



The Role of Electron Structure of Polymers at Their Biodegradation in Living Organisms

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Abstract

Based on the results of experimental studies, comparison of electronic structures and computer simulation of cellulose macromolecules and its derivatives, the possibility of creating composite biodegradable forms of hemostatic agents is shown.

It has been established that the rate of biodegradation of cellulose and its derivatives is directly dependent on molecular parameters, electro negativity and the number of substituents contributing to the displacement of the electron cloud towards electronegative atoms leading to a weakening of the acetal bonds between anhydroglucose units of cellulose and its derivatives. It was shown that the rate of biodegradation of macromolecules decreases in the order OC> NCC> CMC> CEC> cellulose.

It has been established that cellulose macromolecules are not subject to biodegradation in body tissues, and biodegradation of non-crystalline cellulose is, probably, explained by phagocytosis (absorption of small particles of nanoscale size of the body cells).

It is also shown that biodegradation of macromolecules of cellulose derivatives is directly dependent on the number of electronegative substituent's and their electro negativity.

Keywords

Electronic structure; Biodegradation; Cellulose; Carboxymethylcellulose; Polymer

Introduction

Currently, in the world medical practice, a large number of hemostatic agents are used, which differ in the dosage form, methods of use, composition, structure and properties [1-3].

Hemostatic agents include drugs and medical products that promote blood coagulation. These include coagulants of direct (thrombin, fibrinogen) and indirect (menadione, phytomenadione) effect - means of stimulating the formation of fibrin clots, inhibitors of fibrinolysis - synthetic and animal origin, promoters of platelet aggregation such as serotonin adipate, calcium chloride and substance binder and cauterants as tannin and its derivatives, alum, solutions of iron oxychloride and hydrogen peroxide [4,5].

This report presents the results of studies of new polymeric forms of hemostatic agents based on compositions of bio-divisible polysaccharides containing chemically bound calcium ions.

Calcium preparations are referred to as "weak aggregates" such as serotonin, adroxin, and belong to stimulators of platelet aggregation.

It is known that calcium ions as a hemostat are directly involved in the aggregation and adhesion of platelets, as well as contribute to the formation of thrombin and fibrin. Thus, they stimulate the formation of platelet and fibrinogenic thrombus. Calcium preparations are used for bleeding associated with a decrease in its level in the blood plasma. In such cases, calcium compounds are administered intravenously, intramuscularly, or orally.

The disadvantages of calcium ions when used as a hemostatic agent include the following factors:

- Calcium ions at low concentrations in the body do not show the necessary level of hemostaticity;
- At high concentrations - show the necessary level of hemostatic, however, with the simultaneous manifestation of toxicity.

In order to reduce the level of toxicity and at the same time preserve the necessary

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hemostatic properties, we have conducted research on the creation of biodegradable polymeric forms of drugs with high adhesive properties, where calcium ions in the polymer structure are in a bound state.

Materials and Methods

As a polymer substrate, we selected compositions of biodegradable polysaccharides from carboxymethylcellulose (CMC), oxidized cellulose (OC) and nanocrystalline cellulose (NC), carboxyethylcellulose (CEC) [6,7].

In the preparation of calcium salts of polysaccharides, calcium chloride [8] and ethyl alcohol [9] are used. Obtaining a hemostatic composition using purified CMC, OC, and NC powder, followed by adding a 50% aqueous solution of calcium chloride in a 1: 1 volume of ethyl alcohol and a mixing, composition at $25 \pm 1^\circ\text{C}$ for 90 minutes with drying of the product at a temperature. The solubility of the composition is determined by the method [10].

Biodegradation of the hemostatic composition was determined according to the methodology at the Medical Academy of the Republic of Uzbekistan carried out biomedical tests of hemostatic agents synthesized by us, in order to identify their biodegradability and absorbability in the body, by injecting their suspensions under the skin of white rats by injection.

