(390) B. L. Kennedy and S. Ellis, *Federation Proc.*, **22**, 449 (1963).
(391) K. R. Hornbrook and T. M. Brody, *Biochem. Pharmacol.*, **12**, 1407(1963).
(392) K. R. Hornbrook and T. M. Brody, *J. Pharmacol. Exptl. Therap.*, **140**, 295(1963).
(393) E. W. Sutherland and T. W. Rall, *Pharmacol. Rev.*, **12**, 265(1960).
(394) S. Mayer, N. C. Moran, and J. Fain, *J. Pharmacol. Exptl. Therap.*, **134**, 18(1961).
(395) J. J. Burns, K. I. Colville, L. A. Lindsay, and R. A. Salvador, *ibid.*, **144**, 163(1964).
(396) T. R. E. Pilkington, R. D. Lowe, B. F. Robinson, and E. Titterington, *Lancet*, **2**, 316(1962).
(397) V. Classen and E. L. Noach, *Arch. Intern. Pharmacodyn.*, **126**, 332(1960).
(398) G. Northrop and R. E. Parks, Jr., *J. Pharmacol. Exptl. Therap.*, **145**, 87(1964).
(399) R. J. Havel and A. Goldfien, *J. Lipid Res.*, **1**, 102(1959).
(400) H. M. Goodman and E. Knobil, *Proc. Soc. Exptl. Biol. Med.*, **102**, 493(1959).
(401) H. Ali, A. Antonio, and N. Haugaard, *J. Pharmacol. Exptl. Therap.*, **145**, 142(1964).
(402) A. B. Craig, Jr. and P. L. Mendell, *Am. J. Physiol.*, **197**, 52(1959).
(403) S. Ellis, S. B. Beckett, and J. H. Boutwell, *Proc. Soc. Exptl. Biol. Med.*, **94**, 343(1957).
(404) M. C. Schotz and I. H. Page, *J. Lipid Res.*, **1**, 466(1960).
(405) N. Haugaard and M. E. Hess, *Pharmacol. Rev.*, **17**, 27 (1965).
(406) W. R. Kukovetz and G. Poch, *Arch. Exptl. Pathol. Pharmakol.*, **256**, 310(1967).
(407) J. J. Lech, P. Somani, and D. N. Calvert, *Mol. Pharmacol.*, **2**, 501(1966).
(408) P. Bjorntorp, L. Olsson, L. Ek, and G. Schröder, *Acta Pharmacol.*, **25**, 51(1967).
(409) R. A. Salvador, K. I. Colville, S. A. April, and J. J. Burns, *J. Pharmacol. Exptl. Therap.*, **144**, 172(1964).
(410) J. J. Burns, R. A. Salvador, and L. Lemberger, *Ann. N. Y. Acad. Sci.*, **139**, 833(1967).
(411) W. D. Meester, H. F. Hardman, and J. J. Barboriak, *J. Pharmacol. Exptl. Therap.*, **350**, 34(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the *Department of Pharmacology, School of Medicine, University of Hawaii, Honolulu, HI 96816*

* East-West Center Grantee.

† Present address: Research Triangle Institute, Research Triangle Park, NC 27709

RESEARCH ARTICLES

Dissolution Rates of High Energy Polyvinylpyrrolidone (PVP)-Sulfathiazole Coprecipitates

A. P. SIMONELLI, S. C. MEHTA, and W. I. HIGUCHI

Abstract □ The apparent solubility and rate of solution of sulfathiazole from compressed tablets containing polyvinylpyrrolidone (PVP) were found to be greatly increased if sulfathiazole was previously coprecipitated with PVP. The increase noted was found to be a function of the chain length of the PVP used as a coprecipitate and the sulfathiazole to PVP weight ratio of the coprecipitate powder mixture used to compress the tablet. The 10,000-mol. wt. PVP yielded the most rapid sulfathiazole dissolution rate. The sulfathiazole rate of solution was (*a*) independent of the PVP weight fraction in the coprecipitated mixture at low PVP weight fractions; (*b*) increased with increasing PVP weight fraction at intermediate PVP weight fractions; and (*c*) decreased with increasing PVP weight fractions at high PVP weight fractions. A model was presented which utilized a controlling sulfathiazole external layer at lower PVP weight fractions and a controlling PVP external layer at higher PVP weight fractions. Several techniques were developed and used to elucidate the mechanisms involved and include (*a*) dissolution rate studies of mechanical mixes as well as coprecipitated mixtures of a number of sulfathiazole to PVP ratios; (*b*) X-ray diffraction studies of powders and tablets both before and after dissolution; (*c*) solubility determination of the various forms of sulfathiazole as a function of the PVP weight fraction in the coprecipitate and as a function of the PVP concentration in solution; (*d*) simultaneous release rates of PVP and sulfathiazole to determine regions of congruency and noncongruency; and (*e*) rates of solution using PVP solutions as a solvent. The data not only agreed very well with the model, but permitted a detailed characterization of all systems at all times during the dissolution process.

Keyphrases □ Sulfathiazole-PVP—coprecipitates □ Dissolution rates—sulfathiazole-PVP coprecipitates □ Solubility—sulfathiazole-PVP coprecipitates □ Tablets, sulfathiazole release rates—PVP effect □ X-Ray diffraction—sulfathiazole-PVP coprecipitates □ UV spectrophotometry—analysis □ Optical rotation—analysis

The interaction of polymers with chemical compounds to increase solubility has been reported for some time (1–3). More recently it has also been shown that the rates of solution of drugs were appreciably increased by coprecipitating the drug with polymers (4–6). This increase in dissolution rate of some systems, however, appears to be significantly greater than the expected increase calculated from the solubility increase due to the presence of polymer. Moreover, the increase was found to be sensitive to the method of preparation and the

particular ratio of drug to polymer utilized in the experiment (6). Needless to say, the potential value of any method that can significantly alter dissolution rates can not be overestimated.

There have been many suggestions (2, 7, 8) of why these increases occur and include the presence of complexes, solid solutions, colloidal dispersions, *etc.* The object of this study was to investigate this area to develop new approaches, methodology, and concepts, and hopefully to determine the mechanism.

For this study the sulfathiazole-polyvinylpyrrolidone (PVP) system was chosen for several reasons. Sulfathiazole has been extensively studied in these laboratories. It has several well characterized crystalline forms and rates of solution which are significantly different for each form (9, 10). The presence of polymorphism may in itself add several interesting possibilities to the authors' system and serve to further generalize their results. PVP, on the other hand, has been widely reported as generally interacting with a wide range of organic compounds (1–3, 11) and, therefore, the results of any investigation involving PVP should be more generally applicable to other drugs as well. Finally the authors' crystal growth inhibition studies showed that PVP strongly interacted with sulfathiazole and inhibited crystal growth at low concentrations (12). It seemed logical then to extend these studies to include coprecipitated mixture studies.

THEORETICAL CONSIDERATIONS

Analysis of the above reveals that there are several possibilities which can occur. The drug in the solid phase can exist bound to the polymer, only in one of its unbound forms, or lastly as a combination of the above states.

If the drug and polymer coexist as a complex, the dissolution of drug can occur by either of two methods; the bound drug can be removed from the polymer at the surface by solvent interaction and thereby precede the polymer into solution, or the drug polymeric complex can dissolve intact followed by dissociation of the drug-polymer complex in solution.

The mechanism involving the dissolution of the complex followed by dissociation lends itself to a simple solution if the assumption is made that the diffusion layer model is operative, as the dissolution rate will be governed by the solubility of complex and the diffusion coefficients of all polymeric species. The system can then be quantitated by consideration of the equations of the continuity existing in the diffusion layer. The mechanism which allows the drug to be removed from the polymer by solvent interaction will depend on the rate of interaction. To be operative this rate must obviously be faster than the rate of intact complex dissolution.

In either mechanism the rate may be restricted by the amount of free drug in solution for if the free drug concentration exceeds its solubility, this may cause precipitation of the unbound drug on the surface. If this occurs a layer of unbound drug will be produced that can appreciably influence the drug release rate.

This layer can also develop if the drug initially was present in an unbound as well as in the bound state and in such a ratio that the bound drug is preferentially released. The release of drug in this situation will depend on the concentration of bound as well as unbound drug in solution at the interface. The concentration of unbound drug at the interface will be equal to the solubility of the unbound form of the drug present in the layer. The concentration of bound drug at the interface, on the other hand, will not only depend on the solubility of the unbound form of the drug present in the layer, but also the concentration of the polymer at the interface and the stability constant of the complex. This means if more than one polymorphic form of the drug is possible, the reversion of one form to a more stable form must also be considered as it can considerably decrease the release rate of drug.

The above analysis clearly shows the need to characterize the phases present in the solid phase at all times. Many attempts to do so, however, have been clouded because powders were used (6). In these systems factors such as rate of wetting, effect of particle size and hence specific surface area, disintegration, clumping, *etc.*, are unnecessarily complicating.

To avoid these complications mounted tablets were utilized in these studies as they provide a constant surface area, permit a constant hydrodynamic system, and in general avoid many of the problems associated with powders.

EXPERIMENTAL

Preparation of Coprecipitates from Aqueous Solutions—A weighed quantity of sulfathiazole was dissolved in a quantity of hot sodium hydroxide solution. After the solution was allowed to cool to room temperature, the desired amount of PVP was added to the solution. Finally a calculated quantity of concentrated hydrochloric acid was added to this solution with continuous and vigorous stirring to neutralize the sodium hydroxide and precipitate the free base of sulfathiazole. It was found that the result of this procedure depended on the w/w ratio of sulfathiazole to PVP used. Below a ratio of 1:2 sulfathiazole to PVP a uniform light yellow solution was obtained which was then frozen by placing in a cold storage unit at 0°. Above a ratio of 1:2 sulfathiazole to PVP, however, a thick viscous mass was produced which settled to the bottom of the container. The supernatant solution above the viscous mass was decanted in these systems prior to freezing.

The frozen samples were then lyophilized from 2 to 3 days using a freeze drier[1] to produce a dry mass which was powdered for future studies. All powders were analyzed for both sulfathiazole and PVP.

