CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20716

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 26 1997

Clinical Pharmacology/Biopharmaceutics Review

Hydrocodone Bitartrate 7.5mg &
Ibuprofen 200mg Tablets
NDA 20-716 Orig.
Vicoprofen® Tablets
Reviewer: E.D. Bashaw, Pharm.D.
APW

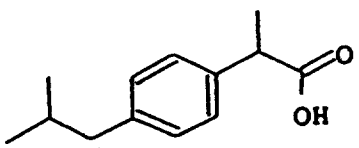
Knoll Pharmaceutical
Mt. Olive, NJ

Submission Date:
April 26, 1996

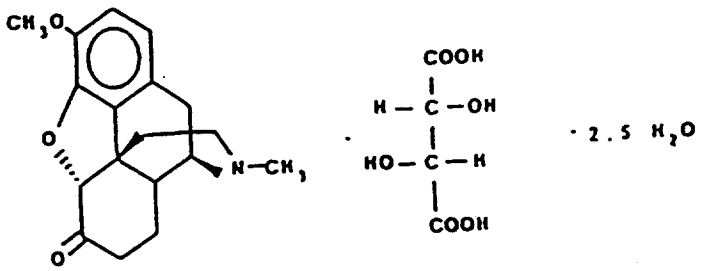
Review of an NDA

I. Background

Knoll Pharmaceutical currently markets a number of analgesic products including Dilaudid® (hydromorphone) and Vicodin® (hydrocodone bitartrate and acetaminophen). The combination of an opioid analgesic and a non-steroidal anti-inflammatory agent is a rational combination of analgesics with two different modes of action. Products related to the one proposed in this application include Percodan® (oxycodone and aspirin), Percocet® (oxycodone and acetaminophen) and the applicant's own product Vicodin®. The product that is the subject of this NDA is intended for use in the treatment of moderate to severe pain. Because of its obvious similarity this product, to some degree, can be considered a pseudo-line extension of the Vicodin® product line. The substitution of a NSAID for acetaminophen should offer some advantages by the inclusion of anti-inflammatory activity to the dual mode analgesic effect. The proposed product will be produced as only 1 strength (hydrocodone 7.5mg/ibuprofen 200mg). Based on the rating of Vicodin®, it is anticipated by the applicant that this product will be classified as a schedule-III narcotic combination under the Controlled Substances Act. Throughout the review the following abbreviations will be used: HC for hydrocodone, IBU for ibuprofen. Reproduced below are the associated chemical structures of HC and IBU:



Benzeneacetic acid,
1-methyl-4-(2-methylpropyl),(±)



Morphinan-6-one,4,5-epoxy-3-methoxy-17methyl-,(5α)-,[R-(R*,R*)]
-2,3-dihydroxybutanedioate

As part of this NDA the applicant has submitted the results of four in vivo pharmacokinetic studies. These studies were designed to investigate the pharmacokinetics of both the individual components of the product given singly and in combination. In addition the

effect of gender and formulation effects were also investigated. As part of the clinical development of this product a pk/pd study was conducted to investigate the additive effects of combining an opioid analgesic with a NSAID. This information along with in vitro dissolution data makes up the core of information regarding the biopharmaceutic portion of this application. At this time the application is incomplete in two respects:

1.) All of the pharmacokinetic studies and most of the clinical development of this product was carried out using doses of two tablets (15mg HC and 400mg IBU). As single tablet doses are going to be used, it should have been investigated to demonstrate the dose proportionality of the finished dosage form.

2.) The applicant did not perform a food effect study. Such a study has been a pre-approval requirement for controlled release drug products for a number of years and has over the last two years been extended into the immediate release category.

These "deficiencies" in the package were noted in the filing memo for this application. In negotiation with the applicant prior to the filing date they admitted that these requests had been made during the development of this product but they had "slipped through the cracks". A decision was made by the reviewing medical division that as the applicant is making a good faith effort to correct these deficiencies and that completion of these items is expected shortly, that the submission of them should not be a condition of approval. This finding was based partly on the well known nature of both drugs, given both singly and in combination with other agents. It was decided that until completion the outstanding nature of these items would be reflected in the proposed package insert. These statements will indicate that the effect of food on the dosage form is unknown and that dose proportionality has not been demonstrated.

II. Recommendation

At the present time the sponsor is rapidly bringing these two "deficiencies" into compliance. A protocol was submitted to the Agency for review in Sept. for a three-way crossover study comparing a single tablet to two tablets with and without food. At the present time (Jan. 1997) the clinical portion of the study is done and the applicant is expecting submission of the data in the first 2 months of 1997. As both of the components of this product are well known and are not considered "bio-problem" drugs, the filing of this application was acceptable given that the applicant has initiated positive action to resolve these issues in a rapid manner.

Given this agreement with the applicant, the only outstanding issue from a biopharmaceutic perspective is the final selection of an appropriate in vitro dissolution method. The proposed method has been evaluated by both this reviewer and the reviewing chemist (Ms. Charlotte Yaciw) and found to be deficient (i.e., it lacks sensitivity). This was conveyed to the applicant in a memo dated Oct. 3, 1996. Until this issue is resolved the application can only be considered approvable from a biopharmaceutic perspective.

INDEX

I. Background * * * * * * * * * 1
II. Recommendation * * * * * * * * 2

III. PK Studies Overview * * * * * * * * 3
IV. Analytical Methods * * * * * * * * 3
V. Summary of In Vivo Pharmacokinetic Trials
VP-02:Interaction between individual tablet components * * 6
VP-30:Bioequivalency of two tablet formulations * * * 7
VP-22:PK/PD evaluation in acute post-operative dental pain * 11
VP-27:Bioavailability and formulation * * * * 15
VI. In Vitro Dissolution * * * * * * * * 16
VII. Conclusions * * * * * * * * * 17
VIII. Comments * * * * * * * * * 18

Appendix I-Studies

Study #	Short Summary Title	Page No.
VP-02	Interaction between individual tablet components	2
VP-30	Bioequivalency of two tablet formulations	8
VP-22	PK/PD evaluation in acute post-operative dental pain	21
VP-27	Bioavailability and formulation	28
	In Vitro Dissolution	38

III. PK Studies Overview

As noted in the background section of this NDA, the applicant submitted four in vivo pharmacokinetic studies. These studies encompass two different strengths of product, two different formulations, and differences in manufacture. The final product was studied pharmacokinetically in a head-to-head manner with the clinically studied formulation in study VP-30. From a pharmacokinetic standpoint the studies were well designed and incorporated adequate numbers of subjects. Although one of the four studies used a dose ratio of HC to IBU that is not being approved, it is being included in this review as this study addresses the issue of individual components vs. finished product (i.e. an interaction study). While it is true that the Agency is awaiting the results from a single dose pk study and a food effect study, there is sufficient breadth of information present in the NDA for review given the nature of the products involved.

IV. Analytical Methods

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

IV. Summary of In Vivo Pharmacokinetic Trials

Study#VP-02: *Single-dose, Three-Way Crossover Bioavailability Study of Vicoprofen® (hydrocodone bitartrate 5mg with ibuprofen 200mg) and Its Active Components.*

As noted in the title above, this study was designed to investigate the interaction between the individual components of the dosage form and the proposed dosage form. This study is noteworthy as it is one of the first studies done in the development of this NDA and as such uses a ratio of HC to IBU that was subsequently abandoned. The product in this study uses 5mg of HC compared to 7.5mg of HC in the final to-be-marketed dosage form, but is otherwise the same product. This increase in the opioid component of the product was done based on both a revised potency ratio for HC and also with clinical evidence of a need to increase the HC to maintain/achieve effective analgesia. The study's continued applicability to this application is that, as a "drug interaction" study, the end-point of interest is not strict bioequivalence (although it would be preferable) but to detect if either component hinders or accelerates the absorption/elimination of the other. As such, the formulation differs only in the amount of HC present in each tablet, and as gross measures of "equivalence" are employed, it is acceptable.

The study itself was a straight forward three-way bioequivalency study. A total of 26 healthy male subjects were enrolled in this trial and successfully completed all three phases of the trial. Attached as pages 2-7 of Appendix I are the study summary sheets and supportive data from this trial. Reproduced below is a summary data table detailing the observed differences seen between the test (Vicoprofen-5®) and reference products:

Study VP-02, Mean Pharmacokinetic Data (%C.V.)

	Hydrocodone			Ibuprofen		
	Vicoprofen-5® (2 tablets)	Hydrocodone (2x5mg tabs.)	Log Transformed 90% C.I.	Vicoprofen-5® (2 tablets)	Ibuprofen (2x200mg tabs.)	Log Transformed 90% C.I.
AUC0-inf*	123(38%)	121(36%)	94-107	99(18%)	108(20%)	89-99
Cmax*	18.6(22%)	16.9(22%)	101-117	27.2(20%)	23.7(16%)	105-127**
Tmax (hrs)	1.3(35%)	1.7(52%)	n.a.	2.2(53%)	2.3(55%)	n.a.
T1/2 (hrs)	4.4(36%)	4.2(35%)	n.a.	1.6(24%)	1.9(21%)	n.a.

*AUC0-inf units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml
**Confidence Interval outside the 80-125% acceptance limit.

Technically, the study that the sponsor performed here, a three-way crossover study, to investigate the effect of drug-drug interaction in a combination product, is not properly designed. Instead of using a three-way model, the study should have been a randomized four-way trial. The leg of the trial that is missing is the administration of hydrocodone and ibuprofen concomitantly as two immediate release components administered together. Although seemingly repetitive, this treatment leg would be able to establish whether or not there was a drug interaction that was not formulation based. It would also establish the degree of in vivo bioavailability by using an "idealized" i.e., solution reference treatment for each component. Ideally such a treatment leg would utilize commercially available liquid dosage forms administered in a combined manner. The failure of the sponsor to do so in this study is critical but not fatal to the application. With the existence of in vivo clinical data supporting the approval of this application the need for definitive bioavailability is somewhat reduced but not removed. The study itself does demonstrate the relative bioavailability of the test product to "reference products", but the reference products used were manufactured by the applicant and were not approved products. While the two reference products do meet the USP specifications for hydrocodone and ibuprofen tablets, this is not an assurance of in vivo bioequivalency with an approved product. Had there not been adequate in vivo clinical data and had the two components in question not been drugs with a long history of marketing and use, then the acceptance of this study for the purposes of establishing the lack of a combination drug interaction would not be possible.

As noted earlier, strict bioequivalence is not a requirement for this study, per se. At the request of this reviewer the applicant did provide a supplemental analysis of the data from this trial that included calculation of log transformed confidence intervals. From their analysis there appears to be a slight difference in the peak plasma levels produced by IBU. Examination of the individual plasma concentration profiles (Appendix I, page 6) shows a fair degree of variability in the data. This variability is reflected here in the calculation of Tmax which for both products has a %CV in the 50's. This variability is not especially surprising as the pka for IBU is approximately 5.5 and as such is poorly soluble in the gastric fluid. Gastric emptying time and accordant transit time into the high pH in the small intestine is being translated into both the Cmax and Tmax values. The fact that the Vicoprofen-5® tablets show higher Cmax values than those from the reference ibuprofen treatment, suggests that the formulation of the ibuprofen product may be less than ideal. In any case the magnitude of the difference between the two products is small and there is no sign of any significant differences beyond this. From a therapeutic standpoint, there does not appear to be any meaningful interaction between the individual components.

Study#VP-30: *A Single Oral Dose, Two-Way Crossover Bioequivalence Study Comparing Direct Tablets to Tablets of Vicoprofen® (hydrocodone bitartrate with ibuprofen).*

As part of the manufacturing scale up for this product the applicant switched from . Prior to the change the applicant was purchasing IBU drug substance from . This material came from the supplier ready for use where 318mg of the : contained 200mg of actual IBU. This change in formulation is discussed in more detail in the chemistry review.

Attached in Appendix I, page 9 is a comparative formulation between the

This study was designed to demonstrate bioequivalence between the two formulations given as a dose of two tablets of either formulation (15mg Hydrocodone and 400mg ibuprofen) in a random manner with a 7 day washout period between treatment groups. A total of 33 subjects were enrolled in this trial (14 males and 19 females). Two subjects were withdrawn from this trial (1 male and 1 female) due to abnormal lab values prior to the second treatment phase, leaving 31 complete sets of data. Due to the number of subjects present in this study the applicant was asked to undertake a secondary analysis of the data to evaluate gender effects. Attached in Appendix I as pages 8-18 are the associated study summary sheets and supportive data from this trial. Reproduced below is a summary data table from the appendix.

Study VP-30, Mean Pharmacokinetic Data (%C.V.)

	Hydrocodone			Ibuprofen		
			Log Transformed 90%C.I.			Log Transformed 90%C.I.
AUC0-inf*	211.7(33%)	216.2(25%)	99.1-109.8	131(29%)	135.6(26%)	98.7-108.4
Cmax*	27(35%)	27.3(22%)	96.8-110.6	28.5(23%)	30.2(23%)	97.4-115.1
Tmax (hrs)	2.1(83%)	1.7(65%)	n.a.	2.8(81%)	1.78(101%)	n.a.
T1/2 (hrs)	4.6(29%)	4.5(25%)	n.a.	2.5(39%)	2.2(18%)	n.a.

*AUC0-inf units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml

Examination of the data from this study indicates that the two formulations are bioequivalent. What is of interest from this data is the continued variability seen in the Tmax values. In this study, unlike the previous one, there is not a statistical difference in Cmax for IBU, even though the Tmax values are different. Interestingly, HC also shows wide variability in Tmax and yet has a relatively tight confidence interval for Cmax, suggesting, but not necessarily proof of, the proposed solubility and formulation issues of IBU raised in the review of Study#VP-02. In any event, the applicant, through this study, has successfully linked their to-be-marketed formulation to their clinically studied formulation.

As noted before the applicant at the request of the FDA used the data obtained in this trial to assess the presence or absence of a gender effect on the pharmacokinetics of HC and IBU. The applicant did not understand the FDA guidance properly and initially did an analysis within gender across dosage form, that is male vs. males and females vs. females While an interesting way to look at the data, this analysis (referred to by the applicant as the primary gender analysis) does not answer the question of is there a difference in the pharmacokinetics of HC and IBU based on gender alone? This issue was addressed by the applicant by a second analysis (referred to by the applicant as the secondary gender analysis) after input from the Agency. Appendix I page 17 contains the summary statistical data tables for the so-called "primary analysis". As it does not really address the issue at hand it is included in the appendix for interest only. The proper gender analysis (the so-called "secondary analysis") is summarized below (the supportive statistical tables are attached in Appendix I as page 18):

Study#VP-30, Secondary Gender Analysis

	Females (n=18)	Males (n=13)	Log Transformed 90% C.I.
Hydrocodone			
AUC0-inf(ng*hr/ml)	210.53	213.41	78.5-116.9*
Cmax(ng/ml)	26.53	27.69	80.9-118.8
Tmax(hrs)	2.61	1.44	-
Cl(ml/min/kg)	1.85	1.4	
Ibuprofen			
AUC0-inf(ug*hr/ml)	143.89	117.51	102.7-141.7*
Cmax(ug/ml)	27.99	29.26	80.9-110.2
Tmax(hrs)	1.89	1.39	-
Cl(ml/min/kg)	0.72	0.68	
	Females (n=18)	Males (n=13)	Log Transformed 90% C.I.
Hydrocodone			
AUC0-inf(ng*hr/ml)	220.63	210.03	89.7-122.9
Cmax(ng/ml)	28.41	25.7	94.3-124.8
Tmax(hrs)	3.57	1.81	-
Cl(ml/min/kg)	1.77	1.42	
Ibuprofen			
AUC0-inf(ug*hr/ml)	144.91	122.84	99.5-137.9*
Cmax(ug/ml)	30.39	29.93	88.2-118.2
Tmax (hrs)	2.67	1.08	-
Cl(ml/min/kg)	0.71	0.64	

*Outside of standard Bioequivalency acceptance limit of

Examination of the data presented above indicates that for ibuprofen there is not a detectable gender difference. The data for hydrocodone does suggest a possible gender difference with Cl being approximately 25% faster for females than males on a per kilogram basis. The high degree of agreement between the calculated Cl values between the two dosage forms indicates that this is a reproducible difference and is not likely to be an artifact of the data. Whether or not this is a clinically significant difference is impossible to tell from this data. Beyond this alteration in Cl there does not seem to be "gender" based difference for any of the other parameter values contained either in this summary table or in the appendix.

Picking up on an issue raised earlier in this review is the apparent high degree of variability present in the Tmax data. Although split up into a number of different comparisons there appears to be some difference in the Tmax values for HC and especially for IBU. Whether or not these differences are gender linked or is more a function of formulation issues inherent in each dosage form is unknown at this time. Attached as pages 19 and 20 in Attachment I are the individual subject plots of IBU from both the formulations. For both males and females there appears to be quite a bit of variability in the plasma levels. In regards to Tmax the subjects break down as follows:

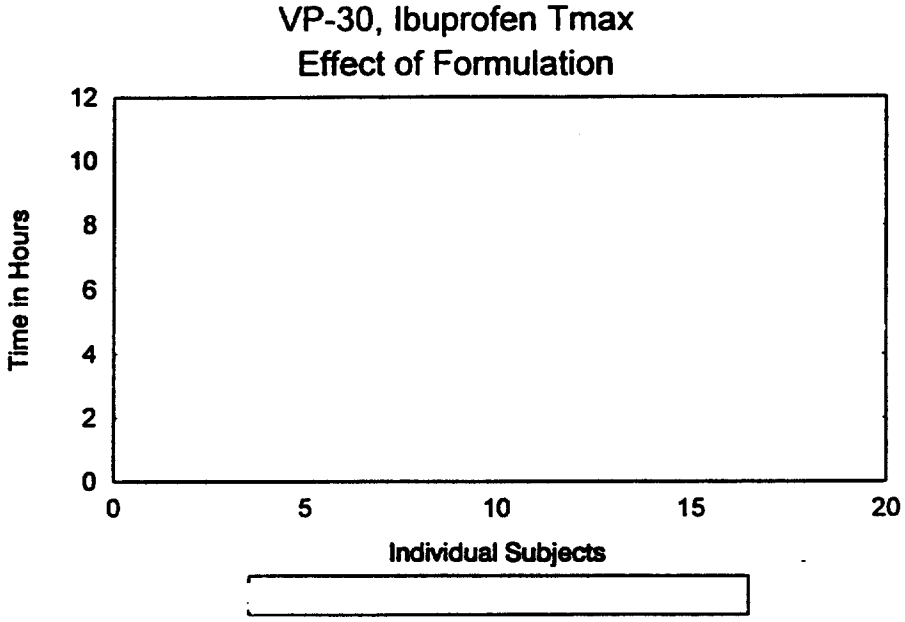
Study#VP-30, Ibuprofen Tmax Comparison

Time in hrs.	# of Observations Females (n=18)	# of Observations Males (n=13)	# of Observations Females (n=18)	# of Observations Males (n=13)
0				
0.5	5	4		1
1	4	7	4	7
1.33	2	1	2	1
1.67			2	1
2				
2.33				
2.67				
3	2			1
3.33			1	
3.67	1	1		
4	1			
5	2		7	2
6			1	
8	1			
10			1	
12				

If we use 2 hrs. a break-point for Tmax it works out that for the formulation only 44% of female subjects and 77% of male subjects have peak concentrations occurring at 2 hours or less. The formulation does improve this situation somewhat by raising the 2hr. rates to 61% and 92% for females and males, respectively. Considering that this product is intended as an analgesic, this data suggest that there may be problems with either onset of effect or the peak magnitude of effect in females. Possible explanations of this finding for IBU include solubility issues, retention of the dosage form in the stomach, formulation related issues, and/or gender related issues such as retention time or gastric pH .

As mentioned in the discussion on page 9, it is impossible to tell whether or not the variation seen in Tmax is due to gender or to other formulation specific issues or a combination of both. While an assessment of Tmax variability is not specifically part of a general gender analysis, it was decided by this reviewer to look at the intra-subject distribution of Tmax values as primarily a formulation issue. The reasoning being that if a formulation related pattern developed then one could more easily remove gender as a cause of Tmax variability. Reproduced below is a plot of the Tmax values for each subject and treatment. Inspection of the figure reveals that of the 18 pairs, 13 of them show a reduction in Tmax from

3 pairs are unchanged, and 2 pairs show a prolonged Tmax with the



While other factors certainly are playing a part in this issue, i.e. the inherently poor solubility of IBU, it appears from this perspective that the formulation and/or method of /manufacture, in addition to intrasubject variability, is the underlying issue with regards to changes seen in the distribution of Tmax values. Due to the study design used in this trial the relative contributions of intrasubject variability and "formulation" effects cannot be separated. While they both contribute to the observed variability, it is this reviewers opinion that the "formulation" effects are driving the differences observed in the data.

Study#VP-22: *A Characterization of the Pharmacokinetic/Pharmacodynamic Relationship of Single Oral Doses of Vicoprofen® (hydrocodone bitartrate 15mg with ibuprofen 400mg) Tablets for the Treatment of Acute Postoperative Dental Pain*

This study was undertaken as part of the clinical development plan to investigate the use of Vicoprofen® in the treatment of dental pain. The pain model used was the standard impacted molar extraction model. Anesthesia was accomplished with a combination of nitrous oxide and either a short acting barbiturate or benzodiazepine. The only opioid analgesic allowed in the trial was small doses of sufentanil citrate. A total of 72 subjects were enrolled in the trial (36 males and 36 females) and completed all phases of the trial. As part of the trial all subjects were asked to rate their pain according to two scales: 1.) a four point categorical scale for pain intensity and 2.) a five point categorical scale for pain relief. In addition the subjects were asked to indicate the time when first noticeable pain relief occurred and to provide an overall

assessment of their pain relief at the conclusion of the study. Attached as pages 21-27 in Appendix I are the associated study summary sheets and supportive pk/pd data from this trial.

It should be noted that this trial employed a "double-dummy" design, in that all treatments had a corresponding placebo. That is the subjects randomized to receive Vicoprofen® tablets also received a placebo suspension and the subjects who received the active ibuprofen suspension had a placebo tablet. By implication there was also a true placebo treatment group which received both the placebo tablet and placebo suspension.

