A NEW CONCEPT FOR RADIONUCLIDE GENERATOR SYSTEMS

Bontchev G. D.¹, S. G. Bontcheva²

¹Dept. of Pharmacology, chemistry, biochemistry and biology, ²Dept. of Physics and biophysics, Medical University "Prof. P. Stoyanov" - Varna

Reviewed by: Assoc. Prof. M. Stancheva

ABSTRACT

Radiodiagnostic methods of nuclear medicine use short-lived isotopes for variety of imaging purposes. In medical centers these isotopes are produced commonly by special equipment, as known as "radionuclide generators". The radionuclide generated by them can be periodically extracted and, after simple chemical processing, used for appropriate medical application. In developed and commercially available radionuclide generators, the separation and extraction of isotopes is set up on the principles of forced column chromatography, i.e. by means of positive (or negative) pressure-driven elution. Although these sorption-type generators work fine and, in general, accomplish most of the requirements for medical application, yet another principle of generator’s construction appears to be also possible. In this paper a new concept for developing a generator system, in which the separation and extraction of radionuclides is carried out on an electrophoretic basis is discussed. Details such as construction possibility, theoretical motivation as well as expected effectiveness are considered. Some possible advantages, concerning radiopharmaceutical usage of proposed electrophoretic generators are outlined.

Key words: radionuclide generators, electrophoresis, nuclear medicine

INTRODUCTION

Radioisotopes are successfully used in nuclear medicine for many years. Generally, three main areas of their application could be clearly recognized: radioimmuno-assay, radiotherapy and radiodiagnostic.

Radioimmuno-assay (RIA) uses variety of radionuclides (Table 1) for different in-vitro biochemical analyses, based mostly on radiolabeling of biologically active molecules for tracing and detecting. It is highly popular, simple and effective technique: about 15 million radioimmuno-assays procedures are undertaken in Europe each year (7). Most important nuclide appears to be I-125, but role of beta emitters as H-3 and C-14 increases from some years now, because radiolabeling with hydrogen/carbon avoids introduction of heavy hetero-atom into sensitive biomolecules.

Radiotherapy exploits the fact that rapidly dividing cells are particularly sensitive to damage by radiation. For this reason, some cancerous growths can be controlled or eliminated by irradiating the area containing the growth. Extracorporeal irradiation (focused or hemi-body) can be managed by high energy gamma-beam from shielded and collimated Co-60 source. Nowadays linear accelerators as a source of high-energy X-rays are preferred for this purpose.

Table 1. Major isotopes used for radioimmuno-assay (RIA) /bold: most important/.

<table>
<thead>
<tr>
<th>Isotopes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3</td>
<td>Ca-47</td>
<td>In-111</td>
</tr>
<tr>
<td>C-14</td>
<td>Co-57</td>
<td>In-113m</td>
</tr>
<tr>
<td>Na-22</td>
<td>Co-58</td>
<td>I-125</td>
</tr>
<tr>
<td>P-32</td>
<td>Fe-59</td>
<td>I-131</td>
</tr>
<tr>
<td>S-35</td>
<td>Ga-67</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Major isotopes used for traditional radiotherapy /bold: most important/.

<table>
<thead>
<tr>
<th>Isotopes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P-32</td>
<td>Sn-117m</td>
<td>Ho-166</td>
</tr>
<tr>
<td>Co-60</td>
<td>I-125</td>
<td>Er-169</td>
</tr>
<tr>
<td>Cu-67</td>
<td>I-131</td>
<td>Yb-175</td>
</tr>
<tr>
<td>Sr-89</td>
<td>Pm-149</td>
<td>Lu-177</td>
</tr>
<tr>
<td>Y-90</td>
<td>Sm-153</td>
<td>Re-186</td>
</tr>
<tr>
<td>Pd-103</td>
<td>Dy-165</td>
<td>Re-188</td>
</tr>
<tr>
<td>In-111</td>
<td>Dy-166</td>
<td>Ir-192</td>
</tr>
</tbody>
</table>

Address for correspondence:
G. Bontchev, Dept. of Pharmacology, Chemistry, Biochemistry and Biology, Faculty of Dental Medicine, Medical University "Prof. P. Stoyanov" - Varna, 55 Marin Drinov Str., 9002-Varna, Bulgaria e-mail: bontchev@mu-varna.bg
though. *Intracorporeal* irradiation is administered by many forms – drugs, seed implants, needles, etc. Usually long-lived gamma and beta emitters are used (Table 2), although recently developed Targeted Alpha Therapy (TAT) appears to be very promising, especially for the control of dispersed cancers (Table 3).

