Dissolution of Slightly Soluble Powders under Sink Conditions III: Transport of Drug Solution across Screens and Membrane Barriers

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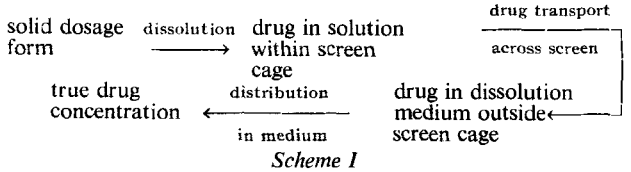
Abstract □ Transport studies were carried out with a three-compartment apparatus developed for dissolution studies of slightly soluble powders under sink conditions. Effects of different pore-size screens and membrane barriers, propeller placement, and rate of agitation were investigated. Experiments were also carried out to study the effect of temperature and the presence of polysorbate 80 in the dissolution medium. Screens and barriers proved to be potential hindrances to the transport of drug molecules in solution. Increases in the barrier pore size and rate of agitation decreased the time for development of equilibrium across the barriers. The presence of an additional impeller, above and close to the barrier, was found to be much more effective than rate of agitation alone. An increase in the temperature of the system also lowered the equilibrium time, while the presence of polysorbate 80 in the dissolution medium increased the time for equilibration.

Keyphrases □ Powders, slightly soluble—dissolution, sink conditions □ Dissolution, slightly soluble powders—sink conditions □ Drug transport, screens, membrane barriers—effect of impeller, agitation, temperature, polysorbate 80

The development of an apparatus to study the dissolution kinetics of slightly soluble powders under sink conditions was the subject of a prior report from this laboratory (1), and dissolution studies were carried out on salicylic acid and griseofulvin powders (1, 2). The dissolution apparatus was designed on the assumption that if a screen or membrane barrier was placed in the dissolution medium below the interface and the sample under study was introduced below this barrier, then, if flotation occurred, the sample would not come in contact with the organic phase. Assemblies recently were reported (3, 4) which utilize screens in their construction, and USP XVIII (5) and NF XIII (6) recommended one such assembly for dissolution testing.

In dissolution studies using such assemblies, the drug first dissolves from the dosage form into the surrounding dissolution medium which is caged by the screen. The drug molecules then pass from the caged area into the remaining bulk of dissolution medium. The dissolution of the dosage form is determined by testing the drug concentration in the medium outside the screen. The sequence of steps involved in such dissolution studies is shown in Scheme I.

To detect any dissolution from the dosage form, the drug molecules must cross the screen after dissolution takes place in the immediate surrounding medium. The screens could possibly create hindrances to the



Scheme I

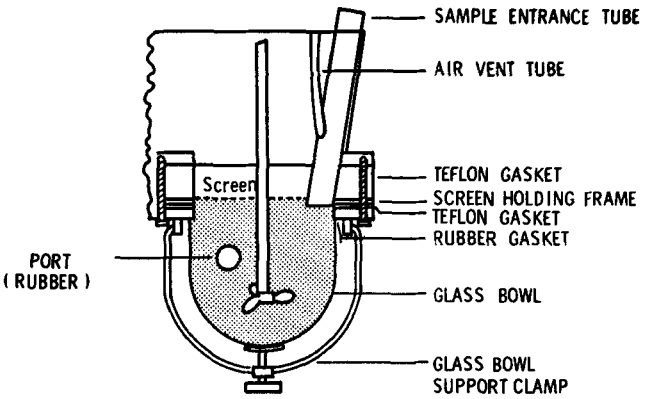


Figure 1—*Apparatus for transport studies (taken in part from Fig. 1,* Reference 1).

passage of drug molecules across them. The presence of such screens in dissolution assemblies could, therefore, be rate limiting if the drug transport problems are not solved properly. Preliminary studies using the earlier reported apparatus (1) showed that screens do, in fact, create a barrier to the transport of drug across them. Recently there was a report (7) about the reproducibility problem in using the USP apparatus (5). The problems were attributed to the slight bends in the shafts which result in additional vibrations. These vibrations could possibly affect the transport phase more than the dissolution phase in the dissolution scheme.

