The Design and Performance of a Portable Handheld $^{11}\text{CO}_2$ Delivery System

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Abstract (80 words max)

We constructed a hand-held device to efficiently trap [^{11}C]CO₂ from the cyclotron target, safely transport up to 3.7 GBq (100 mCi) doses to remote sites and release it without the need for a liquid cryogen. The system consists of a 180 watt furnace and a miniature molecular sieve trap (80 - 100 mg; 80-100 mesh 13X) placed inside a lead pig weighing 11.1 kg. The overall [^{11}C]CO₂ delivery efficiency of the device is ~ 82% (> 99% trapping efficiency). Radiation dose rates measured at 30 cm from the surface of the pig are < 43.5 $\mu\text{Sv/hr}$ (5 mR/hr) up to 2.59 GBq (70 mCi).

Highlights (85 characters max w/spaces each highlight - min 3)

- * A portable handheld [^{11}C]CO₂ delivery system suitable for 3.7 GBq was constructed
- * 90 mg of molecular sieves trap >99% of [^{11}C]CO₂ at room temperature at 1L / min
- * [^{11}C]CO₂ is released (90 s; 82% efficient) using a 180W tube furnace built into the pig

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1. Introduction

Carbon-11 labeled carbon dioxide ($[^{11}\text{C}]\text{CO}_2$) is conveniently produced by the $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ reaction on nitrogen gas targets using a charged particle accelerator such as a cyclotron (Christman et al., 1975). It is an important molecule used both by radiochemists as a precursor for synthesizing radiolabeled compounds of biological significance (Rotstein 2013), and by plant biologists as a radiotracer for studying the transport and allocation of ^{11}C -photoassimilate from recently fixed carbon in plants (Troughton, 1974; Jahnke, 1981; Minchin, 2003; Ferrieri, 2005; Babst, 2005; Kiser, 2008; Dirks, 2012). Because of the short half-life of carbon-11 ($t_{1/2} = 20.4$ min), the availability of $[^{11}\text{C}]\text{CO}_2$ to the scientific community is limited by the need for laboratories to be located at or near the accelerator facilities needed to produce carbon-11 (Schlyer, 2003; Qaim 2011). Even when laboratories are nearby radionuclide production facilities, the transport of $[^{11}\text{C}]\text{CO}_2$ across campus appears not to be common, presumably in part because of the technical constraints that arise when considering the design of a safe and convenient device for moving doses 0.37 GBq – 37 GBq (10 - 100 mCi) of radioactivity needed by researchers. A search of the literature finds few descriptions of such devices that could expand the application of $[^{11}\text{C}]\text{CO}_2$ in the plant sciences beyond the laboratory into the field, and bring $[^{11}\text{C}]\text{CO}_2$ into the laboratories of organic chemists who may have only limited access to shielded hot cells dedicated to large-scale production.

The most recent description of a transportation device for $[^{11}\text{C}]\text{CO}_2$ is more than 25 years old. In this work, McKinney and coworkers (McKinney, 1989) presented details of the design and performance of a movable (wheeled cart) system capable of transporting up to 37 GBq (1Ci) of activity. This device used liquid nitrogen to trap $[^{11}\text{C}]\text{CO}_2$ and incorporated a redundant valve system that minimized the chance that activity would leak if the cryogen evaporated during transport. The system was used routinely to ferry activity from an accelerator facility to a plant growth laboratory where administration of tracer was performed. This early work served as an excellent example of the utility and importance of transportation devices for $[^{11}\text{C}]\text{CO}_2$. The design of a smaller, more portable system for trapping and transporting has also been described (Clark, 1975), although no performance data or results using this device has been reported. In both previously reported systems, transported activity becomes volatile after the liquid cryogen in device evaporates. Although this design feature simplifies the release of radioactivity at the site of use, it does increase the chance that radioactivity could leak during transport.

The goal of this work was to design a simple device that could transport up to 3.7 GBq (100 mCi) of $[^{11}\text{C}]\text{CO}_2$ in a hand-held device without the need for liquid nitrogen. This device was developed to support plant imaging experiments at Brookhaven's clinical Positron Emission Tomography (PET) facility located ~ 100 meters from the cyclotron facility. The transport path includes a series of steps and stairs, and because of that a handheld system was preferred.

