Dissolution Apparatus with Multiple Testing Stations

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An apparatus in which 20 dissolution tests may be conducted simultaneously is described. A single set of controls maintains the test conditions in all 20 dissolution vessels. Provisions have been made to sample automatically and simultaneously from each vessel at predetermined time intervals. Results obtained for the dissolution of experimental potassium chloride tablets using this apparatus are in good agreement with those obtained when tablets were tested individually.

IT HAS BECOME increasingly evident that the rate and extent of the dissolution of drug compounds from solid dosage forms such as capsules or tablets are important criteria for optimum absorption and therapeutic effect. For example, Levy *et al.* (1) have used the dissolution rate of prednisone to differentiate between therapeutically active and inactive tablet formulations. Moore *et al.* (2) demonstrated the value of dissolution tests in evaluating various formulations of nalidixic acid. Under some circumstances, it has been shown (3) that the dissolution data for a given formulation may be injected directly into a relatively complex pharmacokinetic model for the prediction of biological disposition of a drug.

In the course of the development of a dosage form, the examination of dissolution properties may be helpful in various ways. Dissolution may be used to study the effects of formulation and process changes, to evaluate the reproducibility within a batch as well as between batches, and to verify the physical quality of a product. When the dissolution characteristics correlate with the absorption or clinical effectiveness of the dosage form, it may be desirable to include the dissolution test as a regular quality control requirement for that product. The apparatus to be described was designed with this need in view and particularly to accommodate those situations where a large number of individual dissolution tests may be required for proper statistical assessment of the dosage form.

Specifically, this communication describes a mechanical unit in which 20 individual dissolution tests may be conducted simultaneously. A master panel controls the rate of agitation, the position of the agitators, the duration of the dissolution test period, the frequency of sampling, and also provides for the automatic withdrawal of samples at predetermined times. The dissolution vessels are immersed in a constant temperature water bath and are held in fixed positions relative to the stirring mechanism.

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APPARATUS

The apparatus (Fig. 1) consists of four parts: (*a*) a stand and raising mechanism; (*b*) an agitator support and d.c. motor drive; (*c*) electric controls; and (*d*) a sampling device.

The agitators are raised and lowered by a vertical screw which is driven by a 1/4-hp. Boston Ratiomotor with a 10 to 1 ratio. Upper and lower limit switches which are mounted on the stand allow for maximum vertical travel of 16 in. The electrical equipment is mounted on a sliding tray in the lower part of the stand. All operating controls are mounted on a control panel on the right-hand side of the stand.

The 20 agitators are driven by a single Bodine 1/4-hp. d.c. gear motor with a ratio of 10 to 1. The extended armature shaft is connected by a flexible coupling to a tachometer. The extension on the agitator support is equipped with a knurled adjusting and lock screw that operates the lower limit switch and controls the agitator heights. Agitators operate only with the agitator support at the lower limit of travel.

All operational functions, such as raising and lowering, fast and slow agitation speeds, timing and signals, are accomplished through Allen-Bradley relays and Eagle "Cycl-Flex" timers. Using elec-

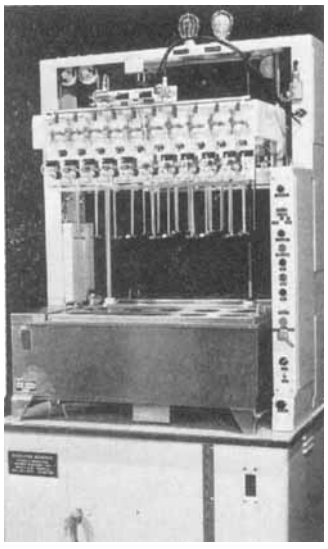

Fig. 1—Dissolution apparatus.

trical interlocks, only one function can be operated at any one time. The speed of the agitators is controlled by a d.c. motor control. Two ranges of speed, slow and fast, provide maximum rates of agitation of 100 and 250 r.p.m., respectively. Speed control is accomplished by balancing the output of the tachometer against a variable voltage obtained from zener diodes by adjusting a potentiometer. The agitator speed can be read directly in r.p.m. on a meter. Speed is maintained to ±2% regardless of line voltage between 105–130 v.

