Notes

[Chem. Pharm. Bull. 26(5)1598—1603(1978)]

UDC 615.453.2.011.3.014.2 : 539.215.08

Determination of Particle Size and Its Distribution of Drug Powder by Dissolution Rate Measurements[1]

Keiji Sekiguchi, Motoharu Iwatsuru, and Kenichi Shirotani

School of Pharmaceutical Sciences, Kitasato University[2]

(Received August 17, 1977)

It was confirmed that the particle size distributions could be effectively obtained by dissolution rate analysis.

If the drug dissolves by a diffusion-controlled mechanism and the absorbance E of its solution obeys the Beer's law, the absorbance change with respect to time t will be proportional to the surface area S and be expressed as $dE/dt=k'S$, where k' is a constant. When a drug powder is composed of n uniform and spherical particles the following equation $d^2E/dt^2=k'dS/dt=Kn(\tau-t)$ will hold, where τ is the disappearance time of the particles and K is a constant.

Any powder can be considered as a set of n_1, n_2....particles having the diameter of D_1, D_2...., and the equation can be transformed into $d^2E/dt^2=K\{n_1(\tau_1-t)+n_2(\tau_2-t)+n_3(\tau_3-t)+....\}$. Thus the size distribution of a powder on the number basis can be determined from the tangent on the d^2E/dt^2—time curve.

The proposed method was applied to benzoic acid crystals and the results were compared with those from microscopic analysis, and the agreement was fairly good. The mechanical trituration effects on the sulfanilamide crystals were also studied by this procedure. Thus it was found that the method gave the effective diameter for dissolution and the results could be obtained in much shorter time as compared with the ordinary methods such as microscopic analysis.

Keywords——particle disappearance time; second derivative of absorbance-time curve; particle size; particle size distribution; dissolution rate analysis; microscopic analysis; sulfanilamide; benzoic acid; ball-mill; effective diameter for dissolution

The dissolution rate and accordingly the bioavailability of a drug are recognized to be highly dependent on particle size and its distribution. For this reason, these properties are very important for dosage forms that contain the drug as a separate phase and have hitherto been measured by several methods such as microscopic dimension analysis, sedimentation method and gas adsorption analysis. However, the particle sizes and their distributions determined by those methods are not always directly related to dissolution rates of the powder, moreover, each of the methods has other disadvantages of its own. For example, the gas adsorption analysis by BET method is not only unsuitable for coarse particles but also gives no information about size distribution.

A thermal method was recently introduced by Suito *et al.*[3] and attempts of its applications to pharmaceutical field[4,5] were immediately made by several workers. Though the method is excellent in that it measures the heat evolved or absorbed due to dissolution of the sample, the apparatus and procedure adopted are not simple and some experimental errors will be accompanied due to non-selectivity and imcomplete seizure of the heat evolved or absorbed.

1) Dissolution Behavior of Solid Drugs VIII. Part VII: K. Sekiguchi, K. Shirotani, and M. Kanke, *Chem. Pharm. Bull.* (Tokyo), **25**, 1782 (1977). Presented partly at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, 1975.
2) Location: *9-1, Shirokane 5 chome, Minato-ku, Tokyo, 108, Japan.*
3) E. Suito, N. Hirai, and K. Taki, *Nippon Kagaku Zasshi*, **72**, 713 (1951).
4) H. Nogami, J. Hasegawa, and Y. Nakai, *Chem. Pharm. Bull.* (Tokyo), **7**, 331 (1959).
5) H. Nogami, J. Hasegawa, and Y. Nakai, *Chem. Pharm. Bull.* (Tokyo), **7**, 338 (1959).

Previously, the authors developed a simple method for determining effective surface area of a drug powder by measuring the initial dissolution rate.[6] The principle was based on comparing the initial dissolution rate of the sample with that in the calibration curve predetermined with compact disks of the same powder which had constant surface area.

