Solid Dispersion of Pharmaceutical Ternary Systems II: Dissolution Studies on Aspirin–Acetaminophen–Urea System

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Abstract □ Solid dispersions of an aspirin–acetaminophen–urea ternary system were prepared by the solvent method. The different phases in the solid state of some selected samples were characterized, and their compositions were determined in the light of information deducted from a previously constructed phase diagram. Studies carried out on physically mixed and coprecipitated aspirin–acetaminophen samples in ratios of 2:1, 3:1, and 9:1 without urea revealed that the dissolution rate of both drugs is a function of their concentrations. Aspirin from coprecipitated samples dissolved 1.8–2.6 times as rapidly as the pure drug, while the initial dissolution rate of acetaminophen decreased 10–35%. Simultaneous dissolution rates of aspirin and acetaminophen from the three binary and the ternary eutectics were studied. The dissolution rates of both drugs, except for that of acetaminophen from its binary eutectic with aspirin, obviously improved. Dissolution rates of both drugs from coprecipitated aspirin–acetaminophen (2:1 and 9:1) as a function of the urea concentration also were considered. The mechanism of the observed improvement in their initial dissolution rates and their T_{90} values is described. About a sixfold increase in the dissolution rate of aspirin and about a threefold increase in that of acetaminophen were achieved when both drugs were coprecipitated with 5% urea.

Keyphrases □ Solid dispersions—aspirin–acetaminophen–urea ternary system, dissolution rates □ Dissolution rates—aspirin–acetaminophen–urea ternary system solid dispersions □ Analgesics—aspirin–acetaminophen–urea ternary system, dissolution rates □ Dosage forms—solid dispersions, aspirin–acetaminophen–urea ternary system, dissolution rates

In 1961, Sekiguchi and Obi (1) proposed that particle-size reduction of sparingly soluble drugs *via* solid dispersion techniques resulted in faster dissolution rates. This concept was later applied successfully by others (2). Almost all reports on this technique are limited to binary systems. Different solid dispersions of phenindione were studied (3). Some of these solid dispersions were prepared using random ratios of mixtures of two carriers. However, excellent work on ternary systems in other disciplines (4) stimulated interest in pharmaceutical ternary solid dispersion systems.

Previously (4), the phase diagram of aspirin–acetaminophen–urea was constructed to contribute information regarding the physical nature of this ternary system. The present work concerned the dissolution rates of aspirin and acetaminophen from ternary solid dispersions with urea in ratios chosen in light of the previously constructed phase diagram. Correlation between dissolution rate data and other information from the phase diagram also are discussed.

EXPERIMENTAL

Materials—Aspirin BP, acetaminophen NF, and urea (GR) were used as obtained (4). Absolute ethanol, hydrochloric acid, and sodium hydroxide were analytical grade.

Sample Preparation—The choice of samples of various compositions to study the dissolution rate of both aspirin and acetaminophen from solid dispersions with urea was based on information obtained from the previously constructed phase diagram (4). The solvent method was applied because of possible aspirin decomposition in samples prepared by the melt method (5). IR spectra[1] of aspirin samples, prepared by both the solvent and melt methods, were identical.

Coprecipitates of aspirin and acetaminophen in ratios of 65:35, 75:25, and 90:10 (for simplicity, 2:1, 3:1, and 9:1, respectively) with urea, ranging in concentration from 0.0 to 30% (w/w), were selected. Samples representing the three binary eutectics E_1, E_2, and E_3 of the aspirin–acetaminophen, aspirin–urea, and acetaminophen–urea binary systems, respectively, as well as the ternary eutectic E_t were included for comparison. The coprecipitates were prepared by dissolving the components in the minimum volume of absolute ethanol and evaporating the solvent *in vacuo* at room temperature using a rotary evaporator. The residue was finely ground, sieved to a particle-size range of 80–125 μm, and stored in a desiccator over anhydrous calcium sulfate.

Physical mixtures were prepared by simple mixing of ingredients possessing the same particle-size range (80–125 μm). Pure crystalline aspirin and acetaminophen (80–125 μm) served as controls.

Dissolution Rate Studies—Dissolution rate studies were carried out on samples containing aspirin, acetaminophen, and urea in the various compositions listed in Table I. All samples contained an equivalent of 100 mg of aspirin. Samples I_1–I_4, J_1–J_4, and E_1–E_t contained acetaminophen in quantities equivalent to 53.84, 11.11, and 33.33 mg, respectively. The dissolution fluid consisted of 450 ml of 0.1 *N* HCl maintained at 37° in a 500-ml beaker immersed in a constant-temperature water bath.

The dissolution fluid was stirred by a glass spiral paddle, attached by a ring to a metal rod joined with a side constant-speed motor. With this arrangement, the spiral paddle made 30 up and down movements/min, accompanied by two horizontal rotations through an arc of 180° with each up and down cycle (6). Samples of 2 ml were withdrawn at appropriate time intervals and replaced by an equal volume of dissolution fluid.

Assay Procedure—Samples were transferred to a 50-ml volumetric flask containing 3 ml of distilled water. A 0.5-ml quantity of 50% (w/v) NaOH was added to each flask and mixed thoroughly. After 15 min, 1.5 ml of concentrated hydrochloric acid was added, and the volume was brought to the mark with 0.1 *N* HCl (7). Preliminary investigations showed that only aspirin is hydrolyzed under these conditions. The absorbance of the solution was determined spectrophotometrically[2] at 302 and 242 nm using an appropriate blank.

