Educational and Research Aspects of Homemade Modular PC-controlled Radiochemistry Systems for the Processing of Irradiated Electroplated Solid Cyclotron Targets

R. Adam-Rebeles [1], P. Van den Winkel [1], L. De Vis [1], R. Waegeneer [1]

[1] Vrije Universiteit Brussel, Cyclotron Laboratory, 1090 Brussels, Belgium

Email contact of main author: radamreb@vub.ac.be

Abstract. Homemade modular PC-controlled radiochemistry systems, used to separate the non-carrier added radionuclide of interest from irradiated electroplated solid cyclotron target layers such as ^{203}Tl, ^{67}Zn, ^{112}Cd and ^{64}Ni , illustrate that classical analytical separation and sampling techniques can be carried out remote-controlled with a minimized risk of operator errors within 1.5 hours, with excellent processing yields (> 90%) and resulting in chemical and radiochemical purity levels that meet the requirements of the Pharmacopoeia.

1. Introduction

Due to the rapid increase of the use of nuclear medicine techniques in modern clinical diagnosis and in a selected series of therapies, researchers' efforts are focused on the standardization and optimization of different production routes for a series of relevant radioisotopes such as ^{64}Cu, ^{67}Cu, ^{114m}In and ^{211}At.

Although a large part of the radioisotopes used in nuclear medicine is currently produced by neutron induced reactions, the increasing availability of the cyclotrons raises the conviction that some of these isotopes (e.g. ^{99}Mo, ^{99m}Tc) could be produced in acceptable quantities by charged particles induced reactions. Amongst others, the main advantage of charged particle activation is that it delivers a carrier free end product.

Nevertheless, the separation of target and activation products is required. Therefore classical analytical separation techniques such as selective dissolution of target layers, precipitation/co-precipitation and re-dissolution of precipitates, liquid extraction, ion exchange chromatography et cetera can be used.

Even if such techniques can be easily applied in a modern research laboratory, when dealing with highly radioactive materials special care should be taken of appropriate shielding to minimize the exposure risk of the staff. Therefore remote controlled and reliable radiochemistry systems must be developed. Moreover these systems should have a limited size (limited by the inner dimensions of the hot-cells) and should allow the safe introduction of target and reagents form outside the hot-cell. Last but not least, operator errors should excluded by the use of a sequential computer-controlled system of checks governed by appropriate software.

As the recently developed, home-made ^{111}In VUB radiochemistry system (^{111}In is produced by the threshold reaction ^{112}Cd(p,2n)^{111}In) includes all the aforementioned features, it will be presented in some detail in this presentation. It clearly demonstrates that a small cyclotron facility fitted with well-equipped electronic and mechanic workshops and having a limited staff (two chemists, one physicist, one mechanic and one electronic engineer) can realize appropriate radiochemistry systems. It should be mentioned that the sub-modules presented here are also used in radiochemistry systems for the preparation of non-carrier-added ^{201}Tl, ^{67}Ga and ^{64}Cu.

2. Homemade modular PC-controlled radiochemistry system for ^{111}In production

The control system for the ^{111}In-radiochemistry consists of a specific *Electromechanical Setup* and a common used *Control Unit*. Both units are connected by appropriate distribution cables (FIG.1).
The *Electromechanical Setup* includes two main parts, the *Manifold* (mounted inside a hotcell with appropriate shield thickness), an assembly of electromechanical components, that allows to carry out remote-controlled the physico-chemical steps required to separate the non-carrier-added (NCA) ^{111}In from the irradiated ^{112}Cd and an *External Panel* (mounted outside the hotcell) necessary to introduce safely the required chemicals into the Manifold.
The *Control Unit* is composed of two major parts: the *Electronic Interface* allowing the bi-directional non-galvanic transmission of signals between the Manifold / External Panel assembly and the *Personal Computer* (PC) loaded with the appropriate Visual Basic Software to generate the correct sequence of the commands required to perform the chemistry steps. Interactive processing is feasible using the PC Keybord, Mouse and the PC Monitor.