All the necessary push-button switches are mounted on the panel (Fig. 2). Briefly their functions are as follows: (*a*) The main selector switch energizes the whole unit. (*b*) A wing lever selector switch selects the mode of operation—"manual" or "automatic." (*c*) The "sample" push button is used to take samples at any time when the wing lever switch is in the "manual" position. (*d*) The "agitator" push button operates agitators manually while depressed and is active only on "manual" operation. (*e*) The "down" push button is used to lower the carrier while depressed and is active on "manual" operation only. (*f*) The "up" push button raises the carrier while depressed but does not have to be held and is operational only in the "manual" mode. (*g*) "Start cycle" push button starts the automatic cycle if the wing lever switch is in the "automatic" position.

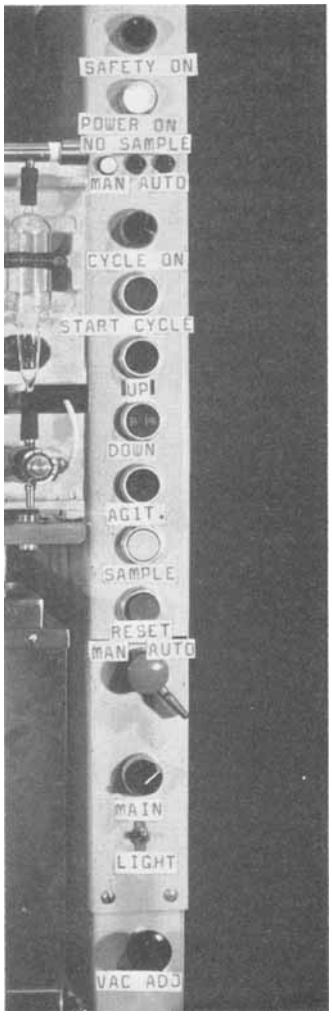

Fig. 2—Operational panel of dissolution apparatus.

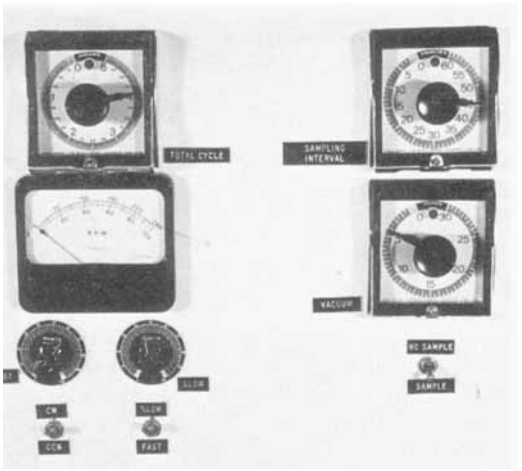

Fig. 3—Preset controls of dissolution apparatus.

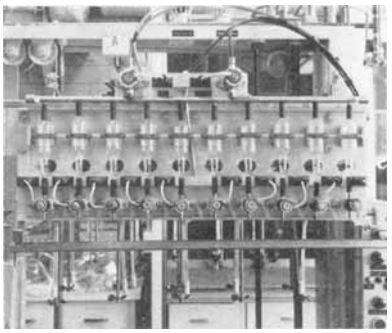

Fig. 4—Sampling device.

Preset controls are all mounted on the front panel of the electrical equipment tray (Fig. 3). A total cycle timer controls the length of agitation during the automatic cycle. A sample interval timer energizes the sampling device to take samples at set intervals and may be bypassed at the operator's discretion. The vacuum timer activates a vacuum pump for a set period of time and controls the level of fill in the sampling bulb. A toggle switch controls the direction of motion of the agitators.

