

POLYVINYLPIRROLIDONE METAL COMPLEXES. FORMATION STABILITY AND THEIR BIOLOGICAL ACTIVITY

V.A.Lee, S.Sh.Rashidova

Institute of Polymer Chemistry and Physics of Uzbek Academy of Sciences,
7b, A.Kodyrii str., Tashkent, 700128, Uzbekistan
tel.: 7-3712-418642, 7-371-1851230;
fax: 7-3712-632526, 7-371-1442661,
E-mail: director@icpp.silk.glas.opc.org. or
dayton@tools.silk.org.

ABSTRACT

The peculiarities of the polyvinylpyrrolidone (PVP) interaction with transition metal ions of the first row in solution were studied. It was shown that PVP macromolecules due to their swelling conformation in organic solvents form the stable metal complexes. Metal ions were bonded with oxygen and nitrogen atoms of PVP lactam rings. In water solution every metal ion interacts with one or two oxygen atoms out of 10-12 monomer units of the polymer. The additional contraction of PVP macromolecule coils in water have been found out by dissolving of the polymer metal complexes (PMC) synthesized in organic media.

Toxicity, blood forming and immune stimulating activity and pharmaco-kinetic too of obtained polymers and their metal complexes have been investigated. The factors and effects that responsible for changing of PMC physical-chemical and biological properties have been estimated.

Introduction

The important role of such trace metals as manganese, cobalt and copper in biological systems has been shown by several investigators. A surplus or deficiency of the metals, and disturbances in their metabolism, lead to alternations in the normal processes within an organism and to various diseases. Thus the use of metal and metal derivatives as drugs has been introduced. However, metal salts used as drugs have a number of shortcomings: high toxicity, poor assimilation and absence of selective action [1,2].

On the other hand the intensive development of pharmacological active polymers chemistry in last 10-20 years give the hope that many shortcomings of the metal ions can be overcome by using polymers for their caring. The alternation of the nature, content and distribution of functional (complexing) groups, molecular-mass characteristics of macromolecules allows to change forming structures of the metal complexes, their stability and at the end their behavior in the biological systems [3,4]. So, using such approach we can create polymer-metal systems with regulating properties.

Results and Discussion

Analysis of known methods [5] of the PMC synthesis in organic solvents (acetone - methylenechloride, acetone - ethanol) shows that at obtaining complexes with low content of metal ions less than 5%, the yield sharply falls up to 5 -

10%. And attempts to obtain of complexes with metal content less than 1% weren't successful. So, we have developed new method of synthesis of PMC with low metal content and quantitative yield. The method is concluded in mixing of polymer and metal salt solutions in polar organic solvent or solvent mixture, in which initial compounds and forming complexes are soluble.

Study of magnetic properties of the PVP metal complexes shows that at metal content up to 6% the favorable conditions on structure formation of tetrahedral configuration for Co, Ni, Mn and square - planar for Cu are realized. At metal content growing the complexes of mixed structures are appeared: for Co, Mn - tetrahedron - octahedron, for Ni - tetrahedron - square - planar and even intra-nuclear clusters for Cu at metal content near to upper limit.

Estimation of changes in IR spectra of PVP during metal ions coordination witnesses about frequency decreasing of valence vibration of carbonyl groups (1670 cm^{-1}), at the same time two new picks are appeared in the region of 1060 cm^{-1} and 1225 cm^{-1} . The spectra decoding allows to propose that cobalt ions interact as with oxygen atom (movement of valence vibration frequency in the field of 1670 cm^{-1} and the pick appearance at 1225 cm^{-1}), so with nitrogen atom (absorption band at 1060 cm^{-1}) of the PVP lactam ring.

Influence of polymer molecular weight, metal ions nature, ionic strength of solution and temperature on binding constants of the forming complexes in aqua media was studied by using of

equilibrium ions exchange method. It was found out that in region of PVP molecular weight from 12600 up to 90000 the changes in values of the stability constants were insignificant. According to the stability the PVP metal complexes can be placed in the following row: $Mn^{+2} < Co^{+2} < Ni^{+2} < Cu^{+2}$ that mainly has the same as for low molecular metal complexes, where donor atoms are the nitrogen and oxygen.

Analysis of thermodynamic functions changes during metal ions interaction with PVP shows that changes in enthalpy is commensurable with hydrogen bonds energy (5-6 kcal/mole), and entropy changes has negative values. It means that water molecules located in coordination sphere of the metal ions was substituted by water molecules located in solvate cover of polymer and subsequent interaction of the metal ions with oxygen atom of carbonyl group.

Using an equilibrium dialysis method it was determined that approximately one bond metal ion is distributed among 10-12 monomer units of the polymer. And at the same time every metal ion interacts with 1-2 functional group of the PVP.

Investigation of PVP cobalt complexes behavior in aqua solutions shows that at metal content up to 2% the PMC were stable in strong basic media - 1-2 mole/l of NaOH. This peculiarity allows to study of O_2 absorption by the complexes. Using IR-, UV- and ESR spectroscopy methods and also volumetric and magneto-chemistry technique it was found out that an oxygenated Co^{+2} complexes was initially formed and then transformed into peroxide compounds of the three valence cobalt.