Preparation of Coprecipitates from 95% Alcoholic Solutions—A weighed quantity of sulfathiazole was dissolved in a minimum volume of 95% v/v ethyl alcohol solution on a steam bath. A sufficient quantity of PVP to yield the desired ratio of sulfathiazole to PVP was then added to the solution. After the PVP dissolved the solution was further heated on the steam bath to evaporate the solvent. Care was exercised not to overdry the sample to prevent charring. The final traces of solvent were removed by placing the beaker containing the remaining material in a vacuum desiccator and applying a vacuum by means of a vacuum pump. The dried mass thus produced was powdered and uniformly mixed and stored for future use.

Dissolution Studies—Weighed quantities of the above coprecipitated sulfathiazole-PVP mixtures were compressed into tablets using a 0.93 cm. (0.375 in.) die at a force of 3,000 lb. in a press (Carver). The tablets were not removed from the die after compression; instead, one tablet face was made flush with the die surface. The other end of the die, however, was sealed with a cork. In this way the die and tablet could be completely submerged in the dissolution media and yet expose only one tablet surface allowing for a constant surface area throughout the dissolution run.

The apparatus (13) used in all dissolution studies is shown in Fig. 1. The die was placed in the methylmethacrylate (Plexiglas) holder. Two hundred milliliters of solvent was added to the 600-ml. water-jacketed beaker. The temperature of the solvent was maintained at 37° by circulating water through the jacketed part of the beaker from a constant-temperature water bath. The methylmethacrylate motor assembly containing the tablet holder previously described and the stirring apparatus was introduced into the solvent and the timer started. Ten-milliliter samples were removed as a function of time for analysis using the sampling port. The volume was kept constant throughout a dissolution run by replacing the removed samples with an equal quantity of new solvent.

The solution was stirred at 150 r.p.m. by means of a stainless steel stirrer with polytetrafluorethylene (Teflon) propeller blades driven by a synchronous constant speed turret motor. The fixed position of tablet holder and stirrer blade along with a constant stirring speed assures constant hydrodynamic conditions.

Analysis of Samples—After suitable dilution, samples were assayed for sulfathiazole using a spectrophotometer[2] at the wavelength of 282 mμ. At this wavelength, PVP did not show any absorption of light and sulfathiazole yielded excellent Beer's law plot.

[1] The Virtis Mechanically Refrigerated Freeze-Mobile model 10-145MR-SA, The Virtis Co., Gardner, N. Y.
[2] Hitachi, Ltd., Tokyo, Japan.

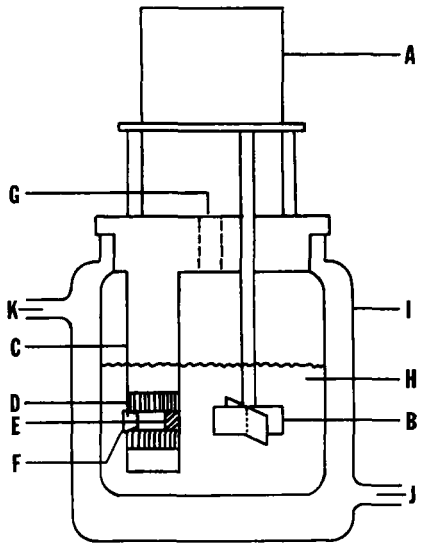

Figure 1—*Dissolution apparatus. Key: A, synchronous motor; B, stirrer; C, die holder; D, die; E, tablet; F, cork; G, sampling port; H, solvent; I, jacketed beaker; J, inlet for water (37°); K, outlet for water (37°).*

To analyze for PVP, the total differential refractive indexes of the above samples were also measured in a differential refractometer,[3] using water as the solvent blank. This was necessary as PVP did not show any useful UV absorption peaks. This method was feasible because the differential refractive index *versus* concentration was found to be linear for both PVP and sulfathiazole. In addition the individual contributions to the differential refractive index were found to be additive for mixtures of PVP and sulfathiazole.

PVP concentrations were determined in the following manner. The sulfathiazole concentration, determined from its UV absorption, was multiplied by the proportionality constant obtained from the differential refractive index *versus* concentration plot to obtain the sulfathiazole contribution to the differential refractive index of the sample. Subtracting this value from the total differential refractive index yields the PVP contribution to the differential refractive index of the sample. The PVP concentration is then calculated using its differential refractive index proportionality constant.

These calculations were automatically made, using an electronic calculator,[4] by inserting a previously prepared perforated tape program, punching in the UV absorbance of sample measured at 282 mμ, and the measured sample differential refractive index, and touching automatic. A teletype accessory tabulated the concentrations and total release of both species as a function of time.

RESULTS AND DISCUSSION

Effect of PVP Molecular Weight on the Sulfathiazole Release Rate—Since a wide range of molecular weight polymers of PVP are available, it was important to determine if any behavioral differences existed with a variation in chain length. If a difference did exist, the polymer chain length that appeared to produce the most significant solubility increase would be utilized for this study. Toward this end powders containing a 1:2 ratio of sulfathiazole to PVP using PVP of 10,000, 40,000, and 360,000 mol. wt. were prepared using the aqueous coprecipitate method, compressed into tablets, and their dissolution rates determined.

The milligrams of sulfathiazole dissolved as a function of time for tablets of all three mixtures are shown in Fig. 2. The dissolution of a tablet made of pure crystalline sulfathiazole Form I was also included for purposes of comparison. It is seen that all plots are linear and that all tablets containing PVP exhibited faster dissolution than that of pure crystalline sulfathiazole Form I. It is also seen that the chain length indeed significantly changes the dissolution rate of sulfathiazole, the 10,000-mol. wt. polymer being the most rapid of the three studied. For this reason the 10,000-mol. wt. PVP was utilized for all studies reported in this paper.

Effect of PVP Weight Fraction on Sulfathiazole Release Rate—The effect of sulfathiazole to PVP ratio on the release rate was next investigated. The alcohol coprecipitate method was utilized as it provides a definite control of the composition of the solid obtained, whereas the aqueous coprecipitate method provides an uncontrolled composition which can only be determined by assay after the solid is produced.

Tablets were made using powders composed of sulfathiazole to PVP ratios of 3:1, 2:1, 1.5:1, 1:1, 1:1.5, 1:2, and 1:3 and their dissolution profiles obtained. Figure 3 shows the milligrams of sulfathiazole released as a function of time for these tablets. Again the pure crystalline sulfathiazole Form I is included as a point of reference. It should be noted that the 1.5:1 sulfathiazole to PVP ratio initially exhibits a fast rate as shown by the higher slope but then tapers off to approximately the same rate as the pure crystalline sulfathiazole Form I. The 1:1 ratio similarly shows a nonlinear plot. The 3:1 and 2:1 mixture ratios also showed nonlinear curves and were omitted so as not to over-congest the plot. They are shown, however, in Fig. 13. The 1:1.5, 1:2, and 1:3 ratios, however, are linear for the length of time studied and pass through the origin. It should also be noted that, as one would expect, the sulfathiazole dissolution rate increases with increasing PVP weight fraction in tablet for this range of PVP. Unexpectedly, however, this trend did not continue as it was found that the sulfathiazole release rate actually decreased as the PVP weight fraction in tablet was further increased. This is shown by the release profiles for the 1:3, 1:5, 1:10, and 1:20 sulfathiazole to PVP ratios plotted in Fig. 4. It should be noted, however, that the curves remained linear for these sulfathiazole-PVP ratios. In addition all tablets yielded faster sulfathiazole dissolution rates than the pure crystalline sulfathiazole tablet, the 1:20 ratio, although the slowest being about 3.5 times faster.

Before proceeding it was felt that the method of preparation may in part be responsible for the nonlinear behavior of the solids containing a lower concentration of PVP, as the evaporation technique may not discourage the possibility of multiphase solids. For this reason the solid coprecipitates were prepared using the aqueous technique which appears to produce a homogeneous viscous gel in the critical region which can be equilibrated and hence more likely to produce a mono-phased solid. A higher concentration of PVP solid was also included so that a proper reference point of the aqueous and alcohol systems can be made where linear release profiles are exhibited. The milligrams of sulfathiazole dissolved as a function of time for these systems are shown in Fig. 5, and clearly show that essentially the same release profiles are exhibited by both systems indicating that the results are independent of the method of prepara-

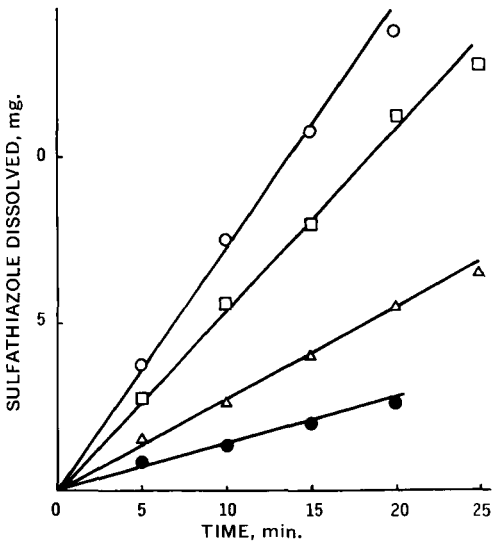

Figure 2—*Milligrams of sulfathiazole released from tablets as a function of time. Tablets were prepared from a 1:2 sulfathiazole to PVP ratio coprecipitate using PVP of different molecular weights. Key: ○, 10,000; □, 40,000; Δ, 360,000; ●, sulfathiazole Form I with no PVP as a reference.*

[3] Brice-Phoenix, model BP2000V, Phoenix Precision Inst. Co.
[4] Mathatron 4280.

