ON PRODUCTION ULTRASHORT- AND SHORT-LIVED ISOTOPES FOR NUCLEAR MEDICINE AT CYCLOTRON CV-28

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The paper presents a survey of experimental methods for cyclotron production of ultrashort-lived (USL) and short-lived (SL) radionuclides recommended by the IAEA as most widely used in nuclear medicine. The data on radionuclide-producing nuclear reactions, the required energy range and targets are given. The undertaken analysis of experimental studies carried out at different scientific centers as well as the comparison with the parameters of the cyclotron CV-28 to be put into operation at the NSC KIPT suggest the conclusion about the operational capabilities of the isochronous cyclotron CV-28 to produce the mentioned radionuclides and the possibility of creating the positron-emission tomography (PET) with the CV-28 as the base.

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1. INTRODUCTION

At the present time there are more than 2300 radionuclides (RN) known to us, of which more than 200 RN are employed in different fields of science, technology and medicine.

These RN are predominantly of artificial origin at the expense of their production in the reactions of charged particle/neutron interaction with the target material, realizable at accelerators or in nuclear reactors.

The RN find the widest use in nuclear medicine and biochemistry. Considerable recent attention has been focussed on radionuclide diagnostics of human diseases through introduction of radioisotopes into the human body [1]. The radionuclide diagnostics makes it possible to investigate not only structural failures in all human internals and body tissues, but also functional failures in the life support systems (blood circulation, nerves, digestion, breathing, etc.), which are difficult if not possible at all to be diagnosed otherwise. The radionuclide diagnostics consists in the analysis of the information obtained after introduction of a certain chemical or biological compound labeled with a gamma-emitting radionuclide into the body, with a subsequent registration of space-time distribution of the compound in the body by a position-sensitive gamma-ray detector. Relying on the results obtained, conclusions are drawn about both the failures in the metabolism systems and functional failures in the body.

Positron-emission tomography is the method of radionuclide diagnostics that is most efficient and gaining an increasing advancement. The method is based on the detection of annihilation photons resulting from the positron decay of RN, which are registered by many pairs of coincidence detectors that form a circular system [1]. Presently, the PET is the most informative method of radionuclide diagnostics, which provides a three-dimensional image of the body's organ, a possibility of measuring the absolute activity of the organ under study, a quantitative estimate of physiologic processes. It is of importance for PET studies to choose the RN with a low maximum positron energy, that provides a high resolution of the image.

Another factor, which must be taken into account when choosing the RN for the PET studies, is a low radiation dose. On the basis of radiation exposure estimates for the man, all other conditions being equal, the preference is given to ultrashort- and short-lived radionuclides, which are capable of entering into vital complex molecules, without changing their chemical and functional properties. These are the so-called organic radionuclides (carbon-11, nitrogen-13, oxygen-15, fluorine-18) with the decay time of tens of minutes [2].

The production of radionuclides and radiopharmaceuticals (RP) based on them, is impossible without the equipment that permits the automated insertion and removal of targets; irradiation; handling of irradiated targets, including various chemical operations; and also, when the occasion requires, sampling of radioactive products in the process of irradiation; production of final preparations and their

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quality control. This equipment is created on the basis of electronic and computer hardware provided with appropriate software for stable operation with high-activity materials [1].

There exist nuclear data for ultrashort-lived isotopes [1]. Nuclear reaction cross-sections have been defined to a high accuracy, the target operation has been investigated. Developed and automated are the methods of on-line extraction of USL RN and preparation of numerous radiopharmaceuticals on their basis.

2. PRODUCTION OF USL RADIONUCLIDES AT THE CYCLOTRON CV-28

Artificial radioactive isotopes came into use in nuclear medicine shortly after creation of the first cyclotron by Lawrence (1930) and discovery of the neutron by Chadwick (1932). The pioneer work of Joliot-Curie (1934), where he obtained the ^{30}P isotope with $T_{1/2} = 2.5\,min$ in the $^{27}Al(\alpha, n)^{30}P$ reaction, gave rise to cyclotron radionuclides that had certain advantages in their properties over the reactor radionuclides [2].