Animals were injected with 1% aqueous sterile suspension of nanocellulose subcutaneously in the back between the shoulder blades and buttocks. Preliminary histological studies of ultrathin sections of white rat tissue over time were carried out at the Republican Pathological and Anatomical Center of the Ministry of Health of the Republic of Uzbekistan.

For histological examination, ultra-thin sections of muscle tissue were taken, which were fixed in a 10% formalin solution. Paraffin sections of tissues with a thickness of 7-8 μm were stained with general histological methods. The state and the nature of the tissue reaction of the muscle wall and subcutaneous tissue were studied. On the 1st day after the injection, electron microscopic studies showed that nanocellulose is homogeneous, has a rounded shape, is colored pink, the initial stages of regional resorption are visible. After 30 days, the presence of hemostatic agents was not detected on animal tissues, and during the study period there were no cases of lethal outcome of white rats even after 6 months of injection. Based on the results obtained, the possibility of biodegradation of hemostatic agents when administered subcutaneously to animals within 30 days was first shown for the first time [11]. The content of carboxyl and carboxymethyl groups in the structure of polysaccharides was determined by the methods of [12,13]. The electronic characteristics of cellulose and its derivatives were modeled using the methods of quantum mechanics, molecular mechanics, and dynamics using the Huperchem 8.0 software [14] and Chem Draw and Chem 3D Pro, which are part of the Chem Bio Office 2010 layout [15].

Results and Discussion

The polysaccharides included in the structure of the biodegradable composition belong to the class of hetero-chain polyanions, and the terms of their biodegradation can be controlled by varying the content of carboxyl and carboxymethyl groups.

It is also known that the ionic carboxyl and carboxymethyl groups of these polymers can exhibit weak hemostatic properties as aminocaproic, aminomethylbenzoic and Tranexamic acids, which are used in medical practice as hemostatic inhibiting the fibrinolysis process. The chemical combination of calcium ions with carboxyl and carboxymethyl groups can lead to an additive increase in their hemostatic properties.

The solubility of these polysaccharides in water and their susceptibility to biodegradation in the body can be explained on the basis of the structure of their elementary units in the polymer chain

and the shift of the electron cloud of the glucopyranose ring towards the electronegative substituent groups (Table 1).

It is known that cellulose, when introduced into the human body orally and intramuscularly, is practically not subject to biodegradation. The biodegradation of cellulose in animals is due to the presence of the enzyme-cellulose in their gastrointestinal tract.

The unbiodegradation of cellulose in humans' organisms from a microscopic point of view is also explained by the fact that in cellulose macromolecules the distribution of the electron cloud in anhydroglucose cycles is localized in such a way that the 1,4 β -glycosidic bond between the anhydroglucose cycles is stable in both acidic and alkaline media and therefore, it is difficult to biodegrade. In addition, a large number of intramolecular and intermolecular hydrogen bonds are present in the macromolecules of cellulose that interfere with the cleavage of intermolecular β -glycosidic bonds.

In the case of an elementary cellulose unit, one primary and two secondary hydroxyl groups weakly attract the electron cloud of the glucopyranose ring, due to the localization of the unpaired oxygen electrons of the hydroxyl groups and practically do not affect the chemical stability of β -glycosidic bonds. This explains the insolubility and non-susceptibility to the biodegradation of cellulose in water.

Unlike cellulose, the OC unit element at the sixth carbon atom contains electronegative carbonyl oxygen, which, due to an unpaired electron pair, strongly attracts the electron cloud of the glucopyranose ring, which weakens the 1-4 β -glycosidic bonds between the anhydroglucose cycles, which leads to gradual the cleavage of 1-4 β -glycosidic bonds of oxycellulose, both in conditioned and in wet conditions. Ultimately, the OC turns into a powdered bio-exploitable state, soluble in weak solutions of whole.