2.1. Manifold and External Panel

A *Manifold* (FIG.1) is an appropriate assembly of components such as receptacles, valves, relays, stirrers, micro switches, drop counters, conductivity transmitters, current comparators/detectors, potentiometers, peristaltic pumps, motors, ... mounted on a rectangular PVC parallellepipedum inside a hotcell and that can rotate over 360 degree. It contains the electromechanical units to perform physico-chemical processes such as stripping (dissolution unit), co-precipitation/filtration/re-dissolution, extraction and back-extraction and chromatographic separation. Moreover a volume monitor **(**to estimate accurately the volume of ^{111}In-bulk at the end of the chemistry**)** and a drop-counter **(**to sample an appropriate bulk volume to perform purity analysis**)** are included.

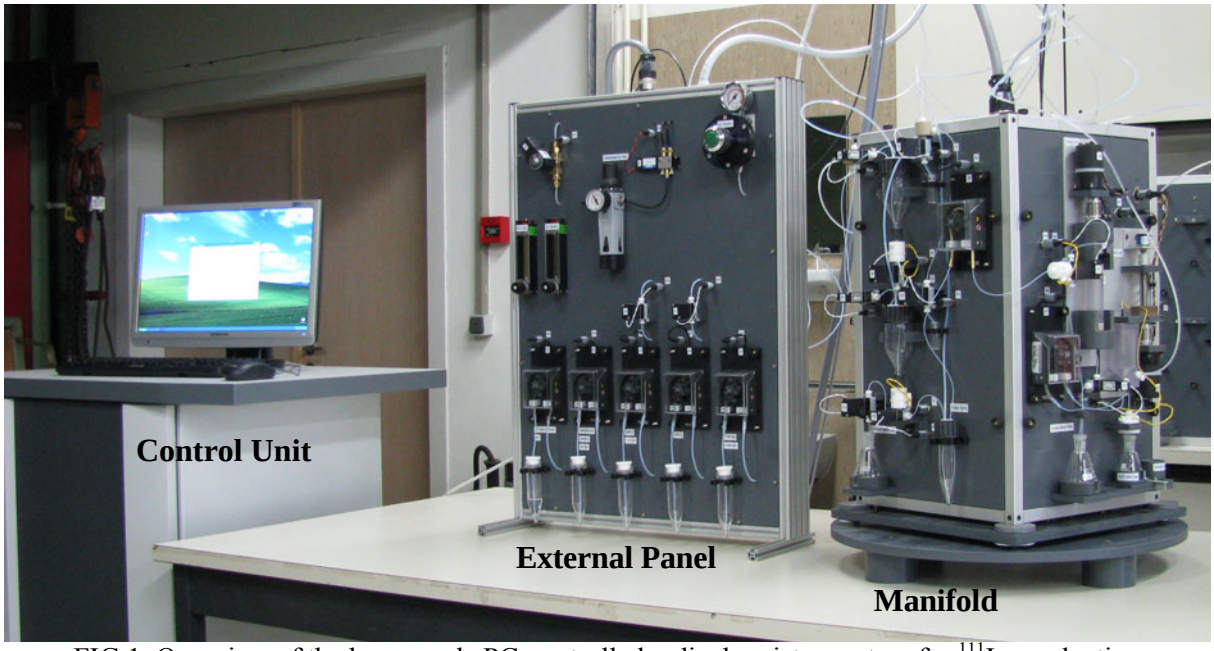

FIG 1. Overview of the homemade PC-controlled radiochemistry system for ^{111}In production

The *External Panel* (FIG.1) contains the vials, valves, flow-meters and pumps necessary for the safe transfer of the solvents, solutions and gasses into the manifold.

2.2. Electronic Interface and Control Software

The output signals from micro switches, conductivity sensors, volume measuring unit, drop counter et cetera on the Manifold/External Panel are collected by the *Electronic Interface* and converted to digital signals used as input to the control software in the computer (see FIG.2). By processing these inputs, taking into account the commands entered by the operator by means of the keyboard/mouse combination, the control software activates the proper pump, motor, valve, relay and so on to control the chemistry process. The outputs from the computer are also transmitted through the Electronic Interface and are converted to suitable signals to control the chemistry process elements. The electronic interface consists of electronic cards that provide the hardware interface between the digital/analog I/O cards (inside the computer) and the chemistry installation. Four different plugged-in digital/analog I/O cards are used as interface between the electronic interface and the computer.