Generally, the required amounts of USL RN are produced at small cyclotrons [2]. A regular use of cyclotrons for the production of medical radionuclides has begun since 1950. Small medical-only cyclotrons, the so-called "baby"-cyclotrons ($E \leq 20\,MeV$), are convenient for their location directly at medical centers, where they serve for generation of USL RN and PET studies with the RN produced. In current nuclear medicine, more than 50 cyclotron radionuclides having the half-life from a few minutes to several years are applied for scientific research, diagnostic and therapeutic purposes.

In practice, to produce RN in nuclear reactions, beams of charged particles (p, d, ^3He, ^4He) are used, of which protons find the widest application [2]. In the nearest future, the NSC KIPT will put into operation the isochronous cyclotron CV-28 with a regulated energy of light ions p, d, ^3He, ^4He. The characteristics of the cyclotron are given below in Table 1 [3].

In this connection, it appears of interest to consider the possibility of generating the USL and SL radionuclides at the cyclotron CV-28 with their subsequent use for medical diagnostics. Table 2 gives the USL and SL RN, their half-lives, RN-producing nuclear reactions, and the required energy range [4].

Table 1

Accelerated particles	Particle energy (MeV)	External target current (μA)	Internal target current (μA)
p	2-24	40-60	200
d	4-14	50-100	300
^3He	6-36	5-50	135
^4He	8-28	6-40	90

Table 2

Radionuclides	Half-life, $T_{1/2}$	Nuclear reactions	Energy (MeV)	Yield from a "thick" target, $\mu Ci/\mu A \cdot hour$
USL				
^{11}C	$20.4\,min$	$^{11}B(p, n)$	22	756
^{13}N	$9.96\,min$	$^{16}O(p, \alpha)$	18	24
^{15}C	$2.03\,min$	$^{14}N(d, n)$	15	4
^{18}F	$109.7\,min$	$^{18}O(p, n)$	15	56
SL				
^{123}I	$13.2\,hour$	$^{124}Te(p, xn)$	5.2	
^{124}I	$4.2\,day$	$^{124}Te(p, n)$		
^{89}Sr	$50.5\,day$	$^{89}Y(p, n)$		
^{64}Cu	$12.7\,day$	$^{64}Ni(p, n)$	19	
^{67}Cu	$61.9\,hour$	$^{70}Zn(p, \alpha)$	26.5	
^{169}Yb	$32\,days$	$^{70}Tm(p, n)$		

The USL RN ^{11}C, ^{13}N, ^{15}O, ^{18}F are the "organic" nuclides, which are positron emitters in their nuclear-physical properties.

The main problems in the process of RN production are the operations of target preparation, irradiation and preparation of the final radioactive product.

The design of targets and target complexes is determined by physical-chemical properties of the target material.

In practice, targets of three types of the state of aggregation (solid, liquid, gaseous) are used [1, 5].

When possible, it is metals that are used as solid targets. In this case, the amount of working target nuclei makes up nearly 100% (impurities may constitute an insignificant portion). Besides, the target compactness, and hence, the small size of the target facilitate the design.

Various salts and oxides have received wide acceptance. In recent years there have appeared specially prepared ice targets - these are H_2O (^{18}O) and CO_2 (^{18}O) to produce ^{18}F [1].

Gaseous targets such as O_2, Ne, the CF_4-H_2 mixture are also widely used to obtain ^{18}F [1, 2].

In accordance with a particular program of RN production and the accelerator parameters, the target material is chosen and target complexes of various degrees of complexity are created. To extract the RN from the target material, to purify and concentrate them, various combinations of physical-chemical methods are used, i.e., deposition, extraction, ion-exchange chromatography, distillation, electrodeposition, electromagnetic separation of isotopes. The choice of the methods is governed by physical-chemical properties of the target material and radioactive isotopes produced in it, and also, by the requirements for the quality of the final preparation (high degree of purity, carrier-free RN condition, high specific activity). Of importance are the factor of time, especially in the case of SL isotopes, and environmental standards requiring radioactive waste minimization. The issues connected with the solution of all these problems are regularly discussed at international meetings "Target devices and chemistry of targets" [1].

