MODERN GAS-TARGET TECHNOLOGY FOR THE PRODUCTION OF HIGH QUALITY RADIOPHARMACEUTICALS

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ABSTRACT

Routine production of radioisotopes for medical diagnostics places high demands on target technology and chemistry, with regards to reliability, production efficiency and quality. The following topics will be discussed: automation, material problems and radiation damage in the target area, target window, cooling problems, safety philosophy, chemistry and quality control. Examples of targets for the production of I-123, Br-77 and the Rb-81/Kr-81m generator system will be presented.

1. INTRODUCTION

The Karlsruhe compact cyclotron is an H^--machine which is variable in energy between 15 MeV to 40 MeV. This cyclotron is dedicated for applications in medicine and industry.[1)]
The radioisotopes produced for medical applications are used in nuclear medicine for diagnosis. In contrary to X-ray studies where only static information can be obtained, nuclear medicine provides dynamic information and hence allows time-dependent study of the function of organs. The labelled biomolecules and the radioisotopes involved should have the following ideal characteristics:

- no β^--particle emission
- short effective half-life
- γ-energy in the range between 100 and 300 keV

The above characteristics result in a maximum efficiency in the diagnosis and a minimum radiation dose to the patient. For example, (fig. 1) shows a comparison between I-131 and I-123. The physical properties show that I-123 (γ-energy 159 keV; no β^-, short half-life) is more favourable than I-131 (γ-energy 364,637; β^--emission, long half-life) for use in nuclear medical diagnosis.

2. GAS TARGETS

The production of radioisotopes used in nuclear medicine can be achieved with solid, liquid or gaseous targets. There are three types of gas targets which can be considered (table 1). A gas target configuration consists of two main parts: the target body and the target window (foil) including seal.

<u>Target bodies and windows</u>

The choice of material for both the target body and window is dependent on the particular nuclide production process. Although a general rule does not exist, there are some aspects of the target bodies like activation, contamination, corrosion and cooling, which have to be considered. The parameters are influenced by the choice of bombarding particle, beam energy, beam current, material and solvent. The criteria for target window materials should be the following:

- thickness of 1 - 200 µm
- pin-hole free
- high mechanical strength
- good thermal conductivity
- high melting point
- chemical resistance to oxidation

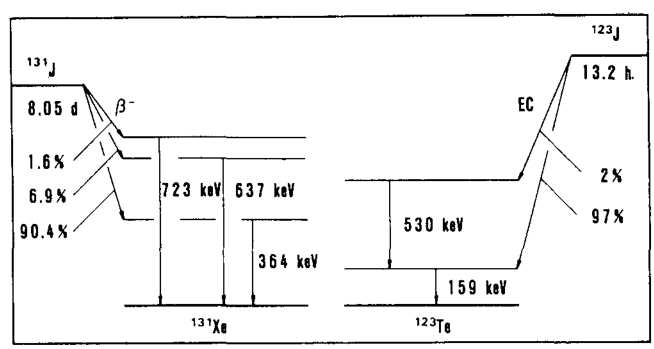

Fig. 1: Comparison of the physical properties between I-131 and I-123

types of gas target	target material	produced isotopes	removal from target
A	solid	gaseous	sweeping
B	gaseous	gaseous	sweeping
C	gaseous	solid	washing

Table 1: Different types of gas targets for the production of radioisotopes

The target windows can be sealed either by O-ring or welding. This depends on the particular boundary conditions like cooling, temperature, pressure and radiation effects.
For routine (daily) and reliable production a microprocessor controlled system is absolutely necessary. Moreover a remote handling of window changes is mandatory to assure a reliable production regime and to prevent personnel from obtaining too high a radiation dose. An overview on targetry and target chemistry in research and commercial applications is presented in detail in references [2,3].

3. KIPROS

An example for a gas target arrangement (cat.C, table 1) for routine production is the Karlsruhe Iodine Production System KIPROS (fig.2)
This system provides ultra pure iodine-123 in large batch sizes (1 - 3 Ci in 6 h). The production process uses the following nuclear reaction: Xe-124(p,2n)Cs-123

$$\text{Cs123} \xrightarrow{5.9\ \text{min}} \text{Xe-123} \xrightarrow{2.08\ \text{h}} \text{I-123}$$