The *Control Software* is the main controller that acts as an interface between the computer and the operator. The control system, in general, is a semi-automated one mostly using the operator commands to control the chemistry process. User messages, showing the present operation procedure and the current state of the chemistry process are displayed on a monitor. These messages guide the operator in issuing proper commands on the keyboard. The control software offers a menu-driven interface to the operator for a first selection to perform one of the radionuclides chemistries followed by a second pop-up menu allowing the selection of:

- the preparation of the ^{111}In system;
- the execution of the ^{111}In chemistry;
- the rinsing of the system after execution of the ^{111}In chemistry;
- the calibration of the volume measuring unit.

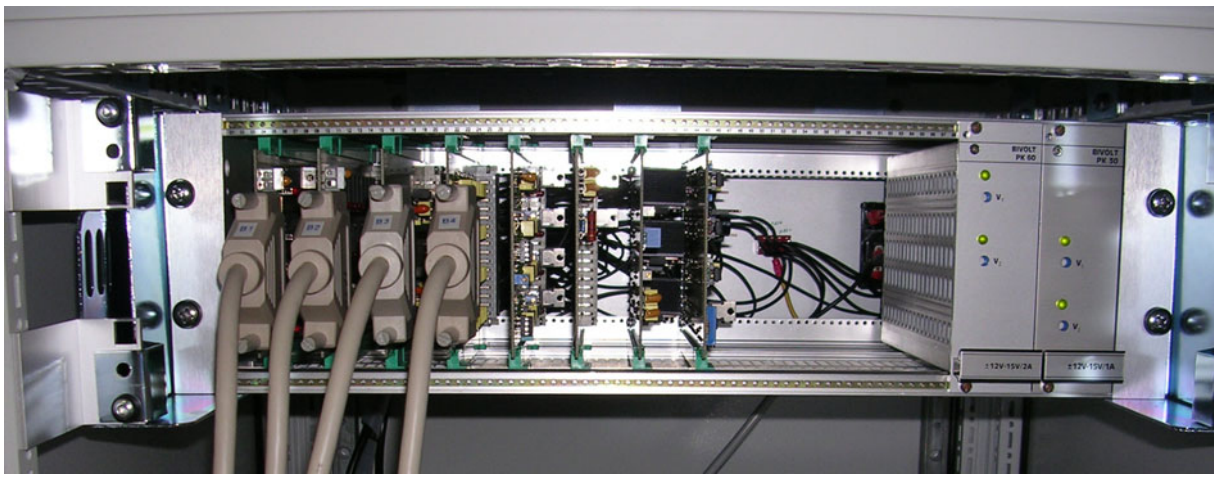

FIG.2 Electronic Interface

Each selection calls a specific Visual Basic project, which is visual to the operator by its main form on the screen: selecting an item in the menu bar of the main form gives access to appropriate pull-down menus in which each item selects one of the basic forms that executes a production step. The operator initiates and controls the production step by activating buttons on the basic form that calls functions and procedures from other Visual Basic modules to communicate with the manifold by digital input and output ports. The operator should follow a well-defined sequence from which he can deviate whenever it seems necessary.

3. ^{111}In separation radiochemistry

The chemistry involves the quasi-selective dissolution of enriched irradiated ^{112}Cd in diluted nitric acid followed by a three step separation/purification of non-carrier-added ^{111}In from enriched ^{112}Cd target material, from iron, copper and NCA zinc.

3.1. Dissolution of an irradiated ^{112}Cd-target

In general a copper carrier is used as a substrate for the target layer. At VUB the latter is produced by Constant Current AC Electro-plating (CCE) from alkaline ammonia solutions. Depending on the exit energy of the protons, reactions like ^{65}Cu(p,n)^{65}Zn may occur in the target carrier. Therefore, a compulsory demand is to minimize the quantity of copper solubilised together with the target layer. This can be achieved by using a flow through stripper.
The ^{112}Cd target layer is dissolved in diluted nitric acid solution containing trace amounts of Fe^{3+} as hydrated ferric nitrate. The diluted acid solution is pumped at low speed by means of a peristaltic pump through a non-heated flow-through stripper (FIG.3 a,b).

