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MEDICAMENT RELEASE FROM SUPPOSITORY BASES: III. IBUPROFEN - PHYSICOCHEMICAL CHARACTERISTICS AND BIOAVAILABILITY IN RABBITS

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ABSTRACT

This investigation was designed to determine the in vitro release of ibuprofen from suppository bases, and their in vivo bioavailability in rabbits. Suppositories containing ibuprofen were made by the fusion method with Theobroma oil, Witepsol H-15 and PEG 1540. In order to produce an exact dosage form, the displacement value was determined. The suppository hardness was determined by utilizing the SBT (Erweka) apparatus and it was found that the Witepsol H-15 allows the formation of brittler suppositories. The release rates were determined with the USP

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dissolution apparatus and with cellophane membrane and it was found to be: PEG 1540 > Witepsol H-15 > Theobroma oil. The bioavailability of Indomethacin after rectal administration was: PEG 1540 > Witepsol H-15 > Theobroma oil which correlates with the in vitro release.

INTRODUCTION

Ibuprofen, 2-(4-isobutylphenyl) propionic acid is a nonsteroidal agent with anti-inflammatory, analgesic and antipyretic properties [1-3]. It is being used in the treatment of rheumatoid arthritis[4-7], osteorthritis[7,8], acute gouty arthritis[9], and mild to moderate degrees of pain[10]. Recent studies indicate its use in dysmenorrhea[11,12].

Though it has been suggested that it is a relatively safe drug, like all other anti-inflammatory agents, it produces gastrointestinal side effects, ulceration and bleeding being the most common[13,14]. This limits its value in patients who are prone to gastric irritation, peptic ulcer, etc. Rectal therapy in such clinical situations could be of great value. Hence, the purpose of this study was to formulate ibuprofen suppositories using three bases: theobroma oil, PEG 1540, and Witepsol H-15, and to evaluate their physicochemical properties and bioavailability in rabbits.

EXPERIMENT

Material and Reagents

Ibuprofen[1], PEG 1540[2], Witepsol H-15[3], theobroma oil[4], ethanol[4], buffered solution pH=8[4], acetic acid[4], methanol[5], and acetonitrile[5].

Acetic acid, acetonitrile and methanol were of chromatographic grade, while the other chemicals were of analytical grade.

Apparatus

U.S.P. tablet dissolution apparatus[6], U.S.P. tablet disintegration apparatus[7], fracture point testing apparatus[7], suppository melting tester[7], Dynac centrifuge[8], recirculating thermostat[7], and spectrophotometer[9]. The high-performance liquid chromatograph[5] consisted of a constant flow pump[5], a universal injector[5], C-18 reversed phase column in series[5], and a U.V. detector[5] set at 254 nm.

In Vitro Studies

All suppositories were prepared by a fusion method using three bases: theobroma oil, PEG 1540, and Witepsol H-15. The displacement value of ibuprofen in these bases was calculated, as previously described[15,16].

After calculating the displacement value, the weight of each base was determined. The base was carefully melted on a steam bath taking precautions not to overheat. The drug was incorporated and the resultant mass allowed to cool. When the mass began to solidify, it was poured into molds and allowed to congeal. The excess amount was trimmed away with a sharp blade. After initial cooling, the suppositories were removed from the molds and stored in a well closed container.

Weight Determination

Twenty suppositories from each base were weight individually. The average weight and the percentage variation was calculated. Though the U.S.P. does not specify the weight variation for rectal suppositories a ± 5.0% deviation is quite reasonable.

Content Uniformity

Ten randomly selected suppositories from each base were assayed individually. A preweighed suppository was placed in a 100 ml volumetric flask containing 20 ml of phosphate buffer solution (pH=8). The suppository was melted with gentle heat on a water bath. The volume was adjusted to 100 ml with phosphate buffer. The flask was agitated on a reciprocating shaker for 4 hours; 10 ml of this solution was diluted to 50 ml, centrifuged and filtered. Its absorbance was measured at 272 mμ on the spectrophotometer. The concentration was determined with reference to a standard curve obtained by plotting abosrbance versus known concentration of ibuprofen.

A simultaneous blank was run to determine if there was any interference. No significant interference was found.

There are no U.S.P. specifications for content uniformity of suppositories, but as it has specified in other solid dosage forms a ± 10% limit was set.

