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Solid Phase Extraction - An Alternative to the Use of Rotary Evaporators for Solvent Removal in the Rapid Formulation of PET Radiopharmaceuticals

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Summary

Solid phase extraction (SPE) was used for the formulation of several radiopharmaceuticals. The method involves dilution of the previously purified HPLC compound with water, trapping of the activity on an SPE bed, washing off the support, elution of the radiopharmaceutical with a small volume of ethanol (< 1 mL) and dilution with sterile isotonic saline solution. Recovery of the radiopharmaceuticals was always higher than 97%. Two different methods of automation were developed for the formulation of [^{11}C] and [^{18}F]radiopharmaceuticals. In all cases, organic solvent levels in the injectable solution were below the recommended limits. This fast (3-6 min.) and easy to automate process can be considered as an alternative to the conventional methods (rotary evaporators).

Introduction

Preparation of radiopharmaceuticals from cyclotron-produced radionuclides is a complex process involving various steps starting from the direct in-target production of radionuclides. It includes the synthesis of the compound through a single or multi-step radiochemical pathway, the purification of the radioactive product, the formulation of the injectable solution and the quality controls. Because of the short half-lives of the radionuclides used in PET [^{15}O (T=2 min), ^{13}N(T= 10 min), ^{11}C (T=20 min), ^{18}F (T= 110min)] and of the radioactive decay throughout the procedure, time is an important constraint in the synthesis making, ^{15}O and ^{13}N not suitable for the labelling of complex radiopharmaceuticals. Furthermore, the overall synthesis time has a direct impact both on

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the amount of activity available for the PET studies and on the final specific activity of the radiopharmaceutical. These points are of prime importance as far as radiopharmaceuticals dedicated to human use are concerned.

Apart from some rare exceptions such as [^{18}F]FDG, most of the [^{11}C] and [^{18}F]labelled radiopharmaceuticals are purified by preparative HPLC (high performance liquid chromatography) methods. In this case, normal or reverse phases are used with appropriate mobile phases. Sometimes, the HPLC eluent is compatible with an injection to animals or humans (6-[^{18}F]fluorodopa and [^{11}C]methionine, for example). More often, formulation of radiopharmaceuticals dedicated to PET consist in a removal of organic solvent using a rotary evaporator under reduced pressure or an inert gas stream (1- 3). These evaporation techniques, frequently used for the formulation of short-lived radiopharmaceuticals, nevertheless present several drawbacks.

1) Volatile or heat sensitive molecules cannnot undergo the process safely. For example, radiopharmaceuticals labelled with high specific activity such as [^{18}F]altanserin are very sensitive to radiolytic decomposition when submitted to such a procedure (4),

2) Resolubilisation of the dry residue requires the use of ethanol, mixture of propylene glycol/ethanol or other organic solvent (2,3,5). As removal of the HPLC buffer salts used in the final HPLC purification cannot be done with rotary evaporation, the choice of the HPLC buffer salt is restricted to a few cations and anions. Futhermore, the presence of these salts requires a very strict control of the solution isotonicity..

3) To avoid cross contamination between the different evaporations resulting from multiple radiopharmaceutical productions (e.g. [^{11}C]methylation), a careful cleaning of the rotary evaporator and a process validation are required. Moreover, the overall procedure is relatively slow and not very easy to automate.

Solid phase extraction (SPE) is a preparative technique frequently used to clean up a sample prior to analysis and/or further concentrate samples before analysis (6). In radiochemistry, the efficiency of the SPE process is so good that, in some cases, this simple and fast SPE method replaces the final HPLC purification (for example: 7-8). The SPE is also commonly used for the fast pre-purification of intermediate compounds in multi-step syntheses or for more specific utilisations like in [^{18}F]FDG preparation (9).

As an alternative to the rotary evaporation method, this paper presents the results obtained with the SPE approach for the formulation of different radiopharmaceuticals. Full experimental details for the formulation of [^{18}F]altanserin and of [^{11}C]flumazenil are provided as examples. Residual organic solvent levels in the injectable solutions for these two compounds and for other [^{11}C] and [^{18}F]radiopharmaceuticals, routinely synthesized in our laboratory, and formulated with the SPE technique are also presented. The SPE results are also compared with those of the evaporating method.

