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COMMUNICATION

IBUPROFEN TABLETS

DISSOLUTION VERSUS BIOAVAILABILITY

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ABSTRACT

Dissolution studies and a 24 patient randomized double-blind crossover bioavailability study were performed using two commercially-sized batches of an ibuprofen 200 mg tablet formulation (sugar-coated). The batches were equivalent with respect to the USP dissolution test, but differed, particularly from tablet-to-tablet, when a paddle at 50 rpm was substituted, one batch consistently giving a high dissolution and the other consistently giving a low dissolution.

The bioavailability study showed the batches to be bioequivalent, thus prompting an investigation as to why the substitution of a paddle at 50 rpm gave no correlation with

bioavailability and should therefore be unsuitable as a standard dissolution test. It was found that soaking tablets in acid prior to using the paddle at 50 rpm (thus simulating more closely the in vivo pH sequence) increased the dissolution rate. The increase is such that the maximum dissolution rate, which also approximates that given by the USP method, is achievable within five minutes, even when the presoak medium is an unbuffered solution of hydrochloric acid at pH 4. A standard presoak procedure was then developed consisting of soaking each tablet for five minutes in 5 ml of USP gastric fluid without pepsin at room temperature and with no agitation. A comprehensive application of this procedure to both batches consistently produced results equivalent to those obtained by the USP method. In particular, there was very little tablet to tablet variation. Studies with formulations of varying bioavailability will be necessary before it can be determined whether this new acid presoak procedure will provide a more meaningful dissolution test compared with the current USP method.

INTRODUCTION

The pharmaceutical industry has long sought a rapid, inexpensive and precise means of measuring the pharmacological effectiveness of different formulations and batches of solid oral dosage forms. The most widely accepted reference

methodology that has emerged is the in vivo approach of measuring drug levels in body fluids at various times after ingestion (i.e., bioavailability testing). Both blood serum and urine have been used, but blood serum has become the more popular approach because it involves a simpler pharmacological model. Bioavailability testing has limitations. First, body fluid drug levels do not necessarily correlate quantitatively with pharmacological response. Second, the data tend to be study-specific so that data from one set of patients and study conditions may not be comparable to those of another set of patients and study conditions. Third, in addition to being rather imprecise, bioavailability testing is relatively time-consuming and expensive principally because of institutional practices and the number of patients required. Consequently, bioavailability testing is used for reference purposes rather than for routine monitoring.

The other method that has emerged is the in vitro approach of dissolution testing whereby the rate at which the drug passes from the dosage form into solution is determined under a given set of conditions including simulated digestive media (e.g., gastric and/or intestinal media), agitation mechanism (e.g., rotating basket or paddle), agitation speed and vessel dimensions. Such testing attempts to simulate the digestive process in a simplistic way. It is understood that this technique should not be used to make in vivo predictions unless

the parameters chosen permit a correlation with bioavailability data. Both Skelly et al[1] and the AAPS Task Force[2] have emphasized this point. It follows that caution must be exercised in selecting dissolution methodology for evaluating and optimizing formulations and for monitoring batch consistency. Chemburkar et al[3], have given examples of how accelerated stability samples of methaqualone tablets (both thermal and humidity stress) showed declining dissolution with increasing stress, even though all the samples were bioequivalent. They obtained a correlative dissolution method only after radically altering the test parameters. Hekimoglue et al[4], have described how a commercial acetaminophen product showed a poor (and failing) dissolution in the USP dissolution test (paddle at 50 rpm) but was nevertheless bioequivalent to two competitive products which gave high (and passing) dissolution in the same test. Clearly, it is possible to create dissolution methodology which is so sensitive that it detects differences which are not meaningful from a bioequivalence standpoint.

For ibuprofen tablets, the official USP dissolution method prescribes, among other conditions, the use of a rotating basket at 150 rpm and a pH 7.2 phosphate buffer. The latter was chosen because neither the use of water nor acid was considered to be feasible due to the relative insolubility of ibuprofen in both media. Recently, Velagapudi et al[5] proposed a modification

(paddle @ 50 rpm) which reportedly detects batch or tablet-to-tablet differences not discernible by the USP method.

