ANALYTICAL APPLICATIONS OF CYCLOTRONS IN
BIOMEDICAL FIELDS - CHARGED PARTICLE ACTIVATION ANALYSIS

M. Anwar Chaudhri

Department of Medical Physics, Austin Hospital,

Melbourne and University of Melbourne,

Vic. 3084, Australia

ABSTRACT

Activation analysis of biomedical materials is another important and useful application of modern cyclotrons. Various methods and theories of charged particle activation analysis are discussed and some practical examples are given. Activation sensitivity curves, for one-particle-emission reactions through proton, deuteron and alpha bombardment of any element with $Z=20$ to $Z=92$ in a tissue matrix are given for bombarding energies of up to 35 MeV.

1. INTRODUCTION

Production of short-lived neutron deficient radio-isotopes for diagnostic studies is by far the most commonly used application of medical cyclotrons, and almost all such cyclotrons are engaged in this activity. However, there are other important applications of cyclotrons in medicine and biology which are also being pursued successfully in many cyclotron establishments around the world. These are production of fast neutrons for therapy, and activation and reaction analyses using accelerated charged particles and neutrons. The neutron therapy aspects of cyclotron applications has been recently described by Chaudhri [1]. In this paper, we are presenting some of the analytical applications of cyclotrons - that is the elemental analysis of biological materials with cyclotron produced beams of charged-particles. Activation analysis of biomedical material with cyclotron produced fast neutrons is described in another paper of the Proceedings.

Particle induced X-ray emission analysis (PIXE) is another accelerator based analytical technique which is commonly used for trace element analysis. However, small accelerators (Van de Graaffs, etc), rather than cyclotrons, are generally used for PIXE. With this method most elements heavier than F can be conveniently determined with detection limits of a few ppm. The sample preparation for PIXE analysis is relatively simple and small quantities of the sample are required. A great deal of useful work on the analysis of biomedical samples can be carried out, and in fact has been carried out, with PIXE. However, there are many elements of interest in biomedical fields which cannot be conveniently, or at all, determined by PIXE as it is not sensitive enough. Furthermore, for elements lighter than F, PIXE is not practical.

Charged particle activation analysis (CPA), using modern cyclotrons, tend to overcome the shortcomings of PIXE. With CPA not only elements lighter than F can be determined but also sensitivities of as low as ppb can be achieved in favourable circumstances. Furthermore, certain elements, such as Al, Si, Ti, Cd, Tl, Pb, Bi, etc., which cannot be conveniently or at all determined with slow neutron activation analysis (by far the most commonly used nuclear analytical method) can also be measured with CPA. In this paper the technique of charged particle activation analysis of biomedical materials, using cyclotrons, is described. Different theories of CPA and some examples, where this method has been successfully applied, are presented. The Activation Sensitivity Curves, for the detection of most elements with atomic numbers between 20 and 90 in a tissue matrix, when activated with proton, deuterons and alphas of up to 35 MeV and one-particle emission reactions, are presented in graphical form. Full comprehensive data, including two and three particle emission reactions, would be published elsewhere [3].

Although there are many papers in the literature on CPA, including a recent book by Vandecasteele [4], most of the authors deal with metals and semiconductors and not with biomedical samples. In fact, Vandecasteele devotes only a few lines in his book on CPA as applied to biomedicine [4].

2. CHARGED PARTICLE ACTIVATION ANALYSIS

As already mentioned CPA using a cyclotron offers many possibilities for carrying our trace elements determination in biomedical material. Up until now mostly protons have been used for CPA, though other projectiles, such as deuterons, He-3 and He-4 particles, offer a great deal of potential too. However, unlike neutron activation analysis, there are a number of practical difficulties in CPA which has to be overcome. These are:

i. Energy loss and heat generation: The charged particles lose their energy rapidly in the biological material thus generating a great deal of heat in a small volume and damage the sample. This effect/damage can be minimized by cooling the sample,[5] and or by mixing the sample (usually dried and powered) with analytical grade graphite powder to conduct away heat.

