

Development of a process using electron beam for a terminal sterilization for parenteral formulations of pharmaceuticals

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Abstract

As pharmaceutical technology advances and sensitive drug formulations demand ever-greater stability, radiation processing is likely the only alternative that can be used to terminally sterilize thermo-labile pharmaceutical products intended for parenteral administration.

To this end, a radiation process using e-beam technology has been developed. A key feature of this process is the elucidation of defined conditions of radiation processing in order to achieve the homogeneity of the absorbed dose inside a single vial and throughout a tray containing several vials.

Results of several dosimetry studies, using e-beam technology, demonstrate the beneficial effects of the use of aluminum or stainless-steel plates to scatter the beam and therefore to obtain an excellent D_{\max}/D_{\min} across all dose-monitoring positions within the vial and throughout a tray containing 260 vials filled with a dry powder or a tray containing approximately 30 vials filled with an aqueous solution.

This ionizing radiation process can be directly applicable, at a manufacturing level, for a terminal sterilization of parenteral formulations of pharmaceuticals.

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1. Introduction

Current international standards, EN 552 (CEN, 1994) and ISO 11137 (ISO, 1995) recommend an irradiation dose of 25 kGy as a reference dose for terminal sterilization. Dose mapping studies to demonstrate regions of low- and high-absorbed doses in the product load are also required by regulatory agencies (Miller, 1999). A dose range of 25.0–32.0 kGy (D_{\max}/D_{\min} of 1.28) is given by a CPMP guidance document (CPMP, 2000) to use a minimum of 25 kGy dose if the product can withstand it, and the 32 kGy upper-dose limit is based on German government regulations.

For pharmaceuticals, the geometry of the vials as well as the nature of the packaging material (glass or plastic vial, stopper, sealing) can also affect the distribution of the absorbed doses (Strelczyk et al., 1990). In addition, with some accelerators, the angular divergence of the emitted beam from “beam centerline” impacts the uniformity of the doses received.

Therefore the objective was the elucidation of defined conditions of radiation processing in order to achieve the homogeneity of the absorbed dose inside a single vial and throughout a tray containing several vials filled either with a dry powder or an aqueous solution.

Such a process could be very useful, in manufacturing, for a terminal sterilization of parenteral forms of pharmaceuticals.

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2. Material and methods

Electron beam processing: IBA Rhodotron TT 300 (10 MeV) at Studer Hard-Switzerland Irradiation dose range: 25–32 kGy.

Dosimetry method: (Mc Laughlin et al., 1989; Regulla and Deffner, 1982).

- Radiochromic film dosimeter: FarWest™ FWT-60.
- Alanine dosimeter: Alanine tablet dosimeters from Risø National Laboratory—Denmark.

Scatter plates:

- Aluminum plate: thickness: 0.2 cm; dimensions: 199 × 48 cm;
- Stainless-steel plate: thickness: 0.1 cm; dimensions: 159 × 48 cm.

Packaging material

Dry powder: PLGA microspheres (500 mg) were filled into cerium oxide (CeO) glass vials (Wheaton), which were placed into a HDPE plastic tray (43.5 × 33.8 × 6.0 cm), which can hold 260 vials.

Aqueous solution: 5 ml of water filled into CeO glass vials (Wheaton) placed into an aluminum tray (13.5 × 13.5 × 4.7 cm), which can hold 25–30 vials. Thickness: 0.2 cm.

Other primary containers, for both dry powders and liquids, COC (Schott) and CZ (West) plastic vials were also evaluated.

Closure system: Gray rubber 20 mm serum stopper (West 4023/50 B2-40) sealed with aluminum seal with a plastic flip top.

3. Results

3.1. Dry powder forms of pharmaceuticals

First studies were conducted with sheets of polyethylene foam placed in the path of the beam to scatter the beam prior to entering the tray. The data indicated for a single vial a large difference between the measured doses in the cap and the bottom, but with a relative homogeneity of the dose throughout the tray. A max/min ratio of 1.33 was, however high according to the initial criteria. A dose of 25 kGy was not achieved in the bottom region while 31.1 kGy were already recorded in the cap of the vial.

The final process developed to provide the lowest possible D_{\max}/D_{\min} incorporated two thin plates of aluminum (effective thickness 1.1 g/cm²) on top of the vials in order to scatter the beam as well as an aluminum plate as reflection plate (Fig. 1).

The measured absorbed doses in these conditions show an excellent improvement in dose uniformity obtained by inserting the aluminum scattering plates between the accelerator and the product (Fig. 2).

