composite solution in 10 separate cups. The usual sequence used in this laboratory is as follows: three standards, five tablets, standard, five tablets, *etc.*, composite, and two standards. The composite is a weighed portion of 20 tablets ground to fine powder, equivalent to one tablet weight. The coefficient of variation for 10 determinations of one composite solution was 1.72 (Table I).

The accuracy of the procedure was studied by comparing the automated assay with the NF column method on 10 different product composites. Both analyses were made on the same mixed powdered composites. The results of the automated method were in general agreement with those by the NF procedure (Table II). The deviation, expressed as percent of declared, was less than ±2.6%.

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Dissolution Rate Studies IV: Solvent Flow Patterns in a Column-Type Apparatus

J. TINGSTAD▲, J. DUDZINSKI, L. LACHMAN, and E. SHAMI

Abstract □ Solvent flow patterns in a column-type, continuous flow apparatus were determined using a flow visualization technique. A supporting bed of glass spheres in the dissolution chamber ensures laminar flow, and this is preferred over the complex, poorly defined flow found with static beaker methods.

Keyphrases □ Dissolution rate studies—solvent flow patterns and laminar flow conditions, column-type equipment □ Tablet dissolution—solvent flow patterns and laminar flow conditions, column-type equipment □ Solvent flow in column-type dissolution equipment—flow patterns, laminar flow conditions □ Column-type dissolution equipment—solvent flow patterns, laminar flow conditions

The advantages of the column-type, continuous flow method for determining the dissolution characteristics of solids have been repeatedly emphasized (1–4). One important advantage is that solvent flow is columnar as opposed to the complex, poorly defined flow found with static beaker methods (5). However, some problems have been encountered with columnar flow because of turbulence (4), problems that would be minimized under conditions of laminar flow. This report describes, for a column-type apparatus, (*a*) solvent flow patterns under various experimental conditions, and (*b*) the necessary conditions for laminar flow.

EXPERIMENTAL

Equipment—The dissolution apparatus was the column type described previously (3). The light sources were a common laboratory microscope light and an electronic tachometer and motion analyzer[1]. The latter was calibrated with respect to the powerline frequency according to the instruction manual. The reflecting spheres were polystyrene base beads[2] (diameter 90–125 μ; specific gravity 1.06).

[1] Strobotac, General Radio Co., West Concord, Mass.

[2] Duke Standards Co., Palo Alto, Calif.

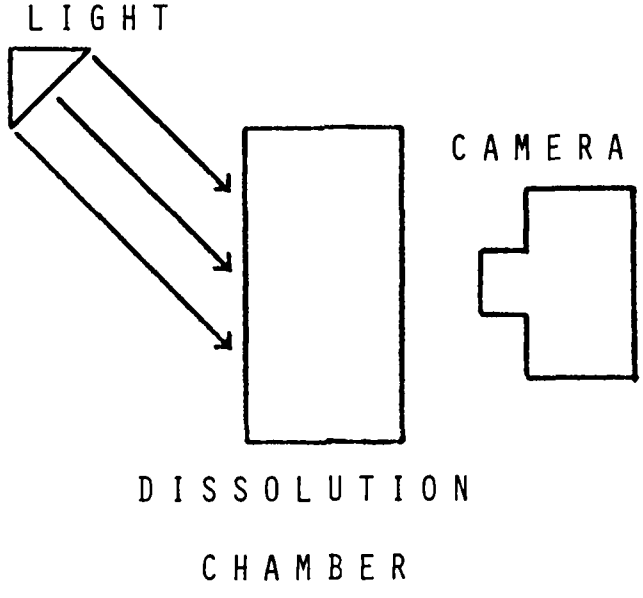

Figure 1—*Arrangement of equipment for photographic and television work.*

A lens hood was used to reduce flare with the still camera[3]. Depending on the tachometer flashing rate, apertures varied between f-11 and f-22 and exposure times between 0.5 and 0.25 sec. All photographs were taken at one-half life size image.

The television camera[4] had a 75-mm. f-1.9 lens and a video tape recorder[5].

