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COMPARISON OF IN VITRO RELEASE RATES OF MULTISOURCE SUSTAINED-RELEASE PAPAVERINE HYDROCHLORIDE PRODUCTS.

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ABSTRACT

The extent of differences in the in vitro release rate among 24 lots of 150 mg sustained-release papaverine hydrochloride products from six manufacturers was investigated.

The rotating bottle method for timed-release capsules, official in N.F. XIV, was used. Quantitation of papaverine hydrochloride in solution was done using ultra-violet spectrophotometry at two wavelengths to assure that there was no interference from other components of the formulation.

While in vitro dissolution data by itself cannot predict in vivo performance, variations from one manufacturer to another and also for the same manufacturer were observed. These included variations in the amount released both in the first hour and also in the total amount released.

Of the six products tested, Pavabid and Cerespan demonstrated the most consistent release patterns with slightly better con-

sistency observed for the former. Observed differences may or may not be of clinical significance.

INTRODUCTION

It is generally accepted that the dissolution rate of a drug from a formulation may affect both its absorption and therapeutic characteristics. It is also well known that *in vitro* dissolution data by itself cannot be used as a predictor of *in vivo* performance of a dosage form[1]. However, dissolution tests are useful and valid, as a quality control procedure; in product development for the rejection of unsuitable formulations; in the detection of lot to lot variation; and in the demonstration of differences among products of various manufacturers.

The present study was undertaken using the N.F. method to determine the extent of differences in the *in vitro* release rate among various marketed papaverine hydrochloride sustained-release products as well as to determine lot to lot variation in the dissolution profiles for a given manufacturer.

EXPERIMENTAL

Reagents. The reagents were: papaverine hydrochloride[a]; hydrochloric acid[b], AR; potassium phosphate monobasic[b], AR; sodium chloride[b], AR; and sodium hydroxide[b], AR. All reagents were used without further purification. All dosage forms were purchased on the open market.

Dissolution Procedure. The rotating bottle dissolution procedure described in NF XIV for the *in vitro* testing of timed-release capsules was followed[2]. Sixty ml of 37°C dissolution

medium is placed into each of five bottles containing one dosage unit. The bottles are capped and rotated end over end at approximately 40 rpm in a 37°C water bath. The pH of the dissolution medium is varied according to the following schedule: pH 1.2 (1 hour); pH 2.5 (1 hour); pH 4.5 (1.5 hours); pH 7.0 (1.5 hours) and pH 7.5 (2 hours). At each pH change, the dissolution medium from a single bottle is appropriately analyzed. Thus, each point on a dissolution profile is from a single dosage unit. The simulated gastric and intestinal fluids were prepared without enzymes as directed in USP XIX[3].

Analytical Procedure. Papaverine hydrochloride can be quantitated directly in the dissolution medium using ultraviolet spectrophotometry[c]. Beer's law plots were determined at each pH because of slight spectral shifts caused by the changing pH. Two wavelengths were used to insure that there was no interference from the other components of the formulation. The wavelengths used at each pH were: pH 1.2 and 2.5 (277, 307 nm); pH 4.5 (281, 307 nm); and pH 7.0 and 7.5 (279, 313 nm). All pH values[d] were within ± 0.1 pH units at 37°C.

An empty capsule shell from each lot was dissolved in 60 ml of simulated gastric fluid, appropriated diluted and utilized as the blank at pH 1.2, since all capsule shells contained colored matter. No capsule shell remained in the dissolution medium at all subsequent pH values, so all other blanks were simply pure buffer at that pH.

Calculation. Conversion of the absorbance to mg of papaverine hydrochloride was made by:

$$\text{Mg Drug} = \frac{(A)(MW)(V)(DF)(1000)}{a}$$

where

A = absorbance

a = molar absorptivity

MW = molecular weight of papaverine hydrochloride

V = volume of dissolution medium in liters

DF = dilution factor

RESULTS AND DISCUSSION

The determination of dissolution profiles for 150 mg papaverine hydrochloride sustained-release products was carried out in duplicate for 24 lots from six manufacturers. There was no observed interference from other components of the formulations. Plots of the duplicate averages of the cumulative amount of drug in solution for each lot from each manufacturer are shown in Figures 1-6.

