# Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices IV

## Some Studies Involving the Polyvinyl Chloride Matrix

By SAURABH J. DESAI*, PARVINDER SINGH, ANTHONY P. SIMONELLI, and WILLIAM I. HIGUCHI

**The mechanism of drug release from tablets made from mixtures of drug and polyvinyl chloride particles was investigated. Experimental data were evaluated by means of the Higuchi relationship for the process. The S-shaped nature of the amount released *versus* (time)$^{1/2}$ plots was studied, and it appears that this behavior was the result of the relatively slow release of air from the tablets. Matrix tortuosities ranging from about 1.5 to 3.0 were found for these polyvinyl chloride matrices.**

IT HAS BEEN previously shown that polyvinyl chloride (PVC) matrices have exhibited peculiar behavior compared to those of polyethylene (1). The drug release from the PVC tablets showed S-shaped curves which are contrary to the predicted linear plots when the amount of release is plotted *versus* the square root of time. In addition, the PVC matrices did not show the surfactant effect observed with those of polyethylene. Finally, the PVC release rates were 4–6 times faster. These plots are shown in Fig. 1. Since this behavior may be representative of a general class of matrices, it was felt that this phenomenon should be thoroughly investigated.

Comparison of PVC and polyethylene powders reveals that the PVC powder has a much higher density (about 50%), a larger particle size (50–200 mesh as compared to smaller than 270 mesh), and a larger particle size distribution. This suggested that their respective matrices may also differ. The PVC powder should produce a more compact tablet due to its higher density and should be better bonded due to its wider particle-size distribution. Examination of their respective matrices shows that, although PVC is more compact, it exhibits poorer bonding. Polyethylene produces a tablet which has a very smooth surface, appearing as a fused solid, but PVC tablets seem rather friable and are easily repowdered by scraping.

### EXPERIMENTAL

The release rates from PVC matrices containing solid drug as well as solutions were studied using the techniques and the evaluation of parameters described previously (1, 2). All studies were conducted using water as the release medium unless specified otherwise, and all percentages reported are on a w/w basis.

### RESULTS AND DISCUSSION

The relatively poorer bonding characteristics of PVC may be partly responsible for its behavior. In an effort to improve its bonding characteristics, the effect of pressure was studied. Tablets containing 10% sodium salicylate were made at compressional forces of 2000-lb. increments between 4000 and 20,000 lb. Their release rates were independent of the compressional force. Figure 2 displays the curve obtained from the composite of all data and shows the range of random variations for each point. These results indicate that PVC is elastic throughout this range of compressional forces, and, therefore, its porosity should remain constant in these tablets. This was confirmed by the constancy of the dimensional measurements of all tablets.

Physical measurements of PVC tablets not only showed the presence of air, but also that the amount was considerably higher than in a similar matrix of polyethylene. The porosity of a 500-mg. 20% sodium salicylate tablet in PVC was 0.37, whereas the corresponding tablet made using a polyethylene matrix had a porosity of 0.22. The relatively large amount of air in the PVC tablet theoretically suggested that a large surfactant effect on the release rates might be observed. However, no such effects were found. This lack of surfactant effect implies that the surfactants used did not increase the wetting characteristics of PVC and that the removal of air was not facilitated. The discussion of this aspect will be deferred to a later portion of this paper.

The S-shaped curves exhibited by PVC tablets show that the slopes are not constant with time, but initially increase, then become constant, and then finally decrease with time. The beginning of the last phase corresponds to where essentially all of the solid drug in the matrix had just dissolved.

