The advantages provided by pellet-type pharmaceuticals have led to a renewed interest in several techniques for agglomerating powders, including the subjecting of wet powders to a vibrating surface or a cascading motion inside a tilted rotating drum (8). This agglomerating process has been called balling, glomulation, or pelletizing. The term spheronizing has been used (9), and it seems to be suited to the process performed by this system, particularly since the particulate product usually has a spherical shape, narrow size distribution, and increased density (10).

SUMMARY

The use of a complete factorial analysis to define the significant main effects and interactions between the variables of water content, extruder speed, screen size, spheronizer speed, and spheronizer residence time on various properties of pelletized granulations of acetaminophen produced by the spheronizing process was studied. Water content and spheronizer speed had a significant effect on all primary granulation properties studied and were involved in most of the first-order interactions noted.

The utility of factorial analysis as a tool for modifying product properties *via* changes in process conditions was given further support by a final experiment using intermediate values for the variables. All data from tests on the final batch fell within the ranges exhibited by the original series.

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Dissolution Studies with a Multichannel Continuous-Flow Apparatus

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Abstract □ A multichannel continuous-flow apparatus for dissolution rate measurements is described. Typical data are presented to demonstrate its utility for studies with bulk drug powders as well as with tablets and capsules without any change of setup. Procedures are given for the preparation of powder samples for dissolution studies and for a simple method of changing pH for "retard" tablets. The precision in dissolution rates obtained with this apparatus and method is 1–10% mean *RSD*. The advantages of the method are flexibility, reproducibility, and ability to obtain data in integral or differential form.

Keyphrases □ Dissolution rate measurements—design and evaluation of multichannel continuous-flow apparatus, application to powders, tablets, and capsules □ Tablet dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to powders and capsules □ Capsule dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to powders and tablets □ Drug powder dissolution rates—design and evaluation of multichannel continuous-flow apparatus, also applied to tablets and capsules

During the past several years, several dissolution rate testing methods have been developed. The beaker method (1, 2), the rotating-basket method (3–5), the rotating-flask method (6), the pressure change method (7), continuous-flow methods with or without cumulating reservoirs (8–22), and others (23–25) are important.

The continuous-flow (7, 8) and pressure change (7) methods have been stated to possess several advantages over the other methods. These advantages include flexibility, reproducibility, the possibility of obtaining data in differential or integral form, the ability to discriminate between similar formulations of the same drug, and the maintenance of sink conditions in the system.

Although a modified beaker method is both simple and adaptable for dissolution rate testing with solid dosage forms, this method gave poorly reproducible dissolution measurements with micronized and difficult-to-wet substances in bulk form. Therefore, a continuous-flow apparatus suitable for both drug substances (powders) and solid dosage forms was developed. The cell is designed to obtain a free flow of the dissolution medium even with large tablets, and

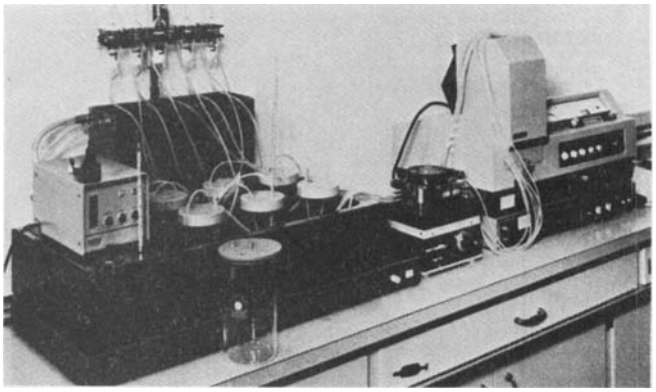

Figure 1—*Multichannel continuous-flow apparatus.*

it is leakproof under the pressure generated when using membrane filters of a very small pore size.

The apparatus is multiple channel, so up to five samples can be studied at one time, and it is capable of being automated. Several automated dissolution devices are described in the literature where spectrophotometry (26–35), potentiometry (4, 36), conductometry (37, 38), and other methods (39, 40) are employed for the measurement of drug in solution. Since most drug substances possess a chromophore in the UV region, spectrophotometry is widely used.

Examples of the determination of the dissolution rate of compressed powders (41, 42) and pellets (43) are known. Some trials have been reported concerning bulk drug powders, but a satisfactory and reproducible method has not been described (7, 8, 10–16, 24), especially for difficult-to-wet powders.