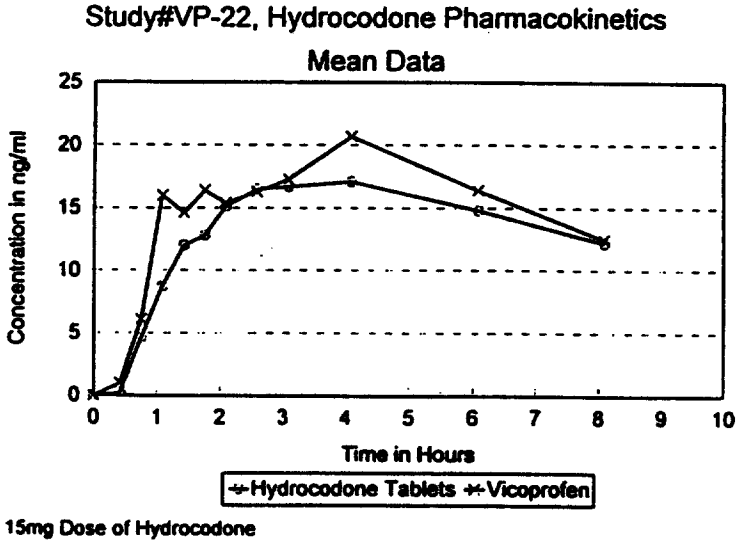
Pharmacokinetic Analysis

The pharmacokinetic results for HC from this study are very comparable to those in the previous study (VP-30). The only obvious difference in the data is the prolonged Tmax and $T_{1/2}$ noted in this study. The significance of this prolonged Tmax will become evident in the analysis of the pharmacodynamic portion of this NDA. It is likely due to the combination of the effects of dental surgery and pain on gastric secretions and G.I. transit time (i.e, a fight or flight response). In general these factors tend to slow down gastric transit and can result in prolonged Tmax values. Reproduced below is a summary data table for HC:

Study#VP-22, Hydrocodone-Mean Pharmacokinetic Data (%CV)

15mg Dose	Cmax (ng/ml)	Tmax(hrs)	AUC_{0-inf}	AUC_{0-t}	$T_{1/2}$ (hrs)
Hydrocodone Tablets	22.31(40%)	3.43(64%)	217.55(37%)	106.1(44%)	6.21(30%)
Vicoprofen	28.28(35%)	2.94(58%)	283.79(94%)	120.33(25%)	7.71(128%)

From the table above the calculation of AUC_{0-inf} by the applicant appears to be flawed. Inspection of the raw data indicates that this value of AUC is being driven by two "outliers". They do not appear to be due to analytical error and the overall shape of their plasma level time curves does not appear out of the range of possibilities. For this reason and the fact that there was not a good criteria to use to reject the data, these two subjects were retained in the analysis. Reproduced below is a plot of the mean HC data from this study:

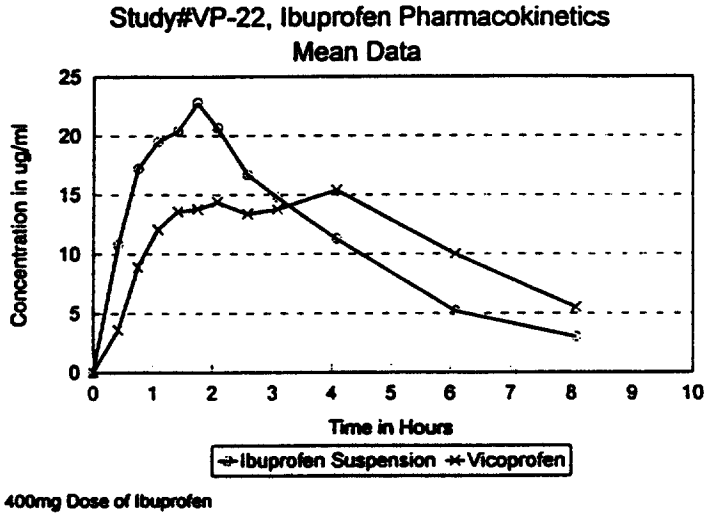


As for the ibuprofen component of this study, the data results are somewhat mixed. Some of the results (Cmax, half-life) tend to agree with the previous study, while other parameters do not (AUC0-inf, and Tmax). Reproduced below is a summary data table from this trial:

Study#VP-22, Ibuprofen-Mean Pharmacokinetic Data (%CV)

400mg Dose	Cmax (ng/ml)	Tmax(hrs)	AUC_{0-inf}	AUC_{0-t}	$T_{1/2}$ (hrs)
Ibuprofen Suspension	29.09(24%)	1.49(60%)	98.07(29%)	89.16(25%)	1.88(26%)
Ibuprofen (Vicoprofen®)	28.12(31%)	2.74(62%)	105.94(29%)	87.87(26%)	2.15(28%)

On the surface of the data there does not appear to be any remarkable differences between the two treatments except for Tmax. When the mean data is plotted out, however, a slightly different picture emerges:



This data clearly shows a lag for the plasma concentrations for ibuprofen from the Vicoprofen® tablets. The clinical implications of this could be dramatic as dental pain, i.e. "bone pain", is usually more response to NSAID's than to opioids. Admittedly the comparison is between that of a tablet and a suspension, and one could in general expect quicker levels with the suspension treatment, but the magnitude of the difference in mean levels is more than one would normally expect. Examination of the individual subject data (page 24, Appendix I) does show a delay in the inital rise in plasma concentrations for the mean data, but it also shows that there is a high degree of inter-subject variability. This suggests that while the mean data may be suppressed, this "suppression" in plasma levels is due to averaging concentrations across the timepoints. For any individual subject it is equally likely that they will get "rapid" pain relief or pain relief of a somewhat slower onset.

Pharmacodynamics

The pharmacodynamic endpoints of interest in this study are time to onset of measurable pain relief (a measure of rate), pain intensity difference (a measure of the extent of pain relief), and time to remedication (a measure of duration). In order to collect information in all groups, including placebo, all subjects were encouraged to refrain from re-medication until 2

hours post-dose. Once re-medication/rescue occurred, the subject was dropped from the pharmacodynamic assessment portion of this trial.

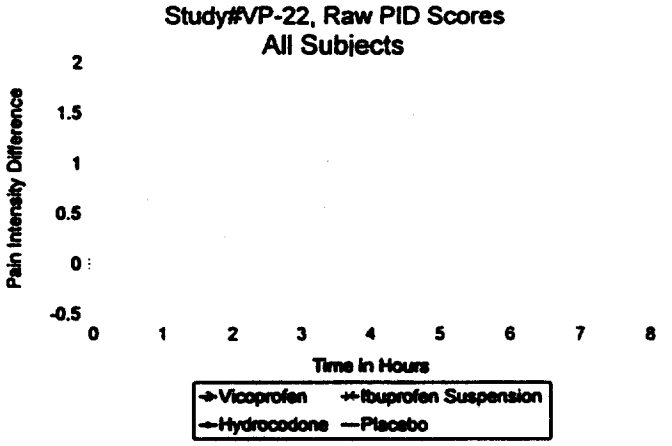
Onset of pain relief was assessed by asking all subjects to record on their case report forms when they first noticed pain relief. This data was then tabulated and a median value was calculated.

Study#VP-22 Time to Onset (hrs.)

	Placebo n=18	Hydrocodone n=18	Ibuprofen n=18	Vicoprofen® n=18
Patients with positive pain relief	12 (66.7%)	9 (50%)	18 (100%)	15 (83.3%)
Median Time	0.84	>1.67	0.33	0.33

From this data an interesting result is that placebo actually beats the hydrocodone treatment phase. While it is not suprising that the pure opioid did poorly in this assessment, it is unusual that the median time to pain relief was >1.67hrs. Calculation of a time to onset after this timepoint was not possible due to dropouts. As for Vicoprofen® it shows a high percentage of early onset scores that are comparable to the ibuprofen suspension. While not a definitive test, one of the desirable properties of any analgesic is an early onset/perception of pain relief. On the basis of this data it can be concluded that Vicoprofen® does demonstrate an early onset of pain relief in this model. It also suggests that the majority of its activity in this model is due to the ibuprofen component and not the opioid component.

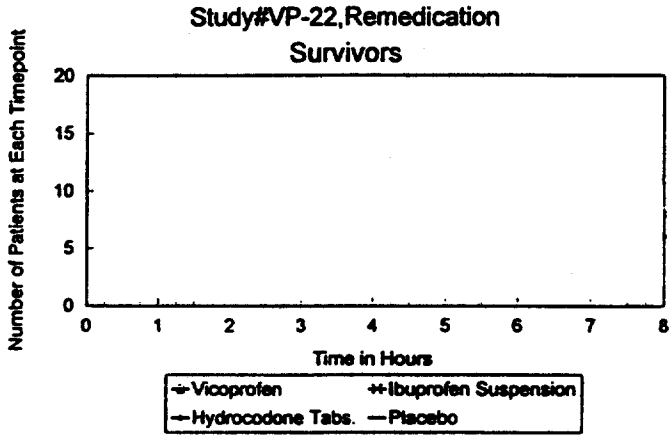
As for the actual pattern of pain relief, each subject was asked to initially rate their pain on a 4 point scale. Subsequent to dosing the subjects were asked to reassess their pain relative to their original score. This difference in pain is referred to as the Pain Intensity Difference or PID. In a general sense, using this pain model, a good analgesic is one that can cause a reduction in pain of 1 unit. Attached in Appendix I as pages 25-27 are the PID scores for all subjects over time and by sub-set (see below). A graphical representation of the PID scores for all subjects and all treatments is presented below:



Analysis of the PID data reveals an unexpected finding that the IBU suspension performed better than the Vicoprofen® combination product (unexpected in that one would normally assume that hydrocodone, a known opioid analgesic, would be expected to potentiate the analgesic effect of ibuprofen). The reason for this is unclear but is thought to be due to the

observation that the peak plasma levels of IBU produced by the suspension are superior to those from the Vicoprofen® tablet. In an attempt to find an association between the PID scores and treatments the applicant did alternative analyses of the PID data using initial assessment of pain as a variable. Copies of the results of these analyses are attached as pages 26 and 27 of Appendix I. Neither attempt by the applicant to use stratification by initial pain rating appreciably improved the scoring of this trial. As it was the conclusion drawn from this study by this reviewer that the combination of HC with IBU was inferior to IBU suspension in terms of overall pain relief. Considering that the dose of IBU is identical across the two treatment groups it implies that rate is a primary determinant.

As for the final pharmacodynamic measure, time to remedication, a plot of time to remedication as the number of subjects remaining in the trial versus time was prepared:



The data represented here is consistent with that seen with the PID scores, that is that the IBU suspension was superior to all treatments. Vicoprofen® on the other hand was inferior to IBU suspension for the majority of the observation internal as measured by dropout rate. It was superior to placebo and to single entity HC.

The net results of the pharmacodynamic analysis is that Vicoprofen® is an analgesic, it has a rapid onset of action, and it is superior to placebo and single entity HC in acute postoperative dental pain. It is, surprisingly inferior to IBU suspension. A possible explanation of this finding may be related to the double dummy nature of this protocol. An examination of IBU pharmacokinetics from both the IBU suspension and the Vicoprofen® tablet suggests that the placebo suspension may have impeded the absorption of IBU from the tablet. In an effort to assess this the applicant undertook a study to investigate the formulation interaction effects of the suspension formulation.

Study#VP-27: A Single Oral Dose, Three Way Crossover Pharmacokinetic Study Comparing Vicoprofen (hydrocodone bitartrate with ibuprofen) Administered Alone and in Conjunction with a Sorbitol-Containing Suspension.

This study was designed to investigate the impact of a sorbitol containing placebo suspension on the absorption of IBU from the Vicoprofen® tablet and from IBU tablets. This study was an outgrowth of the inconsistent clinical results seen in study VP-22. This was

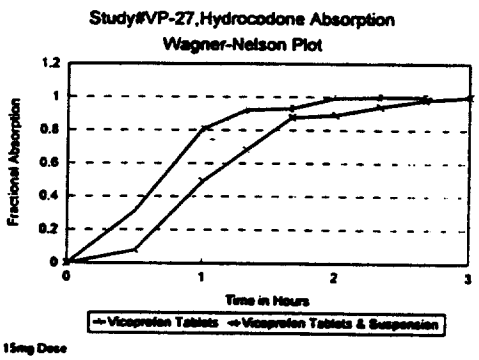
designed as a three-way crossover study using doses of two tablets of Vicoprofen® versus the combination of Vicoprofen® tablets with a sorbitol suspension and ibuprofen tablets administered alone to 34 healthy male and female subjects. Attached as pages 28-37 are the study summary sheets and supportive data tables. A summary data table is presented below:

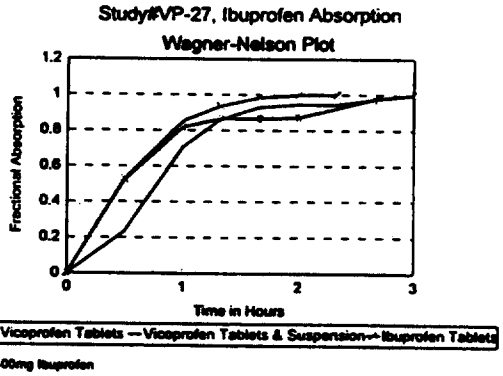
Study#VP-27, Mean Data (%CV)

	Hydrocodone		Ibuprofen		
	Vicoprofen	Vicoprofen & Suspension	Vicoprofen	Vicoprofen & Suspension	Ibuprofen Tablets
Cmax*	29.7(23%)	28.9(23%)	32.5(24%)	33.2(19%)	35.8(16%)
Tmax (hrs.)	1.73(45%)	2.58(40%)	1.73(69%)	1.98(60%)	1.67(54%)
$T_{1/2}$ (hrs.)	4.22(23%)	4.09(29%)	2.01(32%)	2.03(44%)	1.92(20%)
AUC_{0-inf}*	211.1(28%)	212.7(28%)	118.2(29%)	122.1(32%)	129.2(30%)

*AUC_{0-inf} units for HC=ng*hr/ml, for IBU=ug*hr/ml
Cmax units for HC=ng/ml, for IBU=ug/ml

The results of this study suggest that the placebo suspension that was used in the clinical study (VP-22) did not significantly impact the AUC or Cmax of IBU from Vicoprofen® tablets. There was, however an impact on the rate of absorption of both HC and IBU as manifested by results of a Wagner-Nelson analysis performed by this reviewer:





Examination of the Wagner-Nelson plots suggests a modest absorption related effect that tends to slow the initial rate of drug absorption. Even so it should be noted that in the dynamic portion of the last study the Vicoprofen® leg of the study was able to demonstrate onset of pain relief within the first half-hour. The fact that it was able to so undercuts the applicant's hypothesis that sorbitol exhibited an inhibitory effect on the absorption of drug from the GI tract. Clearly there was some effect, but Vicoprofen® itself has a significant degree of variability built into it as measured by Tmax in Study#VP-30 (page 7).

The possibility remains that the reduced absorption seen in Study#VP-22 was due to some physiological stress factor related to the "trauma" of the dental procedure itself. The suspension treatment, with drug already in the solubilized and dispersed particulate states would be less effected by such changes. A solid tablet that has to undergo the various stages of dissolution prior to absorption would be subject to changes in the rate and composition of gastric secretions and gastric motility brought about by the body's natural response to injury and

inflammation secondary to the procedure. The present study was not designed to detect such changes and only demonstrates a modest lag in absorption rate.

In conclusion, the results of this study indicate that the relatively poor performance of the Vicoprofen® tablet in Study#VP-22 is not due to an interaction between the tablet and the sorbitol containing suspension treatment.

VI. In Vitro Dissolution

As part of this NDA the applicant, Knoll Pharmaceutical, has submitted in vitro dissolution data on both the ibuprofen and hydrocodone bitartrate components. The method and specification the applicant has proposed for both entities is as follows:

	USP23 Method (Proposed Method)	USP23 Revised Method
Apparatus	USP-1 (basket)	USP-2 (paddle)
Speed	150rpm	50rpm
Media	pH 7.2 phosphate buffer	pH 7.2 phosphate buffer
Volume	900ml	900ml
Specification	Q=70% at 30min.	Q=80% in 60min

This method is essentially the old USP 23 method for ibuprofen tablets. In the most recent USP 23 supplement (Official Nov. 15, 1996) this method was dramatically revised as shown in the table above (see Appendix I, page 38). Even before this revision the applicant was notified by the Agency on Oct. 3, 1996 that the original specification (and the method) were inadequate. Inadequate in that the in vitro performance of the product was very different from the proposed specification. Reproduced below is a summary table of the individual tablet component dissolution from two lots of Vicoprofen® that were used in the in vivo biopharmaceutics portion of the NDA:

Lot Number & Study	Component	Mean % Dissolved* (%CV)	Range
55-0392 Study #VP-22, 27, & 30	Hydrocodone	98% (3.4%)	
	Ibuprofen	97% (2.7%)	
055-K1080-PI-0295 Study #VP-30	Hydrocodone	103% (0.7%)	
	Ibuprofen	101% (0.7%)	

*% Dissolved at 30min using OLD USP 23 Method.

Analysis of the provided dissolution data clearly indicates that the proposed in vitro method is inadequate of assuring product quality except in the most gross manner. Additional dissolution profile data provided in the chemistry portion of the NDA demonstrated that the dissolution rate was fast enough to meet the proposed specification at 15min with little or no possibility of failure.

Unlike many products, the onset of effect of an analgesic is highly correlated with peak plasma levels and by extension with drug release from a dosage form. The current proposed in vitro dissolution specification (OLD USP Method) would allow for lots of drug to have a markedly different in vitro release profile and still past the "test". It is the opinion of both the chemistry and pharmacokinetic reviewers that prior to NDA approval the sponsor should initiate and report on alternative dissolution methods and medias that would provide a better basis for a release specification. This information has been conveyed to the sponsor (see Comment #2, below).

VII. Conclusions

Based on the four pharmacokinetic trials that were submitted in this NDA the following conclusions can be supported.

1. Neither hydrocodone or ibuprofen interact with the absorption or phamacokinetics of each other (Study VP-02).
2. The to-be-marketed formulation is bioequivalent to the clinically studied Vicoprofen® tablets
3. There is not a significant difference in the pharmacokinetics of ibuprofen based on gender. There does seem to be a somewhat faster clearance of hydrocodone (~20%) in female subjects. The cause of this increased clearance is unknown (Study VP-30).
4. Vicoprofen® tablets beat placebo in an acute dental pain model of analgesic effect but are generally inferior to ibuprofen suspension in terms of the onset of analgesic effect and dropout rate (Study VP-22).
5. The pharmacokinetics of Vicoprofen® tablets following a single two tablet dose have been determined.

VIII. Comments

1. At the present time the Agency is still awaiting a response from the applicant concerning a revised in vitro dissolution specification and revised labeling. Until these issues are resolved the application can only be considered approvable from a biopharmaceutic standpoint.
2. Although not a condition of approval, the Agency is also awaiting submission of the results of a single tablet pharmacokinetic study and a food-effect study for this product.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

CC: NDA 20-716(ORIG),
HFD-550/DIV File
HFD-550/CSO/Lissante
HFD-880(Bashaw)
HFD-880(Fleischer)
HFD-850 (Mira Millison, Drug, Chron Files)
HFD-344(Viswanathan)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix I-Studies

Study #	Short Summary Title	Page No.
VP-02	Interaction between individual tablet components	2
VP-30	Bioequivalency of two tablet formulations	8
VP-22	PK/PD evaluation in acute post-operative dental pain	21
VP-27	Bioavailability and formulation	28
	In Vitro Dissolution	38

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.15

Study Type: Bioavailability Study # VP-02

Study Title: A single dose, three-way crossover study of Vicoprofen® to its active components

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: Seven days

Cross-Over Y Parallel N Other Design:

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? 10hrs.

Subject Breakdown

Normal Y Patients N Young Y Elderly N Renal Hepatic

Subject Type		Males		Group	Males	N=	26	M=	26	F= 0
Weight	Mean	168	Range	Group		N=		M=		F=
Age	Mean	24.8	Range	Group		N=		M=		F=
Subject Type				Group		N=		M=		F=
Weight	Mean		Range	Group		N=		M=		F=
Age	Mean		Range	Group		N=		M=		F=

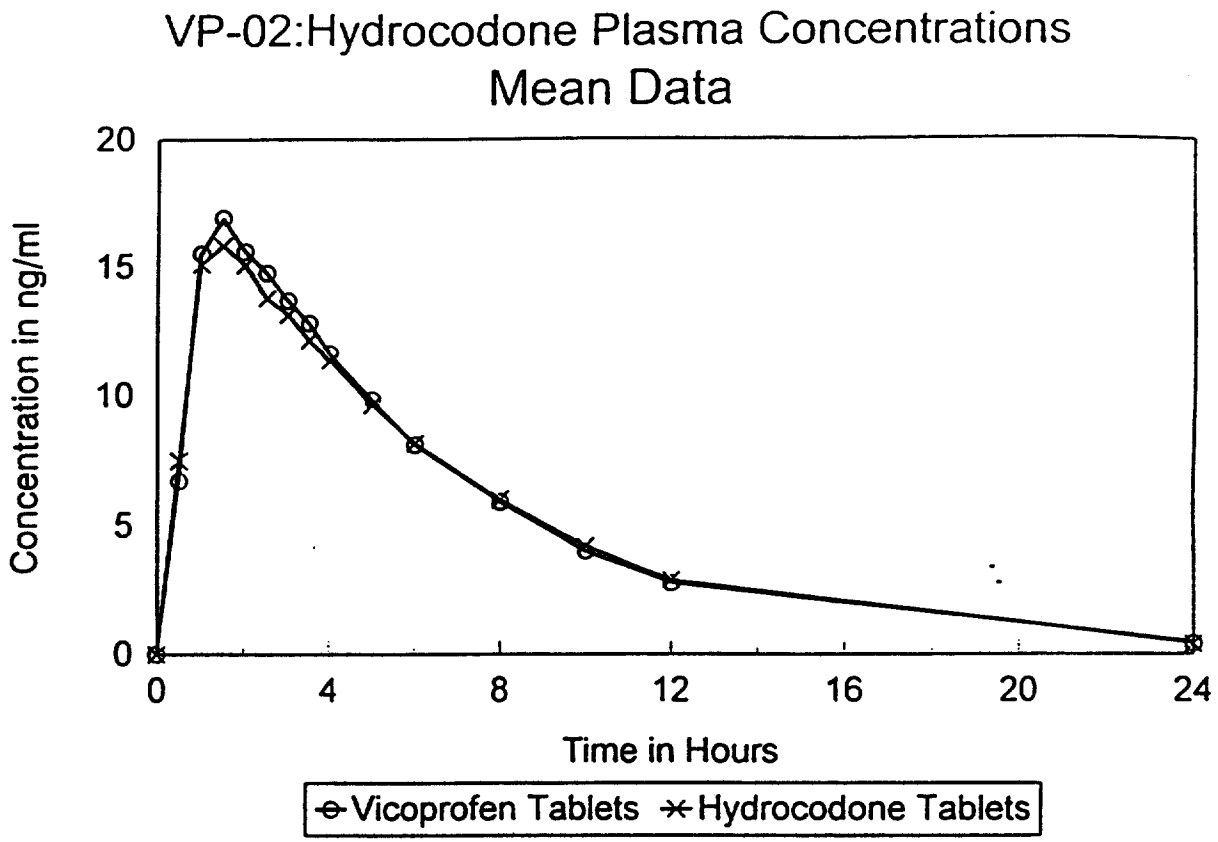
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Hydrocodone	10mg	tablet	5mg	02-0186	
Ibuprofen	400mg	tablet	200mg	29-0286	
Vicoprofen®*	10mg HCl/ 400 IBU	tablet	5mg HC/ 200mg IBU	H46-226	

*Experimental tablet formulation

Sampling Times

Plasma: 15ml samples, prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours after dosing.