Fracture Point Determination

The fragility of suppositories was determined by using the fracture point testing apparatus. The apparatus consists of a double walled chamber which maintains the desired temperature when connected to a recirculating thermostatically controlled

bath. The suppository placed in the chamber is subjected to an initial load of 0.6 Kg. After one minute, a disc weighing 0.2 Kg is added and the process continued until the suppository collapses. If the breaking occurs within the first 20 seconds after the application of the additional disc, only the sum of the previous weights is considered. If it collapses between 20-40 seconds, only half the value of additional weight was added to the sum. If the breaking occurs after 40 seconds, the additional weight is fully considered.

It is important that the suppositories maintain their shape under various ambient temperatures and that the melting time is controlled after insertion[17]. In fact, suppositories must be formulated to melt completely at a temperature about one degree below normal body temperature.

The melting range can be determined by immersing the suppository in a thermostatically controlled waterbath. For theobroma oil and Witepsol H-15, the U.S.P. Tablet Disintegration Apparatus was used, and the suppository melting tester was utilized for PEG 1540.

Release Rate

Procedure I: Using U.S.P. Rotating Basket Dissolution Apparatus

Each suppository was placed in a wire basket and lowered into a beaker containing 600 ml of phosphate buffer solution (pH=8), maintained at a constant temperature of 37° ± 0.5°C. The basket was rotated at 100 r.p.m. 10 ml samples were drawn at time intervals and replaced with equal amounts of buffer solution. The

samples were centrifuged, filtered and assayed by using a spectrophotometer (absorbance at 272 λ) to obtain a dissolution profile.

Procedure II: Employing Dialyzing Tube

The dialyzing bags were prepared from dialyzing cellophane tubing and soaked overnight in phosphate buffer solution. After rinsing the bags twice, 20 ml of the buffer was introduced in each. One suppository was placed in every tube, which was then tied and immersed in beakers containing 400 ml of buffer solution. The solutions were constantly stirred and maintained at 27° ± 0.5°C. 5 ml samples were drawn and assayed as is.

In Vivo Studies

Healthy, white, male, New Zealand rabbits weighing about 3-4 Kg were used as test animals. They were divided into four groups of three animals each: group A for PEG 1540 suppositories, group B for Witepsol H-15 suppositories, group C for theobroma oil suppositories and group D for oral administration of ibuprofen suspension.

A 2.0 ml blood sample was drawn for each animal before administration of the drug to serve as control. At time zero one suppository was inserted rectally and observed for expulsion. Similarly, a suspension containing an equivalent amount of drug was administered orally. Blood samples were collected at ¼, ½, 1, 1½, 2, 3, 4, 5, 6, and 24 hours by cardiac puncture, allowed to clot at room temperature for about twenty minutes, and then centrifuged at 2000 r.p.m. for half an hour. The serum was separated and analyzed by HPLC or deep frozen until assayed.

Apparatus and Chromatographich Conditions

A high pressure liquid chromatograph equipped with a UV-detector (model 440) set at 254 nm was employed. The mobile phase was acetonitrile - 0.1 M acetic acid (55:45 v/v). The flow rate was 1 ml/min at a pressure of 1500 psi, and the column was Boudapak C-18.

Internal Standard Solution

10 mg of the internal standard (1-(p-fluorobenzoyl-5-methoxy-2-methyl indol acetic acid[10] was dissolved in methanol in a 10 ml volumetric flask. 0.1 ml of this 1 mg/ml solution was diluted to 10 ml with methanol and used as the internal standard solution.

Plasma Assay

To 0.5 ml of a plasma sample, 0.1 ml of the internal standard solution was added and the volume was made up to 2.0 ml with methanol. The sample was mixed well and centrifuged for 30 minutes. The supernate was separated and filtered through an organic filter[11]. The filtrate was chromatographed on to the HPLC under the previously described condition.

The concentration of ibuprofen was determined by a previously described calibration curve.

RESULTS AND DISCUSSION

In Vitro Studies

The U.S.P. does not specify weight variations for rectal suppositories. The German and the Russian Pharmacopeias allow for a ± 5% deviation from the average weight, a principle which is generally applied to all solid forms.

