

# Investigation of Drug Release from Solids V

## Simultaneous Influence of Adsorption and Viscosity on the Dissolution Rate

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The simultaneous influence of several factors including chemical reaction, adsorption, and viscosity on the dissolution rate of a slightly-soluble acidic solid was investigated using bentonite, a montmorillonite clay. Adsorption isotherms, determined by a dialysis procedure, were developed for a benzoic acid and bentonite system. The viscosity of various bentonite and neutralized bentonite suspensions was determined.

THE INFLUENCE of adsorption on the dissolution rate was shown in a previous report from this laboratory (1). Experimental evidence obtained from a diffusion controlled dissolution process indicated that an adsorbent, when used in adequate amounts, was capable of increasing the dissolution rate obtained under a decreasing concentration gradient to the maximum rate obtained at a constant concentration gradient by removing solute molecules from solution. In the case of the viscosity parameter, the current study showed the dissolution rate for 96% of the total viscosity range studied (1 to 260 cps.) to be a function of the viscosity raised to the  $-0.5$  power. However, a nearly linear relationship was obtained at low viscosities (1 to 5 cps.).

In most pharmaceutical and *in vivo* systems it would not be possible to separate the viscosity influence from that caused by the adsorbent. Therefore, a study of the simultaneous influence of these factors on the dissolution rate was attempted.

### EXPERIMENTAL

**Apparatus and Procedure.**—The apparatus, tablet production, and general experimental procedure for determining the dissolution rate were identical to that used in previous investigations (1, 2).

**Adsorption Isotherms.**—Adsorption isotherms were determined at  $25 \pm 1^\circ$  for benzoic acid by bentonite U.S.P. (3-7) using a dialysis procedure. A 50-ml. quantity of distilled water was added to a 125-ml., wide mouth, ground glass-stoppered container, containing 750 mg. of bentonite. A cellulose bag<sup>1</sup> containing 25 ml. of a standard benzoic acid solution was placed in the bentonite suspension. Control runs using distilled water instead of benzoic acid solutions were also included in order to correct the alkalinity of bentonite. The containers were

closed and shaken until equilibrium was reached. Although preliminary studies demonstrated equilibrium after only 4 hours, each flask was shaken for 24 hours. A sample of the clear fluid from inside the dialysis bag was taken for analysis at the end of this time. The amount of benzoic acid in solution was determined by titrating with a standard sodium hydroxide solution under an atmosphere of nitrogen using phenolphthalein as the indicator. The amount of benzoic acid adsorbed by the bentonite was calculated by difference. The amount of benzoic acid adsorbed was verified by assaying the suspension outside the dialysis bag for benzoic acid using a back titration technique.

**Dissolution Studies in Bentonite Suspensions.**—The bentonite suspensions (2 L. of freshly boiled distilled water plus an accurately weighed quantity of bentonite) were prepared 2 days before using. Agitation of the solvent medium was started 15 minutes before zero dissolution time. This was done to allow any shearing of the suspension by the stirrer to occur before the initial viscosity was measured.

Using an Epprecht rheometer, the viscosity was determined at zero dissolution time and after completion of each run. Bentonite suspensions, at sufficient concentrations, exhibit thixotropic flow. A standard method for measuring viscosity was necessary since various concentrations were to be studied; therefore, the following method was used throughout. The shear rate was increased until the pointer was deflected approximately half scale in order to remove entrapped air; the instrument was then stopped. After 2 minutes, the instrument was again started and the appropriate shear rate selected so that the pointer was deflected approximately half scale. The initial reading was recorded and the bob was allowed to rotate for 30 seconds. All lower shear rates were then measured in rapid succession. This was repeated twice, at 2-minute intervals. Cup and bob "O" were used for all measurements.

The dissolution rates of benzoic acid tablets in bentonite suspensions of increasing concentration were determined as previously described (2).

**Dissolution Studies in Neutralized Bentonite Suspensions.**—The procedure was the same as given above, except for the following. The alkalinity introduced by the bentonite was eliminated by titrating to pH 7.0 using a standard HCl solution. Twenty-four hours were allowed for the neutralization. The suspensions were brought to their final volume at the end of the neutralization period.

The dissolution rates of benzoic acid tablets in

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neutralized bentonite suspensions of increasing concentration were then determined.

## RESULTS AND DISCUSSION

The method of calculating the dissolution rate including the surface-weight and shape-volume factors have been discussed previously (1, 2).