This report deals with a six-channel apparatus for the determination of the dissolution rate of drug powders as well as of tablets and capsules. The special treatment of powder samples is described in detail.

EXPERIMENTAL

Apparatus—The dissolution system (Fig. 1) consists of a six-channel peristaltic pump[1], a thermostatted water bath[2] with a magnetic stirring plate for six beakers, an additional smaller water bath[2], a spectrophotometer[3] equipped with an automated cell changer[4] and a recorder[4], and five identical independent dissolution units with a sixth one for circulation of a reference solution.

The dissolution cell (sample compartment: height 60 mm, i.d. 25 mm) is shown in an exploded view in Fig. 2. A filter[5] is placed between the upper and the lower flanges to restrict the dissolution process to the cell by preventing any undissolved particles from being carried over to the reservoir containing the dissolution medium. A stainless steel sieve is placed above the filter to provide mechanical strength against pressure which may develop from the use of membrane filters. Strong clamps are used to make the system leakproof.

From the reservoir, the dissolution medium goes (*via* the pump) to the flow-through quartz cell, to the bottom of the dissolution cell, and, from its top, returns to the reservoir. All connections are made by silicone tubing (3 mm i.d., 5 mm o.d.).

[1] Model MP-6, Ismatec Ltd., Zürich, Switzerland.
[2] No. 01 T 643 TB and No. TD 6/1000, Type K, Heto Ltd., Birkerød, Denmark.
[3] Beckman DB-GT or DB-G.
[4] W & W Electronics Ltd., Basle, Switzerland.
[5] Cellulose fleece filter, Schleicher and Schuell Ltd., Feldmeilen, Switzerland (for tablets). Membrane filters (0.47 μm), Millipore or Sartorius (for powders and capsules).

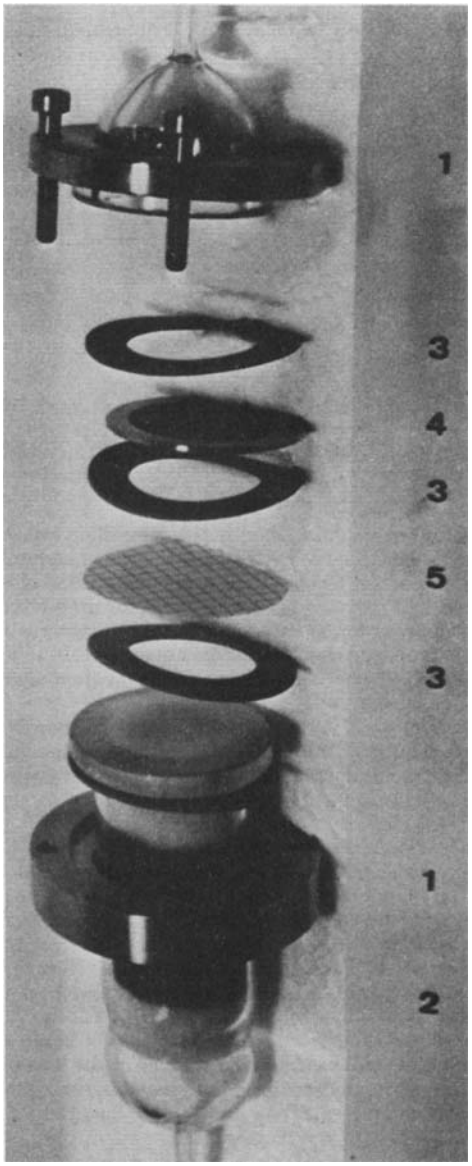

Figure 2—*Dissolution cell filled with drug powder–glass beads mix (exploded view). Key: 1, stainless steel clamp; 2, upper and lower parts of dissolution cell (sample compartment in lower part: height 60 mm, i.d. 25 mm); 3, rubber gaskets; 4, stainless steel sieve (18 mesh U.S.); and 5, filter.*

Preparation of Drug Powder Samples—About 35 g of glass beads (0.2 mm diameter) are divided into two portions. The first portion is placed in a special mixing flask (Fig. 3), and a calculated amount of drug powder is weighed onto these beads. Then the second portion is poured on top of the powder. The flask is rotated at the lowest speed on a rotary evaporator[6] without vacuum for 5 min. The mixture is then quantitatively transferred over a 1-cm bed of glass beads in the lower part of the dissolution cell. The remaining space is filled with more glass beads to the ground joint. A membrane filter (0.47 μm) and a stainless steel sieve are placed between rubber gaskets, the upper portion of the dissolution cell is placed in position, and the flanges are securely clamped (Fig. 2).