In the present study, the dissolution rate measurement was continued untill the sample powder was completely dissolved. By the use of the mathematical treatment proposed by Suito *et al.*, determination of particle size and its distribution would thus be possible. The method was tested with powders of sulfanilamide and benzoic acid and satisfying results were obtained as shown in the following.

Theoretical

When a drug powder composed of n uniform spherical particles having a diameter of D is dissolved into an excess amount of water, the decreasing rate of the total surface area S is written,

$$-dS/dt = 2n\pi D(dD/dt)^{7)} \quad (1)$$

Since the decrease in diameter of each particle is given by

$$D = D_0 - kt \quad (2)$$

where D_0 is the initial diameter and k is a constant, Eq. (1) becomes

$$dS/dt = 2n\pi k^2(D_0/k - t) = 2n\pi k^2(\tau - t) \quad (3)$$

where τ is the disappearance time or the time required for complete dissolution of the particles.

If the drug dissolves by a diffusion-controlled mechanism and the absorbance E of its solution obeys the Beer's law, the absorbance change with respect to time will be proportional to the surface area and expressed as follows,

$$dE/dt = k'S \quad (4)$$

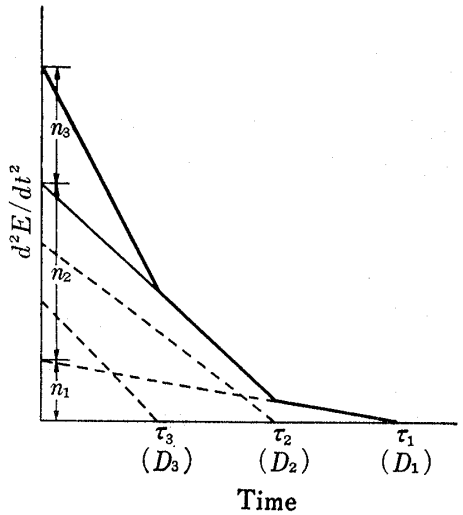

Fig. 1. Theoretical d^2E/dt^2–Time Curve

——— d^2E/dt^2-time curve of mixed particles having diameter D_1, D_2, and D_3.
------- d^2E/dt^2-time curves of particles having a diameter D_1, D_2, and D_3, respectively.
τ_i: the time required for complete dissolution of the particles.
n_i: the number of particles of diameter D_i.

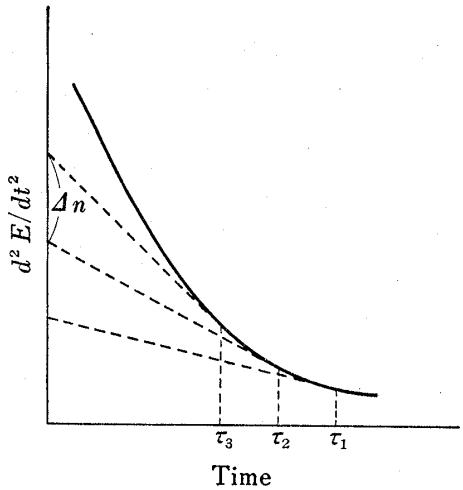

Fig. 2. Theoretical d^2E/dt^2–Time Curve of Particles having Wide Range of Diameters

6) K. Sekiguchi, K. Shirotani, and M. Kanke, *Yakugaku Zasshi*, **95**, 195 (1975).
7) $S=n\pi D^2$: The negative sign in Eq. (1) represents decrease.

where k' is a constant. Accordingly, from Eq. (3) and (4), the following equation is obtained,

$$d^2E/dt^2 = k'dS/dt = Kn(\tau - t) \quad (5)$$

where K is a constant.