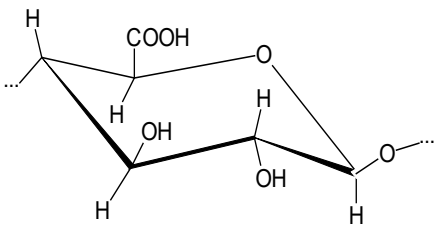
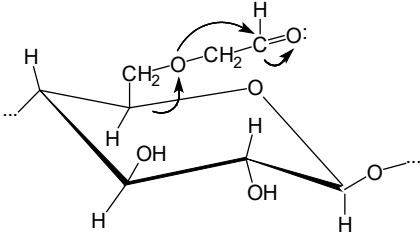
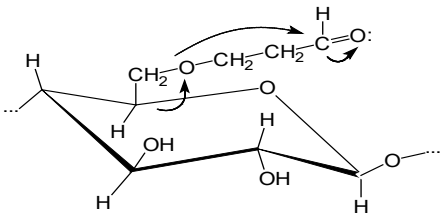
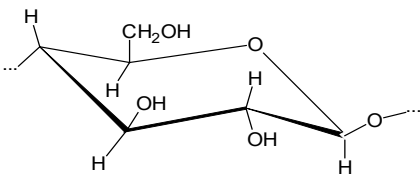
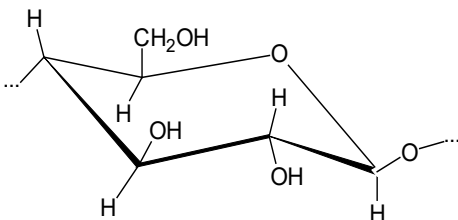
The inclusion of carboxymethyl groups, in the case of obtaining Na-CMC, also contributes to the displacement of the electron cloud of the anhydroglucose cycle towards the carbonyl oxygen of the carboxymethyl groups. However, this shift of the electron cloud will be weaker than in the case of the OC, due to the removal of the carboxyl group from the core of the anhydroglucose cycle.

Due to the weak displacement of the electron cloud of the anhydroglucose cycle towards the carbonyl of the carboxymethyl group, CMC is relatively stable in the dry state and in aqueous solutions as compared to OC, but, depending on the degree of substitution, the carboxymethyl groups are soluble in water and alkali aqueous solutions for the destruction of intra and intermolecular hydrogen bonds under the influence of ionogenic carboxymethyl groups, which probably explains their susceptibility to biodegradation in the body.

Confirmation of the influence of substituted carbonyl groups distance relatively to anhydroglucose ring in carboximethylcellulose is that electron negative oxygen of the carbonyl group of carboxyl is substantially removed from anhydroglucose ring in comparing to oxycellulose. Apparently, carboxymethylcellulose swells, but poorly dissolves in water, and resists to dry and wet conditions by maintaining to a greater degree of intra- and intermolecular hydrogen bonds. All this contributes to the slow biodegradation of CEC in the body.

In the case of NC, the electronic structure of the anhydroglucose cycle remains unchanged. With the transition from macroscopic to nanoscale values, the number of intramolecular and intermolecular hydrogen bonds in the NC is significantly reduced, and in accordance with the general principles of nanotechnology: at reducing the size of the object, the dependence of its properties don't only on its size (through the confinement of electronic excitations) [16], but also depending on its dimension (fractality), is manifested non-monotonically. At the present time to denote a single concept of "nanofactories" [17].

Apparently, reducing the size of cellulose molecules to nanoscale values contributes to the emergence of a new property -

Empirical structure	ΔE , eV	Duration of biodegradation, days	Degree of substitution and polymerization
 Oxycellulose	10,20437	14-20	Oxycellulose. Content of carboxyl groups 18-23%. Degree of polymerization - 160 ± 10 .
 Carboxymethylcellulose	10,0339	35-45	Carboxymethylcellulose. Degree of substitution 0.85 ± 2 . Degree of polymerization - 450-650.
 Carboxyethylcellulose	9,9287	60-75	Carboxyethylcellulose. Degree of substitution - 0.80 ± 2 . Degree of polymerization - 450 ± 10 .
 Cellulose	7,8164	25-30	Cellulose. Degree of substitution - 0. Degree of polymerization - 1860.
 Nanocellulose	7,8164	16-20	Nanocellulose. The content of carboxyl groups - 10-12%. Degree of polymerization 60-80.