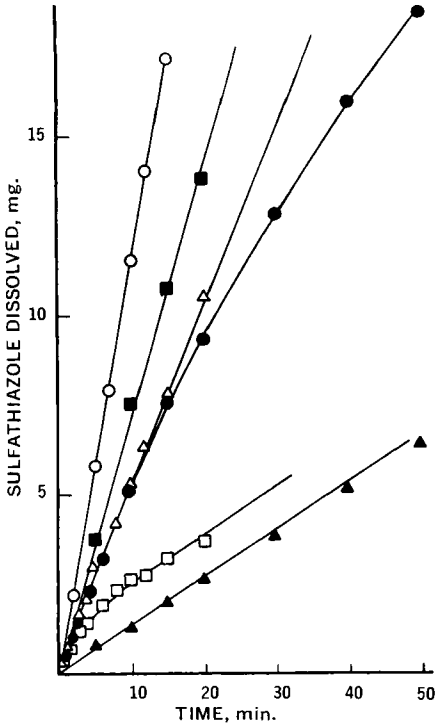

Figure 3—*Effect of sulfathiazole to PVP ratio ($\geq 1:3$) on the release profile of sulfathiazole from tablets made from 95% alcohol coprecipitated mixture. Key: ○, 1:3 ratio; ■, 1:2 ratio; Δ, 1:1.5 ratio; ●, 1:1 ratio; □, 1.5:1 ratio; ▲, 1:0 ratio crystalline Form I.*

tion. This means that the nonlinear behavior is a function of the sulfathiazole-PVP ratio only.

Examination of the slopes of the previous sulfathiazole release plots clearly shows that a linear relationship does not exist between the release rate and the sulfathiazole to PVP ratio in the solid mixture. To more clearly show this relationship, the sulfathiazole dissolution rates were calculated and tabulated in Table I. In addition, the relative rates obtained by calculating the ratio of the observed

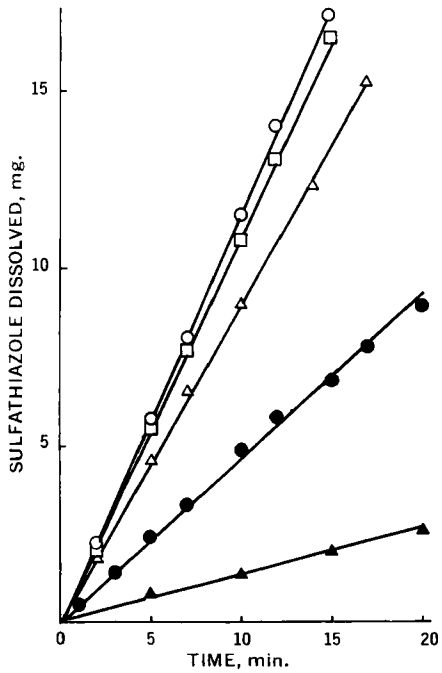

Figure 4—*Effect of sulfathiazole to PVP ratio ($\leq 1:3$) on the release profile of sulfathiazole from tablets made from 95% alcohol coprecipitated mixture. Key: ○, 1:3 ratio; □, 1:5 ratio; Δ, 1:10 ratio; ●, 1:20 ratio; ▲, 1:0 ratio crystalline Form I.*

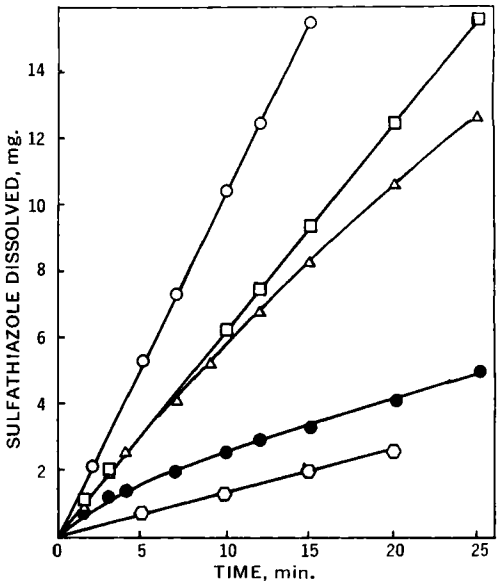

Figure 5—*Effect of sulfathiazole to PVP ratio on the release profile of sulfathiazole from tablets made from aqueous coprecipitated mixture. Key: ○, 1:5 ratio; □, 1:1.5 ratio; Δ, 1:1 ratio; ●, 2:1 ratio; ○, crystalline sulfathiazole Form I as reference.*

rate to the rate of the pure crystalline sulfathiazole Form I were plotted *versus* the weight fraction of PVP in the tablet (see Fig. 6). To provide some insight as to all possibilities the initial and limiting slopes of the nonlinear rate curves are both shown. The shape of this plot indicates that indeed this is a complex system and most likely involves more than one mechanism. It is interesting to note that both the initial (except the 3:1 ratio mixture) and limiting slopes appear to fall on a plateau. The apparent plateau of the limiting slopes fell on the relative rate of one indicating that in these cases the sulfathiazole rates were not influenced by the presence of PVP in the tablets. If this is the case, then, it implies that the surface is covered by a sulfathiazole Form I layer that is controlling the rate of dissolution.

Mechanical Mix Studies—If this is true a mechanical mix of sulfathiazole and PVP in the same ratios should provide limiting dissolution rates corresponding to the lower plateau. For this purpose tablets compressed from mechanical mixes of the above ratios were run, and the results are shown in Fig. 7. Unlike the coprecipitated systems, the mechanical mix systems did not show nonlinear plots, and unexpectedly there was no appreciable enhancement of the sulfathiazole dissolution rate due to the presence of PVP in the tablet. This may indicate that a layer of sulfathiazole I is controlling the release rate after the break shown in the nonlinear release plots.

X-ray Diffraction Studies—The nonlinear curves are yet to be explained. One possibility may be that phase changes in the nonlinear systems are occurring during the dissolution process. In addition the role of PVP in the apparent enhancement of the sulfathiazole dissolution rate of coprecipitated mixtures remains unanswered. Since the mechanical mix dissolution rates were not

Table I—Experimental Relative Release Rates of Sulfathiazole as a Function of PVP Weight Fraction

PVP Wt. Fraction	Absolute Sulfathiazole Release Rate		Relative[a] Sulfathiazole Release Rate	
	Initial	Limiting	Initial	Limiting
0.25 (3:1)	0.135	—	—	—
0.40 (1.5:1)	0.510	0.138	3.78	1.02
0.50 (1:1)	0.520	0.140	3.85	1.04
0.60 (1:1.5)	0.520	—	3.85	—
0.67 (1:2)	0.680	—	5.04	—
0.75 (1:3)	1.155	—	8.90	—
0.83 (1:5)	1.100	—	8.15	—
0.91 (1:10)	0.934	—	6.91	—
0.95 (1:20)	0.450	—	3.33	—

[a] Relative to a pure sulfathiazole crystalline Form I tablet.

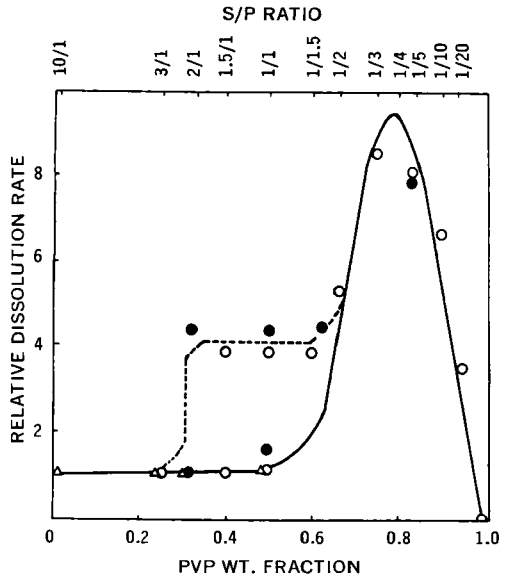

Figure 6—*Relative release rate of sulfathiazole (compared to a 1.0 crystalline Form I) as a function of PVP weight fraction in tablet. Key: ○, coprecipitated from 95% alcohol solution; ●, coprecipitated from water; △, mechanical mixture.*

appreciably enhanced, there is a possibility that again different phases are present in the coprecipitated mixtures.

At this point X-ray diffraction studies were undertaken in an attempt to unravel some of these factors. X-ray diffraction patterns for all powders including pure PVP, all forms of sulfathiazole, and all mixtures were obtained. Figures 8 and 9 show that sulfathiazole Forms I and II can be readily differentiated. Figure 10 shows that pure PVP does not show any crystallinity, and that its presence should therefore not interfere with the characterization of the form of sulfathiazole present. Interestingly all powder mixtures, which exhibited a break in their tablet release curves, showed diffraction peaks indicating the presence of crystallinity, supposedly due to the form of sulfathiazole present. All the coprecipitated powder mixture ratios which showed some degree of crystallinity exhibited essentially sulfathiazole Form I diffraction peaks, except the 3:1 which also exhibited sulfathiazole Form II diffraction peaks. The powder mixtures which exhibited linear tablet release curves, on the other hand, showed no diffraction peaks. For example the diffraction pattern of a 1:2 sulfathiazole to PVP ratio powder mixture which did not exhibit any crystallinity is also shown in Fig. 10.

This implies that sulfathiazole may be present in the higher PVP mixtures in the amorphous form of either the free or complexed sulfathiazole. The absence of apparent crystallinity also could be due to an extremely fine dispersion of sulfathiazole in these systems as opposed to a coarse dispersion of sulfathiazole in systems exhibiting crystallinity.

