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SYNTHESIS OF RADIOACTIVELY LABELLED UNIFORMS OF THE POLYMER COMPLEX OF AZIDINE WITH POLYMETHACRYLIC ACID AND THEIR PHARMACOKINETICS

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ABSTRACT

The paper proposes methods for the synthesis of the labelled uniform forms of H^3-azidine and ^{14}C-methacrylic acid with high radiochemical purity and specific activity. The ^{14}C-polymethacrylic acid was synthesised by means of radical polymerisation. A polymeric dosage form of azidine, immobilised on polymethacrylic acid, was synthesised by complexation. The in vivo distribution and elimination of the uniform forms of the radioactive azidine and the polymer carrier were examined. The process of the high-molecular-weight polymer fractions being deposited at the injection site, along with the slow elimination of the low-molecular-weight substance in the process of its complexation with the high-molecular-weight compound, was confirmed, which ensures the prolongation of the action of the drug. The process of the drug leaching out of the complex with the polymer was simulated by means of the steady-state desorption method. The results of the study can be used to create new forms of polymeric drugs based on PMAA. Pharmaceutical science, including pharmaceutical technology, is characterised by an increased trend towards the creation of new dosage forms with improved biopharmaceutical properties. In this context, prolonged-release and sustained-release dosage forms occupy a special position, having a number of advantages over conventional dosage forms. For example, polymeric excipients are often used for the creation of controlled-release dosage forms. Among the methods for creating polymeric dosage forms, complexation between a functionally active polymer and a dosage form finds significant scientific and practical significance, allowing for a "gentle" immobilisation of a dosage form within a polymer network, retaining its specific activity while acquiring new properties, including an increased residence time within an organism. Based on these principles, a polymeric dosage form of an antiprotozoal drug, Azidine, a diaceturic salt of 4.4-diamidinodiazoaminobenzene, was synthesised with a water-soluble carboxyl-containing polymer, PMAA. However, its practical application in pharmacy is absolutely forbidden without elucidation of its fate, including that of its components, after administration. The solution to this problem is possible only through pharmacokinetic studies involving labelled forms of its components, which is of significant scientific and practical interest.

Keywords: Labelled Uniforms, Polymethacrylic Acid, Azidine, Polycomplex, Dosage Form, Pharmacokinetics.
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INTRODUCTION

Polymers used as drugs, which by their chemical composition are examples of high molecular compounds

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with a molecular weight of several thousand to one million, are rapidly finding their place in pharmacology.[1,2] There are many scientific publications on the synthesis and application of polymers of various forms in human and veterinary medicine.[3,4,5,6] For example, polymers are used as a carrier for drugs[7], which extends the effect of drugs and lowers the degree of inactivation in the body (povidone-iodine, polyfer).[8,9,10] The immobilisation of highly toxic antitumor drugs such as cis-platinum[11], rubomycin, on polymers gives them immunostimulant properties and properties of an interferon inducer.[12] The complex of polymers with antiviral drugs - adamantane derivatives increases the activity and lowers the toxicity of drugs[13], also imparting immunoadjuvant properties to them in combination with antiviral vaccines.[14] Polymeric compounds with a high level of polymerization[15], belonging to the dextran group[16], are used in arterial and venous circulation disorders[17], as well as detoxifying agents[18], because of their hemodynamic and antiplatelet activity on blood cells.[19,20] High-molecular homopolymers[21], capable of exerting volumetric and hemodynamic effects[22], with a high level of circulation in the blood for a long period of time[23], and slow excretion from the body[24], often after fragmentation[25], are the basis for the development of plasma substitutes[26], high-molecular dextrans, polyhydroxyethyl starch, etc.[27] The veterinary drug azidina, with a high level of specific activity, is an antiprotozoan drug in the form of a diacetur salt of 4,4-diamidinodiazoaminobenzene, with a short period of action (5-7 days) and high toxicity (LD50 = 94 mg/kg in white muscles), causing difficulties in practical use. In order to improve its physiological properties, based on its chemical structure and the formation of positively charged functional groups during its dissolution process, polymethacrylic acid has been used as a polymer carrier. In this regard, one of the promising ways to solve this problem is to complex the medicinal substance with a polyelectrolyte, which enhances solubility in water and biological fluids, prevents early degradation by enzymes, gives a prolonged effect to the medicinal substance, and in most cases enhances and softens its physiological effect on the body.[28] The choice of a polyelectrolyte, for example, PMAA, as a polymer carrier to solve this problem is due to its ability to change conformation and solubility with changes in pH and ionic strength.[29,30] The effectiveness of azidin immobilisation on a water-soluble carboxyl-containing polymer has been established by conducting extensive physicochemical research.[31]

