j, α, and τ) can then be determined directly from nonsink dissolution data (W/W_0 *versus* t) using a suitable nonlinear regression program.

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Bioavailability of Sulfadiazine in Rabbits Using Tablets Prepared by Direct Compression and Fluidized-Bed Granulation

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Abstract □ Experimental sulfadiazine tablets prepared by direct compression, using a commercially available direct compression tablet mass, were compared with experimental sulfadiazine tablets prepared by fluidized-bed granulation and commercially available sulfadiazine tablets USP. The values for friability and the time required to release 10 and 50% of the direct compression tablets were between those of the fluidized-bed tablets and the commercial product. With the commercial tablet as a standard, the extent of bioavailability was determined in rabbits; it was slightly higher for both the direct compression and fluidized-bed tablets. A statistically significant difference was found between the direct compression tablets and the standard with respect to the extent of bioavailability and the time of the peak.

Keyphrases □ Sulfadiazine—bioavailability of tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits □ Bioavailability—sulfadiazine, tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits □ Tablets—sulfadiazine, prepared by direct compression and fluidized-bed techniques, bioavailability compared to commercial product, rabbits □ Antibacterials—sulfadiazine, bioavailability of tablets prepared by direct compression and fluidized-bed techniques compared to commercial product, rabbits

Sulfadiazine tablets are considered to present actual or potential bioequivalence problems (1). The use of a direct compression technique for their preparation seemed of particular interest, since numerous formulation factors influencing the *in vitro* dissolution rate and bioavailability previously were studied with sulfadiazine as a model substance. The compression pressure and binder concentration of acacia affected the dissolution rate of sulfadiazine tablets (2). The effects of disintegration agents, binders, fillers, and lubricants on the *in vitro* disintegration time and dissolution rate and the *in vivo* availability of various formulations were investigated (3). The highest blood levels in rabbits were found with formulations that did not contain magnesium stearate as the lubricant and lactose as the filler.

The influence of different lubricants in various concentrations on dissolution rate and bioavailability was studied (4). The highest bioavailability was obtained when the lubricant was kept at the minimum concentration with improved flow properties; a lubricant concentration resulting in optimum flow properties resulted in decreased bioavailability. Increasing amounts of starch paste, carboxymethylcellulose sodium, gelatin, or polyethylene glycol decreased *in vitro* drug release, whereas increasing amounts of povidone increased sulfadiazine release (5). Increasing amounts of carboxymethylcellulose sodium resulted in decreased bioavailability in rabbits (5).

The influence of the granulation method on the *in vitro* drug release and bioavailability of sulfadiazine tablets in rabbits was studied (6, 7). *In vitro* drug release decreased in the following order of granulation method: fluidized bed, nodulation, shaking, sieve pressure, and hole disk. *In vivo*

Table I—Composition of Experimental Tablets

Ingredients	Weight, mg/Tablet Preparation I (Fluidized Bed)	Preparation II (Direct Compression)
Sulfadiazine[a]	250	250
Sorbitan monolaurate[b]	1.2	1.2
Lactose[c] USP	126.075	—
Direct compression mass[d]	—	193.575
Starch[e] USP	50[f]	5
Povidone[g]	22.5	—
Magnesium stearate[h]	0.225	0.225
2-Propanol[g]	q.s.	—

[a] USP, Lederle. [b] Atlas Chemical Ind. [c] Foremost. [d] Lot B 262-X, E. Mendell Co. [e] Merrell Co. [f] Ninety percent internal phase, 10% external phase. [g] Matheson, Coleman and Bell. [h] Witco Chemical.

tablets prepared by fluidized-bed granulation showed a statistically significant higher bioavailability than tablets prepared by hole disk granulation. Differences in bioavailability in humans of commercially available sulfadiazine tablets were reported (8, 9).

Literature reports on the use of direct compression tablet masses are limited and are concerned with physical properties of the tablets and *in vitro* release (10). The purpose of this study was to compare the extent of bioavailability of sulfadiazine tablets prepared by direct compression, using a commercially available direct tableting mass[1], with those prepared by fluidized-bed granulation; a commercial preparation served as the standard.

EXPERIMENTAL

The composition of Preparations I and II is given in Table I. Preparation III was a commercial[2] 500-mg sulfadiazine USP tablet.