2. Materials and Methods

2.1 *Lead pig design*

A cylindrical lead pig with handle and dimensions of 177 mm height x 86.8 mm outside diameter x 36 mm inside diameter was modified as shown in Figure 1 to accommodate a screw top lid and a bracket for electrical and plumbing connections. The threaded plastic collar and screw-top lid from a Biodex (Shirley, NY, USA) PET Vial Pig (Part # 001-706) were adapted for use with the cylindrical pig. The inner dimensions of the Biodex pig did not provide sufficient space to be used directly. The threaded plastic shroud was removed from the Biodex pig and fastened to the base of the lead pig using 6 x 6-32 stainless steel machine screws. Previously the steel clad (3.175 mm thick) of the lead pig was drilled and tapped to accommodate the screws. In this manner the Biodex screw-top lid could be used with the larger lead pig. Two small notches were made in the top of the pig leading to a penetration in the plastic collar that provided access for tubing and electrical wiring to connectors mounted on a custom bracket (see Figure 1). A 1.5875 mm thick annulus of lead vinyl was used as a spacer between the bottom of the lid and the top of the pig to provide additional clearance for tubing and electrical wiring. A small “slice” of the annulus corresponding to the location of the notches in the pig for the electrical cabling and plumbing was removed. During assembly the screw-top lid was tightened just until the lead vinyl spacer was contacted.

An aluminum bracket was machined from 37 mm angle bracket stock and attached to the existing pig handle using two bolts (see Figure 1). The bracket provided space for mounting a thermocouple bulkhead connector (Omega, Stamford, CT; Part # RMJ-K-R) and an A/C power connector (www.digikey.com, CCM1402-ND) on the side, and 2 x Swagelok (Solon, OH, USA) 3.175 mm quick disconnect unions (stem: SS-QM2-S-200, bulkhead body: SS-QM2-B1-200) including 2 x Swagelok 1.5875 mm to 3.175 mm reducers (SS-100-R-2) mounted on the top. The total weight of the pig and bracket assembly is 11.1 kg.

2.2 *Molecular sieve trap and furnace construction*

Molecular sieve (90 - 120 mg; Aldrich 80/100 mesh 13X) was packed in a 50 mm length of 3.175 mm O.D. copper tubing that was bent in half to form a “U” shaped trap (see Figure 2). Quartz wool (~ 10 mm) was packed on top of the molecular sieve. A 3.175 mm to 1.5875 mm stainless steel reducing union (Swagelok part # SS-200-6-1) was used on each side of the “U” trap to join the end of the trap with 1.5875 mm stainless steel tubing that connected to the bracket-mounted quick disconnect.

A custom furnace was constructed by winding ~2250 mm of 27 gauge Kanthal (Hallstahammar, Sweden) wire (9.5 ohms/ft) around a 40 mm length x 17.5 mm O.D. x 11.1 mm outer diameter Alumina tube (McDanel Ceramics, Beaver Falls, PA; part # 98A310530) using a 1 mm pitch. During the winding, the furnace wire was also wrapped around a smaller Alumina cylinder 40 mm length x 2.39 mm I.D. 4.75 mm O.D (McDanel Ceramics part # AXS074130) that served as a housing for a type-K thermocouple (Omega, Stamford, CT. part # TJC36-CAIN-062U-2). The wire-wound cylinders were coated with Fiberfrax QF cement (Unifrax I LLC, Niagara Falls, NY) several times, allowing each coat to dry at room temperature overnight. After the final coat of Fiberfrax was applied and allowed to dry overnight, the furnace was connected to a temperature controller and heated gradually over a period of 10 hours to >300 °C.

Fiberfrax QF cement is an aluminosilicate ceramic fiber product used in high temperature (up to 1430 °C) insulation and sealing applications. Here it serves to hold in place and electrically insulate the furnace's wire windings. About 60 mm length of wire was electrically insulated with 1.5875 mm ID Teflon tubing and connected to the power connector mounted on the external bracket. The total resistance of the furnace was 70 ohms and delivered a maximum of 180 watts of power during heating when connected to line voltage (115 VAC) with a heat zone of ~ 36 mm. To regulate and display the temperature, the furnace and thermocouple wires were connected via the bracket-mounted connectors to an Omega model CN7533 temperature controller.

Figure 3 shows the assembled system ready for transportation of [^{11}C]CO₂. A small control box (230 x 130 x 50 mm) was constructed that housed the temperature controller, a power switch and electrical connectors. The operating furnace temperature was preset to 250 °C (on-off mode) and control was affected by operating the main power switch.