A D_{\max}/D_{\min} ratio of 1.14 (alanine) or 1.13 (film) was obtained when considering all the combined measured absorbed doses throughout the tray and inside the vials (cap, shoulder, bottom). Within a single vial a slightly higher absorbed dose is observed in the cap (29.5 kGy) as compared to the shoulder (28.7 kGy) or the bottom (28.5 kGy).

3.2. Aqueous solutions of pharmaceuticals

The liquid parenteral forms of pharmaceuticals present more difficulties for a terminal sterilization by e-beam radiation processing. Including the container and the volume of liquid in the vial, the homogeneity of

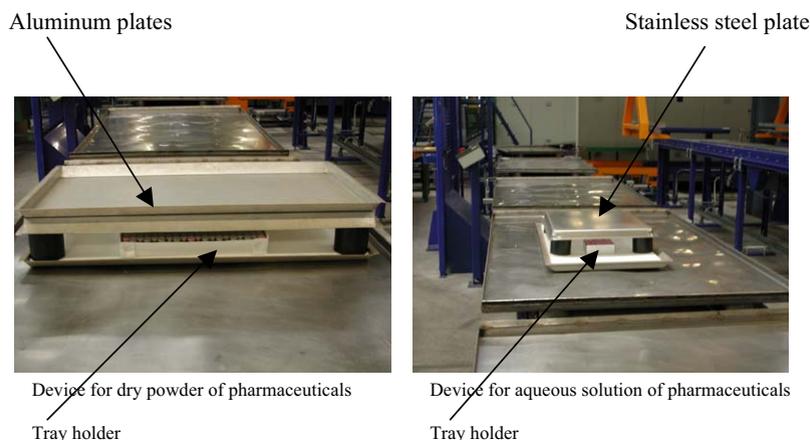


Fig. 1. Device with scattering and reflection plates.