Eq. (5) implies that the term d^2E/dt^2 should decrease linearly with time. However, in reality the particle size of a powder is not uniform but distributed. Any powder can be considered as a set of $n_1, n_2, \ldots$ particles having the diameter of $D_1, D_2, \ldots$ as shown in Fig. 1. And Eq. (5) will be represented as follows,

$$d^2E/dt^2 = K\{n_1(\tau_1 - t) + n_2(\tau_2 - t) + n_3(\tau_3 - t) + \cdots\} \quad (6)$$

When diameters of the particles in a powder are continuously distributed, the relation between d^2E/dt^2 and t will be shown by a curve as in Fig. 2. Thus the size distribution of a powder on the number basis will be determined from the length of ordinate dissected by two tangent lines on the curve at the points corresponding to two consecutive τs.

Experimental

Dissolution Rate Measurements——Using the same apparatus as previously reported,[6] sample powders were dissolved in 1000 g of distilled water with 240 rpm stirring at 25.5±0.1°. A flow cell attached to a UV spectrophotometer was used and the flow rate of 300 ml/min was maintained by pumping. The absorbances were recorded at 258 nm for sulfanilamide or 246 nm for benzoic acid.

Preparation of Samples for Particle Size Determination——(1) Samples obtained by Recrystallization: Sulfanilamide was recrystallized from methanol and classified into 20—28 mesh or 16—20 mesh crystals, which were employed to confirm whether d^2E/dt^2-time curves corresponded to the disappearance of particles during dissolution process.

(2) Samples obtained by Triturating in a Mortar: Recrystallized sulfanilamide was triturated in a mortar and passed through a 100 mesh screen. The powder of under 100 mesh size was used for the determination of the particle size distribution. The further triturated product of which the size was under 100 mesh, was sieved with a 170 mesh screen, and the powder of under 170 mesh size was also used independently.

(3) Samples ground in a Ball-mill: Benzoic acid recrystallized from water was placed in a pot (9 cm in diameter) of a ball-mill and ground with rotating of 180 rpm. Sample powders were withdrawn at certain time intervals and the change of the particle size distribution with the grinding time was determined.

Results and Discussion

Correspondence between d^2E/dt^2–Time Curve and Disappearance of Particles During Dissolution

To ascertain that the d^2E/dt^2-time curve at each time just after the commencement of dissolution reflects the fraction of particles still remained in the dissolving medium, preliminary experiments were done with mixtures containing known numbers of two sizes of sulfanilamide crystals. In Fig. 3 one of the representative results are shown in which was used a sample mixture composed of 11 particles of 16—20 mesh and 30 particles of 20—28 mesh, respectively. As was expected, the curve obtained had two straight portions and their intersection was found at about 7 min on the time axis. The two straight portions indicated that two different sizes of crystals were present in the sample mixture. By extrapolating the second line to the ordinate, the fraction undissolved at the time of intersection was calculated to be 34.5%: namely, 14 particles of sulfanilamide still remained in the solution after 7 min exposure to the medium.

When the same crystal mixture was dissolved in the same volume of water and stirring was stopped at 7 min, the number of undissolved particles were counted to be 13—15 for three trials by visual inspection. From these results, it is clear that the d^2E/dt^2-time curve corresponds to disappearance of particles during dissolution process.

Comparison of Determination Method of Particle Size Distribution by Microscopic Analysis and by Dissolution Rate Analysis

The determination of particle size distribution often gives different results according to the method employed. So the attempts were made to compare the results from dissolution

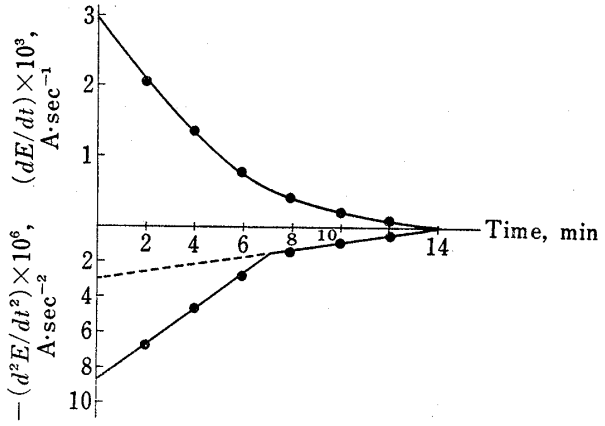

Fig. 3. dE/dt-Time and d^2E/dt^2-Time Curves of Sulfanilamide Crystal Mixture of 16—20 Mesh and 20—28 Mesh (dE/dt-Time Curve was constructed from Absorbance-time Curve during Dissolution of Sulfanilamide Crystals)