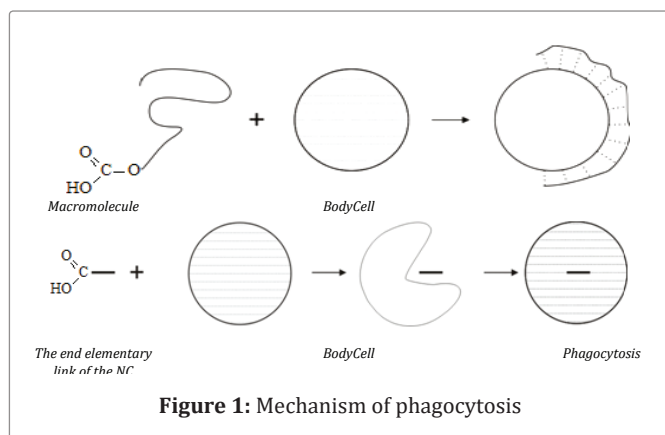
biodegradation. The possibility of NC biodegradation is probably explained not by weakening of 1-4 β -glucosidic bonds, but by weakening of intermolecular hydrogen bonds, the appearance of carboxyl groups at the end of macromolecules and the possibility of their phagocytosis by certain cells of the body (Figure 1).

To confirm the assumption of biodegradation and resorption in the body of cellulose derivatives containing electronegative substituents, we simulated the electronic properties of cellulose and its derivatives and revealed the influence of the nature of the substituents on the change in the electronic structure of glucopyranose rings. Based on calculations of the electron energy of molecular orbitals of glucopyranose cellulose rings and its derivatives (E_{homo} ; E_{umo}) and such characteristics as interatomic distances, charges on atoms and dipole moments, the change in donor-acceptor properties, excitation potential and excitation energy of molecules is established [17].

electronegative atoms and the rate of their biodegradation decreases in the OC < NC < CMC < CEC < cellulose. At the same time, cellulose is practically not subject to biodegradation.

All the main experimental results (in the perspective of theoretical interpretations) can be summarized as follows:

- 1) The degree of biodegradation (K) has a specific dependence on the length of the substituent chain, measured from zero length (corresponds to cellulose) to the maximum long chain (corresponding to carboxyethylcellulose) (Figure 2).
- 2) The bioagent that splits the -C - O - C- bond, which is a link between anhydroglucose units, is not precisely known.
- 3) The biodegradation of NC proceeds by a mechanism different from the degradation of the macromolecule.



$$\Delta E = E_{\text{homo}} - E_{\text{lumo}} \text{ (eV)}.$$

It was found ΔE values for oxycellulose, carboxymethylcellulose, and carboxyethylcellulose and nanocrystalline cellulose equal to 10.20437, 10.0339, 9.9287 and 7.8164, (eV) respectively.

Changing of distance from the glucopyranose ring to electron attracting carbonyl oxygen in carboxymethyl group alters the electronic structure in such way that results in high occupied molecular orbital (HOMO) and unconnected molecular orbital (UMO), have numerical values which can be compared with quantum chemical reactivity capacity.

The HOMO and UMO orbits are distributed among the functional groups of substituents depending on their molecular structures, which indicates a shift of the electron density to the most negative oxygen atoms, which subsequently weakens 1-4 β -glycosidic bond due to the shift of the electron cloud of glucopyranous rings towards the electronegative atom oxygen carboxyl group.