Equations for determining the concentration of aspirin and acetaminophen as a two-component mixture were derived from the following absorptivity indexes: α_1, 0.552; α_2, 0.265; β_1, 0.657; and β_2, 0.000; α_1 and α_2 are the absorbances of a 1-mg % solution of salicylic acid in 0.1 *N* HCl at 242 and 302 nm, respectively, while β_1 and β_2 are the absorbances of a 1-mg % solution of acetaminophen at the same wavelengths. The following working equations were valid:

$$C_s = 3.770A_2 \qquad \text{(Eq. 1)}$$

$$C_a = \frac{A_1 - 0.552C_s}{0.657} \qquad \text{(Eq. 2)}$$

where C_s is the concentration of salicylic acid (milligrams percent), C_a is the concentration of acetaminophen (milligrams percent), A_1 is the absorbance at 242 nm, and A_2 is the absorbance at 302 nm. Urea did not interfere with the assay under test conditions. All samples were run at least in duplicate.

RESULTS AND DISCUSSION

To elucidate the mechanism involved in the dissolution process of aspirin and acetaminophen from their solid dispersions with urea, samples with compositions lying within the six areas of the previously constructed phase diagram were chosen (4). Accordingly, the compositions

[1] Perkin-Elmer model 237 IR spectrophotometer.
[2] Unicam SP 1800 UV spectrophotometer.

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Table I—Initial and Final Composition of Coprecipitated Samples Employed in the Dissolution Studies

	Composition[a], % (w/w)														
	Initial			Final											
				Solid			Binary Eutectic						Ternary Eutectic		
Sample	A	P	U	A	P	U	A–P		A–U		P–U		A–P–U		
I_1	65.0	35.0	—	—	13.3	—	65.0	21.7	—	—	—	—	—	—	—
I_2	61.8	33.2	5.0	—	11.0	—	46.7	17.3	—	—	—	—	15.0	5.0	5.0
I_3	52.0	28.0	20.0	—	7.6	—	—	—	—	—	3.0	2.3	52.5	17.3	17.3
I_4	45.5	24.5	30.0	—	—	5.8	—	—	—	—	9.3	9.0	45.5	15.2	15.2
J_1	90.0	10.0	—	60.0	—	—	30.0	10.0	—	—	—	—	—	—	—
J_2	85.5	9.5	5.0	56.0	—	—	14.5	4.5	—	—	—	—	15.0	5.0	5.0
J_3	72.0	8.0	20.0	15.2	—	—	—	—	32.8	12.0	—	—	24.0	8.0	8.0
J_4	63.0	7.0	30.0	—	—	8.1	—	—	42.0	14.9	—	—	21.0	7.0	7.0
E_1	75.0	25.0	—	—	—	—	75.0	25.0	—	—	—	—	—	—	—
E_2	75.0	—	25.0	—	—	—	—	—	75.0	25.0	—	—	—	—	—
E_3	—	52.0	48.0	—	—	—	—	—	—	—	52.0	48.0	—	—	—
E_t	60.0	20.0	20.0	—	—	—	—	—	—	—	—	—	60.0	20.0	20.0

[a] A = aspirin, P = acetaminophen, and U = urea.

of the selected finely crystallized solid dispersions were calculated, applying previously discussed principles (4) (Table I).

Although the final physical properties of solid dispersions prepared by the solvent method may differ from those obtained by the melt method (2), the solvent method has been used often in the preparation of solid solutions or mixed crystals of organic or inorganic compounds (8). Moreover, solid dispersions prepared by the solvent method can be characterized and their interactions in the solid state can be identified by phase diagrams constructed by thermal techniques (9). From various areas of the phase diagram, random samples prepared by the solvent method had the same melting characteristics as those obtained by the fusion method.

Simultaneous Dissolution Rate of Aspirin and Acetaminophen as a Function of Their Ratios—Melts or coprecipitates of acetaminophen (10, 11) or aspirin (12) with highly soluble inert carriers were previously reported. In the present work, the dissolution rates of these two drugs were studied simultaneously. Therefore, the effect of each drug on the dissolution behavior of the other was evaluated in their physical mixtures and solid dispersions without a carrier.

Physical mixtures and coprecipitates of aspirin with acetaminophen in ratios of 2:1, 3:1, and 9:1 were prepared, and their dissolution rates were determined. The amounts of aspirin and acetaminophen (in milligrams percent) dissolved as a function of their ratio are shown in Figs. 1 and 2. The relative dissolution rates, obtained by calculating the ratio of the observed rate to the rate of the pure crystalline aspirin or acetaminophen, are shown in Table II.

Physical Mixtures—The dissolution curve of pure crystalline aspirin was linear during the entire experimental time (Fig. 1). Curves of pure acetaminophen showed two linear segments; the initial rates tapered off at a time depending on the amount of the drug in the dissolution medium. When particles of pure aspirin were physically mixed with particles of pure acetaminophen in different ratios, no apparent change in the dissolution rate of aspirin was observed. However, the initial dissolution rate of acetaminophen decreased, ranging from about 30% for the aspirin–acetaminophen 2:1 ratio to 60% for the 9:1 ratio (Table II).