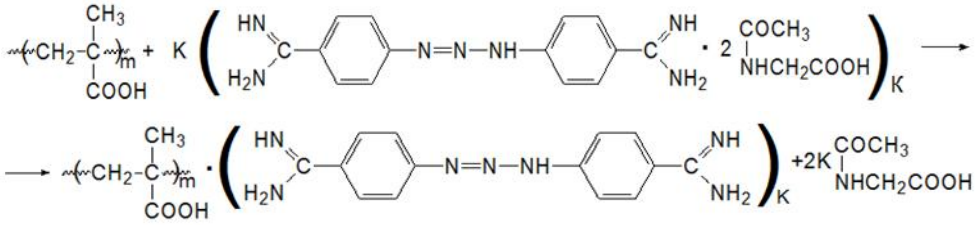


Fig.-1: The Interaction Scheme Between the Studied Reagents During the Immobilisation of Azidin on PMAA can be Represented as Follows

The structure of the polymer complex under investigation has been confirmed by various physicochemical methods.[32] Nevertheless, to be able to recommend it for veterinary practice, pharmacokinetic investigations are necessary.[33]

EXPERIMENTAL

One of the most important objectives of contemporary pharmacology is to enhance the effectiveness of chemotherapy. This may be achieved by creating new systems of drug delivery. The optimal rates of drug elimination from dosage forms enable one to reduce the therapeutic and total doses of the drug, reduce the likelihood of accumulation in organs and the development of allergies, rapidly adapt the body to the drug, and extend the duration of action of the drug. The objectives of our study were to design a low-toxicity and mild-acting drug dosage form with the maximum duration of physiological activity. One of the important problems that may arise when using polymers in pharmacology is the distribution of the drug in the body and its excretion from the body in its original form or in the form of metabolites. It has been well established that the molecular weight, biocompatibility and bioinertness of the initial polymer determine the fate of the polymer in the body. The use of the polymer carrier PMAA may result in its deposition at

the site of injection as a result of its high molecular weight. The pharmacokinetics of ^{14}C-polymethacrylic acid (^{14}C-PMAA) were studied to determine the features of the bioelimination of the synthesised drug.

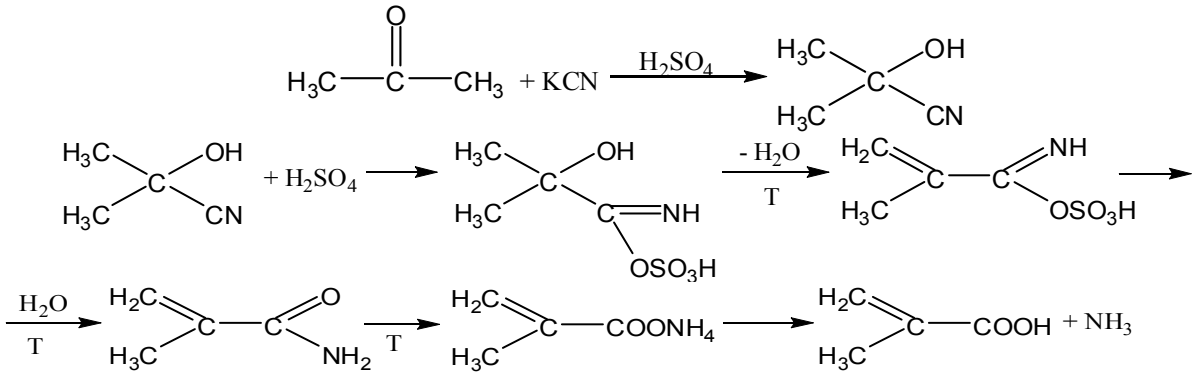


Fig.-2: To produce a Labelled Uniform form of PMAA, we Developed Methods for the Synthesis of ^{14}C-PMAA with Localization of the Radioactive Label in Positions 1 and 2 at the Stage of ^{14}C-acetone Cyanohydrin Synthesis According to the Following Scheme

For synthesis, 7.35 ml of 40% sulfuric acid solution was added within 15 min to a solution of 2.6 g of potassium cyanide, 2.5 ml of 2-^{14}C-acetone with a total radioactivity of 1000 MBq, in 3.2 ml of water at a temperature of 257-277 K, with stirring, to obtain 2-^{14}C-acetone cyanohydrin. The reaction mixture was kept at this temperature for 180 min with stirring, then at a temperature of 333 K for 120 min, then cooled to room temperature, filtered, extracted with diethyl ether, dried on anhydrous sodium sulfite, then distilled in vacuum at 15 mm Hg at a temperature of 347-349 K, with identification of the substance by gas chromatography (GLC) and refractometry:

PI20 = 1.3993-1.3998.

