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Good manufacturing practices (GMP) utilized on human blood irradiation process

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Irradiation of human blood is used to avoid the TA-GVHD (transfusion-associated graft-versus-host-disease), a rare but devastating adverse effect of leukocytes present in blood components for immunocompetent transfusion recipients. Usually this irradiation practice is performed to a physical elimination of lymphocytes. The implementation of the GMP will assure that the properly dose in a range of 25Gy to 50Gy will be delivered to the blood in the bag collected in a blood tissue bank. The studies to establish the GMP were developed under the guidelines of the standard ISO 11137 – Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization. In this work, two dosimetric systems were used for dose mapping during the studies of irradiator qualification, loading pattern, irradiation process validation and auditing. The $CaSO_4$: Dy dosimeter presented difficulties concerning to uncertainty on dose measurement, stability, trace ability and calibration system. The PMMA and gafchromic dosimetric systems have shown a better performance and were adopted on establishment of GMP procedures. The irradiation tests have been done using a Gammacell 220 Irradiator. The developed GMP can be adapted for different types of gamma irradiators, allowing to set up a quality assurance program for blood irradiation.

Key words: Dose mapping. Dosimeter. GMP. Irradiation.

1 Introduction

In many human diseases and health cases, terapy of blood tranfusion becomes necessary. In spite of the necessity, there are some riscs associated with blood used in blood transfusion process.

The TA-GVHD (transfusion-associated graft-versus-host-disease) is a problem when a blood transfusion occurs.

The blood irradiation with gamma rays in blood bags can eliminate this risk. The effect of irradiation of the blood inhibits the proliferation of lymphocytes and consequently stops the TA-GVHD.

To guarantee the irradiation of blood components, the qualification of the irradiator is necessary to assure that this process of irradiation is carried through in appropriate way such a GMP (Good Manufacturing Practices) program must be implemented.

In the GMP activities properly registered in a program of work conceived to demonstrate that the process of radiation happened inside the specified limits. This allows the treated products absorb the doses of radiation in a previous defined interval. The lower limit defines the value from which it provides the desired benefit and the upper limit to the value of the dose that turns it improper for its purpose.

The AABB – American Association of Blood Bank (1992) presents general direction for irradiation process of blood components. The AAMI/ISO11137 (1994) standard of Association for Advancement of Medical Instrumentation and International Standards Organization establishes the requirements for validation and routine control, using the ionizing radiation for sterilization of products for health providing with details and severity all the necessary procedures for implementation of a sterilization GMP. It includes the procedures toward the definition for dose sterilization that are from 25kGy to 50kGy. In case of blood irradiation, the available literature and AABB defines the interval of required doses from 15Gy to 50Gy, to observe that magnitude is 1000 times lower than sterilization doses of medical-surgical products.

The irradiation was carried out in irradiator Gammacell 220 model (^{60}Co) from Atomic Energy of Canada Limited (AECL), Ottawa-Canada, from Radiation Technology Center, IPEN-CNEN/SP.

To perform the irradiator qualification, one of GMP stages, three types of dosimeters were used to know if the doses had been well absorbed in all the blood bag content after irradiation. In the "experimental" section, the types of analysis are shown to evaluate if all blood was radiated well. The used dosimeters were the $CaSO_4$: Dy thermoluminescent dosimeter (TLD), PMMA (Polimetyl Methacrylate) Amber and film standard Gafchromic HD-810.

2 Experimental

The characteristics of each dosimeter had been studied to evaluate its advantages and disadvantages to be used as routine dosimeter for monitoring and for quality assurance in blood components gamma rays processing.

2.1 $CaSO_4$: Dy dosimeter

To study the adequacy of the dosimetric system and its respective calibration, the ASTM E668 – 97 standard was used that establishes the use of termoluminescent dosimeters (TLDs) to estimate the absorbed dose in processed materials by ionizing radiation. They are used for the measurement of the absorbed dose by gamma rays, X-rays and electrons irradiated materials. The range of absorbed dose is approximately from 10^{-2} a 10^{4} Gy (1 to 10^{6} rad) and applicable for absorbed doses rates from approximately 10^{-2} a 10^{10} Gy/s (1 to 10^{12} rad/s).

In the calibration procedure of the dosimetric system, a batch of 60 dosimeters were used to verify the uniformity of response for the radiation dose, in accordance with item 8 of ASTM E668 – 97 standard, that establishes for the lot acceptance the following condition: the standard deviation of response about 30 dosimeters (randomly chosen), that cannot exceed 8% of the average of the readings about these dosimeters.

