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MEDICAMENT RELEASE FROM SUPPOSITORY BASES: II. NAPROXEN PHYSICOCHEMICAL CHARACTERISTICS AND BIOAVAILABILITY IN RABBITS.

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Abstract - Suppositories containing 25mg naproxen were prepared by the fusion method with tehobroma oil, PEG 1000, and witepsol H-15. The liquefaction point and the time for complete liquefaction at temperatures from 37°C to 47°C were determined. By utilizing the SBT (Erweka) apparatus it was determined that the witepsol H-15 formed suppositories which were more brittle.

The in vitro release rates were determined by using the USP method and by a modified one with dialyzing cellophane tubing. Samples withdrawn at definite time interval for up to 6 hours, and were analyzed by the spectrofluorometric method. The in vivo

drug release was studied in rabbits. Ten blood samples were collected over a 24 hour period following administration of a 25mg dose of each suppository and of oral suspension. Plasma samples were assayed by spectrofluorometric method. A student "t" test was conducted on all data from the four different formulations and indicated significant difference between theobroma oil and oral suspension.

Significant correlation was obtained between the in vivo absorption and in vitro release when the suppository was placed in a dialyzing cellophane membrane.

In a previous paper we investigated the in vitro and in vivo release of indomethacin by suppository bases (1). This paper reports the release of naproxen from suppository bases.

Naproxen is a new non-steroidal antiinflammatory agent for use in rheumatoid arthritis, degenerative joint disease, and ankylosing spondylitis. The drug has low toxicity, and its side effects are mild and mostly appear in the upper GI tract. However, in cases where patients cannot swallow, have GI ulcerations and/or are uncooperative, the use of a temporary or permanent alternate route to oral administration is advisable or convenient. Rectal administration as an alternate mode of treatment is of value. Therefore, the purpose of this study was to formulate naproxen suppositories with three different bases (theobroma oil, witepsol H-15 and PEG 1000) and determine their weight variations, content uniformity, breaking point, melting range, in vitro drug release

from the three bases, in vivo bioavailability of the naproxen suppositories and naproxen suspension in rabbits. Furthermore in the light of some previous studies indicating that the in vitro drug release cannot be correlated to the in vivo drug absorption (2,3), an attempt was made to correlate the in vitro release of naproxen from the suppository bases with its in vivo bioavailability.

EXPERIMENTAL

Chemicals and Materials - Naproxen[1], theobroma oil[2], 0.1N sodium hydroxide[2], 1N hydrochloric acid[2], benezene[2], isoamyl alcohol[2], certified buffered solution[2], pH 8, PEG 1000, acacia U.S.P.[3], and witepsol H-15[4], were used as received.

Equipment - Dynac centrifuge[5], U.S.P. tablet dissolution apparatus[6], U.S.P. tablet disintegration apparatus[7], fracture point testing apparatus[7] (SBT), suppository melting tester[7] (SBP), recirculating thermostat[7], and spectrophotofluorometer[8].

Preparation of suppositories - Suppositories containing 25mg of naproxen were prepared by fusion method with three different bases: theobroma oil, witepsol H-15, and PEG 1000. Twenty-five mg of the drug was mixed with melted suppository base, and the mixture was

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1 Syntex Laboratories, Inc., Palo Alto, California
2 Fisher Scientific Co., Fairlawn, N.J.
3 Ammend Drug and Chemical Co., Irvington, N.J. 07111
4 Kay-Fries Chemicals, Inc., Montvale, N.J.
5 Kay Adams, Division of Becton, Dickinson and Co., Parsippany, N.J. 07054
6 American Optical Corporation, New York, N.Y.
7 Erweka Chemical and Pharmaceutical Co., New York, N.Y.
8 American Instrument Co., Silver Spring, Maryland 20910

poured into a mold. The same base was carefully filled into this mold. The cooled suppositories were weighed. The average weight of the prepared suppositories were: 1.3840 ± 0.023 gms, 1,4273 ± 0.024 gms and 1,79818 ± 0.029 for theobroma oil, witepsol H-15 and PEG 1000 respectively. The displacement (D.V.) value was then calculated by using the following equation (4)

$$D.V. = \frac{\text{weight of drug}}{\text{weight of suppository - weight of suppository without drug}} \qquad \text{Eq. 1}$$

The displacement value for theobroma oil was 0.9470, witepsol H-15 was 0.9030 and PEG 1000 was 0.8528. After calculating the displacement value of naproxen, the weight of each base used in the preparation was calculated.

Weight variation - Twenty suppositories of each base were individually weighed by using Mettler weighing apparatus. The percentage variation was calculated for each suppository. The weight should be within the range of 95.0 - 105.0% of the average weight (5).