	Hydrocodone	Ibuprofen
Assay Method:		
Assay Sensitivity		
Assay Accuracy		



10mg dose

HYDROCODONE PLASMA CONCENTRATIONS (ng/mL)
Mean (Std. Dev.)

Treatments:	VICOPROFEN® X 2 Tablets	HYDROCODONE 5 mg X 2 Tablets
TIME (HOURS)		
0.00	0.00 (0.00)	0.00 (0.00)
0.50	6.69 (4.85)	7.47 (4.18)
1.00	15.51 (5.48)	15.08 (4.14)
1.50	16.89 (4.28)	15.80 (4.35)
2.00	15.58 (3.94)	15.05 (3.60)
2.50	14.74 (3.74)	13.76 (3.61)
3.00	13.68 (3.70)	13.12 (3.35)
3.50	12.79 (3.85)	12.12 (3.07)
4.00	11.60 (3.33)	11.35 (3.24)
5.00	9.82 (2.89)	9.61 (2.70)
6.00	8.08 (2.97)	8.14 (2.06)
8.00	5.90 (2.49)	6.00 (2.28)
10.00	4.01 (2.01)	4.21 (1.66)
12.00	2.76 (1.51)	2.89 (1.61)
24.00	0.41 (0.63)	0.38 (0.61)

VP-02 Subjects Plasma Hydrocodone Concentration from Vicoprofen 400/10mg

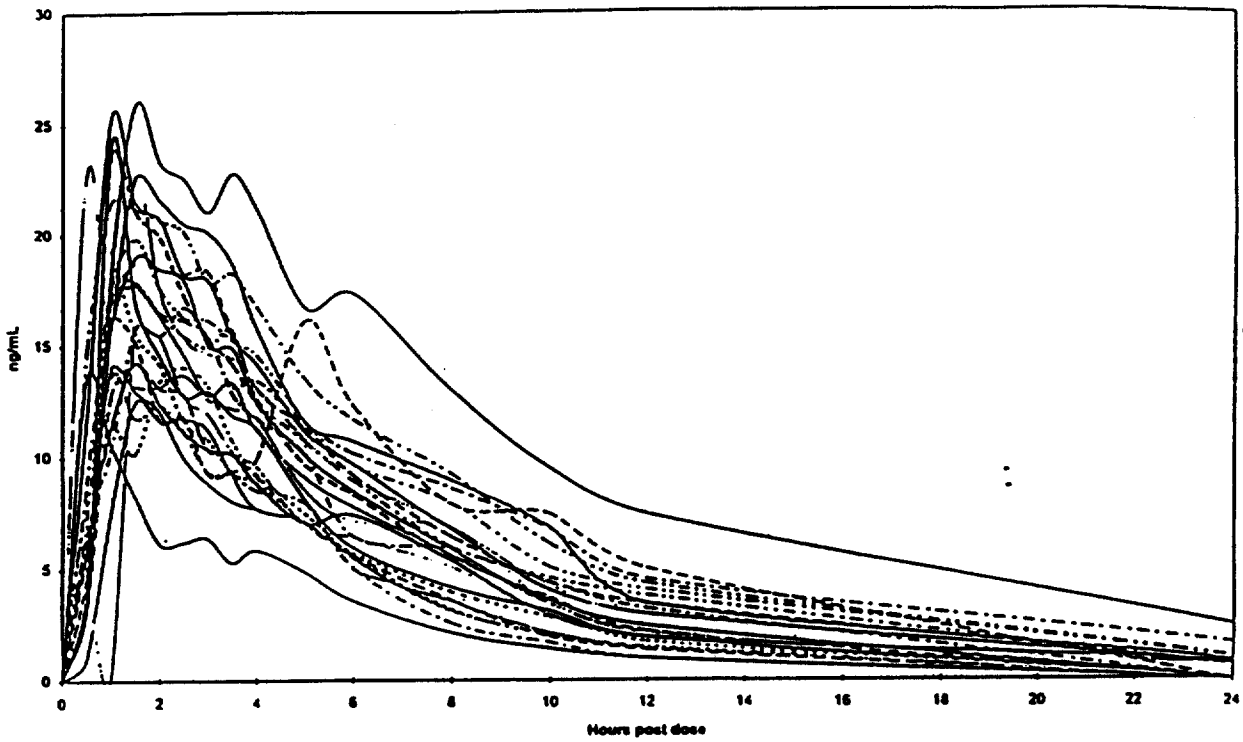


Figure 5

VP-02 Subjects Plasma Hydrocodone Concentrations from Hydrocodone 10mg

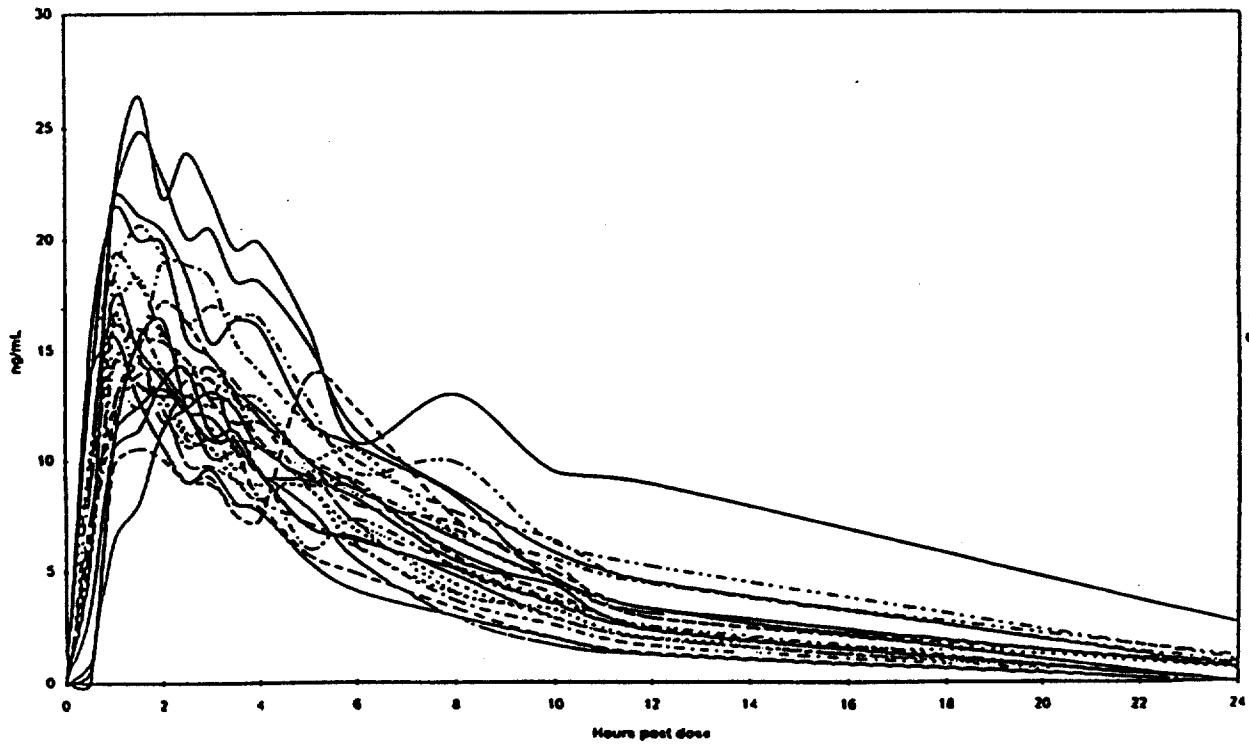
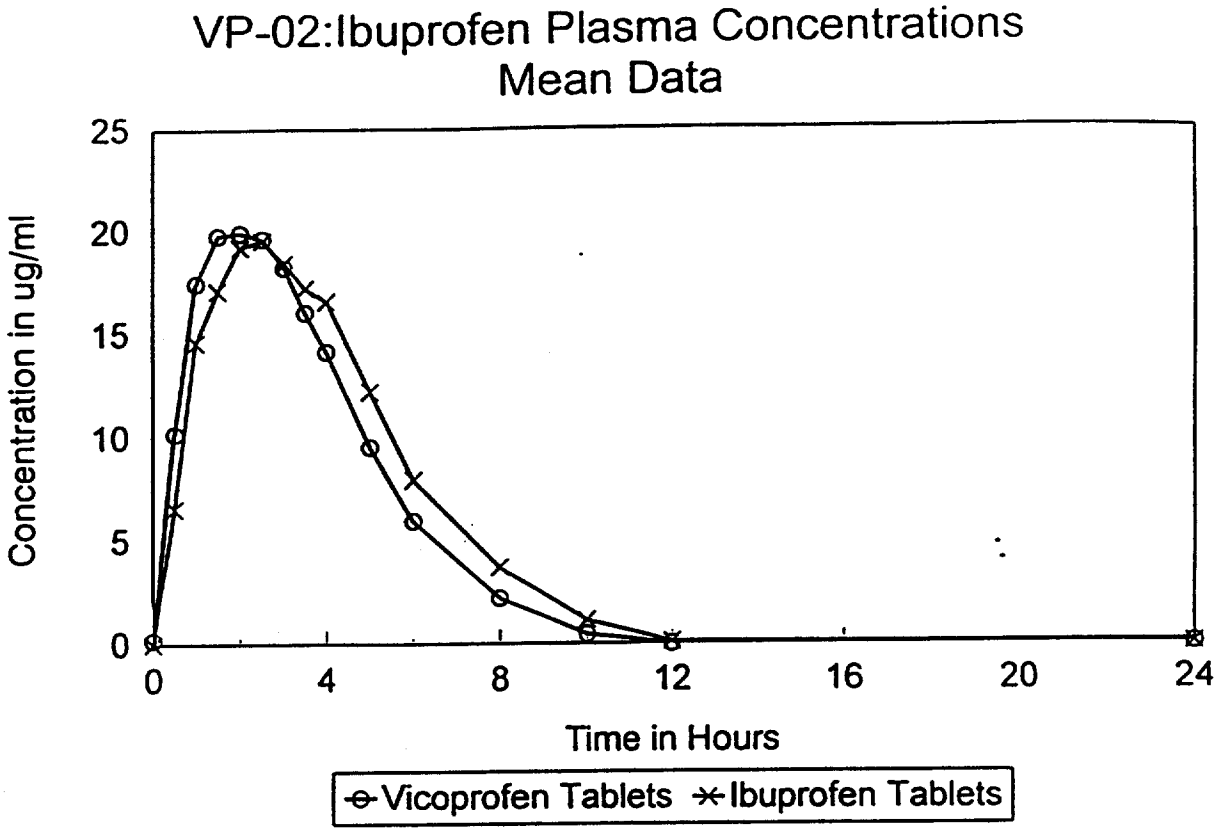


Figure 6



400mg Dose

IBUPROFEN PLASMA CONCENTRATIONS (mcg/mL)
Mean (Std. Dev,)

Treatments:	VICOPROFEN® X 2 Tablets	IBUPROFEN 200 mg X 2 Tablets
TIME (HOURS)		
0.00	0.19 (0.93)	0.00 (0.00)
0.50	10.17 (8.87)	6.55 (5.54)
1.00	17.44 (10.27)	14.58 (7.66)
1.50	19.76 (8.42)	17.07 (8.14)
2.00	19.89 (6.89)	19.19 (6.88)
2.50	19.61 (7.14)	19.51 (5.87)
3.00	18.21 (5.60)	18.42 (5.21)
3.50	16.04 (4.81)	17.20 (4.86)
4.00	14.14 (4.74)	16.57 (4.64)
5.00	9.50 (3.58)	12.20 (4.51)
6.00	5.95 (2.57)	7.92 (3.19)
8.00	2.22 (1.76)	3.70 (1.81)
10.00	0.45 (1.11)	1.15 (1.53)
12.00	0.00 (0.00)	0.10 (0.50)
24.00	0.00 (0.00)	0.00 (0.00)

VP-02 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/10mg

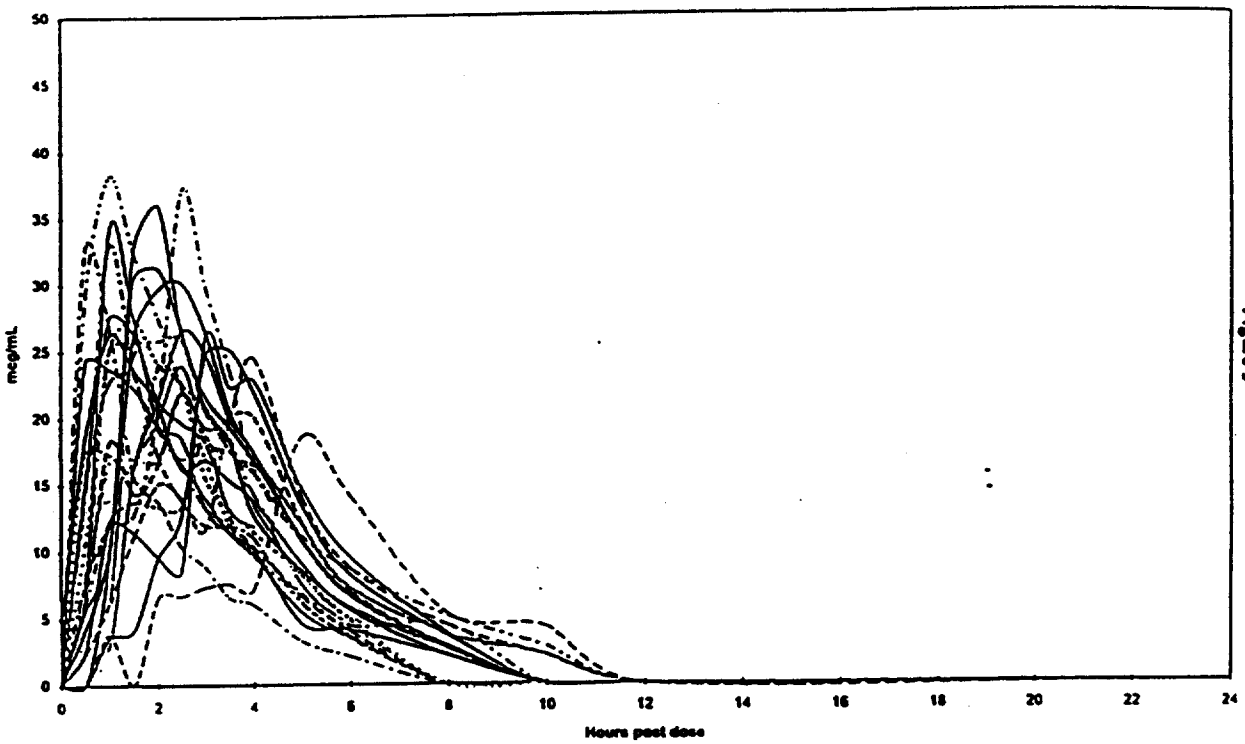


Figure 3

VP-02 Subjects Plasma Ibuprofen Concentrations from Ibuprofen 400mg

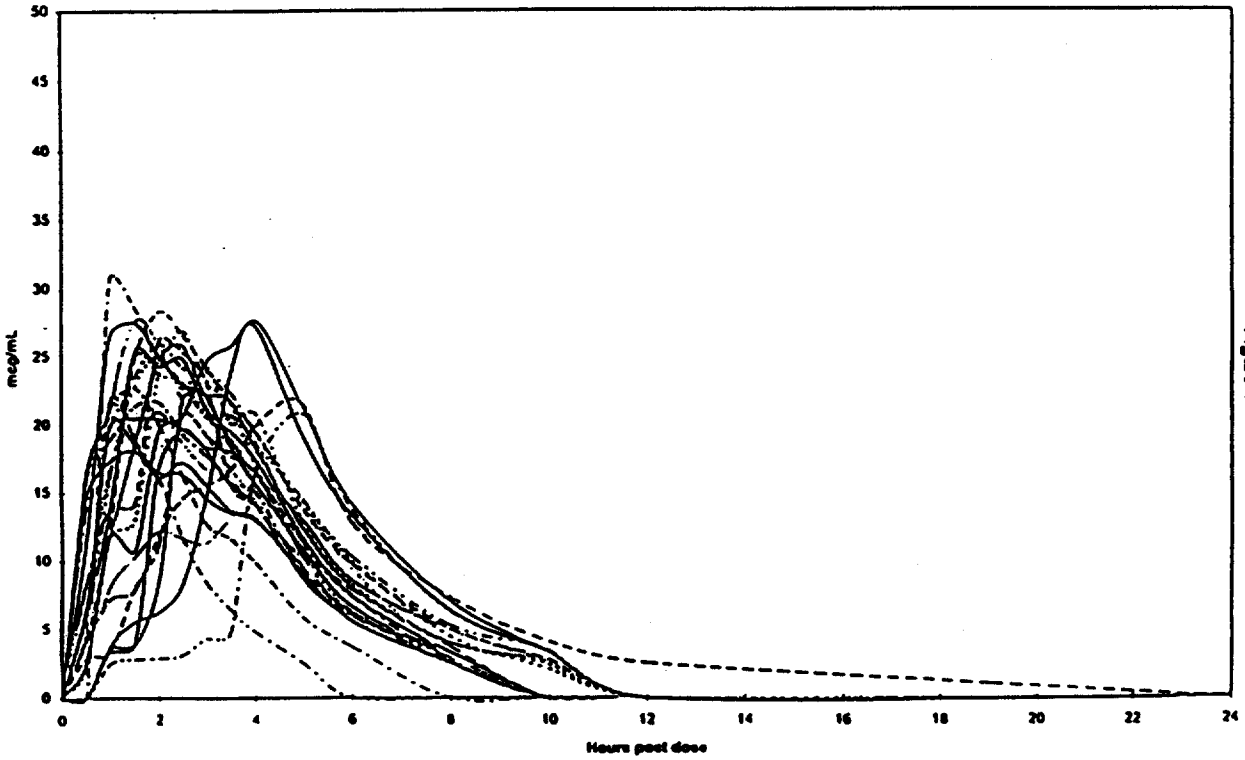


Figure 4

HYDROCODONE SUMMARY STATISTICS

PARAMETERS (UNITS)	VICOPROFEN® X 2 Tablets	HYDROCODONE 5 mg X 2 Tablets	ANOVA PR>F BY TREATMENT	POWER TO DETECT 20% DIFFERENCE
	MEAN (S.D.)	MEAN (S.D.)		
C_{max} (ng/mL)	18.55 (4.11)	16.88 (3.70)	0.043	SIG
T_{max} (Hour)	1.34 (0.47)	1.65 (0.87)	0.157	31
$t_{\frac{1}{2}}$ (Hour)	4.40 (1.61)	4.24 (1.49)	0.649	66
$AUC_{0-\infty}$ (ng/mL * Hr)	123 (47)	121 (44)	0.716	99

NOTE: SIG = Statistically significant.

	Hydrocodone LS Means		Hydrocodone Mean Ratio	90% Confidence Interval	
Parameter	VP 400/10mg	HC 10mg		lower	upper
ln C_{max}	2.895	2.807	1.09	1.01	1.17
ln $AUC_{(0-inf)}$	4.749	4.745	1.00	0.94	1.07

IBUPROFEN SUMMARY STATISTICS

PARAMETERS (UNITS)	VICOPROFEN X 2 Tablets	IBUPROFEN 200 mg X 2 Tablets	ANOVA PR>F BY TREATMENT	POWER TO DETECT 20% DIFFERENCE
	MEAN (S.D.)	MEAN (S.D.)		
C_{max} (mcg/mL)	27.18 (5.51)	23.65 (3.83)	0.017	SIG
T_{max} (Hour)	2.16 (1.16)	2.33 (1.26)	0.625	25
$t_{\frac{1}{2}}$ (Hour)	1.63 (0.39)	1.85 (0.38)	0.022	SIG
$AUC_{0-\infty}$ (mcg/mL * Hr)	99 (18)	108 (22)	0.008	SIG

NOTE: SIG = Statistically significant.

	Ibuprofen LS Means		Ibuprofen Mean Ratio	90% Confidence Interval	
Parameter	VP 400/10mg	Ib 400		lower	upper
ln C_{max}	3.291	3.150	1.15	1.05	1.27
ln $AUC_{(0-inf)}$	4.592	4.657	0.94	0.89	0.99

NDA/IND# 20-716 Suppl/Amend.# Orig. Submission Date: 4/26/96 Volume: 1.9

udy Type: Bioequivalence Study # VP-30

Study Title: A single oral dose, two-way crossover bioequivalency study of formulations.

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: 7 days

Cross-Over Y Parallel N Other Design: n/a

Fasted Y Food Study N FDA High Fat Breakfast n/a

If fasted, how long (hrs.)? 10hrs.