**Table 3. Major isotopes used for Targeted Alpha Therapy (TAT)** /bold: most important/.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Product</th>
<th>Decay Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tb-149</td>
<td>Bi-213</td>
<td>202 keV</td>
</tr>
<tr>
<td>At-211</td>
<td>Ra-223</td>
<td>558 keV</td>
</tr>
<tr>
<td>Bi-212</td>
<td>Ac-225</td>
<td>161 keV</td>
</tr>
</tbody>
</table>

**Radiodiagnostic** uses the gamma rays emitted by some nuclides to make internal body organs and tissue visible in a manner similar to the way X-rays provide images of bones. The difference is that in radiodiagnostic procedures the source of radiation is located within the body. The nuclides (Table 4), linked to a specific chemical compound and introduced in patients (by injection, inhalation or orally) allows to screen the corresponding body zones in which this particular compound is naturally accumulated. The detector, known as “gamma camera”, builds up a 3D (or 3+1 D) image of the points from which radiation is emitted. This summarizes the Single Photon Emission Computed Tomography (SPECT).

**Table 4. Major isotopes used for Single Photon Emission Computed Tomography (SPECT)** /bold: most important/.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Product</th>
<th>Decay Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na-24</td>
<td>Gd-68</td>
<td>1275 keV</td>
</tr>
<tr>
<td>K-42</td>
<td>Se-75</td>
<td>93 keV</td>
</tr>
<tr>
<td>Cr-51</td>
<td>Kr-81m</td>
<td>356 keV</td>
</tr>
<tr>
<td>Fe-59</td>
<td>Te-99m</td>
<td>106 keV</td>
</tr>
<tr>
<td>Cu-64</td>
<td>In-111</td>
<td>490 keV</td>
</tr>
</tbody>
</table>

A more recent development is Positron Emission Tomography (PET) which is a more precise and sophisticated technique using cyclotron-produced isotopes (Table 5). It has been proven that PET is the most accurate non-invasive method of detecting and evaluating cancers. New procedures (PETCT) combine PET with computer assisted X-ray tomography (CT), enabling 30% better diagnosis than with traditional gamma camera alone (7).

**Materials and Methods**

An automatized device for horizontal zone electrophoresis in a free electrolyte was used for measuring ion mobility (3). The equipment as well as the methodic used allows determining the electrophoretic ion mobility with an unique relative error less than 0,5% (6). All of the experiments were done at the temperature (25,00 ± 0,05) °C and gradient of the electric field kept constant near 10 V.cm⁻¹. pH of the solutions was measured with an accuracy of 0,02 pH-units. Isotopes used in electromigration runs described in the present paper: \(^{111}\text{In} (T_{1/2}=2,83 \text{ d; E} = 171,3 \text{ keV (90,3%)}, \quad \text{245,4 keV (94,0%)})\), \(^{11}\text{Cd} (T_{1/2}=49 \text{ m; E} = 150,8 \text{ keV (29,1%)}, \quad \text{245,4 keV (94,0%)})\), \(^{89}\text{Zr} (T_{1/2}=83,4 \text{ d; E} = 392,9 \text{ keV (97,3%)})\) and \(^{176}\text{Hf} (T_{1/2}=70 \text{ d; E} = 89,4 \text{ keV (2,4%)}, \quad \text{343,4 keV (84%)}, \quad \text{433,0 keV (1,4%)})\) were produced at U-200 cyclotron (Flerov Laboratory of Nuclear Reactions, Dubna, Russia) via \((\alpha, \text{xn})\) reactions using 30-35 MeV \(\alpha\)-particles. Radionuclide species were concentrated and purified by means of ion-exchange chromatography (14). Chemical reagents: HClO₄, HNO₃, NaClO₃, KNO₃, NaOH, KOH, DTPA (diethilenetriaminepentaacetic acid) were of p.a. grade (in some cases – Merck®, Suprapur®). All solutions were prepared using bidistilled and deionized water.

**Results and Discussion**

Technically speaking, radionuclide generator systems are portable chemical separators. Mother isotope generates daughter isotope via spontaneous radioactive decay, forming in such a way a homogenous mixture. The main generator’s role is to separate obtained chemical entities; that is,
A new concept for radionuclide generator systems

to set apart daughter from mother nuclides. The separation procedure must be simple and effective one, as well as should ensure that mother isotope will remain within generator’s container. The generator’s construction itself must guarantee an efficient shielding from mother and daughter radioactive radiation.