General Procedure—*Capsule Dissolution Studies*—One capsule, weighted by a ring of stainless steel wire slipped carefully over it, is placed on a bed of glass beads (0.2 mm, 20 g) in the dissolution cell. A membrane filter (0.47 μm) is used. The cell is closed as described previously.

Tablet Dissolution Studies—One tablet is placed on top of a

[6] W. Büchi Ltd., Flawil, Switzerland.

Table I—Dissolution Data of Bulk Drug Substances

Minutes	Drug Substance A, a Modified Ergot Alkaloid		Drug Substance B, a Neuroleptic Drug
	Nonmicronized	Micronized	
	Percent Dissolved		
2.5	14	35	61
5	33	68	93
7	49	83	99
10	58	91	102
15	67	94	
20	79	95	
25	86	96	
30	92	97	
Mean *RSD*	7.4% (8 runs)	4.7% (10 runs)	1.6% (10 runs)
$t_{63.2\%}$	12.5 min	4.7 min	2.6 min

bed of glass beads (0.2 mm, 20 g) in the dissolution cell. A cellulose fleece filter is used. The cell is closed as described earlier.

Measurement of Drug Dissolution—One liter of simulated gastric fluid USP (without pepsin) is used for drug powders. Less liquid is employed for capsules and tablets so that the maximum concentration of drug in solution does not exceed 10–15% of its saturation solubility. The temperature of the medium is maintained at 37°.

A flow rate of 8.0 ± 0.2 ml/min is used for drug powder, and the same rate or 16.0 ± 0.5 ml/min is used for capsule dissolution studies. These rates minimize a buildup of pressure at the membrane filter and provide enough points of measurement to characterize the dissolution curve.

For tablet dissolution studies, a flow rate of 33.0 ± 1.0 ml/min (about 2 liters/hr) and a cellulose fleece filter are used. The cellulose fibers are randomly arranged, and the pores are small enough to prevent particles formed by tablet disintegration from passing through the filter.

Changing pH of Dissolution Medium for "Retard" Tablets and Capsules—Simulated gastric fluid USP (without pepsin) is used for the first 2 hr. To change the pH, 22.50 g of trisodium phosphate ($Na_3PO_4 \cdot 12H_2O$) is added per liter of fluid.

The circulating pumps should be stopped at the time of addition and restarted when all trisodium phosphate has gone into solution. After circulation of the medium for 3–5 min, the pH is 7.5 ± 0.1.

RESULTS AND DISCUSSION

Apparatus—The apparatus as described has been used successfully during the past 3 years for various dissolution studies. Before that time, several trials using a Millipore cell[7] had been made. Experience showed that the inside of the cell was easily scratched by the glass beads. A more serious drawback was the low recovery observed in the powder studies, due to the retention of the undissolved drug in scratches on the inner wall of the cell and the adhesion of powder particles to the polycarbonate material. Tingstad *et al.* (11, 44) recently employed the same cell for tablets (but without using glass beads).

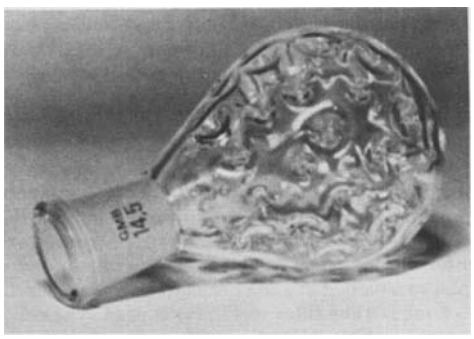

Figure 3—*Mixing flask for powders.*

[7] Part XX 4202500, Millipore Corp.

