Title

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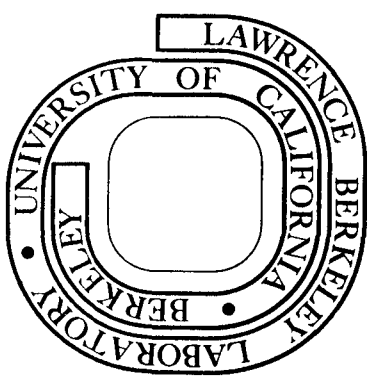

DISCLAIMER

ELECTRONICALLY COMPENSATED POWER SUPPLY FOR ELECTROLYTICALLY LABELED 99m TECHNETIUM RADIOPHARMACEUTICALS

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ABSTRACT

An apparatus was developed for the preparation of technetium (Tc) radiopharmaceuticals by the electrolytic deposition of a precise amount of stannous ion (Sn(II)) into the solution. Preparations of substances which weakly complex Tc demonstrated an enhanced labeling and stability when using this method.

The device is composed of a detector, timer, counter, comparator and control circuit. It is capable of supplying up to 0.1 mg $\pm$10% of Sn(II) in less than 60 sec. The major advantages of this system are the automatic compensation for changes in the conductivity of the preparation, ease of operation, high reliability and low fabrication costs.

Key words: Electrolytic Sn(II); Tc 99m radiopharmaceutical; timer-detector; counter; comparator; control circuit

INTRODUCTION

Currently, technetium 99m (Tc) is the most widely used, gamma emitting, radionuclide in nuclear medicine. There is general agreement that Tc must exist in a +IV valence state, for high labeling yields of radiopharmaceutical preparations.[1] Commercially available generator systems yield Tc as TcO_4^- (Tc in the +VII valence state). Most reactions utilize tin (Sn(II)) as $SnCl_2$ to accomplish the reduction of Tc(VII) to Tc(IV). The major disadvantage of this method is the rapid oxidation of Sn(II) to Sn(IV) and the formation of tin oxides (SnO). To prevent this reaction, most labeling is attempted at an acid pH, possibly with the addition of a stabilizing agent, utilizing the procedures of Eckelman, et al.[2] When attempting to label substances which weakly complex Tc, we have observed the formation of large amounts of insoluble Sn-Tc complex. At a pH of neutral or above, an increase in the pH produced an increase in the formation of insoluble SnO which was evidenced by the increase in the loss of Tc during filtration.

In an effort to better control the amount and the oxidation state of the Sn present in solution, we have also tested the electrolytic method of labeling. As described in the literature, a typical labeling current source consists of a direct current supply, usually a battery or regulated power supply.[3-6] In our experiments the output of this source is applied to two electrodes* which pass through the stopper of a sterile vial** and into the labeling solution similar

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*Tin wire, 0.030 in. diameter, 99.9% pure, United Mineral & Chemical Corporation, New York, NY.
**Thirty milliliters steril vial, New England Nuclear, North Billerica, MA.

to the method of Schneider.[4] The average current passing through the labeling solution is determined with an ammeter. Using Faraday's Law the number of coulombs corresponding to a given concentration of Sn are calculated using Eq. (A).

> Faraday's Law states that one gram equivalent weight (gew) of matter is chemically altered at each electrode for each 96,500 coulombs (c) of electrically passed through the electrolyte.[7]

$$\text{grams of Sn} \; \frac{1 \text{ gew}}{\frac{118.7 \text{ grams Sn}}{\text{valence of Sn (2)}}} \; \frac{96{,}500}{1 \text{ gew}} = \text{coulombs} \qquad \text{(A)}$$

The time required for the plating operation is calculated from the above information and the definition of a coulomb (see Eq. (B)).

> One coulomb is defined as a current of one ampere passing for 1 sec.

$$\text{coulombs} = (\text{amps}) \times (\text{sec}) \quad \text{or} \quad c = I \cdot T \qquad \text{(B)}$$

The inaccuracies and sources of error in this system are obvious. However, we feel that the following contributed most, and were the most readily corrected electronically.

1. The change in conductivity of the labeling solution during the plating process;
2. the inaccuracy of the current measurement;
3. inaccuracy in the manual timing operation.