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Experimental

General

Methanol, acetonitrile, tetrahydrofuran, and all other high purity grade HPLC solvents were obtained from Acros. Absolute ethanol was from Riedel-deHaën. Sep Pak Vac tC_{18} cartridges (trifunctional, 200mg, 3mL) were purchased from Waters. Filtrations were performed with 0.22 μm Millex-GS units from Millipore.

Formulation of [^{11}C]flumazenil

[^{11}C]Flumazenil was purified at a flow rate of 4.5 mL/min on a semi preparative column with a mobile phase consisting of CH_3CN/0.006M H_3PO_4 (35/65). The six mL fraction collected from the C18 reversed phase column was diluted with water (30 mL; buffer vol 1, Figure 1) to reach a final concentration of organic modifier (acetonitrile) below 10%. After stirring, the homogenous solution was transfered (with pressure) to buffer vol 2 and passed through the tC_{18} Sep Pak Vac [previously activated with ethanol (5 mL) and water (5 mL)], the eluate being directed to the waste. In buffer vol 2, the liquid level was automatically detected with a conductivity probe which, before dryness, closes the two way valve after the Sep Pak. After two successive washings with saline (0.9% NaCl, 5 mL, directed to the waste), the [^{11}C]flumazenil was eluted with ethanol (1 mL) and driven to the final step which consisted of an aseptic dispensing process (described below). After dilution with 0.9% NaCl, the percentage of ethanol in the final solution was adjusted below 10% of volume.

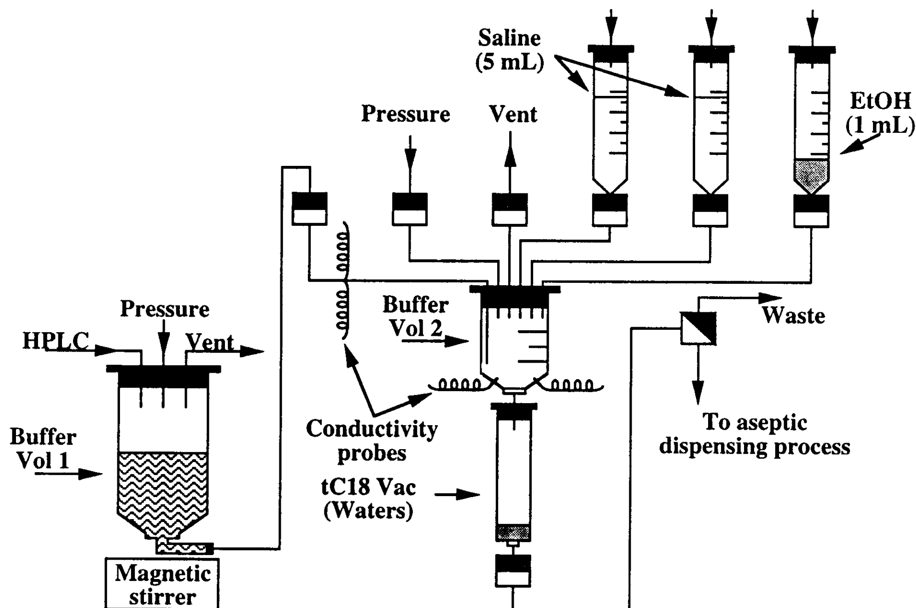

Figure 1: Remote controlled system used for the formulation of [^{11}C]flumazenil.

