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COMPARATIVE DISSOLUTION OF COMMERCIALLY AVAILABLE HYDROXYZINE HYDROCHLORIDE TABLETS

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ABSTRACT

A comparative dissolution study was conducted on commercially available hydroxyzine hydrochloride tablets using USP Apparatus 2 (Paddle Method) at 50 rpm and two dissolution media: Water and Simulated Intestinal Fluid (SIF) and the USP recommended method employing the disintegration apparatus. The dissolution characteristics of 22 samples of hydroxyzine hydrochloride tablets representing four dosage levels and seven manufacturers were profiled.

The study illustrated that the Modified Disintegration apparatus is not able to distinguish slow dissolving formulations from fast dissolving formulation and, consequently, does not provide assurance of bioequivalence and does not perform as an adequate manufacturing control to insure lot to lot uniformity.

Introduction

In vitro dissolution testing can be a valuable predictor of the **in vivo** bioavailability and bioequivalence of solid oral dosage forms. Once the formulation has been shown to be bioavailable, dissolution testing is the method of choice in assuring lot-to-lot bioequivalence. However, in order for dissolution testing to remain a valuable predictor of bioavailability and bioequivalence, it must be able to discriminate formulations which have good bioavailability from those formulations which may have **in vivo** problems. Several methods are available for measuring the dissolution of solid oral dosage forms. The two methods which have received wide recognition by FDA and USP are USP Apparatus 1 (Basket Method) and USP Apparatus 2 (Paddle Method). Other methods such as the rotating bottle method, the rotating filter-stationary basket method, modified disintegration method and the flow-through method have occasionally been used for dissolution testing of various dosage forms.

Hydroxyzine hydrochloride tablets are marketed for the symptomatic relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested. It is useful in the management of pruritus due to allergic conditions such as chronic urticaria and topic and contact dermatitis, in histamine-medicated pruritus and as a sedative prior to, or following, anesthesia.

A Drug Efficacy Study Implementation Notice (DESI 10392) published in the Federal Register outlined the conditions for marketing hydroxyzine hydrochloride solid oral dosage forms (1). The notice indicated that the dissolution data on three consecutive production lots of the product (hydroxyzine hydrochloride tablets) should be carried out by the Paddle Method at 50 rpm using 900 ml of water as the dissolution medium. Using this procedure, the FR notice required that the product be not less than (NLT) 50% dissolved in 30 minutes and NLT 80% dissolved in 60 minutes. Manufacturers failing to meet these dissolution specifications, were required to conduct an **in vivo** bioavailability study comparing the product to the marketed hydroxyzine hydrochloride syrup. The USP dissolution method, on the other hand, utilizes a modified disintegration apparatus, Apparatus 3 (2) and requires that the dissolution be not less than (NLT) 75% in 45 minutes. With the state-of-the-art knowledge today, the disintegration procedure cannot be relied upon to provide assurance of lot-to-lot uniformity of the products. It has been clearly shown that the bioavailability of the products can be correlated with dissolution of the products, and not with the disintegration (3).

This paper presents the findings of a comparative dissolution survey performed on commercially available, chemically equivalent brands of hydroxyzine hydrochloride tablets. The dissolution characteristics of twenty-two samples of hydroxyzine HCL tablets representing four dosage

levels: 10 mg, 25 mg, 50 mg and 100 mg; and seven manufacturers, are profiled. The "dissolution" of all samples was also determined using the USP disintegration procedure and the results compared to the paddle method.