The samples were irradiated in agreement ASTM E668-97

a) The dosimeters were numbered from 1 to 60;
b) The first lot of 30 dosimeters (1 to 30) was irradiated with 40 Gy;
c) The second lot (31 to 60) was irradiated with 60 Gy;
d) The first lot (1 to 30) was irradiated with 20 Gy;
e) The second lot (31 to 60) was irradiated again with 40 Gy.

In the irradiation practice, the dosimeters were positioned in a device in order to accommodate 6 units and to allow the simultaneous irradiation of these dosimeters in the Gammacell 220 irradiator. Fig. 1 shows the irradiator device with the dosimeters in the central position that coincides with region inside the irradiator chamber.

After reading the dosimeters, they were submitted to a heating process to be re-used for the generation of a calibration curve.

The TLDs readings of the doses were highly dispersed, complicated the accomplishment of the calibration tests and the dose mapping of the irradiator for this kind of dosimeter.

Figure 1: Device with 6 TLDs dosimeters
Source: Dosimetrical Lab. at Centro de Tecnologia das Radiações – IPEN-CNEN/SP.

2.2 PMMA dosimeter

The PMMA dosimeter selected have been used routinely by the Technology Centre of Radiations (CTR-IPEN), to control the radiation doses of irradiation activities toward research and service.

The used dosimeters were the PMMA Amber (English manufacture), from Harwell Dosimeter Company. They had been previously calibrated by CTR-IPEN in accordance with ASTM-E1276/93 standard "Standard practice for use of polymethyl/methacrylate Dosimetry System", with tracking carried through International Dose Assurance Service (IDAS) from IAEA (International Atomic Energy Agency – Viena – Austria).

In the comparative aspect about the criteria of selection for the dosimetric system established by AAMI/ISO11137 (1994) standard, the PMMA system is similar to TLD system, differing on the dose range application about the dose range (2 kGy to 30 kGy), while the TLD is from 10^{-2} Gy to 10 kGy. The dosimeter used was Amber type 3042 bath P.

For the present work, the required dose range is from 10 Gy to 100 Gy, and in this case the PMMA exceeds in 200 times the lower value of the interval of required dose, however, its use was accepted increasing the irradiation time for the corresponding factor. This increase did not affect the realization of the experiments of irradiator dose mapping, because the materials used to simulate the blood bag are not affected by radiation doses above 25 kGy (usual dose for disposable medical products).

Based on AAMI/ISO1137 (1994) standard and Guidance for Industry (2000), the following activities had been carried through to characterize the process:

a) Studies for determination of the best way of blood bags load inside the irradiation chamber, with the intention to get the lower relation between maximum and minimum absorbed doses.
b) For the dose mapping of product, it was used a device, which does not suffer interference by the load of the irradiation chamber with blood bags having the same density. This allows to accommodate enough amount of dosimeters to indicate with precision the regions of minimum and maximum absorbed doses by the product. The Fig. 2(a) shows the numbered dosimeters to be irradiated.

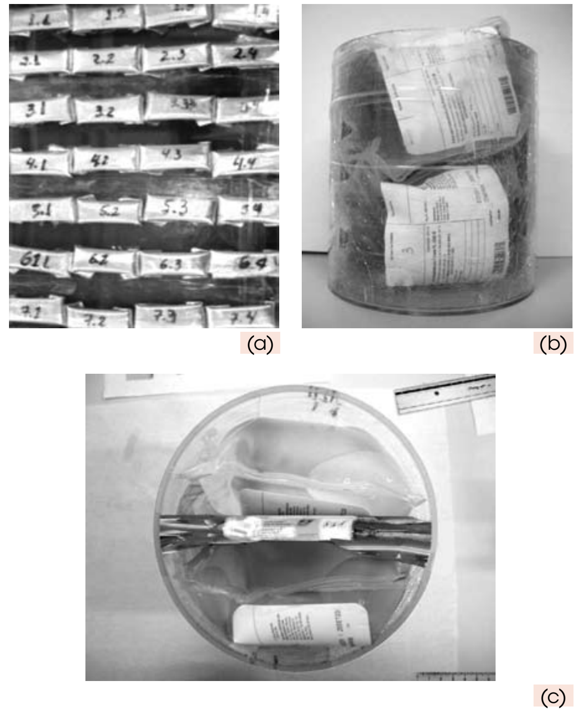

Figure 2: (a) Numbered PMMA Dosimeters; (b) Arrangement dose mapping; (c) Bags and dosimeters distribution inside the device

Source: Dosimetrical Lab. at Centro de Tecnologia das Radiações – IPEN-CNEN/SP.

