

## Medical and pharmaceutical application of oxidized cellulose

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## INTRODUCTION

Cellulose is a linear homopolysaccharide, composed of anhydroglucose units linked by 1,4- $\beta$ -D glycosidic bonds. Each anhydroglucose unit consists of three hydroxyl groups: primary at position C6, and two secondary at positions C2 and C3. These hydroxyl groups can be oxidized to carboxyl, aldehyde or keto groups. Very often, different groups are formed at the same time, and the oxidation product is sometimes referred to as oxycellulose.

Oxidation has a significant role among different processes of chemical modification of cellulose, since the oxidized cellulose is a biodegradable product that can be resorbed by the human body (Kumar & Yang, 2002; Lai et al., 2015; Wu & Wang, 2019). Since the discovery of these unique properties, the oxidized cellulose is used as a hemostatic agent in clinical practice from the 1950s until today (Wu et al., 2018; Zhang et al., 2019). In addition to this most frequent application of the oxidized cellulose, interest in new applications, particularly pharmaceutical, continues to grow.

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Cellulose is the most abundant natural polymer and versatile starting material for chemical modification for obtaining products with various applications. The oxidation of cellulose results in derivatives with improved properties, including the products with new, specific features that can be used for medical and pharmaceutical purposes. Due to its biocompatibility and biodegradability, the oxidized cellulose (6-carboxycellulose) is widely used as a hemostatic agent, as a barrier for the prevention of postsurgical adhesion, in bandage products for covering different wounds, as an excipient in the production of tablets, various gels and pharmaceutical suspensions. In addition to these applications, the oxidized cellulose may be used for the production of surgical sutures, as a drug carrier in products with gradual/controlled release, and as a material in tissue engineering.

This paper offers an overview of the medical and pharmaceutical application of the oxidized cellulose, obtained by introducing a carboxyl group into the position C6 (Figure 1).

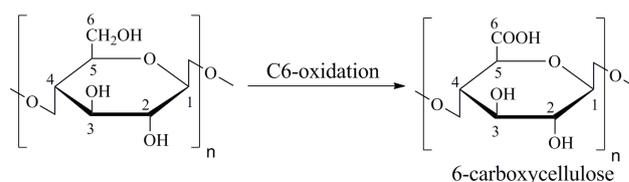


Figure 1. Selective oxidation of cellulose into position C6

### Obtaining oxidized cellulose (6-carboxycellulose)

The oxidation of cellulose enables a modification of the physical and chemical properties of cellulose, that are important for medical and pharmaceutical applications (Bajerová et al., 2009). In most cases, the action of oxidizing agents on cellulose leads to the simultaneous oxidation of primary and secondary hydroxyl groups, i.e. a non-selective oxidation takes place. More significant is a selective oxidation of cellulose by using specific oxidants which oxidize hydroxyl groups in specific carbon atoms and which result in products of uniform chemical composition and characteristics. Still, the selective oxidant does not ensure absolute selectivity because every oxidation is followed by side

reactions important for the characteristics of the final product. Thus, for example, the presence of a small amount of carbonyl groups in 6-carboxycellulose enables its resorption in the human body (Dimitrijevič et al., 1990a; Dimitrijevič et al., 1990b), necessary for medical and pharmaceutical application.

6-carboxycellulose can be obtained by oxidation using nitrogen dioxide ( $\text{NO}_2$ ) in a non-polar solvent, such as tetrachloromethane. This oxidation implies a rather complex mechanism, which includes adsorption of nitrogen oxides on the surface of cellulose, diffusion of oxidants into the structure of cellulose particles or fibers, whereby unstable cellulose nitrites are formed as intermediates (Kaverzneva & Salova, 1959). The literature provides a description of several oxidation processes with nitrogen oxides (Coseri et al., 2013), some of which are applied in industrial conditions, while some of them are used only in laboratories due to their complexity.

