e) Other necessary matters

7.2.1.2 Conditioning

a) If pressure reduction is performed, the pressure achieved and required time

b) Reduced pressure maintenance period

c) Time, temperature, pressure, humidity

d) Sterilization loading temperature and humidity

e) Other necessary matters

7.2.1.3 Sterilization cycle

a) Pressure increase, injection time, and final pressure for the injection of the sterilization gas

b) Concentration of the ethylene oxide gas (it is desirable to analyze directly the gas concentration inside the sterilization chamber, but the following alternatives are acceptable if direct analysis is difficult)

i) Mass of gas used

ii) Volume of gas used

iii) Conversion calculation using the initial low pressure level and the gas injection pressure

c) Temperature within the sterilization chamber

d) Temperature of the loaded products to be sterilized

e) Effect time (exposure time)

f) Product loading pattern/loading density

g) BI placement points and cultivation results

h) Other necessary matters

7.2.1.4 Aeration

a) Time, temperature

b) Loaded sterilized substance temperature

c) Pressure variation in the sterilization chamber and/or the aeration room

d) Rate of change of the air or other gases in the aeration room

e) Other necessary matters

7.2.2 Utilities

The utilities and control devices required for ethylene oxide sterilization determine the quality and precision.

a) Quality of the ethylene oxide gas

b) Quality of the injected vapor or water

c) Quality of the replacement air after the completion of sterilization

d) Quality of the BI

e) Precision of the temperature control devices

f) Precision of the pressure control devices

g) Precision of the humidity control devices

h) Precision of the time control devices

i) Other

7.3 Irradiation Sterilization

Irradiation sterilization refers to methods of killing microorganisms through exposure to ionizing radiation. The types of ionizing radiation used are gamma-rays (γ-rays) emitted from a radioisotope such as ^{60}Co or ^{137}Cs, or electron beams and bremsstrahling (X-ray) generated from an electron accelerator. In the case of γ-rays, the cells are killed by secondarily generated electrons, while in the case of the electron beam, the cells are killed by the electrons generated directly from the electron accelerator. For this reason, the processing time for electron beam sterilization is generally shorter than that for γ-ray sterilization; but, since the penetration of the γ-rays is better than that of the electron beam, there must be appropriate consideration of the density and thickness of the substance being sterilized when choosing between these methods. For an irradiation sterilization process, the control procedures primarily make use of dosimeters and measure the absorbed dose in the substance being sterilized. This is called dosimetric release.

7.3.1 Important control points

The important control points for the irradiation sterilization are indicated below.

7.3.1.1 γ-ray radiation

a) Irradiation time (timer setting or conveyor speed)

b) Absorbed dose

c) Product loading pattern

d) Other necessary matters

7.3.1.2 Electron beam and X-ray radiation

a) Electron beam characteristics (average electron beam current, electron energy, scan width)

b) Conveyor speed

c) Absorbed dose

d) Product loading pattern

e) Other necessary matters

7.3.2 Utilities

A traceable calibration, performed according to national standards, must be performed for the radiation devices and dose measurement systems. This calibration must be performed as specified in a written plan in order to verify that the equipment is kept within the required range of accuracy.

7.3.2.1 Required calibration items for gamma-radiation equipment

a) Cycle time or conveyor speed

b) Weighing device

c) Dose measurement system

d) Other

7.3.2.2 Required calibration items for electron-beam and X-ray radiation equipment

a) Electron beam characteristics

b) Conveyor speed

c) Weighing device

d) Dose measurement system

e) Other

References

1) Validation Standards, PAB Notification No.158, Ministry of Health and Welfare 1995

2) Sterilization Validation Standards, PMSB/IGD Notification No.1, Ministry of Health and Welfare 1997

3) Quality Assurance Standards for Medical Devices, PAB Notification No.1128, Ministry of Health and Welfare 1994

4) ISO 9000 series, International Standards for Quality Assurance

5) ISO 11134 Industrial moist heat sterilization

6) ISO 11135 Ethylene oxide sterilization

7) ISO 11137 Radiation sterilization

8) ISO 11138 Biological indicators

9) ISO 11140 Chemical indicators

10) ISO 11737-1 Microbiological Methods Part 1: Estimation of population of microorganisms on products

11) USP 〈1222〉 Terminally Sterilized Pharmaceutical Products - Parametric Release

14. Tablet Friability Test

The Tablet Friability Test is a method to determine the

physical strength of uncoated tablets upon exposure to mechanical shock or attrition.

