isothermal titrating calorimetry (ITC) has been used to study adsorption of soluble insulin onto NPH crystals and obtain estimates for the thermodynamic parameters associated with this process (20).

Scanning Probe Microscopy

The scanning probe microscopy (SPM) techniques of scanning tunneling microscopy (STM) and atomic force microscopy (AFM) provide added advantages with specific applications to pharmaceutical systems. The AFM technique is appropriate for characterizing protein crystal packing and growth mechanisms. For example, tapping-mode AFM (TMAFM) was used to identify polymorphs of bovine insulin (21), study crystal growth characteristics of $Lys^{B28}Pro^{B29}$ insulin (22), characterize Ultralente crystals prepared from human, porcine, and bovine insulin (23), and assess interfacial structure, morphology, and growth characteristics associated with $Lys^{B28}Pro^{B29}$ protamine crystals (24). The in situ imaging capabilities of the technique allows the direct visualization of the effects of additives and other parameters as crystal growth occurs.

In Vitro Dissolution

In the development of sustained or controlled-release suspensions, it is useful to have an in vitro assay available for quickly approximating dissolution properties. Analogous to dissolution testing for solid dosage forms, the procedure requires some detection method to continuously monitor release of drug. As an example, a continuous-flow spectrophotometric method was developed that can categorize insulin suspension preparations based on clinical time-action classifications (25). Prabhu et al. (26) describe the use of a spin-filter device to study the factors controlling dissolution of zinc-complexed insulin suspensions.

SUSPENSION MANUFACTURE

Developing and validating parenteral commercially viable suspension manufacturing processes present significant challenges. A schematic example of suspension manufacture is seen in Figure 9-6. As pointed out earlier, crystallization of drugs at small scale is not simple, but the difficulty of the problem is magnified by virtue of the large volumes needed and the strict controls required for the preparation of pharmaceutical products. Generally, incremental increases in scale are attempted starting from the bench process and progressing upward in volume to the required batch size. Changes in container composition (e.g., glass vs. stainless steel) and geometry will occur during the transition and this could impact the crystallization. In addition, one must consider how certain operations performed with ease in the laboratory such as additions, mixing, transfers, and temperature control will be conducted under aseptic conditions of a manufacturing facility.

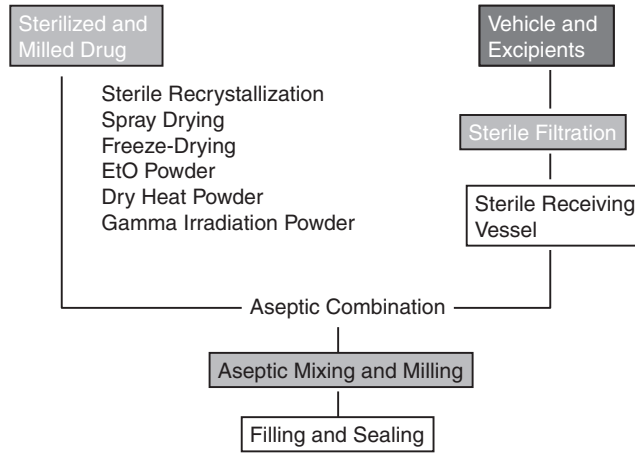

Figure 9-6 Flow diagram schematic of sterile suspension manufacture.