For the fluidized-bed granulation, the powder mixture of the internal phase of the tablets was transferred into the fluidized-bed granulator[3], and 2-propanol was sprayed through a nozzle into the fluidized powder bed. The conditions were: drying temperature, 50°; fan capacity, position 10; and 2-propanol, 50 ml/min. The desired granule size range of 0.3–0.7 mm was screened out. After mixing with the external phase (lubricant plus 10% disintegrant), the granules were compressed on a single-punch machine[4] to biconvex tablets of 11 mm in diameter and a pressure resistance of 3.5 kg.

For the direct compression tablets, the ingredients were mixed in a cube mixer[5] for 30 min and compressed as described.

Powder and Granule Testing—The moisture content[6], pour and stamp volumes, flow time[7], flow factor, and angle of repose were determined for the direct compression powder, the mixture of the direct compression powder plus sulfadiazine, and the fluidized-bed granulation.

***In Vitro* Tablet Testing**—The following physical tablet tests were performed: weight uniformity, pressure resistance[8] (hardness), friability[9] at 20 rpm expressed in percent after 30 min, and dissolution time of six tablets using the USP dissolution rate tester and artificial gastric fluid without enzymes[10] at 37° and 100 rpm.

***In Vivo* Testing**—White male New Zealand rabbits kept under identical conditions were used for blood level studies. Rabbits were studied because this species metabolizes sulfadiazine qualitatively and quantitatively similarly to humans (11). Although a crossover design would have been desirable, it was not feasible due to the relatively large volume of blood taken for each study, prohibiting the reuse of the animal for at least 4 weeks.

Each tablet preparation was tested in three rabbits. Blood samples of 2.5 ml were obtained by heart puncture taken prior to the experiment and 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr after dosing. The tablets were administered in the morning after overnight fasting using a self-made appli-

[1] Emcompress, E. Mendell Co.
[2] Lilly, Control 5HJ61A.
[3] Aeromatic labor model, Muttenz, CH-Switzerland.
[4] Korsch, type EKO-M.
[5] Erweka, type KB 15.
[6] Ohaus determination balance model 6010.
[7] Erweka flowmeter model 21920, type GDT.
[8] Heberlein model 2E/205.
[9] Roche friabilator.
[10] USP XIX.

Table II—Properties of Powders and Granules

Parameter	Direct Compression Powder	Direct Compression Powder plus Sulfadiazine	Fluidized-Bed Granulation
Moisture content, % ± *SD*	4.4 ± 0.2	2.4 ± 0.1	1.7 ± 0.1
Pour volume, ml/g ± *SD*	1.22 ± 0.04	1.93 ± 0.05	2.0 ± 0.04
Stamp volume, ml/g ± *SD*	1.04 ± 0.02	1.35 ± 0.02	1.75 ± 0.015
Flow time, sec ± *SD*	9.7 ± 1.0	24.38 ± 2.2	5.3 ± 0.7
Flow factor ± *SD*	—	0.975 ± 0.004	0.913 ± 0.003
Angle of repose, degrees ± *SD*	31.6 ± 1.75	40.2 ± 2.0	26.0 ± 1.5

Table III—Properties of Tablets Tested

Parameter	Preparation I	II	III
Potency, mg	252	251	496
Weight uniformity, mg ± *SD*	454.5 ± 0.98	451.8 ± 1.75	654.81 ± 0.79
Pressure resistance (hardness), kg ± *SD*	3.52 ± 5.65	3.51 ± 7.6	5.845 ± 12.01
Friability, % within 30 min at 20 rpm	6.5	23.7	63.8
$T_{10\%}$, min	1	24	45
$T_{50\%}$, min	7	53	760

