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DISSOLUTION TESTING OF IBUPROFEN TABLETS

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ABSTRACT

Dissolution testing (using three different methods, USP, FDA and a suggested method) was performed on eight different brands of commercially available ibuprofen tablets as purchased and also after storage at 37°C and 75% Relative humidity. Two dissolution values were determined at time 15 and 30 minutes.

Statistical interpretation was performed using a Student's t test and Duncan multiple range test with an ANOVA on a SAS program.

Some batches tested, notably, sugar coated tablets appeared to be particularly sensitive to the storage conditions used in this study and concern may be felt about possible loss of clinical efficacy.

Of the three dissolution testing methodologies, the present USP method was the least discriminating, the FDA method was intermediate and the new proposed method was the most discriminating.

INTRODUCTION

The approval of ibuprofen for sale as an OTC product at the 200 mg dose has greatly stimulated commercial demand for this drug.

Two types of ibuprofen tablets were examined in this study: film coated and sugar coated. Previous research reported from FDA laboratories and USP laboratories, indicates that the dissolution of drugs from sugar coated tablets is sometimes very sensitive to storage at even mild stress conditions (1,2).

In view of the above factors the design of a dissolution test for ibuprofen is of critical importance. Skelly and coworkers showed that dissolution could be a useful tool to predict biological data (3). At the FDA bioequivalence hearing held in Washington, D.C. in September 1986 (4) the possibility of substantial therapeutic differences between several brands of the same product was also discussed. Clearly since ibuprofen is available on the U.S. market from at least ten different manufacturers, the potential for therapeutic bioavailability differences is significant.

The objectives of this study were to:

1. compare three dissolution methodologies for ibuprofen tablets,
2. investigate the effect of short term storage at moderate stress conditions on the dissolution of ibuprofen tablets,
3. evaluate, in a preliminary way, the dissolution of commercially available ibuprofen products.

Three dissolution methodologies were used in this study

1. The present official USP method (USP)
2. The FDA method (FDA)
3. A suggested method developed by the Upjohn Company (UPJ)

(Table I provides data on the three tests)

TABLE I

Methods of Dissolution Testing Used in this Study

Name	Equipment	Stirrer Speed (rpm)
USP	Basket	150
FDA	Paddle	50
Suggested, UPJ	Basket	50

TABLE II

Ibuprofen Tablets Used in This Study

Brand	Company	Type of Coating
Advil	Whitehall	Sugar
Trendar	Whitehall	Sugar
Unipro	U.R.L.	Sugar
Haltran	Upjohn	Film
Ibuprin	Thompson Medical	Film
Medipren	McNeil	Film
Midol 200	Glenbrook	Film
Nuprin	Bristol Myers	Film

EXPERIMENTAL

Materials

The ibuprofen tablets were purchased from several community pharmacies in Wakefield, Rhode Island; their identity is disclosed in Table II, and information on their composition is given in Table III and IV.

Monobasic potassium phosphate and sodium hydroxide for the phosphate buffer preparation, were obtained from the Fisher Scientific Company. All chemicals were of analytical grade. The prednisone standard powder and 50 mg standard tablets for

TABLE III

Components of 200 mg Ibuprofen Sugar Coated Tablets

(as disclosed on label)

TRENDAR	ADVIL	UNIPRO
Ibuprofen (200 mg), acetylated monoglycerides, beeswax, Ca sulfate, colloidal silicon dioxide, pharmaceutical glaze, povidone, sodium benzoate, NaCMC, starch, stearic acid, sucrose, titanium dioxide		"composition not disclosed on the label"

TABLE IV

Components of 200 mg Ibuprofen Film Coated Tablets

(as disclosed on label)

NUPRIN	MEDIPREN	HALTRAN	MIDOL 200	IBUPRIN
		Ibuprofen	200 mg	(identical components)
	Colloidal silicon dioxide stearic acid, titanium dioxide			
HPMC	HPMC, MCC	HPMC	--	--
D and C yellow No.10	FD and C blue No. 10	--	Ca Phosphate Cellulose	Ca Phosphate Cellulose
D and C yellow No.2	D and C yellow No. 10	--	--	--
Corn Starch	pregelatinized starch	pregelatinized starch	Corn starch	--
Propylene glycol	--	Propylene glycol	--	--
Carnauba wax	--	Carnauba wax	--	--
	glycerol		Mg Stearate	Mg stearate
	Na Lauryl-sulfate		Na Lauryl-sulfate	Na Lauryl-sulfate
	Na starch		starch	Na starch
	--		glycolate	glycolate

the apparatus calibration, as well as ibuprofen for the standard solutions, were directly provided by the Drug Standard Division of USP.

Equipment

An Easy-lift dissolution test station model 63-734-100 from Hanson Research Corp. was used. Some runs were also performed on a Distek model 2000.

All the analytical determinations were conducted on an Hewlett Packard 8541 Diode Assay ultraviolet spectrophotometer.

The moderate stress conditions, four weeks, consisted of $37^{o}C \pm 1^{o}C$ and a 75% Relative Humidity $\pm$ 3%. The dissolution medium was a USP phosphate buffer at pH 7.2 and $37^{o}C$.

The glass filters were Millipore, model GF-F, 0.45µm filters. The ibuprofen assay method was developed as follows. The tablets were ground to a powder in a mortar and transferred into 900 ml of dissolution fluid. The mixture was stirred for three hours using USP paddles rotating at 100 RPM. Triplicate aliquots were either filtered through 0.45µm glass or cellulose acetate filter, or centrifuged for twenty minutes at 2000g.

Figure 1 is a typical spectrum of an ibuprofen standard and Figure 2 shows the superpositions of all spectra as compared to a USP ibuprofen standard spectrum. The results showed no interference within the range of working wavelength and the filtration operation did not affect the observed spectra.

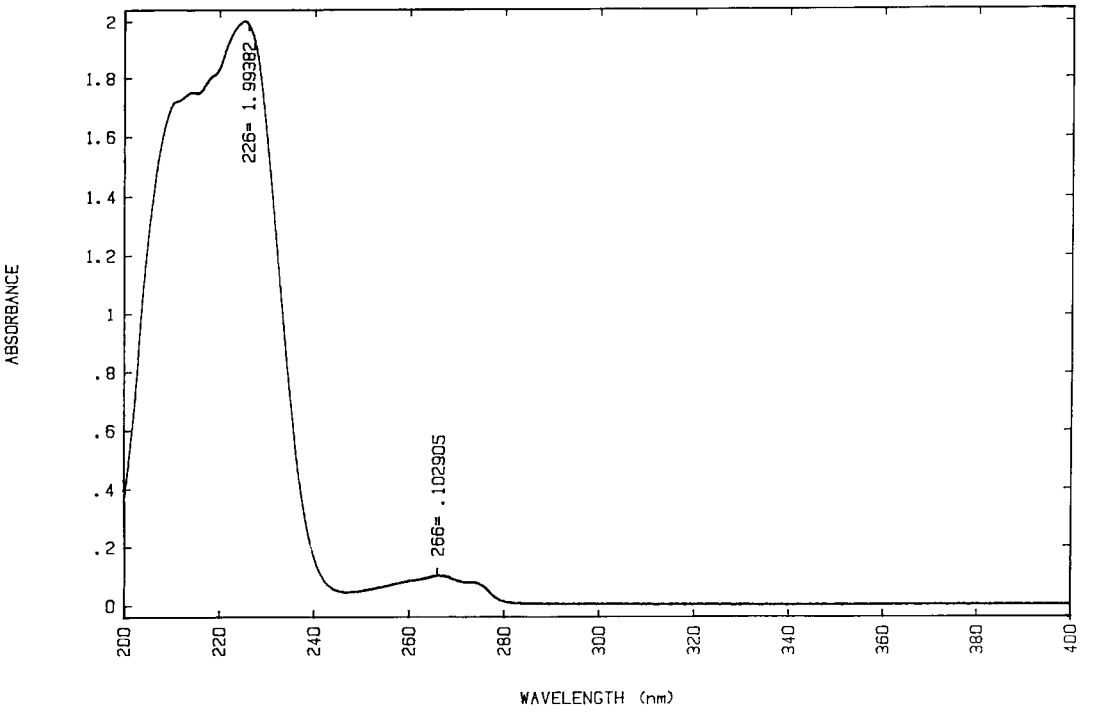


Figure 1 : Spectrum of an ibuprofen standard at 58 µg/ml

In order to avoid dilutions a wavelength of 264nm was selected for the analytical method. A Beer Lambert plot gave good evidence of linearity with a correlation coefficient of 0.999 at this wavelength. Calibration of the dissolution apparatus was effected using paddles and baskets at 50 RPM.

METHODS

Dissolution testing was performed on unstressed and stressed tablets. There are three replicates for each sample unless otherwise specified. Samples were withdrawn at 15 and 30 minutes with 10 and 30 ml syringes respectively (10 ml of

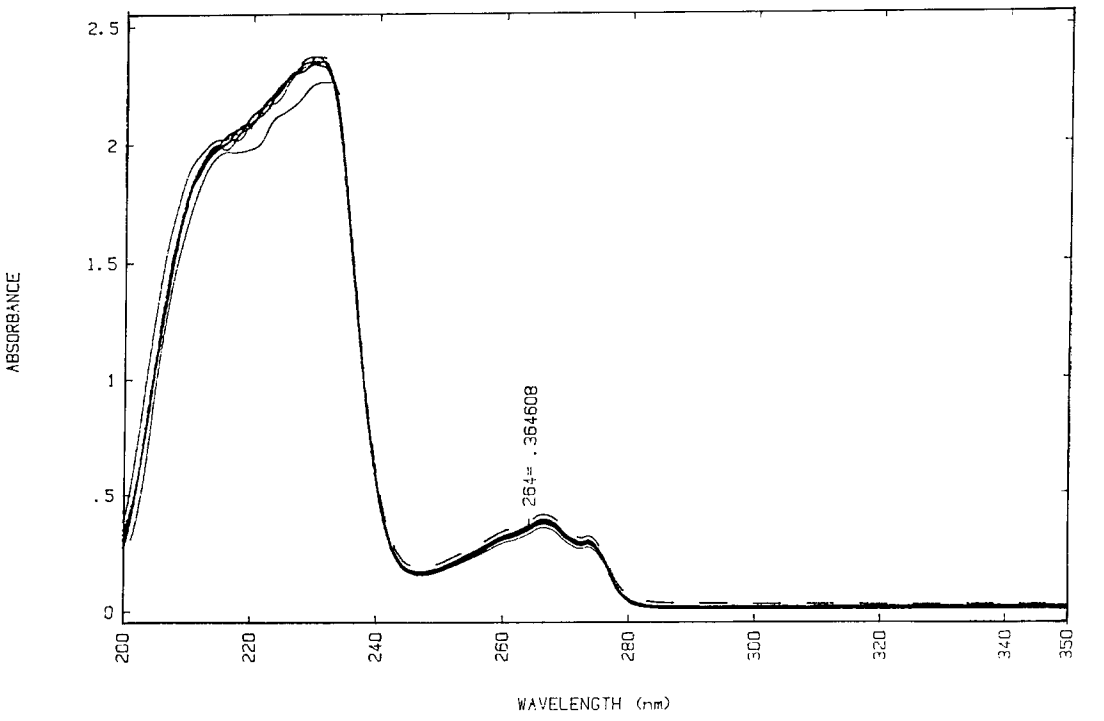


Figure 2 : Preliminary Testing - Superposition of ibuprofen spectra

solvent at 37°C being added at 15 minutes to compensate for the volume removed), then filtered (the first 3 ml was discarded) and assayed. All results are reported with respect to label claim.