Several possible explanations were considered and investigated for the initial curvature of the S-shaped curves. One possible explanation may

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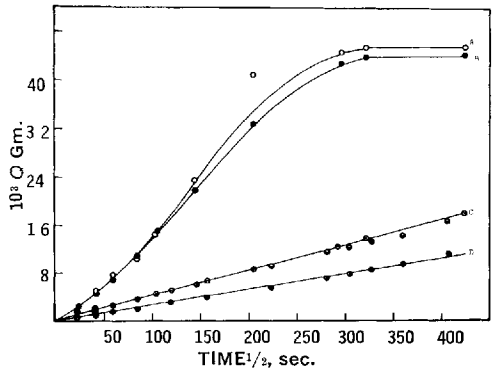


Fig. 1.—Effect of surfactants on sodium salicylate release rates. Key: A, 5% w/w sodium salicylate in PVC matrix using water as solvent; B, 5% w/w sodium salicylate in PVC matrix using 0.2% w/w benzalkonium chloride as a solvent; C, 5% w/w sodium salicylate in polyethylene matrix using the following solvents: ⊙, 0.2% benzalkonium chloride and ⊖, 0.2% sodium lauryl sulfate; D, 5% w/w sodium salicylate in polyethylene matrix using water as a solvent.

be the partitioning of drug between the PVC and the release medium. Theoretical considerations have shown (2) that the release dependence remains linear with respect to the square root of time if reversible drug partitioning should occur. If, however, the rate of partitioning is slow, then the linearity may be disturbed and the S-shaped curve may result. This possibility was ruled out on the basis of liquid leaching experiments using the same tablets which showed linear release plots. If partitioning was the cause of the S-shaped curve, the same result would be expected to occur in both solid and liquid leaching experiments.

This S-shaped curve can be due to any factor which governs the release rates not remaining constant as required, but changing as a function of time. A critical examination of all these factors clearly indicated that porosity would most likely be a variable. As an example, any swelling of the matrix due to the presence of water would alter the porosity, decreasing it with time. This possibility was investigated by accurately measuring the dimensions of tablets prior to and after soaking overnight in water. Blank PVC tablets and PVC tablets containing 10% sodium salicylate were used for these experiments. No change was noted in their dimensions due to the water exposure, and swelling was clearly eliminated as a factor in this system.

Another possibility for porosity variation may be due to a difference in the physical properties of the surface and interior portions of the matrix. This can be brought about by a difference in the flow properties of the matrix components during compression. If there is poor flowability, the effective pressure is not uniformly distributed throughout the matrix. As a result, the surface portion would be subjected to a greater pressure. This would produce smaller porosities and larger tortuosities at the surface and account for initial rates being slower.

If the above is true, it would predict that the release rate of a matrix whose surface was removed by scraping would yield a more rapid initial release of drug and would display linear behavior. For this purpose, matrices containing 10% sodium salicylate were compressed from the same mixture and then treated in the following manner. From one tablet about 6% w/w was scraped from the surface (surface to be exposed to the leaching action of the solvent) so that a uniform layer was removed and a new surface produced. Another had 12.5% w/w removed, and from a third 25% w/w was removed. As a control, one tablet utilized its original surface. Examination of Fig. 3 reveals that the release rates were not affected by the above treatment. This indicated that the physical properties of the surface and interior layers are not different, and that this is not an important factor in the experiments.

To further confirm this finding, the effect of lubri-

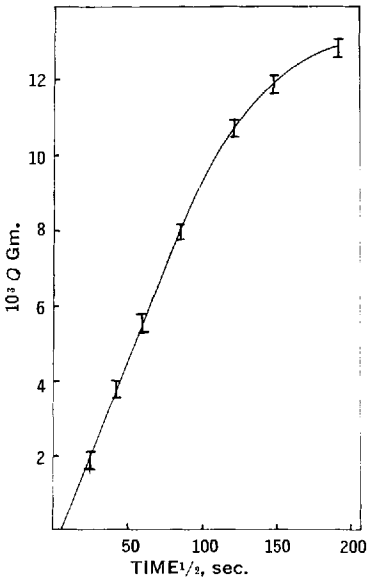


Fig. 2.—Effect of compressional force on release of 10% sodium salicylate–PVC tablets in water. Range of random spread of the data is indicated by the bars.