Any factors that would affect the transport of drug molecules through the screens could possibly affect the resultant dissolution rate. Factors such as screen mesh size, number and type of propellers, rate of agitation, temperature, and presence of surfactant in the dissolution medium could be quite critical for drug transport in the dissolution assemblies.

This report is concerned with the experiments conducted to investigate such factors in the three-compartment apparatus reported earlier (1, 2) and to demonstrate how the transport problem is circumvented by mechanical modifications of the dissolution apparatus which allow equilibrium to be established rapidly.

EXPERIMENTAL

Chemicals and Materials—The salicylic acid was USP grade[1]; polysorbate 80 also was used[2]. The other chemicals were reagent or certified ACS grade.

The various screens and filter membranes used in this study are listed in Table I.

Apparatus and Studies—The dissolution apparatus was described in detail in a previous paper (1). The transport study assembly con-

[1] Obtained from Fisher Scientific Co.
[2] Atlas Chemical Co.

Table I—List of Screens and Filter Membranes Used in Transport Studies

Mesh Size or Membrane Code	Pore Size, μ	Wire Diameter, μ	Material	Type
160[a]	96.50	63.50	Stainless steel	Plain
180[a]	83.80	58.42	Stainless steel	Plain
200[a]	68.60	58.42	Stainless steel	Twilled
Acropor AN-3000[b]	3.00	—	Acryl polyvinylchloride	Nylon cloth, reinforced
Acropor AN-800[b]	0.80	—	Acryl polyvinylchloride	Nylon cloth, reinforced
Acropor AN-450[b]	0.45	—	Acryl polyvinylchloride	Nylon cloth, reinforced

[a] Cambridge Wire Cloth Co. [b] Gelman Instrument Co.

sisted of the right-hand portion of the dissolution apparatus (Fig. 1). One or two propellers were attached to the stirrer shaft. A three-blade propeller, 3.8 cm. in diameter, was positioned 2.2 cm. from the bottom of the glass bowl in Compartment A. A three-blade turbine impeller, 6.0 cm. in diameter, was attached 0.2 cm. above the barrier.

The apparatus was immersed in a constant-temperature bath adjusted to 37.0°. A 455.0-ml. volume of 7.24×10^{-3} M (0.1%) salicylic acid solution in distilled water (previously equilibrated at 37.0°) was gently poured into Compartment A through the sample entrance tube with the help of a long-stem, 500-ml. separator[3]. This volume was just enough to fill the openings of the screen or filter. A 145.0-ml. volume of distilled water (previously equilibrated at 37.0°) was poured on the top of the screen or membrane using a liquid diffusion apparatus (Fig. 2).

The liquid diffusion apparatus consisted of a 1.2-cm. gas dispersion tube with fritted cylinder. The upper portion was formed into a funnel; the bottom, but not the sides, of the porous portion of the tube was flame sealed. The use of this apparatus prevented any appreciable disturbance of the solution beneath the barrier. The stirrer, previously set at the desired speed, was started, and 1.0-ml samples were removed from the solution above the screen at appropriate intervals. The samples were diluted with distilled water and assayed spectrophotometrically at 297 nm. using a Beckman DU-2 spectrophotometer. A volume of distilled water (37.0°) equal to the sample volume was added immediately after each sampling. From the concentration of salicylic acid in the samples, the percent of equilibrium concentration (5.49×10^{-3} M) was calculated as a function of time.

Using this procedure, the effects of propeller(s) and their placement, agitation, screen or membrane pore size, and a surfactant (polysorbate 80) were studied. Several experiments were also carried out at 25.0°.

