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RECEIVING ELASTOVISCOUS SYSTEMS ON THE BASIS OF AQUEOUS SOLUTION OF ACETATE AND SUCCINIMIDE OF CHITOSAN IN THE PRESENCE OF POLYHYDRIC ALCOHOLS

Roman Lazdin¹, Marina Bazunova¹, Valentina Chernova¹, Angela Shurshina¹, Vadim Zakharov¹, Elena Kulish^{1, *}

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Abstract. The rheological behavior of acetate and succinimide of chitosan in mixed solvents was investigated. It is shown that the replacement of a part of the solvent by two- or three-atom alcohols is accompanied by an increase in the relative and dynamic viscosity of the succinimide chitosan solution, an earlier formation of the net of links, a transition from viscoelastic systems to elastoviscous ones at lower polymer concentration values and an increase in the relaxation time.

Keywords: chitosan, succinimide chitosan, rheological behavior, mixed solvent, gel.

1. Introduction

Creation of new highly effective dosage forms is one of the top-priority directions in the development of modern chemistry, medicine and pharmacology [1-3]. The soft dosage forms which differ in high viscosity and thereof have a number of advantages compared to liquid dosage forms are highlighted [4, 5]. Physical and chemical processes proceeding in a viscous medium occur significantly more slowly and the viscous bases provide a prolonged release of drugs, which means high efficiency and minimum complexity of application. Moreover, at high viscosity, sedimentation processes practically do not occur, which means that the dispersed drug will be distributed in a viscous medium evenly.

Gels on the basis of bio- and haemocompatible biopolymers, for example, polysaccharides or proteins, occupy a specific place among various soft dosage forms. However, the direct dissolution of polymer does not always lead to high-viscosity solution. The use of cosolvents, which play the role of the modifying additives capable a forming of "bridge" connection between macromolecules, can become a solution in this situation. As a result of such "crosslinking", the macromolecules lose their kinetic independence, which in turn leads to an increase in viscosity. Some polyhydric alcohols – ethylene glycol, propylene glycol, and glycerin were used as cosolvents – polymer modifiers in our work. Polysaccharides, namely chitosan (ChT) and its watersoluble derivative – succinimide chitosan (SChT) were taken as gelling polymer. The choice of polymers was caused by a spectrum of unique properties, one of which is biocompatibility with body tissues, bacteriostaticity, ability to biodegradation, and much more [6-8].

The aim of the work was to study the rheological behavior of chitosan and succinimide chitosan in a mixed solvent to find conditions for formation of high-viscosity gels suitable for creation of soft dosage forms.

2. Experimental

SChT with M.M. = 207 kDa and the intrinsic viscosity $[\eta] = 3.20$ dl/g produced by Bioprogress (Shchelkovo, Russia) was used as the objects of the study. The degree of SChT substitution for the amino groups is 75 %. The degree of deacetylation of the initial sample of chitosan from which SChT was obtained was 82 %.

Bidistilled water and 1% acetic acid were used as the solvents for SChT and ChT, respectively. Glycerin, propylene glycol, and ethylene glycol was used as a modifier (co-solvent).

The intrinsic viscosities of the polymer were determined using a Ubellode viscometer at the temperature of 298 ± 1 K and calculated using the Baranov method [9], which eliminates the effect of the polyelectrolyte swelling on the value of the intrinsic viscosity of the polymer [10].

Rheological investigations of solutions of polymers were carried out on a module dynamic rheometer Haake Mars III (THERMO Fisher, Germany) at 298 K in two modes: continuous shear deformation in the range of shear rates from 0.1 to 100 s^{-1} and oscillation mode. For creation of concentration curves and calculation of activation

¹Bashkir State University, 32, Zaki Validi, 450076 Ufa, Russia * onlyalena@mail.ru

 $[\]ensuremath{\textcircled{\sc l}}$ Lazdin R., Bazunova M., Chernova V., Shurshina A., Zakharov V., Kulish E., 2019

energy we used the values η determined at shear rate equal to 0.1 s⁻¹. Since tests in the oscillation mode must be performed in the region of linear viscoelasticity, optimal values of the amplitude corresponding to the invariant values of the modules (linear viscoelasticity region) were initially determined on the basis of the dependences of the accumulation modules and losses on the amplitude of the stresses obtained at a constant oscillation frequency.

The activation energies of the viscous flow of the studied systems (ΔE_a) in the temperature range from 288 to 318 K were estimated by Arrenius-Frenkel-Airinga equation (1) and were calculated by the method of the least squares:

$$h = A e^{\frac{\Delta E_a}{RT}} \tag{1}$$

where R is the universal gas constant, A is a constant.