According to the results of computer simulation and the results of the analysis of the electronic structures of cellulose and its derivatives, the study of the influence of the various nature of substituents on the glucopyranous ring of cellulose has established that cellulose cannot be biodegradable in the body due to the nature of its structure and the absence of specific enzymes that contribute to their biodegradation.

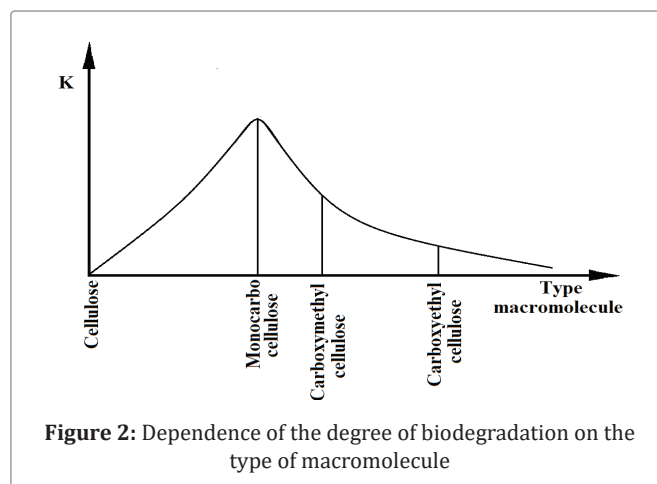
The biodegradability of an NC can be explained on the basis of the following assumptions:

1. Unlike to cellulose, its derivatives such as CMC, CEC, oxycellulose, have sufficiently higher molecular weights and particle sizes (in micron range), they are not able to penetrate into the cell nucleus by phagocytosis, and act on the cell surface.
2. Unlike to cellulose and its derivatives, the particle size of which is a micron-scale, nanoparticles of cellulose can penetrate over the cell barriers into the nucleus by phagocytosis. They are apparently degradable inside the cell due to unknown mechanisms.
3. It was established experimentally that cellulose with DP=1600 may contain carboxyl groups of up to 0.017 %.

In the case of cellulose nanoparticles with DP=80 content of end carboxyl groups is 0.35%. Consequently, in nanoparticles of cellulose the content of end carboxyl groups for 20 times higher than in cellulose. In oxycellulose, if all hydroxyl groups of anhydroglucose unit oxidized to carboxyl groups, their content reaches 25.8%.

Consequently, the content of carboxymethyl groups in the oxidized cellulose in compare to CMC, nanoparticles of cellulose, and cellulose is more than 1.21, 73 and 1500 times, respectively.

In accordance with the experimental data and the results of theoretical studies, it has been established that the rate of biodegradation of cellulose and its derivatives is explained by a decrease in the strength of the acetal bond between the anhydroglucose cycles due to the shift of the electron cloud towards



Modeling the electronic structure of some polysaccharides

The solubility of these polysaccharides in water and their susceptibility to biodegradation in the body can be explained on the basis of the structure of their elementary units in the polymer chain.

The presence of functional groups of various structures and their number changes the electronic structure of antiglucose units. The cellulose lived (electron density) distributed over a 6-membered pyranose cycle.

We can assume the following scenario of biodegradation of the macromolecule.

The main process of degradation consists in the phagocytosis of a macromolecule fragment, and the effectiveness of this elementary act of phagocytosis depends on the size (length) L of this fragment, i.e. K_i is a function of $K_i = f(L_i)$.

At the same time, small fragments are easily absorbed, whereas the effectiveness of phagocytosis drops to zero for very large fragments. That is, large fragments, which must again undergo phagocytosis, can be broken up by splitting the $-C-O-C-$ bonds. At the same time, as the length of the fragments decreases, the probability of phagocytosis increases.

The very act of splitting the intermolecular $-C-O-C-$ bond under the action of a certain biofactor is a chemical reaction, which is determined by the magnitude of the reaction barrier (Q) (Figure 3).

As with any reaction, a modern analysis of the magnitude of the reaction barrier Q can be studied in terms of the approach of Dewar, Fukui, Bader, and Bersuker [18], which are based on quantum concepts.

