The Theory and Practice of Industrial Pharmacy

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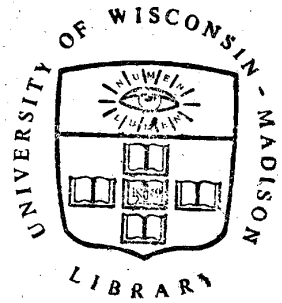

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Dry Heat. Substances that resist degradation at temperatures above approximately 140°C (284°F) may be rendered sterile by means of dry heat. Two hours exposure to a temperature of 180°C (356°F) or 45 min at 260°C (500°F) normally can be expected to kill spores as well as vegetative forms of all microorganisms. This total sterilizing cycle time normally includes a reasonable *lag time* for the substance to reach the sterilizing temperature of the oven chamber, an appropriate hold period to achieve sterilization, and a cooling period for the material to return to room temperature.

Factors in Determining Cycle Time. The cycle time is composed of three parts: (1) the thermal increment time of both the chamber and the load of material to be sterilized, assuming both start at room temperature, (2) the hold period at the maximum temperature, and (3) the cooling time. The material lags behind the increasing temperature of the chamber. The time required for all of the material to "catch up" with the temperature of the chamber is longer with larger quantites of material, poorer thermal conductance properties of the material, and lower heat capacity. The relationship of these factors must be carefully determined during validation studies so that effective cycle times can be planned.

The cycle time is most commonly prescribed in terms of the hold time, for example, 2 hours at 180°C dry heat. The hold time may be shown by sensors detecting the temperature of the chamber at its coolest spot; however, a better indication of the actual thermal condition is obtained by sensing, usually with a thermocouple, the coolest spot in the load of the material to be sterilized. When such a location is used, and when this coolest spot is known from previous validation studies, the timing required for sterilization is correctly programmable. It should be remembered that other parts of the load of material may be heated for a longer period, and if it is thermally unstable, degradation could occur. Therefore, the thermal stability of the material to be sterilized must be known and the optimum method of sterilization selected to achieve effective sterilization throughout the entire mass of material while maintaining its stability and integrity.

Sterilizer Types. The ovens used to achieve hot air sterilization are of two types, natural convection and forced convection. Circulation within natural convection ovens depends upon the currents produced by the rise of hot air and fall of cool air. This circulation can be easily blocked with containers, resulting in poor heat distribution efficiency. Differences in temperature of 20°C or more may be found in different shelf areas of even small laboratory ovens of the natural convection type.[14]

Forced convection ovens provide a blower to circulate the heated air around the objects in the chamber. Efficiency is greatly improved over natural convection. Temperature differences at various locations on the shelves may be reduced to as low as ±1°C. The lag times of the load material therein also are greatly reduced because fresh hot air is circulated rapidly around the objects. The curves shown in Figure 21-3 illustrate the difference in lag time for some of the same containers of corn oil when heated in a natural convection oven as compared with the same oven equipped for forced circulation.[14]

Another type of sterilizer is the tunnel unit with a moving belt, designed to thermally sterilize glass bottles and similar items as they move through the tunnel. The items are cooled with clean air before they exit the tunnel, usually directly into an aseptic room and linked in a continuous line with a filling machine. Such units require careful validation.[15]

Effect on Materials. The elevated temperatures required for effective hot air sterilization in a reasonable length of time have an adverse effect on many substances. Cellulose materials, such as paper and cloth, begin to char at a temperature of about 160°C (320°F). At these temperatures, many chemicals are decomposed, rubber is rapidly oxidized, and thermoplastic materials melt. Therefore, this method of sterilization is reserved largely for glassware, metalware, and anhydrous oils and chemicals that can

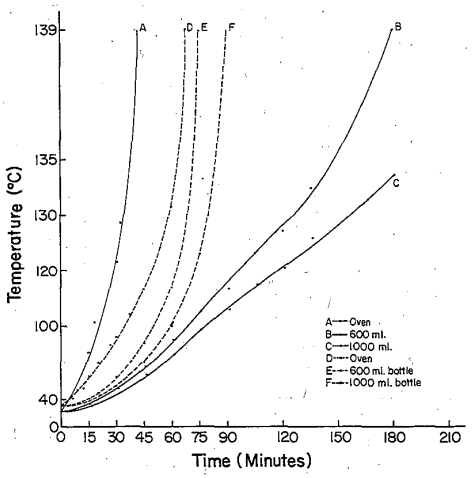

FIG. 21-3. *Rate of heating corn oil in Pyrex liter bottles in the same hot air oven with natural convection (——●——) and forced circulation (--●--).*

withstand the elevated temperature ranges without degradation. Expansion of materials is also appreciable, as they are heated from room to sterilizing temperatures. Therefore, glassware must not be wedged tightly in the oven chamber, containers for oils must be large enough to permit expansion of the oil, and provision must be made for the expansion of other substances.