### Adsorption Isotherms

Before the adsorption isotherms were determined, several exploratory experiments were carried out. Adsorption of benzoic acid by the cellulose dialysis bag did not occur. This was determined by placing a standard benzoic acid solution in the glass container and distilled water in the dialysis bag and allowing the system to equilibrate. All the benzoic acid was accounted for by assaying the inside and outside solutions. Also, significant amounts of bentonite did not pass through the wall of the dialysis bag. Experimentally, this was determined by gravimetric analysis of the solids content when a dialysis bag containing distilled water was immersed in a bentonite suspension and allowed to come to equilibrium. The osmotic pressure effect was negligible, too. This was determined by measuring the volume of the solution inside the dialysis bag after attaining equilibrium with a bentonite suspension. A significant difference in the volume of the solution was not found.

A typical adsorption isotherm is shown in Fig. 1. The adsorptive capacity ranged from 26.1 to 28.9 mg. of benzoic acid per 750 mg. of bentonite. Thus, while bentonite did adsorb benzoic acid from aqueous solution, the adsorption was only moderate. The adsorption of this relatively small amount was, however, readily reproducible.

### Viscosity

The viscosity was determined with a rheogram; the viscosities of various bentonite and neutralized bentonite suspensions are shown in Fig. 2. The average scale reading at each rate of shear was used to determine total  $\tau$ . The bentonite suspensions exhibited both Newtonian and plastic flow; the tendency for plastic flow increased as the bentonite concentration increased. The yield values ranged from 0 to 1 dyne/cm.<sup>2</sup>, whereas the neutralized

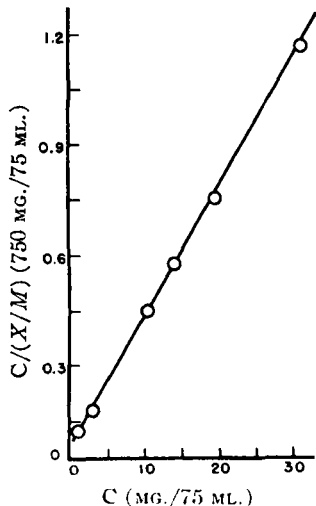


Fig. 1.—Typical adsorption isotherm for benzoic acid by bentonite.

bentonite suspensions gave yield values from 0 to 7.6 dynes/cm.<sup>2</sup>

### Dissolution Studies in Bentonite and Neutralized Bentonite Suspensions

**Chemical Reaction, Adsorption, and Viscosity.**—Figure 3 shows the dissolution rate plotted against the concentration of the suspensions for both bentonite and neutralized bentonite. The point where both curves intersect the ordinate is, of course, the dissolution rate in water under conditions of a decreasing concentration gradient. This figure shows that an initial increase, followed by a leveling off, and subsequently, a decline in the dissolution rate occurred. The initial increase in rate in the upper curve is a result of the combined effects of the alkalinity of the bentonite and its adsorbent property; both of these properties result in an increased dissolution rate. The theoretical aspects of these effects are thoroughly treated in previous papers from this laboratory (1, 8). The decrease in rate results from the increase in viscosity. As stated previously, a near linear relationship existed between the decrease in dissolution rate of benzoic acid and the viscosity of methylcellulose solutions varying between 1 to 5 cps. The more rapid decline of the dissolution rate in the case of the neutralized bentonite resulted from the slight increase in viscosity over that of the bentonite suspensions at the same concentration, as shown in Fig. 2. How-

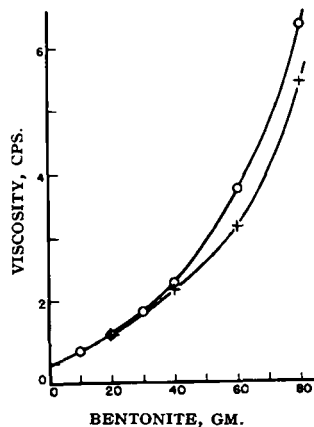


Fig. 2.—Viscosity of bentonite suspension vs. concentration of bentonite in 2 L. of distilled water. +, bentonite suspensions; O, neutralized bentonite suspensions.

ever, the main difference between the two curves in Fig. 3 is due to the alkalinity of bentonite.

