# Automation of NF Method I–USP Dissolution-Rate Test

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**Abstract** □ The construction and operation of an automated dissolution-rate system are described. The system incorporates the NF XIII Method I–USP XVIII dissolution apparatus, using stirring basket assemblies and 1000-ml. resin flasks. Six tests are conducted simultaneously, using a commercially available spectrophotometer capable of monitoring seven separate cells at programmed intervals and a six-channel pump. Data are presented, demonstrating the application of the system using UV analysis.

**Keyphrases** □ Dissolution-rate testing—automated, multiple system □ UV spectrophotometry—monitoring, automated dissolution-rate testing □ Tablets, dissolution-rate testing—automated, multiple system

Dissolution-rate measurements are used extensively in the pharmaceutical industry to help control manufacturing processes and to detect changes in production conditions. They also are used to evaluate changes in ingredient properties, packaging materials, and storage conditions with respect to drug release from solid dosage forms. A multitude of methods for dissolution-rate testing have been employed, all having the following essential features: a dissolution vessel, a dissolution fluid, a means of agitation, a means of sampling or transporting the dissolution fluid, and an analytical procedure to measure the dissolved drug.

To reduce manpower or to produce more dissolution-rate data per unit time, some methods have been automated to varying degrees (1–9). Among the first to recognize the need for automated instrumentation to provide sufficient amounts of dissolution-rate data were Schroeter and Wagner (1). They used the USP disintegration apparatus to provide agitation and circulated the filtered sample of test fluid through a flow cell, with UV absorbances recorded on a strip chart. In the dissolution-rate testing apparatus of Pernarowski *et al.* (8), agitation was achieved by rotating a 10-mesh wire basket containing the solid dosage form. Additional agitation was gained by the attachment of stirring blades to the top of the basket. The design of this basket assembly was modified by replacing the 10-mesh screen with 40 mesh and removing the stirring blades, and it was incorporated into the dissolution-rate apparatus of NF XIII Method I (9) and USP XVIII (10).

The increased need for dissolution-rate testing in these laboratories prompted a survey of procedures applicable to automation. The NF–USP method was selected because of its flexibility and its apparent widespread acceptance by the pharmaceutical industry. Following the assembly of a single unit, the need for additional dissolution-rate data prompted the construction of a system capable of multiple testing. The mating of commercial modules and the construction of new units to give the capability of monitoring dissolution rates in six separate vessels, using UV analysis, are the subjects of this report.

## EXPERIMENTAL

**Equipment**—The assembled system is shown in Fig. 1. The commercially available units consist of the following:

1. Beckman Kintrac VII[1]. This spectrophotometric system is capable of monitoring seven separate cells, six test solutions and one reference, at programmed intervals. Recorder chart values of absorbance readings are linearized electronically, thereby permitting expansion or attenuation, depending on the dissolution characteristics of the sample. The absorbance of each cell, corresponding to a particular flask, is recorded on a strip chart and represents percentage dissolution of a tablet or capsule at recorded time periods.
2. Pump, six channel[2]. The original plunger gaskets were replaced with Teflon–asbestos cord packing.
3. Water baths, three: (*a*) 95 l.[3]—holds the six dissolution vessels while dissolution rates are determined; (*b*) 20 l.[4]—maintains a second set of six dissolution flasks with fluid at the proper temperature; and (*c*) 8 l.[5]—circulates water to a separate 11-l. insulated reservoir; the water is brought to the proper temperature for use in the preparation of dissolution media.
4. Flow cells, 10, 1.0, and 0.5 mm.[6].

