INTELLIGENT CONTROL OF LIQUID TRANSFER

Ren Iwata, Tatsio Ido
CYRIC, Tohoku University, Sendai, 980 Japan

Shigeki Yamazaki
Engineer Research Center, NKK Corp. Kawasaki, 210 Japan

INTRODUCTION

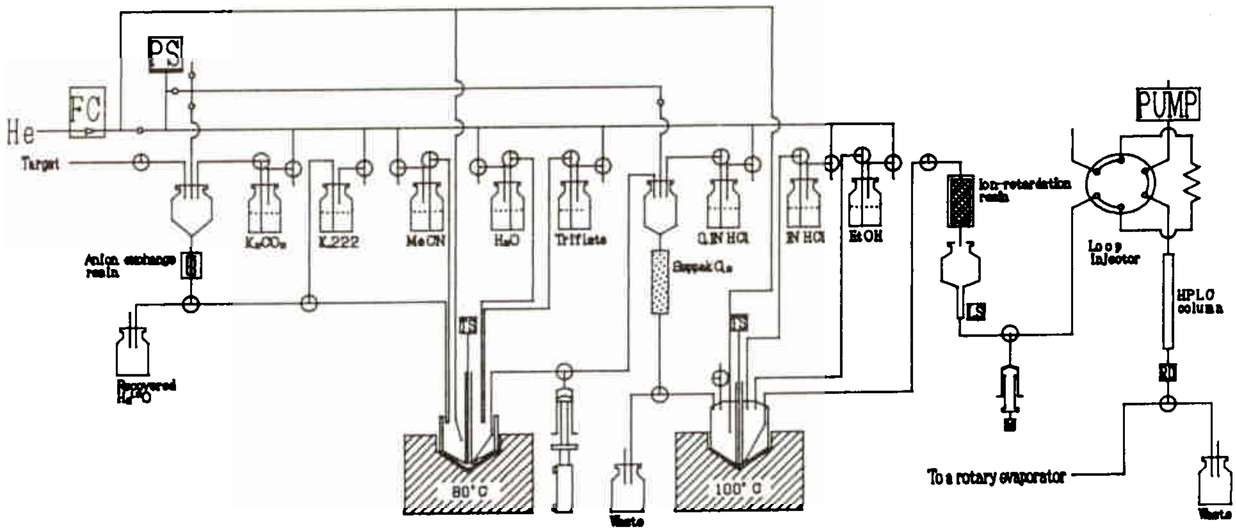
Since we embarked on the development of automated systems for the preparation of positron-emitting radiopharmaceuticals almost 10 years ago, we have realized the importance of sensors for feedback control. In fact, we have tried to exclude time sequence control by using sensors coupled with a computer. Among many useful radiopharmaceuticals, 2-deoxy-2-[^{18}F]fluoro-D-glucose(^{18}FDG) have always been our target for automation. Our first model of the fully automated system for the preparation of ^{18}FDG using computer control was developed based upon this concept.[1] The sensors of pressure, radiation, and liquid level were adopted for control of target recovery, solvent evaporation, chromatographic separation and liquid transfer procedures. Although the whole synthetic procedure was considerably simplified in our second automated ^{18}FDG system by adopting the improved method using [^{18}F]acetyl hypofluorite, many liquid level sensors were still used for control of transferring liquids. Transfer of liquid if a fundamental and accordingly most frequently used procedure in chemical synthesis. A liquid level sensor consists of a photo transistor and a photo diode, and it can inform a computer whether or not liquid exists at the very position of a level sensor by detecting it from outside a glassware. Recently the preparation of ^{18}FDG using no-carrier-added [^{18}F]fluoride has been developed by the Julich group,[2] and the automated synthesis systems have already been reported.[3-5] In our development of the automated system, we have adopted a new approach to intelligent control of transferring many liquid reagents as shown in Figure 1 using a thermal mass flow controller.

