Experimental Studies on Absorbed Dose in Radiation Sterilization of Pharmaceutical Preparation

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(Received June 15, 1991)

For radiation sterilization, it is necessary to decide the irradiation conditions considering a balance between sterilization efficiency and chemical changes of samples by irradiation. These effects may be estimated by the product of two factors (D_{10} and G value) and absorbed dose. In this work, it has been found experimentally by using Fricke dosimeter that the absorbed doses of the samples in vessels different in size, material, volume, etc. are not equal under the same gamma-ray irradiation condition. The correction factor from exposure to absorbed dose was estimated to be 6-7% for organic vessels (a polyethylene bag and a polystyrene vial) and a 20-ml glass vial, 9% for a 10-ml glass vial, and 10% for the 5-ml glass vial. These values of the correction factor were confirmed by using the changes of enzymic activity of saccharated powder pepsin preparation. In the cases of using organic vessels and the 10-ml glass vial, G-values for the change of the enzymic activity were calculated to show similar values in the range from 0.79 to 0.82. However, in the case of a small glass vial (5-ml), the value was 0.93.

1. Introduction

In radiation sterilization, it is necessary to decide the radiation doses considering a balance between sterilization efficiency and chemical changes of samples by irradiation. These effects may be estimated by the product of two factors (D_{10} and G values) and the radiation dose, for which the absorbed dose (in units of Gy) is employed. When more accuracy is required, one of the following methods is used: (1) to measure the absorbed dose with the radiation sensors having physico-chemical properties similar to those of the sample or (2) to convert the exposure to the absorbed dose by calculation considering the electron density in the irradiated sample. Generally, the latter is simpler and more convenient. On the other hand, chemical changes of irradiated materials are influenced by their moisture contents. The specimens are irradiated in the packed condition of an airtight vessel made of glass or plastic. However, when the vessels with high electron density materials or small volume are used, the scattering effects of gamma-rays and secondary elec-

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trons connot be disregarded. In this work, measurements of the absorbed dose by the Fricke dosimeter were made to estimate the correction factor of the exposure to the absorbed dose. The changes of enzymic activities of saccharated pepsin preparation in small vessels were also measured, and the calculation of G-values was carried out. The kinds of examined vessel were glass vials, a polystyrene vial and a polyethylene bag.

2. Conversion of Exposure to Absorbed Dose

In the conversion of the exposure to the absorbed dose, the difference in the electron densities in the sample material and air must be corrected by multiplying the correction factor f given by $f=(\mu_{en}/\rho)_{med}/(\mu_{en}/\rho)_{air}$, where$(\mu_{en}/\rho)_{med}$ and $(\mu_{en}/\rho)_{air}$ are ther atios of the absorption coefficient to the densities of sample material and air, respectively*. When the irradiated material is aqua solution or organic material, 1.0 C/kg is equivalent to 33.7 Gy. On the other hand, the energy absorption rate is not uniform near the boundary of two media under gamma-ray irradiation. In using gamma-rays of ^{60}Co, secondary electrons are generated mainly by the Compton effect. Electrons have higher ionization ability and the shorter range compared with gamma-rays. Thus, the non-uniformity is produced in the dose distribution near the boundary of media with different Compton cross sections. The absorbed doses near the boundary of two media are shown in Fig. 1 [1] for the gamma-rays incident from the left side, where, curve(a) shows the case for gamma-rays only, and curve(b) for a mixture of gamma-rays and electrons. For a three-medium system consisting of, for example, air, the wall of the vessel and the irradiated material, the distribution near the boundaries is more complicated and behaves as shown schematically in Fig. 2. When parallel rays are incident on aqua solution in the vessel of higher density

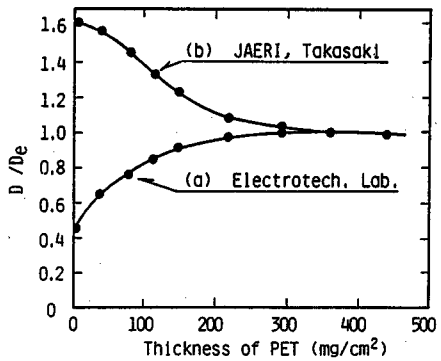

Fig. 1 Dose distribution near the boundary of two media

* For the simplicity of calculation, we express the exposure and absorbed doses in old units of Roentgen (R) and rad; 1 R is equivarent to 0.87 rad for air, and to 0.97 rad for aqua solution or organic materials.

material such as glass, the doses near the boundary ((a) in Fig.2) are different from the dose at the center of the vessel ((b) in Fig.2).

