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THE PROLONGATION OF THE ACTION OF PHARMACEUTICAL PREPARATIONS BY MIXING OR COMBINING THEM WITH POLYMERS

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In the past decade considerable progess has been made in work on prolonging the action of pharmaceutical preparations. By the use of long-acting compounds, not only can the total amount of a preparation introduced into the body during a course of treatment and the number of doses or injections be reduced, but there are also other substantial advantages. Variations in the blood and tissue concentration of an active compound, which are unavoidable with periodically repeated doses of ordinary preparations, can be reduced or eliminated by the use of long-acting preparations; a constant concentration of the active compound that does not exceed the therapeutic dose, as frequently occurs with ordinary preparations, can be maintained with these long-acting preparations[1-4]. Their use also reduces the probability of unwanted effects, if the patient neglects to take medicine at the right time. Long-acting preparations should rapidly establish the required concentration of active compound in the blood and tissues; if this is not possible an ordinary preparation must be used at the beginning of a course of treatment so as to produce a rapid rise of concentration in blood and tissue. Moreover, the use of long-acting preparations saves much routine time; for example, a single dose or injection may replace four or five; this is of great practical importance in treatment in clinics.

The following methods may be used to prolong the action of pharmaceutical preparations: (1) introduction of various substituents into the molecule to retard the rate of excretion; (2) preparation of complexes or salts of pharmaceutical preparations with low-molecular-weight compounds; (3) use of special compounded preparations; (4) administration as a mixture with polymers; (5) formation of compounds with polymers.

The preparation of special long-acting compounded preparations and the use of these compounded preparations in medical practice have been dealt with in a number of reviews[2-7]. However, there are no systematic reviews on long-acting preparations made by methods (4) and (5). The present review is intended to fill this gap.

In the USSR, work in this field has been initiated by Ushakov and coworkers, who have worked on this problem over a long period, and also by Mokhnach, who has prepared and examined complexes of iodine with various polymers.

ADMINISTRATION OF PHARMACEUTICAL PREPARATIONS IN MIXTURES WITH POLYMERS

The action of many pharmaceutical preparations may be prolonged by administering them simultaneously with polymers; for example, procaine, morphine, insulin, adrenaline, antibiotics, and other preparations may be administered with polyvinylpyrrolidone[8-16]. However, the mechanism of action of polyvinylpyrrolidone has not yet been elucidated. Sheinaus and Sperandio[11] studied the effect of polyvinylpyrrolidone on the *in vitro* antibacterial action of 26 compounds against *M. pyogenes* var. *aureus*; the compounds included antibiotics, quaternary ammonium salts, phenols, mercury compounds, dyes, etc. Polyvinylpyrrolidone did not reduce the antibacterial activity of most of the preparations, but it did reduce the activity of iodine and zinc sulphate.

Malek and Kol'ts[17] showed that the rate of excretion of streptomycin and neomycin is reduced when the antibiotic is given mixed with heparin; the penetration of the antibiotic into lymph is also increased. This effect is explained by the formation of a salt of the antibiotic and heparin in the body.

It has also been shown[18] that the addition of polygalacturonic acid to the tannates of codeine, atropine, or morphine retards the excretion of these compounds; the retardation appears to be due to the formation of salts of polygalacturonic acid in the body. In a number of cases a polymer administered simultaneously with the pharmaceutical preparation increases its solubility and lowers its toxicity[16,19,20]; for example, heparin lowers the toxicity of polymyxin, streptomycin, and neomycin[17].

LONG-ACTING PREPARATIONS CONSISTING OF COMPOUNDS WITH POLYMERS

Long-acting preparations consisting of compounds with polymers may be divided into three groups: (1) complexes with polymers; (2) ionic compounds with polymers; (3) covalent compounds with polymers.