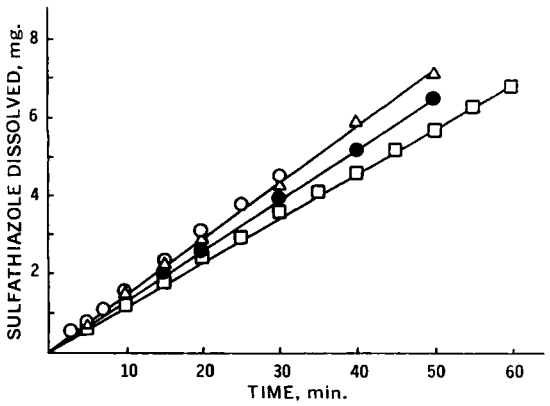

Figure 7—*Milligrams of sulfathiazole released as a function of time from mechanical mixtures containing different ratios of sulfathiazole to PVP. Key: □, 10:1 ratio; △, 3:1 ratio; ○, 1:1 ratio; ●, 1:0 ratio.*

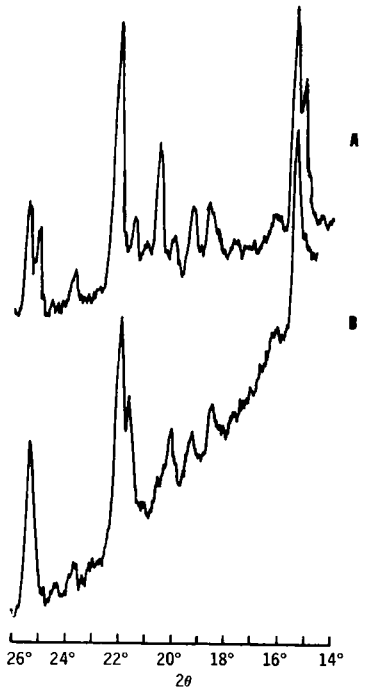

Figure 8—*Comparison of X-ray diffraction spectra of powder and tablet, sulfathiazole Form I. Key: A, powder; B, tablet.*

It would be highly desirable if the degree of crystallinity could be determined as a function of the dissolution time. For this purpose a special holder was devised so that several tablets could be placed in a holder permitting X-ray diffraction spectrograms to be obtained for tablets. For this technique the glass slide normally used for powder samples was replaced by a methylmethacrylate slide of the same dimensions. Three holes of the same diameter as the tablets used for the dissolution studies were drilled in a vertical straight line and close enough to each other so that all three tablets touched each other when put in place (see Fig. 11). This minimized diffraction peaks caused by the methylmethacrylate itself. Figures 8 and 9 show that this technique is valid as tablets made of sulfathiazole Form I or II exhibited the same X-ray diffractograms as their powders.

The 1.5:1 sulfathiazole-PVP ratio mixture was used to make a complete study; that is, comparing the powder X-ray diffraction pattern of the above powder before compression with the tablet X-ray diffraction pattern after compression and then with the tablet

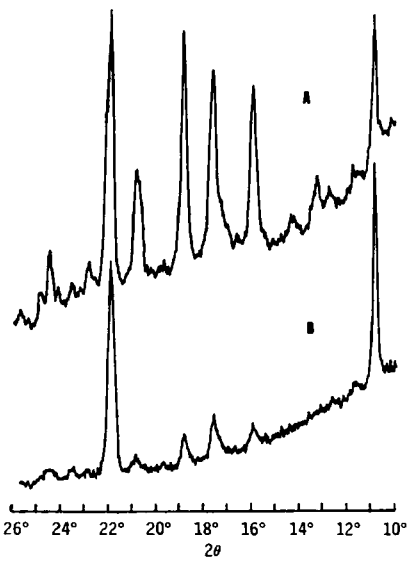

Figure 9—*Comparison of X-ray diffraction spectra of powder and tablet, sulfathiazole Form II. Key: A, powder; B, tablet.*

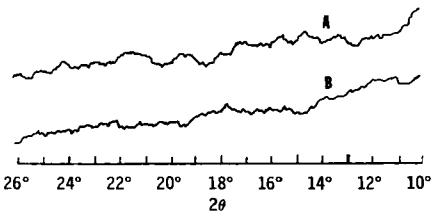

Figure 10—*X-ray diffraction spectra. Key: A, 1:2 sulfathiazole to PVP ratio of a coprecipitated powder; B, PVP (mol. wt. 10,000) powder.*

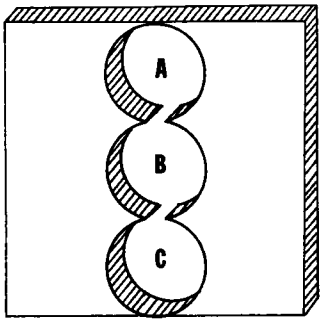

Figure 11—*Methylmethacrylate holder for X-ray diffraction studies on tablets. Tablets are mounted in openings A, B, and C so that their edges touch each other in the center thereby exposing maximum tablet surface to the X-ray beam.*

X-ray diffraction pattern after dissolution was allowed to proceed. The three patterns so obtained were superimposed on the same plot, one above the other to facilitate comparison, and are shown in Fig. 12. All instrument controls were maintained at the same settings for all runs to permit a direct comparison. Interestingly the degree of crystallinity initially seemed to be considerably less than pure sulfathiazole tablets and was definitely enhanced by the dissolution process as shown by the increase in the sharpness and height of all peaks.

The above study was also made using the 3:1 sulfathiazole to PVP ratio. Interestingly Form II as well as Form I of sulfathiazole was present suggesting the presence of both forms in the 3:1 ratio mixture. Again the sharpness and height of all peaks increased, but peaks of both forms continued to remain.

Solubility Studies—None of the above, however, explains the initial rate plateau. It cannot be due to PVP in solution greatly increasing the solubility of sulfathiazole as this was not supported by the mechanical mix data. Nevertheless, the solubility of crystalline sulfathiazole Form I was investigated as a function of PVP concentration at 37°, the temperature of the authors' dissolution experiments. These results are given in another communication (14). It was found that the apparent sulfathiazole Form I solubility doubled with each 3% PVP in solution. This obviously could not explain the initial plateau or the following sharp increase with increasing PVP concentration in the solid phase (see Fig. 6), and indicates that the observed phenomenon could not be explained on the basis of simple complex formation in the solution phase. Comparison of the two apparent plateaus indicates that the rate of sulfathiazole release is initially about 4.0 times faster than the limiting sulfathiazole release rates. These initial rates can only be due to the dissolution of a sulfathiazole-PVP complex or some other high energy form of sulfathiazole. The crystalline sulfathiazole Form II can be ruled out as its solubility is only 1.7 times higher than the Form I (10). For this reason the solubility of the noncrystalline sulfathiazole-PVP coprecipitates was studied. The results are published in another communication (14). They clearly show that in these systems there exists a higher energy form of sulfathiazole which indeed exhibits a solubility that is about 4 times greater than that of crystalline sulfathiazole Form I. This agrees well with the ratio of the initial and limiting rates of the sulfathiazole release in the plateau region.

Comparison of the Simultaneous Sulfathiazole-PVP Release Rates—The above indicates that in the plateau regions the rates are controlled by either the high energy form or crystalline Form I being out front.

This implies that the PVP initial release as compared to the sulfathiazole release is relatively faster than that predicted by the sulfathiazole-PVP solid ratio. This must be true if the outer layer is to be depleted of any PVP. In addition the outer layer must be sufficiently thick so as to cause the concentration of PVP in solution at the tablet interface to be negligible; otherwise, the sulfathiazole release would be much greater than that of the free sulfathiazole.

This can be confirmed by comparing the sulfathiazole and PVP initial release for the same tablets as a function of time. For this purpose the simultaneous release of sulfathiazole and PVP from tablets were plotted for the 3:1, 2:1, and 1:1 sulfathiazole to PVP ratios. These are shown in Fig. 13.

For the 3:1 sulfathiazole to PVP ratio tablet the initial release of sulfathiazole should have been 3 times as fast as the initial release of PVP if both of their solid-liquid interfaces are to remain at the surface of the tablet. Instead the opposite relative rate is observed as Fig. 13 shows that the PVP is released about 2.7 times faster than the sulfathiazole. It has been shown (15) for binary drug mixtures that the relative movement of their solid-liquid boundaries can be calculated from the following relationship:

$$\frac{S_2}{S_1} = \frac{Q_2/A_2}{Q_1/A_1}$$

where S is the distance the drug boundary has moved, Q is the amount of drug released per area of tablet surface at time, t, and A is the concentration of drug in tablet expressed as g./ml. of tablet. The subscripts 2 and 1 refer to Drugs 2 and 1, respectively. Since the initial rates of sulfathiazole and PVP release are linear, the respective Q's can be replaced by the corresponding initial rates of release. This indicates that the PVP solid-liquid interface in the 3:1 system is initially receding 8 times faster than the sulfathiazole solid-liquid interface. A similar analysis using Fig. 13 for the 2:1 and 1:1 sulfathiazole-PVP ratio tablets reveals that the PVP solid-liquid interface is initially moving about 5 times faster in the 2:1 ratio and 1.7 times faster in the 1:1 ratio. Figure 13 also shows that the initial relative rates are not maintained, but decrease with time. This is to be expected. As the PVP boundary moves away from the sulfathiazole boundary its release rate would decrease as it must pass through the formed sulfathiazole layer which obviously must be becoming larger with time. The release of sulfathiazole, on the other hand, occurs through the diffusion layer on the tablet surface which remains constant with time. Only the concentration of complexed sulfathiazole at the surface can change due to the decrease in PVP concentration caused by the increase in the sulfathiazole layer thickness with time. The relative release of PVP as compared to sulfathiazole will decrease until the steady-state condition is reached. At this point the PVP boundary will have sufficiently moved away from the sulfathiazole boundary so that its release rate has decreased to that of "congruent" release, *i.e.*, the ratio of the dissolution rates of the two components is proportional to the mixture ratio in the tablet at this congruent dissolution point, the two

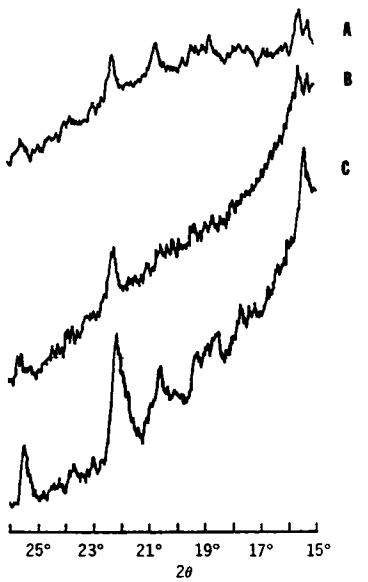

Figure 12—*X-ray diffraction spectra for 1.5:1 ratio of sulfathiazole to PVP (coprecipitated mixture). Key: A, prepared powder; B, compressed tablet before dissolution; C, compressed tablet 30 min. after dissolution.*

