Production of intense mass separated ^{11}C beams for PET-aided hadron therapy

S. Stegemann^{a,*}, T.E. Cocolios^a, K. Dockx^a, G. Leinders^b, L. Popescu^c, J.P. Ramos^{a,d}, K. Rijpstra^c, T. Stora^d, M. Verwerft^b, J. Vleugels^e

^a*KU Leuven, Institute for Nuclear and Radiation Physics, Celestijnenlaan 200d, 3001 Heverlee, Belgium*

^b*Belgian Nuclear Research Centre SCK•CEN, Institute for Nuclear Materials Science, Boeretang 200, 2400 Mol, Belgium*

^c*Belgian Nuclear Research Centre SCK•CEN, Institute for Advanced Nuclear Systems, Boeretang 200, 2400 Mol, Belgium*

^d*CERN, EN-STI, Geneva 23 CH-1211, Switzerland*

^e*KU Leuven, Department of Materials Engineering, Kasteelpark Arenberg 44, 3001 Heverlee, Belgium*

Abstract

A novel production system based on the Isotope Separation On-Line (ISOL) method is being developed to produce intense mass separated ^{11}C beams for PET-aided hadron therapy. In this work, we present a systematic study of the target that was developed for optimized ^{11}C beam production. A solid boron nitride target (BN) with approximately 21% open porosity was manufactured by spark plasma sintering to provide maximized in-target production yield with enhanced isotope release properties. Operational limitations with respect to high temperatures and oxidizing atmospheres were studied, revealing that the BN target can withstand temperatures up to 1500 °C and can be operated with a controlled O_2 leak, providing O_2 potentials up to -300 kJ/mol, measured at 1000 °C.

Keywords: Radioactive ion beam production, ^{11}C production, target material

1. Introduction

Cancer is one of the major causes of death. In 2014 more than 1 in 4 deaths were caused by cancer in the European Union, which corresponds to a total number of almost 1/3rd million deaths [1]. Radiation therapy plays an important role in the treatment of cancers. Hadron therapy, and particularly carbon therapy, is a very precise treatment for localized tumors where the tumor is irradiated with a pure, monoenergetic and high intensity particle beam [2]. Carbon therapy significantly reduces the dose exposure to healthy tissue compared to conventional photon therapy. This is the direct result of the energy loss of heavy charged particles in matter. Such particles have a sharp peak at the end of the particle's trajectory (Bragg peak), where most of the energy is deposited. Treatments are performed according to complex treatment planning systems that simulate the beam trajectory through the human body, and thus, calculate the dose distribution of the particle beam to the human body and to the target cells. However, these treatment planning systems suffer from range uncertainties, which originate for instance from anatomical changes throughout the treatment fractions. Consequently, the verification of the actual dose distribution in the tissue is an important feature which remains difficult. Current attempts involve PET-imaging (Positron Emission Tomography imaging) with secondary β^+ -emitters, such as $^{10,11}\text{C}$ or ^{15}O , which are produced by the primary ^{12}C beam interacting with water contained in human tissue [3, 4]. Studies on off-line and in-beam PET-imaging of these secondary

β^+ -emitters showed promising results [5, 6]. However, limiting statistics and the washing out of the β^+ -emitter distribution remain fundamental issues in such an approach [5, 7]. The subject of this work is an alternative approach, in which the stable ^{12}C beam is entirely replaced with its radioactive isotope ^{11}C ($T_{1/2} = 20.4$ min). By using the β^+ -emitter directly as therapeutic beam, treatment can be combined with on-line PET-imaging. The PET-images, acquired during treatment, provide 3D dose distribution maps of the irradiation field, which allow to validate the correctness of the treatment planning [4].

The challenge remains to produce a radioactive particle beam of sufficient intensity. Effective treatments require $4 \cdot 10^8$ ions/s delivered to the patient [4]. As radioisotope beam production is a multi-step process (see Fig. 1), with inevitable beam losses at each step, optimization of each individual process is essential. This work focuses on the production system (highlighted in red, in Fig. 1) tailored for high intensity ^{11}CO beams.