Procedure—The experimental procedure was similar to that described by Withey and Bowker (5) but was appropriately modified for the column-type apparatus. The basic arrangement of the equip-

[3] A Nikon FTN with a 105-mm. Novoflex short-mount lens on a Novoflex bellows. The film was Kodak 2475 recording film developed in Acufine to an ASA index of 2400.

[4] Apeco VF-200.

[5] Tele-Tape.

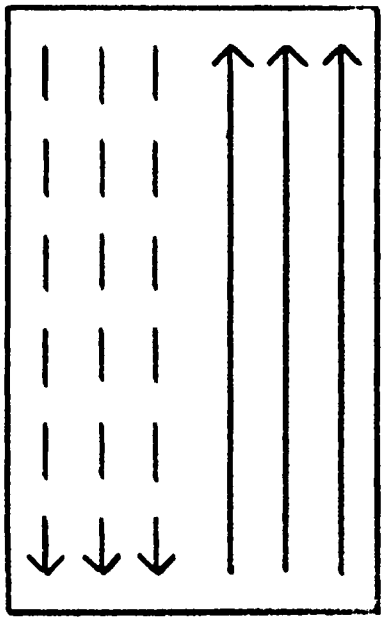

Figure 2 *Diagram of flow patterns with 25-mm. dissolution chamber at a flow rate of 9 ml./min.*

ment for the photography and television work is shown in Fig. 1. The angle between the tachometer and the camera was approximately 135°. The microscope light was used for making simple visual observations.

The polystyrene spheres reflect the light and, since their specific gravity is close to that of water, their flow patterns are essentially representative of the solvent molecules. The tachometer, properly pulsed for a given set of experimental conditions, reveals the paths of the particles as a series of images (usually streaks) on photographic film or video tape. However, the most accurate method for determining flow patterns is simple visual observation.

The solvent reservoir was a 150-ml. beaker containing 100 ml. of a 1-mg./ml. suspension of the polystyrene spheres in distilled water, with 0.05% polysorbate 80 added to reduce air entrapment. After determining that flow patterns were essentially identical with or without filters, all experiments were performed without filters (but with screens) at ambient temperature. The suspension could then

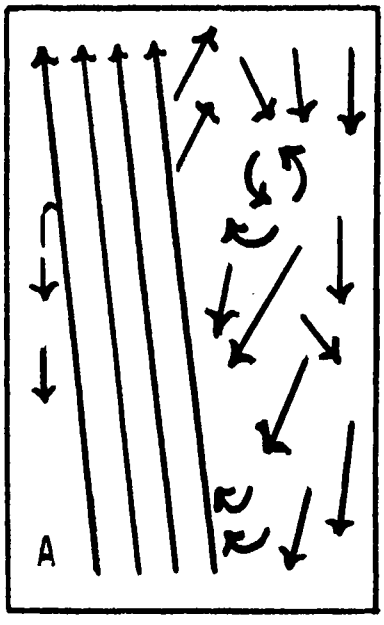

Figure 3—*Diagram of flow patterns with 25-mm. dissolution chamber at a flow rate of 55 ml./min. "A" is an area of low solvent velocity.*

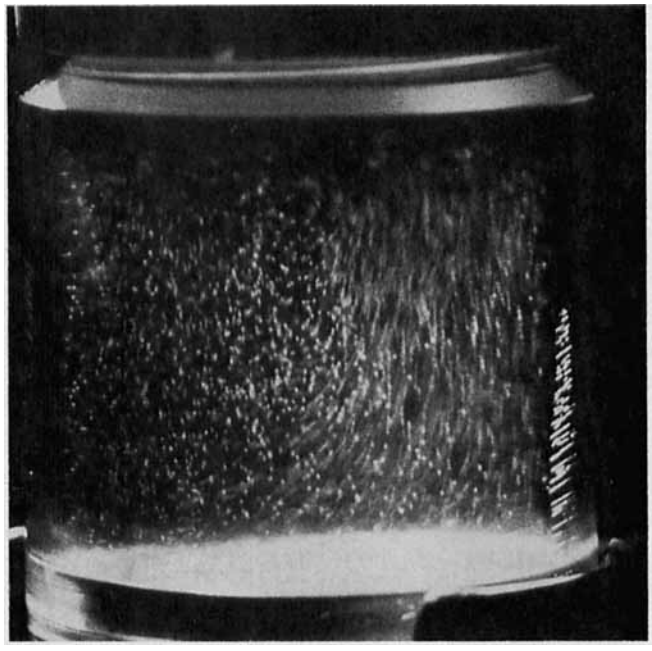

Figure 4—*Photograph of flow patterns with 25-mm. dissolution chamber at a flow rate of 48 ml./min. The tachometer flashing rate was 6000/min., the aperture was f-11, and the exposure time was 0.25 sec.*

