In Vivo–In Vitro Correlations for Trisulfapyrimidine Suspensions

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Abstract □ A UV method is described for measuring total sulfa drug concentration in dissolution samples. This *in vitro* measurement was found to correlate well with several *in vivo* parameters obtained after administration of commercial trisulfapyrimidine suspensions to humans. The UV method, which is rapid, simple, inexpensive and easily automated, is recommended for studying the dissolution of trisulfapyrimidine suspensions.

Keyphrases □ Trisulfapyrimidine—*in vivo–in vitro* correlations, UV method for the measurement of the dissolution of trisulfapyrimidine suspensions

Several reports (1–8) have appeared in the literature dealing with the bioavailability and dissolution of sulfa drugs. We have observed (9) significant bioavailability differences among seven commercial trisulfapyrimidine suspensions and have reported a dissolution method that provided good *in vivo–in vitro* correlation. This method was subsequently recommended for *in vitro* screening of trisulfapyrimidine suspensions. However, the dissolution samples were analyzed by a specific high-performance liquid chromatographic (HPLC) method which measured the concentrations of each component [sulfadiazine (I), sulfamerazine (II), and sulfamethazine (III)] of trisulfapyrimidine suspensions. The present study was undertaken to determine the suitability of a more rapid and readily available UV spectrophotometric procedure for measuring dissolution samples of trisulfapyrimidine suspensions, and to determine whether dissolution data collected in terms of total sulfa drug could be correlated with the *in vivo* parameters reported previously.

EXPERIMENTAL

***In Vivo* Study**—Details of the *in vivo* study are given elsewhere (9). Briefly, seven commercially available trisulfapyrimidine suspensions (A–G)[1] were each administered to 14 healthy male volunteers in a complete cross-over study design. Fourteen blood samples were then collected over a 48-hr period, and serum was analyzed for I, II, and III by a specific HPLC procedure (10).

Dissolution Methodology—Details of the dissolution method employed have been reported previously (9). Studies were done using the rotating paddle method (11) at 25 rpm in 900 ml of 2.2×10^{-4} *M* HCl, pH 3.4 at 37°. Samples were analyzed spectrophotometrically as described below.

Analytical—For the *in vivo* study, all serum samples were analyzed for sulfadiazine, sulfamerazine, and sulfamethazine by an HPLC method described previously (9, 10). For the *in vitro* study, all dissolution samples were analyzed for total sulfa drug content by a UV spectrophotometric procedure. A solution of trisulfapyrimidines was prepared by dissolving 100 mg each of I[2], II[3], and III[4] in the dissolution medium and adjusting the volume to 100 ml in a volumetric flask. This solution was quantitatively diluted with dissolution medium to obtain a stock solution containing 30 μg of total sulfa drug per milliliter. Standards (1.5, 3.0, 4.5, 6.0, 7.5, and 9.0 μg/ml total sulfa drug) were prepared by further diluting the stock solution with the dissolution medium. The absorbance of each standard solution was measured[5] at 254 nm and a calibration plot constructed. Unknown dissolution samples were measured in similar fashion, dilutions being performed with the dissolution medium where necessary. Prior to use, the spectra of each commercial suspension were examined in the dissolution medium for possible interference by excipients. All preparations gave similar spectra, and no interfering peaks were observed.

Table I—Mean [a] (± SD) Percent of Total Sulfa Drug Dissolved in 15 and 30 Min as Measured by the UV Assay for Seven Commercial Trisulfapyrimidine Suspensions

Product	15 min	30 min
A	68.3 ± 1.1	88.4 ± 0.9
B	86.8 ± 1.3	95.9 ± 1.0
C	47.9 ± 3.2	69.2 ± 4.8
D	88.0 ± 1.4	97.8 ± 1.9
E	30.7 ± 0.9	35.8 ± 1.9
F	22.1 ± 2.5	42.1 ± 4.1
G	9.9 ± 1.2	28.3 ± 1.6

[a] Mean of three determinations.

RESULTS

***In Vivo* Study**—Detailed results of the observed maximum serum concentration (C_{max}), the time for maximum serum concentration (t_{max}), and normalized areas under the curve ($AUC_0^\infty \times K_e$), have been presented previously (9) for I, II, and III.

***In Vitro* Study**—The mean percentages of total sulfa drug (IV) dissolved in 15 and 30 min for the seven trisulfapyrimidine suspensions are shown in Table I. It is observed that there were large differences in the dissolution rate among the seven suspensions. Product G showed the slowest rate of dissolution, while products A, B, and D showed the most rapid dissolution.

***In Vivo–In Vitro* Correlations**—For the three drugs (I, II, and III), each *in vivo* parameter was correlated with the percent of total sulfa drug (IV) dissolved in 15 and 30 min. Significant values of the linear correlation coefficient were observed between: (*a*) percent of IV dissolved in 30 min and C_{max} for I ($r = 0.83$, $p < 0.05$); (*b*) percent of IV dissolved in 15 min and C_{max} for I ($r = 0.80$, $p < 0.05$); (*c*) percent of IV dissolved in 30 min and t_{max} for I ($r = -0.80$, $p < 0.05$); (*d*) percent of IV dissolved in 15 min and t_{max} for I ($r = -0.79$, $p < 0.05$); (*e*) percent of IV dissolved in 30 min and C_{max} for II ($r = 0.77$, $p < 0.05$); (*f*) percent of IV dissolved in 30 min and t_{max} for II ($r = -0.85$, $p < 0.02$); (*g*) percent of IV dissolved in 15 min and t_{max} for II ($r = -0.81$, $p < 0.05$). Other combinations of *in vivo* and *in vitro* parameters did not give significant correlations.