3. Results and Discussion

It is known that the rheological behavior of solutions of polyelectrolytes (for example ChT and SChT) has its own characteristic features that distinguish them from solutions of non-ionic polymers. Manifestation of these features depends on concentration area in which the polymer is located. For example, in the field of the diluted solutions rheological behavior of both nonionic and ionic polymers is close to each other - macromolecular coils do not overlap and move independently of each other. Differences of solutions of polyelectrolyte from solutions of nonionic polymers begin to be shown at achievement of the critical concentration called by concentration of the crossover c^* , at which all volume of solution is filled with polymeric coils. In solutions of uncharged polymers the intermolecular association and formation of links net (at concentration of polymer in solution c_e) begin practically right after excess of polymer concentration above c*, i.e. $c^* \approx c_e$ (Fig. 1). Existence of extended area of the semidiluted solutions (at concentration bigger than c^*), in which coils already adjoin with each other but grids of gearings do not form yet, is characteristic of solutions of ionic polymers [11, 12].

The reason of such feature of rheological behavior of polyelectrolyte is connected with electrostatic repulsion of the same loaded chains interfering to penetration of one ball of polymer into another ball and with formation of a net of links. Earlier existence of such area of the semidiluted solutions without formation of a net of links has been revealed for chitosan solutions in acetic acid.

The dependence of the greatest Newtonian viscosity η_0 on concentration of SChT in individual (water) and the mixed solvent (water-glycerin) is presented in Fig. 2.



Fig. 1. Schematic representation of the dependence of the greatest Newtonian viscosity on concentration in double logarithmic coordinates for solutions of ionic (1) and nonionic (2) polymers





From the figure it is visible that the concentration dependence according to the standard approaches can be described by a power function of $C \sim C^n$ and broken into three sites. In the field of the diluted and concentrated solutions of polymer (site I and III on graphics, respectively) the viscosity actually linearly depends on concentration c (in double logarithmic coordinates) that corresponds to the area of the diluted solutions of the macromolecules, which are not interacting among themselves and the area of the concentrated solutions with

completely created net of links, characterized by the reptational mechanism of movement of macro chains, respectively. Intermediate site II is characteristic of the semi-diluted area in which macromolecules interact with each other and form a fluctuation network of links starting concentration $c_e \approx 0.8$ g/dl (value lgc = -0.1). On this site there is a continuous increase in an exponent of ntestifying to the intermolecular association taking place. Considering that value of characteristic viscosity [n] for SChT was 3.20 dl/g, *i.e.* the crossover point $(c^* = 1/[\eta])$ corresponds to concentration of 0.3 g/dl, it is visible that achievement of a point of the crossover does not affect the mechanism of polymer solution flow. In this regard, and in case of solutions of SChT in water, it is possible to speak about existence of transitional area from site I to site II, in which macromolecules already adjoin each other, but net of links does not form yet.

Dissolution of SChT in the mixed solvent waterglycerin leads to some increase in dynamic viscosity (Fig. 2, *curves* 2-4). Several moments attract attention here. Firstly, increasing dynamic viscosity is followed by increase of relative viscosity (Fig. 3). It is important as it is worth remembering that the viscosity of glycerin is significantly higher than viscosity of water owing to what observed increase in dynamic viscosity upon transition from individual solvent of water to mixed – waterglycerin could be caused just by increase in viscosity of the mixed solvent.



Fig. 3. Dependence of the relative viscosity of solutions of SChT of concentrations 1 (1), 2 (2), 10 (3) and 15 g/dl (4) on the volume ratio of components in mixture of water: glycerin in semi logarithmic coordinates

Secondly, addition of co-solvent to solution of SChT leads to reduction of values of concentration c_e that testifies to earlier formation of a net of links.

Similar regularities are observed in case of solutions of ChT in the mixed solvent of 1% acetic acid-glycerin (Fig. 4).



Fig. 4. Dependence of the dynamic viscosity measured at a share rate of 0.1 s^{-1} on the concentration of ChT in the individual (1) and the mixed solvent of 1% acetic acid: glycerin with a components ratio (v/v) 90:10 (2), 80:20 (3) and 70:30 (4)

There can be at least two reasons causing earlier formation of a net of links: physical "cross linking" of macromolecules by glycerin and enhanced aggregation of chains of ionic polymer in solvent with smaller dielectric permeability (relative dielectric permeability of water is 80 and glycerin -47).

The strengthening of aggregation processes caused by reduction of extent of ionization of macromolecules at decrease in dielectric permeability of solvent is a more probable cause because the earlier formation of a net of links also takes place when ethyl alcohol is used as the modifying additive which is incapable to "cross-link" macromolecular chains.

