Dissolution Rate Studies II

Dissolution of Particles Under Conditions of Rapid Agitation.

By P. J. NIEBERGALL,† G. MILOSOVICH, and J. E. GOYAN

Dissolution data for sized fractions of three different compounds were obtained using the method of Niebergall and Goyan. The Hixon-Crowell "cube root law" did not describe the data. Deviation from this law was accounted for by deriving a rate expression assuming that the thickness of the diffusion layer was proportional to the square root of the mean volume diameter. Experiments were performed to verify the applicability of the equation so derived.

NOYES AND WHITNEY (1) were the first to report a differential equation relating the rate of dissolution of solid solute to concentration of dissolved solute in the surrounding solvent

$$\frac{dC}{dt} = K(C_s - C) \qquad \text{(Eq. 1)}$$

The rate constant, K, contains several variables which have been the subject of study by succeeding workers. While Noyes and Whitney assumed that the rate would be proportional to surface, it was Brunner and St. Tolloczko (2–5) who showed this dependence and also that K depended upon temperature and rate of stirring. Nernst (6) considered dissolution as a special case of heterogeneous reaction and suggested that Eq. 1 could be written

$$\frac{dC}{dt} = \frac{DA}{V\delta} (C_s - C) \qquad \text{(Eq. 2)}$$

where: D = diffusion coefficient; A = area of the interface; V = volume of solvent; and δ = thickness of a stagnant film of solvent on the solid surface. Brunner (7) showed this rate dependence on the diffusion constant and presented data to show that K was also proportional to (stirring rate)$^{2/3}$.

The Nernst-Brunner layer has been the subject of controversy over the years but, as pointed out by King (8), it is not necessary to the theory that the layer be stagnant on the solid surface. Perhaps the Nernst-Brunner layer may be identical with a hydrodynamic boundary which, rather than being stagnant, merely reflects a velocity gradient between the bulk fluid and the surface of the solid.

In many dissolution studies conditions are

chosen such that $DA/V\delta$ remains essentially constant during the experiment. This is accomplished by using single large particles such as compressed tablets or crystal masses grown from the melt. The fraction of the particle which dissolves is so small that surface can be assumed constant as long as the particle remains intact. The thickness of the Nernst-Brunner layer is kept constant by maintaining the position of the particle with respect to the stirrer. When dissolution from powders is studied these conditions may not be obtained. Thus, both surface area and rate of shear on the particles may be expected to change during an experiment.

Hixon and Crowell (9) considered the change in surface as small particles dissolve. They pointed out that the surface area of a particle was proportional to its weight to the $^{2}/_{3}$ power, the proportionality constant being composed of density and volume shape factor. If the shape factor remains constant as the particle dissolves the substitution of $W^{2/3}$ for A in Eq. 2 can be made. Then, under the condition that $C_s >> C$ and D, V and δ are constant, the equation can be integrated to give

$$W_o^{1/3} - W_t^{1/3} = kt \qquad \text{(Eq. 3)}$$

where: W_o is the initial weight of solute, W_t is the weight at time t. Equation 3 may also be written

$$W_o^{1/3} - W_t^{1/3} = \frac{k' N^{1/3} D C_s t}{\delta} \qquad \text{(Eq. 4)}$$

for N particles, where k' is a constant containing surface and volume shape factors and particle density. The validity of Eqs. 3 and 4 depend on the constancy of k and k'. Shape factors for cubic or spherical particles will remain constant as long as the particles dissolve equally from all sides. This is not true for other particle shapes, and the equations would not be expected to hold for nonequant habits after dissolution has occurred.

While δ was ignored or assumed constant by Hixon and Crowell, inspection of their data (10) shows that their rate constants increased as dissolution proceeded. Since they were working with cubic salt crystals, this drift probably was not due to shape-factor effects. It could be due, however, to a δ dependence on particle size.

Wilhelm, *et al.* (11), reported an empirical relationship between δ and particle size

$$\frac{D}{\delta} = f(d^{1/4})$$

where the symbols have their usual meaning. Their results, however, predict that the Hixon-Crowell rate constant would decrease with dissolution.

