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Aspirin—A National Survey IV: *In Vitro* Dissolution of Aspirin Formulations

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Abstract □ The results of a national survey of the *in vitro* dissolution rates of aspirin tablets are presented. Dissolution profiles by both the proposed USP XX basket method and a paddle method are compared. The methods were used to analyze 59 tablet formulations representing 38 manufacturers. Each tablet was subjected to the dissolution procedure in 500 ml of pH 4.5 buffer solution, and an aliquot was sampled automatically and analyzed by an automated system. In 30 min, 22% of the samples tested using the basket method failed the proposed USP XX dissolution requirement. Seventy-five percent of the samples tested by the paddle method also failed the proposed dissolution requirement.

Keyphrases □ Aspirin—*in vitro* dissolution, comparison of basket and paddle methods □ Analgesics—*in vitro* dissolution of aspirin formulations □ Dissolution—aspirin formulations, *in vitro*, basket and paddle methods compared

A national survey (1) of aspirin tablet products was conducted at the National Center for Drug Analysis during the summer and fall of 1978. The purpose of the survey was to ascertain the quality of these products and the adequacy of the USP monograph (2). The USP presented a dissolution test in the *Pharmaceutical Forum* (3) that specifies use of a basket and requires 80% dissolution in 30 min.

During the survey, selected aspirin samples representing each manufacturer and dosage level were assayed for their dissolution rates *in vitro* using both a basket and a paddle and the dissolution medium (pH 4.5 buffer) and speed of rotation (50 rpm) specified in Ref. 3. The guidelines (4) for the dissolution testing were followed. The dissolution rate for each sample was determined by taking aliquots automatically (5) every 10 min over 60 min and analyzing the dissolution medium for aspirin by an automated procedure. The purpose of this experiment was to compare the dissolution characteristics of the selected marketed samples by the proposed USP XX dissolution test using the proposed basket method and the paddle method. The paddle method also was used because it has been a more discriminating test for differentiating drug products than the basket method in this laboratory.

EXPERIMENTAL

Apparatus—A dissolution apparatus[1] and a 76-liter aquarium tank with a constant-temperature water bath maintained at 37° were used.

For the sampling[2], an automatic analyzer with a sampler[3], three pumps[4], a manifold, and a timer[5] was used together with a cycle timer[6] for the sampling interval timer. Six sampling probes with filters[7] were required.

For the determinative step, an automatic analyzer with a sampler[3], pumps[8], a manifold, and a timer[5] was connected to a spectrophotometer[9] equipped with a quartz flowcell[10]. A 100-mv recorder[11] was connected to the spectrophotometer.

Reagents—ACS grade chloroform was washed with water and filtered through paper on the day of use. The pH 2.2 buffer solution was prepared by diluting 250.0 ml of 0.2 *M* KCl and 39.0 ml of 0.2 *M* HCl to 1 liter with water. The 0.2 *M* KCl was prepared by dissolving 14.911 g of potassium chloride in water and diluting it with water to 1 liter. The 0.2 *M* HCl was prepared by diluting 17.0 ml of concentrated hydrochloric acid to 1 liter with water. The pH 4.5 buffer solution was prepared by adding 2.99 g of sodium acetate to 1.66 ml of acetic acid and diluting to 1 liter with water. The buffer solution used for the dissolution medium was boiled to remove air bubbles.

Standard Preparation (324-mg Tablets)—Approximately 325 mg of USP reference standard aspirin was weighed accurately and dissolved in 5.0 ml of 95% ethanol. This solution was diluted to 1 liter with the pH 4.5 buffer solution. The standard was prepared fresh daily and was used immediately.

Sample Preparation (324-mg Tablets)—One tablet was placed in each dissolution vessel or basket. For 60 min, samples were withdrawn

