

A Computerized Radiochromatographic System For Radiopharmaceutical Quality Control

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An automated system for the determination of radiochemical composition of microcurie samples of medical radionuclides and/or radiopharmaceutical preparations is described. The system incorporates a multichannel analyzer, a NaI (TI) detector, a lead collimator, a motor-driven rack, and associated electronic components to provide a fast, accurate, and reproducible method for the identification of radiochemical species. When analyzing a radiochromatogram, the system provides both graphic and hard-copy qualitative and quantitative information. The system is applicable to the needs of most nuclear medicine and radiochemistry laboratories, is easy to operate, reduces radiation exposure to personnel, enhances versatility, and decreases the time required to perform radiochemical quality control tests. Results indicate this system provides better analytical data than the strip-counting technique and comparable quality information of more expensive systems.

Currently, many nuclear medicine and radiochemistry laboratories are confronted with the need to perform a variety of quality control (QC) procedures on short-lived radiopharmaceuticals. Measuring the radiochemical purity of radiopharmaceuticals constitutes a major part of these procedures. Additional QC procedures are required to properly assay and document both the radiopharmaceutical's identity and conformance to set specifications prior to its release and administration. In practice, however, the time limitation imposed when using short-lived radionuclides results in some QC procedures being performed post-release and/or post-administration. This is generally due to the lack of a fast QC system with which to carry out the needed protocols. Considering the time limitations involved in the daily testing operation of radiopharmaceuticals, a system for radiochemical quality control must meet the following criteria: 1) simple and safe operation, 2) rapid data-analysis capability, 3) reproducibility, and 4) versatility.

Scientific publications (1,2) have discussed the necessity of reliable and accurate radiochromatographic systems needed

for assaying different radiochemical compounds. However, information on computer assistance to perform radiopharmaceutical quality control is scarce, though some does exist (3-6).

The system described here, when coupled to standard nuclear detection instrumentation, provides accurate, reliable, reproducible, and less time- and labor-consuming radiochemi-

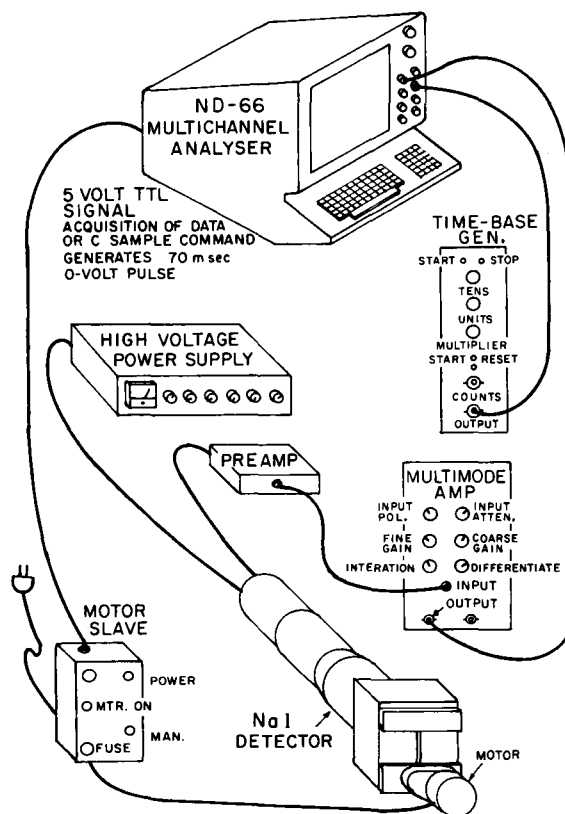


FIG. 1. Schematic view of the different components of the computerized radiochemical quality control system. Most of these components are common items in radiochemistry and/or research laboratories, with the exception of the motor slave (Fig. 3).

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cal quality control. Sophisticated systems capable of performing these tests with a great deal of automation are commercially available at considerable expense. Significant savings can be realized by integrating standard laboratory instruments with easily fabricated assemblies to create a functional and capable system for radiochemical quality control. The system described here is applicable to most current QC methods presently being conducted in clinical and research applications.

