Dissolution Profiles and Specifications for Dihydroergotoxine Sublingual Tablets Using a New *In Vitro* Method

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Received February 28, 1980, from the *Biopharmaceutics Laboratory, Food and Drug Administration, Washington, DC 20204.* Accepted for publication December 29, 1980.

Abstract □ A dissolution method (paddle method) for determining the dissolution rate profile for 0.5- and 1.0-mg dihydroergotoxine methanesulfonate sublingual tablets was developed. A fluorometric method was used for measuring drug concentration in the dissolution medium, distilled water. It was essential to filter the dissolution sample to avoid interference from undissolved excipients. When different kinds of filters were used with the dissolution samples and standards, different degrees of apparent drug binding to the filter occurred. The dissolution rate profiles for several different products were compared to the innovator's product. The *in vitro* method and data obtained were used to propose dissolution specifications for these sublingual products.

Keyphrases □ Dihydroergotoxine—*in vitro* dissolution method for sublingual tablets, dissolution profiles □ Dissolution—dihydroergotoxine sublingual tablets, *in vitro* method □ Psychotherapeutic agents—dihydroergotoxine, *in vitro* dissolution method for sublingual tablets

Dihydroergotoxine is a psychotherapeutic agent used in the treatment of mood depression, confusion, and unsociability in elderly patients. Dihydroergotoxine sublingual tablets contain equal amounts of the mesylate forms of the dihydrogenated ergot alkaloids dihydroergocristine, dihydroergocornine, and dihydroergokryptine (*i.e.*, sum total of dihydro-α-ergokryptine and dihydro-β-ergokryptine) (1).

This drug is not in the official compendia, but the number of applications received by the Food and Drug Administration (FDA) for marketing approval for these products[1] has increased. Since there is no published method for *in vivo* bioavailability determination of dihydroergotoxine, firms seeking FDA approval were required to meet an *in vitro* dissolution specification as an interim minimum (2). This paper describes the development of a discriminatory *in vitro* dissolution method.

EXPERIMENTAL

Apparatus—A dissolution apparatus described in USP XX Method II was used to establish dissolution specifications. The apparatus was equipped with a transparent constant-temperature water bath, which held six dissolution assemblies so that six dissolution tests could be run simultaneously. The water bath was connected to a free-standing water bath pump[2]. Each stirring shaft[3] of each dissolution assembly and its attached paddle[4] were positioned so that the bottom edge of the paddle was 4.5 ± 0.2 cm from the lowest inner surface of the dissolution vessel[5]. The dissolution profile of dihydroergotoxine tablets was determined in 500 ml of distilled water at 37° and 50 rpm. A volume of 500 ml of dissolution medium was selected due to the size of the dosage strengths tested (0.5 and 1.0 mg) and the assay sensitivity limit.

Sampling—A sampling system was designed with a proportioning pump[6] so that filtered dissolution test specimens from six dissolution assemblies could be collected simultaneously. The pumping system had an on-line filter adapter[7], which contained a disposable filter (glass fiber[8], polytef[9], cellulose[10], or nylon[11]) for each dissolution assembly. Filters were replaced for each dissolution test.

Dissolution specimens (2–3 ml) were collected at each time, and an equivalent volume of dissolution medium was replaced immediately. Collected specimens were allowed to equilibrate to room temperature (25°) in a water bath before being read directly in a spectrophotofluorometer[12]. Prior to reading the filtered standard solutions and collected dissolution specimens, the spectrophotofluorometer was set for an emission intensity reading of 100 for a 1.0-μg/ml unfiltered standard solution.

Standard curves were linear over a concentration range of 0.05–4.0 μg/ml for both filtered and unfiltered standard solutions. A typical equation for an unfiltered standard curve was $y = 97.9x + 1.64$ ($r = 0.9980$); for a filtered standard curve using glass-fiber filters, it was $y = 91.3x + 0.450$ ($r = 0.9993$).