[1] Model 72RL, Easi-Lift multiple-spindle dissolution drive, Hanson Research Corp., Northridge, CA 91324.
[2] C. E. Wells, T. W. Moore, and W. E. Juhl, unpublished data.
[3] AutoAnalyzer sampler II, 127-A000, Technicon Instruments Corp., Tarrytown, NY 10591.
[4] AutoAnalyzer proportioning pump I, 105-A200-01, Technicon Instruments Corp., Tarrytown, NY 10591.
[5] Flexopulse timer, model HG93A603, Eagle Signal Time Division, Gulf Western Industries, Davenport, IA 52803 (5).
[6] Three-cam, 10-min cycle timer, Westbrook Timer Sales, Westbrook, CT 06498.
[7] Filter tips, 20 μm, Centauer Chemical Co., Stamford, CT 06902.
[8] AutoAnalyzer proportioning pump III, 133-A014-04, Technicon Instruments Corp., Tarrytown, NY 10591.
[9] Model PM2DL, Carl Zeiss, Oberkochen, West Germany.
[10] Ten millimeters, 18 μl (886881) or 80 μl (886878), Beckman Instruments, Fullerton, CA 92634.
[11] Servo/Riter II, PS01W6A, Texas Instruments, Houston, TX 77001.

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Table I—National Survey Results[a] (Percent of Label Declaration) for Dissolution of Aspirin Tablets