The dissolution data were interpreted statistically using first a Student t Test and then a computerized SAS program.

An ANOVA and a Duncan multiple range test were conducted. The independent parameters were the eight brands, the two time

points, the storage conditions and the three methods, the dependent variable being the percentage dissolved.

RESULTS AND DISCUSSIONS

The results summarized in Tables V and VI are means of percentage dissolved and standard deviations. The number of replicates was three unless otherwise noted. It is appreciated that there is some risk in estimating a standard deviation from only three values. However, in the case of the film coated tablets, the variability was small and thus this process is unlikely to introduce substantial errors. When substantial intra-batch tablet variability was detected (e.g.: Advil, Unipro) four or six replicates were taken. A preliminary statistical screening, was performed comparing the means of percentage dissolved at a 95% confidence level.

Effect of Methodologies

Tables VII and VIII compare the effect of the three methods and stress storage on the sugar coated brands. Data on film coated tablets are shown on Tables IX and X. Tables XI, XII, XIII compare the two types of formulations, before and after storage, using the three methods.

The corresponding analysis of variance are presented on tables XIV and XV. The keys for tables VII, VIII, IX, X, XI, XII and XIII are given as follows:

TABLE V

DISSOLUTION OF SUGAR COATED TABLETS

UNSTRESSED AND UNDER STORAGE AT 37°C 75% R.H.

(means of % dissolved & standard deviaton)

Method	USP		FDA		UPJ	
Time-points	15	30	15	30	15	30
	Means SD		Means SD		Means SD	
Advil O	86 ± 5.0	93 ± 5.0	79 ± 3.5*	86 ± 10.0	27 ± 5.0*	69 ± 10.0*
Advil 4W	75 ± 4.0	89 ± 3.0	3 ± 1.0[a]	4 ± 1.0	4 ± 1.0[a]	4 ± 0.5[a]
Unipro O	96 ± 5.0	97 ± 5.0	81 ± 7.0	89 ± 5.0	49 ± 7.0	54 ± 4.7
Unipro 4W	89 ± 2.6	96 ± 1.7	89 ± 9.0	92 ± 2.6	51 ± 6.0	95 ± 5.0
Trendar O	85 ± 2.5	88 ± 1.0	20 ± 9.0	46 ± 4.0	31 ± 10.0[x]	62 ± 13.0[x]
Trendar 4W	93 ± 8.0	101 ± 2.0	1 ± 1.1	40 ± 3.7	3 ± 1.8	2 ± 0.8

* 1 tablet of the six tested did not disintegrate

[a] very small peaks - no disintegration at all

[x] large difference and high standard deviation

Advil, Unipro: six replicates

Trendar: four replicates

O: unstressed

4W: stress storage during four weeks

TABLE VI

DISSOLUTION OF FILM COATED TABLETS

UNSTRESSED AND UNDER STORAGE AT 37°C 75% R.H.

(means of % dissolved & standard deviation)

	USP		FDA		UPJ	
	Means SD		Means SD		Means SD	
	15	30	15	30	15	30
Nuprin 0	94 ± 3.0	97 ± 1.6	94 ± 1.3	96 ± 3.5	86 ± 8.9	92 ± 1.4
Nuprin 4W	103 ± 1.7	104 ± 1.0	76 ± 7.0	89 ± 3.0	53 ± 14	90 ± 3.0
Midol 0	90 ± 1.8	91 ± 3.0	77 ± 2.0	79 ± 2.3	55 ± 3.0	59 ± 0.5
Midol 4W	93 ± 7.0	91 ± 8.0	83 ± 2.0	95 ± 1.0	75 ± 1.1	83 ± 2.3
Haltran 0	68 ± 2.1	83 ± 3.3	77 ± 3.7	88 ± 3.5	51 ± 5.0	82 ± 8.0
Haltran 4W	71 ± 14	91 ± 3.4	83 ± 5.0	93 ± 5.0	38 ± 1.0	59 ± 1.7
Medipren 0	90 ± 2.0	93 ± 3.5	92 ± 1.1	94 ± 1.1	87 ± 1.0	89 ± 0.3
Medipren 4W	97 ± 0.1	99 ± 1.3	93 ± 3.6	96 ± 2.7	92 ± 4.0	95 ± 4.0
Ibuprin 0	83 ± 2.0	97 ± 3.6	75 ± 7.0	85 ± 1.1	25 ± 5.0	77 ± 2.3
Ibuprin 4W	88 ± 5.0	92 ± 2.5	60 ± 6.0	85 ± 4.0	74 ± 5.0	82 ± 1.7

0: unstressed

4W: stress storage during four weeks

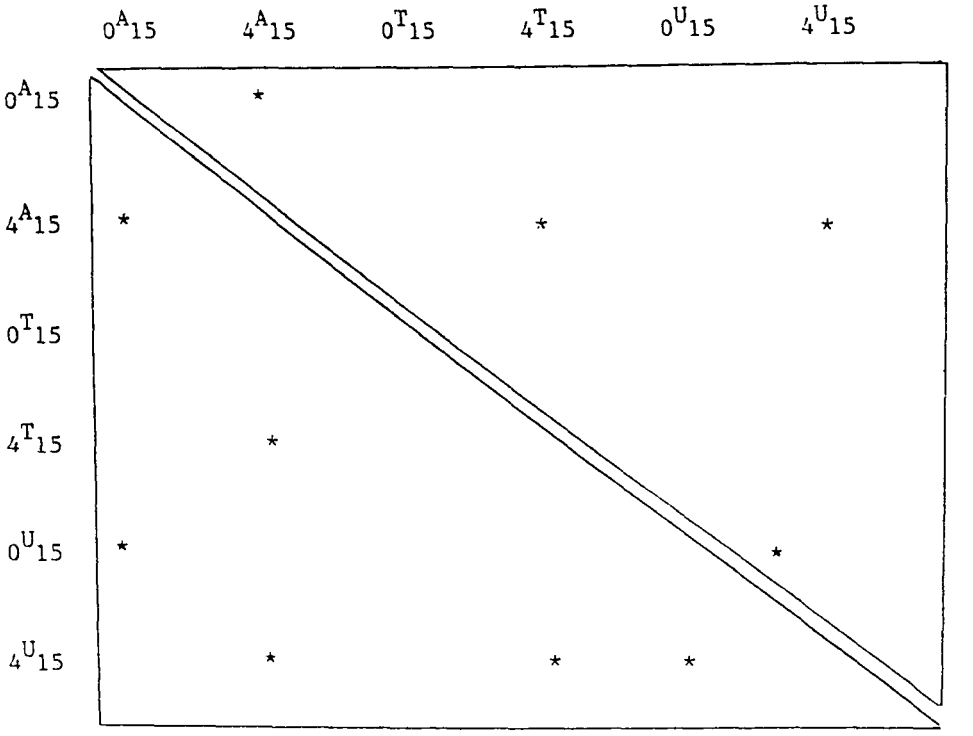
In tables VII, VIII, IX and X each triangle corresponds to a method of dissolution, and compares the means of percentage dissolved between brands before and after storage.

The upper triangle in all cases corresponds to the data from the official present USP test. The lower triangle in

Table VII (a)

Student's T test results for sugar coated tablets

comparison of USP and FDA method



Key Each triangle corresponds to a method of dissolution, and compares means of percentage dissolved between brands before and after storage.
The statistical t was calculated between means of percentage dissolved and compared to the theoretical t at a 95% confidence level.
A "star" indicates a significant difference between the corresponding means.

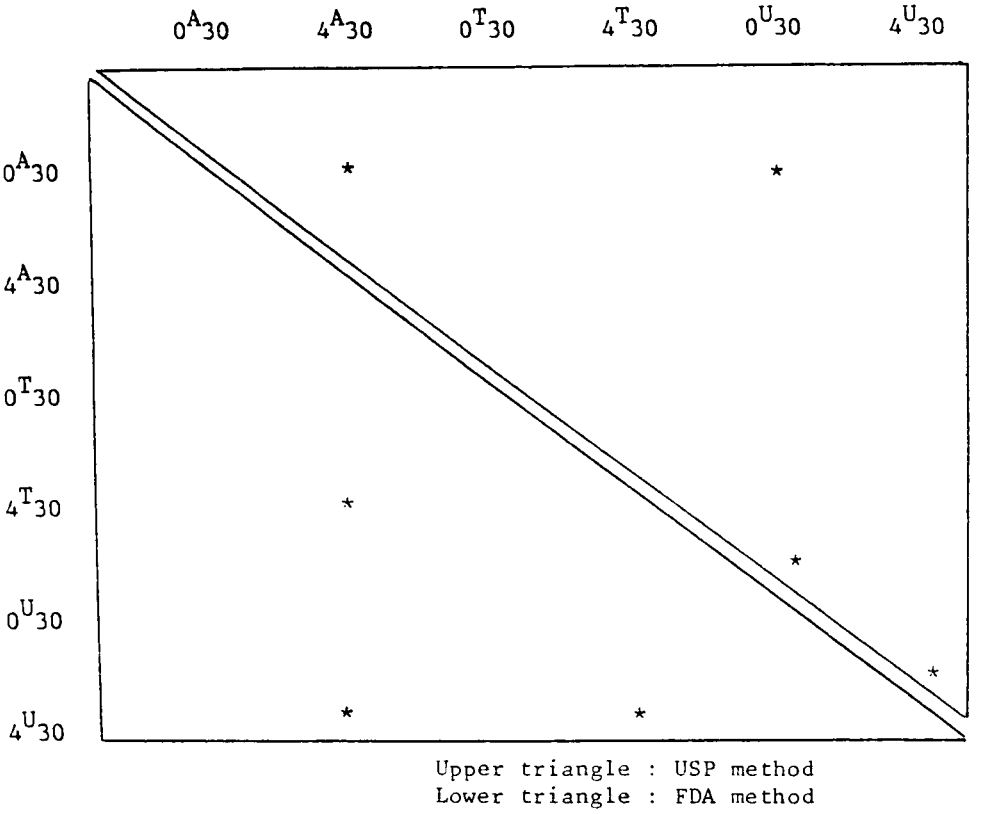
Notation (Nu) Nuprin, (Mi) Midol, (H) Haltran, (Me) Medipren, (I) Ibuprin, (A) Advil, (T) Trendar, (U) Unipro
0 - No stress storage
4 = four weeks of storage under 37°C and 75% Relative Humidity
15 = 15 minutes time point
30 = 30 minutes time point