In nuclear medicine ^{11}C is a well-known radioisotope, commonly used for PET-imaging. The production is usually done in the hospital by irradiating a nitrogen gas target with a low-energy proton beam [11, 12]. Once a sufficient quantity is being produced, the gas cell is dismantled from the target station for further chemical separation and the labelling to the carrier molecule. However, for radioactive ion beam (RIB) production this method is unpractical since such gas targets are under much higher pressures and therefore cannot be directly coupled to the ion source [4]. Furthermore, while it is in principle possible to produce a sufficient activity with one gas cell to deliver enough ions per spill to treat one patient, it remains unpractical with respect to a continuous treatment of several patients per day. An-

*Corresponding author.

Email address: simon.stegemann@kuleuven.be (S. Stegemann)

Figure 1: Schematic layout of a ^{11}C based hadron facility, as it is proposed within the MEDICIS-Promed network [8]. The highlighted part shows the production system discussed in this paper. The beam cooling [9] and charge breeding [10] are further research projects within MEDICIS-Promed. The different parts are not to scale.

other technique to produce radioactive ion beams is projectile fragmentation. However, such beams suffer from low production cross sections and poor quality [13]. Hence, we propose a production system based on the Isotope Separation On-Line method (ISOL), which allows to produce intense, continuous and pure radioactive ion beams. In detail, a thick, usually solid target is mounted in a target chamber which is connected to the ion source. Protons are impinging on the target, producing various (radio-)isotopes via different nuclear reactions. The isotopes are diffusing to the surface of the material, from where they vaporize. Once the isotopes are released, they effuse to the ion source where they are ionized to the 1+ charge state before they can be accelerated by a low extraction voltage, followed by mass separation with a dipole magnet. High temperatures enhance the diffusion and effusion processes. In this way, radioactive ion beams for physics research have been produced for more than 50 years at CERN-ISOLDE (Isotope Separator On Line DEvice) [14], which serves as an example for the ^{11}C beam production. The ISOL type production unit, schematically illustrated in the highlighted part of Fig. 1 will consist of a solid boron nitride (BN) target, an electron cyclotron resonance (ECR) ion source and a controlled oxygen leak for molecular isotope extraction. This target-ion source unit is chosen to maximize the C^+ yield to meet the requirements for effective cancer treatments and will be discussed in the following. In detail, a systematic study on the feasibility of the target material is presented, by investigating operational limitations with respect to high-temperatures and oxidizing atmospheres.

2. Materials and Methods

2.1. Target development

BN has been identified as a promising target material, due to its two reaction channels with high cross sections for ^{11}C production ($^{11}\text{B}(p,n)^{11}\text{C}$ and $^{14}\text{N}(p,\alpha)^{11}\text{C}$) [15]. Both cross sections reach their maximum around $E = 6 - 8$ MeV, which are low-energy and will result in high energy deposition in the target material. Low-energy beams have a higher stopping power

and therefore lose more energy in comparison to high-energy beams. To optimize the isotope production versus energy deposition, the proton beam energy and target thickness are chosen so that the beam energy is in the interval $E \in [5, 15]$ MeV. Such proton beams can be provided by compact cyclotrons, routinely used in hospitals for PET-isotope production. The corresponding physical in-target production yield can be expressed as:

$$Y_{\text{phys}} = \frac{N_A}{M} \int_{E_f=5}^{E_i=15} \frac{f_b \cdot \sigma_{^{11}\text{B}}(E) + f_n \cdot \sigma_{^{14}\text{N}}(E)}{S(E)} dE, \quad (1)$$

with N_A the Avogadro's number, M the molar mass, $S(E)$ the stopping power expressed in $\text{MeV cm}^2 \text{g}^{-1}$, σ_i the cross sections in millibarn and $f_{b,n}$ the fractional isotopic abundances. Previous studies by Loiselet et al. in the Centre de Recherche du Cyclotron (CRC) at Louvain-la-Neuve with BN, yielded already a 10^7 pps ^{11}C beam [16]. However, BN was used as powder [17, 18], which introduces limitations on beam energy and intensity to prevent the powder from escaping the target chamber. To overcome this, and furthermore, to facilitate target handling and waste management, a BN powder compact is investigated in this work.