Fig. 2(b) presents the used array for dose mapping of the irradiation chamber of Gammacell 220.

To verify the distribution in distinct plans of the irradiation chamber, the mapping tests were carried through three positions: with the following angles of rotation: 0º, 90º e 45º. The reference to the angles is the horizontal axle by the irradiation chamber. The Fig. 2(c) shows how the blood bags and the numbered dosimeters had been distributed in the arrangement.

3 Results and discussion

3.1 Dose mapping of the PMMA dosimeter

The radiation dose distribution of Gammacell 220 is shown in Table 1 (0º, 90º and 45º), according to Fig. 2 (a). For the 0º position, the dose uniformity factor value (maximum to minimum dose relation) is 1.50. For the 90º position, the dose uniformity factor value was 1.45. And for the 45º position, the dose uniformity factor value was 1.47.

Table 1: Dose distribution for rotation angles of 0°, 90° and 45°

	1	2	3	4	1	2	3	4	1	2	3	4
1	2.1	1.4	1.5	1.6	3.7	2.9	3.0	3.4	5.5	4.4	4.3	5.0
2	1.8	1.6	1.6	2.0	3.6	3.4	3.3	4.2	6.2	4.8	4.9	5.7
3	1.8	1.8	1.8	2.1	4.0	3.6	3.7	4.0	5.9	5.2	5.2	6.1
4	2.1	1.9	1.8	1.9	4.2	3.7	3.7	4.0	6.3	5.4	5.3	6.0
5	1.9	1.7	1.8	1.9	4.2	3.4	3.6	4.2	6.1	5.4	5.1	5.9
6	1.9	1.6	1.7	2.1	1.2	3.2	3.3	4.2	6.0	5.1	4.9	5.6
7	2.0	1.6	1.5	1.8	3.9	2.9	3.0	3.7	5.3	4.6	4.4	5.1

Source: Dosimetrical Lab. at Centro de Tecnologia das Radiações - IPEN-CNEN/SP.

Marking of major and minor of absorbed dose values are presented in yellow color.

These values are inferior to the dose factor uniformity established by standards for blood irradiation, which is from 25 Gy to 50 Gy, that is, factor 2 (AAMI/ISO1137 standard).

3.2 Gafchromic dosimeter

The films of the Gafchromic dosimeter HD-810 had been projected for use with gamma radiation, X-ray and electron beam. When the transparent film is exposed to the ionizing radiation, a polymerization reaction is initiated, coloring to blue. The amount of reaction and the depth of the color change are proportional to the absorbed dose in the active layer.

Uniformity response are in agreement with the ASTM E1310-89, the results of dosimeters reading for the target doses of 5 Gy, 10 Gy, 20 Gy, 25 Gy, 30 Gy, 50 Gy, 70 Gy, 100 Gy, 120 Gy, 140 Gy, 160 Gy, 180 Gy and 200 Gy were used to generate the calibration curve shown in Fig.3 (polynomial expression) and to determinate the coefficient of variation (CV).

3.3 Dose mapping for gafchromic dosimeter

For the dose mapping, the arrangement shown in Fig. 4 was used in the positions 0°, 45° and 90°. The target dose was 25 Gy. The dose distribution of Gammacell 220 showed in Table 2 (0°, 90° and 45°). For the 0° position, the dose uniformity factor value ratio between greater and lesser value is 1.79. For the 90° position, the dose uniformity factor value was 1.88. And for the 45° position, the dose uniformity factor value was 1.69.

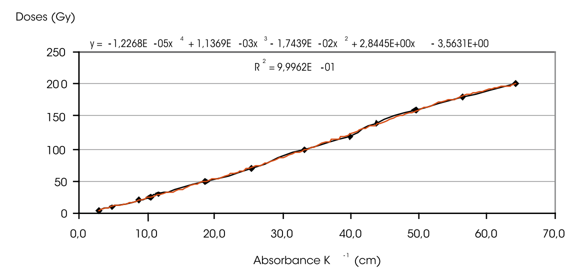

Figure 3: Calibration Curve of the Gafchromic dosimeter
Source: The authors.