The average weights of theobroma oil, PEG 1540 and Witepsol H-15 suppositories are 1.4171 Gm, 1.8009 Gm and 1.5884 Gm respectively. The standard deviations as calculated are ± 0.0242, ± 0.236 and ± 0.0327 for the three bases, respectively. The percentage deviations of all suppositories are within the ± 5% limits.

There are no U.S.P. specifications for content uniformity of suppositories, but generally a ± 10% limit could be applied as with other solid dosage forms. The averages for theobroma oil PEG 1540, and Witepsol H-15 suppositories are 99.7%, 100.28%, and 99.12% respectively. The highest and lowest percentages for theobroma oil are 108.04 and 92.89; for PEG 1540 they are 106.63 and 93.82; for Witepsol H-15, 104.76 and 95.04, therefore, all are within the ± 10% limit.

The fracture point of a suppository is important since it must withstand handling during production, packaging, cartoning, shipping, etc. As can be seen in Figure 1 the fracture point decreases in the order: Witepsol H-15.> PEG 1450.> and theobroma oil. Furthermore it is apparent that the fracture poins is inversly proportional to the temperature. Witepsol H-15 shows a steeper slope indicating that it is more brittle that the other two. The PEG 1540 curve shows greater elasticity indicating a longer softening interval than theobroma oil and Witepsol H-15.

The melting range of ibuprofen-containing suppositories made with the three bases was compared to the corresponding blank suppositories. Figure 2 represents melting range as a function of temperature. As the temperature increases, the time a suppository takes to melt de-

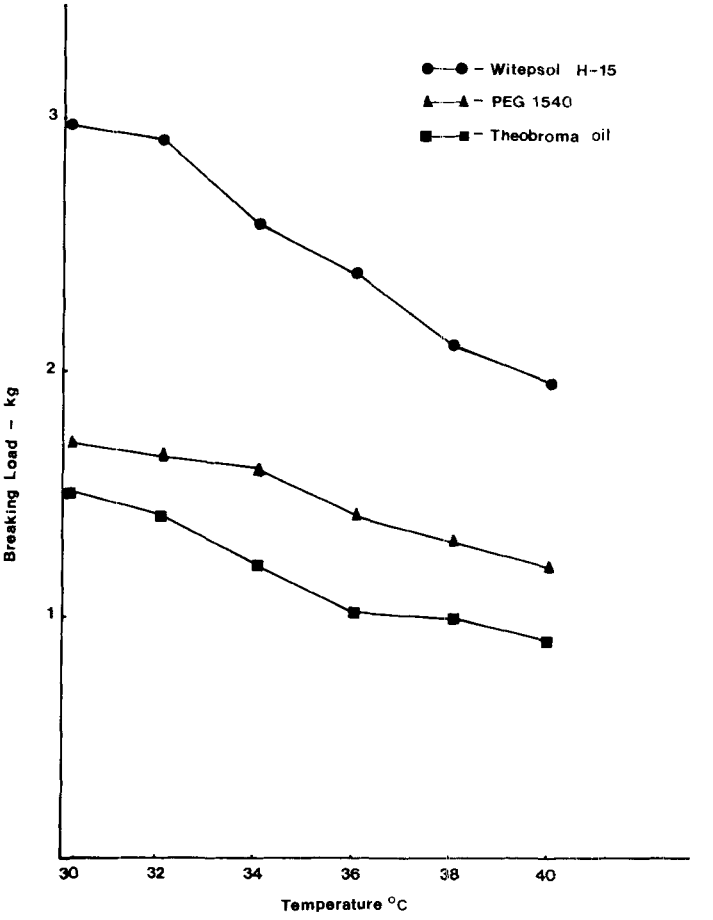

Figure 1 - Comparison of Fracture Points of Ibuprofen Suppositories

creases. Blank suppositories of theobroma oil and Witepsol H-15 have a higher melting range than the corresponding ibuprofen-containing suppositories. The addition of ibuprofen, it can be deducted, lower the melting range of these bases.

In the case of PEG 1540 the opposite is true. This could be explained on the ability of PEG 1500 to form complexes with drugs[18].