EXPERIMENTAL

Dissolution:

1. **USP Apparatus II (Paddle Method)**

Dissolution profiles were determined at 37±0.5°C in 900 ml of water and in 900 ml of simulated intestinal fluid (SIF) without enzymes. The SIF was prepared as directed in the USP (5). All media were deaerated prior to use. Commercially available dissolution equipment[1] employing the paddle apparatus as described in the USP (4) was used to conduct the market survey. A controlled-temperature bath maintained the medium at 37± 0.5°C. The paddle was positioned to extend to exactly 2.5 cm above the flask bottom. Rotation speed was maintained at 50 rpm. Samples were taken with a graduated glass syringe [2] fitted with a metal cannula. The cannula was removed and the syringe fitted with a plastic filter holder containing a 25 mm diameter nylon[3] or membrane[4] filter. The first 4-5 ml of the sample filtrate was discarded and a portion of the remainder added to 2.0 ml plastic sampling cups[5]. The sample was acidified

1. Hanson variable speed Spindle Dissolution Drive Model (Motor) 37-300-101, Hanson Corp., Northridge, CA
2. Luer-Lok, Becton Dickinson and Co., Rutherford, NJ
3. Nylon-66, 0.45 pore size, Rainin, Woburn, MA
4. SSAE91 0.8 micron pore size, Schleicher-Schuell, Keene, NH 03431
5. Technicon Instrument Corp, Terrytown, NY 10591

with one drop (c.a. 0.02 ml) of 50% HCL and stirred will with a narrow bore, closed glass tube. A standard solution of hydroxyzine HCL was added to the 2.0 mark on the plastic sample cup and acidified in the same manner. Between timed samplings, the syringe, filter holder, and cannula used for each vessel were shaken well to remove excess liquid.

System Suitability Test: The suitability of the paddle apparatus was checked using the USP prednisone and salicylic acid "Calibrators for System Suitability Test of Basket and Paddle Dissolution Apparatus"[6] and the Division of Drug Analysis (DDA's) Performance Standard II[7], a prednisone tablet identified by DDA as a better calibrator for assessing system suitability for the paddle apparatus (6).

2. **USP Method: Disintegration Apparatus**

The apparatus consisted of a basket-rack assembly, a 1000 ml low-form beaker for the immersion fluid, water, and a constant temperature bath maintained at 37±0.5°C. The basket-rack assembly was raised and lowered in the immersion fluid at at constant frequency rate between 29 and 32 cycles per minute. The apparatus was adjusted so that the basket-rack assembly descended to 1.0 ±0.1 cm. from the inside bottom surface of the vessel on the downward stroke. The volume of the fluid was 630 ml. The basket-rack assembly consisted of six open-ended tubes as specified in the USP (2).

6. United States Pharmacopeia, Fishers Lane, Rockville, MD
7. Division of Drug Analysis, Market Street, St. Louis, MO

Attached to the under surface of the lower plate was a 40-mesh woven stainless-steel wire cloth having a plain square weave. A 40-mesh woven stainless-steel cloth was fitted to the top of the basket-rack assembly to prevent any dosage unit from floating out of the tubes of the assembly. One tablet was placed in each tube (6 tablets per run) and analyzed after 45 minutes.

Sample Analysis

Tablets with a dark orange film coating (Manufacturer D: 25, 50, and 100 mg tablet) showed UV interference in the SIF medium and were analyzed by HPLC rather than by the UV method. In the case of all other tablets, an aliquot of the SIF medium from one tablet of each dosage strength (except 10 mg), was analyzed by both the HPLC method and the UV method.

1. **UV Method**

The Technicon autoanalyzer and UV spectrophotometer[5] was used to determine the absorbance of the samples. 1:100 HCL:H_2O with 3 ml of Brig-32[8] added per liter was used as a diluent.

A PDP-8 (Digital) was used to track the absorbance output, and a computer program (SASDRA-BA)[9] was used for the calculations.

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8. Brig-35, Pierce Chemical Co. Rockford, IL 61105
9. SASDRA-BA computer program developed for in-house use by Dan Brown

2. **High Pressure Liquid Chromatographic Method (HPLC)**

The high-pressure liquid chromatograph consisted of a three piston pumping system[10], and automatic injector[11], and a variable wavelength UV detector set at 232nm. The data was collected and reduced by a microprocessor[12], and the peaks were recorded on a Heath track strip recorder. The stainless steel column[13] was packed with fully porous 10 um silica particles to which was chemically bonded a monomolecular layer of octadecysilane. The isocratic mobile phase consisted of 60% acetonitrile and 40% aqueous phosphate buffer (0.01M $Na_2HPO_4 \cdot 7H_2O$) adjusted to pH 3.5 with phosphoric acid (H_3PO_4). The mobile phase was filtered and degassed by vacuum. All assays were performed at ambient temperature.

