nm/PRELIMINARY NOTE

THE SYNTHESIS OF ^{18}F-5-FLUOROURACIL. VII.

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The method for the rapid synthesis of 5-fluorouracil-^{18}F is reported.

Heidelberger and coworkers first synthesized 5-fluorouracil (II) in 1957 (*1*). Subsequently it was shown that 5-fluorouracil decreased the growth rate of certain tumors (*2*). The study of the metabolism and mechanism of action of 5-fluorouracil by using the 2-^{14}C analog showed that either 5-fluorouracil or its radioactive metabolites localize to some extent in certain tumors (*3*). The medical value of 5-fluorouracil has recently received considerable documentation (*4,5*). This communication is the first report of a rapid method for labeling 5-fluorouracil with the short half-lived radioactive isotope ^{18}F.

For some time we have been preparing radiopharmaceuticals labeled with ^{18}F for evaluation as scanning agents for various organs (*6,7*). Interest in ^{18}F-5-fluorouracil is prompted by its potential as a tumor localization agent and the possibility that it might be useful as an in vivo drug dose agent (*8*). Until recently the known methods (*1*) for preparing this compound involved time-consuming procedures which could not be used to incorporate the 110-min half-life ^{18}F. However, Schuman and coworkers (*9,10*) recently reported a procedure for the direct fluorination of uracil using elemental fluorine. The development of a new method for synthesizing the required ^{18}F-F_2 intermediate, allowed the use of this method for the rapid synthesis of ^{18}F-5-fluorouracil. Since there is active interest in the general availability of ^{18}F-5-fluorouracil, we are reporting the salient features of the synthetic method at this time in order that interested parties can begin clinical investigations with this radiopharmaceutical.

MATERIALS AND METHODS

Preparation of ^{18}F-5-Fluorouracil. The target, consisting of neon (Matheson Research Grade) containing 7.6% (0.29 mmole) of fluorine scavenger, was irradiated with deuterons at the Brookhaven National Laboratory 60-in. cyclotron. The ^{18}F-labeled fluorine was produced from the ^{20}Ne(d,α)^{18}F nuclear reaction. The beam was degraded from 9.7 to 7.8 MeV in the target. Approximately 80–90% of the ^{18}F-F_2 produced was slowly purged from the target chamber (total time, 15 min) into the solution of 1.73 mg (0.0133 mmoles) of uracil in 0.3 ml of TFA at −10°C. The consumption of uracil was monitored by thin-layer chromatography (TLC). After all of the uracil had reacted, the solution was transferred to a sublimation tube using a minimum amount of TFA to wash the reaction vessel. This was blown to dryness with a stream of nitrogen and the residue sublimed at 210–215° (1 mm) to give 1.80 mg (90%) of crude ^{18}F-5-fluorouracil, mp 270–275° (dec) (Ref. *2*, mp 282–283°). The infrared and ultraviolet spectra were identical with authentic samples of 5-fluorouracil. The mass spectrum* showed m/e = 130. Radiochemical purity was determined by TLC Eastman Chromagram Sheet Silica Gel with ethyl acetate:acetone:water (70/40/5) as developing solvent (*11*). The TLC showed 1–5% of the total activity on the plate to be an impurity concentrated at the plate origin and the remainder in the 5-fluorouracil band. The impurity was removed by filtering a water solution (1 ml) of the sublimed material through a 0.5 × 3.5-cm column of Dowex

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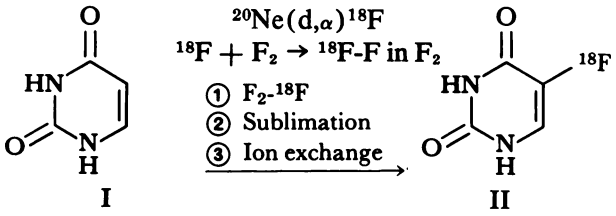
1-X-8 anion exchange resin (50–100 mesh; chloride form) followed by elution with 5 ml of water. This gave a 67% chemical yield of ^{18}F-5-fluorouracil in >99% purity. A second sublimation of (II) can also be used to improve its purity, but this is not as effective as ion exchange.

RESULTS AND DISCUSSION

The ^{20}Ne(d,α)^{18}F nuclear reaction is used to produce high specific activity, anhydrous ^{18}F-F_2. By purging the ^{18}F-fluorine through a solution of uracil (I) in trifluoroacetic acid (TFA), sublimation of the solvent free product, followed by passage of the sublimed material in water through an ion exchange resin results in the production of ^{18}F-5-fluorouracil (II) in 70% chemical yield in >99% purity (see experimental section), and in high specific activity. The sequence is depicted in the scheme



More than 40 experiments were performed with short cyclotron irradiations in order to optimize the chemical yield and purity of II. For example, an average of six experiments gave 5-fluorouracil at a specific activity of 64 ± 23 μCi/mg (per μA-hr) with a radiochemical yield of 17.5 ± 3%. The sublimation step serves both as a means of producing 5-fluorouracil from the initially formed unstable fluorine addition compound (*8*) and as a crude purification step. The ion exchange step removes other radioactive impurities (<5%) which probably result from overfluorination of uracil.

This convenient method can readily be used to provide about 1.5 mg ^{18}F-5-fluorouracil with specific activity of 1.1 mCi/mg at t_0. A 10.0 μA-hr irradiation suffices for ^{18}F production. The synthesis, purification, and delivery of the radiopharmaceutical requires only 35 min from the end of the cyclotron irradiation (t_0). The yield of the ^{18}F-5-fluorouracil represents an incorporation in II of 17.5% of the initial ^{18}F activity recoverable from the target*.

* % incorporation $= \frac{\text{total activity in II} \times 100}{\text{total activity}}$

$= \frac{\text{mg II} \times \mu\text{Ci/mg}(t_0) \times 2^a \times 100}{\text{total activity}}$,

where a is the statistical correction for ^{18}F-F_2 attack on uracil or on the solvent to form a reactive fluorinating species.

Therefore, the specific activity can probably be increased by at least a factor of 5, by (A) using a thicker target, thereby using a larger fraction of the (d,α) excitation function; (B) using a higher total irradiation dose; and (C) improving the radiochemical yield. Indeed the method can provide 5-fluorouracil-^{18}F in very high specific activity.

Details of the radiochemistry, targetry, methods, and precautions for handling radioactive ^{18}F, as well as the synthesis of other novel fluorinating agents, will be subsequently published. A complete evaluation of the parameters affecting the rapid (and kit) synthesis of ^{18}F-5-fluorouracil using ^{18}F-F_2 or ^{18}F-CF_3OF and a clinical evaluation of the compound are in progress.

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