of nonreactive materials such as borosilicate glass or stainless steel. Modern coatings, such as AMCX2286, are used to coat stainless steel needles for products that are affected by contact with metals, for example, formulations containing chelating agents or having very acidic or alkaline pH values. In addition, they should easily be demountable for cleaning and sterilization.

FILLING MECHANISMS

Filling machines are classified by the type of driving device or filling mechanism used to deliver the drug-containing formulation into the primary package. There are at least four driving devices and four filling mechanisms:

Driving device	Filling mechanism(s)
Gravity (solids and liquids)	Gravimetric, time–pressure, fill-by-weight
Piston (liquids and gases)	Rotary piston
Rotary pump (liquids and gases)	Rotary peristaltic
Auger screw or vibrator (solids)	Vibratory/mechanical force

Gravity/Time Pressure Filling

The gravity-based filling machine is the oldest type and most economical. The filling principle is simple; the amount of product flowing through the filling nozzle is driven by gravity and will always be the same for a fixed amount of time. The finished bulk solution is pumped into a holding tank above a set of pneumatically operated valves. Each valve is independently timed by a master computer for the filling machine so that precise amounts of liquid will flow by gravity into the container. The amount of product dispensed is controlled by adjusting the time for closing the valve. In more precise systems, weight feedback is used to control the volume of dispensed product. Independent timing of each filling valve/nozzle corrects for minor variations in flow rates so that each container is filled accurately and uniformly. Improvements in holding tank headspace pressure control and feedback control have made time pressure filling machines more accurate than pump systems.

The disadvantage of this type of technology is that the dynamics of the fluid path and nozzle actuation characteristics continuously change over time. This requires the operator to make adjustments to the machine's stored parameters more frequently than other filling mechanisms.

Fill-by-Weight

This is a very simple system where the bulk solution tank is controlled by a valve to release product through a filling nozzle into the container that sits on a balance that controls the volume of product actually filled. This filling method is not used much anymore because of significant disadvantages using a balance or load cell (Table 19-1). However, there is better accuracy and control of the fill volume per container compared with other methods.

Piston Filling

Piston filling includes pumps with lapped rotary or check valves and pumps that use a rolling diaphragm. Lapped rotary pumps involve a cylinder that is lapped by both the piston and the rotary valve to produce an exceedingly tight fit. Pumps with check valves are not used for injectable filling because the valves are difficult to clean. Pumps with the rolling diaphragm use a flexible membrane attached to the pump at its outside diameter and to the piston at its inside diameter (1). A space between the piston and the body internal cylinder allows the diaphragm to be doubled and to roll as the piston moves up and down. Vacuum is required to maintain the shape of the diaphragm and to pull the piston downward on the refill part of the filling cycle.

Piston pumping machines are the most commonly used filling machines for liquids. They are not the best choice as a filling mechanism for shear-sensitive liquids and suspensions because of the tight clearances between the piston and the cylinder. In piston-driven filling machines, the product enters the dispensing cylinder by opening an infeed valve moving the piston in a reverse direction, closing the infeed valve, opening a discharge valve, and driving the piston in the opposite direction so that the product is propelled to the nozzle and into the collection