Results and Discussion

The dissolution profiles of 22 commercially available hydroxyzine hydrochloride tablets, from 10-100 mg, 7 manufacturers, were determined by the paddle method in water **(Figure 1)** and in SIF **(Figure 2)**. Tablets of all dosage strengths from manufacturers A dissolved significantly faster in water than in SIF compared to other manufacturers. All strengths from manufacturer E as well as the lowest strength of manufacturer F and the 50 mg strength of manufacturer A, were slow dissolving. The

10. DuPont Model 850, DuPont-DeNemors, Willmington, DE
11. WISP 710 Automatic Injector, Waters Associates, Millford, MA
12. Hewlett-Packard 3380A Integrator, Hewlett-Packard Co, Palo Alto, CA
13. uBondapak C_{18}, Waters Associates, Millford, MA

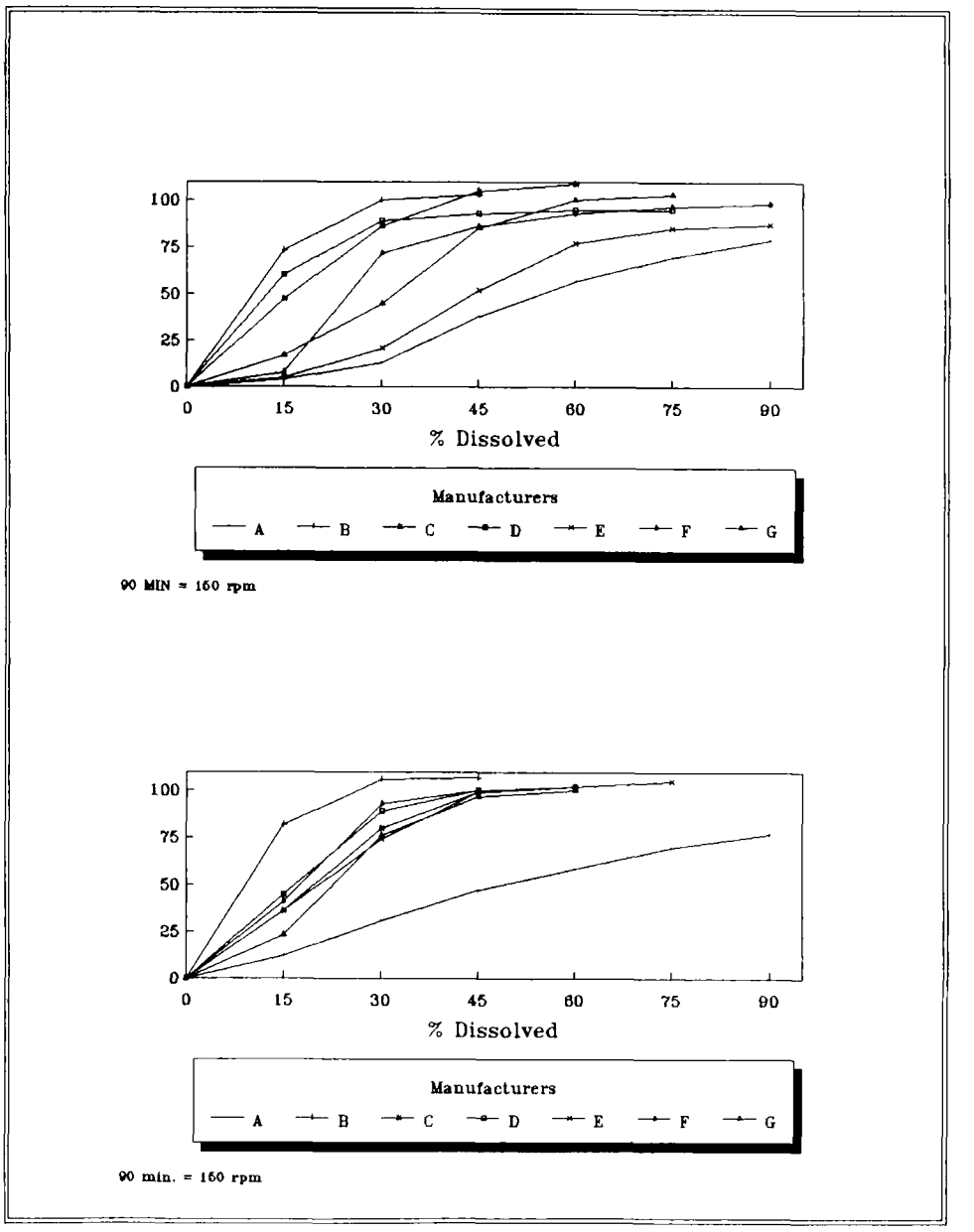

FIGURE 1:
In vitro dissolution of marketed hydroxyzine HCL tablets;
Paddle Method, 50 rpm, Water