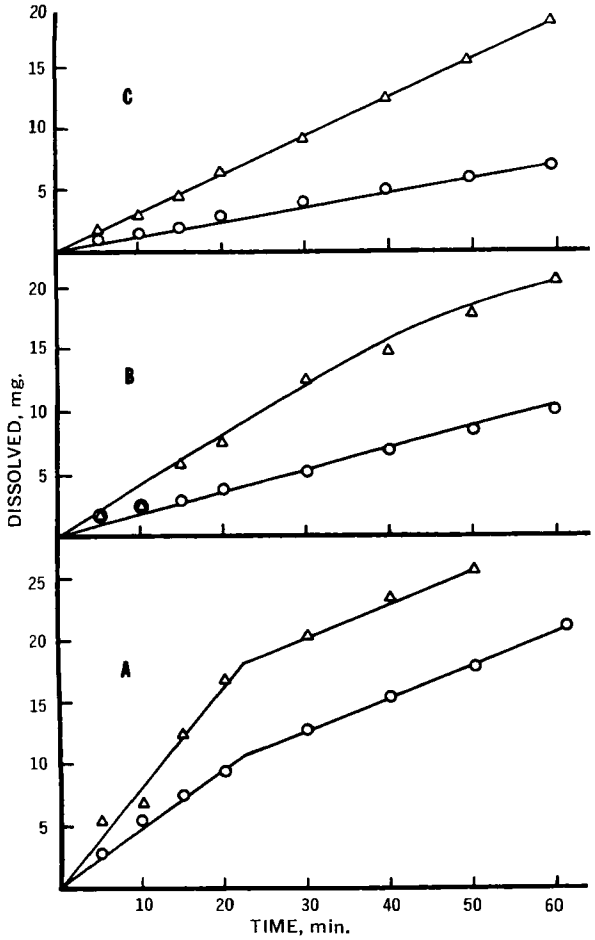

Figure 13—*Release profiles of both sulfathiazole and PVP from tablets made from the higher ratios of sulfathiazole to PVP (coprecipitated mixtures). Key: A, 1:1 ratio curves; B, 2:1 ratio curves; C, 3:1 ratio curves; ○, sulfathiazole release data; Δ, PVP release data.*

boundaries remain at a fixed distance away from each other, and the individual release rates will be given by (13):

$$G_{\text{sulfathiazole}} = \frac{D_s C_s + D_s^* C_s^*}{h}$$

$$G_{\text{PVP}} = \frac{D_{\text{PVP}}\, C_{\text{PVP}}^{\circ}}{h + (\tau/\epsilon)(S_2 - S_1)}$$

Figure 13 shows that only the 1:1 sulfathiazole to PVP ratio actually reached the above steady state as the other ratios did not reach congruent release. Although the 2:1 and 3:1 ratios showed greater relative boundary movements, it is postulated that the other two systems had as yet not reached the steady state. The need for more time to establish the steady state in these systems can be explained on the basis of two factors. First, the PVP boundary must recede much further from the sulfathiazole boundary before the steady state is reached. Second, as the concentration of sulfathiazole in the tablet increases, it presents a tighter and more dense barrier to the release of PVP; that is, the porosity of the sulfathiazole layer will decrease. As an example, the relative porosity of the proposed external layer of the 1:1 ratio tablet will be 25% less than the 2:1 ratio tablet and 50% less than the 3:1 ratio tablet. This effect is magnified by the fact that generally the tortuosity of the resulting outer matrix increases with a decrease in porosity (16). Calculations using the above result indicate that the relative ratio of the porosity to tortuosity of the 1:1, 2:1, and 3:1 ratio tablets are, respectively, 9, 4, and 2. This indicates that the tortuosity of the 2:1 ratio tablet outer matrix is 50% greater than the 1:1 ratio tablet, and the 3:1 system is 50% greater than the 2:1 system.

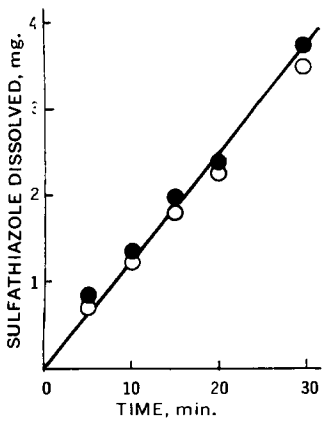

Figure 14—*Milligrams of sulfathiazole released as a function of time from a crystalline Form II tablet in 0.1% PVP as compared with crystalline Form I tablet in water. Key: ●, Form I in water; ○, Form II in 0.1% PVP.*

Unlike the other high sulfathiazole to PVP ratio system, the 3:1 sulfathiazole to PVP weight ratio tablet did not yield higher initial rates, but showed only the limiting rate which appears to be controlled by the crystalline Form I of sulfathiazole. This would indicate that the PVP weight ratio in this system is sufficiently low to cause the PVP solid-liquid boundary to move rapidly enough relative to that of sulfathiazole to immediately reach the condition where the PVP concentration at the tablet surface is too low to influence the sulfathiazole release. Since there is appreciable sulfathiazole crystalline Forms I and II initially present as shown by the X-ray diffraction patterns, the crystalline Form I rapidly establishes control. In addition the concentration of PVP at the interface is not high enough to prevent sulfathiazole reversion from the amorphous or crystalline Form II to crystalline Form I. This conversion has been shown to be very rapid in systems lacking PVP (10).

Sulfathiazole Release into PVP Solutions—In order to better confirm some of the postulates made regarding the sulfathiazole release from high sulfathiazole to PVP ratio tablets, their sulfathiazole release rate was determined using PVP solutions as the release media.

Figure 14 shows the sulfathiazole release from a pure sulfathiazole Form II tablet using 0.1% PVP as the solvent system. For comparison purposes the release of a pure sulfathiazole Form I tablet into water is also shown. Since both yield identical rates, it can be safely assumed that sulfathiazole Form II will convert to sulfathiazole Form I so rapidly that the faster release of Form II is not at all detected. When these studies were repeated but using 10% PVP rather than 0.1% PVP, it was found that the sulfathiazole Form II tablet yielded a faster release rate than a Form I tablet (see Fig. 15). Evidently the reversion of Form II to Form I is blocked by PVP at these concentrations.

Next the 3:1 sulfathiazole to PVP weight ratio tablet was run using a 10% PVP solution. If the precipitation of Form I sulfathiazole is prevented by the 10% PVP solution we should observe the dissolution rate of a Form II surface layer and Fig. 16 clearly confirms this possibility as the initial rate is doubled in 10% PVP solution as compared to its release in water. Interestingly the 3:1 system

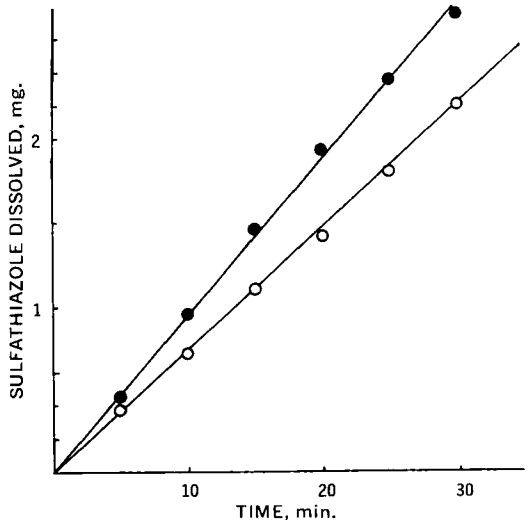

Figure 15—*Effect of 10% PVP solution on the release profile of sulfathiazole from tablets made from crystalline sulfathiazole Forms I and II. Wax-mounted tablets (17) were used. Key: ○, Form I; ●, Form II.*

yielded a limiting slope which was equal to that of the pure sulfathiazole Form II tablet and left little doubt of the conclusion that Form II was the controlling form of sulfathiazole.

A tablet made from a 1.5:1 sulfathiazole to PVP weight ratio mixture was then run in 10% PVP solution. In this system X-ray diffraction powder patterns indicated crystallinity due to the presence of Form I sulfathiazole crystals. The results of dissolution in 10% PVP solution and separately in water are shown in Fig. 17 and clearly show that the break in the curve was still present. This confirms the initial presence of sulfathiazole Form I in the tablet and indicates that the limiting release rate is due to preferential leaching of PVP leading to outer layer enrichment with respect to sulfathiazole and not due to reversion, as the 3:1 system has shown it does not occur.

As would be expected the initial and limiting rates are higher (due to higher PVP concentration in the solution) in 10% PVP solution. In addition the break in the release curve occurs at a later time due to a slower PVP boundary movement caused by the lower concentration gradient of PVP and a faster sulfathiazole boundary movement caused by an increase rate of solution.

Finally the 1:1 sulfathiazole to PVP weight ratio tablets were run in 10% PVP solution and compared to release in water (see Fig. 18). X-ray diffraction patterns have shown no indication of crystallinity and this was confirmed by this run, as the 10% PVP run showed no breaks in the release curve. Evidently the break in the water runs was due to reversion of sulfathiazole to Form I.

Sulfathiazole Release Via the PVP Carrier Effect—The above results indicate that as the sulfathiazole to PVP ratio in the tablet decreases the PVP boundary movement relative to the sulfathiazole boundary is also decreasing. In view of this, it appears safe to assume that at the higher PVP weight fractions the PVP is close enough to the unbound sulfathiazole layer to significantly contribute to the release profile and cause sulfathiazole release rates to be greater than those of the plateau region (see Fig. 6). That is, the increase in rate can be attributed in part to the presence of sufficiently high concentrations of PVP at the interface to increase the effective solubility of sulfathiazole and hence its apparent dissolution rate. It is proposed that

$$G_S^T = G_S + G_S^{PVP-S}$$

where G_S^T = rate of total sulfathiazole that is dissolving; G_S° = rate of sulfathiazole leaving the tablet as unbound sulfathiazole; G_S^{PVP-S} = rate of sulfathiazole leaving the tablet as bound sulfathiazole. The carrier effect of PVP (*i.e.*, the sulfathiazole transported as PVP complex) can be significant as the apparent solubility of sulfathiazole should be doubled with each increment of 3% increase in PVP concentration in solution (14).