The explanation of these results is probably related to effective, rather than absolute, surface area. Both aspirin and acetaminophen have hydrophobic surfaces, and their particles float on the surface of the dissolution medium during the test. Theoretically, in such a system containing an abundant amount of aspirin particles relative to that of acetaminophen, acetaminophen would not influence the dissolution rate of aspirin particles. However, as a result of a decreasing acetaminophen ratio in the physical mixture, the surface area available to the dissolution fluid decreases and so does the dissolution rate.

Coprecipitates—Aspirin coprecipitated with acetaminophen in a 9:1 ratio exhibited a fast initial dissolution rate (3.25 mg/min), showing an increase 2.6 times greater than that of pure aspirin of comparable particle size (Table II). This sample contained 60% aspirin deposited as a primary phase together with 30% aspirin and 10% acetaminophen in the eutectic (Table I). The small amount of acetaminophen occupied in the interaspirin particulates resulted in decreasing aggregation of aspirin particles, increasing its effective surface area and, consequently, its initial dissolution rate.

This mechanism was confirmed by the 35% decrease of the initial dissolution rate of entrapped acetaminophen particles relative to that of pure crystalline acetaminophen. However, such a decrease in the initial dissolution rate of acetaminophen was still less than that observed with the physically mixed sample of identical composition (Fig. 1). This result was probably due to the relatively better wettability of the nonfloating coprecipitated sample.

The initial dissolution rate of acetaminophen from the coprecipitated aspirin–acetaminophen (2:1 ratio) was reduced to only 10% (Table II). This sample contained 35% acetaminophen (13.3% deposited as a primary phase and 21.7% in the eutectic), holding with it the whole 65% aspirin in the eutectic. In this case, some type of competition possibly existed between the two solutes in the dissolution fluid, decreasing the initial dissolution rate of aspirin (which was still 1.8 times greater than that of pure crystalline aspirin). Consequently, aspirin and acetaminophen in the coprecipitated sample of the 3:1 ratio, consisting mainly of 100% eutectic, exhibited intermediate dissolution behavior. In all studied ratios,

Table II—Relative Dissolution Rates of Aspirin (A) and Acetaminophen (P) as a Function of Their Ratios as Well as from Their Binary and Ternary Eutectics

			Relative Dissolution Rate			
			Aspirin		Acetaminophen	
Sample	Description	Condition	Initial	Limiting	Initial	Limiting
A	A	Crystalline	1.0	1.0	—	—
	A	Coprecipitate	1.4	0.8	—	—
P	P	Crystalline	—	—	1.0	1.0
	P	Coprecipitate	—	—	2.3	1.0
I_1	A_2:P_1	Physical mixture	1.0	1.0	0.7	0.7
E_1	A_3:P_1	Physical mixture	1.0	1.0	0.5	3.5
J_1	A_9:P_1	Physical mixture	1.0	1.0	0.4	2.0
I_1	A_2:P_1	Coprecipitate	1.8	0.8	0.9	10.0
E_1	A_3:P_1	Coprecipitate	2.5	0.8	0.8	3.7
J_1	A_9:P_1	Coprecipitate	2.6	0.8	0.6	4.0
E_2	A_3:U_1	Coprecipitate	5.6	0.6	—	—
E_3	P_1:U_1	Coprecipitate	—	—	2.1	1.0
E_t	A_3:P_1:U_1	Coprecipitate	6.6	0.2	2.3	1.0
E_t	A_3:P_1:U_1	Physical mixture	2.4	0.7	2.2	1.0

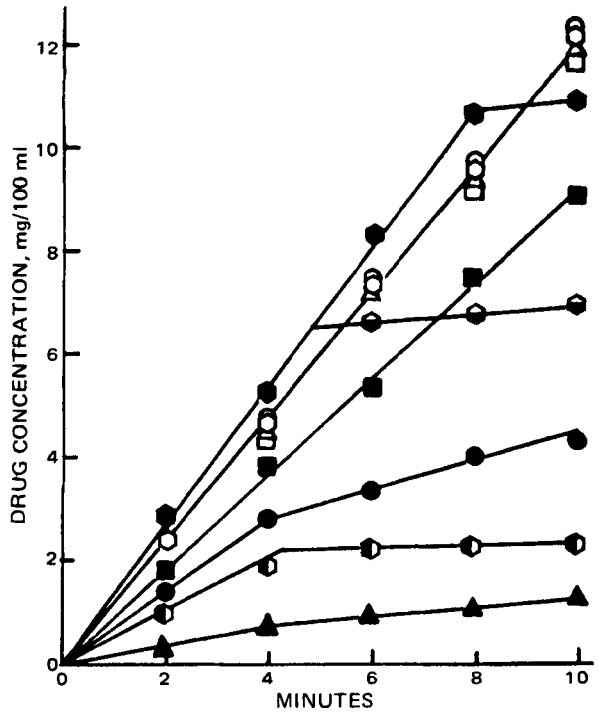

Figure 1—*Dissolution rates of aspirin and acetaminophen as a function of their ratios in physical mixtures. Key: aspirin from 1:0 (○), 2:1 (□), 3:1 (○), and 9:1 (△) ratio and acetaminophen from 0:1 (●, ⊖, and ◐; 54, 33, and 11 mg, respectively, in the dissolution fluid), 2:1 (■), 3:1 (●), and 9:1 (▲) ratios.*

once the second phase of acetaminophen dissolution started, showing high limiting dissolution rates, the dissolution of aspirin tapered off to approximately the same rate as that of the pure crystalline aspirin (Table II).