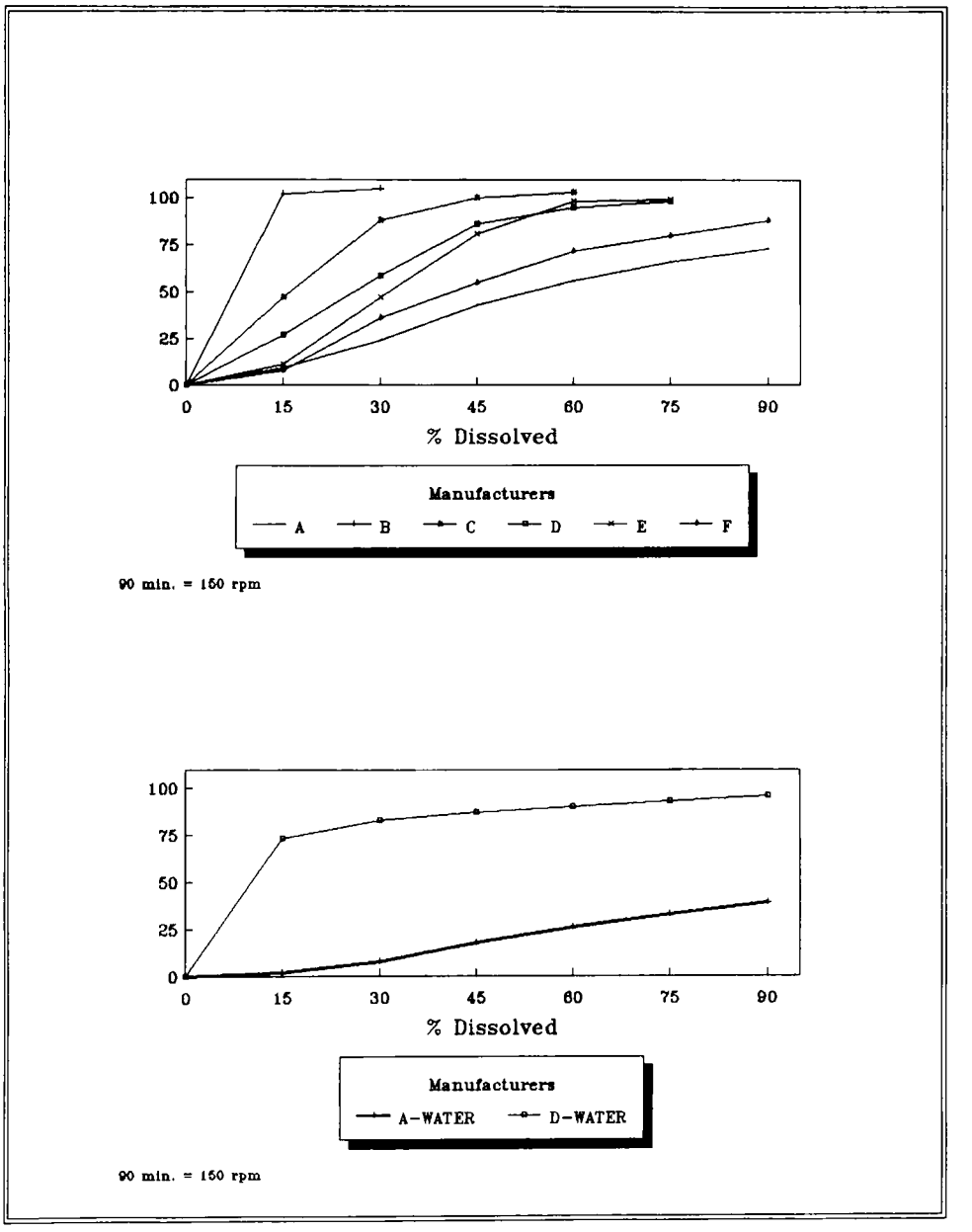

FIGURE 1 (continued)