Subject Breakdown

Normal Y Patients Young Y Elderly Renal Hepatic

	Subject Type	Males		Group	ALL	N=	33	M= 14	F= 19
Weight	Mean	184.3	Range	Group		N=		M=	F=
Age	Mean	31.7	Range	Group		N=		M=	F=
	Subject Type	Females		Group		N=		M=	F=
Weight	Mean	141	Range	Group		N=		M=	F=
Age	Mean	34.8	Range	Group		N=		M=	F=

Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
	2 tablets	tablet	7.5mg HC/ 200mg IBU	55-0392	35,000
1	2 tablets	tablet	7.5mg HC/ 200mg IBU	055K1080P10295	2,700,000

Sampling Times

Plasma 12ml samples, prior to dosing and at 30, 60, 80, 100, 120, 140, 160, 180, 200, 220min., and 4, 5, 6, 8, 10 and 12 hours after dosing

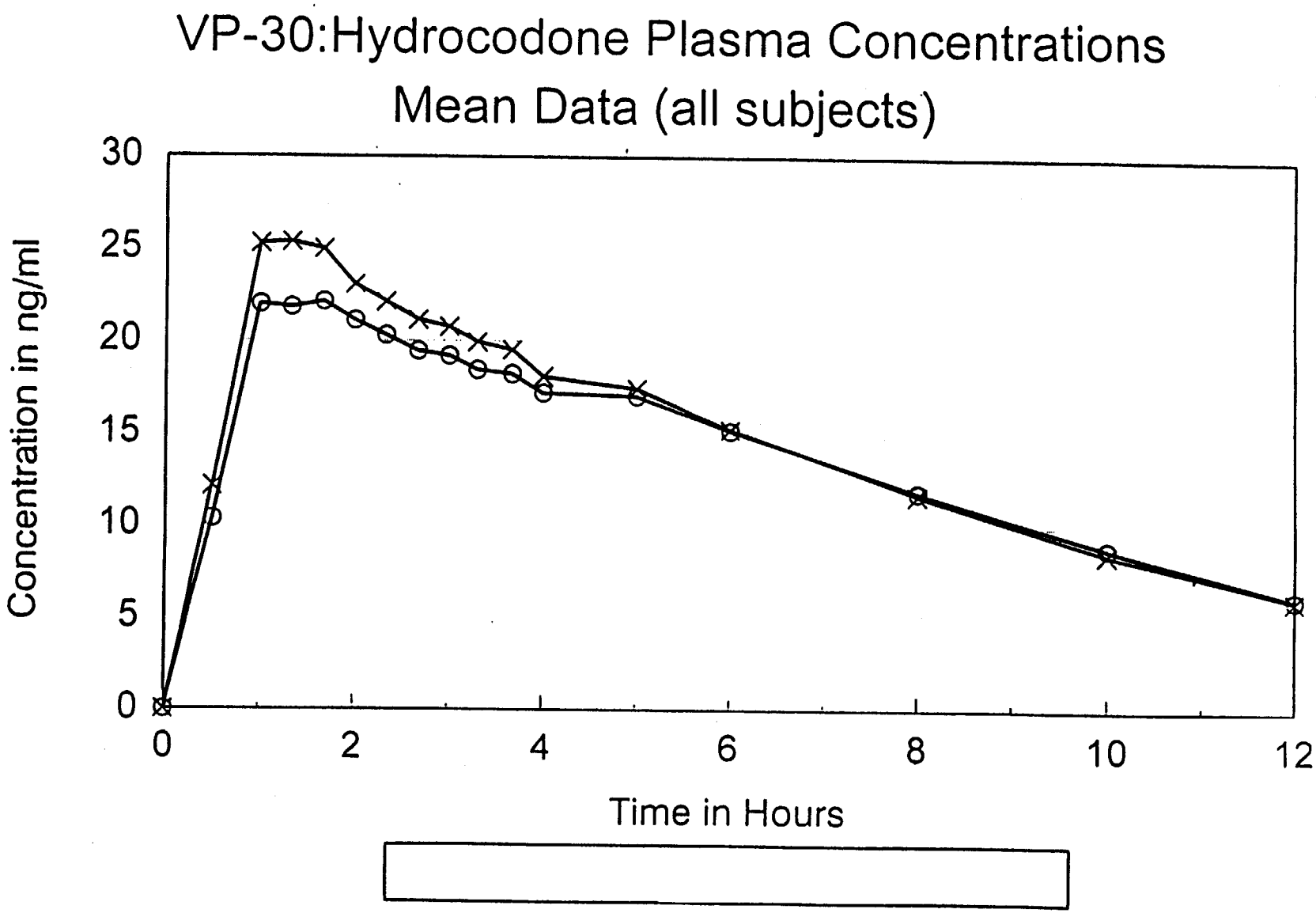
Assay Method:

Assay Sensitivity

Assay Accuracy

TABLE 2.8.3. Vicoprofen® Clinical and Market Formulations

	CLINICAL FORMULA	MARKET FORMULA	
CORE			
		Ibuprofen	200 mg
		Corn starch	
		Croscarmellose sodium	
		Microcrystalline cellulose	
		Hydroxypropyl methylcellulose	
		Magnesium stearate	
		Hydrocodone bitartrate	7.50 mg
		Colloidal silicon dioxide	
COATING			
TOTAL			



2 Tablet Dose (15mg Hydrocodone)

Individual and Mean Plasma Hydrocodone Concentrations (ng/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.0
1	BA	2																	
2	AB	1																	
3	AB	1																	
4	BA	2																	
5	BA	2																	
8	BA	2																	
9	AB	1																	
10	BA	2																	
11	AB	1																	
12	BA	2																	
13	BA	2																	
14	AB	1																	
15	BA	2																	
16	AB	1																	
17	BA	2																	
18	AB	1																	
19	BA	2																	
20	AB	1																	
21	AB	1																	
22	BA	2																	
23	AB	1																	
24	BA	2																	
25	AB	1																	
27	AB	1																	
28	BA	2																	
29	AB	1																	
30	BA	2																	
31	AB	1																	
32	BA	2																	
33	AB	1																	
34	BA	2																	
Mean			0.00	10.34	21.95	21.79	22.09	21.07	20.27	19.44	19.19	18.44	18.22	17.21	17.05	15.19	11.81	8.80	6.1
S.D.			0.00	12.81	10.38	8.73	8.37	7.99	7.17	6.46	6.02	5.46	5.65	5.25	4.34	4.42	4.02	3.66	2.-
C.V.(%)			.	123.84	47.29	40.07	37.88	37.90	35.37	33.25	31.37	29.63	31.03	30.50	25.43	29.07	34.07	41.52	44.-
S.E.M.			0.00	2.30	1.86	1.57	1.50	1.43	1.29	1.16	1.08	0.98	1.02	0.94	0.78	0.79	0.72	0.66	0.-
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.-
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

Individual and Mean Plasma Hydrocodone Concentrations (ng/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	1																	
2	AB	2																	
3	AB	2																	
4	BA	1																	
5	BA	1																	
8	BA	1																	
9	AB	2																	
10	BA	1																	
11	AB	2																	
12	BA	1																	
13	BA	1																	
14	AB	2																	
15	BA	1																	
16	AB	2																	
17	BA	1																	
18	AB	2																	
19	BA	1																	
20	AB	2																	
21	AB	2																	
22	BA	1																	
23	AB	2																	
24	BA	1																	
25	AB	2																	
27	AB	2																	
28	BA	1																	
29	AB	2																	
30	BA	1																	
31	AB	2																	
32	BA	1																	
33	AB	2																	
34	BA	1																	
Mean			0.00	12.11	25.27	25.34	24.96	23.03	22.09	21.11	20.74	19.93	19.52	18.09	17.47	15.27	11.65	8.50	6.0
S.D.			0.00	10.44	6.00	6.21	5.94	5.51	5.39	4.91	4.90	4.54	4.50	4.07	3.30	3.28	2.74	2.46	2.0
C.V.(%)			.	86.23	23.75	24.53	23.78	23.91	24.41	23.23	23.61	22.76	23.05	22.48	18.87	21.51	23.51	28.90	33.0
S.E.M.			0.00	1.88	1.08	1.12	1.07	0.99	0.97	0.88	0.88	0.81	0.81	0.73	0.59	0.59	0.49	0.44	0.3
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.0
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

VP-30 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

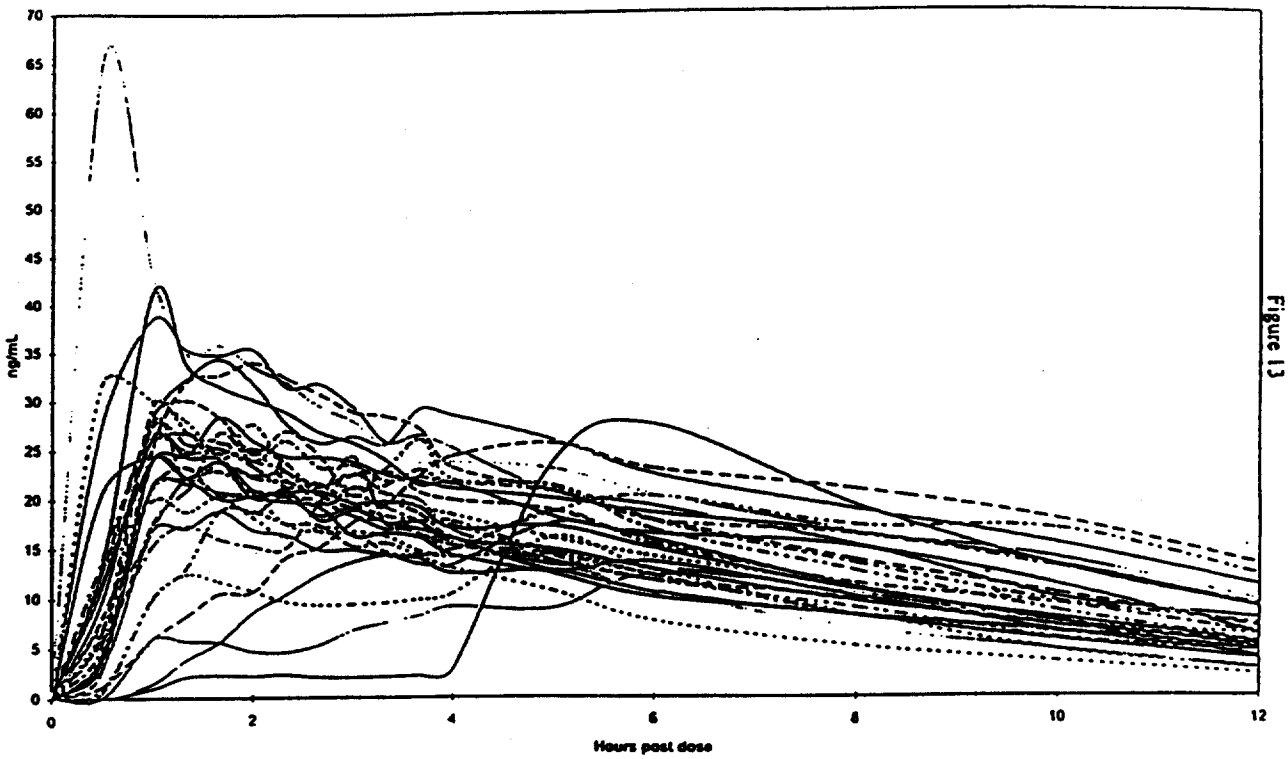


Figure 13

VP-30 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

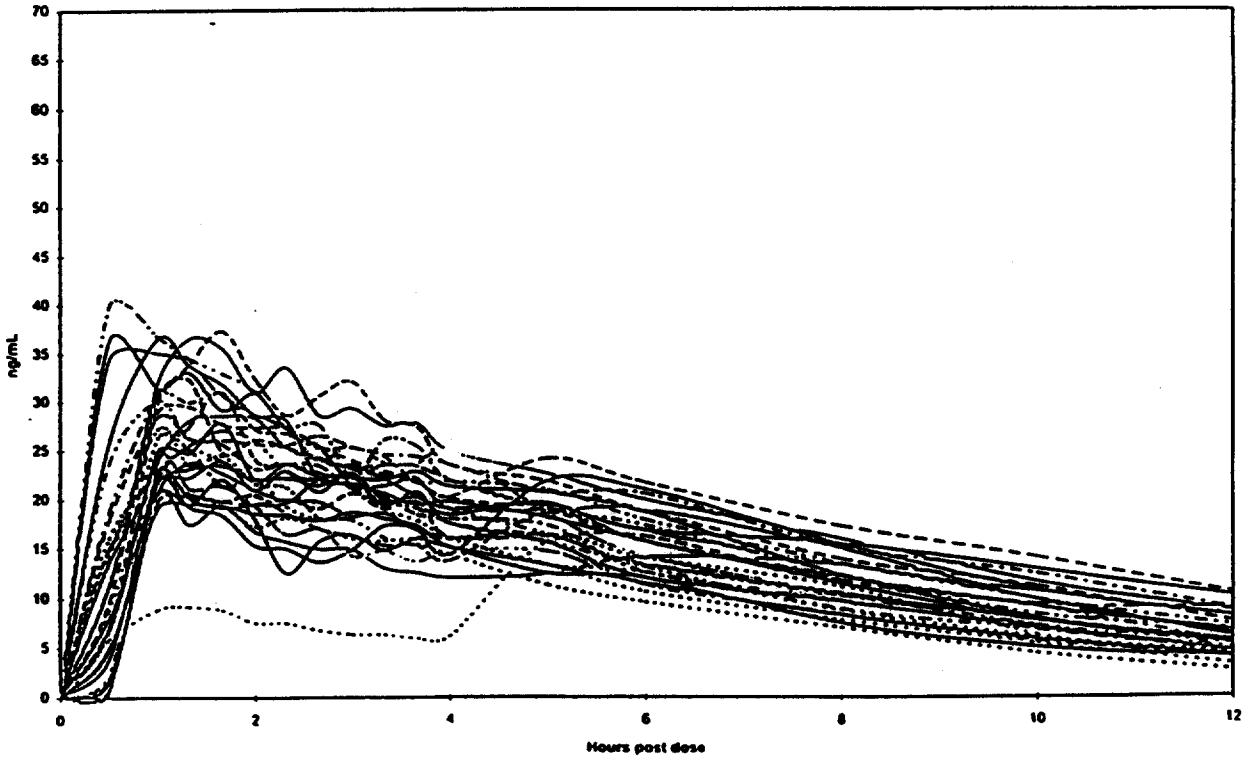
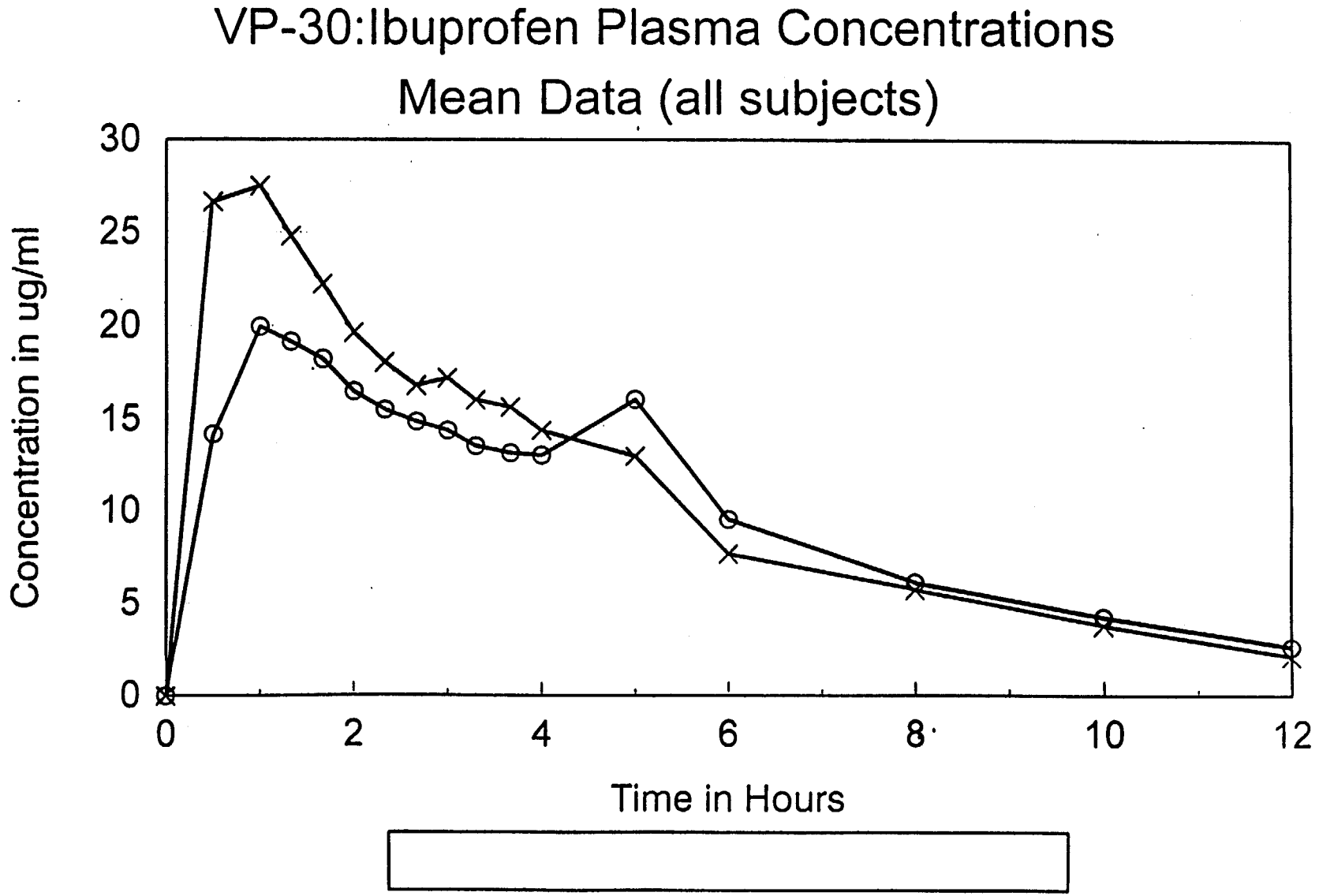


Figure 14



2 Tablet Dose (400mg Ibuprofen)

Individual and Mean Plasma Ibuprofen Concentrations (ug/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	2																	
2	AB	1																	
3	AB	1																	
4	BA	2																	
5	BA	2																	
8	BA	2																	
9	AB	1																	
10	BA	2																	
11	AB	1																	
12	BA	2																	
13	BA	2																	
14	AB	1																	
15	BA	2																	
16	AB	1																	
17	BA	2																	
18	AB	1																	
19	BA	2																	
20	AB	1																	
21	AB	1																	
22	BA	2																	
23	AB	1																	
24	BA	2																	
25	AB	1																	
27	AB	1																	
28	BA	2																	
29	AB	1																	
30	BA	2																	
31	AB	1																	
32	BA	2																	
33	AB	1																	
34	BA	2																	
Mean			0.00	14.18	19.95	19.15	18.23	16.50	15.51	14.86	14.37	13.52	13.14	13.02	16.09	9.53	6.09	4.22	2.60
S.D.			0.00	10.75	11.42	10.15	9.36	8.37	7.52	6.82	6.51	6.47	5.83	5.61	9.36	5.52	4.53	3.73	2.99
C.V.(%)			.	75.76	57.25	53.01	51.33	50.71	48.47	45.94	45.29	47.85	44.37	43.08	58.18	57.92	74.35	88.38	115.06
S.E.M.			0.00	1.93	2.05	1.82	1.68	1.50	1.35	1.23	1.17	1.16	1.05	1.01	1.68	0.99	0.81	0.67	0.54
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

Individual and Mean Plasma Ibuprofen Concentrations (ug/mL)
for Vicoprofen(R) Tablets

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) -1.00	0.50	1.00	1.33	1.67	2.00	2.33	2.67	3.00	3.33	3.67	4.00	5.00	6.00	8.00	10.00	12.00
1	BA	1																	
2	AB	2																	
3	AB	2																	
4	BA	1																	
5	BA	1																	
8	BA	1																	
9	AB	2																	
10	BA	1																	
11	AB	2																	
12	BA	1																	
13	BA	1																	
14	AB	2																	
15	BA	1																	
16	AB	2																	
17	BA	1																	
18	AB	2																	
19	BA	1																	
20	AB	2																	
21	AB	2																	
22	BA	1																	
23	AB	2																	
24	BA	1																	
25	AB	2																	
27	AB	2																	
28	BA	1																	
29	AB	2																	
30	BA	1																	
31	AB	2																	
32	BA	1																	
33	AB	2																	
34	BA	1																	
Mean			0.00	23.63	27.49	24.80	22.23	19.64	18.05	16.81	17.22	16.04	15.66	14.38	12.97	7.65	5.69	3.76	2.09
S.D.			0.00	9.62	8.13	7.05	5.93	4.75	4.57	4.65	6.70	4.88	5.24	5.34	6.37	3.84	4.93	3.03	1.94
C.V.(%)			.	40.72	29.59	28.45	26.67	24.21	25.32	27.66	38.89	30.42	33.44	37.13	49.11	50.21	86.61	80.49	92.44
S.E.M.			0.00	1.73	1.46	1.27	1.07	0.85	0.82	0.84	1.20	0.88	0.94	0.96	1.14	0.69	0.89	0.54	0.35
N			31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00	31.00
Minimum																			
Maximum																			