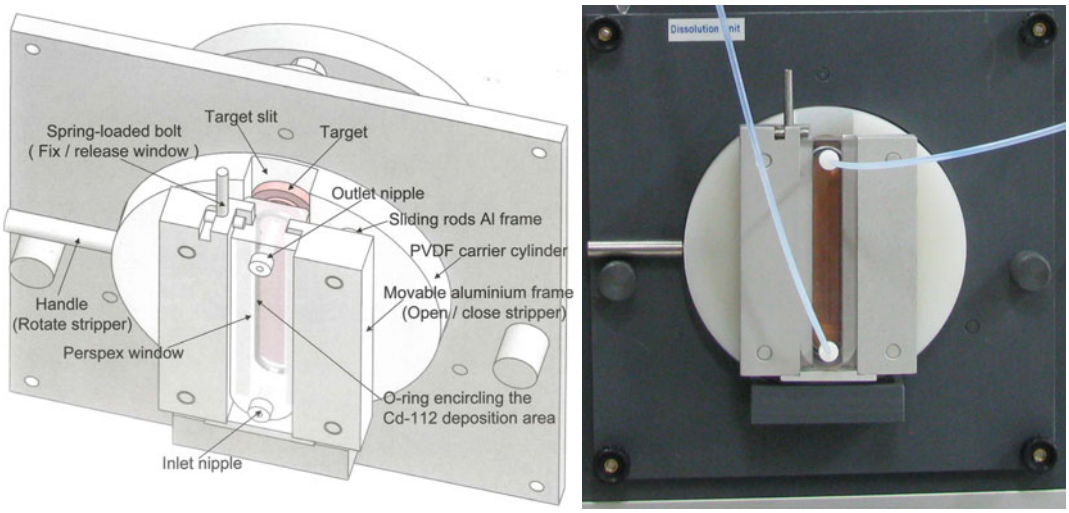

FIG.3 Flow through stripper. a) technical drawing (left) b) picture(right)

The cadmium and the non-carrier added ^{111}In do dissolve according the reactions:

$$Cd^0 - 2e \rightarrow Cd^{++}$$
$$2HNO_3 + 2e \rightarrow 2NO_3^- + 2H^0$$
$$2H^0 - 2e \rightarrow 2H^+$$
$$HNO_3 + 2H^+ + 2e \rightarrow HNO_2 + H_2O$$
$$Cd^0 + 3HNO_3 \rightarrow Cd(NO_3)_2 + HNO_2 + H_2O \quad (1)$$

Reaction (1) shows that the dissolution of cadmium in diluted nitric acid does not result in hydrogen gas evolution as the hydrogen in *statu nascendi* (H^0) is oxidized on its turn by nitric acid giving rise to nitrous acid. Near the end of the stripping process a few mg of the stripped copper target carrier are also dissolved. Hence, the stripping solution contains an excess of nitric acid, nitrous acid, ^{112}Cd as cadmium nitrate, mg amounts of iron and copper as nitrate, non-carrier added ^{111}In and some *NCA* ^{65}Zn formed in the copper target carrier during irradiation through threshold reaction ^{65}Cu(p,n)^{65}Zn.

3.2. Co-precipitation of NCA ^{111}In with $Fe(OH)_3$ and re-dissolution of the precipitate in HBr

The solution emerging from the flow-through stripper is pumped directly into a heated and stirred co-precipitation / filtration unit (FIG.4) filled with a mixture of 10 ml % NH_4OH and 2 ml 30% of hydrogen peroxide. The latter is added to ensure the iron to be present in the trivalent state.