The great values of an indicator of n in dependence $\eta_0 \sim C^n$ in the field of the concentration corresponding to concentration c_e also testify to more intensively proceeding aggregation processes in the presence of co-solvent (Figs. 2 and 4).

Thirdly, the viscosity of the studied systems of ChT and SChT in the mixed solvents measured at big rates of shift (about 100 s^{-1}), corresponding to completely destroyed net practically coincides with viscosity of solution of polymer in individual solvent of the corresponding concentration (Figs. 5 and 6).

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It allows assuming that observed effects of increase in viscosity in systems polymer–mixed solvent in comparison with viscosity of solution of polymer in individual solvent are caused by formation or destruction of an additional network whose nodes are physical crosslink between the macromolecules.

Small values of energy of activation of a viscous current also testify to the physical nature of nodes of an additional network (Figs. 7 and 8).

It is important that the aggregation of macrochains forms system with elastic and viscous properties. The rheological measurements taken in the oscillation mode prove it.



Fig. 5. Dependence of the dynamic viscosity on the shear rate for 5% solutions of SChT in the individual (1) and the mixed solvent (2, 3) with water:glycerin ratio (v/v) 90:10 (2) and 70:30 (3)



Fig. 7. Calculation of the energy of activation of viscous flow for solutions of SChT of concentration 1 g/dl in water (1) and in mixed solvent with water: glycerin ratio (v/v) 80:20 (2)

Therefore, from Fig. 9 it is visible that for solutions of SChT in individual solvent the value of the module of accumulation becomes more than loss modulus only at achievement of concentration of SChT in solution $C_{el} = 9 \text{ g/dl}$ (value of $\lg c = 0.95$), that indicates the formation of elastic and viscous system and loss by the system of fluidity (see Fig. 10).

Replacement of a part of water by co-solvent (glycerin) leads to earlier transition of system from viscoelastic liquid to elastoviscous body. As can be seen from the data in Fig. 11, for the system SChT-water-glycerin with the ratio of components 80:20 (v/v) already in the field of concentration of SChT in solution of 6 g/dl a non-flowing elastoviscous system is formed.



Fig. 6. Dependence of the dynamic viscosity on shift rate for 2% solutions of ChT in the individual (1) and the mixed solvent (2, 3) with 1% acetic acid:glycerin ratio (v/v) 90:10 (2) and 70:30 (3)



Fig. 8. Concentration dependence of activation energy of viscous flow of SChT solution in water (1) and mixed solvent with water: glycerin ratio (v/v) 80:20 (2)



Fig. 9. Concentration dependence of the modulus of accumulations (1) and losses (2) for solutions of SChT in water in double logarithmic coordinates. The values of the module of accumulation and losses are determined in the field of linear viscoelasticity at the frequency of 1 s⁻¹. The arrow indicates the concentration at which the system acquires elastoviscous properties



Fig. 10.8% solution of SChT in water having elasticity properties



Fig. 12. Concentration dependence of the modulus of accumulations (1) and losses (2) for solutions of ChT in 1% acetic acid in double logarithmic coordinates. The values of the modulus of accumulations and losses are determined in the field of linear viscoelasticity at the frequency of 1 s⁻¹. The arrow indicates the concentration at which the system acquires elastoviscous properties



Fig. 11. Concentration dependence of the modulus of accumulations (1) and losses (2) for solutions of SChT in mixed solvent with water:glycerin ratio (v/v) 80:20 in double logarithmic coordinates. The values of the modulus of accumulations and losses are determined in the field of linear viscoelasticity at the frequency of 1 s⁻¹. The arrow indicates the concentration at which the system acquires elastoviscous properties

Similar regularities take place also for solutions of ChT in the mixed solvents. As can be seen from the data in Fig. 12, if for solutions of ChT in individual solvent the module of accumulation becomes more than loss modulus at concentration of polymer in solution more than 3 g/dl (lg3 = 0.47), then in the mixed solvent (for example, 80 % of 1% of acetic acid–20 % of glycerin) this transition happens in the field of much smaller concentration (Fig. 13).



