A Study of the Preparation of Disofenin and Gluceptate Cold-Unit Doses

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This study evaluated the feasibility of preparing cold-unit doses (CUDs) of disofenin (DISIDA) and gluceptate (GHA) in syringe form. DISIDA and GHA reagent kits were reconstituted with normal saline and divided into single-unit doses (UDs) in accordance with the recommended volume of the manufacturers. These UDs were immediately frozen at −10°C after preparation. After 5, 10, 12, 24, and 31 days of storage, 4 CUDs from the DISIDA group were randomly selected and radiolabeled with technetium-99m (^{99m}Tc) pertechnetate. The CUDs from the GHA group were similarly radiolabeled after 7, 16, 22, and 38 days of storage. Radiochemical impurities of these ^{99m}Tc-labeled CUDs were determined and analyzed. The DISIDA CUDs produced ^{99m}Tc-DISIDA CUDs with acceptable radiochemical purity (90%) for up to 31 days but the GHA CUDs produced acceptable ^{99m}Tc-GHA CUDs only up to 16 days.

Based on proven pharmaceutical and pharmacy dispensing principles, some multiple-dose kits used for compounding technetium-99m (^{99m}Tc) radiopharmaceuticals can be dispensed as unit doses (UDs) before radiolabeling. These UDs may be stored at cold temperatures as cold-unit doses (CUDs) for future radiolabeling. This concept of unit dosing can be a very efficient and economical way to compound certain ^{99m}Tc-labeled radiopharmaceuticals.

The concept of CUDs for preparing radiopharmaceuticals is particularly attractive in small hospitals where few patient procedures are performed on a daily basis. Even in large hospitals, this method may still be useful for preparing emergency doses and ^{99m}Tc radiopharmaceuticals that are not routinely used. Previous studies have shown that medronate (MDP) CUDs, pentetate (DTPA) CUDs and exametazime (HMPAO) CUDs could be prepared in evacuated vials (*1–3*). However, the stability of these CUD preparations differ from each other. These studies have suggested that the preparation and storage conditions of CUDs prepared from different radiopharmaceuticals should be individualized in order to achieve optimal results. In this study, we evaluated the radiochemical stability of CUDs stored in syringe form prepared from disofenin (DISIDA) and gluceptate (GHA) kits.

The goal of the study was to investigate the feasibility of preparing CUDs of DISIDA and GHA in disposable syringes. In previous published studies (*1–3*), evacuated vials and nitrogen purging were used to prevent the introduction of air during the preparation procedures. While these procedures are useful and can prolong the shelf life of CUDs, they are not very practical or convenient for preparing CUDs on a daily basis. Nitrogen purging requires a nitrogen tank, laminar flow hood, sterile air filter, and accessories, which may not be readily available in most small nuclear medicine laboratories.

Using evacuated vials has a major disadvantage; a significant portion of the prepared dose is lost in the vial. This problem is particularly acute since most CUDs demand rather small volumes of preparation to avoid unacceptable dilution of tin content. Therefore, nitrogen purging and evacuated vials were purposely not used in this study for the practical reasons of easy preparation and radiolabeling. The CUDs were prepared in syringes and dispensed in the original syringes for injection. This decreased the dispensing time by eliminating the step of dispensing from the reaction vial.

The specific objectives of this study were as follows.

1. Prepare CUDs of DISIDA and GHA in syringes to be stored at −10°C.
2. Compound ^{99m}Tc-labeled DISIDA CUDs and GHA CUDs from their respective CUDs on different days after preparation.
3. Determine the radiochemical purity (RP) of the ^{99m}Tc-labeled DISIDA CUDs and GHA CUDs immediately after radiolabeling.