This effect has also been reported in studies on crystal growth (12) under diffusion control. McCabe and Stevens (13) verified that the cube root law applies for growth of various sized crystals under conditions of constant shear. On this basis they postulated that larger crystals grow faster because of a thinner Nernst-Brunner layer due to greater shear imposed on the larger particles in a slowly stirred system. This leads to the analogous situation of dissolution, *i.e.*, larger particles dissolving faster because of thinner diffusion layer.

Thus, a review of the literature indicates that the dissolution process for small particles is still not theoretically well defined. It is most apparent that the influence of agitation is important, yet the effect of various degrees of agitation is still unanswered. Certainly, if larger particles dissolve faster under conditions of agitation present in the intestinal tract, one must question the practice of reducing size to
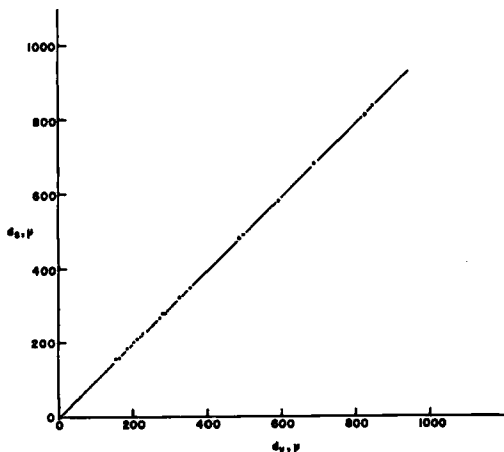
effect faster dissolution of drug particles for oral dosage.

This paper reports the initial investigation on the effect of stirring on the dissolution process for small particles. It was the objective of this study to test the applicability of the cube root law to dissolution of particles moving freely in rapidly stirred systems.

EXPERIMENTAL[1]

The continuous recording spectrophotometric procedure described by Niebergall and Goyan (14) was used in this study with one modification. The pump introduced a considerable amount of heat into the solution and made temperature control in the dissolution vessel inadequate. It was decided, therefore, to collect the returning solution in a graduated cylinder. It was then necessary to make corrections for volume changes and loss of solute to the cylinder. These corrections were simplified by the fact that the concentration in the dissolution

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[1] Equation 5 is more correctly written

$$W_o - W_t = C_t\,[V_o - ft] + \int_0^t \frac{dC_t}{dt}\,ft\,dt \quad \text{(Eq. 6)}$$

which is equivalent to

$$CV_o = C_t\,[V_o - ft] + f\int_0^t \frac{dC_t}{dt}\,t\,dt \quad \text{(Eq. 7)}$$

Differentiating Eq. 7 with respect to time

$$V_o\frac{dC}{dt} = [V_o - ft]\frac{dC_t}{dt} - f\,C_t + f\,t\,\frac{dC_t}{dt}$$

$$= V_o\frac{dC_t}{dt} - C_t$$

and

$$\frac{dC_t}{dt} = \frac{dC}{dt} + \frac{fC_t}{V_o} \quad \text{(Eq. 8)}$$

Now, squaring Eq. 14 and rearranging gives

$$W_o - W_t = 2\,W_o^{1/2}\,k''N^{1/2}t - (k'')^2Nt^2$$

or

$$C\,V_o = 2\,W_o^{1/2}k''N^{1/2}t - (k'')^2Nt^2$$

Thus,

$$\frac{dC}{dt} = \frac{2\,W_o^{1/2}k''N^{1/2}}{V_o} - \frac{2(k'')^2Nt}{V_o} \quad \text{(Eq. 9)}$$

Combining Eqs. 8 and 9 gives

$$\frac{dC_t}{dt} = \frac{2\,W_o^{1/2}k''N^{1/2}}{V_o} - \frac{2(k'')^2Nt}{V_o} + \frac{fC_t}{V_o} \quad \text{(Eq. 10)}$$

Under the experimental condition that

$$2\,(k'')^2Nt = f\,C_t$$

dC_t/dt would be constant and a plot of C_t *versus* time would be linear. If f is approximately constant as was the case in these experiments, a linear plot would be expected only in the case where

$$\left(\text{Since } C_t = \int_0^t \frac{2W_o^{1/2}\,k''N^{1/2}}{V_o}\right)$$

However, at the relatively small t and C_t values and the average flow rate used in this study, the deviation from linearity is negligible. Nonlinear plots were evident only with the smallest size materials and in these cases the corrections were made using Eq. 7 and graphical integration.

