

DEVICE FOR STERILISING FLEXIBLE BAGS BY ELECTRON BEAM
IRRADIATION AND METHOD FOR STERILISING THEM

DESCRIPTION

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The present invention relates to the pharmaceutical sector, specifically to a device for sterilisation by electron beam irradiation of flexible bags, in particular flexible bags of the type that can contain solutions of human plasma proteins for therapeutic use. Furthermore, the present invention relates to a method of sterilisation by electron beam irradiation of said flexible bags and to an in-line method for filling flexible bags that uses the sterilisation device and method of the present invention.

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Electron beam irradiation, also abbreviated to "E-beam", is a form of ionising energy generally characterised by its low penetration and high doses of energy applied. Said beam is a stream of concentrated, highly charged electrons. The electrons are generated by an accelerator capable of producing beams that can be continuous or pulsed. The material to be sterilised absorbs the energy of the electrons and said energy absorption, also known as absorbed dose, eliminates any micro-organisms, destroying their DNA strands.

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Commercial electron beam accelerator equipment usually operates with a single energy and, in the case of sterilisation of pharmaceutical products, a high-energy electron beam is usually required to successfully penetrate the product and its packaging. A higher-energy electron beam will lead to greater penetration by said electron beam into the product.

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When the electron beam is assessed with a view to carrying out sterilisation, account has to be taken of various parameters such as the density, size and orientation of the product, and the packaging. E-beam irradiation generally works better when used for low-density products, packed uniformly.

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In the particular case of flexible bags suitable for containing a solution of human plasma proteins, these are formed from various materials in various thicknesses. For example, the walls of the bag can be approximately 130 µm thick, the tube of the outlet port of the bag, which is sealed to the latter, can be 1.24 mm thick, whilst the twist-off cap is the zone of greatest thickness, which can be approximately 3 mm. All these portions have to be decontaminated and sterilised before the bags are filled with said human plasma protein solutions.

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The electron beam energy needed to carry out sterilisation of said flexible bags is therefore different for each of the portions mentioned, being lowest for the walls of the bag and greatest for the outlet port tube and the cap. A conventional electron beam accelerator, which emits a single energy, may not be suitable for these cases, given that the energy would be higher than necessary to perform the sterilisation for some portions of the bag or insufficient for others.

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The authors of the present invention have developed an electron beam sterilisation device that allows sterilisation of this type of bags and a sterilisation method for said bags without the need to apply high

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energies, since the energy necessary for sterilisation will be applied to each portion according to the characteristics of said portion, specifically its thickness.

The invention will be explained below with reference to the figures, in which:

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Fig. 1 is a perspective view of an empty flexible bag suitable for containing human plasma proteins.

Fig. 2 is a view from above of the sterilisation zone of one embodiment of the electron beam sterilisation device according to the present invention.

Fig. 3 is a view from above of the sterilisation zone of another embodiment of the electron beam
 10 sterilisation device according to the present invention.

An example of the flexible bags to be sterilised using the sterilisation device of the present invention is shown in Fig. 1. Said bags can have a volume of 50 mL to 500 mL. Fig. 1 shows an empty bag -2- that contains a port/cap structure. The walls -1- of said bag can be approximately 130 μ m thick, the tube of
 15 the outlet port -4- of the bag can be approximately 1.24 mm thick, whilst the twist-off cap -3- can have a thickness of approximately 3 mm.

In a first aspect, the present invention relates to a device for sterilising flexible bags, characterised in that it comprises a sterilisation zone formed by at least two electron accelerators that emit electron beams at
 20 different energies.

In a first embodiment, said sterilisation device comprises at least one accelerator that emits an electron beam at an energy of between 450-500 keV and at least one other accelerator that emits an electron beam at an energy of 700-750 keV. Preferably, said sterilisation device has one accelerator that emits an
 25 electron beam at an energy of between 450-500 keV and another accelerator that emits an electron beam at an energy of 700-750 keV.

Fig. 2 is a view from above of the sterilisation zone of one embodiment of the sterilisation device according to the present invention. Said sterilisation zone is formed by a lower-energy electron beam
 30 accelerator or emitter -5- (450-500 keV), a higher-energy electron beam accelerator or emitter -6- (700-750 keV) and a zone -7- in which the flexible bags to be sterilised are placed. In this embodiment, the two accelerators are positioned on opposite sides of the bags in a position facing each other.