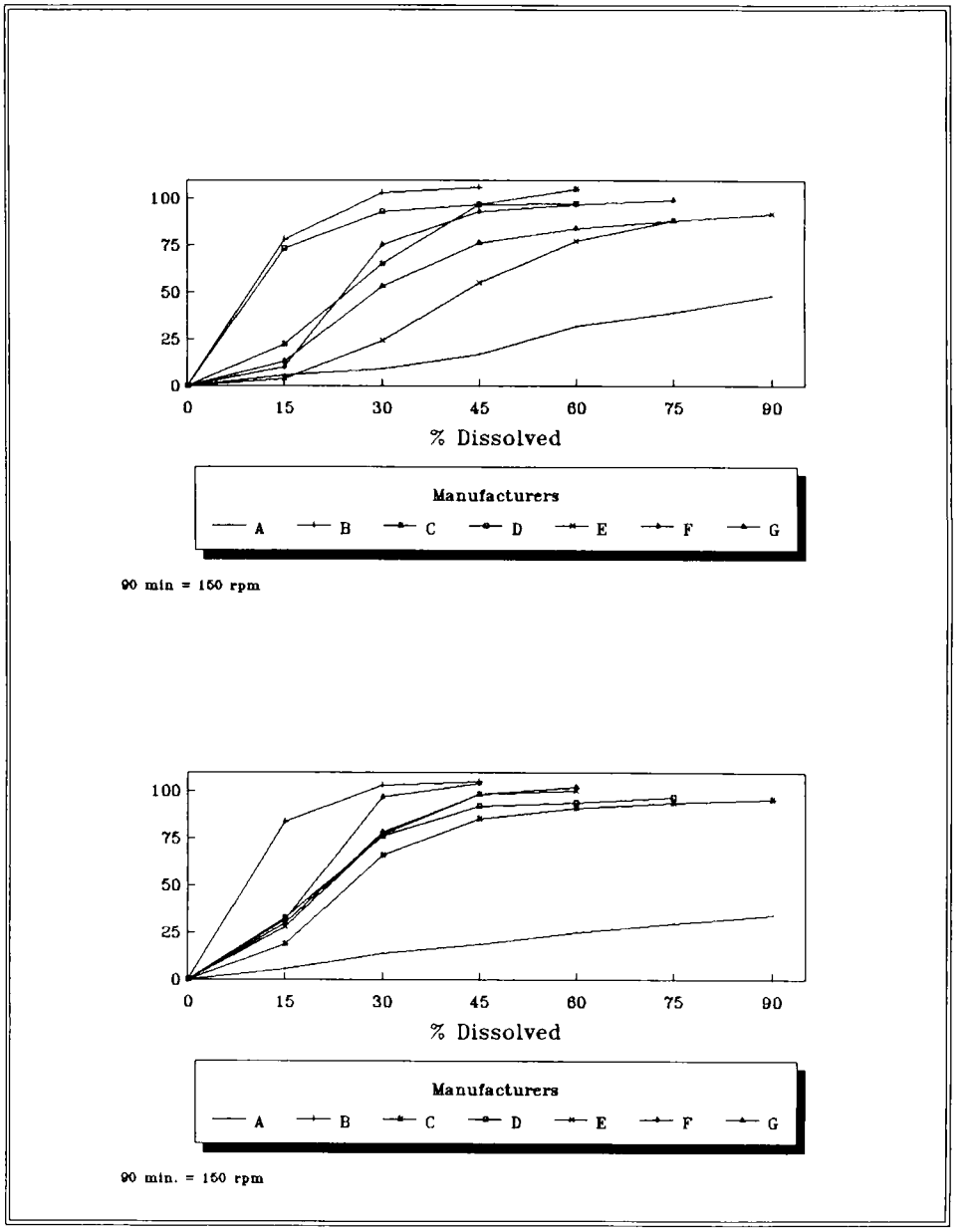

FIGURE 2:
In vitro dissolution of marketed hydroxyzine HCL tablets;
Paddle Method, 50 rpm, SIF

