

- The NanoTek Microfluidic Synthesis System is a modular microfluidic chemistry system with the ability to combine both microscale and macroscale process steps. Modular components give the user maximum flexibility for both discovery and clinical applications.

Simultaneous Preparation of Two C-11 Radiotracers, Raclopride and Dihydropyridazinone (DTBZ), on NanoTek® LF

Introduction

In this application note, we describe a method for the simultaneous preparation of the [C-11] radiotracers raclopride and dihydropyridazinone (DTBZ) from a single batch of [C-11] methyl iodide on the NanoTek LF. These experiments were conducted at the TRIUMF Cyclotron facility (Vancouver, BC) with the assistance of Salma Jivan and Thomas Ruth.

Equipment

NanoTek LF System
Version 1.3.2 Control Software
Reactor: 2 m X 100 µm (2)
TR-13 cyclotron

HPLC Analytical System

Waters 600E Multisolvant Delivery Unit consisting of controller and pump with a Waters 2487 dual wavelength absorbance detector.

Dihydropyridazinone Analysis

Waters Nova-Pak C18 4µm, 3.9x150mm P/N WAT086344
Solvent: 22:78 Acetonitrile/0.1M ammonium formate (0.5% acetic acid)
Flow: 1.0mL/min UV: 280nm

Raclopride Analysis

Waters Xterra RP18, 3.5µm, 3.0x100mm. P/N 186000420
Solvent: 37:63 Acetonitrile/5mM KH2PO4 (pH2.8)
Flow: 0.5mL/min UV: 214nm

Reagents

Desmethyl Raclopride (ABX)
DTBZ Precursor (ABX)
Dimethyl Sulfoxide, anhydrous (Acros)
5N Sodium Hydroxide (Fisher)
Acetonitrile, anhydrous (Acros)
Tetrabutyl ammonium fluoride (Sigma-Aldrich)
C-11 Methyl iodide (prepared from "in-target" methane using a "in-house" methyl iodide system) and trapped in ~250 µl of acetonitrile.

Results and Discussion

The optimum conditions for each of the radiotracers was determined by running each compound in the Discovery Mode through the reactor. The systems were optimized for temperature and flow rate through the reactors in Discovery Mode.

The synthesis of each radiotracer was optimized by determining which conditions would give the maximum radiochemical yield when corrected for radiochemical decay¹. For radiotracers with longer half lives this effect does not have a major impact. However, for isotopes such as C-11 this must be taken into account during the optimization process.

After optimization the instrument was modified to perform under dual batch mode conditions. In this modification, pumps 1 and 2, are independently plumbed and programmed to draw up methyl iodide, mix it with precursor, then push each combined solution through their own reactor (see Figure 2 for plumbing diagram). This mode of operation also allows different ratios of the methyl iodide to be apportioned to each precursor. In some tests 70% of the methyl iodide was used in the synthesis of [C-11]Raclopride and the remaining activity was used for the preparation of [C-11] DTBZ.

The initial conditions chosen for the synthesis of the two tracers, were 60 µl/min flow rate corresponding to a reactor residence time of approximately 15 seconds and a reactor temperature of 100 °C for DTBZ and 80 °C² for raclopride.

Reaction conditions were optimized for reaction yield by changing reaction temperature and precursor concentration. The results are shown in Tables 1 and 2, and a sample of the analytical HPLC trace of the two tracers is shown in Figure 1.

Conclusions

The NanoTek LF system is capable of simultaneously preparing two [C-11] radiotracers from a single batch of [C-11] methyl iodide. For raclopride, there seemed to be no effect on the radiochemical yield when 0.35 mg or ~0.7-0.8 mg of the desmethyl precursor was used, and the optimal reaction temperature was found to be 40 °C.

For DTBZ, there seemed to be no significant effect on the radiochemical yield when the amount of precursor was dropped from 0.7 mg to 0.05 mg per run. The best yields were obtained at a reactor temperature of 100 °C.