When radiochemical equilibrium between the mother and daughter radioisotopes is established, the extraction procedure could be started: an appropriate eluant, e.g. pH-adjusted 0,9% NaCl, is forced through the system by means of positive pressure (syringe, attached to inlet) or negative pressure (evacuated vial, attached to outlet). Thus, daughter nuclide is washed out from the system and mixed with a specific kit (a chelating agent + buffer solution) to form as a result an injection-ready tracer. Mother nuclide remains within the generator and, in relatively short period of time, accumulates fresh amount of daughter isotope. In described procedure the separation of daughter from mother nuclides is taking place due to their different sorption behavior; that is why the generators organized on such principle are called “sorption-type” or “chromatographic type”.

Principles of new generators

During investigation on electrophoretic methods for separation, a new radionuclide generator concept has been raised. Proposed generators are based on principles of electrophoresis. Avoiding macroscopic fluid fluxes during work cycle ensures even further simplification of their construction (Fig. 2). Initially, a specific amount of mother radionuclide is dissolved in an appropriate electrolyte (chelating agent + buffer solution) and is encapsulated together with two elec-

### Table 6. Common radionuclide generators used in nuclear medicine.

<table>
<thead>
<tr>
<th>mother</th>
<th>half life</th>
<th>decay mode</th>
<th>daughter</th>
<th>half life</th>
<th>decay mode</th>
<th>terminator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-32</td>
<td>153 (19) y</td>
<td>β</td>
<td>P-32</td>
<td>14,262 (14)</td>
<td>β</td>
<td>S-32 (st)</td>
</tr>
<tr>
<td>Zn-62</td>
<td>9,186 (13) h</td>
<td>EC</td>
<td>Cu-62</td>
<td>9,67 (3) m</td>
<td>EC</td>
<td>Ni-62 (st)</td>
</tr>
<tr>
<td>Ni-66</td>
<td>54,6 (3) h</td>
<td>β</td>
<td>Cu-66</td>
<td>5,120 (14) m</td>
<td>β</td>
<td>Zn-66 (st)</td>
</tr>
<tr>
<td>Ge-68</td>
<td>270,95 (16) d</td>
<td>EC</td>
<td>Ga-68</td>
<td>67,71 (9) m</td>
<td>EC</td>
<td>Zn-68 (st)</td>
</tr>
<tr>
<td>Rb-81</td>
<td>4,570 (4) h</td>
<td>EC</td>
<td>Kr-81m</td>
<td>13,10 (3) s</td>
<td>IT</td>
<td>Kr-81 (*)</td>
</tr>
<tr>
<td>Sr-82</td>
<td>25,55 (15) d</td>
<td>EC</td>
<td>Rb-82</td>
<td>1,273 (2) m</td>
<td>EC</td>
<td>Kr-82 (st)</td>
</tr>
<tr>
<td>Sr-90</td>
<td>28,90 (3) y</td>
<td>β</td>
<td>Y-90</td>
<td>64,053 (20) h</td>
<td>β</td>
<td>Zr-90 (st)</td>
</tr>
<tr>
<td>Mo-99</td>
<td>65,94 (1) h</td>
<td>β</td>
<td>Te-99m</td>
<td>6,0058 (12) h</td>
<td>IT</td>
<td>Te-99 (*)</td>
</tr>
<tr>
<td>Sn-113</td>
<td>115,09 (3) d</td>
<td>EC</td>
<td>In-113m</td>
<td>99,476 (23) m</td>
<td>IT</td>
<td>In-113 (st)</td>
</tr>
<tr>
<td>Tc-132</td>
<td>3,204 (13) d</td>
<td>β</td>
<td>I-132</td>
<td>2,295 (13) h</td>
<td>β</td>
<td>Xe-132 (st)</td>
</tr>
<tr>
<td>W-188</td>
<td>69,78 (5) d</td>
<td>β</td>
<td>Re-188</td>
<td>17,003 (3) h</td>
<td>β</td>
<td>Os-188 (st)</td>
</tr>
<tr>
<td>Ac-225</td>
<td>10,0 (1) d</td>
<td>α</td>
<td>[Fr-221, α] ↓ [At-217, α] ↓ Bi-213</td>
<td>45,59 (6) m</td>
<td>β</td>
<td>[Po-213, α] ↓ [Pb-209, β] ↓ Bi-209 (st)</td>
</tr>
<tr>
<td>Th-227</td>
<td>18,68 (9) d</td>
<td>α</td>
<td>Ra-223</td>
<td>11,43 (5) d</td>
<td>α</td>
<td>[Rn-219, α] ↓ [Po-215, α] ↓ [Pb-211, β] ↓ [Bi-211, α] ↓ [Ti-207, β] ↓ Pb-207 (st)</td>
</tr>
</tbody>
</table>