Even though the dissolution profiles by themselves are not able to predict in vivo dosage form performance, much useful information of a quality control nature can be obtained. Differences among manufacturers are readily apparent upon examination of Figures 1-6. For example, it is interesting to note that one of the lots, Lederle #455-178, appears to dump over 90% of its drug in the first hour under the conditions of the study, in-

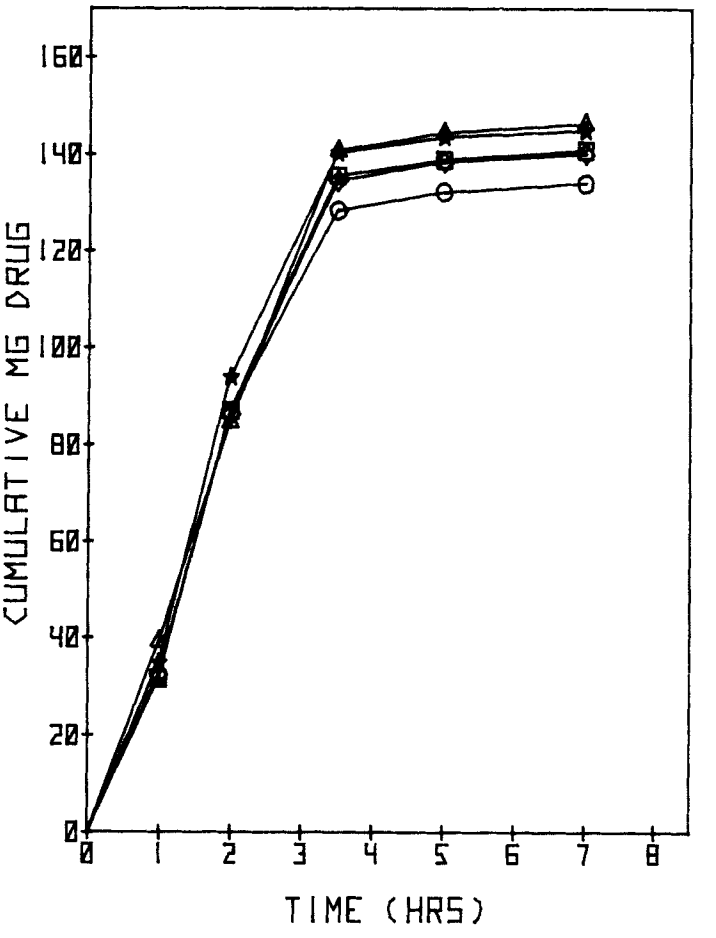

FIGURE 1

Cumulative amount of papaverine hydrochloride in solution for five lots of Pavabid. Key: ○, A7043; □, E7002; △, E7003; ☆, C7005; ◇, E7004.

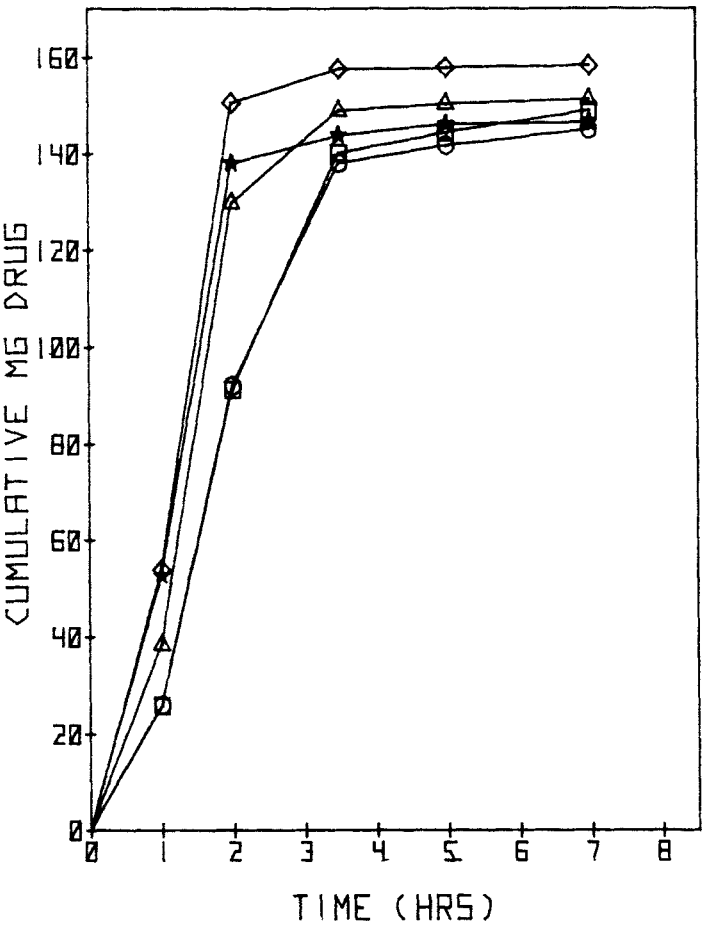

FIGURE 2

Cumulative amount of papaverine hydrochloride in solution for five lots of Cerespan. Key: ○, 55595; □, 55593; △, 55267; ☆, 55285; ◇, 55283.