Chemically, we have shown that the insoluble SnO-Tc varies directly with the Sn concentration while the free untagged Tc varies inversely with the Sn concentration. For these reasons we desired to deposit a more precise concentration of Sn in our labeling solution. The

purpose of this investigation was to design an electrolytic labeling apparatus which would deliver a more precise amount of Sn into the labeling solution. The system we were using consisted of a 0-40 volts dc regulated power supply, an electro-mechanical timer, and a Hewlett Packard model 3476A digital multimeter. When the run button was pressed the timer would energize the power supply, for a preset time. Our experience with this apparatus resulted in the establishment of the following ideal design criteria:

1. variations in the conductivity of the labeling solution should not alter the concentration of Sn deposited into the solution;
2. the time required for deposition of the Sn should not exceed 60 sec;
3. the system should be reliable;
4. the system should be inexpensive;
5. the system should be electrically safe to operate;
6. the amount of Sn deposited should be controlled to deliver in the range of 0.01 mg to 0.1 mg ± 10%.

THEORY OF OPERATION

The following discussion will refer to both the functional block diagram (Fig. 1), which gives a brief summary of this system's operation, and the schematic diagram (Fig. 2), which illustrates the system's wiring. The control bistable (7474) is a D-type edge triggered flip flop which is used as a bistable multivibrator. The term bistable means that the flip flop has two stable states and must be actively changed from one state to the other. One state (in our case the "Set" state) exists when the Q output (7474 pin 5) is hi and the $\bar{Q}$ (Q-not) output (7474 pin 6) is lo. The other state (in our case the "Clk" (Clock state) occurs when the Q output is lo and the $\bar{Q}$ output is hi. Pressing the "RUN" button "Sets" the control bistable (Q hi and $\bar{Q}$ lo). A hi at the Q output causes the coil of relay K to be energized which closes contacts K1. The closure of contacts K1 completes the labeling current (I_L) path. This path, consisting of the tin electrodes, the labeling solution, resistor R1, and capacitor C1, is also the charging path for capacitor C1. The timer (555) controls the charge on C1 by allowing C1 to charge until it reaches 2/3 of the reference voltage, which is the supply voltage for the timer (555 pin 8). The upper waveform in Fig. 3 is a graphical representation of the timer's input (or the voltage across C1) as visualized on an oscilloscope. The lower portion of Fig. 3 demonstrates the negative going pulse which occurs at the output of the timer when capacitor C1 is discharging. The charge on capacitor C1 is directly proportional to the number of coulombs applied to the labeling solution and is expressed mathematically in Eq. (C).

$$CV = IT \qquad (C)$$

where

C = capacitance in fards

V = voltage in volts across the capacitor

I = current in amperes

T = time in seconds.

Note: the coulombs applied to the labeling solution equal the product of the current and the time.

The number of coulombs (area under upper waveform Fig. 3) represented by one timer output pulse may be calculated by first applying Ohm's Law to find the current equivalent of the voltage waveform across C1 (Fig. 3 upper waveform)

Ohm's Law: $E = IR \qquad (D)$

where

E = voltage in volts. In this case we use the average which is 1/2 Vmax + Vmin (from Fig. 3 upper);

I = current in amperes (the unknown);

R = resistance in ohms. In this case we use the sum of the resistance of the labeling solution (measured by multimeter) and R1.

This current equivalent is then multiplied by the duration of one cycle of the waveform across C1 (Fig. 3 upper). The product is the approximate area under the curve. The area's diminsion is in coulombs because 1 coulomb equals 1 ampere second. Thus the timer indirectly measures the coulombs applied to the labeling solution and gives one output pulse when the required number of coulombs have been collected

by C1. The required number of coulombs is set during calibration of the system.

Once the number of coulombs represented by one timer output pulse has been calculated it is a simple matter to use the information in Eq. (A) to calculate the number of pulses corresponding to a desired amount of tin. The counter counts the timer's output pulses and outputs the binary coded decimal (BCD) equivalent of the count. As shown in Eq. (E) a BCD is the binary number composed of the binary equivalents of each digit of the decimal number, going from the largest to the smallest digit.