1. Complexes of pharmaceutical preparations with polymers. With many polymers iodine forms complexes possessing antimicrobial activity. Much work has been devoted to the preparation and study of iodine complexes of different polymers: polyvinylpyrrolidone[21-28], poly(ethylene glycol)[29], dextran[30], polyethoxypolypropoxyethanol[31], poly(vinyl alcohol)[32,33], and starch and its components[34-36]. The synthesis of iodine–polymer complexes, their properties, antimicrobial action, and field of application are discussed in detail in Mokhnach's monograph[37]. Mokhnach showed that the antimicrobial properties of coloured iodine–polymer complexes are due to the presence of the cation $I(I^+)$;[37-40] he also showed that the toxicity of iodine is reduced when it is combined with polymers.

Ushakov[41,42] has proposed a complex of iodine with polyvinyl alcohol ("iodinepolyvinyl alcohol") as a thixotropic gel which is melted for subcutaneous or intramuscular injection. Thixotropic gels of "iodinepolyvinyl alcohol" are prepared by cooling solutions of "iodineopolyvinyl alcohol" to which are added compounds (borax, boric acid) that form labile cross-links between the polymer macromolecules; these links are readily destroyed by heating and re-established at body temperature. The thixotropic gels melt at a temperature (usually 38–42°) which depends on the molecular weight of the polymer, its concentration in solution, and the number and kind of cross-links. To increase the iodine content of the gel and to prolong its absorption by the body[43,44], two-phase gels were prepared which contained an insoluble solid phase, consisting of an iodine complex of a three-dimensional copolymer of vinyl alcohol with diallylacetals or hydroxymethylcrotonamide, in addition to the "iodinepolyvinyl alcohol" thixotropic gel. Ordinary and two-phase gels of "iodinepolyvinyl alcohol" have been used in the treatment of tuberculosis, atherosclerosis, and other diseases.

Complexes of polyvinylpyrrolidone with halogen halides have been proposed as antiseptics; iodine monochloride and other halides have been used[19,45]. The preparation of iron–dextran complexes for the treatment of anaemia by injection has been described[46-48], and also the preparation of cobalt–dextran[49] complexes and complexes of polyhydroxyethylene-40-polystearate with various pharmaceutical preparations[50].

2. Long-acting preparations consisting of ionic compounds with polymers. Polymeric materials with ion-exchange properties have been used in the treatment of dermatitis, oedema due to cardiac insufficiency, kidney diseases, cirrhosis of the liver, and other diseases[51-56]. Blood anticoagulants, the preparation of which has been described, include sulphate esters of partially hydrolysed dextran[57-60], "dextranic acid"[61] (obtained as a by-product in the depolymerisation of dextran by an enzyme separated from *Asperigillus wentii*), glycogen, starch[62,63], xylan[64], chitin, chondroitin[65,66], sulphates and acetates of alginic acid[67], and carboxymethylcellulose[68]. Alkali metal salts of the sulphate esters of partially degraded polysaccharides have been proposed as haemostatics[69]. Dextran phosphates that increase the glucose content of the blood have been synthesised[70], and the synthesis of physiologically active amylose sulphate has been described[71].

Recently, the use of polymeric materials with ion-exchange properties, or ion-exchange resins, for the prolongation of the action of ordinary pharmaceutical preparations has been attracting increased interest. The salt of a pharmaceutical preparation and an ion-exchange resin is gradually decomposed in the organism and the liberated drug exhibits its therapeutic action. The decomposition of these salts in the gastro-intestinal tract may be represented by the following schemes:

in the stomach:

$$P\text{–}SO_3^-{}^+H_3N\text{–}A + HCl \rightleftharpoons P\text{–}SO_3H + A\text{–}NH_3^+Cl^-,$$

$$P\text{–}NH_3^+{}^-OOC\text{–}B + HCl \rightleftharpoons P\text{–}NH_3^+Cl^- + B\text{–}COOH;$$

in the intestine:

$$P\text{–}SO_3^-{}^+H_3N\text{–}A + NaCl \rightleftharpoons P\text{–}SO_3Na + A\text{–}NH_3^+Cl^-,$$

$$P\text{–}NH_3^+{}^-OOC\text{–}B + NaCl \rightleftharpoons P\text{–}NH_3^+Cl^- + B\text{–}COONa,$$

where P is the polymer and A and B are pharmaceutical preparations.