The constructed units consist of the following:

1. A rack for the 95-l. water bath holds and positions the six, 1000-ml. dissolution flasks in a straight line, 14.6 cm. apart, at their centers. A coil spring is located under each flask to raise it above the top surface of the rack for ease of loading and unloading. The flasks are pressed against the springs by the weight of the stirring unit when it descends into position.
2. A manifold plate covers the dissolution flasks and provides inlet and outlet connections for sampling the six flasks. Inlet and outlet tubes consist of 4.8-mm. o.d., 0.5-mm. wall, stainless steel tubing, with 60-mesh stainless steel cylindrical screen filtering devices attached to the outlet tubes. The manifold is correctly positioned relative to the dissolution flasks by pins extending through holes in the manifold. The manifold, with inlet and outlet tubing attached, can be picked up manually, brought forward, and placed in a tank for cleaning of lines and for standardization between tests.
3. A vertically movable platform supports the six NF–USP dissolution baskets and their drive train. The platform is raised and lowered by a pair of worm gear screw jacks[7] positioned at the ends of the platform and mounted on the table top. So that the jacks rise in unison, each is driven by a timing belt from a single, totally enclosed, 0.33-hp., ball-bearing motor[8]. Microswitches, located above

[1] Beckman Instruments, Fullerton, Calif.
[2] Hughes, Marton Equipment Inc., Beverly, Mass.
[3] Precision Scientific Co., Chicago, Ill.
[4] Blue M Electric Co., Blue Island, Chicago, Ill.
[5] Tamson model P29, Witt Sales, Cleveland, Ohio.
[6] Hellma, Jamaica, N. Y.
[7] Model WJ62-18, Joyce, Crulland Co., Dayton, Ohio.
[8] Reliance Electric Co., Cleveland, Ohio.

and below the table top, stop the units at the ends of travel. Due to the momentum developed when moving the platform, it was necessary to apply a brake[9] on the motor shaft when stopping. As safety measures, additional microswitches were installed at both ends of travel of the movable platform and on a dual idler running on the two belts powering the screw jacks. If either belt breaks, the microswitch causes the main power supply to be disconnected and the motor brake to be applied.

4. A common motor assembly drives the six stirring baskets[10], which are connected in line with flexible couplings[11]. The vertical output shaft of each drive is provided with a bushing to hold the shaft of the dissolution basket. A 0.05-hp. motor[12] drives the angle gears by means of a timing belt. Direct current power is supplied to the motor by a speed controller[13]. The speed is infinitely variable from 0 to 325 r.p.m. Visual readout of the basket rotation is provided by a tachometer generator[14], mounted on the drive motor, and a speed dial in revolutions per minute, located on the main control panel.

5. Polyethylene tubing of approximately 3.2 mm. is used for all flow lines, except for 3.2-mm. Tygon tubing[15] attached to exit and entrance ports of the flow cells. Fifteen-gauge stainless steel tubing, bent at a 45° angle and embedded in a plastic block, connects the Tygon and polyethylene tubing (Fig. 1). The polyethylene tubing is fully inserted into the 4.8-mm. stainless steel tubing of the common manifold, which extends into the dissolution vessels, at a level approximating the midpoint of the stirring basket assembly. Insertion of the polyethylene tubing into the entrance and exit tubes of the manifold facilitates isolation of individual flow lines for cleaning and testing purposes. Hold-up volume of the flow system is also reduced. All lines are of equal length polyethylene and Tygon tubing and have equal hold-up volume.

6. Two emergency stops are provided for the operator, one at the control panel and one on the vertically moving head. Stainless steel guarding covers all electrical and moving parts.

7. A special table to hold the constructed units and the 95-l. water bath was assembled from welded 6.4 × 6.4-cm., 11-gauge steel tubing, providing a rigid, vibration-free mounting surface.

**Operating Procedure**—Prior to determining dissolution rates of solid dosage units, the six flow cells are corrected for their absorbances against an air blank while fluid is pumped through them. Appropriate standards are pumped through the flow cells, with exit lines leading to waste. Span adjustments of the spectrophotometer are made so that desired values for the standard are recorded on the chart. Lines are rinsed and placed in the dissolution vessels containing the specified volumes of dissolution fluid, pumping is continued, and a zero baseline for all flow cells is verified. Tablets or capsules are placed in the basket assemblies, which are automatically lowered into the flasks. Basket rotation automatically begins when the baskets are 2 cm. from the bottom of the flasks. The absorbance of each solution is determined at approximately 1-min. intervals.

**Interpretation of Results**—The percent of tablet dissolved within the desired time period is interpolated from the chart. Each series of six bar graphs represents absorbance readings for the six dissolution vessels. As an aid in determining dissolution rates as a function of time, a template was constructed so that only the desired absorbance recordings on the strip chart could be viewed. Openings were made in a translucent overlay at regular intervals, thereby exposing only absorbance recordings from a single flow cell.