Manufacturer[b]	Tablet Dosage, mg	Appararus[c]	Dissolution Time, min 10	20	30	40	50	60
A	324	P	38.6 (2.6)	50.2 (3.8)	59.0[d] (4.2)	66.3 (4.5)	72.4 (4.3)	77.7 (4.3)
	324	B	71.2 (3.7)	93.4 (2.4)	97.5 (2.0)	97.4 (1.9)	96.8 (2.1)	96.2 (1.7)
B	421	P	41.3 (10.9)	51.0 (8.0)	58.1[d] (7.3)	62.9 (7.3)	65.9 (7.3)	68.6 (5.8)
	421	B	33.6 (4.0)	56.3 (6.7)	72.3[d] (9.8)	85.4 (12.8)	90.4 (13.2)	92.3 (12.7)
C	324	P	41.6 (3.6)	54.6 (8.1)	61.7[d] (7.9)	66.5 (8.0)	69.6 (7.6)	73.0 (7.2)
	324	B	61.8 (4.2)	94.4 (3.1)	100.3 (1.1)	100.3 (1.4)	99.6 (2.3)	98.6 (1.9)
	81	P	56.6 (4.6)	78.0 (8.1)	88.0 (8.1)	94.4 (7.2)	97.3 (6.8)	98.9 (6.4)
	81	B	55.4 (1.0)	85.2 (1.6)	96.5 (2.0)	100.0 (2.3)	100.8 (2.3)	100.8 (2.2)
	160	P	67.0 (2.4)	80.4 (3.3)	85.0 (3.8)	86.9 (3.7)	88.1 (3.7)	88.9 (3.6)
	160	B	61.8 (2.5)	87.9 (4.0)	98.0 (3.4)	101.2 (3.4)	101.9 (3.6)	102.6 (3.5)
D	486[e]	P	89.7 (6.0)	90.7 (5.2)	92.1 (5.5)	92.0 (5.0)	91.9 (4.9)	92.2 (5.1)
	486[e]	B	62.8 (16.9)	77.2 (14.2)	84.7 (10.3)	88.0 (6.7)	90.2 (3.6)	91.4 (2.3)
	324[e]	P	74.0 (12.2)	77.2 (10.0)	78.0[d] (9.2)	78.9 (8.5)	79.2 (7.7)	79.0 (7.8)
	324[e]	B	85.9 (13.3)	96.3 (4.9)	97.5 (2.6)	97.7 (1.5)	97.6 (1.8)	98.0 (2.0)
F	324[e]	P	98.6 (2.2)	100.3 (1.5)	100.8 (1.9)	100.5 (1.6)	100.7 (1.9)	99.2 (2.4)
	324[e]	B	79.7 (2.4)	87.3 (2.4)	91.4 (2.3)	92.1 (2.1)	92.2 (2.6)	92.9 (1.7)
G	324	P	17.6 (3.1)	27.0 (5.6)	35.4[d] (7.6)	42.3 (6.2)	48.2 (7.2)	54.2 (7.3)
	324	B	11.2 (1.0)	20.2 (2.0)	27.5[d] (3.4)	36.0 (4.8)	44.5 (5.7)	52.4 (6.9)
H	324	P	17.2 (8.7)	34.5 (14.8)	47.0[d] (18.3)	55.4 (19.2)	60.8 (17.8)	65.0 (16.3)
	324	B	37.9 (7.9)	72.9 (7.7)	91.1 (5.2)	96.7 (2.2)	99.4 (1.3)	98.9 (1.4)
	81	P	69.0 (18.7)	90.8 (11.4)	97.1 (7.7)	98.5 (9.1)	100.0 (9.2)	100.3 (8.6)
	81	B	56.2 (7.1)	84.6 (7.5)	93.4 (6.2)	97.6 (6.0)	100.1 (6.1)	102.0 (5.5)
I	81	P	9.1 (2.4)	12.5 (1.2)	16.9[d] (1.5)	20.5 (1.4)	24.2 (2.1)	27.3 (2.5)
	81	B	7.3 (0.4)	12.1 (0.6)	16.6[d] (0.6)	19.8 (0.4)	22.8 (0.5)	25.7 (0.7)
	324	P	16.0 (2.3)	27.4 (4.7)	36.6[d] (6.1)	43.6 (6.6)	49.3 (6.7)	54.2 (6.5)
	324	B	36.5 (14.7)	75.2 (13.9)	93.3 (6.2)	99.1 (1.3)	98.8 (0.7)	98.4 (0.5)
J	324	P	38.1 (3.2)	59.4 (6.3)	72.2[d] (7.8)	80.7 (7.6)	84.8 (6.0)	88.2 (5.4)
	324	B	59.9 (7.3)	81.7 (6.9)	90.4 (6.1)	93.9 (5.7)	95.1 (5.2)	95.0 (4.9)
K	81	P	12.3 (0.9)	24.1 (2.7)	32.4[d] (3.3)	38.7 (2.7)	44.2 (3.1)	47.2 (3.4)
	81	B	37.8 (3.1)	86.1 (6.7)	105.7 (8.5)	107.2 (6.1)	108.0 (6.1)	109.4 (6.6)
	324	P	23.2 (2.3)	34.3 (2.9)	41.4[d] (4.8)	47.3 (5.3)	52.1 (6.5)	55.9 (7.3)
	324	B	62.3 (6.2)	86.5 (5.5)	96.6 (2.6)	99.2 (1.7)	100.1 (1.1)	100.0 (1.5)
L	324[e]	P	93.4 (7.4)	95.0 (6.2)	95.4 (6.4)	95.2 (5.6)	95.1 (6.1)	95.8 (5.5)
	324[e]	B	83.7 (5.9)	90.0 (4.5)	93.0 (4.1)	95.6 (3.3)	96.7 (3.1)	95.4 (3.1)
M	324	P	31.5 (3.5)	46.7 (5.7)	56.5[d] (5.9)	64.4 (5.9)	70.6 (5.5)	75.9 (5.0)
	324	B	55.0 (1.8)	85.7 (3.4)	93.6 (1.5)	95.9 (2.1)	96.6 (2.4)	96.7 (2.2)