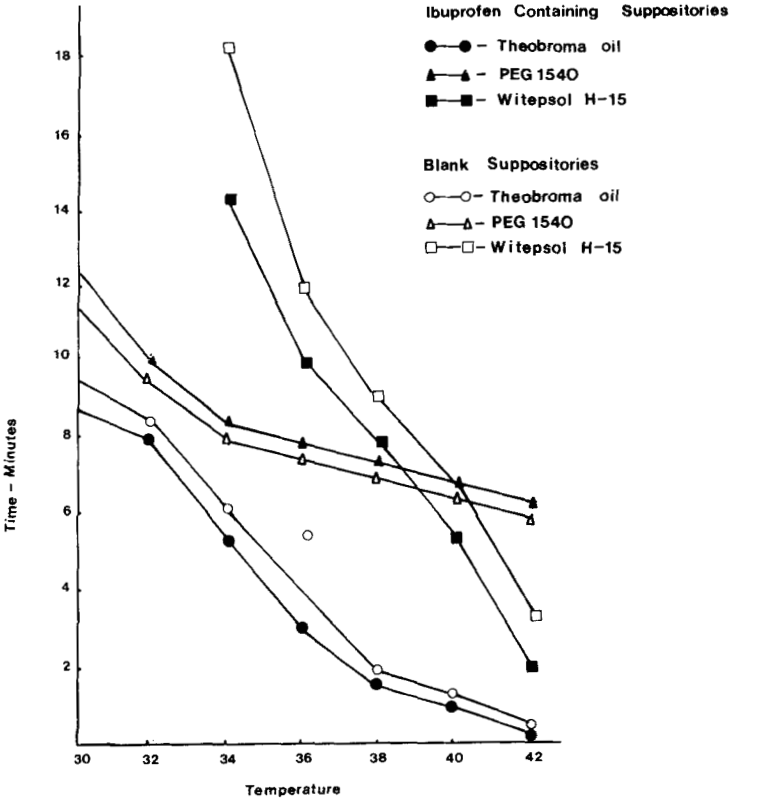

Figure 2 – Comparison of Melting Range of Ibuprofen Suppositories

Figure 3 presents the release profile of ibuprofen suppositories as determined by Procedure I. The percentage release has been rounded to the next highest tenth of a percent, beyond which there can not be any practical significance. Whereas, Table I represents the release constants (K) and T_{50}, the time required for the suppository to release half of its contents in the medium. It is evident that ibuprofen is released more readily from PEG 1540 than from the other two bases because PEG 1540 is a water soluble base and ibupro-

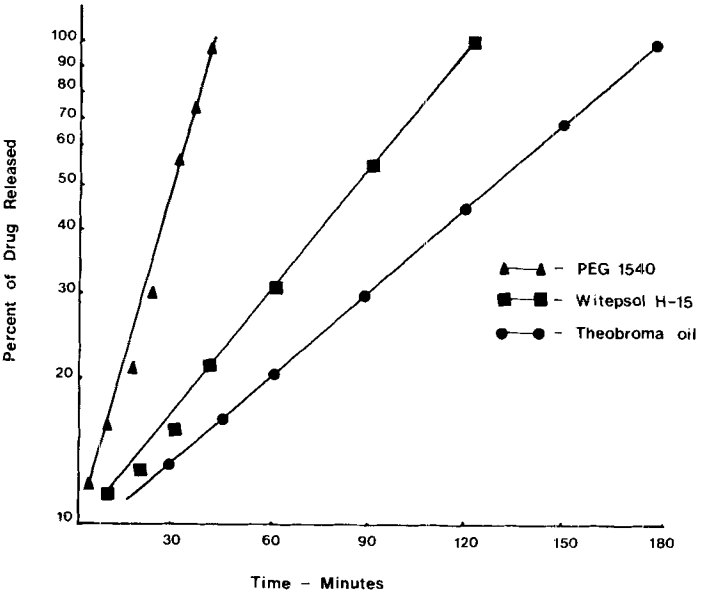

Figure 3 - Release Profile of Ibuprofen Suppositories in Procedure I

TABLE I
First Order Values
Obtained from In Vitro Release
Using Procedure I

Base	Release Rate Constant (K) x 10^{-3} mg%/min	T_{50} (minutes)
Theobroma Oil	5.40	123.91
PEG 1540	24.30	28.5
Witepsol H-15	8.06	85.91

fen is freely soluble in the medium of pH=8. PEGs are known to form complexes with the drugs[18]; a soluble complex leads to an increase in the release rate. Ibuprofen was released faster from Witespol H-15 than theobroma oil, which may be due to emulsifying and water absorptive properties of the former[19].