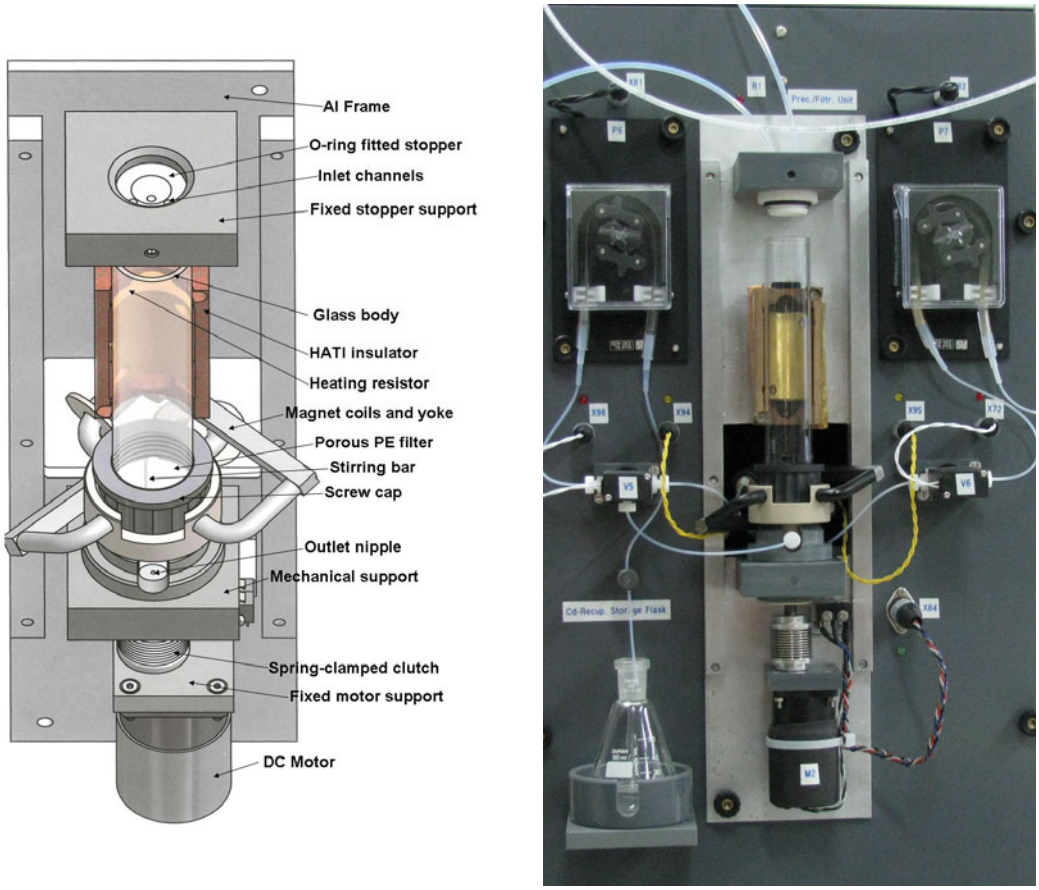

FIG.4 The co-precipitation / filtration unit a) technical drawing (left) b) picture (right)

The bottom of this unit is fitted with a 0.45µm HV filter supported by a porous PE membrane (35µm pores) and its outlet is closed by means of an electromagnetic 3 way valve. Co-precipitation of *NCA* $^{111}In^{3+}$ occurs according the reaction:

$$Fe(NO_3)_3 + 3NH_4OH + {}^{111}In^{3+} \rightarrow Fe(OH)_3.{}^{111}In^{3+} + 3NH_4NO_3 \quad (2)$$

Upon completion of reaction (2) the iron hydroxide precipitate is collected on the 0.45 µm filter of the co-precipitation / filtration unit by opening the outlet valve and pumping out the supernatant ammonia solution by means of a peristaltic pump (PP) into a ^{112}Cd recovery receptacle. Finally the precipitate is washed with hot 1% NH_4NO_3, pH > 9. From the combined filtrates in the ^{112}Cd recovery receptacle the enriched material will be recovered by Controlled Cathode Potential Electrolysis (CCPE) after a suitable decay time.
Next the precipitate is dissolved under stirring in three times using small amounts of 6 M HBr added by means of a peristaltic pump. After each HBr addition the resulting solution is transferred through the 3-way valve to a first extractor (FIG.3) by a PP. The precipitate and any trace of co-precipitated copper and zinc are solubilized by complex formation:

$$Fe(OH)_3 \cdot {}^{111}In^{3+} + 4HBr \rightarrow FeBr_4^- (+ {}^{111}InBr_4^-) + 3H_2O + H^+$$
$$Cu^{++} + HBr \rightarrow CuBr^+, CuBr_2 + H^+$$
$$^{65}Zn^{++} + HBr \rightarrow {}^{65}ZnBr^+, ZnBr_2 + H^+$$