N	324	P	21.0 (4.8)	31.7 (7.0)	39.6[d] (7.6)	45.4 (8.0)	49.9 (8.0)	53.8 (7.9)
	324	B	43.5 (4.4)	62.5 (5.5)	73.7[d] (6.5)	80.6 (6.9)	84.8 (6.0)	91.9 (8.5)
O	324	P	24.0 (4.8)	42.3 (7.9)	55.8[d] (9.3)	65.5 (9.3)	72.6 (9.2)	78.2 (8.3)
	324	B	27.5 (6.6)	49.6 (9.2)	64.8[d] (10.2)	76.8 (9.3)	84.8 (8.2)	90.6 (6.6)
P	324	P	22.6 (2.6)	38.1 (5.5)	49.8[d] (6.2)	58.5 (6.4)	65.4 (6.6)	71.3 (5.5)
	324	B	26.6 (4.9)	45.7 (6.2)	59.5[d] (6.1)	69.9 (5.8)	77.9 (4.9)	84.2 (3.5)
Q	324	P	23.6 (2.2)	35.8 (3.8)	45.2[d] (4.9)	52.0 (6.2)	57.4 (7.2)	61.5 (7.6)
	324	B	40.0 (3.7)	69.6 (4.1)	84.1 (4.3)	91.0 (3.4)	94.5 (2.3)	95.9 (1.1)
R	324	P	20.0 (2.1)	29.5 (3.0)	37.1[d] (3.2)	42.5 (3.3)	46.9 (3.1)	50.7 (3.5)
	324	B	52.3 (7.7)	76.6 (10.5)	88.8 (8.5)	95.6 (7.0)	98.4 (5.4)	99.3 (4.2)
S	324	P	38.2 (10.9)	48.2 (11.0)	54.3[d] (10.4)	59.1 (9.9)	63.0 (9.3)	66.7 (9.0)
	324	B	66.0 (7.7)	93.4 (3.9)	97.6 (2.5)	97.1 (2.7)	97.1 (2.2)	96.7 (2.5)
T	81	P	56.4 (8.2)	67.5 (7.2)	75.7[d] (10.1)	79.8 (8.9)	83.0 (8.0)	84.5 (6.7)
	81	B	45.5 (7.8)	64.9 (8.1)	74.6[d] (7.8)	80.4 (6.1)	85.1 (5.5)	87.5 (4.0)
	324[e]	P	87.9 (2.3)	88.7 (2.9)	88.2 (2.8)	88.0 (2.9)	88.0 (2.7)	87.4 (2.5)
	324[e]	B	85.7 (2.3)	93.4 (2.3)	93.9 (2.2)	93.7 (2.0)	93.8 (1.6)	93.3 (1.9)
	81	P	46.9 (8.5)	61.9 (9.0)	70.1[d] (8.5)	74.3 (7.4)	77.3 (7.5)	80.1 (6.3)
	81	B	47.3 (7.8)	63.0 (9.5)	76.2[d] (10.3)	84.0 (9.4)	89.6 (9.1)	90.8 (7.9)
U	324[e]	P	103.7 (5.0)	107.5 (5.7)	105.6 (6.0)	103.6 (4.7)	105.9 (4.6)	107.4 (3.8)
	324[e]	B	90.4 (3.6)	96.4 (4.6)	98.9 (4.3)	99.0 (4.2)	99.9 (4.3)	100.2 (4.4)
	81	P	45.4 (5.6)	67.3 (7.2)	73.5[d] (7.5)	78.0 (7.7)	79.1 (7.1)	79.4 (7.8)
	81	B	50.5 (8.8)	70.9 (10.1)	80.0 (10.0)	84.6 (8.6)	88.1 (7.9)	90.8 (7.7)
V	324[e]	P	74.2 (9.0)	84.8 (7.0)	86.9 (6.8)	87.1 (6.2)	87.6 (5.8)	88.1 (5.1)
	324[e]	B	63.7 (4.8)	98.2 (2.8)	102.4 (1.4)	101.0 (3.0)	100.5 (1.8)	—
	81	P	44.6 (2.0)	68.8 (10.8)	74.2[d] (13.0)	76.9 (13.3)	79.2 (13.6)	80.2 (13.0)
	81	B	77.9 (4.0)	98.8 (3.6)	101.8 (2.8)	101.1 (2.2)	99.7 (2.5)	100.7 (2.7)
W	324	P	8.1 (0.7)	14.0 (2.5)	18.5[d] (3.5)	22.3 (4.3)	25.8 (4.8)	28.5 (5.1)
	324	B	4.1 (1.1)	9.6 (1.5)	14.4[d] (2.0)	19.2 (2.4)	23.1 (3.0)	27.3 (4.0)
X	324	P	16.3 (1.6)	25.9 (2.6)	33.1[d] (2.8)	39.3 (3.2)	44.5 (3.2)	48.9 (3.8)
	324	B	57.9 (4.9)	83.1 (3.1)	93.1 (2.0)	96.0 (2.5)	97.2 (2.1)	97.7 (1.3)
	81	P	60.5 (5.6)	75.2 (5.2)	81.9 (5.6)	85.0 (5.1)	85.9 (4.5)	87.9 (4.8)
	81	B	76.7 (4.1)	94.6 (1.8)	98.9 (2.5)	100.9 (2.1)	100.3 (1.6)	99.1 (1.9)
Y	81	P	37.7 (4.7)	56.7 (4.6)	65.6[d] (5.2)	71.4 (4.8)	73.8 (4.3)	75.1 (4.7)
	81	B	58.2 (6.8)	83.6 (4.0)	92.7 (3.6)	96.7 (1.9)	96.6 (2.5)	96.5 (1.3)
	324	P	19.2 (4.6)	32.1 (4.4)	40.4[d] (4.6)	47.3 (5.0)	52.6 (5.1)	57.0 (5.6)
	324	B	52.3 (12.0)	78.1 (9.8)	91.6 (4.7)	98.0 (1.5)	99.2 (1.5)	97.9 (1.5)
	486	P	48.3 (8.8)	67.7 (6.4)	76.9[d] (5.8)	81.7 (5.4)	84.4 (4.4)	84.9 (4.1)
	486	B	35.0 (3.1)	65.5 (9.4)	80.9 (11.9)	87.1 (9.4)	89.4 (5.4)	91.7 (4.4)

