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The influence of hyaluronic acid molecular mass on the rheological properties of bases for soft dosage forms

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Hyaluronic acid (HA) is a biologically active extracellular elastic material. It fills the space between cells and collagen fibers, covers the epidermal tissues, protects and lubricate cells, stabilizes the collagen network and protects it from mechanical damage. It is the main lubricant in the tendons and on the surface of the synovial membrane, and also it is a factor contributing to the rheological mechanics of tissues. Mixtures of HA with different molecular weight are used for the effective treatment of various types of diseases and the manufacture of medical preparations.

The aim of the present research was to establish the influence of the HA molecular parameters on the rheological and structural-mechanical properties of its aqueous solutions. For this purpose, the rheological characteristics of low molecular weight hyaluronic acid (LMW-HA) solutions with molecular weight $M=8\cdot10^3$ *Da* and high molecular weight hyaluronic acid (HMW-HA) with molecular weight $M=1{,}15\cdot10^6$ *Da* (Truthful Concepts and Nutritional Integrity, USA) and mixtures thereof with the calculated average values $M=1\cdot10^4\ldots3{,}9\cdot10^4$ *Da* were studied. The study of the solutions viscosity in the concentration range of 0.0156 to 1 % by weight was performed on a rotational viscometer "Rheotest-2". The study of the rheological dependences between the viscosity and shear rate of 1% HMW-HA solutions along with its LMW-HA mixtures was carried out within the ratio of HMW/LMW acids 80/20 → 20/80 at a temperature of 20–35 °C.

The forces of intermolecular interaction in hyaluronic acid dilute solutions are very weak, so the formation of fluctuation networks is not observed. The introduction of HMW-HA with long macromolecular chains into the LMW-HA solution increases the viscosity of solutions and determines the point of critical concentration, above which the viscosity increases sharply.

Compared to dilute HA solutions, which exhibit properties close to Newtonian fluids, moderately concentrated HA solutions are capable of forming gel-like structures with a certain ultimate shear stress value.

The value of HA molecular weight has decisive influence on ultimate shear stress value of such structures. For 1% HMW-HA solution with $M=1{,}15\cdot10^6$ *Da* this value 9,3 Pa. Increasing in the content of LMW-HA in the mixture of solutions from 20 % (M_a=35412 *Da*) to 60 % (M_a=12568 *Da*) ultimate shear stress decreases to 1.4 Pa. Fluctuation networks of gel structures from 1% solutions are destroyed as a result of exposure to temperature and shear stresses exceeding their ultimate shear stress, so the system goes over to a viscous flow. Mixture containing of LMW-HA up to 40% (M_a=19240 *Da*) exhibit properties of structured systems. Increasing in the content of LMW-HA up to 60% and more (M_a=12680 *Da*) the nature of their flow is more and more approaching Newtonian fluids. The values of the structural and plastic constituents of viscosity are calculated, and the effect of temperature and shear rate on the change in their ratio is determined.

Conclusions:

1) aqueous solutions of HMW-HA with a concentration of 1% are capable of forming fluctuation networks in gel-like structures characterized by ultimate shear stress of up to 9.3 Pa. The introduction of LMW-HA ($M=8\cdot10^3$ *Da*) into HMW-HA solution ($M=1{,}15\cdot10^6$ *Da*) leads to a weakening of the intermolecular forces and the strength of fluctuation networks;

2) fluctuation networks are not formed due to weak intermolecular interactions in LMW-HA solution with short molecular chains at a concentration of 1%;

3) weak fluctuation networks formed in HMW-HA solutions and its mixtures with LMW-HA are easily destroyed under the action of temperature and shear stresses exceeding their ultimate shear stress.