

Minimization of the Amount of Kryptofix 2.2.2/KHC03 for Microscale Radiosynthesis of 18F-Labeled Probes

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| 著者 | Iwata R., Pascali C., Terasaki K., Ishikawa Y., Furumoto S., Yanai K. |
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VI. 2. Minimization of the Amount of Kryptofix 2.2.2/KHCO₃ for Microscale Radiosynthesis of ¹⁸F-Labeled Probes

Iwata R.¹, Pascali C.², Terasaki K.³, Ishikawa Y.¹, Furumoto S.¹, and Yanai K.⁴

¹Cyclotron and Radioisotope Center, Tohoku University

²Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

³Cyclotron Research Center, Iwate Medical University

⁴Graduate School of Medicine, Tohoku University

Nowadays the ¹⁸O(p,n)¹⁸F reaction on enriched [¹⁸O]water is widely used for the production of no-carrier-added [¹⁸F]fluoride ([¹⁸F]F⁻). The labeling use of this [¹⁸F]F⁻ requires a rapid and efficient separation and recovery from the target water mostly by the combined use of a disposable anion exchange cartridge Sep-Pak QMA (HCO₃⁻) and a Kryptofix 2.2.2-KHCO₃ complex (K.222/KHCO₃) dissolved in a mixture of water and acetonitrile (MeCN). Since the presence of water spoils the subsequent reaction of [¹⁸F]F⁻ in an aprotic solvent such as MeCN and DMSO, the eluate from the cartridge is usually evaporated to dryness by repeated azeotropic distillation. To avoid this laborious procedure two alternative methods were reported: an electrochemical concentration method¹⁾ and a minimalist approach²⁾. The former method is based on trapping [¹⁸F]F⁻ on the surface of a carbon electrode and releasing it into a small amount of dry MeCN or DMSO containing K.222/KHCO₃. The [¹⁸F]F⁻ ready for reaction is prepared in <100 μL within 6 min but the recovery yield of reactive [¹⁸F]F⁻ is unsatisfactorily low (<60%). On the other hand, the minimalist approach, which avoids repeated evaporations by applying a precursor in an “onium” form dissolved in dry methanol (MeOH) to the elution of [¹⁸F]F⁻ from the QMA cartridge, yields a recovery higher than 95%. MeOH can be then rapidly evaporated and a suitable aprotic solvent added to the residue for subsequent ¹⁸F-substitution. Weak point of this approach is the limited applicability since only few precursors are available in an “onium” form. Thus, based on this minimalist approach, we developed a more general method starting from the K.222/K[¹⁸F]F that can be applied to the radiosynthesis of various ¹⁸F-labeled probes while minimizing also the amount of K.222/KHCO₃ for microscale radiosynthesis (see next report).

A 1-1.5 mL portion of the diluted $[^{18}\text{F}]\text{F}^-$, which was produced in $[^{18}\text{O}]\text{H}_2\text{O}$ (98 atom%-enrichment, Taiyo Nippon Sanso) with the Cypris HM-12 cyclotron at CYRIC, was passed through either a silica-based anion exchange cartridge of Sep-Pak Plus Light QMA (HCO_3^- , 46 mg, Waters) or a polymer-based anion exchange cartridge of Oasis MAX (HCO_3^- , 10 mg, Waters). The cartridge was washed with dry MeCN or MeOH (2-3 mL) to remove water and the $[^{18}\text{F}]\text{F}^-$ was then eluted with K.222/ KHCO_3 in MeCN or MeOH (5-40 mM, 50-300 μL) followed by further rinse with MeOH (70 μL). Figure 1a clearly indicates that dry MeOH was a much better solvent than MeCN for eluting $[^{18}\text{F}]\text{F}^-$ from the cartridge with K.222/ KHCO_3 . As expected, higher concentrations of K.222/ KHCO_3 allowed for better elutions of $[^{18}\text{F}]\text{F}^-$ and Fig. 1b also shows that the relatively larger ion exchange capacity of QMA lowered the recovery yields than that of Oasis MAX. As expected, this difference in performance becomes even more critical at low concentrations or volumes. The minimum amount of K.222/ KHCO_3 -MeOH still affording a high recovery yield was determined as 40 mM-200 μL for QMA and 10 mM-200 μL for MAX (Fig. 1b).

