USE OF A ZYMARK ROBOT TO PRODUCE RADIOPHARMACEUTICALS

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Large amounts of radioactivity with a radiation field at contact of greater than 10 R/hr make it necessary to work remotely when producing PET radiopharmaceuticals. Because of the speed required when working with short half-life radionuclides, human error is a potential problem for manual remote production of these pharmaceuticals . Remote automation both reduces the exposure, resulting in a safer working environment, and helps to ensure consistent synthetic yields.

We routinely produce thirteen radiopharmaceuticals as well as develop new radiopharmaceuticals in 60 square feet of hot cell space. Due to personnel and space limitations we have chosen to develop our automated syntheses modularly, rather than creating a different automated system for each synthesis. Each module performs a chemical step, such as; drying, purification, heating of reaction vessels, and pH adjustment. Often there are chemical steps common to the different syntheses, and these modules are usable in several syntheses. When space is limited, only modules required for the synthesis underway need to be installed in the hot cell. As the foundation for our modular system, we purchased a Zymark Zymate II Pytechnologyt robot (Zymark Corporation, Hopkinton, MA), which permits convenient swapping of modules.

The Zymark robot consists of an arm which moves along polar coordinates. The company has many stations available which perform operations which are useful in the radiochemistry lab. Some that are tailored for repetitious tasks tend to be too large for efficient use in the hot cell or for syntheses with small (< 10 mL) reaction volumes and need to be modified for work in a hot cell. We have built several stations for our robot which handle single samples, but which include more than one "modular" function, to save on space. The modules we have bought, modified and developed are as follow:

Purchased From Zymark and Used Without Modification:

Pipet hand: A robotic hand which can attach a plastic pipet tip, draw up and dispense liquids of up to 1 mL in volume into a tube or vial and then discard the pipet tip.

Master lab station (MLS): A station containing three 1 mL syringe pumps and valves which can individually and repetitively deliver liquids in volumes of a few μL to 1mL through tubing.

Power and event controller (PEC): A unit which is stationed outside the hot cell and contains digital and analog I/O inputs for controlling switches and valves used in the syntheses.

Purchased From Zymark and Used With Minor Modification:

General purpose hand: This hand picks up test tubes or vials of a limited range of diameters, we have added another set of grips so we can pick up two sizes of vials without changing hands.

Syringe hand: The syringe hand was built to pipet volumes up to 100μL. It was modified from a Zymark pipet hand to which a 100 μL Hamilton gas tight syringe (Hamilton, Reno, Nevada) was mounted. Zymark pipet hand programs have been used for this module by changing the program and variable names to prevent conflict with the other pipet hand. A hand definition was required. This is a set of offset values to a common point on the wrist that the Zymate system uses to allow rack positions to be accessed with different hands without teaching the positions for each hand.

Vortex station: This station was modified to accept 5 mL mini-vials by replacing the original cup with one machined to fit a mini-vial. Also the steadying bracket above the cup was removed for robot access.

A set of variables for describing the vial came with the Pytechnologyt setup program. These variable values were changed to describe the new container, the absolute robot position was re-taught, and the software was re-installed.

Capping station: This station is used to cap or uncap screw top vials. We purchased the Zymark capping station for use with scintillation vials, but modified the grippers for this station to work with 5 mL mini-vials and the container descriptions in the Pytechnologyt setup program were changed to match the dimensions of the mini-vial and the robot capper position was re-taught.

Made at the University of Washington for the Zymark Robot:

Dry baths: We have purchased several hot and cold dry baths which are mounted on plates to establish a fixed position and which are machined to precisely hold our reaction vials. Cyanide trap: At the cyanide trap, a vial is held up to a septum and H11CN gas is bubbled into the 5 mL mini-vial through a needle which is threaded through a 1 mL pipet tip. The septum is pierced by the pipet tip from which the bottom half of the tip has been cut off to prevent the liquid from being bubbled out of the vial.

Liquid dispensers: The dispensers add <1 mL of liquid. The liquid is loaded into tubing before the synthesis begins; the tube leads to a pressurized gas source, with a solenoid valve acting as a shutoff valve in the path. Gas flow is controlled by a pressure regulator and needle valve to add the liquid without splashing. The collection vial is held under the dispenser by the robotic arm. The solenoid valve is actuated by the Zymark PEC, and liquid is dispensed into the vial.

Titration station: A narrow pH probe is used with a teflon tube attached to it and connected to the Zymark MLS. The probe is placed in a vial on the magnetic stirrer and the pH determined by taking a reading of the analog signal provided by a voltage output on the pH meter through the A/D converter of the Zymark PEC. Variable microliter volumes of acid are added until the desired pH is reached.