3.3. Extraction of Fe^{3+} and In^{3+} into di-isopropylether from 6N HBr (separation of iron and indium from Cu and Zn)

To the combined HBr solutions in Extractor-1, 15 ml of di-isopropylether (DIPE) saturated with 6N HBr are added.(FIG. 5) Mixing of both phases is done by nitrogen bubbling followed by a short time delay to allow the separation of the phases. In 6N HBr the elements iron and indium are transferred for more than 90% into the organic phase (OP) by oxonium salt formation if the volumes of aqueous and organic phases are equal.[1]
Copper and zinc do not form stable oxonium salts from hydrobromic acid and thus remain in the aqueous phase (AP). Upon phase separation the aqueous HBr solution is transferred to Extractor-2 under gravity flow by opening the electromagnetic valve at the outlet of Extractor-1. The phase boundary is thereto detected by a mini-conductivity cell mounted at Extractor-1's outlet and associated feedback electronics. The extraction of iron and indium is repeated in Extractor-2 whereupon the aqueous HBr solution is transferred to the waste.

3.4. Back-Extraction of In^{3+} into 7.7N HCl (separation of iron and indium)

The separation of iron from indium is done by back-extraction of $^{111}In^{3+}$ with 7.7 N HCl where the volume distribution coefficient D_V for Fe^{3+} in HCl / DIPE is maximum.[2] At that hydrochloric acid normality and due to the low and comparable order of magnitude of the stability constants of bromide and chloride complexes of both elements ($K_{stab} \approx 10^2$) and the large excess of Cl^-, the bromide complexes are turned into chloride complexes:

$$FeBr_4^- + 4Cl^- \rightarrow FeCl_4^- + 4Br^-$$
$$^{111}InBr_4^- + 3Cl^- \rightarrow {}^{111}InCl^{++}, {}^{111}InCl_2^+, {}^{111}InCl_3 + 4Br^-$$

The anionic $FeCl_4^-$ forms again a stable oxonium salt with protonated DIPE and, as a result, remains in the organic phase while neutral or cationic indium-chloro complexes are transferred to the aqueous phase. The global exchange reaction can be represented as:

$$[(C_3H_7)_2 = OHFeBr_4]_{OP} + [4Cl^-]_{AP} \rightarrow [(C_3H_7)_2 = OHFeCl_4]_{OP} + [4Br^-]_{AP}$$
$$[(C_3H_7)_2 = OH{}^{111}InBr_4]_{OP} + [4Cl^-]_{AP} \rightarrow [(C_3H_7)_2 = OHCl]_{OP} + [{}^{111}InCl_3 + 4Br^-]_{AP}$$

Practically, the back-extraction is done by adding 10 ml 7.7 N HCl to Extractor-1, mixing and phase separation followed by transfer of the aqueous HCl phase containing the ^{111}In under gravity flow to Extractor-2. The back-extraction is repeated in Extractor-2 whereupon the HCl phase is transferred to a temporary storage vial. This two-step procedure is repeated with a second volume of 10 ml 7.7 N HCl that is also collected in the temporary storage vial. Next the DIPE phases are combined in Extractor 2 and transferred to the organic waste subsequently.
The residual DIPE present in the 20 ml 7.7 N HCl containing the ^{111}In in the temporary storage vial is removed by nitrogen flushing.