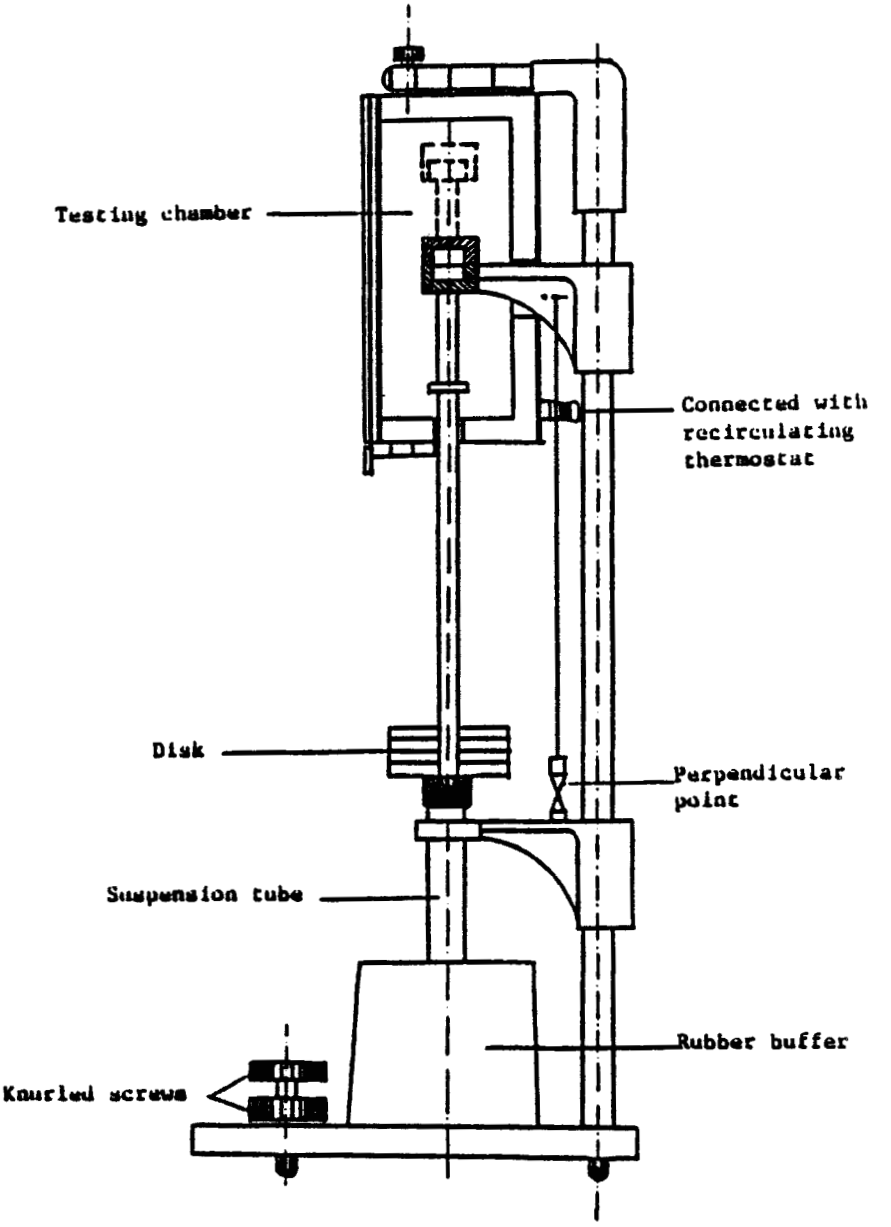
Content uniformity - Each suppository was placed in a 100 ml volumetric flask which contained 90 ml of 0.1N NaOH solution. The flask was shaken for 10 minutes on a modified reciprocating shaker and one ml of the water phase was pipetted into a 100 ml volumetric flask, and was diluted with 0.1N NaOH to 100 ml. The fluorescent intensity of a representative sample was measured in a spectrofluorometer at the excitation and emission maxima of 330 and 355 nm, respectively (5). The concentration of naproxen in 0.1N NaOH solution was determined from a calibration curve previously constructed.

Breaking point - Each suppository, stored atleast 24 hours at room temperature, was placed in the testing chamber of a fracture point