The importance of quantum theory lies in the fact that it allows us to study the magnitude of the barrier Q on the basis of the ideas about the electronic structure of both the attacking factor (components of the biostructure) and the electronic structure of the $-C-O-C-$ bond, which can be regulated using functional substituents monomers - links. Note that the degree of regulation can be dosed and the chain length - the degree of distance of the substituent from the monomer - the main link.

A complete analysis of the experimental results of the work in the framework of the above concept should be carried out on the basis of a simulation combining the kinetic approach of cleavage and phagocytosis with the quantum chemical theory of the cleavage reaction of the $-C-O-C-$ bond.

Kinetic analysis

Let the original macromolecule have a length L_0 . Consider the evolution of this macromolecule taking into account two types of processes: one is the possibility of its phagocytosis, and the other competing is the fragmentation by breaking the $-C-O-C-$ bond,

followed by phagocytosis.

The analysis scheme is as follows. Suppose that at the initial moment ($t = 0$) there are N identical macromolecules containing "weak bonds", we will call them I - generation.

Let, as a result of interaction with the biological environment,

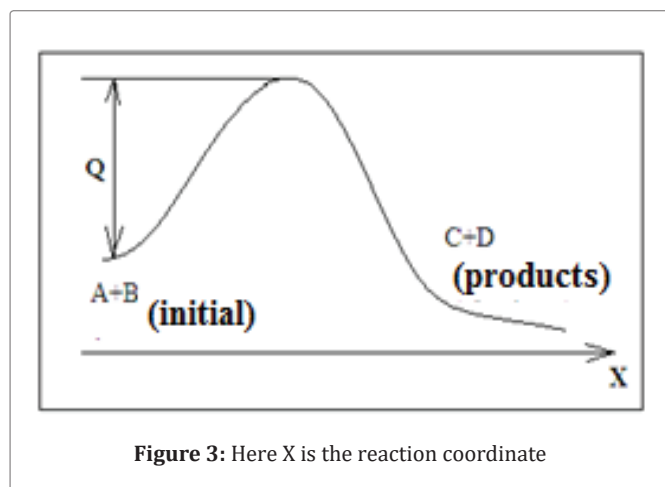


Figure 3: Here X is the reaction coordinate

each of these N molecules (on average) is divided into $N_2 = K_p \cdot N_1$ fragments (it is clear that $K_p > 1$) - this will be the second generation of molecules. (K_p is the fraction determining the transition from the I state to the II state).

Consider now that in each generation (I and II) phagocytosis can occur (with a certain probability a). Then N_2 is reduced by $a \cdot N_1$ and becomes.

$$\tilde{N}_2 = (K_p - a_1) N_1$$

If this process goes further, then for the third generation of fragments we get:

$$\tilde{N}_3 = (K_p - a_2) (K_p - a_1) N_1 \text{ and so on.}$$

For some n -th generation of macromolecules, we have:

$$\tilde{N}_n = (K_p - a_{n-1}) (K_p - a_{n-2}) \dots N_1$$

It is important to note that since phagocytosis is more powerful for smaller fragments, then $a_{n-1} < a_{n-2} < \dots$ and so on. The length of some n th fragment is defined as $L_n = L_1 / K_p^{n-1}$.

Now, let the time required for the transition from $i-1$ generation to i -th is τ_{i-1} . It is obvious that the value (transition time) from $i-1$ generation to i generation is equal to $1 / K_p$.

Then the total time of transition from the I generation of molecules (their number $\tilde{N}_1$) to the n -th generation (the number of such molecules $\tilde{N}_n = (K_p - a_{n-1}) (K_p - a_{n-2}) \dots N_1$) will be $t_n = \sum_{i=1}^n \tau_i$, i.e. is the sum of all successive phases. Now we note an important consequence: if phagocytosis effectively begins only with the n generation (i.e., for sufficiently small fragments of the macromolecule), then the waiting time for the onset of biodegradation cannot be less than t_n .

