Electrostatic binding of doxorubicin and bovine serum albumin by self-organizing N-vinyl-2-pyrrolidone copolymers with acrylic acid in aqueous media

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The relevance of the research and the current state of the matter.

Despite the active development of medicine and technology, cancer mortality worldwide remains at a high level. According to statistics, the cause of death of almost 10 million people in 2020 was precisely oncological diseases. One of the key strategies to combat this problem is the development of carriers for the delivery of antitumor drugs. The immobilization of a drug substance on a polymer carrier has the potential to address a multitude of challenges that impede the advancement of pharmacotherapy, including enhancing solubility, bioavailability, and circulation time of medicinal substances; directing their accumulation in target areas through active or passive targeting; and reducing the toxicity of the drug in relation to healthy cells. Amphiphilic polymers are macromolecules that are capable of self-organization in aqueous solutions to form nanoscale aggregates with a hydrophobic core and a hydrophilic shell. Such aggregates can serve as "containers" for the delivery of a wide range of medicines and diagnostic labels. Currently, the majority of amphiphilic macromolecules utilized in the synthesis of drug delivery systems comprise PEG fragments, which may induce an immune response in the body upon introduction. Consequently, the development of novel carriers comprising non-immunogenic, non-toxic, biocompatible hydrophilic polymers remains a necessity. One of these polymers is poly-N-vinyl-2-pyrrolidone (PVP), which has been recognized by the World Health Organization (WHO) as safe for use as a dietary supplement and as part of pharmaceutical and cosmetic preparations. Despite the obvious potential of PVP as a material for creating delivery systems, the absence of reactive groups in its structure significantly limits its use. To date, a significant amount of research has been accumulated related to the use of PVP in dosage forms, including nanoscale ones. However, there is a lack of information on the use of amphiphilic copolymers of N-vinyl-2-pyrrolidone containing functional groups capable of interacting with drugs, vector ligands, diagnostic labels, and other molecules and macromolecules.

The objective of this research is to identify the patterns of electrostatic binding of the model antitumor drug doxorubicin and bovine serum albumin by self-organizing copolymers of N-vinyl-2-pyrrolidone with acrylic acid in aqueous media for possible use in the treatment of oncological diseases and the production of contrast agents in demand in ultrasound diagnostics.

The tasks are:
– Using the du Noüy ring method to determine the patterns of self-assembly of chains of diphilic macromolecules based on copolymers of N-vinyl-2-pyrrolidone with acrylic acid of various compositions and average molecular weights in aqueous media;
– to develop a kinetic model of the process of release of doxorubicin electrostatically immobilized by aggregates of chains of amphiphilic copolymers of N-vinyl-2-pyrrolidone and acrylic acid;
– to evaluate the cytotoxicity of aggregates of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid containing electrostatically immobilized doxorubicin;
– to determine the rate constants of the processes of binding and release of electrostatically immobilized doxorubicin by varying the concentration and composition of chains of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid, as well as the pH of the medium and temperature, to calculate the standard thermodynamic functions for the release of doxorubicin in a neutral medium;
– to obtain complexes of amphiphilic copolymers of N-vinyl-2-pyrrolidone and acrylic acid with bovine serum albumin and to develop an approach to the formation of ultrasonic contrast agents (microbubbles) based on them.

The scientific novelty:
– it was found that the release of electrostatically immobilized doxorubicin obeys the kinetic equation for reversible first-order reactions, the rate constants of release and binding of doxorubicin at various concentrations and compositions of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid were calculated, and standard thermodynamic parameters for the process of doxorubicin release were calculated;
– It was found that in a neutral environment, the release of electrostatically immobilized doxorubicin occurs in the kinetic region, whereas binding is control by diffusion, and the equilibrium conversion of drug release increases significantly in an acidic environment, which can serve as a factor in targeting the delivery of doxorubicin to cancer cells;
– the formation of complexes of bovine serum albumin and amphiphilic copolymers of N-vinyl-2-pyrrolidone and acrylic acid, which can be the basis for the creation of contrast agents for ultrasound diagnostics, has been shown.

The theoretical significance for the first time, kinetic patterns were established and standard thermodynamic functions were calculated for the release of electrostatically immobilized doxorubicin by chain aggregates of the amphiphilic copolymer N-vinyl-2-pyrrolidone with acrylic acid with a terminal hydrophobic n-octadecylthiogroup. It was found that changes in the composition and concentration of the amphiphilic copolymer, as well as the temperature and pH of the medium, have a significant effect on the release rate of electrostatically immobilized

doxorubicin. The formation of interpolymer complexes of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid in interaction with bovine serum albumin is shown.

The practical significance of the dissertation is to detect the dependence of the release rate of electrostatically immobilized doxorubicin on the pH of the medium, which may be of interest for targeted therapy of tumor diseases. Approaches to the creation of microbubbles based on complexes of bovine serum albumin with amphiphilic copolymers of N-vinyl-2-pyrrolidone and acrylic acid, which are of interest for ultrasound diagnostics, have been developed.

The main provisions for the defense:

1. Patterns of changes in critical aggregation concentrations with varying chain composition, as well as the length of hydrophilic and hydrophobic fragments of synthesized amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid;
2. Patterns of changes in the distribution of aggregates by diameter with varying concentrations, average molecular weight and composition of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid;
3. Determination of cytotoxicity of nanosomal forms of electrostatically immobilized doxorubicin by aggregates of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid in in vitro experiments on cell lines C6 (rat glioma) and U87 (human glioblastoma);
4. Kinetic patterns of the release of doxorubicin immobilized by chain aggregates of amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid through electrostatic interionic interactions;
5. Preparation of complexes of bovine serum albumin with amphiphilic copolymers of N-vinyl-2-pyrrolidone with acrylic acid and their use to create ultrasonic contrast agents.