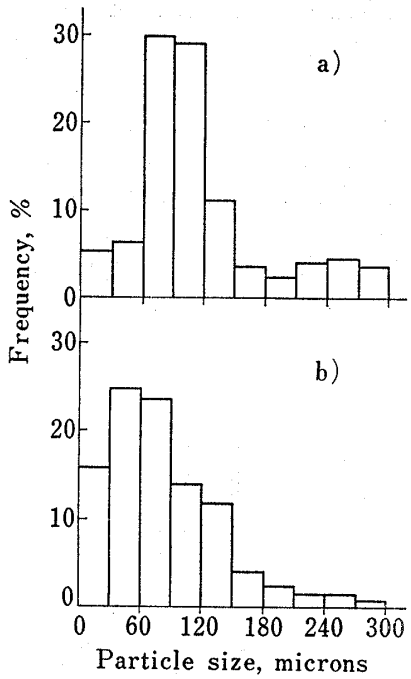

Fig. 4. Comparison of Particle Size Distributions by Dissolution Rate Analysis and Microscopic Analysis

a) From dissolution rate analysis.
b) From microscopic analysis.

rate analysis and those from microscopic analysis. Benzoic acid crystals ground in a ball-mill for 20 min were used as the test sample. In dissolution rate analysis, the particle diameters are primarily given by the time required for complete dissolution. The assumption was made that the largest particle by microscopic analysis corresponded to the longest time requiring particle for dissolution. Both results, one from dissolution rate analysis, and the other from microscopic analysis, are shown in Fig. 4. It can be said that the agreement is fairly good, though as a whole, the proposed method showed the tendency to give somewhat larger values.

The patterns of absorption and/or appearance of effect(s) of medicinal powders given to a subject are of pharmaceutically great concern. However, it is generally accepted that the particle size distribution determined by microscopic analysis is not necessarily related to dissolution rates. On this standpoint, as the proposed method gives the effective diameter for dissolution, the utility of this method is evident.

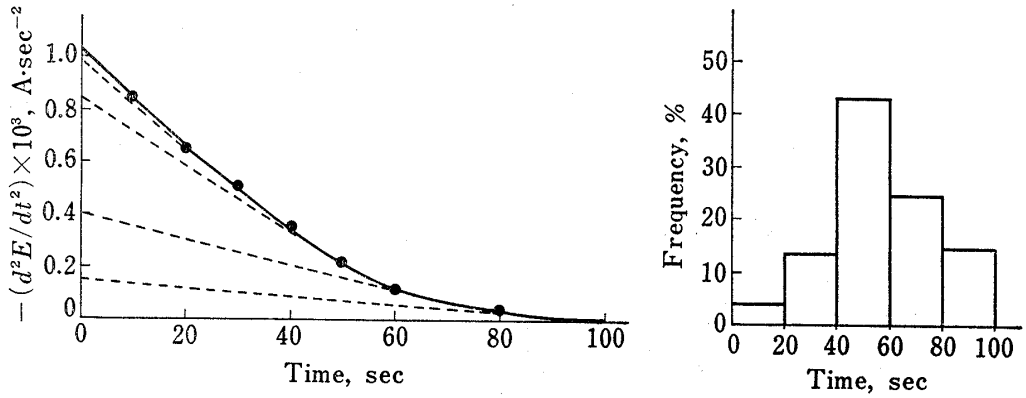

Fig. 5. d^2E/dt^2-Time Curve of Sulfanilamide Powder sieved with 100 Mesh Screen and Its Particle Size Distribution (in Time Scale. See Text for Explanation)