To see if a relationship existed between the dissolution rate and the aspirin to acetaminophen ratio in both coprecipitated and physically mixed samples, the relative initial dissolution rates were plotted *versus* the weight fraction of acetaminophen in the studied samples (Fig. 3). No linear relationship was observed for aspirin in the coprecipitated samples. Coprecipitation of aspirin with the minimum amount of acetaminophen highly improved its initial dissolution rate, but a further increase in the acetaminophen content decreased such improvement.

On the other hand, acetaminophen showed a linear relationship between its initial dissolution rate and its weight fraction in both coprecipitated and physically mixed samples. Generally, an increase in the acetaminophen content diminished the observed reduction in its initial dissolution rate.

Simultaneous Dissolution Rates of Aspirin and Acetaminophen from Binary and Ternary Eutectics—Figure 4 shows the dissolution rates of aspirin from the eutectics with acetaminophen (E_1) and with urea (E_2) and the ternary eutectic (E_t). For comparative purposes, the dissolution rate of aspirin precipitated from ethanol is also shown. The pure crystalline aspirin sample yielded an initial dissolution rate constant of 1.25 mg/min, while the precipitated sample demonstrated an initial rate constant of 1.7 mg/min, showing an increase of approximately 35%.

Tawashi (13) reported that polymorph I of aspirin, prepared by slow crystallization from its saturated solution in 95% ethanol, was very similar to commercial aspirin in its dissolution rate from tablets and in its X-ray diffraction pattern. The experimental discrepancy between the former study and the present work may be ascribed to differences in the method of aspirin crystallization. The relative initial dissolution rate data (Table II) indicate approximately a sixfold increase in the dissolution rate of aspirin from the eutectic mixture aspirin–urea (3:1) over that of crystalline aspirin, a fourfold increase over that of precipitated aspirin, and a twofold increase over that from the eutectic mixture aspirin–acetaminophen (3:1). However, the highest increase in the initial dissolution rate of aspirin (approximately seven times greater than the crystalline drug) was achieved with the ternary eutectic sample.

These results may reflect the significant reduction in the size of aspirin particulates during sample preparation. In addition to the increase in surface area of aspirin particles, local solubilization by urea appears to

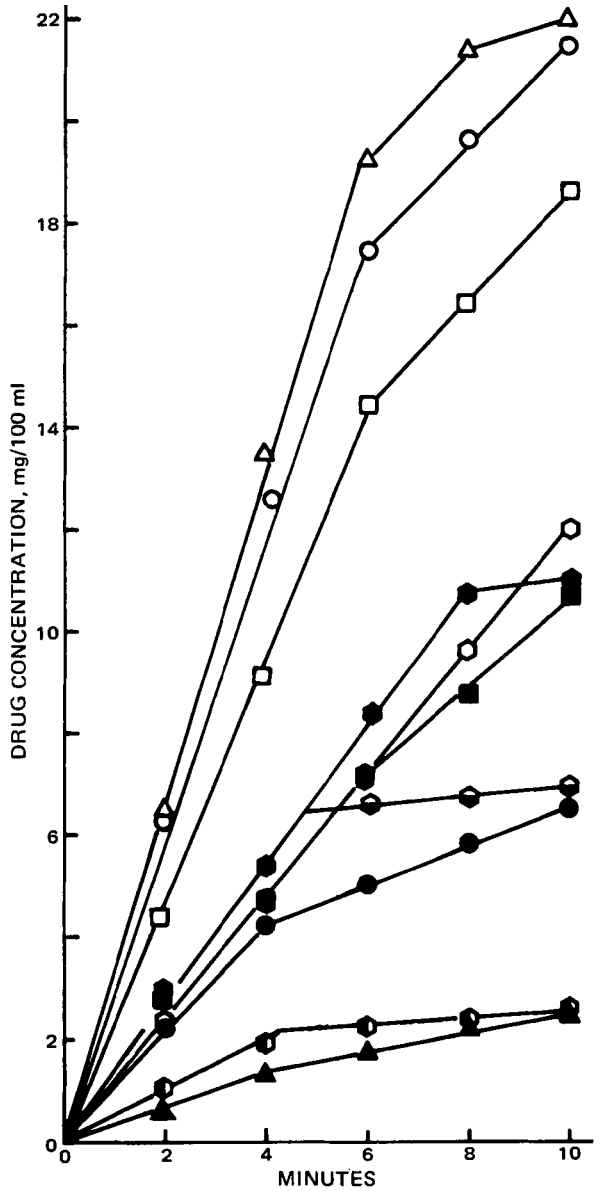

Figure 2—*Dissolution rates of aspirin and acetaminophen as a function of their ratios in coprecipitates. Key: aspirin from 1:0 (○), 2:1 (□), 3:1 (○), and 9:1 (△) ratios; and acetaminophen from 0:1 (●, ⊖, and ◐; 54, 33, and 11 mg, respectively, in the dissolution fluid), 2:1 (■), 3:1 (●), and 9:1 (▲) ratios.*

be responsible for the observed potentiation. The importance of the microenvironmental effect of urea on the dissolution of aspirin may be appreciated by considering the behavior of the physically mixed ternary eutectic sample. The initial dissolution of aspirin from this sample was almost twice as rapid as that of pure crystalline aspirin (Table II) but still lower than that of the coprecipitated sample of the same composition.

