



Development of an Electronic Technique for Determining Rate of Solution of Solid Products

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During the development of a product that requires constitution or reconstitution by the user, the question of rate of solution invariably arises. This is of primary concern when the in-situ preparation of intravenous injections is involved. Because of continued controversy about differences in rates of solution determined by various operators and laboratories, a more objective method was sought to assess differences in dissolution behavior. The present study concerns the rate of solution for sterile powders that must be constituted for injection. The method is applicable to dissolution of solids in general.

The effect of various process changes on dissolution rates is of particular interest because in various stages of product development the raw material process is scaled up and improved. Data collected by manually dissolving the solids and observing the time of dissolution often prove inconclusive, in part because the data are too subjective: different operators (or the same operator on different days) can come to different conclusions. The duration of shaking and observation periods cannot be well controlled. Differences of opinion can arise based on such questions as: "When shaking is discontinued to permit observation, should this time be counted?"; "How many shakes per minute should be used?"; and "What length, direction, and force of shaking stroke is required?" The most difficult question to answer is: "When and where is the end point?" The proposed method allows one to assess the effects of process changes on dissolution rate and minimizes the subjectiveness of the data used in decision making.

Our laboratory obtained a laser particle counter (Spectrex Corporation, Redwood City, California, USA) for use in another type of particle testing. This equipment seemed to be appropriate for the present study because of its ability to perform settling counts. That is, one can count particles in a series of equal time intervals and determine both the size and number of particles in a given volume of a settling or dissolving system. A preliminary study showed that by monitoring the disappearance of particles with time, one could estimate the time of dissolution. Only particles $>50 \mu\text{m}$, the approximate threshold of visibility, were counted.

PARTICLE COUNTER

The laser counter used in this study employs the principle of near-angle light scatter and is unique insofar as it can determine particle counts inside the sample bottle. The counter's optional particle profile analyzer can separate the counts into channels of $5\text{-}\mu\text{m}$ size increments. (The standard counter, without the options, gives total counts above a single, selectable threshold.)

The laser light source is focused into a *sensitive zone*, and the unfocused pulses are electronically filtered out. The container walls are not seen by the sensor. There have been questions about the possible lens effects created by the container walls. In this study, large-

volume containers, which have a minimum of curvature in the light path, were used. As will be discussed in more detail, each individual sample evaluated in this method becomes its own control. Because the container is stationary during the entire count sequence, any possible lens effects are normalized. Even if such effects were present, they would not affect the time to reach base-line count level.

A clear sample container is preferable, but minor opacity can be accommodated. An opacity meter supplied with the counter permits such adjustments. Figure 1 shows an overall schematic of the counting system. Figure 2 is a representation of the laser beam optics and the sensitive zone.

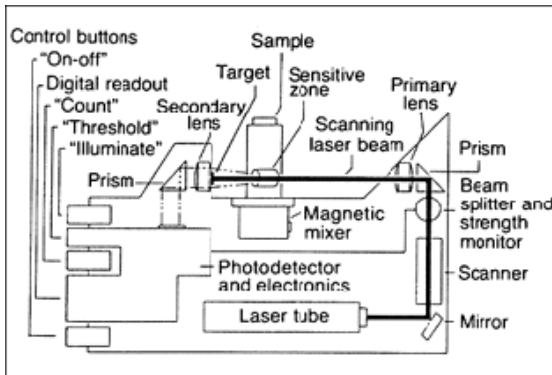


Figure 1: Schematic of the laser particle counter.

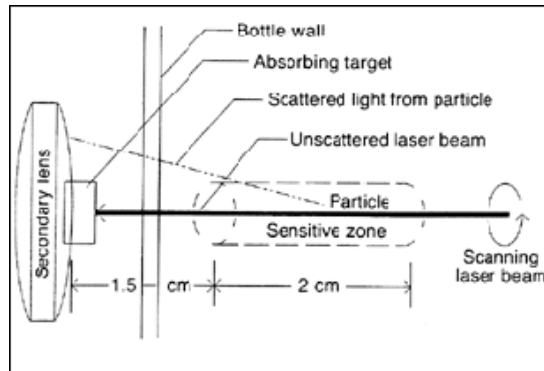


Figure 2: Schematic of the laser beam optics.