Sipping station: The sipping needle is used to transfer liquid to other devices, such as a rotary evaporator by means of a vacuum. A vial is raised under the needle until it touches the bottom of the vial. Vacuum is applied to transfer the liquid. Any vial that fits in the robot hand and is shorter than the needle can be held up to the sipper without reprogramming, as positioning is determined by the description of the container.

Separation module: This module has a holder for a small solid phase or ion exchange column with a two-position rack that moves vials under the column, with the other vial position becoming available for access by the robot hand. The Zymark PEC runs two switches which move the motor in either direction. Rack position is sensed by two microswitches. Sample and the rinses are placed on the columns using the Zymark pipet hand.

Filtration module: This module removes solids from samples. It consists of a 5/8" nylon cylinder for the robot hand to grip. The cylinder is tapped through to hold two 1/4-28 to male luer fittings. A needle is attached to the bottom luer fitting and a 0.2 μm luer fitting syringe filter is attached to the top luer fitting. The other end of the filter is connected by tubing to another 22 G needle piercing a septum . The septum is fixed to a horizontal plate. A vial is placed in a holder and the filter placed into the vial. A second vial is then held tightly up against the septum to form a seal, and vacuum is applied. The liquid is transferred into the second vial, free of any solids.

Drying module: After the robot places a test tube in the heat block, it is used to place a gas line in a holder over the tube or holds it over the tube to blow Ar over the liquid and thereby speed evaporation. If the gas line is in a holder, the pipet hand is available to add organic solvent in portions, as the liquid evaporates for azeotropic drying of F-18 .

Inert atmosphere reactions: This station provides an inert gas at a low flow rate for reactions that require an oxygen free and dry atmosphere . The needle is attached to a nylon cylinder and tubing identical to that described for the filtration module. The general purpose hand grips the cylinder and pushes the needle through a septum containing a vent hole, on a capped vial.

Our robot works in "pysections". At this time we mount several modules on one plate. Thus, we use less space than these functions would normally take if each were on its own station plate. Grouping the functions on one plate reduces the modularity of the system, but we group the stations by function to maximize modularity. We model the programs after the Pytechnology station programs and each of the functions are treated as a separate station, except for using the same station id and one setup program for all of the functions. One or all of the functions could be physically split up and installed as separate stations with a minimum of reprogramming. We are saving space to prolong the time when stations will have to be swapped in and out for different syntheses.

FUTURE DEVELOPMENTS

We plan to develop more convenient integration of the robot to feedback systems such as those available with generic PC I/O boards to collect temperature, pressure, pH, and radiation data. We plan to use these data for determining when to end reaction steps. Quite a bit of radioactivity is left behind in the hot cell hood after a synthesis is complete. As our schedule for the production of radiopharmaceuticals becomes heavier, we hope to develop routines for the robot to clean up after one synthesis and prepare for a second, in order to continue to reduce radiation dose to our chemists.

OVERALL EVALUATION OF THE ROBOT

We have found several disadvantages of the Zymark system. The robot arm uses about three square feet of dead space which cannot be used for synthesis in the hot cell. The robot has a limited programming capability. The language that Zymark uses is linear; while loop functions are available, the robot must complete a command before the next one can be entered. Entering programs into the computer is cumbersome and the memory is limited. In our experience, a maximum of two synthesis programs can be entered into the computer at one time without running out of memory. The menu driven system is primitive. The robot takes slightly more time to perform a function than a person would take to do the same task.

Our group is not committed to any particular brand of automated synthetic system. We are however, committed to working with modular systems. The Zymark system has worked well for us. We have limited personnel time for development of automated systems. The Zymark robot was the automated system with the most features and modules applicable to our use which was available at the time we needed to begin automation, in summer of 1988.

We purchased a Zymark demonstration system for about $30,000 which we were able to use for parts of syntheses within two weeks of purchase. However, we find that it takes about 3 full months of a technician's time to fully program a synthesis such as [C-11]-thymidine. The Zymark robot has been very reliable and the mechanical and technical support available from the company has been excellent. Given sufficient time, personnel and money, a remote automated system developed in an individual laboratory for an individual synthesis should be better than any commercial product; but, given our limits of time, money and personnel, the Zymark was the best choice for our laboratory situation. Producing radiopharmaceuticals remotely using a robot has decreased the radiation dose received by personnel doing these syntheses by a factor of ten to the whole body, and we expect to reduce the dose even further. At the same time the reliability of radiopharmaceutical production has increased, albeit with a modest decrease in radiochemical yield at end of synthesis. Robotic stations that have multiple modular functions and have the capability to be used in different syntheses allows several syntheses to be performed by one device in a limited space.

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