Rapid Quality Control of Technetium-99m-2-Methoxy Isobutyl Isonitrile (Technetium-99m-Sestamibi)

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Objective: Technetium-99m-sestamibi (^{99m}Tc-MIBI) is a radiopharmaceutical imaging agent useful for assessing myocardial perfusion. We present a simple, rapid and accurate SepPak® method to confirm the radiochemical purity of ^{99m}Tc-MIBI.

Methods: Technetium-99m-MIBI preparations of high (>95%), intermediate (83–90%) and low (25–43%) radiochemical purity were evaluated by the recommended thin-layer chromatography (TLC) procedure. Radiochemical purities were simultaneously determined by Alumina-N and C-18 SepPak treatment using 95% ethanol and 0.9% sodium chloride injection, USP as eluents. Statistical analysis was used to determine concordance between TLC and corresponding SepPak values for the entire range of ^{99m}Tc-MIBI purity studied.

Results: For all purity groups studied, a significant difference was found when ^{99m}Tc-MIBI radiochemical purity values by the C-18 SepPak method were compared to values obtained by the recommended TLC procedure. However, no statistical difference in ^{99m}Tc-MIBI radiochemical purity values were found when Alumina-N SepPaks, treated with sufficient eluent, were compared to values obtained by the recommended TLC procedure.

Conclusion: This study demonstrates that an Alumina-N SepPak method can be routinely used as an alternative to the recommended TLC method for the radiochemical purity determination of ^{99m}Tc-MIBI.

Key Words: technetium-99m-sestamibi; radiochemical purity; quality control

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Technetium-99m-sestamibi (^{99m}Tc-MIBI; Cardiolite®, DuPont Merck Pharmaceutical Co., N. Billerica, MA) is a cationic complex approved for myocardial perfusion imaging. This agent is routinely used in the nuclear medicine laboratory for myocardial risk stratification (*1–3*) and to evaluate myocardial blood flow following coronary artery angioplasty or thrombolytic therapy (*4*).

To ensure acceptable radiolabeling, Cardiolite is heated. The heating step facilitates the reduction of ^{99m}Tc-pertechnetate and the formation of the ^{99m}Tc-MIBI complex. Inadequate heating will result in solutions with radiochemical purity values less than the recommended ≥90% ^{99m}Tc-MIBI. This decrease in radiochemical purity is associated with an increase in levels of radiochemical impurities. For Cardiolite this includes residual ^{99m}Tc, hydrolyzed-reduced ^{99m}Tc (^{99m}Tc-HR) and one or more ^{99m}Tc-MIBI intermediate complexes (^{99m}Tc-IC).

To ensure that radiolabeled kits meet the radiochemical purity ≥90% criteria, the manufacturer has validated a quality control procedure (*5*) for the determination of ^{99m}Tc-MIBI radiochemical purity. The quality control procedure uses an aluminum oxide thin-layer chromatography (TLC) plate developed in 95–99% ethanol. After development, the TLC plate is analyzed for activity in the upper portion of the plate compared with the total activity applied to the plate. In this procedure, the ^{99m}Tc-MIBI migrates to the upper portion of the plate while the radiochemical impurities (^{99m}Tc, ^{99m}Tc-HR and ^{99m}Tc-IC) remain in the lower portion of the plate. Although the TLC procedure has proven accuracy, it requires up to 40 min to perform and is not designed to separate radiochemical impurities from each other.

Several investigators have evaluated and recommended either reversed phase (*6,7*) or normal phase (*8*) SepPak® methodology to replace the recommended TLC procedure. These systems have either overestimated TLC values and/or were not validated with ^{99m}Tc-MIBI kits of <90% radiochemical purity. Other investigators (*9,10*) have proposed the use of mini-paper chromatography (MPC) as a replacement for TLC. Although this method was validated with kits containing ^{99m}Tc-IC, the system underestimated TLC values and requires a solvent hazardous to health (*11*).

This study was designed to develop a procedure for the determination of ^{99m}Tc-MIBI radiochemical purity using solid-phase extraction methodology. Our aim was to develop a system that would: (a) compare favorably with the approved

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TLC method for preparations having a wide range of ^{99m}Tc-MIBI radiochemical purity; (b) adequately separate ^{99m}Tc-MIBI from potential impurities; (c) allow quantitation of radiochemical impurities; and (d) require less time than the current TLC procedure. Systems for study were chosen based upon technical simplicity, safety and ease of access to required materials.