An improved version of oxidation with nitrogen oxides includes the treatment of cellulose with phosphoric acid with  $\text{NaNO}_2$ , whereby  $\text{N}_2\text{O}_3$  is generated as an oxidant (Painter et al., 1985). This process results in the increase of the oxidation degree with the increase of the molecular weight of the initial cellulose. This type of oxidation can be performed by using sodium nitrite in a mixture with  $\text{HNO}_3$  (Sharma et al., 2017),  $\text{HNO}_3/\text{H}_3\text{PO}_4$  (Kumar & Yang, 2002) or in a mixture with  $\text{HNO}_3/\text{H}_2\text{SO}_4$  (Son et al., 2004).

In the last few years, great attention has been paid to the process of oxidizing primary hydroxyl groups by using 2,2,6,6-tetramethylpiperidine-1-oxyl-radicals,

known as TEMPO radical. Unlike the oxidation with nitrogen oxides, TEMPO oxidation offers numerous advantages, such as higher reaction rate and yield, high selectivity and less cellulose degradation during the oxidation process (Bragd et al., 2004). Various TEMPO oxidation systems for cellulose substrates were most studied by Isogai and Saito (Isogai & Kato, 1998; Isogai et al., 2018; Saito et al., 2006; Saito et al., 2010).

The typical TEMPO oxidation with  $\text{NaBr}/\text{NaOCl}$  of pH at 10-11 implies the effective conversion of primary hydroxyl groups first to aldehyde, and then to carboxyl groups (Saito & Isogai, 2004). However, the implementation of the system TEMPO/ $\text{NaBr}/\text{NaOCl}$  is usually related to the problem of cellulose depolymerization. By using the modified system TEMPO/ $\text{NaClO}/\text{NaClO}_2$  of pH at 4-7 it is possible to decrease the extent of oxidized cellulose depolymerization (Hirota et al., 2009), but this also reduces the content of carboxyl groups (Isogai et al., 2011). Figure 2 (Ruan, 2017) shows two typical TEMPO oxidations, with  $\text{NaBr}/\text{NaOCl}$  in an alkaline medium of pH at 10-11 (Saito et al., 2006) (a), and with  $\text{NaClO}/\text{NaClO}_2$  in an acidic or neutral medium (Saito et al., 2010) (b).

New, more environmentally friendly, TEMPO systems include the use of enzymes such as oxidases and peroxidases. One such process of cellulose oxidation, in which enzyme has the role of co-catalyst instead of hypochlorite, uses the TEMPO/lacaza/oxygen system (Aracri et al., 2012; Quintana et al., 2017).

The introduction of carboxyl groups on cellulose fiber, without using toxic reagents, can be performed

