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Dissolution of Slightly Soluble Powders under Sink Conditions I: Development of an Apparatus and Dissolution Studies of Salicylic Acid Powders

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Abstract □ A three-compartment apparatus was developed for dissolution studies of slightly soluble powders under sink conditions. The apparatus was designed to accommodate up to three phases to provide sink conditions. The apparatus could accommodate a barrier in the dissolution medium to prevent floating powders from entering and dissolving directly into the sink phase. Dissolution studies were conducted with several particle size grades of salicylic acid under nonsink as well as sink conditions. Effects of the rate of agitation and methods of introducing samples (dry or wetted suspensions) were also investigated. The data indicated that under diffusion-controlled rate of agitation, using the appropriate placement of propellers, it was possible to establish a rank order for *in vitro* dissolution times of different particle size salicylic acid powders.

Keyphrases □ Powders, slightly soluble—dissolution, sink conditions □ Particle-size effect—powder dissolution □ Diagram—powder dissolution apparatus □ UV spectrophotometry—analysis

In recent years, much attention has been focused on the problem of drug availability from solid dosage forms. The importance of *in vitro* dissolution-rate studies for solid dosage forms in determining the drug availability has been recognized (1–5), but it is now generally accepted that the *in vitro* results should be correlated to some physiologic parameter. It has been shown that unless appropriate sink conditions are maintained in certain cases, *in vitro* dissolution studies might bear little relationship to *in vivo* dissolution results (6).

Recently, several methods have been developed (3–17) to study the *in vitro* dissolution rates of drugs from solid dosage forms; however, most of these methods lack sink conditions. Only a few methods (6, 15) have been reported for dissolution studies under sink conditions, but these are not suitable for powders. Due to flotation and flocculation of slightly soluble powder, the determination of a rank order in the dissolution rates of slightly soluble powders is a problem even under nonsink conditions. Unless these floating

floccules could be broken up, and the powders distributed in such a way that the relative surface areas of different particle-size powders would be available for dissolution, a rank order in the dissolution rates would not be possible. Finholt *et al.* (18, 19) encountered these problems in their attempt to study the effect of particle size on dissolution rates and while comparing the dissolution rates of powders with granules and tablets. Lin *et al.* (20) also found similar problems in the rank order in the dissolution rates of different particle-size powders.

Because certain properties of drug powders play an important part in their dissolution rates from the dosage forms, it is important that the dissolution behavior of powders be studied. An apparatus, which could give a rank order in the *in vitro* dissolution rates of powders and could also accommodate sink phases, would be of value in the development and evaluation of dosage forms where control of certain powder characteristics is important.

The objectives of this investigation were to develop an apparatus which could be used to carry out dissolution studies of slightly soluble powders under sink conditions, and to demonstrate the utility of this apparatus by obtaining an appropriate rank order in the dissolution rates of different particle-size powders of a model drug.

EXPERIMENTAL

Chemicals and Materials —The salicylic acid[1] used was USP grade. The different particle-size grades were obtained by sieving twice through Ro-Tap testing sieve shaker, using U. S. standard sieves. Isopropyl myristate[2] and polysorbate 80[3] were used. All other chemicals were reagent or certified ACS grade.
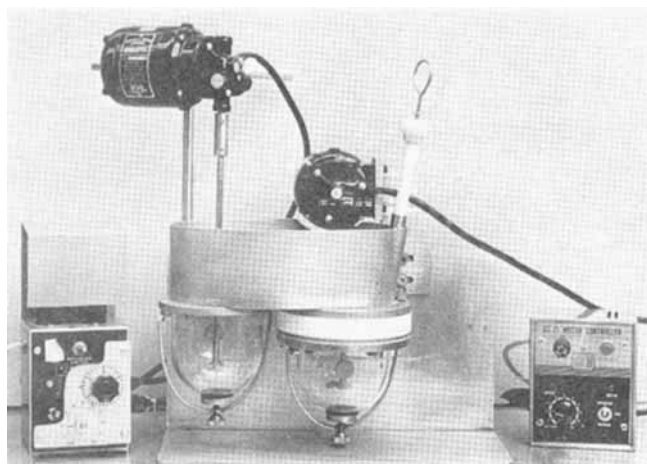
Figure 1—*Dissolution apparatus.*

Apparatus—The dissolution apparatus developed for this study is illustrated in Fig. 1, a schematic diagram of the assembly is shown in Fig. 2, and the dismantled apparatus is given in Fig. 3. The basic parts of the apparatus consist of a main frame; two glass bowls; a pair of Teflon gaskets; a screen or a filter membrane-holding frame; two controlled speed stirrers with stirring shafts, propellers, and impellers; and a sample injector.