Note that data giving a linear C_t *vs.* t plot may not necessarily be described by Eq. 14, nor will data fitting Eq. 14 necessarily give linear C_t *vs.* t plots. The results reported in this paper were obtained under a fortuitous choice of experimental conditions which gave good correlation between Eqs. 5 and 14.

Fig. 1.—Plot of mean surface diameter *vs.* mean volume diameter for all sized fractions used in this study. Slope = 0.99.

vessel increased linearly with time. The amount of solute dissolved in time, t, is then given as

$$W_o - W_t = C_t(V_o - ft) + \tfrac{1}{2}kft^2 \quad \text{(Eq. 5)}$$

where: C_t = concentration in the vessel at time, t; V_o = initial volume in the vessel; f = flow rate determined by timing the flow into the cylinder; and $k = dC_t/dt$, obtained by plotting concentration against time.

After this modification was made, continuous temperature recording using a thermistor in a wheatstone bridge circuit and a Varian strip-chart recorder showed a maximum temperature variation of $-0.1°$.

The three materials used in this study were selected on the basis of solid state, particle shape, and suitable spectral curves. Potassium dichromate (absorption minimum 317.5 mμ) reagent grade was obtained as equant triclinic prisms. Salicylamide U.S.P. (absorption minimum 262.5 mμ) was spray-congealed to obtain spherical aggregates of microcrystals. Potassium ferricyanide (absorption minimum 418 mμ) reagent grade was obtained as equant rectangular prisms (maximum length to width ratio of about 1.5) with rounded edges. While the latter particles were not as symmetrical as the others it was felt that for the size ranges used the amount of dissolution required for a determination would not significantly alter the shape factor. These materials were sieved three times to obtain sized fractions in which particle sizes were then determined microscopically. Figure 1 is a plot of d_s against d_v, and shows by its slope (0.99) that these fractions were essentially monodisperse (monodisperse slope = 1.00). Size data is presented in Table I.

The solvent selected for these three materials was 50% v/v aqueous ethanol, 750 ml. being used in each run. This solvent was chosen because it wetted the particles and was not a "good" solvent for these compounds (solubility $\sim$2–4%). One-gram samples of each size fraction were used and the stirrer was operated at 500 r.p.m. This speed was chosen as being rapid enough to insure complete suspension of the particles, instantaneous mixing, and representative sampling, yet slow enough that the dissolution process was diffusion controlled. This is seen in the plot of rate constant against r.p.m. in Fig. 2.
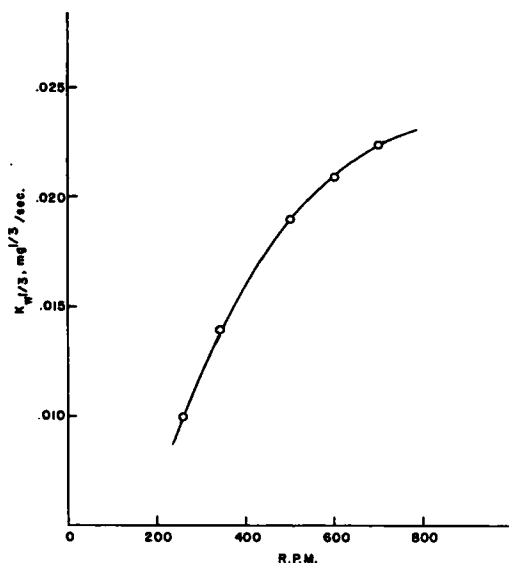

Fig. 2.—Effect of stirrer r.p.m. on the Hixon-Crowell rate constant for dissolution of 681μ potassium dichromate. Complete suspension of particles at 400 r.p.m. T = 24.8°.