2.3 *Production of [^{11}C]CO₂*

[^{11}C]CO₂ was produced by irradiating a 150 mm long custom conical target (2.76 MPa [400 psi] 99.9999% pure N₂ with 760 ppm O₂) with 17 MeV protons using an EBCO TR-17/9 cyclotron. Cyclotron irradiations for all performance tests (below) were carried out until an integrated target dose of 32- 34 $\mu\text{A} \cdot \text{min}$ was reached. [^{11}C]CO₂ target gas was delivered through ~ 61 meters of 3.174 mm O.D. copper line and passed through a trap to remove nitrogen oxides from the gas stream (Tewson, 1989). The target gas flow was throttled by two preset, manually operated metering valves - one located near the cyclotron target, and the second located near the hot lab complex, about 50 m away from the target.

2.4 *Performance testing*

The gas flow rate through the molecular sieve trap was measured using a glass flow tube (Allborg, Orangeburg, NY; flow tube # 092-04) attached directly to the trap outlet and vented to atmosphere. Since the target flow is not regulated during unloading, flow measurements were recorded every 10 s for 5 minutes. Typically the target is depressurized for 30 s then re-pressurized with pure nitrogen to 2.07 MPa (300 psi) and expanded again into the 3.175 mm delivery line to move activity into the hot lab. This re-pressurization and expansion is repeated 3 times in total every 30 s until after the final pressurization the target is let to bleed down to near atmospheric pressure before being ready to reload for the next beam.

In one experiment using [^{11}C]CO₂, a Si PIN diode (PIN refers to an intrinsic semiconductor layer sandwiched between p-type and n-type semiconductor layers: Carroll Ramsey Associates, Inc, Berkeley, CA, USA; Standard Si PIN diode: 2.7 x 2.7 mm active element) was placed near the top of the portable trap (lid off) to detect activity accumulating in the portable trap during target unloading. The output of the pin diode was connected to a pre-amp (101HDC-3) whose output was connected to a data acquisition system (National Instruments Corporation, Austin, TX, USA; USB-6008). Data from the data acquisition system was displayed and recorded using a LabView program running on a personal computer. This data was used to determine a standardized time to unload the target through the portable trap.

The trapping efficiency of the portable delivery system was measured using a simple test system installed inside a shielded hood (see Figure 4). Activity trapped on the molecular sieve trap was not measured directly, but was determined by comparing results from portable trapping experiments with direct measurements of the total target [^{11}C]CO₂ using standardized target irradiation conditions. Trapping efficiency was determined by measuring the amount of [^{11}C]CO₂ activity that did not trap on the portable device, and comparing that value to the amount of [^{11}C]CO₂ activity trapped directly from the target using the same cyclotron irradiation dose (~ 33 $\mu\text{A} \cdot \text{min}$). The same soda lime trap (203.2 - 304.8 mm 10 mL syringe) was used to measure both the breakthrough activity for trapping experiments and the total target activity for direct unload measurements. The portable [^{11}C]CO₂ system was by-passed manually (see Figure 4) to allow direct measurements of total target activity. For all experiments a standard time of 4 minutes was allowed for target unloading, a time determined to be sufficient for complete unloading of the target under both conditions. Direct target unloading and portable [^{11}C]CO₂ trapping experiments were interleaved to minimize the variability of the activity produced and recovered from a standard 33 $\mu\text{A} \cdot \text{min}$ target irradiation. Each experiment was carried out 3 times and the results averaged for comparison.

The release efficiency was determined by comparing the activity released after heating the furnace to 250 °C to the activity trapped (see above) on the portable device. A slow flow (10 - 20 mL/min) of dried argon was introduced through the trap at the same time heating was started. This argon flow was directed through a soda lime trap sitting inside a Capintec Radioisotope Dose Calibrator CRC-15W (Capintec, Inc, Ramsey, NJ, USA) so that the activity released from the portable trap could be measured directly (see Figure 4). Argon flow was continued until the activity measured by the Capintec reached a maximum. In a separate experiment the maximum temperature rise of the lid of the pig was measured using a K-type thermocouple after heating for 10 minutes, a time much longer than needed for release of activity.

Prior to its first use the molecular sieve trap was conditioned for 1 hour by heating to 290 °C under dry argon flow (10 - 20 mL /min). The trap was cooled under the same argon flow for > 1 hour after 1 hour of heating. In between each trap and release experiment the molecular sieve trap was cooled under argon for 30 minutes, a time determined to bring the trap temperature < 30 °C.

The exposure rate ($\mu\text{Sv} / \text{hr}$) during transport of activity was measured after approximately 3.7 GBq (100 mCi) of activity was trapped using a portable ion chamber (Eberline: RO-20) meter.

