New oligomeric carriers and nanosized systems of targeted drug delivery

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Abstract – A series of new water-soluble oligoelectrolytes-surfactants of linear, block and comb-like structure that can bind low-molecular substances by solubilization and ionic interactions with formation of nanoscale systems that can be used in medicine for diagnosis and for targeted drug delivery were synthesized. Biological activity of the developed systems was investigated in vitro and in vivo.

Key words – targeted drug delivery, nanosized systems, polymerization, surface active oligomers, solubilization, doxorubicin.

I. Introduction

Today the relatively large number of biologically active substances with high anti-cancer, antituberculous or antiviral activity are known. However, the possibility of pre-clinical research and implementation in the medical practice of many of these drugs is constrained by their poor solubility in water, the general- and cyto-toxicity, inability to overcome the natural biological barriers and acquired resistance of bacteria and cells [1]. Natural, synthetic or semi-synthetic water-soluble polymers are the most common carriers in aqueous systems of controlled delivery and release of drugs and deoxyribonucleic acids in target organs [2, 3]. Therefore, research aimed at the creation of nanoscale systems for targeted delivery of drugs is a promising area of modern chemistry.

II. Methods of investigation

Polymerization kinetics was studied by dilatometric and gravimetric methods. Molecular mass characteristics of copolymers were determined by gel permeation chromatography. The structure and function of linear and comb-like copolymers was confirmed by IR and NMR spectroscopy. The composition of copolymers was determined by elemental analysis, potentiometric titration and thermal decomposition using gas-liquid chromatography. Formation process of interaction products of polymers and drugs was investigated by conductometric titration methods, Raman, UV spectroscopy and fluorescence analysis. Size of micelle-like structures was investigated by DLS, TEM and SEM microscopy. Toxicity and therapeutic effects of aqueous delivery systems for anticancer drugs were investigated *in vitro* and *in vivo*.

III. Results and Discussions

Oligoelectrolytes of anionic (cooligomers of vinyl acetate, acrylic acid (AA) and maleic anhydride) and cationic (cooligomers of N,N-dymethylaminoethyl methacrylate (DMAEM) and butyl acrylate) type, linear, block and branched structure were synthesized using peroxide-containing monomers and monoperoxine as telogen. Influence of synthesis conditions on the molecular weight and colloidal-chemical properties of oligomers was investigated. According to the proposed mechanism of telechelic oligoperoxides obtaining, equations that describe the kinetics of polymerization and the molecular mass and structural parameters of oligomers were derived.

Synthesis of novel branched polymers with polyethylene glycol (PEG) and polyelectrolyte chains expands the range of their solubility, surface activity, rheological characteristics and the ability to bind drugs and biopolymers. It is important for the use of novel surface-active branched polymers as universal carriers of drugs and nucleic acids. Branched surfactants with PEG and anionic polyelectrolyte chains are interesting in terms of creating drug carriers that are both thermo-and pH-sensitive, can deliver drugs to the target and releases them under the influence of the external environment.

We have synthesized, on the basis of vinyl monomers, (5-*tert*butylperoxy)-5-methyl-1-hexene-3-ine (VEP) and glycidyl methacrylate (GMA), PEG-containing comb-like soluble surface-active copolymers (Fig. 1) which have already proven themselves as an effective vehicle for delivery of anticancer drugs of different structure. The presence of peroxide moiety in the structure of such polymers allows their subsequent use as macroinitiators of graft-polymerization and grafting side chains of varying functionality.

The dependence of kinetic parameters of polymerization initiated by PEG-containing macroinitiators on its concentration was shown. A significant decrease of the polymerization rate constant occurs when a certain critical concentration of PEG-containing poliperoxide in solution is reached. The degree of grafting of carboxyl-containing polymer chains is relatively high and depends slope opposite on the concentration of macroinitiator.

As experimental drug for drug delivery testing doxorubicin was chosen [4]. Study of structural and colloidal-chemical characteristics of novel PEGylated polymeric carriers confirmed their ability to bind water soluble anticancer medicine doxorubicin forming highly stable nanosized waterborne systems. The influence of the oligomeric carrier's nature, binding method and the components ratio in oligomer:drug system on the properties of the obtained systems was studied. Testing developed drug delivery systems based on novel PEGylated carrier *in vitro* and *in vivo* showed that specific structure and controlled size of doxorubicin bearing conjugates provides their low toxicity, the acceleration of cytostatic action on cancer cells and high therapeutic effect at the dose lesser in 2-10 times in comparison with using of free doxorubicin.