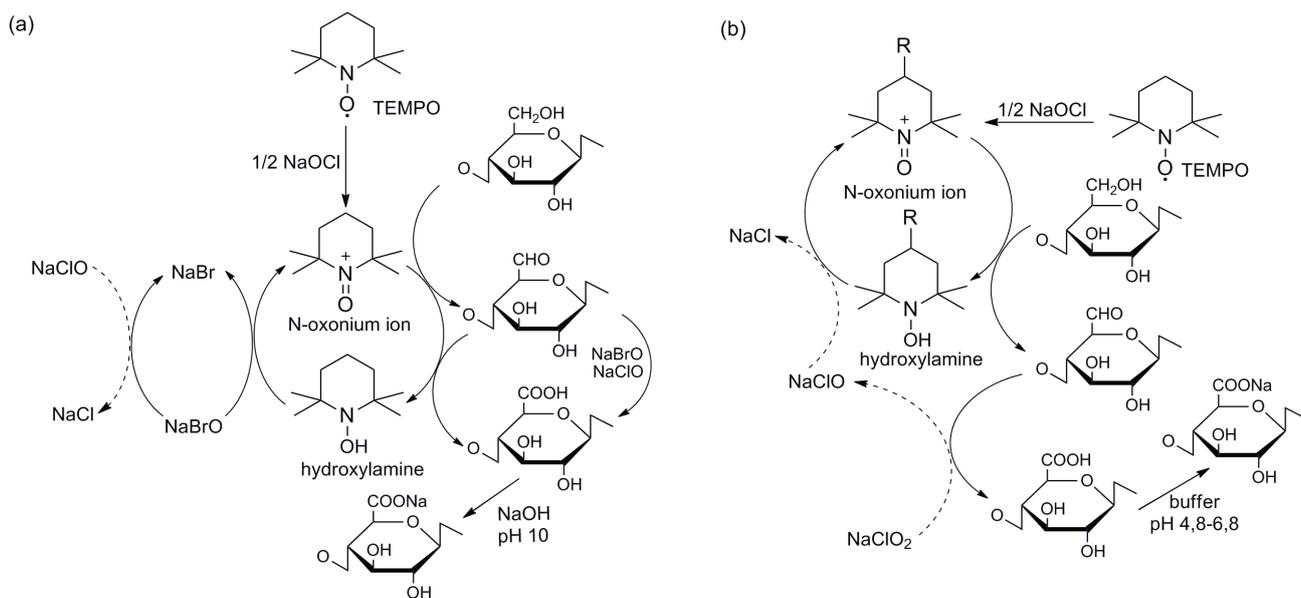


Figure 2. Selective oxidation of C6 primary hydroxyl groups of cellulose into carboxyl by using (a) TEMPO/ $\text{NaBr}/\text{NaOCl}$  in aqueous solution of pH 10-11, and by using (b) TEMPO/ $\text{NaClO}/\text{NaClO}_2$  (Ruan, 2017)

by applying a dielectric barrier discharge (plasma treatment). This process enables the obtaining of the oxidized cellulose suitable for different biomedical applications (Pavliňák et al., 2015; Vosmanska et al., 2014).

### The medical and pharmaceutical use of 6-carboxycellulose

To date, the oxidized cellulose obtained by oxidation with nitrogen oxides has been most widely used for medical and pharmaceutical purposes. In recent years, there is an increasing number of papers dealing with the potential applications of products produced by TEMPO oxidation of cellulose, specifically in the field of cellulosic nanomaterials. Although the testing of biocompatibility and long-term non-toxicity of these materials for the human body is still ongoing, the results obtained so far indicate that they could be successfully applied in the future (Yang et al., 2019).

### Hemostatic and bandage materials and the treatment of chronic wounds

The oxidized cellulose (OC) was first used as hemostatic in 1942, and in 1960 the oxidized regenerated cellulose (ORC) was produced (Kunio & Schreiber, 2013). *The ORC is obtained through oxidation of the regenerated cellulose, most commonly of rayon. This fiber, unlike cotton, has a uniform chemical and physical composition and provides the oxidation product of better absorption characteristics* (Havelka et al., 2010).

According to the American Pharmacopeia the oxidized cellulose (OC) used as a hemostatic must contain 16-24% COOH groups (USP29-NF24, 2020a), while the oxidized regenerated cellulose (ORC) must have 18-24% COOH groups calculated on the dried basis (USP29-NF24, 2020b).

Due to its simple application, biocompatibility and bactericidal properties, the oxidized cellulose has become a standard hemostatic material in surgical practice, so nowadays it is used in the form of a powder, gauze, mesh, sponge etc. (Table 1).

Oxidized cellulose acts as a passive hemostatic by providing substrate for the adhesion and aggregation of platelets (Masci et al., 2018), and when used in acid form (6-carboxycellulose) it promotes hemostasis by lowering pH value (Bajerová et al., 2009). All forms of the oxidized cellulose are resorbed and completely degraded in a period of 1-6 weeks, depending on the place of application and amount used (Kunio & Schreiber, 2013).