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Formulation of [^{18}F]altanserin

In this case, the column (Lichrosorb RP Select B- C8) was eluted at 16 mL/min with a mixture of CH_3OH/ THF/ 0.05 M NaOAc pH 5 (13/ 32/ 55) (4). The final formulation was conducted with SPE extraction on a robotic system (Zymate II Laboratory Robot, Zymark Corp.) as illustrated in Figure 2. All the operations were conducted by the « robot arm ». The HPLC fraction (15 mL) was diluted up to 100 mL with water and the entire volume transfered into a 100 mL syringe. The lid (pneumatically actuated) was closed and the solution pushed through the tC_{18} Sep Pak with a slight nitrogen flow. The liquid level was automatically detected by the conductivity probe. The SPE cartridge was washed twice with 0.9% NaCl / 0.1% ascorbic acid (20 mL) and [^{18}F]altanserin eluted with ethanol (600 µL). The eluate was then directed to the aseptic dispensing process including dilution with saline up to a final volume of 15 mL.

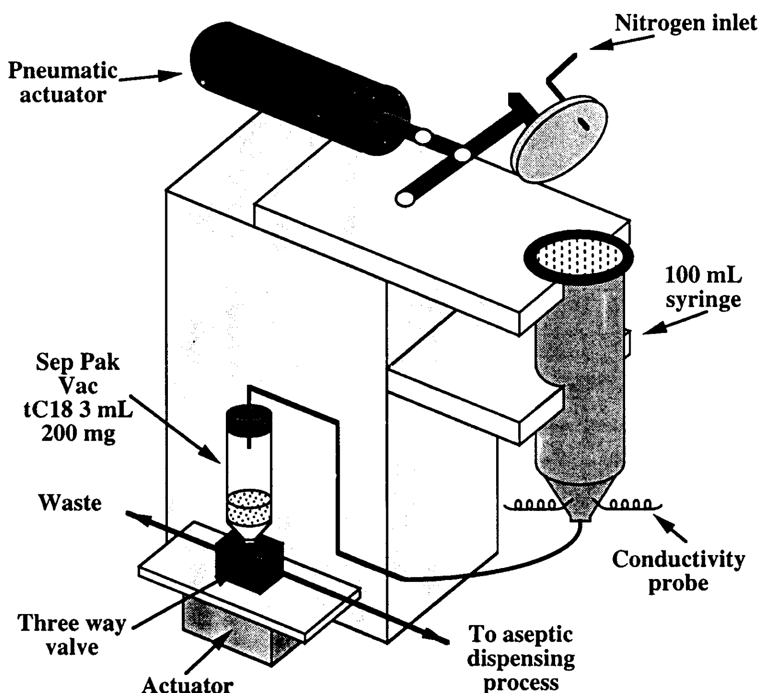

Figure 2: Final formulation station dedicated to SPE extraction on a Zymate II Laboratory Robot (Zymark Corp.)

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Aseptic dispensing process

The final solution was filtered first through a 0.22 μm filter and transfered into a single use container (a syringe without piston closed with the rubber head of the piston). This bulk solution, characterised by a low bioburden, was diluted with saline to reach a final ethanol concentration below 10% and finally underwent a second 0.22 μm filtration under a laminar flow of HEPA-filtered air.

Quantification of organic solvent residues

Residual solvent assays in the injectable solution were performed by gas chromatography (GC) analyses. Chromatographic separations were carried out on a Hewlett-Packard 5880 gas chromatograph equipped with a glass column (i.d. 2 mm, o.d. 1/4'', 6 ft) packed with 60-80 mesh Hayesep P (Alltech). The temperatures of the injector and FID detector were of 250 and 200°C respectively. Nitrogen gas was used as carrier at a flow rate of 30 mL/min. The column temperature was held at 80°C for 5 minutes and heated to 110°C at 30°C/min (gradient 1). Isocratic temperature was kept for 7 minutes and the oven heated again up to 170°C at 30°C/min (gradient 2). After 3 minutes, gradient 3 was applied (30°C/min, final value 190°C) and the final temperature kept for 8 min. Quality controls of the routine productions were realized by direct injection of an aliquot (3 μL) of the injectable solution sampled from the bulk solution after the first 0.22 μm filtration.

The GC system was calibrated for methanol, ethanol, acetonitrile, acetone, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide from direct injection of aqueous solutions (3 μL) containing concentrations of each solvent averaging between 0,03 and 3 mg/mL.