## RESULTS AND DISCUSSION

With the multiple testing system, six dosage units can be tested simultaneously. Selection of this number was geared to the capabilities of the commercial spectrophotometric system and to the fact that the NF–USP specifications are expressed in units of six tablets or capsules.

[9] Model 50603, Able Manufacturing Co., River Edge, N. J.
[10] Six model R-3100 type 3-way "Anglegear" units, having 1:1 ratios, Airborne Accessories Corp., Hillsdale, N. J.
[11] Model A-060 couplings, Lovejoy Flexible Coupling Co., Chicago, Ill.
[12] Type NSH-33R, Bodine Electric Co., Chicago, Ill.
[13] Model SL-32, Minarik Electric Co., Los Angeles, Calif.
[14] Bodine Electric Co., Chicago, Ill.
[15] Manifold Tubing, Technicon Corp., Tarrytown, N. Y.

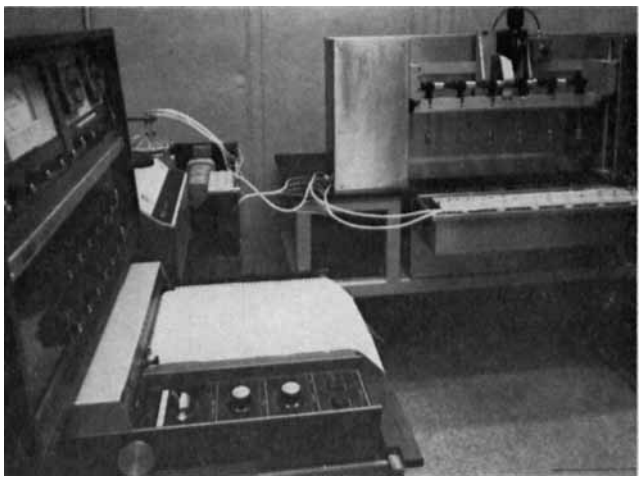

**Figure 1**—*Instruments comprising the automated six-unit dissolution-rate apparatus.*

The entire flow system (flow lines, pump heads, and flow cells) is flushed in approximately 0.5 min. Absorbance plateaus for standards are recorded in this period.

The dwell time of each flow cell is optimized so that satisfactory absorbance readings are recorded and subsequent ones are made as rapidly as possible. Routinely, a dwell time of approximately 7 sec., giving identical recordings for continuous or intermittent sampling, is used. After a reading is made for the last cell, the cell compartment stops, reverses the direction of rotation, and returns to the reference position for a new series of readings. Any of the cell positions can be bypassed, read continuously, or read at programmed intervals. The latter function is particularly useful in determining dissolution rates for sustained-release products.

Initially, rotation of the basket assemblies were checked frequently by other means than the tachometer generator. Slow rotation speeds were checked by counting revolutions. A strobe light was used for determining revolutions per minute in excess of 75 r.p.m.

Two modifications were made in the Beckman Kintrac VII system which aided reliable, long-term dissolution-rate testing: (*a*) the electronic system was altered so that the chart drive could be stopped

**Table I**—Dissolution Rates for Steroid Tablets and Antibiotic Capsules Using the Mechanized Six-Unit Dissolution-Rate Testing System (NF–USP Method)