Materials and Methods

The different components of the computerized radiochemical quality control system are shown schematically in Fig. 1. The central component of the system is the microcomputer-based multichannel analyzer (Nuclear Data 66 8192, Schaumburg, IL) with multichannel scaling capabilities. The detector consists of a 2×2 in NaI(Tl) scintillation crystal in an aluminum housing surrounded by a 0.75 cm thick lead shield with a 0.3×4.0 cm collimator slit. Additional collimation is provided by two lead blocks ($5.0 \times 10.0 \times 0.2$ cm) fastened to the face of the collimator. In order to allow for variable slit openings, either lead block can be adjusted with set screws. With the collimator in place, the total distance between the NaI(Tl) detector and the chromatographic strip is approximately 0.95 cm, allowing for good counting efficiency even with μ Ci-level samples. Because the half-value layer in lead for 500 keV gamma rays is only 0.43 cm, the collimator thickness (0.75 cm) provides sufficient attenuation for most of the currently useful medical radionuclides, which have characteristic emissions of < 200 keV.

An electric clock motor was adapted to drive a metal rack assembly supporting the radiochromatographic strip. This allows for either a continuous or a step-motion assay of the radioactivity distribution on the chromatogram. The entire collimator and rack assembly is shown schematically in Fig. 2. A schematic of the electronic slave to drive the motor from the keyboard commands is shown in Fig. 3. This is a rather simple electronic device which can be fabricated using standard off-the-shelf components. Additional components are clearly indicated in Fig. 1 and are common items found in nuclear medicine and radiochemistry laboratories. The physical space needed for the system installation and operation is approximately 60×60 cm. For radiation-safety considerations, the multichannel analyzer may be located far from the detector-scanning system.

The system is adaptable for scanning a variety of different chromatographic media as used in paper and thin-layer chromatography (either plastic or glass supported), column chromatography, and electrophoresis. For scanning a column, some minor modifications are needed in order to secure the column in position with the motor-driven rack assembly.

A properly developed radiochromatograph strip, with a clearly marked solvent front and origin, is covered with plastic tape to prevent contamination and facilitate handling. The strip is then placed on the collimator rack and fastened with metal clips. Careful consideration should be given to ensure that the amount of radioactivity present in the sample is within an acceptable range. Below the 1μ Ci level, small peaks are difficult to resolve due to poor counting statistics, and above the 2 mCi

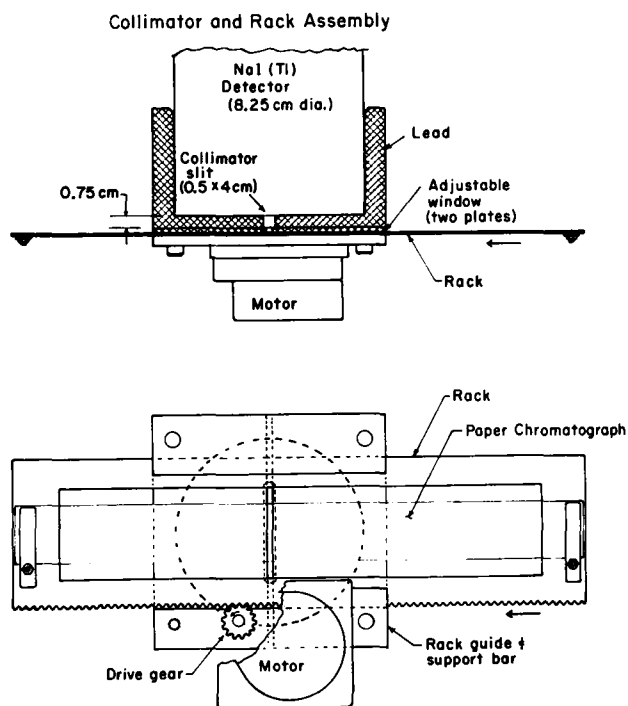


FIG. 2. Schematic of the collimator and rack assembly. The collimator is constructed of sufficiently thick lead to allow for scanning all of the currently used, medically useful radionuclides. The rack assembly can support all of the different chromatographic media for the scanning operation.