Table I—Influence of Filter Composition on Dihydroergotoxine Binding [a]

	Polytef	Glass Fiber	Cellulose	Nylon
N[b]	22	55	20	6
Mean percent unbound	93.2	92.2	74.0	44.3
Range	85–98.5	84–100	58–93.5	25–70
SD	4.0	4.3	10.1	15.7
SE	0.9	0.6	2.3	6.41
CV[c]	4.3	4.6	13.6	35.5

[a] Percent of apparent drug filter binding was determined using an aqueous 1.0-μg of dihydroergotoxine/ml standard solution. The standard's filtered fluorescence reading for each filter was compared to the standard's unfiltered fluorescence reading of 100. Binding = 100 − observed reading. [b] Number of filters tested. [c] Coefficient of variation.

RESULTS AND DISCUSSION

Spectrophotofluorometric scans demonstrated that an aqueous solution of dihydroergotoxine methanesulfonate[13] (with the assumption that all three drug moieties have the same dissolution characteristics) had maximum excitation and emission wavelengths of 283 and 353 nm, respectively.

Initial studies revealed that dihydroergotoxine standard solutions gave lower relative emission intensity readings when filtered with cellulose filters than when read as unfiltered solutions. Further investigations were conducted using standard solutions to determine the effects other filters had on fluorescence readings. Study results indicated an apparent drug filter binding effect, which was dependent on the type of filter used (Table I). For cellulose and nylon filters, there appeared to be significant binding (~25 and 55%, respectively). For polytef and glass-fiber filters, slight binding seemed possible when the small assay variability (coefficient of variation of 4.3 and 4.6%, respectively) and the differences between unfiltered and filtered fluorescence readings for those filters (~7 and 8%, respectively) were considered.

Sublingual tablets, 0.5 and 1.0 mg, from several manufacturers were

[1] FDA files.
[2] GCA/Precision Scientific, Chicago, Ill.
[3] Part 65-700-001, Hanson Research Corp., Northridge, Calif.
[4] Part 65-700-300, Hanson Research Corp., Northridge, Calif.
[5] Part 33710-S1, Owens Illinois, Vineland, NJ.
[6] Technicon Instrument Corp., Chauncey, N.Y.
[7] Part SX0001300, Millipore Corp., Bedford, Mass.
[8] Part 61628, Gelman Instrument Co., Ann Arbor, Mich.
[9] Teflon, Part LCWP01300, Millipore Corp., Bedford, Mass.
[10] Part SCWP01300, Millipore Corp., Bedford, Mass.
[11] Part NCWP01300, Millipore Corp., Bedford, Mass.
[12] Perkin-Elmer model 204A spectrophotofluorometer with 1.0-cm quartz cells.
[13] Riker Laboratories, Northridge, Calif.

0022-3549/81/0700-0796$01.00/0

Table II—Dissolution Rates (Mean ± *SD*) of 0.5-mg Dihydroergotoxine Tablets in 500 ml of Distilled Water at 37° Using Rotating-Paddle Method

Minutes	Product[a] S1	S2	S3	S4	M1	M2	P	R	B1
2	4.6[b] ± 1.3	8.1 ± 2.6	9.7 ± 3.2	12.5 ± 4.8	2.3 ± 1.5	13.5 ± 5.8	3.0 ± 2.0	39.8 ± 9.4	4.2[b] ± 2.0
5	12.3 ± 4.4	28.6 ± 5.0	30.1 ± 2.9	40.1 ± 9.2	14.1 ± 5.8	43.6 ± 15.3	14.4 ± 4.0	76.3 ± 7.0	20.7 ± 4.6
10	34.1 ± 5.1	52.9 ± 6.9	61.7 ± 7.4	72.8 ± 13.0	31.0 ± 6.3	68.1 ± 16.3	38.5 ± 8.7	81.2 ± 10.4	54.6 ± 9.2
15	55.0 ± 7.4	75.6 ± 4.1	84.3 ± 7.7	90.2 ± 8.0	49.5 ± 13.5	83.6 ± 6.0	50.8 ± 11.3	87.6 ± 4.1	74.6 ± 5.2
20	73.0 ± 7.2	83.3 ± 7.1	91.1 ± 8.1	97.5 ± 5.2	61.8 ± 12.4	90.0 ± 6.0	56.3 ± 10.5	82.8 ± 9.3	80.6 ± 6.2
30	97.7 ± 7.0	90.4 ± 4.9	89.9 ± 7.6	99.4 ± 4.1	77.7 ± 7.1	94.0 ± 6.3	59.9 ± 11.0	84.9 ± 5.0	84.3 ± 7.2
60	102.8 ± 5.7	89.1 ± 3.2	92.8 ± 6.0	101.0 ± 5.8	91.1 ± 5.8	94.4 ± 4.1	76.1 ± 9.8	86.5 ± 7.5	81.4 ± 4.2
∞[c]	98.5 ± 6.8	91.0 ± 5.2	91.9 ± 6.2	98.9 ± 4.4	98.2 ± 3.7	98.6 ± 7.8	76.2 ± 14.9	89.1 ± 8.5	86.9 ± 7.5