The second phase of dissolution of aspirin from the coprecipitated sample aspirin–urea (3:1) and the physically mixed ternary eutectic sample showed relative dissolution rate values favorably comparable to the rate found with the precipitated aspirin. This result suggests that once urea is completely depleted from the diffusion layer immediately surrounding the dissolved solid particles, the dissolution behavior of aspirin from these samples is almost identical. However, the coprecipitated ternary eutectic sample exhibited a much lower limiting dissolution rate.

The relative initial and limiting dissolution rates of acetaminophen from its precipitated sample, the binary eutectic sample with urea (E_3), or the ternary eutectic samples (physically mixed or coprecipitated) showed no significant difference in their dissolution behavior (Table II). These samples yielded an initial dissolution rate constant of 3.2–3.4 mg/min, showing approximately a twofold increase in the dissolution rate

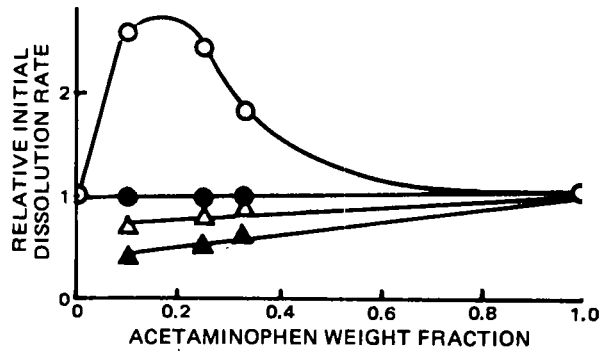

Figure 3—*Relative initial dissolution rates of aspirin and acetaminophen (compared to the crystalline drug) as a function of their weight fraction. Key: ○, aspirin from coprecipitates; ●, aspirin from physical mixtures; △, acetaminophen from coprecipitates; and ▲, acetaminophen from physical mixtures.*

of acetaminophen. In all cases, the second phase of dissolution had a rate constant of 0.1 mg/min, a value quite close to that of pure crystalline acetaminophen of equal particle size.

Goldberg *et al.* (10) reported that there is no evidence of particle-size reduction of acetaminophen by eutectic formation with urea. IR studies on precipitated acetaminophen showed that no ethanol solvates were formed under the present experimental conditions. The observed increase in the initial dissolution rate of acetaminophen, therefore, may be due to coprecipitation and/or better wetting of the drug by urea.

Simultaneous Dissolution Rate of Aspirin and Acetaminophen as a Function of Urea Concentration—The amounts of aspirin and acetaminophen dissolved from the 2:1 and 9:1 ratios as a function of the urea concentration are shown in Figs. 5 and 6, respectively. The relative initial dissolution rates and the time required to dissolve 90% of the drug (designated by T_{90}) were calculated (Table III). In general, the presence of urea in the studied ratios increased the dissolution parameters of both drugs. This result could be attributed mainly to the wetting effect of the highly water-soluble urea in intimate contact with the drugs.

Aspirin–Acetaminophen (2:1 Ratio)—Approximately a sixfold increase in the initial dissolution rate of aspirin from Sample I_2, coprecipitated with 5% urea, over that of pure crystalline aspirin was observed (Table III). This sample also exhibited a threefold increase in the initial dissolution rate of aspirin over that of Sample I_1, free from urea. This potentiation (also shown by the decrease in the T_{90} value from 18 to 8) could be attributed to the participation of urea in depositing a portion of aspirin as the ternary eutectic (Table I), previously shown to exert an accelerated initial dissolution rate (Fig. 4).

A comparison of the relative initial dissolution rates and T_{90} values of the physically mixed and coprecipitated I_2 samples again reflects the significance of solid dispersion in enhancing the dissolution rate of poorly soluble drugs (Table III). Samples I_3 and I_4, containing 20 and 30% urea, respectively, actually had most of their aspirin content in the form of a ternary eutectic (approximately 87 and 76%, respectively, Table I). Consequently, these two samples were expected to exhibit similar initial dissolution rates. However, I_4 showed a T_{90} value almost half that of I_3, probably because of the presence of free urea (6%) in I_4 deposited as a primary phase (Table I).

The dissolution profiles of acetaminophen from the coprecipitated samples, containing urea concentrations of 5–30%, were almost the same, as is evident from their initial relative dissolution rates (Table III).

