The effect of hardness on the dissolution profile must be considered for each viable tablet core formulation, and the formulation that demonstrates the least variation in release rate and extent over the widest possible hardness range (while still retaining the desired appearance and disintegration characteristics) will invariably become the "final formulation." It is this formulation and associated manufacturing process that must be scaled up in the course of further development.

Equipment Selection for Formulation Development

During the early era of generic drug product manufacture, formulation development was often commenced using different equipment to that used for pilot production, exhibit batch, and/or in the commercial-scale manufacturing facility. The process of scale-up is more often than not a daunting task even when employing equipment of the same type and operating principle during the initial stages of formulation development (small-scale) through pilot-batch (exhibit-batch) production to final full-scale (commercial) batch manufacture. As far as possible, the type of tablet compression equipment and tooling or encapsulator machinery should be identical in principle to those used for scale-up manufacture of the exhibit-batch/commercial batches, resulting in technology transfer from pilot scale to production batch occurring with few difficulties for the formulation scientist. Hence, the use of different types of equipment between the different phases of development is not recommended. A comprehensive account of scale-up and technology transfer is portrayed in Chapter 5.

Of all the processes that need to be controlled, the most critical is wet granulation because it is particularly vulnerable with respect to consistency using different types of equipment. Careful monitoring of (a) mixer and chopper speeds, (b) rate of addition of the granulating vehicle, (c) the quantity of granulating vehicle, and (d) the processing time is necessary to yield an evenly textured granulate to result in satisfactory granules after subsequent drying [72–76]. It is, however, possible to vary the type of mill used and yet achieve the desired granulometry by adroit use of screen dimension and milling rate [77].

Drying of wet granulate can be undertaken effectively using either a fluid-bed dryer or a circulating air oven, the most noticeable difference between the two techniques manifesting itself in the granulometry of the dried granule, because the fluid-bed technique tends to provide a "finer" (less dense) granule than an oven [78,79].

Wet granulation formulations tend to suffer less from nonhomogeneity of (active) distribution than do direct-compression formulations, because the active/excipients are far more intimately mixed before granulation than can be effected by traditional dry blending. Each granule yielded by wet granulation should thus comprise a homogenous blend of active and excipients, whereas, in the case of direct-compression formulations, the blending is far less vigorous and the materials being blended are usually not of the same size and morphology, these two differences being the main contributing factors to dry blends demonstrating greater (active) variation than those produced by wet granulation [80].

The type of blender used can also affect the compressibility and, to a lesser extent, the encapsulation characteristics of a granule/powder blend. Blenders that offer too intimate a mix between granule and intergranular excipients (as in the case of wet