

INDUSTRIAL SCALE PRODUCTION OF RADIOACTIVE ISOTOPES AT THE INSTITUTE OF NUCLEAR PHYSICS OF ACADEMY OF SCIENCES AND ITS ENTERPRISES

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The radioactive isotopes are widely used in various fields of the human activity. The methods with application of chemical compounds labeled with the different radionuclides are highly effective for a solution of scientific and practical problems in a science, medicine, agriculture and engineering. Without any doubt the fulfilment of a number of key discoveries as well as progress in development of a molecular biology and genetics as a whole, development and use of reliable methods of diagnostics and the treatments of heavy human diseases were directly or indirectly predetermined by application of radionuclides.

A new "know-how" and methods development for practical use of radioactive isotopes take place in all technically developed countries of the world constantly.

The main role in it has without any doubt:

1. An availability of research nuclear reactors and cyclotrons with acceptable level of power and flux of particle.
2. Competent staff experienced in processing of radioactive materials that could work in adjacent areas of physics, chemistry and biology.

In Uzbekistan Republic the Institute of Nuclear Physics of an Academy of sciences meets completely to these demands. The constantly acting nuclear reactor WWR-SM (Water-Water Reactor of Medium Power), accelerator U-150, «RADIOPREPARAT» and «TEZLATGICH» enterprises were specialized for production of reactor and accelerator isotopes accordingly. There are the ideal facilities for development of modern technologies for production of radionuclides and labeled compounds on their base.

It is necessary to note that in spite of impressive age Tashkent nuclear reactor, due to reconstruction conducted in 1980, quite approaches for a solution of modern problems. The modernization of the nuclear reactor has allowed to increase its power up to 10 Megawatts and to create channels for targets irradiation with a flux of neutrons up to 10^{14} neutrons/cm²·sec⁻¹. It has increased considerably the production potential for installation majority of known radionuclides. The indicated factors and the existing industrial facilities at «Radiopreparat» enterprise had ensured conditions for acceleration of works connected with development of

technologies and organization of production of labeled compounds. The acute shortage of isotope products in the country owing to export limitation from the foreign manufacturers had been as the additional stimulus. The engaging of the competent experts has allowed in the shortest time to carry out the development of the up-to-date technologies and to arrange providing of the scientific and medical centres of country by labeled preparations for scientific researches in a molecular biology, genetic engineering and biochemistry. On the base of P-32 or P-33 carrier free Orthophosphoric Acid of the special grade and Ammonium Sulphate high specific radioactivity labeled with S-35 the manufacture of several tens items of the labelled biologically active compounds had been organized within 2-3 years at the «Radiopreparat» enterprise. Moreover the experts have ensured themselves with full independence from the external sources of enzymetic preparations that had been necessary for synthesis.

At the same time medical organisations of the country were supplied with therapeutic labeled preparations and with the immunodiagnostical kits for determination of markers of Hepatitis B virus, infarct of the myocardium, diabetes and some of human cancer diseases. Physician of Uzbekistan Republic are using widely till now the radioimmunological kits for determination of markers of Hepatitis B virus.

Scientific - technological enterprise «TEZLATGICH» acts on basis of the classic cyclotron U-150 that had been started in a 1960 for the experiments on photons of low energies. The cyclotron could accelerate protons up to 20 MeV, deuterons - up to 24 MeV and nucleus of helium - up to 50 MeV. Before the modernisation had been completed the current accelerated particles was low and reached till 10-20 MKA and it was a main obstacle in use of the cyclotron for production of isotopes. The modernisation of various systems of the cyclotron has allowed to achieve a current of the protons flux up to 800-1000 MKA and to use it as the industrial irradiating device for production of the cyclotron isotopes. The targets irradiated at the cyclotron are represent a copper base on which by means of electrochemical way the stable isotopes are put as the initial raw material. The target isotopes are received by chemical processing of targets after bombardment by the flux of protons.