Grinding Time and Particle Size Reduction

In order to study the particle size change sa a function of grinding time, dissolution rate analysis was applied to the sample triturated in a motar or ground in a ball-mill. As an example of an ordinary powder, sulfanilamide crystals were triturated with circular strokes of 100 times in a mortar and the powder was sieved with a 100 mesh screen. The results are shown in Fig. 5. The particle sizes or diameters are expressed by the time required for complete dissolution as mentioned above, and the results are shown by seconds without conversion to length. Time axis is segmented by 20 sec. Taking the purpose of the proposed method into consideration, it is evident that the diameter expressed by time is of greater use than

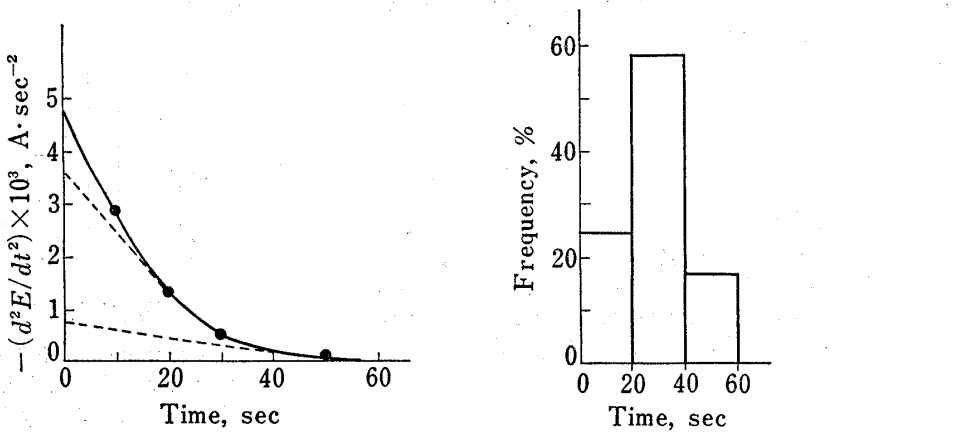

Fig. 6. d^2E/dt^2–Time Curve and Particle Size Distribution of Sulfanilamide Powder sieved with 170 Mesh Screen