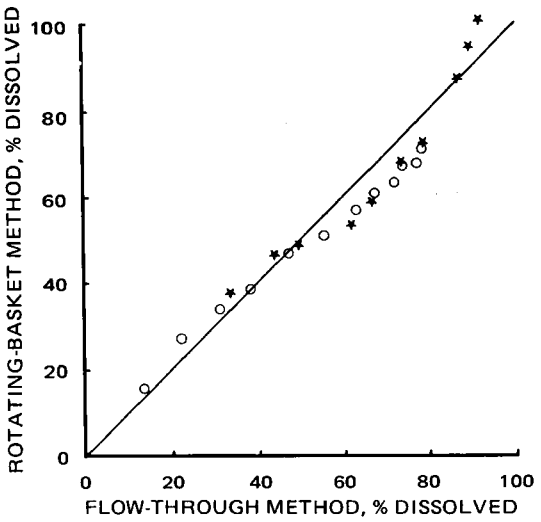

Figure 4—*Correlation plot of flow-through method at 33.0 ml/min* versus *rotating-basket method at 60 rpm. Percent dissolved values of equal sampling time are plotted against each other. Compression-coated tablets were Type I (★) and Type II (○). Straight line shows 100% correlation.*

Drug Powder Dissolution Studies—Measurement of dissolution of drug powders in media of high surface tension (such as water or simulated gastric fluid) is frequently difficult because of irregular wetting of the powder by the medium. Even weak agglomerates, which are present in every fine powder or are formed when the substance is poured, dissolve very slowly (at a rate comparable to the dissolution of similarly sized large single crystals), thus yielding unrealistic dissolution times. In some cases there was no complete solution even after 24 hr.

This effect is especially observed with particles carrying small electrostatic charges, *e.g.*, very fine and micronized powders. When such powders are mixed with small glass beads (average weight about 10 μg) as described under *Experimental*, the effective surface for dissolution is considerably increased. The majority of clusters and single substance agglomerates is destroyed by the mixing process, and the buildup of new ones is substantially reduced. Sim-

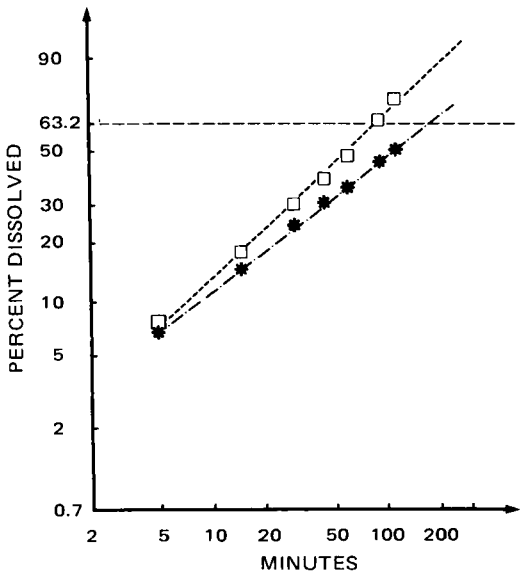

Figure 5—*Dissolution of nicotinic acid from equally composed retard tablets manufactured on different tablet machines (RRS diagram). Key: □, Tablet A, excentric machine, $t_{63.2\%}$ = 86 min; and *, Tablet B, rotary machine, $t_{63.2\%}$ = 170 min (extrapolated).*

Table II—Dissolution Experiments with Aspirin of Different Particle Sizes and at Differing Flow Rates

Particle Size	Flow, ml/min	Percent Dissolved at 5 min	7 min	10 min	15 min	20 min	30 min	$t_{63.2\%}$, min
Micronized	8	6.4	37	71	85	91	97	9.6
	14	60	81	89	96	98	100	5.0
	20	82	91	96	99	100		2.9
	30	93	98	99	100			1.5
Sieve fraction 297–420 μm	8	2	13	40	75	93	100	14.5
	14	21	41	67	92	99	100	9.8
	20	34	55	78	97	100		7.9
Sieve fraction 420–595 μm	8	1	7	22	55	74	96	18.7
	14	11	26	47	70	87	98	13.9
	20	14	33	57	81	95	100	11.6

ilar phenomena take place during dry powder mixing for a solid formulation.

At this point, checking by microscope showed no instance of any breakdown of primary particles during the mixing step. Therefore, the increase of the dissolution-affecting surface area of a powder is exclusively due to the disintegration of agglomerates and not to a size diminution of primary particles. So the mixing procedure helps to create better defined starting conditions (and more similarity to a formulation mix), thus providing a more reproducible drug powder dissolution process than without pretreatment.