Fig. 13. Concentration dependence of the modulus of accumulations (1) and losses (2) for solutions of ChT in the mixed solvent with 1% acetic acid:glycerin ratio (v/v) 80:20 in double logarithmic coordinates. The values of the modulus of accumu-

lations and losses are determined in the field of linear viscoelasticity at the frequency of 1 s⁻¹. The arrow indicates the concentration at which the system acquires elastoviscous properties



Fig. 14. Dependence of the modulus of accumulations (1, 3) and losses (2, 4) on the angular rate (frequency) of oscillations for solutions of SChT with the concentration of 2 g/dl in an individual (1, 2) and a mixed solvent with water:glycerin ratio (v/v) 80:20 (3, 4) in semi logarithmic coordinates. The arrow





Fig. 15. Dependence of the dynamic viscosity measured at the shear rate of 0.1 s^{-1} on the concentration of SChT in the mixed solvent water:glycerin (1), water:propylene glycol (2), water:ethylene glycol (3), and water:ethanol (4) with the components ratio (v/v) 90:10

Table

System	Volume ratio of components in mix water:co-solvent	c _e , g/dl	C_{el} , g/dl	$t^* \cdot 10^2$, s
SChT-water	100:0	0.80	9.0	6
SChT-water-glycerin	90:10	0.70	7.5	16
	80:20	0.60	6.0	25
	70:30	0.55	5.8	37
SChT-water-propylene glycol	90:10	0.68	7.4	20
	80:20	0.63	5.5	34
	70:30	0.60	5.2	42
SChT-water-ethylene glycol	90:10	0.60	5.5	35
	80:20	0.57	5.1	46
	70:30	0.48	4.8	68

The characteristics of elastoviscous properties of SChT received from rheological data

Note: * the value of relaxation time is given for 2% solution of SChT

Reviewing the dependence of modules of accumulation and losses from the frequency (Fig. 14) allows to state that in the range of concentration of SChT in solution, corresponding to the area from $c_e \approx 0.8$ g/dl to $c_e \approx 3$ g/dl, the tangent of angle of the frequency dependence of the module of accumulation in double logarithmic coordinates is equal to 2, and the module of losses is 1. It testifies that the behavior of the system is well described by simple model of Maxwell for viscoelasticity liquid with time of relaxation τ , for which G' = G''. For solutions of ChT this field of intensive formation of a net of linkages corresponds to area of concentration from $c_e \approx 0.4$ g/dl to $c_e \approx 1$ g/dl.

From the data provided in the Table it is visible that replacement of a part of solvent by the modifying additive (glycerin) leads to increase in time of relaxation of the macromolecules τ that will be coordinated with the increased values of viscosity and the accelerated formation of a net of links. The data on values c_e and C_{el} , which undergo natural changes, are provided in the Table as well.

The observed regularities qualitatively coincide in case of use of propylene glycol and ethylene glycol as cosolvent. At the same time, for all studied structures (a water:co-solvent ratio (v/v) is equal to 90:10, 80:20 and 70:30) the increase in dynamic and relative viscosity, shift value c_e and C_{el} to the area of smaller values of concentration and increase in time of relaxation in comparison with solution of SChT in individual solvent takes place (Table). The concentration dependence of the greatest Newtonian viscosity for solutions of SChT in the mixed solvent water:propylene glycols and water:ethylene glycol with the volume ratio of 90:10 is given in Fig. 15. As an example the dependence of viscosity on concentration for the system SChT-water-ethanol is given by *curve* 4.

The fact that rheological characteristics of the system SChT-mixed solvent correlate with value of dielectric permeability of the mixed solvent attracts attention.

Introduction of co-solvents in the system SChTwater, except increase in viscosity in system polymersolvent and earlier formation of a net of links, allows solving some problems. The first problem concerns instability of solutions of chitosan, namely: as the solution of the polymer is maintained, its viscosity gradually decreases with time. Instability of solutions of ChT is a fact repeatedly noted in the literature. However, while for solutions of ChT in strong acids (e.g., hydrochloric acid) reduction of viscosity is unambiguously connected with the course of acid hydrolysis, concerning the reasons of change of viscosity of polymer in solution of weak acetic acid, there was no uniform view point among researchers. Most of researchers see the reason of "inconstancy" of values of characteristic and relative viscosity in changes of a conformational condition of macromolecules, formation of intra chain and/or inter chain hydrogen



