Dissolution Studies of Povidone–Sulfathiazole Coacervated Systems

A. A. BADAWI ˣ and A. A. EL-SAYED

Received February 22, 1979, from the *Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo, Egypt.* Accepted for publication November 20, 1979.

Abstract □ Sulfathiazole and povidone were coacervated by many methods, indicating complexation of the two compounds. The coacervated complex had a higher solubility and dissolution rate than did sulfathiazole. It resisted the action of dilute acids and alkalies, suggesting a helical structure with sulfathiazole situated between two povidone chains and a hydrogen bond linking the amino groups of the sulfathiazole to the oxygen of povidone. Upon addition of precipitants for sulfathiazole, the povidone portion attempted to compensate and to solubilize the whole complex; hence, partial precipitation or coacervation occurred. A model is given to describe the dissolution profile of the different coacervate systems prepared.

Keyphrases □ Povidone—coacervation with sulfathiazole, dissolution of coacervated system □ Sulfathiazole—coacervation with povidone, dissolution of coacervated system □ Coacervation—povidone and sulfathiazole, dissolution of coacervated system

The interaction of povidone with drugs is of theoretical and practical importance since it may influence their availability, efficacy, and transport (1).

Povidone reduced the dissolution rate of salicylic acid. This reduction was attributed to increased viscosity or to complex formation (2). When incorporated into compressed disks of ephedrine hydrochloride, potassium chloride, and sodium chloride, the polymer reduced their dissolution rates (3, 4).

However, several investigators described increases in solubility of various compounds by povidone (5, 6). A solid dispersion of reserpine, a poorly water-soluble drug, with the polymer enhanced its *in vitro* dissolution and absorption (7). A povidone–digitoxin coprecipitate exhibited enhanced dissolution and absorption, as indicated by a decrease in the LD_{50} value (8). Increased dissolution of hydroflumethiazide (9), hydrochlorothiazide (10), and ellipticine (11) was achieved by incorporation of the polymer into similar products.

Simonelli *et al.* (12, 13) described the preparation of a high energy form of sulfathiazole when it is dissolved in an alcoholic solution of povidone and evaporated to dryness or when an aqueous solution of its sodium salt and povidone is acidified. There was no explanation for the precipitation of the polymer along with the sulfathiazole, although the polymer by itself is not affected by acids. The nature of this high energy form and the mechanism of its formation were not given. Only the possible formation of a complex was reviewed.

The present study attempted to explain the coprecipitation from another viewpoint. The study was based on the facts that povidone is a linear polymer and that, when its complex with sulfathiazole is treated with acids that precipitate sulfathiazole, the whole molecule coils to form a coacervate. When dried, the coacervate droplets give colloidal particles of sulfathiazole complexed with the polymer, and a higher dissolution rate results.

In this study, sulfathiazole and povidone were mixed to form solutions. Different precipitants for sulfathiazole or for the polymer then were added separately. The products were examined microscopically to follow the development of the coacervate droplets and their transformation to solid colloidal particles.

EXPERIMENTAL

Interaction of Sulfathiazole and Povidone—*Method 1*—Sulfathiazole[1] and povidone[2] (mol. wt. 25,000), 5 g each, were dissolved in 25 ml of alcohol, which was evaporated on a water bath. When the volume was reduced to ~5 ml, a sample was taken and examined microscopically. Evaporation was continued, and a dried alcohol coacervate was obtained.

Method 2—Five grams of each of the two materials was dissolved by heating in 15 ml of alcohol. Water was added dropwise, the colloidal dispersion formed, and this precipitate coacervate was examined.

Method 3—Sulfathiazole, 5 g, was placed in a beaker, and 8 *N* NaOH was added until dissolution was complete. Povidone, 5 g, was added and dissolved by stirring. An equivalent quantity of 8 *N* HCl was added dropwise with continuous stirring to give the pH coacervate.

Method 4—Sulfathiazole, 5 g, was dissolved using an equivalent amount of 8 *N* NaOH. Povidone, 5 g, was added and dissolved by stirring. Resorcinol[1] solution, 20%, was added dropwise, and the colloidal dispersion obtained was investigated microscopically. This dispersion is referred to as the resorcinol coacervate.

Each process was repeated using different ratios of sulfathiazole and povidone. Each ratio will be described by its percent content of povidone.

Microencapsulation of Sulfathiazole—Sulfathiazole powder, 3 or 10 g, was suspended in 50 ml of 2% povidone solution. Resorcinol solution, 20%, was added dropwise with continuous stirring until complete phase separation was obtained. The microcapsules were filtered and air dried. The product was used without sieving because it was free flowing and very fine.

Separation of pH Coacervate into Its Components—Sulfathiazole, 7 g, was dissolved in 50 ml of water containing an equivalent quantity of sodium hydroxide. Povidone, 3 g, was added and dissolved by stirring. Hydrochloric acid, 5 *N*, was added dropwise with continuous stirring. When the povidone was consumed, the sticky mass that formed was withdrawn. The rest of the equivalent volume of the acid was added, and the fine particles that precipitated were filtered and dried.

Dissolution Study—Weighed quantities of each prepared sample were compressed into tablets using a single-stroke compression tablet machine[3] with a 1-cm die. The tablets were compressed to an average hardness of 5–6 kg. Each tablet was fixed to the top of a test tube with melted wax and placed at a constant level into a 600-ml beaker containing 400 ml of water as the dissolution medium.