The data were plotted initially as $\Delta W^{1/3}$ vs. t and good straight lines were obtained in all cases. The slopes of these lines would then be equal to $(k'N^{1/3}DC_s)/\delta$ as seen from Eq. 4 and are given as $k_w^{1/3}$ in Table I. Since linear plots were obtained, even though particle size changed with time, it would appear that δ does not depend on size. To test this further, the rate constants for different sized fractions were plotted against the reciprocal of the respective mean volume diameters. The expected linear relationship was not obtained. A logarithmic plot of rate constant vs. d_v showed for all the materials that the rate constant depended on $d_v^{-3/2}$, Fig. 3.

One way that this relationship may be obtained from Eq. 4 is to set δ proportional to $d_v^{1/2}$. Equation 4 can then be modified as follows:

TABLE I.—SIZE DATA AND DISSOLUTION RATE CONSTANTS FOR THE THREE MATERIALS USED IN THIS STUDY

Material	Screen Size	d_s, μ	d_v	$K_w^{1/3}$, mg.$^{1/3}$/sec.	$K_w^{1/2}$, mg.$^{1/2}$/sec.
Spray-congealed salicylamide, 24.8°	50–60	278	281	0.108	0.482
	60–70	227	230	0.157	0.691
	70–80	208	211	0.172	0.750
	80–100	184	187	0.206	0.880
	100–140	158	159	0.245	1.02
Potassium dichromate, 23.4°	20–30	838	846	0.0063	0.030
	30–40	681	686	0.0088	0.042
	40–50	482	489	0.0122	0.056
	50–70	322	326	0.0246	0.113
	70–100	269	272	0.0363	0.163
	100–140	209	213	0.0503	0.230
	140–200	159	164	0.0713	0.330
Potassium ferricyanide, 23.4°	20–30	814	829	0.023	0.110
	30–40	581	592	0.035	0.187
	40–50	490	500	0.049	0.220
	50–70	349	355	0.080	0.347
	70–100	280	288	0.112	0.503
	100–140	201	207	0.209	0.890

$$-\frac{dW}{dt} = \frac{3k'N^{1/3}DC_sW^{2/3}}{\delta} \quad \text{(Eq. 11)}$$

since $d_v{}^3 = \dfrac{W}{\alpha_vN}$, α_v being the volume shape factor

$$\delta = k\, d_v{}^{1/2} = \frac{k\, W^{1/6}}{\alpha_v{}^{1/6}N^{1/6}} \quad \text{(Eq. 12)}$$

combining Eqs. 11 and 12

$$-\frac{dW}{dt} = \frac{3k'\alpha_v{}^{1/6}N^{1/2}DC_sW^{1/2}}{k} \quad \text{(Eq. 13)}$$

which upon integration gives

$$W_o{}^{1/2} - W_t{}^{1/2} = k''N^{1/2}t \quad \text{(Eq. 14)}$$
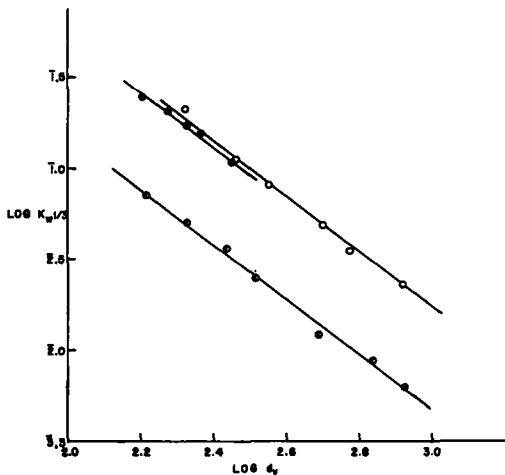
where