The main frame was fabricated from stainless steel. When the glass bowls were clamped to the main frame, the apparatus consisted of three compartments. The main frame served as the compartment (Compartment C) for an organic sink phase.

The glass bowls were 9.0 cm. in diameter with round bottoms. The bowl for Compartment A was 7.3-cm. deep, and the bowl for Compartment B was 9.1-cm. deep.

The Teflon gaskets had 9.1-cm. open diameter. One gasket was 2.0-cm. thick, while the other was 0.16 cm. The screen-holding frame, to which a screen was secured, was 0.3-cm. thick, had four support arms, and had a central hole for a stirrer shaft. As seen in Fig. 3, this screen-holding frame was combined with the sample entrance tube through which samples being studied could be introduced directly into the dissolution medium. To prevent injecting air below the screen when introducing the samples, a side tube was affixed to the sample entrance tube to vent the air. The level of this air vent tube corresponded to the level of the liquid in the apparatus. A 200-mesh screen[4] was used as the barrier throughout these studies. This screen was selected on the basis of transport and equilibrium studies carried out using various membranes and screens as barriers. The results of these studies will be reported in a forthcoming paper.

Two propellers were attached to the left-hand stirrer shaft. A three-blade propeller, 1.9 cm. in diameter, was positioned 2.5 cm. from the bottom of the glass bowl in Compartment B. A three-blade turbine impeller, 2.6 cm. in diameter, was used in the organic phase and positioned 0.9 cm. above the interface in Compartment B.

Two, three, or four propellers were attached to the right-hand stirrer shaft. A three-blade propeller, 1.9 cm. in diameter, was placed 2.2 cm. from the bottom of the glass bowl in Compartment A. A three-blade turbine impeller, 3.0 cm. in diameter, was attached 0.2 cm. above the screen. Other additional impellers were used, depending on the particular experimental conditions, and will be described in detail under other headings.

The sample injector is shown in Fig. 4 and consists of a syringe-like assembly made of Teflon. A Teflon piston was attached to a stainless steel rod, which could be unscrewed to clean the assembly. A Teflon disk or Whatman No. 1 filter paper disk was used to cover the tip of the injector assembly. The fitting of these disks was such that they could be ejected with a slight pressure but would remain intact while the samples were being introduced.

Dissolution of Salicylic Acid Powders under Nonsink Conditions—These experiments were carried out in Compartment A with the apparatus immersed in a $37 \pm 0.5°$ water bath. A 600.0-ml. volume of 0.2 M Clark-Lubs pH 2.0 buffer containing 0.05% polysorbate 80 (dissolution medium), which was previously equilibrated[5] at 37.0°, was poured into Compartment A through the sample entrance tube with the help of a separator[6] (there was approximately 145 ml. of dissolution medium above the screen). The stirrer, which was previously set at 55 r.p.m., was started. One gram of salicylic acid powder of desired mesh size was placed in the sample injector. The closed end of the injector was gently tapped three times on a firm surface to give uniform packing. The piston rod was pushed to bring the powder to the tip of the injector, and a Whatman No. 1 filter paper disk was placed over the opening. The sample injector was then introduced into the aqueous phase through the sample entrance tube with the lower tip of the injector placed 4.5 cm. above the bottom of the glass bowl; the sample was then slowly injected into the aqueous phase over a 30-sec. period. One-milliliter samples were removed from the solution above the screen at appropriate intervals. The samples were diluted with pH 2.0 buffer and assayed spectrophotometrically at 302 mμ using a Beckman DU-2 spectrophotometer. A volume of the buffer used for dissolution (37.0°) equal to the sample volume removed was replaced immediately after each sample was taken. Using this method, the effect of particle size on dissolution of salicylic acid was investigated.

Dissolution of Salicylic Acid Powders under Sink Conditions—Three different methods were used for these experiments. In Compartment A, three propellers were used for Methods A and B while four propellers were used for Method C. The third propeller was a three-blade turbine-type impeller, 2.2 cm. in diameter, and was placed 0.6 cm. above the interface. The fourth propeller was also a three-blade turbine-type impeller. This impeller was 4.3 cm. in diameter and was attached 0.1 cm. below the screen-holding frame.

