Chemical Processes of Sterilization

Gas Sterilization

Gas sterilization is not new. Such gases as **formaldehyde and sulfur dioxide** have been used for sterilization for many years. **These gases are highly reactive chemicals, however, and are difficult to remove from many materials after exposure.**

Therefore, their usefulness is limited.

Two newer gases, ethylene oxide and beta-propiolactone, have fewer disadvantages than the older agents and therefore have assumed importance in sterilization.

Ethylene Oxide.

Ethylene oxide (EtO) is a cyclic ether ($[CH_2]_2O$) and is a gas at room temperature. Alone, it is highly flammable, and when mixed with air, explosive.

Admixed with inert gases such as carbon dioxide , or one or more of the fluorinated hydrocarbons (Freons) in certain proportions, ethylene oxide is rendered nonflammable and safe to handle.

As a gas, **it penetrates readily such materials as plastic, paperboard, and powder.**

Ethylene oxide dissipates from the materials simply by exposure to the air. It is chemically inert toward most solid materials. **On the other hand, in the liquid state, as compressed in cylinders, ethylene oxide dissolves certain plastic and rubber materials and requires particular care in handling.**

Mechanism of Action.

Ethylene oxide is believed to exert its lethal effect upon microorganisms by **alkylating essential metabolites, affecting particularly the reproductive process**. The alkylation probably occurs by **replacing an active hydrogen on sulfhydryl, amino, carboxyl, or hydroxyl groups with a hydroxyethyl radical**. **The altered metabolites are not available to the microorganism, and so it dies without reproducing.**

Application.

Alkylation may also occur with drug molecules in pharmaceutical preparations, particularly in the liquid state. Therefore, ethylene oxide sterilization of pharmaceuticals is **limited essentially to dry powders of substances shown to be unaffected. It has extensive application, however, to plastic materials, rubber goods, and delicate optical instruments**. **It has also been found that stainless steel equipment has a longer useful life when sterilized with ethylene oxide instead of steam.** The effective penetrability of ethylene oxide makes it possible to sterilize parenteral administration sets, hypodermic needles, plastic syringes, and numerous other related materials enclosed in distribution packages of paperboard or plastic.

Beta-propiolactone.

Beta-propiolactone ($[CH_2]_2OCO$) is a cyclic lactone and **is a non-flammable liquid at room temperature**. It has a low vapor pressure, but since it is bactericidal against a wide variety of microorganisms at relatively low concentrations, no difficulty is experienced in obtaining bactericidal concentrations of the vapor.

It is an **alkylating agent and therefore has a mode of action against microorganisms similar to that of ethylene oxide**.

The penetrability of beta-propiolactone vapour has been found to be poor. Therefore, its principal use appears to be the sterilization of surfaces in large spaces, such as entire rooms.

Clarification and Filtration

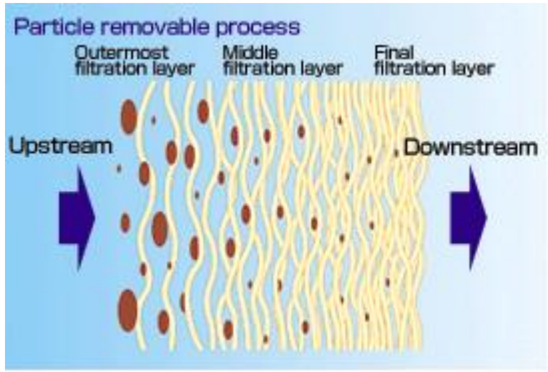
The preparation of pharmaceutical dosage forms frequently requires the separation of particles from a fluid. The usual *objective is a* sparkling liquid that is free of amorphous or crystalline precipitates, colloidal hazes, or insoluble liquid drops. Sterility specifications may expand the objective to include removal of microorganisms.