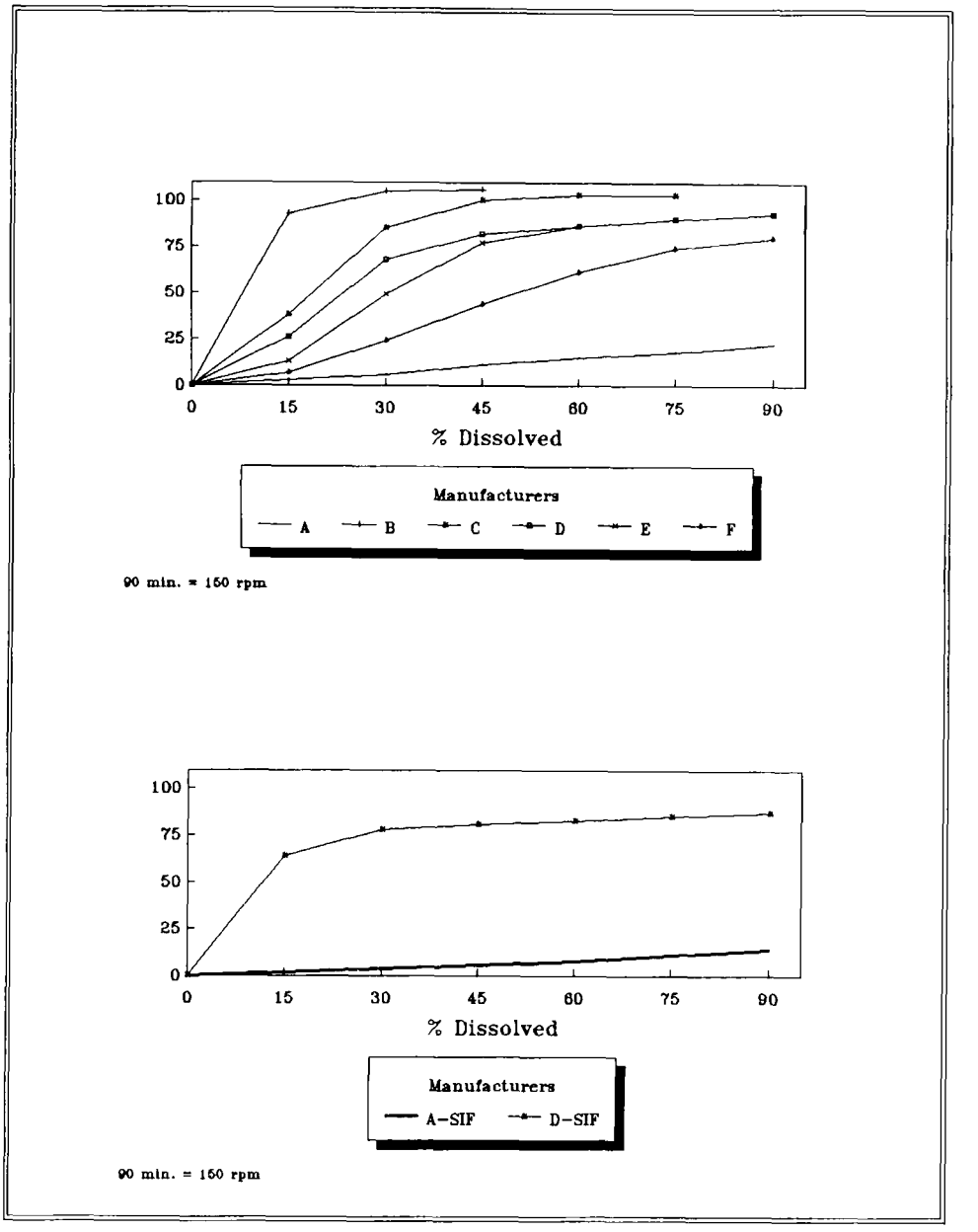

FIGURE 2 (continued)

TABLE 1

Firm	Control No.	Dosage	% Dissolved in 45 minutes		
			Disintegration Apparatus	Paddle Method Water	Paddle Method SIF
A	2918-21	10 mg	103.0	86.4	93.1
	2919-27	25 mg	104.8	100.8	103.7
	2920-17	50 mg	101.8	55.6	44.3
B	26968	10 mg	103.0	102.8	106.8
	26873	25 mg	103.2	107.6	104.5
	26644	50 mg	109.6	105.3	106.2
C	840475	10 mg	106.0	102.3	93.2
	840722	25 mg	104.8	104.4	102.0
	840931	50 mg	113.8	107.0	103.5
D	3L30111	10 mg	97.7	93.4	97.1
	3L29821	25 mg	104.0	100.5	91.8
	3E29917	50 mg	108.6	86.3	82.3
	3E30018	100 mg	103.7	87.6	81.0
E	33034	10 mg	102.0	38.4	17.6
	41162	25 mg	88.8	47.5	19.4
	46022	50 mg	103.8	43.3	11.2
	3404118	100 mg	103.4	18.0	5.9
F	404015	10 mg	95.9	51.2	55.4
	312063	25 mg	106.0	99.7	98.0
	312062	50 mg	101.2	81.5	77.2
G	742230	10 mg	85.2	85.0	76.1
	742230	25 mg	107.6	97.0	98.7

Legend:
Manufacturer
A: Pfizer
B: Danbury
C: Par
D: Barr
E: Chelsea
F: Zenith
G: KV Pharm

% dissolved at 45 minutes using these two method was compared to the % dissolved using the modified disintegration apparatus **(Table 1)**. The dissolution results obtained using the USP method (modified disintegration apparatus) indicate little or no difference between manufacturers or between dosage strengths. However, a difference is observed when the dissolution is carried out using the paddle method. **Figure 3** is a graphic comparison of the three method