The chemical yield of 2-^{14}C-acetone cyanohydrin was 2.1 g, or 75%, with a radiochemical purity of 96% and a specific activity of 28.6 MBq/mmol. 2-^{14}C-methacrylic acid is obtained from 2-^{14}C-acetone cyanohydrin by hydrolysis and dehydration. 2.0 g of 2-^{14}C-acetone cyanohydrin is mixed with 0.02 g of copper powder, then with 2 ml of 98% sulfuric acid solution within 15 minutes, with stirring, then kept at 342-353 K for 15 min, then at 363-373 K for 25 min, then at 508-513 K for 35 min, then rapidly cooled to 333 K, with addition of 0.008 g of hydroquinone to prevent polymerization, then with addition of 1.1 ml of water at 503 K for 180 min, then cooled, with extraction of the resulting substance with benzene, then drying, then distillation at 331-333 K at a pressure of 12 mmHg. The chemical yield of 2-^{14}C-methacrylic acid is 0.63 g, or 31.6%, with a radiochemical purity of 95% and a specific activity of 26 MBq/mmol. 1-^{14}C-methacrylic acid was synthesised in a similar way from 2.2 g of K^{14}CN with a total radioactivity of 2000 MBq. 0.54 g (30.0%) of 1-^{14}C-methacrylic acid with a radiochemical purity of 96% and specific activity of 53 MBq/mmol was obtained. The chemical purity of the synthesised radioactive uniform forms of 1-^{14}C-methacrylic acid was determined by GLC analysis and refractometry: P_d^{20} = 1.4308-1.4315. The synthesis of ^{14}C-PMAA was carried out by a radical mechanism in benzene by the classical method from the uniform forms of ^{14}C-methacrylic acid synthesised above.

Labelled H^3-azidine was obtained by performing an isotope exchange reaction with a heterogeneous catalyst, which was 5% Pd on $BaSO_4$, in a tritium-containing solvent. To remove labile tritium, the sample was subjected to repeated washings with ethyl alcohol, which resulted in a negative reaction for the label. To remove H^3-aceturic acid, an alkali solution was added to the sample, and the resulting precipitate, which was labelled H^3-azidine, was separated by centrifugation. The resulting product was subjected to repeated washings with water, which resulted in a negative reaction for aceturic acid. When a solution containing non-substituted aceturic acid was added, H^3-azidine was converted into a complex salt, which was H^3-azidine. The specific activity of the sample was 33 MBq/mol. The experiments were carried out on albino male rats with a weight of 200-230 g, with 10 animals per group, in metabolic chambers. The labelled drug was injected subcutaneously with water injections into the hind legs of the animals. The radioactivity was measured every 24 hours by incising the tail and taking a sample, and

analysing the urine sample. Moreover, at regular time intervals after injection, two animals were sacrificed by decapitation, and a sample was taken for analysis by dissolving an aliquot of organs in formic acid, adding scintillation fluid JS-8, and then measuring after 24 hours with a Beta-1 radiometer.