| Lot Number | $T_{20\%}$[a] Average of Six Tablets | $T_{20\%}$[a] Slowest Tablet | $T_{40\%}$ Average of Six Tablets | $T_{40\%}$ Slowest Tablet | $T_{60\%}$ Average of Six Tablets | $T_{60\%}$ Slowest Tablet |
|---|---|---|---|---|---|---|
| | | | **Prednisolone, 5 mg./C.T.** | | | |
| 1 | 0.7 | 1.0 | 1.3 | 1.6 | 1.9 | 2.2 |
| 2 | 1.2 | 1.7 | 2.0 | 2.7 | 2.9 | 3.8 |
| 3 | 1.2 | 1.8 | 2.1 | 2.8 | 2.9 | 3.9 |
| 4 | 1.6 | 2.6 | 2.6 | 4.2 | 3.9 | 6.7 |
| 5 | 3.2 | 5.1 | 5.0 | 7.2 | 7.0 | 9.7 |
| 6 | 0.8 | 0.9 | 1.2 | 1.4 | 1.8 | 2.2 |
| 7 | 1.3 | 4.4 | 2.3 | 7.9 | 3.4 | 11 |
| 8 | 1.0 | 1.5 | 1.8 | 2.7 | 3.0 | 4.3 |
| 9 | 1.4 | 2.2 | 2.5 | 3.9 | 3.8 | 5.6 |
| 10 | 2.3 | 7.0 | 4.6 | 15 | 7.0 | 24 |
| | | | **Tetracycline Hydrochloride, 250 mg./cap.** | | | |
| 1 | 3.4 | 3.7 | 4.1 | 4.4 | 5.0 | 5.3 |
| 2 | 3.6 | 4.3 | 4.4 | 5.3 | 5.4 | 6.5 |
| 3 | 4.1 | 5.6 | 5.3 | 7.2 | 6.4 | 8.1 |
| 4 | 3.6 | 4.4 | 4.6 | 5.3 | 5.9 | 6.9 |
| 5 | 3.3 | 4.3 | 4.4 | 5.8 | 5.6 | 6.7 |
| 6 | 3.6 | 4.8 | 4.9 | 6.3 | 5.9 | 6.9 |
| 7 | 3.4 | 4.3 | 3.9 | 5.1 | 5.2 | 5.9 |
| 8 | 3.2 | 3.7 | 4.3 | 5.2 | 5.6 | 6.9 |
| 9 | 2.6 | 3.1 | 3.8 | 4.6 | 5.0 | 5.6 |
| 10 | 2.5 | 2.8 | 3.4 | 4.1 | 4.7 | 5.3 |

[a] $T$ = time in minutes.

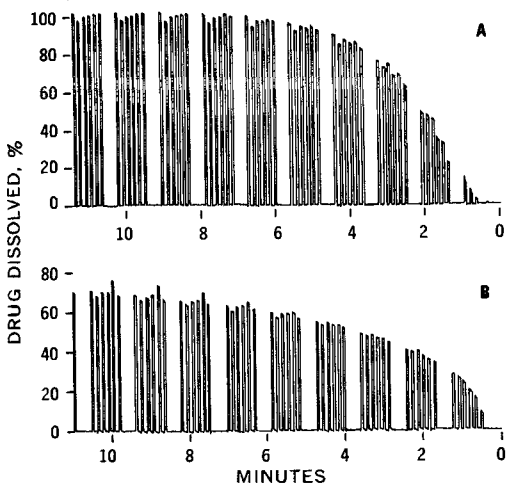


**Figure 2**—*Dissolution profiles for tablets showing: (A) little tablet-to-tablet variation, with rapid tablet dissolution and plateauing of responses; and (B) little tablet-to-tablet variation but with somewhat slow tablet dissolution and gradual plateauing of responses.*

in between bar graph recordings at programmed intervals (for example, for readings made only once each hour for sustained-release formulations); and (*b*) a reliable recorder pen was constructed from a 23-gauge stainless steel tube. The tube was rolled shut, and a capillary opening was made. The constructed pen was connected to the original ink supply line and inserted into a specially constructed aluminum mount, machined to fit into the original pen holder.

The automated dissolution-rate apparatus was used extensively in testing steroid and antidiabetic tablets and antibiotic capsules. It was used almost daily for the last 18 months. Recorded instrumental drift was negligible in routine testing of tablet and capsule dissolution rates. For long periods of continuous operation (for example, with sustained-release formulations), recorded drift can be corrected by adjusting the baseline by using the "off zero" of the reference absorbance. (Drift never exceeded 2% of full chart for 8 hr. of continuous operation.) Among the various steroid tablets tested were hydrocortisone, methylprednisolone, prednisone, and prednisolone. Water was the dissolution fluid, the cell lightpath was 10 mm., the wavelength was at absorbance maxima (approximately 246 nm.), and the basket rotation was 100 r.p.m. Tolbutamide tablets were tested using the tromethamine buffer at a pH of 7.6. The cell lightpath was 0.5 mm., the wavelength was 226 nm., and the basket rotated at 150 r.p.m. Tetracycline hydrochloride capsules were tested in 0.1 *N* hydrochloric acid, with basket rotation