The percentage released ibuprofen using Procedure II is presented in Figure 4. Again, the percentage released has been rounded to the next highest tenth of one percent. It is apparent that the fastest release is obtained again from PEG 1540, followed by Witepsol H-15. The first order release rate (K) and T_{50} are listed in Table II.

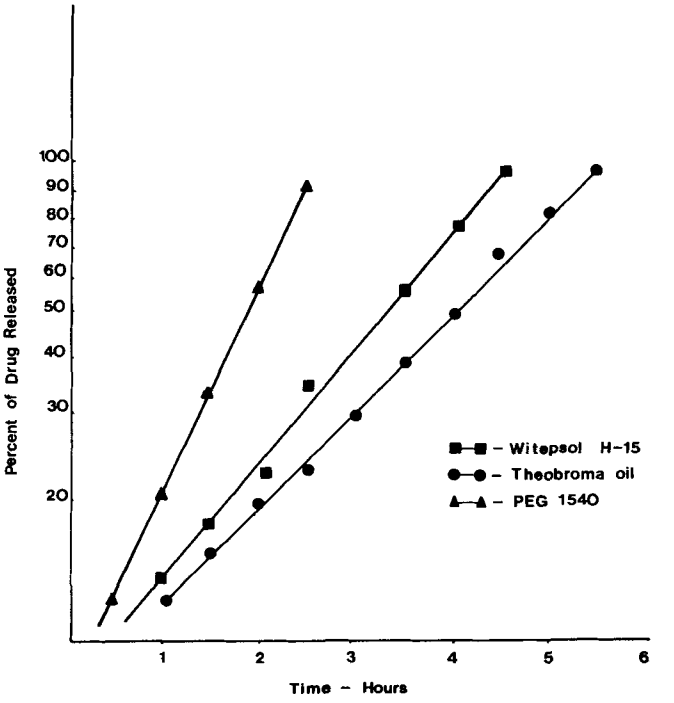

Figure 4 - Release Profile of Ibuprofen Suppositories by Procedure II.

TABLE II
First Order Values Obtained from In Vitro Release
Using Procedure II

Base	Release Rage Constant (K) x 10^{-3} mg%/min	T_{50}* (minutes)
Theobroma Oil	2.88	240.1
PEG 1540	6.08	113.3
Witepsol H-15	3.50	198.6

*Rounded to the nearest tenth of a minute

In Vivo Studies

The serum levels obtained with the three bases and the oral suspension in rabbits are presented in Figure 5. The values of AUC measurements, as well as the average peak time, the average of individual peak serum concentration and the average of individual peak times are given in Table III.

Ibuprofen suspension produces the highest peak which is 28.2 ug/ml, followed by PEG 1540, Witepsol H-15 and theobroma oil with peaks 26.9 ug/ml, 25.6 ug/ml, and 21.9 ug/ml respectively. The time of the peak serum concentraition which is closely related to the rate of the drug from a particular formulation, is 90 minutes from the oral suspension and PEG 1540 and 120 minutes from theobroma oil and Witepsol H-15. The area under the plasma concentration-time curve (AUG) was meas-