A large number of peroral long-acting drugs have been patented in Great Britain; these consist of salts of ion-exchange resins and various therapeutically and physiologically active compounds, including vitamins (thiamine, riboflavine, and pyrodoxine)[72], alkaloids (morphine, ephedrine, normorphine, dihydromorphine, and dihydromethylmorphine)[72-75], lucanthone[76], barbiturates[74,77], and

salicylates[77,78]. These preparations are known under the general name "resinates". Drugs with basic groups are usually combined with a sulphonated copolymer of styrene and divinylbenzene, or with a copolymer of divinylbenzene and acrylic or methacrylic acid or maleic anhydride, but other cation-exchange resins may also be used[79]. Combination of a drug with a polymer containing ionogenic groups may eliminate an unpleasant odour and taste as well as prolonging the action of the drug. Becker and Swift[80] have shown that some resinates are less toxic than the unmodified compounds.

A long-acting preparation of adrenocorticotropic hormone (ACTH) with enhanced activity may be obtained by interaction of the hormone with modified proteins (gelatin, albumin, globulin)[81]. A long-acting ACTH preparation has also been obtained by interaction of ACTH with hyaluronic acid[82]. Salts of polyuronic acids and choline, calcium, iron, magnesium, and cobalt have been proposed for the treatment of diseases of the liver, arteriosclerosis, and disorders due to the deposition of cholesterol in the vascular system[83].

According to patent information[84], long-acting antihistamine preparations may be obtained by the action of diphenylpyraline on sulphonated copolymer of styrene and divinylbenzene. Cobalt salts of carboxyl-containing polymers have been proposed for the treatment of dermatitis[85]. A mixture of polyacrylic acid cross-linked by polyhydroxy-compounds, and magnesium oxide, hydroxide, or carbonate has been proposed as an antacid to reduce the acidity of the gastric juice to pH 4–5 and maintain it at this level[86].

The preparation of salts of polysaccharide sulphates, used as anticoagulants, and aminobenzoic acid esters, used as local anaesthetics, has been patented[87].

Alkylsulphonated or acylated polymers containing basic groups, for example polyethylenimine[88], have been proposed for prolonging the action of pharmaceutical preparations and removing toxins from the body. Antibacterial compounds have been prepared by the interaction of quaternary ammonium bases with polysaccharides containing carboxy-groups, for example carboxymethylcellulose, carboxymethylstarch, and polyuronic acids[89].

Compounds containing ion-exchange resins and neomycin or sulphadiazine have been proposed for the treatment of skin diseases[90]. *In vitro* experiments have shown that the long-acting compounds have a greater antibacterial activity than the ordinary preparations.

Thus both natural and synthetic polymers are used to prolong the action of drugs. When synthetic polymers are used, their absorption and excretion is of great importance, but this has been little studied. Probably, it would be advantageous to use modified natural polymers such as polysaccharides and proteins.

Much work has been devoted to decomposition of salts of drugs and ion-exchange resins and to the liberation of drugs from the resins. It has been shown that 0.1 *N* hydrochloric acid very rapidly elutes drugs such as ephedrine and methapyrilene from cation-exchange resins containing carboxy-groups[1,91]. For this reason, many workers consider that polymers containing carboxy-groups cannot be used in making long-acting peroral preparations. The rate of decomposition of salts of drugs and polymers containing sulpho-groups in 0.1 *N* hydrochloric acid is much slower[1,91]; these polymers are therefore more useful for long-acting peroral preparations. Nash and Crabtree[92] have studied the liberation of tritium-labelled α-deoxyephedrine from these two types of cation-exchange resin in the body. It was found that the salt bond between α-deoxyephedrine and the polymer carboxy-groups is very rapidly destroyed in the stomach, but the liberation of α-deoxyephedrine from the sulphonated polymer is much slower. In the intestine the rate of liberation is the same for both types of polymer.

