Focus on COVID-19: Antiviral polymers in drugs and vaccines

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Abstract

Pathogenic viral factors pose a serious epidemiological threat and challenge to the world population, as proven by the scale and rapidity of COVID-19 pandemic outbreak. Polymer macromolecules can be an alternative to the accepted forms of treatment. Polymeric substances can be used as drugs or as adjuvants in vaccines. The most important feature of polymers is their advanced structure and the ability to construct the molecule from scratch, giving it the desired properties. Antiviral properties are influenced by, among other things, electrical charge, form and structure, and composition with other polymers or heavy metals. Depending on the expected properties, molecules can be built from scratch to be capable of transporting drugs or improve the effectiveness of the right drug. They can also be antiviral drugs in themselves. Polymeric compounds allow to reduce the frequency of adverse effects and improve the effect of the drug. They can have a direct antiviral effect by upsetting the lipid membrane of the surrounding viruses. Antiviral action of polymers occurs because of the properties of the polymers alone or in combination with other molecules. Viral epidemics are a motivation for research that can help stop a global pandemic in the future.

Key words: polymers, coronavirus, pandemics, antivirals, antiviral agents

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Introduction

Recurring pandemics threaten public health as known and hitherto unknown pathogens hit the world's population with great force. The danger is multidimensional and requires broad-spectrum counteraction. Researchers look for new solutions or rediscover old ones. At the moment of danger, attention is paid to polymeric compounds. Polymeric materials have a wide range of possible applications and are susceptible to modification. In medicine, they can be used for the transfer of drugs as supportive substances, e.g., as adjuvants in vaccines.[1] Their great advantage is the possibility to adjust the properties of the material according to needs – by enrichment with metal ions or nanoparticles, or by combining these materials with other compounds. Polymeric compounds can act as auxiliary compounds – as transporters of specific substances or vaccine adjuvants. The transport possibilities are determined by the chemical nature of the polymer – they allow for crossing the lipid membrane or for reaching the target cells selectively. Polymers improve the body response to the vaccine and may reduce the number of side effects or reduce the toxicity of the drug. They can be antivirals in themselves. In this work, we have focused on the aspect of the use of polymers as agents in patients. We also discussed the use of polymer compounds in the diagnosis and detection of pathogens. This study focuses on the antiviral effect of polymers, alone or in combination with other molecules, and their usefulness in reducing epidemiological threats. Attention was paid to substances capable of inhibiting coronaviruses and viruses causing respiratory diseases.

Methods

The article discusses the use of polymers in the production of drugs against human coronaviruses (HCoVs), where they act as active or auxiliary substances. In addition, the protective role against the side effects of some drugs and vaccines was emphasized. The systematic search of the literature was performed in October 2020. Research terms comprised a combination of words „polymers", „antiviral" and „coronavirus". We considered SARS epidemics from 2003, MERS-CoV from 2012 and SARS-CoV-2 outbreak from 2019.[2]

Chemical characteristics

The inactivation function of antiviral agents depends on the structure of the polymer chain. The distribution of the electric charge affects the virucidal properties of the substance. Crucial factors are the anionic characteristic of the polymer charge and the hydrophobicity of the backbone. The inhibitory effect of polymers is related to the concentration of glycoproteins in the viral envelope. Non-enveloped viruses are resistant to polymers which are virucidal against enveloped viruses. The interaction of the polymers with the viral envelope makes it difficult for the virion to attach to a cell receptor.[3] Polymers combined with heavy metals affect viral proteins and the genetic material of the virus. Also, salts of toxic ions are more effective in disinfection than nonionic metals. Elevated temperature in environment increases antiviral activity of these polymers. Combining the drug with a polymer reduces toxicity and side effects, but does not reduce drug activity. It has a positive effect on the distribution of the drug in body compartments.[4]

Many faces of virucidal polymers

Polymer compounds show different properties depending on the chemical structure and physical conditions of the environment. The polymers can be virucidal against one type of viruses or have a broad spectrum of activity. Poly(vinylbenzoic acid) (PVBzA) could be a potential antiviral agent with a broad antiviral range (Table 1). It has the ability to inhibit enveloped viruses ZIKV (Zika virus), HIV-1, Flu, Lyssa, Ebola, and SARS. This polycarboxylate showed the broadest spectrum of activity against all viruses. Among the polyphosphates, poly(vinylphosphonic acid) (PVPA) shows a high inhibitory capacity against herpes simplex virus 2 (HSV-2) and SARS; however, due to its very low effectiveness against other viruses, it can only be used to a limited extent. These compounds can be used in drug development.[3] Polymeric compounds can be obtained by deacetylation of naturally occurring chitin. The polymeric compound based on chitosan HTCC (N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride) efficiently inhibitsthe respiratory infection caused by the human coronaviruses HCoVs.[5]