MATERIALS AND METHODS

Our methodology is shown in Figure 1. The volumes of reconstitution for both GHA and DISIDA kits were based on the allowable reconstitution volumes recommended by the manufacturers. Ten GHA kits (Glucoscan™, Du Pont Co., Billerica, MA) were reconstituted with 2 ml of normal saline and each kit was divided into four 0.5 ml unit doses in disposable syringes. Ten DISIDA kits (Hepatolite, Du Pont Co., Billerica, MA) were reconstituted with 4 ml normal saline

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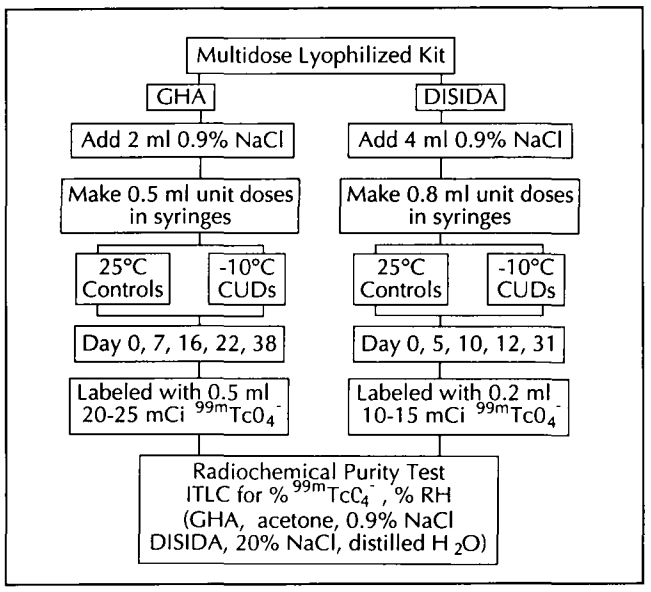

FIG. 1. Methodology flow chart.

and divided into five 0.8 ml unit doses in syringes. All of the unit doses were immediately stored in the freezer at −10°C.

After storing at −10°C for different time periods, four CUDs from each reagent were randomly selected and thawed out at room temperature for 2–5 min. An appropriate volume of ^{99m}Tc pertechnetate was transferred from another syringe, with a needle, into the CUDs in the original syringes (through the needle hub without a needle) for radiolabeling. The reaction mixture was mixed well by inverting the CUD syringe several times.

The volume of ^{99m}Tc pertechnetate used was calculated so that when each CUD was radiolabeled with the appropriate volume of ^{99m}Tc pertechnetate, the total volume of all ^{99m}Tc-labeled CUDs from a single multidose kit would be within the range of the recommended reconstitution volume for the multidose kit. The GHA CUDs were radiolabeled with 0.5 ml of 20–25 mCi of ^{99m}Tc pertechnetate. Thus, the total volume of all four ^{99m}Tc-GHA CUDs prepared from a single multidose kit was 4 ml, which was within the range of the recommended volume (3–7 ml). The DISIDA CUDs were radiolabeled with 0.2 ml 10–15 mCi ^{99m}Tc pertechnetate. The total volume of all five ^{99m}Tc-labeled DISIDA CUDs from one kit was 5 ml. The recommended reconstitution volume for the DISIDA multidose kit was 4–5 ml.

RP tests using the instant thin layer chromatography (ITLC) method described by Kowalsky and Perry (*4*) were carried out 5 min after radiolabeling. The percent of free $^{99m}TcO_4$ and percent of reduced hydrolyzed ^{99m}Tc (^{99m}Tc-RH) species were determined using different solvent systems. For ^{99m}Tc-GHA CUDs, acetone and normal saline were used to determine the free $^{99m}TcO_4$ and ^{99m}Tc-RH species, respectively. The stationary phase of ITLC-SG was used for both solvent systems. In the acetone ITLC-SG system, only the free pertechnetate migrated to the solvent front. In the saline ITLC-SG system, only the ^{99m}Tc-RH species stayed at the origin.

For ^{99m}Tc-DISIDA CUDs, 20% NaCl (ITLC-SA) and distilled water (ITLC-SG) were used to determine the free $^{99m}TcO_4$ and ^{99m}Tc-RH species, respectively. In the 20% NaCl ITLC-SA system, only free $^{99m}TcO_4$ migrated to the front. In the H_2O ITLC-SG system, only the ^{99m}Tc-RH species stayed at the origin.

An identical number of unit doses were prepared but stored at room temperature, serving as controls. They were radiolabeled on the same days as the CUDs.