RESULTS AND DISCUSSION

Most drugs that enter a living body undergo some form of biotransformation. Different drugs are metabolised by different percentages, while some drugs are almost completely converted into metabolites within the living body. Moreover, a single drug may be converted into different kinds of metabolites. Drugs and their metabolites are eliminated from a living body through different channels, including the kidneys, gastrointestinal tract, lungs, etc. The main route for elimination of drugs and their metabolites is renal excretion. Therefore, with pathological processes occurring in renal tissue, including nephritis and nephrosis, a drug may accumulate in the living body because of its failure to be eliminated. However, most drugs do not remain in the same form once they are introduced into an organism, as they are metabolised. The rate of metabolism varies among different drugs, with some being metabolised to a small degree, e.g., just several per cent of the dose, and others being almost completely metabolised. In addition, different metabolites of the same drug are possible. At the same time, the body eliminates the drugs and their metabolites in different ways, including the kidneys, gastrointestinal tract, lungs, and other routes. The primary route of excretion of most drugs and their metabolites is the kidneys. Therefore, if kidney tissue suffers from diseases like nephritis or nephrosis, the rate of excretion of the drugs slows, and the drugs may accumulate in the body. Another significant aspect of the excretion of drugs from the body is the role of the liver, not only in metabolising the drugs but also in their excretion. Drugs with molecular weights lower than 300 are not excreted in the bile, which leads to enterohepatic circulation of the drugs, increasing their concentration in the bloodstream and body tissues. Such drugs may lead to poisoning of the body with repeated doses, and that is why we focused our research in this area. During our experiments, an aqueous solution of ^{14}C-PMAA was injected subcutaneously, and some of the tracer was found in the bloodstream, liver, kidneys, and spleen, as shown in Fig.-1, with minimal radioactivity in the brain and intestines.

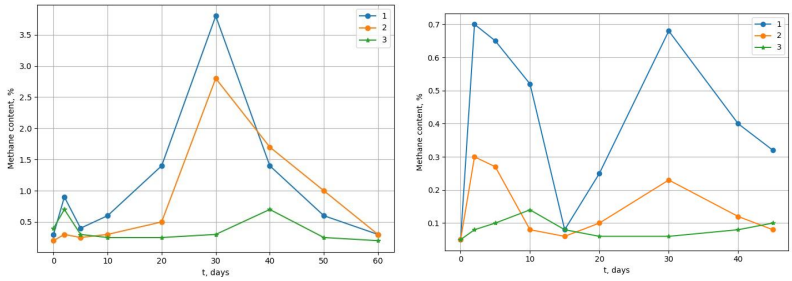


Fig.-3: Kinetic Curves of the Label Content in the Organs: Liver (1), Kidneys (2) and Spleen (3) of Animals from the Time of Administration of Aqueous Solutions of ^{14}C-PMAA (A) and the Polymer Complex ^{14}C-PMAA-azidine (B)

As depicted in Fig.-1, a brief, barely perceptible accumulation of label occurs in the organs at first, which can be explained by the entry and rapid clearance of low molecular weight fractions of polymer (<10.000) into the bloodstream. Over a period of 30-40 days, however, the amount of label retained by the organs increases, probably because PMAA fractions up to 50.000 Da distribute between tissues and gradually clear from the body. When you add everything up, i.e., label retained by organs plus that eliminated in urine, you get a total of about 15-20% of the original dose. This is roughly consistent with that fraction of low molecular weight fractions (<50,000 Da) present in PMAA polymer, as determined by similar experiments with ^{14}C-PMAA fractionation methods. The decrease in label retained by organs over time probably results from the elimination of macromolecules by urine and the reticuloendothelial system. This is also seen in the amount of labelled polymer present in the bloodstream, as depicted in Fig.-2, and that present in urine, as depicted in Fig.-3. Here, we see a sharp increase in the amount of label leaving the injection site and entering the bloodstream over a few days, followed by a gradual decrease. In the urine, we also see a sharp increase over the first four days, with a gradual decrease over the remainder of the 30-day period.

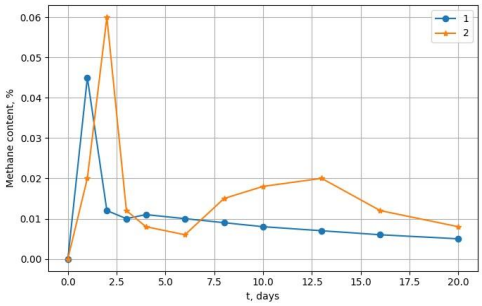


Fig.-4: Kinetic Curves of the Label Content in the Blood Upon Administration of ^{14}C-PMAA Solutions (1) and the ^{14}C-PMAA-Azidine Polymer Complex (2) to Animals

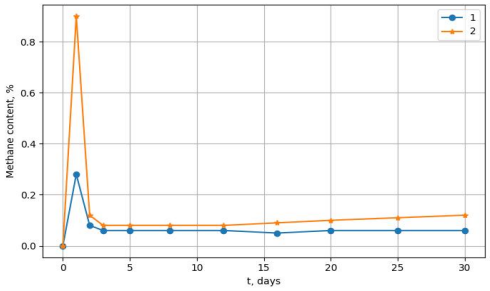


Fig.-5: Kinetic Curves of the Label Content in Urine Upon Administration of ^{14}C-PMAA Solutions (1) and the ^{14}C-PMAA-Azidine Polymer Complex (2) to Animals

Thus, pharmacokinetic investigations demonstrate that PMAA, being of high molecular weight, about 200.000–220.000, or its cross-linked derivatives remaining at the injection site, are applicable pharmacologically. With regard to the cross-linked forms of PMAA, their particle size, ranging from 2 to 20 micrometres, makes them unable to penetrate biomembranes or to be subjected to bio-transformation.