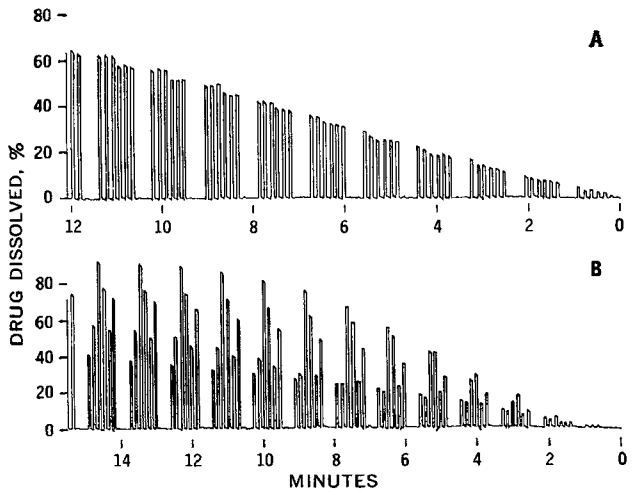


**Figure 3**—*Dissolution profiles for tablets showing: (A) dissolution of active ingredients at a relatively slow, uniform rate; and (B) considerable tablet-to-tablet variation and relatively slow dissolution.*

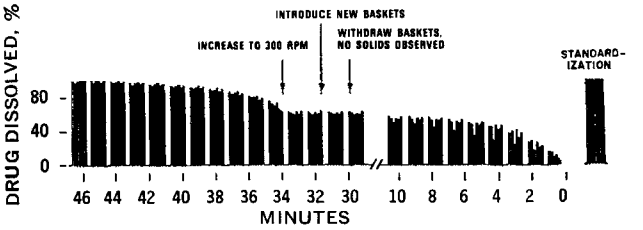


**Figure 4**—*Dissolution profiles suggesting complete dissolution at approximately 60% of label. Increased stirring rate (increased agitation) caused an additional 40% of drug to dissolve.*

at 150 r.p.m. The cell lightpath was 1.0 mm., and a wavelength of 268 nm. was used.

Table I gives individual data for prednisolone tablets and tetracycline hydrochloride capsules from 10 lots of each. The table gives the average for the six tablets and the slowest dissolving tablet. Data for the slowest tablet are also given since slow dissolving tablets —not the averages—determine passage or rejection of lots by NF and USP criteria. Requirements are that the lot passes if not more than two of 12 tablets fail to meet the test limits.

Figures 2 and 3 give recorder tracings of dissolution profiles as examples of four lots of differently dissolving tablets from commercial sources. Figure 2 gives data for rapidly and uniformly dissolving tablets (A) and for uniform, initially faster, but eventually slower dissolving tablets (B) than those of the first group. Figure 3 gives the results for uniformly dissolving tablets, which dissolved at a constant rate (A), and nonuniformly dissolving tablets (B).

Use of the automated unit has provided opportunities for observations which are considered pertinent. The rigidly constructed, mechanized basket assembly was nearly free of vibration as comparted to a single unit constructed with Fisher Frame. Vibration that was visually nonperceptible was rated as severe by a commercial vibration analyzer[16]. Vibration with the single unit had an enhancing effect on the dissolution rate of particular tablets when stirred at low rates. The effect of vibration was largely eliminated when the rotation speed was increased (11).

Occasionally, tablet fragments passing through the 40-mesh baskets remained on the bottom of the vessels, undisturbed by the agitation provided. Figure 4 shows portions of dissolution profiles obtained for methylprednisolone tablets in which this condition was observed. At a stirring rate of 100 r.p.m., the dissolution profiles plateaued, indicating a drug content of approximately 60% of label. Although the baskets were observed to be entirely free of tablet remnants, material from disintegrated tablets could be seen lying undisturbed on the vessel bottoms. When the rotation speed was increased to 300 r.p.m., thereby increasing agitation, the absorbance values increased sharply, reaching new plateaus corresponding to 100% of label.