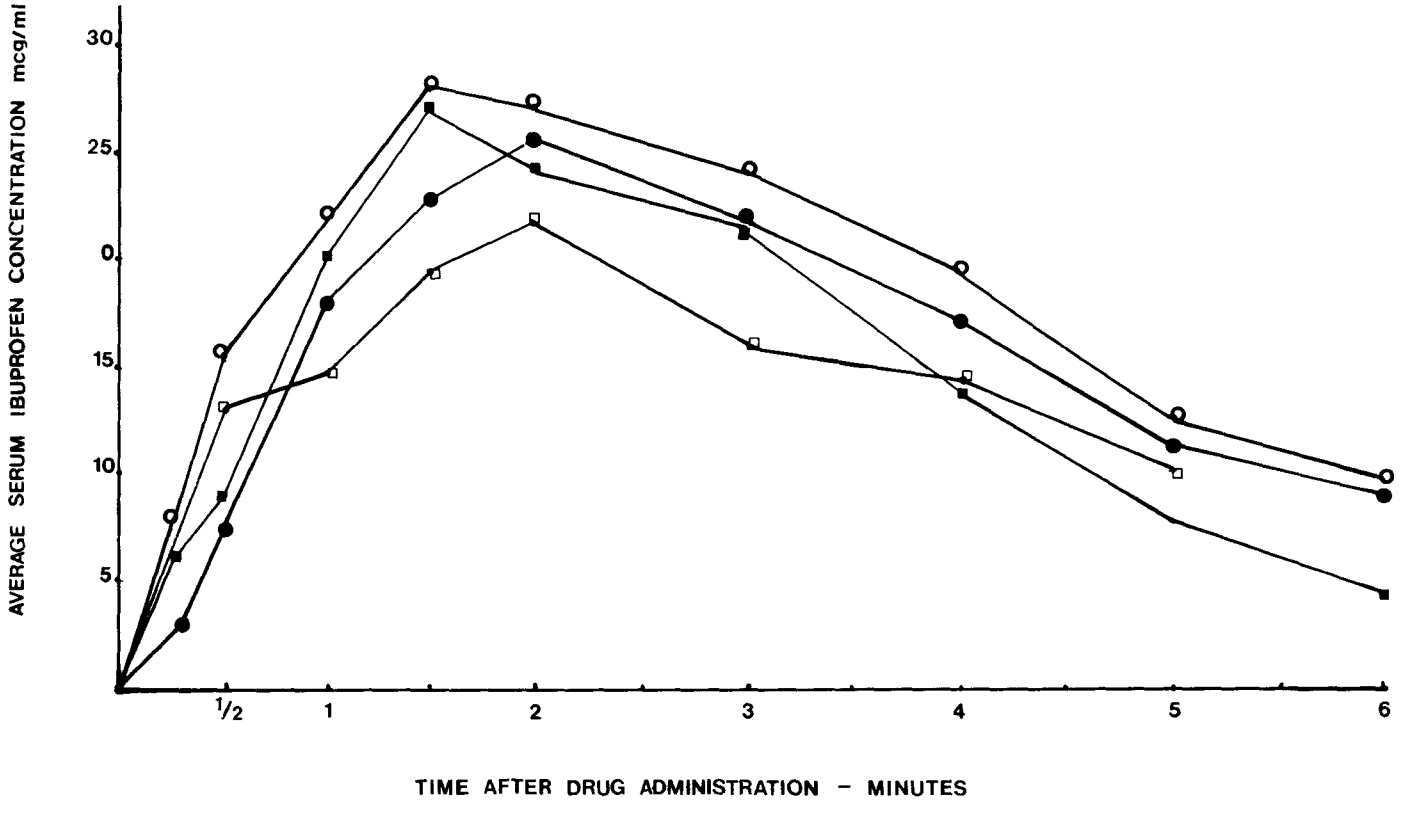

FIGURE 5 - Average serum ibuprofen concentration (mcg/ml) obtained for 3 rabbits after receiving 150mg of ibuprofen given as:
o-oral suspension; ●-widepsol H-15; ■-PEG 1540;
-theobroma oil

TABLE III
Bioavailability Parameters of Ibuprofen Suppositories and Suspension

	Peak of the Average Serum Concentration-Time Curve (ug/ml)	Time of the Peak of the Average Serum Concentration-Time curve (minutes)	Average of the area under the curve (0-360 min, ug/ml)	Percentage of the Suspension
Theobroma Oil	21.9	120	74.37	57.68
PEG 1540	26.9	90.0	89.77	69.62
Witepsol H-15	25.6	120.0	96.50	74.85
Oral Suspension	28.2	90	128.93	100.00

ured by trapezoidal rule. The areas under the curve (AUG) theobroma oil, PEG 1540 and Witepsol H-15 are 57.68%, 69.62% and 74.85% of the oral suspension, respectively. This indicates that the total amount of ibuprofen absorbed rectally is less than that absorbed from oral administration. Release from theobroma oil may be impaired, as it tends to form a barrier between the drug and rectal mucosa due to its fatty nature[20]. Release from PEG 1540 may be hampered by the small amount of rectal fluid[17]. In part, the total amount of the ibuprofen absorbed may also be influenced by its interaction or complex formation with these bases.