As a hemostatic material, the ORC is easily adjusted to uneven surfaces and hard-to-reach areas of application (Masci et al., 2018). According to some authors (Lewis et al., 2013; Pameijer US patent, 2007), OC has better hemostatic properties than ORC, while others prefer ORC based on evaluation of cytotoxicity, bactericidal and hemostatic properties (Sezer et al., 2019; Wagenhäuser et al., 2016). The irritation and cytotoxicity of ORC due to the low pH may be reduced

Table 1. Commercial hemostatic materials based on the oxidized cellulose currently available on the market (Zhang et al., 2019).

Product name	Composition and form	Producer	Country
Oxycel®	oxidized cellulose (gauze)	Becton Dickinson	USA
Surgicel®	oxidized regenerated cellulose (gauze, mesh, powder)	Johnson& Johnson	USA
Evarrest®	oxidized regenerated cellulose (medical plaster)	Johnson& Johnson	USA
ActCel®	oxidized regenerated cellulose	Coreva Helth Science, LLC	USA
Traumacel®	oxidized regenerated cellulose with calcium (powder)	Bioster 1.s.	Czech Republic
Gelita-Cel®	oxidized cellulose (gauze, mesh, powder)	Gelita Medical	Germany
Okcel®	oxidized cellulose (gauze, medical compress, powder)	Sinthesia	Czech Republic
CuraCel®	oxidized regenerated cellulose (gauze, mesh)	CuraMedical BV	The Netherlands
Emosist®	oxidized regenerated cellulose (gauze)	Mascia Brunelli Spa	Italy
Taikeling®	oxidized regenerated cellulose (gauze, mesh, powder)	Hangzhou Singclean Medical Products Co., Ltd	China

by neutralization with NaOH ethanol solution. In this way it is possible to obtain a product with reduced content of free COOH groups and acidity of about pH 6, which does not cause skin irritation or inflammation (Wu et al., 2018).

New hemostatics in powder form, ORC based on K- and Na-salts, in addition to excellent hemostatic properties also show bactericidal activity against *S. Aureus* (Basagaoglu et al., 2015).

The hemostatic properties of the pure oxidized cellulose can be improved by incorporating some additional substances. The oxidized cellulose can serve as a carrier for binding trypsin, a proteolytic enzyme that helps the healing of surgical wounds (Nikolić et al., 2017). Also, there are some composite hemostatic materials in which oxidized cellulose is intermolecularly bound to collagen (Li et al., 2017) and alginate (Cheng et al., 2017). The ORC in combination with collagen in the treatment of chronic wounds helps healing in a way to inactivate harmful proteolytic enzymes, absorbs free oxygen radicals, and eliminates excess metal ions (Cullen et al., 2002). Products based on the combination of the ORC and collagen are commercially available under the trade name Promogran® (Johnson & Johnson).

The antimicrobial properties of the OC and ORC have been known for quite some time and are explained by their acidity and sorption properties (Abaev et al., 1986; Spangler et al., 2003). Numerous microorganisms can hardly survive in the environment with pH lower than 4, while the oxidized cellulose in its acidic form provides pH of approximately 3.

The carboxyl groups of 6-carboxycellulose enable the binding of various cations and substances that can enhance its antimicrobial properties. Thus, by incorporating zinc, silver and copper into the OC, it is possible to obtain fibers of enhanced antimicrobial properties (Markovic et al., 2018; Motková et al., 2017; Praskalo-Milanović et al., 2010). Combination of the ORC with carboxymethyl-chitosan results in a composite hemostatic gauze with antibacterial properties (Cheng et al., 2016).

