

PHOTONUCLEAR METHOD OF PRODUCTION Cu-67

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The efficient separation of ^{67}Cu is achieved by using diantipyrylpropylmethane (DAPPM). Experimental separation of ^{67}Cu from sulphuric solution (1 mol./L) of zinc (2 mol./L) with addition potassium iodide (0.1 mol./L) is realized with help DAPPM (0.02 mol./L), which dissolve in chloroform. The 84.4% ^{67}Cu was extracted from water phase of ZnSO_4 into organic phase (solution DAPPM in chloroform). The ^{67}Cu remainder in organic phase is 4.6%. Effective extraction of protonated forms of reagent and ionic associate of metal+halide was realized by means of antipyrin forms in acid halide solution. The decrease of acidity of a water phase is necessary for effective re-extraction. Re-extraction was realised by means of consecutive washing of organic phase (DAPPM in chloroform) by means of distilled water. Some amount of ZnSO_4 in process of extraction gets in organic phase that causes a low level re-extraction in first two tests. These tests re-extraction have low values pH. Re-extraction ^{67}Cu from solution DAPPM in chloroform is carried out consistently four times by distilled water. The activity of ^{67}Cu in third and fourth re-extraction tests was 72.7%.

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INTRODUCTION

Copper is the irreplaceable microelement necessary for normal vital functions of the person. Copper is mainly involved in redox reactions throughout the body, but also plays a role in iron transportation in blood plasma. Copper is part of hormones and influences growth, development, reproduction, an exchange, processes of formation of haemoglobin, phagocytic activity of leukocytes.

^{67}Cu is one of the most promising isotopes for radioimmunotherapy. The half-value period of ^{67}Cu is 61.5 h and it well matched to the residence time of a typical antibody on the tumour. ^{67}Cu emit β -particles as well as a moderate abundance of 93 and 184 keV gamma rays. These gamma rays permit radiation dosimetry to be predicted from the information obtained from quantitative imaging studies on pretherapy doses of ^{67}Cu . This pretherapy imaging and kinetics, followed by similar pharmacokinetics of the actual therapy doses, allows treatment planning and on-going verification of that planning with actual dosimetric information on the radiation delivered.

Various ways of use of ^{67}Cu for therapy and diagnostics of cancer diseases are used. For example ethylglyoxal bis(thiosemicarbazone) has potential utility as radiopharmaceutical with the various isotopes of copper [1]. ^{64}Cu TETA-Octreotide is a chelate that has been shown to bind to the somatostatin receptor [2]. CB-TE2A a stable chelation system for ^{67}Cu was incorporated with Bombesin analogs for in vitro and in vivo studies of prostate cancer [3]. ^{67}Cu -ATSM (diacetyl-bis (N4-methylthiosemicarbazone)) has been shown to increase the survival time of tumor-bearing animals with no acute toxicity [4]. ^{67}Cu is widely used in radioimmunoassay therapy and in early diagnosis and treatment of lung cancer. For this purpose the unicellular suspension was treated by solution 5, 10, 15, 20-tetrakis (4-carboxyphenyl) porphine for a time sufficient to substantially capture by malignant cells. The treated cell suspension was irradiated by UV irradiation. Diagnosis of malignant lung cells realize by the number of fluorescent cells. The localization of malignant process of

lung in the whole organism was performed by means of introducing in a patient's blood of porphyrin derivatives with subsequent analysis of the image produced in the emitted gamma radiation. In the case of treatment of the patient is administered complex 5, 10, 15, 20-tetrakis (4-carboxyphenyl)- ^{67}Cu (-II) porphine in the form of an aerosol.

Low cost and high specific activity is necessary conditions of wide use of ^{67}Cu in nuclear medicine. NSC KIPT is developing a process for production of ^{67}Cu using an electron linac. The two most significant criteria are the specific activity of the ^{67}Cu and the absence of other metals that could compete with the chelating agent that medical researchers plan to use to target the delivery of the ^{67}Cu . Moreover yield and waste disposal requirements necessitate the use of an isotopically enriched target, which must be recovered and reused.

The purpose of the present work is development of method of production of ^{67}Cu with low cost, with high specific activity and absence of metal impurity in solution.