Method A—A 600.0-ml. quantity of dissolution medium was poured into Compartment A as described earlier. A 480.0-ml. volume of 0.2 M Clark-Lubs pH 7.4 buffer was used in Compartment B, while 300.0 ml. of isopropyl myristate was placed above the two aqueous phases. The stirrers were started and the three phases allowed to equilibrate for 45 min. The stirrer for Compartment B was adjusted to 100 r.p.m., while the Compartment A stirrer was varied for different experiments as indicated in the particular experiment. One gram of salicylic acid powder of desired particle size was packed and introduced into the dissolution medium as described earlier. One-milliliter samples were removed from each phase[7] at appropriate intervals, and the sample volume was replaced immediately with the appropriate solvent. The samples from Compartments A, B, and C were diluted, respectively, with pH 2.0 buffer, pH 7.4 buffer, and isopropyl myristate and assayed spectrophotometrically at 302, 297, and 306 mμ using a Beckman DU-2 spectrophotometer. Using this method, the effects of various particle sizes and two Compartment A agitation rates (55 and 100 r.p.m.) on the dissolution rate of salicylic acid powder were studied.

Method B—These experiments were carried out as described under Method A except that the samples were introduced as suspensions. A suspension of 1.0 g. of salicylic acid powder and 1.5 ml. of the dissolution medium was made in the sample injector by stirring with a melting point capillary tube. The piston rod was moved to bring the suspension level up to the tip of the injector, and a Teflon disk was placed over the opening. The samples were then shaken vigorously before introducing them into the dissolution medium in Compartment A. The suspensions were slowly injected into the dissolution medium over a 30-sec. period, and samples from each phase were removed at appropriate intervals and assayed spectrophotometrically as described earlier.

Method C—With this method the experiments were carried out as described under Method A, with the exception that an additional three-blade impeller, as described earlier, was attached to the stirrer shaft below the screen in Compartment A. An agitation rate of 30 r.p.m. in Compartment A was used in these experiments.

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[4] This screen was obtained from Cambridge Wire Cloth Co. The screen had twilled weave, 68.6-μ pore size and was made from a 58.42-μ diameter wire.

[5] This was necessary so that dissolved air in the buffer would not be evolved and block the screen.

[6] The separator had a 20.0-cm. long stem which, when introduced through the sample entrance tube, would rest on the bottom of the glass bowl. There was no formation of foam below the screen when the dissolution medium was introduced in this manner.