METHOD DEVELOPMENT

Recent models of the counter can be interfaced to an IBM or Apple microcomputer for data collection and display. After initial evaluation and development, the instrument was modified by the addition of a Hewlett-Packard computer system (Model 9836, Portland, Oregon, USA). The counter was calibrated using standard monodispersed spheres in sealed bottles. These standards were prepared, and several counts were made on a light obscuration—based counter that used a polychromatic light source (Model PC-320, HIAC/Royco Instrument Division of Pacific Scientific Company, Silver Spring, Maryland, USA). This counter was used for calibration because *USP XXII* (788) suggests the use of this type of equipment for the determination of particulate matter in small-volume injectables. Successive counts on this instrument showed good agreement with each other; the standards were then used to calibrate the Spectrex counter.

Adjustments were made to the gain and threshold of the Spectrex counter to approximate the distribution of particles found using the PC-320. Once the distribution curve was established, the time of counting was adjusted to give the same total particle count by both methods. This was easily accomplished by controlling the delay interval between the start and stop of the counting register.

Next, a section of programming code was written to draw a graph and plot the appropriate data. For ease of scaling, all counts greater than 900/mL were equated to 900 (the top of the y-axis). This was justified by the fact that the area of decision occurred when the counts reached background for that individual sample: this took place in the range of 0-20 counts/mL.

Initial evaluation of the curves was done by visual interpretation. After several curves were reviewed, the standards for decision making were outlined, and program code was written to make these decisions. For example, the visual standard for dissolution was established as 'when the counts/mL reach the base line for this sample.' Mathematically this was done by scanning the curve in reverse order and comparing each data point to the remaining base line. Further

inspection of the curves indicated that dissolution was deemed to be complete when the curve showed no more than five counts from the average base line.

Some base lines were not completely flat because of the mixing pattern in the sample container. These fluctuations represented gentle slope changes when compared with the general curve approaching the base line (as material dissolved). The program was modified to incorporate a comparison of the slope between each point while assessing that point's relationship to the average base line. The combination of the two parameters allowed the computer to calculate the dissolution time more precisely than could be done by visually interpreting the graph. Figure 3 is a schematic view of the decision points used in this evaluation.

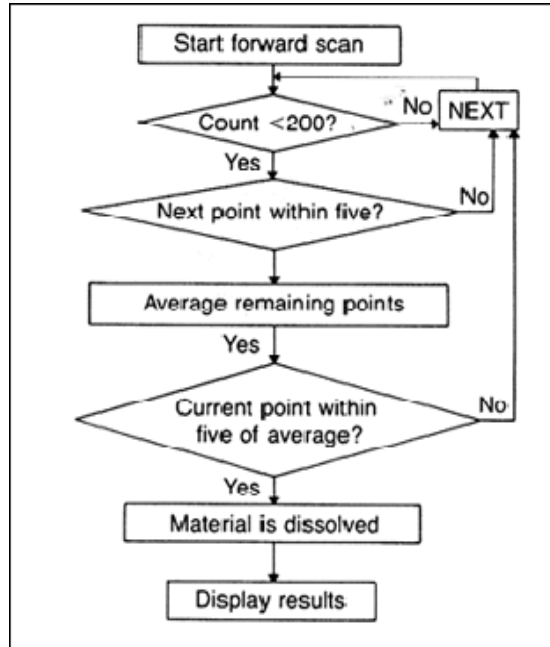


Figure 3: Flow chart of dissolution analysis

One additional phenomenon occurred during the development phase for the graphic display. Certain samples, which contained a very high concentration of fine particles, masked the sensor in the first few count sequences because of turbidity. This was represented by an initial sharp drop in counts (sometimes to almost zero), followed by a return to count levels above 900. This return occurred when the turbidity cleared to the point at which discrete pulses could be sensed by the optics. During visual observations, this portion of the curve was simply ignored, because the cause was observed during the count sequence. In order to clarify the final output, a programmed routine was incorporated to replot the curve. This was justified on the basis that the counts during the period of turbidity were obviously greater than the 900-count limit established for graphic purposes.

All counts to this point had been made on the basis of 15-s intervals, which approximated a 1.0-mL volume scanned by the laser. An appropriate calculation factor had been applied to bring the data to a per-mL basis (using the HIAC standard).

