THE GEL GENERATOR OPTION

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Abstract

The development of a national policy for guaranteeing an ample supply of ^{99m}Tc to nuclear medicine, involves issues which go beyond the means by which radioactivation is achieved. Indeed, in such an exercise the pragmatic dictates of business and the sensitivities of politics must also be taken into account. Furthermore where a preference towards the nuclear reactor or the potential of cyclotrons is being questioned, the debate is incomplete if the only options that are considered are the fission-based ^{99}Mo generator versus the direct cyclotron production of ^{99m}Tc. There is a third option (also neutron γ-based), an alternative to the fission ^{99}Mo generator, which ought not be overlooked. The application of low specific activity (n,γ) ^{99}Mo to a new type of generator, the Gel Generator, has been the focus of much research, particularly in Australia and more recently in China. After the initial concept had been established in the laboratory, the Australian researchers then undertook a comprehensive program of tests on the Gel Generator to assess its potential, either in the clinical laboratory or the centralised radiopharmacy, for supplying ^{99m}Tc suitable for nuclear medicine. The outcome of this program was a clear indication that the Gel Generator innovation had the capability to provide both technical and economic advantages to the nuclear medicine industry. These advantages are described. Since that time the Gel Generator has been selected for routine use in China where it now satisfies more than 30% of the ^{99m}Tc demand.

1. INTRODUCTION

The majority of the world's supply of ^{99m}Tc is derived from generators containing fission-based ^{99}Mo. While such systems consistently produce ^{99m}Tc with excellent physico-chemical and biomedical qualities, the process of manufacturing fission-based ^{99}Mo involves so many complications that few commercial organisations are willing to be involved, despite the size of the world market. The need for elaborate heavily shielded processing facilities, the need to protect the environment from volatile fission products and the generation of medium level, liquid and solid radioactive wastes are all attendant difficulties which incur substantial economic penalties. These penalties are endured because the nuclear medicine industry has traditionally accepted the view that the fission-based ^{99}Mo generator is the unique solution to the continuously growing demand for an efficient, clinically acceptable and user-friendly source of its mainstay radionuclide. This view is still current, as reflected by the US Government's decision [1] to establish an indigenous capability for manufacturing fission-based ^{99}Mo; but it is also being challenged.

There are modern alternatives to the fission-based ^{99}Mo generator which deserve to be given serious consideration by the nuclear medicine industry. Novel alternatives utilising the particle accelerator, either to produce ^{99m}Tc directly by the proton bombardment of molybdenum [2] or by inducing uranium-238 to fission under the influence of proton bombardment [3], are being proposed. Another alternative follows on from research conducted in Australia in which reactor irradiated molybdenum (ie low specific activity) was incorporated into a zirconium molybdate gel [4]. It was shown that ^{99m}Tc can be separated from such a gel in an exactly the same manner (saline elution) and with identical qualities to that obtained from the fission-based ^{99}Mo generator [5].

Although some general comments are offered on the relative values of the cyclotron and the nuclear reactor as a tool for producing radionuclides, the main thrust of this work is to increase the general awareness of the reactor-based alternative to the present fission-based ^{99}Mo generator. It is intended to demonstrate that this alternative can offer the nuclear medicine industry all the operational advantages of today's generators without the more obvious disadvantages incurred through the processing of irradiated uranium.

2. THE NUCLEAR REACTOR VERSUS THE ACCELERATOR

The production of a radioactive product is more easily achieved via neutron irradiation of a target in a nuclear reactor than by a cyclotron bombardment with charged particles for the following reasons:-

- Reactor targets are easier to design and construct
- Reactor targets require less cooling during activation
- Reactor targets are easier to load and unload

In general, neutron activation cross-sections are orders of magnitude greater than those for charged particles; this leads to higher yields. There are fewer channels of activation with neutrons and as a result it is easier to predict the outcome(s) from neutron activation; this implies lower impurity levels. Nuclear reactors are invariably used to perform simultaneous activation of many targets and as a consequence the nuclear reactor is better suited to large scale commercial production programs.