This paper describes work we have conducted to establish the relationship of bioavailability to these methods and to a third procedure consisting of presoaking the tablet in acid prior to using the paddle at 50 rpm. Our rationale was to test the effect of more closely simulating the in vivo pH sequence.

STUDY DESIGN

Ibuprofen Tablets Studied

Two commercial-sized batches (A & B) of a standard sugar-coated formulation containing 200 mg ibuprofen/tablet were studied. They were chosen because each was known to consistently give a high dissolution rate with the USP method and because they were also known to consistently behave differently with regard to the use of the paddle at 50 rpm. Both batches fully conformed with the USP monograph "Ibuprofen Tablets".

Dissolution Methods Used

METHOD I - USP XXI (includes use of a rotating basket and 900 ml of pH 7.2 phosphate buffer).

METHOD II - USP XXI modified as proposed by the Velagapudi et al (use of paddle at 50 rpm).

METHOD III - Method II preceded by soaking the tablet in 5 ml USP gastric fluid without pepsin (static and at RT).

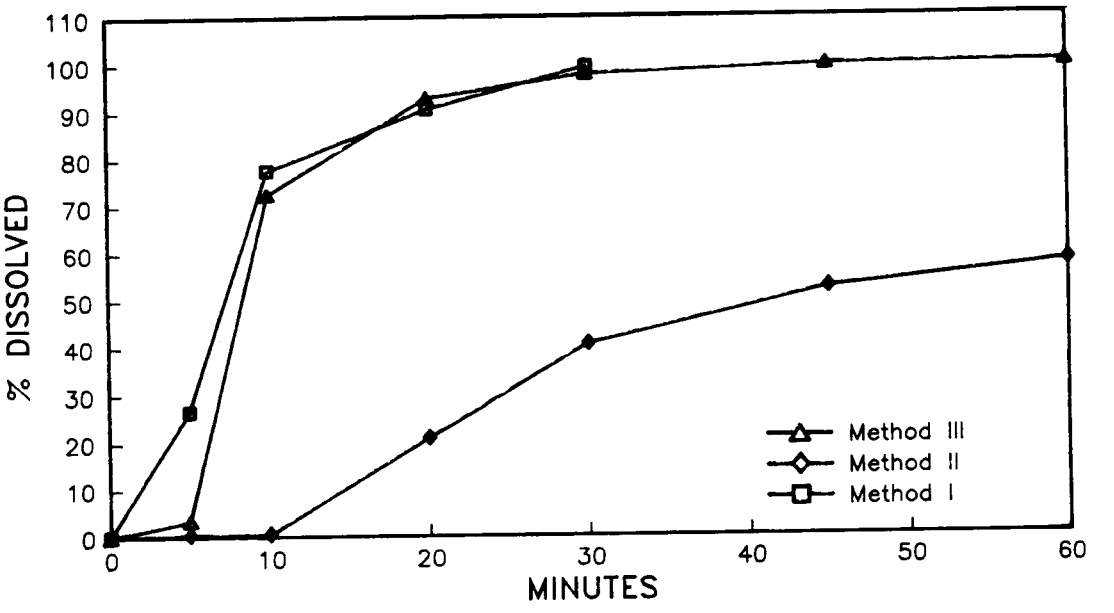
Bioavailability Study Conditions

The two batches of ibuprofen tablets were compared in a double-blind crossover study in 24 healthy volunteers. Volunteers were randomly assigned to receive two 200 mg tablets from each batch separated by a one-week wash-out period. Plasma samples were drawn at baseline and at 5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours following dosing. The samples were randomly numbered so that the identities of the samples handled by the analysts were disguised.

RESULTS

Dissolution Versus Bioavailability

Comparisons of the time means for the bioavailabilities of Batches A and B with the means for the applications of dissolution Methods I, II, and III are shown in Figures 1 and 2. Summaries of the data upon which the graphs are based are shown in Tables 1 and 2.