The radiochemical purity of ^{99m}Tc-GHA CUDs and ^{99m}Tc-DISIDA CUDs was calculated and presented as the percent of RP (%RP). The %RP was calculated with the following formula.

$$\%RP = 100\% - (\%^{99m}TcO_4^- + \%^{99m}\text{Tc-HR})$$

The data were analyzed using the Newman Keul ANOVA (*5*).

RESULTS AND DISCUSSION

This study demonstrated that both GHA CUDs and DISIDA CUDs could be successfully prepared in syringes and stored at −10°C. The preparation procedure was a simple two-step method: thawing out the frozen syringe of CUD; and injecting the appropriate amount of $^{99m}TcO_4^-$ from another syringe directly into the CUD syringe. By putting on the appropriate needle, the radiolabeled CUD in the original syringe was ready to be used. The entire preparation procedure took 5–10 min including the thawing of the CUD.

Results of the radiochemical purity test of ^{99m}Tc-GHA CUDs are tabulated as %RP in Figure 2. The RP of ^{99m}Tc-GHA CUDs (98.3% ± 3.4, N=4) on Day 0 was the same as that of the normally prepared (multidose kit) ^{99m}Tc GHA (97.1% ± 2.5, N=4). The %RP of the ^{99m}Tc-GHA CUDs was slightly decreased from Day 0 to Day 16, but the %RP values were acceptable (within 90% RP). However, there was a significant decrease in radiochemical purity on Day 22 (61.8%

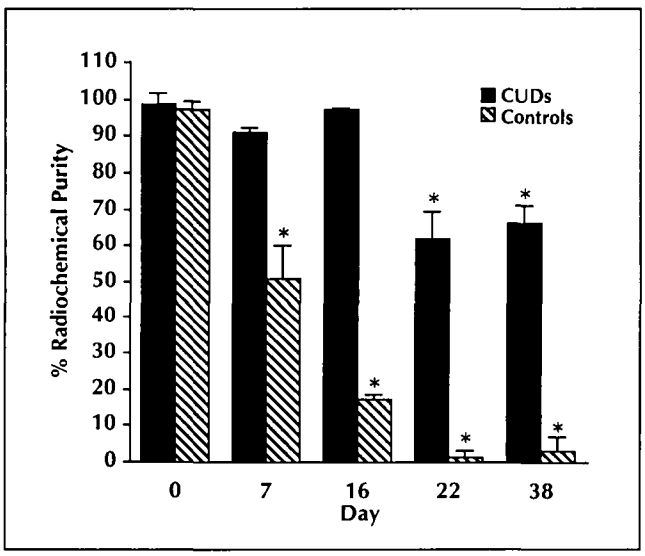

FIG. 2. Radiochemical purity of ^{99m}Tc-GHA CUDs on different days after preparation, * $p<0.05$, Newman Keul ANOVA, n = 4.

RP). The RP of the controls, ^{99m}Tc-labeled GHA UDs stored at room temperature, deteriorated rapidly to 50% within 7 days.

The results from ^{99m}Tc-DISIDA CUDs are presented in Figure 3. Again, the radiochemical purity on Day 0 (96.0% ± 1.8, N=4) was similar to the normally prepared (multidose kit) ^{99m}Tc DISIDA (96.8% ± 1.4, N=4). DISIDA CUDs appeared to be more stable than GHA CUDs. The %RP of ^{99m}Tc-DISIDA CUDs remained acceptable (90%) up to 31 days after preparation. The RP of the controls at room temperature deteriorated rapidly to 1.5% within 3 days. The major radiochemical impurity in all cases was $^{99m}TcO_4^-$ (90%) and less than 10% was ^{99m}Tc-RH species.

In a separate experiment, we investigated CUDs prepared in evacuated vials and purged with nitrogen. All materials and methods used were the same as above except that the CUDs were dispensed in evacuated vials and then purged with nitrogen for 10 min before storage. These CUDs were only studied for two time points. As we expected, the results appeared to show that the CUDs in the evacuated vials with nitrogen purging would be more stable and have a longer shelf life (at least for GHA) than the syringe preparations.