Discussion

Traditional liquid-solid extraction involves admixing a surface-active solid adsorbent with a sample solution. Sample components partition between the liquid and the solid phases. Sometimes, the desired component remains in the liquid phase; in other cases, the molecule of interest is removed with the solid via filtration. In the latter case, selective desorption leads to sample recovery. One of the principal advantages of liquid-solid extraction is that, by choosing suitably selective adsorbents, the partition equilibrium of specific sample components can be driven to effect nearly complete adsorption or desorption. This leads to a simple isolation process with promise of higher recoveries and greater enrichment of the desired compounds.

The use of solid adsorbents in the batch adsorption method (described above) still can lead to incomplete sample recovery and purification, due to unfavorable partition equilibria, insufficient sample capacity or liquid entrapment within the solid matrix. A better approach is the column adsorption mode of liquid-solid extraction which takes advantages of chromatographic principles. The term « solid-phase-extraction » usually abbreviated « SPE », has come to be applied to this mode of extraction.

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Today, to meet the broader sample preparation requirements, the sorbent beds are most often encapsulated in single use « mini column » that perform high recovery solid phase extraction. These SPE cartridges are available from different suppliers in a large variety of sizes (1 mL up to 60 mL) containing nominal weight of sorbents (30 mg up to 10 g) and designs for manual syringe procedure (pressure or vacuum assisted techniques) to automated protocols. Chromatographic sorbents which are surface modified are also available with different chemical selectivities (silica, florisil, alumina, diol, NH_2, CN, C_{18}, tC_{18}, C_8, C_2, tC_2, cylohexyl, phenyl, cation and anion exchange phases, ...) allowing the component of interest to be either retained or removed under very mild conditions. Each application should be considered with respect to chromatographic principles in order to drive the selection of the polarity of the sorbent, its amount and the volume of aqueous or organic phase required for the dilution.

The case of [^{11}C]flumazenil and [^{18}F]altanserin is presented in detail as examples of our experience in this field. [^{11}C]Flumazenil is a well-known radiopharmaceutical used to study the benzodiazepine receptors with PET. Its routine preparation relies on a conventional N-methylation with [^{11}C]iodomethane followed by a final HPLC purification on a C18 preparative column and a final evaporation step (10-12). In our laboratories, [^{11}C]flumazenil is prepared through the Suzuki *et al.* technique (10) and the final HPLC purification realized with a mobile phase consisting of acetonitrile and aqueous H_3PO_4 (see experimental part). The remote controlled system used for the final formulation is presented in Figure 1.

No-carrier-added [^{18}F]altanserin, a radiotracer used for mapping the 5-HT_2 serotonin receptors with PET (13), is prepared through a one step nucleophilic substitution reaction of the corresponding nitro precursor with [^{18}F]fluoride in dimethyl sufoxide (4). After labelling, this organic solvent is removed by fast SPE cleaning on a tC_{18} Sep Pak. The final purification of the [^{18}F]labelled compound from the starting nitro substrate is realized by HPLC on a C8 column with a mobile phase consisting of methanol , tetrahydrofuran, and aqueous acetate.

For the SPE formulation of these two radiopharmaceuticals, three basic steps after the column conditioning are concerned: application with retention of the sample (step A), washing of the support (step B) and elution of the purified labelled compound (step C). In order to optimise the radiopharmaceutical recovery, all these points were considered in detail.

Conditioning the adsorbent

Purifications of [^{11}C]flumazenil and of [^{18}F]altanserin, two lipophilic radiopharmaceuticals, were conducted by HPLC on a reversed phase column. As solid-phase-extraction follows the same analyte/sorbent interactions rules that govern HPLC, the same type of packing sorbent (C18) was selected for the SPE.

In the case of chemically modified silica supports, SPE sorbents can only function properly if the packing material surface is fully wetted. Solvation with an organic solvent e.g. acetonitrile or methanol is recommended prior to the conditioning of the adsorbent with water or buffer solution.