Filtration **is defined as the process in which particles are separated from a liquid by passing the liquid through a permeable material.** **The porous filter medium is the permeable material that separates particles from the liquid passing through it and is known as a *filter.* Thus, filtration is *a* unit operation in which a mixture of solids and liquid, the *feed, suspension, dispersion, influent* or *slurry,* is forced through a porous medium, in which the solids are deposited or entrapped. The solids retained on a filter are known as the *residue.* The solids form a *cake* on the surface of the medium, and the clarified liquid known as *effluent* or *filtrate* is discharged from the filter. If recovery of solids is desired, the process is called *cake filtration.* The term *clarification* is applied when the solids do not exceed 1.0% and filtrate is the primary product.**

Ultrafiltration **may be defined as the separation of intermicellar liquid from solids by the *use of* pressure on a semipermeable membrane.**

Filtration is frequently the method of choice for sterilization of solutions that are chemically or physically unstable under heating conditions.
In many applications, *sterile filtration* is an ideal technique. Sterile filtration of liquids and gases is commonly used in the pharmaceutical industry.
Final product solutions or vehicles for suspensions are sterile-filtered prior to an aseptic filling process. Sterile filtration of bulk drug solution prior to an aseptic crystallization process eliminates the possibility of organisms being occluded within crystals.

Surface filtration **is a screening action by which pores or holes in the medium prevent the passage of solids. The *depth filter* permits slurry to penetrate to a point where the diameter of a solid particle is greater than the diameter of a tortuous void or channel. The solids are retained within *a* gradient density structure by physical restriction or by absorption properties of the medium.**



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Theory

Even today, filtration is more an art than a science. The filtration theory, with all its mathematical models, has a deficiency. The deficiency is its preoccupation with resistance to flow, almost to the exclusion of considerations of filtrate quality. It is possible to estimate the resistance to flow of a clean filter medium but impossible to estimate with comparable accuracy what the resistance will be as the filter begins to trap solids.

The mathematical models do provide a means of showing apparent relationships between variables in a process and may be valuable decision-making tools in the selection of apparatus and techniques for a particular filtration application.

The mathematical models for flow through a porous medium, cake filtration, and granular bed filtration may differ, but all follow this basic rule. The energy lost in filtration is proportional to the rate of flow per unit area.

The flow of liquid through a filter follows the basic rules that govern flow of any liquid through a medium offering resistance. The *rate* of flow may be expressed as:

$$\text{rate} = \frac{\text{driving force}}{\text{resistance}} \qquad (1)$$

The rate may be expressed as volume per unit time and the driving force as a pressure differential.

The apparent complexity of the filtration equations arises from the *expansion of the* resistance term.

Resistance is not constant since it increases as solids are deposited on the filter medium.

An expression of this changing resistance involves a material balance as well as factors expressing permeability or coefficient of resistance of the continuously expanding cake.

The rate concept as expressed in modifications of Poiseuille's equation is prevalent in engineering literature:

$$\frac{dV}{dT} = \frac{AP}{\mu\,(\alpha W/A + R)} \qquad (2)$$

$$\frac{dV}{dT} = \frac{AP}{\mu\,(\alpha W/A + R)} \qquad (2)$$

where:
V = volume of filtrate
T =time
A = filter area
P = total pressure drop through cake and filter medium
μ = filtrate viscosity
α = average specific cake resistance
W = weight of dry cake solids
R = resistance of filter medium and filter

$$\frac{dV}{dT} = \frac{AP}{\mu\,(\alpha W/A + R)} \qquad (2)$$

Interpretation of the basic equation, however, leads to a general set of rules:

1. **Pressure increases usually cause a proportionate increase in flow unless the cake is highly compressible. Pressure increases on highly compressible, flocculent, or slimy precipitates may decrease or terminate flow.**

2. An increase in area increases flow and life proportional to the square of the area since cake thickness, and thus resistance, are also reduced.