Upper triangle: USP method
Lower triangle: FDA method

Table VII (b)

Student's T test results for sugar coated tablets

comparison of USP and FDA method



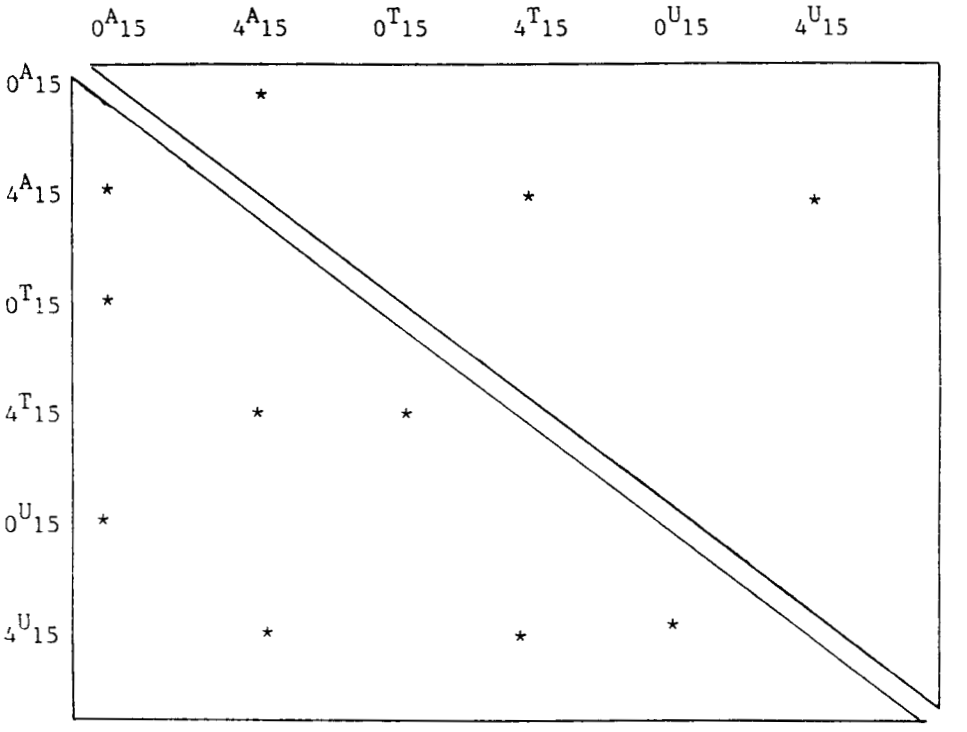
tables VII and IX represents data from the FDA method. In tables VIII and X the data in the lower triangle is from the new proposed method.

The statistical t was calculated between means of percentage dissolved and compared to the theoretical t at a 95%

Table VIII (a)

Student's T test results for sugar coated tablets

comparison of USP and UPJ method



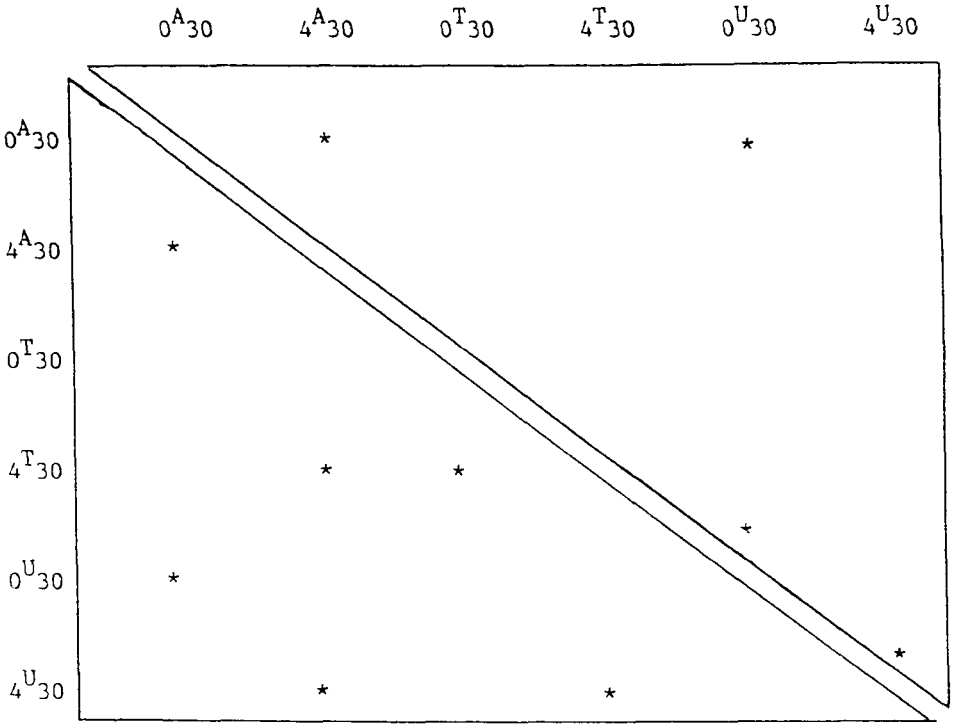
confidence level. A star (*) indicates a significant difference between the corresponding means.

Each of the three tables (XI, XII, XIII) corresponds to a single method. All tables are divided into two: (a) compares the 15 minute time points (b) compares the 30 minute time points. For example in Table VIIa:

Table VIII (b)

Student's T test results for sugar coated tablets

comparison of USP and UPJ method



Horizontal line: $0^{A}15$: Results obtained from the dissolution of Advil (no stress storage) at 15 minutes showed a significant difference with $4^{A}15$ (Advil, 4 weeks of storage) at 15 minutes, but no difference with any other brands when using the USP method (upper triangle).

Table IX (a)
Student's T test results for film coated tablets comparison of USP and FDA method

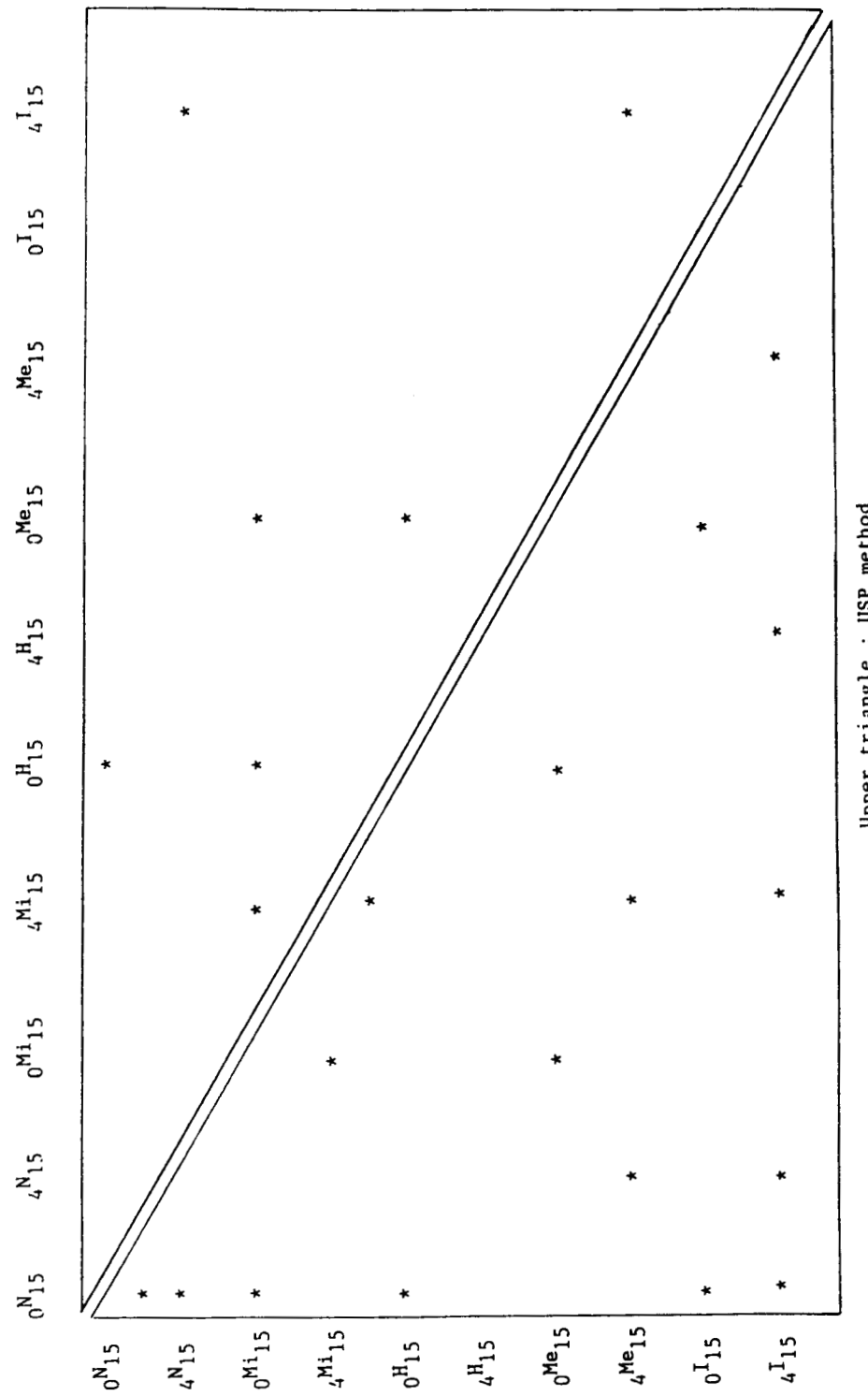


Table IX (b)

Student's T test results for film coated tablets comparison of USP and FDA method