At present on the base of the raw materials that are being received after irradiation of targets in the nuclear reactor or at the cyclotron there are produced in industrial scale or can be produced by developed technologies the isotopes: Phosphorus-32, Phosphorus-33, Sulphur-35, Iron-55, Iodine-125, Iodine-131, Cobalt-57, Cobalt-58, Gold-198, Cadmium-109, Molibdenum-99, Germanium-68 and Tungsten-188 (for generators of Technetium-99m, Gallium-68 and Rhenium-188, accordingly). First seven items of radionuclides are subjects of export and the compounds labeled with these isotopes are delivered according to the determined schedules to several leading companies in USA, England, Germany, Finland and Japan. Very specific problem is limiting the development of the export shipments of the Iodine-131 preparations owing to deficiency of the reliable transport containers. That is the main constraining factor in the extension of this isotope production. Most part of the export

shipments are provided by Phosphorus-32 and Phosphorus-33. It is known also that most of Phosphorus-33 is used as the raw material for synthesis of biologically active compounds that are necessary for scientific researches. On the other hand the Iodine-125 preparations are used mainly for manufacturing of the metal microcapsules (so called «seeds») that are used with the extremely high efficiency in the therapy of prostate cancer. The organization of «seeds» production on the basis of «Radiopreparat» enterprise not only real but could be one of the most perspective directions of development in the nearest future.

The completeness of the article would be obviously insufficient without granting some of the technological and manufacturing-oriented moments concerning labeled compounds production. The production of any radioactive isotope consists of the following key moments.

- Choice of an initial stable isotope with a necessary degree of enrichment and approaching natural and chemical characteristics.
- Preparing of the targets for irradiation in the appropriate channels of nuclear reactor. This stage is connected with the loading of the stable isotope into vacuumated quartz ampoule with the following sealing in the high temperature flame. The quartz ampoule can be located directly into aluminium container for irradiation or the same action can be done after sealing it into the aluminium tube by means of welding.
- Location of the aluminium container into the channel of the nuclear reactor with the following irradiation during the certain time. The choice of optimum time of the irradiation is determined by the different factors. At first the dependence of the accumulation as the function of irradiation time and flux of neutrons should be determined for each isotope. It is known that for each radionuclide there exists the optimum of irradiation for radioactivity accumulation per unit of the irradiated raw material from the time. However, for example, for Sulphur-33 targets the optimum time of irradiation is determined not only by parameter of accumulation - disintegration (depending on the half-life of the radionuclide) but also by activation of the certain undesirable processes in samples depending on the time of irradiation as well. Partially it leads to the burning out or to the charring of Sulphur-33 or the destruction of the ampoules owing to, as we assume, the strains in crystal structure of the quartz ampoule that become apparent just after 500 hours of the irradiation.
- Treatment of the irradiated targets or processing of the samples is carried out with the purpose of separating of the radionuclide from the raw material isotope and its most complete restoration for the new production cycle. Recycle of stable isotopes - targets for the production of Phosphorus-33 and Iodine-125 is dictated mainly by the reason of the extremely high seller's prices. By this reason the loss even small part of Sulphur-33 sample as the result of the ampoule destruction during the irradiation leads to the hardly recovered economic losses. Definitely there are the regeneration stages of the raw

material in the technological process, however, for the indicated example the degree of regeneration usually does not exceed 50-60 % owing to accompanying irreversible chemical processes.

- Chemical processing and purification of the labeled compounds. Usually it is effected by means of the number of the procedures such as dissolution, filtration, evaporation and chromatographic purification of the labeled compounds from the chemical impurities.
- The analysis of the quality of the final preparations. Consists of the determination of chemical, radiochemical and radionuclidic purity, biological activity of preparations and radioactive concentration. The quality of the produced preparations is that unique, indisputable and constant criterion which should be ensured and be independent on any circumstances. It is necessary to note that during almost seven-years export experience there were only few problems in the practice of «Radiopreparat» enterprise that concerns to some extent the quality of the preparations and they were settled without any consequences for further activity. It is necessary take into account that for last six years there had been effected more than two hundred deliveries of the isotope products to the distant foreign countries.

It would be desirable separately to pay the attention to the problems concerning the process of the labeled compounds delivery to the consumers. It is the special and extremely important theme.

In spite of the exportation dispatch procedure is organized at present very well, periodically there are appears the certain problems which could cause the delay or even the failure of the goods transposition on the planned date of dispatch and also to complicate delivery by the reason of the certain circumstances. It is possible to determine the following key moments in the delivery preparations procedures.

- Availability of the packing sets including high quality vials, ensuring preservation of preparations and safety of their transportation. But first of all it is necessary for the consumers the convenience in manipulations with obtained packages. Some variants of package sets were developed at «Radiopreparat» enterprise step by step during the latest time. They were realized in practice and met to all necessary requirements. There was created the octagonal vial with the V-shaped bottom insertion made from high-quality glass and closed by teflon covered silicone. It represents the last variant of the vials offered to the consumers for delivering of any labeled compounds.
- The second is the necessity of correct registration of the set of the regulating documents during shortest time, customs registration of the consignment and dispatch of the consignment by airline guaranteeing delivery to the point of destination, with double transshipment frequently.