is developed for a drug, generally the scale-up of this process to a commercial scale can be achieved with relative ease. Equipment for filling liquids in a capsule on both small and large scales is readily available. However, the challenge encountered in this approach is achievement of adequate solubility and stability in the cosolvent system that can be contained in a specified capsule volume. This dosage form also limits the quantity of water as an enabling solvent.

As formulation scientists engage themselves in formulation and process development activities, in-process controls begin to assume major importance for demonstrating quality during the manufacturing process. Current GMPs state that in-process controls must exist to assure batch uniformity and quality of drug product (21 CFR 211.110 and EU GMP Guidelines Annex 13). The in-process controls are to be implemented to monitor and control critical process parameters during manufacturing of drug product. In-process controls assume a greater level of importance in ensuring that each manufactured lot meets all its specifications since limited process validation is available for exploratory clinical lots. In-process controls are dependent on previous experience with the particular dosage form, formulation characteristics, manufacturing process complexity, and batch size.

In-process controls are of two types: (1) in-process *monitoring* during the manufacturing and (2) in-process *testing* of the intermediate material. Monitoring is defined as periodic checks performed during manufacturing to ensure that the process conforms to the preestablished ranges and, if necessary, to adjust the manufacturing parameters before further processing. An example of in-process monitoring would be machine adjustment to ensure that tablet weight or capsule fill weight is maintained in the specified range. In-process testing can be defined as GMP testing performed during manufacturing to assess the performance of key manufacturing steps by ensuring compliance to a specified target range before further processing. An example of the in-process testing would be the verification of blend uniformity for compliance to target acceptance range before an encapsulation or tablet compression step. Authors' suggested examples of common in-process monitoring and testing controls for tablet and capsule dosage forms are listed in Table 23.4.

Blend uniformity testing is intended to demonstrate content uniformity and adequate mixing of ingredients at the blending unit operation. However, research has proven that one cannot rely only on this assurance as segregation of API could happen in the downstream processing during compression and/or encapsulation. Product blend during these processes can be subjected to machine vibration during manufacturing and thus have potential for impacting the overall quality of the drug product. Stratified sampling and testing is an approach to demonstrate that quality (batch uniformity) is maintained throughout the encapsulation or compression run. Stratified sampling is defined as the process

TABLE 23.4
In-Process Monitoring and Testing Controls for Tablet and Capsule Dosage Forms

Unit Process	In-Process Monitoring	In-Process Testing
Blending		Blend uniformity
Compressing	Appearance	Stratified sampling and testing
	Friability	
	Hardness	
	Weight variation	
	Thickness	
Granulation		
Dry granulation	Solid fraction	Compliance to target solid fraction range
	Thickness	
Wet granulation	Moisture assessment	Drying endpoint target (moisture test)
	Granule size	Sieve analysis
Encapsulation	Appearance	Blend uniformity
	Weight variation	Stratified sampling and testing