Fig. 3 is a view from above of the sterilisation zone of another embodiment of the sterilisation device according to the present invention. Said sterilisation zone is formed by a lower-energy electron beam
 35 accelerator or emitter -5- (450-500 keV), a higher-energy electron beam accelerator or emitter -6- (700-750 keV) and a zone -7- in which the flexible bags to be sterilised are placed. In this embodiment, the two accelerators are positioned on opposite sides of the bags in a position in which they do not face each other.

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In another aspect, the present invention discloses a method for sterilising flexible bags containing a solution of human plasma proteins, using the above-mentioned electron beam accelerator device. Said method is characterised in that it comprises the following steps:

- a) at least one emission of an electron beam at an energy of 450-500 keV;
- b) after a period of approximately of 10 ns , emission of a second electron beam at an energy of 700-750 keV.

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A person skilled in the art will understand that the higher-energy electron beam is aimed at the zone of the bag of greatest thickness, i.e. at the tube of the outlet port and the cap, whereas the lower-energy electron beam is aimed at the walls of the bag.

- 10 In one embodiment of the electron beam accelerator device of the present invention, the distance from the flexible bag to be sterilised to the irradiation source is between 1.5 cm and 2.5 cm. Preferably, said distance is 2 cm.

- 15 The sterilisation method of the present invention can be carried out before or after filling the bag and is preferably performed in a sterile environment.

The flexible bag to be sterilised by the method of the present invention can be made from any of the materials that are appropriate for the pharmaceutical industry and known in the state of the art.

- 20 Furthermore, said flexible bag can contain pharmaceutical solutions of biological origin, such as blood or blood products such as plasma, serum, red blood cells, albumin, α 1-antitrypsin, von Willebrand factor, coagulation factors such as factor VII, factor VIII and factor IX, immunoglobulins, plasminogen, plasmin, antithrombin III, fibrinogen, fibrin, thrombin or combinations thereof. It is also provided for the pharmaceutical liquid or product to be of non-biological origin, and obtained by any other process or
- 25 method known in the state of the art, for example, chemical synthesis, recombinant production or transgenic production.

- In a final aspect, the present invention relates to an in-line method for filling flexible bags with human plasma proteins, which comprises a step of electron beam sterilisation using a device as mentioned
- 30 above.

Said in-line method for filling flexible bags comprises the steps of:

- a) labelling the bags;
- 35 b) sterilising the bags by electron beam;
- c) filling the bags with the solution of human plasma proteins in a sterile environment; and
- d) sealing the bags.

- The flexible bags that can be sterilised by the method of the present invention can have a volume of
- 40 50 mL to 500 mL. Fig. 1 is a perspective view.

Furthermore, said flexible bag can contain pharmaceutical solutions of biological origin, such as blood or blood products such as plasma, serum, red blood cells, albumin, α 1-antitrypsin, von Willebrand factor,

coagulation factors such as factor VII, factor VIII and factor IX, immunoglobulins, plasminogen, plasmin, antithrombin III, fibrinogen, fibrin, thrombin or combinations thereof. It is also provided for the pharmaceutical liquid or product to be of non-biological origin, and obtained by any other process or method known in the state of the art, for example, chemical synthesis, recombinant production or transgenic production.

To aid understanding, the present invention is described below with reference to the following example, which in no way purports to restrict the present invention.

10 EXAMPLE. Determination of the electron beam energy needed for each portion of the flexible bag.

Bags having four different volumes (50, 100, 250 and 500 mL), produced by Grifols S.A., were tested. However, the thicknesses of all the bags are the same in all four formats, the characteristics of which are summarised in Table 1 below. The walls of the bags are formed by a film of multiple layers bonded together by a layer of adhesive.

Table 1. Characteristics of the walls of the flexible bags.

Bag	Layer 1 (PET-SiO)	Layer 2 (OPA)	Layer 3 (PP-SiO)	Layer 4 (PP)
Formula	$C_{10}H_8O_4SiO$	$C_8H_6O_2$	C_3H_6SiO	C_3H_6
Density (g/cm ³)	1.42	1.13	0.889	0.894
Thickness (µm)	12	15	18	85

The total thickness of the bag wall is 130 µm, without taking into account the intermediate layers of adhesive, which can be ± 12 µm thick. On the other hand, on measurement, the total thickness of the cap was found to be 2.85 mm.