ii. Simultaneous or controlled similar irradiation of the sample (to be analysed) and the "standard" (with known trace elements composition) is required. This can generally be achieved by keeping the irradiation conditions (energy, current, etc) stable during irradiation and monitoring the beam carefully. Simultaneous irradiation of the "standard" and sample can also be accomplished by mounting the two on a special holder and rotating the holder at a constant speed during irradiation. In this way both the standard and sample are bombarded with identical amount of charged particles.

iii. The trace element which is being determined has to be ;uniformly distributed in the sample to be analysed. This condition is generally met in biological fluids while for organs the sample is freeze dried and/or ashed, and then homogenized.

iv. A knowledge of the major constituents of the matrices of the sample and the 'standard' is required in order to calculate the range of charged particles in them for estimating the activation depths.

As shown by Chaudhri et al,[6] the induced activity at saturation A, in an element/isotope Y, uniformly distributed in a thick sample X, after irradiations with a beam of charged particles of atomic number z and energy E(MeV), is given by the activation equations:

$$A = cf\,(N_A/W) \cdot (6.25/z)\,10^{12}\,I \int_{E_o}^{E_i}\sigma_E(-dE/dx)^{-1}dE \quad (1)$$

where c = the concentration of Y in X (in ppm or ppb)

f = the natural abundance of the isotope in nuclide Y undergoing nuclear transformation

N_A = the Avegadoo's number

W = the atomic weight of Y

E_i = the incident energy of the projectiles

E_o = the lowest energy for which an appreciable amount of activity in Y would be produced.

I = the current in microamperes of the incident charged particle beam falling on the target/sample.

σ = activation cross section for the element/isotope Y

dE/dx = the stopping power of the incident charged particles in the matrix X.

The Eq.1 can be written as

$$A = CKIF \quad (2)$$

where $\qquad K = f\,(N_A/W) \times (6.25 \times 10^{12})/z$

and $\qquad F = \int_{E_o}^{E_i}\sigma_E\,(-dE/dx)^{-1}dE$

The induced activity for any given irradiation time t is given

$$A_t = CKIF\,(1-e^{-\lambda t})$$

where λ is the decay constant of the activity being induced in Y.

In order to obtain the values of A for different bombarding energies F has to be evaluated at these energies. This cannot be done by exact integration as neither the σ nor dE/dx have simple and useful analytical forms. Therefore this integral has to be calculated by numerical integration. The values of σ-, the reaction cross section, at different bombardment energies can be taken from the known excitation functions and those of the stopping powers from the tabulations of Andersen and Zigler[7] Zeigler[8]. If A is measured experimentally under known bombarding and measuring conditions then using eqn.U, the value of c the concentration of Y in X can be calculated.However, in practice it is generally more convenient to use the "comparator method" for activation analysis with charged particles as is the case of neutrons.In this method a standard thick sample Xs is irradiated simultaneously or under similar (identical if possible) conditions as the unknown sample X containing an unknown concentration c of Y. The induced activity in the two cases A_s and A can be related by Eq. 2 as

$$A_s/A = C_s I_s F_s/CIF \quad (3)$$

which can also be written as

$$A_s/A = C_sQ_sF_s / CQF \qquad (4)$$

where Qs and Q are the beam charges collected at the Standard and sample respectively during irradiation at identical or similar beam currents.

In order to make use of Eq. 4) the integrals F_s and F have to be calculated for the standard and the sample matrices, which is a relatively laborious and complex task. To simplify this Chaudhri et al[6] used some approximations and presented a modified equation

$$\frac{A_s}{A} \simeq \frac{C_sQ_s}{CQ}\frac{(dE/dx)}{(dE/dx)_s} \qquad (5)$$

where (dE/dx)s and (dE/dx) are the stopping power values for the standard and the sample at the mean energy (Ei + Eo)/2.

They showed, though extensive calculations, that more accurate results could be obtained with Eqr.5 than with previous approximations.[9]

Using Eq.1, we have calculated the activation sensitivities of all the elements with atomic numbers between 20 and 90 assumed to be uniformly distributed in a tissue matrix, by bombardment with protons deuterons and alphas of up to 34 MeV. The results for a "thick" biological sample (tissue matrix) and for one particle emission - reactions are shown in Fig.1 and 2. The results for 2 and 3 particle emission reactions and for other matrices would be published elsewhere.[3]

Thick target activation sensitivities can be read directly from the "Activation Curves" at given irradiation conditions. These curves can also be applied to thin samples of known thickness simply be taking the difference between activation sensitivities at the energies at which the charged particle beam enters and leaves the target sample.