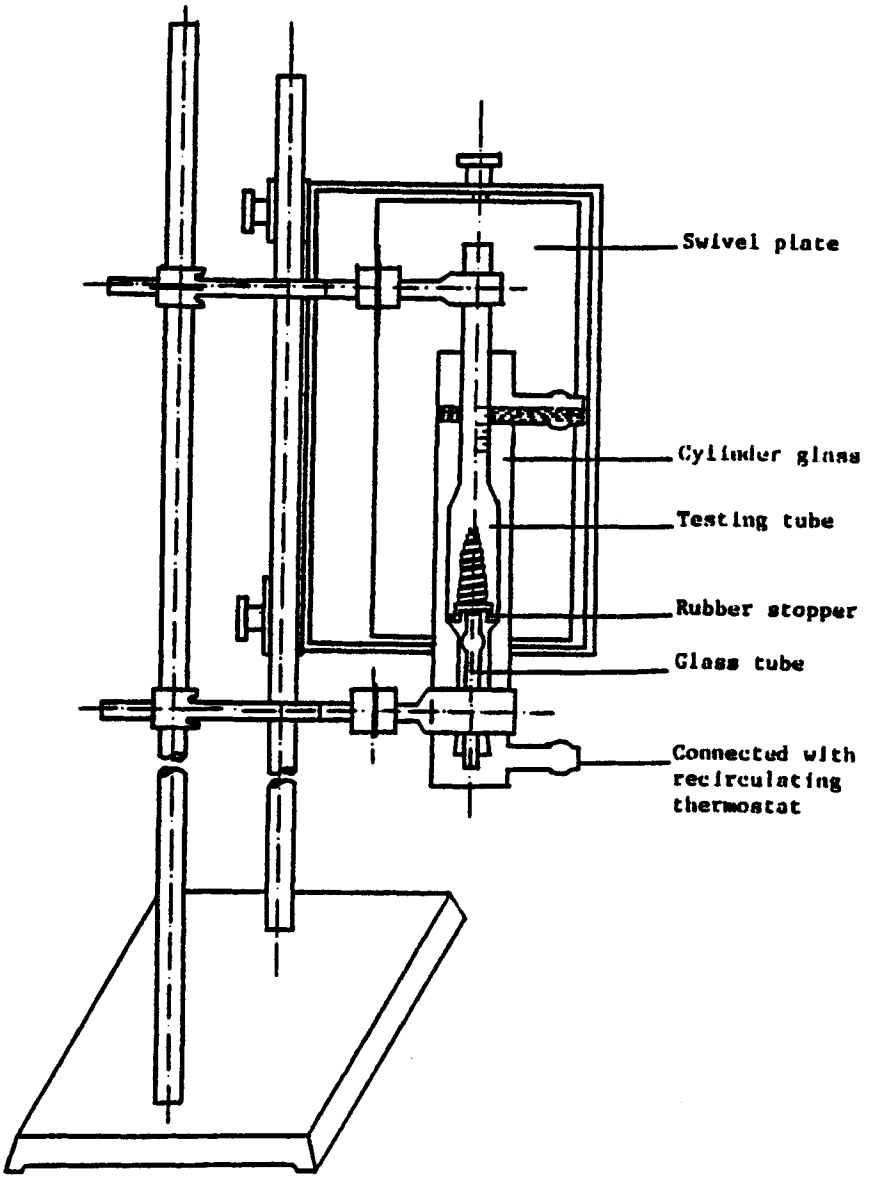
testing apparatus, as shown in Scheme 1 which was connected with a recirculating thermostat to control each temperature of the testing chamber. The temperatures used in this experiment was 25°C - 32°C. The chamber was then closed and the time was measured by using a stopwatch. The initial load, which was given by the weight of the entire suspension block, was 600 grams. After a full minute, a disk weight of 200 grams was added, and after another minute, the next weight and so on until the suppository collapsed under the load of the weight. If the breaking occurred within the first 20 seconds after application of the last weight, the latter was not considered in the total sum of the weight. If it occurred between 20-40 seconds, only the one held of the last weight was considered. If the breaking occurred after 40 seconds, the total weight was considered.

Melting range - a) Theobroma oil and witepsol H-15 suppositories by using U.S.P. tablet disintegration apparatus.

The apparatus was set as required in U.S.P. XIX, using water as the immersion fluid. A suppository, stored at least 24 hours at room temperature, was placed in each tube of the basket and each tube was covered with a disk. The water temperature was maintained between 32°C - 40°C for theobroma oil, and between 34°C - 42°C for witepsol H-15. The time required for each suppository to completely melt was measured. b) PEG 1000 by using suppository melting tester (SSP) - Each suppository, stored at least 24 hours at room temperature, was inserted in the spiral shaped glass of the testing tube of the suppository melting tester as shown in Scheme 2. The testing tube was closed by a rubber stopper with a glass tube. This glass



Scheme 1: Fracture point testing apparatus for suppository



Scheme 2: Suppository melting tester

tube was suspended in a cylinder glass which was filled with water. The water of each constant temperature was regulated by a recirculating thermostat and flowed into the inner space of the testing tube The temperature range used in this experiment was 37°C - 47°C. The time was measured as soon as the water level in the testing tube reached the water level in the outer cylinder until the suppository melted completely.

Release Rate - Procedure 1 - using a tablet dissolution apparatus. A 900 ml of certified buffered solution pH 8 was put in a vessel which was immersed in a constant temperature water bath. This solution was used as a melting medium, and was allowed to come to a temperature of 27.0 ± 0.5°C. A suppository was put in each basket which was then immersed into the vessel with a distance of 2.0 ± 0.2 between the basket and the bottom of the vessel. The baskets were rotated at the rate of 68 rpm. A sample of 0.9 ml was pipetted to a tube at different time intervals for up to 3 hours for theobroma oil and witepsol H-15, and up to 16 minutes for PEG 1000. The volume of vessel was maintained constantly be replacing the samples with the melting medium. Each sample was diluted to 10 ml with 0.1N NaOH and was analyzed immediately spectrofluorometricly if not, stored at room temperature.

Procedure II, using a tablet dissolution apparatus - The same as procedure I, only each suppository was placed in a cellophane tubing. Both ends of the tubing were tightened with white thread before putting it in the basket. The collection times were every 15 minutes for the first hour, every 20 minutes for the second hour, and every hour for the next four hours for each suppository base.

Procedure III - A 300 ml of melting medium was put in a vessel which was immersed in the constant temperature of 7.0 ± 0.5°C water bath. The melting medium was allowed to come to this temperature. A suppository was put in a cellophane tube which contained 15 ml of melting medium. Both ends of this tube were closed by clippers before putting it into the vessel. The melting medium in the vessel was constantly stirred. A sample of 0.9 ml was withdrawn at the same time intervals as in procedure II. Each sample was diluted and analyzed in the same as in procedure II. The cellophane tubing was soaked in water overnight before using in both procedures II and III.

In-vivo Studies - Health adult, white male, New Zealand rabbits were used as the test animals. Each rabbit weighed between 3.0-4.5 kg. If a rabbit was reused a one-week washout period was observed between dosing of the formulation under test. A 1.5 ml of blood was initially withdrawn by cardiac puncture as a control sample before any administration.