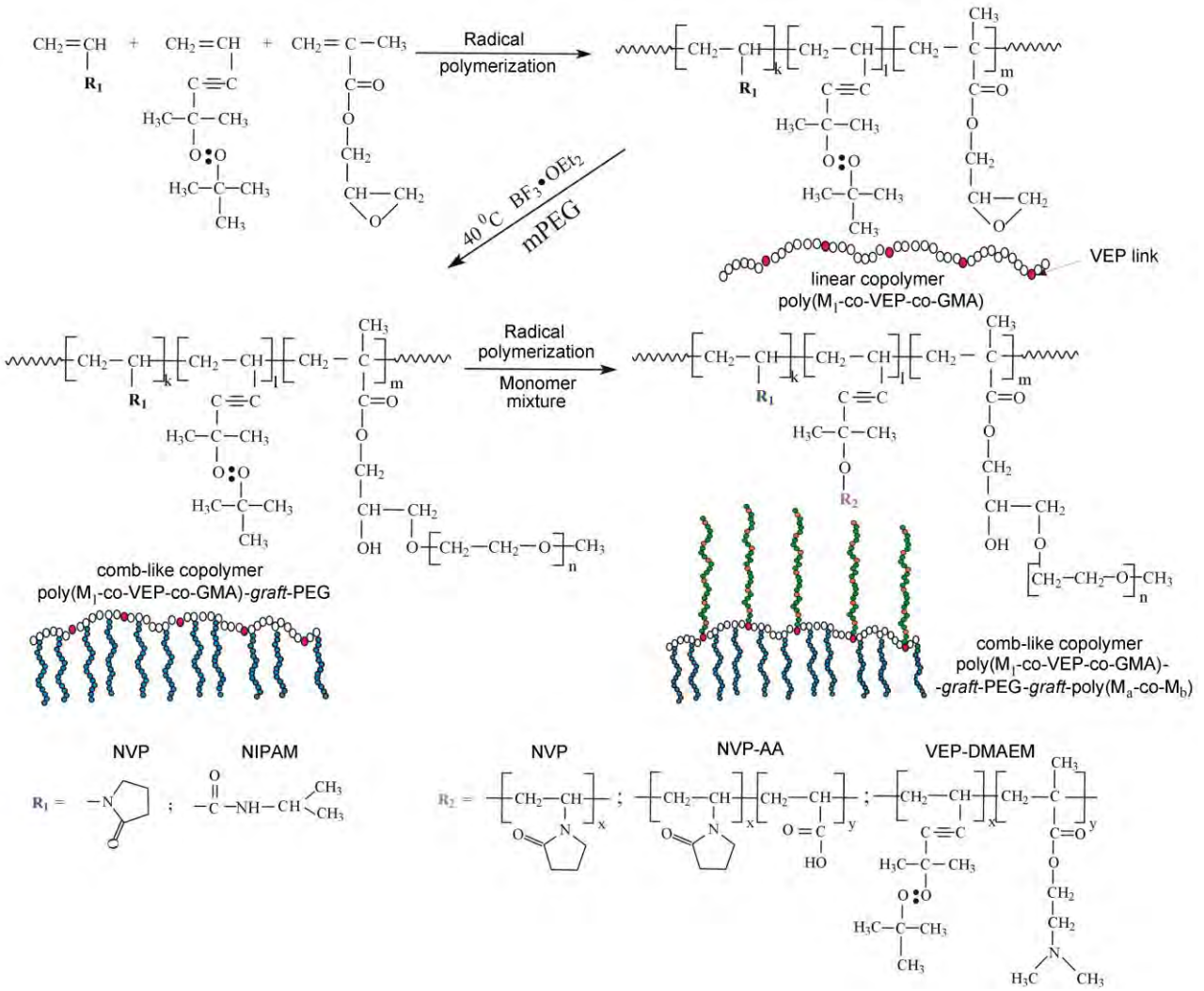

Fig. 1. The general scheme of synthesis of comb-like polymeric carriers with ionic and non-ionic side chain

Methods of filling of polymer composites with nanopigment by dispersion in solution or polymer radical block-polymerization were developed, colloid-chemical and special physical properties of composites were studied and possibility of their practical application as biologically inert markers in cancer cells was shown.

Conclusion

Implementation of linear, block and comb-like oligomeric carriers with polyethylene glycole and polyelectrolyte chain obtained via radical copolymerization reactions and polymer-analogous transformations with epoxy and peroxide reactiony fragments, found that polymeric carriers and delivery systems of anticancer agents are non-toxic, provide cardioprotection from exposure to doxorubicin, accelerate drug delivery into cells, reducing the therapeutic dose and overcome acquired resistance of cells to drugs.

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