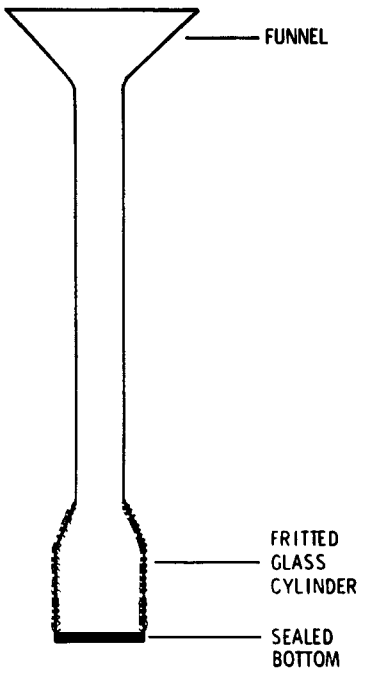


Figure 2—*Liquid diffusion apparatus.*

[3] 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.

RESULTS AND DISCUSSION

Effect of Barriers on Development of Equilibrium—Equilibrium studies with salicylic acid solutions (Fig. 3) showed that the screens and membranes, if placed in the dissolution medium, create a substantial barrier to the transport of drugs through the medium. The pore size of these barriers seems to have a direct relationship to the time needed for the required equilibrium to be established. Data in Fig. 4 show a log linear relationship between pore size and t_{30} (time for 30% equilibrium); however, there does not appear to be a

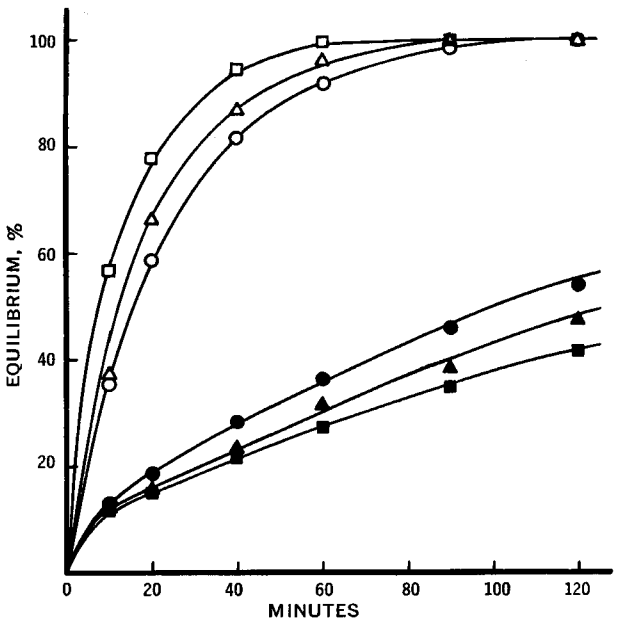


Figure 3—*Effect of screen mesh size or membrane pore diameter on the development of an equilibrium of salicylic acid solution at 55 r.p.m. and 37°. Key: □, 160 mesh; △, 180 mesh; ○, 200 mesh; ●, 3.0 μ; ▲, 0.8 μ; and ■, 0.45 μ.*