2.1.1. Target preparation

One possible way to obtain a rigid target is by sintering of a powder compact. Sintering is a complex process, in which parameters such as temperature, pressure and time have a strong impact on the material properties and densification of the powder compact [19, 20]. In that respect, the isotope release properties are essential, as they are often considered as a bottleneck in RIB production [21, 22]. Generally, small grain sizes for short diffusion times in combination with large pore sizes and high open porosity for fast effusion, enhance the isotope release [22, 23]. Therefore, it is desirable to process a powder compact that is not fully densified, i.e., sintering does not reach the theoretical density, and which microstructure is stable at typical ISOL target operational conditions [19]. To obtain such a powder compact, hexagonal BN (h-BN) targets were manufactured by spark plasma sintering (SPS), often also denoted as field-assisted sintering technique (FAST) [24]. This technique sends high DC currents through a punch/die system in which the powder is compacted to rapidly heat up the material. High heating/cooling rates up to 1000 $^{\circ}\text{C}/\text{min}$ and 400 $^{\circ}\text{C}/\text{min}$, respectively, can be applied, reducing grain coarsening at lower temperatures. We explored three h-BN powders from different suppliers and concomitant particle size distributions¹, and optimized the SPS sintering cycle's temperature, dwell-time and pressure. The following parameters were used: Momen-tive HCP powder, a SPS cycle under 2 mbar air pressure, 100 $^{\circ}\text{C}/\text{min}$ heating rate, $T_{\text{final}} = 1700$ $^{\circ}\text{C}$ and a sintering-pressure of 25 MPa with 5 minutes dwell-time. In this way, a BN powder pellet with bulk density of 1.3 g cm^{-3} corresponding to a

¹Momentive: Grade HCP, D50 = $8.3 \mu\text{m}$, purity 99.5 %. Asbury: BTBN5003 D50 = $2.5 \mu\text{m}$, purity 99 %. Goodfellow: max. particle size $10 \mu\text{m}$, purity 99.5 %

total porosity of 40 % was manufactured². With respect to isotope release, open porosity is an important property, which was determined to be 21 % by He-gas pycnometry. Based on these results, the target thickness to absorb 10 MeV of the initial proton beam can be calculated and corresponds to 2 mm. Fig. 2 shows the expected in-target production yield as a function of irradiation time. Note that the 8.55 GBq/ μ A saturation yield is proportional to the applied beam current, which will depend on the maximum applicable target temperature and the cooling efficiency.

Figure 2: In-target production yield resulting from irradiating a 2 mm thick SPS pre-sintered BN target having 40 % porosity with a 15 MeV proton beam. The target thickness is chosen to optimize the isotope production versus energy deposition.

2.1.2. Heat management

Using low-energy beams for ^{11}C production from BN results in high power deposition and consequently, rapid heating of the target material. Hence, heat management has to be considered. Generally, ISOL targets are operated at pressures $P = 10^{-6} - 10^{-4}$ mbar and at temperatures just below their melting point since high temperatures enhance diffusion. An equilibrium calculation of h-BN at a pressure of 10^{-6} mbar, performed with HSC7 [25], suggests that BN dissociation: $2\text{BN} \rightarrow 2\text{B} + \text{N}_2(\text{g})$ starts already at $T \approx 1000$ °C (see Fig. 3). This phenomenon is especially important as the target container will be coupled with a short transfer line to the ECR ion source, whose efficiency depends crucially on the injected gas load [26]. To study the extent of BN dissociation at high temperatures and low pressures, a heat test was performed using an experimental setup which was used in another study to assess TiC mass losses and phase dynamics [27]. The aim of this study was to determine the maximum temperature at which the target can be operated to prevent overloading the ion source. The experimental setup consisted of an Al_2O_3 tube inserted in a furnace that could be heated up to 1500 °C with a rate of 8 °C/min. A vacuum system with two turbo pumps and two evacuation lines allowed to evacuate the tube to a base pressure of 10^{-6} mbar, and to measure residual gases and the relative pressure change with a quadrupole mass spectrometer (QMS) and a full-range gauge. The results are shown in Fig. 4. The detected mass-over-charge (A/q) signals were corrected