$$k'' = \frac{3k'\alpha_v{}^{1/6}DC_s}{2k}$$

Fig. 3.—Dependency of log initial Hixon-Crowell rate constants on log initial mean volume diameter. Lines have slope of -1.5. —O—O— potassium ferricyanide, 23.4°; —●—●— spray-congealed salicylamide, 24.8°; —◑—◑— potassium dichromate, 23.4°.
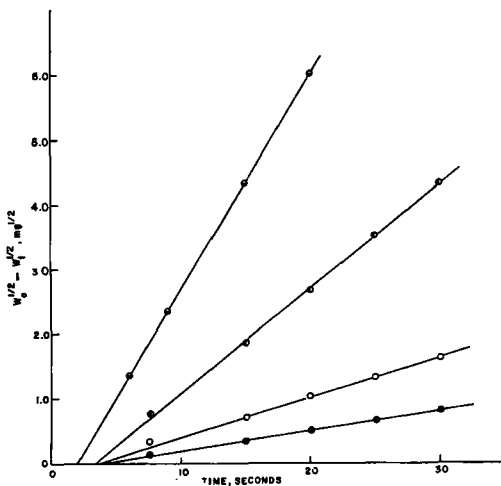

Fig. 4.—Typical dissolution data for potassium dichromate plotted according to Eq. 14. T = 23.4°. ◐— 164μ, ◑— 272μ, O— 489μ, ●— 846μ.

All of the data were replotted as $\Delta W^{1/2}$ vs. t according to Eq. 14 and were found to be described by this equation even better than by Eq. 4. Figure 4 shows typical data plots of Eq. 14. These rate constants are listed in Table I as $K_w{}^{1/2}$.

Figure 5 is a model plot of fraction initial diameter against time calculated from Eqs. 4 and 14. It is seen from Fig. 5 that appreciable deviation from the cube root law is not encountered until dissolution has progressed to a region where $d_t \sim 0.6\,d_v$ or 80% of the particle has dissolved. This explains why Eq. 4 described the data within a run but did not correlate data between runs of sufficiently different size material.

As additional tests of Eq. 14, two experiments were run. From Eq. 14 it may be seen that the rate constant depends on the square root of the total number of particles. Since N is proportional to weight, aqueous dissolution rate constants were determined for different initial weights of a single size fraction of crystalline salicylamide (needle habit). Figure 6 shows a plot of $k_w{}^{1/2}$ against $W_o{}^{1/2}$ and shows by its linearity that Eq. 14 is valid.

The number of particles can be kept constant for different size fractions by calculating equivalent weights from the size data. When this is done the rate constant given by Eq. 14 should be independent of size while the constant given by Eq. 4 would be independent of size only if δ were constant. Table II gives data obtained from dissolution runs on samples of potassium dichromate in which the number of particles was kept constant.

It can be seen from the data in Table II that $k_w{}^{1/2}$ is constant but that $k_w{}^{1/3}$ increases as particle size is decreased. The most exacting test of the experimental method and Eq. 14 would be their ability to describe the complete dissolution curve. One run was made using 0.1000 Gm. of 140–200 mesh potassium dichromate in the previous experiment. In this system the particles completely dissolved to give a solution which could still be assayed directly in the instrument. Figure 7 compares the experimental data using the Hixon-Crowell $\Delta W^{1/3}$ plot and the $\Delta W^{1/2}$ plot derived above.
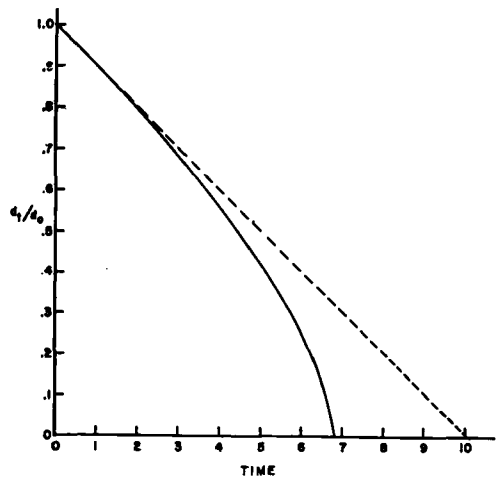