Based on the above considerations, the biodegradation kinetics may look like this (Figure 4).

The specific form of the graph (Figure 2 and 4) can only be obtained on the basis of the quantum chemical theory of the $-C-O-C-$ bond splitting reaction, which makes it possible to calculate $a^{(i)}$.

Quantum-chemical modeling of the $-C-O-C-$ bond cleavage reaction

We use the vibronic model, based on the approach of Bersuker [18]. Let's draw the electronic spectrum of the joint system consisting of the $-C-O-C-$ bond and the biodegradation factor (Figure 5).

In the vibronic model, the following scheme and methodology is used.

It is necessary to depict the electronic spectrum of the combined system (spectra A and B are in direct contact) (Figure 5).

Now we have to determine the electronic gap D between molecules A and B. From figure 5 it is seen that $D = \text{HOMO}_A - \text{LUMO}_B$.

Knowing this, D and vibronic constant a , which is calculated by quantum-chemical methods (taking into account 3 things: the symmetry of the wave function HOMO_B and LUMO_A , as well as the symmetry of the fluctuations, i.e. coefficient of the reaction at H (Figure 5), can be written as the reaction barrier - value barrier of the cleavage reaction bond $-C-O-C-$

$$Q = (1/2) \cdot (M \cdot a^2 / D) \cdot x^2$$

It is clear that without taking into account the vibronic effects ($a=0$), we will get $Q_0 = (1/2) \cdot M \cdot x_{\text{MAX}}^2$.

If Δ is a large quantity, then the reduction of the reaction barrier

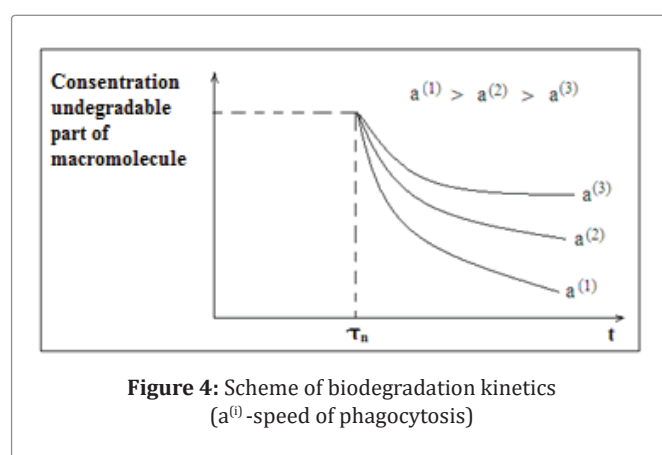


Figure 4: Scheme of biodegradation kinetics ($a^{(i)}$ - speed of phagocytosis)

is small, and we believe that this is exactly the situation characteristic of the original cellulose, for which there is no biodegradation.

Now, let the group that converts cellulose to OC is included in the anhydroglucose ring. According to our calculations using computer quantum chemistry (see Table 1), the electron cloud is shifting to this group. This necessarily affects the decrease in electron density in the HOMO_A (possibly until the electron leaves), so that the HOMO_A -cellulose turns into $\text{HOMO}_A - \text{OC}$, and this immediately reduces the value of Δ , which: $\Delta > \Delta' < \Delta$ (see Figure 5). We obtain a sharp decrease in the reaction barrier:

$$Q = (1/2) \cdot (M \cdot a^2 / \Delta') x^2$$

And the growth of K_p , i.e. biodegradation.