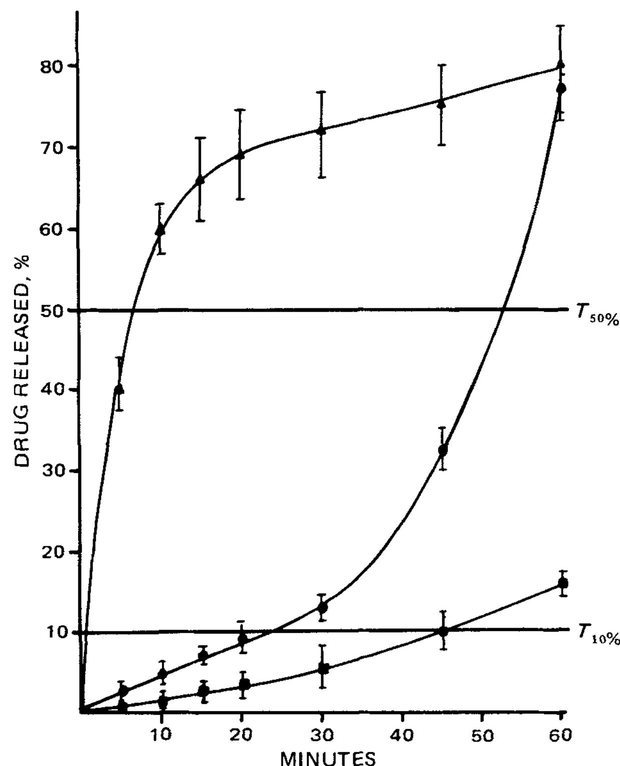

Figure 1—*Percent sulfadiazine released* versus *time of different tablet preparations. Key:* ■, *commercial product;* ▲, *tablets prepared by fluidized-bed granulation; and* ●, *tablets prepared by direct compression.*

Table IV—Average Blood Free Sulfadiazine Levels in Micrograms per Milliliter at Corrected Sampling Time

Preparation	Body Weight, g	Dose Size (Potency), mg	Rabbit	Hours							
				1	2	3	4	6	8	10	12
I	1780	252	1	7.26	25.40	32.24	33.24	29.16	23.04	17.68	13.30
	1900		2	2.93	22.67	29.74	30.67	25.81	19.44	114.11	10.10
	1800		3	8.76	25.44	31.77	32.74	28.24	21.87	16.28	11.92
			$\bar{x}$	6.315	24.50	31.25	33.27	27.74	21.45	16.02	11.77
			$\pm SD$	±3.0	±1.58	±1.32	±0.47	±1.73	±1.84	±1.79	±1.6
II	2300	251	1	4.65	24.78	31.18	31.075	24.35	16.93	11.25	7.34
	2150		2	11.39	26.23	30.67	29.99	23.31	16.12	10.62	6.83
	2450		3	6.44	22.24	27.13	26.86	21.15	14.89	10.07	6.69
			$\bar{x}$	7.49	24.42	29.66	29.31	22.94	15.98	10.64	6.95
			$\pm SD$	±3.40	±2.02	±2.20	±2.18	±1.63	±1.03	±0.59	±0.34
III	3380	496	1	13.42	30.11	35.40	35.01	28.14	20.32	14.08	9.57
	3550		2	13.28	30.00	35.31	34.94	28.09	20.30	14.07	9.57
	3480		3	15.34	32.88	38.69	38.45	31.1	22.47	15.48	10.43
			$\bar{x}$	14.01	31.0	36.43	36.13	29.11	21.03	14.54	9.85
			$\pm SD$	±1.15	±1.63	±1.87	±2.0	±1.72	±1.24	±0.82	±0.49

cator. Immediately after dosing, a stomach catheter was introduced and 5 ml of water was administered. Food was withheld for 6 hr after dosing; water was available *ad libitum*.

Assay of Sulfadiazine—A 2-ml aliquot of blood was mixed with 30 ml of water. After hemolysis, 8 ml of 15% (w/v) trichloroacetic acid was added. The precipitate was filtered off, and the filtrate was assayed by the Bratton–Marshall method (12).

Pharmacokinetic Analysis—The blood level–time data were computer[11] analyzed according to the one-compartment open model. Since it is difficult to keep the sampling time accurate to the minute, actual blood levels were corrected from the computer-fitted curves to the specified times.

RESULTS AND DISCUSSION

The physical properties of the powders and granules are listed in Table II. The smaller ratio of pour volume to stamp volume for the fluidized bed suggests that the weight uniformity should be higher than that of the direct compression mixture. The flow time and the angle of repose for the direct compression powder were much larger than for the fluidized-bed granulation, indicating that the latter is more suitable for compression for a high-speed tableting machine.

The tablet properties are listed in Table III. As suggested by the powder and granule testing, the tablets prepared by fluidized-bed granulation showed somewhat higher weight uniformity than those prepared by direct compression. However, all were within the general accepted limits. The pressure resistance (hardness) was maintained for both experimental preparations at 3.5 kg because any further increase in compression force resulted in capping of the direct compression preparation. The commercial preparation had a much higher pressure resistance. The friability of the tablets prepared by direct compression was between those prepared by fluidized-bed granulation and the commercial tablets.