(continued)

Table I—*Continued*

Manufacturer[b]	Tablet Dosage, mg	Apparatus[c]	Dissolution Time, min 10	20	30	40	50	60
	648	P	26.5 (4.9)	44.5 (5.6)	52.8[d] (6.1)	57.5 (7.1)	61.2 (6.9)	63.7 (6.5
	648	B	34.4 (6.2)	65.3 (10.0)	85.3 (9.9)	97.5 (6.7)	103.7 (4.1)	105.4 (1.2)
Z	324	P	25.9 (4.6)	36.8 (5.5)	45.8[d] (5.8)	52.6 (5.8)	58.0 (5.9)	63.1 (5.7)
	324	B	67.5 (1.9)	88.8 (3.9)	93.1 (2.7)	94.5 (2.2)	95.2 (2.4)	95.5 (2.8)
	486	P	10.8 (2.0)	20.8 (5.6)	28.5[d] (8.6)	35.7 (10.1)	41.7 (11.0)	47.7 (12.2)
	486	B	5.7 (0.9)	10.7 (1.4)	15.5[d] (1.8)	20.2 (2.2)	24.5 (2.9)	28.8 (3.5)
AA	300	P	36.9 (2.7)	51.8 (2.8)	60.6[d] (3.1)	66.8 (3.1)	72.4 (2.7)	76.6 (2.1)
	300	B	59.9 (2.7)	87.7 (2.8)	98.9 (2.2)	100.6 (2.4)	100.4 (1.9)	100.3 (2.0)
	81	P	33.6 (3.4)	50.0 (4.3)	61.6[d] (5.6)	70.2 (5.1)	76.8 (5.0)	80.6 (4.8)
	81	B	77.6 (6.3)	98.6 (2.9)	99.5 (1.9)	99.1 (2.1)	98.5 (2.2)	98.1 (2.1)
BB	324	P	40.8 (2.3)	55.1 (3.5)	63.8[d] (3.9)	69.6 (4.1)	73.6 (4.3)	77.8 (4.5)
	324	B	47.3 (1.0)	74.6 (4.3)	91.1 (5.6)	97.0 (3.8)	98.8 (2.1)	99.3 (2.5)
CC	324[e]	P	81.8 (4.5)	84.7 (4.1)	85.3 (3.5)	85.0 (3.5)	84.8 (3.5)	84.3 (3.2)
	324[e]	B	77.7 (3.5)	89.5 (4.2)	92.4 (3.8)	93.7 (4.1)	94.3 (3.7)	96.4 (4.4)
DD	324[e]	P	90.6 (1.7)	89.8 (1.2)	88.4 (1.7)	88.7 (1.9)	90.8 (2.1)	93.2 (2.3)
	324[e]	B	82.6 (4.0)	94.2 (4.1)	94.3 (3.3)	93.1 (2.4)	93.8 (4.4)	95.4 (2.4)
EE	81	P	15.8 (4.1)	45.8 (7.6)	67.1[d] (7.2)	79.3 (7.7)	82.2 (7.7)	84.5 (7.3)
	81	B	56.0 (13.7)	85.0 (9.9)	95.9 (6.3)	99.1 (3.7)	99.3 (5.0)	100.4 (4.7)
	324	P	38.9 (8.4)	46.6 (10.1)	56.5[d] (6.3)	62.6 (6.4)	68.1 (5.6)	72.2 (4.9)
	324	B	62.1 (6.8)	92.0 (2.8)	100.1 (2.8)	101.2 (2.7)	101.3 (1.8)	101.4 (2.4)
FF	324	P	40.3 (2.6)	53.6 (3.3)	63.6[d] (5.0)	71.9 (6.4)	78.1 (6.2)	82.6 (5.5)
	324	B	70.6 (3.9)	97.3 (1.3)	100.4 (1.1)	99.6 (1.1)	99.7 (1.2)	98.7 (1.0)
GG	324[e]	P	29.0 (2.7)	48.9 (1.6)	63.8[d] (2.6)	73.6 (1.8)	77.8 (2.5)	81.3 (2.3)
	324[e]	B	50.5 (4.1)	71.9 (6.8)	83.2 (5.2)	88.7 (6.5)	91.8 (4.5)	92.5 (4.1)
	81	P	12.0 (1.7)	17.5 (2.9)	31.7[d] (5.9)	42.3 (4.1)	53.1 (3.8)	64.3 (4.1)
	81	B	8.1 (1.1)	17.8 (2.0)	33.2[d] (3.7)	54.5 (7.6)	78.4 (4.1)	89.9 (2.3)
	81	P	8.5 (0.6)	17.2 (3.9)	28.5[d] (3.8)	40.0 (6.4)	49.7 (7.0)	54.3 (6.3)
	81	B	6.2 (0.4)	9.9 (0.2)	13.8[d] (0.6)	19.8 (1.2)	30.9 (1.9)	46.4 (4.3)
HH	320	P	13.7 (1.3)	22.4 (2.2)	29.7[d] (4.1)	34.5 (3.1)	39.5 (3.6)	43.9 (3.7)
	320	B	33.1 (6.2)	63.6 (8.0)	80.7 (6.9)	89.7 (6.9)	93.3 (4.2)	95.6 (3.3)
	65	P	45.9 (11.0)	69.6 (11.5)	81.7 (9.3)	88.0 (7.1)	92.6 (6.0)	94.8 (5.1)
	65	B	59.1 (24.7)	79.0 (24.4)	88.1 (21.9)	92.3 (18.8)	93.1 (15.7)	94.2 (13.5)
II	324[e]	P	47.4 (5.2)	58.7 (5.4)	63.5[d] (5.4)	66.3 (4.9)	68.4 (5.0)	70.2 (5.0)
	324[e]	B	41.8 (5.0)	65.2 (4.3)	78.6[d] (5.6)	85.3 (7.2)	89.5 (8.1)	91.1 (8.7)
JJ	324	P	30.5 (2.7)	44.2 (2.8)	55.3[d] (4.9)	65.5 (6.9)	74.3 (8.0)	80.2 (6.9)
	324	B	66.6 (3.8)	92.6 (2.9)	97.2 (1.0)	98.3 (2.8)	97.8 (1.3)	97.8 (1.8)
	81	P	31.5 (2.6)	61.5 (9.1)	70.6[d] (9.6)	73.5 (8.8)	76.3 (8.6)	76.8 (9.1)
	81	B	45.9 (7.6)	74.7 (9.5)	85.6 (8.4)	90.4 (6.5)	92.8 (4.4)	95.5 (3.1)
KK	486[e]	P	81.0 (4.3)	84.9 (4.8)	87.4 (4.4)	88.3 (4.3)	89.0 (4.4)	89.8 (4.6)
	486[e]	B	34.5 (8.5)	77.5 (11.7)	96.6 (3.4)	99.2 (2.8)	99.8 (3.2)	99.0 (2.8)
LL	324[e]	P	47.8 (2.0)	62.2 (2.8)	70.2[d] (3.2)	74.9 (2.8)	78.6 (2.6)	80.9 (2.6)
	324[e]	B	38.3 (3.5)	58.9 (4.1)	70.9[d] (5.3)	78.1 (5.6)	82.4 (5.4)	85.0 (5.6)