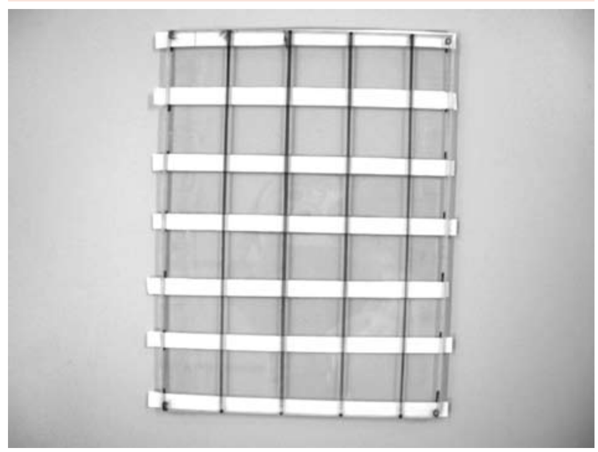

Figure 4: Assembly for Gafchromic Dosimeter
Source: Dosimetrical Lab. at Centro de Tecnologia das Radiações - IPEN-CNEN/SP.

Table 2: Dose distribution for rotation angles of 0°, 90° and 45°

	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1	20,11	17,07	16,54	15,15	18,82	21,78	18,56	19,15	19,00	21,85	19,42	19,79	16,61	17,18	20,23
2	23,95	18,76	16,82	16,76	21,25	26,63	20,61	19,76	20,51	27,09	22,49	17,77	17,64	19,10	24,57
3	24,14	19,33	17,84	17,55	21,62	28,26	21,17	21,94	23,55	29,42	22,60	18,97	16,96	20,23	24,92
4	26,13	20,53	19,44	19,91	22,71	25,49	22,48	17,24	23,44	28,70	23,11	20,12	19,25	20,70	26,19
5	25,06	20,63	19,67	20,73	23,84	25,65	20,81	20,91	23,33	30,33	25,31	20,78	20,20	21,33	25,68
6	27,11	21,08	17,82	18,05	22,54	23,68	18,23	18,47	17,88	27,57	25,05	20,41	17,47	19,24	28,03
7	23,85	17,55	15,99	16,12	20,09	21,03	16,17	18,57	17,15	24,44	22,14	17,16	16,59	16,94	23,00

Source: Dosimetrical Lab. at Centro de Tecnologia das Radiações - IPEN-CNEN/SP.

Marking of major and minor of absorbed dose values are presented in yellow color.

Equipment used in the reading of the dosimeter:

a) TLD Dosimeter: Nuclear Harshaw System, model Bicron QS 3500.
b) PMMA Dosimeter: Thermo model Spectronic Genesys 20.
c) Grafchromic Dosimeter: Shimadzu UV-1601 PC.

3.4 $CaSO_4$: Dy dosimeter

The TLDs readings of the doses were very dispersed, complicating the accomplishment of the calibration tests and the dose mapping of the irradiator for this kind dosimeter.

3.5 PMMA dosimeter

In the comparative aspect about the criteria of selection for the dosimetric system established by AAMI/ISO11137 standard, the PMMA system is similar to TLD system, differing on the dose range application about the dose range (2 kGy to 30 kGy), while the TLD is from 10^{-2} Gy to 10 kGy.

3.6 Gafchromic dosimeter

Uniformity response are in agreement with the ASTM E1310-89, the results of dosimeters reading for the target doses of 5 Gy, 10 Gy, 20 Gy, 25 Gy, 30 Gy, 50 Gy, 70 Gy, 100 Gy, 120 Gy, 140 Gy, 160 Gy, 180 Gy and 200 Gy were used to generate the calibration curve shown in Fig.3 (polynomial expression) and to determinate the coefficient of variation (CV).

4 Conclusions

The Gammaccel 220 irradiator of the CRT-IPEN is appropriate to be used in the routine blood irradiation, because the safe design and operation has make it a good choice for high dose rate radiation studies.

The dosimetric system TLD revealed to be inappropriate for utilization in blood irradiators dosimetry, due to the lack of response uniformity.

However, the PMMA and Gafphcromic dosimeters had revealed to be adequate for dosimetry in irradiations of blood components, assuring that the Gammacell 220 irradiator can be used in the blood irradiation.

References

AAMI/ISO11137. *Sterilization of health care products*. Requirements for validation and routine control. Radiation Sterilization, 1994.

ASTM International. Designation: E 668-97. *Standard practice for application of thermoluminescence-dosimetry (tld) systems for determining absorbed dose in radiation-hardness testing of electronic devices*.

ASTM International. Designation: E 1310-89. *Standard practice for use of radiochromic optical waveguide dosimetry system*.

BALDWIN, M. L.; JEFFERIES, L. C. Irradiation of blood components. Bethesda: American Association of Blood Bank. Washington, DC: Library of Congress Cataloging, 1992.

GUIDANCE FOR INDUSTRY – *Gamma irradiation of blood and blood components: a pilot program for licensing*. Food and Drug Administration, February 2000.

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