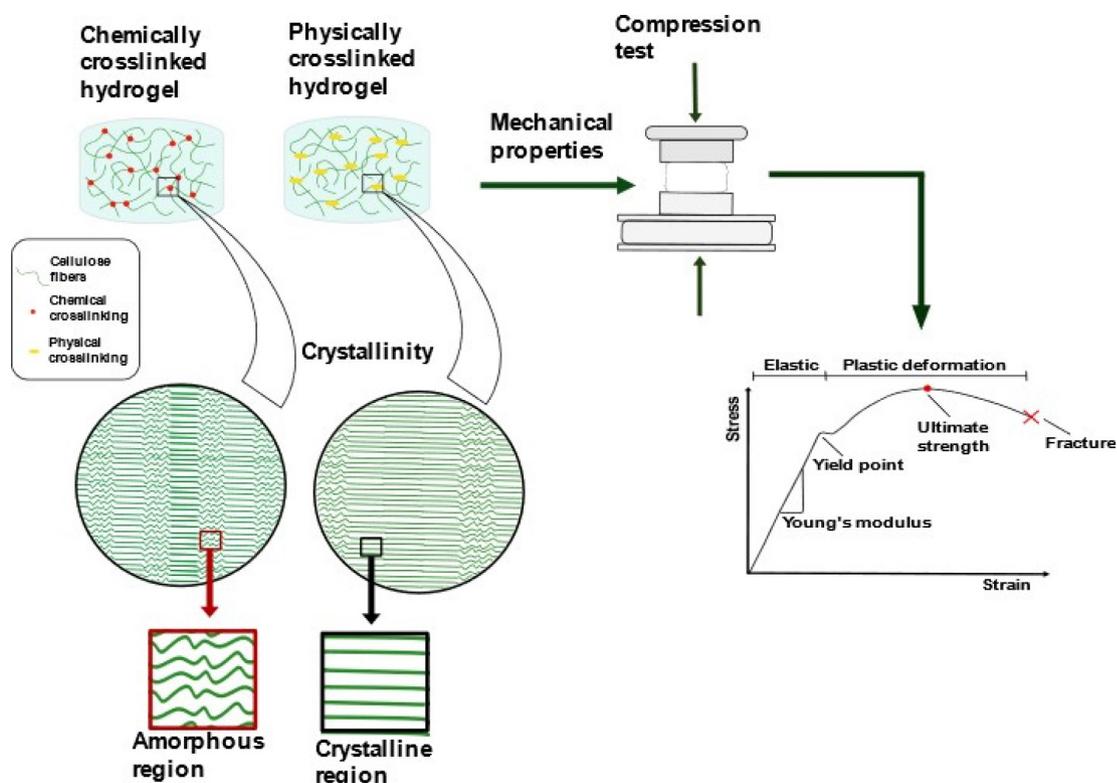

Figure 2. Pictorial summary of general trends observed between the type of crosslinking with changes in the ordered/disordered regions in cellulose-based materials and mechanical properties

11. Final Remarks

Specific properties of cellulose and its straightforward modification strategies have motivated a great deal of studies. In this mini-review an examination of works using cellulose and its derivatives crosslinked with ECH was proposed aiming to show the effects of this important crosslinker on the resultant materials. Crosslinking with ECH allows the formation of variable materials such as hydrogels, films, foams beads and membranes. In hydrogels, for instance, ECH influences positively the swelling degree while leading to weakening of some mechanical properties such as compressive strength. Moreover, ECH contributes to the improvement of thermal stability and decrease of crystallinity also influencing mechanical performance. In order to mitigate the negative effects, the double crosslinking approach has been found to be effective but it is worth to mention that positive and negative effect must be balanced taking into account each desired application. In summary, the versatility of ECH-modified cellulose materials enables opportunities for application in many different fields. However, some challenges must be overcome in order to improve crosslinking efficiency and optimize the properties of crosslinked materials, in view of the desired application, such as adaptations in crosslinking conditions, mixed crosslinking studies to take advantage of the positive features of each crosslinker, in addition to evaluating the long-term performance and stability of materials as well as searching for new applications.

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