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METHOD OF STERILE PACKAGING

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28 Claims

ABSTRACT OF THE DISCLOSURE

A method of sterile packaging which involves the steps of partially filling a container with any of a number of anti-bacterial agents in liquid or semi-liquid form, then sealing the container so that an air space is formed above the liquid within the container, and finally heating the container and its contents (which may include a solid object to be sterilized immersed or partially immersed in the liquid) to a temperature substantially below the boiling point of the liquid, and at a pressure of about one atmosphere, until the interior surfaces of the container above and below the liquid level, and the entire contents of such container, are sterilized.

RELATED APPLICATION

This application is a continuation-in-part of our co-pending application Ser. No. 873,786, filed Nov. 4, 1969, now U.S. Pat. No. 3,618,283.

BACKGROUND

The aforementioned co-pending application discloses a method for the sterile packaging of surgical sponges and other articles in sealed flexible wrappers. During the packaging operation, and immediately following the sealing of the wrappers, the packages are squeezed or compressed so that all of the surfaces within the package will be flushed or wetted by the germicidal soap solution contained within the package. Subsequent heating of the package at a low enough temperature to avoid rupturing the flexible walls of the wrapper results in sterilization of all of the surfaces contacted by the liquid or, in other words, all of the surfaces within the package.

SUMMARY

A main aspect of this invention lies in the discovery that all surfaces within such a package will be sterilized by a procedure similar to the one described even where some of the surfaces are not flushed or contacted by the anti-bacterial solution. Obtaining complete sterilization under such conditions is believed most unexpected, not only because true sterilization is achieved with anti-bacterial agents which, at least in some instances, are considered only moderately effective in killing microorganisms, but also because such results are achieved with agents in which the active ingredient is of low volatility. The word "sterilization" as used herein means a method wherein no organisms are found living after treatment and in which even the most resistant organisms (spores) give no evidence of viability following such treatment.

The method involves the steps of first partially filling a bottle, bag, or other sealable container with a solution, usually but not necessarily an aqueous solution, of a standard anti-bacterial agent. While a wide variety of such agents are believed to be suitable, effective results are known to be obtainable with solutions of iodine (iodoform), halogenated bis-phenols such as hexachlorophene, quaternary ammonium salts such as benzalkonium chloride, and sodium ethylmercurithiosalicylate (marketed under the trademark "Merthiolate"). After partially filling the con-

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tainer with the anti-bacterial agent solution, and after placing in the container those items (if any) to be sterilized, the container is sealed so that an air (or gas) space is disposed above the liquid. Thereafter, the container and its contents are heated to a temperature well below the boiling point of the liquid and at a pressure of about one atmosphere. In general, the temperature to which the container and its contents are heated will fall within the range of about 130 to 210 degrees F., but usually below 180 degrees F., the particular temperature selected depending upon the anti-bacterial agent used and the duration of the heating step. The heating operation is continued until all organisms, including spores, are killed, the interval normally falling within the range of 2 to 24 hours.

DESCRIPTION

The anti-bacterial agents used in connection with the present method are conventional. Of the numerous agents known to have anti-bacterial properties and which are believed suitable for use in connection with the invention, experimental work has been successfully performed in connection with four of the more common of such agents. On the basis of such experimental work, it is believed that the following general conditions are applicable.

Where the anti-bacterial agent is sodium ethylmercurithiosalicylate in aqueous solution, a concentration within the range of 1:100 to 1:2000 has been found effective. The heating step should exceed 12 hours at a temperature within the range of about 160 and 210 degrees F.

For hexachlorophene, a halogenated 2,2'-bis-phenol, the aqueous solution should have a concentration within the range of about 0.25 to 4.0 percent (w./v.). The container and its contents should be heated to a temperature within the range of about 160 to 210 degrees F. for a time interval exceeding 12 hours.