Smith *et al.*[91] studied the decomposition of a salt of methapyriline and a sulphonated copolymer of styrene with divinylbenzene in 0.1 *N* hydrochloric acid under static conditions. Chaudry and Saunders carried out analogous studies on ephedrine salts under static and dynamic conditions[1]. It was found that the rate of decomposition of both salts decreased as the particle size of the ion-exchange resin and the number of cross-links in the polymer increased, that is, as the total surface of the polymer particles and the rate of diffusion of acid in the polymer decreased. When a polymer with a large number of cross-links was used, the rate of elution of methapyrilene from the ion-exchange resin fell sharply as the particle size of the resin increased. The effect of the number of cross-links in the polymer on the elution rate decreases as the resin particle size is reduced. Under static conditions, when a salt of ephedrine and a cation-exchange resin was treated with 0.1 *N* hydrochloric acid, the rate of decomposition, and therefore the rate at which the ephedrine is liberated, decreased sharply after only two hours; at this point equilibrium is established between the ephedrine in solution and ephedrine bound to the sulpho-groups of the copolymer. When a sulphonated polymer containing ephedrine is treated with 0.1 *N* HCl under dynamic conditions, the sharp reduction in the rate of ephedrine liberation is not observed. In the presence of a polymer with free sulpho-groups the elution of ephedrine from resin under dynamic conditions is much slower. According to Chaudry, if a polymer with free sulpho-groups is added to a polymer containing ephedrine bound by saltlike bonds, a constant rate of ephedrine liberation in 0.1 *N* HCl can be achieved under dynamic conditions; this is a good model of the process occurring in the gastro-intestinal tract.

Chaudry and Saunders showed also that a salt of ephedrine and a sulphonated copolymer of styrene and divinylbenzene decomposes at about the same rate in 0.1 *N* solutions of hydrochloric acid, sodium chloride, or sodium bicarbonate. Swift[93], who studied the action of four antihistamine resinates on guinea-pigs, showed that the degree of prolongation depends on the particle of the resin; for example, granulated phenyltoloxamine and pyrilamine resinates were unsatisfactory, but the powdered resinates gave good results.

The rate at which a salt formed from a drug and an ion-exchange resin decomposes, and therefore the rate at which the drug is liberated, depends entirely on the presence of ions and is independent of the action of enzymes, peristalsis, or other physiological factors[94]. Since the total concentration of ions in the gastric juice changes within very narrow limits, the rate of liberation of drugs from ion-exchange resins in the gastro-intestinal tract must be fairly constant. The liberation of drugs from tablets and granules with special coatings cannot be uniform, since the decomposition of the coatings depends on a number of physiological factors[94]. Experiments *in vivo* have shown that, when acetylsalicylic acid and amphetamine resinates are administered, the rate of excretion of the drugs in the urine is much lower than when the same

drugs are given not combined with polymers[95,96]. It has been shown that the breaking of the salt bond between amphetamine and a cation-exchange resin proceeds at a constant rate[97]. Experiments on dogs and rabbits have shown that amphetamine resinate is more long acting than amphetamine sulphate in specially coated tablets[98,99]. With amphetamine resinate the daily therapeutic dose is much lower, and the curative effect much greater, than that obtained with ordinary amphetamine[99].

Methapyrilene resinate has about the same therapeutic activity as methapyrilene hydrochloride[91] Experiments *in vivo* showed that a salt of methapyrilene and a sulphonated copolymer of styrene and divinylbenzene had an action lasting 6.5 h, compared with 5.5 h for methapyrilene hydrochloride; there was therefore no significant increase in duration of action.

Malek[100,101] has prepared long-acting compounds by reacting antibiotics containing basic groups, like streptomycin and neomycin, with polymers containing acid groups (polyacrylic acid, polysaccharide sulphates and phosphates, polyuronic acids, and carboxymethylstarch). With these long-acting preparations a high concentration of antibiotic in the lymph was achieved; they were therefore termed "antibiolymphins".