The above relationship may thus explain the increase in the sulfathiazole release rate with the increase in the PVP-sulfathiazole mixture ratio from the plateau region to the peak in the curves of Fig. 6.

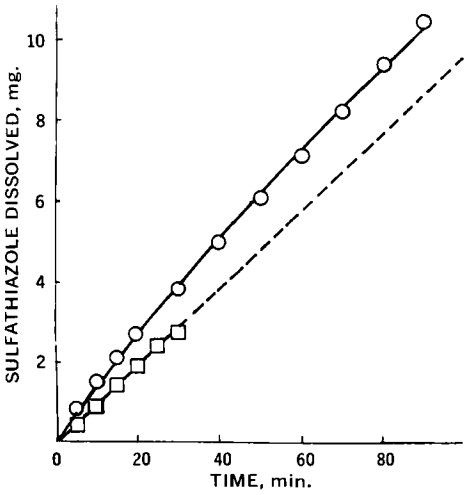

Figure 16—*Milligrams of sulfathiazole released in 10% PVP solution as a function of time made from 3:1 ratio of sulfathiazole to PVP alcoholic coprecipitate. Release of sulfathiazole from a Form II tablet in 10% PVP solution is shown as reference. Wax-mounted tablets (17) were used. Key: ○, 3:1 ratio; □, crystalline Form II.*

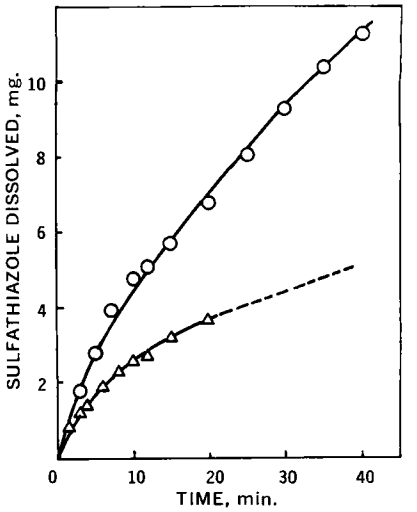

Figure 17—*Milligrams of sulfathiazole released from a 1.5:1 sulfathiazole to PVP (alcoholic coprecipitate) as a function of time using water and 10% PVP as the release medium. Key: △, water; ○, 10% PVP solution.*

It would also appear from the above that the steady state would be reached very rapidly and that the higher PVP weight fractions should exhibit congruent PVP-sulfathiazole release. The relative rates of PVP and sulfathiazole were compared for tablets containing high PVP weight fractions (above 1:1.5 sulfathiazole to PVP weight ratio) and found to be congruent confirming the authors' viewpoint (see Fig. 19).

Theoretical Calculations of Sulfathiazole Release Rate—Theoretical calculations of the apparent sulfathiazole dissolution rate were then made for each sulfathiazole to PVP ratio tablet independent of the experimental release rate of either sulfathiazole or PVP. The following method was used: diffusion coefficients of sulfathiazole and PVP were independently determined in a diffusion cell (12).

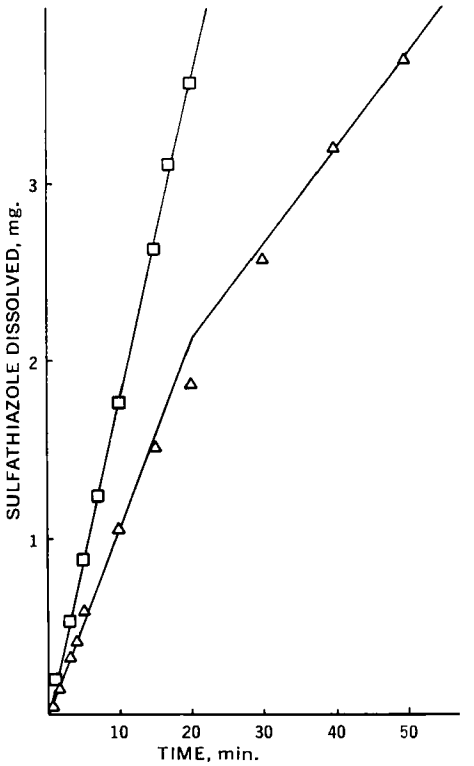

Figure 18—*Milligrams of sulfathiazole released from a 1:1 sulfathiazole to PVP (alcoholic coprecipitate) as a function of time using water and 10% PVP solution as the release medium. Key: △, water; □, 10% PVP solution.*

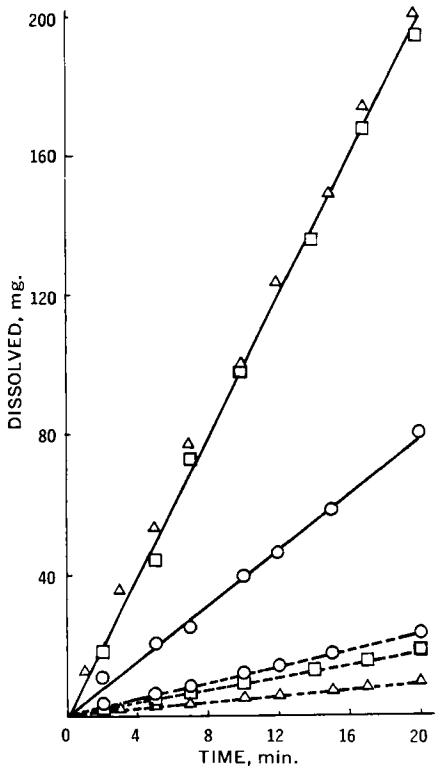

Figure 19—*Release profile of both sulfathiazole and PVP from tablets made from the smaller ratios of sulfathiazole to PVP (95% alcohol coprecipitated mixture). Key: △, 1:20 ratio; □, 1:10 ratio; ○, 1:3 ratio; —, PVP release; - - - sulfathiazole release.*

The concentration of PVP at the tablet interface necessary to provide congruent release can be roughly estimated by assuming that the sulfathiazole concentration at the interface is equal to the solubility of the unbound sulfathiazole. Since the PVP at the surface, however, carries sulfathiazole with it into solution, the first estimate of the PVP concentration at the tablet surface based only on unbound sulfathiazole must be readjusted. This calculation process of alternately calculating the PVP and sulfathiazole concentration at the tablet surface based on the newest estimate of the other species concentration must be continually repeated until the values converge. These calculations were automatically performed by a reiteration process using a programmed tape on the electronic calculator for all sulfathiazole to PVP ratios. It should be emphasized that the above process determines the expected sulfathiazole release rate based only on the diffusion coefficient, solubility of unbound sulfathiazole Form I, and the sulfathiazole to PVP ratio in the tablet. The above was repeated using the solubility of unbound sulfathiazole Form II and again using the solubility of unbound amorphous sulfathiazole. The results are shown in Table II. Theoretical curves based on the solubility of the above three forms are shown by Fig. 20 as smooth curves. For comparison purposes the experimental data are shown by the plotted points. Examination of the agreement of the theoretical curves with the experimental data at the lower PVP weight fractions strongly indicates that the release rate is controlled by a layer of free sulfathiazole, the initial rate being controlled by the amorphous form and the limiting rate by the crystalline Form I.

Table II—Calculation of Theoretical Relative Release Rates of Sulfathiazole from Tablets Containing Low PVP Weight Fractions

PVP Wt. Fraction[a]	—Sulfathiazole Relative Release Rates— Crystalline Form I	Crystalline Form II	Amorphous
0.20 (4:1)	1.01	1.73	3.88
0.30 (7:3)	1.01	1.75	4.02
0.40 (1.5:1)	1.02	1.78	4.22
0.60 (1:1.5)	1.04	1.90	4.54
0.70 (3:7)	1.07	2.10	5.12
0.80 (1:4)	1.12	2.36	14.23

[a] Numbers in parentheses indicate the sulfathiazole to PVP ratio.

Low Sulfathiazole-PVP Ratio Mechanical Mix Studies—The question now remains—what of the behavior of the system beyond the peak in Fig. 20 as the theoretical curves go up to infinity rather than drop as shown by the experimental points in this region?

To investigate this latter region, mechanical mixes of the high sulfathiazole to PVP ratio tablets were studied. Unfortunately tablets made from these mechanical mixes did not produce tablets which were stable when undergoing dissolution. Within 20 sec. after immersion, tablets released a fine powder which was emanating from the surface. It appeared that the PVP was rapidly released leaving the crystalline sulfathiazole behind. Since the tablet had lost its binding structure provided by the PVP prior to dissolution, the sulfathiazole was released as a fine powder. Obviously the release of sulfathiazole at the higher concentration of PVP in these mechanical mix systems due to the above phenomenon has no meaning in the context of the present study as there is a large increase in the surface area which would accompany the transformation of the system from a tablet to a powder.

The Effect of Sulfathiazole to PVP Ratio on the PVP Release Rate—It would be expected that the rate of sulfathiazole release at the very high PVP weight fraction is controlled by the rate of release of PVP itself. At the very high PVP-sulfathiazole ratios, despite the high solubility of PVP, the sulfathiazole boundary would tend to recede more rapidly than the PVP boundary. This situation would tend to make the PVP dissolution rate the rate-determining step for the release of both components. Presumably when the PVP-sulfathiazole mixture corresponds exactly to the peak in Fig. 6, both boundaries would coexist at the surface.

It would be highly desirable at this point to be able to semiquantitate the dissolution rate process if possible. Since the rate of PVP release may very well be the rate-determining step, the release of PVP rather than the release of sulfathiazole was studied as a function of the sulfathiazole-PVP ratio. The milligrams of PVP dissolved as a function of time were plotted for the previous tablets made from alcohol coprecipitated mixtures with sulfathiazole to PVP solid ratios of 1:20, 1:10, 1:5, 1:3, and 1:2, and they are shown by Fig. 21.

