Dissolution Behavior of Commercial Enteric-Coated Aspirin Tablets

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Abstract □ Dissolution behavior was studied for four commercial batches of enteric-coated aspirin tablets from two companies. The USP XIX dissolution procedure was modified by including pretreatment in simulated gastric juice. The effects of five pretreatment times were studied. Pretreated tablets yielded higher dissolution profiles and fewer undissolved fractions than nonpretreated tablets. Among pretreatments, 15 min was adequate and 60 min produced the highest dissolution profiles. None of the pretreatments differed significantly from each other. An F test conducted on the data indicated that Product X was significantly better than Product Y at the $p = 0.05$ level. Batch C was ranked as the best batch irrespective of pretreatment time, followed by Batch D. Batches A and B were equal, although Batch A appeared to be better than B for the 60-min pretreatment, as indicated by the lower $t_{80\%}$ value.

Keyphrases □ Aspirin—tablets, commercial, enteric coated, dissolution procedures, dissolution times, pretreatment with simulated gastric juice □ Dissolution studies—aspirin tablets, commercial, enteric coated, dissolution times, pretreatment with simulated gastric juice □ Dosage forms, solid—tablets, aspirin, enteric coated, commercial, dissolution procedures, dissolution times, pretreatment with simulated gastric juice

Historically, enteric-coated tablets have not enjoyed the same success as other dosage forms. From time to time, new enteric coatings have been presented, but they have not been entirely successful. In 1964, Levy and Hollister (1) pointed out the failure of the USP disintegration test to assess the physiological availability of enteric-coated tablets. Subsequently, the product evaluated by these investigators was reformulated to yield a new tablet, which was said to be physiologically available (2).

In 1973, Wagner *et al.* (3) demonstrated the failure of the USP disintegration test to assess the *in vivo* availability of commercial enteric-coated aminosalicylic acid tablets. They showed that a tablet could pass the dissolution test at a high rotation speed (200 rpm) but failed to do so at the slower speed of 50 rpm. Hence, the failure of the dissolution test provided an explanation for the lack of *in vivo* availability.

Since the official compendia do not provide a method or criteria by which to judge the dissolution performance of this dosage form *in vitro,* baseline dissolution data on commercial enteric-coated aspirin tablets were needed to use as a comparison for future development of enteric coatings. In so doing, the *in vitro* dissolution profiles of two commercially available enteric-coated aspirin tablets were evaluated after varying pretreatment periods. The usual USP procedure for uncoated tablets was adapted for this purpose. Additionally, the product-to-product and batch-to-batch variations were observed.

EXPERIMENTAL

Reagents—Purified resin powder[1] (pepsin) and pancreatin[2] obtained from porcine pancreas (Grade II) stored below 0° were used without further treatment. All other materials, sodium chloride, sodium hydroxide, monobasic potassium phosphate, and hydrochloric acid, were reagent grade and were used as obtained. The commercial enteric-coated aspirin tablets were purchased over the counter from various pharmacies, and the batches were selected at random. Two brands were involved; Brand X consisted of Batches C and D, and Brand Y consisted of Batches A and B.

Equipment—The dissolution equipment[3] was manufactured to USP XIX (4) standards, which included the dissolution motor and variable-speed controller with a stainless steel basket assembly. The dissolution vessel was a 900-ml round-bottom resin flask fitted with an appropriate glass cup. Two dissolution apparatus, designated left (L) and right (R), were matched in their performance using a single batch of tablets and modified to reduce unwanted vibrations by the incorporation of a 1000-μF capacitor in the speed control circuit (5).

The rotation speed of the basket assembly was fixed at 50 ± 1.5 rpm throughout the experiment. The dissolution assembly was immersed in a water bath at 37 ± 0.1°. The UV absorbance was measured with a spectrophotometer[4]. All absorbance data were processed using a desktop computer[5]. The final statistical analysis was conducted by the statistical analysis system[6] (SAS) program package.

Method—The USP XIX (4) dissolution procedure for uncoated tablets was used with the modification noted later. The dissolution study involved a pretreated and a nonpretreated regimen. A total of 200 tablets was tested.

Two experiments were conducted. The first involved the direct introduction of the enteric-coated tablets into the simulated intestinal juice for 10 hr. The second involved the pretreatment of the enteric-coated tablet in simulated gastric juice for variable intervals of 15, 30, 60, and 120 min, followed by immersion in simulated intestinal juice for 10 hr. A single gastric juice sample was analyzed for salicylate content after pretreatment. This test was followed by the analysis of the simulated intestinal juice samples collected every 2 hr.