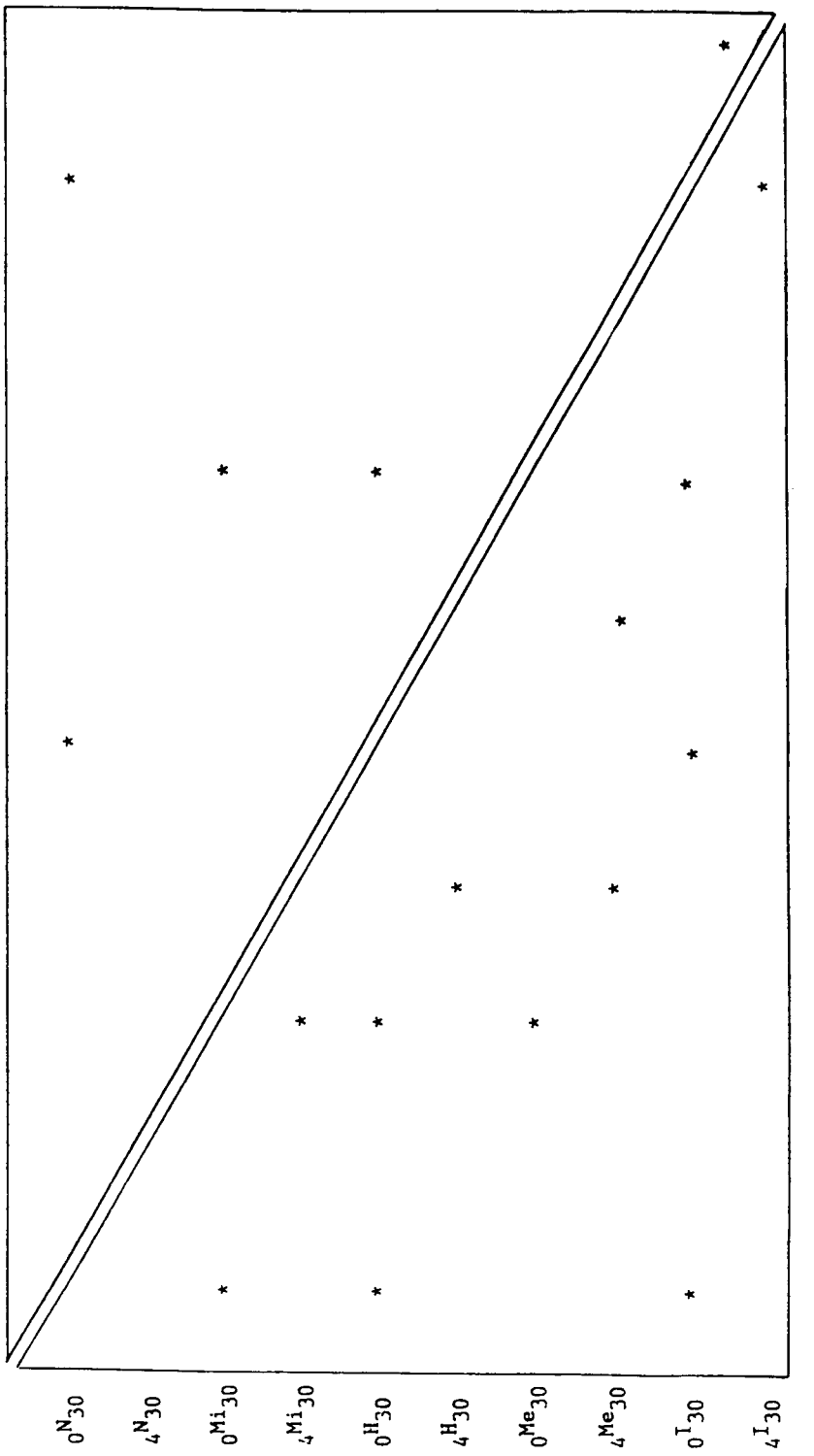
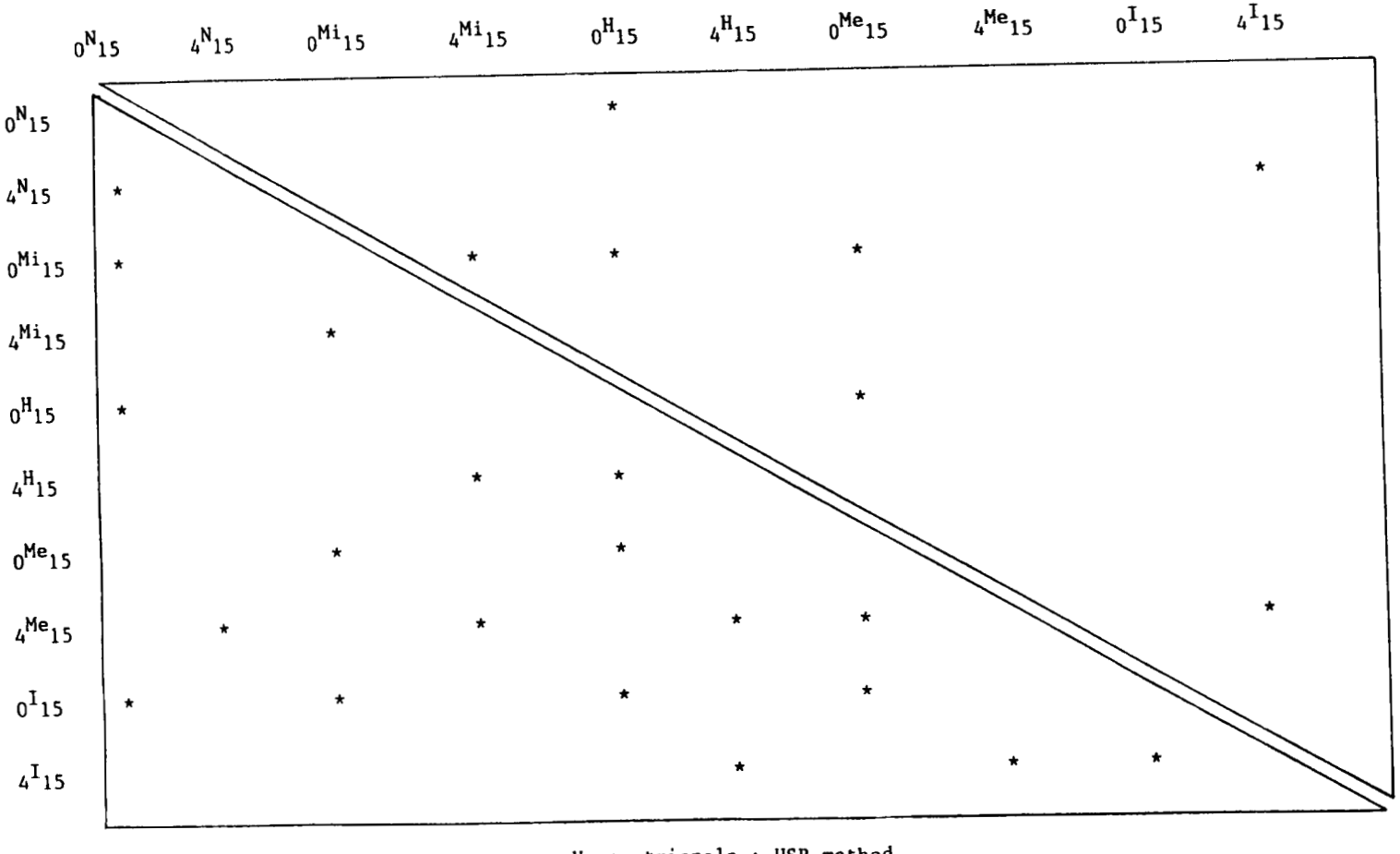


Table X (a)

Student's T test results for film coated tablets comparison of USP and UPJ method



Upper triangle : USP method
Lower triangle : UPJ method

Table X (b)
Student's T test results for film coated tablets comparison of USP and UPJ method

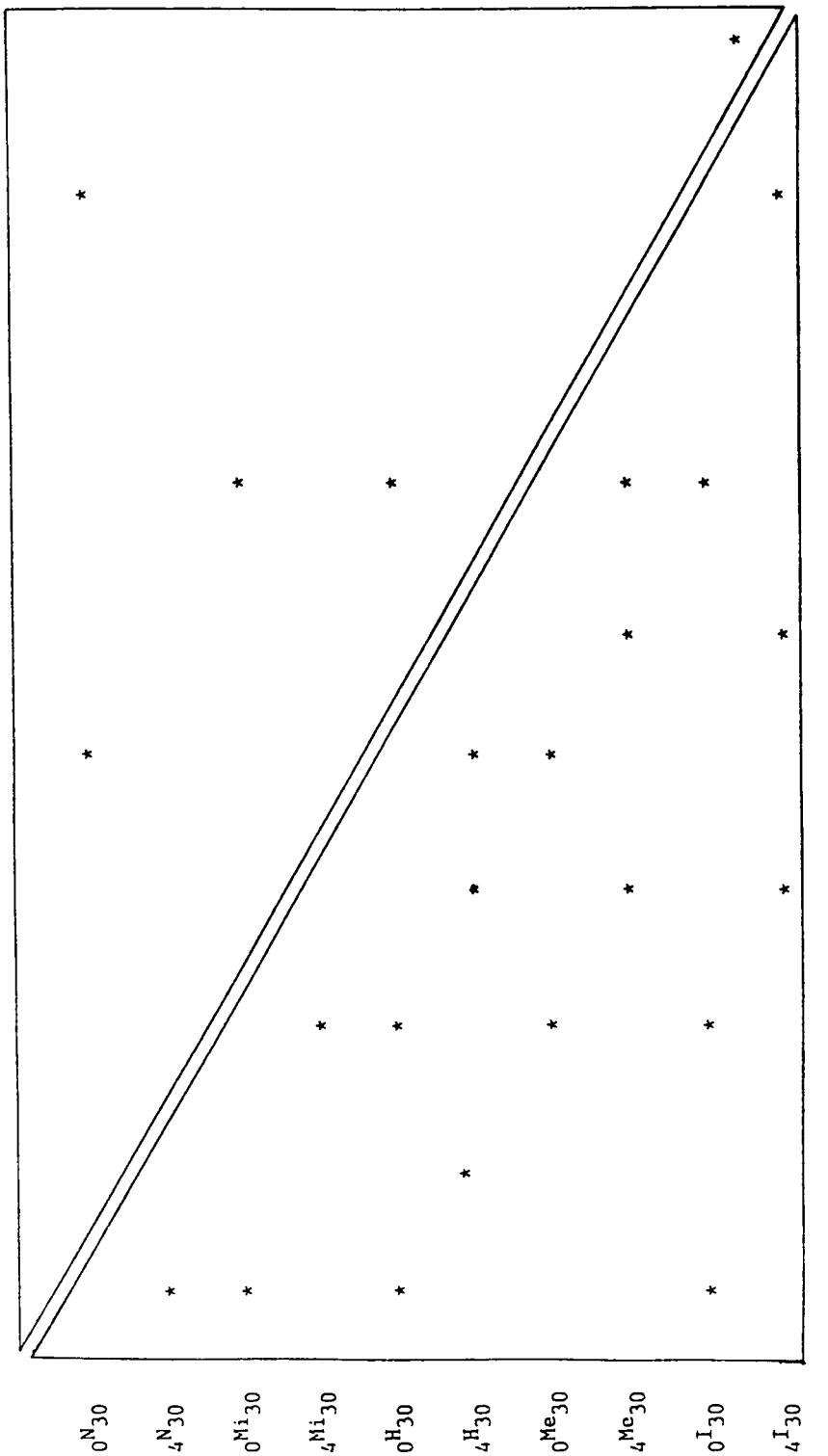


Table XI (a)