MATERIALS AND METHODS

Technetium-99m-MIBI was prepared according to the manufacturer's instructions (*12*) by the addition of ^{99m}Tc in 2 ml 0.9% NaCl injection, USP to each lyophilized kit vial of Cardiolite for study. Each kit vial contained 1.0 mg tetrakis (2-methoxy isobutyl isonitrile) copper (I) tetrafluoroborate, 2.6 mg sodium citrate dihydrate, 1.0 mg 1-cysteine hydrochloride monohydrate, 20 mg mannitol, and 0.075 mg stannous chloride dihydrate under a nitrogen atmosphere. Preparations of low radiochemical purity ^{99m}Tc-MIBI were prepared as described by Hung, et al. (*9*). Following the addition of ^{99m}Tc, vials were swirled for 1 min and incubated in an ice bath containing a precooled lead pig. Samples for radiochemical purity determination were obtained after a 25-min incubation period. Technetium-99m-MIBI solutions of intermediate purity were prepared by mixing samples from kits of known high and low radiochemical purity. Final ^{99m}Tc-MIBI purity was determined by the recommended TLC method.

Technetium-99m was obtained from a ^{99}Mo/^{99m}Tc generator (Technelite®, DuPont Merck Pharmaceutical Co., N. Billerica, MA) using standard technique. Radiochemical purity was evaluated using Tec-Control (Atomic Products Corp., Shirley, NY) MPC systems. Hydrolyzed-reduced ^{99m}Tc was prepared by the method of Robbins (*13*) with modification. Radiochemical purity was evaluated using MPC.

Radiochemical Impurities With Sep-Pak® Systems

The characteristics of ^{99m}Tc and ^{99m}Tc-HR with normal phase (Alumina-N, Waters, Milford, MA; catalog no. 20510) and reversed phase (C-18, Waters, Milford, MA; catalog no. 20515) chromatography SepPaks were evaluated respectively using the manufacturer's recommendations (*14*). Alumina-N SepPak cartridges were: (a) conditioned with 10 ml 95% ethanol; (b) 50 μl of sample loaded; (c) the eluate of interest extracted with 10 ml (Method I) or 20 ml (Method II) 95% ethanol followed by 10 ml of room air; and (d) extractable impurities removed with 10 ml 0.9% NaCl injection, USP followed by 10 ml of room air. For reversed-phase chromatography using the C-18 cartridge (Waters, Milford, MA; catalog no. 20515): (a) columns were conditioned with 10 ml 95% ethanol followed by 10 ml 0.9% NaCl injection, USP; (b) 50 μl sample loaded; (c) extractable impurities removed with 10 ml 0.9% NaCl injection, USP followed by 10 ml of room air; and (d) the eluate of interest extracted with 10 ml 95% ethanol followed by 10 ml of room air. All eluates were collected in counting tubes.

The distribution of elutable and nonelutable ^{99m}Tc species in SepPak systems was studied with application of 537 to 1684 μCi samples of ^{99m}Tc and 230–824 μCi samples of ^{99m}Tc-HR to Alumina-N and C-18 cartridges, respectively. Cartridges were treated with 95% ethanol and 0.9% NaCl injection, USP as previously described. Activity in each SepPak and associated counting tubes were measured in a dose calibrator and percent activity in each fraction determined.

Evaluation of High, Intermediate and Low Technetium-99m-Sestamibi Purity

To demonstrate the accuracy of an alternate method for the determination of ^{99m}Tc-MIBI radiochemical purity, it is necessary to compare the radiochemical purity found by the proposed method with that obtained by the recommended TLC method for preparations having a wide range of purity. TLC was performed using the procedure described in the Cardiolite package insert (*12*). Briefly, a predried plastic plate coated with aluminum oxide (Bakerflex® 1B-F, J.T. Baker Chemical Co., Phillipsburg, NJ) was first spotted with 95% ethanol. Two drops of ^{99m}Tc-MIBI were applied side-by-side on top of the wet ethanol spot. The plate was allowed to dry in a desiccator for approximately 15 min and subsequently developed in 95% ethanol for a distance of 5 cm from the origin. The plate was cut at Rf 0.5 and each half measured in a dose calibrator. Purity of ^{99m}Tc-MIBI is represented by the activity on the top half of the plate with respect to the total activity on the plate.