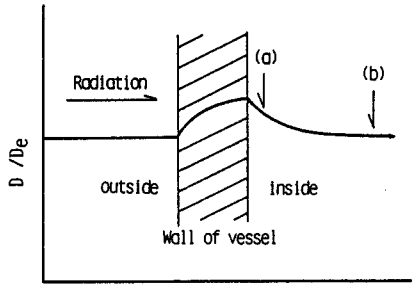

Fig. 2 Schematic diagram of the dose distribution near the wall of the sample vessel

3. Experiment

3. 1 Irradiation condition

As shown in Fig.3, Pencil-type sources of ^{60}Co were inserted in the wall of a cylindrical container placed at the bottom of a water pool. Irradiation of sample was carried out in a stainless-steel basket put in the middle of the source container. As shown in Fig.3, the exposure rate in the basket was higher by about 10% near the wall in the horizontal plane and lower by about 10% near the bottom or top wall in the vertical plane. The samples were set in the middle of the basket packed with formed styrol resin having an apparent density of 0.032g/㎤. The exposure rate was 49.0C/kg•hr(0.19MR/hr) at the center of the basket, and the ranges of exposure were from 1.29 to 7.74C/kg(from 0.5×10^4 to 3.0×10^4R). The temperature of pool water was 25±1 °C.

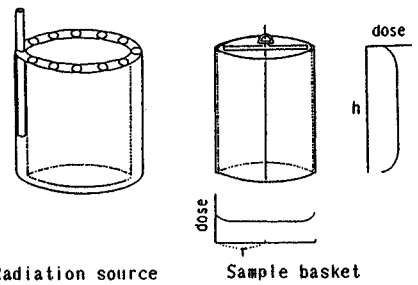

Fig. 3 Schematic diagram of the radiation source and the sample basket

3. 2 Sample vessel

The vessels used in this experiment were a commercial light brown glass vial, a transparent polystyrene vial and a polyethylene bag. The volumes, sizes, wall thicknesses and specific gravities of these vessels are shown in Table 1.

Table 1 Sample vessels used in the experiment

Light brown glass vial	Vol. 5ml, diameter 14mm, wall thickness 0.80mm
〃	〃 10ml, 〃 18mm, 〃 1.00mm
〃	〃 20ml, 〃 24mm, 〃 1.25mm
Polystyrene vial	Vol. 8ml, diameter 16mm, wall thickness 1.20mm
Polyethylene bag	Size 100×70mm, wall thickness 0.04mm

3. 3 Method of determining absorbed dose

Fricke dosimeters were employed for the measurement of the absorbed doses in the sample vessels. As the theory and procedure of the dosimeters are well known, they need not be explained here in detail. The principle is the determination of the oxidated rate of iron ions produced in Fricke solution by gamma-ray irradiation. The range of applicability is from 40 to 400Gy (from 4×10^3 to 4×10^4R). [2)]

4. Results and Discussion

4. 1 Relationships between exposure and absorbed doses

If the Compton electrons produced near the wall of the sample vessel under gamma-ray irradiation are neglected, the absorbed dose can be theoretically calculated with the relation 1R =0.97 rad. The relationships between the exposure and the absorbed dose measured by Fricke solution are shown in Fig.4. In this figure, the broken line shows the theoretical relation under the above assumption (1 R=0.97 rad). There are slight differences between the theoretical and experimental absorbed doses, and also between the experimental values for different vessels. The yield of Compton electrons are directly proportional to the surface area of the sample vessel,

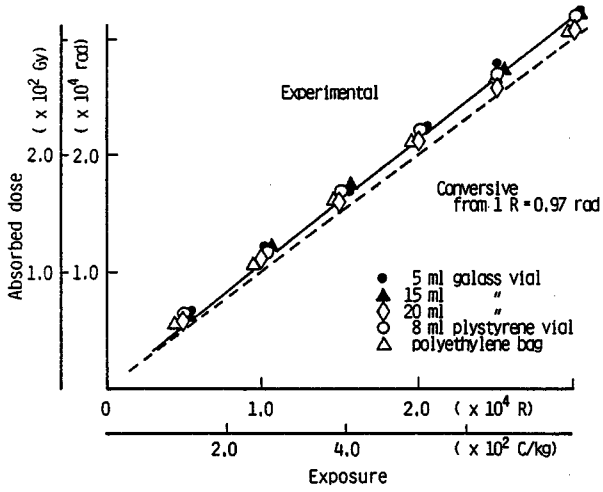

Fig. 4 Relation between exposure and absorbed doses (1R=2.58×10^{-4} C/kg, 1rad=0.01Gy)

