Determination of *In Vivo* and *In Vitro* Release of Theophylline Aminoisobutanol in a Prolonged-Action System

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A system has been described in which the dissolution rate of theophylline aminoisobutanol is applied as a parameter of the blood level concentration. The time-lag factors required to obtain maximum cumulation between the *in vitro* dissolution rate and the biopharmaceutical observations warrant further investigation as a yardstick of *in vivo* levels. The slopes of the linear regression curves and the semilog plots of the sustained fraction of the formulation and the blood level data suggest constant rate arithmetic functions in which the fitted curves conform to the laboratory observations. The calculated linear regression curve of the urine concentration data does not fit the observed findings. The semilog plot suggests an exponential function with a delayed and subsequently increasing rate of urinary excretion.

THE PHARMACEUTICAL dosage evaluated in this report is a dual-action pediatric formulation[1] containing theophylline aminoisobutanol (60 mg.) in combination with methylethylaminophenylpropanol HCl (25 mg.) and doxylamine succinate (6 mg.). The product design shown in Fig. 1 is one in which the dosage is divided equally between an outer layer (C) designed to provide rapid drug availability and a slow dissolving inner core (A) protected by a barrier coating system (B).

The inner core contains a matrix of hydrophilic gums in combination with the three active ingredients. The composition of this matrix is a high-viscosity methyl cellulose[2] gum system which swells in contact with the fluids of the intestinal tract. It rapidly absorbs aqueous fluids and forms a soft mucilaginous gel barrier on the surface. This prevents the rapid dissolution of the inner core tablet and results in slow diffusion of the medicaments over a period of 4 to 5 hr. *in vitro* following the breakdown of the barrier coating.

The outer layer system is applied to the protected inner core tablet in a pharmaceutical pan coating process. A hydroalcoholic carbohydrate gum solution is applied as the wet binder in this process. This solution consists of 5% acacia and 32% sucrose in a menstruum of 70% distilled water and 30% alcohol by volume. Finally, a conventional sugar coating is applied to impart the external appearance of the dosage form.

Theopylline aminoisobutanol is a white crystalline compound soluble in water and sparingly soluble in alcohol. "It is a loosely connected compound of theophylline, 67% and, β-aminoisobutanol, 33%, and is said to offer advantages over other theophylline salts in terms of stability, tolerance, and freedom from epigastric irritation. It is not affected by atmospheric moisture, and is particularly superior to theophylline ethylenediamine in this regard" (1). The drug was found to be completely stable at the pH of gastric fluid and intestinal fluid during the *in vitro* dissolution rate determinations described under *Experimental*. The aliquot sample solutions were stored at room temperature for 24-hr. periods. No degradation of the theophylline aminoisobutanol was noted during the analytical procedures.

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[1] Marketed as Dila-min by Walker Laboratories, Division of Richardson-Merrell, Inc., Mount Vernon, N. Y.

[2] Methocel 15,000 cps., 90HG, Dow Chemical Co., Midland, Mich.

EXPERIMENTAL

The *in vitro* rate of dissolution was determined using the U.S.P. tablet disintegration apparatus (2), modified for this study with a No. 40 mesh screen. Eighteen tablets were used, three in each disintegration basket tube. The disintegration basket was placed in an 800-ml. beaker containing 600 ml. of simulated gastric fluid U.S.P., and the apparatus was operated as directed in the official compendium. After 1 hr., the simulated gastric fluid was replaced with simulated intestinal fluid U.S.P. and the apparatus operated until all 18 tablets had disintegrated. During this *in vitro* tablet disintegration procedure, the beaker and apparatus were covered with aluminum foil to prevent the evaporation of water from the disintegration fluids.

At time-span intervals of 1, 2, 4, and 6 hr., 2-ml. aliquots were removed from the disintegration fluids by pipet and assayed for theophylline (3). The analytical results were extrapolated to yield the dissolution rate per tablet in the *in vitro* disintegration fluids.

The *in vivo* blood and urine levels were determined on humans at intervals of 1, 4, 8, and 12 hr., as reported by Holloman *et al.* (4). Blood level and urinary excretion data were reported in terms of milligrams per 100 ml. (mg.%). These data are transformed in this report to relative value indices based on a maximum cumulative concentration of 100 to permit direct comparison of the *in vitro* dissolution rate data with the blood level and urine level concentrations.

RESULTS

The outer layer fraction of the tablet disintegrated within the first hour of exposure to the *in vitro* gastric fluid media. The exposed barrier coating retained its integrity during this first hour and prevented the leaching of active medicament from the inner core tablet. Upon introduction into the intestinal fluid media, the barrier coating system dissolved within 15 min., permitting the onset of

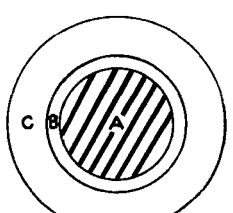

Fig. 1.—Dosage form design. Key: A, sustained-release inner core; B, delayed barrier coating; C, immediate release outer layer.