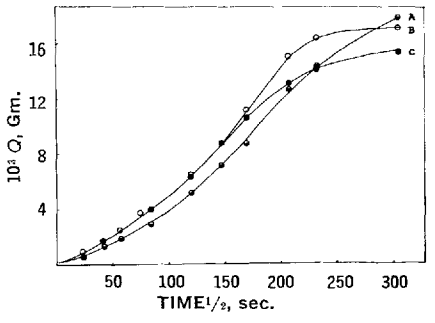


Fig. 3.—Effect of removal of the tablet surface layers on the release rates of 5% sodium salicylate tablets in PVC. Key: A, 6% w/w tablet surface removed; B, 12.5% w/w tablet surface removed; C, 25% w/w tablet surface removed.

cant addition to the matrix was studied. If the flowability of the PVC powder–drug mixture is not adequate, the addition of lubricant would improve flowability under compression and alter the matrix release profile. Figure 4 shows the release of 10% sodium salicylate matrices containing 3% talc or magnesium stearate. Comparison of these curves with the included plot of the matrix not containing any lubricant confirm the previous finding of sufficient flowability of the powder mixture under pressure.

It was finally reasoned that the initial incomplete removal of air from the matrix may be the cause of the S-shaped curves. This view was supported by the fact that a resaturated matrix yielded a linear plot. Such a matrix would have been exposed to solvent for a sufficient length of time to allow for the complete removal of air.

It is believed that the availability of air channels

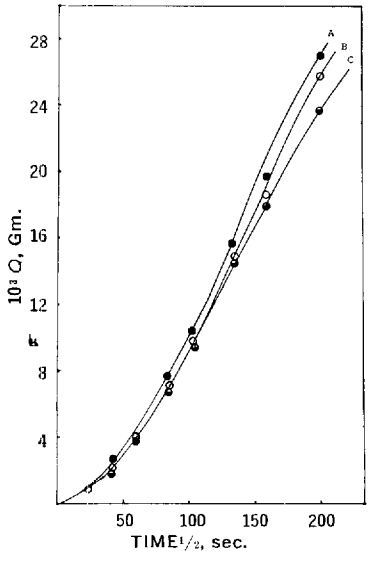


Fig. 4.—Effect of lubricant on the release of 10% sodium salicylate tablets in PVC. Key: A, 10% sodium salicylate; B, 10% sodium salicylate + 3% talc; C, 10% sodium salicylate + 3% magnesium stearate.

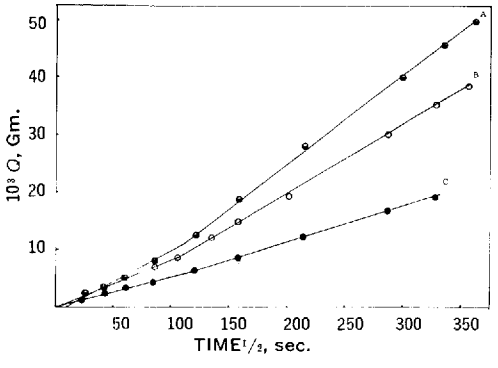


Fig. 5.—Release of 20% calcium benzoate (A), 20% caffeine (B), and 20% sulfanilamide (C) from PVC matrices into water.

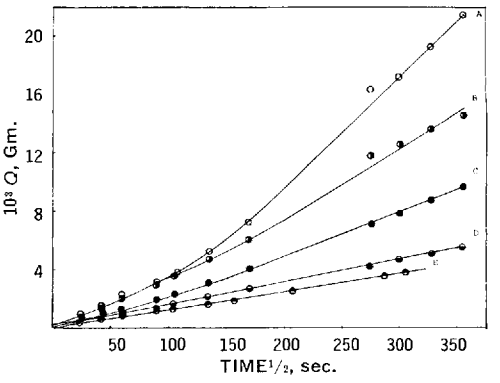


Fig. 6.—Effect of $K_2HPO_4$ concentration on release of 10% salicylic acid in PVC tablets. Key: A, 1.00 *M* $K_2HPO_4$; B, 0.50 *M* $K_2HPO_4$; C, 0.10 *M* $K_2HPO_4$; D, 0.01 *M* $K_2HPO_4$; E, water.

to the solvent depends on the rate of liquid boundary movement which should be a function of the drug solubility and would be expected to increase with an increase in solubility. If the drug is poorly soluble, the movement of the liquid boundary may be sufficiently slow to permit the prior removal of air. This would provide the linear plots predicted by theory. If the drug is very soluble, on the other hand, the drug solution boundary may move faster than the process of air removal, producing an increasing porosity with time and causing the observed curvature.