Advantage may be taken of the anhydrous state achieved with this method of sterilization to provide dry glassware and metalware at the end of an adequate heating cycle. Dry equipment and containers are essential in the manufacture of an anhydrous product, but they are also desirable to prevent dilution of an aqueous product. Also, dry equipment can be kept sterile during storage more easily than wet equipment. Further, dry heat effectively destroys pyrogens, usually requiring about twice the hold time for sterilization.

To maintain a sterile condition after sterilization, environmental contamination must be excluded. The openings of equipment must be covered with a barrier material such as aluminum foil. As an alternative, items to be sterilized may be placed in a covered stainless steel box or similar protective container.

Moist Heat. Moist heat is more effective than dry heat for thermal sterilization. It should be remembered, however, that normal moist heat cycles do not destroy pyrogens.

As previously noted, moist heat causes the coagulation of cell protein at a much lower temperature than dry heat. In addition, the thermal capacity of steam is much greater than that of hot air. At the point of condensation (*dew point*), steam liberates thermal energy equal to its heat of vaporization. This amounts to approximately 540 calories per gram at 100°C (212°F) and 524 calories per gram at 121°C (250°F). In contrast, the heat energy liberated by hot dry air is equivalent to approximately only 1 calorie per gram of air for each degree centrigrade of cooling. Therefore, when saturated steam strikes a cool object and is condensed, it liberates approximately 500 times the amount of heat energy liberated by an equal weight of hot air. Consequently, the object is heated much more rapidly by steam. In addition, when steam under pressure is employed, a rapidly changing fresh supply of heat-laden vapor is applied to the object being heated. This is due both to the pressure under which steam is applied and to the partial vacuum produced at the site where steam is condensed, for it shrinks in volume by about 99% as it condenses.

Air Displacement. The density of steam is lower than that of air. Therefore, steam enters an autoclave chamber and rises to the top, displacing air downward, as illustrated by the gravity displacement autoclave shown in Figure 21-4. Objects must be placed in the chamber with adequate circulation space around each object, and so arranged that air can be displaced downward and out of the exhaust line from the chamber. Any trapped air, e.g., air in containers with continuous sides and bottoms or in tightly wrapped packs, prevents penetration of the steam to these areas and thus prevents sterilization. The air trapped in this manner is heated to the temperature of the steam, but hot air at a temperature of 120°C (248°F) requires a cycle time of 60 hours to ensure a lethal effect on spores.[16] A 20-min exposure at this temperature with hot dry air, therefore, would be entirely inadequate.

Factors Determining Cycle Time. Spores and vegetative forms of bacteria may be effectively destroyed in an autoclave employing steam under pressure during an exposure time of 20 min at 15 pounds pressure (121°C [250°F]) or as little as 3 min at 27 pounds pressure (132°C [270°F]). These time intervals are based on the assumption that the steam has reached the innermost recess of the material to be steri-

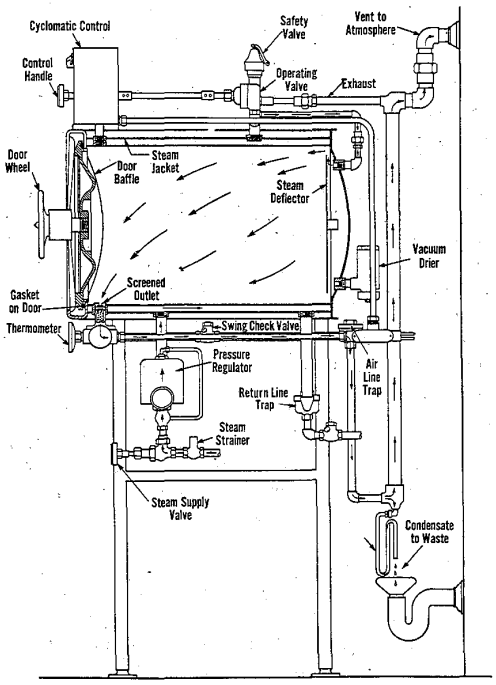

FIG. 21-4. *Cross-sectional diagram of the functional parts of an autoclave. (Courtesy of American Sterilizer Co.)*

lized, and that the temperature of the material is held for at least one half of that time interval. In the case of bottles of solution, the heat must be conducted through the wall of the container, raise the temperature of the solution to that of its environment, and generate steam within the container from the water therein. Therefore, a significant lag time is involved before the solution reaches the sterilizing temperature.