2.5 *MicroPET imaging*

PET imaging was performed on the MicroPET R4 (Concorde Microsystems, Knoxville, TN) small animal scanner using a second molecular sieve trap of similar geometry to the portable trap. Imaging was carried out to visualize the spatial distribution of [^{11}C]CO₂ activity trapped on the molecular sieve in order to assess the feasibility of reducing the size of future portable devices and to better understand the trapping process. The molecular sieve imaging trap was made from a quartz tube (3.2 mm OD x 1.3 mm ID) and packed with 80 mg of 80/100 mesh

13X molecular sieve. The path length of the molecular sieve in the quartz tube was 67 mm, slightly longer than the path length of the portable trap due to the smaller tube inner diameter. Each end of the quartz tube was packed with ~ 20 mm of quartz wool and outfitted with low pressure, chemically inert fittings (1/4 - 28 thread) used to connect to target and argon gas plumbing. The quartz tube trap was conditioned using a suitable furnace for about 40 minutes under dried argon similar to the conditions described above.

[^{11}C] CO_2 for the imaging experiment was trapped directly from the target in a Capintec chamber using the conditions described above using a standardized 1 min target irradiation. The activity was allowed to decay to <37 MBq (1 mCi) before it was delivered to the MicroPET suite for imaging. The tube was positioned on the bed for imaging by aligning the upstream quartz wool / molecular sieve interface with the MicroPET laser. The bed was then moved under computer control to put the laser-aligned point at the center of the field of view. Image data was collected for 5 minutes and processed using the default MicroPET R4 parameters as detailed previously (Alexoff, 2003) with the exception that scatter correction was not done. Images were displayed and analyzed using ASIPro version 6.2.5 software (Concorde Microsystems).

In a second imaging experiment, the laser and bed systems of the MicroPET R4 were calibrated using a dual point source phantom made from [^{18}F]fluoride (~ 925 kBq [25 μCi] total) deposited on a plastic thin layer chromatographic plate. The F-18 phantom was also used to confirm the pixel size of the reconstructed images from which the penetration distance and distribution of the $^{11}\text{CO}_2$ activity on the molecular sieve trap was determined.

3. Results and Discussion

3.1 *Trapping and release efficiency*

The results from the flow testing experiments are shown in Figure 5. The presence of the portable [^{11}C] CO_2 system restricted flow and limited the maximum target unload flow rate to ~1500 mL / min, reached at about 2 minutes after the start of isotope delivery. Peak [^{11}C] CO_2 was reached at about the same time, demonstrating that most of the [^{11}C] CO_2 is trapped at flow rates 0.5 - 1.0 L / min. The trapping efficiency of [^{11}C] CO_2 under these conditions was determined to be 99.7 +/- 0.085 %. Quantitative trapping of [^{11}C] CO_2 at high flow rates (> 0.5 L / min) is routine using molecular sieves (Marazona et al., 1977, Dahl et al., 1993), whereas efficient trapping at high flow rates using liquid nitrogen only requires some optimization (Smith et al. 1991). McKinney et al. (1989) report using a significantly lower flow rate to trap of [^{11}C] CO_2 using their liquid nitrogen based transportation system. The release efficiency of the portable trap was determined to be 81.8 +/- 2.28 %. This efficiency for these experiments was somewhat lower than expected, but is similar to what has been reported (85%) by McKinney et al. (1989). Quantitative release of [^{11}C] CO_2 and $^{12}\text{CO}_2$ from aluminosilicate molecular sieves has been reported (Dahl et. al., 1993 - see discussion - and Bauer et al., 1992 respectively) using standard laboratory apparatus. Moch and coworkers (1995) also report nearly quantitative release of [^{11}C] CO_2 (>98%) using carbon molecular sieves, although 1 g of sieves was required for efficient trapping, and the apparatus was not part of a portable delivery system.

The total time to reach maximum activity after heating was ~ 2.5 min using 10 – 20 mL / min argon. This time includes the 40 s for the furnace to reach 250 °C and is comparable to processing times reported by Moch and coworkers (1995). For plant studies the portable transport system was flushed with 400 mL / min of air after the furnace reached release temperature. Under these conditions all of the activity was introduced to the plant leaf in ~40 s. The maximum temperature increase of the pig lid was measured to be 1.5 °C after 10 min of continuous heating with no gas flow. Even though it is normally not necessary to handle the pig during or immediately after heating, this measurement shows that no special precautions need to be taken when handling the assembled device.