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This is the first necessary step for a reproducible adsorption of the analyte on the cartridge. In the scope of the final injection into animals or humans, the conditioning was realized with ethanol and water ([^{11}C]flumazenil). For [^{18}F]altanserin, which is very sensitive to radiolytic decomposition, the conditioning was realized with ethanol and saline containing 0.1% of ascorbic acid.

Application of the sample (step A)

The best way to load samples containing lipophilic compounds in a high organic solvent concentration [flumazenil (35%); altanserin (55%)] is to dilute them with water. The amount of water necessary for the dilution is related to both the volume collected from the HPLC and to the concentration of organic modifier in the HPLC eluent. As organic solvent concentration decreases, retention of the analytes increases exponentially. The dilution factor will depend on the polarity or lipophilicity of the compounds but for all the molecules presented here, an organic modifier concentration averaging between 5-10% afforded high sample extraction (step A, >98%). As high specific radioactivity [^{18}F]altanserin may be sensitive to radio-decomposition on the support, the same saline/ascorbic solution as for the conditioning was used for the dilution of the fraction collected from the HPLC. Pure water was used for the dilution of flumazenil.

Washing (step B)

The washing process was conducted twice with an equal volume of sterile - pyrogen free physiological saline (0.9%, 10-20 mL) or mixture of saline/ascorbic acid. With these small volumes of solution, all interfering residual HPLC solvents were removed from the surface of the cartridge. This point is discused in detail in the next part of this paper.

Elution of the purified labelled compound (step C)

In the final step of the solid-phase extraction process, the substance of interest should be desorbed with a suitable solvent and eluted. For our applications, the final elution was realized with a small volume of ethanol. Although parenteral solutions containing up to 50% of ethanol have been formulated, lower levels (5-10% v-v) are prefered (14). Such concentrations are easily reached after dilution up to 15 mL with 0.9% NaCl. Lower ethanol contents can also be achieved by eluting the SPE cartridges with a smaller volume of ethanol. This point was only optimized for altanserin which can be recovered quantitatively from the support with 600 μL of ethanol. Another alternative would be to trap all the activity on an SPE column containing a lower amount of sorbent (eg 50 or 100 mg). In this case the eluting volume of ethanol would be also reduced. This approach, which has not been investigated yet, would lead to less ethanol in the final injectable solution than with an automated mini rotary evaporator. Membranes impregnated with C18, silica or cation exchange particles incorporated or not into a syringe filter housing that fits on the end of the syringe are also available. These membranes with large cross sectional area increase sample throughput. They would also allow lower ethanol volume for the final elution.

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One could argue that for [^{11}C]flumazenil, the use of ethanol is dangerous because it is known to interact with central benzodiazepine (Bz) receptors. Although it was demonstrated that chronic alcohol consumption has multiple effects on the Bz receptor complex (15-17), the picture is rather different in the case of acute administration of ethanol. Farde and collaborators have shown with PET (positron emission tomography) and the radioligand [^{11}C]flumazenil, that in healthy humans, acute ingestion of alcohol did not alter total radioactivity uptake or specific [^{11}C]flumazenil binding (18). Furthermore, another study conducted in man with the same radioligand, demonstrated that the acute ingestion of 1.0 g/kg body weight of ethanol did not modify either total radioactivity uptake or specifically bound Bz receptor related radioactivity (19).

Usually, the injection of [^{11}C]flumazenil formulated with the SPE technique, results in an acute administration of less than 0.5 g of ethanol (5 mL injection and 10% v-v). For a 75 kg body mass, the dose is about 150 times lower than in the study of Pauli (19). From this point, it seems reasonable to estimate that the ethanol concentration arising from the SPE technique, is not a major issue. The efficiency of the different steps (A-C) involved in the formulation of [^{11}C]flumazenil and of [^{18}F]altanserin are presented in Table 1.

Results concerning the formulation of other lipophilic radiopharmaceuticals, which have also been purified by HPLC on a reverse phase column (C18) such as [^{11}C]raclopride, [^{11}C]deprenyl, [^{11}C]flumazenil, 4-[^{18}F]fluorotropapride or p-[^{18}F]MPPF, a new potential $5HT_{1A}$ antagonist (20) are also presented (Table 1).