Quaternary ammonium surface-active disinfectants have also been found effective. Thus, benzalkonium chloride in aqueous solution having a concentration falling within the range of 0.0025 to 0.2 percent may be used. The temperature of the heating step should fall within the range of about 150 to 210 degrees F. and heating should be carried out for a period exceeding 12 hours.

Iodine preparations or complexes which liberate free iodine in aqueous solution are highly effective for use in connection with the method of this invention. An aqueous iodoform solution having an iodine concentration within the range of 0.0012 to 3.0 percent is suitable. The heating step should be carried out at a temperature within the range of approximately 130 to 150 degrees F. for a period in excess of 2 hours.

Sterilization is complete even though surface portions within the container are never directly contacted by the liquid anti-bacterial agent. Normally the space above the liquid in the container will be filled with air; however, other gases might be substituted if desired. As previously mentioned, it is particularly significant that the gas and all surfaces on which the gas impinges become sterile at temperatures far below what is normally considered a sterilizing temperature (autoclaving temperature is about 220 degrees F.) and below the boiling temperatures of the liquids at normal atmospheric pressure.

The effectiveness of the sterilization procedure, and the details of specific applications of the operative procedure, will be evident from the following illustrative examples:

Example I

The following steps were carried out using an aqueous solution of a quaternary ammonium salt marketed under the designated "Zephiran" by Winthrop Laboratories, Inc., New York, N.Y. Ninety milliliters (ml.) of Zephiran, estimated to have a quaternary ammonium salt concentration

of about 1:750, were placed in a 200 cubic centimeter (cc.) large mouth bottle. A *Bacillus subtilis* (globigii) spore strip was secured by wire to the inside of the bottle cap so that when the cap was fitted tightly upon the bottle the spore strip was disposed half the length of the bottle above the liquid. Ten such bottles were partially filled and provided with spore strips as thus described. Five of them were inverted, thus wetting the spore strips with the solution. After being left in inverted position for 30 minutes, each was returned to an upright position. The five were then placed in upright position in a rack in an oven.

The other five bottles were not inverted and care was taken to avoid wetting of the spore strips. Such bottles were placed in the oven at the same time and under the same conditions as the preceding five bottles.

Two additional bottles were prepared for use as controls. Each contained 90 ml. of Zephiran and was provided with a *Bacillus subtilis* (globigii) spore strip secured to the underside of the cap as described above. One such control was inverted for 30 minutes and then returned to upright position as described above; the other was carefully maintained in upright position to avoid wetting of the spore strip. Neither control was heated, each being maintained at room temperature during the heating step performed on the other ten bottles and their contents.

The ten bottles and their contents were heated in the oven at a temperature of 166 to 172 degrees F. for 24 hours. Following such treatment, each of the containers was opened and its spore strip examined for growth. None of the first ten spore strips (those in containers subjected to heating) showed any evidence of growth and none revealed any viable microorganisms. Evidence of spore growth was clearly apparent on the spore strips in each of the controls.

It is evident from the above that the germicidal agent, in the absence of heat, was ineffective to prevent spore growth but that the combination of such agent with a moderate application of heat was not only sufficient to kill spores in direct contact with the agent but also to kill such spores suspended in the air space above such agent.

Example II

The procedure of Example I was repeated using a liquid hexachlorophene preparation marketed under the designation "Dermassage" by S. M. Edison Chemical Company, Jersey City, N.J. The concentration of hexachlorophene in such preparation was estimated to be about 3.0 percent. The test was conducted using ten bottles (200 cc.) each partially filled (90 ml.) with the Dermassage solution and each having a *Bacillus subtilis* (globigii) spore strip wired to the inside of the bottle cap. The spore strips of five of the bottles were wetted and the spore strips of the other five were left dry in the manner described in Example I. A single control bottle was prepared in the same manner and its spore strip was left dry.