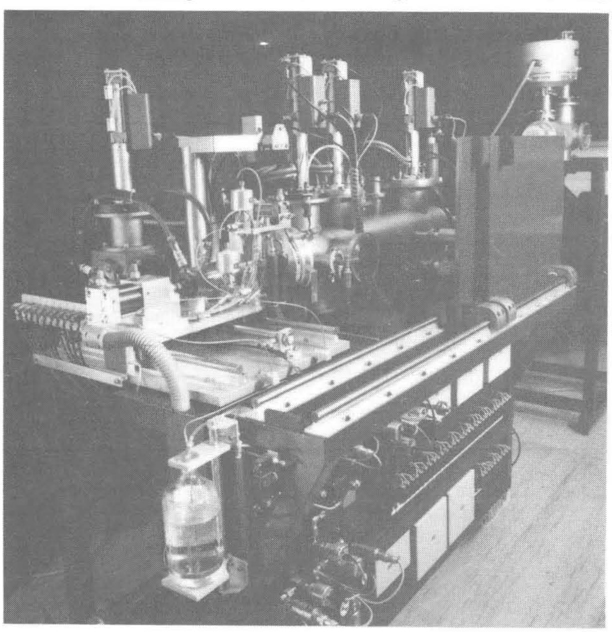

Fig. 2: High pressure gas target system KIPROS for the production of ultra pure I-123. A sophisticated beam diagnostic system in front of the target assures a proper alignement of the beam. KIPROS is completely operated with a Simatic S-135 microprocessor controller.

The Xe-124 gas as target material is highly enriched (> 99,8 %) which results in an ultra pure I-123 end product. According to measurements of the Physikalisch-Technische Bundesanstalt in Braunschweig (The German National Bureau of Standards) the impurity for I-125 and I-124 is 1.4×10^{-5} and 5×10^{-7}, respectively, at 24 hours after EOB.
KIPROS consists of a high pressure gas target, a sophisticated diagnostic system for proper adjustment of the beam onto the target and a chemistry unit for the delivery of I-123 as iodide in 0.02 n NaOH. The target body is made out of nickel-plated aluminium to reduce activation and radiochemical contaminations, and to assure proper cooling. The target is operated at a pressure of 14 bars with beam currents up to 50 microamperes. The production yield for I-123 with 30 MeV protons is 10 mCi/µAh.
To prevent gas losses in case of target window ruptures a dedicated safety system is provided. It consists of a safety chamber in front of the target and a fast closing valve (12 ms closing time) about 8 m upstream in the beam line. The target window can be changed remotely with a robot (fig. 3) within one minute, so that a foil rupture during irradiation does not considerably influence the production schedule. The KIPROS system is completely microprocessor-controlled via a SIMATIC S-135.

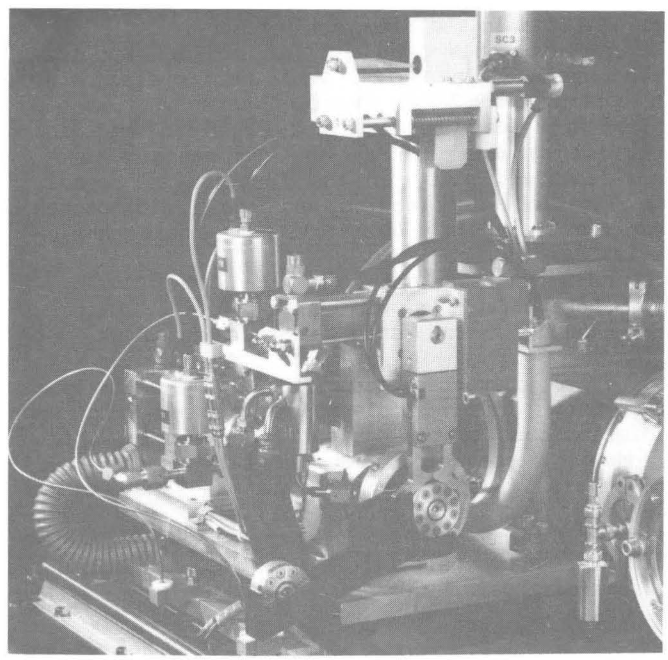

Fig. 3: Nickel-plated aluminium target with window flange in front. A robot changes automatically the target window in case of foil rupture. As part of the target volume there is a coldfinger for gas transfer from the storage vessel into the target (left side).

4. CHEMISTRY AND QUALITY CONTROL

The hardware configuration of the chemistry unit for the production of I-123 is shown in fig. 4.