Student's T test results comparison of sugar and film coated brands

USP method

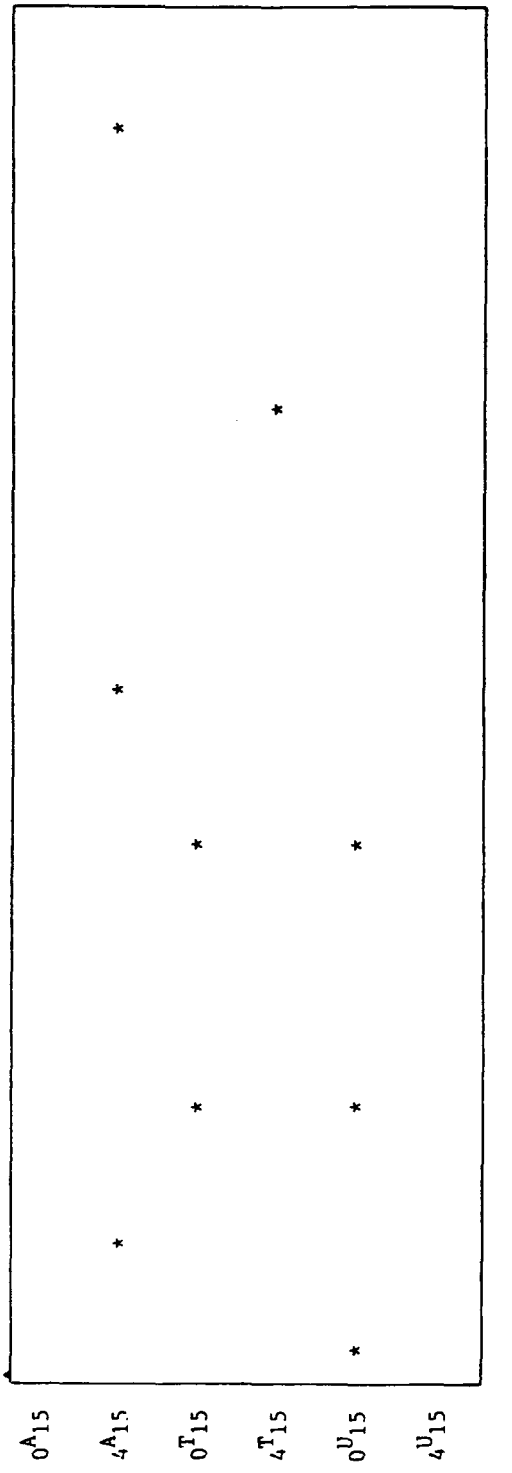


Table XI (b)
Student's T test results comparison of sugar and film coated brands
USP method

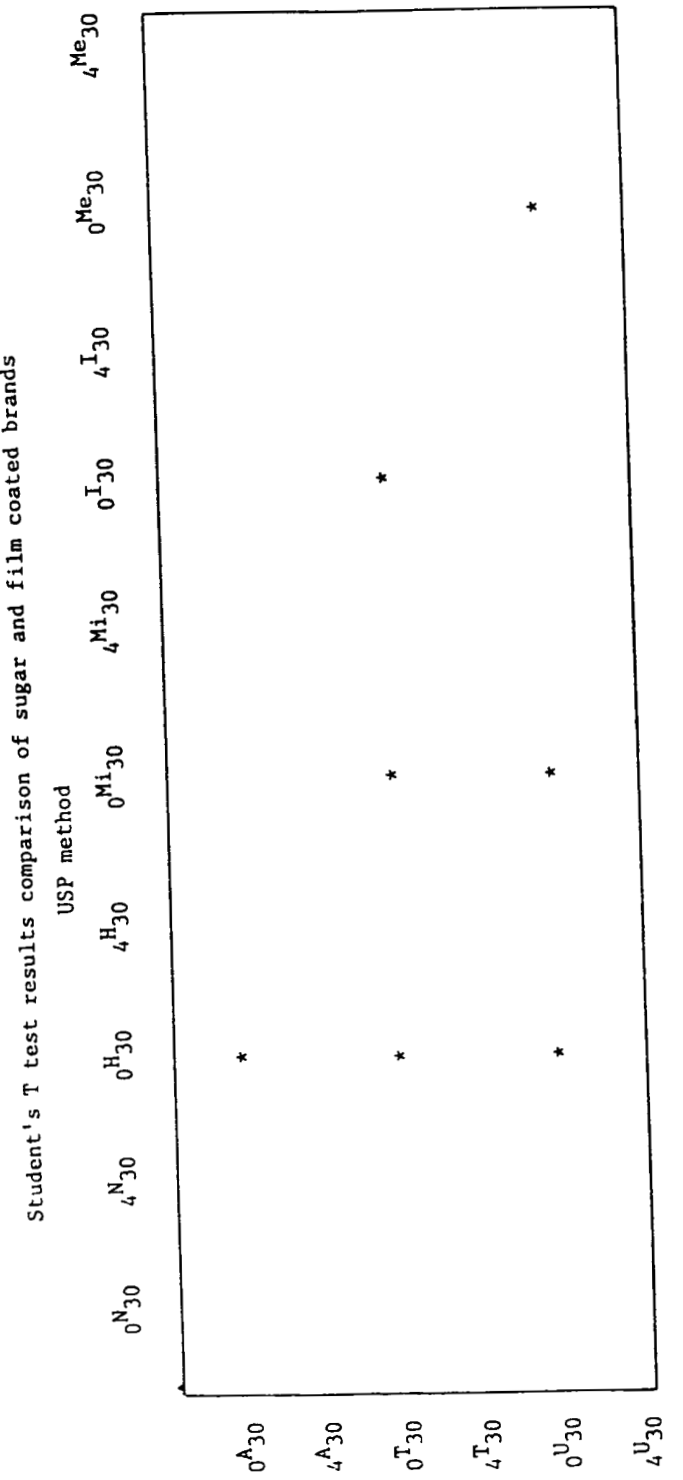


Table XII (a)
Student's T test results comparison of sugar and film coated brands
FDA method

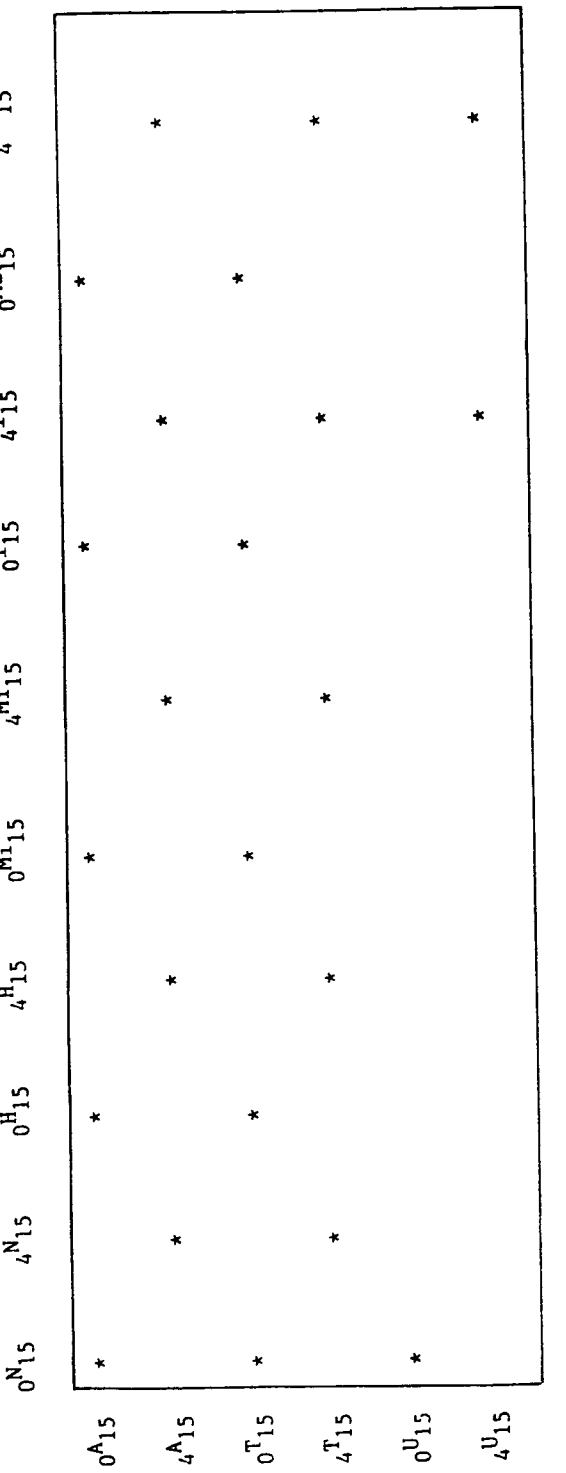


Table XII (b)