All bottles but the control were heated in an oven for 24 hours at a temperature within the range of 170 to 180 degrees F. Inspection thereafter revealed no evidence of spore growth or of viable microorganisms in any of the bottles except for the control where such growth was clearly present.

Example III

The procedure of Example II was repeated in every respect except for the substitution of a different hexachlorophene preparation marketed under the designation "Dermisurgical" by S. M. Edison Chemical Company, Jersey City, N. J. The anti-bacterial solution was prepared by mixing the Dermisurgical preparation with water in the volume-volume ratio of 3:8. After heating all but the control for 24 hours in an oven at a temperature of 170 to 180 degrees F., inspection revealed that no spore growth existed on any of the spore strips

except for the spore strip in the control bottle which clearly evidenced spore growth.

Example IV

An iodoform soap solution marketed under the designation "GSI" by Huntington Laboratories, Huntington, Ind., was mixed with water in the proportions of three parts water to one part iodoform. The aqueous solution was then placed in ten test bottles and one control bottle, all as described in Example II. After carrying out the procedure described fully in Example II, but heating the test bottles and their contents for only three hours at a temperature of 140 to 150 degrees F., none of the spore strips in any of the ten test bottles revealed any evidence of spore growth or an indication of viable microorganisms. Spore growth was clearly apparent on the spore strip in the control bottle.

Example V

The test procedure of Example II was performed using as the anti-bacterial agent an aqueous solution of sodium ethylmercurithiosalicylate marketed under the designation "Methiolate" by Eli Lilly & Company, Indianapolis, Ind. The concentration of sodium ethylmercurithiosalicylate in such solution was given as 1:1000 and, following the procedure of Example II, 90 ml. of such solution were placed in each of eleven 200 cc. large mouth bottles. All of the steps of Example II were carried out, the ten test bottles and their contents being heated for 24 hours in an oven at 170 to 180 degrees F. Thereafter, the spore strips of all bottles were examined. None of the spore strips from the ten test bottles showed any indication of spore growth or any evidence of viable microorganisms. The spore strip of the unheated control bottle showed clear evidence of spore growth.

The numbered spore strips of all of the tests carried out in Examples I through V were designated as having a spore count of one million spores per square millimeter. All of such strips were incubated in fluid thioglycollate with neutralizers (Tween-80, Azolectin, and sodium thiosulfate) for growth of spores within seven days at 32 degrees C.

Example VI

The procedure of Example II was conducted as set forth therein, except that a heating temperature of about 180 degrees F. was maintained for a period of 20 hours. Results the same as reported in Example II were observed.

While in the foregoing we have disclosed the method of the invention in considerable detail for purposes of illustration, it will be understood by those skilled in the art that many of these details may be varied without departing from the spirit and scope of the invention.

We claim:

1. A method of sterile packaging comprising the steps of partially filling a container with a solution of a standard anti-bacterial agent selected from the group consisting of halogenated bis-phenols, quaternary ammonium salts, and sodium ethylmercurithiosalicylate; then sealing said container to provide a gas space above said solution within the sealed container; and thereafter heating said container and its contents to a temperature substantially below the boiling point of said solution and at a pressure of about one atmosphere until the interior surfaces of said container above and below the liquid level, and the entire contents of said container, are sterilized.

2. The method of claim 1 in which said container and its contents are heated to a temperature within the range of 130 to 150 degrees F.

3. The method of claim 1 wherein said gas space contains air.

4. The method of claim 1 wherein said container and its contents are heated to a temperature within the general range of about 130 to 210 degrees F.

5. The method of claim 1 in which said liquid comprises an aqueous solution of sodium ethylmercurithiosalicylate having a concentration within the range of 1:100 to 1:2000.

6. The method of claim 5 in which the container and its contents are heated to a temperature within the range of 160 to 210 degrees F.

7. The method of claim 1 in which said liquid comprises an aqueous solution of a halogenated 2,2'-bis-phenol having a concentration within the range of 0.25 to 4.0 percent.

