RADIOISOTOPE METHOD RESEARCHES OF PHARMACEUTICAL PREPARATES

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1. INTRODUCTION

The development of modern stage of nuclear medicine is characterized by the increasing role of methods using radionuclides [1]. Radioactive nuclides used in nuclear medicine may be divided into 2 groups. Radionuclides used for diagnostic researches and radionuclides used for therapeutic purposes. These two directions are considered to be the main ones in usage of radionuclides in medicine. However there is another direction in the research of new medical products where the radionuclides are used to study their pharmacological kinetics [2] In these researches radionuclide is applied as a radioactive label at the stage of study pharmacological kinetics of a new medical product.

In Institute of Nuclear Physics AS RU the works are being carried out in the recent years focused on study of pharmacology of some new medical preparations, which are synthesized in Tashkent Pharmaceutical Institute. Syntheses these preparations are based on use microelements. Its compounds are possessed expressed biological activity and be of great importance in the pharmaceutical science of Uzbekistan. The reception of all preparations labeled by radioisotopes is made by introducing of radioisotope at the stage of their synthesis. The output of the final product reached the yield of no less than 70-80 % in all cases of synthesis.

This work presents the results of research on synthesis and study of pharmacology of radioactively labeled preparations – Piracin, labeled by radioisotope ^{69m}Zn; Feramed, labeled by radioisotope ^{59}Fe; Cobavit, labeled by radioisotope ^{57}Co and ^{58}Co; CO-101, labeled by radioisotope ^{57}Co and ^{58}Co. These labeled compounds of medical preparations were used in the study of their pharmacological kinetics. In all cases, preliminary irradiation of corresponding nuclear targets in the nuclear reactor and cyclotron, radiochemical procedures on separation, purification and concentration of radioactive isotopes, and reception of its radioactive solution for synthesis of labeled compounds of preparations were carried out.

This work presents the results of investigations on obtaining radioactively labeled compounds following pharmaceutical preparations:

- Piracin, labeled by radioisotope ^{69m}Zn.
- Feramed, labeled by radioisotope ^{59F}e.
- Cobavit, labeled by radioisotope ^{57C}o and ^{58}Co.
- CO-101, labeled by radioisotope ^{57}Co and ^{58}Co.

2. EXPERIMENTAL

^{69m}Zn, ^{59}Fe and ^{58}Co radionuclides were received in the Nuclear Reactor WWR-SM INP AS RU by irradiating of $Zn(NO_3)_2$ samples and metallic Iron of high pure and enriched ^{58}Ni isotope by nuclear reactions:

$$^{68}\text{Zn}\ (n,\gamma)\ ^{69m}\text{Zn};$$
$$^{58}\text{Fe}\ (n,\gamma)\ ^{59}\text{Fe and}$$
$$^{58}\text{Ni}\ (n,p)\ ^{58}\text{Co}.$$

^{57}Co radionuclide was received in cyclotron U-150 by irradiated enriched ^{58}Ni isotope by nuclear reaction:

$$^{58}\text{Ni}\ (p,pn)\ ^{57}\text{Co}$$

To Obtain of radioactive solutions for synthesis labeled compounds the irradiating targets are processing by radiochemical procedures.

1. Start reagents for synthesis labeled Piracine (^{69m}Zn):

- Pyridokcin hydrochloric - $B_6 \cdot HCl$
- $NaHCO_3$
- $Zn(NO_3)_2 \cdot 6H_2O$
- Radioactive solution $^{69m}Zn(NO_3)_2$.

2. Start reagents for synthesis labeled Feramed (^{59}Fe):

- Amido Nicotine acid
- Ascorbic acid (Vitamin "C") - $C_6H_8O_6$
- $FeCl_2 \cdot 4H_2O$
- Radioactive solution $^{59}FeCl_2$.