A suppository was administered to a rabbit rectally. The animal was observed not to have a rectal leakage or an expulsion of the suppository. To a group of animals, a naproxen suspension prepared by mixing 0.02 mg of acacia with 25 mg of naproxen in 5 ml of purified water was orally administered by using a tube syringe. A blood sample of 1.5 ml was withdrawn by cardiac puncture. The samples were collected at the time ½, 1, 1½, 2, 3, 4, 6, 8, and 24 hours after rectal administration. Blood samples were allowed to clot for 10 minutes and were then centrifuged at 2500 rpm for 15 minutes. A 0.1 ml of each serum sample was pipetted into a tube for analysis

immediately or the serum samples were frozen at temperature - 20°C.

Plasma Samples Analysis by Using Spectrofluorometric Method - Naproxen in plasma sample were extracted into organic phase by adding a 0.1 ml of plasma sample to a 1.0 ml of 1N hydrochloric acid and a 5.0 ml of benzene containing 1.5% of isoamyl alcohol, before shaking for 10 minutes on a reciprocating shaker and centrifuged for 5 minut at 2000 rpm. The naproxen in the organic phase was then reextracted by adding 4 ml of organic phase to a 3.0 ml of 0.1N NaOH before shak ing and centrifuging. A 1.0 ml of water phase of each sample was diluted to 10 ml by 0.1N NaOH. The fluorescent samples were measure immediately or stored at room temperature. The measurements were made with a spectrofluorometer at excitation and emmission maxima of 330 and 355 nm, respectively. The sample concentrations were determined from a calibration curve obtained by assaying blood plasma containing known amounts of naproxen and plotting the relative fluorescent intensity against known concentration of naproxen. A linear relationship was obtained over the range .1 - 7 ug/ml of naproxen in plasma.

RESULTS AND DISCUSSION

In vitro studies - The U.S.P. does not specify the weight variation of rectal suppositories. Only the German and Russian Pharmacopeias state individual weight variation of rectal suppositories at ± 5.0% of the average weight, whereas the Pharmacopeia Nordica allows ± 10.0% of the average weight for 90.0% of the suppositories, but these deviations must not exceed ± 20.0%. However, the weights of the suppositories should fall within ± 5.0%

of the average weight, generally applied to other solid dosage forms (5,7,8). The percentage deviations of theobroma oil, witepol H-15, and PEG 1000 are 0.023, ± 0.024, and ± 0.029 respectively, which indicates that all suppositories are within the control limits of the average weights.

As in the weight variation, the U.S.P. does not specify the content uniformity, but as in other solid dosage forms, the content of each of 10 suppositories should be within limits of 85.0% and 115.0% of the specified dose (9). It was found that the content of each of 10 suppositories from three different bases is within the limits of 85.0% and 115.0% of the dose of 25 mg of naproxen.

The breaking point of a suppository is important since the suppository must withstand the forces caused by production, packing, shipping and patient use in handling. The breaking points of naproxen suppositories from three bases are presented in Figure 1. Between the temperatures 26°C - 32°C, witepsol H-15 suppositories require higher forces than theobroma oil and PEG 1000 suppositories, and PEG 1000 suppositories require greater forces than theobroma oil suppositories. From the curves of three bases, witepsol H-15 curve has a greater slope indicating that this base is more brittle than the other two bases. Theobroma oil and PEG 1000 appear more elastic than witepsol H-15. The PEG 1000 curve is flatter than theobroma oil curve indicating that PEG 1000 is more elastic and requires a longer softening interval.

The melting ranges of theobroma oil suppositories and witepsol H-15 suppositories were performed by using the U.S.P. tablet dis-