TABLE I.—RELATIVE VALUE INDEX (RVI) TRANSFORMATION OF THE OBSERVED DATA TO COMPARATIVE VALUES WITH A MAXIMUM CUMULATIVE CONCENTRATION OF 100

In Vitro Dissolution			Blood Concn.			Urine Concn.		
hr.	mg.	RVI	hr.	mg.	RVI	hr.	mg.	RVI
1	35	59	1	.15	22	1	0	0
2	42	70	...	...	...	4	1.1	5.7
4	49	82	4	.45	66	8	4.2	22.0
6	60	100	8	.68	100	12	19.1	100

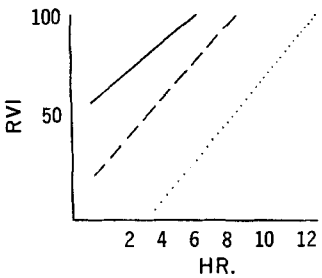

Fig. 2.—Arithmetic linear regression curves. Key: ——, *in vitro*; — —, blood level; . . ., urine level.

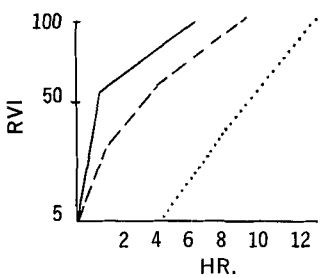

Fig. 3.—Semilog plot. Key: ——, *in vitro*; — —, blood level; . . ., urine level.

dissolution of the inner core medicament into the disintegration solution. The elapsed time required for complete dissolution of the inner core was in terms of 5 hr. following the 1 hr. in gastric fluid.

The *in vitro* dissolution pattern and the *in vivo* blood and urine levels are presented in Table I. These observations were determined following administration of one tablet, and the data tabulated are the mean values of the laboratory findings. The presentation of these observations in terms of relative values permits comparison and time series analysis. The *in vitro* dissolution achieved the maximum cumulative value 100 after 6 hr., the blood level concentration after 8 hr., and the urine concentration after 12 hr. The preceding interval observations were assigned relative percentage values based upon the actual laboratory findings.

DISCUSSION

The cumulative *in vitro* and *in vivo* data and the linear regression fitted curves are plotted in Fig. 2 in terms of their relative value indices.

Theophylline, in the form of its soluble salts, has been shown to be absorbed rapidly following oral administration, yielding fairly high blood levels (5). This is reflected in the 22% relative value blood level observed in the first hour, following the physical dissolution of half of the total theophylline aminoisobutanol which is present in the immediate release outer layer. The linear regression slopes of the dissolution rate of the slow release inner core tablet and the blood level data indicate time-lag factors of about 3 hr. at the 60% relative value index level, and 2 hr. at the maximum cumulative concentration, observed after 8 hr. These linear regression curves fit the observed data closely with respective slopes (y/x) of 0.65 for the dissolution rate and 0.85 for the blood levels; the decreasing time-lag factors are a function of the convergency of the slopes. The linear regression curve of the urinary excretion data falls well below the 12 hr. laboratory observation and indicates an increased rate of urinary excretion in the 4- to 12-hr. period. The time-lag factor at the maximum urine concentration level is in terms of 4 hr. following the maximum blood level concentration.

The semilogarithmic plot of the observed RVI data in Fig. 3 describes the rate of change of the *in vitro* dissolution pattern and the *in vivo* blood and urine data. The similarity in the rate of dissolution release and blood level cumulation suggests the application of this *in vitro* parameter to the pharmacodynamic activity of the theophylline moiety in this formulation. These curves, straight lines on the arithmetic plot, become concave downward on the semilog plot, an indication of constant rate arithmetic progression functions.

The urine concentration semilog plot, as a straight line function, suggests a geometrically increasing rate of excretion of the drug and appears to be a delayed exponential function. These observations, although based on limited data, conform with previously reported studies that theophylline compounds attain appreciable blood levels with slow excretion from the body following the oral route of administration (6).

The rationale in formulating this prolonged-action dosage form to include theophylline aminoisobutanol, which itself is slowly excreted in the urine, is based upon the dual-action nature of this formulation. Following the initial blood levels obtained from the outer layer, the barrier coating delays the release of the inner core ingredients until the tablet has passed to the alkaline environment of the intestinal tract. The *in vivo* data presents this time-lag in terms of 4 hr., making the inner core theophylline content available for blood level maintenance at the time when the outer layer fraction begins to disappear from the blood stream and appears in the urine. The *in vitro* release pattern developed to achieve this *in vivo* data indicates the retarding action of the gum system in which the diffusion effect is retarded and controlled.

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