As already mentioned only a limited number of papers have been published on CPA of biomedical samples. Most of the studies are confined to the analysis of standard reference materials, calculating the minimum detection limits and pointing out the potential of this method rather than its application to particular biomedical problem. [10-14]

By using protons of 10-13 MeV at 500nA - 1uA intensity and irradiation of up to 1 - 2 hours, detection limits of as low as a few ppb to many ppm were obtained for many elements.

Most of the authors have used protons for activation analysis. But with modern cyclotrons which are equally capable of providing beams of deuterons, He3 and He-4 particles, activation with these particles can also be

carried out. However, again as is the case for proton activation analysis, there are very few papers in the literature on the applications of these particles on the activation analysis of biomedical materials. Deuterons and He-3 particles, which are both loosely bound would induce many nuclear reactions in most elements throughout the periodic table and therefore should be quite useful for the purpose of activation analysis. However, in practice this is not the case and relatively fewer (compared to protons) activation analyses have been carried out with d + He-3. Perhaps, one of the main reasons could be that these particles produce positron activities from many elements/isotopes, thus involving the complex task of separating a number of exponentials with different half lives, if radiochemical separation was to be avoided.

As early as the mid sixties Ricci and Hahn [9] promoted the idea of activation analysis with 18MeV He-3 particles. For a number of elements they determined the sensitivities of detection, both experimentally and theoretically, with good agreement between the two methods. Sastri et al [15] used 14 MeV He-3 beams for activation analysis of a number of elements with Z between 12 and 47. For irradiation time of 1 hour or 1 half life of the product nuclides (which ever is shorter), at 2μA they calculated the detection limits to be

1 - 50 ppb for Al, Ti, V, Mn, Ni, Zn and Nb,

50 - 100ppb for Mo,

100 - 500ppb for Mg, Cr, Fe, Zr, Ag.

Kosmali and Schweihart[16] compared the potential of 20MeV protons and deuterons with 40MeV alphas and He-3 particles for activation analysis of medium Z elements. Only those product nuclides with half lives between 10 min and 3 days were considered. They concluded that the protons provided an optimum compromise between sensitivity and selectivity.

Recently we have developed a new method for the determination of carbon in dental hard tissue by activation analysis with He-3 beams and applied it to study the role of carbon in tooth decay.[17]

3. SAMPLE HANDLING AND TREATMENT

As already mentioned, unlike neutron activation, in CPA a large amount of energy is deposited in a small volume in the sample. Therefore, biological material, which are predominantly organic, are liable to decompose unless appropriate steps are taken to avoid it. Chaudhri et al[5] pelleted the sample, covered it with a thin Al-foil, mounted it on a Cu-holder and cooled the sample holder and thus the sample with liquid nitrogen. In this way they observed that even after 1 hour of irradiation with 8.5 MeV protons at up to 1uA intensity, there was no decomposition and/or deterioration of the sample material.

The specially designed container could hold enough nitrogen to last for more than a couple of hours.

Zikovsky et al[10] mixed freeze dried biological materials, standard reference materials, (SRM) with nuclear grade graphite, pressed into pellets and wrapped them in Al-foils. They showed that this sort of set up could withstand 12 MeV protons at 0.6 uA for 1 hour. Cantone et al[12] pressed freeze dried serum a 0.7 mn thick pellet, sandwiched it in a 6um Mylar and an aluminized Mylar foil of 30um thickness, and cooled the samples to -5°C with freon. They demonstrated that such a system could withstand irradiation with 23 MeV proton at 300nA for 3 hour. Bonardi et al[11] successfully used high purity graphite container in which various SRM's were pressed, cooled it with freon, in order to determine Pb by using 31 MeV protons at 0.5 - 0.6 uA. Besides cooling, and mixing the freeze dried biological samples with a heat conducting material such as graphite[10] in order to avoid the damage to the sample under irradiation, one can also use an internal standard in order to compensate for the loss of the sample material[13].