DISCUSSION

Significant bioavailability differences among the commercial trisulfapyrimidine suspensions have been reported (9). These differences were

[1] A, Trisem, lot C53747, Beecham-Massengill Pharmaceuticals, Bristol, Tenn.; B, Terfonyl, lot 60080, E. R. Squibb and Sons, Princeton, N.J.; C, Sulfaloid, lot 17612, Westerfield Laboratories, Cincinnati, Ohio; D. Trisureid, lot 5M249, Reid-Provident Laboratories, Atlanta, Ga.; E, Quad-Ramoid, lot 28431, Paul B. Elder Co., Bryan, Ohio; F, Sulfose, lot 1951619, Wyeth Laboratories, Philadelphia, Pa.; and G, Neotriazine, lot 9ND79A, Eli Lilly and Co., Indianapolis, Ind.

[2] Lot R02114, Eli Lilly and Co., Indianapolis, Ind.

[3] Lot M07059, Eli Lilly and Co., Indianapolis, Ind.

[4] Lot R02011, Eli Lilly and Co., Indianapolis, Ind.

[5] DB-G grating spectrophotometer, Beckman Instruments Inc., Irvine, Calif.

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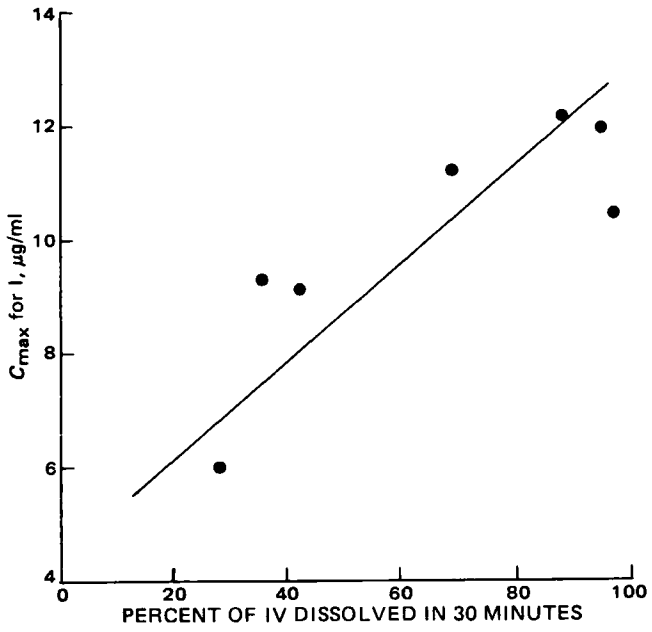

Figure 1—*Relationship between the* in vivo *measure of* C_{max} *for I and the* in vitro *measure of percent IV dissolved in 30 min for the seven trisulfapyrimidine suspensions, showing the regression line for the correlation coefficient of +0.83 (*$p < 0.05$*).*

observed in the rate and extent of absorption of individual suspension components. An *in vitro* dissolution test procedure was developed and dissolution samples analyzed by HPLC. Several significant correlations were reported between *in vivo* and *in vitro* parameters for individual sulfa components. Results of the present investigation show that when using the same dissolution procedure but a different method of detection (UV spectrophotometric) statistically significant correlations could be achieved between the *in vitro* values of percent of total sulfa drug dissolved (in 15 and 30 min) and the *in vivo* parameters reported previously for I and II.

As reported previously, the greatest bioavailability difference among the seven products was observed for the C_{max} parameter for I, for which good correlation was shown with the percent of I dissolved in 30 min (as measured by HPLC). The results of this study also show good correlation ($r = 0.83$, $p < 0.05$) between C_{max} for I and percent of IV dissolved in 30 min, as shown in Fig. 1. Thus, the UV method can be employed for studying the dissolution of trisulfapyrimidine suspensions. The method offers certain advantages over the HPLC procedure in that it is more rapid, less expensive, readily available in most laboratories, and more easily applicable to automation technology. Except for the fact that it could not detect differences in the individual sulfa components of trisulfapyrimidines, the UV method was found to be suitable for the determination of dissolution properties of commercial products.

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Quantitative Assessment of the Effect of Some Excipients on Nitrazepam Stability in Binary Powder Mixtures

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Abstract □ The decomposition rate constants, normalized for dilution and relative specific surface effects, of nitrazepam in simple binary powder mixtures with talcum, lactose·H_2O, microcrystalline cellulose, corn starch, mannitol, and saccharose are shown to be linearly related to the nitrogen adsorption energy of the excipients.

Keyphrases □ Nitrazepam—effect of excipients on stability in binary powder mixtures □ Excipients—effect on nitrazepam stability in binary powder mixtures

Recently, considerable effort has been made to precisely describe the chemical properties of excipients and how these excipients influence the technical and biopharmaceutical characteristics of the dosage forms. Excellent reviews list the "inert compounds" of pharmaceutical preparations (1), describe the difficulties concerning the "choice of excipients for international use" (2), "the influence of excipients on the design and manufacture of tablets and capsules" (3), and the "problems of drug interactions with excipients" (4). Many studies describe the influence of excipients, *e.g.* the acid-catalyzed decomposition of digoxin by montmorillonite (5), the effect of water adsorption properties of silica gel on the stability and the biological availability of ascorbic acid (6), and the influence of the solubility of some excipients on *in vitro* and *in vivo* properties of bendroflumethiazide tablets (7). Additional references were cited by Carstensen (8, 9).

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