be pumped through the dissolution chamber and recycled to the reservoir. The flow rate was varied, and the flow patterns in the 13- and 25-mm. chambers were observed and (when desirable) photographed or recorded on video tape.

RESULTS AND DISCUSSION

With the 25-mm. chamber at relatively low flow rates (5–9 ml./min.), the flow patterns shown in Fig. 2 was observed. While the solvent flow coming into the chamber (solid arrows) had essentially laminar characteristics, solvent was dispersed as it struck the upper screen and filter holder, and some returned to the bottom of the cell, still with the characteristics of laminar flow. This two-directional flow is, of course, undesirable. At intermediate flow rates (14–34 ml./min.), the same general pattern held except that turbulence increased and, in general, downward flow was much slower than upward flow. The degree of turbulence progressed with an increasing flow rate until (*e.g.*, at 48–55 ml./min.) a column of solvent moved rapidly upward and randomly dispersed after striking the upper screen and filter holder. Turbulence was much more wide-

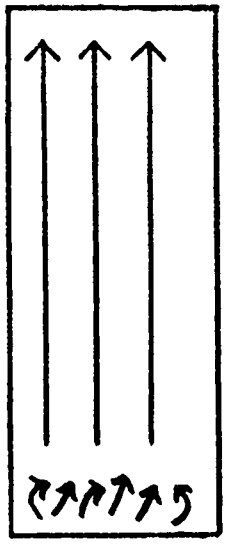

Figure 5—*Diagram of flow patterns with 13-mm. dissolution chamber at a flow rate of 13 ml./min.*

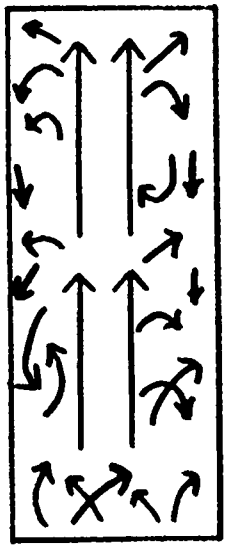

Figure 6—*Diagram of flow patterns with 13-mm. dissolution chamber at a flow rate of 36 ml./min.*

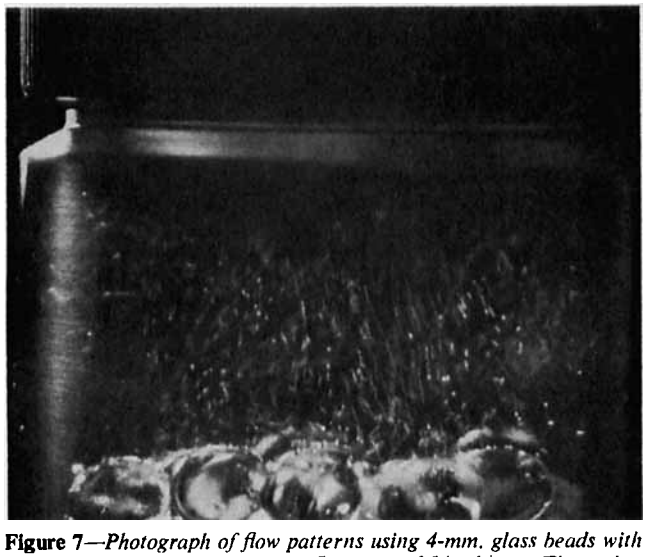

Figure 7—*Photograph of flow patterns using 4-mm. glass beads with 25-mm. dissolution chamber at a flow rate of 54 ml./min. The tachometer flashing rate was 6000/min., the aperture was f-16, and the exposure time was 0.5 sec.*