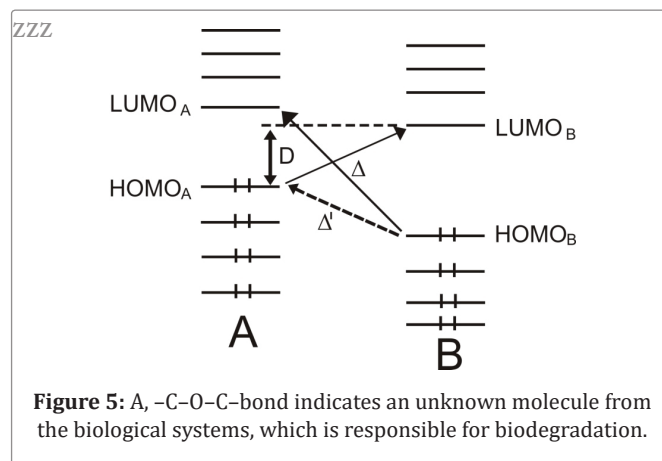


Figure 5: A, $-C-O-C-$ bond indicates an unknown molecule from the biological systems, which is responsible for biodegradation.

Further, after lengthening the chain (OC → CMC → CEC), if the corresponding conductive chain has a HOMO smaller than the HOMO group that turns cellulose into the OC, the electron outflow from the glucopyranose ring will be less and less as the chain elongates (HOMO_A of this chain decreases as it lengthens - a purely quantum effect).

This leads to a “partial” return of the electron density to the HOMO_A, so that Δ again turns (partially!) into Δ. The latter revives the –C – O – C– bond to the original, poorly degraded state. This characteristic describes well the situation in (Figure 2).

Regarding the model being developed, the weakening of the chemical bond due to a change in the electronic composition of the pyranose ring requires an important generalization. Since the upper occupied molecular orbital (HOMO) can be both binding and loosening, the transition from HOMO to an acceptor in the electron orbital leads to two opposite results: if HOMO is binding, the transition weakens the chemical bond then the transition of electrons from it enhances the chemical bond, i.e. the modulus of its energy |ε_i|. This circumstance is easy to describe mathematically:

$$|E_{c6}| = \sum_i |\varepsilon_i| n_i (-1)^m$$

and besides $m = +1$ (if the orbit is loosening); $m = 2$ (if the orbit is connecting); $|E_{c6}|$ is the binding energy, n_i is the number of fillings of the electron orbital. With such a record, it is necessary to take into account that the energy of each i -th orbital $\varepsilon_i < 0$ (as is the case in the calculations of quantum chemistry; in addition, n_i is the populated i -th orbital (equal to either 0 or 1 or 2).

Conclusion

The material presented above is essentially one of the first attempts to use purely quantum laws in the field of “polymer nanopharmacology”. Indeed, the whole set of ideas is based on a combination:

- The phenomena of different localization of electron clouds on polymeric structures;
- Using the ideas of the interference of electronic states along the polymer chain with a different number of monomers;
- Using the vibronic (Jan-Teller) interpretation of the chemical reaction of the destruction of the C-O-C bond in cellulose.
- There are always two possibilities for weakening the required chemical bond: either by outflow of electron density from the binding orbital, or by filling up the loosening orbital, which extends the engineering of joining the chains to the control point of the macromolecule.

It should be noted that this set of ideas is much broader than those commonly accepted in quantum chemical pharmacology based on only the Conclusion indicates on the nanofractal structure of the molecule [17] or the ideas on transfusion [18]. In our opinion, it is the combination of ideas about the electronic spectrum of polymers [19] with vibronic ideas that seems to be the most effective.

Since the reactivity of a polymer required for a given purpose is related to the concentration of functional groups of a certain length, for a small sample (nano-chain) the probability of such group formation is always greater than for a large (long) chain, i.e. the probability of any fluctuations with the sample size (N) decreases according to the law $\sim 1/\sqrt{N}$ (where N is the concentration of functional groups). Note that this circumstance radically distinguishes the properties of polymer nanoparticles from all other types of nanoparticles. Note that this nano-effect is especially clearly manifested in quasi-one-dimensional structures.

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Conflict of interest

The author declares that there is no conflict of interests regarding the publication of this article.

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