and the ratio $\Delta D/D_t$ of the dose difference ($\Delta D = D_m - D_t$) to the absorbed dose (D_t) calculated from the exposure gives the fractional correction for the true absorbed dose, where D_m is the measured dose. The relation between $\Delta D/D_t$ and the ratio of the wall surface area to the volume of the vessel, 2(r+h)/rh, is shown in Fig.5, where r and h are the radius and the height of the sample vessel. The value of 2(r+h)/rh on the polyethylene bag cannot be estimated, so its data is plotted at the margin of this figure. When the value of 2(r+h)/rh is smaller, the ratio $\Delta D/D_t$ is small, and it is almost constant in the range 2(r+h)/rh>0.13. In other words, the results show that the dose difference ΔD is small for the 20-ml glass vial and the polyethylene bag, but large for vials of the sizes from 5ml to 10ml. The values of the fractional correction for the true absorbed dose are shown in Table 2.

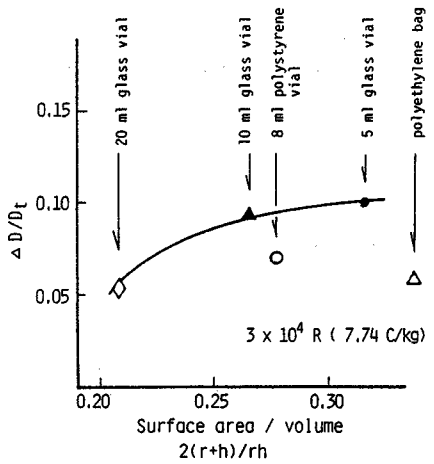

Fig. 5 Deviation of absorbed dose for each sample vessel (1R=2.58×10⁻⁴ C/kg)

Table 2 Fractional correction for convertion of exposure to absorbed dose

Vessel	Fractional Correction($\triangle D/D_t$)
Glass vial (5ml)	0.10
〃 (10ml)	0.09
〃 (20ml)	0.06
Polystyrene vial (8ml)	0.07
Polyethylene bag	0.06

4. 2 Difference of the irradiation effects for different vessels used

The variation levels of activity of pharmaceutical material or the radiolysis of organic materials by gamma-ray irradiation are calculated by using the G-value. Then, as the G-value is defined as the numbers of molecules that are resolved or produced per absorbed energy of 100eV by irradiation, the ratio of the resolved moleculer number to the number in the non-irradiated sample is given by

$$A = 1.04 \times 10^{10} \cdot M \cdot G \cdot D, \quad (1)$$

where M is the molecular weight, and D is the absorbed dose (Gy). With regard to the variations in activity of phamaceutical preparation by gamma-ray irradiation, the same expression can be used for the process. Therefore, the residual rate of the activity after irradiation is given by

$$(N/N_0) = 1 - 1.04 \times 10^{10} \cdot M \cdot G \cdot D. \quad (2)$$

The variations of the rate of residual enzymic activities of saccharated pepsin powder preparation as a function of exposure are shown in Fig.6, where the vessels

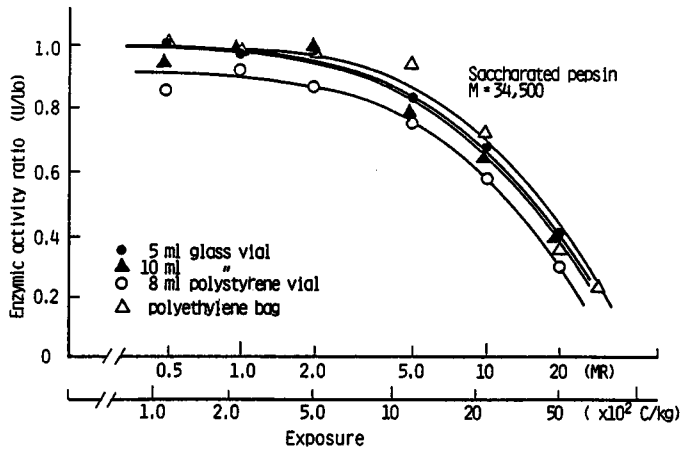

Fig. 6 Relationships between enzymic activity ratio of saccharated pepsin preparation and exposured dose