Both Alumina-N and C-18 SepPak systems, stored at ambient temperature and humidity, were compared with the recommended TLC procedure for purity levels of ^{99m}Tc-MIBI in the high (>95%), intermediate (83–90%) and low (15–43%) ranges. Samples from each purity range were prepared and studied by the C-18 SepPak method and by Alumina-N SepPaks using Methods I and II, as previously described. The reproducibilities of the two Alumina-N SepPak procedures were evaluated by analyzing five replicate high-purity samples by Methods I and II. Additional samples were obtained and treated by Method II to determine label integrity over time.

RESULTS

Evaluation of ^{99m}Tc and ^{99m}Tc-HR by MPC systems demonstrated each to be radiochemically pure. In studies designed to demonstrate recovery of ^{99m}Tc from conditioned SepPaks, 99.9% ± 0.2% and 98.7% ± 2.0% of activity were found in 0.9% NaCl injection, USP eluates following Alumina-N and C-18 SepPak treatments, respectively. When ^{99m}Tc-HR recovery was evaluated, 100.0% ± 0.0% of activity was bound to the Alumina-N SepPak while only 81.0% ± 5.8% of activity was associated with the C-18 SepPak. Activity not associated with the C-18 SepPak was found in the 95% ethanol (16.2% ± 3.2%) and 0.9% NaCl injection, USP (2.9% ± 2.5%) eluates (Table 1).

Fifteen high-purity ^{99m}Tc-MIBI kits were prepared according to the manufacturer's instructions (*12*) with the addition of 2 ml of ^{99m}Tc activity ranging from 44 to 142 mCi. Activity loaded onto Alumina-N and C-18 SepPaks ranged from 751 to 1941 μCi and 675 to 1336 μCi, respectively. The labeling efficiency, as determined by TLC and Method I, was 98.8% ±

TABLE 1
Evaluation of Radiochemical Impurities with SepPak® Systems

Component counted	Percent recovery	
	^{99m}Tc	^{99m}Tc-HR
Alumina-N SepPak	0	100.0 ± 0.0
EtOH eluate	0	0
NaCl eluate	99.9 ± 0.2	0
C-18 SepPak	0	81.0 ± 5.8
NaCl eluate	98.7 ± 2.0	2.9 ± 2.5
EtOH eluate	0	16.2 ± 3.2

0.4% and 98.4% ± 0.6%, respectively (Table 2A). Studies designed to demonstrate the reproducibility of five replicate, high-purity ^{99m}Tc-MIBI solutions provided a labeling efficiency of 98.7% ± 0.2% and 98.8% ± 0.1% for Methods I and II, respectively. Samples of high-purity ^{99m}Tc-MIBI obtained at 0, 2 and 4 hr after preparation and studied by Method II demonstrated a labeling efficiency of 98.1%, 98.5% and 98.6%, respectively. For eight kits, where Method II was used, labeling efficiency was 98.9% ± 0.2% (Table 2B). Nine kits were evaluated by the C-18 SepPak method. Labeling efficiency, as determined by this method, was 97.8% ± 1.0% (Table 3).

Twelve low-purity ^{99m}Tc-MIBI kits were prepared by the addition of 2 ml ^{99m}Tc containing 44 to 139 mCi of activity. Samples for radiochemical purity determination ranged from 767 to 1433 μCi and 895 to 1020 μCi for Alumina-N and C-18 SepPaks, respectively. Labeling efficiency, as determined by TLC and Method I was 25.5% ± 8.9% and 24.0% ± 7.5%, respectively (Table 2A). For five kits, where Method II was used, labeling efficiency was 25.0 ± 8.1% (Table 2B). Three kits were evaluated by the C-18 SepPak method and provided a labeling efficiency of 79.4% ± 5.2% (Table 3).