Curves A and B in Fig. 4 were obtained from the data given in Fig. 3. Here the dissolution rate is plotted as a function of viscosity. The viscosity is that of the corresponding bentonite concentration given in the previous figure. Curve C was obtained from the dissolution rate studies in methylcellulose solutions and shows only the effect of viscosity on the dissolution rate. In general, the explanation given for Fig. 3 also explains curves A and B; however, several other points should be mentioned.

In a previous study (1) it was shown that an adsorbent is capable of increasing the dissolution rate up to a maximum. The maximum is the rate obtained in pure water under such conditions that no appreciable buildup of the solute occurs, and a constant concentration gradient (Nernst-Brünner film theory) is maintained. When the concentration of the solute increases to the point where the concentration gradient decreases significantly, the

dissolution rate is also decreased. However, an adsorbent in adequate concentration is capable of increasing the rate to the maximum by removing solute molecules from solution and thereby maintaining the concentration gradient at the maximum. A further increase in the adsorbent concentration will not increase the dissolution rate above this maximum. This is apparently the explanation for the plateau region in curve *B*. The maximum dissolution rate of benzoic acid in these neutralized bentonite suspensions was 0.0462 Gm./cm.<sup>2</sup>/hour. This compares favorably to the value of 0.0459

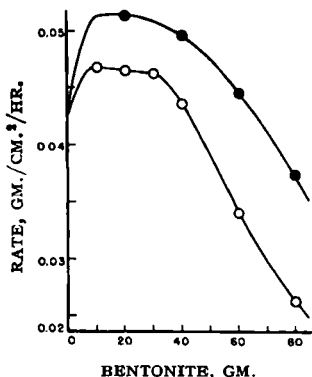


Fig. 3.—Dissolution rate of benzoic acid vs. concentration of bentonite in 2 L. of distilled water. Key; ●, bentonite suspensions; ○, neutralized bentonite suspensions.

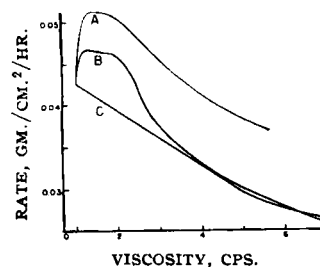
Gm./cm.<sup>2</sup>/hour obtained with Norite (1) and the rate of 0.0456 Gm./cm.<sup>2</sup>/hour in water.

At low viscosities adsorption appeared to be the dominant factor; ultimately the influence of viscosity overcomes this factor. Above 3.5 cps., for the viscosity range studied, curves *B* and *C* are nearly identical. This indicates that viscosity is the controlling factor for these concentrations of neutralized bentonite. This behavior would be expected, theoretically, since a linear relationship between the amount adsorbed and the concentration of the adsorbent would exist. A linear relationship between the dissolution rate and viscosity over the range of 1 to 5 cps. also exists; however, the viscosity increases at a faster rate with an increase in the bentonite concentration.

The difference between curves *A* and *B* can be accounted for by the alkalinity of the untreated bentonite. Also, since the influences of alkalinity and adsorption are superimposed upon the viscosity influence, the dissolution rate of a solid weak acid will be greater in bentonite suspensions than that indicated solely by the viscosity of the medium.

**Salt Effect.**—In the case of neutralized bentonite suspensions another possible effect on the dissolution rate should be mentioned. This is the salt effect. Again it was shown previously (2) that the dissolution rate decreased in a linear manner as the equilibrium concentration decreased. The latter concentration decreases as the concentration of various salts increases and thus decreases the water concentration (1, 8). For a suspension containing 80 Gm. of bentonite in 2 L. and neutralized with HCl, the amount of salt formed in terms of NaCl was approximately  $7 \times 10^{-3}$  moles/L. On the basis of the above-mentioned experiments this salt concentration would not cause a significant change in the dissolution rate of the benzoic acid. For example, a 0.154 *M*/L. concentration of NaCl caused the dissolution rate under the existing

Fig. 4.—Simultaneous influence of chemical reaction, adsorption, and/or viscosity on dissolution rate. Key: A, chemical reaction, adsorption, and viscosity; B, adsorption and viscosity; C, viscosity.



conditions to change from 0.0426 to 0.0414 Gm./cm.<sup>2</sup>/hour (8).