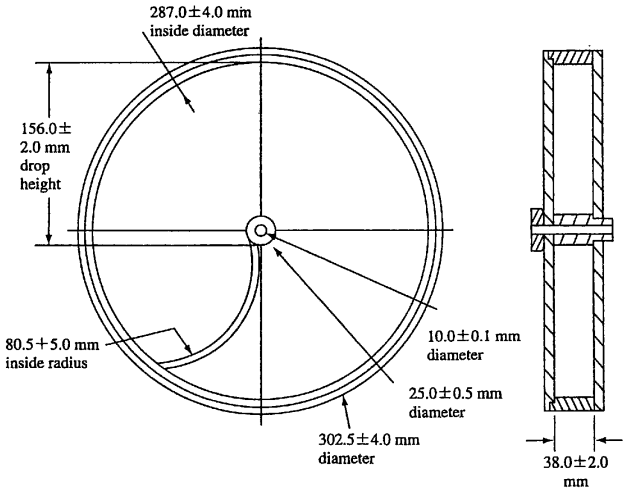
Apparatus

The apparatus consists of a drum and a motor. Use a drum with an inside diameter of about 287 mm and about 38 mm in depth, made of a transparent synthetic polymer with polished internal surfaces and not subject to static build-up, as illustrated in the figure. One side of the drum is removable.

Procedure

The drum is attached to the horizontal axis of a device that rotates at 24 - 26 revolutions per minute. For tablets weighing up to 650 mg each, take a sample consisting of the minimum number of tablets that makes a total mass of more than 6.5 g. For tablets weighing more than 650 mg each, take a sample of ten tablets. Dust should be carefully removed from the tablets prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before. If no tablets are cracked, split or broken, accurately weigh the tablets, and determine the friability (mass per cent of the lost mass with respect to the initial mass).

If the tablet size or shape results in irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the bench top and the tablets can fall freely when the drum is rotated. A drum with dual scooping supports for the running of two samples at the same time is also available. In the case of hygroscopic tablets, a humidity-controlled environment (relative humidity less than 40%) is required for testing.



15. Terminal Sterilization and Sterilization Indicators

Sterilization is a process whereby the killing or removal of all forms of viable microorganisms in substances is accomplished. It is achieved by terminal sterilization or a filtration method. For substances to which terminal sterilization can be applied, an appropriate sterilization method should be selected in accordance with the properties of the product, including the packaging, after full consideration of the advantages and disadvantages of each sterilization method, from among the heat method, irradiation method and gas method. After installation of the sterilizer (including design and development of the sterilization process), validation is required to confirm that the sterilization process is properly performing its designed function, under conditions of loading and unloading of the product, on the basis of sufficient scientific evidence. After the process has been validated and the sterilization of the product commenced, the process must be controlled correctly, and qualification tests of the equipment and procedures must be performed regularly. The bioburden per product, prior to terminal sterilization, must be evaluated periodically or on the basis of batches. Refer to the ISO standard (ISO 11737-1) relevant to bioburden estimation. For a substance to which terminal sterilization can be applied, generally use sterilization conditions such that a sterility assurance level of less than 10^{-6} can be obtained. The propriety of the sterilization should be judged by employing an appropriate sterilization process control, with the use of a suitable sterilization indicator, and if necessary, based on the result of the sterility test. The filtration procedure is used for the sterilization of a liquid product, to which terminal sterilization can not be applied. Concerning the disinfection and/or sterilization necessary for processing equipment and areas of pharmaceutical products, and performing microbiological tests specified in the monographs, see Disinfection and Sterilization Methods.

1. Definitions

The definitions of the terms used in this text are as follows.

Terminal sterilization: A process whereby a product is sterilized in its final container or packaging, and which permits the measurement and evaluation of quantifiable microbial lethality.

Product: A generic term used to describe raw materials, intermediate products, and finished products, to be sterilized.

Bioburden: Numbers and types of viable microorganisms in a product to be sterilized.

Sterility assurance level (SAL): Probability of a viable microorganism being present in a product unit after exposure to the proper sterilization process, expressed as 10^{-n}.

Integrity test: A non-destructive test which is used to predict the functional performance of a filter instead of the microorganism challenge test.

D value: The value which shows the exposure time (decimal reduction time) or absorbed dose (decimal reduction dose) required to cause a 1-logarithm or 90% reduction in the population of test microorganisms under stated exposure conditions.

Sterilization indicator: Indicators used to monitor the sterilization process, or as an index of sterility, including biological indicators (BI), chemical indicators (CI), dosimeters and the like.

2. Sterilization

2-1. Heat Method

In the heat method, microorganisms are killed by heating.

(i) Moist heat method

Microorganisms are killed in saturated steam under pressure. In this method, factors which may affect the sterilization include temperature, steam pressure and exposure time.