Student's T test results comparison of sugar and film coated brands

FDA method

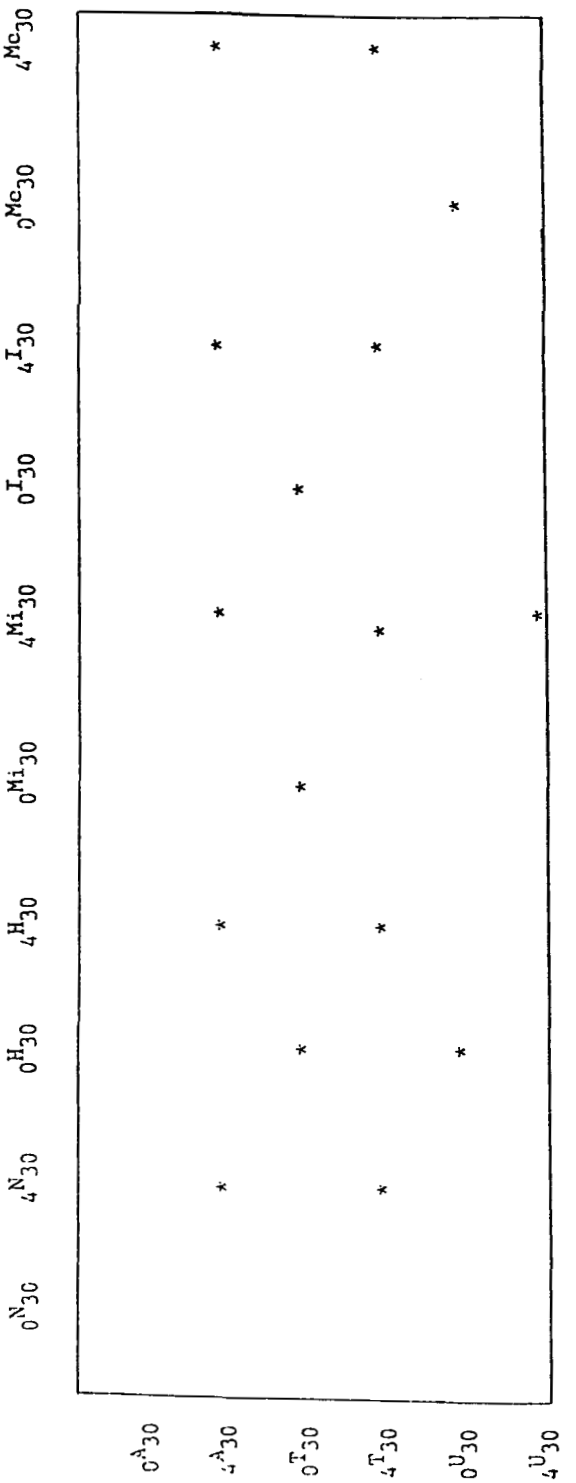


Table XIII (a)

Student's T test results comparison of sugar and film coated brands

UPJ method

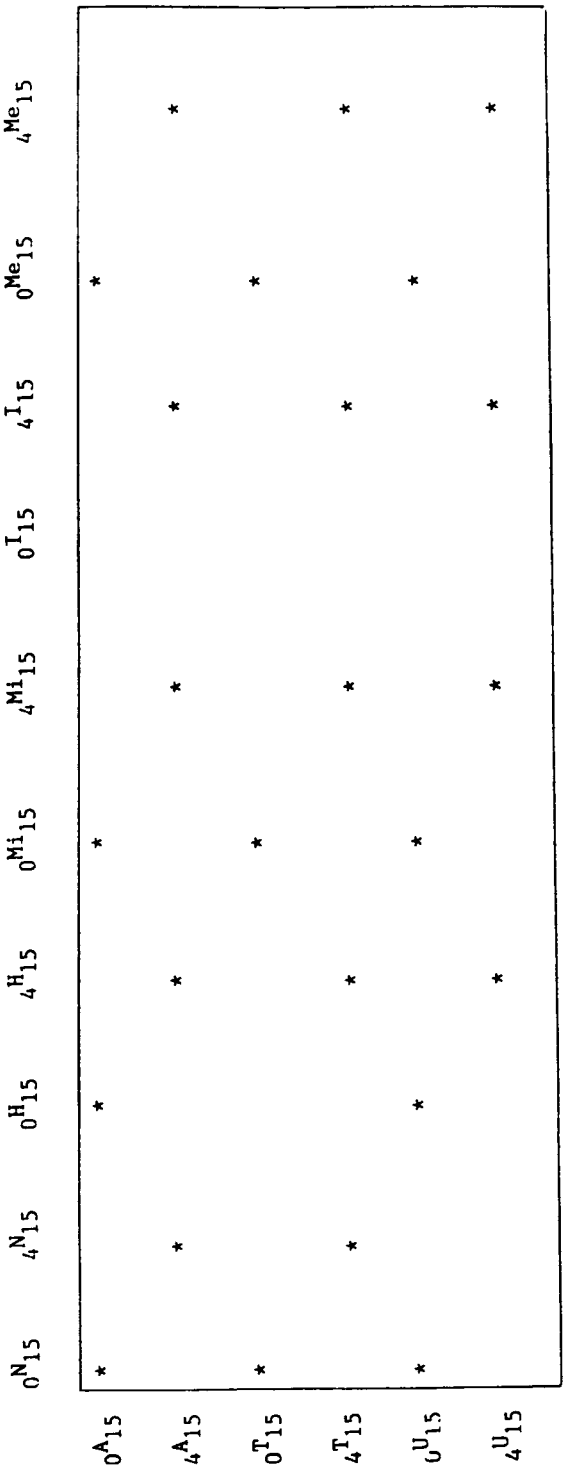


Table XIII (b)

Student's T test results comparison of sugar and film coated brands

UPJ method

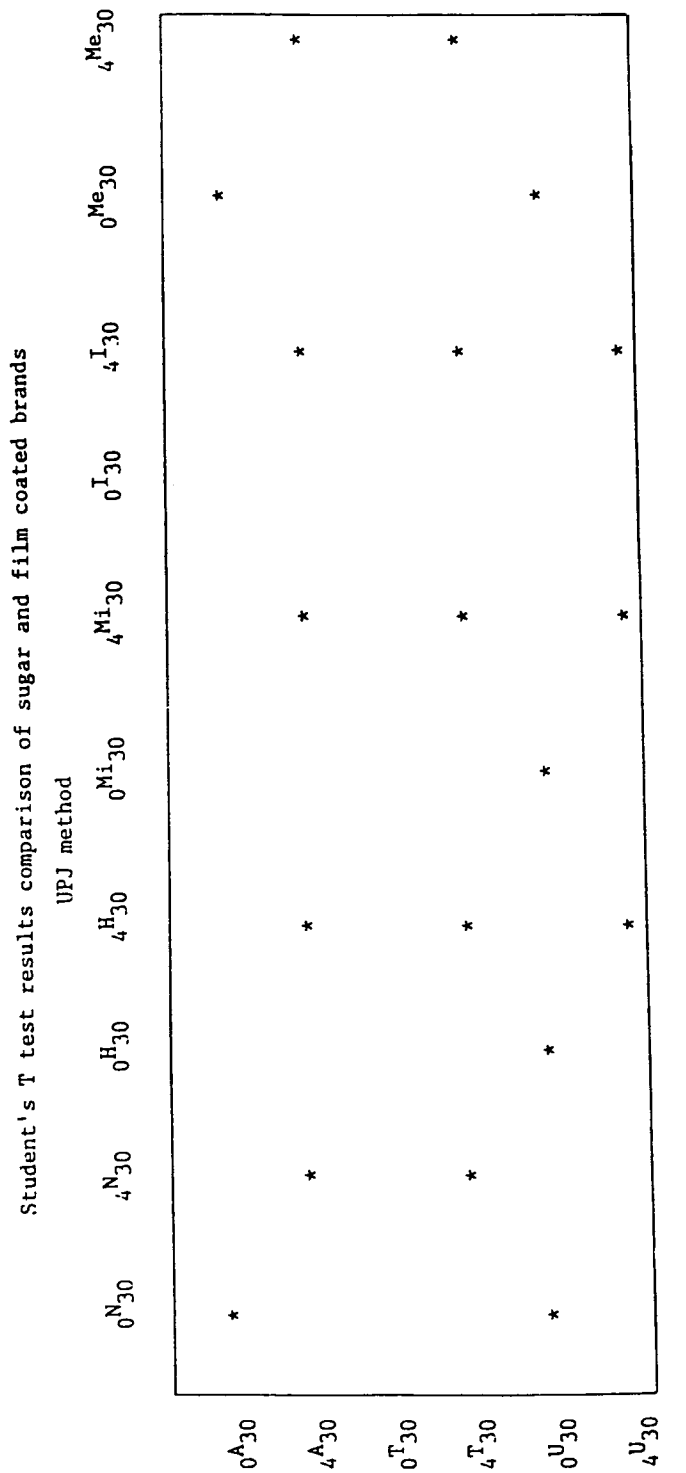


Table XIV

Analysis of Variance (ANOVA)
Effect of Methodologies
Sugar coated tablets

Duncan's multiple range test on variable: % Dissolved
alpha = 0.05, DF = 24
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
USP Method			
time 15	A	87.6	3.6
time 30	B	94.7	3.6
No storage	A	92.3	3.6
Storage	A	90.1	3.6
Advil	A	89.3	4.7
Trendar	A	90.9	4.7
Unipro	A	93.5	4.7
FDA Method			
time 15	A	40.0	12.7
time 30	B	64.2	12.7
No storage	A	65.5	12.7
Storage	B	38.7	12.7
Advil	A	28.8	16.3
Trendar	A	41.0	16.3
Unipro	B	86.1	16.3
UPJ Method			
time 15	A	28.3	4.9
time 30	B	50.0	4.9
No storage	A	51.1	4.9
Storage	B	27.2	4.9
Advil	A	24.5	6.4
Trendar	A	27.4	6.4
Unipro	B	65.6	6.4

Table XV

Analysis of Variance (ANOVA)
Effect of Methodologies
film coated tablets

Duncan's multiple range test on variable: % Dissolved
alpha = 0.05, DF = 40
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
USP Method			
time 15	A	87.5	4.2
time 30	B	94.8	4.2
No storage	A	89.9	4.2
Storage	A	93.1	4.2
Haltran	A	80.7	7.3
Ibuprin	B	89.8	7.3
Midol	B	91.4	7.3
Medipren	B C	94.6	7.3
Nuprin	C	99.3	7.3
FDA Method			
time 15	A	80.8	2.0
time 30	B	90.1	2.0
No storage	A	85.7	2.0
Storage	A	85.1	2.0
Ibuprin	A	76.2	3.6
Midol	B	83.2	3.6
Haltran	B	85.1	3.6
Nuprin	C	88.8	3.6
Medipren	D	93.7	3.6
UPJ Method			
time 15	A	63.5	2.6
time 30	B	81.0	2.6
No storage	A	70.1	2.6
Storage	B	74.4	2.6
Haltran	A	57.6	4.5
Ibuprin	B	64.5	4.5
Midol	B	67.7	4.5
Nuprin	C	80.8	4.5
Medipren	D	90.7	4.5

Vertical line: $0^{A}15$ results showed a significant difference with $4^{A}15$ and $0^{U}15$ (Unipro, no stress storage) at 15 minutes when using the FDA method (lower triangle).