3. The filtrate flow *rate* at any instant is inversely proportional to viscosity.

4. Cake resistance is a function of cake thickness; therefore, the average flow rate is inversely proportional to the amount of cake deposited.

$$\frac{dV}{dT} = \frac{AP}{\mu\ (\alpha W/A + R)} \qquad (2)$$

5. Particle size of the cake solids affects flow through effect on the specific cake resistance, α. A decreased particle size results in higher values of α and proportionally *lower* filtration rates.

6. The filter medium resistance, R, usually negligible or about 0.1 α in cake filtration, is the primary resistance in clarification filtration.

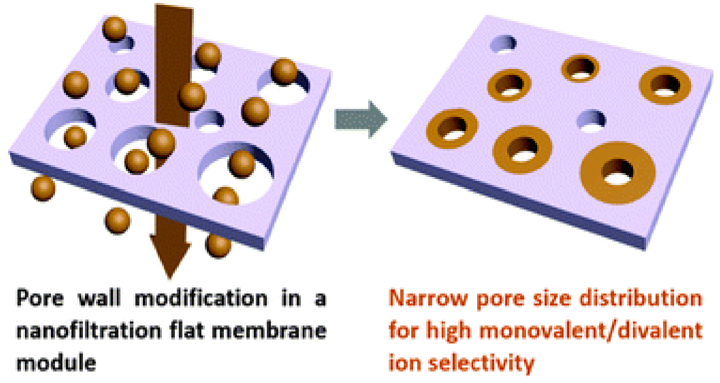
In the latter case, flow rate is inversely proportional to R.

It is convenient to summarize the theoretic relationship as:

$$\text{Rate of filtration} = \frac{(\text{area of filter}) \times (\text{pressure difference})}{(\text{viscosity}) \times (\text{resistance of cake and filter})} \qquad (3)$$

The membrane filters are highly porous. A number of methods are used for establishing the pore size and pore size distribution. Most methods are derived from the interfacial tension phenomenon of liquids in contact with the filter structure.
Each pore in the filter acts as a capillary.
For a nonwetting fluid, the following equation was established by Poiseuille:

$$p = \frac{-2\gamma \cos \theta}{r} \qquad (4)$$



where:
p = applied pressure
γ = liquid surface tension
θ = contact angle between liquid and solid
r = radius of the pore

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Filter Media

The surface upon which solids are deposited in a filter is called the *filter medium*. For the pharmacist selecting this important element, the wide range of available materials may be bewildering. The selection is frequently based on past experience, and reliance on technical services of commercial suppliers is often advisable.

A medium for cake filtration must retain the solids without plugging and without excessive bleeding of particles at the start of the filtration.

In clarification applications, in which no appreciable cake is developed, the medium is the primary factor in achieving clarity, and the choice is limited to materials that will remove all particles above a desired size.

Sterile filtration imposes a special requirement, since the pore size must not exceed the dimension of microorganisms unless the filter is adsorptive, and since the medium should be sterilizable.

Filter media are available in different materials and forms. The filter fabrics are commonly woven from natural fibers such as cotton and from synthetic fibers and glass. The properties of these fibers and glass applicable for media selection are tabulated in Table 7-1.

***Filter cloth*, a surface type medium, is woven from either natural or synthetic fiber or metal.**

Cotton fabric is most common and is widely used as a primary medium, as backing for paper or felts in plate and frame filters, and as fabricated bags for coarse straining.

Nylon is often superior for pharmaceutical use, since it is unaffected by mold, fungus, or bacteria, provides an extremely smooth surface for good cake discharge, and has negligible absorption properties. Both cotton and nylon are suitable for coarse straining in aseptic filtrations, since they can be sterilized by autoclaving. Monofilament nylon cloth is extremely strong and is available for openings as small as 10 microns.

Teflon is superior for most liquid filtration, as it is almost chemically inert, provides sufficient strength, and can withstand elevated temperatures.

