Formulation of ^{18}F-FDG: pH Adjustment of Buffered Solution

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The steam-sterilized ^{18}F-FDG of our laboratory frequently has a pH of around 6.5. To avoid decomposition, we studied the possibility of adjusting the pH by adding a pharmaceutical compound but without modifying the usual production sequence and reagents. **Methods**: Citric acid in 4 concentrations (0.01, 0.03, 0.05, and 0.06 M) was added to routine batches of ^{18}F-FDG. Established pharmacopeia quality controls at 0 and 12 h after synthesis were run, and the dilution effect was checked. **Results:** A 0.06 M concentration of 1:15 v/v citric acid brought about a pH range of 5.46–5.68; did not change significantly after 1/10 dilution; and did not interfere with quality control. The results of quality control 12 h after dispensing were in the desired range. **Conclusion:** A 0.06 M concentration of 1:15 v/v citric acid modifies pH in a buffered ^{18}F-FDG solution without the need to change the synthesizer protocol or reagent composition. This new formulation allows pH adjustment; is an easy, reliable, and safe method with no technical difficulties; and does not interfere with the quality of the radiopharmaceutical.

Key Words: buffer; ^{18}F-FDG; citric acid; pH

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Temperature, pH, and specific volume play an important role in ^{18}F-FDG stability. Impurities from epimerization and hydrolysis have been observed at a more alkaline pH (*1*). The rate of decomposition due to steam sterilization is diminished in an acidic environment, and radiolysis of high-activity ^{18}F-FDG solutions is significantly lower at pH 5.5 than at a neutral pH. pH 5.5 appears to be optimal and gives ^{18}F-FDG of high radiochemical purity (~99%) (*2*).

The steam-sterilized citrate-buffered ^{18}F-FDG solution synthesized in a commercial module in our laboratory repeatedly shows a pH higher than 6.5, with the presence of undesirable ^{18}F-fluorodeoxymannose. We proposed to adjust the pH closer to 5.5 by adding citric acid to ^{18}F-FDG before sterilization by heat, without modifying the synthesis sequence and reagent composition.

Citric acid monohydrate (reagent specification as per the European Pharmacopoeia; Merck) was chosen because of the reagent composition of the TRACERlab MX synthesizer (GE Medical Systems) (buffer vial contains disodium hydrogen citrate-1,5-hydrate and trisodium citrate-2-hydrate; ABX Advanced Biochemical Compounds), its acidity and dissociation constants (pH 2.2 in 0.1N solution; pK_a1 = 3.09, pK_a2 = 4.75 (*3*), where pK_a is the negative logarithm of the acid dissociation constant), and its recognition as an excipient in pharmacopeias (*4,5*).

MATERIALS AND METHODS

Citric acid monohydrate in 0.01, 0.03, 0.05, and 0.06 M solution was added in various ratios to three ^{18}F-FDG solutions with pH higher than 6.5 (1:1, 1:15, 1:30, and 1:60 citric acid:^{18}F-FDG [v/v] [30.00–0.16 mM]). pH was tested in all cases (pH meter 3520 [Jenway], with a glass electrode).

TABLE 1
pH of ^{18}F-FDG with Citric Acid Added

Initial citric acid concentration (M)	Ratio of citric acid to ^{18}F-FDG (v/v)	pH of ^{18}F-FDG		
		Batch 1	Batch 2	Batch 3
0	0	6.58	6.59	6.61
0.01	1:1	4.98	4.94	4.94
	1:15	6.27	6.25	6.26
	1:30	6.27	6.28	6.24
	1:60	6.29	6.28	6.29
0.03	1:1	3.91	3.90	3.91
	1:15	5.84	5.83	5.84
	1:30	5.89	5.90	5.88
	1:60	5.88	5.87	5.87
0.05	1:1	3.54	3.49	3.47
	1:15	5.70	5.71	5.66
	1:30	5.65	5.65	5.65
	1:60	5.62	5.65	5.65
0.06	1:1	3.36	3.33	3.32
	1:15	5.5	5.51	5.52
	1:30	5.58	5.57	5.58
	1:60	5.57	5.57	5.58

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TABLE 2
Data of Formulation Tested in ^{18}F-FDG Routine Production

Parameter	1:15 v/v citric acid:^{18}F-FDG		
	0.06 M	0.05 M	0.03 M
Number of batches studied	10	10	10
Radioactivity concentration of batches studied (MBq/mL)	2,600–4,000	2,600–4,000	2,600–4,000
pH range	5.46–5.68	5.51–6.22	5.68–6.52
^{18}F-fluorodeoxymannose (median ± SD)	0.83% ± 0.73%	1.78% ± 0.81%	1.94% ± 0.81%
Pharmacopeia quality control	Passed	Passed	Passed
pH and radiochemical purity 12 h after synthesis	Passed	Passed	Passed

The use of 1:15 v/v citric acid in 0.03 M ($n = 10$), 0.05 M ($n = 10$), and 0.06 M ($n = 10$) concentrations was studied in 30 batches of ^{18}F-FDG (2,600–4,000 MBq/mL), and pharmacopeia quality controls were run in all cases.

RESULTS

^{18}F-FDG at 1:1 v/v reached a pH lower than 5.5 (pH 4 ± 1) for the 4 chosen concentrations. A 0.01 M concentration of 1:15, 1:30, and 1:60 v/v citric acid did not decrease pH enough (6.20 ± 0.10). However, 0.03, 0.05, and 0.06 M concentrations of 1:15 v/v citric acid brought about suitable pH values, as indicated in Table 1.

In routine batch production, the addition of a 0.06 M concentration of 1:15 v/v citric acid produced a pH range of 5.46–5.68, a 0.05 M concentration produced a pH range of 5.51–6.22, and a 0.03 M concentration produced a pH range of 5.68–6.52. Pharmacopeia quality controls had results similar to those for ^{18}FDG with no citric acid added (Table 2).

Dilution with physiologic saline to at least 1/10 was well tolerated.

pH, ^{18}F-FDG, and free ^{18}F-fluoride met pharmacopeia requirements 12 h after dispensing.

DISCUSSION

Formulation with a 0.06 M concentration of 1:15 v/v citric acid produced pH values closer to 5.5 in batches of ^{18}F-FDG ranging from 2,600 to 4,000 MBq/mL. Dilution with physiologic saline to at least 1/10 was well tolerated, but batches of higher activity should be tested.

To avoid degradation, the use of some acidic species is common in the formulation (*2,6,7*), but differences in formulation can have a profound effect on the radiochemical purity of ^{18}F-FDG (*8*). In our case, pharmacopeia quality controls showed results similar to those of ^{18}F-FDG with no citric acid added. Therefore, the substance did not interfere in quality tests (endotoxin test included; no inhibition was detected). The new formulation retained radiochemical purity for at least 12 h.

CONCLUSION

This new formulation can be considered acceptable for routine production. It is an easy, reliable, and safe way to adjust the pH of ^{18}F-FDG produced in a TRACERlab MX synthesizer, without changing the cassette and reagent composition.

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