From these results, it appears that the activity trapped on the support (step A) is very high for all the compounds; that no activity is lost during the washing process (step B) and that the activity recovered from the support with ethanol (step C) is almost quantitative. The overall formulation process required only three or six minutes (depending upon the dilution volume) using the remote

	n	Activity trapped (%) step A	Activity after washing (%) step B	Activity recovered (%) step C	Time (min)
[^{11}C]Flumazenil	30	> 98	97 ± 2	97 ± 2	3
[^{11}C]Raclopride	6	> 98	> 98	92 ± 2	6
[^{11}C]Deprenyl	4	> 98	> 98	96 ± 2	3
[^{18}F]Altanserin	20	> 98	> 98	97 ± 2	6
p-[^{18}F]MPPF	15	> 98	> 98	97 ± 2	6
4-[^{18}F]Fluoro tropapride	10	97 ± 2	97 ± 2	96 ± 3	6

Table 1. Results of radiopharmaceutical formulations using the SPE technique (tC_{18})
Step cumulative yields (corrected for decay %) are related to activity after HPLC (100%)

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controlled unit ([^{11}C]labeled molecules, Figure 1) and about six minutes with the robot ([^{18}F]labeled molecules, Figure 2). Both systems have been presented to show that different approaches can be successfully used for the automation of the radiopharmaceutical formulation relying on the SPE method. Space requirement for the automated formulation devices depicted in Figure 1, is similar to that required for a mini rotary evaporator. The robotic system described in Figure 2 is even more compact.

The major advantage presented by the SPE over evaporation is that the process can be fully conducted (from the end of the preparative HPLC up to the final filtration) under remote controlled conditions without hands on. One of the key point in the design of the automation device is the very reliable conductivity probe consisting of two small electrodes connected to a liquid level controller type « Multi-safe 91-12 » from Turck. The detection of the liquid levels is of prime importance because the reliability of the SPE process depends upon the fact that the SPE cartridges must not drained to dryness. For [^{18}F]altanserin preparation with very high specific activity (2 Ci/μmol), this point is critical, the compound being destroyed by radiolytic decomposition if the SPE cartridge reaches dryness after the trapping or during the washing processes.

At this point a major question had to be addressed: is the efficiency of the SPE formulation technique high enough and reliable enough to reach the tolerated limits for the organic solvent residues?

Although this topic can be a matter of active discussion, the acceptable organic solvent levels in injectable solutions of radiopharmaceuticals presented here are based on the maximum acceptable daily intake (ADI) reported by Gachon for a short-term administration (21). For methanol and tetrahydrofuran, the maximum acceptable intake for an injection of 10 mL is of 30 and 10 mg respectively. According to the same paper, dimethyl sulfoxide does not appear to be critical because of its low toxicity. The LD50 reported for administration of i.v. dimethyl sulfoxide is above 5 g/kg for rat and above 11 g/kg for monkey (22).

For acetonitrile, the current value proposed by the European Pharmacopoeia for an unique injection like in PET is 3.8 mg in the total injected volume (23). For dimethylformamide, the ADI is 6.7 mg/day for a 70 kg body mass. This value is issued from a proposal of the European Pharmacopoeia Commission dealing with guidelines for residual solvent levels in drug substances and excipients used for the preparation of pharmaceutical products (24).

The GC system was calibrated for seven solvents as described in the experimental section. The retention times obtained in these conditions are presented in Figure 3.

Although the GC system was calibrated for seven solvents only the results for the four directly implicated in the preparation of the considered radiopharmaceuticals are presented (Table 2). The quantification and detection limits measured with our GC system were in the range 0.1 to 0.03 mg/mL for each solvent respectively. Considering an injected volume of 10 mL, which is quite large for a PET radiopharmaceutical injection in humans, the detection limit of our system is 0.3 mg of