Aspirin was assayed by hydrolysis of acetylsalicylic acid (aspirin) to

Table I—Analysis of Variance for Overall Data Collected (1000 Observations)

Source of Variation	Degrees of Freedom	F Value[a]	Probability, $>F$
Batch	3	39.83+	0.0001
Pretreat	4	70.99+	0.0001
Time	4	1450.98	0.0001
Machine	1	43.77+	0.0001
Batch–pretreat	12	7.93+	0.0001
Batch–time	12	4.22	0.0001
Pretreat–time	16	6.14	0.0001
Batch–pretreat–time	48	3.09	0.0001
Pretreat–machine	4	1.35+	0.2531
Time–machine	4	7.15	0.0001
Batch–machine	3	1.72+	0.1641
Pretreat–time–machine	16	0.12+	1.0000
Batch–pretreat–machine	12	12.31	0.0001
Batch–time–machine	12	1.64	0.0755
Batch–pretreat–time–machine	48	1.41	0.0393
Tablet (batch–pretreat–machine)	160	15.39	0.0001
Error	640		
Corrected total	999		

[a] The plus sign indicates test of hypotheses using analysis of variance sum of squares for the tablet (batch–pretreat–machine) as the error term.

[1] Fisher Scientific Co., Orlando, Fla.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Hanson Research Corp., Northridge, Calif.
[4] Beckman DB-GT connected to a 25.4-cm Beckman recorder.
[5] Hewlett-Packard 9815A attached to a model 9862 desktop calculator plotter.
[6] Amdahl 470 computer.

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Table II—Effect of Pretreatment on Dissolution ($t_{80\%}$)

Batch	Pretreatment Time			
	15 min	30 min	60 min	120 min
A	448	374	232	330
B	322	206	264	370
C	224	188	153	176
D	252	212	208	218

salicylate ion and subsequent UV spectrophotometry. A dissolution medium aliquot was filtered into a 25-ml volumetric flask to which, just prior to UV analysis, 10 ml of 2 *N* NaOH was added to achieve the pH 14 necessary for rapid and complete hydrolysis. The UV absorbance of this solution was measured at 302 nm. Constant dissolution volume was maintained by the addition of fresh dissolution fluid. Simulated gastric and intestinal juices were prepared fresh and were brought to temperature just prior to the actual dissolution experiment.

Statistical Analysis—The analysis of variance (ANOVA) study was conducted using a mixed model to analyze statistically the dissolution experiment data. To stabilize the variances, the data were transformed by taking the arc sine of the square root of 1/100 of each observation. The overall analysis of variance was conducted for all 1000 observations. The *F* statistic for the mixed model was calculated by dividing the sum of squares for the effect by the sum of squares for the tablet (batch–pretreatment–time) nested triple interaction term for the values indicated by the plus sign in Table I. All other values were calculated in the usual fashion by dividing the sum of squares for the effect by the sum of squares for the error term (6).

The overall analysis of variance was designed to determine the independent variable that caused the most interactions. All observations could be sorted by that variable, enabling inferences to be drawn with more accuracy. A point-by-point analysis for significance was conducted for percent dissolved at each time interval using Duncan's multiple-range test (7). Finally, an *F* test was conducted to determine if the two brands were significantly different in performance based on the four batches tested.

RESULTS AND DISCUSSION

The overall analysis of variance indicated that batch, pretreatment time, dissolution time, and apparatus all significantly affected the dissolution profiles of commercial enteric-coated aspirin tablets (Table I). Because most interactions were caused by batch-to-batch variations, the data were sorted by batches, and an analysis of variance was conducted for each batch. Pretreatment significantly altered the dissolution profiles from all batches except D.

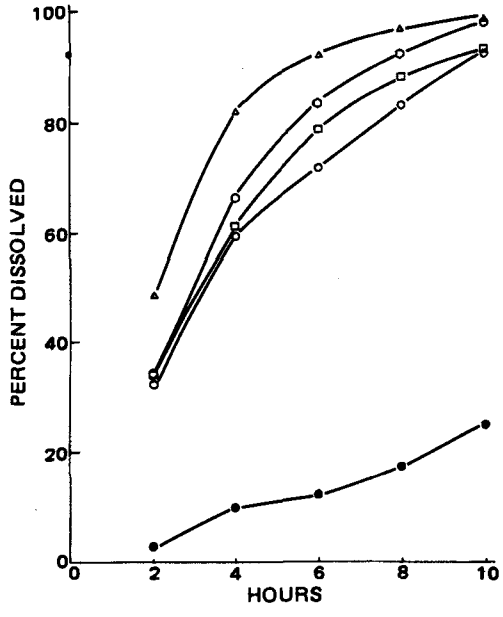

Figure 1—*Dissolution profile of Batch A in simulated intestinal juice after different gastric juice pretreatment times. Key: ●, no pretreatment; ○, 15-min pretreatment; □, 30-min pretreatment; △, 60-min pretreatment; and ○, 120-min pretreatment.*