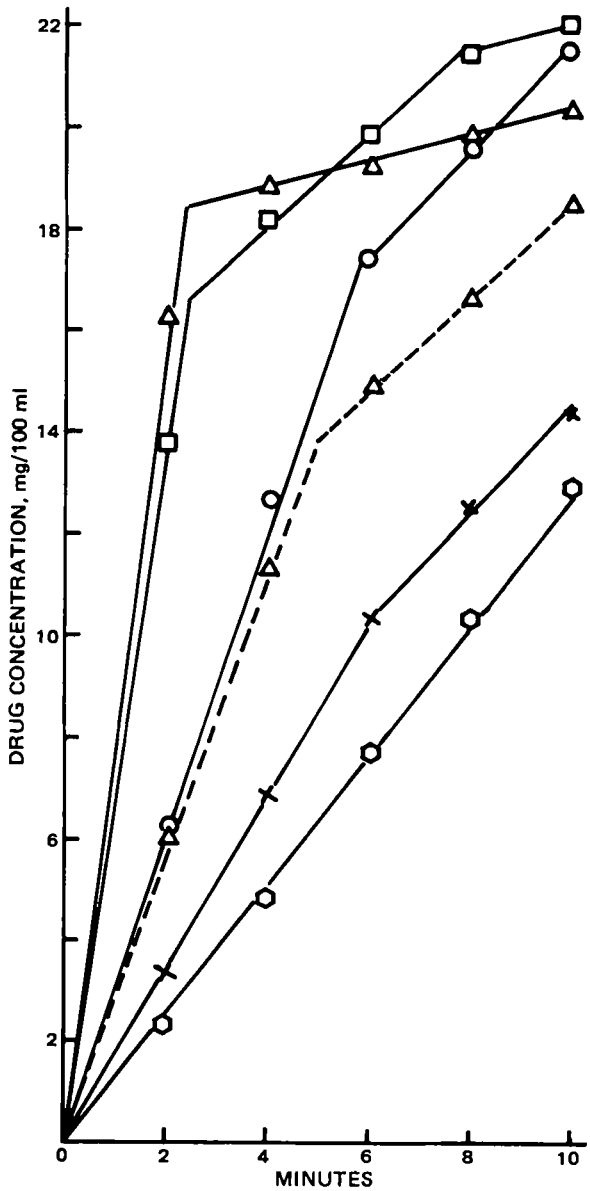

Figure 4—*Dissolution rates of aspirin from binary and ternary eutectics. Key: ○, crystalline aspirin; ×, precipitated aspirin; ○, aspirin–acetaminophen (E_1); □, aspirin–urea (E_2); and △, aspirin–acetaminophen–urea (E_t). The dotted line represents the physical mixture.*

Samples I_3 and I_4 had their acetaminophen content deposited as a ternary eutectic, a binary eutectic with urea, and/or a primary phase (Table I), which were shown to exhibit equal dissolution rates (Table II). The only difference was observed from the relatively high T_{90} value for Sample I_2, which contained approximately half of its acetaminophen in the form

Table III—Relative Initial Dissolution Rates (RIDR) and T_{90} Values of Aspirin (A) and Acetaminophen (P) as a Function of Urea (U) Concentration

A:P Ratio	Sample	[U], %	Condition	[A] RIDR	[A] T_{90}, min	[P] RIDR	[P] T_{90}, min
—	A	—	Crystalline	1.0	18.0	—	—
—	P	—	Crystalline	—	—	1.0	6.8
	I_1	—	Coprecipitate	1.8	15.0	0.9	10.0
	I_2	5	Physical mixture	1.8	10.0	1.4	15.0
2:1	I_2	5	Coprecipitate	5.8	8.0	3.2	7.5
	I_3	20	Coprecipitate	6.8	5.0	3.5	3.0
	I_4	30	Coprecipitate	7.7	2.3	3.7	2.5
	J_1	—	Coprecipitate	2.6	6.5	0.6	6.0
	J_2	5	Coprecipitate	5.8	3.5	1.7	4.0
9:1	J_3	20	Coprecipitate	6.7	5.0	2.0	2.4
	J_4	30	Coprecipitate	6.8	5.0	2.0	2.4