However, generally speaking it is advantageous to mineralize the biological sample either by LTA (low temperature ashing) or by careful incineration at 400 - 450° Naturally some volatile elements, such as Br, Se, Hg, etc., would be partly lost, but a considerable increase in the sensitivity of detections would also be obtained.

For example the residual ash is only about 1% referred to the original liquid and about 10% referred to the freeze dried sample.

4. CONCLUSIONS

It has been pointed out that CPA of biological materials, using cyclotrons, is a practical and worthwhile analytical method. It has certain difficulties, such as the excessive heating of the samples during the irradiation. However, as demonstrated it can easily be overcome by mixing the samples with graphite and/or cooling the sample holder. Good sensitivities of detections for many elements (e.g. as low as a few ppb in favourable circumstances) can be obtained. Up until now about 15 elements have been determined in biological materials, mostly by proton activation and instrumental analyses. This method is specially useful for the determination of those elements which can not be detected at all, or with sufficient sensitivities with fast neutron activation analysis.
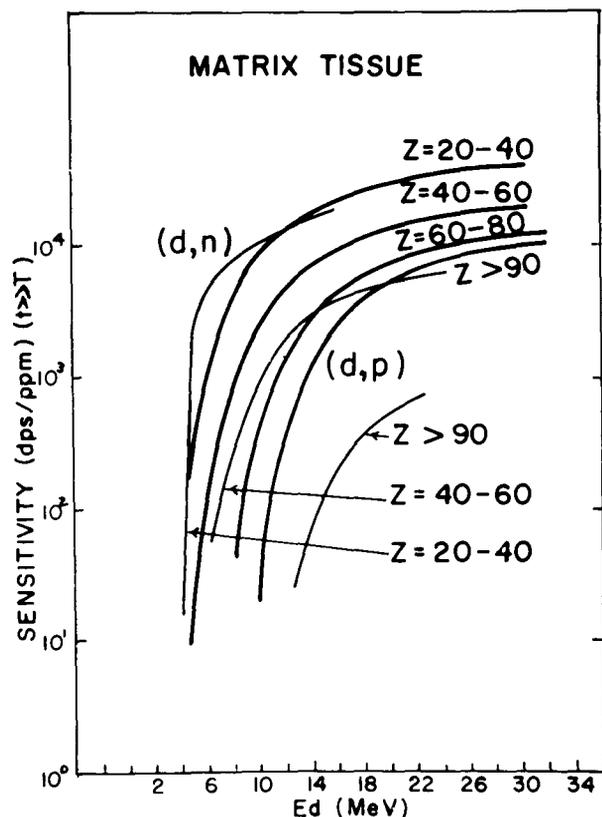

Fig. 1. The sensitivity curves at saturation for all the elements with atomic numbers from 20 to greater than 90 activated by protons and alphas of different energies through the (p,n) and (α,n) reactions.
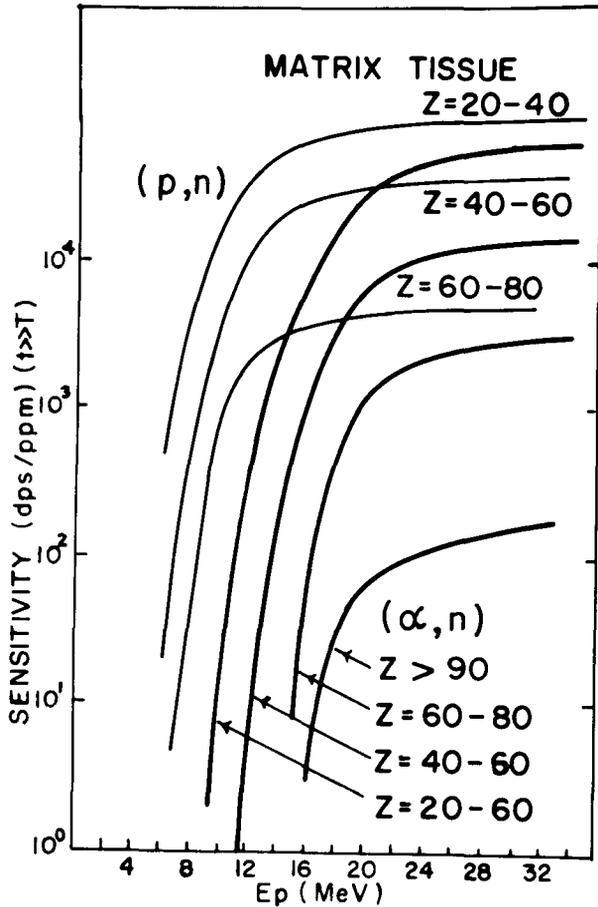
Fig. 2. The sensitivity curves at satu-
ration for all the elements with atomic
numbers from 20 to greater than 90 act-
ivated by deuterons of different ener-
gies through the (d,n) and (d,p) react-
ions.