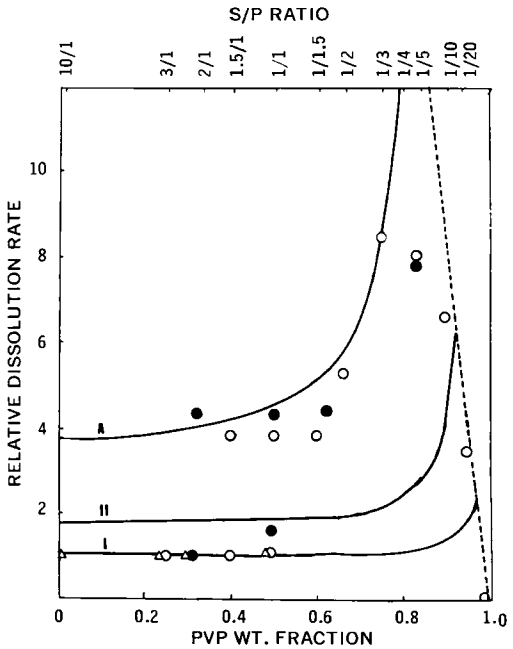

Figure 20—*Comparison of theoretical and experimental relative release rates of sulfathiazole compared to a 1:0 crystalline Form I as a function of PVP weight fraction in tablet. Key: Experimental points: ○, 95% alcohol coprecipitated mixtures; ●, aqueous coprecipitated mixtures; △, mechanical mixtures. Theoretical curves for controlling layers: I, sulfathiazole Form I; II, sulfathiazole Form II; A, amorphous sulfathiazole.*

Comparison of these plots show that the release rate of PVP generally decreases as its concentration in the solid phase decreases. In addition all release curves are linear and pass through the origin. As in the sulfathiazole release a plot of the relative PVP release rate *versus* the PVP weight fraction was made. Superimposed on the same figure a plot of the sulfathiazole to PVP ratio in the solid is also shown (see Fig. 22). Interestingly these two plots clearly show that although the PVP release rate is increasing rapidly, the fraction of possible PVP binding site occupied by sulfathiazole is rapidly decreasing.

Figure 22 also shows that the PVP release ceases to increase at high PVP weight fractions and appears to plateau. This indicates at this point that the PVP release is independent of the concentration of sulfathiazole in tablet. As in the sulfathiazole release pattern, a PVP plateau implies that a layer of PVP is out front. If the steady-state condition is reached, the PVP layer should be controlling the rate of release of both species. As previously stated this steady state can readily be characterized as it requires that the sulfathiazole and PVP must be simultaneously released in a congruent ratio. For this purpose the milligrams of PVP and sulfathiazole released as a function of time for tablets made from alcohol coprecipitated mixtures of sulfathiazole to PVP, ratios of 1:20, 1:10, and 1:3 were plotted and, are shown in Fig. 19. It is seen that the rates are congruent and therefore have reached the steady state.

Sulfathiazole Release at Very Low Sulfathiazole to PVP Ratios—If the above is true, the grams of sulfathiazole released with each gram of PVP is given by the sulfathiazole to PVP ratio existing in the solid phase. Obviously the product of the above ratio and the PVP release rate experimentally observed at the same PVP fraction of the solid will yield the corresponding sulfathiazole release that should agree with the experimental value. The above calculations were made and presented in Table III. The relative sulfathiazole release rates as a function of the PVP weight fraction in the solid were also calculated and are presented in Table III.

These calculated relative sulfathiazole release rates are shown by the smooth curve represented by a dashed line at the high PVP weight fractions in Fig. 20. It is seen that there is excellent agreement between the calculated curve and the experimental points in the corresponding region which indicates that a PVP layer out front can be used to quantitatively explain the sulfathiazole release rates in this region.

Proposed Model—The results of an extensive study involving the sulfathiazole-PVP system have been presented in this report. These results can be best summarized by simply presenting a physical model that satisfactorily explains the observed release rates of all sulfathiazole to PVP weight ratio systems.

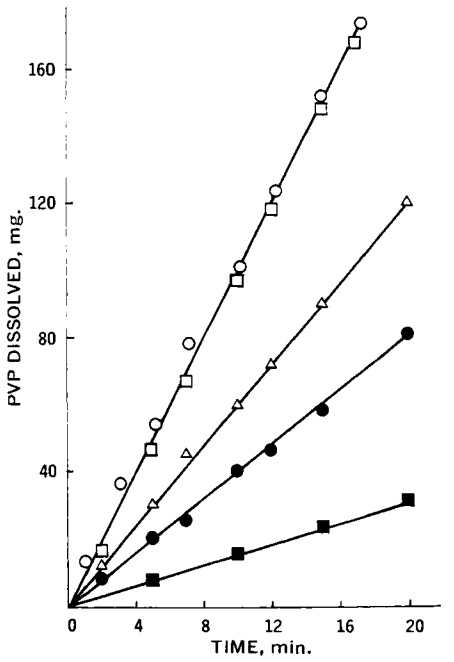

Figure 21—*Effect of sulfathiazole to PVP ratio ($\leq 1:2$) on the release profile of PVP from tablets made from coprecipitated mixtures. Key: ○, 1:20 ratio; □, 1:10 ratio; △, 1:5 ratio; ●, 1:3 ratio; ■, 1:2 ratio.*

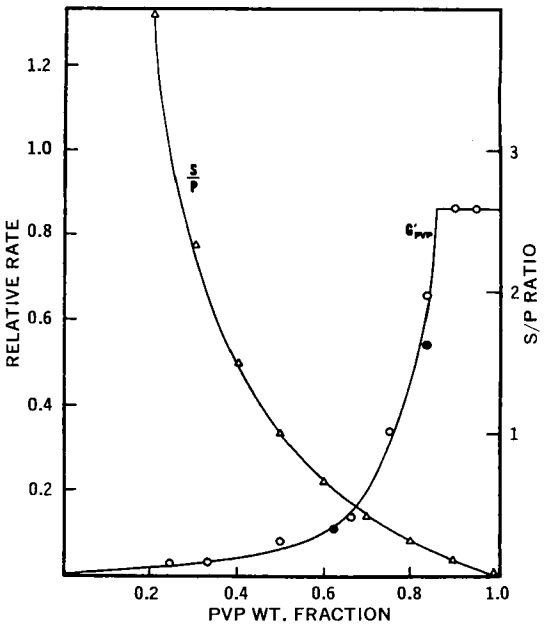

Figure 22—*Relative release rate of PVP compared to 95% alcohol-treated pure PVP as a function of PVP weight fraction in tablets. Superimposed the sulfathiazole to PVP ratio as a function of PVP weight fraction in tablet. Key: ○, coprecipitated from 95% alcohol; ●, coprecipitated from water; △, sulfathiazole to PVP ratio.*

In these solid mixtures there can be a number of phases present and include unbound and bound PVP, bound and unbound sulfathiazole in any of its known forms. As a result of these possibilities a tablet which initially has all of the phases homogeneously dispersed throughout the tablet can develop segregation of these phases as the dissolution proceeds, particularly at or near the exposed regions of the tablet due to preferential dissolution rates of one phase. As a matter of fact this segregation can produce layers of phases. Whenever this occurs the outermost layer (the layer containing the component whose boundary moves the slowest) will have the greatest influence on the dissolution process particularly if the next layer has sufficiently receded to prevent any significant contribution to the overall rate. Schematics of proposed models are shown in Fig. 23 and show the changes that can occur in a tablet as dissolution proceeds. Initially at zero time, the tablet can contain unbound PVP, unbound sulfathiazole, and the sulfathiazole-PVP complexes. The mechanical mixture tablets initially will not contain any complexes and the coprecipitated mixture tablets may not initially contain any unbound sulfathiazole or PVP.

As time progresses to a finite time, t_1, Fig. 23 shows that a layer can develop whose composition is different from the original composition of the tablet. The inner region, however, maintains its original composition unchanged. The formation of this layer can be the result of one or more components of the original composition being preferentially released due to a more favorable combination of factors, such as solubility, diffusion coefficients, degree of dis-

Table III—Comparison of Calculated and Experimental Relative Release Rates of Sulfathiazole from Tablets Containing High PVP Weight Fractions

PVP Wt. Fraction[a]	PVP Release Rate[b]	S/PVP Ratio	Sulfathiazole Relative Release Rate—— Calcd.	Exptl.
0.83 (1:5)	10.2	0.2	15.10	8.15
0.91 (1:10)	10.2	0.1	7.55	6.91
0.95 (1:20)	10.2	0.05	3.78	3.33

[a] Numbers in parentheses indicate the sulfathiazole to PVP ratio. [b] PVP release rate obtained from the plateau region exhibited by the higher PVP weight fraction tablets, see Fig. 22.

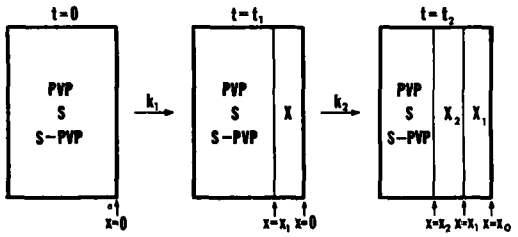

Figure 23—*Physical model that describes the release of PVP, sulfathiazole, and complex from a tablet as a function of time. Initial conditions are shown at* $t = 0$. *A primary barrier layer,* X_1, *is formed at* $t = t_1$, *and a secondary barrier layer,* X_2, *is formed at* $t = t_2$.

sociation, *etc.* On the other hand, this layer can be the result of possible phase reversions brought about by new components being precipitated at the tablet interface or even the result of changes occurring in the solid phase at the interface. An example of this first process would be the dissolution of unbound amorphous sulfathiazole and simultaneous precipitation of crystalline sulfathiazole Form I. An example of the second process would be the release of sulfathiazole from the PVP complex at the surface by dissociation, the PVP remaining behind in the solid phase. Regardless of the mechanism by which a new layer is produced, its thickness will continue to grow and in doing so will decrease the release rates of components releasing from the rear. The thickness will continue to grow until large enough to sufficiently slow down the release of other components to that of congruent release. At this point the layer thickness will remain constant.

As time further progresses, the possibility of a secondary layer appearing either in front or behind the above primary layer must also be considered. This is illustrated by the schematic in Fig. 23 representing the system at time equal to t_2. This can be exemplified by utilizing the same examples used to illustrate the primary layer. If at t_1 the primary layer is composed of amorphous sulfathiazole and then the precipitation of crystalline sulfathiazole Form I occurs, it would obviously produce a secondary layer in front of the primary layer.