The sampling device (Fig. 4) will take a volumetrically controlled sample from each of the 20 dissolution flasks simultaneously and transfer all samples to corresponding sample cups. This is accomplished in the following manner: when the vacuum timer is energized the vacuum pump starts and two vacuum valves open. A vacuum is thus created in a manifold and in all 20 sample bulbs (Fig. 5). Liquid from the flasks is transferred through the suction tubes adjacent to each agitator into the sample bulbs. By setting the vacuum timer or the vacuum adjust valve, the volume of fill can be regulated. When taking samples it is only necessary to let the liquid rise slightly above the narrow portion of the sample bulb. When the vacuum timer stops, the two

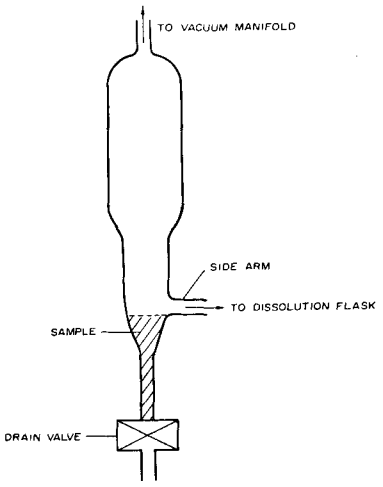

Fig. 5—Schematic drawing of sample bulb.

vacuum valves close and the vacuum pump stops. At the same time, two vent valves open to allow the excess sample fluid to drain back into the flasks leaving only the desired quantity of sample in the bulbs. After a delay of 5 to 10 sec., the 20 drain valves open and the liquid empties from each bulb into 20 sample cups. Suction tubes may be back flushed with air prior to sampling to avoid dead volume in the line; or, alternatively, up to three samples may be flushed through the sampling device prior to actual taking of the analytical specimen to avoid dilution effects. The sample size is fixed by the location of the horizonal extension of the sample bulb.[1]

APPLICATION

Use has been made of the apparatus described to monitor the dissolution behavior of several new dosage forms, but especially an experimental, slow-releasing potassium chloride tablet formulation. Such a tablet was selected for study because it enabled us to use an automated assay procedure where the potassium concentration was measured by flame photometry. For this particular preparation, 20 individual tablets were tested in the apparatus simultaneously. The agitators (2 in., three-blade impellers, A. H. Thomas, 9240-K) were individually adjusted to a height of 3 cm. from the bottom of each of 20 dissolutions flasks (reaction flask, Corning 6947). The flasks were individually centered with respect to the agitator shaft and then fixed in this position. Each flask contained 750 ml. of 0.01 *M* sodium phosphate buffer at pH 7.2 and maintained at 37° in a constant temperature water bath. The rate of agitation was adjusted to 180 r.p.m. in the counterclockwise direction, when viewed from above. Samples were withdrawn automatically at the beginning of the dissolution cycle and at 30-min. intervals during the dissolution test for a total of 4 hr. The sample bulbs were designed to deliver 1.5 ml. of sample into the sample cups for assay. The concentration of potassium in solution in the cups, and consequently in the dissolution flasks at each time was determined by flame photometry. The rates of dissolution measured with this apparatus were compared with those obtained when 20 individual tablets were tested one at a time and consecutively in a single dissolution test apparatus which involved timed sampling by pipet. Dissolution results on samples withdrawn from a single batch of the experimental potassium chloride tablets by both methods illustrate good agreement (Table I) and validate the use of the automated apparatus for large-scale dissolution testing.

[1] Built by Mr. P. J. Dockery, Glass Blowing Shop, Merck Sharp & Dohme Research Laboratories.