TABLE 3
Comparison of Technetium-99m-MIBI Purity by TLC and C-18 SepPak® Methods*

Preparation purity	TLC (% purity)	C-18 SepPak (% purity)
High (>95%)	98.8 ± 0.5	97.8 ± 1.0†
Intermediate (83–90%)	85.7 ± 3.0	93.9 ± 2.0†
Low (15–43%)	22.4 ± 7.4	79.4 ± 5.2†

*Conditioned SepPaks were loaded with sample and eluted with 10 ml 0.9% NaCl injection, USP followed by 10 ml 95% EtOH.
†Significantly different from TLC; paired t-test ($p < 0.05$).

Nine ^{99m}Tc-MIBI solutions of intermediate purity were prepared for study. Activity loaded onto Alumina-N and C-18 SepPaks ranged from 716 to 1830 μCi and from 929 to 1300 μCi, respectively. The labeling efficiency, as determined by TLC and Method I, was 87.1% ± 2.0% and 85.2% ± 2.7%, respectively (Table 2A). For four solutions, where Method II was used, labeling efficiency was 85.2% ± 2.4% (Table 2B). Five solutions were evaluated by the C-18 SepPak method. Labeling efficiency, as determined by this method, was 93.9% ± 2.0% compared to 85.7% ± 3.0% by the TLC method (Table 3).

Table 2 provides percent elutable (^{99m}Tc) and non-elutable (^{99m}Tc-HR and ^{99m}Tc-IC) radiochemical impurities from high-, intermediate- and low-purity ^{99m}Tc-MIBI preparations following treatment by Methods I and II, respectively.

Comparison of SepPak and TLC Methods

Labeling efficiency values obtained by TLC treatment of high-, intermediate- and low-purity ^{99m}Tc-MIBI preparations were compared (paired t-test, $p > 0.05$) with corresponding

TABLE 2
Comparison of Technetium-99m-MIBI Purity by TLC and Alumina-N SepPak® Using Methods I and II

2A. Method I*

Preparation purity	TLC (% purity)	SepPak elutable activity		SepPak non-elutable activity
		EtOH	NaCl	
High (>95%)	98.8 ± 0.4	98.4 ± 0.6†	0.3 ± 0.2	1.2 ± 0.5
Intermediate (83–90%)	87.1 ± 2.0	85.2 ± 2.7†	1.3 ± 0.5	13.4 ± 2.7
Low (15–43%)	25.5 ± 8.9	24.0 ± 7.5	7.8 ± 3.6	68.2 ± 9.7

2B. Method II‡

Preparation purity	TLC (% purity)	SepPak elutable activity		SepPak non-elutable activity
		EtOH§	NaCl	
High (>95%)	98.8 ± 0.4	98.9 ± 0.2	0.2 ± 0.1	0.9 ± 0.1
Intermediate (83–90%)	87.1 ± 2.0	85.2 ± 2.4	1.2 ± 0.5	13.6 ± 2.0
Low (15–43%)	25.5 ± 8.9	25.0 ± 8.1	6.0 ± 3.1	68.9 ± 11.1

*Conditioned SepPaks were loaded with sample and eluted with 10 ml 95% EtOH followed by 10 ml 0.9% NaCl injection, USP.
†Significantly different from TLC; paired t-test ($p < 0.05$).
‡Conditioned SepPaks were loaded with sample and eluted with 20 ml 95% EtOH followed by 10 ml 0.9% NaCl injection, USP.
§Values are not significantly different from TLC.

values obtained by Alumina-N and C-18 SepPak treatments. Radiochemical purity values obtained from high- and intermediate-purity ^{99m}Tc-MIBI preparations, following treatment by Method I, were slightly, but statistically, lower than TLC values (Table 2A). In all cases, however, there was concordance between the two methods as to the clinical acceptability of the kits. No statistical difference was observed for either high or intermediate radiochemical purity values and TLC values when SepPaks were treated by Method II (Table 2B). Low-purity ^{99m}Tc-MIBI preparations studied by TLC and Method I (Table 2A) or Method II (Table 2B) demonstrated radiochemical purity values that were not statistically different.

Technetium-99m-MIBI preparations of high, intermediate and low radiochemical purity demonstrated values by the C-18 SepPak method that were statistically different from those obtained by the TLC procedure (Table 3). While SepPak values for high-purity ^{99m}Tc-MIBI underestimated TLC values, preparations of intermediate- and low-purity demonstrated values by the SepPak procedure that overestimated TLC values. Technetium-99m-MIBI solutions of intermediate purity found unacceptable for clinical use by the TLC method were found satisfactory when evaluated by the C-18 SepPak method.