To test this concept, the release rates of sulfanilamide, caffeine, and calcium benzoate tablets were obtained and the corresponding data are shown in Fig. 5. The respective solubilities are $1.08 \times 10^{-2}$, $2.50 \times 10^{-2}$, and $3.08 \times 10^{-2}$ Gm./ml., as compared to $65.0 \times 10^{-2}$ Gm./ml. for sodium salicylate. In agreement with the previous discussion, the curves in Fig. 5 show the expected correlation between solubility and degree of curvature. As the solubility increased, nonlinearity also increased showing the most marked change for sodium salicylate.

This correlation can be shown in another way. The solubility of a drug can be varied by using different concentrations of buffer in the release medium. In this manner, the solubility of the drug can be varied and yet have the identical matrix properties operative in all cases.

The release rate of 10% salicylic acid dispersed in PVC was studied in different concentrations of $K_2HPO_4$ solutions. The results are given in Fig. 6, and they show that the release rates increase as the concentration of $K_2HPO_4$ is increased. In the presence of $K_2HPO_4$, salicylic acid in solution is converted to salicylate ion, the extent of the conversion being essentially proportional to the concentration of $K_2HPO_4$. Again, as the effective solubility increases, each plot displays increasing curvature in the release patterns. The rates are linear in water and at low $K_2HPO_4$ concentrations.

If the rate of air removal is the controlling factor, then the complete removal of air by vacuum before exposing the matrix to solvent should produce a linear square root of time dependence. To test

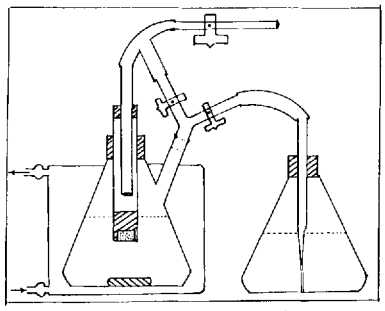

Fig. 7.—Schematic diagram of the apparatus used to study release rates after vacuum treatment.

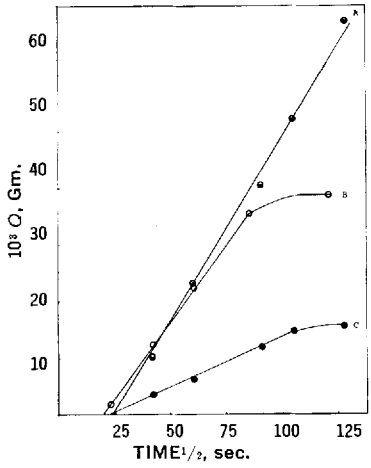


Fig. 8.—Release of 5, 10, and 20% sodium salicylate in PVC tablets into water after vacuum treatment. Key: A, 20% sodium salicylate; B, 10% sodium salicylate; C, 5% sodium salicylate.

this, a modified apparatus was made, and its schematic diagram is shown in Fig. 7. A tablet inserted in a glass tube as previously described (1) was mounted on a 125-ml. conical flask with a side arm. The flask was jacketed to maintain a constant temperature. The side arm was fitted with a Y-joint. One of the arms of the joint was connected to a vacuum pump and the other to a flask containing a measured amount of water. Vacuum was also applied to the top of the glass tube by means of a T-tube so as to maintain equal pressure on either side of the mounted tablet preventing any movement or damage of the tablet. Prior to the final application of vacuum, the connecting tube and stopcock bore from the water supply to the flask was completely flushed to remove the entrapped air. All connecting joints were sealed with "Apiezon" vacuum sealing material. A McLeod gauge was used to measure the pressure. A vacuum pressure of 0.9 mm. Hg was obtained before the water was allowed to flow into the sample flask. Immediately after the addition of water, the magnetic stirrer was started. The height of the tube containing the tablet had been previously adjusted to insure complete immersion of the tablet in water before the vacuum was released.