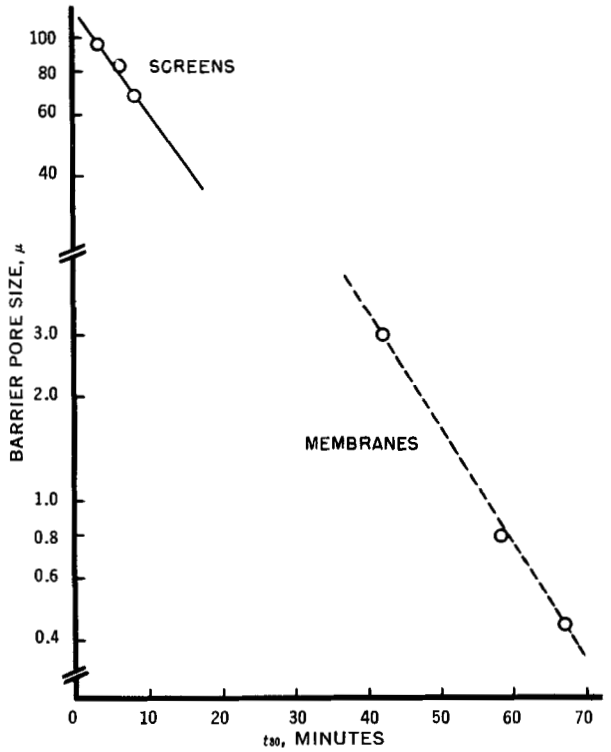


Figure 4—*Plots of logarithm of barrier pore size* versus *logarithm of* t_{30} *for the development of an equilibrium of salicylic acid solution at 55 r.p.m. and 37°. The* t_{30} *values were obtained from Fig. 3.*

direct linear relationship between the data obtained for the screens and the membrane barriers (*i.e.*, the lines when extrapolated do not meet). The slope for the screen curve was slightly less than the slope for the membrane barrier curve. These discrepancies could be due to relatively different amounts of open areas in screens and membrane barriers. The t_{30} values were used since the slow equilibrium times with the membrane barriers did not allow higher t values, common to both screens and membrane barriers, to be obtained.

Effect of Agitation on Development of Equilibrium—Agitation also seems to be a rate-limiting factor for the development of equilibrium. As expected, the equilibrium time for salicylic acid decreased with an increase in the rate of agitation (Fig. 5). This result was probably due to the increased circulation of the solution through the barrier pores under an increased rate of agitation. Figure 5 shows that it takes more than 1 hr. for equilibrium to be achieved across a 200-mesh screen at 25° even at 100 r.p.m. Under these conditions, it apparently would not be possible to develop a rapid equilibrium using high rates of agitation for these diffusion-controlled dissolution studies.

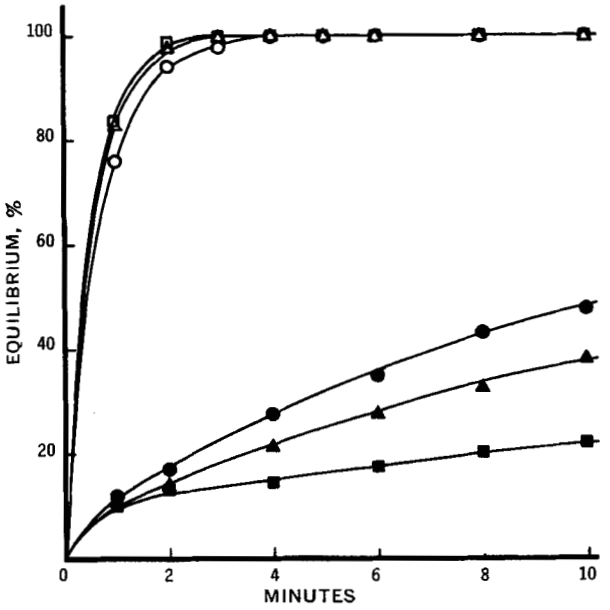


Figure 6—*Effect of an additional top impeller on the development of an equilibrium of salicylic acid solution across different barriers at 55 r.p.m. and 37°. Key: □, 160 mesh; △, 180 mesh; ○, 200 mesh; ●, 3.0 μ; ▲, 0.8 μ; and ■, 0.45 μ.*

Effect of Additional Top Impeller on Development of Equilibrium—The use of an additional impeller attached to the stirrer shaft above and close to the barriers caused equilibrium to be established rapidly (Fig. 6). With the screens used, which had relatively large pore sizes, it was possible to develop equilibrium in a reasonably short period (less than 4 min.). Although the development of equilibrium was