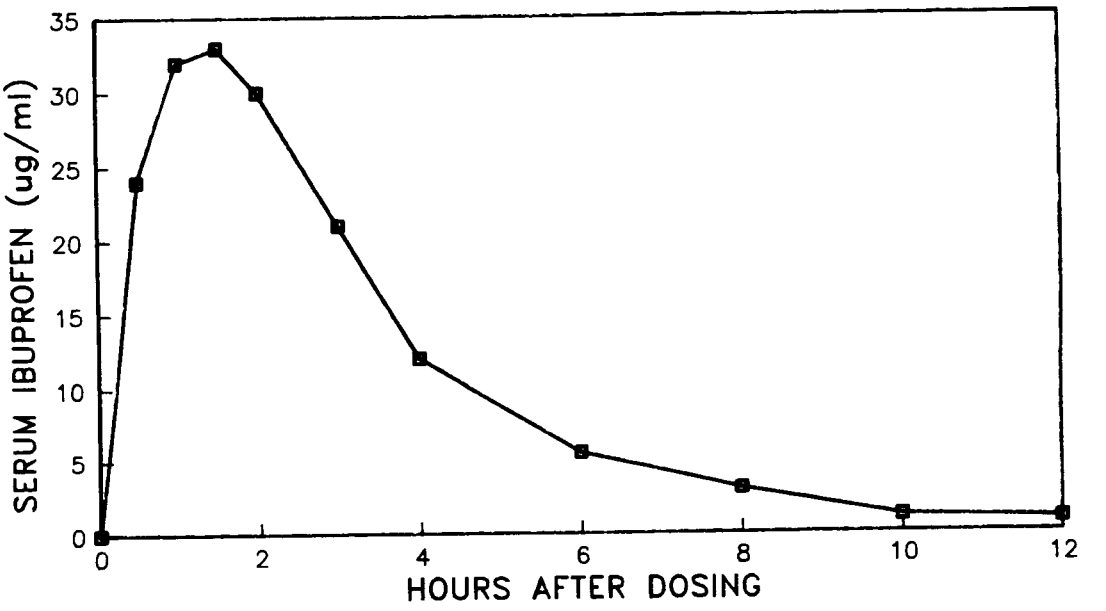
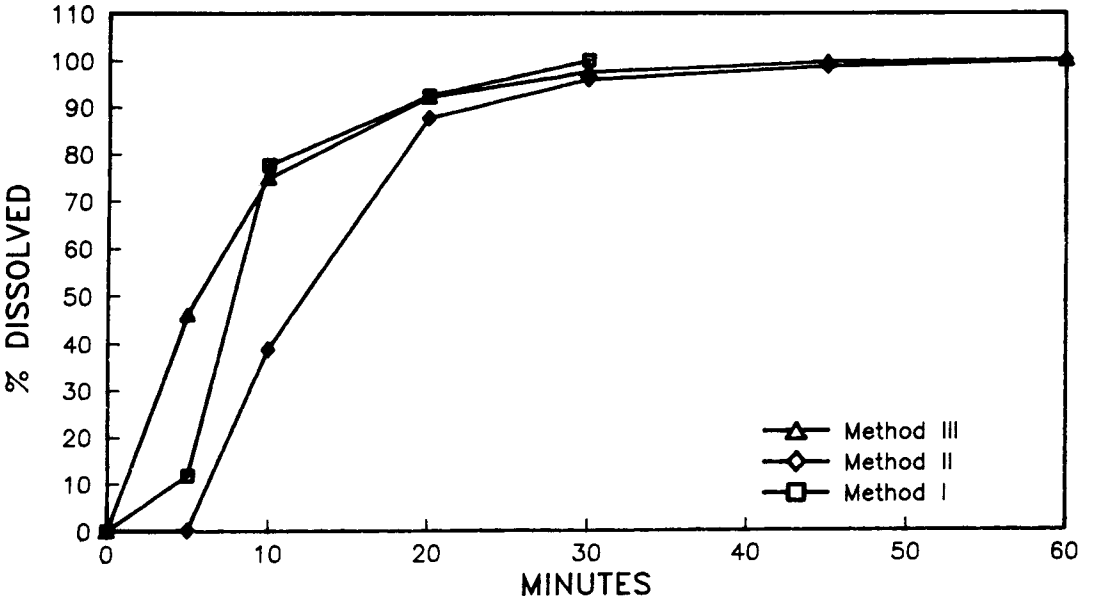