[7] The samples from aqueous phases were removed by dipping pipets into the respective phases through the organic phase. The sides of these pipets were wiped off before delivering the samples.
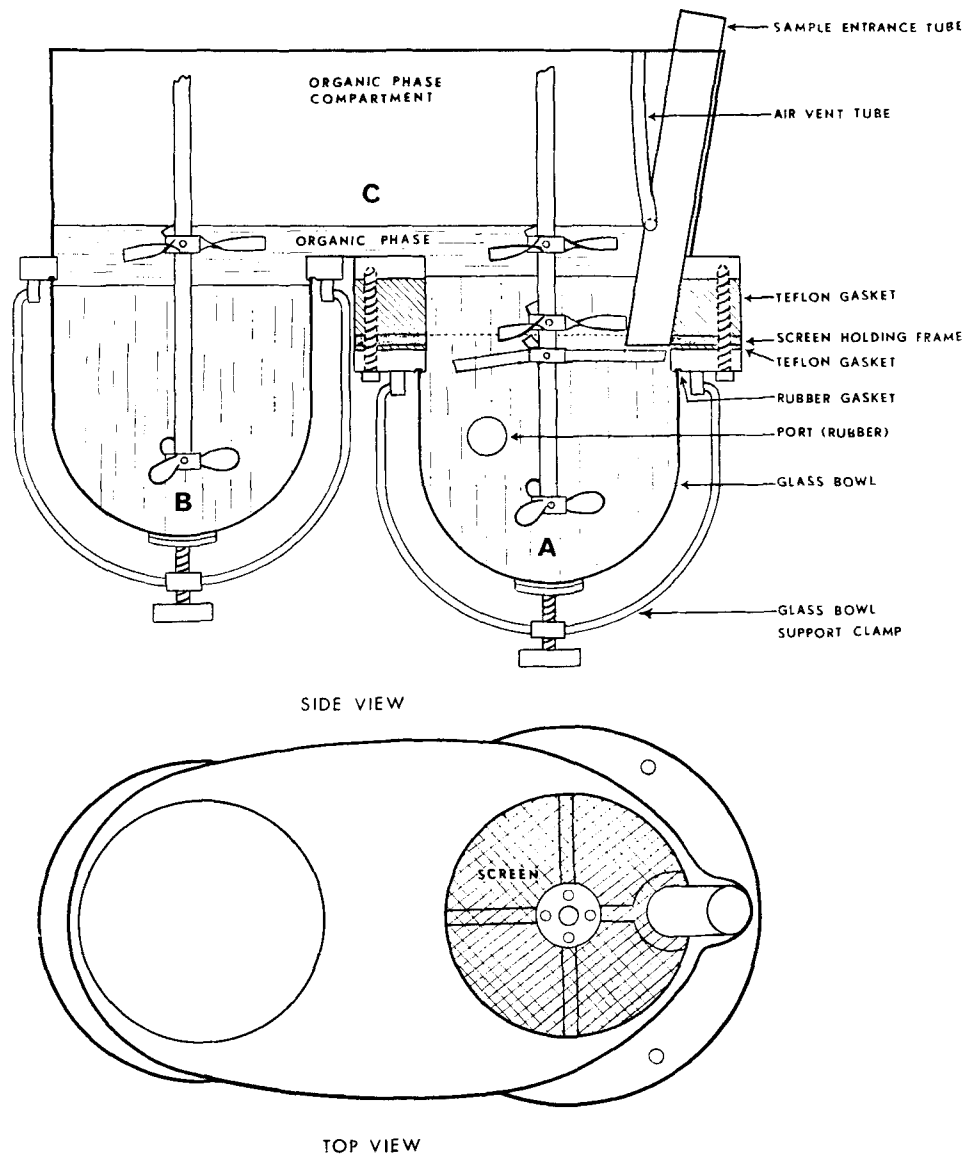
Figure 2—Schematic diagram of the dissolution apparatus.

The sample injector was positioned just below the lower edge of the screen-holding frame, so the lower impeller would scrape off the powder sample as it was slowly introduced into the dissolution medium over a 30-sec. period.
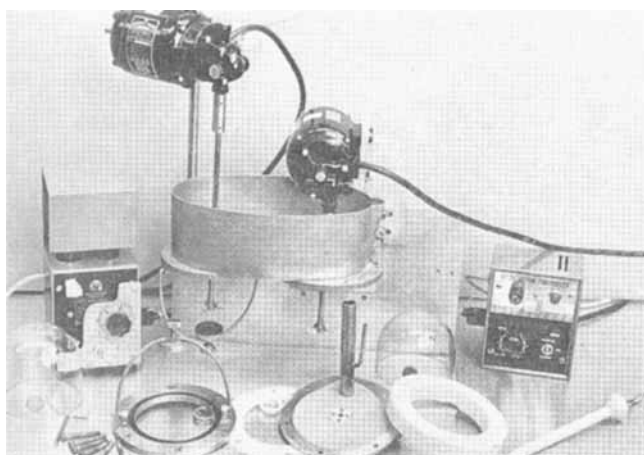

Figure 3—Dissolution apparatus dismantled.