In the context of ^{99}Mo $\rightarrow$ ^{99m}Tc production, the nuclear reactor offers two independent, high yielding routes of activation both of which have been commercially exploited on a world-scale. On the other hand we see the method proposed for the direct cyclotron production of ^{99m}Tc as having only limited application in a few specialised circumstances. The production of high specific activity ^{99}Mo by the proton induced fission of ^{238}U is still too new a concept to be evaluated with any certainty.

3. THE GEL GENERATOR CONCEPT

The Gel Generator utilises low specific activity (n,γ)^{99}Mo which is processed post-irradiation into an insoluble zirconium molybdate hydrous gel structure. The dried gel contains about 25% by weight of molybdenum and has properties consistent with a cation exchanger*. The process for synthesising the gel is shown in Fig. 1.

The passage of an aqueous eluant (typically either pure water or physiological saline) through a column of the gel releases the ^{99m}Tc; the chromatographic separation can be performed with the same degree of ease as that applying with the fission ^{99}Mo generator.

The gel generator may experience radiolytically induced losses in efficiency similar to those exhibited by the fission ^{99}Mo generator however this effect can be minimised by replacing 5% of the zirconium in the initial gel reactants with cerium [Ce(IV)].

*Synthesising the gel prior to neutron activation produces a relatively useless product because of damage sustained by the gel from the effects of nuclear heating which cause it to lose its ion-exchange properties.