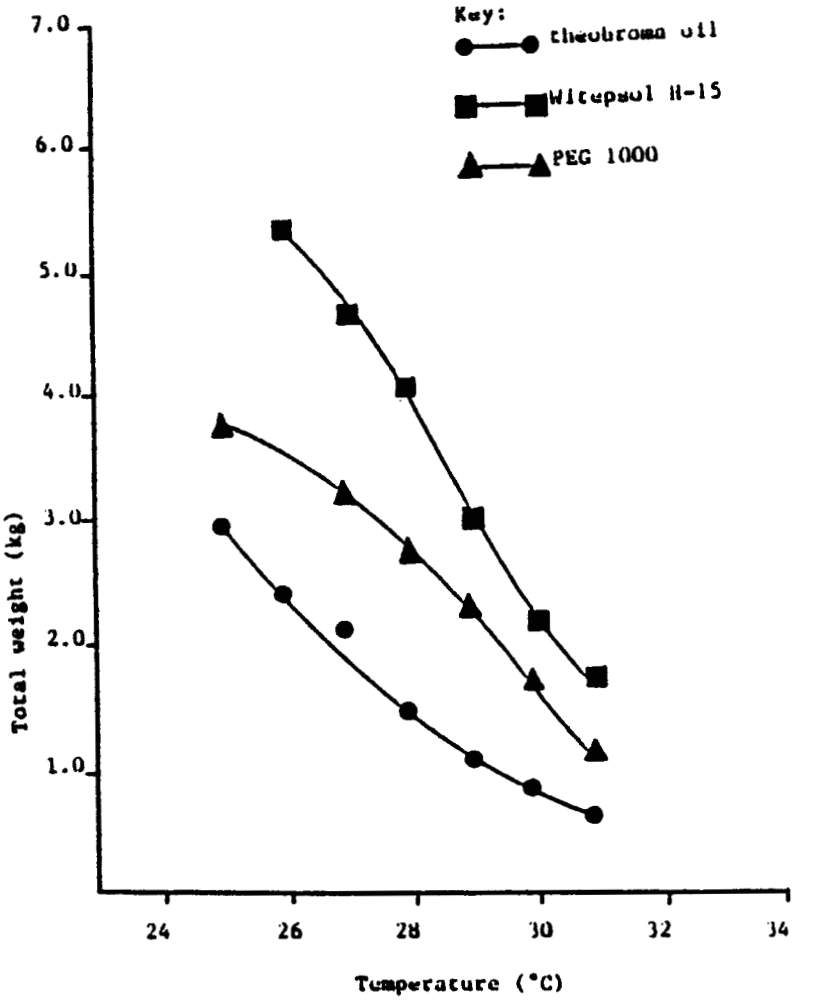


Figure 1: Comparison of breaking point of naproxen suppositories

integration apparatus and the melting range of PEG 1000 suppositories were performed by using a suppository melting tester. The comparison of the melting ranges of naproxen suppositories with blank suppositories and the comparison of the melting range between three bases

are presented in Figure 2. It is apparent that as the temperature increased, the time required for melting the entire suppository decreased. The theobroma oil with naproxen and witepsol H-15 with naproxen curves are higher than their blank suppositories curves,

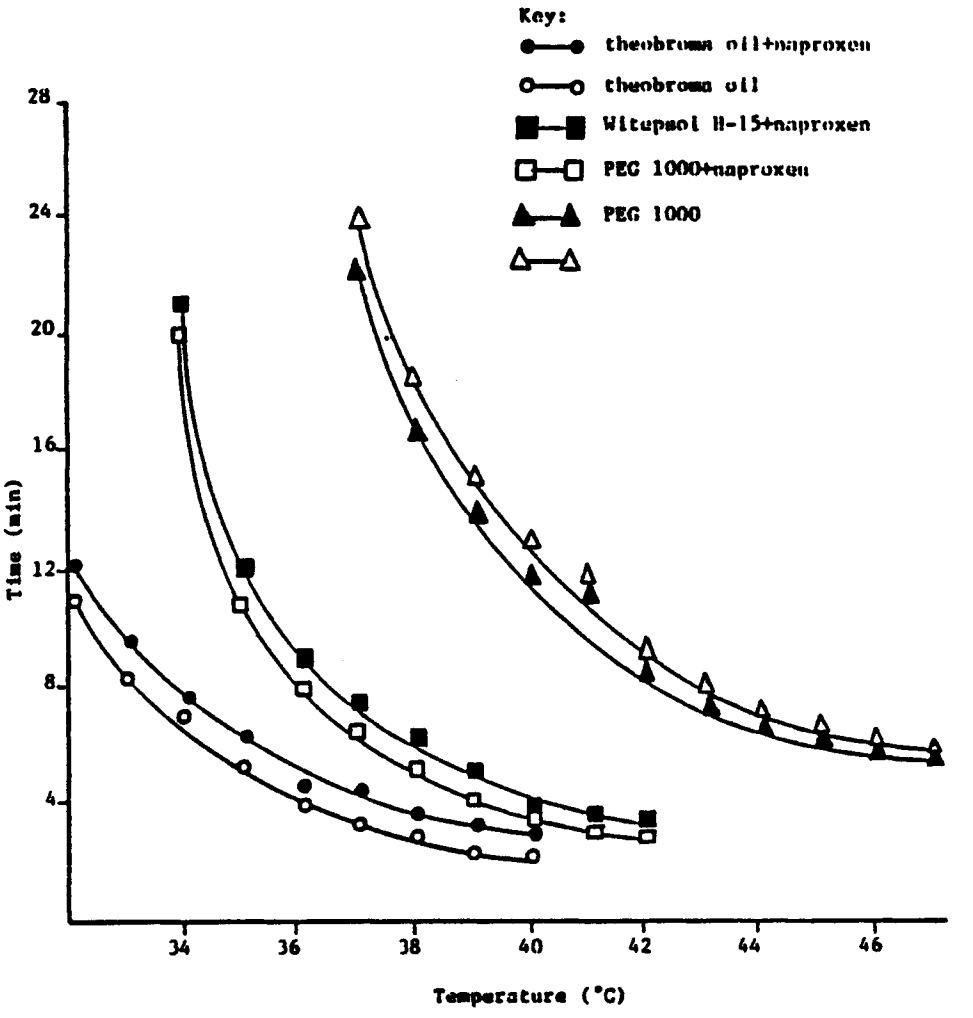


Figure 2: Comparison of melting range of naproxen suppositories

whereas PEG 1000 with naproxen curve is lower than its blank suppositories curve. This is possible due to the formation of eutectic mixture of naproxen and PEG 1000 because naproxen lowers the melting range temperature of the base, it may facilitate the release rate of the suppositories and increase the absorption of the medicament (10-12). Furthermore, at any temperature, PEG 1000 suppositories require more time to melt than the other two bases, and at body temperature, 4.3, 7.3, 22.3, minutes are required to melt theobroma oil, witepsol -H15, and PEG 1000 respectively.