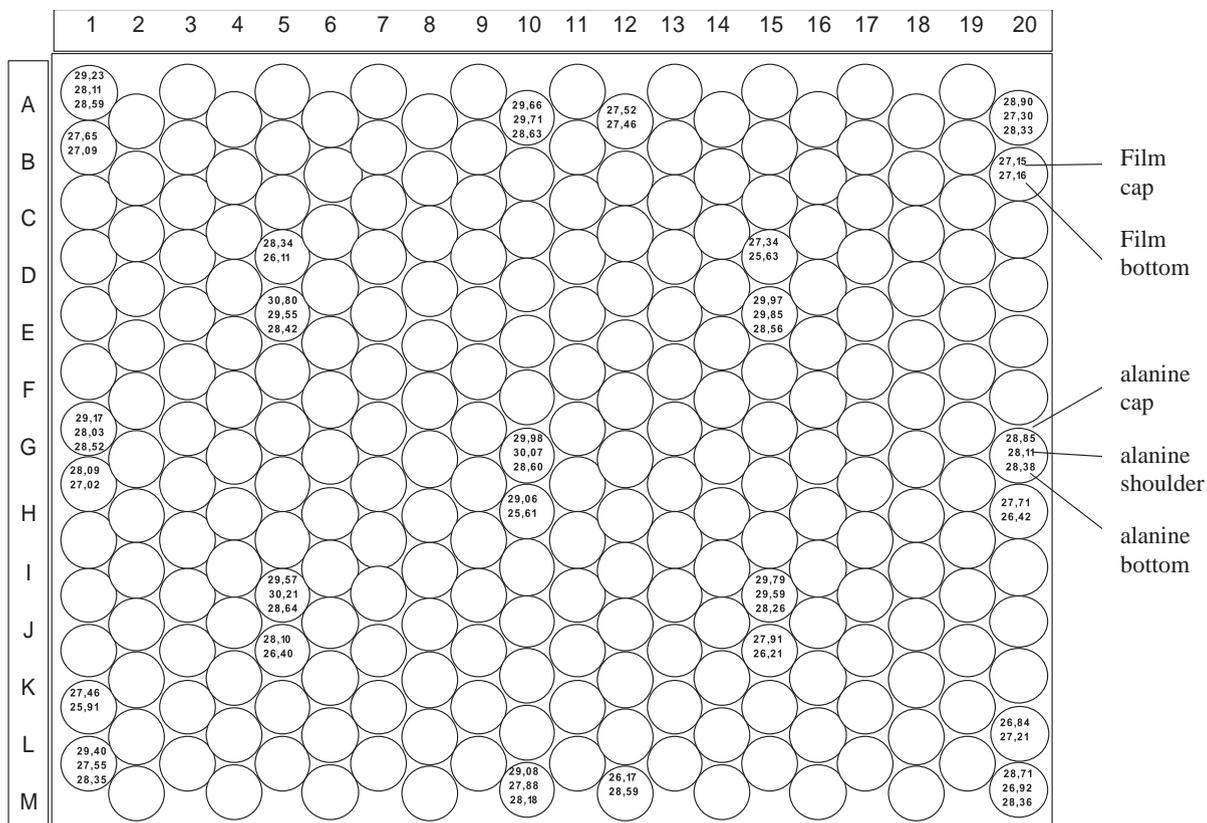


Fig. 2. Dosimetry results for dry powder of pharmaceuticals.

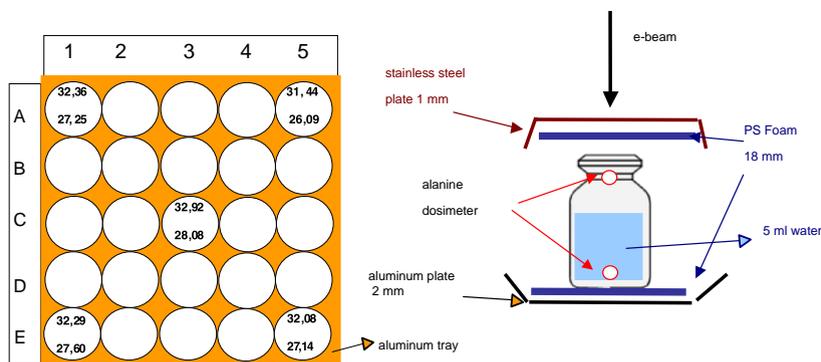


Fig. 3. Dosimetry results for aqueous solution of pharmaceuticals.

the materials is more complex. In addition, the limited penetration depth of e-beam radiation could produce in these conditions greater variations in absorbed doses.

Preliminary studies using the same device as for dry products did not show an acceptable max/min ratio (1.59).

The optimum treatment (D_{\max}/D_{\min} ratio of 1.26) was achieved by using a 1 mm stainless-steel scattering plate (effective thickness 0.8 g/cm^2) on top of the vials and a 2 mm aluminum reflection plate (Fig. 3). The vials are

placed in a tray made of aluminum (wall thickness 2 mm).

3.3. Packaging material

Dry products or aqueous formulations can be filled into suitable primary packaging including glass or plastic (Fig. 4). The primary packaging must be able to withstand exposure to ionizing radiation.

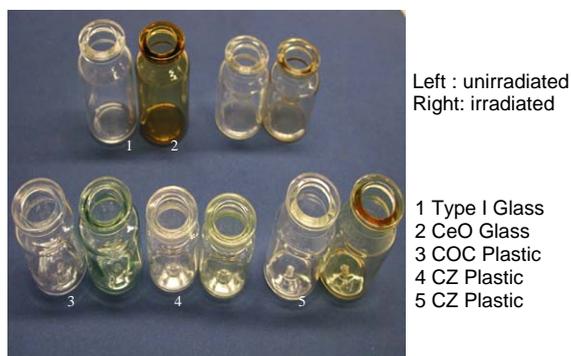


Fig. 4. Irradiation of packaging material.

While type I standard glass vials present strong discoloration after radiation processing, CeO glass, COC and CZ plastic vials retain their optical clarity.

4. Conclusion

Terminal sterilization of injectable products, unless it can be shown products cannot tolerate it, is mandated by FDA policy in the United States and by the CPMP and Ph Eur in Europe.

Documentation of the efficacy of the sterilization process (e.g. an effective absorbed dose of 25 kGy) is a critical cGMP requirement, as it directly affects the product safety for use in humans.

The use of e-beam for a terminal sterilization process has several advantages in comparison to gamma rays: higher throughput rates and reduced product degradation.

However, because of a limited penetration depth of accelerated electrons, the homogeneity of the absorbed

dose by pharmaceuticals, filled in primary containers with complex shapes like vials, can be affected. The use of beam scattering and reflection tools in combination with an accelerator delivering a parallel beam greatly improves the uniformity of the absorbed dose as shown by the D_{\max}/D_{\min} ratio obtained and close to 1.15.

With this process the objective to get a max/min ratio below 1.28 is thus achieved while having the minimum requested dose of 25 kGy for a terminal sterilization.

This ionizing radiation process can be directly applicable, at a manufacturing level, for a terminal sterilization of parenteral formulations of pharmaceuticals.

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