For this study, four electron beam energies were chosen: 250 keV with a current of 5.5 kA, 450 keV with a current of 8.5 kA, 650 keV with 12.5 kA and 850 with 16 kA. The distance from the irradiation window was 2 cm.

At the 250-keV energy, approximately half the electrons were stopped by the bag wall, producing a lower flux (3.5×10^{-3} electrons/cm²). However, at an energy of 450 keV, sufficient energy was produced to treat the inner portion of the bag, even bonding the two walls of the bag having a thickness of 260 µm.

The electron beams of 250 keV and 450 keV were not penetrative enough to pass through the tube of the outlet port of the bag. On the other hand, a large difference between the 650-keV and 850-keV beams was found with respect to the dose deposited (approximately 30 times), and therefore a study of two intermediate energies of 700 keV and 750 keV was conducted. It has been observed that, at the 700-keV energy, the electrons are able to pass through the inner tube of the cap, which is 2.85 mm thick, and at 750 keV a deposited dose that is 10 times higher is produced.

CLAIMS

1. Device for sterilising flexible bags, characterised in that it comprises a sterilisation zone formed by at least two electron accelerators that emit electron beams at different energies.
2. Device for sterilising flexible bags according to claim 1, characterised in that it comprises at least one accelerator that emits an electron beam at an energy of between 450-500 keV and at least one other accelerator that emits an electron beam at an energy of 700-750 keV.
3. Device for sterilising flexible bags according to claim 1, characterised in that it has an accelerator that emits an electron beam at an energy of between 450-500 keV and an accelerator that emits an electron beam at an energy of 700-750 keV.
4. Device for sterilising flexible bags according to any one of claims 1 to 3, characterised in that the accelerators are positioned on opposite sides of the bags in a position facing each other.
5. Device for sterilising flexible bags according to any one of claims 1 to 3, characterised in that the accelerators are positioned on opposite sides of the bags in a position in which they do not face each other.
6. Method for sterilising flexible bags containing a solution of human plasma proteins by electron beam, characterised in that it comprises the following steps:
 - a) at least one emission of an electron beam at an energy of between 450-500 keV;
 - b) after a period of approximately of 10 ns, emission of at least one second electron beam pulse at an energy of between 700-750 keV.
7. Method according to claim 6, characterised in that the distance from the flexible bag to be sterilised to the irradiation source is between 1.5 cm and 2.5 cm.
8. Method according to claim 7, characterised in that the distance from the flexible bag to be sterilised to the irradiation source is 2 cm.
9. Method according to any one of claims 6 to 8, characterised in that the bags to be sterilised can contain a volume of 50 mL to 500 mL.
10. Method according to any one of claims 6 to 9, characterised in that the solutions contained in said flexible bag are pharmaceutical solutions of biological origin, such as blood or blood products such as plasma, serum, red blood cells, albumin, α 1-antitrypsin, von Willebrand factor, coagulation factors such as factor VII, factor VIII and factor IX, immunoglobulins, plasminogen, plasmin, antithrombin III, fibrinogen, fibrin, thrombin or combinations thereof.

11. Method according to claims 6 to 10, characterised in that the pharmaceutical solutions are obtained by chemical synthesis, recombinant production or transgenic production.
12. In-line method for filling flexible bags, characterised in that it comprises the steps of:
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- a) labelling the bags;
 - b) sterilising the bags by electron beam, using the method according to claims 6 to 11;
 - c) filling the bags with the solution of human plasma proteins in a sterile environment; and
 - a) sealing the bags.
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13. Method according to claim 12, characterised in that the bags to be sterilised can contain a volume of 50 mL to 500 mL.
14. Method according to either claim 12 or claim 13, characterised in that the solutions contained in said
- 15 flexible bag are pharmaceutical solutions of biological origin, such as blood or blood products such as plasma, serum, red blood cells, albumin, α 1-antitrypsin, von Willebrand factor, coagulation factors such as factor VII, factor VIII and factor IX, immunoglobulins, plasminogen, plasmin, antithrombin III, fibrinogen, fibrin, thrombin or combinations thereof.
- 20 15. Method according to claims 12 to 14, characterised in that the pharmaceutical solutions are obtained by chemical synthesis, recombinant production or transgenic production.