The mean of the uncorrected released concentrations of naproxen from the bases were subjected to a cumulative correction for the previously removed samples in determining the total amount released by using the following equation (13):

$$C_n = C_n \text{ (meas.)} + \frac{0.9}{900} \sum_{S=1}^{n-1} C_{s(meas.)} \qquad \text{(Eq. 2)}$$

where $C_{n(meas.)}$ is the concentration measured through the spectrofluorometer and C_n is the concentration of the n^{th} sample expected in the medium if previous samples has not been removed. The factor $\frac{0.9}{900}$ represents a 0.9 ml from a 900 ml total volume in procedure I and II. This dilution factor is $\frac{0.9}{300}$ in procedure III. The $\sum_{S=1}^{n-1} C_n$ (meas.) represents the sum of the uncorrected concentration of all previous samples but not including the n^{th} sample. The log of the unreleased concentration versus time are shown in Figure 3. The slopes and the Y-intercepts were obtained from the least square lines of best fit. The Y-intercepts, representing the amount of the

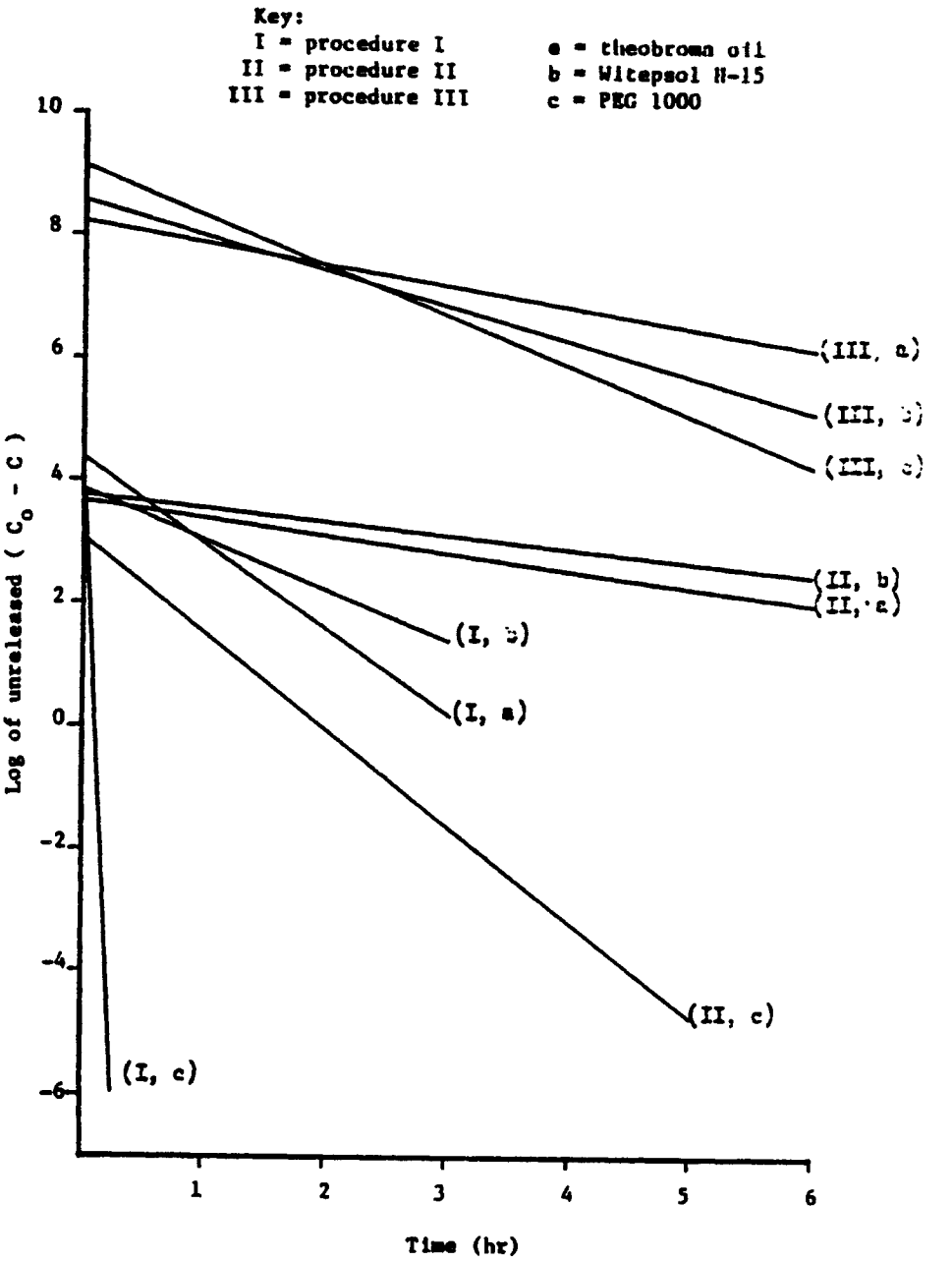


Figure 3: In-vitro release of naproxen suppositories

unreleased drug at time 0, are theoretically 0.40 or log of the initial concentration 2.5 ug/ml in procedure I and II, and 0.88 or log of the initial concentration of 7.5 ug/ml in procedure III. They vary slightly from these numbers since this method is designed to find the "line of the best fit" which may not intercept exactly the same in the theory. The rate constants were calculated from the slopes (Table I).