Regardless of the number of phases present, however, only the outer phase will control the release rates of all components at the steady state, *i.e.*, congruent release rates will be observed with the outer layer component setting the absolute rate. Prior to the steady-state condition only those phases whose solid-liquid boundaries are sufficiently close to the tablet surface to yield appreciable solution concentration of its component at the tablet surface will have any influence on the release rates of other tablet components.

Correlation of Data with Proposed Model—For sulfathiazole to PVP ratios equal to or greater than 3, it would appear that only Step 1 occurs with crystalline sulfathiazole Form I as the outer layer X. For this reason the sulfathiazole release in this region is equivalent to a pure sulfathiazole crystalline Form I tablet.

For sulfathiazole to PVP ratios between 3 and 1, Step 2 in addition to Step 1 also occurs. First, amorphous rather than the crystalline Form I sulfathiazole outer layer, X, is apparently produced in Step 1, but in Step 2 a secondary layer, X, of crystalline sulfathiazole Form I is then apparently formed in front of the previous amorphous sulfathiazole layer, X_2. For these reasons the initial sulfathiazole release in this region is equivalent to a pure amorphous sulfathiazole tablet, whereas the limiting sulfathiazole release in this region is equivalent to a pure sulfathiazole crystalline Form I tablet.

For sulfathiazole to PVP ratios from 1:0.3, Step 2 does not apparently occur, *i.e.*, only Step 1 producing an amorphous sulfathiazole layer out front. In this range of tablet weight ratios, however, the thickness of the outer layer at the steady state is not thick enough to prevent appreciable concentrations of PVP in solution at the tablet surface. As a result the sulfathiazole release is increased by the carrier effect of PVP. This contribution of the carrier effect to the overall sulfathiazole release rate is greatly compounded as the PVP weight fraction in the tablet is increased because the steady-state thickness of the amorphous sulfathiazole outer layer decreases. This decrease in steady-state thickness is very sensitive to the PVP weight fraction for the following reasons: as the weight fraction of sulfathiazole in the tablet decreases, its boundary recedes faster, whereas, the weight fraction of PVP is increasing at the same time causing its boundary to recede more slowly. This decrease in the steady-state thickness as the PVP weight fraction increases causes the PVP concentration at the interface, on the other hand, to greatly increase as the PVP weight ratio increases. Recalling that a doubling of the sulfathiazole solubility occurs for each 3% incremental increase of PVP in solutions the above increase in PVP concentration at the surface in turn causes the sulfathiazole boundary to recede even faster. This combination of events causes the rate of sulfathiazole release to rise exponentially with PVP weight fraction increase in tablet.

As the PVP weight fraction is further increased the thickness of the amorphous sulfathiazole layer continues to decrease until it becomes zero. At this point the sulfathiazole and PVP boundaries recede at the same rate, and as a result, the tablet retains the integrity of the original composition of the tablet at its surface throughout the duration of the experiment. Interestingly, this precise PVP weight fraction will yield maximum sulfathiazole release rates. The unbound sulfathiazole in solution at the interface will be equal to the solubility of the amorphous form which is the maximum possible, and the PVP concentration will also be a maximum yielding a maximum PVP carrier effect, *i.e.*, at lower PVP weight ratios the concentration of PVP at the interface decreases which will yield a smaller carrier effect; whereas at higher PVP weight ratios the concentration of sulfathiazole at the interface decreases. Figure 20 indicates that the above condition occurs at a PVP weight fraction between 0.78 and 0.80.

At PVP weight fractions above 0.80, it appears the PVP is out front, and the sulfathiazole boundary moves further behind as the PVP weight fraction increases so that its release eventually drops to zero.

Application and Importance of Results—The results of this investigation show that the rate of solution of sulfathiazole can be greatly increased by the use of coprecipitation techniques with PVP. Since others have shown that similar results have been obtained with other drugs and materials, it appears that the coprecipitation technique can be made generally applicable.

Before this technique can be generally applied, however, it is necessary not only to elucidate the possible mechanisms by which this increase in solubility can occur, but also the necessary techniques must be developed to allow future investigators the tools to adequately define their preliminary systems before meaningful changes can be scientifically designed rather than using the state of the art as it is now done.

It is felt that the major contribution of this report lies in the techniques developed and described and the application of these techniques in successfully delineating the various mechanisms operative in the different sulfathiazole-PVP systems. By using a parallel approach it is hoped that other investigators will be able to increase solubility and dissolution rates of poorly soluble drugs.

Many times the treatment of a patient requires that a solution of a drug be administered. A solution is also required specifically for intravenous injections. An example of this need would be neoplastic agents which can not be given orally in many instances due to poor stability and absorption from the gastrointestinal tract and must be given by intravenous injections. As a result a number of potentially effective drugs have not as yet been tested in humans.

REFERENCES

(1) T. Higuchi and R. Kuramoto, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 393(1954).

(2) *Ibid.*, **43**, 398(1954).

(3) D. Guttman and T. Higuchi, *ibid.*, **45**, 659(1956).

(4) J. M. Stone, U. S. pat. 3,089,818 (1963).

(5) T. Suyama, Japanese pat. 411656 (1963).

(6) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55**, 1323 (1966).

(7) J. Chambron and C. Sadron, *Compt. Rend.*, **252**, 3247(1961).

(8) T. Tachibana and A. Nakamura, *Kolloid-Z.*, **203**, 130(1965).

(9) G. Milosovich, *J. Pharm. Sci.*, **53**, 484(1964).

(10) W. I. Higuchi, P. D. Bernardo, and S. C. Mehta, *J. Pharm. Sci.*, **56**, 200(1967).

(11) P. Molyneux and H. P. Frank, *J. Am. Chem. Soc.*, **83**, 3169 (1961).

(12) S. C. Mehta, A. P. Simonelli, and W. I. Higuchi, to be published.

(13) W. I. Higuchi, N. A. Mir, and S. J. Desai, *J. Pharm. Sci.*, **54**, 1405(1965).

(14) S. C. Mehta, A. P. Simonelli, and W. I. Higuchi, to be published.

(15) P. Singh, S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *J. Pharm. Sci.*, **56**, 1542(1967).

(16) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55**, 1230(1966).

(17) S. J. Desai, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **54**, 1459(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received January 21, 1969, from the *College of Pharmacy, University of Michigan, Ann Arbor, MI 48104*

Accepted for publication March 3, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.

This investigation was supported by contract PH 43 68 1284 with the National Cancer Institute, U. S. Public Health Service, Bethesda, Md.

Degradation Mechanisms for Water-Soluble Drugs in Solid Dosage Forms

J. THURØ CARSTENSEN,* MODEST OSADCA, and S. H. RUBIN

Abstract □ Thiamine hydrochloride, when tableted with magnesium stearate and microcrystalline cellulose, degrades in a pattern whereby an apparent equilibrium is reached. The amount of intact thiamine at equilibrium depends on the amount of moisture present and exhibits a minimum at about 5.5 percent moisture content. A model is proposed to explain this phenomenon. Thiamine dissolved in the water present adsorbs on the microcrystalline cellulose and the thiamine present in the monolayer degrades totally, whereas the thiamine in layers beyond the monolayer does not degrade.

Keyphrases □ Solid dosage forms—water-soluble drug degradation □ Degradation, drug—solid dosage forms □ Thiamine degradation, tablets—moisture effect □ Model—thiamine degradation, tablets □ Mechanism—thiamine degradation, solid dosage forms

The manner in which drugs degrade in solid dosage forms is still rather obscure. Systematic investigations in this field have been made with pure drug by Leeson and Mattocks (1), Kornblum and Sciarrone (2, 3), Reinstein and Higuchi (4), and Garrett (5). Two phenomena seem to prevail in degradation of pure crystals: (*a*) the degradation is mostly zero order (2–5) although, at higher temperatures, three phases (induction period, acceleration period, and decay period) occur; (*b*) degradation is hypothetically confined to a liquid layer on the crystal (1, 4). Leeson and Mattocks (1) demonstrated that, in the presence of moisture in the vapor phase, the degradation of acetylsalicylic acid crystals took place in the sorbed moisture layer.

Publications dealing with degradation patterns in solid dosage forms are more plentiful, although by no means common. Tardif (6) and Carstensen *et al.* (7–9) have described the logarithmic decay patterns (*i.e.*, apparent first-order degradations) of vitamins in solid dosage forms, the effect of moisture, and the existence of equilibria and have pointed out that such data are amenable to Arrhenius (or Van't Hoff)-type treatment. These type investigations are of practical interest, in the sense that treatment is facilitated for those investigators primarily interested in product stability. The fact that many of these patterns are first-order types seems, however, to imply that phenomena other than those prevalent in degradation of the pure crystals are the determining factors. For, if the solid dosage form was to be considered a dry, noninteracting system, then zero-order patterns should prevail. If, on the other hand, sorbed moisture layers, saturated with drug, were the media of decomposition, then (drawing an analogy with a very concentrated "suspension") the degradation should also be a zero-order type.

The fundamental question then, is, what actual physical phenomena, aside from the purely chemical reaction, are involved? This has not been the subject of published reports in the case of solid dosage forms, and it is the intent of this study to examine whether some of the principles established for pure, solid drugs, by some model, might apply to solid dosage forms as well. In this type endeavor it is, of course, important to select a simple system, since, the more components are present, the more difficult the task of assigning effects to one particular species or interaction. For this reason, microcrystalline cellulose[1] was selected as the tablet base for the study.

The properties and uses of microcrystalline cellulose in tablet formulations have been described by Reier and Shangraw (10), Richman *et al.* (11), and Enezian (12), and the use of microcrystalline cellulose as a direct compression excipient is by now common practice in the pharmaceutical industry. The important feature here is that it is possible to prepare tablets consisting of only drug, the microcrystalline cellulose, a disintegrant, and a lubricant.

[1] Marketed as Avicel by the American Viscose Corp., Marcus Hook, Pa.