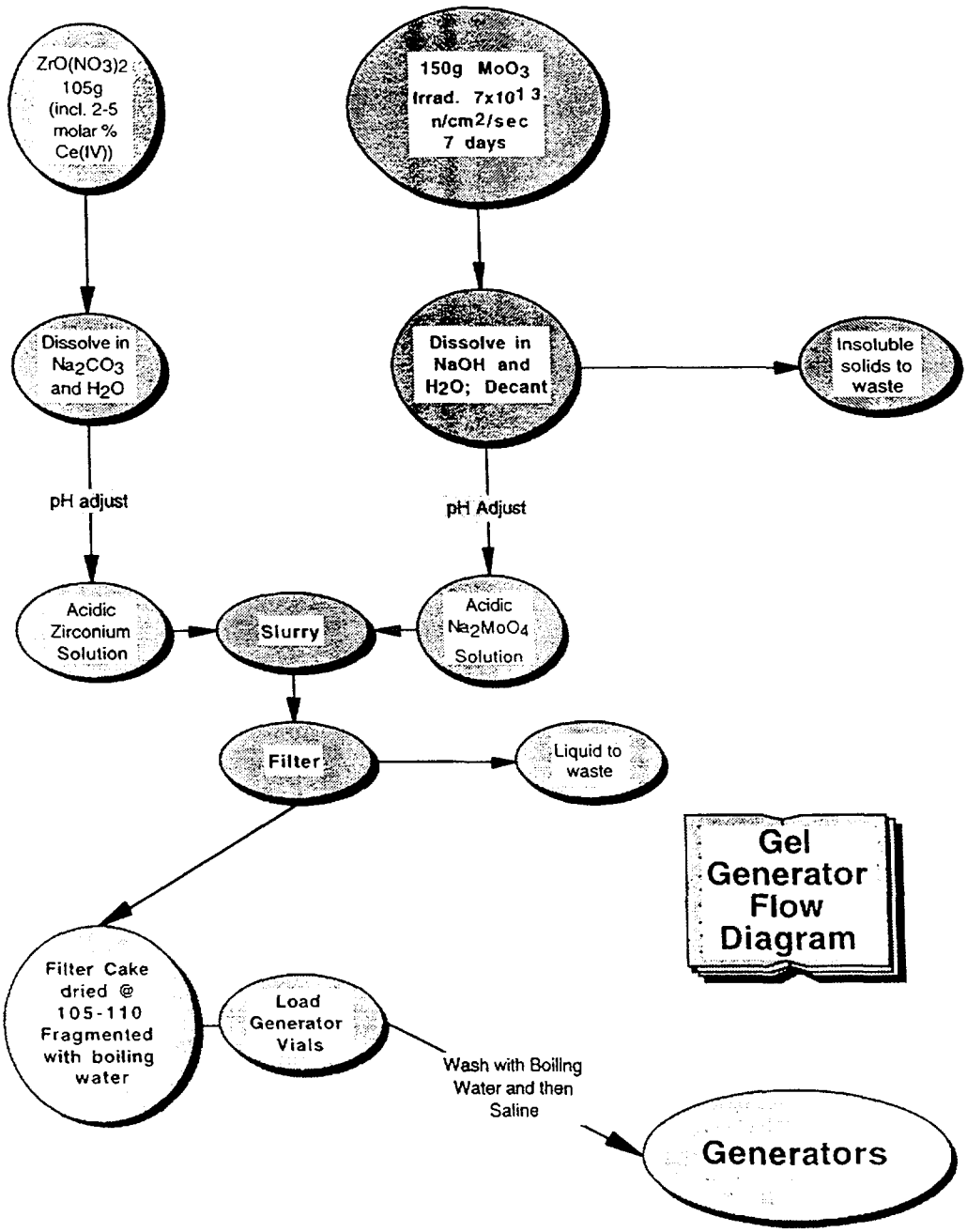

FIG.1. Flow diagram for the preparation of zirconium molybdate (^{99}Mo) gel.

The gel is insoluble and chemically stable within the pH range 2-9. It successfully withstands thermal (wet steam) autoclaving; consequently the gel generator may be presented as a terminally sterilised product.

4. PERFORMANCE TESTING THE GEL GENERATOR

Following the initial research period in which the gel was chemically characterised and its optimum preparation conditions established, a pilot plant was constructed to produce prototype generators in two ranges of activity-firstly a range covering the radioactivities routinely used within nuclear medicine departments (ie the transportable ^{99m}Tc generators) and

then another range of much higher radioactivities typical of those used in centralised radiopharmacies (the "jumbo" generators). A comprehensive program of performance testing was applied to the prototype generators with the following results:

4.1. Elution efficiency

The efficiency with which ^{99m}Tc could be separated from the generators is summarised in Tables I and II.

TABLE I. ELUTION EFFICIENCY OF TRANSPORTABLE GEL GENERATORS

No. of Generators	Range of Activities GBq	Total No. of Elutions	Mean Efficiency %
43	15 to 64	411	82.4 ± 1.2

TABLE II. ELUTION EFFICIENCY OF "JUMBO" GEL GENERATORS

No. of Generators	Range of Activities GBq	Total No. of Elutions	Mean Efficiency %
5	669 to 2023	45	89.3 ± 7.4

TABLE III. ^{99}Mo BREAKTHROUGH

No. Eluates Tested	^{99}Mo Breakthrough		Mean Expiry Time
	Range of Values %	Mean Value %	(h)
408	0.000 to 0.014	0.003	44

4.2. Molybdenum-99 breakthrough

The ^{99}Mo content of the eluates was measured gamma-spectroscopically and the results are summarised in Table III*.

*Because the ^{99}Mo level in an eluate increases with the age of the sample, an alternative statement of radionuclidic purity is employed. The **Expiry Time** is that period of time post-elution necessary before the ^{99}Mo reaches the maximum level allowed by the pharmacopoeia monograph- typically 0.1%)

4.3. Other radionuclidic impurities

After the short-lived radioactivities had decayed (a few days), several of the eluates were re-examined for the presence (identity and concentration) of other radionuclidic impurities. The results of these measurements are shown in Table IV.

TABLE IV. LONG-LIVED RADIO-CONTAMINANTS

No. Eluates Tested	Frequency of Making a Positive Finding	Radionuclide(s) Identified	Concentration %
133	17/133	^{134}Cs	<0.005

TABLE V. CHEMICAL PURITY OF THE ELUATES

No. Eluates Examined	131 Samples
pH	4.5 to 6.0
Zr^{4+} ppm	<5
NO_3^- ppm	<20
Ce^{3+} and Ce^{4+} ppm	<5 to <10

TABLE VI. RADIOCHEMICAL PURITY

Early Eluates		Mid-cycle Eluates		Late Eluates	
No. Samples	% ^{99m}Tc as $^{99m}TcO_4^-$	No. Samples	% ^{99m}Tc as $^{99m}TcO_4^-$	No. Samples	% ^{99m}Tc as $^{99m}TcO_4^-$
42	99.2 to 99.9	43	99.1 to 99.9	43	99.1 to 99.9

4.4. Chemical purity

Eluate samples, taken at the beginning, the mid-point and at the end of a series of elutions were assayed for trace chemical impurities likely to compromise pharmaceutical quality. The results of these tests are summarised in Table V.