Fig. 5.—Hypothetical plot of the ratio of diameter at time, t, to initial diameter vs. time. ——— calculated from Eq. 4. – – – – calculated from Eq. 14.
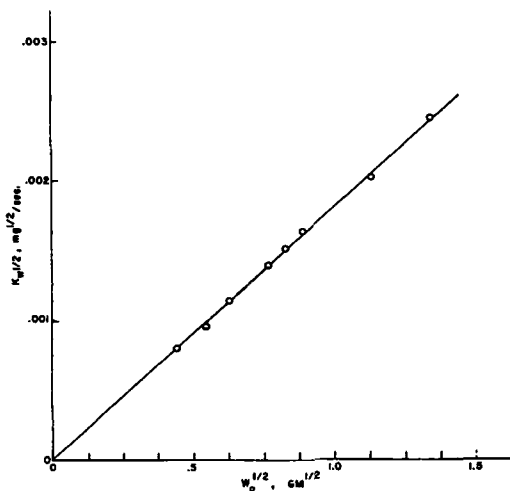
Fig. 6.—Dependency of the rate constant from Eq. 14 on the square root of the initial weight of salicylamide needles. Dissolution in water at 23.4°.

TABLE II.—DISSOLUTION RATE CONSTANTS FROM EQUAL NUMBERS OF POTASSIUM DICHROMATE PARTICLES OF DIFFERENT SIZES[a]

d_v, μ	W_o, Gm.	$K_{w}^{1/3}$, mg.$^{1/3}$/sec.	$K_{w}^{1/2}$, mg.$^{1/2}$/sec.
846	13.6292	0.017	0.13
686	7.8053	0.021	0.14
489	2.6407	0.024	0.13
326	0.7810	0.027	0.13
272	0.4560	0.032	0.13
213	0.2181	0.042	0.13
164	0.1000	0.044	0.12

[a] At 25°.

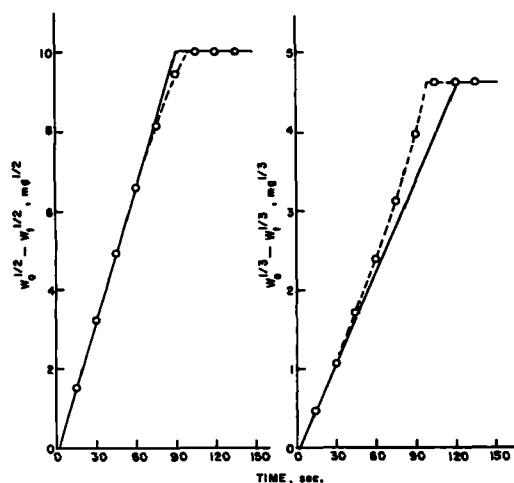Fig. 7.—Comparison of the ability of Eqs. 14 and 4 to describe the complete dissolution curve for 164μ potassium dichromate. T = 25.0°. – – – – experimental line, ——— line calculated from data obtained in the first 30 seconds.

As seen in Fig. 7 neither equation exactly described the data over the complete run. While the results from the $\Delta\Pi^{-1/3}$ plot cannot be explained at this time unless the δ dependency is accepted, there is a valid reason for the deviation in the $\Delta W^{1/2}$ plot. At the point where deviation first occurs, 96% of the material has dissolved and it is not unreasonable to expect that the smaller particles are disappearing. Thus, N would no longer be constant and the curve would be expected to fall off as shown. It was also of interest to note in this run that the final three data points showed that exactly 0.100 Gm. of potassium dichromate had dissolved. This indicates the accuracy of dissolution data obtained with the apparatus.