Hydrodynamic equilibrium was established with a constant stirrer placed at a fixed distance from the tablet surface. At each time interval, a 0.5-ml aliquot was withdrawn, diluted suitably, and assayed spectrophotometrically at 283 nm.

Solubility Study—Weighed excesses of sulfathiazole and of each sample of the coacervated systems were placed in 25-ml ampuls containing 10 ml of water. The ampuls were sealed and placed on a rotating shaft (42 rpm) immersed in a water bath at 25 ± 1°. Duplicate samples were withdrawn, filtered, and assayed spectrophotometrically at 283 nm.

RESULTS AND DISCUSSION

Figure 1 shows the coacervate formed in all cases. These coacervates

[1] BP 1963.
[2] BASF (West Germany)
[3] Diaf, Copenhagen, Denmark.

0022-3549/80/0500-0492$01.00/0

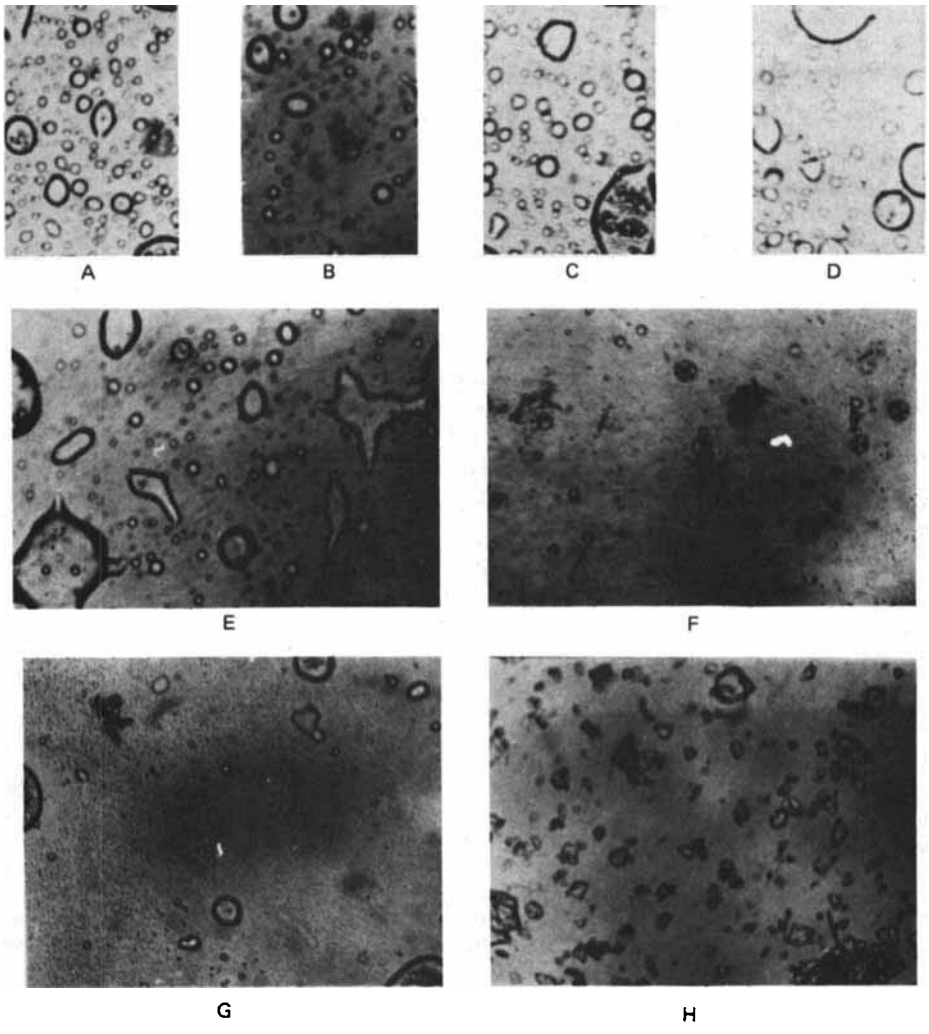


Figure 1—*Photographs (×40) of sulfathiazole–povidone coacervated systems. Key: A, alcohol coacervate; B, pH coacervate; C, precipitate coacervated; D, resorcinol coacervate; E, coalesced coacervate; F, dried coacervate; G, dried coacervate treated with water; and H, sulfathiazole precipitated with pH change.*

exhibited brownian motion. Upon continuous stirring, they coalesced into larger drops, which dried to give very fine particles. These particles were distributed in water to give spherical colloidal particles in the submicron range, which rapidly went into solution.

Coacervation can be considered as an intermediate state between true solution and complete precipitation, or it can be described as partial precipitation. When a solution of the sodium salt of sulfathiazole is treated with hydrochloric acid or when its hydrochloride salt solution is treated with sodium hydroxide, precipitation of amorphous or crystalline sulfathiazole normally occurs. On the other hand, povidone is not affected by acids or alkalis.

The coacervate formed when sulfathiazole and povidone both are present can be explained only by the interaction of povidone and sulfathiazole to form a complex with intermediate properties. Povidone retains its linear polymeric structure, which may be coacervated. Sulfathiazole still is affected by its precipitants. The povidone portion counteracts the precipitation of sulfathiazole and tries to solubilize the whole complex. The molecule thus is coiled around itself, thereby reducing its surface area that holds minimal water and reducing the total free energy of the coacervated system.