4.5. Radiochemical Purity

Radiochemical impurities often arise due to the effects of radiation on the solvent(radiolysis), changes in temperature or pH, or the presence of reducing/oxidising agents. The pertechnetate ion is a strong oxidising agent capable of reacting with traces of reducing substances to produce lower valency species. Using thin layer chromatographic techniques the radiochemical species present in the eluates were investigated (Table VI).

4.6. Elution Profile

The elution profile of column based generators is influenced strongly by physical size and shape [6]. In the case of the gel generator a third factor applies: the bed can be pre-conditioned by extensive washing with saline to remove pertechnetate-retarding anion exchange sites. Following this treatment the elution profile is substantially sharpened and the elution efficiency improved.

At moderate levels of ^{99}Mo specific activity (circa 75GBq ^{99}Mo per g Mo) the elution process is essentially complete within the passage of 10 mL. Some complications arise with very low specific activities because the ^{99m}Tc concentration of the eluates is too low for practical application. However an important property of the gel generator is its ability to be eluted effectively with pure water, in place of saline. This difference can then be exploited to provide the means for overcoming the low ^{99m}Tc concentrations that are characteristic of the large bed "Jumbo Generator".

The following technique for concentrating ^{99m}Tc was developed:-

- A 1g Al_2O_3 column is located downstream of the main generator bed,
- The generator is eluted with just 50mL of pure water,
- Issuing from the base of the generator, the aqueous ^{99m}Tc is pumped through the Al_2O_3 column which strips out the ^{99m}Tc activity. The water is recycled to the top of the generator column and the elution process is repeated 3-4 times.
- A highly concentrated ^{99m}Tc solution can then be recovered ,simply by flushing the small Al_2O_3 column with 5 mL saline.
- The process is amenable to automation and laboratory results indicate that the ^{99m}Tc can be recovered with >90% efficiency and be concentrated by a factor of 20.

4.7. Pre-clinical biological testing

Experiments were performed* in which the relative bio-distributions were compared for several radiopharmaceutical 'cold-kits' reconstituted with either gel ^{99}Mo-derived or fission ^{99}Mo-derived pertechnetate solutions.

The respective bio-distributions, in age-matched groups of 12 rats, were shown not to be significantly different (Unpaired Student t-Test) [5].

*According to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes

The quality of the ^{99m}Tc produced by the gel generator is sufficiently high to presume that this generator should anticipate receiving a wider clinical acceptance than it currently enjoys. When presented either for use in the nuclear medicine clinic or in the setting of a centralised radiopharmacy, the gel generator deserves to be considered as a potential adjunct to, or replacement for the fission ^{99}Mo generator.