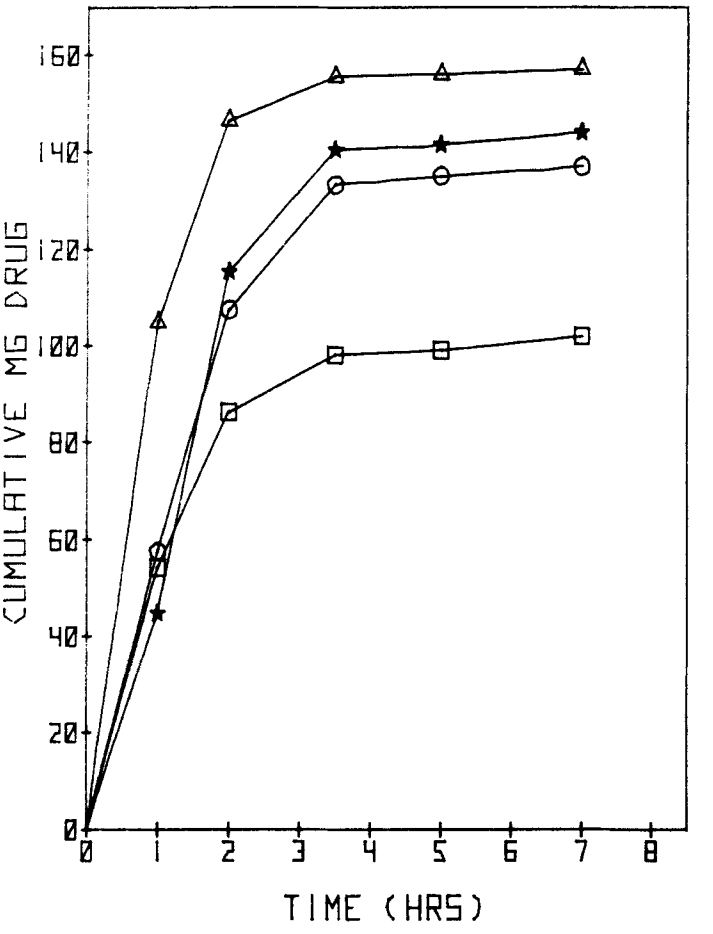

FIGURE 3

Cumulative amount of papaverine hydrochloride in solution for four lots of Pavasule. Key: ○, 09501; □, 05701; △, 02603; ☆, 12603.

