DEVELOPMENT METHODS LABELED TECHNETIUM-99M MAGNETICALLY NANOCOLLOIDS FOR MEDICAL DIAGNOSIS

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ABSTRACT

The opportunity of drawing of a radioactive label ^{99m}Tc on a surface nanoparticles of iron Fe_2C, covered by a carbon environment, and also particles Fe_2C (IDA), modified arenediazoniumtosylates is investigated. It is shown, that on not modified particles about 11,2 % ^{99m}Tc from its entered quantity are adsorbed. Thus the size of atomic adsorption does not exceed 0,736·10-9 g-at/g ^{99m}Tc on 1 g Fe_2C. On the modified particles Fe@C (IDA) physical adsorption is not observed. At their chemical interaction with ^{99m}Tc at presence of reducing agent of tin (II) output labeled a product increases more than in 1,5 times and makes 21,3 % from the general entered activity radionuclide. For achievement of higher output carrying out of the researches connected with selection of optimum concentration and conditions of preparation of a reducer or selection of other more effective reducer is necessary.

Key words: nanoparticles of iron Fe@C, particlesFe@C (IDA), modified aryldiazoniumtosylates, nanocolloid labeled technetium-99m

INTRODUCTION

Last years significant strengthening interest to use radioactive nanocolloidin medicine [1] all over the world is marked. They have found wide application for labeledautoleykotsitywith the purpose of diagnostics of inflammatory processes, revealings of "sentry" lymph nodes at oncological sick, lymphoscintigraphyand other areas [2]. The most simple method of reception labelednanocolloidwith the set sizes and properties is immobilisation^{99m}Tc on a surface nanomaterials. For a basis of such materials in work have been chosen nanoparticlesthe iron, (Fe@C) covered by carbon. The technology of their reception has been developed in Institute of physics of metals UROthe RussianAcademy of Science. The general view of a particle is shown in a photo (*fig. 1*).

As have shown researches on experimental animals, nanopowdersFe@C are not toxic and, basically, can be used as carriers^{99m}Tc if the problem of drawing of it radionuclideon their surface will be solved.

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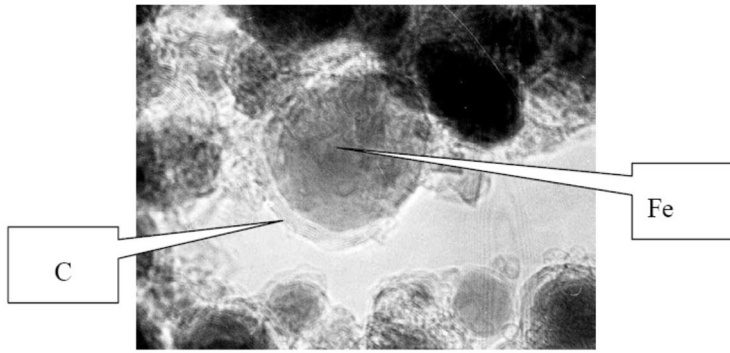

Fig.1– Photo nanoparticlesFe@C

The choice nanoparticleson the basis of iron is caused also by that they, possessing magnetic properties, can be simultaneously used as radio-opaqueagents for carrying out of a magnet -resonant tomography. All this opens ample opportunities for their application in two parallel kinds of diagnostics with the subsequent reception of the information not only on topography of the center of an inflammation, but also its functional condition.

For giving iron-carbon to particles lipophilicproperties and increase of their stability in a solution in colloidto the form, on faculty of organic chemistry TPUthe technique of preliminary drawing on a surface of these particles of organic radicals - aryldiazoniumtosylateshas been developed, which are capable to react spontaneously with carbonaceoussurfaces with allocation of nitrogen and covalentprishivkoyfossil (fragments benzildimethylenaminouksusnayaacids - IDA) to a carbon environment. It was supposed, that connection ^{99m}Tc to such modified particles will occur by formation of complexes to the sewn radicals, instead of by physical adsorption for a case of a pure carbon surface. The general scheme of synthesis of particles Fe@C (IDA) and their subsequent interaction with ^{99m}Tc is shown on *Figure 2*.