The results of the release of 5, 10, and 20% sodium salicylate tablets, obtained by the above vacuum procedure, are plotted in Fig. 8. The release rates of 20% sulfanilamide and 20% calcium benzoate tablets under similar conditions are shown in Fig. 9.

As predicted, all the release rates follow the square root of time dependence, strongly suggesting that the S-shaped curve is produced by the proposed mechanism. To further investigate this, liquid release rates of sulfanilamide and calcium benzoate tablets were carried out using procedures previously described (1, 2), and these results are plotted in Fig. 10. The quantitative evaluation of tortuosity by solid and liquid leaching procedures were made,

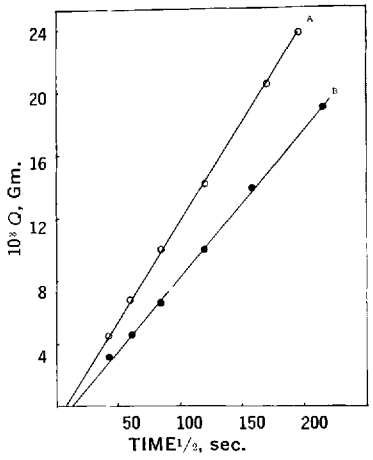


Fig. 9.—Release of 20% calcium benzoate (A) and 20% sulfanilamide (B) from PVC matrices into water, after vacuum treatment.

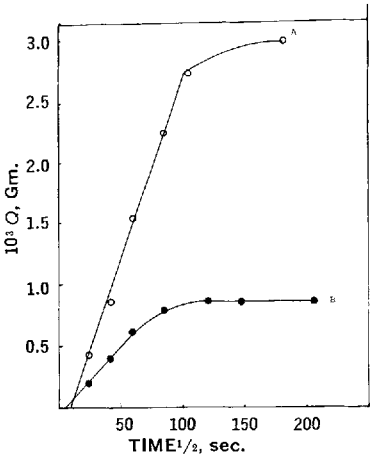


Fig. 10.—Release data from matrices saturated with drug solution. Key: A, tablet originally contained 20% calcium benzoate, which was completely leached (the matrix was equilibrated with saturated calcium benzoate solution prior to studying the liquid release); B, same as A, except sulfanilamide was used as the drug, and saturated sulfanilamide solution was used instead of calcium benzoate solution.

TABLE I.—CALCULATION OF TORTUOSITIES IN POLYVINYL CHLORIDE MATRICES CONTAINING SULFANILAMIDE AND CALCIUM BENZOATE. SOLID RELEASE STUDIED WITH VACUUM PROCEDURE

| Tablet Compn. | $D$ $10^6$ cm.$^2$ sec.$^{-1}$ | $C_s$ $10^2$ Gm. ml.$^{-1}$ | Vol. of Tablet, ml. | $\epsilon$ Due to Air and Drug | $A$ Gm. ml.$^{-1}$ | $C_0$ $10^2$ Gm. ml.$^{-1}$ | $10^5 Q/t^{1/2}$ Solid Leaching | $10_5 Q/t^{1/2}$ Liquid Leaching | $\tau$ By Solid Leaching | $\tau$ By Liquid Leaching |
|---|---|---|---|---|---|---|---|---|---|---|
| 20% Sulfanilamide | 12.90 | 1.08 | 0.4311 | 0.390 | 0.2319 | 0.80 | 6.21 | 9.60 | 2.6 | 1.3 |
| 20% Calcium benzoate | 9.20 | 3.08 | 0.4247 | 0.380 | 0.2354 | 3.28 | 8.5 | 11.3 | 3.2 | 2.0 |