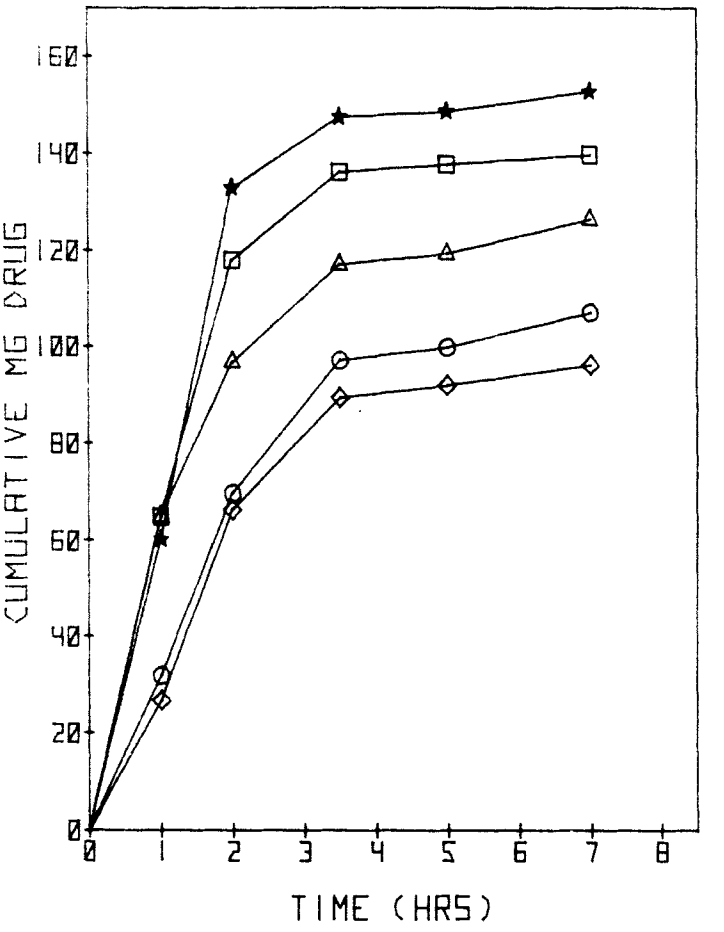

FIGURE 4

Cumulative amount of papaverine hydrochloride in solution for five lots of Purepac. Key: ○, 633161; □, 62251; △, 73005; ☆, 63055; ◇, 61377.

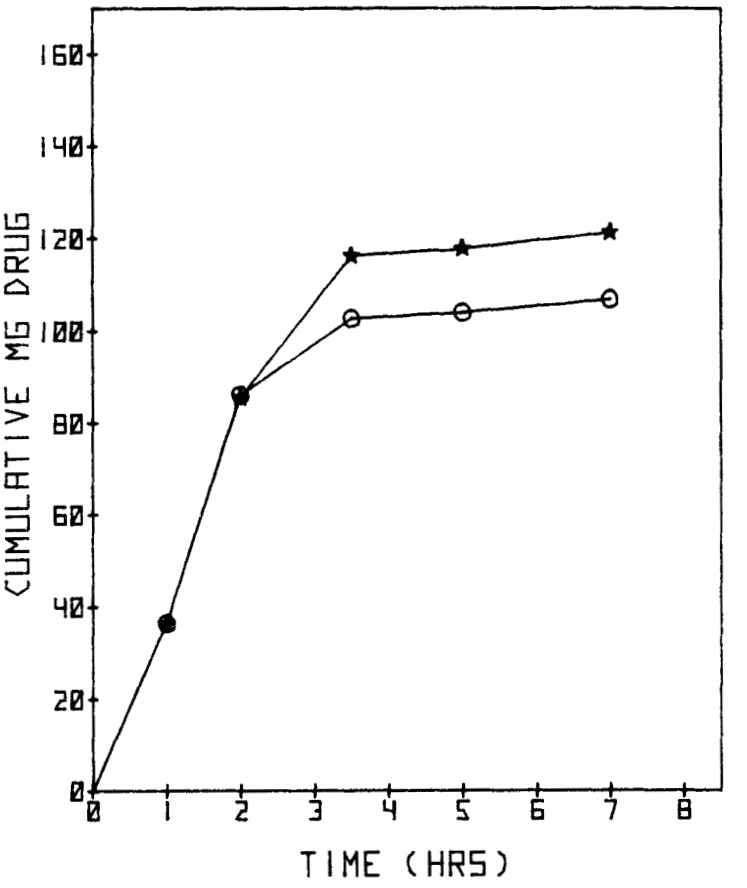

FIGURE 5

Cumulative amount of papaverine hydrochloride in solution for two lots of Towne. Key: ○, 037661; ☆, 027635.