TABLE I—DISSOLUTION OF INDIVIDUAL EXPERIMENTAL POTASSIUM CHLORIDE TABLETS *FROM A SINGLE BATCH*

	% Dissolved, min.							
	30	60	90	120	150	180	210	240
	20 Tablet Apparatus							
	3	2	8	13	20	28	36	47
	0	1	6	12	20	29	37	46
	1	1	8	12	21	31	40	51
	1	1	6	11	18	26	35	43
	1	1	7	14	22	31	41	51
	1	1	6	12	20	28	37	46
	1	0	6	12	20	29	39	50
	1	1	6	12	19	27	36	46
	1	0	3	7	13	19	26	34
	1	1	6	11	19	27	36	46
	1	0	4	9	16	23	32	42
	1	2	9	16	26	37	49	60
	1	2	8	15	24	35	45	56
	1	4	10	18	26	37	46	57
	1	2	7	13	20	29	38	48
	2	5	11	19	29	40	51	60
	1	1	5	9	16	24	33	43
	2	3	8	16	26	26	37	56
	1	0	4	8	15	22	31	40
	1	3	8	15	25	35	45	54
Av.	1	2	7	13	21	30	39	49
	20 Individual Determinations							
	1	6	13	20	29	37	46	54
	0	4	10	17	25	32	41	49
	0	3	9	15	23	30	39	47
	0	3	9	15	23	30	39	47
	0	4	11	17	26	33	42	50
	0	6	14	22	33	42	53	62
	0	3	8	14	21	28	37	44
	0	7	15	24	35	44	57	67
	1	4	10	17	25	32	41	49
	0	4	10	17	24	32	41	48
	0	4	9	14	23	31	40	48
	0	2	8	14	21	29	38	46
	0	4	11	18	26	26	44	53
	0	6	15	23	33	44	55	64
	0	4	10	17	24	33	42	40
	0	5	11	18	25	35	44	52
	0	5	12	19	28	37	47	56
	0	5	12	20	27	37	48	56
	0	2	7	12	18	25	33	40
	0	3	9	16	23	32	42	50
Av.	0	4	11	17	26	33	43	52

SUMMARY

An apparatus capable of performing multiple dissolution tests simultaneously under controlled conditions is described.

This apparatus has the following features: (*a*) 20 individual tests may be performed simultaneously. (*b*) The degree of agitation may be maintained at constant rates up to 250 r.p.m. (*c*) Samples may be withdrawn automatically at any predetermined frequency within a specified length of time. (*d*)

Relative positions of stirrers and dissolution vessels may be adjusted at will. (*e*) Size of samples taken is adjustable.

The dissolution behavior of an experimental potassium chloride tablet was used to illustrate the application of this apparatus in comparison with a more laborious single dissolution flask procedure.

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Keyphrases

Dissolution apparatus—multiple testing
Apparatus, dissolution—photographs
Operating instructions—dissolution apparatus

Development and Evaluation of a Sampling Device for the Analysis of Pharmaceutical Aerosols

By SIDNEY P. TUESLEY, JOHN J. SCIARRA, and ANTHONY J. MONTE-BOVI

Various devices and techniques were studied in an attempt to obtain suitable samples of material from aerosol products. Generally accepted sampling procedures cannot be used since the aerosol product contains propellants that are extremely volatile. Several of these methods were investigated and used as the basis for assaying various aerosol products. A sampling device was developed and evaluated. The sampling device was designed in a manner that made available a sample of aerosol product that could then be assayed directly in the chamber. Openings were fitted with specially designed valves that allow for transfer of the contents without loss of volatile propellant or active ingredients. Various samples of aerosol products containing local anesthetics, steroids, and amines, were assayed by this method and found to give acceptable results. In all cases, the amount of active ingredient contained in each product could be accurately determined. The device makes possible a technique applicable to the analysis of most pharmaceutical aerosols. This method, which can be carried out with ease in a relatively short period of time, was shown to produce accurate results when used in the manner described.

THE ANALYSIS of pharmaceutical aerosols presents many unique problems to the analytical chemist. Generally encountered analytical techniques such as extractions and titrations cannot be performed without modification of the intact aerosol product. Since one or more of the components of an aerosol product may be extremely volatile, it is difficult to obtain a representative sample. The vapor pressure of the system may vary from 15 psig to about 40 psig, depending upon the nature and amount of propellant and other solvents that may be present.

All aerosol products consist of a volatile and a nonvolatile portion. The nonvolatile portion, generally referred to as the product concentrate, consists of the active ingredients dissolved, suspended, or emulsified in various solvents and other ingredients. While this concentrate may contain volatile solvents such as ethyl alcohol, acetone, *etc.*, the vapor pressure of these solvents at room temperature is considerably less than the more volatile propellants.

The propellant may consist of a compressed gas such as nitrogen, carbon dioxide, or nitrous oxide or, more commonly, of a liquified gas of the fluorocarbon type. Hydrocarbons such as propane, butane, and isobutane have not been used for pharmaceuticals at the present time. Dichlorodifluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), and trichloromonofluoromethane (propellant 11) are generally used for this purpose. The positive pressure within the container indicates the need for a sampling procedure by which active ingredients can be determined from a known amount of aerosol product. The form in which the active ingredients are found will vary accord-

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