5. REFERENCES

1. Chaudhri, M.A., "Cyclotron production of neutrons for therapy - Historical development and current status". Acta Radiologica, Supplementum **376**,53(1991)

2. Chaudhri, M.A., "A simple method for estimating activation sensitivities of different elements/isotopes with cyclotron produced neutrons", Proc. XIII Int. Conf. on Cyclotrons and their Applications.

3. Chaudhri, M.A., "Activation sensitivities of all the elements with Z from 20 to 90, in different matrices, activated with protons, deuterons and alphas of up to 34 MeV. To be published.

4. Vandacasteele, C., Activation Analysis with charged particles (Ellis Horwood Ltd., Chichester, 1988).

5. Chaudhri, M.A. and Lee, M., "Trace elements determination in blank Polystyrene air filters by charged particle activation analysis with a cyclotron" in Proceedings of the Twelfth International Conference on Cyclotrons and their Applications (World Scientific, Singapore, 1991)pp.612.

6. Chaudhri, M.A., Burns, G., Reen, E., Rouse, J.L. and Spicer, B.M., "A method for charged particle activation and its application to fluorine determination in biological materials", J.Radioanal. Chem. **37**,243(1976)

7. Andersen, H.H. and Ziegler, J.F., Hydrogen Stopping Powers and Ranges in all Elements (Pergamon Press, New York, 1977).

8. Ziegler, J.F., Helium Stopping Powers and Ranges in all Elemental Matter (Pergamon Press, New York, 1977).

9. Ricci, E. and Hahn, R.L., "Theory and Experiment in rapid, sensitive He-3 activation analysis", Anal.Chem. **37**,742(1965)

10. Zikovsky, L. and Schweikert, E.A. "Comparison of non destructive proton and neutron activation analysis: The case of biological samples", J.Radioanal. Chem., **37**,550(1977)

11. Bonardi, M., Birattari, C., Gilardi, H.C., Pierta, R. and Sabbioni, E., "Development of proton activation analysis for the determination of heavy metals in biological matrices: excitation functions, irradiation system and selective radiochemical separations", J.Radioanal .Chem **70**,337(1982)

12. Cantone, M.C., Molho, N. and Pirola, L., "cadmium and titanium in human serum determined by proton nuclear activation", J.Radioanal. Chem. **91**,197(1985)

13. Masumoto, K. and Yagi, M., "Simultaneous determinations of P, Cl, K and Ca in several control serums by alpha particle activation analysis using the internal standard method, J.Radioanal. Nucl. Chem. **109**,449(1987).

14. Yagi, M. and Masumoto, K. "Instrumental charged particle activation analysis of several selected elements in biological materials using the internal standard method", J.Radioanal. Nucl. Chem. **111**,359(1987)

15. Sastri, C.S., Petri, H. and Erdtmann, G., "Determination of 13 elements with atomic number between 12 and 47 by 14MeV He-3 activations analysis", Anal. Chem. **49**,1510(1977)

16. Kormali, S.M. and Schweikert, E.A., "Charged particle activation of medium Z elements", J.Radioanal., Chem. **31**,413(1976)

17. Chaudhri, M.A. and Crawford, A.C., "Carbon determination in human teeth by activation with He-3 ions", Nuclear Analytical Methods in the Life Sciences, Ed. Zeisler, R. and Guinn, V.P. (Humana Press, Clifton, N.J. 1990)521