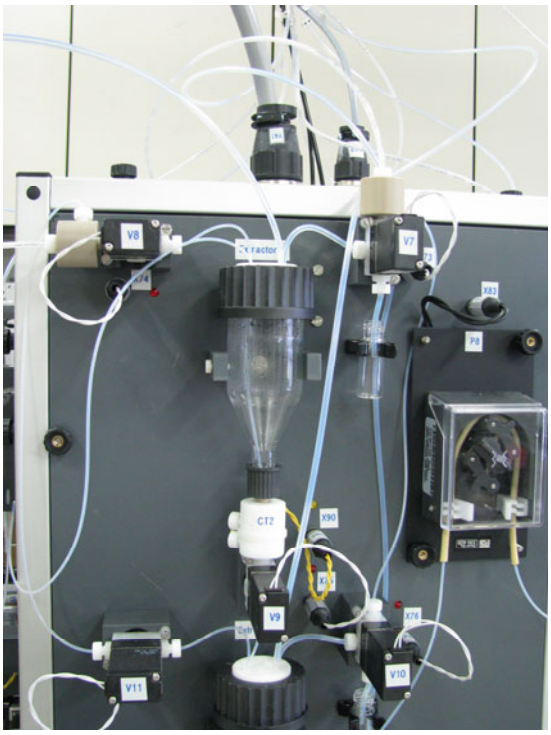

FIG.5 Picture of extractor unit

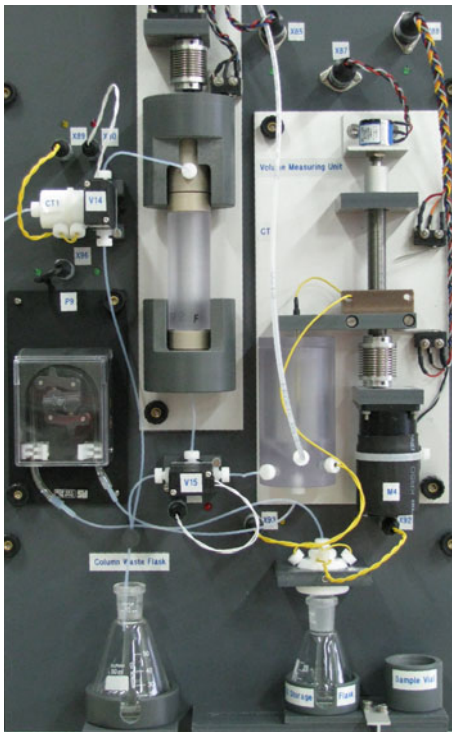

FIG.6 Picture of chromatographic column, volume measuring and drop counter assembly

3.5. Anion exchange chromatography

To reduce the normality of the ^{111}In bulk, the 7.7 N HCl solution collected in the temporary storage vial is applied to a chromatographic column packed with Dowex 1X8, 100 -300 mesh, Cl^- anion exchange beads pre-conditioned with 7.7 N HCl and carried by an porous PE filter disk mounted in the lower screw cap of the chromatographic column. The column setup is shown in FIG. 6. The PMMA column body is provided with two Teflon screw caps fitted with nipples carrying O-rings to ensure liquid tightness upon current-controlled clamping of the column into the column holders. Clamping is done by means of a motor-spindle combination compressing the spring-clamped clutch until the DC motor current reaches a preset cutoff value. The column inlet is provided with a 3 way valve as is the outlet (waste and bulk collection). The 20 ml 7.7 N HCl solution from the back-extraction procedure is applied to the column by means of a peristaltic pump operating at a low flow-rate. At this normality $^{111}In^{3+}$ is adsorbed by the resin according the reaction:

$$R\text{-}N(CH_3)_3{}^+Cl^- + {}^{111}InCl_3 \rightarrow R\text{-}N(CH_3)_3{}^{+111}InCl_4{}^-$$

The corresponding eluate is collected in the waste. The ^{111}In is eluted next by means of 20 ml 0.05 N HCl. Due to the interstitial volume of the column the final HCl concentration is estimated as being 0.5 N HCl. The ^{111}In containing eluate is collected in a volume monitor with a resolution of 50 µl. By means of a peristaltic pump a 4 drop sample from the volume monitor is collected in a sample vial and is used for multiple purity (chemical, radiochemical and radionuclidic) analysis and yield determination (FIG. 6). Both, the volume monitor and the drop-counter sampler are devices based on micro-conductivity measurements.

4. Conclusions

The experience gathered in the last decades in our laboratory allowed us to develop a set of compact, modular radiochemistry systems. The simplicity and interchangeability of the modules makes them attractive from the point of view of research for new isotopes of medical interest.
With a minimum change in the design of the systems, techniques such as precipitation, co-precipitation, liquid-liquid extraction and (ion exchange) chromatography, can be easily combined and applied for the separation of a variety of non-carrier-added radionuclides with an overall yield higher than 90% within 1.5 hour. On the other hand, most of the parts of the assemblies are home made and can be easily adapted whenever required, minimizing in that way the costs of development. The user friendly Visual Basic interface coupled up with the manifold/external panel assemblages via the home made electronic interfaces allows the full control over each step of the chemistry with a minimum risk of operator errors and of radiation exposure for the staff.
Although rather rare, minor hitches such as a defective valve or a broken pumping tube are stated. Repair or replacement of a defective item can be done during the preliminary check-up step which precedes every radiochemistry run.

References

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[2] DE CORTE, F., Activeringsanalyse van Sporenelementen in Silicium, PhD thesis, Institute of Nuclear Sciences, Ghent University, Belgium (1969)