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THE DEVELOPMENT OF TECHNETIUM - 99m RADIOPHARMACEUTICALS: TECHNETIUM - 99m GLUCOHEPTONATE

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ABSTRACT

A radiopharmaceutical kit for Kidney imaging has been developed. The kit provides a predispensed sterile formulation for reconstitution with sterile Tc-99m pertechnetate solution. The resulting injection contains Tc-99m labelled glucoheptonate. Each kit consists of 3 vials and each vial contains 200 mg. of Sodium glucoheptane and up to 1 mg of Stannous Chloride in freeze-dried form.

INTRODUCTION

A radiopharmaceutical of metastable technetium-99, Tc-99m glucoheptonate which is used as a kidney imaging agent, has been prepared at the Philippine Nuclear Research Institute (PNRI) in kit form so that it may be availed of by hospitals which have their own supply of Tc-99m generators.

EXPERIMENTAL PROCEDURE

The radiopharmaceutical is prepared by adding a freshly prepared solution of sodium glucoheptonate (2.0 g in 10 mL TDW) to 10 mg. of stannous chloride solution dissolved in 10 mL dilute HCl. The resulting solution is passed through a millipore filter (0.22 micron). Two mL fractions of this solution are dispensed into borosilicate vials and lyophylized if not used immediately. The filtrate (2 mL) is made to react with 2 mL of Tc-99m pertechnetate in normal saline solution for five to ten minutes after which it is ready for injection.

Formation of Tc-99m glucoheptonate was confirmed by

(1) Establishing the Rf value of the tracer (Tc-99m) by paper chromatography using Whatman No. 1 as the chromatographic support and 70% ethanol as the developing solvent for 7 hours at 25°C;

(2) Comparing the paper chromatograms of the labelled product with that of sodium glucoheptonate using radioactivity to identify and locate the presence of the Tc-99m glucoheptonate in the chromatogram and those of sodium glucoheptonate by spraying with ammonical silver nitrate solution *(sodium glucoheptonate produces brown spots with this reagent due to the reduction of silver ions to silver by the unchelated glucoheptonate).

STRUCTURE OF PRODUCT

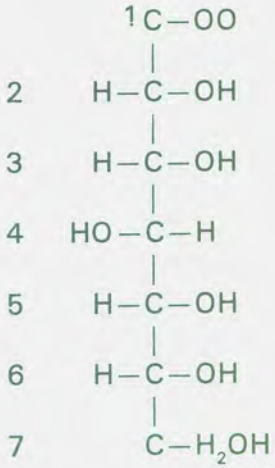
The over-all stoichiometry was inferred from the studies done with Tc-99.

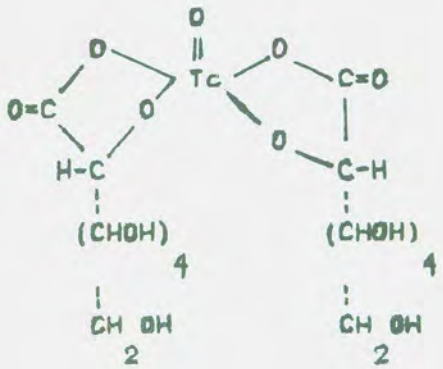
$$TcO_4^- + 2\,(C_7H_{13}O_8)^- + Sn^{2+}$$

$$+ H_2O \text{ - - -> } [TcO(C_7H_{12}O_8)]^- + 2H^+ +$$

$$[SnO_2\,(OH)_2]^{2-}$$

by Kievs who postulated two five-membered ring systems are formed as shown:





TESTS PERFORMED on the Product

1. Paper Chromatography

The chromatographic vessel was previously saturated with the solvent. Whatman # 1 was cut into strips 2.5 cm wide by 20 cm long. The strips were lightly marked with pencil into 1 cm sections. The product was spotted onto the strip about 3 cm from its upper edge. The paper is introduced about 0.5 cm. in the mobile phase and left hanging for a predetermined time. The chromatogram is then taken out, the solvent front is marked and it is allowed to dry in air. The paper is then cut into 1 cm. sections and separately counted in the Gieger-Muller counter. The results were compared with data from Handbook of Radiopharmaceutical Controls of Argentina. See Table 1.