Table I presents results obtained from the same relatively insoluble drug substance (Drug Substance A) in micronized and unmicronized form after mixing with 0.2-mm glass beads. As expected, the micronized powder dissolved more rapidly than the nonmicronized powder; without pretreatment, more than 24 hr was required for the dissolution of both forms due to cluster formation. This trial and other experience led to the conclusion that the more homogeneous the glass bead mix is, the smaller the relative standard deviation of the measurement will be. Drug Substance A has a strong agglomeration tendency, so a mean relative standard deviation of only 4.7% compared to the nonmicronized value of 7.4% was achieved. Fairly soluble and easily wettable drug powders usually yield more reproducible values, with relative standard deviations of about 2% as shown for Drug Substance B in Table I.

Capsule and Tablet Dissolution Studies—In contrast to the procedure used for powder dissolution studies, capsules and tablets have to be placed on top of the glass beads to ensure an unimpeded decay or swelling of the pharmaceutical form. Capsules are weighted by a coil of stainless steel wire so that they will not float in the dissolution medium.

Tablets usually float in the liquid at the beginning of the dissolution rate measurement for about 10 sec. They then become wetted and sink onto the glass beads where they remain. Since this movement of the tablets only occurs in the first few seconds, the dissolution process is not influenced.

The dissolution profile of a drug substance as well as that of formulations is very strongly affected by changes in the liquid flow rate. With aspirin as an example, the dissolution behavior as a function of flow rate is shown in Table II for samples of differing particle size. Due to this interdependence, a highly constant flow rate of the dissolution medium is necessary; this point was considered in establishing the rather tight specifications.

The 8.0-ml/min flow rate was chosen as a standard for powders since—in contrast to higher rates—it permitted the ready recognition of differences in the first, steep range of the dissolution profile. The data in Table II also confirm the well-known findings of the reduction of dissolution rate with increasing particle size (45).

The 33.0-ml/min (2 liters/hr) rate for tablets was chosen because this flow showed an optimum dissolution rate correlation with the USP rotating-basket method, corresponding to the findings described by Tingstad *et al.* (12). Figure 4 gives an example of a typical correlation plot for two kinds of compression-coated tablets tested with both methods.

The reproducibilities of the flow-through method and the USP method were compared measuring the same batch of tablets. The results are listed in Table III for four different tablet series. Obviously, the method described here is capable of providing more reproducible data than the official rotating-basket method, a fact that allows better discrimination between different species.

Even slight variations in manufacturing or in the composition of a formulation can be detected by measuring the dissolution rate. Figure 5 depicts the dissolution profiles of two tablet series having exactly the same composition but manufactured on different tablet machines. The results are plotted by the Rosin–Rammler–Sperling (RRS) method (46, 47). The $t_{63.2\%}$ corresponds to the time for dissolution of 63.2% of the drug. As can be seen from the plot, the variation of dissolution rate from one tablet to the other is significant.

Another example of the discriminating capability of this flow-through method is illustrated in Fig. 6. Here two tablets, differing only in the quality of a single excipient (cellulose acetate phthal-

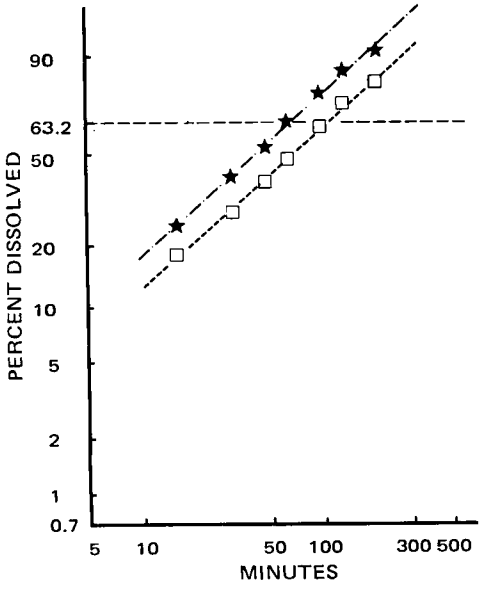

Figure 6—*Dissolution profile of equally composed and identically manufactured retard tablets, differing only in quality of a single excipient (cellulose acetate phthalate) (RRS diagram). Key: ★, Tablet A, cellulose acetate phthalate quality I, $t_{63.2\%}$ = 63 min; and □, Tablet B, cellulose acetate phthalate quality II, $t_{63.2\%}$ = 101 min.*