From the point of view of reception of high activity of a preparation, the degree of filling of a surface nanoparticlesradicals IDA should be whenever possible maximal since it, on the one hand, will raise probability of their interaction with ^{99m}Tc, and with another, - will allow to lower the general concentration nanoparticlesin an entered diagnostic doze.

Experimental studying of process of interaction^{99m}Tc with particles Fe@C (IDA) was spent under the following program. At the first stage adsorption ^{99m}Tc on not modified particles Fe@C with the purpose of their quantitative definition sorptioncapacities on radionuclideand stability of received connection was investigated. These data were necessary for the subsequent comparison with similar parameters of the modified particles.

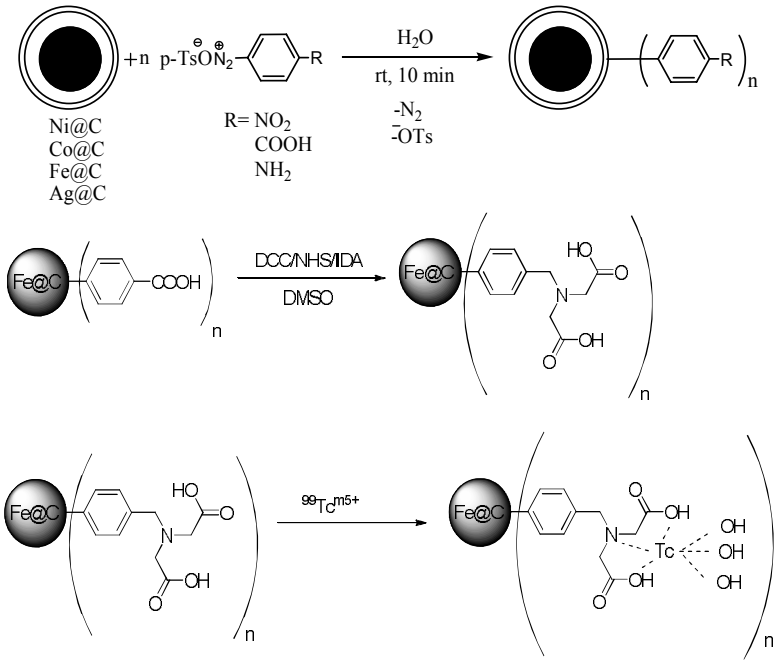

Fig. 2– The scheme of synthesis of particles Fe@C (IDA) and their interactions with ^{99m}Tc

At the second stage conditions of introduction of a radioactive label ^{99m}Tc in structure of organic radicals on a surface Fe@C (IDA) with the subsequent estimation of an output labeleda product were fulfilled.

EXPERIMENTAL RESULTS AND THEIR DISCUSSION

For reception of an initial preparation ^{99m}Tc (eluate) in the form of a solution of sodium pertechnetate, ^{99m}Tc it was used chromatographicthe generator «^{99m}Tc-GT-TOM» manufactures of scientific research institute of nuclear physics TPU.

Quantitative estimation of efficiency of sedimentation ^{99m}Tc on a carbon surface of not modified particles Fe@C spent a method of direct mixing of water suspension of a powder (10 mg to 1 ml of water) about 4 ml eluatefrom the generator having the general activity on ^{99m}TcA = 1,268 GBq. Preliminary from initialeluate^{99m}Tc 3 tests in volume 5 μlfor carrying out of radiometric measurements of their activity by means of the single-channel peak analyzer Strahlungsmessgerat 20 046 which have been adjusted on energy scale-quantums 0,140 МэВ(^{99m}Tc) have been selected. After intensive hashing a mix

and it incubatedduring 5 mines the branch of particles from a water phase has been lead. With this purpose the bottle with suspension has been placed above a constant magnet. After sedimentation of particles the deposit Fe@C has been washed out by the distilled water, and from the received washing waters selection of 3 tests in volume 5 μlalso has been made. By results of measurement activities tests initial eluate (A_{source})and washing waters(A_1), after their normalization on time, calculation of quantity reacted with particles ^{99m}Tc (in %) with use of a parity has been lead:

$$\beta = \frac{\grave{A}_{source} \cdot 4 - \grave{A}_1 \cdot V_1}{\grave{A}_{source} \cdot 4} \cdot 100 \qquad (1)$$

Where 4 – volume of the entered preparation^{99m}Tc, ml;V_1.total amount of washing waters, ml.