Apart from Advil and Trendar there were no significant mean differences, even after storage and between brands, when using the USP method.

The effect of storage was significant on Midol and the sugar coated tablets as measured by the FDA dissolution test.

The new proposed method detected a difference in dissolution after moderate stress condition for all brands tested.

The results indicated that when the surface shear upon the tablets is increased the discriminating power is decreased (USP).

Figure 3,4,5,6 show the percentage of drug dissolved from the various brand as observed using the three different tests, before and after aging. The key for the figures is represented by the following: A. Advil, B. Trendar, C. Unipro, D. Nuprin, E. Midol, F. Ibuprin, G. Haltran, H. Medipren.

The dissolution methods are significantly different in all cases. The USP test did not detect any difference in dissolution before and after storage for any brands. However, both the FDA and the new method did detect statistically significant differences for some brands. It is notable that all

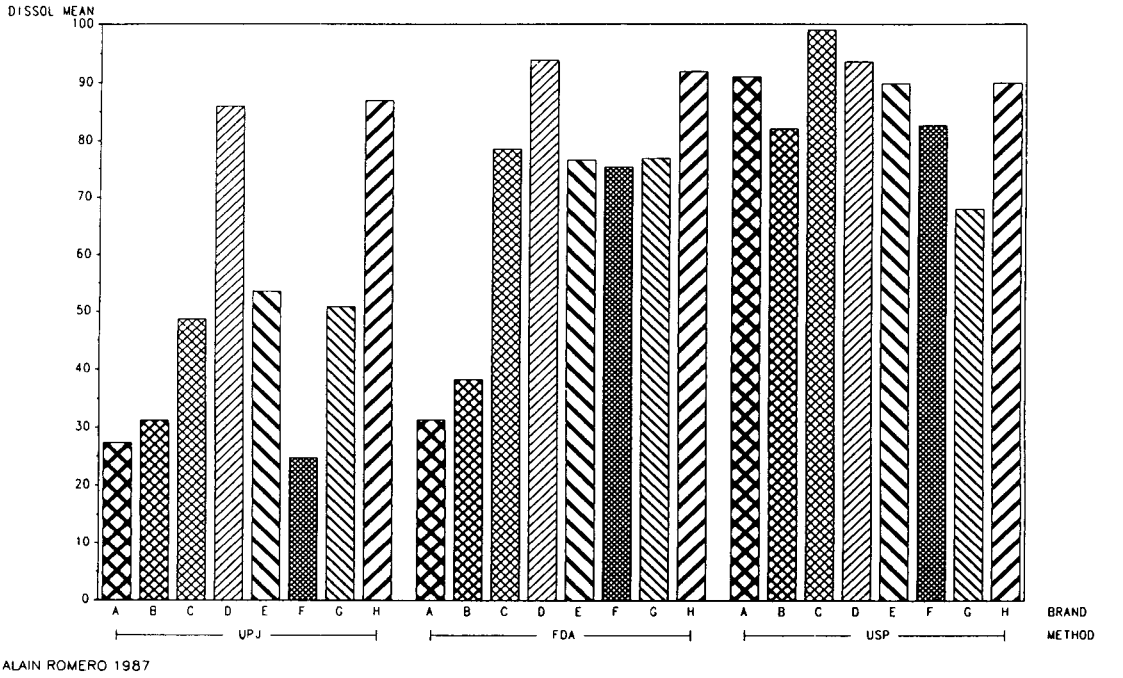


FIGURE 3: EFFECT OF TEST METHOD AND BRAND
TIME=15 MIN; NO-STORAGE

brands complied with the current USP specifications before storage and it has been well established that different dissolution methods can yield to substantially different results (5).

Effect of Formulations

Since the number of replicates was small, the purpose of this paper was not to make a detailed and precise comparison of all brands. Rather the intention was to obtain a general picture of the extent of the variability between a number of

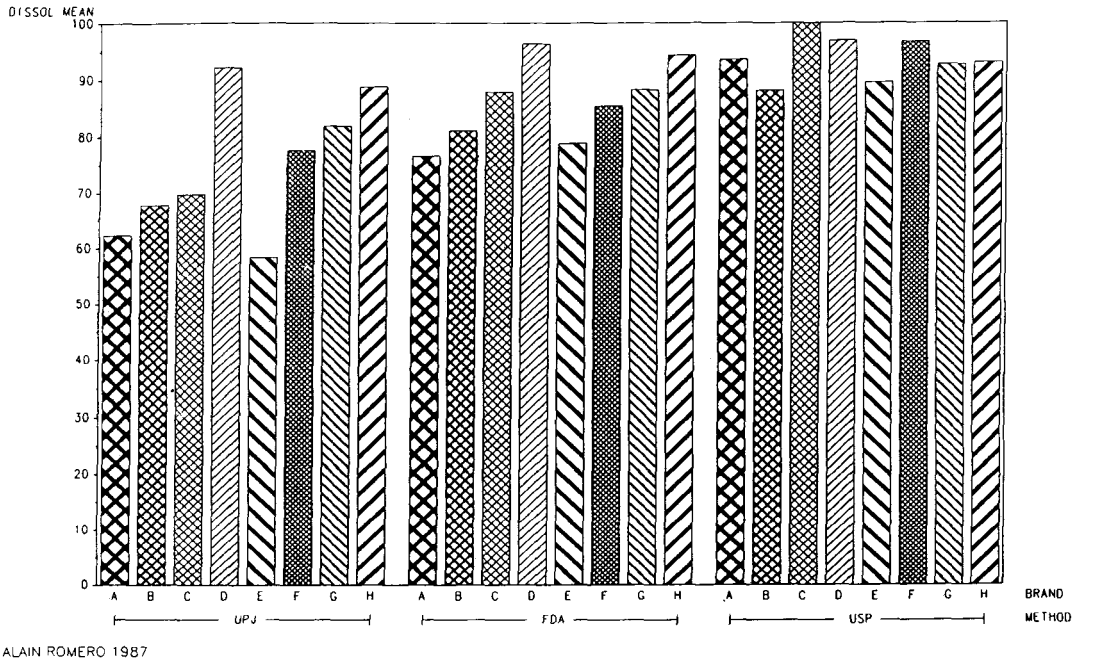


FIGURE 4: EFFECT OF TEST METHOD AND BRAND
TIME=30 MIN; NO-STORAGE

brands. It is appreciated that it would be invalid to induce a general conclusion about the dissolution of any one individual brand of ibuprofen tablets from the present limited study. Before any such conclusion could be reached it would be necessary to test more tablets obtained from a variety of different sources. It is conceivable that some of the samples may be atypical and not representative of the dissolution normally observed.

Apart from Haltran which dissolved slowly the dissolution of all film coated tablets was quite similar.