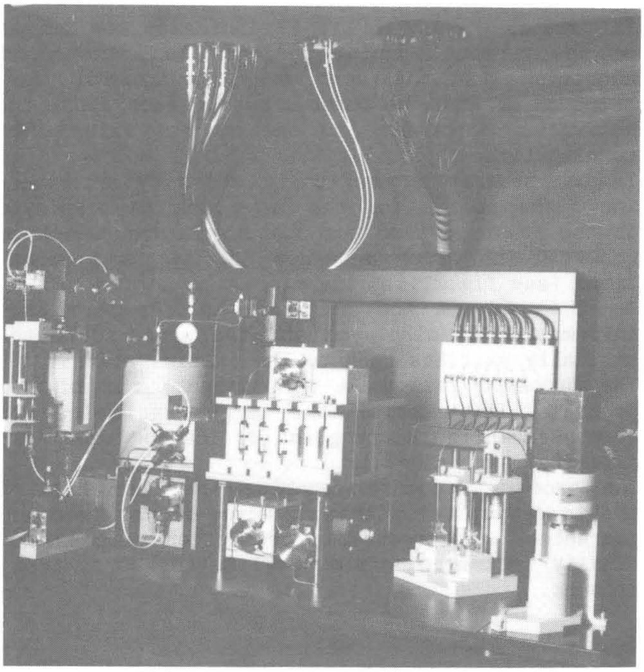

Fig. 4: Concentration unit for I-123 production

The flow diagram which illustrates the function o of the concentration process is shown in fig. 5. At the end of the target wash out procedure the active solution is purged from the target into the glass vessel inside the hot cell. An additional vacuum vessel traps the small amounts of radioactive gas coming from the target. The active solution is pumped through the ion exchanger column. The operator can select between three columns to make the process more variable and to avoid a column replacement in case of a failure during the process runs.
Bio Rex 5 is used as column resin with an absorption efficiency > 99 %.
After the loading procedure the I-123 is eluted with 0.02 n NaOH from the column into the glass vial. The flow direction through the column during the elution process is opposite to the loading direction.

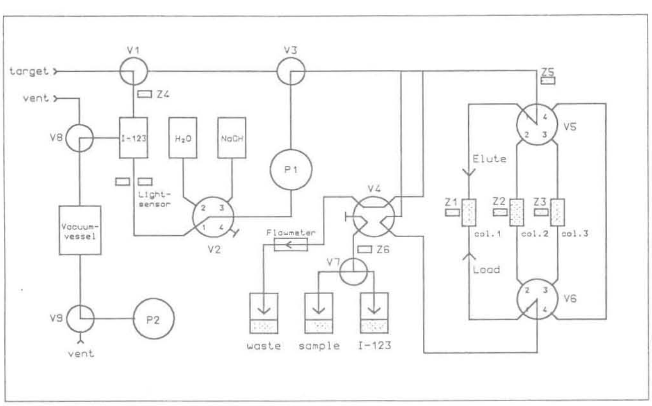

Fig.5: Flow diagram of I-123 concentration unit

The chromatography pump keeps the flow rate constant, which can be preset before the loading or elution process starts. At the end of elution the main part of the activity (> 90%) is dissolved in a final process volume of > 1,6 ml of 0.02 n NaOH. The whole process from the beginning up to the point when the final product is inside the glass vial can be controlled either manually or fully automatically. Valves, pumps, cylinders, positions switches and sensors are connected to the processor (see part 5: control system). The activity is monitored with small GM sensors at a few positions to guarantee a reliable automatic process, which can be stopped in case of a system failure (for example: an accidental column breakthrough during the loading procedure). The configuration of the multiport valves enables to obtain different samples during the automatic run. The samples are used for the quality control.
The quality control includes tests for the product identity, the radionuclide purity, the radiochemical purity and the pyrogen concentration. The radionuclide purity is measured with a Ge-detector while the radiochemical purity is determined by the thin layer chromatography method.

5. CONTROL SYSTEM

The control system consists of the programmable controller type Simatic S5-135 U, the communication station with monitor and keyboard and the printer station (fig. 6). The controller crate contains the following modules necessary for the operation of the production process:

- Central processing unit (CPU) with a 16-bit microprocessor, internal memories, data organisation and an external memory for the user software
- Communication processor 525 for the process documentation which enables the data transfer of all the various process parameters to a printer station
- Communication processor 526 for the communication between the controller and the terminal. Process commands can be entered via a keyboard, while status information (for example: position of valve) and system messages are displayed on the monitor fig.7
- Analog input modules for the measurement of analog process values
- Digital input modules for the connection of status indication signals
- Digital output modules for the connection of switching components.