Calculations have shown, that on particles 11,2 % ^{99m}Tc from its general entered quantity Fe@C are adsorbed.

It is known, that between size of activity *A*and quantity of radioactive atoms *N* the parity is carried out:$A = \lambda N$. From here, proceeding from activityeluate$A$ = 1,268 GBq, the total of atoms ^{99}Tc, entered in initial mix $N = 3{,}97 \cdot 10^{13}$at.has been certain., and also the size of its atomic adsorption on investigated particles is found:

$$G = \frac{3{,}97 \cdot 10^{13} \cdot 0{,}112}{0{,}01 N_a} = 0{,}736 \cdot 10^{-9}\, g \text{ -at}^{99}\text{Tcin1 gFe@C} \qquad (2)$$

WhereNa= $6{,}02 \cdot 10^{23}$–Avogadro's number.

Further similar experiment has been lead with the modified powder Fe@C (IDA). Here too to 1 ml of suspension 4 ml eluate^{99m}Tc have been added. After hashing and incubatedmixes during 5 mines sedimentation of particles has been lead to a field of a constant magnet. Unlike not modified Fe@C, particles Fe@C (IDA) long enough were in a suspension that confirms presence at them lipophilicproperties alongside with display of ability to colloidformation. The calculations lead by subsequent, have shown, that adsorption ^{99m}Tc on a surface Fe@C (IDA) is not observed. From here has been drawn a conclusion, that as a result of the lead updating nanoparticlesFe@Caryldiazoniumtosylates, they have lost ability to physical adsorption ^{99m}Tc on the surface. The reason of it, most likely, is blocking of an initial graphitic environment by organic radicals that testifies to their high concentration on a surface. This fact is extremely important from the point of view of the subsequent introduction ^{99m}Tc in structure of such radicals not in the form of physically adsorbed ions, in summary chemisorption which is steadier.

As is known, ^{99m}Tc, present in initial eluatefrom the generator, has the maximum degree of oxidation (VII). In this chemical form it does not showcomplexingproperties. Therefore for "linkage"^{99m}Tc with organic radicals it was necessary to lead preliminary its restoration up to lower valent condition. As such reducing agents formalin, an ant acid and tin (II) chloride dihydrate($SnCl_2 \cdot 2H_2O$) have been tested. Last from them is the classical reducer widely used in medicine, in particular, for manufacturing of standard sets (lyophilized) for the generatortechnetium-99m [3]. Thus process of introduction of an isotope label ^{99m}Tc in structure of substances can be characterized approximately the scheme:

$$^{99m}TcO_4^- + Sn(II)L \xrightarrow{Subst./H_2O} {}^{99m}Tc - Sn - L + Sn(IV)L$$

Where*L*- the substance which is exposed labeled.

As a result of such reaction, except for expected target products [^{99m}Tc-Sn-L] or [^{99m}Tc-L], the complex^{99m}Tc with tin, and also radiochemical impurity in the form of not reacted ions initial^{99m}Tc (VII) and its restored ions can be formed.