DECAY MODES:
α = alpha-decay
β = beta-decay
EC = electron capture
IT = isomeric transition

SYMBOLS:
(st) = stable
(*) = half-life > 1.10^5 y
↓ = decays further

Principles of existing generators

At present time most of the generator systems, especially one’s used in nuclear medicine, are based on principles of chromatography. They feature a plane construction (Fig. 1) as well as simple maintenance. Initially, a specific amount of mother radionuclide is fixed onto inert (and usually) inorganic adsorbent, e.g. Al₂O₃, and the system is encapsulated within a shielded container.
trodes within a shielded container. When radiochemical equilibrium between the mother and daughter radioisotopes is established, the extraction procedure could be started: a high voltage current is switched on. Daughter nuclide migrates toward one of the electrodes and could be collected as already formed tracer. Mother nuclide migrates toward the other electrode, thus remains within the generator and, in relatively short period of time, accumulates fresh amount of daughter isotope. In described procedure the separation of daughter from mother nuclides is taking place due to their opposite electrophoretic behavior; that is why the generators organized on such principle should be called “mobility-type” or “electrophoretic type”.

Theoretical basis of new generators

However it should be boldly underlined that generators of electrophoretic type will properly work if only the electrolyte’s parameters are carefully chosen. That is, the experimental conditions must guarantee that mother nuclide’s and daughter nuclide’s chemical forms electromigrate in an opposite directions. Such a demand may look extremely complicated one but, in fact, it could be easily arranged in most cases, even when chemically very close species as Zr and Hf are concerned (5).

Kits used in nuclear medicine usually are chelating agents and represents a weak polyvalent acids of type H$_n$Y (e.g. EDTA, DTPA, NTA etc.). In aqueous solution they undergo multi-step dissociation, which we could express in summarized form as follows:

\[ \text{(1) } H_nY = nH^+ + Y^{n-} \]

Metal cations (e.g. mother nuclide) Me$^{m+}$ introduced in solution are engaged in complex formation process:

\[ \text{(2) } Me^{m+} + Y^{n-} \rightarrow [MeY]^{(n-m)-} \]

Conjugated chemical equilibriums (1) - (2) actually describe a competition between two cations (H$^+$ and Me$^{m+}$) for a ligand (Y$^{n-}$). This competition obviously could be manipulated by varying the proton concentration, i.e. adjusting pH of the solution. In other words, we do have a possibility to force the nuclide into positive- or negative-charged ionic form. If a second metal ion (e.g. daughter nuclide) M$^{k+}$ is introduced into solution, an additional equilibrium, equivalent of (2), is established. Depending on pH of electrolyte, this second ion will form positive (M$^{k+}$) or negative ([MY]$^{(n-k)-}$) charged species. However, stability constant of chelates [MeY] and [MY] in general are different, hence altering between cationic and anionic form for each of the nuclides will be occurred at individual pH values. Thus, in general, it is always possible to specify a pH region in which two given nuclides, mixed with a chelating agent, will form an opposite charged species and, consequently, in electric field will show contramigration.

Example

As an example, an investigation on In/Cd separation possibility along with the In/Cd separation itself could be demonstrated. It was shown (2) that in presence of DTPA In and Cd are represented by opposite charged ions ([In-DTPA]$^{2-}$ and Cd$^{2+}$, respectively) within a certain pH region. In order to prove this fact, two sets of experiments were set up. Each of them was aimed on investigation of ion (In, respectively Cd) mobility in presence of DTPA at different pH; all other experimental parameters (ionic strength, temperature etc.) were kept constant. Results for both In and Cd ion mobility are plotted on one graphic (Fig. 3) for comparison. It is clear that within area 1.0 < pH < 1.5 In and Cd species migrate in opposite directions.