Investigation of the PMC hydrodynamic properties shows that the value of intrinsic viscosity of mixtures of the PVP and cobalt salts in water at different metal ions concentration isn't changed. At the same time the intrinsic viscosity of the PMC synthesized in alcohol media falls with growing of the metal content as in aqua solution and so in organic solvents. This phenomena is very strange because of according to traditional laws the process of polymer interaction with metal ions should be described by the following equilibrium: $P + nM \rightleftharpoons PM_n$. And during the system dilution the equilibrium must be moved to the left side. It means that the intrinsic viscosity of the PMC must reach to the value of the initial polymer. It has been observed only in the case of using the mechanical mixtures.

For more detail study we have used method of non-equilibrium dialysis. Estimating the influence

of the media to the polymer was shown that in alcohol media the PVP macromolecules are more expanded than in water one, because of the value of the PMC intrinsic viscosity in alcohol solutions higher than in aqua media. During interaction with metal ions the macromolecule coils are contracted as well as in the water and so in organic solutions due to intramolecular binding of the metal ions. Falling of the intrinsic viscosity values in water and in alcohol solution are witnessed about this. Such kind of behavior can be explained if we will propose that the PVP with cobalt ions forms two types of complexes: - "stable" in organic media due to more swollen conformation of the macromolecule coils and - "weak" in water media due to macromolecules has already "contracted" and so its interaction with metal ions grows weak.

So, there is a favorable condition in organic media for stable PMC formation via possible interaction of oxygen and nitrogen atoms of lactam ring with metal ions, which intramolecular coordination accompanied by contraction of macromolecular coils. At dissolving of these complexes in water the macromolecular coils are additionally contracted due to changes of the solvent quality. These peculiarities are the main reasons of such abnormal viscosimetric properties of the PMC and their stability in strong basic media.

Medical-biological properties

Estimation of medical-biological properties of the PVP and its metal complexes included a following studies:

- investigation of toxic characteristics;
- determination of their specific activity (blood forming, immune and desintoxic activity)
- study of farmacokinetic rules of behavior of the such type compounds in the condition of living organism.

Acute toxicity determination shows that initial PVP is nontoxic compound ($LD_{50} = 10\ 000$ mg/kg) and introduction the metal ions into polymer chain leads to increasing of the toxicity. Treatment of the obtained data allows to make a regression equation that is useful for prediction of the PMC toxicity. It was found out that toxicity of metal salts and their polymer complexes increased in the same row: $Mn^{+2} < Co^{+2} < Cu^{+2} < Ni^{+2}$. It means that the metal ions brings main contribution into compounds toxicity.

It is well known that 3 d metal and their compounds take part actively in the blood forming processes [1-3]. Study of PVP metal

complexes shows that only manganese and cobalt complexes of PVP have expressed haemostimulating activity. Main influence they make on red sprout. Changes in the peripheral blood are mainly marked in hemoglobin and reticulocytes quantity. It was found out that the higher the cobalt content in the PMC the more effective their action in the processes of blood forming stimulation. But it is necessary to remind that at high content of the cobalt ions the toxicity of the PMC also will be high that leads to limit of their administration doses. But nevertheless the application of the polymer matrix allows to decrease the frequency of administration in two times in comparison with low molecular compound preparation of the same action.

For pharmacokinetic investigation the radio-labeled (Co^{60} , J^{125}) PMC were specially synthesized. So, for PMC behavior in living organism we searched according to distribution of the complexes and also according to its components distribution. It was shown that introduction of metal ions into polymer matrix leads to increase of an excretion velocity of the complexes. After intra-peritoneal administration of the PMC on the base of PVP with molecular weight 43000, during 24 hours 61,4% of the PMC was excreted through kidney, and only 31,0% of polymer was excreted after administration of the PVP at the same conditions. It was so due to contraction process of the PVP macromolecule during interaction with metal ions.

On the other hand, during 2 hours the cobalt ions level in the blood stream was in two times higher at the PMC administration than at cobalt chloride administration. And also, the excretion velocity of the cobalt ions from an organism was lower in the case of the PMC.

On the base of these data we suggested a hypothesis that the PMC are mainly circulated with blood during first 3 - 3,5 hours, then are accumulated in liver where they will be metabolized. At this step several equilibrium reactions are possible: $PM_n \leftrightarrow PM_{n-1} + M \leftrightarrow \dots \leftrightarrow P + n M$ and also possible at every steps some recomplexation reactions depending on environmental conditions. So, at this stage, the concentration of free metal ions in solution is very important that should be enough for showing a special activity and lower than the concentration when the toxic properties will be prevailed.

On the base of made studies we recommended the PMC with high cobalt content (10-12%) - as polymer blood stimulators and with low metal content (0,3 - 1,0%) - as plasma substitutor -

desintoxicator with immunogenesis and blood forming stimulation. The polymeric drug as medical - prophylactic remedy for gastric - intestine illnesses of home and agricultural animals was created and allowed to apply in the Republic of Uzbekistan.

References

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