RESULTS AND DISCUSSION

Dissolution of Salicylic Acid Powders under Nonsink Conditions— The apparatus used for these studies, as described under *Experimental*, was essentially a modified form of Levy's beaker stirrer assembly. Using this apparatus, the dissolution studies of different particle size salicylic acid powders under nonsink conditions (Fig. 5) show a good rank order for the dissolution rates of medium particle size range powders (40/60, 60/80, and 100/120). The method however, fails to give relative dissolution rates for coarser (20/30) or finer (120/140) powders. Figure 5 shows that after about an hour, there is a higher dissolution rate for 20/30-mesh powder as compared to 40/60 mesh. Similar discrepancies have been reported by other workers (18-20). This might be due to the packing characteristics of different particle-size powders. The 20/30-mesh powder, being coarser, may not pack as tightly as the 40/60-mesh powder and thus might allow a greater movement of the dissolution medium through its particles, resulting in a higher dissolution rate. It was
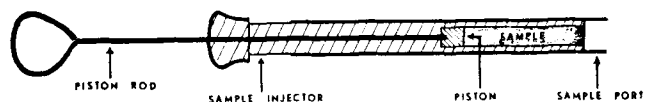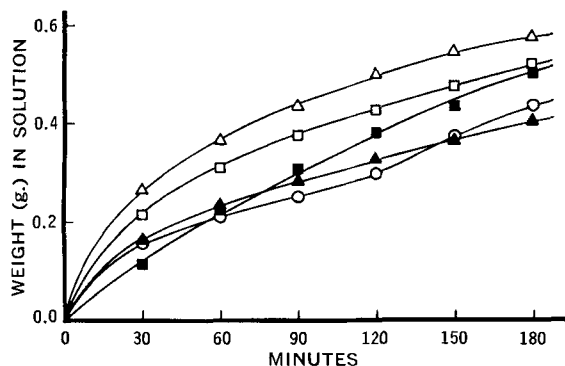

Figure 4—Sample injector.

Figure 5—*Effect of particle size on dissolution of salicylic acid under nonsink conditions at 55 r.p.m. and 37°. Key:* O, *120/140 mesh;* △, *100/120 mesh;* □, *60/80 mesh;* ▲, *40/60 mesh; and* ■, *20/30 mesh.*

observed that a small portion of the 40/60-mesh powder was dispersed over a larger surface area at the bottom of the vessel than the 20/30-mesh powder, and this could be the reason for higher initial dissolution rates for the finer powder.

Figure 5 also shows a lower than expected dissolution rate for 120/140-mesh powder. This lower dissolution rate is due to the greater tendency of this size powder to agglomerate because of greater surface energy and electrostatic charges (21). In these studies, the powder remained mainly as a single large mass against the bottom of the screen, which resulted in a much lower effective surface area for dissolution. This mass slowly, but not uniformly, disintegrated during the dissolution period. After about 2 hr., there was a slight increase in the dissolution rate due to the breakup of the floating mass into smaller particles.

The flotation problem could still be seen with fine powders, even though the dissolution medium used in the studies contained 0.05% polysorbate 80. In these studies, 20/30 and 40/60-mesh powders sank rapidly; but 60/80-mesh powder floated for about 2 min., 100/120-mesh powder floated for about 20 min., and 120/140-mesh powder remained floating during a 3-hr. experimental run. The preliminary experiments showed that in the absence of polysorbate 80, the flotation problem was much greater even in relatively much coarser powders, and a 120/140-mesh powder did not completely disintegrate and sink even after 24 hr. under similar experimental conditions. The presence of the surfactant in the gastrointestinal contents (22–24) and its use in the dissolution studies have been shown (24). In these studies, the presence of surfactant in the dissolution medium does not completely solve the flotation problem; however, it does substantially decrease its magnitude.

Dissolution of Salicylic Acid Powders under Sink Conditions—The studies under sink conditions show that the dissolution rates (Fig. 6) are generally higher than those under nonsink conditions (Fig. 5). However, a close comparison shows that the differences are small. This is due to the fact that after 3 hr. the dissolution medium is never more than 35% saturated for any mesh size salicylic acid powder, even under nonsink conditions.
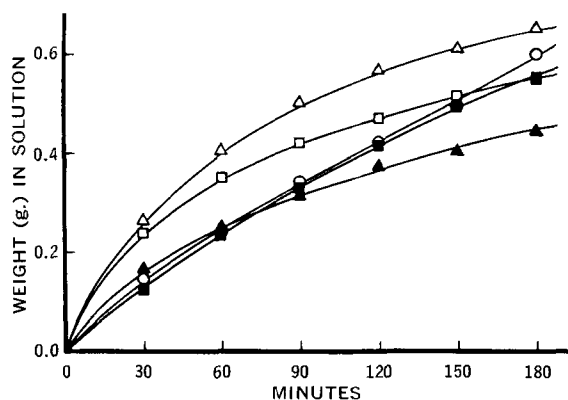