It has been shown[100] that 75% of streptomycin given intravenously to rabbits is excreted in 8 h; the corresponding figure for the salt of streptomycin with dextran sulphate was 22.7%, and for the salt with polymethacrylic acid 45.5%. The toxicity of the long-acting preparations was lower than that of the free antibiotics.

Ushakov and Panarin[102] prepared salts of benzyl- and phenoxymethyl-penicillin with a copolymer of vinyl alcohol and vinylamine; these contained 11.22% of benzylpenicillin and 13.6% of phenoxymethyl-penicillin. The salts were not decomposed by dissolution in water and reprecipitation, and their solutions were stable. Preliminary biological tests at the First Leningrad Medical Institute showed that the benzylpenicillin polymer has the same activity (on a penicillin content basis) against *Staphylococcus* 209-R as standard benzylpenicillin. Thixotropic gels, with a setting temperature of 38–39°, of both polymers were prepared by a method previously described[41,42].

Brudney[103] showed in *in vivo* experiments that when penicillin V resinate is administered, a constant concentration of the active drug is maintained in the body for 3 h, after which there is a gradual fall in concentration. When free penicillin V is administered a high concentration in the body is obtained, which falls in a short time. The use of resinates of octanoic acid and undecenoic acid in intestinal affections has been described[104].

The work reviewed shows that a considerable number of long-acting drugs have been synthesised by linking ordinary drugs to polymers by ionic bonds. However, the literature contains insufficient systematic results of pharmacological and clinical trials of these long-acting preparations.

3. Long-acting pharmaceutical preparations consisting of covalent compounds with polymers. When compounds bound covalently to polymers are introduced into the body, they can act in two ways: (a) the covalent bond between the polymer macromolecule and the drug molecule is gradually destroyed and the drug beings to exercise its therapeutic action; (b) the covalent bond is maintained and the therapeutic action is due to the polymer-drug compound.

The therapeutic effect of a drug is due to its structure, that is, to the presence in its molecule of certain functional groups and of different substituents in positions related to these groups. Therefore, if the covalent bond between the drug and the polymer is maintained in the body, the addition of the drug to the polymer should not destroy or reduce its therapeutic effect.

Ushakov[105] has proposed the modifications of drugs by combining them with polymers used as blood substitutes. Different copolymers of vinylpyrrolidone and vinyl alcohol with crotonic acid, hydroxymethylcrotonamide, and vinylamine were synthesised. The presence in these copolymers of hydroxy-, amino-, carboxy-, and hydroxymethylcarbamoyl groups enabled a number of drugs to be combined with their macromolecules. By the use of these blood-substituent polymers, a number of drug polymers were prepared for the treatment of cardiovascular diseases, tuberculosis, and tumours[102,106–110]. As Ushakov[106] has shown, the drug can also be introduced into this type of macromolecule by copolymerising vinylpyrrolidone with organic drugs containing unsaturated groups.

By reacting polyvinyl alcohol with the lactone of di-(4-hydroxycoumarin-3-yl)acetic acid (pelentanoic acid), Ushakov and Kononova[107,108] synthesised the ester of pelentanoic acid, which is a blood anticoagulant. The ester of pelentanoic acid with the copolymer of vinyl alcohol and vinylpyrrolidone was obtained in the same way. The esters of pelentanoic acid with polyvinyl alcohol dissolve readily in water to form stable solutions and have blood-substituent properties. Trials on rabbits and dogs at the Leningrad Blood Transfusion Institute showed that intravenous administration of an aqueous solution of the ester of pelentanoic acid with polyvinyl alcohol rapdily lowers the blood prothrombin and maintains it at a low level for a considerable time[107]. The hydrogen sulphate esters of polyvinyl alcohol, which are also anticoagulants, were prepared[106] by the reaction of polyvinyl alcohol or polyvinyl acetate with sulphuric or chlorosulphonic acid.