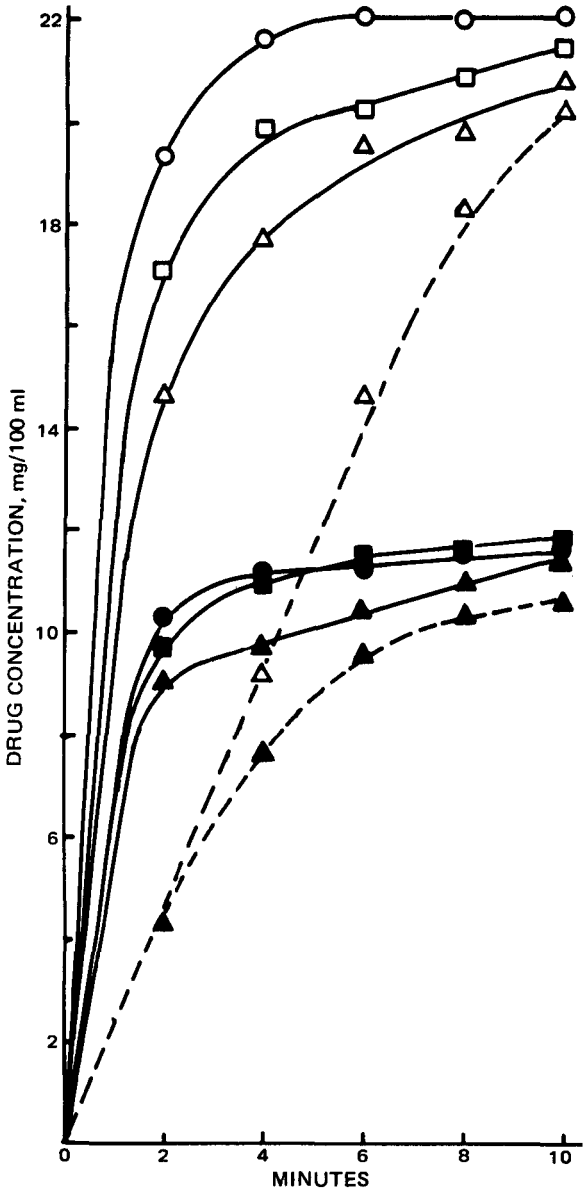

Figure 5—*Dissolution rates of aspirin (open symbols) and acetaminophen (solid symbols) from coprecipitates in 2:1 ratio as a function of urea concentration. Key: △, 5% urea; □, 20% urea; and ○, 30% urea. Dotted lines represent the physical mixture.*

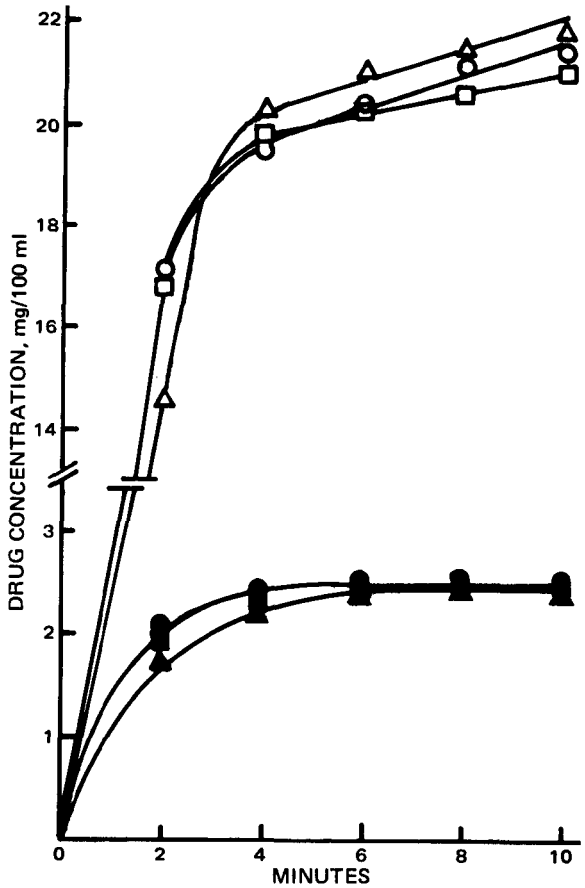

Figure 6—*Dissolution rates of aspirin (open symbols) and acetaminophen (solid symbols) from coprecipitates in 9:1 ratio as a function of urea concentration. Key: △, 5% urea; □, 20% urea; and ○, 30% urea.*

of the binary eutectic with aspirin, previously shown to exert a low acetaminophen dissolution rate (Fig. 2).

Aspirin–Acetaminophen (9:1 Ratio)—Samples I_2 and J_2, coprecipitated with 5% urea, contained an equal proportion of the ternary eutectic (Table I). This composition probably could explain the identical relative initial dissolution rate values of aspirin from both samples (Fig. 6 and Table III). However, the presence of a large amount of aspirin deposited as a primary phase in J_2 would explain the twofold decrease in the T_{90} value in this sample relative to I_2 (Tables I and III).

Samples J_3 and J_4, however, showed similar initial dissolution rates and T_{90} values. Both samples contained more or less equal amounts of the binary eutectic aspirin–urea (3:1) and the ternary eutectic. The possible increase in the dissolution rate due to the presence of free aspirin, deposited as a primary phase in J_3, would make up for the increase resulting from the free urea in J_4.

All of the acetaminophen content in J_3 and J_4 was deposited as the ternary eutectic (Table I), a fact that could explain the identical dissolution behavior of acetaminophen from these samples (Table III and Fig. 6). The acetaminophen content of J_2, on the other hand, was equally distributed between the binary eutectic aspirin–acetaminophen (3:1) and the ternary eutectic. The ternary eutectic would account for the observed increase in the initial dissolution rate of acetaminophen, while the binary eutectic might be responsible for the high T_{90} value relative to the values of J_3 and J_4.

It can be concluded that coprecipitation of aspirin and acetaminophen with only 5% urea markedly improved the dissolution parameters of both drugs. However, a further increase in the urea content (from 5 to 30%) only slightly improved their initial dissolution rates from samples representing the six areas of the phase diagram. Nevertheless, the variation in the T_{90} values of both drugs in these samples was a function of the urea concentration.

The sixfold increase of the initial dissolution rate of aspirin and the threefold increase in that of acetaminophen when aspirin–acetaminophen (2:1) was coprecipitated with 5% (w/w) urea encourage *in vivo* testing of this ternary system. The bioavailability of this combination of drugs is presently under investigation.

Simultaneous dissolution rates of two drugs, possible enhancement in dissolution behavior of one at the expense of the other, and elucidation of possible mechanisms by which accelerated dissolution rates can occur (on the basis of accurate determination of the composition of finally crystallized solid dispersions) are some contributions of the present report. The suggested approach of ternary solid dispersion systems represents a fertile area for possible enhancement of dissolution rates of drug combinations in solid dosage forms and proposes systematic techniques for their evaluation.