On the same basis, povidone is very soluble in both water and alcohol and does not precipitate if its solution in one solvent is treated with the other solvent. Sulfathiazole alone in its alcoholic solution precipitates as amorphous particles or as crystals when it is mixed with water. Again, the coacervate formed when the alcoholic solution of the two materials was mixed with water indicated the formation of a complex that was coacervated by the nonsolvent addition phase separation method. On the other hand, when the aqueous solution of sulfathiazole sodium and povidone was treated with resorcinol solution, which is a coacervating agent for povidone, a coacervate containing sulfathiazole was formed.

When sulfathiazole was suspended in the povidone solution and resorcinol solution was added, the coacervated povidone droplets microencapsulated the sulfathiazole particles, which, upon drying, were free flowing. The dissolution of the microcapsules was exactly the same as that of pure sulfathiazole when the coat to core ratio was 1:10 and slightly higher when the ratio was 1:3 (Fig. 2). This result indicated that the povidone did not interact with sulfathiazole when it was in the insoluble form and that the coacervated povidone microencapsulated the drug to form a protective layer. It rapidly went into solution to give sulfathiazole since the coacervation of povidone by resorcinol is reversible and since solvation of povidone occurs once the equilibrium is disturbed.

During the preparation of the pH coacervate, it was clear that the

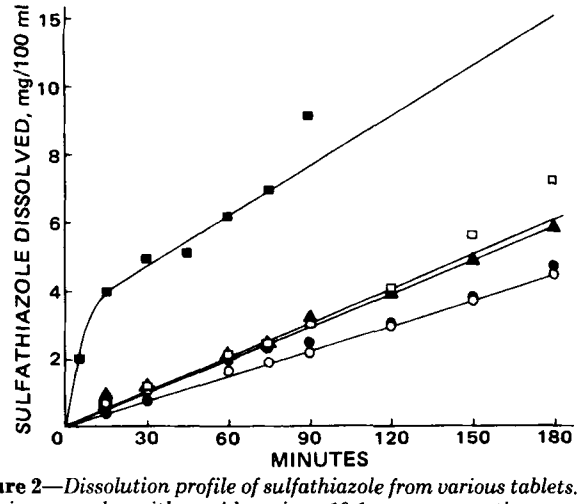


Figure 2—*Dissolution profile of sulfathiazole from various tablets. Key: ●, microcapsules with povidone in a 10:1 core-coat ratio; ▲, microcapsules of povidone in a 3:1 core-coat ratio; ■, alcohol coacervate with 20% povidone; ○, amorphous sulfathiazole; and □, physical mixture containing 20% povidone.*

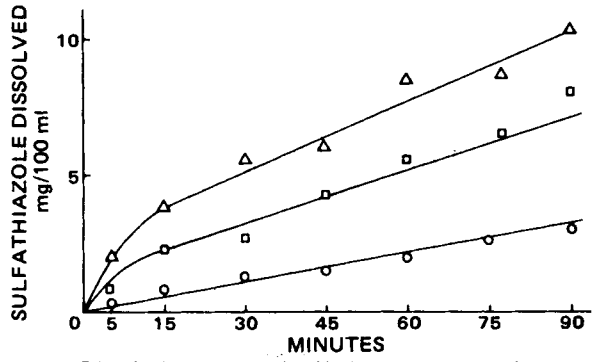


Figure 3—*Dissolution profile of sulfathiazole from a pH coacervate containing 40% povidone made with different volumes of equilibrium liquid. Key: ○, 100 ml; □, 50 ml; and △, 25 ml.*

volume of the equilibrium liquid greatly affected the product (Fig. 3). The large volume caused dissolution of the coacervated complex. Therefore, for preparation of samples for dissolution studies, 12 ml of liquid was used. However, to observe the process sequence, a volume of 50 ml was more suitable. Upon addition of hydrochloric acid by drops, coacervate droplets were formed; they coalesced into a sticky mass upon stirring. When the povidone was consumed, subsequent addition of acid caused the fine precipitated sulfathiazole particles to become enmeshed within the sticky mass. At a low povidone ratio, the sticky mass was small and the fine particles were large. With successive increases in the povidone ratio, the amount of fine particles precipitated was smaller; a homogeneous mass was obtained at 65%.

Figure 4 shows the release profile of sulfathiazole from the two components of the 30% povidone system. The fine particles gave almost the same profile as did sulfathiazole alone, and the sticky mass had a much higher dissolution rate. The mixture of the two compounds had a high initial rate and a slower terminal rate. On this basis, the release profile of sulfathiazole from its alcohol coacervates or its pH coacervates (Figs. 5–8) composed of different weight fractions of povidone could be explained easily.