Drug polymers with antitubercular activity have been obtained[109] by the action of *p*-aminosalicyloyl chloride on polyvinyl alcohol. These compounds contained up to 30% of *p*-aminosalicylic acid and had blood-substituent properties. Trials showed that the rabbit excreted the preparation much more slowly than ordinary PAS. *In vitro* tests on Petran'yani's medium showed that the preparation had an antimicrobial activity against *Mycobacterium tuberculosis*. Thixotropic gels of the preparation, setting at 38–40°, were obtained by a method previously described[42,44].

Blood-substituent polymers with antisclerotic action have been prepared by copolymerising vinylpyrrolidone with vinyl oleate. When the product was introduced into the blood, a fall in cholesterol content was noted and also partial "washing away" of sclerotic platelets, but it was found that the polymer was deposited in the liver and spleen of the experimental animals; the authors consider that this deposition is due to the long side chains. Blood-substituent polymers with antitumour activity and antioxidant properties were obtained by copolymerising vinylpyrrolidone and vinylhydroquinone[110], and also by acetylating polyvinyl alcohol with salicylaldehyde[106].

Jatzkewitz[111,112] combined glycylleucylmescaline with a copolymer of vinyl pyrrolidone and acrylic acid by means of an amide bond. When the product was given subcutaneously to experimental white mice, mescaline was observed in the urine for 17 days; in contrast, mescaline was

eliminated in 16 h when it was given as mescaline hydrochloride, as glycylleucylmescaline hydrochloride, or as a mixture of the copolymer of vinylpyrrolidone and acrylic acid with mescaline. It should be noted, however, that the high-molecular-weight product was more toxic than free mescaline. According to Jatzkewitz, the increased toxicity is due to the presence in the polymer used of a fraction with a very high molecular weight. Later Jatzkewitz[113] proposed other compounds in which physiologically or therapeutically active compounds are linked by an amide bond to the copolymer of vinylpyrrolidone and acrylic acid; the drugs used included 5-hydroxytryptamine, tryptamine, histamine, thyroxine, antibiotics with a free amino-groups, and hormones.

Kratzl and Kaufmann[114] obtained an acetylsalicylic ester of starch containing up to 0.7 acetylsalicylic acid residues by the action of acetylsalicyloyl chloride on soluble starch in the presence of potassium hydroxide. A higher degree of esterification is obtained when pyridine is used but the product is difficult to purify. Labelled ^{14}C was used in the synthesis of this acetylsalicylic ester. The breakdown of the ester was studied in dogs and rabbits[115]. The animals received an intramuscular solution of the ester in glycerol-acetonide and the concentration of acetylsalicylic acid in the blood was determined colorimetrically and radiometrically. It was found that administration of the starch ester gave a concentration of acetylsalicylic acid in the blood 20 times lower than that obtained when the free acid was administered. A vanillin diethylamide derivative of starch carbonate, with two ester residues per unit link[116], was obtained by the action on soluble starch of the product of the reaction between phosgene and vanillic acid diethylamide; the diethylamide was labelled with ^{14}C. Intramuscular administration of the product in glycerol-acetonide gave a much lower concentration of vanillic acid diethylamide in the blood than when an equivalent amount of the free diethylamide was administered. It was therefore shown that only slight cleavage occurs when the starch derivatives are given intramuscularly.

Compounds with antitubercular activity have been prepared by condensing polysaccharides, oxidised with sodium metaperiodate, with thiosemicarbazide, aminobenzaldehyde thiosemicarbazone, and isonicotinic acid hydrazide[117-119]. Starch, alginic acid, and inulin have been used in the preparation of high-molecular-weight pharmaceutical preparations.

Long-acting drugs have also been prepared by condensing compounds containing an amino-group with the aldehyde groups of partially oxidised dextran[120]. A nicotinic acid ester of starch that liberates the free acid in the body has also been described[121].

The work reviewed here shows that the prolongation of the action of drugs by administering them mixed with, or combined with, polymers is attracting the attention of a wide circle of research workers throughout the world. There is no doubt that systematic studies in this field will lead to new valuable long-acting preparations.

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PHYSICOCHEMICAL FEATURES OF THE SPREADING OF A LIQUID METAL ON A SOLID METALLIC SURFACE

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