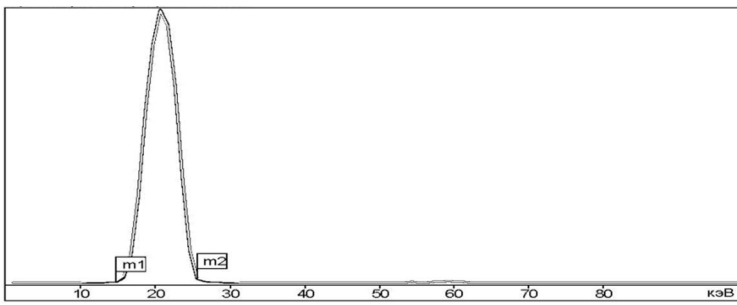

Fig. 3 – The Initial preparation^{99m}Tc

Check of restoring abilities of formalin and ant acid spent by their direct introduction in quantity on 10 μl to the bottles containing on 1 ml initial eluate^{99m}Tc. After hashing mixes and incubated during 5 mines from the received solutions selected tests for removal radiohromatogrammon installation «Гаммаскан-01А». Simultaneously as the sample of comparison selected test from an initial preparation. Expected result, in case of restoration^{99m}Tc, occurrence on chromatogramsadditional peak in the field of a line of start unlike peak ^{99m}Tc (VII) initial preparation located in the end chromatogramsis. On the basis of the lead researches has been drawn a conclusion, that restoration ^{99m}Tc in these environments does not occur.

The positive result has been received at use as reducer $SnCl_2 \cdot 2H_2O$.Radiohromatogrammyof an initial preparation ^{99m}Tc and a preparation with tin (II) are presented on *Figure 3* and *Figure 4*, accordingly.

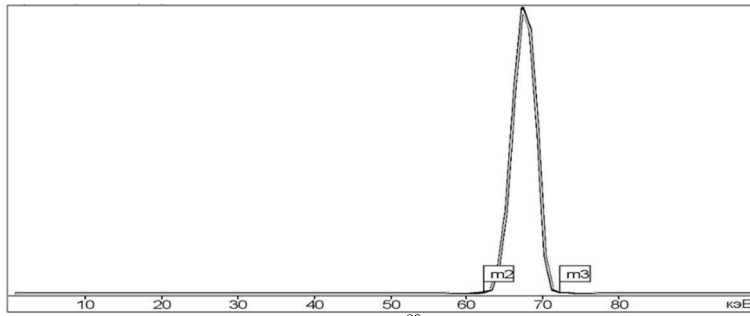

Fig. 4– A preparation ^{99m}Tc with tin (II)

Comparison presented chromatogramsshows, that at mixing eluatewith tin (II) basic peak on chromatogram(fig. 4) is displaced in area of 2 sm (Rf = 0,1), that speaks about formation restored ^{99m}Tc (presumably ^{99m}Tc (IV)) or its complex with Sn which as it is established in work [4], can be presented by the formula: $(\text{-O-TcO-O-SnCl2-O-TcO-})_n$, where n = 2, 3 ,… - the number depending from pH of a solution.

The subsequent introduction of a label ^{99m}Tc to structure Fe@C (IDA) at presence of tin (II) spent by a following technique. With the modified substance (6,8 mg in 1 ml of water) have entered into a bottle 100 µl (0,7 mg) $SnCl_2$ and 4 ml of a solution preparation ^{99m}Tc. After incubatedduring 5 mines of a particle have besieged on a magnet. Behind that have made selection of a water phase and have washed out a deposit water. Have preliminary lead sampling (3 tests on 5 µl) from an initial solution of a preparation, and after - from washing waters for measurement of activity ^{99m}Tc and the subsequent carrying out of calculations of an output labeleda product. From these results it has been found, that at chemical interaction Fe@C (IDA) with ^{99m}Tc at presence of tin (II) size of absorption radionuclidehas increased up to 21,3 % from the general entered activity, that in 1,52 times it is more, than at not modified Fe@C.

CONCLUSIONS

On the basis of the received results, it is possible to draw following conclusions.

The basic lack of not modified particles Fe@C as the carrier of a radioactive label ^{99m}Tc is them not high enough adsorption capacity on radionuclide, that can limit their use at carrying out scale-scintigraphicof researches where the quantity of entered substance should be minimal. Besides physical adsorp-

tion does not provide reliable linkage ^{99m}Tc on a surface of particles, and, hence, there is a danger of uncontrollable hit radionuclidein case of it desorptionin critical bodies. In this plan the modified particles Fe@C (IDA) with chemisorbed^{99m}Tc, possessing lipophilic properties and propensity to colloid-formationin a water solution are more preferable. The subsequent development of works in this direction is connected with selection of optimum concentration and conditions of preparation of a reducer or selection of other more effective reducer which would provide an output labeleda product at a level of 90 - 95 %.

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