After being absorbed, the medicinal substance is transported to various parts of the body, and the manner of its distribution is determined by several factors. The most important of these are the intensity of blood flow to different body areas, the solubility of the medicinal substance in lipids, and its affinity to plasma proteins. In the course of the first minutes of absorption, the majority of the medicinal substance is transported to organs and tissues with the most intensive blood flow, i.e., heart, liver, and kidneys. The saturation of muscles, mucous membranes, skin, and fat takes place gradually. The manner of penetration of medicinal substances into organs and tissues is of significant importance both theoretically and practically, specifically with regard to pharmacotherapy. The tissue-specific effects of many medicinal substances, along with their possible toxicity, are often associated with the accumulation of toxic concentrations of these substances in certain tissues. The tissue's permeability to medicinal substances depends on several factors, including the concentration of the medicinal substance in the blood, its affinity to plasma proteins, its affinity to proteins of the intercellular space and within the cell, as well as its rate of penetration through different cell membranes, and the tissue's own blood flow. To investigate the release of azidin from the polymeric dosage form, the distribution and excretion of uniformly labelled H^3-azidin were studied. The labelling was achieved by exchanging protons with tritium in 4.4-diamidinodiazoaminobenzene with tritiated solvent. The experiments involved tracking the labelled drug, as well as its polymeric complex with PMAA, in white rats over 60 days. During the early stages, 0.2-2.0% of the dose was found in the liver, spleen, heart, and lungs, gradually reducing to 0.1-0.5% per gram of the organ by the end of the study. The minimal distribution of the drug into organs indicates that readministration of the drug during treatment may be safe for the rats. However, the concentration of the label in the blood and urine was higher in both scenarios. The pharmacokinetic study of the H^3-azidine-PMAA polymeric complex revealed that the concentration of the drug in the bloodstream remains high over long periods, as indicated in Fig.-4, while the concentration of the drug in the urine was lower than that of the labelled H^3-azidine, as indicated in Fig.-7. The study of the pharmacokinetics of the polymeric complex was necessary since azidine is an anti-inflammatory drug with chemoprophylactic activity in the

bloodstream of cattle. To simulate the release of the drug from the injection site of the polycomplex, the steady-state desorption method was used. The amount of desorbed drug was determined using UV spectrophotometry, with the concentration of the solution determined using a calibration curve at 370 nm with Shimadzu's UV-1800 instrument. To prevent liquation of the polycomplex, hydrogels of methacrylic acid with very low cross-linking degrees, not more than 2%, were used as the polymeric carriers, with N, N'-methylenebis-acrylamide as the cross-linker.

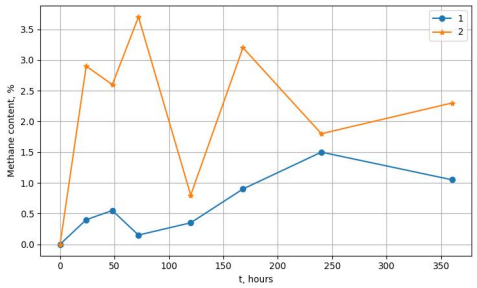


Fig.-6: Dependence of the Label Content in the Blood (in % of the administered dose) on Time Upon Administration of Solutions of H^3-azidine (1) and the Polymer Complex H^3-azidine-PMAA (2)

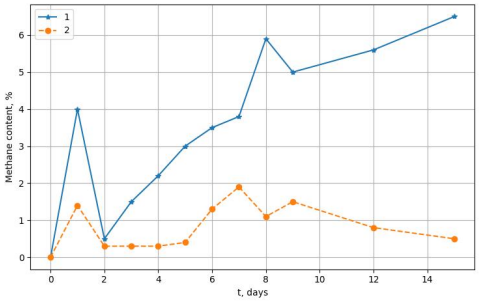


Fig.-7: Kinetic Curves of the Label Content in Urine Upon Administration of H^3-azidine (1) and H^3-azidine-PMAA Polymer Complex (2) Solutions to Animals