Decimal	4	0	6	(E)
BCD	0100	0000	0110	

The counter's output is applied to the "A" inputs of the comparator (74LS283). The comparator's "B" inputs come from the thumbwheel switch. The output of the humbwheel switch is a complimented (inverted, 0 is 1 and 1 is 0) BCD representing the number of pulses which must be counted for deposition of the desired amount of tin. The comparator is wired to give a "carry out" (hi on pin 9, 74LS23) when the pulse count equals or exceeds the count set on the thumbwheel switch. The "carry out" from the comparator is applied to the clock (clk); pin 3, 7474) of the control bistable. When a "carry out" occurs the control bistable shifts to its other stable state and de-energizes relay K. De-energizing relay K opens contacts K1 and stops the flow of labeling current. When the bistable shifts states $\bar{Q}$ (7474, pin 6) goes hi resetting the counters and making the circuit ready for another cycle of operation.

SUMMARY

To summarize, let us consider how the system described meets the ideal design criteria stated previously. Compensation for variations in the conductivity of the labeling solution is made automatically by the timer. The timer acts to alter the time between output pulses inversely with the labeling current. By varying the calibration it is possible to deposit the desired amount of tin in much less than the 60 sec limit. We have experienced no system failures in 6 months of operation and because of the inherent reliability of the solid state technology used, we do not feel reliability is a concern. The system is very inexpensive. With the one additional stage of counter, comparator and thumbwheel we are now using the total cost is less than $50. The system is very safe to operate because external voltages do not exceed 30 volts dc. We have confirmed the amount of tin deposited by our system using iodine titration and found that the system's accuracy is well within the 10% limit. During the 6 months this system has been operational we have used it to reliably label several substances which by the $SnCl_2$ or our older electrolytic method had proved difficult to label predictably.

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FIGURE CAPTIONS

Fig. 1. Block diagram.

Fig. 2. Schematic diagram.

Fig. 3. Calibration waveforms.

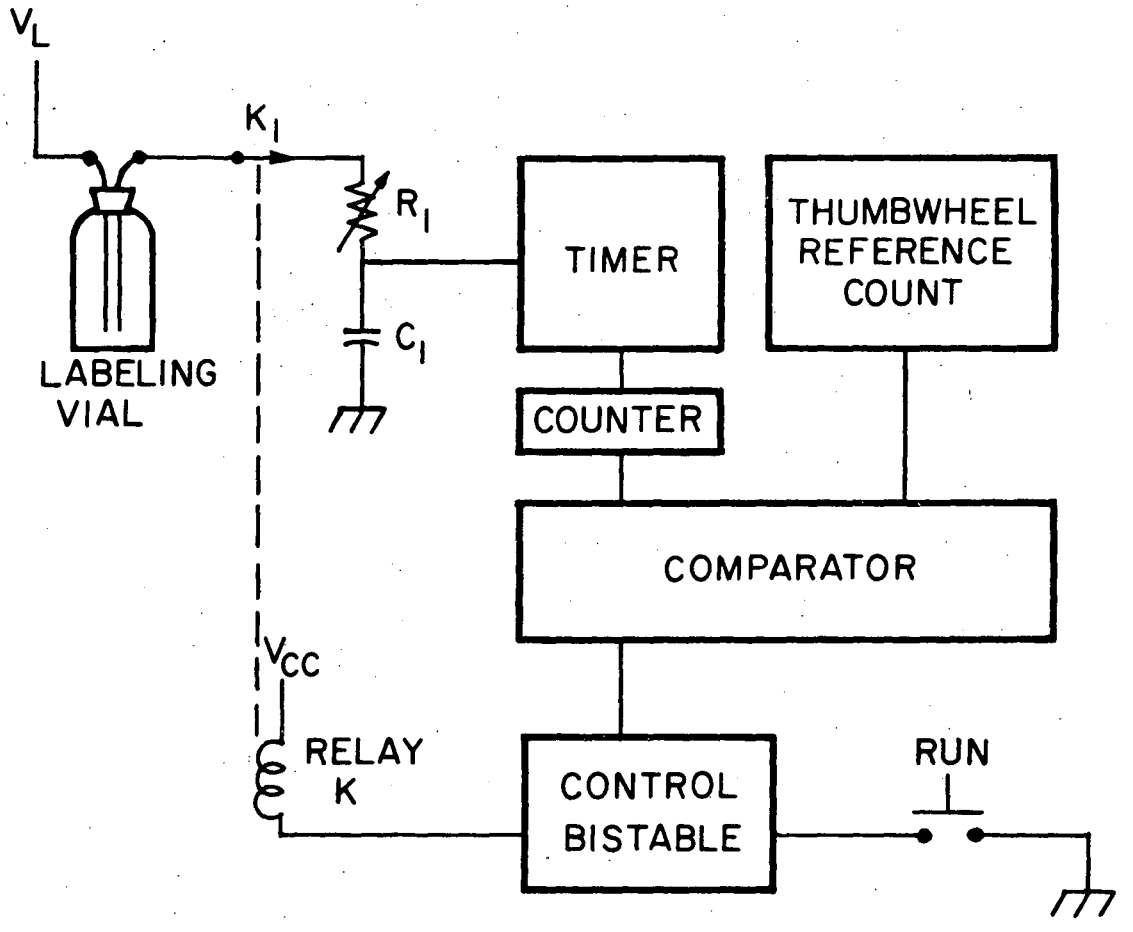
V_L
K_1
R_1
C_1
LABELING VIAL
TIMER
THUMBWHEEL REFERENCE COUNT
COUNTER
COMPARATOR
V_{CC}
RELAY K
CONTROL BISTABLE
RUN
XBL778-3679