ELECTRONIC SLAVE FOR MOTOR

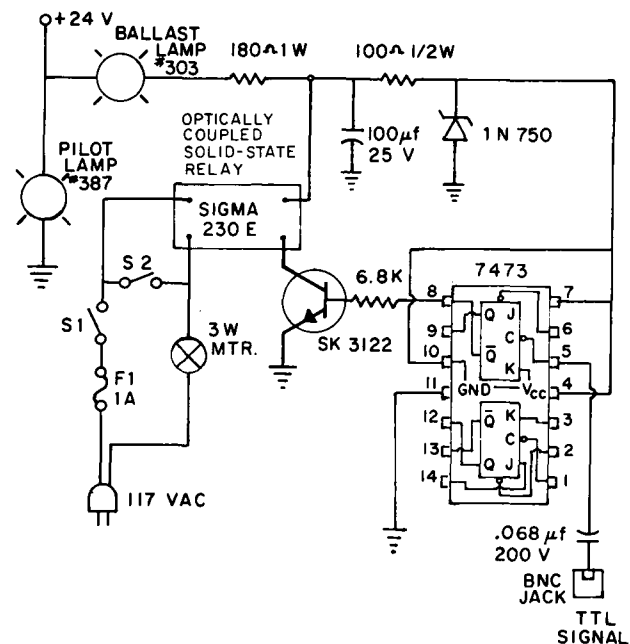


FIG. 3. Diagram of the electronic slave for the continuous or step-motion electric motor. This device can be fabricated with off-the-shelf electric components and mounted accordingly (as shown in Fig. 1).

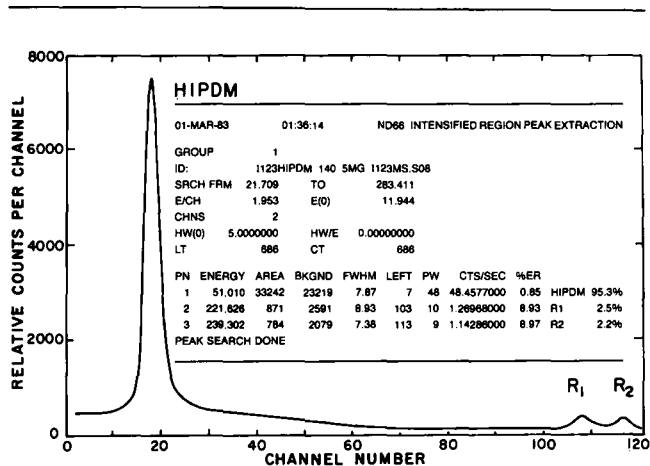


FIG. 4. A typical radiochromatogram of I-123-HIPDM, obtained with the computerized system, using the continuous-mode scanning motion (1 cm/min). The analysis included was performed by using the peak-extraction mode provided by the ND 66 system. PN=Peak Number, AREA=Total number of counts (events) within the peak, ENERGY=Energy in keV, BKGND=Background, FWHM=full-width half-maximum, LEFT=Left marker by channel number, PW=Peak width in channels, CTS/SEC=counts per second, and %ER=percent error.

level, the electronics are close to count rate saturation. The chromatographic strip is placed at the same reference point and distance for each scan. This reference point is needed to assure reproducibility of the QC assay. After manually engaging the rack to the drive gear, the data acquisition and the process control becomes fully automatic. Manual override can be instituted using the computer keyboard.

Routines for multichannel scaling are called from a floppy disk drive and executed by one line commands. System configuration and data acquisition parameters can be selected for specific radionuclides or radiopharmaceuticals either manually or by software. Sample change signals indicating the end of the scan are also displayed on the computer screen. Data analysis of the different peaks is then performed using the region-of-interest peak-extraction mode. During the spectrum analysis, data is stored on floppy disk to be later displayed on a printer, plotter, or on the monitor screen. A typical radiochromatographic analysis of I-123 labeled (N,N,N'-trimethyl-N'-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propane diamine) (I-123 HIPDM), with the corresponding computer peak-extraction results, is shown in Fig. 4. A hard copy is made from the computer via a fast on-line printer and contains all of the important parameters and measurements such as peak number and identification, net integrated peak counts, background counts, peak full width at half maximum, count rate, and percent errors. A sample of this analysis is also shown in Fig. 4.