Table III—Number out of 10 Tablets Remaining Partially Undissolved after 10 hr of Dissolution [a]

Pretreatment	Brand Y		Brand X	
	Batch A	Batch B	Batch C	Batch D
None	0	5	3	0
	10	5	1	0
15 min	2	2	0	0
	0	0	0	0
30 min	0	2	0	0
	0	0	0	0
60 min	1	1	0	0
	0	0	0	0
120 min	2	2	1	0
	0	0	0	0

[a] First row of numbers represents <50% and the second row represents >50% of the tablets that remained undissolved after 10 hr.

Figure 1 demonstrates the typical effect of simulated gastric juice pretreatment on tablet dissolution in simulated intestinal juice. Figure 2 presents the percent dissolved at each pretreatment time after 2 hr of dissolution in simulated intestinal juice and is typical of the results obtained for 4-, 6-, 8-, and 10-hr intervals. Duncan's multiple-range test for significance indicated no significant difference among 15-, 30-, and 60-min pretreatments for Batches A, C, and D. The 60-min pretreatment yielded higher values for percent dissolved, but they were not statistically significant.

The data suggests (Figs. 1 and 2) that a 15-min pretreatment would be adequate for three of the four batches. The 60-min pretreatment was consistently higher than other pretreatment times within a given batch. The 60-min pretreatment was not significantly different from the 15-min pretreatment except for Batch B. However, there was a trend for the dissolution values to peak following the 60-min pretreatment. The percent dissolved value diminished slightly after 120 min of pretreatment. This slight reduction for three of the four batches was not statistically significant from that observed for the 60-min pretreatment. Batch D, on the other hand, did have a significant reduction in the percent dissolved after 120 min of pretreatment and 2 hr of dissolution. This apparently anomalous behavior was not consistent in magnitude or in order with the data obtained at later dissolution intervals up to and including 10 hr. Similar plots of percent dissolved *versus* pretreatment time for the data at 4-, 6-, 8-, and 10-hr dissolution intervals showed the same rank order and confirmed the conclusions drawn from the data presented in Fig. 2.

Percent dissolved *versus* pretreatment time plots were made for all four batches after 15, 30, 60, and 120 min of pretreatment. Figure 3 presents the typical results of the 60-min pretreatment. Batch C gave the highest value at all pretreatment times. Table II summarizes the dissolution profile with respect to $t_{80\%}$, the time for 80% of the tablet to be dissolved for each batch. These values appear to be smallest after 60 min of pretreatment for Batches A, C, and D; Batch B had a minimum $t_{80\%}$ after 30 min of pretreatment. Overall, the $t_{80\%}$ values range from 2 hr and 33 min for Batch C to 4 hr and 24 min for Batch B after 60 min of pretreatment. The tablets pretreated for 15 min had higher $t_{80\%}$ values than the 60-min pretreatment results, suggesting a relationship between pretreatment time and the minimum $t_{80\%}$ values; *i.e.*, increased pretreatment time appeared to reduce the $t_{80\%}$ values.

A similar relationship may exist for the *in vivo* dissolution process.

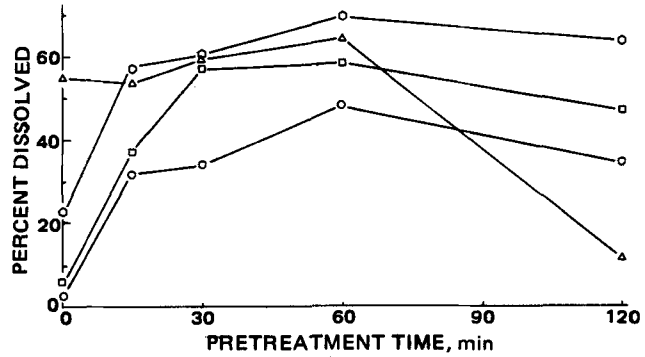

Figure 2—*Percent dissolved* versus *pretreatment time for all four batches after 2 hr of dissolution in simulated intestinal fluid. Key: ○, Batch A; □, Batch B; ○, Batch C; and △, Batch D.*