2. Biological Distribution:

Biological distribution of the product is determined by using white mice of approximately 30 g. body weight as experimental animals. Three mice are used for each run into which 0.2 mL of Tc-99m glucoheptonate in normal saline solution was injected intravenously. Three mice were also used for control into which saline solution was injected intravenously. The animals were sacrificed after 30 minutes and the different organs, e.g. heart, liver, kidneys were removed from the experimental and control mice and weighed and counted separately using the GM counter. The concentration of Tc-99m glucoheptonate in the kidneys is between 16 to 25% (19.44 + 3.78%). See Table II.

3. Toxicity

The toxicity test was done by injecting ten mice each time with the product in doses of 0.3, 0.4 and 0.5 ml. and monitoring their survival one day after. Results are shown in Table III.

DISCUSSION OF RESULTS

Results of the tests performed on the product establishes its identity. Rf values of the product are identical to those of Handbook of

Radiopharmaceutical Controls using Acetone and NaCl as solvents and ITLC and whatman #1 as chromatographic supports respectively (Please refer to Table I). For biological distribution, the value of 19.44 + 3.78 compare fairly well with the value of ~ 15% as specified on Isopharm Radiopharmaceuticals Division, Bhabha Atomic Research Center. It's sterility and pyrogenicity tests together with other tests they wish to underake will be performed by BFAD upon submission of required samples solution of pH 6. An intravenous injection of 5 mCi and 15 mCi for kidney and brain scanning respectively is recommended by HRC.

CONCLUSION

The product after passing tests performed by BFAD may be released for use in the local market.

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Table 1. Experimental Chromatographic Results vs. HRC Controls.

	HRC Controls	Experimental
Backing	ITLC SG	WHATMAN #1
Solvent	Acetone	Acetone
Time	5 minutes	25 minutes
Rf value	$99^m TcO_4$: 1.0	$99^m TcO_4$: 1.0 (97%)
	99^m TcGH : 0.0	99^m TcGH : 0.0 (99.5%)
	$99^m TcO_2$: 0.0	$99^m TcO_2$: 0.0 (0.6%)
Backing	ITLC SG	WHATMAN #1
Solvent	NaCl 0.9%	NaCl 0.9%
Time	5 minutes	25 minutes
Rf value	$99^m TcO_4$: 1.0	$99^m TcO_4$: 0.83
	99^m TcGH : 1.0	99^m TcGH : 0.83
	$99^m TcO_2$: 0.0	$99^m TcO_2$: 0.0

Table 2. Results of Biological Distribution Studies.

Date	% Accumulation/Gm Kidney Runs			Average Accumulation per gram kidney tissue in percentage
	1	2	3	
15/05/90	18.20	13.70	24.30	18.73
24/05/90	23.90	15.00	12.30	16.77
30/05/90	15.60	18.80	17.30	17.23
14/06/90	15.30	10.70	20.50	15.50
26/06/90	21.30	26.40	21.50	23.07
04/07/90	19.00	16.00	12.50	15.83
10/07/90	36.50	16.90	20.80	24.73
13/12/90	32.30	27.50	11.20	23.67

Table 3. Results of Toxicity Runs

Date	Dose (ml)	No. of Mice	
		Alive	Dead
12/02/91	0.30	10	0
11/04/91	0.30	10	0
09/05/91	0.30	10	0
21/02/91	0.40	10	0
27/02/91	0.40	10	0
17/04/91	0.40	10	0
14/03/91	0.50	10	0
25/04/91	0.50	10	0
25/05/91	0.50	10	0