8. The method of claim 7 in which said container and its contents are heated to a temperature within the range of 160 to 210 degrees F.

9. The method of claim 8 in which said halogenated 2,2'-bis-phenol is hexachlorophene.

10. The method of claim 1 in which said liquid comprises an aqueous solution of a quaternary ammonium salt having a concentration within the range of 0.0025 to 0.2 percent.

11. The method of claim 10 in which said container and its contents are heated to a temperature within the range of 150 to 210 degrees F.

12. The method of claim 11 in which said quaternary ammonium salt is benzalkonium chloride.

13. The method of claim 1 wherein the contents of said container include a solid object to be sterilized, said method comprising the step of placing said object within said container prior to said sealing step.

14. The method of claim 13 wherein at least a portion of said object is disposed in said space above the level of said liquid.

15. The method of claim 14 wherein said portion of said object is disposed above the level of said liquid throughout said filling, sealing, and heating steps.

16. A method of sterile packaging comprising the steps of partially filling a container with a solid object to be sterilized and with a liquid consisting essentially of a solution of a standard anti-bacterial agent selected from the group consisting of halogenated bis-phenols, quaternary ammonium salts, and sodium ethylmercurithiosalicylate; then sealing said container to provide a gas space above said solution within the sealed container; and thereafter heating said container and its contents to a non-boiling temperature within the range of about 130 to 210 degrees F. until the surfaces of said object and of the interior of said container above and below the liquid level, and the gaseous and liquid contents of said container, are sterilized.

17. The method of claim 16 in which the gas within the space above said liquid and within the sealed container is air.

18. The method of claim 16 wherein at least a portion of said object is disposed in said space above the level of said liquid.

19. The method of claim 16 in which said liquid comprises an aqueous halogenated 2,2'-bis-phenol solution of a concentration within the range of 0.25 to 4.0 percent; said container and its contents being heated to a temperature within the range of 160 to 210 degrees F.

20. The method of claim 19 in which said bis-phenol is hexachlorophene.

21. The method of claim 16 in which said liquid com-

prises an aqueous quaternary ammonium salt solution having a concentration within the range of 0.0025 to 0.2 percent; said container and its contents being heated to a temperature within the range of 150 to 210 degrees F.

22. The method of claim 21 in which said quaternary ammonium salt is benzalkonium chloride.

23. A method of sterile packaging comprising the steps of partially filling a container with a solid object to be sterilized and with a liquid consisting essentially of a solution of a standard anti-bacterial agent selected from the group consisting of halogenated 2,2'-bis-phenols, quaternary ammonium salts, and sodium ethylmercurithiosalicylate; then sealing said container to provide a gas space above said solution within the sealed container; thereafter heating said container and its contents to a non-boiling temperature within the range of about 130 to 210 degrees F. until the surfaces of said object and of the interior of said container above and below the liquid level, and the gaseous and liquid contents of said container, are sterilized; and maintaining at least a portion of said object above the level of said liquid and within said gas space throughout said filling, sealing, and heating steps.

24. The method of claim 23 in which said liquid comprises a solution of sodium ethylmercurithiosalicylate having a concentration within the range of 1:100 to 1:2000; said container and its contents being heated to a temperature within the range of 160 to 210 degrees F.

25. The method of claim 23 wherein said liquid comprises a solution of a halogenated 2,2'-bis-phenol having a concentration within the range of 0.25 to 4.0 percent; said container and its contents being heated to a temperature within the range of 160 to 210 degrees F.

26. The method of claim 25 wherein said bis-phenol is hexachlorophene.

27. The method of claim 23 in which said liquid comprises a solution of quaternary ammonium salt having a concentration within the range of 0.0025 to 0.2 percent; said container and its contents being heated to a temperature within the range of 150 to 210 degrees F.

28. The method of claim 27 wherein said quaternary ammonium salt is benzalkonium chloride.

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