Figure 6—*Effect of particle size on dissolution of salicylic acid under sink conditions at 55 r.p.m. and 37°. Key:* O, *120/140 mesh;* △, *100/120 mesh;* □, *60/80 mesh;* ▲, *40/60 mesh; and* ■, *20/30 mesh.*
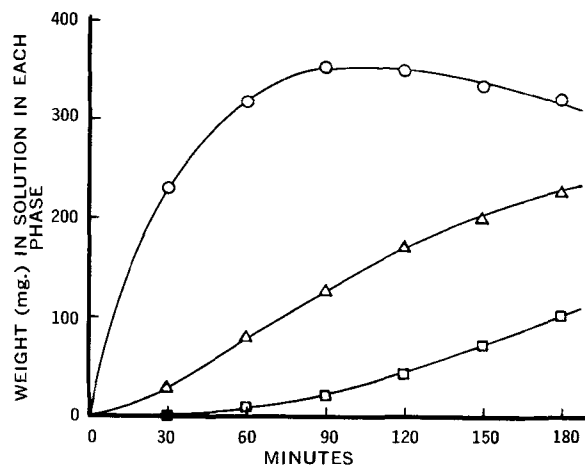

Figure 7—*Dissolution and partitioning of 100/120-mesh salicylic acid powder using Method A at 55 r.p.m. and 37°. Key:* O, *pH 2.0 buffer;* △, *isopropyl myristate; and* □, *pH 7.4 buffer.*

It is apparent from these studies that the failure to obtain a rank order in the dissolution rates of salicylic acid powders under nonsink conditions was not due to the lack of sink conditions but to the packing, agglomerating, and floating characteristics of the powders. Under these circumstances, the presence of a sink condition would not be expected to make a qualitative change in the dissolution results. The method, however, does demonstrate the technique for using sink conditions and the necessity for a screen barrier to prevent the floating powders from entering directly in the organic phase under sink conditions. The experiments also did not indicate any emulsification at the interface.

Figure 7 shows the partitioning of 100/120-mesh salicylic acid powder as the dissolution takes place. The development of concentration in the pH 7.4 buffer seems to be a little slow and could possibly be increased by using a higher pH buffer; however, no such attempt was made because the purpose of these studies was mainly to demonstrate the use of a three-phase sink system and not necessarily to develop a perfect sink system which, of course, would be different from product to product.

Dissolution studies at 100 r.p.m. under sink conditions (Fig. 8) show that, at this rate of agitation, it is possible to have a large rank order difference between coarser powders (20/30 and 40/60). This could be due to a greater distribution of 40/60-mesh powder under the force of agitation. Figure 8, however, shows a decrease in the difference of the dissolution rates of the finer (60/80 and 100/120) powders. This could be due to the fact that, at this rate of agitation,
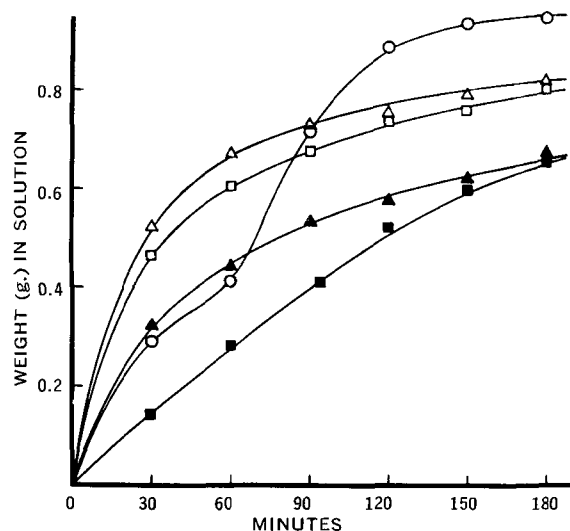

Figure 8—*Effect of particle size on dissolution of salicylic acid under sink conditions at 100 r.p.m. and 37°. Key:* O, *120/140 mesh;* △, *100/120 mesh;* □, *60/80 mesh;* ▲, *40/60 mesh; and* ■, *20/30 mesh.*
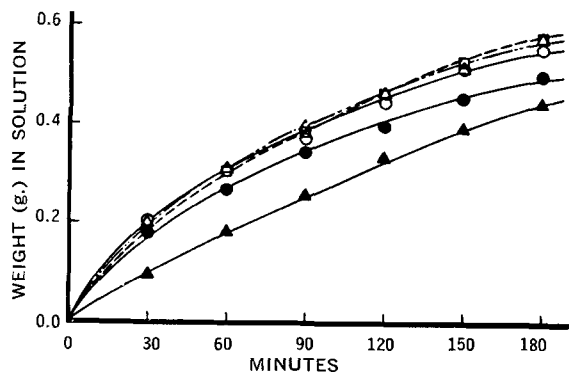
Figure 9—*Effect of particle size on dissolution of salicylic acid under sink conditions using suspension samples at 55 r.p.m. and 37°. Key: O, 200/230 mesh; △, 120/140 mesh; □, 60/80 mesh; ●, 40/60 mesh; and ▲, 20/30 mesh.*