RESULTS AND DISCUSSION

One of effective ways of separation of ^{67}Cu is a method internal electrolysis, which allows receiving pure copper without the carrier [5]. Recently the ^{67}Cu finds more and more wide use for treatment of tumours [6]. The significant number of articles [7 - 13] is devoted to development of methods of synthesis ^{67}Cu . Most frequently at manufacture of isotopes of copper is used extraction and electrochemical sedimentation.

Extraction by organic reagents allows realizing automation of the separation of the radioactive isotope. Extraction by acetone [7] provides the attitude of distribution approximately 100 that does not satisfy to conditions for further use ^{67}Cu as pharmaceutical production. Using diantipyrylpropylmethane provides a distribution coefficient more than 10^3 copper and about 10^4 for zinc, which corresponds to a ratio of zinc for initial and final solution 10^{-7} [14 - 15].

Metal zinc, zinc oxide from closed Joint-stock company "OEZ" "VladMiVa", chemically pure sulfuric acid, pure hydrochloric acid, chemically pure chloroform,

chemically pure (PDS 2930-0002), diantiprylpropylmethane (DAPPM) (C₂₆H₃₀N₄O₂) of analytical grade, dithizone (diphenylthiocarbazone, C₁₃H₁₁N₄S), reagent grade, TU 6-09-07-1684, Pyrex glass, Viton tubing (Cole Parmer Instrument, Vernon Hills), connecting silicone a tube had been used at fulfillment of investigations.

Series of experiments about dissolution of zinc metal and zinc oxide was carried out. This procedure is given special attention, because dissolving the irradiated zinc should take place in the shortest possible time and in a special container made of glass, not containing in the structure of that element. This procedure is being performed in a hot cell and should be as simple as possible. The sample of metal zinc (998 mg) was placed in a bowl with a solution of hydrochloric acid (HCl) which was diluted (1:1). After dilution of zinc the hydrochloric acid was evaporated with addition of 0.6 ml of sulfuric acid to a final volume of aqueous phase of H₂SO₄ with concentration 1...2 mol./L of zinc. Solution was heated until vapours of sulfuric acid and complete dilution of sample. The resulting solution has a transparent lemon colour.

For simplification of procedure of dissolution was used zinc oxide (manufactured by JSC "OEZ" "VladMiVa") in an amount of 8 g. The 7 ml of concentrate sulfuric acid was added in a bowl and was added ~20 ml of distilled water. Heating of a bowl carried out before full dissolution of the zinc sample. In order to enhance the dissolution of zinc in bowl was added a 50% solution of hydrogen peroxide.

The most suitable concentration of hydrogen ions for dilution of zinc is in the range from pH 2 to 3. In the case when metallic zinc after adding sulfuric acid is not completely dissolved it was necessary to add to a cold solution of hydrogen peroxide. Then a mix of solutions in addition warmed up.

For obtaining isotope ⁶⁷Cu the technique of extraction from iodide system is developed. In this case potassium iodide is being entered into a solution of sulfuric acid. In sour iodide solutions the copper is present at a degree of oxidation (+1), forming strong anionic complexes CuI₂⁻. Their stability is much more than of zinc (II). Therefore in this system the greatest contrast is being observed at extraction of copper concerning zinc. Optimum pH for the separation of copper from the zinc is equal to 1 mol./L for H₂SO₄ and 0.1 mol./L for KI. In these conditions the copper extraction was realized in form of ionic associate CuI₂⁻ with protonate form of reagent LH⁺. In less sour area the significant contribution of copper as introduction complex creates difficulties in re-extraction.

The important condition of extraction of copper is the ratio of concentration of reagent L and iodine-ions. Extraction is optimum at 2-3 multiple surplus of I⁻ in relation to L. In these conditions K copper exceeds 10³, and for zinc it is less 10³. Falling of extraction of copper at [L]>[I] is caused by destruction of iodine complex of copper by reagent surplus:

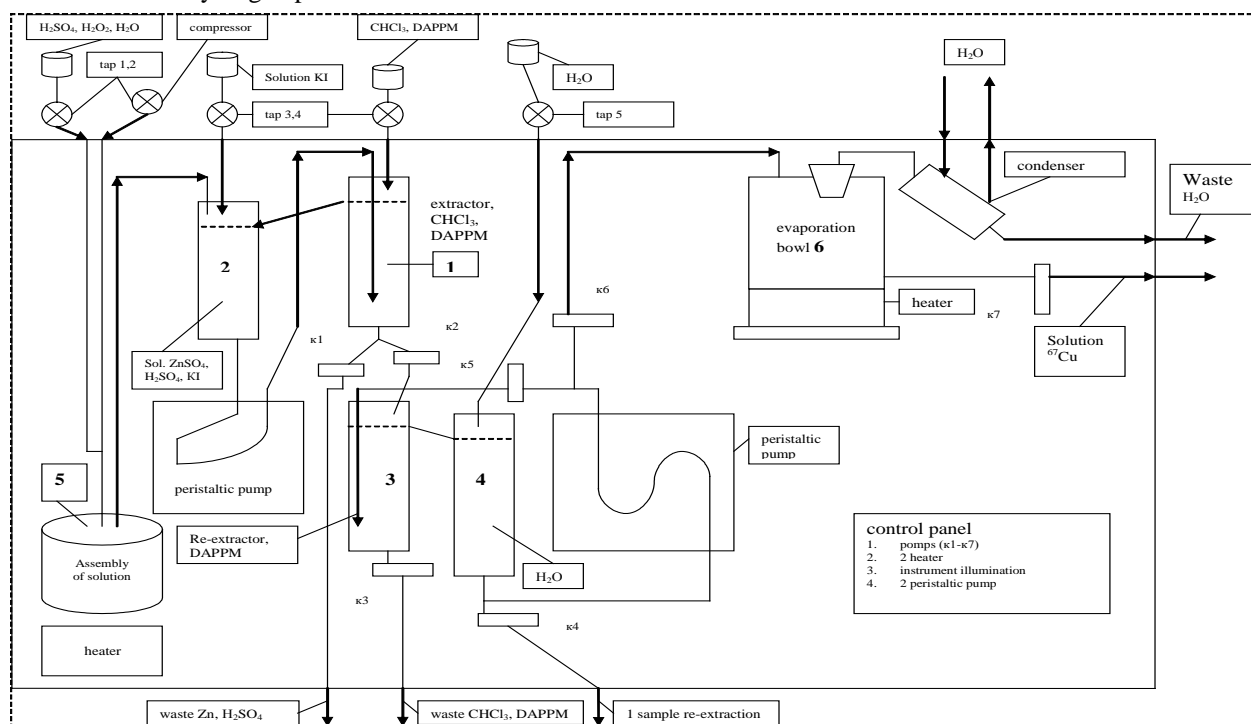
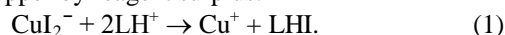
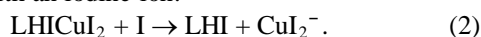


Fig. 1. The scheme of installation

Reduction of copper extraction at [L]<[I] is caused by deficiency of a reagent owing to his linkage in ionic associate with an iodine-ion:



At significant concentration of zinc (to 2 mol./L) the factor of distribution K_p of copper does not change. Also down to concentration of copper 10⁻³ mol./L K_p of

copper remains constant. Essential feature of use of the given system is simplicity re-extraction copper. Decrease of acidity of an organic phase by water results to effective re-extraction copper. The sulfuric water phase with concentration of a sulfuric acid 1 mol./l, of zinc 2 mol./l and of potassium iodide 0.1 mol./l was located in separating funnel (2) (Fig. 1). In extraction column

(1) solution DAPPM in chloroform with concentration 0.02 mol./L was located. Volumes of chloroform and a water phase were equal (130 ml) and allowed to dissolution 20 g of metal zinc. Extraction of copper-67 was carried out by pass of water phase through a capillary extraction column with the help peristaltic pump. Speed of swapping of a water phase is 13 ml/minute. The water passed through solution DAPPM in chloroform and again arrives in separating funnel (2). Time of extraction of copper-67 was 20 minutes. After the termination of extraction the solution DAPPM in chloroform was transported in extraction column (3). In separating funnel (4) was poured 130 ml of distilled water and was included peristaltic pump (7), which pumped water through a capillary extraction column (3) within 10 minutes. In this case the water rose upwards and arrived in separating funnel (5). The first test of a contact mix lowers acidity of a solution up to pH=2, that creates necessary conditions about acidity for transition of copper-67 in the subsequent re-extracts. The first test of a contact mix merges in a glass for waste products. Then in extraction column (3) 130 ml of distilled water are again added and the cycle re-extraction of copper-67 is carried out. After that re-extract from separating funnel (4) with the help peristaltic pump (10) was pumped over in a flask (9). In a result it is carried out four consecutive cycles re-extraction, which transported in a contact solution more than 90% of copper-67.