On Day 16, the radiochemical purity of ^{99m}Tc-GHA CUDs in syringe form was 97.3% (± 1.2, N=4) compared to 98.3% (±1.8, N=4) of ^{99m}Tc-GHA CUDs in evacuated vials. However, on Day 22, the results showed 61.8% (±7.4, N=4) for the syringe form, which was significantly lower ($p<0.05$) than the 97.7% (±1.8, N=4) of the evacuated vials. The RP of ^{99m}Tc-DISIDA CUDs prepared from evacuated vials was at least as stable as the syringe form. On Day 24, the syringe form had 93.4% (± 3.4, N=4) and the evacuated form had 94.3% (± 2.3, N=4). On Day 31, the syringe form had 94.5% (± 0.6, N=4) compared to 96.5% (± 0.6, N=4) of the evacuated forms.

The stability difference between GHA CUDs and DISIDA CUDs may be due, in part, to the higher tin concentration in the DISIDA formulation (0.6 mg tin/20 mg DISIDA) than the GHA formulation (0.07 mg tin/200 mg GHA). This observation appears to support the theory that the success of preparing CUDs is probably dependent on the stability of the tin content. The higher tin concentration in DISIDA CUDs may make them more resistant to oxidation than the GHA CUDs, which have a lower tin concentration during storage.

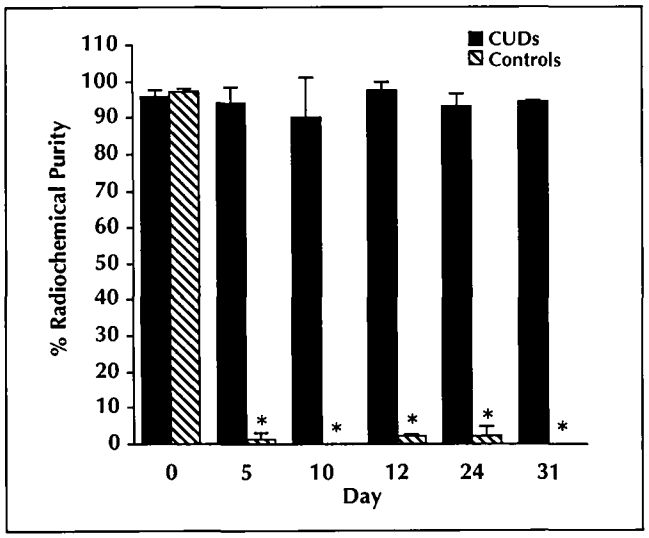

FIG. 3. Radiochemical purity of ^{99m}Tc-DISIDA CUDs on different days after preparation, * $p<0.05$, Newman Keul ANOVA, N = 4.

In another separate study, not presented here, we have also found that GHA CUDs prepared from higher reconstitution volumes (thus, lower tin concentrations) were also less stable than GHA CUDs with higher tin concentrations (lower reconstitution volumes).

Finally, this study demonstrates that the preparation of DISIDA CUDs and GHA CUDs in syringes can be conveniently achieved by storing the UDs at freezing temperatures (at least −10°C) even without evacuation or nitrogen purging. We did not investigate whether ^{99m}Tc DISIDA and ^{99m}Tc GHA, prepared from their respective CUDs, have the same shelf life (kinetics of radiochemical stability) as the ^{99m}Tc-labeled compounds prepared from the multidose kits (the average shelf life is about 6 hr). This will be investigated in the future.

CONCLUSIONS

From the study results, we conclude that the CUD system, whether in syringe form or evacuated form, may be a suitable alternative method for preparing ^{99m}Tc DISIDA and ^{99m}Tc GHA. However, since this preparation method falls outside the package insert instructions, documentation on how to comply with NRC and state regulations and quality control procedures should be strictly followed.

In summary, this study resulted in the following conclusions.

1. GHA CUDs and DISIDA CUDs can be prepared successfully in syringes stored at −10°C.
2. The preparation and compounding process for ^{99m}Tc-GHA CUDs and ^{99m}Tc-DISIDA CUDs is relatively fast and simple.
3. DISIDA CUDs in syringe form (stable up to 31 days) appear to be more stable than GHA CUDs (stable up to 17 days).
4. Using evacuated vials and nitrogen purging may further increase the stability of CUDs and may prolong their shelf life (as in the case of GHA CUDs).

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