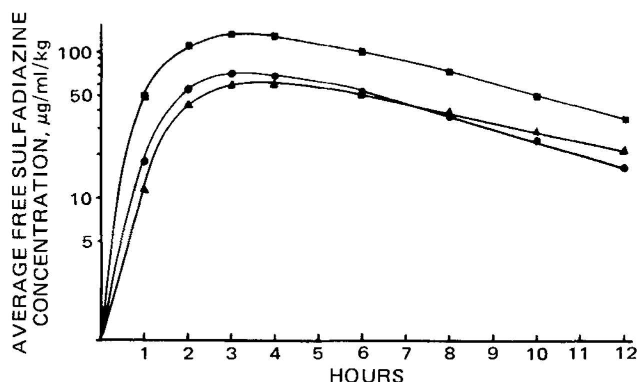

Figure 2—*Average blood free sulfadiazine concentrations* versus *time in micrograms per milliliter per kilogram. Key:* ■, *commercial product (500 mg);* ▲, *tablets prepared by fluidized-bed granulation (250 mg); and* ●, *tablets prepared by direct compression (250 mg).*

The *in vitro* drug release expressed in percent sulfadiazine released into artificial gastric fluid *versus* time (based on potency, not labeled amount) is shown in Fig. 1. Artificial gastric fluid was used as the test medium because sulfadiazine drug release is much higher in this medium than in water or artificial intestinal fluid (4–6, 9). Drug release was characterized by $T_{10\%}$ and $T_{50\%}$ and was highest for fluidized-bed tablets, followed by direct compression tablets and the commercial product.

The blood level data corrected for the specified sampling times are listed in Table IV. The average blood level–time curves, corrected for the body weight, are shown in Fig. 2. The standard deviations were omitted for clarity but are listed in Table IV.

Bioavailability is characterized by the area under the blood level–time curve, the time of the peak, and the concentration at the peak time (Table V). The areas under the curves were determined by the trapezoidal rule for the time from 0 to 12 hr, and the remaining areas were determined by dividing the last blood level point by the overall elimination rate constant, which was reported previously as 0.29 hr^{-1} after intravenous dosing (5, 7).

The extent of bioavailability, E, was determined using:

$$E = \frac{AUC_{\text{test}}^{0\to\infty} \dfrac{\text{dose}_{\text{standard}}}{\text{body weight}_{\text{standard}}}}{AUC_{\text{standard}}^{0\to\infty} \dfrac{\text{dose}_{\text{test}}}{\text{body weight}_{\text{test}}}} 100 \quad \text{(Eq. 1)}$$

The 500-mg commercial preparation of sulfadiazine USP was considered as the standard. The highest extent of bioavailability was obtained with the tablets prepared by direct compression, followed by those prepared by fluidized-bed granulation. A statistically significant difference was found between the direct compression tablets and the standard with respect to the extent of bioavailability and the time of the peak.

Large differences were found in the *in vitro* dissolution studies, but only minimal differences existed *in vivo*. Part of the differences *in vitro* between the two experimental tablet preparations and the commercial preparation may be explained by the dose size differences of 250 and 500 mg, respectively. Saturation may be approached with the 500-mg dose. Since *in vivo* the peak times occurred in all three preparations in less than 3 hr, the drug is absorbed fast enough not to prevent dissolution due to saturation.

In conclusion, the direct compression tablet mass, when compared to a wet granulation (fluidized-bed) and a commercial tablet preparation,

Table V—Bioavailability Data

Preparation	Body Weight, g ± SD	Dose Size (Potency), mg	$AUC^{0\to\infty}$, (μg/ml) hr ± SD	t_p, hr ± SD	c_{tp}, μg/ml ± SD	Extent of Bioavailability, % ± SD
I	1826.6 ± 64.3	252	316.16 ± 26.16	2.97 ± 0.15	31.096 ± 1.85	106.14 ± 5.22
II	2300 ± 150.0	251	252.27 ± 17.82	2.63[a] ± 0.06	28.58 ± 2.15	106.98[a] ± 3.52
III	3470 ± 85.44	496	308.0 ± 17.14	2.83 ± 0.05	36.08 ± 2.0	100

[a] Statistically significant ($p < 0.05$) when compared to the standard.