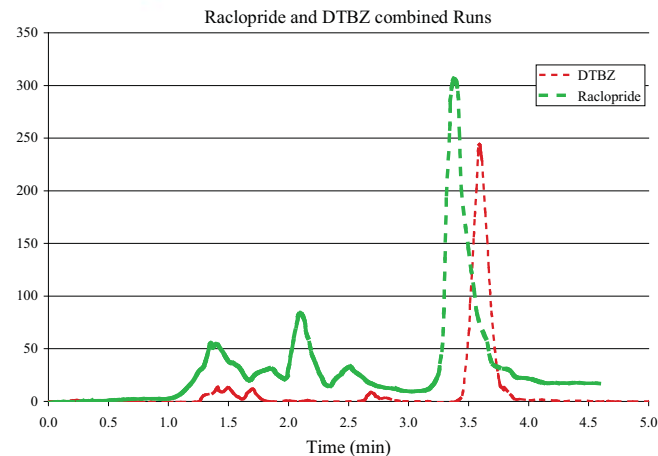
Table 1. Batch Production of Raclopride

Precursor (mg)	Temperature °C	%RCY of Raclopride
0.82	80	21.71
0.82	60	37.73
0.76	40	57.28
0.7	40	58.99
0.35	40	54.37

Table 2. Batch Production of DTBZ

Precursor (mg)	Temperature °C	%RCY of DTBZ
0.7	100	89.64
0.202	100	83.45
0.1	100	78.69
0.05	100	69.22

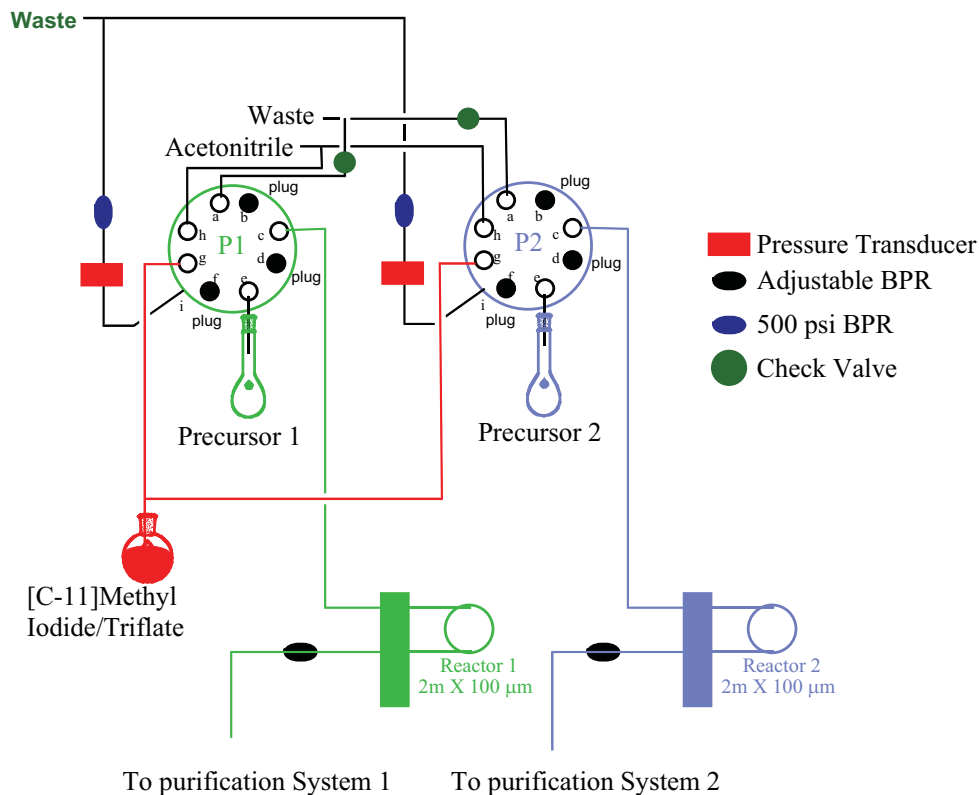
Figure 1: Analytical chromatograms of crude raclopride and DTBZ reactin mixtures



¹ Because we are dealing with short-lived isotopes, the optimum conditions for a reaction may not be those that yield the highest radiochemical yield because the time it takes to flow the entire solution through the reactor increases with increased residence time (slower flow rates). The yields must be corrected for radiochemical decay when determining the optimal conditions.

² Temperature conditions using the Discovery Mode started at 80 °C and was not tested at lower temperatures. During subsequent batch mode reactions, the optimum temperature was found to be 40 °C.

Figure 2: Plumbing diagram for dual [C-11] radiotracer synthesis.



Each of the reactors is set to the optimum temperature and backpressure settings for the radiotracers being prepared. Typically the backpressure regulator is adjusted to maintain a maximum system pressure of below 500 psi. By adjusting the volume of methyl iodide withdrawn by each pump the amount of methyl iodide sent to each reaction system may be tuned to amount of product desired or to the radiochemical yields of the reactions being performed.