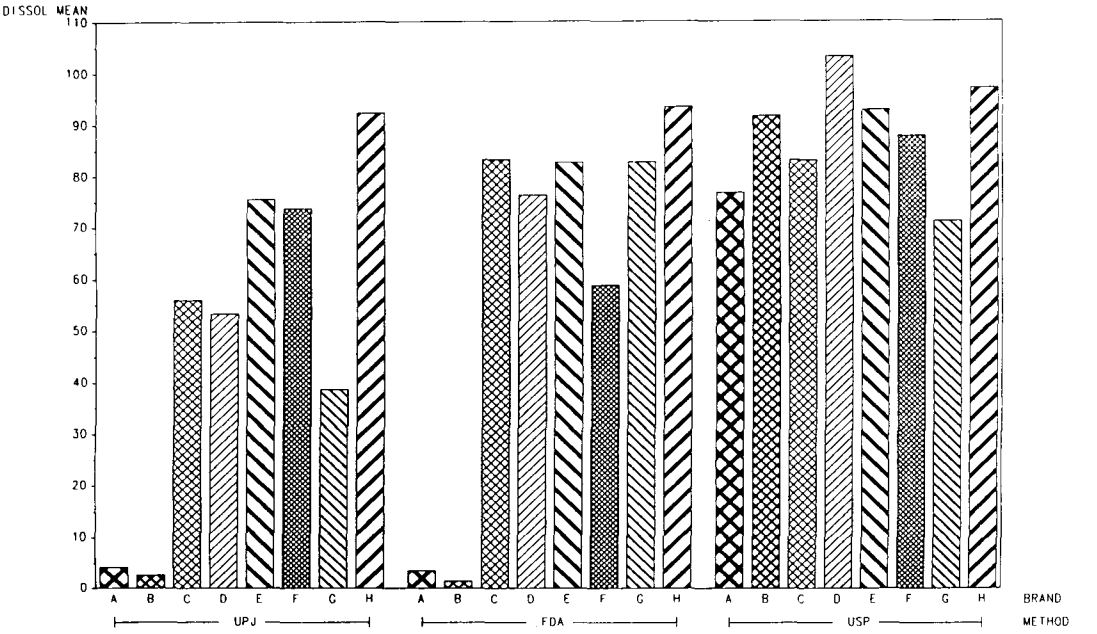


FIGURE 5: EFFECT OF TEST METHOD AND BRAND
TIME=15 MIN; STORAGE

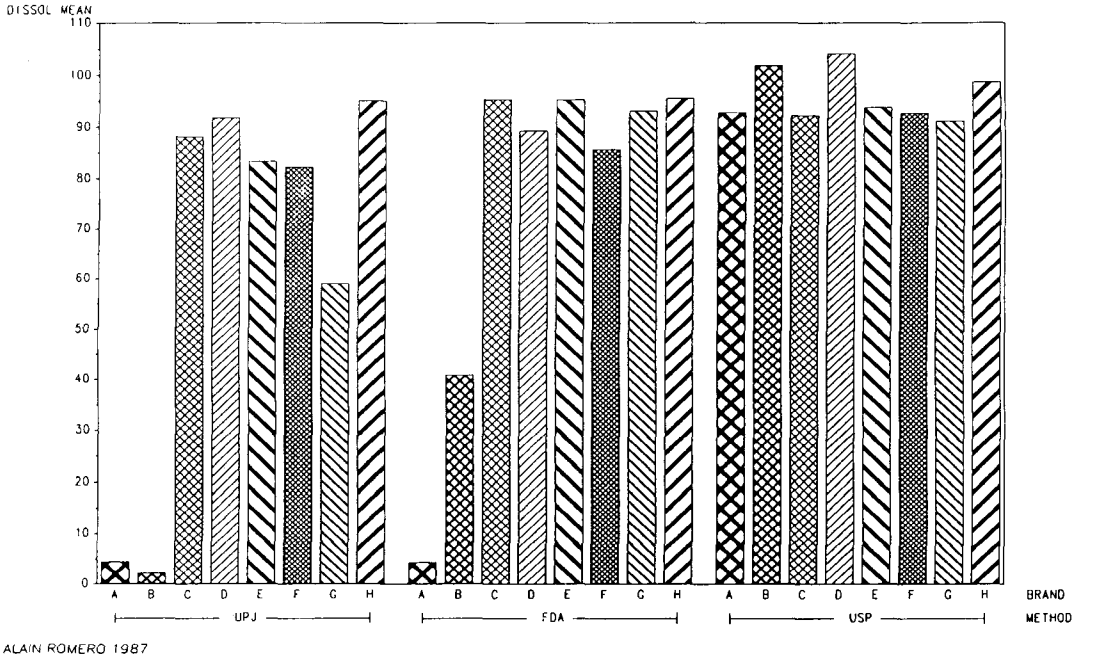


FIGURE 6: EFFECT OF TEST METHOD AND BRAND
TIME=30 MIN; STORAGE

Table XVI

Analysis of Variance
Effect of Formulation
Before Storage

Duncan's multiple range test on variable: % Dissolved
alpha = 0.05
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
Sugar coated brands (df = 36)			
time 15	A	58.6	6.6
time 30	B	80.7	6.6
Advil	A	63.6	8.5
Trendar	A	64.7	8.5
Unipro	B	80.6	8.5
Film coated tablets (df = 60)			
time 15	A	76.0	2.7
time 30	B	87.4	2.7
Ibuprin	A	73.7	4.7
Midol	A	74.4	4.7
Haltran	A	76.4	4.7
Midol	B	90.8	4.7
Nuprin	B	93.1	4.7

Table XVI and XVII show the analysis for the different formulations.

The dissolution of sugar coated formulations presented several problems specifically regarding aging. Those formulations even when they have been submitted to moderate stress conditions showed a general tendency to dissolve less rapidly then the film coated. Also the inter tablet variability for the sugar coated tablets appeared to be greater, and one Advil tablet did not dissolve at all.

Table XVII

Analysis of Variance (ANOVA)
Effect of Formulation
After Storage
Duncan's multiple range test on variable: % Dissolved
alpha = 0.05
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
Sugar coated brands (df = 36)			
time 15	A	58.5	6.6
time 30	B		6.6
Advil	A	28.0	8.5
Trendar	A	29.5	8.5
Unipro	B	82.9	8.5
Film coated brands (df = 60)			
time 15	A	78.5	2.7
time 30	B	89.4	2.7
Haltran	A	72.5	3.98
Ibuprin	A	80.0	3.98
Nuprin	B	86.2	
Midol	C	87.1	3.98
Medipren	D	95.2	3.98

Effect of Storage

Recently there has been an increase of interest in the physical aging of compressed tablets (6), (7) and special attention must be given to coated tablets (2). The present work shows that aging studies can be of value in assuring the quality of tablets throughout the shelflife.

The SAS analysis presented in Tables XVIII and XIX indicated a significant but small decrease in the dissolution of film coated tablets. The sugar coated brands showed significant

Table XVIII

Analysis of Variance
Effect of Storage
Sugar coated tablet

Duncan's multiple range test on variable: % Dissolved
alpha = 0.05, DF = 35
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
time 15			
No storage	A	58.6	7.6
Storage	B	43.8	7.6
time 30			
No storage	A	80.7	5.5
Storage	B	58.9	5.5

Table XIX

Analysis of Variance
Effect of Storage
Film coated tablets

Duncan's multiple range test on variable: % Dissolved
alpha = 0.05, DF = 60
Means with the same letter are not significantly different

Independent variable	Duncan Grouping	Mean	Criteria Range
time 15			
Storage	A	78.6	3.2
No storage	A	76.0	3.2
time 30			
Storage	A	89.9	1.4
Storage	B	87.4	1.4

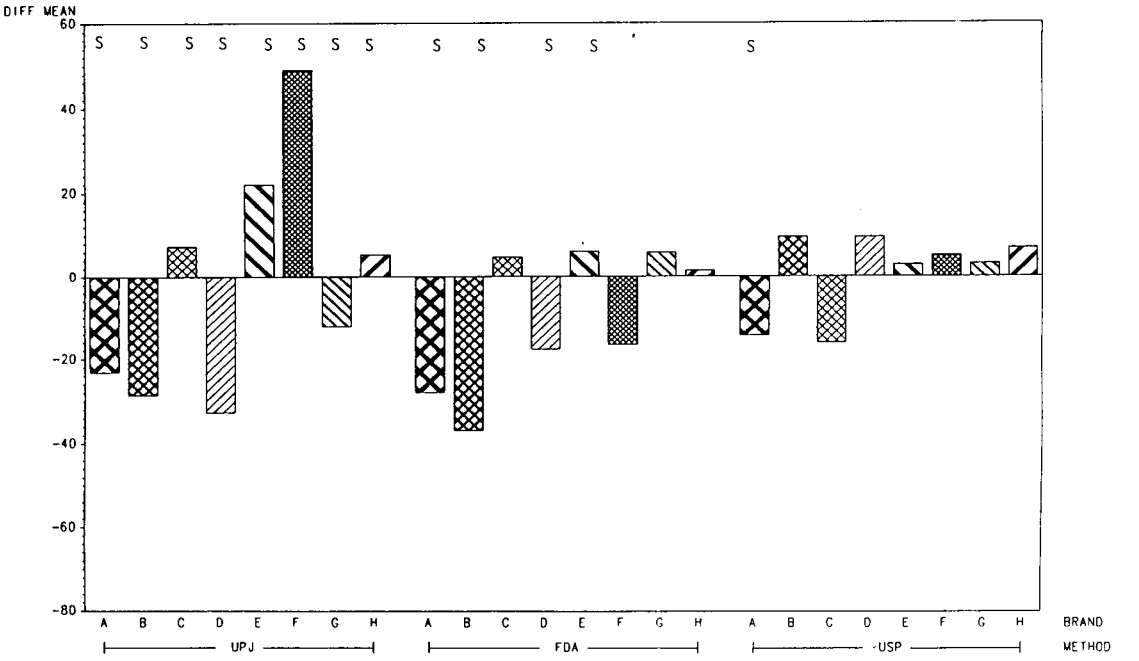


FIGURE 7: EFFECT OF MODERATE STRESS STORAGE ON DISSOLUTION
SAMPLING TIME = 15 MIN

changes in dissolution after storage, especially when FDA and UPJ testing methods were used.

Figures 7 and 8 illustrate the effect of storage on the dissolution of ibuprofen tablets. The Δ % is the difference between the means of percentage dissolved after storage and before storage. The S on the top of the histograms represents significant differences between means. (The key for these figures, is the same as in figures 3, 4, 5, 6).

It is understood that all approvable ANDA's for ibuprofen tablets must contain an acceptable bioequivalence study

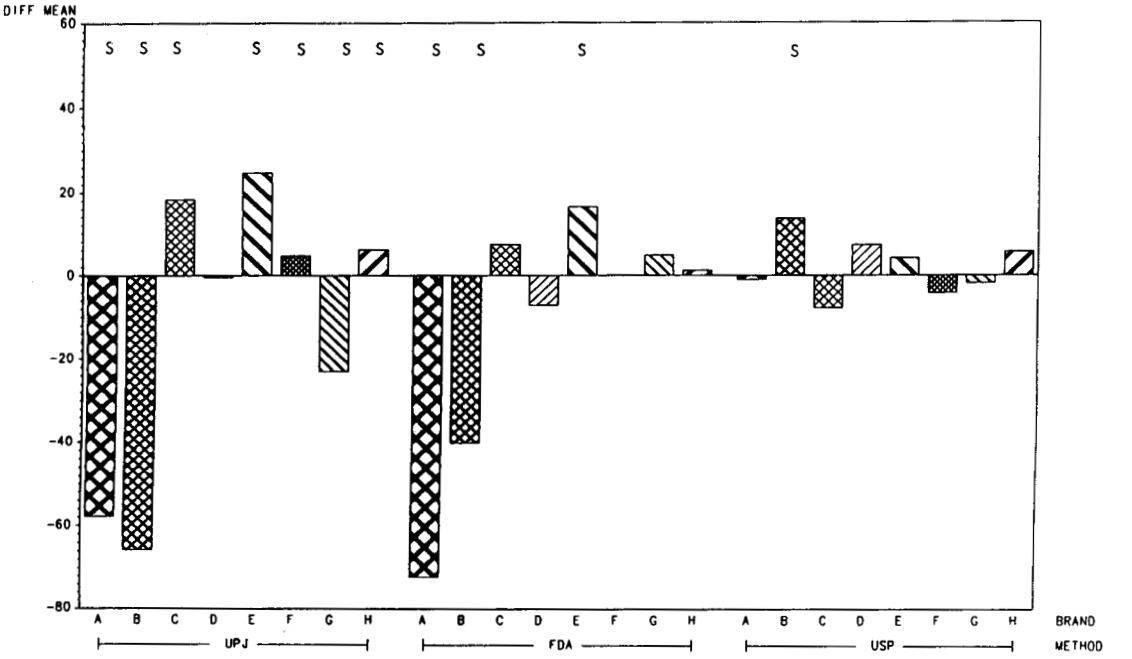


FIGURE 8: EFFECT OF MODERATE STRESS STORAGE ON DISSOLUTION
SAMPLING TIME = 30 MIN

demonstrating that the test product exhibits pharmacokinetic parameters (notably AUC, C_{max} and T_{max}) which are within 20% of the reference product. However, such a test is normally only performed on samples derived from one batch of tablets. Thus if batch to batch variability is substantial, it is indeed possible for bioinequivalence to exist between marketed products. Dissolution tests can therefore perform a valuable function as quality control tools which can hopefully prove of value in reducing batch to batch variability.

Of the three dissolution test methods examined in this study the present official USP method is the least discriminating. This is probably due to the relatively high stirring rate used. The FDA and the UPJ tests are more discriminating and thus there may be merit to modifying the current USP dissolution test for ibuprofen tablets in order to detect formulation differences.

The effect of moderate stress aging on the dissolution of the sugar coated tablets is a cause of some concern. The stress conditions used in this study can not be termed entirely unrealistic and it is by no means inconceivable that these or similar conditions may well apply on the storage of ibuprofen tablets in a consumer's bathroom. Therefore the fact that some sugar coated tablets showed minimal dissolution after such stress could well be construed as indicating the likelihood of clinical failure. This aspect of the present study could well be subjected to more detailed scrutiny.

In conclusion, the present study although not comprehensive in scope, indicates the possibility of problems with some sugar coated ibuprofen tablets.

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