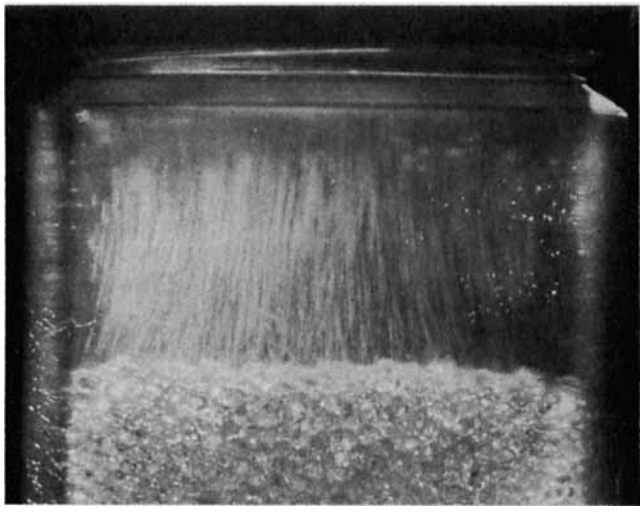

Figure 8—*Photograph of flow patterns using 1-mm. glass beads with 25-mm. dissolution chamber at a flow rate of 73 ml./min. The tachometer flashing rate was 12,000/min., the aperture was f-16, and the exposure time was 1 sec.*

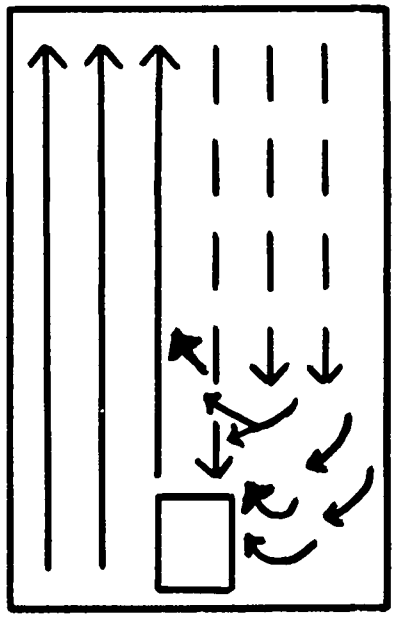

Figure 9—*Diagram of flow patterns with constant-surface pellet in the center of the lower screen of 25-mm. dissolution chamber. Flow rate was 34 ml./min.*

spread and dominant, and areas of low solvent flow developed (Figs. 3 and 4).

With the 13-mm. chamber at low flow rates (5–13 ml./min.), the flow was essentially laminar except for some turbulence in the first 0.5–1 cm. of the cell (Fig. 5). This is also undesirable because the area of turbulence would surround the tablet. At 36 ml./min., the flow was quite turbulent throughout the cell (Fig. 6). The spheres moved in relatively straight lines up the center of the chamber, but there was considerable turbulence on either side and at the bottom. It was not possible to obtain acceptable photographs with the 13-mm. cell because of excessive reflection and glare.

During these investigations, it was noted that flow patterns would vary considerably from one experiment to another (under the same set of conditions) if excessive air was trapped within the lower filter holder and beneath the lower screen. To minimize this variation and attain more laminar flow over a wider range of solvent velocities, a

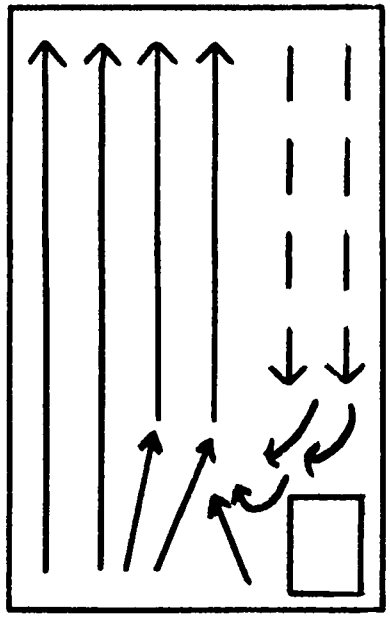

Figure 10—*Diagram of flow patterns with constant-surface pellet at the side of the lower screen of 25-mm. dissolution chamber. Flow rate was 34 ml./min.*

bed of glass beads was added to both cells, occupying about half of the chamber volume. The beads acted as dampers, and the 4-mm. size improved the flow characteristics considerably (Fig. 7 *versus* Fig. 4). However, it was necessary to use 1-mm. beads before proper laminar flow was attained (Fig. 8). Laminar characteristics were observed up to 80 ml./min., the highest flow rate used.