Fig. 16. Dependence of the greatest Newtonian viscosity on time of withstanding the solution of SChT in water of concentrations 0.5 (1), 2 (2), 5 (3), and 10 (4) g/dl

communications, disintegration of units. In the earlier works of our department it has been proved too that the reason of decrease in viscosity of solutions of ChT is connected with the change of its supramolecular structure, owing to slow achievement in the course of dissolution of equilibrium structure [13]. The similar situation is observed in case of solutions of SChT in water. At the same time, as well as in case of ChT, on the nature of change of viscosity the basic value is rendered by concentration of polymer in initial solution. As can be seen from Fig. 16, in the case when SChT in solution has not created a net of links yet (solution with concentration $c < c_e$), or have created already rather developed net of links as a result of which the system has gained elastic and viscous properties (solution with concentration $(c > C_{ol})$, values of dynamic viscosity practically do not change with hold time of solution. In the same case, when the solution of SChT in water is a typical viscoelasticity fluid with a formed net of links (solution with a concentration $c_e < c < C_{el}$), the dynamic viscosity decreases significantly when the solution is held. However, the presence of a cosolvent (glycerin, propylene glycol, ethylene glycol) in the system SChT-water leads to significant changes in the behavior of the systems under study. In this case, solutions with polymer concentration in solution over the whole range of concentrations are stable in all cases studied by us, apparently due to the "crosslinking" of macromolecules taking place through interaction with a cosolvent (Fig. 17).



Fig. 17. Dependence of the greatest Newtonian viscosity on time with solution of SChT concentrations of 1 (1), 2 (2), and 5 (3, 4) g/dl in the mixed solvent water:propylene glycol (1, 2), water:glycerin (3) and water:ethylene glycol (4) with the ratio (v/v) 90:10

Stability of rheological characteristics of polymer in the system SChT-mixed solvent, certainly, has considerable advantages from the technological point of view at process of formation of polymeric materials in comparison with the system SChT-water.

The second problem is connected with solubility of ChT and its derivatives in water environments leading to essential reduction of service life of materials on the basis of these polymers. Several ways of ChT modification leading to the loss of solubility of chitosan materials in water is known. Thermal modification consisting in warming up of the created material at the temperature about 373–383 K within 30–60 min is the most widespread and convenient way of modification. After carrying out of this sort modification, a film of ChT loses solubility in water, but keeps the physico-mechanical and physico-chemical properties at the previous level. However, carrying out thermal modification of SChT does not lead to loss of solubility of materials in water. Even long (during 3-4 h) warming up of films at the temperature of 373-403 K is not followed by noticeable reduction of solubility. Introduction of co-solvent (glycerin) in amount of 20 vol % and more, allows to receive soft and elastic gel materials, well occluding water, but keeping at the same time the integrity and not capable to dissolution in water. At the same time, the effect of loss by material of ability to be dissolved in water takes place only when using as co-solvent of triatomic alcohol - glycerin. When using diatomic alcohols (propylene and ethylene of glycol) elastic gel materials at the long-lived contact with water pass into initial elastoviscous or viscoelastic gels.

Thus, the research of the rheological properties of SChT in the mixed solvent allows to draw a conclusion that replacement of a part of solvent by two- or triatomic alcohols is followed by growth of relative and dynamic viscosity of solution of SChT, earlier formation of a grid of gearings, transition from viscoelastic systems to elastic and viscous at smaller values of concentration of polymer and by the growth of relaxation time. The systems which are formed at the same time are characterized by stability of viscous characteristics in time and, in case of using glycerin, lead to receiving water non-soluble gel materials capable to become the main ones for creation of soft dosage forms.

4. Conclusions

It is established that increase of the dynamic viscosity of polymers (ChT and SChT) and earlier formation of the fluctuation grid of links occurs in the presence of co-solvents - glycerin, ethylene glycol and propylene glycol. According to the nature of the flow curves, it is established that the fluctuation grid has a physical character. It is shown that the addition of a cosolvent is followed by a decrease in the value of the

polymer concentration in the solution, at which the transition from viscous-elastic liquids to elastoviscous systems occurs, and the increase in relaxation. It is shown that the introduction of a co-solvent into a solution of SChT and ChT leads to the formation of solutions with stable viscous characteristics and, in the case of using glycerin as a co-solvent, allows to receive elastic materials that are not capable of dissolving in water.

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ОДЕРЖАННЯ ПРУЖНО-В'ЯЗКИХ СИСТЕМ НА ОСНОВІ ВОДНИХ РОЗЧИНІВ АЦЕТАТУ І СУКЦИНІМІДУ ХІТОЗАНУ У ПРИСУТНОСТІ БАГАТОАТОМНИХ СПИРТІВ

Анотація. Досліджено реологічну поведінку ацетату та сукциніміду хітозану в змішаних розчинниках. Показано, що заміна частини розчинника на дво- або триатомні спирти супроводжується збільшенням відносної та динамічної в'язкості розчину сукциніміду хітозану, більш раннім формуванням сітки, переходом від в'язкісно-пружних систем до пружно-в'язких за менших значень концентрацій полімера і більшого часу релаксації.

Ключові слова: хітозан, сукцинімід хітозану, реологічна поведінка, змішаний розчинник, гель.