Table III—Experimental Comparison of Reproducibilities of Rotating-Basket and Flow-Through Methods Established with Four Completely Different Tablets

Tablet Series	Mean *RSD*, out of Eight Values, %: USP Rotating-Basket Method, 60 rpm	Flow-Through Method, 33.0 ml/min
1	2.9	2.7
2	6.5	5.1
3	4.5	2.4
4	12.2	6.8

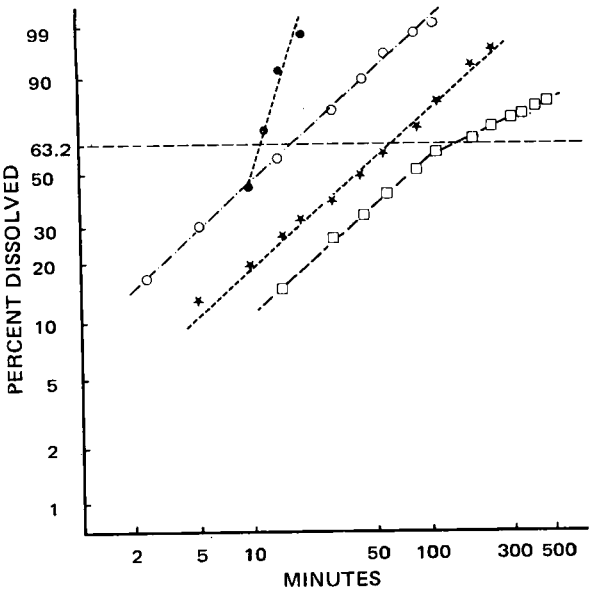

Figure 7—*Dissolution rate data. Key:* ●, *tetracycline capsule;* ○, *Tablet 1, antiobesity drug;* ★, *Tablet 2, neuroleptic drug; and* □, *Tablet 3, retard formulation.*

ate) but manufactured in the same way in every respect, were measured. The plot exhibits a significantly different dissolution behavior.

In Fig. 7, applications are presented of the flow-through method to a hard gelatin capsule, a tablet, a sugar-coated tablet, and a retard tablet.

Dissolution from hard gelatin capsules of tetracycline hydrochloride was carried out using a 16.0-ml/min flow rate. The capsules needed more than 5 min to open, but drug dissolution was rapid thereafter.

The dissolution data of an antiobesity drug (Tablet 1) showed good tablet-to-tablet uniformity (s_{mean} from six values was less than 1%). The slope of the straight line in the RRS plot is about 0.95, indicating an apparent first-order dissolution process. The $t_{63.2\%}$ is 17 min.

The profile for a neuroleptic drug from a sugar-coated tablet (Tablet 2) yielded a slope of 0.9 and a $t_{63.2\%}$ of 70 min in the RRS plot (Fig. 7). The tablet-to-tablet uniformity was not as good as in the previous case (s_{mean} from eight values was about 6%).

Release of phenylpropanolamine from an experimental retard formulation (Tablet 3) is also shown in Fig. 7. The pH of the dissolution medium was changed to 7.5 after 2 hr, as described under *Experimental.* At this point, a decrease in slope indicates a slowdown of the dissolution process at higher pH.

The procedure for the change of pH described here involves a simple addition of solid trisodium phosphate. An increase of about 2% in the volume of the dissolution medium takes place. The resulting pH of 7.5 is equal to that of simulated intestinal fluid USP; the ionic strength is, however, 0.248, almost twice as much as that of the USP solution. This procedure is suitable in all cases where drug dissolution is not affected by ionic strength in the 0.12–0.25 range, and it is applicable to the USP–NF dissolution tests as well as to continuous-flow methods with cumulating reservoirs. For the latter procedure, the well-known half-change method can be used.

Unfortunately, many modern drugs are used in low doses and, therefore, yield only low absorbance values. For the determination of the dissolution rate of such drugs from their retard dosage forms, the described procedure for change of pH is very useful because there is no impediment to the analytical assay by the dilution. Tromethamine has been used to change pH when working with phosphate-incompatible drugs.