Among the USL RN, ^{18}F is a relatively long-lived isotope (see Table 2, $T_{1/2} = 109.7\,min$). The radiopharmaceuticals based on it play the main role in the development of PET studies that may take 1 to 4 hours for scanning from the moment of RP injection. ^{18}F can be obtained in a greater quantity and with a higher specific activity in comparison with ^{11}C, ^{13}N, ^{15}O. Of greatest practical interest for the production of ^{18}F are the nuclear reactions ^{20}Ne (d, ^{4}He) ^{18}F and ^{18}O (p, n) ^{18}F, which can proceed at a particle energy $\leq 15\,MeV$ and at relatively moderate currents providing an acceptable yield of the isotope [1, 4]. When designing targets for ^{18}F production, it is necessary to take into account a high chemical activity of the element, because its interaction with the structural materials of the target and RP production equipment may reduce the real yield of the product and change its chemical form.

The choice of the target is dependent on the way of introducing ^{18}F into the RP molecules. The H_2 ^{18}O target has certain advantages over other materials (low cost, simplicity of the target device, high yield of ^{18}F and its production in the required ionic form). However, there are some problems arising during irradiation with intense particle beams. They are connected with the target heating and water radiolysis, which result in increased gas evolution and pressure inside the target, and hence, in a possible failure of the target [1, 5].

Carbon-11 can be produced in the reactions $^{14}N(p, \alpha)$, ^{11}B(p, n), ^{10}B(p, n), ^{11}B(d, 2n) at energies E 15, 22, 5, 11.5 MeV, respectively [4].

Nitrogen-13 is obtained in the reactions $^{16}O(p, \alpha)$, ^{12}C(d, n), ^{14}N(p, pn) at energies E equal to 18, 7.5 and 22 MeV, respectively.

To obtain oxygen-15, one can make use of the reactions ^{14}N(d, n), ^{12}C (^{4}He, n), ^{16}O(p, pn) at $E = 15$, 25 and 33 MeV, respectively [4].

The production of USL radioisotopes at irradiation of targets (liquid, solid and gaseous) in cyclotrons has been considered in a number of papers [7] - [13].

The radionuclides carbon-11, nitrogen-13, oxygen-15 were produced by irradiation of targets with deuterons of very low energies (0.5 to 2 MeV) [7, 11]. The authors of ref. [12] have discussed the applicability of liquid, solid and gaseous targets for the generation of the mentioned USL RN. In this case, liquid and gaseous targets were shown to have an essential advantage over solid targets. The experimental optimization of gaseous target systems was described.

The production of oxygen ^{15}O-labeled water for PET has been described in ref. [13]. A continuous gas flow O_2 (^{15}O) was produced at the cyclotron by means of the nuclear reaction ^{14}N(d, n) ^{15}O as the neutral nitrogen target (1%O_2 in N_2) was irradiated with a deuteron beam of energy 5 MeV. Paper [10] describes the program requirements for the cyclotron production of USL radionuclides. The clinical need of ^{15}O-labeled water has been demonstrated along with the substantiation of the modification and efficiency of combining two gas target systems: one labeled with ^{15}O resulting from the ^{14}N(d, n) ^{15}O reaction, which is combined with the other gas target labeled with the ^{11}C radionuclide. The system permits the on-line production of an extremely high yield of radionuclides of excellent purity. The characteristics of upgraded cyclotron target systems and the results of radiochemical analyses have been presented.

On account of a short half-life, the application of USL RN in nuclear medicine calls for territorial union of all the processes such as target irradiation, radiochemical extraction of RN, preparation of RP followed by their use in *in-vivo* studies. Thus, the diagnostic complex must include the cyclotron (CV-28 in our case), the PET facility; radiochemical, radiopharmaceutical, analytical laboratories and the nuclear medicine branch. The required amounts of USL RN are generally produced at small cyclotrons [1], and the cumulative volume in the countries with their every-day RN production makes several curies per week.

3. CYCLOTRON CV-28 PRODUCTION OF SL RADIONUCLIDES

The methods of production and use of RN have been described in numerous original and survey papers that comprise results of long-term experimental and theoretical studies. The data obtained at different scientific centers for the last 20 - 25 years have formed the basis for elaborating standard IAEA recommendations concerning the methods of production of a number of most widely used RN [2].