Samples below the quantifiable limit are reported as 0.00

VP-30 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

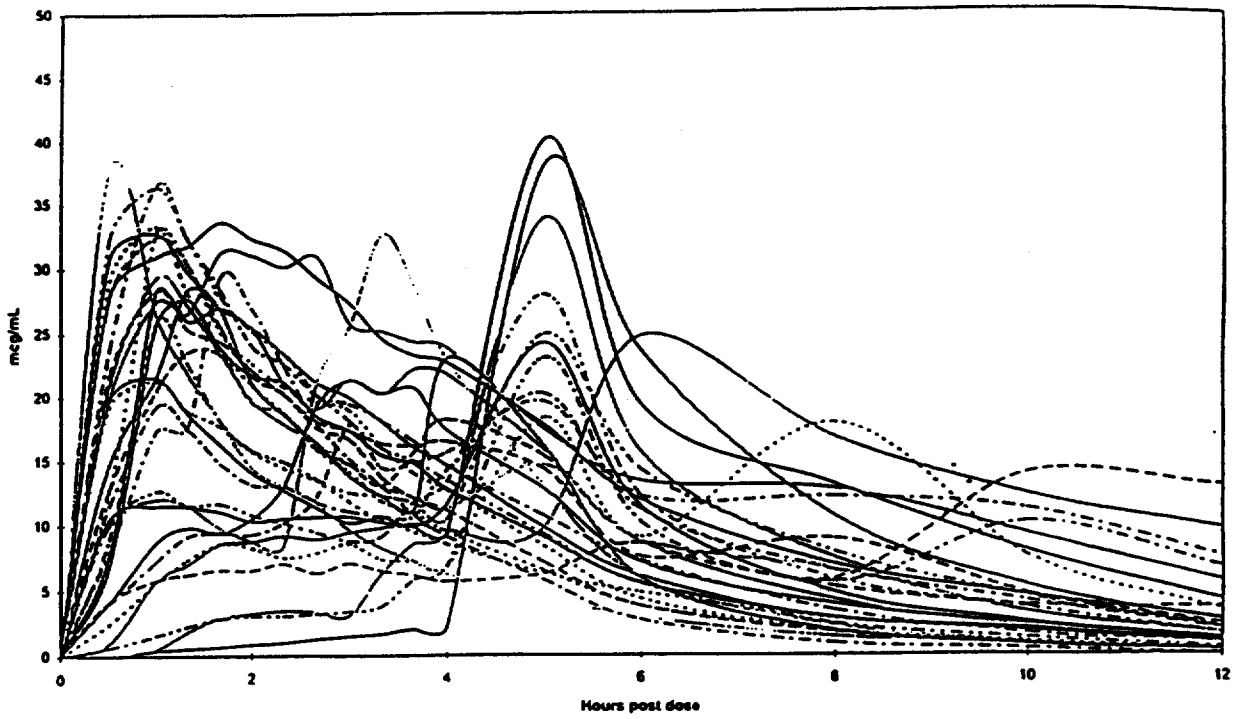


Figure 15

VP-30 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

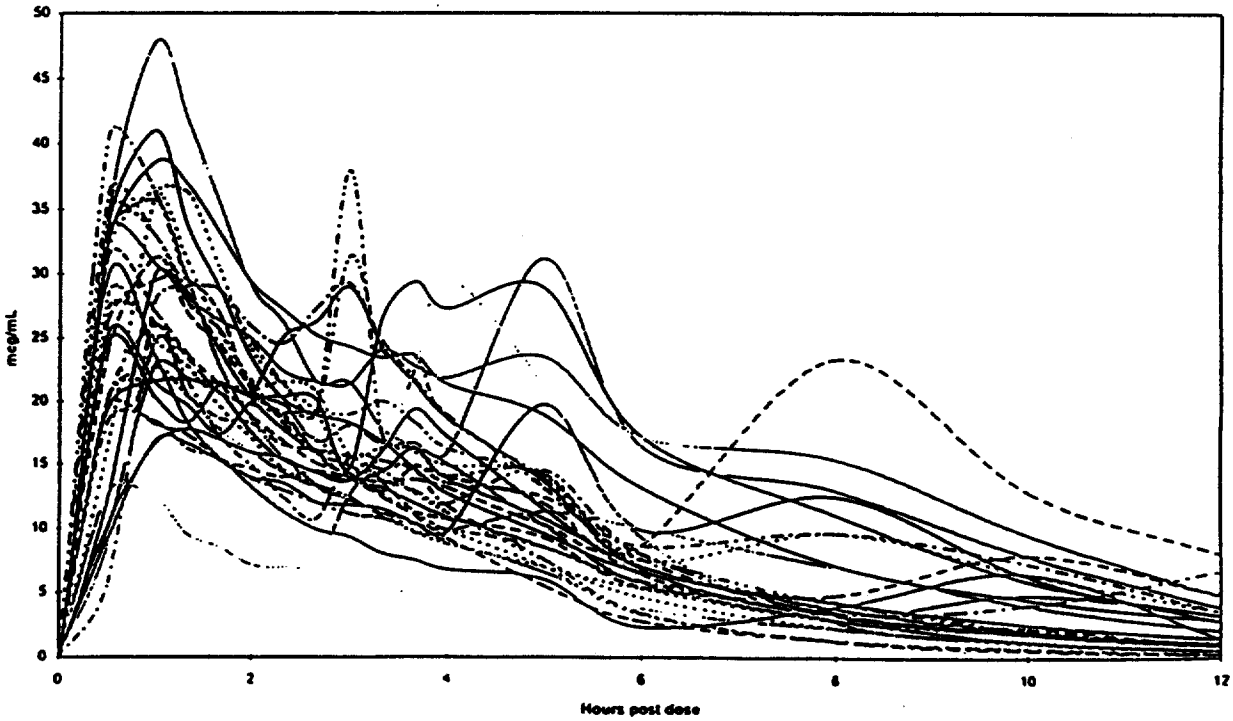


Figure 16

Statistical Comparisons of Plasma Hydrocodone Pharmacokinetic Parameters

Treatment B versus Treatment A

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Confidence Intervals (95% Confidence)	Mean Ratio
Cmax	27.295	27.004	1.08	0.8240	97.84	92.9 - 109.2	91.2 - 110.9	.
Tmax	1.679	2.123	-20.92	0.2271	19.69	50.3 - 107.9	44.4 - 113.8	.
						(-2.2 , 0.0)	(-2.5 , 0.2)	
AUC(0-t)	174.137	166.160	4.80	0.0472*	99.99	100.9 - 108.7	100.1 - 109.5	.
AUC(0-inf)	215.844	210.844	2.37	0.4424	99.99	97.2 - 107.5	96.1 - 108.6	.
Kel	0.162	0.161	0.66	0.8168	99.99	95.9 - 105.4	94.9 - 106.4	.
T 1/2el	4.489	4.605	-2.53	0.5759	98.93	89.9 - 105.1	88.3 - 106.6	.
LN(Cmax)	3.282	3.248	1.04	0.3974	99.76	96.8 - 110.6	95.4 - 112.1	103.4
LN[AUC(0-t)]	5.140	5.081	1.16	0.0202*	99.99	101.8 - 110.5	101.0 - 111.4	106.1
LN[AUC(0-inf)]	5.345	5.302	0.80	0.1717	99.99	99.1 - 109.8	98.1 - 110.9	104.3

Treatment B = Vicoprofen(R) Tablets
Treatment A = Vicoprofen(R) Tablets

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA

. = value was not calculated

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test - reference) for log transformed parameters only

() = 90% and 95% non-parametric confidence intervals for Tmax

Statistical Comparisons of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment B versus Treatment A

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Confidence Intervals (95% Confidence)	Mean Ratio
Cmax	30.154	28.531	5.69	0.2718	96.59	97.1 - 114.3	95.3 - 116.1	.
Tmax	1.773	2.827	-37.27	0.0031*	37.69	43.1 - 82.4	39.1 - 86.4	.
						(-2.3 , -0.5)	(-2.6 , -0.4)	
AUC(0-t)	128.526	119.720	7.36	0.0247*	99.99	102.1 - 112.6	101.0 - 113.7	.
AUC(0-inf)	134.515	131.021	2.67	0.3666	99.99	97.7 - 107.6	96.7 - 108.7	.
Kel	0.329	0.312	5.44	0.1803	99.69	98.7 - 112.2	97.3 - 113.6	.
T 1/2el	2.171	2.455	-11.58	0.1071	79.17	76.6 - 100.3	74.1 - 102.7	.
LN(Cmax)	3.381	3.323	1.73	0.2534	97.35	97.4 - 115.1	95.8 - 117.1	105.9
LN[AUC(0-t)]	4.829	4.763	1.39	0.0366*	99.99	101.5 - 112.5	100.4 - 113.7	106.9
LN[AUC(0-inf)]	4.875	4.841	0.70	0.2236	99.99	98.7 - 108.4	97.8 - 109.5	103.5

Treatment B = Vicoprofen(R) Tablets
Treatment A = Vicoprofen(R) Tablets

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA

. = value was not calculated

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test - reference) for log transformed parameters only

() = 90% and 95% non-parametric confidence intervals for Tmax

2° Analysis

Statistical Comparisons of Plasma Hydrocodone Pharmacokinetic Parameters

Gender F versus Gender M
(Females vs. Males)

Parameter	Gender Means F	Gender Means M	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	26.531	27.699	-4.22	0.7408	32.41	74.1 - 117.2	.
Tmax	2.611	1.436	81.85	0.0662	6.26	109.0 - 254.7	.
AUC(0-t)	164.979	168.599	-2.15	0.8204	53.53	81.9 - 113.8	.
AUC(0-inf)	210.534	213.410	-1.35	0.9108	35.78	78.4 - 118.9	.
Kel	0.170	0.147	15.66	0.1109	52.17	99.5 - 131.8	.
T 1/2el	4.470	4.856	-7.96	0.4134	48.09	75.0 - 109.1	.
LN(Cmax)	3.240	3.260	-0.61	0.8609	39.28	80.9 - 118.8	98.0
LN[AUC(0-t)]	5.069	5.102	-0.64	0.7357	51.94	82.3 - 113.9	96.8
LN[AUC(0-inf)]	5.288	5.332	-0.81	0.7145	36.88	78.5 - 116.9	95.8

Gender F versus Gender M
Formulation (Females vs. Males)

Parameter	Gender Means F	Gender Means M	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	28.412	25.704	10.54	0.2310	60.82	95.9 - 125.2	.
Tmax	1.889	1.385	36.42	0.2146	9.40	87.6 - 185.2	.
AUC(0-t)	180.344	165.897	8.71	0.2600	72.12	95.8 - 121.6	.
AUC(0-inf)	220.634	210.028	5.05	0.5975	52.73	89.0 - 121.1	.
Kel	0.169	0.151	11.68	0.1320	72.63	98.9 - 124.5	.
T 1/2el	4.270	4.813	-11.27	0.1903	62.99	74.5 - 103.0	.
LN(Cmax)	3.316	3.234	2.53	0.3294	64.78	94.3 - 124.8	108.5
LN[AUC(0-t)]	5.173	5.096	1.52	0.3063	73.80	95.2 - 122.6	108.1
LN[AUC(0-inf)]	5.366	5.318	0.92	0.6030	54.54	89.7 - 122.9	105.0

Statistical Comparisons of Plasma Ibuprofen Pharmacokinetic Parameters

Gender F versus Gender M
Formulation (Females vs. Males)

Parameter	Gender Means F	Gender Means M	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	27.998	29.263	-4.32	0.6002	65.67	81.8 - 109.5	.
Tmax	3.574	1.808	97.71	0.0314*	6.22	124.3 - 271.1	.
AUC(0-t)	124.016	113.072	9.68	0.2725	60.38	95.0 - 124.4	.
AUC(0-inf)	143.886	117.506	22.45	0.0607	38.03	102.9 - 142.0	.
Kel	0.298	0.306	-2.46	0.8324	37.72	77.9 - 117.2	.
T 1/2el	2.860	2.321	23.19	0.2302	16.47	91.0 - 155.4	.
LN(Cmax)	3.299	3.356	-1.71	0.5339	55.99	80.9 - 110.2	94.4
LN[AUC(0-t)]	4.798	4.707	1.94	0.2475	70.30	96.1 - 125.0	109.6
LN[AUC(0-inf)]	4.932	4.744	3.96	0.0568	52.62	102.7 - 141.7	120.7

Gender F versus Gender M
Formulation (Females vs. Males)

Parameter	Gender Means F	Gender Means M	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	30.385	29.925	1.54	0.8587	61.25	87.0 - 116.1	.
Tmax	2.269	1.077	110.65	0.0669	4.98	111.9 - 309.4	.
AUC(0-t)	137.252	116.293	18.02	0.0683	52.20	101.8 - 134.2	.
AUC(0-inf)	144.910	122.844	17.96	0.1223	39.07	98.8 - 137.1	.
Kel	0.341	0.305	11.85	0.1389	69.60	98.6 - 125.1	.
T 1/2el	2.101	2.329	-9.77	0.1556	82.13	78.8 - 101.6	.
LN(Cmax)	3.391	3.369	0.62	0.8092	60.68	88.2 - 118.2	102.1
LN[AUC(0-t)]	4.895	4.736	3.36	0.0605	65.88	102.1 - 134.6	117.2
LN[AUC(0-inf)]	4.946	4.788	3.30	0.1111	51.25	99.5 - 137.9	117.1

Gender F = Female: test
Gender M = Male: reference

Values for Genders F and M are the least-square means (LSMEANS) from the ANOVA

. = value was not calculated

Pct Difference = difference between genders (F - M) expressed as a percentage of Gender M

PR>|T| = ANOVA test for significant differences between genders
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between genders (α=0.05)

1° analysis

Statistical Comparisons of Plasma Hydrocodone Pharmacokinetic Parameters

Treatment B versus Treatment A
Male Subjects

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	26.818	27.066	-0.92	0.9364	34.16	78.9 - 119.2	.
Tmax	1.289	1.361	-5.31	0.8665	7.44	39.3 - 150.1	.
AUC(0-t)	166.552	168.519	-1.17	0.7954	98.08	90.9 - 106.7	.
AUC(0-inf)	207.313	208.702	-0.67	0.8940	95.77	90.6 - 108.1	.
Kel	0.153	0.155	-1.65	0.7467	95.17	89.4 - 107.3	.
T 1/2el	4.703	4.589	2.48	0.7386	70.68	89.5 - 115.5	.
LN(Cmax)	3.277	3.255	0.66	0.7803	67.41	89.3 - 116.9	102.2
LN[AUC(0-t)]	5.103	5.109	-0.12	0.8858	99.02	92.4 - 106.9	99.4
LN[AUC(0-inf)]	5.314	5.319	-0.11	0.9059	96.99	91.5 - 108.1	99.4

Treatment B versus Treatment A
Female Subjects

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	28.811	26.494	8.75	0.0743	98.04	100.8 - 116.7	.
Tmax	1.896	2.653	-28.53	0.2323	11.47	31.3 - 111.6	.
AUC(0-t)	185.524	171.203	8.36	0.0100*	99.99	103.4 - 113.4	.
AUC(0-inf)	227.971	226.394	0.70	0.8717	99.02	93.3 - 108.1	.
Kel	0.166	0.158	4.89	0.2456	99.37	97.8 - 112.0	.
T 1/2el	4.337	4.855	-10.67	0.0857	89.60	79.2 - 99.5	.
LN(Cmax)	3.330	3.245	2.63	0.1167	95.15	99.5 - 119.2	108.9
LN[AUC(0-t)]	5.202	5.109	1.81	0.0151*	99.92	103.4 - 116.4	109.7
LN[AUC(0-inf)]	5.399	5.359	0.74	0.3985	98.13	96.1 - 112.6	104.0

Statistical Comparisons of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment B versus Treatment A
Male Subjects

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	30.062	29.224	2.87	0.7682	46.40	85.8 - 119.9	.
Tmax	0.992	1.525	-34.97	0.4082	5.77	-8.0 - 138.1	.
AUC(0-t)	116.332	116.404	-0.06	0.9895	97.13	91.6 - 108.2	.
AUC(0-inf)	122.083	120.844	1.02	0.8155	98.09	93.2 - 108.8	.
Kel	0.312	0.312	-0.24	0.9242	99.99	95.2 - 104.3	.
T 1/2el	2.274	2.267	0.30	0.9257	99.86	94.5 - 106.1	.
LN(Cmax)	3.381	3.361	0.60	0.8384	45.00	85.8 - 121.3	102.0
LN[AUC(0-t)]	4.737	4.741	-0.07	0.9468	95.51	91.2 - 108.9	99.7
LN[AUC(0-inf)]	4.786	4.777	0.20	0.8409	96.95	92.9 - 109.7	100.9

Treatment B versus Treatment A
Female Subjects

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	90% CI	Mean Ratio
Cmax	31.261	27.759	12.62	0.0880	77.07	100.5 - 124.7	.
Tmax	2.312	3.847	-39.89	0.0030*	35.91	40.2 - 80.0	.
AUC(0-t)	136.888	121.124	14.67	0.0033*	99.00	107.2 - 122.1	.
AUC(0-inf)	142.782	137.496	1.84	0.3889	98.53	96.2 - 111.5	.
Kel	0.351	0.312	12.63	0.0293*	94.62	101.5 - 121.7	.
T 1/2el	1.996	2.610	-21.53	0.1069	24.94	52.4 - 100.5	.
LN(Cmax)	3.416	3.287	3.91	0.0581	84.39	101.9 - 127.1	113.8
LN[AUC(0-t)]	4.906	4.772	2.81	0.0046*	99.35	106.5 - 122.8	114.4
LN[AUC(0-inf)]	4.933	4.889	0.90	0.2686	99.55	97.7 - 111.8	104.5

