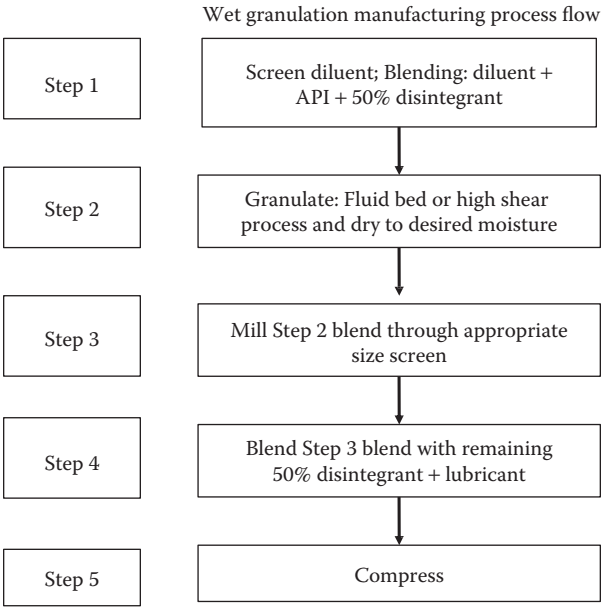

FIGURE 23.4 Example process flow for the wet granulation process.

help in assessing this risk and impact. If the drug loading is very low (i.e., <1%), the preferred technology could be wet granulation to ensure content uniformity. Table 23.3 suggests two broad risk factors where variability in dose and drug loading in standard formulations could pose challenges in the clinical manufacturing environment. Also mentioned are the authors' suggested risk mitigation techniques to ensure quality compliance. The processes and the manufacturing scales vary widely, and process validation is nonexistent at this stage in the development. Hence, the obligation for ensuring quality drug product lies solely on the in-process controls and sound understanding of how the API will behave in the standardized formulation during manufacturing. Although specialized

TABLE 23.3
Phase II Clinical Manufacturing Challenges with Standardized Formulations

	Factors	Clinical Manufacturing Challenge	Suggested Risk Mitigation Approaches
1.	Low dose (<1 mg or below 1% drug loading)	Content uniformity	In-process controls such as stratified sampling, process analytical technology (PAT) application, and blend homogeneity. Assess modification of dissolution through optimization of API characteristics and then perform assessment of specialized technologies [hot-melt extrusion (HME), spray-dried dispersion, solid dispersion, etc.] for long-term resolution.
2.	High dose (>10% drug loading)	Potential risk in process ability during manufacture	API material characterization before manufacturing for potential impact assessment. Process understanding and evaluation of specialized technologies [twin-screw wet granulation (TSWG), extrusion, solid dispersion, etc.] for long-term resolution.