CONCLUSION

The described apparatus is versatile enough to determine the dissolution patterns of drug powders and of tablet and capsule formulations without any change of the experimental setup. The novel preparation of drug powder samples for dissolution studies is given in detail as well as a facile procedure to change pH during dissolution of retard preparations. In 3 years' experience with the apparatus, it has been simple to use and has yielded reproducible dissolution data. In addition to being capable of showing formulation differences, the apparatus is sensitive enough to reveal process changes.

The criteria for a dissolution apparatus proposed by Wagner (48) are satisfied. Although the apparatus has been used with a cumulating reservoir to yield integral dissolution data, it is quite suitable for obtaining data in the differential form. Finally, the multichannel capability allows the determination of up to five dissolution rates concomitantly.

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Enhancing Fluidity of Concentrated Antacid Suspensions

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Abstract □ Highly concentrated antacid suspensions can be fluidized by adding a colloidal polyelectrolyte to alter the charge on antacid particles from positive to negative. A deflocculated state is assumed to exist in such preparations, as supported by electrophoretic and viscometric analyses. When viscosity is directly correlated with the ζ-potential, viscometry becomes particularly useful in confirming that the suspension has been maximally fluidized.

Keyphrases □ Antacid suspensions, concentrated—fluidized by addition of colloidal polyelectrolyte, viscosity correlated with ζ-potential, electrophoretic and viscometric measurements □ Fluidized antacid suspensions—preparation using colloidal polyelectrolyte, viscosity correlated with ζ-potential, electrophoretic and viscometric measurements

Primary goals in formulating stable suspensions of coarse particles are to prevent caking and, thus, to maintain a stable shelflife. Obtaining these objectives becomes particularly difficult when preparations are highly concentrated because the classical techniques of flocculation no longer apply.

Flocculation appears to be the preferred method for preparing coarse suspensions which can be redispersed easily by shaking (1–3). In the phenomenon of flocculation, the force of attraction between particles predominates, causing the particles to form loose aggregates. Should repulsion forces prevail, however, the particles separate or deflocculate, settling slowly. A suspending and/or gelling agent is required to stabilize such a preparation to prevent caking.

In a study of the surface characteristics of particles and the intensity of particle interaction related to the caking of insoluble particles in aqueous dispersion, flocculation was controlled by adding an electrolyte; the resulting product did not cake (4). Martin (5), in reviewing the physicochemical principles applicable to caking and flocculation, emphasized that maximal flocculation occurred within a range of low positive to low negative ζ-potential. Deflocculation and caking occurred at either extreme, *e.g.*, high positive or high negative (Fig. 1). Haines and Martin (6), in studying the electrokinetic behavior of insoluble drug particles, correlated the magnitude of the ζ-potential, as calculated from electrophoresis data, with the tendency to cake.

Table I—Physical Properties of Antacids

Property	Dried Aluminum Hydroxide Gel USP[a]	Magnesium Hydroxide NF[b]	Calcium Carbonate USP[c]
Particle size[d], μm	2.34 (0.28–6.42)[e]	8.12 (1.4–42)	4.39 (0.28–9.2)
Shape	Asymmetric round	Asymmetric round	Barrel shaped
Bulk density, lb/ft³	19–23	17–25	17

[a] J. T. Baker Chemical Co., Phillipsburg, N.J. [b] Mallinckrodt Chemical Works, Jersey City, N.J. [c] Pfizer Mineral, Pigments and Metals Division, Clifton, N.J. [d] Mean volume diameter. [e] Particle-size range.

Flocculation technology evolved from research performed on suspensions containing no more than 10% solids. Thus, current flocculation technology did not seem applicable to the preparation of coarse suspensions containing, for example, 40% solids. Antacid preparations containing 40% solids do not contain enough free water to achieve a low enough viscosity and easy flow. Furthermore, concentrated suspensions cannot be flocculated to a maximal extent since the potential maximum sedimentation volume on dilution would greatly exceed the original total volume (7).

An alternative to flocculation is fluidization. An elegant system was described for a superior barium sulfate suspension used as a diagnostic contrast medium (8). The use of radiographic techniques to evaluate the *in vivo* performance of the system was also described (8). In addition, Brown (9) referred to increased fluidity in the preparation of highly concentrated, gelating, antacid systems.

In an investigation of this system (8, 9), the fluidization technique was evaluated. Highly concentrated antacid suspensions of high fluidity (*e.g.*, marked flowability and low viscosity) can be successfully pre-