[a] S1 (lot 720X5534), S2 (lot 752X6194), S3 (lot 751X6194), and S4 (lot 717X5654) represent four lots of the innovator Sandoz Pharmaceuticals; M1 (lot 3MMJ075) and M2 (lot 3MF0082) were from Mead Johnson; P (lot A61447) was from Premo Pharmaceutical Laboratories; R (lot 57295) was from Riker Laboratories; and B1 (lot 026093) was from Bolar. Twelve tablets of each product were used except that six tablets of M1 and M2 were tested. [b] Mean of six tablets. [c] See Footnote 14.

Table III—Dissolution Rates (Mean ± *SD*) of 1.0-mg Dihydroergotoxine Tablets in 500 ml of Distilled Water at 37° Using Rotating-Paddle Method

Minutes	Product[a] S5	S6	S7	S8	B2	M3	M4
2	8.6 ± 0.7	8.3 ± 0.8	7.9 ± 2.1	11.1 ± 1.4	19.9 ± 2.2	5.2 ± 1.7	18.6 ± 6.1
5	23.9 ± 1.3	25.2 ± 2.0	22.9 ± 2.2	31.3 ± 2.6	45.6 ± 2.0	17.1 ± 2.5	48.7 ± 9.9
10	50.7 ± 1.9	51.5 ± 3.2	46.1 ± 2.0	55.8 ± 2.6	57.2 ± 3.0	32.0 ± 4.4	79.9 ± 6.2
15	66.0 ± 2.1	76.3 ± 2.5	66.0 ± 3.9	83.3 ± 6.4	64.9[b] ± 3.4	42.6 ± 4.9	103.0 ± 7.4
20	84.9 ± 2.7	88.7 ± 3.7	76.5 ± 2.7	96.8 ± 4.0	64.6 ± 2.9	49.2 ± 3.3	107.0 ± 2.3
30	95.8 ± 3.1	91.0 ± 3.4	89.5 ± 3.1	98.9 ± 3.9	69.0[b] ± 5.8	58.4 ± 6.9	112.0 ± 4.7
60	98.6 ± 2.8	92.3 ± 2.1	93.5 ± 3.4	100.0 ± 3.6	62.9 ± 6.4	97.4 ± 4.5	106.0 ± 2.1
∞[c]	102.0 ± 1.5	94.7 ± 1.7	95.0 ± 3.9	98.3 ± 2.6	64.1 ± 7.7	106.0 ± 9.6	110.0 ± 8.8

[a] S5 (lot 040X6375), S6 (lot 039Y6389), S7 (lot 035X6265), and S8 (lot 038Y6389) represent four lots of the innovator Sandoz Pharmaceuticals; B2 (lot 116581) was from Bolar; and M3 (lot 3MMJ082) and M4 (lot 3MF0081) were from Mead Johnson. Six tablets of each product were used except that 12 tablets of S7 were tested. [b] Mean of 12 tablets. [c] See Footnote 14.

tested. Glass-fiber filters were used because of their low apparent drug binding effect. Dissolution profiles from 2 min to infinity[14] were determined. For each dissolution run, at least six tablets were tested and a filtered standard curve was prepared.