The isotope ^{67}Cu allows carry out therapy of many cancer diseases. Extraction diantipyrylpropylmethane (DAPPM) allows to effectively separation of ^{67}Cu . Experimental separation ^{67}Cu from sulfuric solution (1 mol./L) zinc (2 mol./L) with addition potassium iodide (0.1 mol./L) is realized with help (DAPPM (0.02 mol./L), dissolved in chloroform. At extraction of ^{67}Cu from water phase ZnSO_4 passes in an organic phase (solution DAPPM in chloroform) 84.4% ^{67}Cu (Table).

Activity and the content of impurity in re-extract

No sample	Yield ^{67}Cu , %	pH solution re-extract	The share of activity ^{65}Zn in re-extract	Content Zn in re-extract, $\mu\text{g/ml}$	Content Cu in re-extract, $\mu\text{g/ml}$
1	0.7	2	$< 2 \cdot 10^{-4}$	20.8	0.0757
2	0.8	2.5	$< 6 \cdot 10^{-5}$	3.92	0.132
3	33.7	4.5	$< 2 \cdot 10^{-5}$	0.45	0.0052
4	39.0	5	$< 2 \cdot 10^{-5}$	0.05	0.0045
5*	5.6	7	$< 2 \cdot 10^{-5}$	—	—
6**	4.6	—	$< 2 \cdot 10^{-5}$	—	—

5* – solution NaOH for quantitative re-extraction;

6** – solution DAPPM in CHCl_3 after re-extraction.

The activity of ^{67}Cu in organic phase is 4.6%. Derivatives of antipyrine are producing in acidic halide solutions ion associates well extractable metal-halide anions and the protonated forms of the reagent. Therefore, the basic method of re-extraction is a reduction in acidity of the aqueous phase by mixing the organic phase with an alkaline solution or water. The destruction of the copper iodide is achieved by the introduction of excess reagent DAPPM. Some amount ZnSO_4 in process extraction

gets in an organic phase that causes a low degree re-extraction in first two tests. These tests re-extraction have low values pH.

The activity of initial solution ZnSO_4 , of organic phase and of tests re-extract was measured by Ge(Li)-detector in volume of 40 cm^3 with the power resolution 3.2 by 1332 keV (Fig. 2).

Re-extraction of ^{67}Cu from solution DAPPM in chloroform was carried out consistently four times by distilled water (see Table). In third and fourth tests were re-extracted 72.7% of activity ^{67}Cu (Fig. 3). The fifth re-extraction of ^{67}Cu was carried out by quantitatively a solution of caustic soda (pH=7) and its activity was 5.6% from initial activity of ^{67}Cu .