Fig. 1

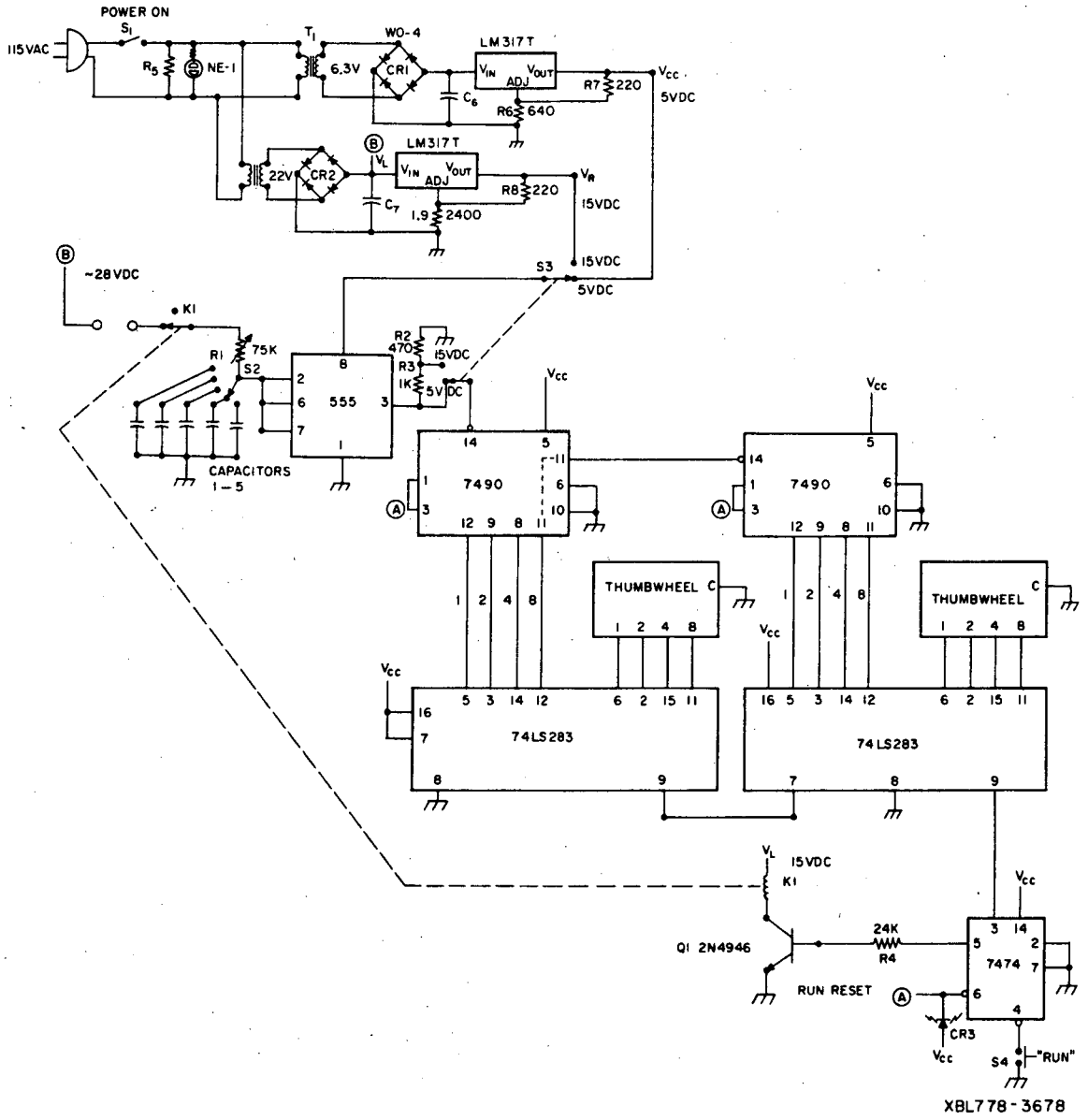
POWER ON
S1
115VAC
R5
NE-1
T1
WO-4
6.3V
CR1
LM317T
VIN
VOUT
ADJ
C6
R7 220
R6 640
VCC
5VDC
22V
CR2
VL
LM317T
R8 220
VR
15VDC
C7
1.9
2400
S3
15VDC
5VDC
~28VDC
K1
R1
75K
S2
CAPACITORS
1-5
555
R2
470
15VDC
R3
1K
5VDC
7490
7490
THUMBWHEEL C
THUMBWHEEL C
74LS283
74LS283
VL
15VDC
K1
Q1 2N4946
24K
R4
RUN RESET
7474
CR3
S4
"RUN"
XBL778-3678