These data indicate that naproxen was released much more readily from PEG 1000 than from the other two bases because PEG 1000 is a water-soluble base and naproxen is freely soluble in the medium of pH 8. Furthermore, an increase in release rate of PEG 1000 is due to the formation of soluble complex with the drug (14), and may be due to the lower melting temperature of eutectic mixture formation through construction of their structures (19). Naproxen was released more readily from theobroma oil than from witepsol H-15. However, during the first 15 minutes of the experiment, naproxen was released from witepsol H-15 faster than from theobroma oil. This occurs because witepsol H-15 possess emulsifying and water absorptive properties (16).

The release rate from procedure II, indicate that the rate constant from PEG 1000 is 7.34×10^{-3} ug/ml-min. from theobroma oil is 1.11×10^{-3} ug/ml-min and from witepsol H-15 is 0.9×10^{-3} ug/ml-min. This is due to the same reasons as in procedure I. Naproxen was released from theobroma oil more readily than witepsol H-15 throughout this procedure because there is no melting medium inside the

TABLE I

FIRST ORDER VALUES OBTAINED FROM IN-VITRO RELEASE STUDIES

Suppository Base	Slope ($X10^{-3}$)	Y-Intercept	Release Rate Constant ($X10^{-3}$ µg/ml-min)
PROCEDURE I			
Theobroma Oil	-2.68	0.43	6.17
Witepsol H-15	-1.26	0.39	2.90
PEG 1000	-59.24	0.45	136.43
PROCEDURE II			
Theobroma Oil	-0.48	0.37	1.11
Witepsol H-15	-0.39	0.38	0.89
PEG 1000	-3.19	0.31	7.34
PROCEDURE III			
Theobroma Oil	-0.59	0.83	1.35
Witepsol H-15	-1.00	0.86	2.30
PEG 1000	-1.35	0.91	3.11

cellophane membrane, the emulsifying and water absorptive properties of witepsol H-15 do not disperse the drug the membrane.

The rate constant obtained from PEG 1000, in procedure II, is 3.11, from witepsol H-15 is 2.30, and from theobroma oil is 1.35. It is apparent that the rate constant from PEG 1000 is greater than from other bases. However, the release rate from witepsol H-15 in the first 3 hours is greater than from the other two bases, because of its emulsifying and water absorptive properties, dispersing the drug throughout the medium in the inner surface of the membrane. The release rate from theobroma oil in the first 1½ hours is more than from PEG 1000 because it melts within a few minutes, spreading itself within the membrane, setting up conditions favorable for naproxen to undergo partition between the base and the medium, whereas PEG 1000, although water-soluble, do not have a solubility great enough to complete with the ability of theobroma oil to rapidly set up conditions favorable for partition of the drug to the medium. After the first 3 hours of the experiment, the release rate from PEG 1000 is greater than from the other bases because PEG 1000 dissolved itself in the medium within the membrane and disperses the drug through the medium. It is possible that PEG 1000 forms a soluble complex with naproxen.

The serum concentration levels time profile obtained after the administrations of theobroma oil, witepsol H-15, PEG 1000 suppositories and naproxen oral suspension in rabbits are presented in Figure 4, and Table II. Naproxen suspension produces the highest peak of the curve which is 1.38 ug/ml, from PEG 1000 is 1.323