Recently, the interest in the application of nanotechnologies for obtaining hemostatic and antimicrobial materials used in surgery has increased (Sun et al., 2018). Regardless of biocompatibility, excellent absorption capacity and hydrophilic property, the oxidized cellulose nanofibrils (OCNF) have poorer hemostatic properties. This deficiency of OCNF can be compensated by combining it with biocompatible materials such as chitosan (Markovic et al., 2018; Sukul et al., 2017) thrombin (Shefa et al., 2019a), ZnO (Shefa et al., 2019b) and silver amid ( $\text{Ag-NH}_2$ ) (Liu et al., 2018). In this way, materials with better hemostatic, antibacterial and mechanical properties were obtained.

### **Material for the production of surgical sutures and tissue engineering**

Although the oxidized cellulose is mostly used as a hemostatic, it is well known that it can be used for the production of surgical sutures (Yasnitskii, 1982). The oxidized regenerated cellulose (ORC) has achieved excellent results in the prevention of post-surgical adhesions and healing of wounds (Li & Cook, 1994), and, recently, surgical sutures made from the ORC have been confirmed to have good mechanical and resorption properties (Cheng et al., 2019).

Thanks to its non-toxicity, biocompatibility and biodegradability, the oxidized cellulose satisfies the main criteria for biomaterials used in tissue engineering. In this application, the biomaterial which is introduced into the wound serves as a scaffolding material for the formation of new tissue, whereby the biomaterial is gradually degraded, after which it disappears. This application requires that the OC must contain 5-10% of COOH groups calculated on the dried basis (Havelka et al., 2010). The oxidized cellulose proved to be an excellent material for the regeneration of bone tissue (Park et al., 2015; Safwat et al., 2018) that could successfully replace collagen which has been mostly used for this purpose so far (Dias et al., 2003). The functionalization of the oxidized cellulose with arginine and chitosan resulted in providing the material suitable for application in tissue engineering with improved stability and biocompatibility (Novotna et al., 2013). Lately, the technology of 3D printing of the carriers for the regeneration of bone tissues has been attracting more and more attention. Different combinations of biopolymers and inorganic materials have been intensively tested for the needs of this technology. Thus, a composite material based on the oxidized cellulose and alginate has shown excellent characteristics in the production of 3D carriers for bone tissue regeneration (Abouzeid et al., 2018).

### **Auxiliary material in pharmaceutical technology and drug carrier**

The oxidized cellulose as an auxiliary material in pharmaceutical technology is compatible with a large number of water-soluble and insoluble pharmaceutical excipients, such as methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, polyacrylates, alginates, polysorbates and many others. These substances can be combined in dispersions or mixed with the powdered form of the oxidized cellulose.

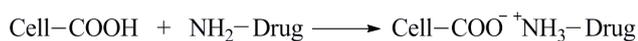
In an aqueous medium, the OC can bind water and form thixotropic gels. These properties allow it to be combined with other pharmaceutical adjuvants in suspension with the content of the OC < 3 % in suspension, 0,5-15 % of the OC in lotions and gels

or with 15-50 % of the OC in creams containing (Gajdziok & Vetchy, 2015).

In the production of solid drug forms, the OC can be used to make coatings for the film-coated tablets in combination with other polymers, since the OC is very fragile and not suitable for this application as such (Bajerová et al., 2009). Gajdziok et al. (2013) have determined that the OC in the form of Na-salt (NaOC) is better as an excipient in tablets than the acidic form of the OC. Thus, NaOC in combination with hydroxypropyl-methyl cellulose as a hydrophilic-lipophilic matrix enables the gradual release of caffeine from the tablets that can be used in professions requiring increased alertness, such as drivers, pilots etc. (Gajdziok & Vetchy, 2015).

The oxidized cellulose has been tested in muco-adhesive tablets (Gajdziok et al., 2010) and in the form of beads with controlled drug release (Trygg et al., 2014; Zhang, 2013) The procedure of spray-drying of aqueous dispersions of the OC provided oxidized cellulose in the form of biocompatible and biodegradable microparticles, suitable to be used as carriers for different drugs in an injectable or implantable delivery systems (Kumar et al., 2001a). Such micro particles in an anti-allergy spray bind grass and mite allergens to the OC and prevent allergic reactions (Shani et al., 2011; Shoseyov & Yosef, 2015).

