by gas or radiation sterilization. Plastic components used in manufacturing are sterilized by steam sterilization with depyrogenation accomplished by prerinsing.

Siliconization

Silicone historically has been used to coat rubber closures in order to provide sufficient lubrication for the closures to feed and flow readily in high-speed filling equipment. Silicone application to syringes and cartridges also has been necessary for facile movement of a plunger rod with a rubber tip through the barrel of the container.

The amount of silicone applied per rubber stopper depends on the formulation size, weight, and design of stopper. Typically, the formulas used are established by trial and error. One example is that for 60000 13-mm lyophilization stoppers being processed in a Getinge stopper processor, with an average stopper weight of 630 mg, 31 mL of silicone oil is used[1]. Typically, the larger the stopper, the smaller the amount of silicone applied per stopper. For example, 13-mm liquid stoppers will contain a target of 0.85% silicone, 20-mm liquid stoppers will contain a target of 0.1% silicone, and 28-mm liquid stoppers will contain a target of 0.05% silicone. However, these are examples and not standards so the amount of silicone applied per stopper load will vary according to manufacturer, stopper processor, and filling speed of product fill.

Despite the ubiquitous usage of silicone in parenteral packaging preparation, it is surprising that very little has been published on the subject. While silicone coating on closures and syringe/cartridge barrels certainly offers significant advantages, there are many disadvantages with the use of silicone. Among these are the following:

1. Cleanability
2. Balance between too much and too little silicone applied
3. Potential incompatibilities with biomolecules
4. Viewed as a particle by electronic particle measuring devices

Mixing

Effective mixing must assure that the entire solution is thoroughly mixed and that there are no areas of stagnation where mixing is minimal or none. Mixing procedures are relatively straight forward for readily soluble components, but much more of a challenge for poorly soluble or slow-to-dissolve components and for biopharmaceutical active ingredients sensitive to the effects of mixing shear. Excessive foaming or entrapped air should be avoided, as denaturation at the air–liquid interface is possible. Precautions in mixing must be taken to prevent foaming. For suspension mixing and re-circulation during filling, a balance must be established between adequate mixing to achieve suspension homogeneity without impacting particle size distribution.

Primary mixing parameters to be controlled are shear rates (rpms), time, and temperature. Electropolished mixing tanks are available in different sizes and shapes with volumes ranging from roughly 100 L to 2000 L (Fig. 12-4). Mixing equipment must be designed to be cleaned-in-place (CIP) and sterilized-in-place (SIP). There should be no retention of liquid when the mixing tank is emptied and must have no "dead" areas or crevices. Materials of construction must be product compatible and corrosion resistant.

Mixing mechanisms include shear (propellers, blades, even magnetic stirring bars), diffusive, and vibratory. High shear mixers (e.g., Ross) are used for dissolving "hard-to-wet" components (e.g., polymers like carboxymethylcellulose). Bottom mount tank mixers (e.g., NovAseptic®, Fig. 12-5), are good general mixing systems where the blade type and configuration can dictate whether mixing includes vortexing. Suspension formulations where compounding and mixing must be aseptic use Rütten magnetic mixers. Rütten also produces the Vibromixer®, an intensive but gentle mixer applicable for shear-sensitive formulations. Mixing systems have now become disposable (e.g., ATMI LifeSciences) based on a single-use mixing bag containing a bottom mounted disposable magnetic impeller on a disposable bearing.

[1] These and other examples used in this book do not necessarily reflect what is true at Baxter BioPharma Solutions, but represent a general view of what is true in the entire sterile products manufacturing industry.