After clarification of In/Cd separation’s condition, a final experiment was done. Into the electrophoretic tube, filled with an appropriate electrolyte, a trace amount of radioac-
tive In³⁺ and Cd²⁺ was introduced simultaneously. The
electromigration progress is presented on Fig. 4. At the be-

ginning, an united radioactive zone, containing homoge-
neous mixture of In and Cd species is observed. After some
12 minutes, due to the opposite electrophoretic behavior of
In and Cd in conditions cited, the corresponding zones are
visibly divided already. Twenty minutes later, two migrating
zones are detected at considerable distance from each

**Effectiveness, limits and comparison**

When considering the medical application of described
electrophoretic separation technique, some major questions
arise. Firstly, is it always possible to separate any given
couple mother/daughter by electrophoresis? The answer is:
“generally, yes”. Even the most chemically similar cations
show differences in their chelate’s stability, considerable
enough to ensure the existence of corresponding pH-region
of contramigration.

Secondly, is it always possible to use gathered solution for di-
rect in-vivo introduction? The answer is again: “generally,
yes”. Described technique has no requirements about salinity
of electrolyte. Separation procedure could be executed in
physiological solution, for example. The only parameter to
take care of is the pH. In the example given above (separation
of couple In/Cd) pH was chosen to be 1,00, which is too acidic
for direct injection. Therefore it is always possible to select
weaker chelating agent, so that pH-region of contramigration
shifts toward the neutral pH area.

And finally, how fast is the electrophoretic separation? Ob-
viously, it depends on type of the ions being separated and
gradient of electric field chosen. It could be shown that at
realistic 10 V.cm⁻¹ most ions (average mobility of 3.10⁻⁴
cm².V⁻¹.s⁻¹) will fully separate for about 90 seconds. In
worst case, when considering well-hydrated, large,
heavy-charged ions (mobility down to 1.10⁻⁵ cm².V⁻¹.s⁻¹)
separation will take less than 20 minutes.
There are some distinctive advantages of proposed new electrophoretic-type generators, which come to live when comparing with existing, chromatographic-type ones. Main advantages could be summarized as follows:

- Due to the migration in opposite directions, two nuclide forms naturally undergo 100% separation. Such effectiveness may not be reachable by chromatographic technique;
- In-vivo application could be done immediately after separation procedure. Daughter nuclide is already engaged in suitable complex, forming a ready tracer during the separation itself. No additional kits are required.
- There is zero chance to inject the patient with radioactive solution containing inappropriate form of the nuclide. That is, the separation will take place if only the target nuclide did take the desired complex form. There is no way to forget adding a kit or observe failure in post-separation nuclide-kit incorporation.
- Collected tracer contains the target radionuclide within relatively small volume, e.g. 1-2 ml. That is a welcome fact, because, from practical point of view, it is easier to maintain a high specific activity samples.
- However, some disadvantages of proposed technique should also be mentioned. At first, the method described is inappropriate for dealing with gaseous isotopes. Such a special cases do exist (e.g. the Rb-81/Kr-81m couple), yet are rare ones. At second, the end-user should have a high-voltage DC supply in his disposal. This type of laboratory equipment is relatively standard one though; moreover there are no special technical requirements.

**CONCLUSION**

The idea to use the electrophoresis in order to construct a radionuclide generator has been outlined for the first time. Investigation carried out has led to the conclusion that such a task is completely possible. The principles of electrophoretic separation conception have been discussed. It has been shown how to track down the optimal parameters of separation procedure. The existing (chromatographic type) generators, and new, proposed (electrophoretic type) ones have been schematically compared. It has been underlined that some advantages could be expected, such as achieving an extremely high separation rate, avoiding kit usage as well as ensuring the high specific activity of the tracer collected. Attention has been drawn upon the ease of maintenance (switch on – wait 5 min – get tracer) as well as the safety of product (zero chance for kit-nuclide engagement failure scenario).

**REFERENCES**


4. Filossofov D.V., Lebedev N.A., Novgorodov A.F., Bontchev G.D., Starodub G.Y., Production, concentration and deep purification of $^{111}$In

---

**Fig. 4.** Electrophoretic separation of In/Cd mixture at pH = 1.00. Analytical concentration of DTPA $3\times 10^{-5}$ M, ionic strength (perchlorate medium) 0.100 mol.l$^{-1}$, temperature 25.0 $^\circ$C, electric field gradient 10.0 V.cm$^{-1}$. 

![Electrophoretic separation of In/Cd mixture](image-url)
5. Ivanov P.I., Bozhikov G.A., Bontchev G.D., Milanov M.V., Maslov O.D., Dmitriev S.N.,
Electrophoretic separation of Zr(IV) and Hf(IV) ions. *JINR FLNR Scientific Reports 2001-2002 “Heavy Ion Physics”*, Dubna (2003), p. 175-176