Due to the free carboxyl groups, the oxidized cellulose can bind different drugs, enzymes and proteins. Binding is mostly performed through electrostatic interactions between COOH group of the oxidized cellulose and  $\text{NH}_2$  group of bioactive substances:



A significant factor in drug binding, besides the content of COOH groups of the oxidized cellulose, is the pH of the solution during binding. The amount of the bound drug decreases below pH 3, since the degree of OC dissociation is decreased. In addition to this, the example of amino acids and  $\beta$ -lactam antibiotics was used to prove that the pH of the solution defines the form of the drug (cationic, anionic or neutral) which also influences the amount of the drug bound to the OC (Zimnitsky et al., 2006). Monitoring over binding various bioactive substances to the OC with different pH values showed that hydrogen bonds, hydrophobic and Van der Waals interactions also participate in binding, in addition to ionic interactions, (Đudić et al., 2015; Kumar et al., 2001b; Rodić-Grabovac et al., 2017; Sailović et al., 2018).

It was proved that in combination with phenylpropanolamine the OC can be used as a carrier for covalent drug binding by an amide bond, which provides gradual drug release by hydrolysis in the acidic

pH range (Zhu et al., 2001). Phenylpropanolamine can also be bound by ionic interaction of the drug amino group with partially neutralised COOH groups of the oxidized cellulose. Thus obtained drug-OC complex allows a gradual drug release, and can potentially be applied in implantable systems with controlled drug release (Zhu et al., 2004).

The antiseptics chlorhexidine (Nizhnikova et al., 2004), cetylpyridinium chloride (Gajdziok et al., 2010), and 2-benzyl-4-chlorophenol (Cassano et al., 2013) were successfully bound to the oxidized cellulose. The OC also served as a carrier for glycosidic (Yurkshtovich et al., 2002; Yurkshtovich et al., 2004) and cephalosporin antibiotics (Rodić-Grabovac et al., 2014; Sailović et al., 2016a; Sailović et al., 2016b; Zimnitsky et al., 2006), and metronidazole (Kumar et al., 2020).

The oxidized cellulose can be used as a carrier for analgesics diclofenac (Bajerová et al., 2011; Sailović et al., 2018), ibuprofen (Celebi et al., 2016) and acetaminophen (O'Donnell et al., 2020), as well as for the anesthetics procaine (Akhlaghi, 2014; Rodić-Grabovac & Đudić, 2008) and lidocaine (Rodić-Grabovac et al., 2006).

The pure 6-carboxycellulose as a hemostatic, proved its anti-tumor activity (Tokunaga et al., 1998), while the anti-tumor substances camptothecin (Kumar et al., 2001c), methotrexate (Zhang et al., 2013; Zimatkina et al., 1996) and cisplatin (Sheleg et al., 2002) were successfully immobilized on the oxidized cellulose.

The gels with the OC in the form of Na-salts proved to be excellent enterosorbents with antiulcer and detoxifying effects (Gert et al., 2005). The gastroprotective activity was improved by combining the OC in the form of oral tablets with glycyrrhizin, triterpene glycosides from licorice (Gajdziok et al., 2013), while the OC in the form of beads with controlled drug release was used as a carrier for ranitidine (Trygg et al., 2014).

## CONCLUSION

The oxidation of the primary hydroxyl group of cellulose in position C6 to carboxyl group results in a product which has found wide medical and pharmaceutical application due to its biocompatibility, biodegradability, antimicrobial and immunomodulatory properties. Although it has been used as a hemostatic for a long time, the oxidized cellulose does not meet all demands of the clinical practice. That is why new procedures of modifying hemostatic materials based on the OC by introducing other functional groups or by combining it with materials that should increase its hemostatic potential have been developed. Besides the fact that there are already some enhancements of the hemostatic properties of new material based on the OC, it is necessary to wait for a greater number of clinical trials in order to approve the mass application.