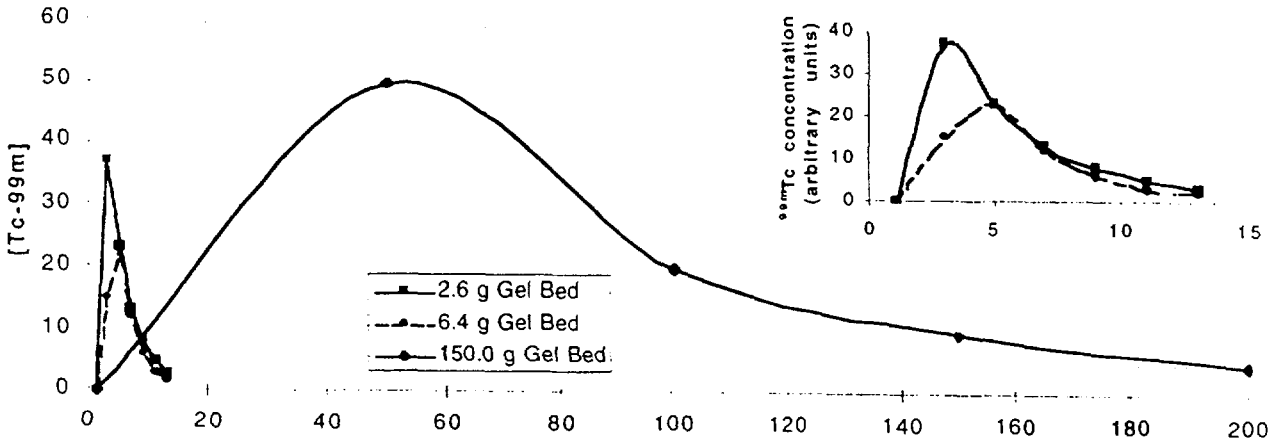

FIG. 2. The effect of bed size on the elution profile.

4.8. Clinical experience

The Gel Generator has not yet progressed to clinical trials in Australia, however it is in routine use in China where it was reported [7] that clinical results are indistinguishable from those obtained from its fission ^{99}Mo counterpart in comparable clinical studies.

4.9. Summary of test results

^{99m}Tc derived from gel generators has been assessed by a battery of tests and has been compared against the international standards of acceptability that would apply to presently available generators. Without exception, the performance characteristics of the gel generator were found to be at least as good as those exhibited by the fission ^{99}Mo generator.

5. OTHER CONSIDERATIONS

Given the close similarity in the technical performances of the two generator types, it is profitable to examine other considerations to find the incentives for change.

5.1. Economic considerations

The cost of producing (n,γ)^{99}Mo is less than that for fission ^{99}Mo. One analysis [5] shows that this differential can be quite substantial; eg $US 0.83 per Ci as compared to $US 57 per Ci. However when the fixed costs associated with generator manufacture are included in the comparison much of this relative advantage is eroded away. Effective costs are also complicated by such considerations as the post delivery calibration time for the ^{99}Mo activity and the type of elution regime. However it would be reasonable to presume that the gel generator technology offers some savings.

5.2. Waste and environmental issues

The processing of uranium targets for the production of fission ^{99}Mo generators gives rise to quantities of medium-level liquid and solid wastes containing uranium, plutonium and several long-lived fission products which require substantial treatment before final disposal can be contemplated.

The gaseous releases from the processing hot-cells are very much reduced by the use of delaying absorbent filters in the dissolver off-gas lines and in the cell ventilation ductwork.

The processing of irradiated molybdenum trioxide to zirconium molybdate gel does not require as sophisticated a waste management strategy.

6. DISCUSSION

The Gel Generator has been shown to be technically equivalent to the fission ^{99}Mo generator.

- From the perspective of the end-user, the Gel Generator retains the simple-to-operate attribute that is an important characteristic of the fission ^{99}Mo generator.
- ^{99m}Tc can be obtained from the Gel Generator with an efficiency close to that of the fission ^{99}Mo generator.
- The overall quality of ^{99m}Tc from the Gel Generator is, to all intents and purposes, indistinguishable from the alternatives.
- There appears to be no special restriction on the field of application for ^{99m}Tc obtained from the Gel Generator.
- Manufacturing zirconium molybdate gel from neutron activated molybdenum trioxide does not require the elaborate processing facilities that are a pre-requisite of all processes treating fissioned uranium.
- The Gel Generator minimizes waste.
- ^{99m}Tc from the Gel Generator is cheaper than that obtained from the fission ^{99}Mo generator
- Gel generator can be presented to the marketplace in the same packaging format, if so required.
- Since more than 80% of nuclear medicine's imaging procedures require the administration of a ^{99m}Tc radiopharmaceutical* the Gel Generator is capable of bringing the benefits of nuclear medicine to a wider population of patients.

China is the first country to attempt to satisfy a significant portion of the national demand for ^{99m}Tc by utilising the gel generator technology. Other Asian countries have also explored the possibility of change.

In the commercial pharmaceutical world, the need to protect society by requiring all new drugs to be formally registered has had the unavoidable side-effect of slowing down the rate of innovation. However the demonstrated potential benefits of the gel generator technology could be sufficient incentive to persuade the radiopharmaceutical industry to consider a change.

**to some 100,000 patients per day world-wide*

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