for background residuals by measuring one full cycle with the empty Al_2O_3 boat. The relative pressure change (top) illustrates only a moderate pressure increase for $T > 1000$ °C. Although the measured pressure does not correspond to the actual vapor pressure we can conclude from experience with this setup that the observed pressure increase indicates slow dissociation kinetics, allowing to operate the BN target at 1500 °C. This is supported by the total mass loss of the samples after heat treatment, which is below 1%. The mass spectrum presents an increased $A/q = 14$ (N), 28 (N_2 , CO) signal, which corresponds to the evaporation of N_2 from the dissociation of BN and, to some extent, to CO. Furthermore, increased signals of $A/q = 12$ (C), 32 (O_2), 44 (CO_2) are observed at high temperatures, and a strong $A/q = 18$ (H_2O) is detected throughout the whole measurement. These may result from corresponding contaminations in the Al_2O_3 tube, as the H_2O signal decreased in subsequent measurements and the blank measurement was taken in the end. Besides that, high masses are detected, which were not present in the background spectrum. The origin of these signals is not clear, however, a pattern of $A/q = 12$, 14 indicates a formation of clusters binding an additional nitrogen or carbon atom.

Figure 3: Equilibrium calculation of h-BN at a pressure of $P = 10^{-6}$ mbar showing that BN dissociation is starting at $T \approx 1000$ °C. Note that B(g), B(A), B(GL), B(B) denote different phases of boron: gas, amorphous, glass, β -rhombohedral. The calculation was carried out with HSC7 [25].

2.1.3. Molecular isotope extraction

For high intensity beam production, molecular isotope extraction and beam formation are considered for two reasons: firstly, carbon is very refractory, resulting in poor release efficiency from the target material, where carbon monoxide is more volatile and is expected to increase the release efficiency; secondly, carbon is very reactive and easily forms refractory carbides with hot metal surfaces. Since carbon monoxide is less reactive, retention times on the surrounding material are reduced, increasing the transport efficiency. Thus, as indicated in Fig. 1, a controlled O_2 leak is foreseen in the production system, to extract ^{11}CO from the target matrix. Introducing O_2 into the system includes the risk of target oxidation. To find operational conditions where BN oxidation is not favorable, Ellingham diagrams can be consulted. They show the thermodynamic stability (standard Gibbs free energy) of metal/metal-oxide couples

²The theoretical density of h-BN powder corresponds to $2.1 - 2.2 \text{ g cm}^{-3}$ at 23 °C

Figure 4: Heat treatment up to 1500 °C of SPS pre-sintered BN in an evacuated furnace. (Top) Relative pressure and (bottom) mass spectrum detected during the heating cycle. At high temperatures, a modest pressure increase and enhanced mass signals $A/q = 14$ (N), 28 (N_2 , CO) are observed. Signals at $A/q = 12$ (C), 18 (H_2O), 32 (O_2), 44 (CO_2) probably result from contaminations in the Al_2O_3 tube.

as a function of temperature. In equilibrium, and assuming negligible reactant and product vapor pressure, the standard Gibbs free energy of such couples corresponds to $RT \cdot \ln(P_{O_2})$, which is commonly denoted as the O_2 potential μ_{O_2} . One can obtain from this plot equilibrium conditions where BN oxidation is not thermodynamically favored. In Fig. 5, the BN/B_2O_3 -line corresponds to the line of stability for BN, where the oxidation can be described by:

Potentials above this line will result in the oxidation of BN, whereas below this line the BN-state is thermodynamically favored, and conditions may be found where O_2 oxidizes the C-content in the BN target matrix to CO or CO_2 . It must be mentioned here that Ellingham diagrams, usually, depict standard state conditions, e.g. all partial pressures equal to one. In such cases, volatile species do not contribute to the Gibbs free energy, due to its logarithmic partial pressure dependency.