Compared to other cellulose derivatives, the oxidized cellulose is rarely used as an excipient, but the increased number of studies indicates its advantages and possibilities of using it as a drug carrier, particularly in the systems for controlled and gradual drug release.

New procedures, such as TEMPO oxidation, resulted in products with improved physical and chemical properties, including TEMPO-nanocellulose. Composite carriers based on the oxidized nanocellulose have shown excellent results in bone tissue regeneration and have confirmed that the oxidized cellulose can successfully replace presently most common material, collagen.

Despite the increased number of research groups dealing with the oxidized cellulose and the large number of patents for the OC-based products, it is rather relatively expensive material. Considering that it is obtained from the most abundant and completely renewable cellulose biopolymer, with more effective and cheaper oxidation procedures, the interest in the application of the oxidized cellulose in different products will certainly increase in the future.

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## Medicinska i farmaceutska primjena oksidovane celuloze

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### Ključne riječi:

6-karboksiceluloza, oksidovana celuloza, hemostatičko sredstvo, nosač lijekova, biomedicinska primjena

Celuloza je prirodni polimer koji karakteriše dostupnost, jednostavnost dobijanja, i molekularna struktura koja omogućava hemijsko modifikovanje u proizvode različite namjene. Oksidovanjem celuloze dobijaju se derivati sa poboljšanim svojstvima, kao i proizvodi sa novim, specijalnim osobinama koje omogućavaju medicinsku i farmaceutsku primjenu. Oksidovana celuloza (6-karboksiceluloza) se može dobiti oksidacijom sa gasovitim azot-dioksidom u nepolarnom rastvaraču ili sa azotnim oksidima koji se generišu reakcijom NaNO<sub>2</sub> sa azotnom, sumpornom ili fosfornom kiselinom. Najširu primjenu u medicini i farmaciji našla je oksidovana celuloza dobijena oksidacijom sa azotnim oksidima.

Posljednjih godina sve veći broj radova bavi se mogućnostima primjene proizvoda TEMPO oksidacije celuloze, naročito u oblasti celuloznih nanomaterijala. Postupkom TEMPO oksidacije celuloze sa 2,2,6,6-tetrametilpiperidin-1-oksil-radikalom postiže se veća brzina i prinos reakcije, kao i visoka selektivnost i manja degradacija celuloze tokom procesa oksidacije.

Zahvaljujući biokompatibilnosti i biodegradabilnosti, 6-karboksi celuloza je našla široku primjenu kao hemostatik, sredstvo za sprečavanje posthirurških adhezija i materijal u proizvodima za previjanje različitih rana. Pored oksidovane celuloze (OC) u praškastoj formi, u obliku gaze ili mrežica, kao hemostatički materijal i za previjanje rana koristi se i oksidovana regenerisana celuloza (ORC). Ona se dobija oksidacijom regenerisane celuloze, najčešće rejonu, i za razliku od pamučnog vlakna, daje proizvod ujednačenog hemijskog i fizičkog sastava i boljih apsorpcijskih svojstava.

Oksidovana celuloza se može koristiti kao ekscipijent u proizvodnji tableta, gelova i farmaceutskih suspenzija ili kao materijal za inkapsuliranje lijekova u obliku perli. Pored ovih primjena, oksidovana celuloza se može upotrijebiti za izradu hirurških konaca, kao nosač različitih ljekovitih preparata u proizvodima sa postepenim/kontrolisanim otpuštanjem, i materijal u inženjerstvu tkiva. Kompozitni nosači na bazi TEMPO oksidovane nanoceluloze pokazali odlične rezultate u regeneraciji koštanog tkiva i potvrdili da mogu uspješno da zamijeni danas najzastupljeniji materijal, kolagen.