3. Start reagents for synthesis labeled Cobavite (57Co):

- Glutaminic acid - $HOOC\text{-}(CH_2)_2\text{-}CHNH_2\text{-}COOH$)
- Vitamin "U" – $HOOC\text{-}CH(NH_2)\text{-}(CH_2)_2\text{-}S(CH_3)2Cl$
- $Na_3[Co(NO_2)_6]$
- NaOH
- Radioactive solution $^{57}CoCl_2$ or $^{58}CoCl_2$

4. Start reagents for synthesis labeled CO-101(^{57}Co):

- Asparaginic acid – $COOH \bullet CHNH_2 \bullet CH_2 \bullet COOH$
- Inosine – $HO \bullet C_5H_2N_4 \bullet C_5H_9O_4$
- $NaHCO_3$
- $CoCl_2 \bullet 6H_2O$
- Radioactive solution $^{57}CoCl_2$ or $^{58}CoCl_2$

3. RESULTS

1. Synthesis of Piracine (^{69m}Zn):

$$B_6 \cdot HCl + NaHCO_3 \rightarrow B_6(basic) + CO_2\uparrow + NaCl \quad (1)$$

$$3B_6(basic) + Zn(NO_3)_2 + {}^{69m}Zn^{2+} \rightarrow {}^{69m}Zn(B_6)_3 \cdot (NO_3)_2 \cdot 2H_2O + H_2O \quad (2)$$

Yield of labeled Piracine (^{69m}Zn) preparation was 65-70%. The preparation was in the form of white powder.

2. Synthesis of Feramed (^{59}Fe):

$$C_5H_4N \cdot CONH_2 + FeCl_2 + 59Fe^{2+} \rightarrow C_5H_4N \cdot CONH_2 \cdot {}^{59}FeCl_2 \quad (3)$$

Yield of labeled Feramed (59Fe) preparation was more than 90%. The preparation is in the form of fine crystalline powder at white-yellow color.

3. Synthesis of Cobavite (^{57}Co):

$$Na_3[Co(NO_2)_6] + 3NaOH + {}^{57}Co^{3+} \rightarrow {}^{57}Co(OH)_3 + 6NaNO_2 \quad (4)$$

$$^{57}Co(OH)_3 + 2[HOOC\text{-}(CH_2)_2\text{-}CH(NH_3)\text{-}COOH] \rightarrow {}^{57}Co(OH) \cdot [OOC\text{-}(CH_2)_2\text{-}CH(NH_3)\text{-}COO]_2 + 2H_2 \quad (5)$$

$$^{57}Co(OH) \cdot [OOC\text{-}(CH_2)_2\text{-}CH(NH_3)\text{-}COOH]_2 + HOOC\text{-}CH(NH_2)\text{-}(CH_2)_2\text{-}S(CH_3)2Cl \rightarrow$$
$$^{57}Co[OOC\text{-}(CH_2)_2\text{-}CH(NH_3)\text{-}COOH]_2 \bullet [OOC\text{-}CH(NH_2)\text{-}(CH_2)_2\text{-}S(CH_3)2Cl] + H_2O \quad (6)$$

Yield of labeled Cobavite (57Co) preparation was 70%. The preparation was in the form of brown powder.

4. Synthesis of CO-101($_{57}$Co) preparation

$$HOOC\text{-}CH_2\text{-}CH(NH_2)\text{-}COOH + 2NaHCO_2 \rightarrow$$

$$\rightarrow NaOOC\text{-}CH_2\text{-}CH(NH_2)\text{-}COONa + \uparrow CO_2 + 2H_2O \quad (7)$$

$$HOOC\text{-}CH_2 + CH(NH_2)\text{-}COONa + {}^{57}CoCl_2 \rightarrow$$

$$\rightarrow CH(NH_2)\text{-}COO \quad \diagdown \; {}^{57}Co + 2NaCl \quad (8)$$

$$CH2\text{-}COO \quad \diagup$$

$$\rightarrow CH(NH_2)\text{-}COO \quad \diagdown$$

$$CH2\text{-}COO \quad \diagup \; {}^{57}Co\ HO \bullet C_5H_2N_4 \bullet C_5H_9O_4 \rightarrow CO\text{-}101({}^{57}Co) \quad (9)$$

Yield of labeled_CO-101(^{57}Co) preparation was 80%. The preparation is in the form of fine crystalline powder at rose-color.

The obtained results allow us to reduce the terms of carrying out of clinical tests of medical products considerably and to speed up their introduction in medical practice [3].

4. REFERENCES

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