This profile greatly resembled that of Simonelli *et al.* (12, 13), whose model was divided into five stages. For up to 25% povidone, amorphous

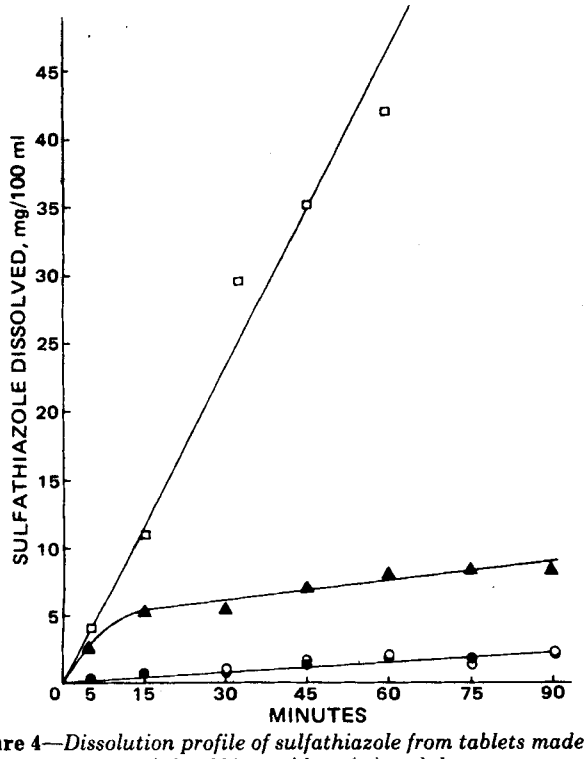


Figure 4—*Dissolution profile of sulfathiazole from tablets made of a pH coacervate containing 30% povidone (▲) and the same proportion separated into a fine powder (○) and a sticky mass (□). The dissolution profile of sulfathiazole is shown for comparison (●).*

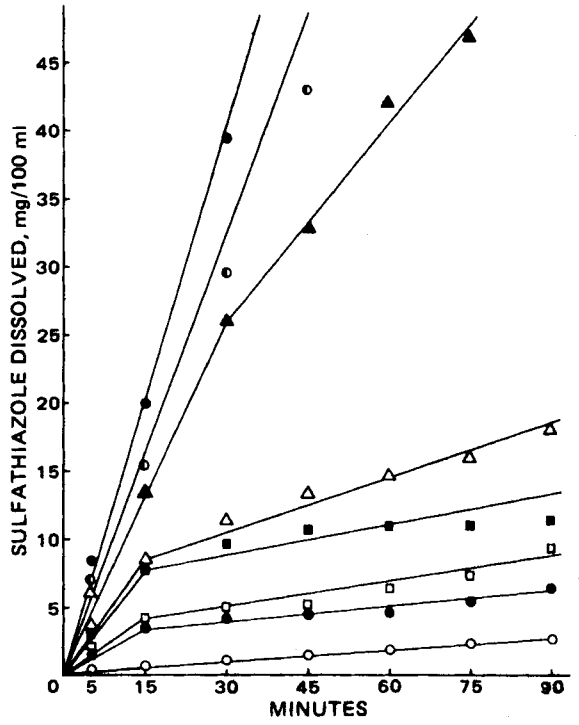


Figure 5—*Dissolution profile of sulfathiazole from tablets made of an alcohol coacervate containing low percentages of povidone. Key: ●, 10%; □, 20%; ■, 30%; △, 40%; ▲, 50%; ◐, 60%; and ⊙, 65%. The dissolution profile of sulfathiazole is shown for comparison (○).*

or unbound sulfathiazole was dissolved to leave an outer layer of crystalline Form I. From 25 to 50% povidone, amorphous sulfathiazole initially formed the outer layer, but a secondary layer of crystalline Form I eventually was formed in front of the previous amorphous layer. From

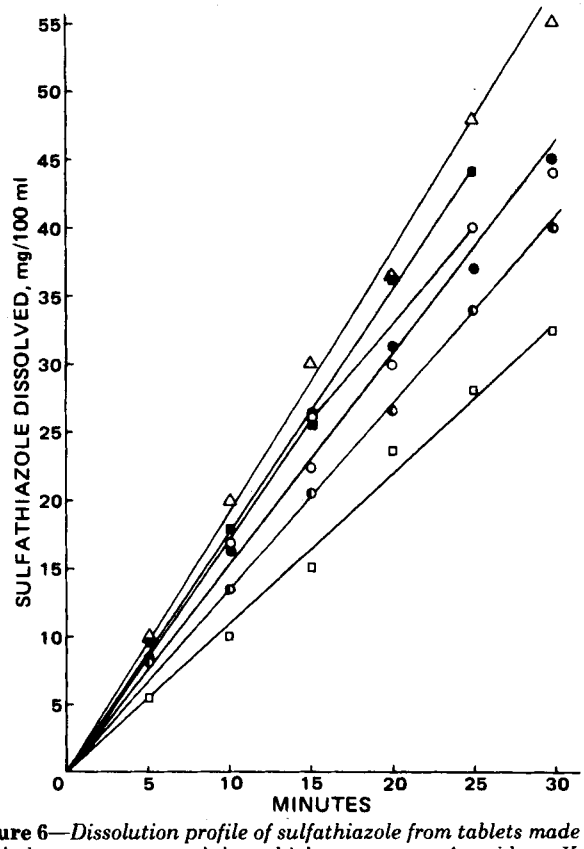


Figure 6—*Dissolution profile of sulfathiazole from tablets made of an alcohol coacervate containing a high percentage of povidone. Key: ◐, 65%; ●, 70%; ■, 75%; △, 80%; ○, 85%; and □, 90%.*