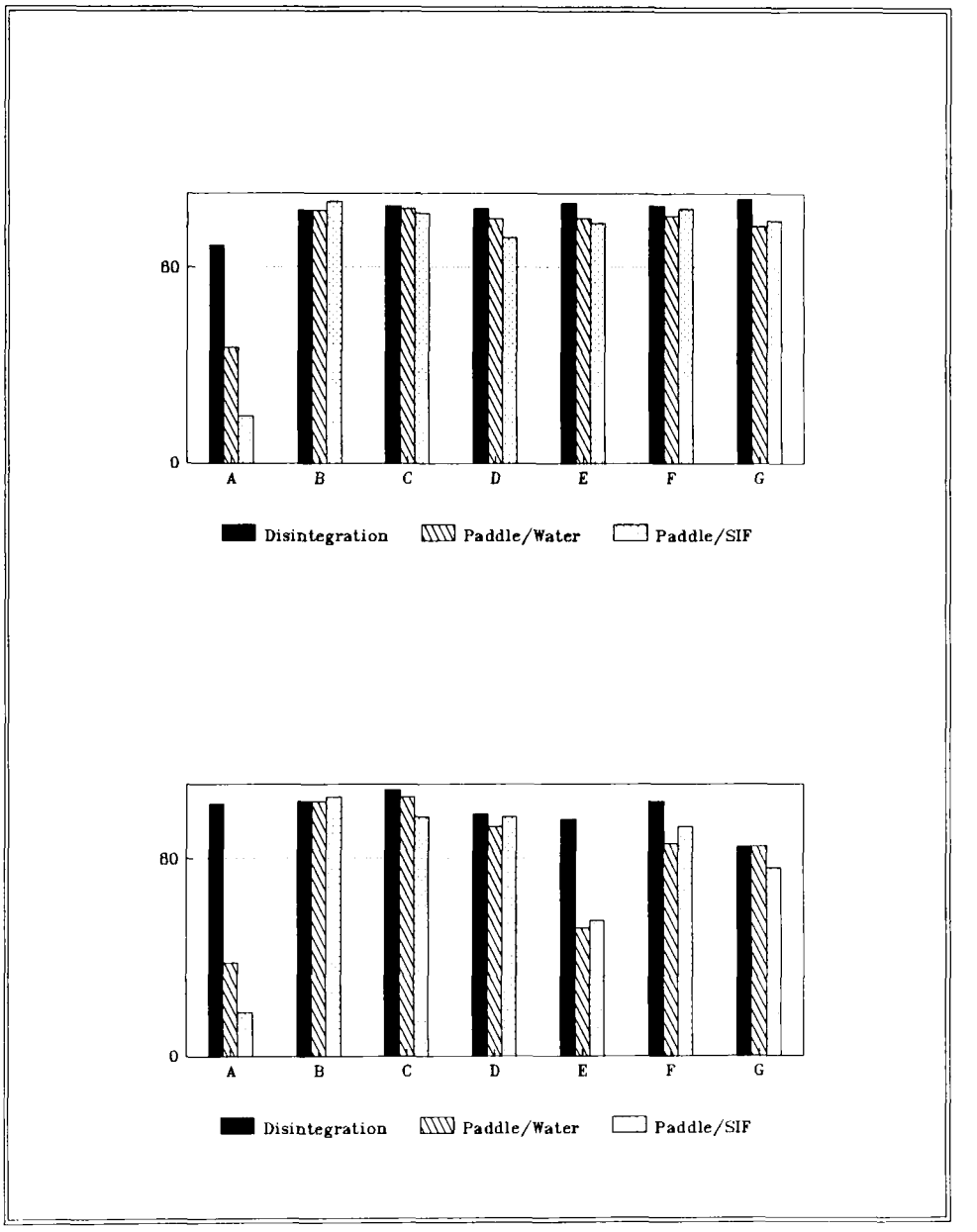

FIGURE 3:
Comparison of the **In vitro** dissolution of
marketed 10 and 25 mg hydroxyzine HCL tablets from all manufacturers

used on the 10 and the 25 mg tablets of all manufacturers. As illustrated by this graph, the modified disintegration apparatus is not able to distinguish slow dissolving lots, lots with potential bioavailability problems, from fast dissolving lots. The modified disintegration apparatus procedure appeared to be abrasive and nondiscriminatory and therefore would not be a good predictor of bioavailability or bioequivalence, nor would it be a good manufacturing control to assure lot to lot uniformity. However, the paddle procedure is able to pinpoint slow dissolving lots or formulations.

Analysis of the dissolution results from the market survey indicate that the test currently proposed in the Federal Register, i.e. the use of the Paddle Method at 50 rpm with water as the medium will assure the bioavailability and the bioequivalence of the hydroxyzine hydrochloride tablets.

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