We have considered the possibility of production of a variety of promising medical SL radioisotopes (Table 2) at the cyclotron CV-28 in accordance with the IAEA recommendations [6].

Along with the use of USL isotopes in nuclear medicine, recent attention has been given to other radionuclides, which decay mostly with emission of β-particles and have the half-life $T_{1/2}$ optimum for PET diagnostics. The usage of RN with these properties makes it possible to investigate the kinetics of physiological and biochemical processes, to study the RN behavior, including the time stability of RP, *in-vitro* and *in-vivo*.

So, in PET studies ^{124}I is used, which is cyclotron produced in the reactions with charged particles, primarily of energies up to 40 MeV. The nuclear data on ^{124}I have been known sufficiently well [2]. This isotope is used in both PET diagnostics and radiotherapy. Among nuclear reactions of ^{124}I production [4] we mention the $^{124}Te(p, n)$ and $^{124}Te(d, 2n)$ reactions as most well studied, with detailed measurements of excitation functions, yield, purity of ^{124}I obtained in the selected energy ranges. In practice, it is the reactions $^{124}Te(p, n)$ and $^{125}Te(p, 2n)$ that are mainly used. The dioxide TeO_2 with enriched tellurium isotope is mostly used as a target. After its irradiation, radioactive iodine is extracted by the dry distillation technique.

^{123}I is considered an ideal radionuclide for clinical diagnostics. Owing to its nuclear-physical properties it is widely used for *in-vivo* multifunctional investigations. As a special advantage, it should be noted its less radiation load on the patients, as opposed to other iodine isotopes, this being of primary importance for children and pregnant women [2].

There are about twenty ^{123}I-producing nuclear reactions, which form the basis for two principal methods of production:

1) direct method, by which ^{123}I is produced directly on antimony and tellurium, and

2) indirect (generator) method, where ^{123}I results from the decay of ^{123}Xe.

For direct production of ^{123}I, it is most common practice to use enriched ^{124}Te targets, and less common - ^{122}Te or ^{123}Te. The radionuclide purity of ^{123}I obtained from tellurium targets does not exceed 96%, the main impurity comes from ^{124}I ($T_{1/2} = 4.1 days$). This fact and also, a high price of highly enriched target material as well as the necessity of its regeneration make the generator method more preferable,

where the extraction of radioxenon needs no special chemical operations and ^{123}I of high radionuclide purity is obtained ($\geq 99.5\%$, $^{125}I \leq 0.2\%$). Owing to this, the ^{123}I preparations obtained by the generator technique are applicable for a wide use in the diagnostics of diseases of different organs, while ^{123}I obtained by the direct method is applicable mainly for the diagnostics of thyroid gland diseases [2, 5].

At generator production of ^{123}I, it appears most optimum from the radionuclide purity viewpoint to irradiate highly enriched ^{124}Xe with protons of energy up to 30 MeV. The target irradiation with intense proton beams at small and medium cyclotrons, the absence of corrosion problems in the target systems, a simple chemistry, a high radionuclide purity of the product (^{125}I content is less than $10^{-3}\%$), a rather high yield, all these factors make the generator method most promising for batch production of ^{123}I [4].

Numerous experiments in a number of scientific centers of different countries are dedicated to the methods of obtaining the mentioned radionuclides at cyclotrons [14] - [27].

The results of three-year studies and the program of synchrocyclotron production of high-purity ^{123}I during proton bombardment of diiodomethane have been presented in ref. [4]. The ways of solving the problems and the equipment were also described.

A relatively simple and inexpensive method of ^{123}I production in the $^{124}Te(p, 2n)$ ^{123}I reaction has been presented in ref. [15].

A regular cyclotron production of ^{123}I isotope has been organized in Orleans [16]. The enriched target of tellurium oxide was irradiated with protons. As a result of the $^{124}Te(p, 2n)$ ^{123}I reaction, the required isotope was produced. The paper [16] also discusses the irradiation equipment and the process of dry extraction of the radioisotope.