Treatment B = Vicoprofen(R) Tablets
Treatment A = Vicoprofen(R) Tablets

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA

. = value was not calculated

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

VP-30 Males Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

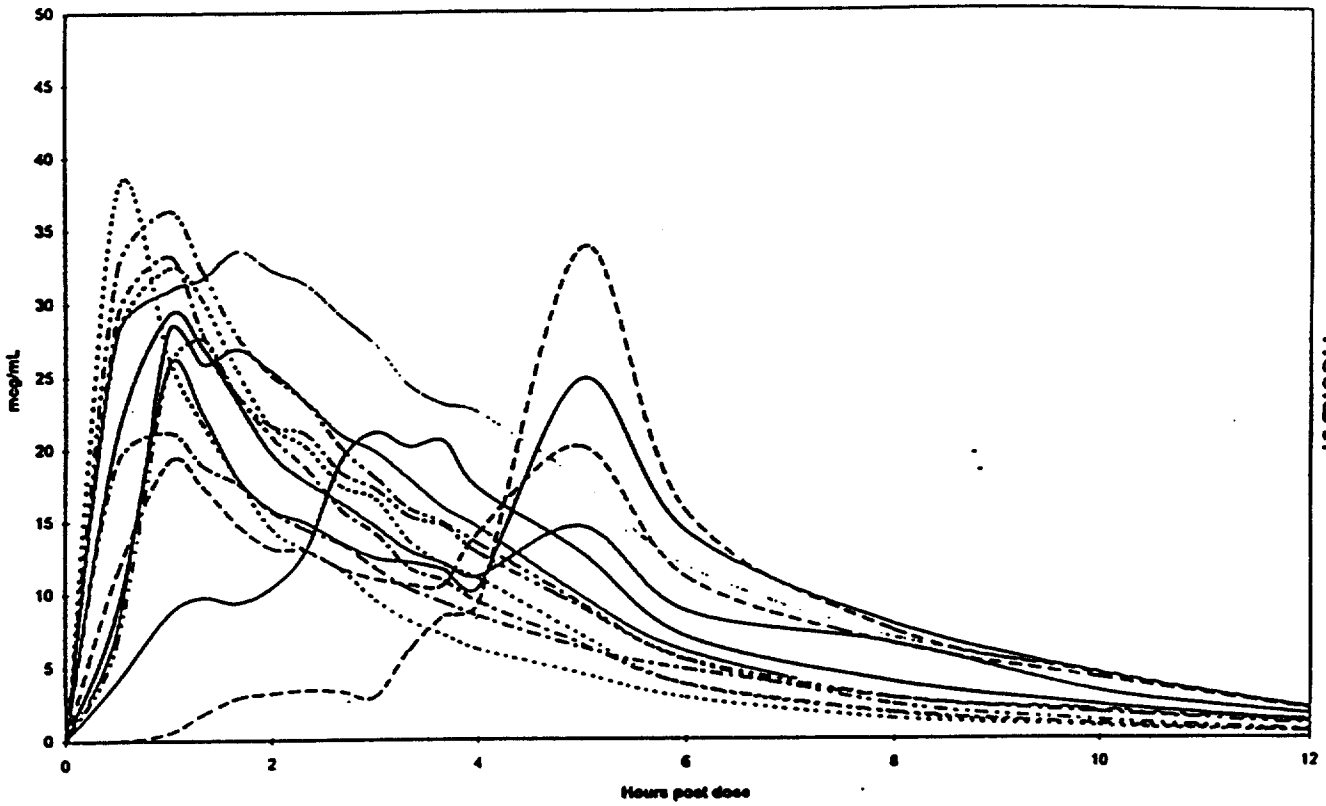


FIGURE 21

VP-30 Females Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

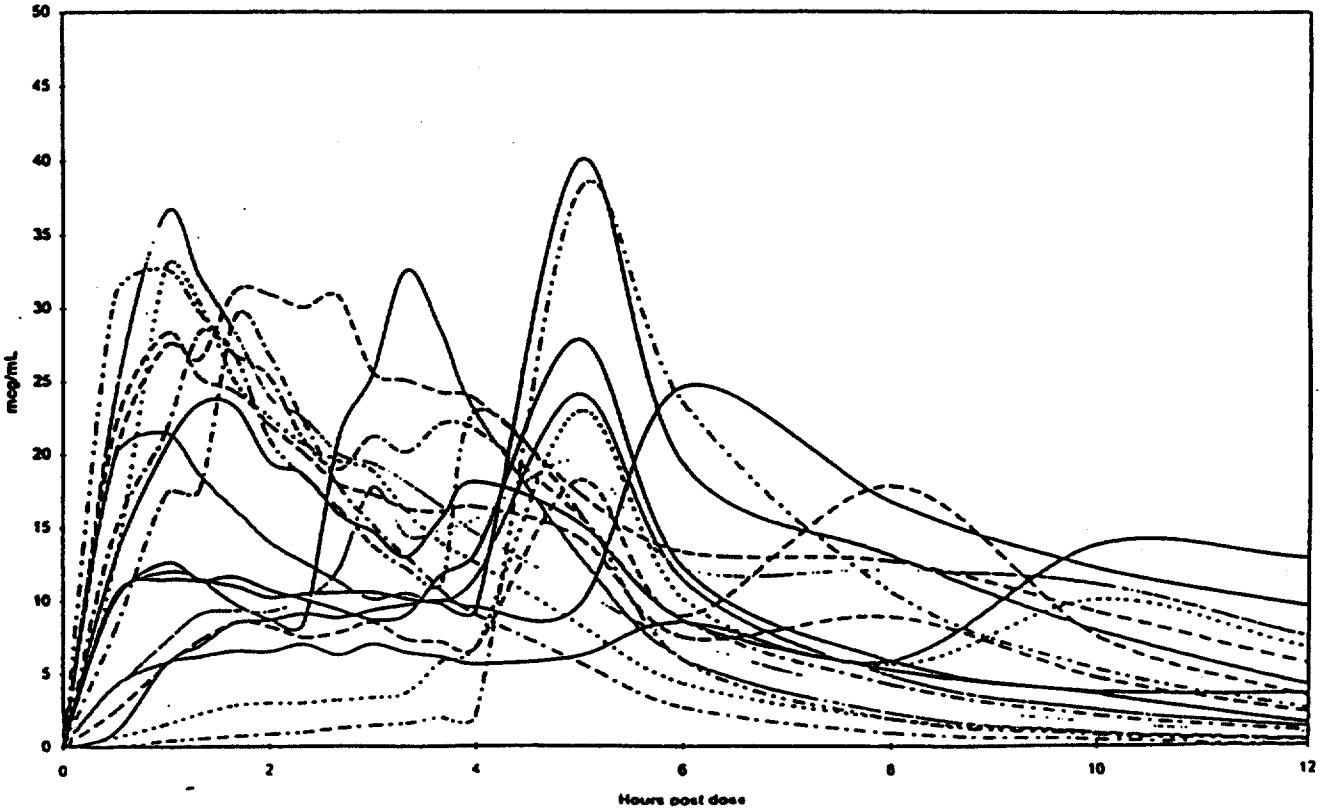


FIGURE 22

VP-30 Males Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

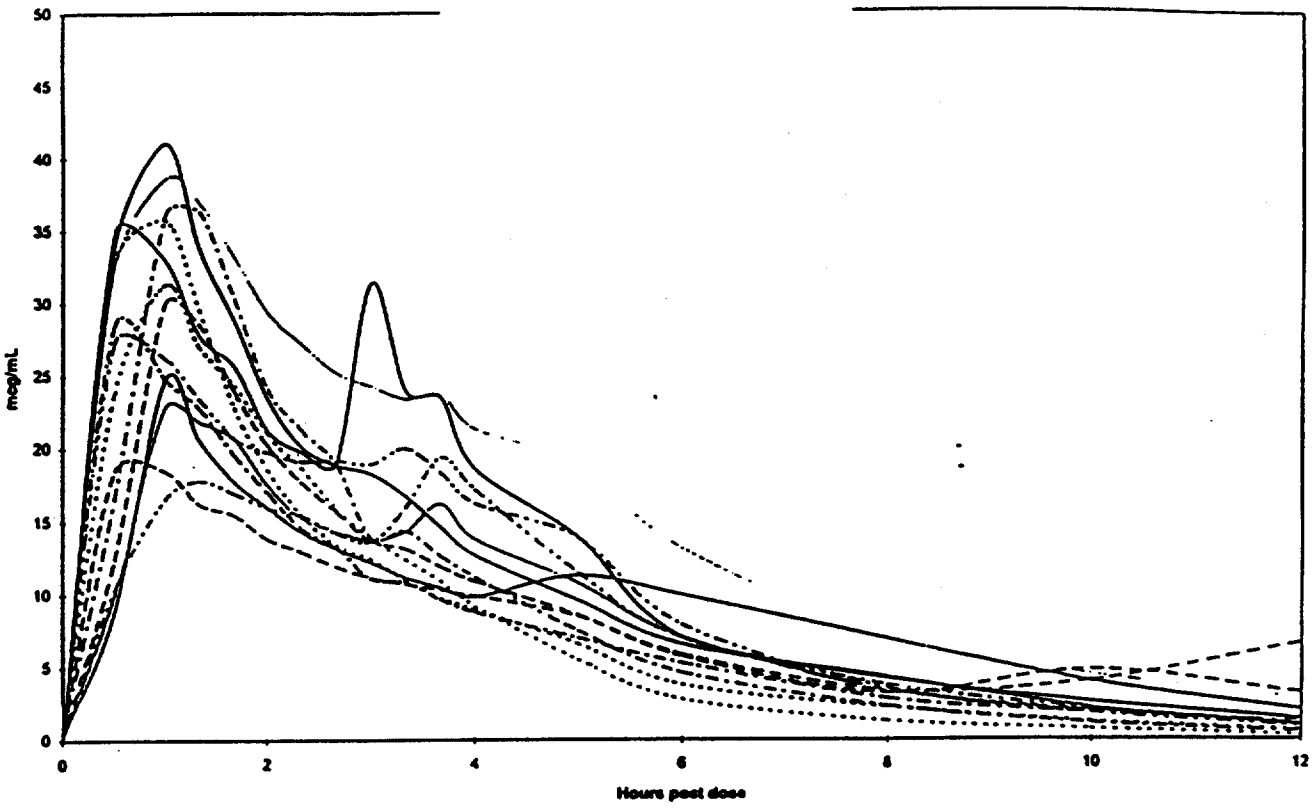


FIGURE 23

VP-30 Females Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

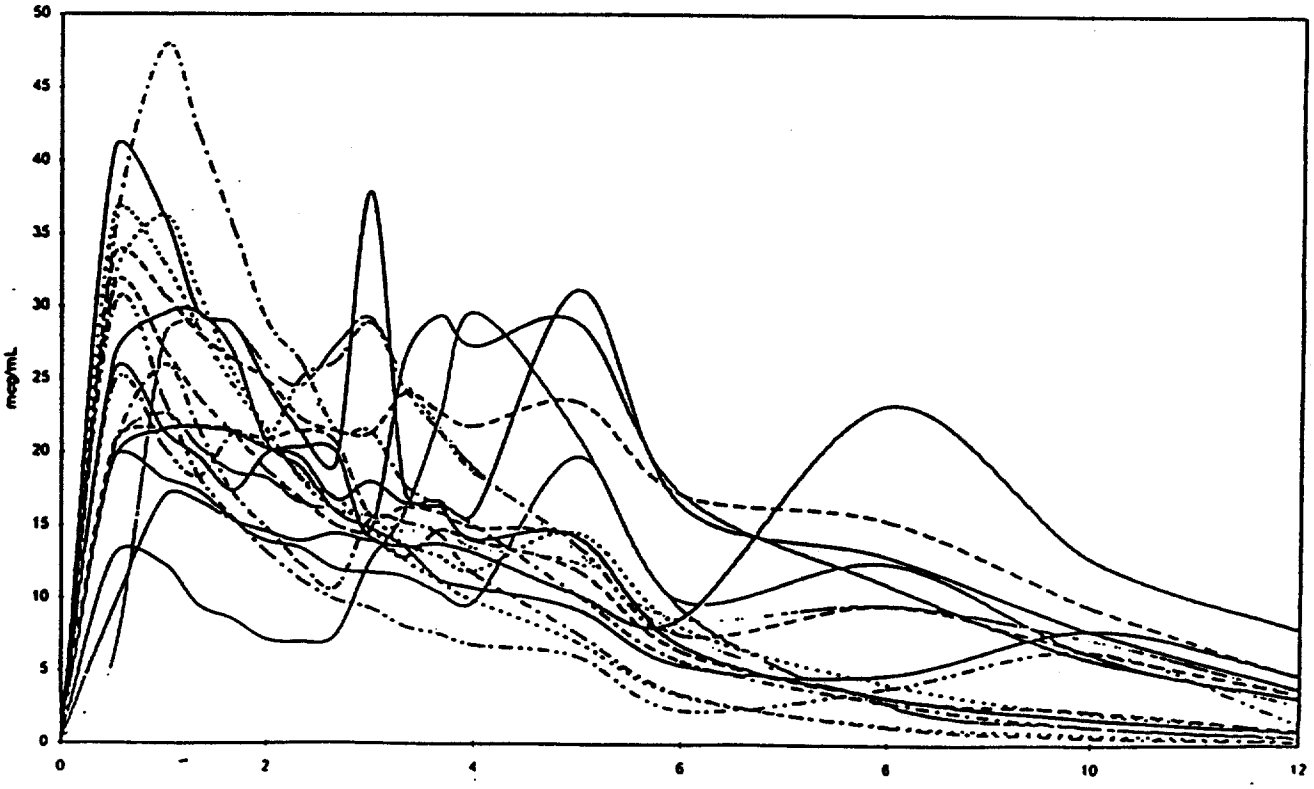


FIGURE 24

NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.16

tudy Type: PK/PD Study # VP-22

Study Title: A PK/PD characterization of Vicoprofen® tablets in acute post-operative dental pain

Clinical Investigator

Site

Analytical Investigator-*Hydrocodone*

Site

Analytical Investigator-*Ibuprofen*

Site

Single Dose: Y Multiple Dose: N Washout Period: N/A

Cross-Over N Parallel Y Other Design: N/A

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? (?)

Subject Breakdown

Normal Y Patients Y Young Y Elderly N Renal Hepatic

	Subject Type	Males		Group	All	N=	72	M=	36	F= 36
Weight	Mean	Range	See Attached	Group		N=		M=		F=
Age	Mean	Range		Group		N=		M=		F=
	Subject Type	Females		Group		N=		M=		F=
Weight	Mean	Range	See Attached	Group		N=		M=		F=
Age	Mean	Range		Group		N=		M=		F=

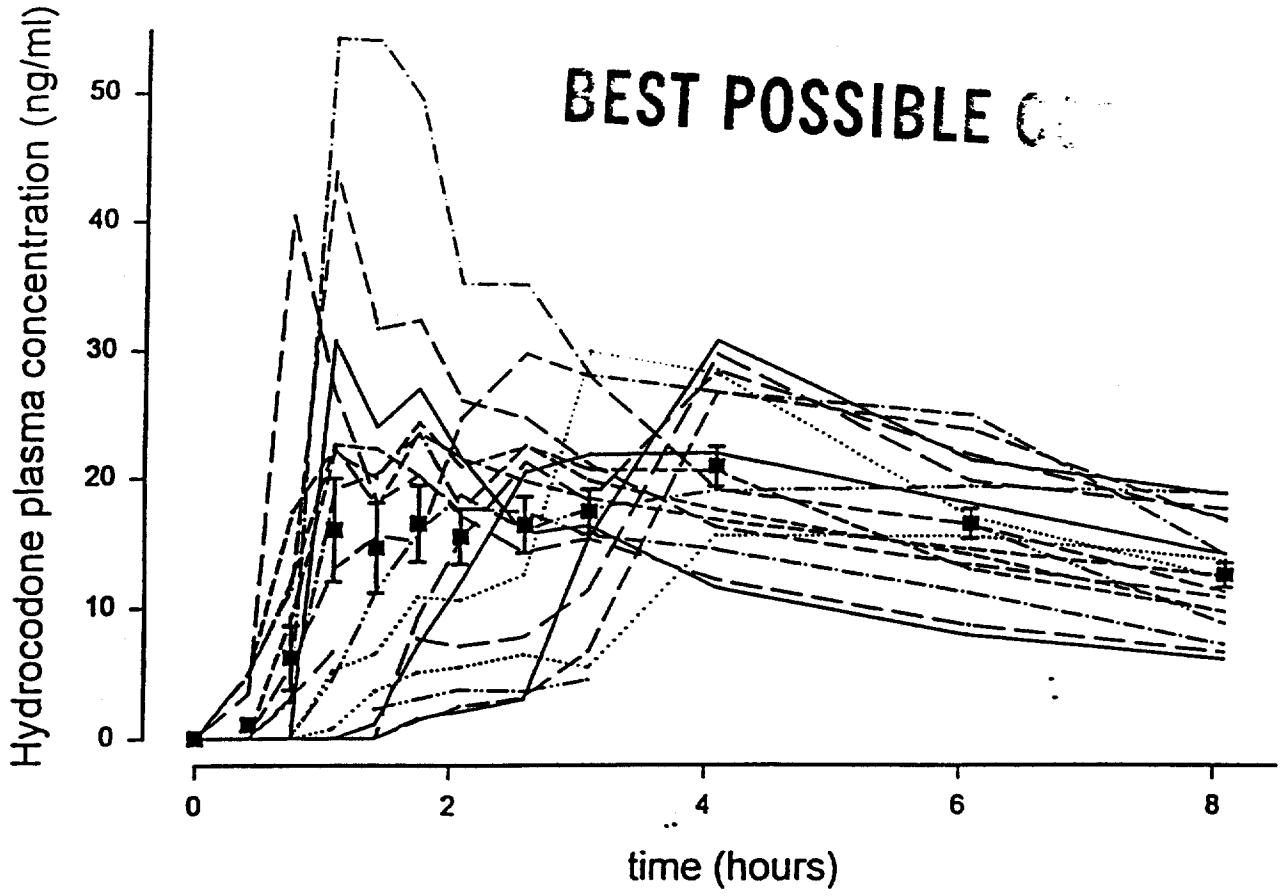
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
Vicoprofen®	15mg HC/ 400mg IBU	Tablet	7.5mg HC/ 200mg IBU	55-0392	
Ibuprofen Susp.	400mg	Suspension	20mg/ml	131-13	
Hydrocodone	15mg	Tablets	7.5mg	128-0191	
Placebo Tablets		Tablets		120-0191	
Placebo Susp.		Suspension		131-01	

Sampling Times

Plasma Prior to dosing and 20, 40, 60, 80, 100, and 120 min. and 2.5, 3, 4, 5, 6, 7, and 8 hrs after dosing.

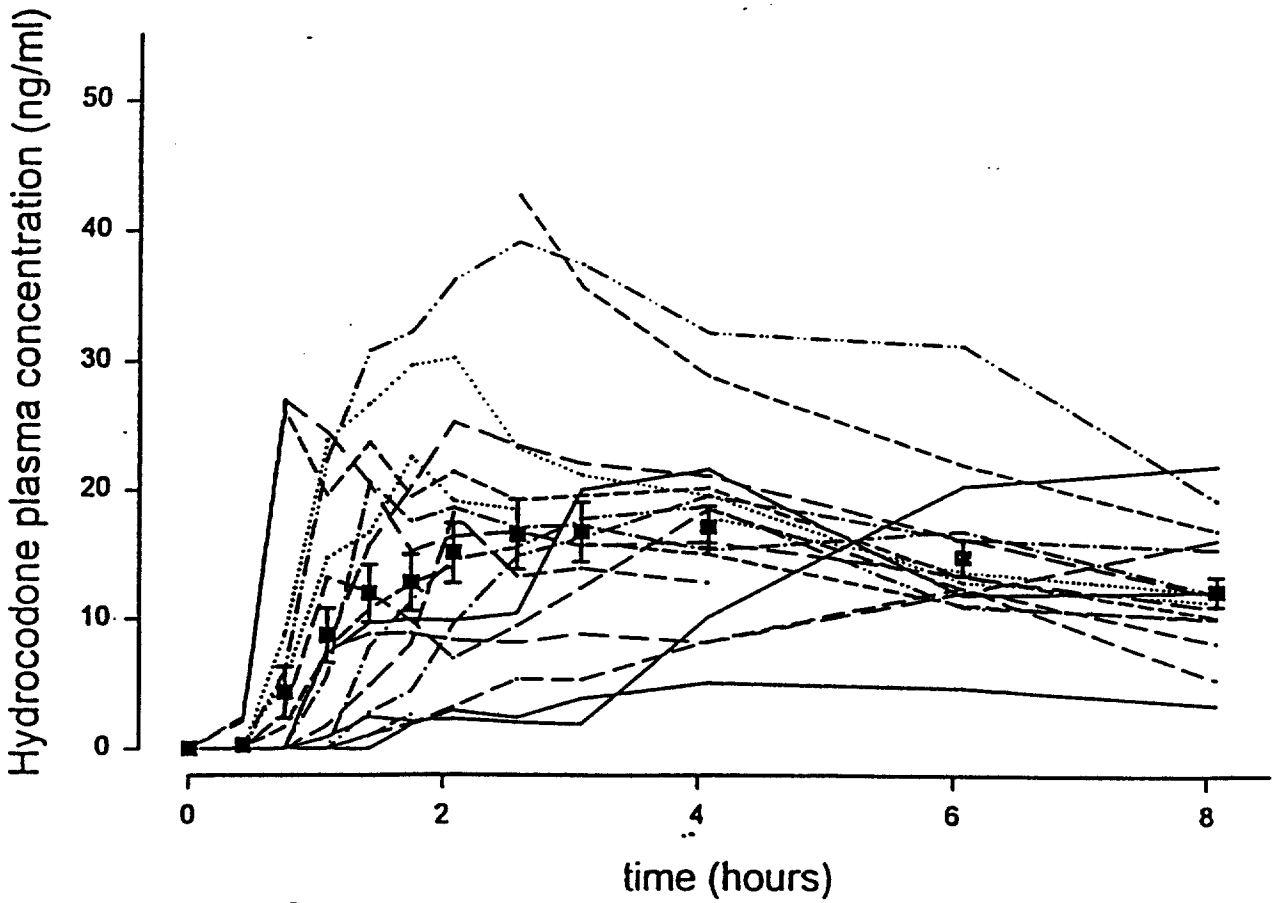
Table C1
Demographic and Background Information

	Placebo (N=18)	Hydrocodone (N=18)	Ibuprofen (N=18)	VICOPROFEN (N=18)	Total (N=72)	Statistic	df	p-value
Age (years)								
Mean	23.1	23.1	23.9	24.9	23.8	F = 0.49	3, 68	0.690 NS
S. D.	4.1	4.6	5.9	6.4	5.3			
Range								
Sex								
Female	10	9	7	10	36			
Male	8	9	11	8	36	X^2 = 1.33	3	0.721 NS
Weight (lbs)								
Mean	153.8	155.8	158.3	155.9	156.0	F = 0.05	3, 68	0.985 NS
S. D.	33.3	30.2	27.7	45.3	34.1			
Range								
Type of Surgery								
Dental	18	18	18	18	72			
Racial Origin								0.897 NS
Caucasian	12	11	11	11	45			
Black	1	4	4	4	13			
Hispanic	2	1	1	0	4			
Asian	1	1	1	1	4			
Other	2	0	1	2	5			
Unavailable	0	1	0	0	1			

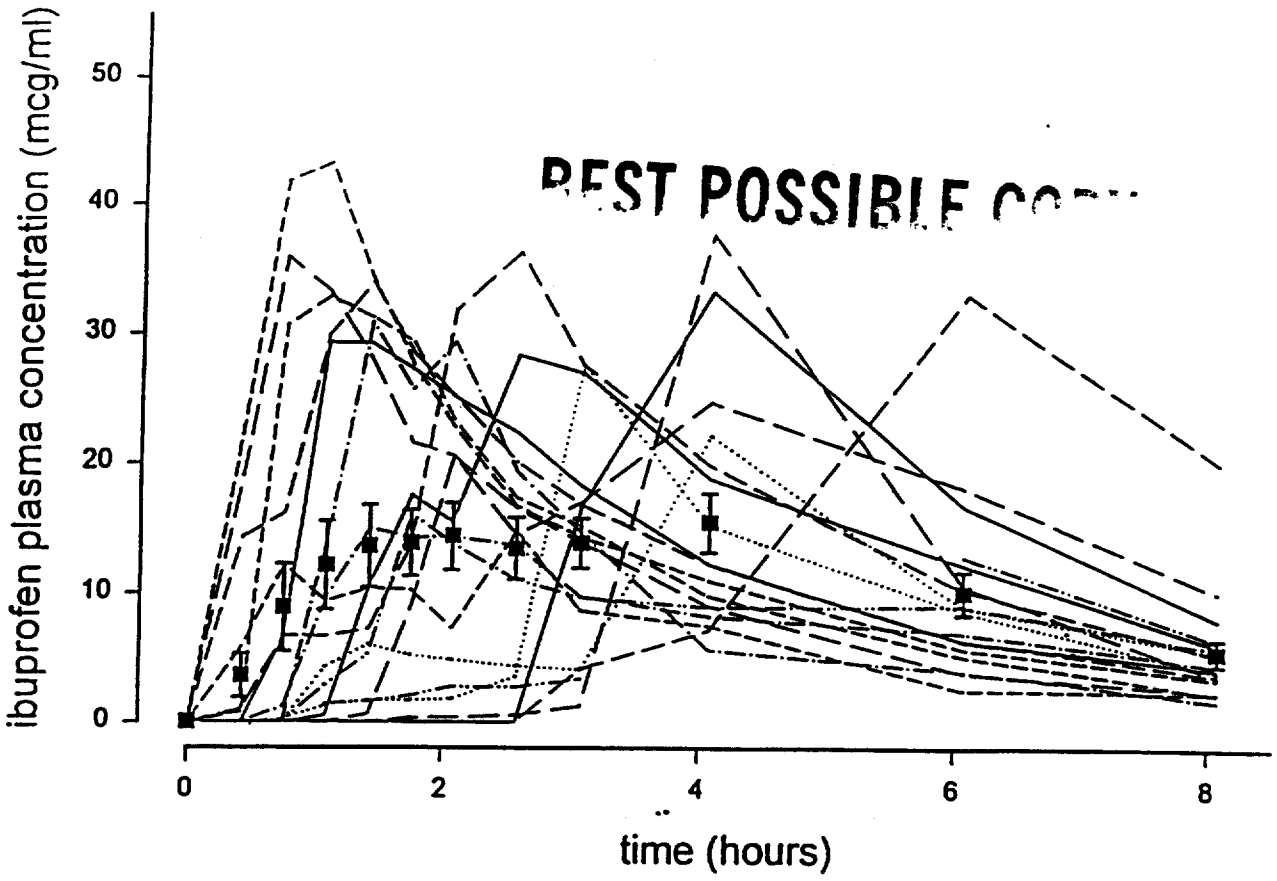


Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

Hydrocodone plasma concentration after vicoprofen 400/15 mg orally.
Each line represents a patient. At missing values the lines are interrupted. The squares indicate the means +/- SE