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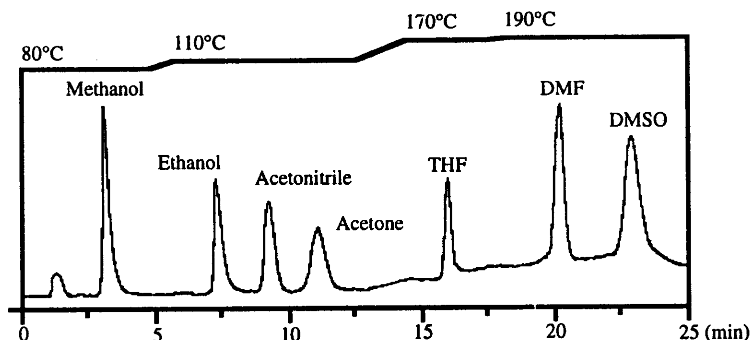

Figure 3: Separation obtained for a single injection (3 µL) of a water solution containing seven solvents (1 mg/mL each) with the GC system described.

residual solvent in the total injected volume. This value is at least tenfold below the acceptable intake reported. Although some positive measures were obtained (Table 2), the levels were consistently below the quantification limits.

		n	CH_3CN	THF	CH_3OH	DMF
Acceptable Intake (mg)			3.8 (#)	30 Daily ($)	10 Daily ($)	6.7 Daily (@)
Quantification limits (mg / mL)			0.1	0.1	0.1	0.1
Detection limits (mg / mL)			0.03	0.03	0.03	0.03
[^{11}C]Flumazenil	SPE	30	d (25)	nd	-	nd
[^{11}C]Flumazenil	Evap	5	0.25 ± 0.08	nd	-	nd
[^{11}C]Raclopride	SPE	1	d	nd	-	-
[^{11}C]Deprenyl	SPE	2	nd	-	d (1)	nd
[^{18}F]Altanserin	SPE	20	-	d (6)	d (7)	-
p-[^{18}F]MPPF	SPE	15	-	nd	nd	-
p-[^{18}F]MPPF	Evap	5	-	d (2)	nd	-
4-[^{18}F]Fluorotropapride	SPE	5	d (3)	nd	-	-

Table 2. Residual solvent levels in the injectable solution after formulation with SPE technique or with classical rotary evaporation (Evap).

d = detectable but below quantification limit (number in parentheses indicates the number of positive detections); nd = below the detection limit; « - » = not involved in the process; mg/mL means ± std.

(#): recommended limit for a single [^{18}F]FDG dose (23). ($): recommended limit for a 10 mL injection (21). (@): recommended limit for a body mass of 70 kg (22)

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The Table includes also the results obtained for the formulation of flumazenil and p-MPPF with the rotary evaporation technique. The final HPLC purification of p-MPPF is conducted under the same conditions as [^{18}F]altanserin (same solvents, 19). The evaporation process was performed under reduced pressure for two extra minutes after dryness (75°C, 15 mm Hg). The evaporation process took about 5 and 8 minutes for flumazenil and p-MPPF respectively. The first comment is that the evaporation procedure is slower than the SPE extraction but, the most important point is that in all cases, the concentration of acetonitrile remaining in the final solution of flumazenil is consistently around 0.25 mg/mL (n = 5). These results are a good illustration of the concrete improvement brought about by the SPE extraction method which is easy to automate and fast. These points are of prime importance as far as the highly radioactive short-lived radiopharmaceuticals are concerned. Furthermore, there is little chance for cross contamination since columns are used once and discarded.

Conclusions

In light of the results presented, it is quite clear that the SPE extraction technique can be considered as an interesting alternative to the classical evaporation procedure for the final formulation of radiopharmaceutical compounds labeled with short-lived cyclotron-produced positron emitters. The SPE formulation proceeds with high yield, allows mild treatment of volatile molecules and heat sensitive compounds. The process, which is fast and easy to automate, relies on the use of single-use materials, avoiding cross contaminations and complex cleaning procedures. Problems of redissolving the radioactive residues are avoided and the injectable solution presents low levels of organic solvents. Moreover, the flexibility of this approach gives the chemist the opportunity of using the best chromatographic conditions to conduct the final HPLC purification regardless of the toxicity of the salt present in the eluent.

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