DISCUSSION

The data obtained in this study clearly show that the cube root law does not describe dissolution of particles under the degree of agitation used. The data were described by an equation derived by making the assumption that δ was proportional to $d_v^{1/2}$. It might be expected that such a simple relationship between δ and d_v should be derivable on a theoretical basis. This type of mathematical treatment has been well developed for flow past a flat surface, but it is generally conceded that flow past a sphere is so complicated that mathematical handling is impossible (15). Solving the Prandtl boundary layer equations for flow past a flat surface result in the relationship (16)

$$\delta = k \frac{L^{1/2}}{v^{1/2}} \qquad \text{(Eq. 15)}$$

where L = the length of the surface in the direction of flow, v = the approach velocity of the flowing liquid. Thus, in the system studied one might expect that the larger particles would be subjected to greater flow velocities as postulated by McCabe and Stevens, but, on the other hand, that their surface dimensions would be larger. These two effects are in opposition as seen from Eq. 15. Certainly, direct measurement of the diffusion layer and correlation of factors affecting it would contribute significantly to the complete understanding of particle dissolution. Until such information is available the possible nonconstancy of δ as dissolution proceeds must be considered in the treatment of particle dissolution data.

SUMMARY

1. Dissolution data for different size fractions of three different compounds were obtained.

2. The data were described by an equation derived on the assumption that the thickness of the diffusion layer was proportional to the square root of the mean volume diameter.

3. Experiments designed to test the equation showed that it was valid under the conditions of study.

4. The applicability of the method of Niebergall and Goyan to dissolution studies was demonstrated.

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Stability of Antibacterial Preservatives in Parenteral Solutions   III

Relationship Between Chemical Loss and Microbiological Activity in Multiple-Dose Vials

By L. LACHMAN, S. WEINSTEIN, T. URBANYI, E. EBERSOLD, and J. COOPER

The loss of preservative content due to degradation in solution and absorption by rubber stoppers was studied by chemical and microbiological analytical methods. The preservatives investigated were chlorobutanol and *p*-chloro-β-phenylethyl alcohol in conjunction with neoprene rubber stoppers. The contribution of rubber extractives and preservative degradation products towards enhanced antimicrobial activity is discussed.

THE LOSS of preservatives from solution due to degradation or absorption by rubber stoppers has been determined by chemical (1–4) and microbiological (4–6) methods. However, there are no reports in the literature quantitatively comparing the loss of preservative as determined chemically and microbiologically. This lack of information can be ascribed to two major factors: (*a*) the time consuming and cumbersome characteristics of microbiological procedures and (*b*) the fact that existing microbiological assay methods have not been of sufficient accuracy or precision to permit valid comparisons.

In a previous investigation (7) a turbidimetric microbiological assay method was described for chlorobutanol and *p*-chloro-β-phenylethyl alcohol. This would now permit a valid correlation between chemical and microbiological determinations of preservative content.

Because of the techniques employed in the manufacture of rubber stock to be used for molding rubber stoppers, it is not uncommon for the rubber to contain appreciable amounts of unreacted accelerators, activators, and antioxidants. It has been recognized that these unreacted materials, as well as certain reaction products (8–12), can be extracted by solutions coming in

contact with the stopper. These materials have been shown to exert deleterious effects on active ingredients (13) and antibacterial agents (10) in injectable solutions.

In this study the influence of rubber closure extractives on the microbiological activity of the preservatives chlorobutanol and *p*-chloro-β-phenylethyl alcohol in vial solutions buffered to a pH 4 and stoppered with neoprene closures was determined. In addition, the contribution of preservative degradation products to antibacterial activity was ascertained. These two preservatives were chosen for study because chlorobutanol is representative of one which degrades in solution as well as being absorbed by the closure, whereas *p*-chloro-β-phenylethyl alcohol is representative of a preservative which essentially undergoes no degradation for the duration of study but which is lost from solution by absorption into the closure. Analyses for residual preservative content were performed both chemically and microbiologically and the results compared to determine whether rubber extractives or preservative degradation products influence the microbiological determinations.

EXPERIMENTAL

Materials.—0.275 M solution of citric acid–sodium phosphate buffer of pH 4.0; *p*-chloro-β-phenylethyl alcohol, Ciba, b.p. 80–83° at 1.07 mm; chlorobutanol, anhydrous U.S.P.; neoprene poly-