[a] Average of six assays. Numbers in parentheses are standard deviations. [b] A = Bell Pharmacal, Greenville, S.C.; B = Block Drug Co., Memphis, Tenn.; C = Bowman Pharmaceuticals, Canton, Ohio; D = Bristol-Myers Co., New York, N.Y.; F = Otis Clapp & Sons, Boston, Mass.; G = Cord Laboratories, Detroit, Mich.; H = Davis Manufacturing Co., Knoxville, Tenn.; I = Dewey Products Co., Grand Rapids, Mich.; J = Ferndale Laboratories, Ferndale, Mich.; K = Freeda Vitamins, New York, N.Y.; L = ICN Pharmaceuticals, Cincinnati, Ohio; M = Lannett Co., Philadelphia, Pa.; N = Eli Lilly & Co., Indianapolis, Ind.; O = Mallard, Detroit, Mich.; P = Manhattan Drug Co., Hillside, N.J.; Q = Marshall Pharmacal Corp., S. Hackensack, N.J.; R = McKesson Laboratories, Fairfield, Conn.; S = Norwich-Eaton Pharmaceuticals, Norwich, N.Y.; T = Oak Park Pharmaceuticals, Fredonia, Wis.; U = Pennex Products Co., Pittsburgh, Pa.; V = L. Perrigo Co., Allegan, Mich.; W = Pill Mill, Grand Rapids, Mich.; X = Plough, Memphis, Tenn.; Y = Rexall Drug Co., St. Louis, Mo.; Z = Richlyn Laboratories, Philadelphia, Pa.; AA = Stein-Mendez Labs, Rio Peidas, Puerto Rico; BB = Stanback Co., Salisbury, N.C.; CC = Standard Pharmacal Co., Chicago, Ill.; DD = Stanley Laboratories, Portland, Ore.; EE = Sterling Drug, New York, N.Y.; FF = E. R. Squibb & Sons, New York, N.Y.; GG = Sun Laboratories, Portland, Ore.; HH = Vale Chemical Co., Allentown, Pa.; II = Walgreen Co., Chicago, Ill.; JJ = West-Ward, Eatontown, N.J.; KK = Whitehall Laboratories, New York, N.Y.; and LL = Zenith Laboratories, Hoboken, N.J. [c] P = paddle, and B = basket. [d] Failed to meet proposed USP XX requirements of 80% dissolution at 30 min. [e] Buffered tablets.