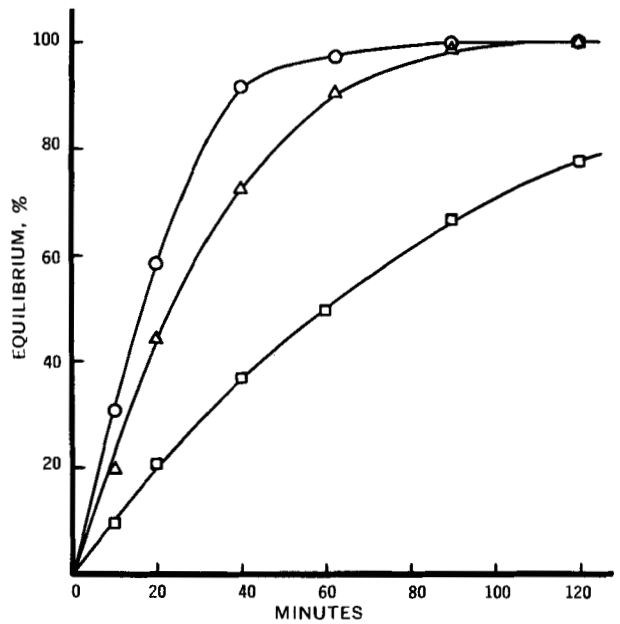


Figure 5—*Effect of agitation on the development of equilibrium of salicylic acid solution across a 200-mesh screen at 25°. Key: ○, 100 r.p.m.; △, 75 r.p.m.; and □, 55 r.p.m.*

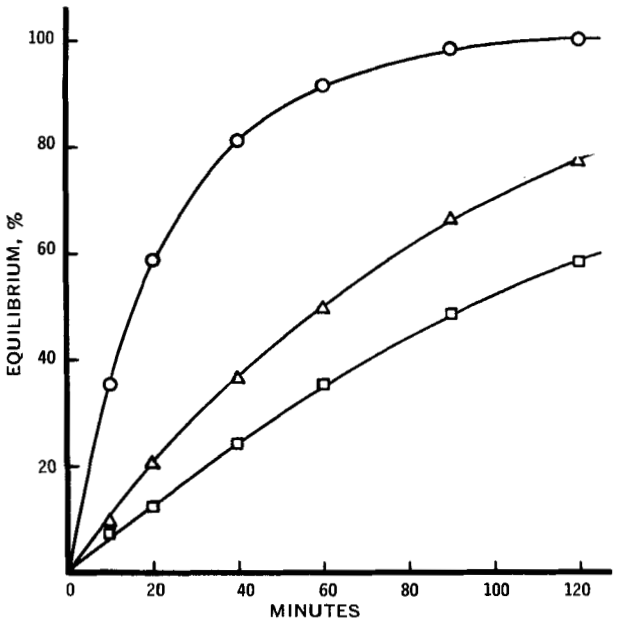


Figure 7—*Effect of temperature and polysorbate 80 on the development of an equilibrium of salicylic acid solution across a 200-mesh screen at 55 r.p.m. Key: ○, without polysorbate 80 at 37°; △, without polysorbate 80 at 25°; and □, with polysorbate 80 (0.05%) at 25°.*