Table I—Reproducibility of Dissolution Method A for the Dissolution of 100/120-Mesh Salicylic Acid Powder at 55 r.p.m. and 37°

Dissolution Time, min.	Mean Weight[a] (mg.) in Solution	SD ± mg.	Percent SD
30	262.9	31.1	11.82
60	406.1	59.7	14.70
90	504.3	86.7	17.39
120	567.3	85.5	15.05
150	610.5	89.7	14.69
180	652.8	92.7	14.20
		Mean =	14.65

[a] Each value is an average of six experiments.

the finer powders cannot remain distributed on the lower sides and bottom of the vessel but are forced into the central vortex, where there is less surface area exposed to the dissolution medium. The 120/140-mesh powder shows an initial lower dissolution rate even at this high rate of agitation. The floating mass is wetted and completely disintegrated after about an hour, resulting in an increased dissolution rate. Although the flotation of powders was partially reduced with the increase in the rate of agitation, the problem of powder distribution was aggravated due to vortexing; the rank order problem was not solved by this experimental method.

Dissolution of Salicylic Acid Powders Using Suspension Samples—Since the problem of rank order in the dissolution rates could be attributed mainly to flotation, flocculation, and poor distribution, it was thought that if prewetted powder samples could be properly distributed, a rank order might be possible. Dissolution studies using samples as wetted suspensions (Method B) did not show any significant difference in the dissolution profiles of powders having particle sizes higher than 40/60 mesh (Fig. 9). A rapid settling of the powders was observed and there was no flotation and flocculation. Due to rapid settling of the powders, however, it appeared that the particles could not be distributed well enough to expose relatively different surface areas; different dissolution rates for different particle size powders above 40/60 mesh did not occur.

A similar phenomenon was observed by Finholt *et al.* (18), who could not differentiate dissolution rates of different particle size acetylsalicylic acid powders in 0.1 *N* HCl containing 0.2% polysorbate 80. These workers mentioned the possibility of a complex formation between acetylsalicylic acid and polysorbate 80 as
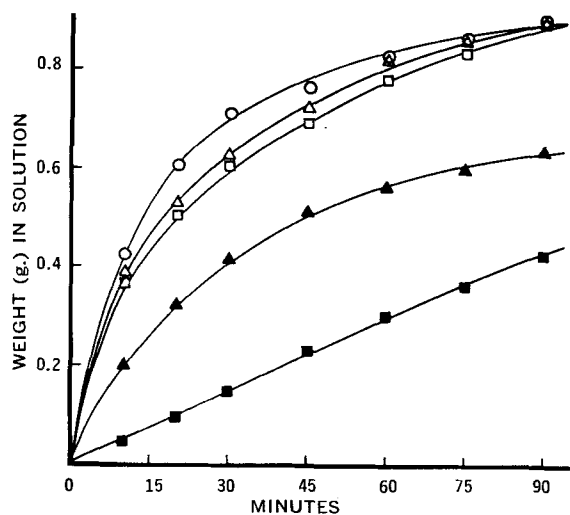

Figure 10—*Effect of particle size on dissolution of salicylic acid under sink conditions using four propellers at 30 r.p.m. and 37°. Key: O, 200/230 mesh; △, 120/140 mesh; □, 60/80 mesh; ▲, 40/60 mesh; and ■, 20/30 mesh.*

being responsible for this unusual behavior. They did not introduce the samples as suspensions, but the powders were spread over the dissolution medium. An alternative explanation for their observation might be that the powders were wetted rapidly and, under the slow rate of agitation used, were not distributed enough in the dissolution vessel to give relatively different surface areas for dissolution.