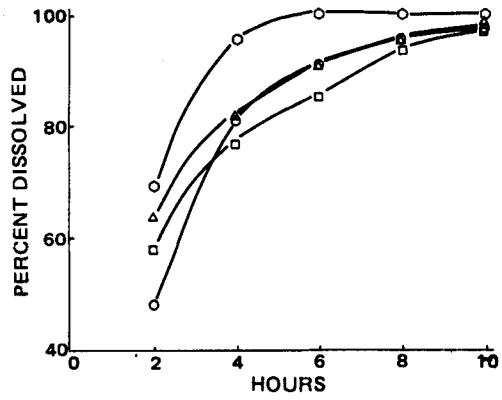

Figure 3—*Dissolution plots of all four batches after 60-min pretreatment. Key:* ○, *Batch A;* □, *Batch B;* ○, *Batch C; and* △, *Batch D.*

Table III shows that the number of tablets undissolved after 10 hr of dissolution with no pretreatment was greater for Product Y than for Product X. For Batches A and B with no pretreatment, all tablets tested were partially undissolved after 10 hr. Batch C similarly yielded four out of 10 undissolved, whereas the tablets in Batch D were totally dissolved. Pretreatment decreased both the number and size of undissolved tablet residues after 10 hr of dissolution. Overall, the 60-min pretreatment resulted in the fewest undissolved residues for all batches tested, suggesting it as the optimum pretreatment time. Furthermore, Product X appeared to perform *in vitro* better than Product Y with respect to the number of undissolved tablet fractions at all pretreatment times. This finding supports the F test result, which indicated that Brand X performed significantly better *in vitro* than Brand Y ($p = 0.05$).

SUMMARY

Pretreated tablets yielded higher dissolution profiles than nonpretreated tablets. The analysis of variance showed that pretreatment significantly increased the tablet dissolution profiles from all batches except Batch D at the $p = 0.0001$ level. Furthermore, Table III indicates that pretreatment in simulated gastric juice reduced both the number and the size of undissolved fractions. The 15-min pretreatment was adequate and was not statistically different from the other pretreatment periods. However, the 60-min pretreatment yielded higher dissolution profiles for all batches and fewer tablet residues. While the tendency for higher dissolution profiles cannot be supported statistically, this trend is consistent with the reduction in tablet residues after 10 hr of dissolution.

A relationship between the pretreatment time and the $t_{80\%}$ reduction appeared to exist, suggesting that a similar relationship may exist *in vivo* and should be studied. Product X performed better than Y, as indicated by higher dissolution profiles. The smaller $t_{80\%}$ values for Product X (Table II) support this argument. The F test using averages obtained after each time interval indicates that Product X was significantly better than Y at the $p = 0.05$ level. Furthermore, Table III shows that there were fewer undissolved tablet residues for Product X than for Product Y after 10 hr of dissolution in simulated intestinal fluid.

The batch ranking indicated that Batch C was the best batch irrespective of the pretreatment times, and it was followed by Batch D. Batches A and B were interchangeable, although Batch A appeared to be better than B for the 60-min pretreatment, as indicated by the lower $t_{80\%}$ value. Since the conclusions are based on *in vitro* data, any extrapolations to the biological system should be confirmed *in vivo*.

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Anomalous Solution Behavior of 2-Palmitate Esters of Lincomycin and Clindamycin

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Abstract □ The aqueous solubilities of lincomycin and clindamycin 2-palmitate esters are compared. Clindamycin 2-palmitate hydrochloride has an unusually high solubility at 25°, which is due to micelle formation. Both compounds are surface active with relatively low critical micelle concentrations. However, since the Krafft point of lincomycin palmitate is ~43°, it does not form micelles below that temperature and appears to be quite insoluble until heated above 43°. The experimental monomeric solubilities of the two compounds agree with calculations based on group contributions to lipophilicity. Clindamycin 2-palmitate hydrochloride solutions are quite sensitive to ions, being salted out as unprotonated base in the form of oily droplets. Salting out correlates well with anionic strength, which is quite constant for the various salts studied. A viscosity maximum occurs with increasing salt addition, with the peaks of the different salts occurring at the same anionic strengths.

Keyphrases □ Lincomycin—palmitate ester, aqueous solubility, pH, temperature, micelle formation □ Clindamycin—palmitate ester, aqueous solubility, pH, temperature, micelle formation □ Antibacterial agents—lincomycin, palmitate ester, aqueous solubility, pH, temperature, micelle formation □ Antibacterial agents—clindamycin, palmitate ester, aqueous solubility, pH, temperature, micelle formation □ Aqueous solubility—lincomycin and clindamycin palmitate esters

Lincomycin and clindamycin are medium spectrum antibiotics whose hydrochloride salts are quite soluble in water. Both compounds have a bitter taste which is difficult to mask. Since clindamycin hydrochloride is considerably more bitter than lincomycin hydrochloride, chemical modification was required to make an acceptable liquid dosage form. A variety of prodrug esters were synthesized to reduce or eliminate the bitter taste of these anti-

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