Even such a small content of K.222/ KHCO_3 in 200 μL MeOH increases its concentration by >10 times up when the MeOH volume is reduced down to <20 μL . This high concentration may affect unfavorably the reaction as demonstrated in the synthesis of protected $[^{18}\text{F}]\text{FDG}$ (Fig. 2)³, where no relevant effect on the yield was observed between 10-80 mM whereas a rapid drop was registered at volumes leading to concentrations above 80 mM. For this reason, a practical method for efficient removal of K.222/ KHCO_3 had to be developed for microscale radiosynthesis of ^{18}F -labeled probes. Three commercially available cartridges of OASIS MCX (H^+ , 10mg), OASIS MCX (H^+ , 30 mg) and Sep-Pak Plus Light CM (H^+ , 130 mg) were examined to remove/decrease the K.222/ K^+ present in the MAX cartridge eluate. A cation exchange cartridge was connected to the MAX cartridge and the target content was passed through the two cartridges. After rinsing with MeOH (2 mL), $[^{18}\text{F}]\text{F}^-$ was eluted with a 20 mM K.222/ KHCO_3 -MeOH solution (200 μL) followed by MeOH (100 μL). Concentration of K.222/ K^+ in the eluate was semi-quantitatively estimated by color spot test and the intensity of its spot was compared with those of 10 standard solutions of known concentrations (0-20 mM) of K.222/ KHCO_3 in MeOH. As shown in Fig. 3, best results were obtained with Oasis MCX (30 mg; 30 μeq of cation exchange capacity). It retained the majority of K.222/ KHCO_3 , with less than 0.2 mM eluting into a reaction vial. The concentration of K.222/ KHCO_3 in the reaction solvent could be readjusted by adding an appropriate amount of a 20 mM K.222/ KHCO_3 -MeOH

solution to the eluate before MeOH evaporation.

In conclusion, the amount of K.222/KHCO₃ was successfully minimized for efficient recovery of [¹⁸F]F⁻ from the target water and readjusted for microscale radiosynthesis using the combined use of Oasis MAX and MCX disposable cartridges. The present results were published in *Applied Radiation & Isotopes*³⁾ and in part presented at 22nd International Symposium on Radiopharmaceutical Sciences, May 14-19, 2017 in Dresden (Germany).

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References

- 1) Saiki H, Iwata R, Nakanishi H, et al., *Appl Radiat isot* **68** (2010) 1703.
- 2) Richarz R, Krapf P, Zarrad F, et al., *Org Biomol Chem* **12** (2014) 8094.
- 3) Iwata R, Pascali C, Terasaki K, et al., *Appl Radiat Isot* **125** (2017) 113.

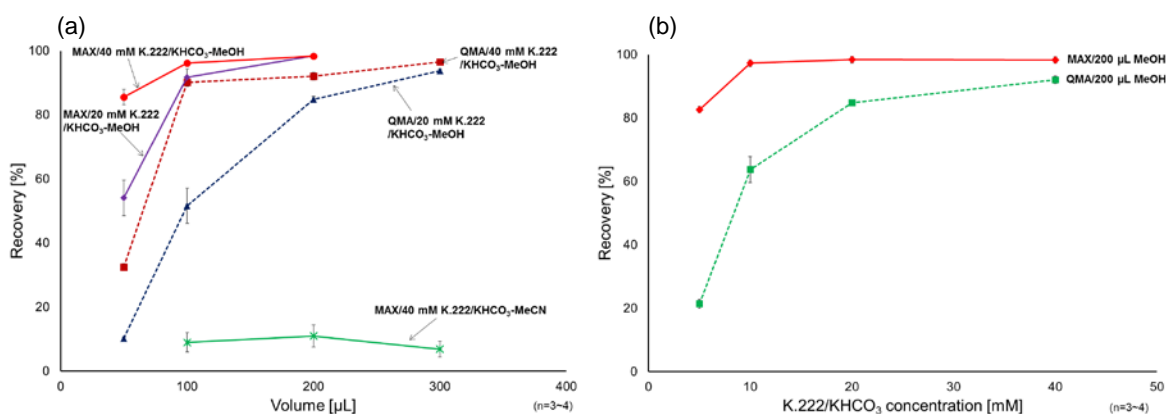


Figure 1. (a) [¹⁸F]Fluoride recovery yield from QMA and MAX cartridges vs a volume of K.222/KHCO₃-MeOH or K.222/KHCO₃-MeCN and (b) [¹⁸F]fluoride recovery yield from QMA and MAX cartridges vs a K.222/KHCO₃ concentration in MeOH.