The precision of analysis by the computerized system was compared to analysis by the strip counting method. A Whatman #1 paper strip was loaded with six different radioactive spots (2 to 50 μ Ci) at different locations using I-123 sodium iodide. This sample was used as a reference control. The reference spots were made from the same I-123 sodium iodide solution (2.4 mCi/ml). Furthermore, the reference spots were "smeared" by immersing the strip in the chromatographic solvent (85% methanol-15% water) and allowing it to dry in the

vertical position. The strip was first analyzed using the multichannel analyzer system, and then by the strip count method using 0.5 cm segments.

In addition, a sample of our radiopharmaceutical-quality I-123 sodium *o*-iodohippurate was contaminated by adding known amounts of I-123 iodide (I^-), I-123 iodate (IO_3^-), and I-123 sodium *o*-iodobenzoate, all of which are possible radiochemical contaminants in hippuran preparations. The resulting solution was then chromatographed with a TLC Bakerflex 1B-F silica gel plate, using a glacial acetic acid:benzene:water:n-butanol (5:5:2:1.5 in volume) solvent mixture. The radiochromatogram was first analyzed using the multichannel analyzer system and then by the strip-counting method.

Results and Discussion

The comparison of analysis by the computerized multichannel analyzer system and strip-counting technique of the strip with six I-123 spots is given in Table 1, along with the deviation with respect to the reference. The data for analysis of the intentionally contaminated I-123 *o*-hippurate sample is listed in Table 2 and shown graphically in Fig. 5. The experiments demonstrate the greater accuracy of the computerized multichannel analyzer system over the commonly used strip-counting method. The comparison of both methods, as shown in Tables 1 and 2, indicates that when the level of a radiochemical impurity decreases, the accuracy of the strip-counting method declines. Because the release criteria is largely based on upper

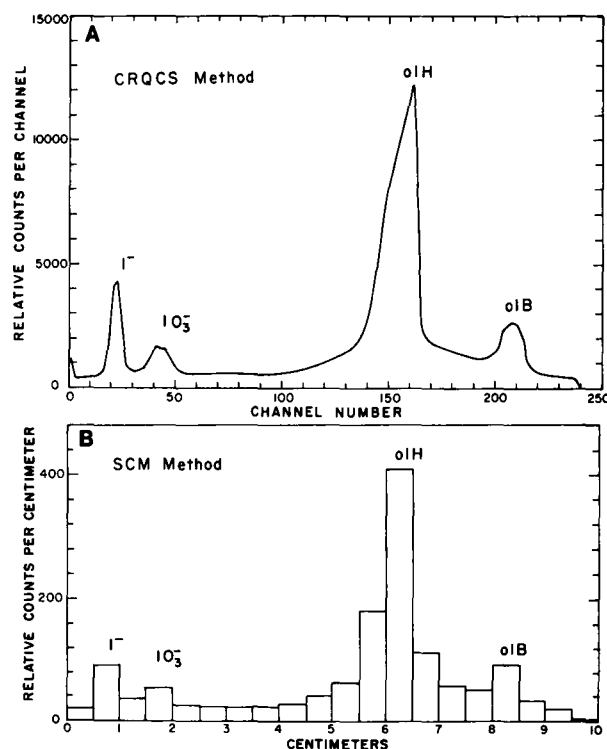


FIG. 5. Comparison of computerized system and the strip-counting mode analysis of a sample of radiopharmaceutical-quality I-123 sodium *o*-iodohippurate, contaminated with I-123 iodide, I-123 iodate, and I-123 sodium *o*-iodobenzoate. (a) Result of the computer analysis. (b) Strip-counting method analysis with 0.5 cm wide strips.

TABLE 1. Comparison of radioassay results using the computerized and the strip-counting method.