**Viscosity.**—The measured viscosity of all bentonite suspensions was essentially the same after the dissolution experiment as before except for the neutralized suspensions containing 60 and 80 Gm. of bentonite. For these suspensions the final viscosity was 0.9 and 2.3 cps. higher, respectively, than the viscosity at zero dissolution time. In these two cases the average viscosity was used.

**Change in pH.**—The pH of the suspensions following the dissolution experiments varied with the bentonite concentration, the pH being higher for those suspensions of greater concentration. The final pH varied from 4.6 to 7.3 over the range of bentonite concentrations studied (10 to 80 Gm./2 L.). The increased pH was due to both increased chemical reaction and adsorption as the bentonite concentration increased.

The pH of the neutralized bentonite suspensions was followed as a function of dissolution time. The results indicated that neutralized bentonite had little or no buffer capacity toward benzoic acid. The final pH varied from 4.0 to 4.6 for the range of neutralized bentonite concentrations studied (10 to 80 Gm./2 L.). The increased pH was due to the increased adsorption of benzoic acid as the bentonite concentration increased which then resulted in a decrease in the equilibrium concentration of the acid.

## SUMMARY

Using bentonite U.S.P., a montmorillonite clay, the simultaneous influence of several factors on the dissolution rate of compressed benzoic acid tablets was investigated.

The adsorption isotherms, determined by a dialysis procedure, showed bentonite to have a moderate and reproducible adsorption capacity for benzoic acid.

When the dissolution rate was determined in bentonite suspensions, the controlling factors were characterized as chemical reaction, adsorption, and viscosity; when the dissolution rate was determined in neutralized bentonite suspensions, only adsorption and viscosity were the controlling factors.

For both bentonite and neutralized bentonite suspensions, the dissolution rate increased, leveled off, and finally decreased as the concentration of bentonite increased.

In methylcellulose solutions of various concentrations where a correction was made for the increased solubility of benzoic acid in this medium, viscosity was made the only variable affecting the rate of solution. A linear relationship between the rate

and the viscosity was found for viscosities of 1 to 5 cps. The dissolution rate was a function of the viscosity raised to the  $-0.5$  power for the rest of the viscosity range studied (1 to 260 cps.).

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## Technical Articles

# Continuous Production of Tablet Granulations in a Fluidized Bed I

## Theory and Design Considerations

By MORTON W. SCOTT\*, HERBERT A. LIEBERMAN, ALBERT S. RANKELL, and JOSEPH V. BATTISTA

**A single step process for the production of tablet granulations on a continuous basis is described. The process is based on the use of a modified fluidized bed dryer. Important considerations in the design and operation of the equipment are derived from material and energy balances and from heat and mass transfer relationships. The report illustrates the usefulness of the pharmaceutical engineering approach in the analysis of new process developments.**

FLUIDIZATION TECHNIQUES have been used in various process industries for over 20 years (1, 2). The unit operation has found applications in areas as diverse as roasting processes (3), refining uranium ores (4), gasification of carbon (5), and ion exchange procedures (6). Fluidized bed drying has been studied extensively (7-9). The usefulness of fluidization techniques for the drying of tablet granulations was also discussed recently (10); rapid rates of drying and reduced operating costs were some of the advantages reported for the process.

Procedures for coating particulate solids in fluidized beds have been developed by Wurster (11) and applied to a variety of pharmaceutical products. When the coating agents have adhesive qualities, the technique also can be used for agglomeration and for the preparation of tablet granulations (12). The Wurster apparatus operates in a batchwise fashion and thus finds major usefulness when numerous small batches of different formulations must be processed.

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The present report introduces a new fluidization process capable of high-volume production of tablet granulations on a continuous basis. The fundamental pharmaceutical engineering relationships which have been applied successfully in designing and operating the fluidized bed granulator are developed in this report. A brief discussion of conventional batch and continuous fluidization processes is presented as background material. An accompanying report reviews the process performance levels and product characteristics obtained in batchwise and continuous operation of the equipment (13).

The analysis of the fluidized bed granulation

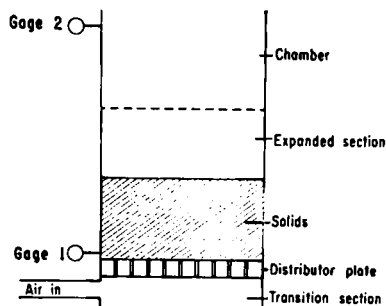


Fig. 1. —Schematic drawing of a simple fluidized bed.