However, this is here not reasonable, as C will only be produced in trace amounts and the N_2 partial pressure P_{N_2} resulting from the BN oxidation and dissociation has to be considered. It is however not clear how to evaluate these partial pressures at equilibrium. As a starting point, an initial N_2 partial pressure of 100 ppm leaking into the thermal analysis tool, which remains unaltered in equilibrium, was assumed for the calculation. Leaks of this magnitude have been measured in the exhaust gas of the experimental setup that was used in this study. Assuming the same partial pressure for P_{CO} and P_{CO_2} yields the diagram shown in Fig. 5 (bottom). The standard state case is shown as a reference in Fig. 5 (top). The green-shaded area

marks conditions where oxidation of C to CO is thermodynamically favored, and BN does not oxidize. While it seems that at 1000 °C desirable conditions exist, such low μ_{O_2} are difficult to probe experimentally. However, the comparison of the top and bottom graph in Fig. 5 shows that the area of interest is increasing when decreasing the partial pressures, which is favorable for selective carbon oxidation. Since it is not clear how to evaluate the partial pressures at equilibrium, as a starting point, thermogravimetric analysis (TGA) of pure BN and carbon-doped SPS pre-sintered BN (BN-C, with [C] = 0.01, 0.1, 1, 5 wt.%) were performed at 1000 °C for O_2 potentials $\mu_{O_2} = -400, -340$ and -300 kJ/mol (indicated at stars in Fig. 5). At the time of the measurements, 1000 °C was still expected to be the maximum applicable temperature, and the O_2 potentials were chosen with respect to CO and CO_2 formation. From the results one can examine, firstly, the high-temperature oxidation kinetics of SPS pre-sintered BN in controlled atmospheres. This is important since the calculations contain no information on the kinetics, which are relevant for target operation. Secondly, conclusions on the release properties of C from BN may be drawn, by measuring the carbon-doped BN material.

Figure 5: Ellingham diagram for BN exposed to O_2 , showing the O_2 potential $\mu_{O_2} = RT \cdot \ln(P_{O_2})$ as a function of the temperature for standard state condition (top) and for $P_{N_2} = P_{CO} = P_{CO_2} = 100$ ppm (bottom). The solid BN/B_2O_3 -line corresponds to the line of stability for BN, and the green-shaded area mark conditions where C oxidation is favored, forming CO. The stars illustrate the conditions that were investigated by thermogravimetric analysis that is explained in the text.

For the measurements, the samples were prepared in an Al_2O_3 crucible, standing on a thermocouple. This assembly was mounted on a precision balance and the assembly was surrounded by a Rh furnace, equipped with a leak-tight fit and controlled gas in- and outlets. The whole system was coupled to a Quadrupole Mass Spectrometer (QMS), allowing to measure the mass change over time and the mass-over-charge ratio (A/q) of the evaporated gases simultaneously (TGA-MS). A gas control system could vary between different atmospheres: (1) Inert (Ar, N_2), (2) reducing (H_2 /Ar), (3) oxidizing (0.01 – 21 vol.% O_2) and (4) vacuum ($> 10^{-5}$ mbar). The samples were heated in Ar-atmosphere up to 1000 °C with a heating rate of 20 °C/min. To stabilize the TG signal, the sample was kept for 30 minutes at 1000 °C. Subsequently, the atmosphere was changed to an oxidizing atmosphere of chosen O_2 potential by mixing gas-flows of 5% H_2 /Ar gas with an O_2 gas mixture and the TGA-MS signals were recorded for 1.5 h. For each O_2 potential, a full

blank measuring cycle was recorded to correct for buoyancy-effects on the sample holder. Additionally, the mass spectrum was recorded to correct for background signals.

The result of this study can be seen in Figures 6-8, where the mass spectra in Figures 7, 8, unfortunately, fail to yield conclusive information. First, the pure BN case shall be discussed. Fig. 6 shows that BN follows parabolic oxidation kinetics. A similar behavior was reported by N. Jacobson et al. [28] who studied the high-temperature oxidation of hot-pressed, high-density CVD (chemical vapor deposition) and low-density CVD BN. The parabolic behavior results from a parabolic weight gain and simultaneous linear weight loss [29, 30]. According to Eq. 2, the weight gain should correspond to the uptake of O_2 , while, according to N. Jacobson et al. [28], the weight loss results from the volatilization reaction: $B_2O_3(l) + H_2O(g) = 2HBO_2(g)$. However, BN shows no oxidation at $\mu_{O_2} = -400$ kJ/mol, while still showing significant weight loss, dismissing the volatilization reaction from above. Only at $\mu_{O_2} = -340$ or -300 kJ/mol moderate parabolic oxidation kinetics with a maximum weight gain of less than 0.1% are observed, where only at $\mu_{O_2} = -300$ kJ/mol, in comparison to the background signal, a prominent N_2 signal can be observed in the mass spectrum (blue line in Fig. 7 (bottom)). It is however not clear whether the mass loss can be assigned to the evaporation of HBO_2 . While an increased $A/q = 44$ (HBO_2) signal is detected (blue line in Fig. 8 (bottom)), we observed a similar trend for the Ar-signal (not shown here), which is unaffected by the oxidation reaction. Therefore, the increased $A/q = 44$ signal is more likely a result of overall fluctuations.