[11] Wang 700C, printer-plotter 702.

resulted in an extent of bioavailability of at least that of the standard. The *in vitro* test revealed acceptable tablet properties with respect to weight uniformity, friability, and *in vitro* drug release. Considering the simple methodology employed in the manufacturing of direct compression tablets, this technique and the direct compression mass tested have a high potential for commercial use of a quality product.

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Mathematical Model for Cyclocytidine Pharmacokinetics

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Abstract □ The pharmacokinetics of the drug cyclocytidine in humans were modeled by using a physiological and anatomical approach. Each pertinent tissue is represented by a single compartment, and these compartments are linked together by the circulatory system. Each compartment is then represented by an ordinary differential equation that represents the rate of change in drug concentration as a function of convecting transport, metabolism, and urinary clearance. The models for cyclocytidine and cytarabine are linked together by a hydrolysis term in each equation set. The resulting equation sets are then solved numerically to predict the concentration of both drug species *in situ*. The models use physiological blood flows, tissue volumes, and clearance parameters. The results of the model show that cyclocytidine can act as a reservoir for cytarabine *in vivo* over the time studied. This effect is confined to relatively long times and relatively low plasma concentrations.

Keyphrases □ Cyclocytidine—pharmacokinetics in humans, mathematical model □ Pharmacokinetics—cyclocytidine in humans, mathematical model □ Models, mathematical—cyclocytidine pharmacokinetics in humans

Cytarabine (I) (NSC-63878), an effective antileukemic agent (1–3), has a very short half-life because of its rapid deamination to a biologically inactive compound. O^2,2′-Cyclocytidine (II) (NSC-145688), which is structurally similar to I, was more effective than I in several animal tumor systems (4, 5). The efficacy of II may be due to its hydrolysis to I (6). If so, its effects may be strongly related to the pharmacokinetics of both I and II *in vivo*.

The enhanced cytotoxic effect of II could possibly be due to its slower urinary clearance compared to the elimination of I by deamination and kidney clearance. Thus, II could act as a reservoir for the production of I *in vivo*. This paper presents a mathematical model to study the distribution and hydrolysis of II to I *in vivo*. This model demonstrates that the pharmacokinetic characteristics of II are important to its effective usage.

PHARMACOKINETIC MODEL

The model, an extension of the work by Dedrick *et al.* (7, 8), is based on the principle that anatomical and physiological parameters should be included to reflect biochemical interactions of the drug. The rationale for modeling on this basis as opposed to classical compartmental analysis was developed previously (9–15).

By using compartments to represent real organs, the actual blood flows and physiological volumes as well as terms to include metabolism, urinary clearance, and binding can be included. Thus, when the model is complete, it can provide predictive capability derived from a quantitative physiological and pharmacological basis. Since a model for the pharmacokinetics of I was described in detail (7, 8, 16), only key assumptions that deal directly with changes for the inclusion of II are discussed.

Scheme I represents the flow diagram of the various compartments used in the model. Each compartment represents a real organ, with the anatomical volume experimentally measured independently. The organs are contained in a network representing the systemic blood circulation. The blood flows are also measured independently for each compartment. A drug mass balance represents the rate of change of the mass of drug in the compartment as a function of the convective inflow and outflow rates, the metabolism rate, the elimination rate by urinary or other clearance, and the rate of drug introduction from external sources.

Dedrick *et al.* (7, 8) used the following assumptions to write differential equations describing the pharmacokinetics of I. Each organ is a volume of distribution for the drug, and deamination can be represented by a Michaelis–Menten expression. Urinary clearance is directly proportional to the concentration in the blood. For II, a similar compartmental network is considered. Since the chemical structures of II and I are closely related, it is assumed that they will act similarly, with no gross differences in distribution and urinary clearance from the body.

Compound II is not deaminated *in vivo* (17), and hydrolysis of II to I is assumed to take place in all tissues. Thus, a production term for I is included in each balance that is first order in II concentration (16). The balance equation on the blood compartment for I is:

$$V_B \frac{dC_B}{dt} = Q_H C_H + Q_{Li} C_{Li} + Q_M C_M + Q_K C_K + Q_{Le} C_{Le} - Q_B C_B - \frac{V_{\max,B}\, C_B}{K_{m,B} + C_B} V_B + Mg(t) + K_h X_B \phi V_B \quad \text{(Eq. 1)}$$