TABLE II.—CALCULATION OF TORTUOSITY FOR 5, 10, AND 20% SODIUM SALICYLATE IN THE POLYVINYL CHLORIDE MATRIX. SOLID RELEASE RATES WERE OBTAINED USING VACUUM PROCEDURE

| Tablet Compn. | $D$ $10^6$ cm.$^2$ sec.$^{-1}$ | Vol. of Tablet, ml. | I Vol. of Drug, ml. | II Vol. of Air, ml. | $\epsilon$ | III Wt. of Drug, Gm. | $C_0$ $10^2$ Gm. ml.$^{-1}$ $\frac{\text{III}}{\text{I} + \text{II}}$ | Solid Release Rate $10^4 Q/t^{1/2}$ | $\tau$ |
|---|---|---|---|---|---|---|---|---|---|
| 5% Sodium salicylate | 13.30 | 0.4385 | 0.0161 | 0.1093 | 0.286 | 0.025 | 0.200 | 1.79 | 1.7 |
| 10% Sodium salicylate | 17.20 | 0.4294 | 0.0323 | 0.1006 | 0.309 | 0.050 | 0.376 | 4.34 | 1.6 |
| 20% Sodium salicylate | 23.00 | 0.4189 | 0.0645 | 0.0908 | 0.371 | 0.100 | 0.644 | 6.55 | 3.8 |

and the results are summarized in Table I. The good agreement of the tortuosity values obtained by the two methods indicate that the total porosity is available when the vacuum procedure is followed.

The $\tau$ values were similarly calculated for the sodium salicylate systems. The calculated values for $\tau$, however, were physically impossible as they were less than unity. Analysis of the situation revealed that when the vacuum procedure is used, the solid release equation should not be applicable. Under these conditions, the water is able to rapidly permeate all available channels. Since the dissolution rate of sodium salicylate is very rapid, the water which penetrated the matrix is rapidly saturated. If the amount of drug in the matrix, however, is not sufficient to produce a saturated solution, then all of the drug will be rapidly dissolved. As a result, a matrix containing no solid drug but only its solution will be produced. In these cases the release rates should follow the liquid release equation rather than that of the solid release.

The concentrations of the resultant solutions in the 5, 10, and 20% tablets were calculated on this basis assuming that all the volume of each tablet initially occupied by air and sodium salicylate became occupied by a solution containing all of the incorporated drug. The concentrations of the solutions in the matrix for 5, 10, and 20% tablets were calculated and found to be 0.20, 0.37, and 0.64 Gm./ml., respectively. In addition, $\tau$ values were calculated using the above solution concentrations in the liquid leaching equation and are listed in Table II. These values are in excellent agreement with those obtained from the sulfanilamide and calcium benzoate studies and provide strong support for the concepts developed here.

An interesting observation can be made by comparing the magnitude of the tortuosity values obtained for these different drugs in a PVC matrix with those that were obtained for the same drugs dispersed in a polyethylene matrix (3). It is seen that the tortuosity values obtained for the PVC matrix vary from about 1.5 to 4, whereas for the polyethylene matrix they vary from about 7 to 10. It has been shown (4) that the value of $\tau$ for a system composed of closely packed spheres is generally above 1.5 to 2.0. This indicates that the structure of a PVC matrix resembles that of a closely packed glass bead bed, and implies that PVC particles are elastic, and, therefore, they are not permanently distorted when compressed. The high $\tau$ values of the polyethylene matrix, on the other hand, indicate that its particles are plastic and are severely distorted when compressed.

## APPENDIX

The equations used in the explanation of the rate process are:

$$Q = \frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t^{1/2} \qquad \text{(Eq. 1)}$$

and

$$Q = 2\,C_0\epsilon\left(\frac{DT}{\pi\tau}\right)^{1/2} \qquad \text{(Eq. 2)}$$

where

$Q$ = amount of drug released per unit area of the tablet surface exposed at time, $t$,
$D$ = diffusion coefficient of the drug in release medium,
$C_s$ = solubility of the drug in the release medium,
$C_0$ = concentration of the solution in the matrix,
$\epsilon$ = porosity of the matrix,
$\tau$ = tortuosity of the matrix.

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