The user software for the sequential and logical run of the process is written in a special language, called "STEP 5", which is optimized for the S5 Simatic controllers. The user software for the communication processors (CP 525 and CP 526) is written by entering values in the different masks which are created by the COM 525 and COM 526 system programs.
In case of using RAMs as external storage medium, the memory is buffered by a back-up battery in the central crate of the S5-135 U controller. The typical cycle time for the CPU is 3-100 msec, which depends on the user program volume.

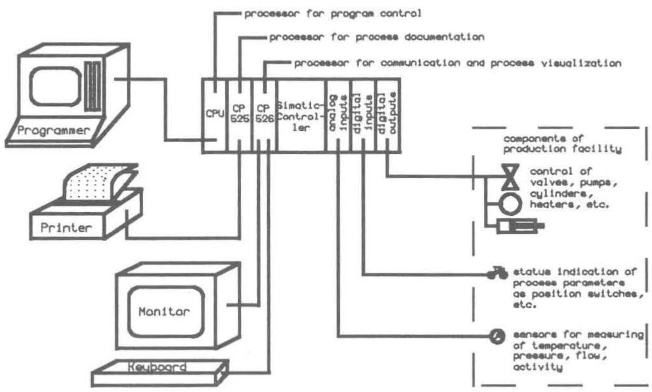

Fig.6: Configuration of the Gas Target Control System

The edition and the transfer of the user program to the processor modules are performed with the programmer unit S5-PG 685 which can also be used for an on-line test of a running programm.

Communication with the Control Processor

The following description illustrates the principle of the processor control und communication during a running program.
At the beginning of any operation the monitor usually displays the main screen with the main menu. The picture lists the possible operations including the programs which can be selected with the function keys of the keyboard. After pressing the function key to select a particular program, the appropriate picture of the program status is displayed.

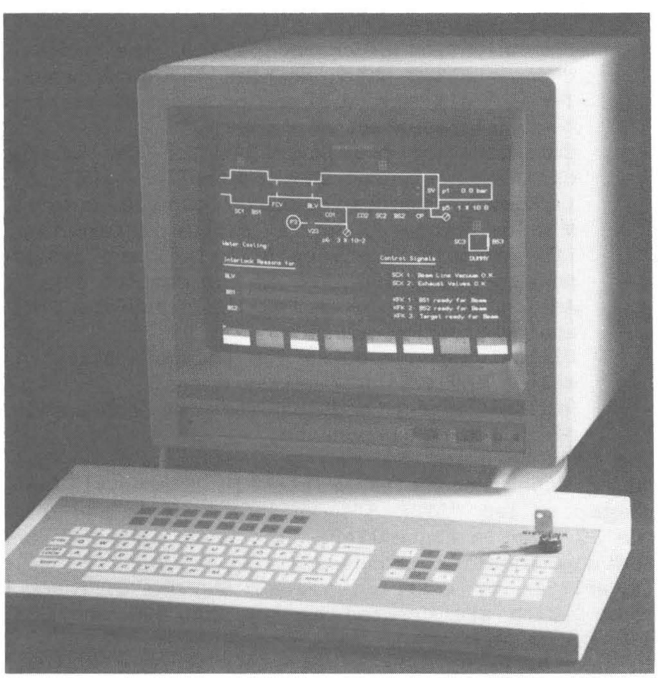

Fig. 7: Colour monitor with keyboard for the communication with the control processor

The status picture (fig. 7) indicates the number of the current running program step, the start condition for the next step, a general description of what is carried out in each step, the activated components and the current value of a running timer.
If the program automatically stops by an interlock, the reason for the interlock is displayed in the lower part of the status picture, which is reserved for error messages and system informations (see fig. 7).
At the end of the program the <Program End> information is displayed and the processor automatically switches back to the initial state.
The processor allows a simultaneous run of two programs. For example, the target system can be evacuated while the program for loading the I-123 activity is running.
The processor control enables the operation of the target system with a minimum of manpower and guarantees a reproducible production process and finally a reproducible quality of the final product.

6. CONCLUSION

The high pressure gas target system KIPROS is usable for highly-enriched target gases in particular, where it is necessary to minimize gas inventory and gas losses. This system is used e.g. for the production of ultra-pure I-123, Rb-81 and Br-77 [4] at different production facilities in Europe, USA and Japan. The appropriate choice of nuclear reaction adapted to a compact cyclotron (maximum energy 30 MeV protons) combined with a sophisticated technique and a microprocessor controlled process, guarantees a realiable and cost-effective production of radioisotopes with high yields and constant product quality.

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