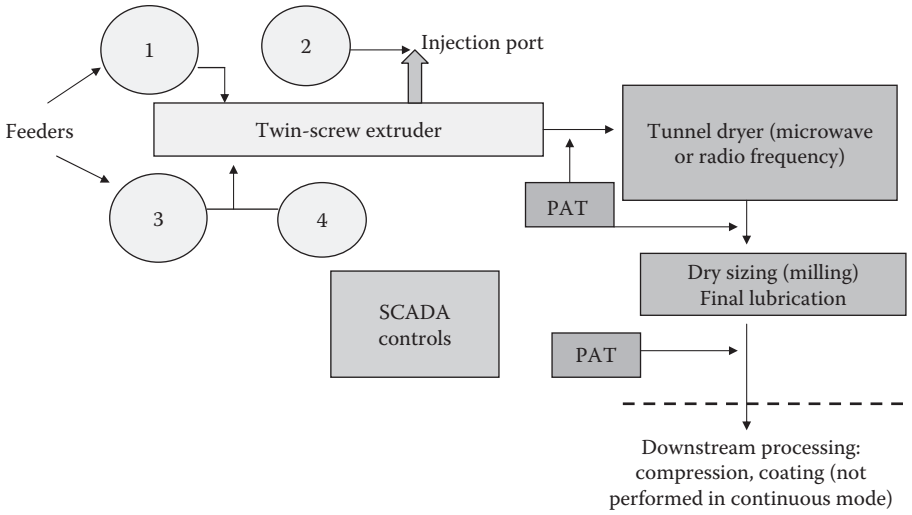

FIGURE 23.6 Process flow schematic based on continuous production of pharmaceutical granulation (From Ghebre-Sellassie, I. et al., U.S. Patent 6,499,984B1, 2002).

The twin-screw extruder provides the following advantages to facilitate scalability and robustness in the wet granulation process:

1. Modular screw design to assist in densification, and distributive and dispersive mixing
2. Efficient granulation endpoint determination
3. Consistent processing of unit mass of material
4. Sustained processing at a steady state for any duration of processing
5. Short residence time, limiting the material's exposure to harsh shear
6. Efficient design to facilitate waste minimization
7. Operation using the FIFO principle
8. Self-cleaning system
9. Flexibility in efficient process optimization

A typical TSE system consists of a feeding port for introducing dry powders into the extruder, a mixing zone where powders are mixed intimately, and a discharge zone for taking the granulation to the next step in the processing. Typically, granulation liquid is also introduced close to the feeding port to allow for sufficient mixing and optimal granule growth. The screw design optimization is a key part of the development activity. The screw design is optimized on the basis of the formulation process requirements.

Dispersive mixing is defined as breakdown of the morphological domains (Manas-Zloczower, 1994). If the active ingredient in the formulation needs to be broken down into smaller-size particles, the screw design needs to include a modular element utilized for dispersive mixing. On the other hand, *distributive* mixing is viewed as a means to achieve blend homogeneity requirements of the process. In this type of mixing, the minor phase (generally active API) gets evenly distributed in the overall mass being processed. To achieve the desired content uniformity, the screw design must include modular elements that will facilitate distribution of the API. The screw design becomes the critical part of process development activity. For formulation with low drug loading, the design will be dominant in screw elements that will facilitate distributive mixing. If the process requires breaking down the API into smaller particles, the design will be dominant in dispersive elements. Formulation and process scientists generally take a balanced approach to achieve the overall quality objective.