at 10-min intervals using the automated sampling system.

Semiautomated Determination—The automated system was assembled as shown in Fig. 1. The solutions were sampled at a rate of 30 cups per hour with a sample-to-wash ratio of 2:1. A sampling pattern of three standards, six samples, one standard, six samples, *etc.*, was used. Two cups of standard were placed at the end. The first two standards and the last standard were not used in the calculations. A polytetrafluoroethylene strip was inserted into the BO fitting to direct the organic phase downward.

To start the system, ethanol was pumped through the chloroform pump tube for 5 min, and the tube then was pumped dry. The chloroform line was placed in the solution and pumped until the solution reached the spectrophotometer cell. The pH 2.2 buffer line was placed in the solution, and the system was allowed to equilibrate.

The sample stream was diluted with pH 2.2 buffer, and chloroform was added. The chloroform containing the extracted drug was pumped through a flowcell, and the absorbance of the drug was read at 280 nm.

RESULTS AND DISCUSSION

Validation Tests—A series of validation tests was performed on the automated system. A linear response was obtained from four standard solutions containing 0.3–1.3 mg of aspirin/ml (corresponding to 50–200% of the label declaration). The results of an assay of 30 individual cups exhibited a relative standard deviation of 0.9%. A standard solution containing 0.65 mg of aspirin/ml gave reproducible peaks whose height reached ~97.0% of the steady state.

Composite Assays—Portions of tablet composites equivalent to single tablets were analyzed by the paddle method and the proposed USP XX (3) method. The ground tablet composites were prepared from available commercial samples. When four samples were analyzed by the USP and the automated methods, the results obtained were (percentage of label declaration): 97.9, 98.2, 101.0, and 100.9 and 99.3, 98.2, 101.5, and 101.2, respectively. Four individual assays of one composite gave an average of 101.2% of the label declaration with a relative standard deviation of 0.27%.

Effect of Alcohol in Standard—Since aspirin is not very soluble in pH 4.5 buffer solution, the aspirin standard was dissolved in ethanol and then diluted with the buffer solution. To test the effect of the alcohol, solutions containing 1% alcohol and no alcohol were analyzed. There was no difference in absorptivity between the two solutions.