FIGURE 1

Dissolution and Bioavailability Data
Means for Batch A



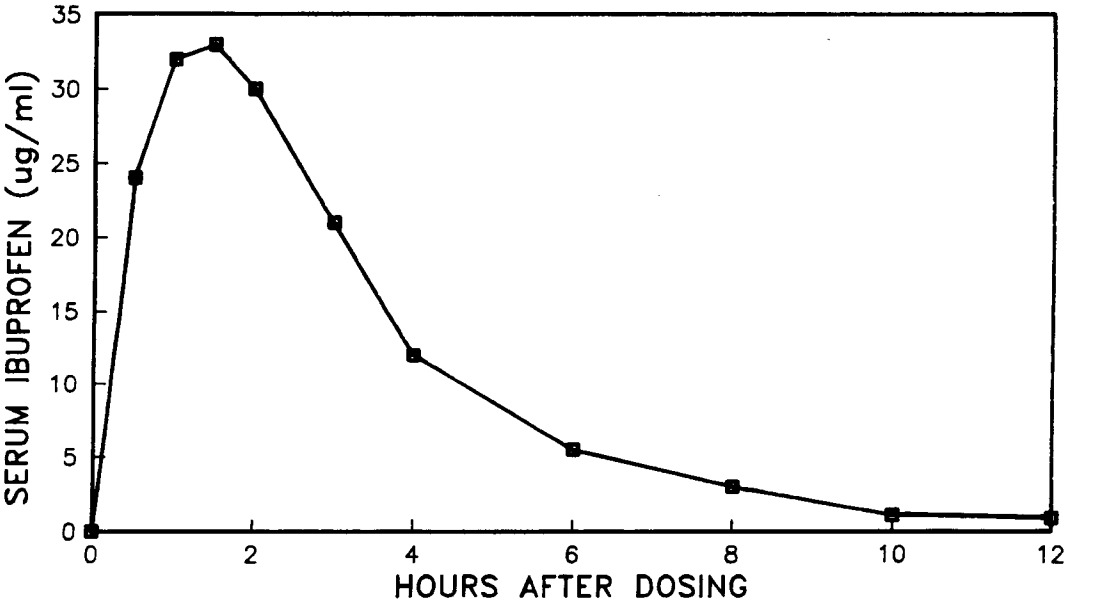


FIGURE 2

Dissolution and Bioavailability Data
Means for Batch B

TABLE 1

Summary Bioavailability Data for Batches A and B
(Means and Standard Deviations)

Batch	$AUC_{0-\infty}$ mg/l x hrs	C_{max} mg/l	T_{max} hrs.
A	130 (31)	43.3 (11.4)	1.3 (0.7)
B	128 (26)	41.0 (8.8)	1.4 (0.8)

NOTES

- Study was a randomized double-blind crossover study with 24 patients.
- $AUC_{0-\infty}$ - Area under plasma concentration curve (extrapolated to infinity) with time calculated by the trapezoidal rule.
- C_{max} - Maximum plasma concentration.
- T_{max} - Time required to achieve C_{max}.
- Means are statistically derived on a per patient basis.

Examples of Individual Tablet Dissolution Data for Methods II and III

Typical examples are shown in Figure 3. Figure 3(a) shows results for the application of Method II to six random tablets of Batch A and Figure 3(b) shows the application of Method III to six random tablets of the same batch.

