Figure 12-5 NovAseptic® GMP mixer. *Source*: Courtesy of Millipore Corporation.

In-process Testing

In-process controls are those operations within a manufacturing process where a critical parameter is controlled to a proven acceptable range or an analytical assay is conducted to determine proper interim conditions prior to progressing onto the next step. Examples of possible in-process controls are drug potency, pH, clarity, appearance, bioburden, and filter integrity. For suspension processes additional process controls may include order and rate of addition of components, location of addition, temperature, heat gain/loss (rate and overall time), agitation (type, rate, intensity, and duration), particle size control, suspension homogeneity, and morphology.

All in-process controls need to be supported by studies designed to establish appropriate specifications that will ensure batch-to-batch reproducibility. The order, rate, and location of additions and temperature control can be extremely important, especially for producing the desired crystalline form of a peptide or protein. Heat gain or loss can result in denaturation or influence particle generation if strict controls are not in place. Agitation is another critical parameter requiring precise control when dealing with peptide or protein suspensions as just described.

As with any finished dosage form, the product specifications must define key attributes of the preparation that ensure safety, identity, strength, purity, and quality. Besides potency, purity, and stability, suspension preparations will also require, at a minimum, specifications for content uniformity, particle morphology, and physical appearance. Specifications might also be established for other parameters such as particle size and distribution, sedimentation rate, and sedimentation volume, or rheological properties depending on the nature of the final suspension.

Filtration

Chapter 18 is devoted to filtration, but lets discuss a few introductory remarks here. The primary purposes of filtration are to clarify (remove all visible particulate matter) and to sterilize. Even if the final product is to be terminally sterilized, the solution is filtered through a sterilizing filter.

Filters are either flat disks or cartridge-type filters of different polymer compositions, sizes (diameters or surface areas), and porosities. Filters are selected based on three primary validations—microbial retention, product compatibility, and low extractables. Filter integrity during processing is determining via nondestructive integrity tests such as the bubble point test or the diffusion test.