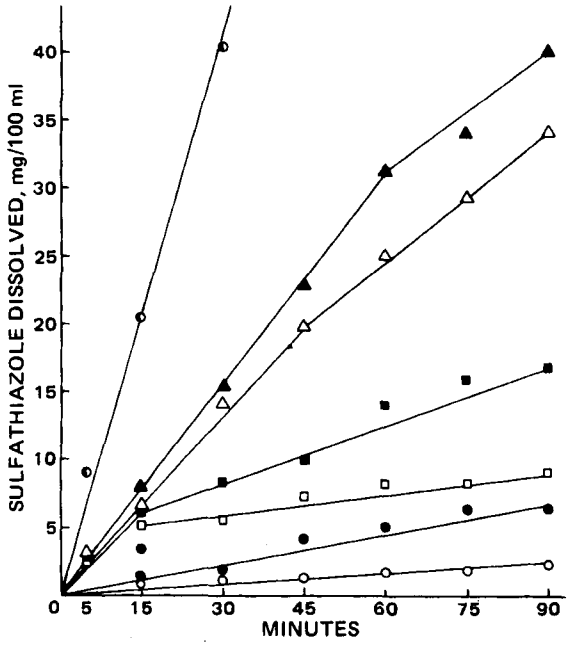


Figure 7—*Dissolution profile of sulfathiazole from tablets made of a pH coacervate containing low percentages of povidone. Key: ●, 20%; □, 30%; ■, 40%; △, 50%; ▲, 60%; and ◐, 70%. The dissolution profile of sulfathiazole is shown for comparison (○).*

50 to 77% povidone, the thickness of the amorphous sulfathiazole layer allowed the povidone to carry the sulfathiazole into solution. As the povidone weight fraction was increased from 78 to 80%, the thickness of the amorphous layer continued to decrease until it became zero. At this point, the sulfathiazole and povidone boundaries receded at the same rate, and the tablet retained the integrity of the original composition throughout the experiment. Above 80% povidone, the povidone boundary was in front and the sulfathiazole boundary moved behind.

In the present work, the dissolution medium was large enough to guard against the precipitation of crystalline Form I. However, the same stages

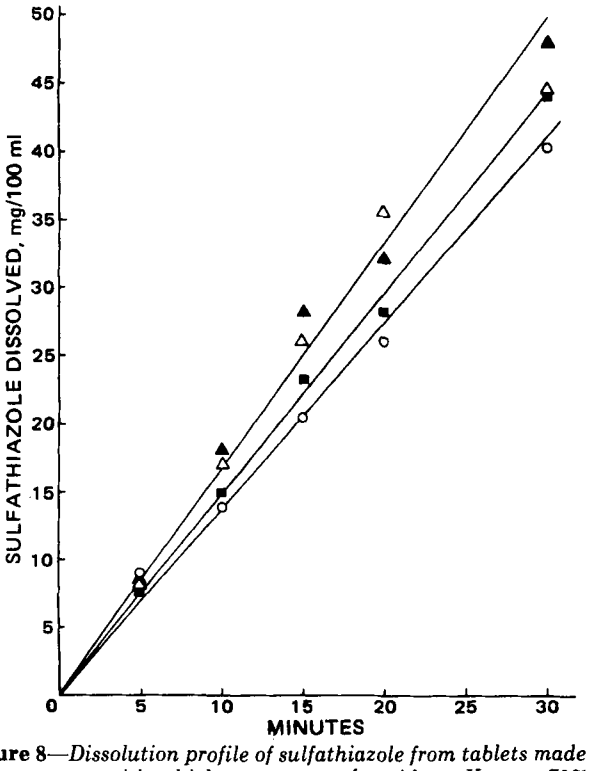


Figure 8—*Dissolution profile of sulfathiazole from tablets made of a pH coacervate with a high percentage of povidone. Key: ○, 70%; ■, 75%; △, 80%; and ▲, 85%.*

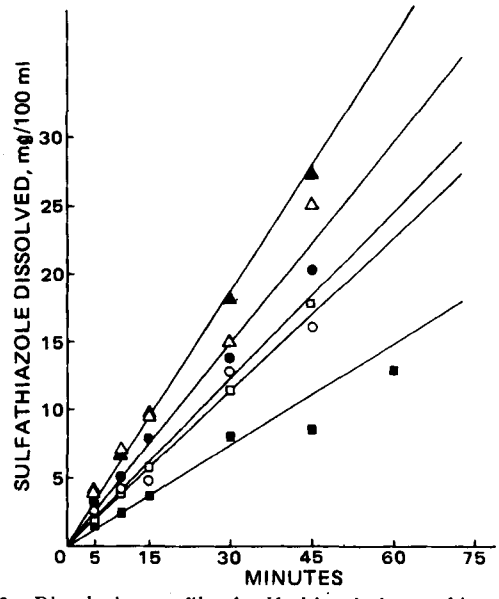


Figure 9—*Dissolution profile of sulfathiazole from tablets made of a resorcinol coacervate containing various percentages of povidone. Key: ○, 10%; ●, 20%; △, 30%; ▲, 40%; □, 50%; and ■, 60%.*

recognized in the dissolution profile (Fig. 9) can be explained by the formation of a highly soluble coacervated complex of sulfathiazole and povidone. At a low povidone content, the coacervated systems contained a lower percentage of the complex and a larger amount of free sulfathiazole. The complex rapidly went into solution, leaving behind the sulfathiazole, which was amorphous in the case of the pH coacervate and was Form I in the case of the alcohol coacervate. Table I shows good agreement between the percent content of the complex within the coacervate and its initial dissolution rate. Also, the solubility of the coacervates tested showed direct dependency on the ratio of the complex.