From the TGA-MS measurements of the BN-C samples, unfortunately, no conclusive information regarding the C-extraction properties could be obtained. The BN-C samples seem to follow parabolic oxidation kinetics as well, where an increased C concentration results in an increased mass gain (see Fig. 6), indicating the formation of carbon oxides. However, a qualitative interpretation of the mass spectra (Fig. 7, 8) is impossible as signals that originate from the detected carbon are expected at $A/q = 28$, 44 (CO and CO_2 , respectively), which cannot be distinguished from N_2 and potential HBO_2 signals. Furthermore, considerable background signals are present, making weak signals indistinguishable from the background.

Nevertheless, we can conclude from this study that BN can be thermally treated under small O_2 potential without risking excessive material oxidation, and that carbon has an effect on the oxidation behavior. Future prospects are to investigate the effect of the N_2 partial pressure as it might be beneficiary with respect to selective C oxidation.

3. Summary & Conclusion

An ISOL type production unit for mass separated ^{11}C beams, comprising a solid BN target and an ECR ion source, is currently under development. BN is a promising target material for high intensity ^{11}C beam production via the ISOL method. To

Figure 6: TG measurement of BN and BN-C (with [C] = 0.01, 0.1, 1, 5 wt.%) for $\mu_{O_2} = -400, -340, -300$ kJ/mol. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture. The graphs show that both, an increased O_2 potential and increased C-content are enhancing the mass gain by O_2 uptake.

Figure 7: $A/q = 28$ MS measurement of BN and BN-C (with [C] = 0.01, 0.1, 1, 5 wt.%) for $\mu_{O_2} = -400, -340, -300$ kJ/mol. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture. Only at $\mu_{O_2} = -300$ kJ/mol, in comparison to the background signal, a prominent N_2 signal is observed. The enhanced signal of BN-C[1] at $\mu_{O_2} = -400$ kJ/mol (top) is in strong contrast to the rest of the series, and is therefore more likely the result of a leak into the setup.

enhance the release properties, BN powder pellets with approximately 21% open porosity were manufactured by spark plasma sintering. From this result, we expect a $8.55 \text{ GBq}/\mu\text{A}$ saturation yield by irradiating a 2 mm thick target with 15 MeV protons. In this context it was experimentally proven that the BN target can withstand temperatures of at least 1500°C in typical ISOL operational conditions. The feasibility of ^{11}CO isotope extraction via a controlled O_2 leak was investigated by measuring the high-temperature oxidation kinetics of BN and BN-C materials. Operating BN in controlled oxidizing atmospheres imposes no limitations on the material itself, whereas no conclusive information on the carbon release characteristics by studying BN-C systems could be made. Consequently, a study with activated pellets from which ^{11}C can be studied is essential to determine the release properties of the material. Such a program is ongoing at the CERN MEDICIS facility [31].

Figure 8: $A/q = 44$ MS measurement of BN and BN-C (with $[C] = 0.01, 0.1, 1, 5$ wt.%) for $\mu_{O_2} = -400, -340, -300$ kJ/mol. Note that $t = 0$ denotes the time when the gas composition is changed to the O_2 active mixture.

4. Outlook

It was mentioned that an ECR ion source is foreseen to be used for the ^{11}C beam production unit (Fig. 1). The advantage of such plasma ion sources is their absence of hot metal surfaces, which may retain CO. At GANIL, in collaboration with PANTECHNIK, a 2.45 GHz ECR ion source for efficient $1+$ ionization was developed (MONO 1000). Based on that, a compact source was developed and tested in an off-line study at ISOLDE. Promising 14% ionization efficiency was achieved [32]. For the study presented in this work, further ionization efficiency measurements of commercial PANTECHNIK ECR ion sources are being prepared.

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