For nuclear medicine diagnostics, the enriched tellurium dioxide target was irradiated in the cyclotron to produce ^{123}I radioisotope [18, 20].

The authors of ref. [21] have discussed the possibility of ^{123}I isotope production at small cyclotrons at proton energies of about 18 to $20\,MeV$. Among possible nuclear reactions for production of this radionuclide, consideration was given to the $^{122}Te(d, n)$ ^{123}I and $^{123}Te(p, n)$ ^{123}I reactions. In comparison with Te, the preference is given to TeO_2 targets. The ^{123}I preparation comprises a certain amount of ^{130}I and ^{124}I. The ^{130}I impurity that gives rise to high-energy gamma-radiation appears to be more dangerous.

The cyclotron production of high-purity ^{123}I with the use of enriched xenon-124 has been described in ref. [22]. Since the production of ^{123}I by using the $^{127}I(p, 5n)$ reaction calls for energies higher than attainable at compact commercial cyclotrons, consideration was given to possible production of ^{123}I in the reactions $^{124}Xe(p, n)^{123}Cs \rightarrow^{123} Xe \rightarrow^{123} I$ and $^{124}Xe(p, pn)^{123}Xe \rightarrow^{123} I$ with the use of xenon comprising 50% of xenon-124. A conclusion has been drawn on the possibility of successful use of

a compact cyclotron with an external beam of energy $24\ldots26\,MeV$ to produce high-quality ^{123}I in the $(p, 5n)$ reaction with the use of a gas target ^{124}Xe.

The production of ^{123}I for medical purposes (diagnostics and RP preparation) was also realized at the isochronous cyclotron [23]. The $^{127}I(p, 5n)^{123}Xe \rightarrow^{123}I$ reaction was used. NaI was used as a target material. The resulting isotope had a high radionuclide purity and was produced in quantities sufficient to carry out medical and biological studies.

For cyclotron production of a variety of radioisotopes, including ^{123}I and ^{124}I radionuclides, a special remote-control system of internal targets has been designed [24]. The target stability conditions at high current values have been considered.

Studies have been made into principal conditions of ^{123}I isotope production in the $^{124}Te(p, 2n)\,^{123}I$ reaction at the cyclotron CV-28 for the proton energy $E = 24MeV$ [25]. The targets of two types (TeO_2 and $TeO_2 + 2\%Al_2O_3$) were used, and the influence of Al_2O_3 on the iodine extraction was investigated. Iodine was separated by dry distillation with the use of the induction furnace in O_2 atmosphere.

In accordance with the IAEA recommendations [6], the SL isotopes ^{64}Cu, ^{67}Cu and ^{169}Yb also hold promise for nuclear medicine.

^{64}Cu is a positron radiator, which is cyclotron-produced in the reactions of charged particles, primarily of energies up to $40\,MeV$ (see Table 2) [2]. The ^{64}Cu RN is applied for labeling biomolecules and monoclonal bodies, and also in PET diagnostics of tumor masses.

^{67}Cu is a beta radiator (Table 2), which is used, similarly to ^{64}Cu RN, for studies of copper metabolism and for labeling monoclonal antibodies used in radioimmunotherapy. However, owing to its nuclear characteristics, ^{67}Cu has some advantages for diagnostic and therapeutic applications. The studies have demonstrated that the greatest amounts of ^{67}Cu can be generated in the (p, α) reaction with irradiation of enriched ^{70}Zn at low-energy accelerators [2].

Experiments at the cyclotron CS-30 capable of accelerating protons up to $26.5\,MeV$ were made to investigate the possibility of producing various radionuclides simultaneously with production of ^{67}Cu on one and the same target. Among those radionuclides there were ^{64}Cu and ^{67}Cu. Both of them are used for obtaining radiopharmaceuticals and have the commercial potential [26].

^{64}Cu is the radioactive label for radiopharmaceuticals in PET studies. This radionuclide was produced at the cyclotron by irradiating the Zn target with deuterons in the nuclear reactions (d, xn) and $(d, 2pxn)$ in the energy range up to $19\,MeV$ [26].