The experimental data with the NF–USP basket assembly also tend to confirm the findings and conclusions of Lin *et al.* (12). They noted that dissolution material occasionally clogged the screen of the 40-mesh basket. On the other hand, when they employed an 8-mesh basket, large drug particles and their aggregates accumulated at the bottom of the dissolution flask. When using the 40-mesh basket, clogging of the screen was experienced with some tablets as rapid disintegration occurred; yet with other tablets, particles passed through the screen and settled at the bottom of the vessels. It is possible that a larger mesh size, perhaps 20, and an additional means of agitation should be provided.

## SUMMARY AND CONCLUSIONS

A detailed description is given of the construction and operation of a dissolution-rate system utilizing the NF–USP apparatus. The system incorporates the stirring basket assembly and 1000-ml. resin flask of NF–USP, a six-channel pump, and a spectrophotometer capable of monitoring seven separate cells at programmed intervals. Data are presented, demonstrating the application of the system for capsules and tablets.

[16] International Research and Development Co., Columbus, Ohio.

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# Dry Powder Aerosols I: A New Powder Inhalation Device


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**Abstract** □ A new portable device is described for administration of powdered drugs by inhalation. Powder contained in a standard hard gelatin capsule is induced to flow from the capsule into the air stream by a vibratory feed mechanism arising from a rotor driven by the inhaled air. The relationship between air flow rate, vibratory cycle, and powder emission was investigated, and the results indicate a good degree of coordination of dose administration with inhalation into the inspired air stream. The ability of the device to dispense size-graded fractions of lactose, in the range of 4–400 μ, was investigated. Poor flow of the finest powders was demonstrated and can be overcome by use of a coarse flow aid.



**Keyphrases** □ Aerosol powder drugs—portable inhaler □ Inhaler, portable—aerosol powder drugs


Aerosol therapy constitutes a major part of the therapeutic program of many patients with airways disease. It is not generally realized that, with the pressurized aerosol or other portable inhalers, the administration of medication requires coordination of activation with the inspiratory cycle of respiration if variation in the quantity and site of drug deposition in the airways is to be minimized. The introduction of medication into the inhaled air near the end of inspiration confines drug entry and deposition to the upper respiratory tract. Many of the finer drug particles in the inhaled air would have insufficient time to deposit by sedimentation in the large diameter airways of this region before being swept out by the exhaled air flow. In contrast, drug introduced at the beginning of deep inspiration could be carried far into the lungs by the inhaled air, increasing the opportunity for fine-particle deposition in the narrow airways of the deep lung and markedly altering the pattern of drug distribution. An ideal inhalation device would ensure administration of inhalant reproducibly and conveniently with minimal patient effort, cooperation, or need for coordination.

The depth and degree of penetration of particulate matter into the respiratory tract and its subsequent deposition are an integrated effect of independent variables concerned with the characteristics of the aerosol cloud and the respiratory cycle (1). In the laboratory, experimental aerosols varying in such properties as particle size and degree of polydispersion can be prepared by selection of a suitable aerosol generator, and the quantity administered to a patient can be accurately controlled by timing the period of inhalation. To achieve reproducible particle deposition, control must be achieved over the physiological events of rate and volume of inspiration, since these play a role in determining the sizes and areas of deposition of particles within the airways. These factors are significant for particles larger than 8–10 μ, which can gain entry to the upper airways during oral inhalation when the protection afforded by the nasal cavities is bypassed. These particles can represent a major fraction of the weight of drug administered in a pharmaceutical inhalant.

Control of the respiratory cycle in man is readily attained in the laboratory by use of a spirometer and metronome, which provide the subject with an immediate indication of breathing depth and rate (2). In clinical practice, however, it is difficult if not impossible to train many patients to inhale to a specific pattern and simultaneously to coordinate dose administration at a particular point in the inhalation cycle. Consequently, the amount and site of drug deposition in in the airways and lungs may be variable, notwithstanding high precision of dose metering by the adminis-