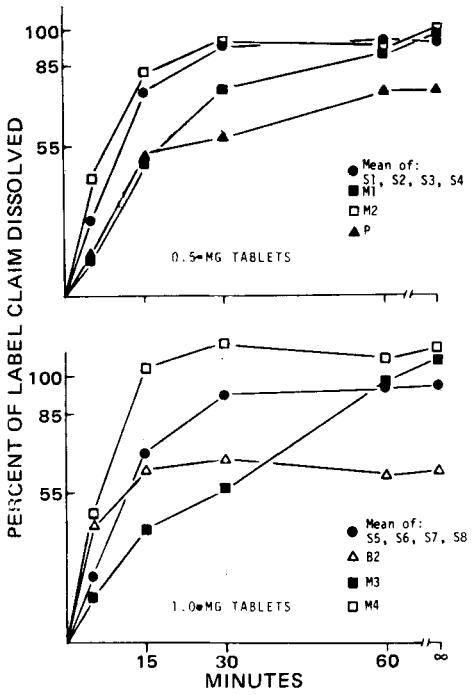

Figure 1—*Dissolution profiles for 0.5- and 1.0-mg dihydroergotoxine mesylate tablets in distilled water at 37° by the 50-rpm paddle method. The data points represent a mean of 48 tablets representing four batches for 0.5-mg tablets and a mean of 30 tablets representing four batches for 1.0-mg tablets for Product S. For all other brands, the values represent a mean of six or 12 tablet determinations.*

[14] Infinity dissolution was determined after stirring the dissolution medium for an additional 30 min at 200 rpm following 60 min of specimen collection.

Table IV—*p* Values for the Significance Tests Associated with Analysis of Variance of Percent Dihydroergotoxine Dissolved

Effect	0.5-mg Tablet 15 min	0.5-mg Tablet 30 min	1.0-mg Tablet 15 min	1.0-mg Tablet 30 min
Brands	0.602	0.020	0.989	0.469
Lots within brands	0.001	0.086	0.005	0.001

The dissolution test results for 0.5- (Table II) and 1.0- (Table III) mg tablets demonstrated that there were brand-to-brand and lot-to-lot dissolution differences (Fig. 1). To establish differences between brands and between lots within a brand, analyses of variance were carried out on the percent of drug dissolved for 0.5- and 1.0-mg tablets at 15 and 30 min using the NESTED procedure previously described (3). The p values for the associated significance tests are summarized in Table IV. There were significant differences ($p \leq 0.005$) between lots within brands for 0.5-mg tablets at 15 min and for 1-mg tablets at 15 and 30 min. In addition, there were significant differences among brands for 0.5-mg tablets at 15 min ($p = 0.02$).

The differences observed under these test conditions were attributed to drug product manufacturing differences, excipients, and other tablet

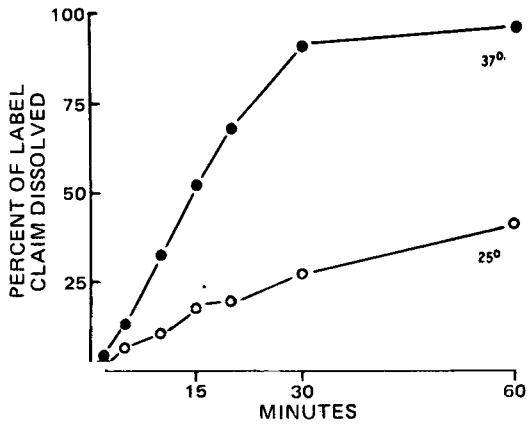

Figure 2—*Effect of temperature on the dissolution rate of innovator's product (S1; lot 720X5534) of 0.5-mg sublingual tablets. Dissolution values represent the average of two tablets.*

Table V—Dissolution Rates of 0.5- and 1.0-mg Dihydroergotoxine Tablets in 500 ml of Distilled Water at 25° Using Rotating-Paddle Method

Minutes	0.5 mg					1.0 mg,
	Product M2[a]	Product P	Product B1	Product R	Product S1	Product M4
2	2.5, 5.5[b]	0.0, 2.0	2.0, 0.6	27.3, 38.8	0.6, 3.0	8.7, 8.3
5	11.0, 13.0	4.0, 7.5	9.5, 5.8	66.8, 67.8	6.3, 6.0	20.2, 20.3
10	23.5, 25.5	16.0, 13.5	22.0, 23.3	75.3, 84.8	8.3, 10.6	37.2, 39.8
15	29.5, 39.0	22.0, 37.5	30.5, 37.8	79.8, 87.8	16.3, 16.0	48.7, 60.8
20	45.5, 56.0	33.5, 57.0	50.5, 59.8	85.3, 82.8	19.3, 16.5	73.2, 73.3
30	74.5, 81.2	41.5, 54.5	71.5, 70.3	75.8, 87.8	27.3, 23.0	94.2, 97.8
60	89.0, 90.5	61.0, 55.5	75.0, 75.3	82.8, 84.3	34.8, 42.0	106, 101