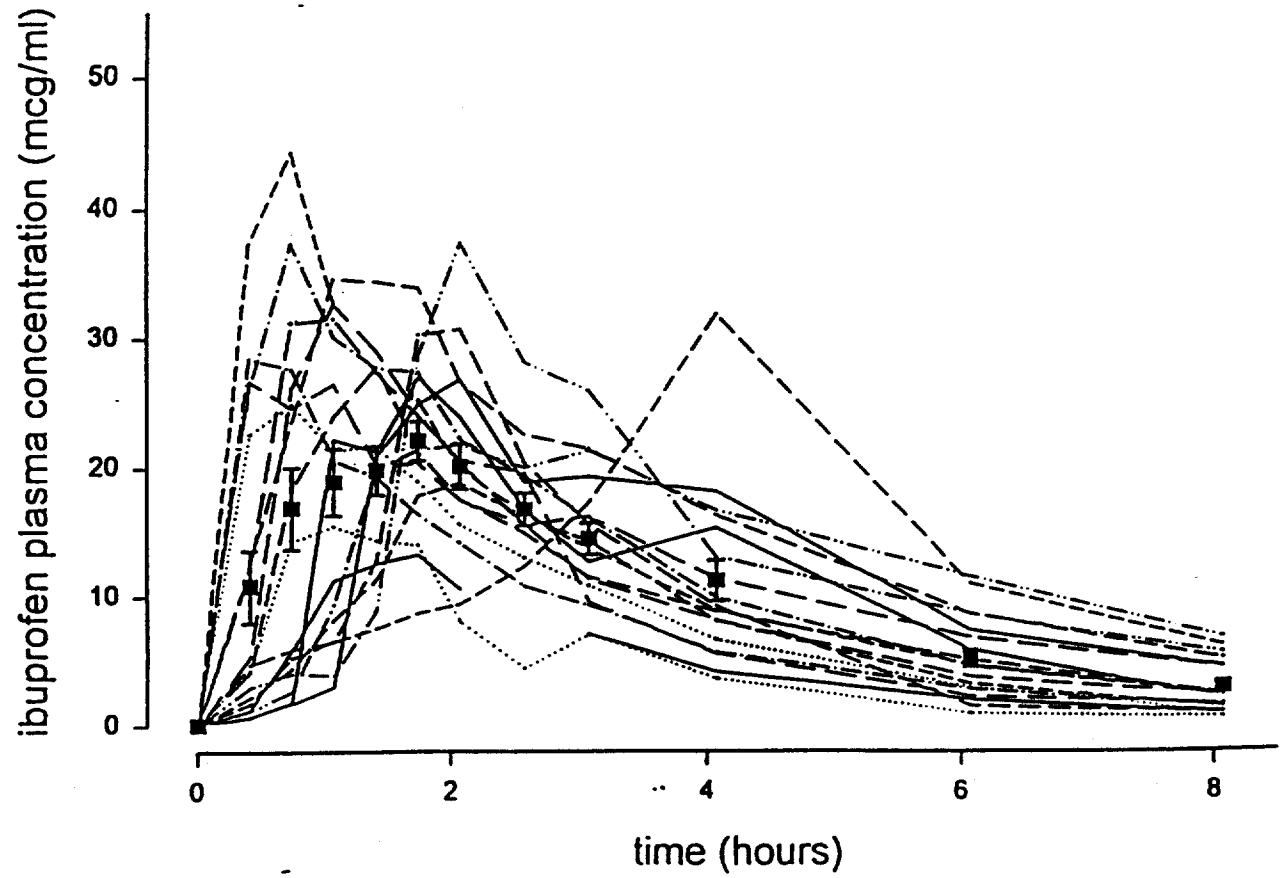


Vicoprofen Protocol VP-22
Plasma Drug Concentration Results



PK 6
Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

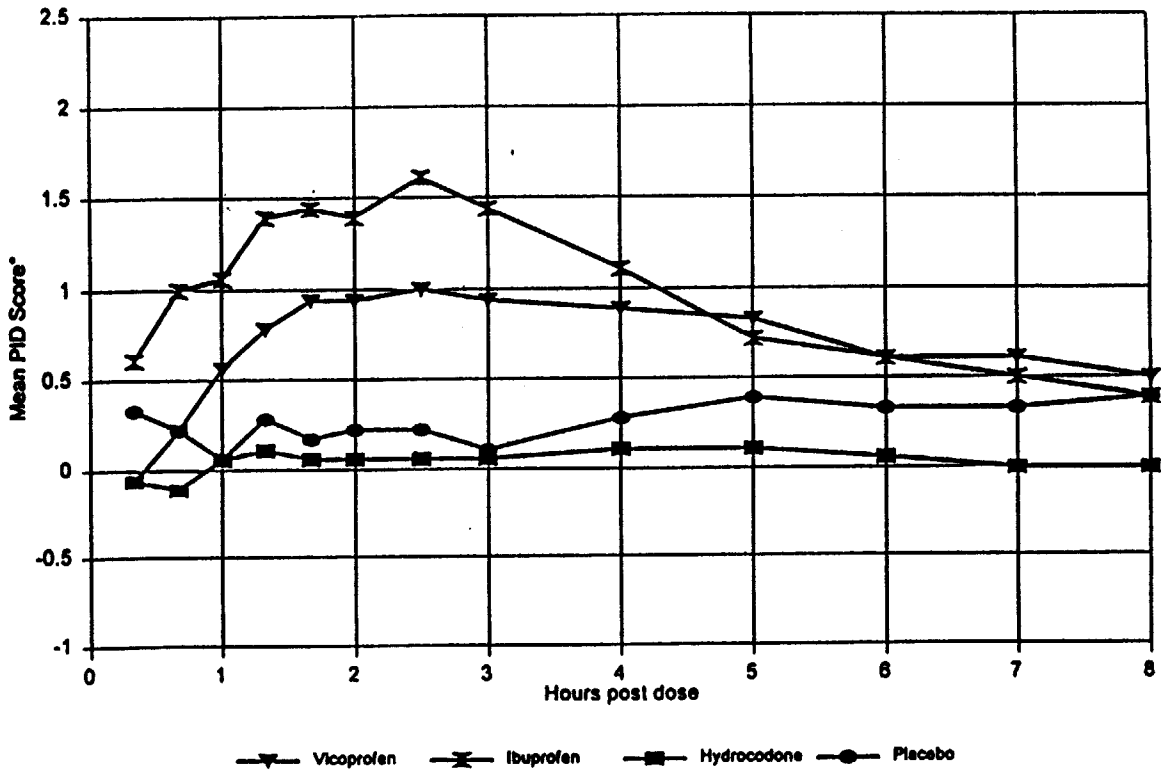
Ibuprofen plasma concentration after vicoprofen 400/15 mg orally.
Each line represents a patient. At missing values the lines are interrupted. The squares indicate the means +/- SE.



PK 5
Vicoprofen Protocol VP-22
Plasma Drug Concentration Results

VP-22-2201 Pain Intensity Differences

All Patients



		Hours post dose																									
		0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd	-0.06	(0.64)	0.22	(0.81)	0.56	(0.96)	0.78	(1.00)	0.94	(1.00)	0.94	(1.06)	1.00	(1.06)	0.94	(1.06)	0.89	(1.13)	0.83	(1.20)	0.81	(1.14)	0.81	(1.04)	0.50	(0.99)
	n sig	18		18		18		18		18	X	18	X	18	X	15	X	13		13		12		11		11	
Ibuprofen (400 mg)	*mean sd	0.61	(0.78)	1.00	(0.84)	1.06	(1.00)	1.39	(0.85)	1.44	(0.78)	1.39	(0.78)	1.61	(0.85)	1.44	(0.98)	1.11	(0.68)	0.72	(0.89)	0.81	(0.98)	0.50	(0.92)	0.39	(0.98)
	n sig	18		18	X	18	X	18	X	18	X	18	X	18	X	17	X	16	X	16		13		11		8	
Hydrocodone (15mg)	*mean sd	-0.06	(0.64)	-0.11	(0.83)	0.06	(1.00)	0.11	(1.06)	0.06	(1.00)	0.06	(1.11)	0.06	(1.16)	0.06	(1.16)	0.11	(1.23)	0.11	(1.28)	0.06	(1.11)	0.00	(1.14)	0.00	(1.24)
	n sig	18		18		18		18		14		13		10		7		7		6		6		6		6	
Placebo	*mean sd	0.33	(0.69)	0.22	(0.73)	0.06	(0.73)	0.28	(0.83)	0.17	(0.86)	0.22	(0.88)	0.22	(0.81)	0.11	(0.68)	0.28	(0.89)	0.39	(0.98)	0.33	(0.97)	0.33	(0.97)	0.39	(0.98)
	n sig	18		18		18		18		16		14		11		11		10		10		9		8		8	
	p-value	0.011		<0.001		0.005		<0.001		<0.001		<0.001		<0.001		<0.001		0.010		0.196		0.337		0.306		0.507	

Mean AUC-PID Scores

	0-4 hr	0-8hr
Vicoprofen	2.72 X	5.36
Ibuprofen	4.85 X	7.01 X
Hydrocodone	0.15	0.34
Placebo	0.68	2.04
p-value	<0.001	0.017

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X=significantly different from placebo (p<=0.05)

FIGURE 1

	*mean +sd	0.33	0.67	1	1.33	1.67	2	2.5	3	4	5	6	7	8
Vicoprofen (400/15 mg)	*mean +sd	-0.33 (0.49)	0.08 (0.90)	0.42 (1.08)	0.83 (1.11)	1.00 (1.04)	1.00 (1.13)	1.00 (1.13)	0.92 (1.08)	0.75 (1.06)	0.67 (1.07)	0.42 (0.90)	0.50 (0.90)	0.42 (0.90)
	n, df	12	12	12	12	12	10	10	10	10	10	9	9	9
	p-value	0.013	0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010	0.154	0.036	0.035
Ibuprofen (400 mg)	*mean +sd	-0.27 (0.47)	-0.55 (0.52) X	-0.55 (0.52) X	-0.45 (0.82) X	-0.36 (0.82) X	-0.43 (0.82) X	-0.55 (0.69) X	-0.55 (0.69) X	-0.36 (1.03) X	-0.45 (0.82) X	-0.36 (1.03) X	-0.55 (0.82) X	-0.64 (0.67) X
	n, df	11	11	11	11	11	11	11	11	11	11	11	11	11
	p-value	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010	0.154	0.036	0.035
Hydrocodone (15mg)	*mean +sd	0.27 (0.65)	0.00 (0.77)	-0.18 (0.75)	0.00 (0.77)	-0.18 (0.75)	-0.09 (0.83)	-0.09 (0.76)	-0.09 (0.76)	0.00 (0.77)	0.18 (0.98)	0.18 (0.98)	0.18 (0.98)	0.27 (1.01)
	n, df	11	11	11	11	10	8	7	7	7	6	6	6	6
	p-value	0.013	0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010	0.154	0.036	0.035
Placebo	*mean +sd	0.27 (0.65)	0.73 (0.47) X	0.73 (0.65) X	1.27 (0.65) X	1.36 (0.50) X	1.27 (0.47) X	1.73 (0.47) X	1.45 (0.82) X	1.18 (0.60) X	0.73 (0.90) X	0.55 (1.04) X	0.45 (0.93) X	0.27 (1.01) X
	n, df	11	11	11	11	11	11	11	11	11	11	9	9	9
	p-value	0.013	0.001	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.010	0.154	0.036	0.035

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X = significantly different from placebo (p<=0.05)

Mean AUC-PID Scores	0-4 hr	0-8hr
Vicoprofen	2.52 X	4.56
Ibuprofen	4.37 X	8.80 X
Hydrocodone	-1.66	-3.57
Placebo	-0.24	0.44
p-value	<0.001	<0.001

FIGURE 2

VP-22-2201 Pain Intensity Differences

Patients with Severe Baseline Pain

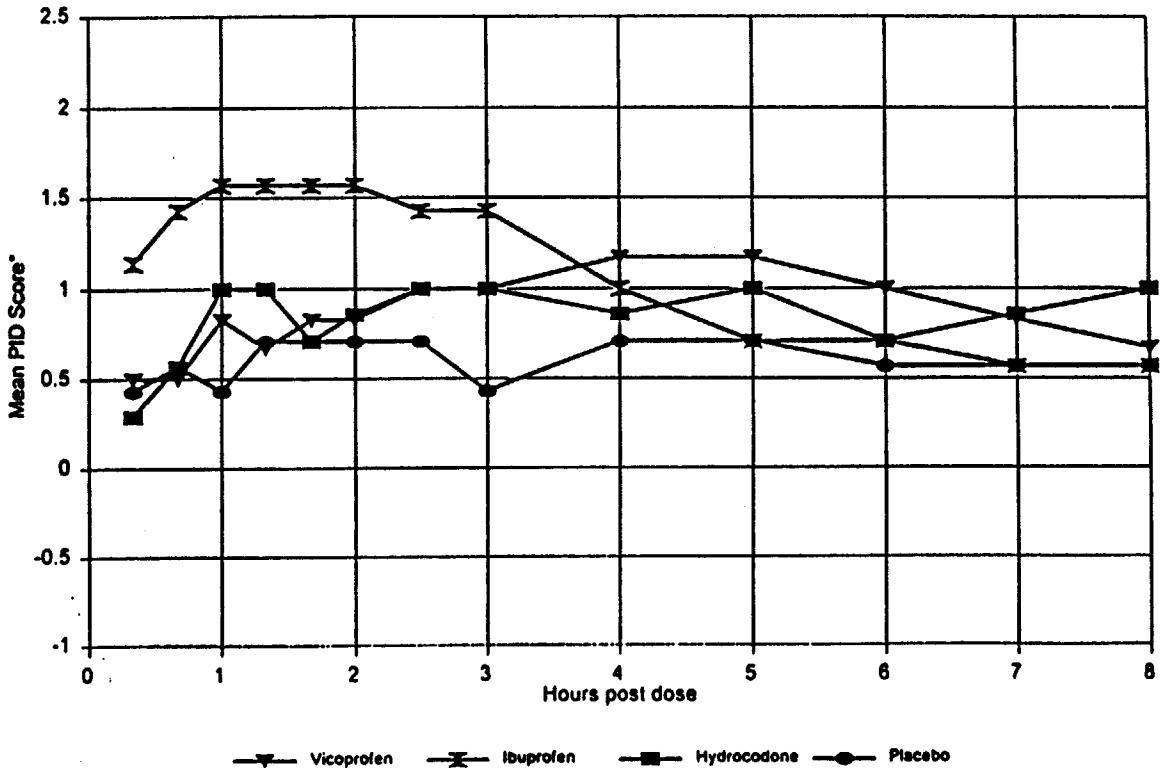


FIGURE 3

		Hours post dose																			
		0.33		0.67		1		1.33		1.67		2		2.5		3		4		5		6		7		8	
Vicoprofen (400/15 mg)	*mean sd	0.50	(0.55)	0.50	(0.55)	0.83	(0.75)	0.67	(0.82)	0.83	(0.98)	0.83	(0.98)	1.00	(1.10)	1.00	(1.10)	1.17	(1.33)	1.17	(1.47)	1.00	(1.55)	0.83	(1.33)	0.67	(1.21)
	n sig	6		6		6		6		6		6		6		5		3		3		3		2		2	
Ibuprofen (400 mg)	*mean sd	1.14	(0.69)	1.43	(1.13)	1.57	(1.27)	1.57	(1.13)	1.57	(1.13)	1.57	(1.13)	1.43	(1.27)	1.43	(1.27)	1.00	(0.82)	0.71	(0.95)	0.71	(0.95)	0.57	(0.98)	0.57	(0.98)
	n sig	7		7		7	X	7		7		7		7		6		5		5		4		3		2	
Hydrocodone (15mg)	*mean sd	0.29	(0.76)	0.57	(0.79)	1.00	(0.82)	1.00	(0.82)	0.71	(0.76)	0.86	(1.07)	1.00	(1.15)	1.00	(1.15)	0.86	(1.21)	1.00	(1.41)	0.71	(0.95)	0.86	(1.07)	1.00	(1.29)
	n sig	7		7		7		7		6		6		5		4		4		3		3		3		3	
Placebo	*mean sd	0.43	(0.79)	0.57	(0.53)	0.43	(0.53)	0.71	(0.76)	0.71	(0.76)	0.71	(0.76)	0.71	(0.76)	0.43	(0.53)	0.71	(0.95)	0.71	(0.95)	0.57	(0.98)	0.57	(0.98)	0.57	(0.98)
	n sig	7		7		7		7		8		6		4		4		4		4		3		2		2	
	p-value	0.140		0.127		0.148		0.251		0.266		0.384		0.677		0.383		0.890		0.860		0.919		0.932		0.874	

Mean AUC-PID Scores		
	0-4 hr	0-8hr
Vicoprofen	3.13	6.96
Ibuprofen	5.10	7.67
Hydrocodone	2.99	6.49
Placebo	2.13	4.56
p-value	0.382	0.871

Sample sizes (n) represent number of patients remaining at each evaluation time point. However, mean values and comparisons are based on all patients, with values extrapolated after remedication.

*X=significantly different from placebo ($p<=0.05$)

NDA/IND# 20-716 Suppl/Amend.# ORIG Submission Date: 4/26/96 Volume: 1.12

tudy Type: Interaction Study Study # VP-27

Study Title: A study of the interaction between Vicoprofen® tablets administered with and without a sorbitol containing suspension

Clinical Investigator

Site

Analytical Investigator

Site

Single Dose: Y Multiple Dose: N Washout Period: Seven Days

Cross-Over Y Parallel N Other Design:

Fasted Y Food Study N FDA High Fat Breakfast N

If fasted, how long (hrs.)? 10

Subject Breakdown

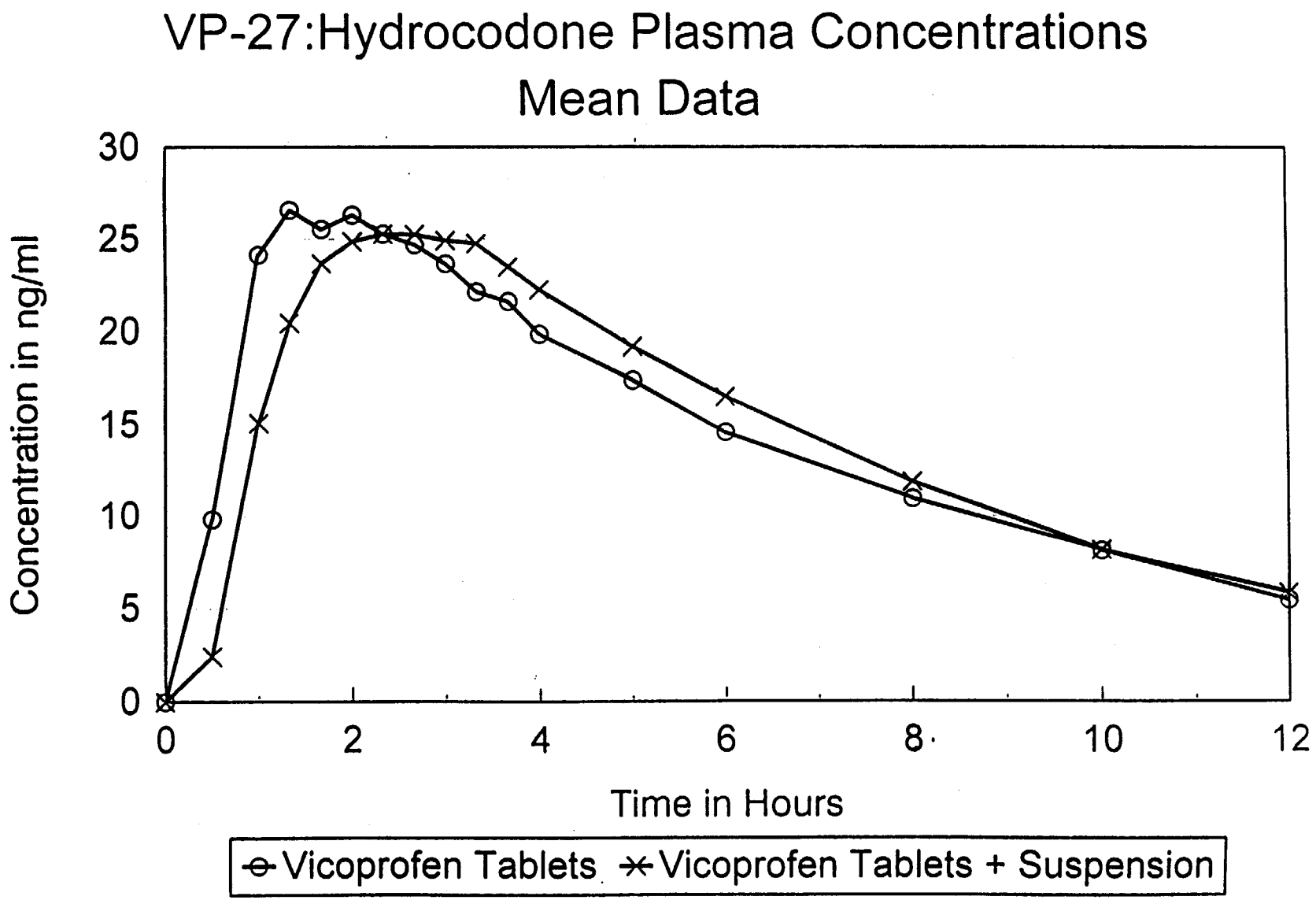
Normal Y Patients N Young Y Elderly N Renal N Hepatic N

	Subject Type	Males		Group	All	N=	34	M= 28	F= 6
Weight	Mean 171	Range		Group		N=		M=	F=
Age	Mean 29	Range		Group		N=		M=	F=
	Subject Type	Females		Group		N=		M=	F=
Weight	Mean 143	Range		Group		N=		M=	F=
Age	Mean 31	Range		Group		N=		M=	F=