  

Teflon

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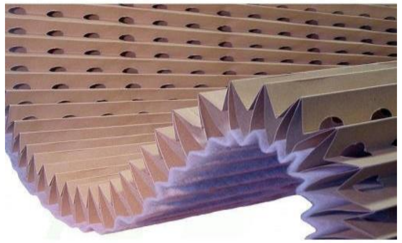
Woven wire cloth, particularly stainless steel, is durable, resistant to plugging, and easily cleaned. Metallic filter media provide good surfaces for cake filtrations and usually are used with filter aids. As support elements for disposable media, wire screens are particularly suitable, since they may be cleaned rapidly and returned to service. Wire mesh filters also are installed in filling lines of packaging equipment. Their function at this point is not clarification, but security against the presence of large foreign particles.

Nonwoven filter media **include felts, bonded fabrics, and kraft papers. A *felt* is a fibrous mass that is free from bonding agents and mechanically interlocked to yield specific pore diameters that have controlled particle retention. High flow rate with low pressure drop is a primary characteristic. Felts of natural or synthetic material function as depth media and are recommended where gelatinous solutions or fine particulate matter are involved.**



Kraft paper

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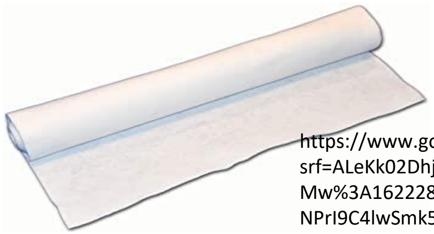

Felt

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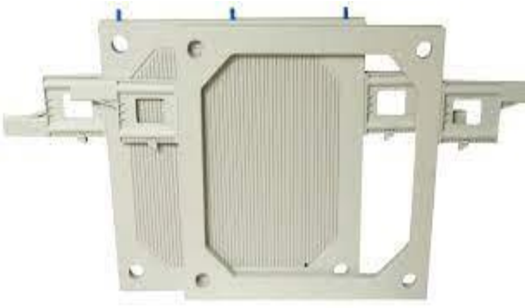
<u>*Bonded fabrics*</u> are made by binding textile fibers with resins, solvents, and plasticizers. These materials have not found wide acceptance in dosage form production because of interactions with the additives.

***Kraft* paper is a pharmaceutical standard. Although limited to use in plate and frame filters and horizontal-plate filters, it offers controlled porosity, limited absorption characteristic, and a low cost. The latter is important since concern over cross-contamination makes a disposable medium attractive to pharmacy.**

White papers are preferred, and they may be crinkled to produce greater filtration area. A support of cloth or wire mesh is necessary in large filter presses to prevent rupture of the paper with pressure.

Porous stainless steel filters are widely used for removal of small amounts of unwanted solids from liquids (clarification) such as milk, syrup, sulfuric acid, and hot caustic soda. Porous metallic filters can be easily cleaned and repeatedly sterilized.



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Membrane filter media **are the basic tools for microfiltration and ultrafiltration. They are used commonly in the preparation of sterile solutions.**

Membrane filters classified as surface or screen filters are made of various esters of cellulose or from nylon, Teflon, polyvinyl chloride, polyamide, polysulfone, or silver.

The filter is a thin membrane, about 150 microns thick, with 400 to 500 million pores per square centimetre of filter surface. The pores are extremely uniform in size and occupy about 80% of filter volume. This high porosity permits flow rates at least 40 times faster than those obtained through other media of comparable particle retention capability.

Because of surface screening characteristics, prefiltration is often required to avoid rapid clogging of a membrane.

The selection of a membrane filter for a particular application is a function of the size of the particle or particles to be removed. An approximate pore size reference guide can be set down as follows:

Pore Size (micron)	Particle Removed
0.2 (0.22)	All bacteria
0.45	All coliform group bacteria
0.8	All airborne particles
1.2	All nonliving particles considered dangerous in i.v. fluids
5	All significant cells from body fluids

The fragility of membrane filters is partially overcome by the use of monofilament nylon as a supporting web within the membrane structure. The distinction between ultrafiltration and microfiltration lies in the nature of the filter medium. Ultrafiltration membranes contain pores of relatively narrow size distribution 10^{-3} to 10^{-2} microns (10 to 100 A) and are formed by etching cylindric pores into a solid matrix.