Certain samples were found to require a shorter count sequence in order to resolve differences. The final modification was made to the method to resolve the time to 0.1 min. This was a simple programming change, but it required additional attention to machine delays. When the counter was used with a 15-s count interval, the delay of about 1 s/count interval (to transfer data and reset the sequence) was reproducible and was not considered significant. The method had only

been used to determine comparative differences. However, the change from 15-s to 6-s intervals caused concern over the interpretation of the data.

The internal clock on the computer was used to define the time involved, and an appropriate decrease in time interval was added so that the actual time of mixing could be represented on the graphic display. Adjustments were made to the factor that converted the counts to a per-mL base. The computer was then programmed to calculate the actual counting time for each test and to print the result on the report.

One final addition was made to the program to allow the performance of counts on several samples in one group. This improved the statistical significance of the data. Statistics were calculated for each group to establish the sample-to-sample variation. The group averages for each count sequence were graphed in a manner similar to that used for the individual samples. An average was obtained for the group, both by the graphic techniques used for the individual samples and also by calculation.

DISCUSSION

The testing interval of 5 min./sample was chosen based on the type of materials being evaluated. Preliminary evaluations had shown dissolution times as long as 4.5 min., with none exceeding 5min. This interval could be shortened (or lengthened) to optimize throughput of samples.

Any computer that allows programmatic control of outputs to the RS-232 interface could be used to control the particle profile analyzer. For this development, the Hewlett-Packard worked very well because it is fast and can be equipped with relatively large amounts of internal memory (RAM). Working in RAM minimizes delays and allows real-time display of the data.

Figure 4 shows the graphs for two solids prepared by different processes. Ranges, standard deviations, and 95% confidence intervals are calculated for each group using standard formulas¹. These data are used in separate statistical routines to determine the significance of subtle differences between groups.

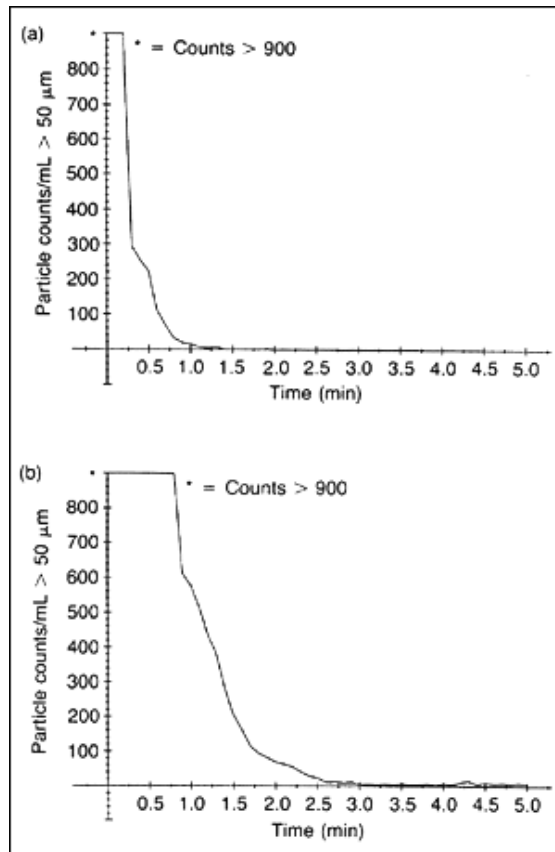


Figure 4: Output curves for samples prepared using two different processes. Dissolution time in (a) = 1.2 min; in (b), 2.6 min.

The shape of the curves generated can also give information about the solids. Certain curves progress toward the base line in a smooth fashion, although others may contain areas of leveling. Further investigation is planned in this area. For example, one could postulate that certain gradations in particle size within the sample are responsible for the leveling effect. A study in which a portion of the sample is tested for particle-size distribution, followed by a plot of dissolution behavior, will be used to test this hypothesis.

The recent addition of a hard disk to the computer system will allow the data to be stored and subjected to comparative statistical routines. This will allow immediate decisions about the significance of differences between groups.

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REFERENCE

1. *Remington's Pharmaceutical Sciences*, 15th ed. (Mack Publishing Co., Easton, Pennsylvania, 1975). p. 123.

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