Effect of Boiling pH 4.5 Buffer Solution—Deaerated water usually is recommended for dissolution of tablets. In the proposed method, if the water is deaerated first and the buffer solution then is prepared using this

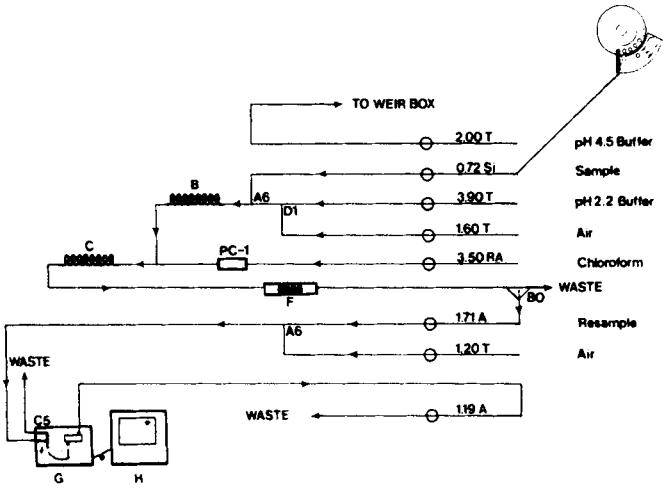

Figure 1—*Flow of automated system for aspirin dissolution. Key: Si, silicon pump tube; T, Tygon tube; A, Acidflex pump tube; RA, red Acidflex pump tube; B, 28-turn × 2.4-mm i.d. mixing coil; C, 28-turn × 2.4-mm i.d. mixing coil with one double end; F, 5.5-turn settling coil; G, UV spectrophotometer; and H, recorder. Pump tube sizes are in milliliters per minute.*

water, air can be introduced into the solution. A test was performed to determine if boiling the pH 4.5 buffer solution affects the pH of the solution. The pH of the freshly prepared solution and the boiled solution was the same.

Survey Results—The automated method was employed to analyze 59 tablet formulations representing 37 manufacturers using both the basket and the paddle techniques (Table I). Of the total samples tested, 22% failed the proposed USP XX dissolution requirement using the basket method and 75% failed using the paddle technique.

Of the 59 formulations tested, 49 were plain aspirin tablets and 10 were buffered tablets. None of the buffered tablets and 26.5% of the plain tablets failed the proposed USP XX requirements by the basket method. Eighty-six percent of the plain tablets and 20% of the buffered tablets failed the proposed USP XX requirements by the paddle method.

During this survey, the basket method gave higher results than the paddle method for ~75% of the samples. For some samples, the basket method results were twice as high as those for the paddle method. Therefore, if the basket method is used as the USP XX requirement, all buffered and most plain tablets would pass the test; but if the paddle method is used, some buffered tablets and most plain tablets would fail the proposed requirement. These results pose the question of which method will predict bioavailability more accurately.

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NOTES

Poloxamer 188 as Vehicle for Injectable Diazepam

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Abstract □ The significant occurrence of thrombophlebitis in patients administered diazepam intravenously was described recently. This side effect has been attributed to the crystallization of diazepam and its subsequent precipitation upon contact with blood or intravenous fluids. The current study was designed to reveal whether the solubilizing capability of poloxamer 188 reduces the incidence of thrombotic and inflammatory effects of diazepam in rabbits. The incidence of early (3-hr) ear vein necrosis was 72% in the diazepam-treated ears, while the incidence of necrosis in the ears that received poloxamer 188 as a vehicle for diazepam was 25%. The occurrence of thrombosis and loss of vessel integrity also was higher in diazepam-treated ears than in those treated with diazepam plus poloxamer 188. Solubilization of diazepam with poloxamer 188 may decrease the incidence of the tested side effects.

Keyphrases □ Diazepam—reduction of thrombosis and inflammation using poloxamer 188 as vehicle, rabbits □ Poloxamer 188—use as vehicle for reduction of thrombosis and inflammation induced by injectable diazepam, rabbits □ Sedatives—diazepam, reduction of thrombosis and inflammation using poloxamer 188 as vehicle, rabbits

Diazepam[1] is generally accepted as an intravenous sedative/anesthetic with usefulness in dentistry and medicine (1–6). Its increased use over the past decade has resulted in support for its benefits in various procedures, but the literature also contains references to side effects.

Pain upon injection is a frequent side effect of diazepam use (3, 7–9), and there have been many reports of thrombophlebitis following diazepam injection (1–3, 9). These side effects have been associated with precipitation of di-

[1] Valium Injectable, Hoffmann-La Roche, Nutley, N.J.

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