Each point in Figure 5 is the average of three determinations and in order to find out if there is any statistical difference between bases and oral suspension and from rabbit to rabbit a 1-way

ANOVA with repeated measures was utilized and the results are summerized as follows:

(a) The 1-way ANOVA with repeated measures for the four preparations gave F=15.29 and probability 0.0000 which indicates that statistically there is significant difference at least in some of the four formulations. Therefore, a student "t" test was conducted on all data from the four formulations; it was found that there is a significant difference in the bioavailability data obtained from theobroma oil and PEG 1540 suppositories, where in the data obtained from Witepsol H-15 and PEG 1540, and from Witepsol H-15 and oral suspension are statistically significant at 0.01 level of significance ($p < 0.001$).

TABLE IV
Evaluation of Student "t" Test*

Suppositories	F	Probability	Level of significance between rabbit		
			1-2	1-3	2-3
Witepsol H-15	20.58	0.0000	0.01	0.001	0.05
Theobroma oil	19.13	0.0002	0.01	0.01	0.05
PEG-1540	9.966	0.0015	ns	0.01	0.05
Suspension	14.22	0.0002	0.01	0.01	0.05

* ns = not statistically significant

Furthermore, the bioavailability data from oral suspension and theobroma oil, and from oral suspension and PEG 1540 are statistically significant at 0.001 level of significance ($p < 0.001$). In addition it was found that the data obtained from Witepsol H-15 and Theobroma oil are statistically significant at 0.05 level of significance ($o < 0.05$).

(b) In order to determine if there is difference from rabbit to rabbit within the same suppository base the same analytical procedure was used and the results are shown in Table IV. It is apparent from the data in Table IV that in any study not only the number o specimens taking part in the study must be reported but also any difference in the data among the specimens.

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FOOTNOTES

1 The Upjohn Company, Kalamazoo, Michigan
2 J.J. Baker Chemical Company, Phillipsburg, N.J.
3 Kay-Fries Chemical Inc., Montvale, N.J.
4 Fisher Scientific Company, Fair Lawn, N.J.
5 Waters Associates, Milford, Mass.
6 American Optical Corporation, New York, N.Y.
7 Erweka Chemical and Pharmaceutical Company, New York, N.Y.
8 Kay Adams, Division of Becton, Dickson & Co., Rutherford, N.J.
9 Bausch & Lomb
10 MSD, West Point, Pa.

REFERENCES

1. S.S. Adams, E.E. Cliffe, B. Lessel and J.S. Nicholson, J. Pharm. Sci. 56, 1687 (1967).
2. S.S. Adams, K.F. McCullough, and J.S. Nicoholson, Arch. Int. Pharmacodyn 17, 115 (1969).
3. S.S. Adams, R.G. Bough, E.E. Cliffe, W. Dickenson, K.F. McCullough, R.F.N. Mills, J.S. Nicholson and G.A.H. Williams, Rheum. Phys. Med (Suppl) 10, 9 (1970).
4. A.A. Goldberg, Practitioner 207, 343 (1971).
5. M.K. Jasani, Ann. Rheum. Dis. 27, 417 (1968).
6. T.M. Chalmers, Ann. Rheum. Dis. 28, 513 (1969).
7. P.L. Board, Ann. Rheum. Dis. 26, 560 (1967).
8. L. Mattara, Clin. Trials J. 14, 30 (1977).
9. S. Schweitz, JAMA 239, 34 (1978).
10. Data on file, The Upjohn Company
11. S.L. Corson and R.J. Bolognese, J. Reprod. Med, 20, 246 (1978).
12. D.R. Halbert and L.M. Demers, J. Reprod. Med, 21, 219 (1978).
13. C.D. Brooks, C.A. Schlagel, N.C. Sekhar and J.T. Sobota, Curr. Therap. Res. 15, 180 (1973).
14. J.R. Lewis, JAMA 233, 364 (1975).
15. N.J. Vidras, F.M. Plakogiannis and V.E. Reid, J. Pharm. Sci. in press.
16. G. Chongsathien and F.M. Plakogiannis, "The Drug Development and Industrial Pharmacy", 6, 255 (1980).
17. I. Setnikar, J. Pharm. Sci., 52, 38 (1963).
18. O.I. Corrigan and R.F. Timoney, Pharm. Acta. Helv., 51, 268 (1968).
19. Suppository Bases, Kay-Fries Chemicals, Inc.