The determination of lag time and its inclusion in the planned total cycle time is no less important for moist heat sterilization than for hot air sterilization, discussed previously. By way of illustration, it has been found that 1200 ampuls, each containing 5 ml of a solution, can be effectively sterilized in an autoclave at 121°C (250°F) during an exposure time of 20 min. A single bottle containing the same total volume of solution (6 L) required an exposure of 60 min at 121°C (250°F).[17]

Air-Steam Mixtures. While air-steam mixtures have a lower temperature and lower thermal capacity than pure steam, the presence of air may be utilized to control the pressure in the chamber when flexible-walled containers of products are being sterilized. For example, plastic bags of large-volume parenterals (LVPs) or collapsible tubes of aqueous jellies would swell and burst in an autoclave utilizing steam only, particularly during the cooling phase. When air is mixed with the steam and the air pressure is independently controlled, the pressure applied to the outside of the containers can be adjusted to equal the internal pressure so that the containers do not burst. Because of the tendency of steam and air to stratify, the mixture must be mixed continuously; this is usually accomplished by means of a blower.

Approaches to Reduction of Cycle Time. Prolonged heating of most objects is detrimental to the material. For example, fabrics and rubber parts deteriorate with loss of tensile strength, solutions may undergo adverse chemical changes, and metal objects may become pitted. Therefore, the total cycle time should be controlled so that the heating period is not unnecessarily prolonged. Usually, this is best accomplished by shortening the cooling period. For nonsealed items of equipment or containers that do not contain solutions, the steam may be exhausted to the outside rapidly at the end of the sterilizing cycle. Objects are thereby cooled rapidly, particularly if removed from the autoclave chamber. Such a procedure cannot be employed for solutions, whether sealed or unsealed in containers, because the rapid release of chamber pressure would cause violent ebullition of the hot solution, with spattering of the contents of unsealed containers and explosion of sealed containers.

One method for rapid extraction of heat from sealed containers of solutions is to spray the containers with gradually cooling water while the pressure in the chamber is concurrently reduced. Another accelerated cooling method employs short pulses of high pressure steam introduced into the loaded chamber. As the steam expands in the chamber it extracts heat from the containers of solution. The steam is exhausted from the chamber at a rate that provides for a gradual reduction of the pressure concurrent with the temperature reduction. By these methods, it is sometimes necessary to introduce pulses of air into the chamber to replace all or part of the steam so that the pressure around the containers is not reduced too rapidly. By the spray cooling method, it has been reported that the cooling time for a load of 200 one-liter bottles of solution may be reduced from about 20 hours to about 20 min.[18]

A relatively new approach to a reduction in the total heating cycle time has been the introduction of a precycle vacuum. In a specially designed autoclave, a precycle vacuum of at least 20 mm Hg is drawn. More recent studies have shown that a double vacuum drawn in sequence prior to the heating cycle removes air more effectively from porous materials.[19] The subsequent introduction of steam permits rapid penetration and load heating with complete elimination of air pockets. Since the total heating period is markedly reduced owing to the reduction in the temperature increment time, a higher temperature (usually 135°C [275°F]) may be employed with less deleterious effects on materials. This method is particularly suited to operating room packs in hospitals, where the total cycle time for large packs has been reduced from about 78 min by the conventional method to about 14 min. Such a method cannot be used for solutions or other objects that cannot withstand the high vacuum employed.

Lower Temperature Sterilization. Moist heat also is used for lower temperature sterilization procedures. Temperatures of 100°C (212°F) or lower are used for these so-called *marginal,* or *fractional,* methods. The term marginal originates from the questionable reliability of the processes. The term fractional is derived from the fact that these processes are normally performed by two or three exposures to moist heat, alternated with intervals during which the material is held at room or incubator temperatures.

Fractional methods of sterilization such as tyndallization, employing a temperature of 100°C (212°F), and inspissation, employing

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