Fig. 2

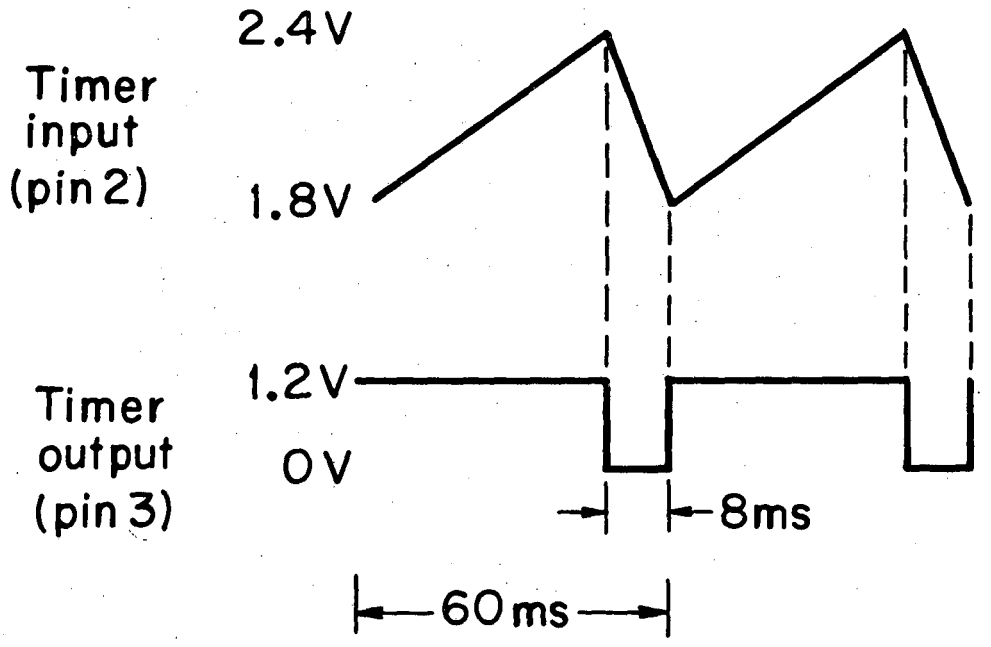
2.4V
Timer input (pin 2)
1.8V
1.2V
Timer output (pin 3)
0V
8ms
60ms
XBL779-3830

Fig. 3

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