In this work quantitative trapping of [^{11}C]CO₂ was achieved with only 90 mg of aluminosilicate molecular sieves, which is less than 1/3 the amount typically used in commercial automated production systems (for example Shao et al, 2011). This small amount permitted the compact trap design required to fit inside a hand-portable lead pig. Experiments to determine the minimum amount of molecular sieve were not carried out, but it is likely that significantly less molecular sieve is required for quantitative trapping, even at these high flow rates. The capacity of molecular sieves (8 - 12 mesh 13X) in competitive adsorption studies (15 % v/v CO₂ in nitrogen) has been reported to be 2 μmol /mg (Siriwardane, 2001). Since most C-11 targets yield < 0.1 μmol of total carbon (Rotstein, 2013), it is theoretically possible to reduce the amount of molecular sieves much further, although the flow rate used to measure 13X capacity for CO₂ during competitive adsorption was only 15 mL /min (Siriwardane, 2001).

To test the hypothesis that the mass of molecular sieves could be reduced further under high (~ 1000 mL / min) flow rates, we imaged the distribution of [^{11}C]CO₂ on a molecular sieve trap using MicroPET. The results depicted in Figure 6 strongly suggest that the molecular sieve amount could be lowered significantly under relevant gas flow conditions. As shown by the overlaid MicroPET image in Figure 6, all the C-11 activity adsorbs to the molecular sieve starting at 5 mm from the beginning of molecular sieve packing ending about 12 mm. A short, straight molecular sieve trap (~ 12 mm length) would be easy to shield for in-situ operation in a shielded chemistry hood, or could be incorporated into a more heavily shielded lead pig, permitting a larger amount of C-11 activity to be transported safely. In our test system, a 12 mm length corresponds to about 14 mg of sieve material. According to Siriwardane (2001), a trap of this size would have the capacity to adsorb at least 280x the maximum mass of $^{12}\text{CO}_2$ expected from a single target delivery (see above).

3.2 Dose rate measurements

The dose rate at 30 cm from the pig was <43.5 $\mu\text{Sv/hr}$ (5 mR/hr) with up to 2.59 GBq (70 mCi) [^{11}C]CO₂ trapped. During routine use the pig is inserted into a 5 gallon plastic bucket with a foam liner so that the dose rate from the edge of the bucket is <43.5 $\mu\text{Sv/hr}$ (5 mR/hr) up to 3.7 GBq (100 mCi).

3. Conclusion

We have constructed a portable handheld pig (11 kg) that efficiently traps and releases up to 3.7 GBq (100 mCi) of [^{11}C]CO₂ giving a dose rate of <43.5 $\mu\text{Sv/hr}$ (5 mR/hr) at 30 cm. We have used the transport pig more than 40 times over a period of several months without failure in

support of our PET imaging studies of [^{11}C]CO₂ fixation in plants. During this time the trap was stored under helium and was conditioned for 30 - 60 minutes every 1 - 2 weeks to maintain maximum trapping efficiency.

The utilization of [^{11}C]CO₂ by radiochemists and plant scientists is restricted by the need to produce it at or near the site of use due to the short half-life of the isotope. [^{11}C]CO₂ trapping and transporting devices like that described here can provide more versatility for radiochemists and biologists to have access to [^{11}C]CO₂ in their laboratories even if they are not physically connected to the accelerator facilities needed to produce [^{11}C]CO₂. In the future, we plan to investigate the design of smaller trapping systems that could be easily shielded in hot cells or incorporated into portable systems capable of transporting higher doses of tracer. Miniature systems for processing cyclotron-produced [^{11}C]CO₂ may also provide a more convenient interface to microfluidic devices that are now being tested to produce C-11 labeled radiotracers (Miller et al., 2011).

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FIGURE CAPTIONS

Figure 1. Drawings of side (A) and top (B) views of lead pig assembly. (C) Front view of bracket assembly only. Dimensions are reported in mm.

Figure 2. Diagram of molecular sieve trap and tube furnace assembly inside the lead pig. Dimensions are reported in mm.

Figure 3. Photograph of the portable device with ruler (inches).

Figure 4. Test system for determination of [^{11}C]CO₂ trapping and release efficiencies.

Figure 5. Results from a [^{11}C]CO₂ trapping experiment using a silicon diode type radiation detector to monitor activity during target unloading. Most of the [^{11}C]CO₂ activity is trapped over a flow rate of 0.4 - 1 L / min.

Figure 6. Composite figure from overlay of MicroPET image (C-11 activity) and scale drawing of experimental trapping tube. A quartz trapping tube was packed with 80 mg of molecular sieves. Most of the activity is trapped starting from 5 mm of the beginning of the packing extending to 12 mm.

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