In the present studies, a lower concentration of polysorbate 80 (0.05%) was used. This low concentration is not enough to complex a major fraction of the sample used and probably does not explain the results. Since good differentiation in the dissolution rates of some powders was achieved using the same concentration (0.05%) of polysorbate 80 (Figs. 5 and 6), it would appear that some other factor is responsible for the lack of differentiation in this case. The most likely factor that would explain the lack of differentiation is the rapid settling of the powders. Figure 9 also shows relatively lower dissolution rates as compared to Fig. 6. This difference can also be explained on the basis of rapid settling and poor distribution of the powders.

Dissolution of Salicylic Acid Powders under Sink Conditions Using Additional Lower Impeller—The preceding studies on dissolution of salicylic acid powders showed that the apparatus was adequate for dissolution studies under sink conditions; however, a rank order in the dissolution rates of different particle size powders could not be obtained. The failure was probably due to a lack of mechanism to wet and disintegrate rapidly the large floating powder masses (in the case of fine powders) and to inadequate distribution of the particles in the dissolution medium. An increase of rate of agitation or prewetting of the samples also did not overcome the problems. Consideration of the previous results indicated that an additional lower impeller just below the barrier might solve these problems. A rate of agitation of 30 r.p.m. was selected on the basis of preliminary equilibrium and dissolution studies using the additional lower impeller.

Dissolution profiles of various particle size salicylic acid powders, using an additional lower impeller (Method C), are shown in Fig. 10. The profiles show a good rank order for the different particle size powders studied. The dissolution profiles do not give conventional linear rate order plots, but this is not surprising since a multiparticulate system is very complex.

Table II—Reproducibility of Dissolution Method C for the Dissolution of 120/140-Mesh Salicylic Acid Powder at 30 r.p.m. and 37°

Dissolution Time, min.	Mean Weight[a] (mg.) in Solution	SD ± mg.	Percent SD
10	392.1	9.5	2.42
20	538.0	8.0	1.48
30	632.0	15.2	2.40
45	730.8	19.6	2.68
60	828.3	26.7	3.22
75	863.0	16.8	1.94
90	891.7	18.4	2.06
		Mean =	2.31

[a] Each value is an average of six experiments.

Since these studies show a rank order for the dissolution of different particle-size powders and the studies were conducted under sink conditions using a diffusion-controlled rate of agitation, it might be possible to correlate such studies with some physiological parameter.

Since the main difference in the dissolution Methods A and C was the presence of an additional lower impeller in the latter method, the achievement of the rank order in the dissolution rates of different particle-size powders can be attributed to the effect of this impeller. This impeller runs very close (0.1 cm.) to the lower end of the sample entrance tube where it scrapes off the powders as they are introduced into the dissolution medium and distributes them evenly on the bottom and sides of the dissolution vessel. In this way, even coarser powders are not allowed to drop to the bottom in the form of small piles but are distributed relatively more widely, resulting in higher dissolution rates as compared to the rates of Method A (Figs. 5 and 6). Since the smaller particle-size powders require relatively longer times for settling, they are distributed differently and relatively more widely by the action of the lower impeller. Another very important effect of the lower impeller on very fine powders (120/140 and smaller), which tend to float, is the slight impact it has on the floating masses due to its proximity (upper edge of this impeller is 0.4 cm. below the screen). Under this gentle impact, the floating masses were rapidly disintegrated and settled evenly on the lower sides of the dissolution vessel.

Figure 10 shows that after about 80% of the sample weight has been dissolved, the dissolution profiles of finer powders converge. This could be due to the fact that in the case of very fine powders (120/140 and 200/230), some glomerates are not completely disintegrated before settling on the bottom portion of the dissolution vessel. After the major portion of the powder has been dissolved, these small glomerates remain at the bottom of the vessel and their surface area is about the same as the large-size powders. However, this does not seem to be a serious problem since it occurs after a major portion (above 80%) of the sample has been dissolved.

Although a fine powder (120/140 mesh) was used for dissolution studies with Method C as compared to a relatively coarser powder (100/120 mesh) for Method A, the comparison of the data in Tables I and II shows that Method C with an additional lower impeller is much more reproducible as compared to Method A which does not have this lower impeller. The mean percent standard deviation is more than 6 times greater than for Method C. Student's t test conducted on percent standard deviation gave the value of 15.95, which shows that Method C is significantly better than Method A even at 99.9% confidence limits. This can be explained on the basis that in the case of Method C, the lower impeller distributes the powders uniformly each time, while in its absence (Method A), the powders disintegrate and distribute in a haphazard and non-uniform fashion.

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