TRANSFER WITH A THERMAL MASS FLOW CONTROLLER

A thermal mass flow controller works based on thermal conductivity of a flowing gas. Output signal from a thermal mass flow sensor is proportional to a number of molecules flowing per unit time and independent of pressure and temperature. Figure 2 demonstrates a typical flow rate correlation curve in transferring 1 mL of water in a vial to the reaction vessel with He. As the inside He pressure is atmospheric at first, He flows in rapidly when the valve-1 is opened and the flow rate is then gradually decreased until the pressure reaches to the regulated He pressure of 1.5 kg/cm^2. When the valve-2 is then opened, He starts to flow again at the same rate as the water is transferred, and finally the flow rate is suddenly increased up to the controlled rate of 100 mL/min., clearly indicating that the transfer is completed.

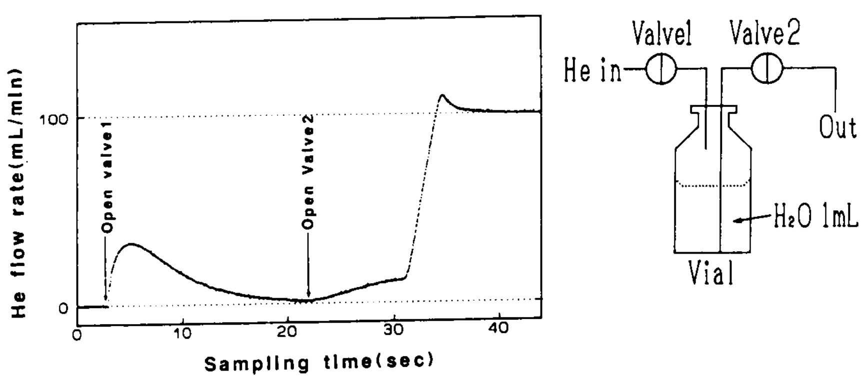
A He flow rate can be correlated with a volume of liquid to be transferred. A spatial dead volume of a reagent vial is equal to an integration of the flow rate, from the time of opening the valve-1 to that of opening the valve-2, divided by the increase in the inside pressure. Therefore, if an empty volume of the vial has been known in advance, the computer can estimate a net volume of the liquid reagent and check whether it is properly charged in each vial before starting the synthesis. The computer can also control a transfer amount of liquid by real time integration of the He flow rate. As shown in Figure 3, a stock solution is dispensed from a reservoir using this method.

One of the excellent characteristics of a thermal mass flow controller is that a single flow sensor enables a computer to control all liquid transfer. As demonstrated above, the control method using this sensor is intelligent compared to a liquid level sensor and therefore it can be said that the present method is suitable for automation with a computer.



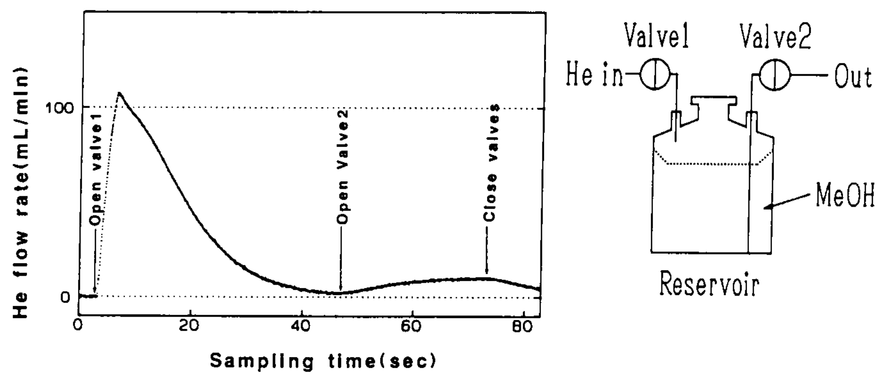
Automated System for NCA^{18}FDG Preparation (CYRIC-NKK)

Figure 1 Automated synthesis system for the preparation of ^{18}FDG from no-carrier-added [^{18}F]fluoride.



Transfer

Figure 2 Typical flow rate correlation curve in transfer of 1 ml water.



Dispense

Figure 3 Flow rate correlation curve in dispensing 1 ml methanol from a reservoir.

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