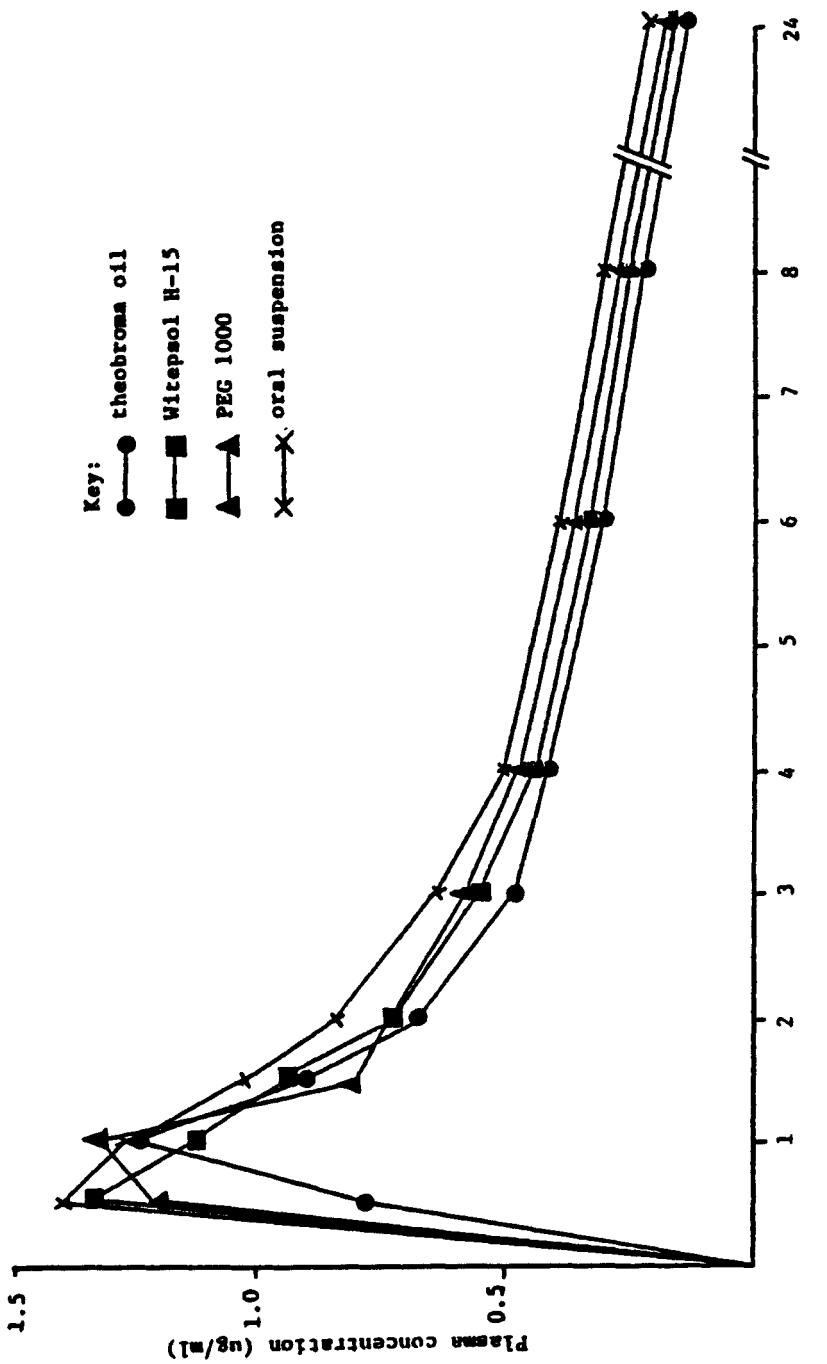


Figure 4: Bioavailability profile after administration of 25 mg of naproxen suppositories and suspension

TABLE II

BIOAVAILABILITY PARAMETERS OF NAPROXEN SUPPOSITORIES AND SUSPENSION*

	Theobroma Oil	Witepsol H-15	PEG 1000	Suspension
Peak of the Average Serum Concentration-Time Curve (g/ml) ± S.D.	1.238 ± 0.233	1.355 ± 0.114	1.323 ± 0.178	1.388 ± 0.265
Time of the Peak of the Average Serum Concentration-Time Surve (min) ± S.D.	60 ± 0	30 ± 0	60 ± 0	30 ± 0
Average of the Area Under the Curve (0-480 min, g/ml) ± S.D.	234.25 ± 8.20	260.37 ± 42.20	261.15 ± 12.40	293.40 ± 7.87
Percentage of the Suspension (0-480 min)	79.85	88.76	89.02	100.00

* each is the average of three animals

ug/ml, from witepsol H-15 is 1.355 ug/ml, and from theobroma oil is 1.238 ug/ml. The time of the peak serum concentration is believed to be closely related to the rate of absorption of the drug from a formulation (17). The times of the peak from suspension and witepsol H-15 are 30 minutes after administration while from PEG 1000 and theobroma oil are 60 minutes. The area under the curve, representing the amount of the drug absorbed after the administration (17), of the suspension, PEG 1000, witepsol H-15, and theobroma oil, which measured mathematically by trapezoidal technique, are 293.3, 261.1, 260.3, and 234.2 ug/ml-min, respectively. The areas under the curves of PEG 1000, witepsol H-15, and theobroma oil are 89.02%, 88.76%, and 79.85% of the oral suspension, respectively.

A student "t" test was conducted on all data from the four different formulations (Table III). As can be seen there is no difference in the peak concentration between each suppository formulation and oral suspension. For the time of the peak, there is no difference between witepsol H-15 and the oral suspension, while there are significant differences between theobroma oil and oral suspension. For the area under the curve, there are no differences between witepsol H-15 and suspension, and between PEG 1000 and suspension. In this investigation, based on the in vivo data, witepsol H-15 suppository appears to deliver the drug at the same rate as in oral suspension, but at a faster rate than the other bases. The reasons are that even though PEG suppository shows a more rapid release rate than witepsol H-15 in in vitro disintegration, it dissolves rather slowly in the small amount of rectal

TABLE III

EVALUATION OF STUDENT "t" TEST

	DIFFERENCE BETWEEN		
	Theobroma Oil & Suspension	Witepsol H-15 & Suspension	PEG 1000 & Suspension
Peak of the Average Serum Concentration-Time Curve (g/ml)	n.s.** p >0.50	n.s. p >0.70	n.s. p> 0.70
Time of the Peak of the Average Serum Concentration-Time Curve (min)	s.*** p <0.0001	n.s. p >0.9995	s. p <0.0001
Average of the Area Under the Curve (0-480 min, g/ml)	s. p <0.01	n.s. p >0.30	n.s. P >0.05

* tested at the 0.05 level of significance

** n.s. = not statisticahly significant at 0.05 level of significance (p>0.05)

*** s. = statistically significant at 0.05 level of significance (p<0.05)

fluid (18), and theobroma oil tends to form barrier between the drug and the rectal membrane due to its fatty character (2). The total amounts of naproxen absorbed from witespol H-15, PEG 1000, and suspension, are almost the same, and are greater than from theobroma oil. This may be due to the interaction of naproxen to theobroma oil and its lack of interaction to other bases, or naproxen may form complex with theobroma oil.

A review of bioavailability profile in Figure 4 and *in vitro* release in Figure 2 indicate that there is a correlation between the *in vivo* absorptions from three suppository formulations and the dissolution release of procedure III, a phenomenon which has been previously reported (3). The *in vitro* testing shows that naproxen was released from witepsol H-15 more readily than from PEG 1000 and theobroma oil. The in vivo investigation indicates that naproxen was absorbed from witepsol H-15 faster than the other two bases.

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