[a] Letter represents manufacturer, and number represents a different production lot. Refer to Tables II and III for explanation of symbols. [b] Values for two tablets.

variations. Other studies, under slightly modified test conditions, also helped to establish that dissolution differences may be due to formulation differences. Two brands, P and B2, failed to achieve total dissolution (Fig. 1). With both preparations, insoluble material in the dissolution medium and a film on the stirring shafts and paddles indicated the possibility of an insoluble complex formation. Total dissolution could be achieved only by further dilution to 900 ml of medium.

The extent of dissolution as a function of temperature was not clear cut and predictable because of the differences in formulations (Table V). For example, Products M2, P, B1, and M4 initially dissolved slowly at 25°; however, after 60 min, the extent of dissolution was comparable to that at 37°. On the other hand, temperature had no influence on Product R (the dissolution profiles at 25 and 37° were identical). However, the rate and extent of dissolution of Product S1 were decreased significantly at 25° when compared to the results obtained at 37° (Fig. 2).

Based on the *in vitro* dissolution results, the FDA implemented a dissolution specification for 0.5- and 1.0-mg sublingual tablets using the paddle method (4) where the dissolution medium is 500 ml of distilled water at 37°. The paddle height is 4.5 cm, and the stirring speed is 50 rpm. The dissolution specimens are filtered with either glass or polytef filters prior to drug content analysis.

In vivo bioavailability data for *in vitro–in vivo* correlations are lacking. Therefore, based on the *in vitro* performance of eight batches representing 0.5- and 1.0-mg tablets of the innovator product[15], a dissolution specification was set. For tablets to be considered acceptable, they must dissolve not less than 55% in 15 min and not less than 85% in 30 min for a mean of 12 tablets. However, no tablet should fall below 45 and 75% at those respective times.

The described *in vitro* dissolution method and its specifications should help ensure both product-to-product and lot-to-lot uniformity and consistency for dihydroergotoxine sublingual tablet dosage forms.

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[15] Sandoz.

NOTES

Loss of Nitroglycerin from Solutions to Intravenous Plastic Containers: A Theoretical Treatment

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Received June 3, 1980, from *American Critical Care, McGaw Park, IL 60085.* Accepted for publication September 10, 1980.

Abstract □ The physical instability of nitroglycerin solutions in plastic containers has been reported extensively. A systematic study of potency loss in plastic infusion bags was reported recently. This paper presents a theoretical treatment of the data and a proposed model consisting of adsorption onto the surface followed by partitioning into the plastic.

Keyphrases □ Nitroglycerin—loss from solution to plastic intravenous containers, a theoretical treatment □ Plastic containers—loss of nitroglycerin from intravenous plastic containers, a theoretical treatment □ Adsorption, potential—nitroglycerin loss from solution in plastic intravenous containers, a theoretical treatment

Numerous studies (1–10) have reported stability problems associated with nitroglycerin solutions in plastic containers meant for intravenous infusions. Adsorption of the drug by plastic containers and infusion sets was suggested as the cause. Yuen *et al.* (8) studied the loss of nitroglycerin from aqueous solutions in immersed strips of plastic. Based on equilibrium and kinetic studies, these workers proposed an adsorption–absorption mechanism in which adsorption plays a minor role. Although their report provided some insight into the phenomenon, it did not deal with the system as a whole, *i.e.*, nitroglycerin solutions contained in intravenous bags.

The loss of nitroglycerin from solutions stored in commercial plastic intravenous bags was reported recently (10). Immediate significant losses were followed by a gradual decrease in concentration. No chemical degradation was observed. In this report, a theoretical treatment of the data and a proposed model are presented.

EXPERIMENTAL

The applicability of the proposed model was tested using recently reported data of nitroglycerin compatibility with intravenous admixture aids (10). In brief, the procedures for obtaining the kinetic data entailed: (*a*) the addition by syringe of an aqueous nitroglycerin preparation to

0022-3549/81/0700-0798$01.00/0