DISCUSSION

It is part of good nuclear pharmacy practice to determine the radiochemical purity of a ^{99m}Tc-labeled radiopharmaceutical before patient administration. Any method selected to make this determination must ensure that an improperly prepared kit would be detected. The method, therefore, should be designed to generate the most complex mixture of radiochemical impurities. For ^{99m}Tc-MIBI, inadequate heating time or temperature promote the formation of radiochemical impurities (*9*). Radiochemicals that may be found in kit vial preparations under these conditions include ^{99m}Tc, ^{99m}Tc-HR and ^{99m}Tc-IC. These radiochemical impurities must be adequately separated from ^{99m}Tc-MIBI to obtain an accurate measure of the product radiochemical purity. Using the recommended TLC method, Proulx, et al. (*6*) described Rf values of 0.00–0.50, 0.00–0.25 and 0.50–1.00 for ^{99m}Tc, ^{99m}Tc-HR and ^{99m}Tc-MIBI, respectively. Based upon our work with ^{99m}Tc-MIBI kits prepared under suboptimal heating conditions, it is possible to assume an Rf of 0.00–0.50 for ^{99m}Tc-IC.

A radiochemical purity specification of ≥90% ^{99m}Tc-MIBI has been recommended for Cardiolite (*12*). As a result, an acceptable procedure must be evaluated with kit preparations having a radiochemical purity <90%. The recommended TLC procedure (*12*) has been validated with samples from kits of at least 85% ^{99m}Tc-MIBI. While the TLC procedure is accurate over the range of interest, its 40-min completion time may delay studies in patients with acute myocardial infarction. Furthermore, the recommended TLC procedure is designed to separate total radiochemical impurities from ^{99m}Tc-MIBI for the determination of radiochemical purity. A new procedure capable of quantifying radiochemical impurities may prove valuable should additional indications for ^{99m}Tc-MIBI include imaging of abnormal parathyroid tissue (*15,16*).

Proulx, et al. (*6*) evaluated a reversed-phase C-18 SepPak, with water as solvent, for the determination of ^{99m}Tc-MIBI purity. With this system lipophilic ^{99m}Tc complexes are retained by the SepPak while polar impurities are eluted with a polar solvent. In studies comparing the TLC system with this SepPak system, labeling efficiencies of 97.1% ± 1.9% and 99.7% ± 0.1% were found for the TLC system and C-18 SepPak system, respectively (n = 15). The higher values for the SepPak system were attributed to the retention of ^{99m}Tc-HR by the SepPak. This is in agreement with Mah, et al. (*17*) who found 33–86% retained activity following SepPak elution. Reilly, et al. (*7*) attributed slight but significantly higher ^{99m}Tc-MIBI purity to ^{99m}Tc-HR when comparing a C-18 SepPak method to the recommended TLC procedure ($n = 9$; $p < 0.005$). The authors suggest that a sample with acceptable radiochemical purity by the approved TLC method should also be acceptable by this SepPak method. However, our data demonstrate that ^{99m}Tc-MIBI preparations of intermediate purity that meet or exceed the radiochemical purity standard of ≥90% using the C-18 SepPak, fail to meet this standard when evaluated by the recommended TLC procedure.

Hammes, et al. (*8*) determined the radiochemical purity of high-purity ^{99m}Tc-MIBI preparations on a normal phase SepPak with ethanol as solvent. With this system lipophilic ^{99m}Tc complexes are eluted from the SepPak while more hydrophilic complexes are retained. When ^{99m}Tc-MIBI preparations of 96.0–98.4% radiochemical purity by TLC were compared with this system, a slight but significantly lower value was found when SepPaks were eluted with 100% ethanol ($n = 11$; $p < 0.025$). No difference in percent ^{99m}Tc-MIBI purity was found between the TLC system and this system when 95% ethanol was used to elute the SepPak ($n = 10$; $p < 0.05$).