Increasing the ratio of povidone, *i.e.*, increasing the ratio of the complex, resulted in approachment of the initial and terminal rates. Above 60% povidone, the coacervates gave a line function whose slope increased with increasing povidone content.

From these findings, it was postulated that, in the presence of its excess, sulfathiazole interacted with povidone in the ratio of one molecule of sulfathiazole to four units of povidone; this ratio corresponded to 63.5% povidone. Above this ratio, a greater number of units of povidone participated in the interaction and many complexes were formed; the more polymer that was included, the more soluble was the coacervate. This region was described by Simonelli *et al.* (12) as the carrier region, and this description held well in the present model in which the povidone carried the complexed sulfathiazole to the dissolution medium.

Above 75% povidone, the alcohol coacervates showed a decrease in their dissolution rates, indicating that saturation of the povidone chain oc-

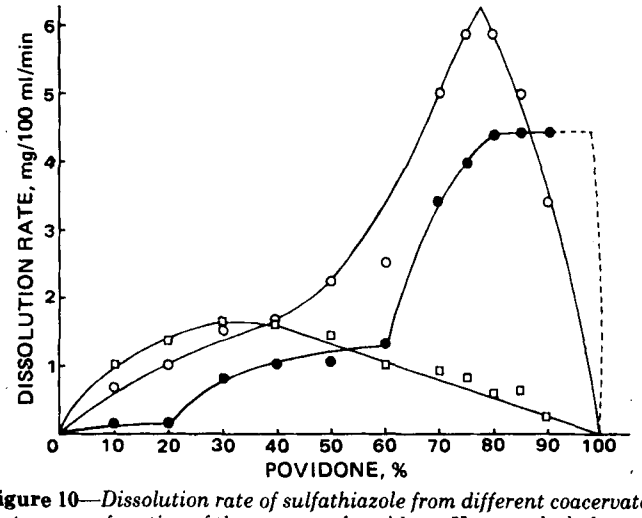


Figure 10—*Dissolution rate of sulfathiazole from different coacervate systems as a function of the percent of povidone. Key: ○, alcohol coacervate; ●, pH coacervate; and □, resorcinol coacervate.*

Table I—Relationship between the Amount of Povidone–Sulfathiazole Complex and the Initial Dissolution Rate and Solubilities of Alcohol Coacervates [a]

Amount of Povidone, %	Amount of Complexed Sulfathiazole, %	Amount of Complex (a), %	Dissolution Rate (b), mg/100 ml/min	Solubility (c) Expressed as Milligrams of Sulfathiazole per Milliliter of Water	a/b	a/c
10	5.74	15.74	0.65	—	24.22	
20	11.48	31.48	1.00	2.45	31.48	12.85
30	17.22	47.22	1.50	—	31.48	
40	22.96	62.96	1.60	5.02	39.35	12.54
50	28.70	78.70	2.25	—	34.98	
60	34.44	84.44	2.50	7.60	37.78	12.43
65	35.00	100.00	4.20	—	23.81	

[a] Solubility of sulfathiazole was 0.78 mg/ml.

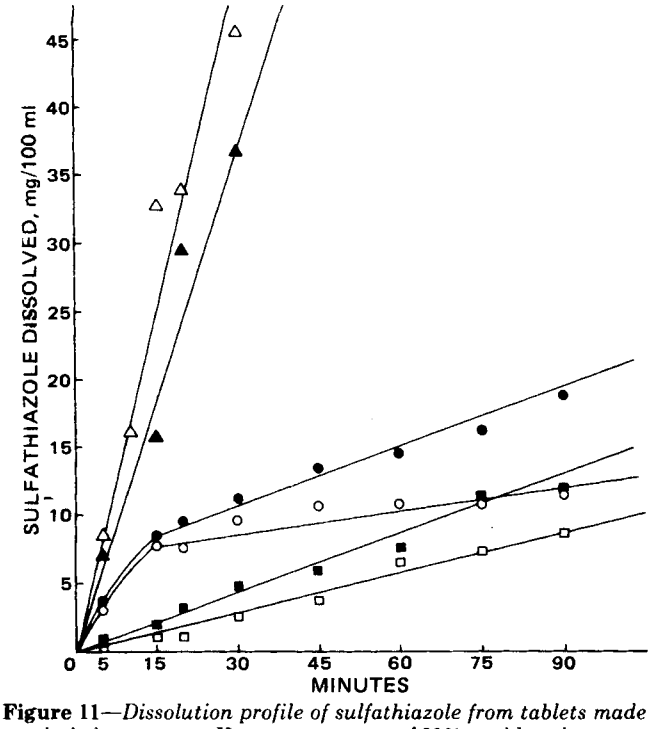


Figure 11—*Dissolution profile of sulfathiazole from tablets made of an alcohol coacervate. Key:* ○, *coacervate of 30% povidone in water;* □, *coacervate of 30% povidone in 0.05* N *HCl;* △, *coacervate of 30% povidone in 0.05* N *NaOH;* ●, *coacervate of 40% povidone in water;* ■, *coacervate of 40% povidone in 0.05* N *HCl; and* ▲, *coacervate of 40% povidone in 0.05* N *NaOH.*