TABLE 2

Ibuprofen Dissolutions for Batches A and B
Expressed as % Label Claim
(Means and Standard Deviations)

Method	Number of Tablets	Batch	Minutes 5	10	20	30	45	60
I	48	A	26.6 (13)	77.6 (5.5)	90.6 (2.8)	99.4 (1.4)	--	--
	48	B	11.7 (12)	80.0 (4.9)	92.4 (2.6)	100 (2.2)	--	--
II	48	A	0.40 (1.5)	0.52 (1.6)	21.0 (25)	40.5 (37)	52.3 (43)	57.8 (45)
	48	B	0.08 (0.4)	38.7 (28)	87.6 (7.7)	95.9 (3.7)	98.7 (2.4)	100 (1.3)
III	48	A	31.4 (13)	72.5 (5.7)	92.9 (2.7)	97.9 (2.1)	99.7 (1.7)	100 (1.4)
	12	B	46.1 (11)	74.8 (4.1)	92.1 (1.3)	97.5 (1.4)	99.7 (1.8)	100 (1.7)

Optimization of Dissolution Method III

Before its routine use for this present study, the acid presoak condition for Method III needed to be optimized. The optimization study was performed on a batch that gave a slow dissolution rate with Method II. The results are shown in Figure 4 and Table 4. Figure 4(a) shows the effect of a five