In this study a statistical difference (underestimation) was demonstrated when radiochemical purity values from samples of high- and intermediate-purity ^{99m}Tc-MIBI obtained by Method I were compared with TLC values. No statistical difference, however, was found when values obtained by Method II were used in this comparison. Furthermore, no difference was found when values obtained following analysis of low-purity ^{99m}Tc-MIBI by either Method I or II were compared with values obtained following analysis by TLC. These data would suggest that in the Alumina-N SepPak system, a large volume of weakly polar solvent is required to elute the ^{99m}Tc-MIBI complex when the radiochemical purity is in the intermediate or high range. Technetium-99m-MIBI in preparations of low radiochemical purity (<40%), however, were effectively eluted with reduced volumes of solvent.

We have determined in this work that 10 ml 0.9% NaCl and 20 ml 95% ethanol, respectively, elute ^{99m}Tc and ^{99m}Tc-MIBI quantitatively from Alumina-N SepPaks while ^{99m}Tc-HR and ^{99m}Tc-IC avidly bind to this packing material. Theoretically ^{99m}Tc-HR could be reoxidized and subsequently eluted from the SepPak. In preliminary studies we have demonstrated removal of bound activity with 20% hydrogen peroxide, however, it is unclear whether one or both radiochemical impurities are

present in the eluate. Additional work in this area may be difficult to perform since ^{99m}Tc-IC, in the presence of kit components, converts to the primary complex at room temperature.

Of practical value from this study is the good agreement between ^{99m}Tc-MIBI purity values obtained by the recommended TLC method and the elution of Alumina-N SepPaks with 20 ml 95% ethanol (Table 2B). This would suggest that a single-solvent elution would provide the same purity information as the recommended TLC procedure. Therefore, for those nuclear medicine studies where quantitation of impurities is superfluous, the single-elution modification could be used and would further reduce the processing time necessary for the determination of ^{99m}Tc-MIBI radiochemical purity.

CONCLUSION

We have developed a simple and rapid method for the determination of ^{99m}Tc-MIBI radiochemical purity based upon Alumina-N SepPak methodology. The investigation evaluated a range of ^{99m}Tc-MIBI purity that included levels below the acceptable limit for clinical use. Our evaluation demonstrated concordance between Method II and the recommended TLC procedure throughout the purity range of ^{99m}Tc-MIBI under study. Although our method can separate ^{99m}Tc-MIBI from ^{99m}Tc, ^{99m}Tc-HR, and ^{99m}Tc-IC, additional studies are necessary to separate ^{99m}Tc-HR from ^{99m}Tc-IC for quantitation.

The recommended method for determination of ^{99m}Tc-MIBI is as follows:

1. Condition an Alumina-N SepPak with 10 ml 95% ethanol and follow with 10 ml of room air.
2. Load two drops of ^{99m}Tc-MIBI preparation on the conditioned SepPak.
3. Elute the SepPak in a dropwise manner with 10 ml 95% ethanol and collect the eluate in Counting Tube 1 and follow with 10 ml of room air.
4. Elute the SepPak in a dropwise manner with a second 10-ml volume of 95% ethanol and collect eluate in Counting Tube 2. Follow this elution with 10 ml of room air.
5. Elute the SepPak in a dropwise manner with 10 ml 0.9% NaCl. Collect the eluate in Counting Tube 3 and follow with 10 ml of room air.
6. Determine the net activity of Counting Tubes 1, 2, 3 and that remaining in the SepPak using a dose calibrator.
7. Calculate percent ^{99m}Tc-MIBI radiochemical purity and percent radiochemical impurities as follows:
   a. Percent ^{99m}Tc-MIBI purity:

$$\frac{\text{Activity Tubes 1 + 2}}{\text{Activity Tubes 1 + 2 + 3 + SepPak}} \times 100$$

   b. Percent elutable impurity (^{99m}Tc):

$$\frac{\text{Activity Tube 3}}{\text{Activity Tubes 1 + 2 + 3 + SepPak}} \times 100$$

   c. Percent non-elutable impurities (^{99m}Tc-HR, ^{99m}Tc-IC):

$$\frac{\text{Activity SepPak}}{\text{Activity Tubes 1 + 2 + 3 + SepPak}} \times 100.$$

For those nuclear medicine procedures requiring only the radiochemical purity determination of ^{99m}Tc-MIBI, step 5 above may be omitted and the calculation may be simplified as follows:

Percent ^{99m}Tc-MIBI purity:

$$\frac{\text{Activity Tubes 1 + 2}}{\text{Activity Tubes 1 + 2 + SepPak}} \times 100.$$

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