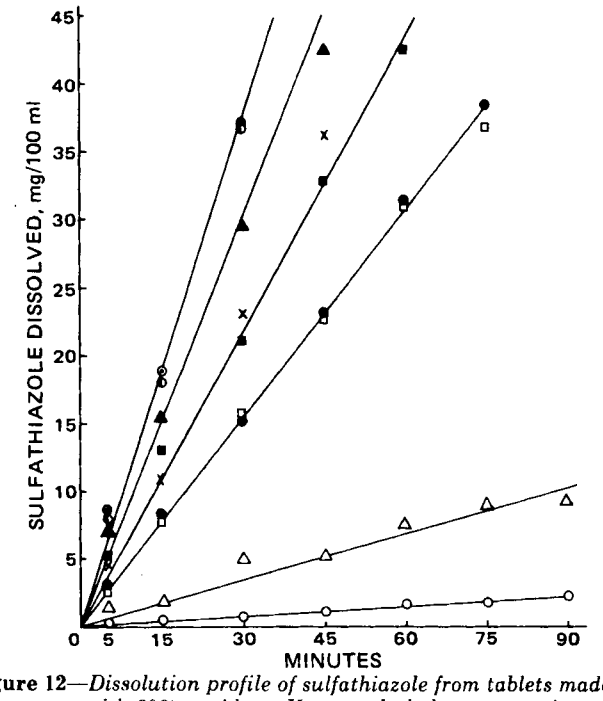


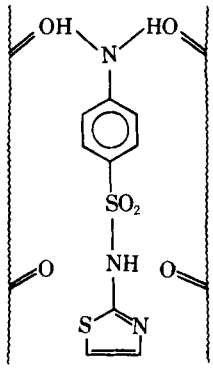
Figure 12—*Dissolution profile of sulfathiazole from tablets made of coacervates with 60% povidone. Key:* ▲, *alcohol coacervate in water;* ◐, *alcohol coacervate in 0.05* N *HCl;* ⊙, *alcohol coacervate in 0.05* N *NaOH;* ●, *pH coacervate in water;* ■, *pH coacervate in 0.05* N *HCl; and* x, *pH coacervate in 0.05* N *NaOH. The dissolution profiles for sulfathiazole tablets in water* (○), *hydrochloric acid* (△), *and sodium hydroxide* (□) *are included for comparison.*

curred at 77.7%, corresponding to eight units of povidone to each molecule of sulfathiazole. The tablet in this region was formed of two entities, the complex and excess povidone, which hindered the dissolution of the complex or its dissolution. With the pH coacervate, such a decline was not noticed. This finding was explained on the basis that the excess povidone was not precipitated with the coacervated complex.

With the resorcinol coacervate system (Fig. 10), a sudden and pronounced increase in the dissolution rate was noticed. A plateau was reached at 40% povidone, and then a linear decline occurred up to 100% povidone. This observation can be explained by the fact that, in the presence of a large excess of sulfathiazole, resorcinol coacervates a complex made of povidone with an equivalent amount of sulfathiazole, leaving its excess in solution as the sodium salt. With an increased povidone concentration, the amount of complexed sulfathiazole increases until the concentration of the two materials are equivalent; this effect yields a product with the maximal dissolution rate. With excess povidone, a mixture of the coacervated complex and coacervated povidone forms, and the access of sulfathiazole to the dissolution medium is hindered. Hence, the decline in the dissolution rate is observed.

Figure 11 shows that 0.05 *N* HCl gave slightly higher dissolution rates of pure sulfathiazole and of the alcohol coacervate containing 30 and 40% povidone. Sodium hydroxide at the same strength had a much higher effect, which was more pronounced in plain sulfathiazole than with the two coacervates. The coacervate with 30% povidone dissolved more rapidly than that with 40% povidone.

Both 60% alcohol and the pH coacervate (Fig. 12) greatly resisted the action of sodium hydroxide and hydrochloric acid. Both reagents had nearly the same dissolution rate, which was slightly higher than that of water. This result may suggest that sulfathiazole is linked by hydrogen bonds through its amino group to the oxygen of the povidone:



The polymer still retains its linearity; upon addition of any precipitant to sulfathiazole, the whole molecule is coiled and coacervated.

REFERENCES

(1) C. H. Hsiao, H. J. Rhodes, and M. I. Blake, *J. Pharm. Sci.*, **66**, 1157 (1977).

(2) M. Gibaldi and H. Weintraub, *ibid.*, **57**, 832 (1968).

(3) A. T. Florence and A. Rahman, *J. Pharm. Pharmacol., Suppl.*, **27**, 55 (1975).

(4) A. T. Florence, P. H. El-Worthy, and A. Rahman, *ibid.*, **25**, 779 (1973).

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

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

(7) E. I. Stupak and T. R. Bates, *J. Pharm. Sci.*, **61**, 400 (1972).

(8) *Ibid.*, **62**, 1806 (1973).

(9) O. I. Corrigan and R. F. Timoney, *J. Pharm. Pharmacol.*, **27**, 759 (1975).

(10) O. I. Corrigan, R. F. Timoney, and M. J. Whelan, *ibid.*, **28**, 703 (1976).

(11) A. Rahman, J. C. Cradock, and J. P. Davignon, *J. Pharm. Sci.*, **67**, 611 (1978).

