and manufacturing factors can affect the disintegration and dissolution of a tablet, including particle size of the drug substance; solubility and hygroscopicity of the formulation; type and concentration of the disintegrant, binder, and lubricant; manufacturing method, particularly the compactness of the granulation and compression force used in tableting; and any in-process variables (12). Together, these factors present a set of complex interrelated conditions that have a bearing on a product's dissolution characteristics. Therefore, batch-to-batch consistency is vitally important to establish dissolution test standards and controls for both materials and processes and to implement them during production and in final testing.

In addition to formulation and manufacturing controls, the method of dissolution testing must be controlled to minimize important variables such as paddle rotational speed, vibration, and disturbances by sampling probes. Dissolution testing for oral dosage forms has been a component of evaluating product quality in the USP since 1970, when only 12 monographs contained such a requirement. Today, the requirement is standard for tablets and capsules.

The USP includes seven apparatus designs for drug release and dissolution testing of immediate-release oral dosage forms, extended-release products, enteric-coated products, and transdermal drug delivery devices. Of primary interest here are USP Apparatus 1 and USP Apparatus 2, used principally for immediate-release solid oral dosage forms.

The equipment consists of (*a*) a variable-speed stirrer motor; (*b*) a cylindrical stainless steel basket on a stirrer shaft (USP Apparatus 1) or a paddle as the stirring element (USP Apparatus 2); (*c*) a 1,000-mL vessel of glass or other inert transparent material fitted with a cover having a center port for the shaft of the stirrer and three additional ports, two for removal of samples and one for a thermometer; and (*d*) a water bath to maintain the temperature of the dissolution medium in the vessel. For use of USP Apparatus 1, the dosage unit is placed inside the basket. For use of USP Apparatus 2, the dosage unit is placed in the vessel.

In each test, a volume of the dissolution medium (as stated in the individual monograph) is placed in the vessel and allowed to come to 37°C ± 0.5°C. Then, the stirrer is rotated at the speed specified, and at stated intervals, samples of the medium are withdrawn for chemical analysis of the proportion of drug dissolved. The tablet or capsule must meet the stated monograph requirement for rate of dissolution, for example, "not less than 85% of the labeled amount is dissolved in 30 minutes."

There is growing recognition that where inconsistencies in dissolution occur, they occur not between dosage units from the same production batch but rather between batches or between products from different manufacturers, most likely because of the many factors of formulation, materials, and manufacturing pointed out earlier. However, since dosage units within a batch are generally not the problem, pooled dissolution testing has emerged. This process recognizes batch characteristics and allows pooled specimens to be tested. The pooled specimens may be sampled from the individual dissolution vessels in the apparatus or from multiple dosage units dissolved in a single vessel (13).

Sophisticated and highly automated equipment is continually being developed to provide high levels of quality assurance and control to dissolution testing (Figs. 8.16 and 8.17).

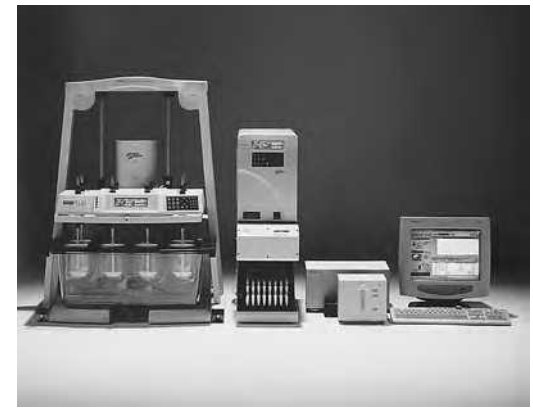

FIGURE 8.16 Hanson Automated Dissolution Test System. It features microprocessor and templates to create, edit, store, and validate dissolution protocols; graphical displays with menus; and icon-based program controls. (Courtesy of Hanson Research.)