Polymeric compounds are susceptible to modification. In this way, the properties of the initial compound can be modified as required. Ye et al. showed that graphene oxide conjugated with polymer has antiviral properties at different stages of viral infection.[6] They indicated that the charge of the polymer conjugated with the negatively charged graphene oxide (GO) is important. Nonionic PVP (polyvinylpyrrolidone composite) showed greater antiviral potential compared to cationic PDDA (poly(diallyldimethylammonium chloride). The inactivation mechanism is based on the cleavage of the virus by single-layer graphene oxide. Ye et al.[6] suggested the use of conjugated GO as a potential virucidal material. Low concentration of povidone-iodine (PVP-I) showed antiviral activity during 15 s of oral rinsing.[7] Such use of PVP-I is recommended for oral procedures and surgical prophylaxis. The PVP-I shows virucidal activity for use in surface and hand disinfection after contact with infectious SARS-CoV material.[8] Such vaccines contain a backbone made of gold nanoparticles, polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyetherimide

Table 1. The chemical characteristics of the polymers and their role in antiviral drugs and vaccines

Author	Compound	Type	Role
Schandock et al.	PVBzA PVPA	polycarboxylates polyphosphates	antiviral agent antiviral agent
Milewska et al.	HTCC	polisaccharides	antiviral agent
Ye et al.	GO-PVP GO-PDDA	composite composite	antiviral agent antiviral agent
Bidra et al. Kariwa et al.	PVP-I	N-vinylpyrrolidone polymer	antiviral agent
Hu et al.	PEG-PLGA	copolymer	drug adjuvant
Honda et al.	delta inulin	polisaccharides	vaccine adjuvant
Garrido et al.	cyclodextrins	oligosaccharydes	drug carrier, antiviral agent, cholesterol trapper, vaccine adjuvants
Wang et al.	metal-organic frameworks	coordination polymer	detector
Lee et al.		DNA-based nanoarchitecture	drug carrier detector

PEG-PLGA – poly(ethylene glycol)-poly(lactide-co-glycolide); PVBzA – poly(vinylbenzoic acid); PVPA – poly(vinylphosphonic acid); HTCC – N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride; PVP – poly(vinylpyrrolidone); PDDA – poly(diallyldimethylammonium) chloride; PVP-I – poly(vinylpyrrolidone)-iodine

(PEI), or protein assemblies. The antiviral agent diphyllin, vacuolar ATPase blocker, is more effective when is encapsulated in poly(ethylene glycol)-block-poly(lactide-co-glycolide) (PEG-PLGA) copolymers than alone.[9]

Polymers as adjuvants for vaccines

As shown above, the polymeric compounds can act directly as an antiviral drug. Polymers are used as auxiliary compounds for other substances, vaccines and drugs. They play the role of adjuvants for vaccines, a transport role, or improve drug distribution in body tissues. Honda-Okubo et al.[10] showed that adjuvants for coronavirus vaccines based on delta inulin can improve the effectiveness of the vaccine by enhancing memory B cells. The addition of an adjuvant speeds up the neutralization of the pathogen. Adjuvant-conjugated vaccines reduce eosinophilic immunopathological side effects in the lungs caused by disproportionate vaccine-induced Th1 response. Inulin delta-based polymers have a positive effect on the efficacy of the vaccine against coronaviruses and reduce the inflammatory response of the body, which causes an adverse immunopathological effect in the form of lung infiltration with eosinophils.

Multirole cyclodextrins

Cyclodextrins (CDs) are oligosaccharides from the dextrin group. A characteristic feature is that CDs form a torus in the solution. Due to the specific distribution of the load, they have a hydrophobic interior. The outer surface can be modified by adding nonionic, anionic or cationic groups. The CDs form inclusion complexes with hydrophobic compounds.[11] Native or modified cyclodextrins can be used as carriers for antiviral drugs. They can enhance drug activity or be used as proper virucidal drugs. The CDs show ability to interact with virus lipid membranes by encapsulating them into cholesterol traps. They can also be used as vaccine adjuvants. Notably, dimethyl-beta-cyclodextrin improves the absorption of low-molecular-weight heparins and can be used as an anticoagulant drug carrier.[12]

Supportive role of polymers

During the pandemic, quick diagnostics is important. It has become crucial to develop low-cost methods of SARS-CoV-2 infection diagnosis, with high sensitivity and specificity. The effective detection from a low number of virions is a great advantage. Coordination polymers can be used as metal–organic framework (MOF) with typical structure porosity. The MOFs in combination with fluorescence technique may be used as virus and antibody detectors in the future. Practical application is hindered by the high detection limit which is practically not available in samples taken for testing.[13] Lee et al.[14] developed modular DNA-based nanoarchitecture that can be used as a secondary carrier or pathogen detector. Their solution allows for building polymers with the desired properties from scratch.

Conclusions

Viral outbreaks are stimulating for research that could help contain future global pandemics. Polymeric compounds reduce the toxicity of the drug and the frequency of side effects. At the same time, they can improve the effect of the actual therapeutic substance. The possibility of modification of the polymer creates an area for the study of nanoarchitecture, which will allow effective targeted therapy.

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