(12) A. P. Simonelli, S. C. Mehta, and W. I. Higuchi, *ibid.*, **65**, 355 (1976).

(13) *Ibid.*, **58**, 538 (1969).

Quantitative Structure–Activity Relationships in Drug Metabolism and Disposition: Pharmacokinetics of *N*-Substituted Amphetamines in Humans

BERNARD TESTA ˣ and BJARNE SALVESEN *

Received August 20, 1979, from the *School of Pharmacy, University of Lausanne, CH-1005 Lausanne, Switzerland.* Accepted for publication November 26, 1979. *Institute of Pharmacy, University of Oslo, Blindern, Oslo 3, Norway.

Abstract □ Pharmacokinetic data of 15 *N*-alkyl-substituted amphetamines in humans have been the object of a retrospective quantitative structure–activity relationship study. The urinary excretion of amphetamines was shown to decrease with increasing lipophilicity; the correlation equations revealed that, for identical lipophilicities, tertiary amines are excreted faster than secondary amines, which are excreted faster than primary amines. The apparent *n*-heptane–pH 7.4 buffer partition coefficient correlates better with urinary excretion than does the true *n*-octanol–water partition coefficient, probably because it includes a pKa term that accounts for the fraction of the drug present in the tubules as nonionic species. The *N*-dealkylation rate increases with increasing lipophilicity of the substrates (enhanced enzyme affinity) but decreases with increasing bulk of the *N*-substituent that is split off (steric hindrance of initial C_α-hydroxylation).

Keyphrases □ Quantitative structure–activity relationships—*N*-substituted amphetamines, pharmacokinetics, humans □ Amphetamines, *N*-substituted—pharmacokinetics, quantitative structure–activity relationships, humans □ Pharmacokinetics—*N*-substituted amphetamines, quantitative structure–activity relationships, humans

Quantitative structure–activity relationships have many pharmacological and toxicological applications. The correlation equations obtained in such studies often provide valuable steps in the rational design of improved drugs (1).

Suitable results of drug metabolism studies also can provide a valuable biological input to quantitative structure–activity relationship studies. While the results thus obtained could help in designing drugs with improved metabolic profiles, previous investigations (2–5) concentrated entirely on interpreting the correlation equations in terms of reaction mechanisms and of the structural factors influencing the biological response.

One prerequisite of any quantitative structure–activity relationship investigation is the need for quantitative and reliable biological data. This fact may help to explain why applications of quantitative structure–activity relationships to drug metabolism and disposition have been based almost exclusively on results from *in vitro* studies (*e.g.*, protein binding, drug–enzyme interactions, and parameters of *in vitro* biotransformation). In contrast, few, if any, *in vivo* studies have led to successful quantitative structure–activity relationship interpretations.

The present report describes the application of quantitative structure–activity relationship methodology to the results of a pharmacokinetic study of *N*-alkyl-substituted amphetamine derivatives in humans (6). The thoroughness of the work of the previous investigators, the quantitative nature of results, the number (15) of molecules investigated, and the large spread in the biological responses made this study an attractive candidate for a quantitative interpretation in terms of molecular properties. Furthermore, the previous investigators measured the apparent

Table I—Physicochemical and Structural Parameters of Amphetamine and Derivatives

	Compound	Log P_H[a]	$f_{RR'}$[b]	V_R[c]	NH[d]	$C_\alpha H$[e]
I	Amphetamine	−2.26	0.94	—	2	—
II	*N*-Methyl	−1.51	1.17	13.67	1	3
III	*N*-Ethyl	−0.92	1.69	23.90	1	2
IV	*N*-*n*-Propyl	−0.20	2.21	34.13	1	2
V	*N*-2-Propyl	−0.41	2.21	34.12	1	1
VI	*N*-*n*-Butyl	−0.32	2.73	44.36	1	2
VII	*N*-2-Butyl	0.07	2.73	44.35	1	1
VIII	*N*-Benzyl	3.18	2.83	56.07	1	2
IX	*N*,*N*-Dimethyl	−0.27	1.40	13.67	0	3
X	*N*,*N*-Diethyl	0.58	2.44	23.90	0	2
XI	*N*,*N*-Di-*n*-propyl	2.38	3.48	34.13	0	2
XII	*N*,*N*-Di-*n*-butyl	3.83	4.52	44.36	0	2
XIII	*N*-Ethyl-*N*-methyl	−0.09	1.92	13.67[f]	0	3[f]
				23.90[g]		2[g]
XIV	*N*-Methyl-*N*-*n*-propyl	0.45	2.44	13.67[f]	0	3[f]
				34.13[g]		2[g]
XV	*N*-*n*-Butyl-*N*-methyl	1.44	2.96	13.67[f]	0	3[f]
				44.36[g]		2[g]

[a] P_H is the apparent *n*-heptane–water partition coefficient measured at pH 7.4 (6). [b] Hydrophobic fragmental constant of the two nitrogen substituents (hydrogen and/or alkyl) (7). [c] Volume in milliliters per mole of substituent that is cleaved by *N*-dealkylation, calculated according to Bondi (9). [d] Number of hydrogen atoms on the nitrogen. [e] Number of hydrogen atoms on the α-carbon of substituent that is cleaved by *N*-dealkylation. [f] *N*-Methyl group. [g] *N*-Alkyl group.

0022-3549/80/0500-0497$01.00/0