Ultrafiltration membranes are fragile and require supporting substrates because of the high-pressured differences required during filtration.

Most types of filter media are also available as *cartridge units*. These cartridges are economical and convenient when used to remove low percentages of solids ranging in particle size from 100 microns to less than 0.2 micron.

The cartridge may be a surface or depth filter and consists of a porous medium integral with plastic or metal structural hardware. Synthetic and natural fibers, cellulose esters and fiberglass, fluorinated hydrocarbon polymers, nylon, and ceramics are employed for the manufacture of disposable cartridges.

Porous materials for cleanable and reusable cartridges use stainless steel, Monel, ceramics, fluorinated hydrocarbon polymers, and exotic metals.

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Surface-type cartridges **of corrugated (uneven), resin treated paper are common in hydraulic lines of processing equipment, but are rarely applied to finished products. Ceramic cartridges have the advantage of being <u>cleanable for reuse by backflushing</u>, and porcelain filter candles are acceptable for some sterile filtrations along with membrane filters in cartridge form. Sintered metal or woven-wire elements are also useful, but fine wire mesh lacks strength. The metallic-edge filters overcome this problem by allowing liquid to pass between rugged (rough) metal strips, which are separated by spacers of predetermined thickness.**

Sintered metal

Depth-type cartridges **consist of fibrous media, usually cotton, asbestos, or cellulose. The cartridge may be formed by felting or by resin bonding fibers about a mandrel. مغزل Effective units are also manufactured by winding (curving) yarn around a central supporting screen. The depth cartridge is always a disposable item since cleaning is not**

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Filter Aids

$$\frac{dV}{dT} = \frac{AP}{\mu\,(\alpha W/A + R)} \quad (2)$$

Justification for use of filter aids may be found in equation (2), which shows the rate of filtration to be inversely proportional to the resistance of the solids cake. Therefore, the pressure drop across the system is directly proportional to the filtration rate, the thickness of the cake, and the liquid viscosity for flow through porous media, when laminar flow conditions exist in the filter media or cake. It is also inversely proportional to the density of the liquid and square of the particle diameter. Poorly flocculated solids offer higher resistance than do flocculated solids or solids providing high porosity to the cake. In the case of cake filtration, the rate varies with the square of the volume of liquid. When the volume of the filter cake solids per unit volume of filtrate is low, the solids formed on the filter medium may penetrate the void space, thus making the filter medium more resistant to flow.

At a higher concentration of solids in a suspension, the bridging over of openings over the void space, rather than blinding of the openings, seems to predominate. Slimy or gelatinous materials, or highly compressible substances, form impermeable cakes with high resistance to liquid flow. The filter medium becomes plugged or slimy with accumulation of solids and *the* flow of filtrate stops. A filter aid acts by reducing this resistance.

Filter aids are a special type of filter medium. Ideally, <u>the filter aid forms a fine surface deposit that screens out all solids</u>, <u>preventing them from contacting and plugging the supporting filter medium.</u> <u>Usually, the filter aid acts by forming a highly porous and noncompressible cake that retains solids, as does any depth filter</u>. The duration of a filtration cycle and the clarity attained can be controlled as <u>density, type, particle size, and quantity of the filter aid are varied.</u>

<u>The quantity of the filter aid greatly influences the filtration rate</u>. If too little filter aid is used, the resistance offered by the filter cake is greater than if no filter aid is used, because of added thickness to the cake. On the other hand, if high amounts of filter aid are added, the filter aid merely adds to the thickness of the cake without providing <u>additional cake porosity.</u>

Figure 7-1 is a typical plot of filter aid concentration versus permeability. In the figure, flow rate and permeability are directly proportional to each other.

FIG. 7-1. *Experimental determination of flow rate as a function of filter aid quantity discloses correct operating level.*