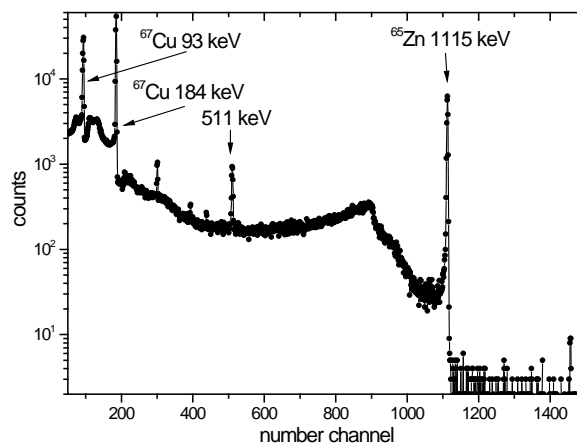


Fig. 2. The spectrum of solution after irradiation of Zn

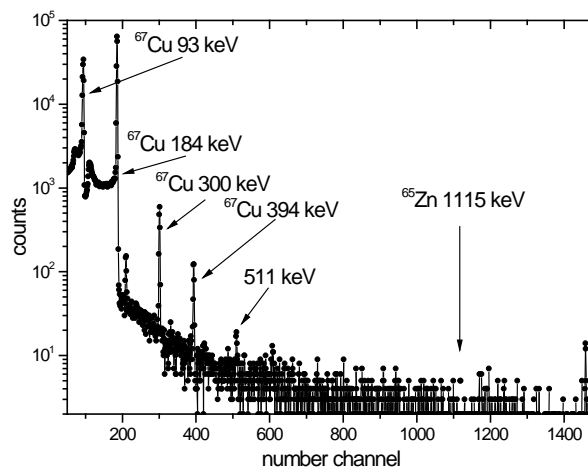


Fig. 3. The spectrum of solution after extraction of ^{67}Cu

Use of ^{67}Cu for radio immune therapy shows the certain requirements about the content of zinc in re-extract. The content of zinc in re-extract of copper should not exceed a level of copper. Therefore for the further downturn of the content of zinc in re-extract is supposed to use silica gel as an absorber [16]. Sorption of zinc by silica gel is realized at pH=7. Therefore pass of re-extraction through activated silica gel will allow reach the set content of zinc in a preparation of ^{67}Cu which can be used for radio immune therapy. Research of influence of masking of zinc for increase in factors of distribution of copper [13] and reduction of factor of distribution for zinc is supposed also.

CONCLUSIONS

1. The model of installation for extraction of copper-67 with use diantipyrylpropylmethane is created and tested.
2. The ratio of the content of zinc in re-extract in relation to initial zinc $3 \cdot 10^{-6}$ is received.
3. The extraction of copper is achieved at level of 90%.

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ФОТОЯДЕРНЫЙ МЕТОД ПРОИЗВОДСТВА Cu-67

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Экстракция диантипирилпропилметаном (ДАППМ) позволяет эффективно выделять ^{67}Cu . Реализовано экспериментальное выделение ^{67}Cu из сернокислого раствора (1 моль/л) цинка (2 моль/л) с добавлением йодистого калия (0,1 моль/л) при помощи ДАППМ (0,02 моль/л), растворенного в хлороформе. При экстракции ^{67}Cu из водной фазы ZnSO_4 переходит в органическую фазу (раствор ДАППМ в хлороформе) 84,4% ^{67}Cu . В органической фазе остается 4,6% ^{67}Cu . Производные антипирина образуют в кислых галогенидных растворах хорошо экстрагирующиеся ионные ассоциаты металл + галогенидного аниона и протонированной формы реагента. Поэтому для эффективной реэкстракции необходимо снижение кислотности водной фазы, что и реализуется при последовательных перемешиваниях органической фазы (ДАППМ в хлороформе) с дистиллированной водой. Некоторое количество ZnSO_4 в процессе экстракции попадает в органическую фазу, что обуславливает низкую степень реэкстракции в первых двух пробах. Эти пробы реэкстракции имеют низкие значения pH. Реэкстракцию ^{67}Cu из раствора ДАППМ в хлороформе проводили последовательно четыре раза дистиллированной водой. В третью и четвертую пробы реэкстрагировалось 72,7% активности ^{67}Cu .

ФОТОЯДЕРНЫЙ МЕТОД ВИРОБНИЦТВА Cu-67

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Екстракція діантипірилпропілметаном (ДАППМ) дозволяє ефективно виділяти ^{67}Cu . Реалізовано експериментальне виділення ^{67}Cu з сірчанокислого розчину (1 моль/л) цинку (2 моль/л) з додаванням йодистого калію (0,1 моль/л) за допомогою ДАППМ (0,02 моль/л), розчиненого в хлороформі. При екстракції ^{67}Cu з водної фази ZnSO_4 переходить в органічну фазу (розчин ДАППМ в хлороформі) 84,4% ^{67}Cu . У органічній фазі залишається 4,6% ^{67}Cu . Похідні антипірину утворюють у кислих галогенідних розчинах добре екстрагуючі іонні асоціати метал + галогенідні аніони і протонізовану форми реагенту. Тому для ефективної реекстракції необхідне зниження кислотності водної фази, що і реалізується при послідовних перемішуваннях органічної фази (ДАППМ в хлороформі) з дистильованою водою. Деяка кількість ZnSO_4 в процесі екстракції потрапляє в органічну фазу, що обумовлює низьку ступінь реекстракції в перших двох пробах. Ці проби реекстракції мають низькі значення pH. Реекстракції ^{67}Cu з розчину ДАППМ у хлороформі проводили послідовно чотири рази дистильованою водою. У третю і четверту проби реекстрагувалося 72,7% активності ^{67}Cu .