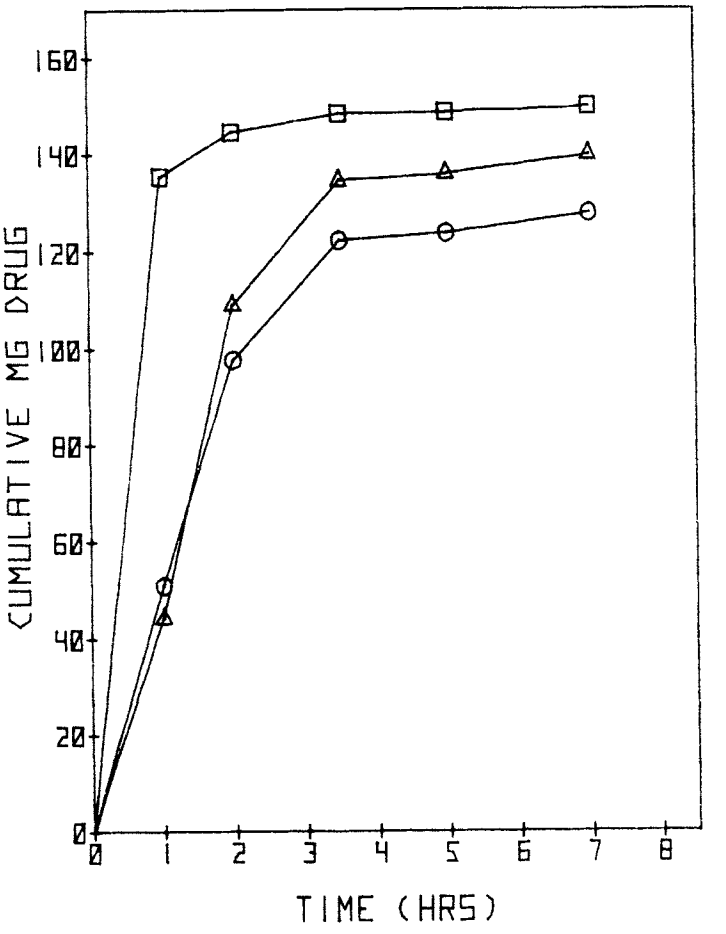

FIGURE 6

Cumulative amount of papaverine hydrochloride in solution for three lots of Lederle. Key: ○, 479-413; □, 455-178; △, 467-615.

TABLE 1. Cumulative Amount of Papaverine Hydrochloride in Solution Averaged Over All Lots from a Single Source.

		Cumulative Amount Papaverine Hydrochloride (Mg ± S.D.)					
Time (Hrs)	pH	Pavabid[a]	Cerespan[a]	Pavasule[b]	Purepac[a]	Towne[d]	Lederle[c]
1.0	1.2	34.1 ± 5.1	39.4 ± 13.8	65.4 ± 24.8	49.7 ± 18.3	36.4 - 36.5	77.0 ± 43.6
2.0	2.5	87.8 ± 3.9	120.4 ± 25.5	113.9 ± 22.6	96.7 ± 27.0	85.6 - 86.2	117.1 ± 22.1
3.5	4.5	135.9 ± 6.9	145.7 ± 7.3	131.8 ± 22.0	117.5 ± 22.8	102.7 - 116.2	135.1 ± 12.8
5.0	7.0	139.6 ± 6.9	148.1 ± 5.9	132.9 ± 21.9	119.5 ± 22.3	104.0 - 117.8	136.2 ± 12.4
7.0	7.5	141.3 ± 6.9	150.0 ± 4.9	135.1 ± 21.3	124.4 ± 21.4	106.8 - 121.3	139.1 ± 11.3

[a]Average of five lots run in duplicate

[b]Average of four lots run in duplicate

[c]Average of three lots run in duplicate

[d]Range of two lots run in duplicate

dicating a possible failure of the sustained-release mechanism for this lot. In addition, four of the lots release less than 75% of their labelled amount of drug during the duration of the study as demonstrated by Pavasule #05701, (68.1%); Purepac #61377, (64.1%) and #633161 (71.4%); and Towne #037661 (71.2%).

Lot to lot variations are also in evidence as shown by a range of release in the first hour of 44.4 mg to 135.5 mg of drug for Lederle #467-615 and #455-178 respectively. Wide variations in the total amount released are also observed as demonstrated by Pavasule #05701 (102.1 mg) and #02603 (157.2 mg); and Purepac #61377 (96.1 mg) and #63055 (152.7 mg).

Table 1 shows the averages over all lots of the cumulative amount of papaverine hydrochloride in solution from a particular source. The most consistent release pattern is obtained from the Pavabid formulation.

CONCLUSION

Although the N.F. rotating bottle method cannot predict *in vivo* performance without correlating *in vivo* data, its usefulness as a quality control tool for determination of intermanufacturer and lot to lot variation is clearly evident. Of the six different products tested, Pavabid and Cerespan demonstrated the most consistent release patterns with slightly better consistency observed for the Pavabid. Observed differences may or may not be of clinical significance.

FOOTNOTES

[a]Sigma Chemical Co., St. Louis, MO 63147

[b]Mallinckrodt Chemical Works, St. Louis, MO 63147

[c]Gilford 240, Gilford Instruments Labs, Inc., Oberlin, OH 44074

[d]Model 4500, Beckman, Beckman Instruments, Inc., Fullerton, CA 92634

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3. Anon: The United States Pharmacopeia, 19th rev, The United States Pharmacopeial Convention, Inc., Rockville, MD, 1975, p. 765.