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Fluorometric Assay for Urinary Indapamide

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Abstract □ A sensitive fluorescence method for the determination of indapamide was developed. Reaction of indapamide with sodium hydroxide at 100° yielded a fluorescent product, and addition of formaldehyde to the fluorescent product increased its fluorescence intensity by a factor of three. The assay is sensitive to levels of indapamide of 0.025 μg/ml in an aqueous solution, and a linear response between 0.025 and 2.0 μg/ml was observed. The procedure was adapted to the analysis of intact indapamide in urine. Concentrations of indapamide of 0.05 μg/ml can be detected in dogs given 20 mg of the drug.

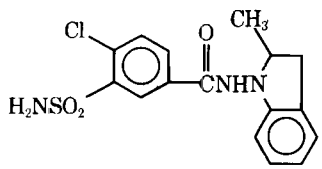
Keyphrases □ Indapamide—fluorometric analysis in urine □ Fluorometry—analysis, indapamide in urine □ Antihypertensive agents—indapamide, fluorometric analysis in urine

Indapamide, 1-(3-sulfamoyl-4-chlorobenzamido)-2-methylindoline (I), is a new agent for the treatment of mild to moderate hypertension (1–4). Drug levels in biological fluids were measured by TLC with a sensitivity of 0.1 μg/ml (5), and plasma ^{14}C-indapamide concentrations following oral administration of the radiolabeled drug also were determined by TLC (6).

It was considered desirable to investigate other highly sensitive assays amenable to analyzing large numbers of samples from pharmacokinetic studies using the unlabeled drug. Accordingly, a spectrofluorometric assay for indapamide in both aqueous solutions and urine was developed.

EXPERIMENTAL

Materials and Instruments—All fluorescent measurements were performed on a scanning fluorescence spectrophotometer[1]. TLC was performed on 0.25-mm silica gel plates[2].



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[1] Model MPF-2A, Perkin-Elmer Corp., Wilton, Conn.
[2] LQD Quanta, Quantum Industries, Fairfield, N.J.

Indapamide[3] was used without further purification. Indapamide tablets[3] were administered to dogs. Indoline[4], alipamide[5], 2-methylindoline[6], and 1-(3-sulfamoyl-4-chlorobenzoyl)-2-methylindoline[6] were studied as model fluorescent compounds. Methanol and all solvents used in the TLC studies were distilled-in-glass grade[7]. The ether used routinely was anhydrous grade[8], and all other reagents were analytical reagent grade[9].

Aqueous Assay—Indapamide was dissolved in 5.0 ml of 0.005 *N* NaOH containing 3 *M* NaCl. This solution was heated at 100° for 45 min in a water bath in screw-capped culture tubes (16 × 150 mm) with polytef liners. After heating, the tubes were removed and placed in ice water for a few minutes; then 0.2 ml of 37% formaldehyde was added. The tubes were reheated at 100° for 8 min, cooled in ice water for a few minutes, and then allowed to remain at room temperature until read on the fluorescence spectrophotometer.

Duplicate samples were run in all experiments. Reaction blanks were prepared by treating the sodium hydroxide–sodium chloride solution without indapamide identically.

The fluorescence of the samples was measured in quartz cells with a 1-cm path length. The excitation wavelength was 284 nm, and the emission spectrum was scanned for each sample. Both the excitation and emission slit widths were set according to the sensitivity required in the assay. Typical values were 4 nm.

The fluorescence intensity for each sample and blank was calculated by subtracting the fluorescence intensity at 300 nm (the baseline following the Rayleigh–Tyndall scattering peak) from that at 356 nm, where the peak occurs. A corrected sample fluorescence intensity was determined by subtracting the fluorescence intensity of the blank from that of the sample.

Extraction of Urine—Different indapamide concentrations were added to urine, which was then adjusted to pH 2 with 6 *N* HCl. Urine without indapamide was used as a control blank. In 16 × 150-mm screw-capped culture tubes with polytef liners, 6 ml of urine was extracted twice with 3.5 ml of ether. The ether previously was washed with 0.1 *N* NaOH [ether–sodium hydroxide (2:3 v/v)]. The combined ether layers were then extracted twice with 0.05 *M* sodium phosphate, pH 7.4 (16.0 ml, 5.0 ml).

The aqueous layer was discarded, and the ether layer was extracted with 6.0 ml of a 0.005 *N* NaOH–3 *M* NaCl solution. A 5-ml aliquot of the aqueous solution was then transferred into 16 × 150-mm tubes and reacted as described. The fluorescence of each sample was measured, and the absorbance between 280 and 360 nm was measured in random samples to test for interference by light-absorbing compounds.

[3] Servier Laboratories, Neuilly Sur Seine, France.
[4] Eastman Kodak Co., Rochester, N.Y.
[5] Parke-Davis, Ann Arbor, Mich.
[6] USV Pharmaceutical Corp., Tuckahoe, N.Y.
[7] Burdick & Jackson Laboratories, Muskegon, Mich.
[8] Fisher Chemicals, Fair Lawn, N.J.
[9] Mallinckrodt Chemical Works, St. Louis, Mo.

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