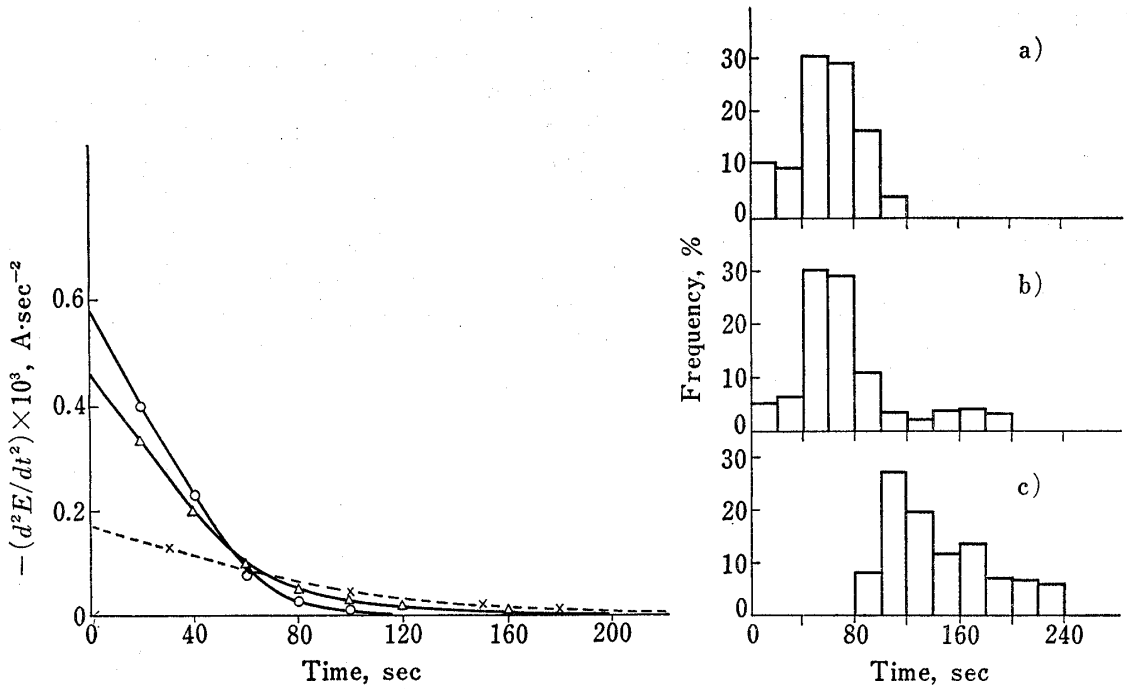

Fig. 7. d^2E/dt^2–Time Curves and Particle Size Distributions of Benzoic Acid Particles ground in a Ball-Mill

—○—: d^2E/dt^2-time curve of particles ground for 60 minutes.
—△—: d^2E/dt^2-time curve of particles ground for 20 minutes.
—×—: d^2E/dt^2-time curve of particles ground for 5 minutes.
a) Particle size distribution of particles ground for 60 minutes.
b) Particle size distribution of particles ground for 20 minutes.
c) Particle size distribution of particles ground for 5 minutes.

the one expressed by length. If necessity arises to show the diameter by length, the conversion can be easily made by the determination with particles of known diameter. For example, as the largest diameter was 150 μ (100 mesh), and the time for complete dissolution was 100 sec in this case, following relation was obtained.

$$D = D_0 - 1.5\,t$$

From the equation, the diameter of particles can be approximately calculated.

In addition, the same sample was further triturated in the mortar for 1 min with strokes of 100 times, then sieved with a 170 mesh screen (Fig. 6). As the biggest diameter was 88 μ (170 mesh) and time was 60 sec, k was calculated to be 1.47. Both values were in good agreement. Evidently the validity of this method was thus shown.

With the purpose of measuring in short time the grinding effect of a ball-mill, the proposed method was applied to benzoic acid crystals. Benzoic acid crystals were placed in a pot of the ball-mill and rotated at 180 rpm and certain quantities of the sample were withdrawn at 5, 20, and 60 min. The results are shown in Fig. 7. The sample at 5 min showed large diameter and deviation. The mean diameter of the sample at 20 min became half as much. The sample ground for 60 min showed the mean diameter as large as that of 20 min grinding, though the deviation became smaller. As for benzoic acid crystals, the grinding effect was not proportional to the grinding time.

The time needed for a measurement by this method will be 2—3 min at most, though it is dependent upon the particle diameters to be analyzed. Accordingly, even with addition of the time needed for the calculation, the result can be obtained in very short time. It will be fairly easy by this method to examine the object has already reached the predetermined diameter or not.

Conclusion

It was confirmed that the particle size distributions could be effectively obtained by dissolution rate analysis. The particle size obtained in this experiment should be evaluated as the effective diameter for dissolution. Up to the present, the dissolution rates have been predicted by the particle size. In pharmaceutical applications, however, the relationship between the dissolution rate and the appearance of the drug effect(s) is important concern, and accurate prediction of dissolution rates is required. In these cases, the diameter obtained from dissolution rate analysis will be readily available as an indicator of the dissolution rate *in vivo*. As previously reported, dE/dt–time curves gave the effective surface area for dissolution. Also, in this report, the particle size distribution was shown to be obtainable from the d^2E/dt^2–time curve. Therefore, dE/dt–time and d^2E/dt^2–time curves will give useful information with regard to dissolution behaviors for powders or solid drugs.

Acknowledgement This work was partly supported by the grant from the Ministry of Education, Science and Culture of Japan in 1976.