The authors of paper [26] have described the outcome of experiments on production of ^{169}Yb radioisotope from the target irradiated at the cyclotron U-120. The ^{169}Yb radioisotope was obtained in the $^{168}Tm(d, n)^{169}Yb$ reaction and was extracted by means of ion-exchange chromatography.

The ^{87}Sr radionuclide was produced for nuclear medicine by exposing the strontium-88 target to protons at the cyclotron [26].

The analysis of literature data on the production and use of USL and SL radionuclides and the above-given information (Table 2) indicates that the cyclotron CV-28 available at the NSC KIPT has the operational capabilities of producing USL and SL radionuclides, including ^{18}F radionuclide.

4. CONCLUSIONS

The advancement of studies on USL isotopes, and particularly, on ^{18}F, is stimulated by the creation of new PET centers in the world, which include a positron-emission tomograph and a small-sized cyclotron for isotope production.

From the literary sources, including the IAEA information, it is known that the nuclear medicine needs make up more than 50% of the world annual production of radionuclides [2]. The demands for USL RN (^{11}C, ^{13}N, ^{15}O, ^{18}F), and also, for other β^+-radiators (^{124}I) have particularly increased in the last decades in connection with the development of PET investigations and creation of new PET centers. Buy 2000, there were more than 150 such centers in the world, and nearly a half of them are operating in Northern America [27].

It should be noted that for the time being, in Ukraine there are no PET centers in combination with a cyclotron for radionuclide production. In view of this, the possibility of creating the PET center for medical diagnostics at the NSC KIPT with the available isochronous cyclotron CV-28 as the basis is of special interest.

It can be seen from Table 2 that, e.g., the cyclotron can efficiently produce about 7000Ci of fluorine-18 annually. Taking into account that one diagnostic run requires about 5 to 10 mCi, it can be easily calculated that the amount of the isotope produced would be sufficient to make about 10^6 examinations of patients.

Therefore, one complex including the PET center and the cyclotron CV-28 can obviously meet the current requirements in Ukraine for SL and USL radionuclides for nuclear medicine.

Besides, being equipped with a special target, the cyclotron can be used for neutron therapy.

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ПОЛУЧЕНИЕ УЛЬТРАКОРОТКОЖИВУЩИХ И КОРОТКОЖИВУЩИХ ИЗОТОПОВ НА ЦИКЛОТРОНЕ CV-28 ДЛЯ ЯДЕРНОЙ МЕДИЦИНЫ

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В работе дан обзор экспериментальных методов получения циклотронных ультракороткоживущих (УКЖ) и короткоживущих (КЖ) радионуклидов, рекомендованных МАГАТЭ как наиболее широко используемых в ядерной медицине. Представлены ядерные реакции, из которых они получаются, необходимый диапазон энергий, мишени для их получения. На основе проведенного анализа экспериментальных исследований в различных научных центрах и сравнения с параметрами циклотрона CV-28, который планируется запустить в ННЦ ХФТИ, делается вывод о реальной возможности наработки этих радионуклидов на изохронном циклотроне CV-28 и создания на его основе ПЭТ-центра для ядерной медицины.

ОДЕРЖАННЯ УЛЬТРАКОРОТКОЖИВУЧИХ ТА КОРОТКОЖИВУЧИХ ІЗОТОПІВ НА ЦИКЛОТРОНІ CV-28 ДЛЯ ЯДЕРНОЇ МЕДИЦИНИ

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В роботі наведено огляд експериментальних методів одержання циклотронних ультракороткоживучих (УКЖ) та короткоживучих (КЖ) радіонуклидів, рекомендованих МАГАТЕ для найбільш широкого використання в ядерній медицині. Представлено дані про ядерні реакції, в яких вони одержуються, необхідний диапазон енергій, мішені для їх одержання. На основі проведеного аналіза експериментальних досліджень в різних наукових центрах і порівняння з параметрами циклотрона CV-28, який планується запустити в ННЦ ХФТІ, робиться висновок про реальні можливості наробки цих радіонуклидів на ізохронному циклотроні CV-28 та створення на його основі ПЕТ-центра для ядерної медицини.