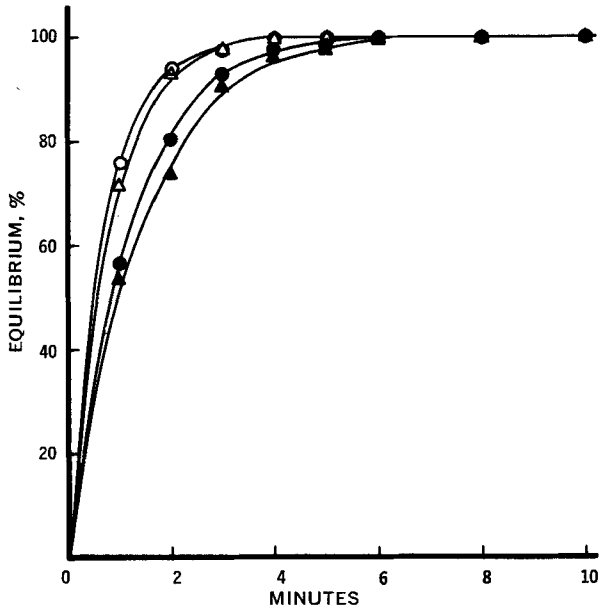


Figure 8—*Effect of temperature and polysorbate 80 (0.05%) on the development of an equilibrium of salicylic acid across a 200-mesh screen using an additional top impeller at 55 r.p.m. Key:* ○, *without polysorbate 80 at 37°;* △, *with polysorbate 80 at 37°;* ●, *without polysorbate 80 at 25°; and* ▲, *with polysorbate 80 at 25°.*

very rapid using screen barriers, the effect of barrier pore size was observed, with the 200-mesh screen effecting a slightly longer equilibrium time than the smaller mesh number screens. Although salicylic acid solution transport was also faster than it was without the additional impeller in the case of membrane barriers, equilibrium was not established rapidly; therefore, these membrane barriers would not be suitable for dissolution studies. Even a 3.0-μ pore-size membrane allowed only about 48% equilibrium in 10 min. and would be a rate-limiting factor in dissolution studies. It appears that a 200-mesh screen would be an appropriate barrier for further dissolution studies, using an additional top impeller.

The very rapid equilibrium in the presence of an additional top impeller must be due to the creation of an increased upward circulation of the solution, which overcomes hindrance created by the barrier to the movement of the drug solution across the screen openings.

Effect of Temperature and Polysorbate 80 on Development of Equilibrium—Temperature seems to have a substantial effect on the development of equilibrium (Fig. 7). Equilibrium time decreases with an increase in temperature. This result might be due to several factors. With an increase in temperature, there is increased molecular motion in the solution and greater probability for the drug solution to pass through the barrier pores and result in a faster development of equilibrium. As the temperature increases, the viscosity of the solution decreases, allowing easier circulation of the solution through the barrier pores. Since some heat of activation is also required to cross the barriers, an increase in temperature could facilitate the transport of the drug molecules across the barriers.

The presence of polysorbate 80 in the solution shows an adverse effect on the development of equilibrium (Fig. 7). This might be due to micelle formation of the surfactant. These micelles could create hindrance to the free molecular motion and result in an increased equilibrium time. Another factor could be due to the possible entrapment of the drug molecules in the micelles, which decreases the kinetic displacement of the molecules and, therefore, decreases the effective diffusion rate of these molecules.

The effect of temperature on the development of equilibrium can be seen even in the presence of the additional top impeller (Fig. 8). However, the transport rate of salicylic acid solution is not appreciably affected by the polysorbate 80 when the top impeller is used.

SUMMARY

1. The presence of barriers in the dissolution medium was found to be rate limiting in the establishment of a drug equilibrium between phases. The pore size of these barriers was established as the rate-limiting factor, and a linear relationship was shown between t_{30} for equilibrium and the barrier pore size.

2. An additional impeller was used above the barrier to develop rapid equilibrium. It was demonstrated that a 200-mesh screen is quite suitable as a barrier when this additional top impeller is used.

3. Agitation, temperature, and polysorbate 80 were found to be rate limiting for the development of an equilibrium. However, it was shown that in the presence of an additional top impeller, the presence of polysorbate 80 (0.05%) in the dissolution medium did not appreciably affect the equilibrium time.

REFERENCES

(1) I. Ullah and D. E. Cadwallader, *J. Pharm. Sci.*, **59**, 979 (1970).

(2) *Ibid.*, **60**, 230(1971).

(3) G. Levy, *J. Pharm. Sci.*, **52**, 1039(1963).

(4) M. Pernarowski, W. Woo, and O. Searl, *ibid.*, **57**, 1419(1968).

(5) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 934.

(6) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 802.

(7) P. J. Weiss, *Drug Cosmet. Ind.*, **107**, 50(1970).

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