used are (a) the 5-ml glass vial, (b) the 10-ml glass vial, (c) the 8-ml polystyrene vial and (d) the polyethylene bag. The results show that the activity decreases with increasing exposure and that the decreasing rate varies with the kind of vessel. Especially, the residual rate for the 5-ml vial is the lowest. The correlations, calculated by the method of least squares, between residual enzymic activity ratio of saccharated pepsin preparation and exposure dose, and G-values are shown in Table 3. It has been assumed that 1 R is equal to 1 rad, that the density of saccharated pepsin preparation is eaqual to that of water, and that the molecular weight M is 34,500. The calculated G-values in the cases of using the glass and the polystyrene vial are larger by 5-25% than in the case of using the polyethylene bag. These results show the same trend as the fractional correction shown in Table 2. The variations in the residual enzymic activity ratio as a function of the absorbed dose obtained from the exposure by using the values of fractional correction in Table 2 are shown in Fig.7. The correlations between the residual enzymic activity ratio and the absorbed dose are given in Table 4 together with G-values. In this table, the G-values for the polystyrene vial, the polyethylene bag and the 10-ml glass vial are almost equal and lie in the range from 0.79 to 0.82. Only the value of the 5-ml glass

Table 3 Correlations between residual enzymic activity ratio of saccharated pepsin preparation and exposure rate, and G-values.

Vessel	Correlation formula	G-value
Glass vial (5ml)	$Y = -0.033X + 0.93$ (r=0.98)	1.0
〃 (10ml)	$Y = -0.031X + 0.99$ (r=0.98)	0.85
〃 (20ml)	—	—
Polystyrene vial (8ml)	$Y = -0.031X + 1.0$ (r=1.00)	0.84
Polyethylene bag	$Y = -0.029X + 1.0$ (r=0.98)	0.84

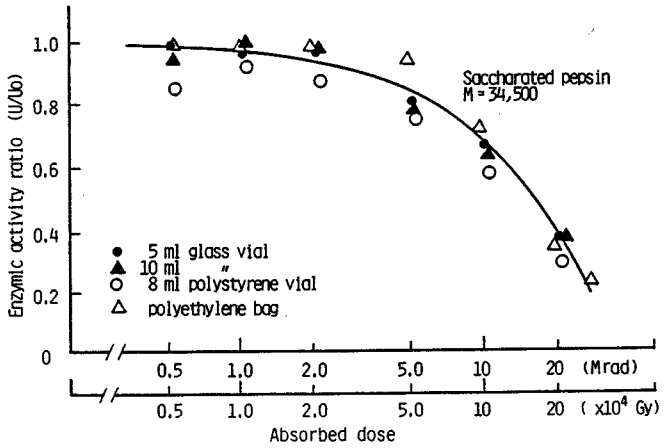

Fig. 7 Relationships between enzymic activity ratio of saccharated pepsin preparation and absorbed dose

Table 4 Correlations between residual enzymic activity ratio of saccharated pepsin preparation and absorbed rate, and G-values

Vessel	Correlation formula	G-value
Glass vial (5ml)	$Y = -0.030X + 0.94$ (r=0.99)	0.93
〃 (10ml)	$Y = -0.030X + 1.00$ (r=0.99)	0.82
〃 (20ml)	—	—
Polystyrene vial (8ml)	$Y = -0.028X + 1.0$ (r=1.00)	0.79
Polyethylene bag	$Y = -0.029X + 1.05$ (r=0.98)	0.79

vial is higher by about 16-17%; a possible reason for this is as follows: Fricke aqua solution was used to determine the fractional correction shown in Table 2, and the absorbed energies due to Compton electrons might be different for Fricke solution and saccharated powder pepsin preparation packed in a small glass vessel, because of the different densities.

5. Conclusion

By using Fricke dosimeter it has been found experimentally that the absorbed doses of the samples in vessels of different sizes, materials, volumes and so on are not equal in the same gamma-ray irradiation condition. The fractional correction of the exposure dose to the absorbed dose was estimated to be 6-7% for organic vessels (the polyethylene bag and the polystyrene vial) and the 20-ml glass vial, 9% for the 10-ml glass vial, and 10% for the 5-ml glass vial. These values were also confirmed by using the changes of enzymic activity of saccharated powder pepsin preparation. In the case of using organic vessels and the 10-ml glass vial, G-values for the change of the enzymic activity were calculated to be almost equal, lying in the range 0.79-0.82. However, for the small glass vial(5-ml), the value has been found to be 0.93.

References

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2) Z.Kuri, "Radiation Chemistry", p.37, Kyoritsu Shuppan, Tokyo (1985)