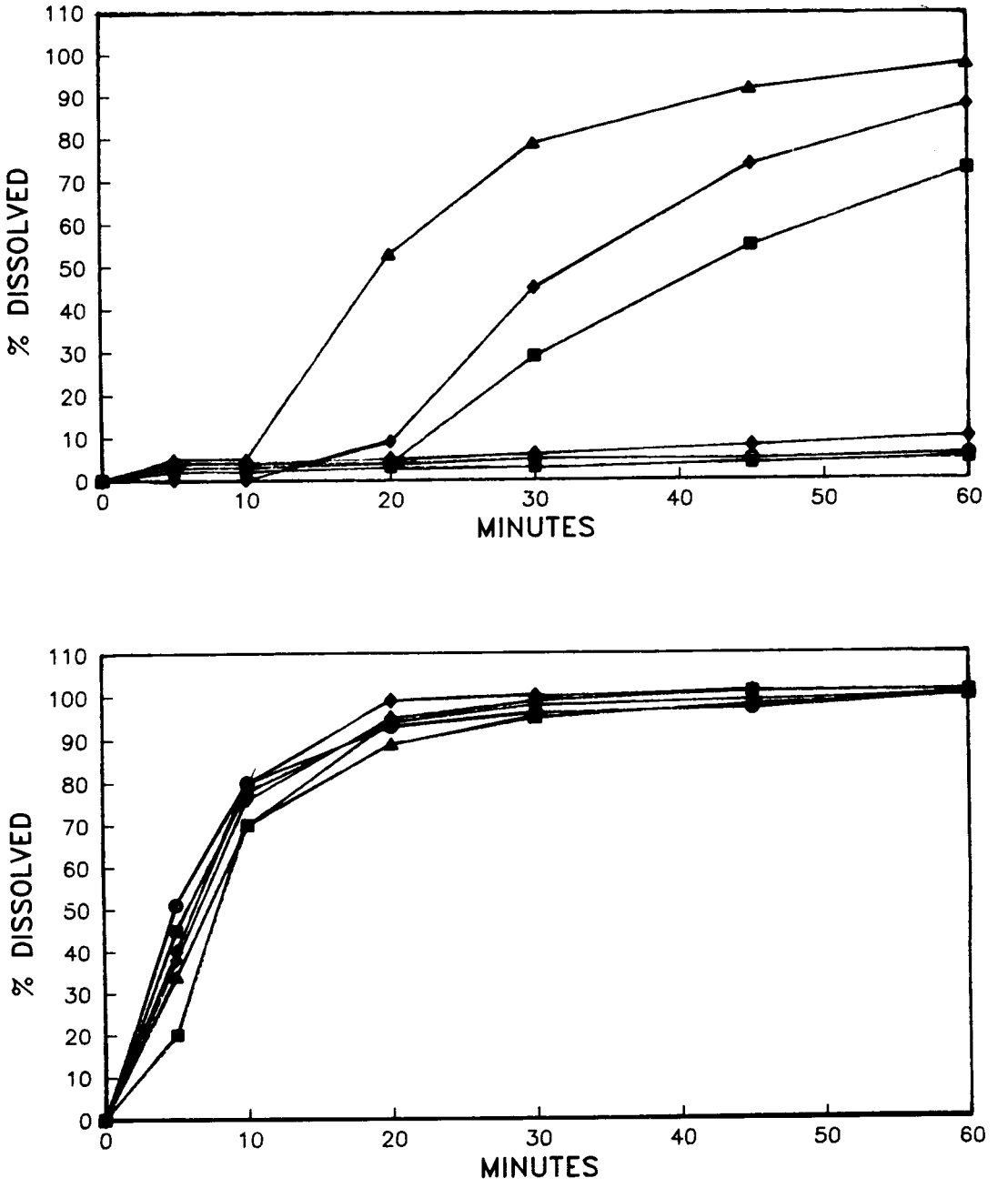


FIGURE 3

Examples of Individual Tablet Dissolution Data (Batch

(a) METHOD II (b) METHOD III

TABLE 3

Ibuprofen Dissolutions for Individual Tablets for Application of Methods II and III to Batch A (Expressed as % Claim)

Method	Tablet No.	Minutes 5	10	20	30	45	60
II	1	2	2	3	3	4	5
	2	0	0	9	45	74	88
	3	5	5	53	79	92	98
	4	4	4	4	5	5	6
	5	3	3	4	29	55	73
	6	4	4	5	6	8	10
III	1	45	78	94	98	99	100
	2	38	76	95	99	101	101
	3	34	70	89	95	98	100
	4	51	80	93	96	97	100
	5	20	70	94	99	101	101
	6	40	80	96	100	101	101

minute presoak at pH 1 (5 ml of USP gastric fluid without pepsin) and pH 4 (5 ml of 0.0001 N HCl). Even though the rates were comparable, pH 1 was selected as a more practical condition for optimization. Figure 4(b) shows the effect of presoak time at pH 1. Since a maximum dissolution rate was essentially