Reference Control			Computerized system		Strip-counting method		Deviations* (%)	
R_f	μCi	%	R_f	%	R_f	%	Computerized system	Strip-counting method
0.08	16.3	17.5	0.10	17.5	0.10	11.5	0.0	-52.0
0.18	10.6	11.4	0.20	12.6	0.20	14.5	+11.0	+27.0
0.45	48.2	51.8	0.45	50.2	0.50	49.6	-3.2	-4.4
0.59	1.7	1.8	0.57	2.0	0.60	2.1	+11.1	+16.7
0.75	7.3	7.9	0.71	8.0	0.76	9.7	+1.3	+22.8
0.93	8.9	9.6	0.87	9.7	0.94	12.6	+1.0	+31.3

*Deviations with respect to the percentages in the reference control.

limits of small level radiochemical contaminants, the computerized system represents a significant improvement in radiochemical quality control.

After several attempts, a decision was made to operate a continuous rather than a step-mode system for the analysis of radiochromatograms. Adjustable scan-speeds also provide a simple way to allow for different count rates of the sample. In addition, data analysis using the smooth continuous functions is more precise than analysis using the step-mode functions.

All the radiochromatograms were run for an approximately 10 cm origin-to-solvent-front distance. The computer multi-scaling mode was also preset to divide the radiochromatogram strip into 25 channels/cm. Under these conditions, peak resolution depends on the scanning rate, collimator width, and counting statistics. The optimum scanning rate was found to be 1 cm/min. A collimator width of 0.3 cm was also found acceptable, although a narrower collimator could be used for improved peak resolution when sampling radiochromatograms containing several hundred microcuries. Under these conditions, the system can function reproducibly with 1-2000 μCi samples. Samples with lower levels of radioactivity could still be successfully analyzed using a step-mode function during the scanning-counting operation. In this mode, the sensitivity of the system was increased to approximately a 10 nCi level.

Many radiochemical QC protocols are normally carried out by using the "destructive" strip-counting technique. A properly developed radiochromatogram is cut into specified regions of interest and defined by the R_f values of the expected radiochemical forms. The radioactivity in every region of the radiochromatogram is measured with a suitable radiation detector. This "destructive" method is normally used to speed up the QC protocol by counting only pre-defined regions of interest.

Peak resolution can be achieved by cutting the strip into small regions (0.5 cm wide segments) and then plotting a radioactivity versus distance histogram. The simplicity of the strip-counting technique, which can even be executed using a dose calibrator and inexpensive standard chromatographic equipment, has found a place in many clinical and research laboratories. In practice, many experimental random errors are introduced via the strip-counting technique. Significant errors in measured R_f values and in peak area calculations are the result of differences in strip preparation and handling techniques, detector systems, counting statistics, and background radioactivity. Other sources of errors, such as variations of electronic dead-time and counting geometry, are rarely taken into consideration. The system described here was developed primarily to solve some of the difficulties commonly encountered with the use of the strip-counting method. This was accomplished by eliminating many of the sources of uncertainties while minimizing the handling of radioactive sources and standardizing the procedures.

Conclusions

By today's standards, radiochemical QC should ideally be performed using complex and expensive high-performance liquid- or thin-layer chromatography systems. Data from this type of chromatography can be obtained by measuring radioactivity distributions and levels. The resulting data can then be processed to obtain an accurate representation of the radiochemical species present. High performance chromatography systems are highly desirable and powerful research tools. However, the systems are expensive and are not adequately structured for serial and/or repetitive analysis as required in the batch-production mode of radiochemicals and radiopharmaceuticals. The radiochromatograph scanning system described

TABLE 2. Comparison of Radiochemical Analyses for I-123 Sodium o-iodohippurate using the computerized and the strip-counting methods.

Radiochemical Species	Reference Sample	Computerized system	Strip-counting method	Deviations	
				Computerized system	Strip-counting method
o-iodohippurate	76.0%	77.4%	83.8%	+1.8%	+10.3%
o-iodobenzoate	9.5%	8.8%	6.0%	-8.0%	-58.3%
iodide	10.2%	9.3%	7.4%	-9.7%	-37.8%
iodate	4.3%	4.5%	2.8%	+4.7%	-53.6%

and evaluated in this work offers the possibility of precise, rapid, and nondestructive quality control testing capabilities using a combination of standard equipment and instrumentation already common in most clinical and research facilities.

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