Because the photographs and drawings are two dimensional and static, they do not accurately represent the total, dynamic, three-dimensional situation. The video tapes from the television work provide a better record of solvent flow patterns because the actual motion is recorded. As mentioned earlier, visual observation is best.

In a previous investigation (4), constant-surface pellets of salicylic acid were used with the column apparatus. To gain more insight into the results of those experiments, flow patterns were observed in the 25-mm. chamber with the pellet in the center of the lower screen (Fig. 9) and at the side (Fig. 10). The results confirmed that, for a given flow rate, the lowering of the dissolution rate when the pellet was moved to the side of the chamber was due to the lower rate of solvent flow in that region.

SUMMARY

These results indicate that using a bed of 1-mm. glass beads with the column apparatus helps ensure laminar flow over a wide range of liquid velocities. This type of solvent flow is much preferred over the poorly defined, random-type flow characteristic of all beaker methods. Because surface tension slows solvent movement near the sides of the chambers, it is preferable to place the tablet well away from the sides of the cell.

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Dustiness of Pharmaceutical Formulations I: Instrumentation

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Abstract □ Instrumentation for evaluating the dustiness of tableting materials is reported. The sample is dropped into a dust chamber where a controlled flow of air carries the resulting dust particles through a beam of light. The scattered light is received by a photodetector which converts light pulses into electrical pulses. The instrumentation was precalibrated in particle-size ranges of 0.5–10, 11–50, and >50 μ, and the number of particles in each size range is displayed on a digital counter. The particle size refers to the equivalent diameter of the dust particle that generates the same electrical response in the photodetector as the reference particle used to calibrate the instrumentation. Eleven commonly used tableting aids were classified into three categories based on their relative dustiness. Data obtained with the dust counter were shown to correlate with the dustiness resulting from the bulk handling of larger quantities of materials.

Keyphrases □ Dustiness of tableting materials—determination using light-scattering method and equipment □ Pharmaceutical technology—method and equipment for determining dustiness of tableting materials □ Tableting materials—measurement of dustiness □ Light-scattering method and equipment—determination of dustiness of tableting materials

Dust of any kind in a pharmaceutical plant is a serious matter. Areas of particular concern are: (*a*) cross-contamination of other products, and (*b*) potential hazards to the health of workers. There is always a risk of cross-contamination occurring with potentially serious consequences in pharmaceutical plants that utilize the same manufacturing facility to produce a variety of pharmaceutical products. Cross-contamination of a product with penicillin, for example, is capable of causing a serious reaction or even death to a person sensitive to penicillin (1). It is essential, therefore, that dust always be kept under control.

In regard to the workers' health, dust may be classified as a lung-depositing dust, toxic dust, primary irritant dust, sensitizing dust, or nuisance dust. A lung-depositing dust is deposited and retained in the lungs, where it may be benign or cause lung pathology. Toxic dust is a systemic poison which enters the circulation by absorption from the respiratory tract or after being swallowed. A primary irritant is limited largely to the mucous membranes of the eyes, nose, and throat. Prolonged exposure to low-grade irritants is capable of producing disturbances in respiratory function and secondary infection (2). A sensitizing dust elicits the antigen–antibody response in susceptible individuals as a result of either inhalation, skin contact, or ingestion. A nuisance dust is primarily discomforting to the worker and is often associated with increased colds and bronchitis. In general, the inhalation of any kind of dust in sufficient amounts for long periods of time can lead to disturbances in pulmonary function (3).

Particle size, frequency of exposure, quantity of concentration, and chemical action on the body tissue and fluids are important factors that influence whether a