To replicate the desorption of the drug from the polycomplex formed at the injection site, the stationary desorption method was selected, with the amount of desorption being determined using UV spectrophotometry, creating a calibration curve with a wavelength of 370 nm using a Shimadzu UV-1800 instrument. Moreover, to prevent an error in the reading of the concentration of the azidin due to its diffusion into the water-soluble form of the polycomplex, which forms as some of the drug liquates, hydrogels of methacrylic acid with minimal cross-linking, no more than 2%, were selected as the vehicle for the polycomplex, with N,N'-methylenebisacrylamide being the cross-linking agent.

0.9% solution of saline was chosen as the model desorption medium (Fig.-8). The drug loading of the saturated complexes in system (1) and system (2) was equal to 0.0041 and 0.0029 g/g, respectively. As a result of the analysis of these results, it became possible to trace the pattern of the liquation process in controlled model conditions (Fig.-9). As can be seen from the results presented in Fig.-8, in both systems, there is an initial rapid desorption of a significant portion of the bound drug, followed by a slower process. This could be due to the rapid desorption of the drug from the surface of the polycomplex particles, and then the slower desorption from the bulk of the particles.

The desorption curve of the immobilised drug from the saturated polycomplexes (Fig.-9) could serve as an indicator of the period for which the drug's effect is prolonged. When performing the acute toxicity test using white mice (10 mice in each group), using subcutaneous injections of aqueous solutions of the polymer and the azidine-containing polymer complex, the LD50 of PMAA amounted to 950 mg/kg, whereas the LD50 of the azidine-PMAA polymer complex was equal to 750 mg/kg, ten times higher than that of the drug under investigation. When examining the chemopreventive activity of the developed azidine-PMAA polymer complex in cattle, the prolonged effect of the drug is maintained for 24-26 days after administration of a single dose of the drug in the course of the therapeutic test.

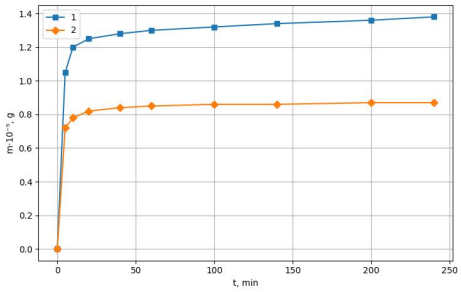


Fig.-8: Presents an Example of the Desorption of the Drug from Saturated Polycomplexes into Saline. The Samples are characterised by Drug Content of 0.0041 g/g (labelled 1) and 0.0029 g/g (labelled 2), with a Mass of Polycomplex of 4 g, a desorbed volume of 200 mL, and a Temperature of 298 K

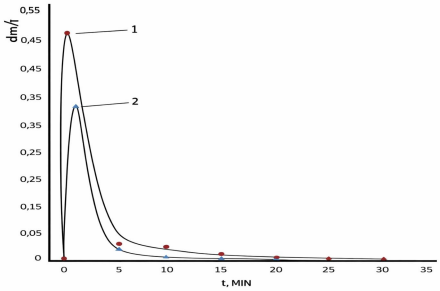


Fig.-9: Dependence of the Desorption Rate of Immobilised Drug from Saturated Polycomplexes: where the Drug Content is 0.0041 g/g (1) and 0.0029 g/g (2) on Time with Saline. The Weight of the Polycomplexes is 4 g, the Volume of Desorbate is 200 ml, and T = 298 K

CONCLUSION

On the basis of the pharmacokinetic studies, the following key findings have been made:

- For the first time, it has been demonstrated that the substance Azidine can be stored in animal hematomas for a long time by attachment to PMAA.
- PMAA with a molecular weight of about 200.000–220.000 or its cross-linked derivatives are recommended for use as a polymer support for the creation of long-acting dosage forms of other drugs.
- High molecular weight PMAA fractions accumulate at the injection site, yet allow for bioelimination, whereas low molecular weight PMAA macromolecules are removed slowly from the animal body.
- The in vivo tests have shown that complexation of a low-weight medicinal substance with macromolecules decreases its toxicity.
- The biological tests have confirmed the fact that the new dosage form possesses a prolonged therapeutic and preventive effect in the fight against protozoal diseases in cattle. These findings enrich the scientific information about the ion-exchange interaction of organic substances with polyelectrolytes.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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