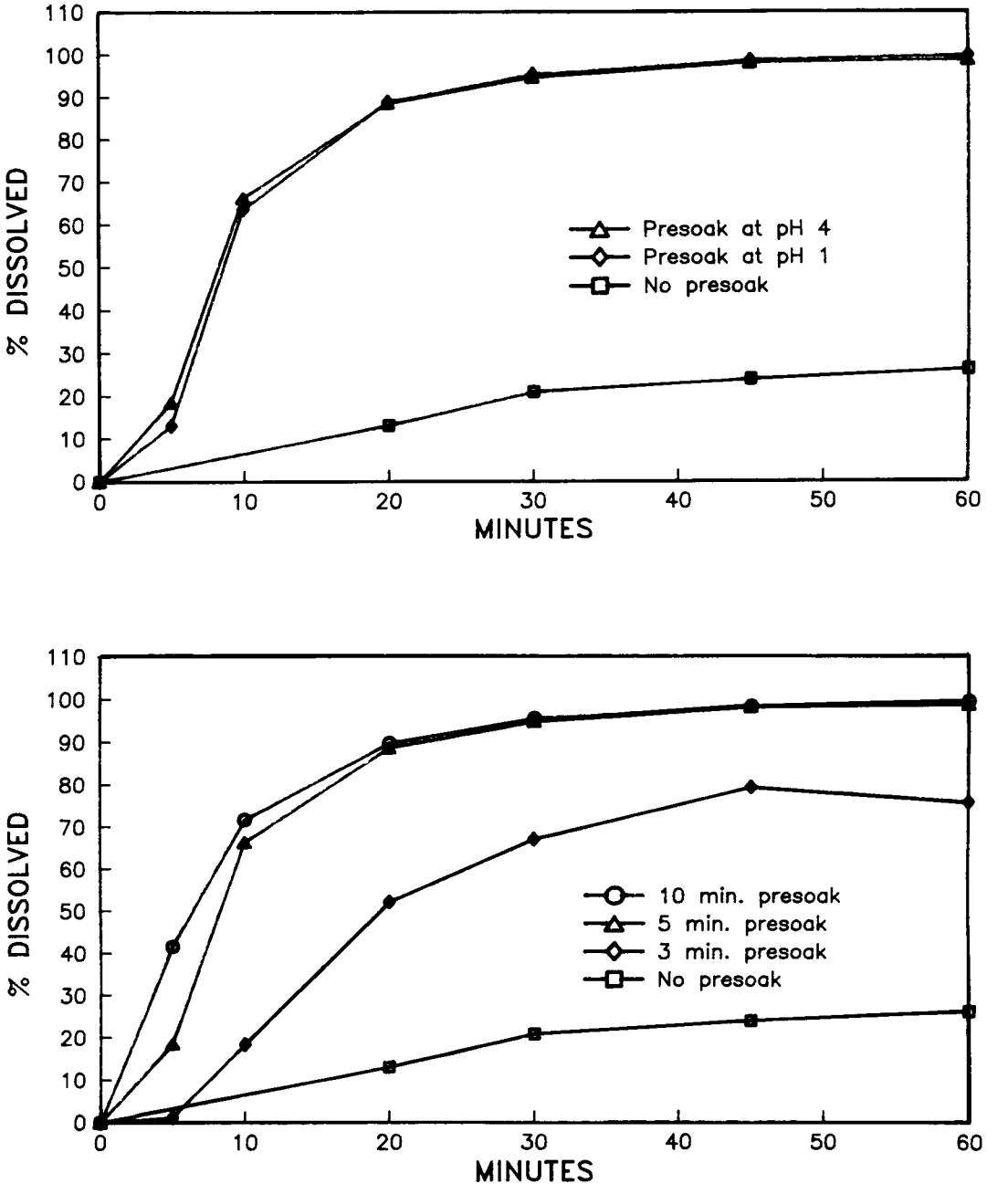


FIGURE 4

Optimization of Dissolution Method III

(a) Effect of 5 Minute Presoak at pH 1 and pH 4

(b) Effect of Presoak Time at pH 1

TABLE 4

Means and Standard Deviations of Ibuprofen Dissolution Data for Optimization of Dissolution Method III (Expressed as % Claim)

Presoak Conditions	Number of Tablets	Minutes 5	10	20	30	45	60
No presoak	12	--	--	13.1 (28)	20.9 (29)	23.9 (40)	26.2 (42)
pH 4 5 min	12	13.1 (6.4)	63.7 (5.0)	89.0 (2.7)	95.5 (2.1)	98.7 (1.2)	99.7 (1.2)
pH 1 3 min	12	1.17 (2.4)	18.5 (25)	52.2 (34)	67.0 (34)	79.3 (37)	75.6 (36)
pH 1 5 min	12	18.6 (11)	66.4 (6.3)	88.7 (2.9)	94.8 (2.0)	98.2 (2.5)	98.7 (1.3)
pH 1 10 min	12	41.6 (6.7)	71.7 (4.3)	89.8 (2.6)	95.6 (2.7)	98.4 (1.6)	99.4 (1.6)

achieved within five minutes, this time was selected for routine use.

DISCUSSION

The dissolution and bioavailability data for the two batches A and B indicate that the batches were bioequivalent but also gave different dissolution results depending on the procedure employed. The application of the USP method (i.e., Method I)

gave very similar results for the two batches. The simple substitution of the paddle at 50 rpm for the rotating basket at 150 rpm gave widely different results. While with batch B it gave results only slightly lower and with a similar inter-tablet variation, with batch A it gave very much lower results with considerable inter-tablet variation. The use of an acid presoak, markedly accelerated the dissolution obtained with the paddle at 50 rpm. Even a presoak at pH 4 gave dissolutions similar to those obtained with the USP method.

Clearly the simple substitution of a paddle at 50 rpm detects batch-to-batch and/or tablet-to-tablet differences which have no meaning from a bioavailability standpoint and thus makes the procedure particularly unsuitable for assessing the releasability of batches for commercial use.

A possible explanation for its unsuitability is that the in vivo process is more stressful to the tablets and readily overcomes the slight differences that the method detects. Based upon this model, both the use of the rotating basket at 150 rpm and the use of an acid presoak prior to the paddle at 50 rpm are more stressful and therefore present better candidates for release testing. Studies with formulations of varying bioavailability will, however, be necessary before it can be determined which of these methods constitutes the more meaningful approach.

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