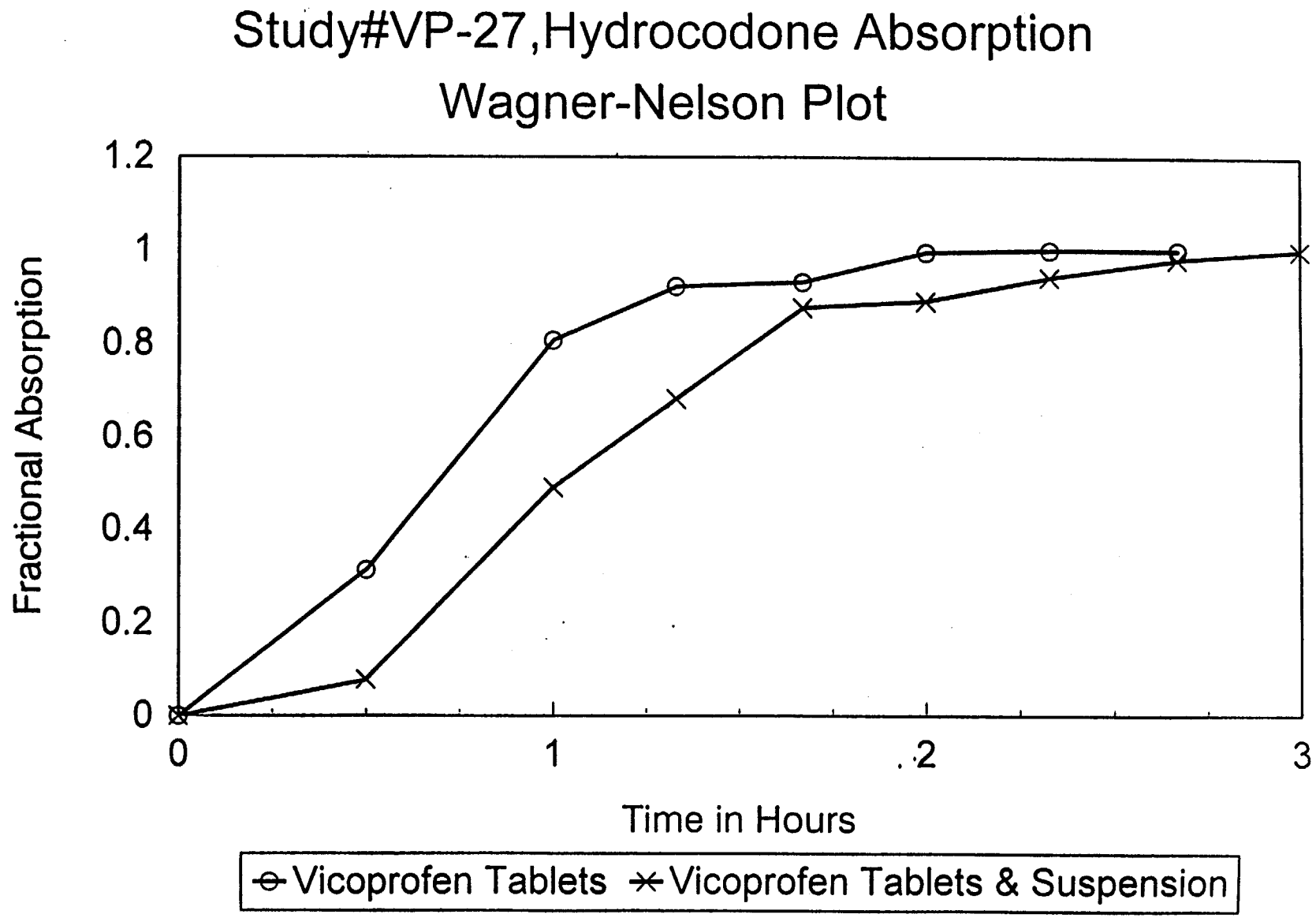
Treatment Group	Dose	Dosage Form	Strength	Lot#	Lot Size
TRT A	2 tablets	tablets	7.5mg HC/ 200mg IBU	55-0932	
TRT B	2 tablets	tablets	7.5mg HC/ 200mg IBU	55-0932	
	20ml	Suspension	Placebo	131-01	
TRT C	2 tablets	tablets	200mg IBU	29-0291	

Sampling Times

Plasma 12ml samples, prior to dosing and at 30, 60, 80, 100, 120, 140, 160, 180, 200, 220min., and 4, 5, 6, 8, 10 and 12 hours after dosing



2 Tablet Dose (15mg Hydrocodone)



15mg Dose

Vicoprofen® Protocol VP-27
Pharmacokinetic Summary Statistics
Mean (+/- S.D.)

Analyte:	Hydrocodone Bitartrate N=32		Ibuprofen N=32			
Parameter (Units)	Vicoprofen	Vicoprofen + Suspension	Vicoprofen	Vicoprofen + Suspension	Ibuprofen	Parameter (Units)
C_{max} (ng/mL)	29.7 (6.9)	28.9 (6.7)	32.5 (7.6)	33.2 (6.2)	35.8 (5.7)	C_{max} (mcg/mL)
T_{max} (hour)	1.73 (0.77) A	2.58 (1.03) B	1.73 (1.19)	1.98 (1.19)	1.67 (0.90)	T_{max} (hour)
$t_{½}$ (hour)	4.22 (0.97)	4.09 (1.17)	2.01 (0.65)	2.03 (0.89)	1.92 (0.38)	$t_{½}$ (hour)
$AUC_{0-\infty}$ (ng/mL.hr)	211.1 (58.4)	212.7 (59.5)	118.2 (34.1)	122.1 (39.2)	129.2 (37.8)	$AUC_{0-\infty}$ (mcg/mL.hr)

Bioequivalence with Respect to Plasma Hydrocodone

Treatment B versus Treatment A

Parameter	Treatment Means B	A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	(95% Confidence)	Mean Ratio
CMAX	28.905	29.653	-2.52	0.4591	99.97	91.8 - 103.2	90.6 - 104.3	.
TMAX	2.588	1.738	48.94	0.0007*	31.36	137.1 - 170.8	122.6 - 175.3	.
AUC	176.345	176.394	-0.03	0.9913	99.99	95.7 - 104.2	94.8 - 105.1	.
AUC-INF	212.924	211.554	0.65	0.8252	99.99	95.7 - 105.6	94.7 - 106.6	.
KEL	0.179	0.171	4.13	0.3012	99.76	97.5 - 110.8	96.1 - 112.2	.
HALF-LIFE	4.092	4.219	-3.01	0.6130	90.79	87.0 - 107.0	85.0 - 109.0	.
LCMAX	3.337	3.365	-0.83	0.4115	99.98	91.9 - 102.9	90.8 - 104.1	97.2
LAUC	5.142	5.144	-0.04	0.9421	99.99	95.4 - 104.4	94.6 - 105.3	99.8
LAUC-INF	5.323	5.316	0.10	0.8620	99.99	95.4 - 106.0	94.4 - 107.1	100.5

Treatment B = 2 x Vicoprofen(R) Tablets + 20 mL Sorbitol Suspension - test
Treatment A = 2 x Vicoprofen(R) Tablets - reference

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'L' prefix are log-transformed parameters
. = value was not calculated

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test - reference) for log transformed parameters only

VP-27 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg

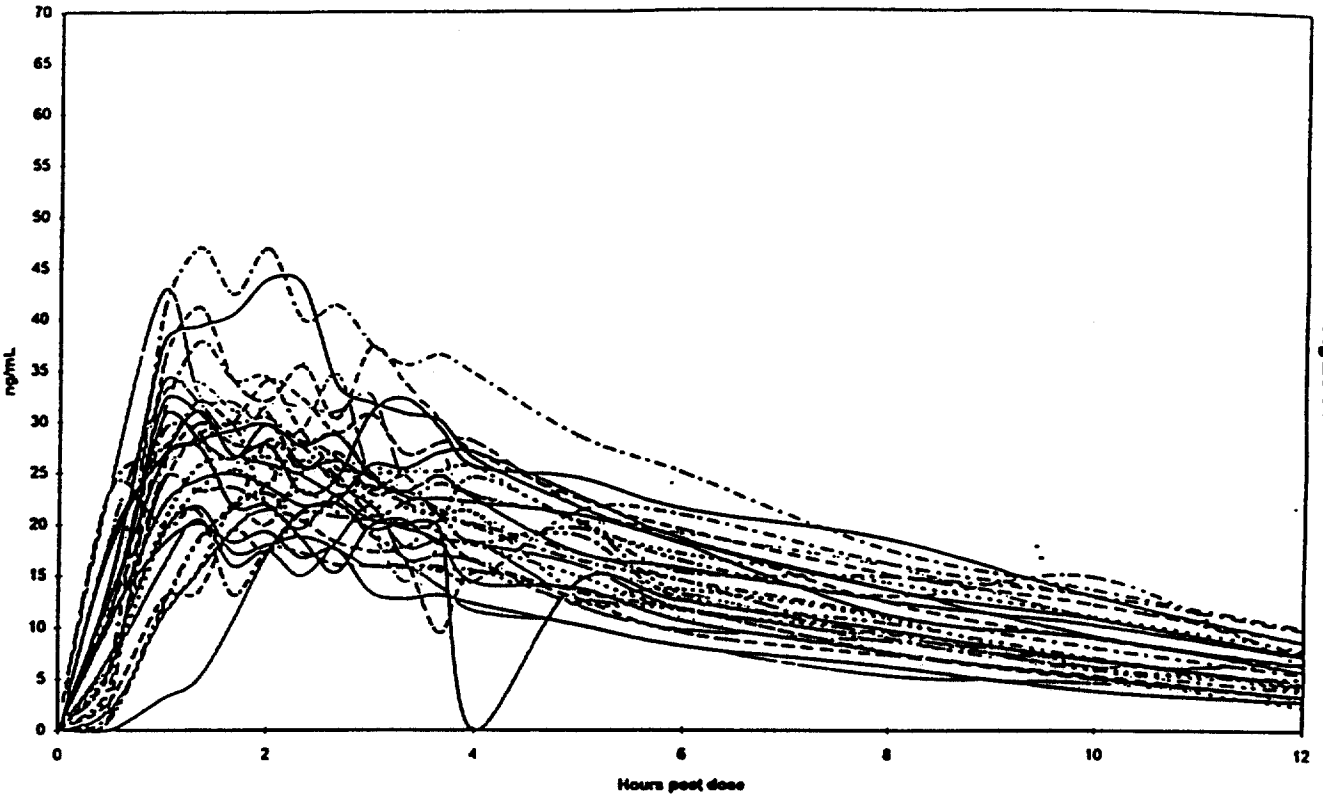


Figure 14

VP-27 Subjects Plasma Hydrocodone Concentrations from Vicoprofen 400/15mg + Placebo Suspension

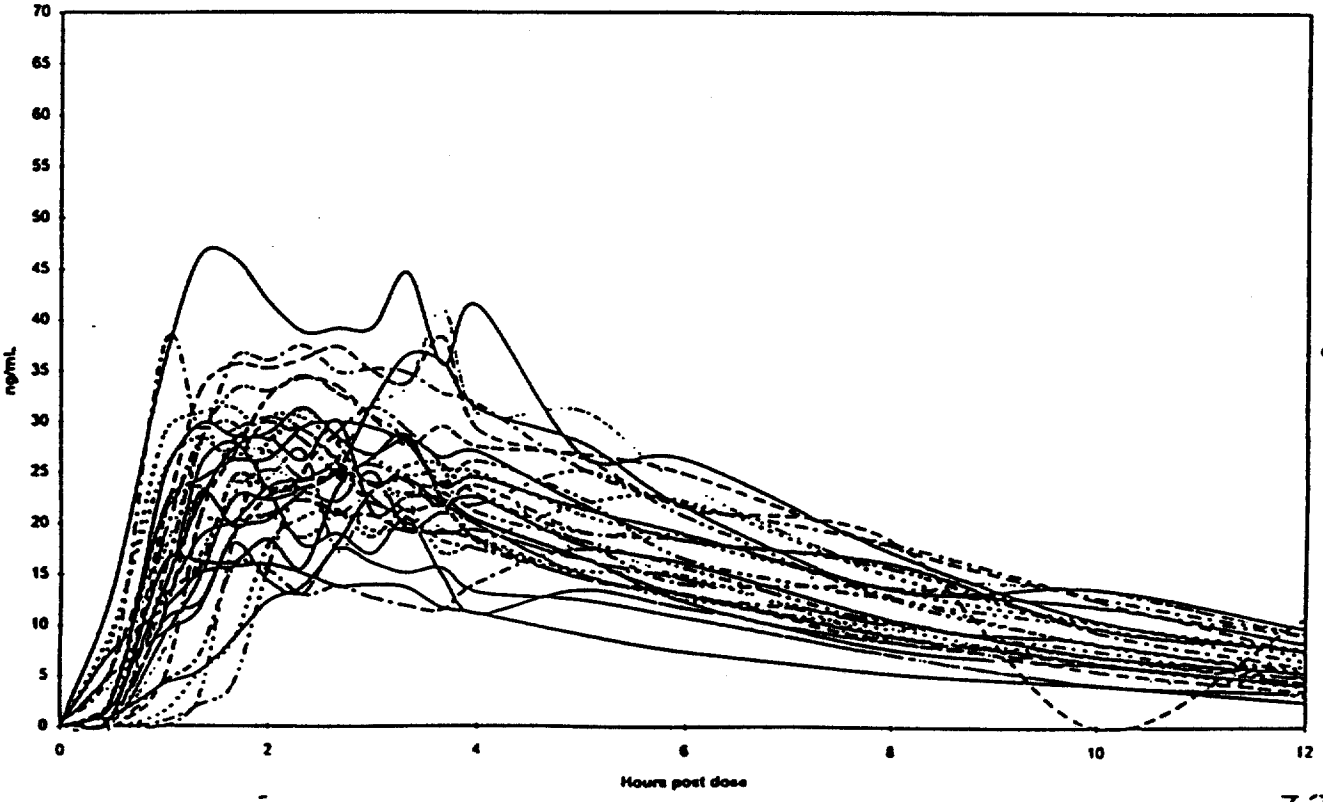
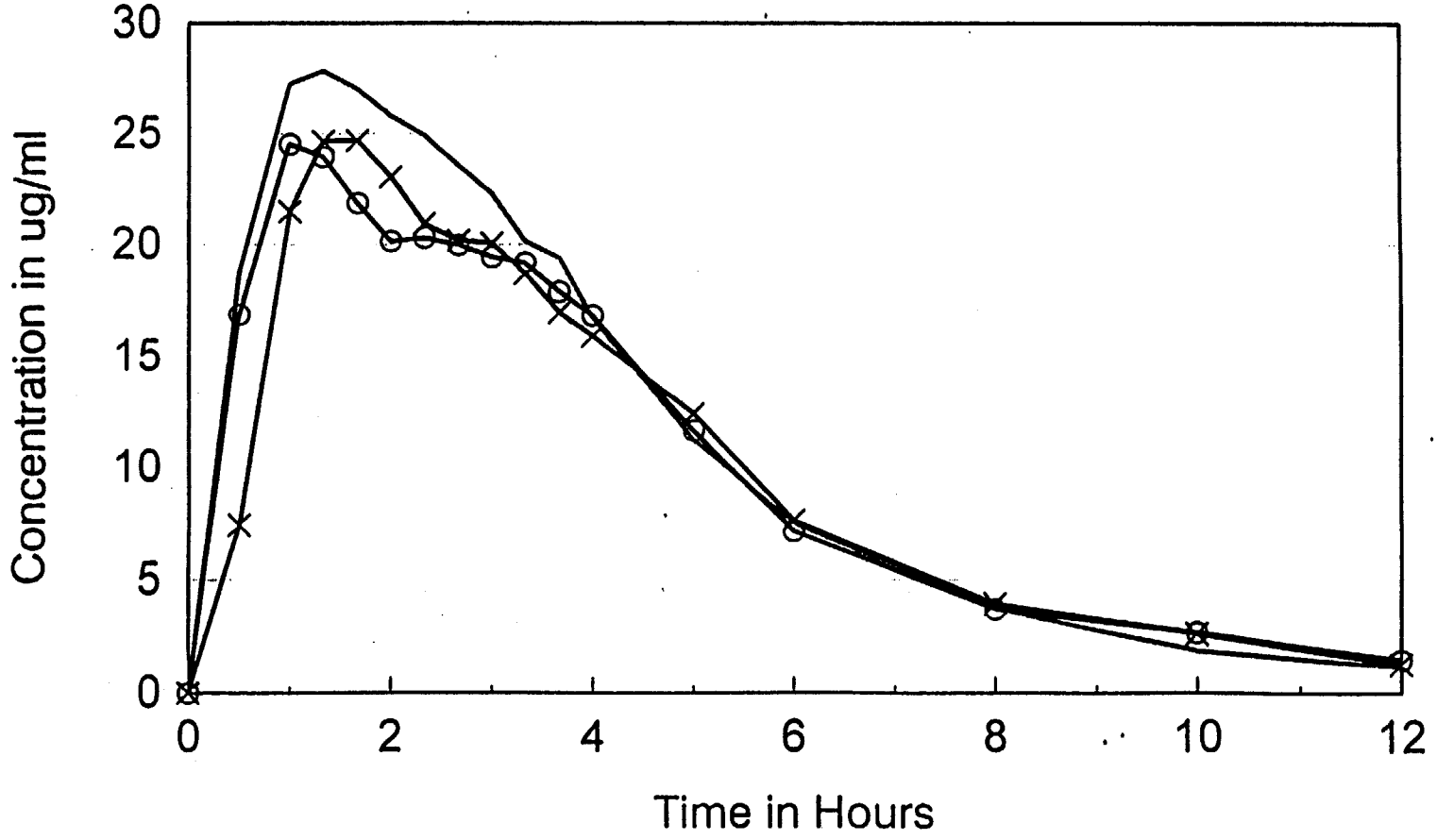


Figure 15

VP-27:Ibuprofen Plasma Concentrations

Mean Data

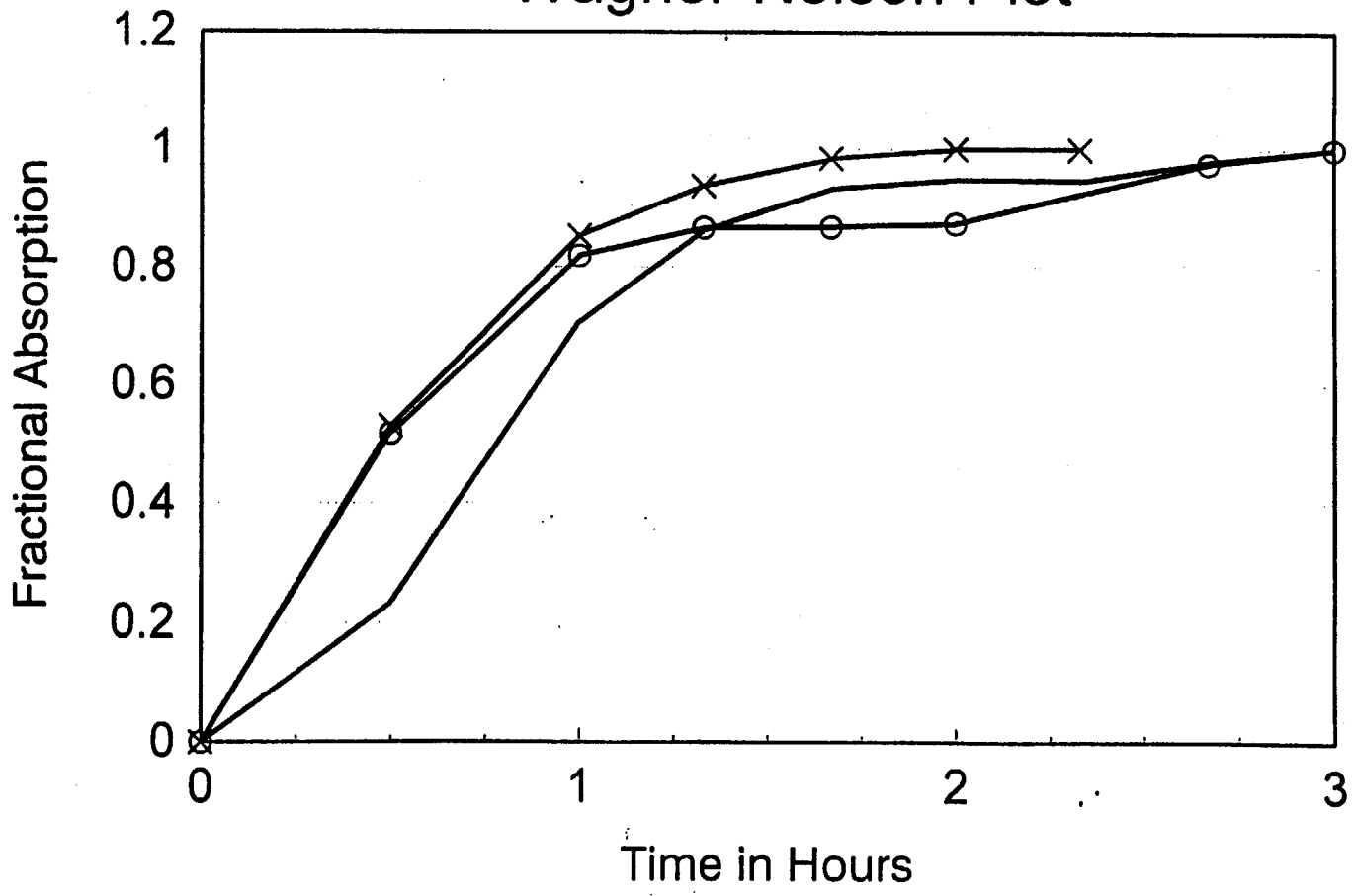


Vicoprofen Tablets Vicoprofen Tablets + Suspension Ibuprofen Tablets

2 Tablet Dose (400mg Ibuprofen)

Study#VP-27, Ibuprofen Absorption

Wagner-Nelson Plot



400mg Ibuprofen

Statistical Comparison of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment A versus Treatment C

Parameter	Treatment Means A	Treatment Means C	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Confidence Intervals (95% Confidence)	Mean Ratio
CMAX	32.006	35.474	-9.78	0.0240*	99.99	85.2 - 95.2	84.2 - 96.2	.
TMAX	1.772	1.735	2.13	0.8909	42.92	83.8 - 120.5	80.2 - 124.1	.
AUC	116.000	125.183	-7.34	0.0034*	99.99	89.8 - 95.5	89.3 - 96.1	.
AUC-INF	122.532	128.705	-4.80	0.0463*	99.99	92.4 - 98.0	91.9 - 98.5	.
KEL	0.361	0.373	-3.25	0.2859	99.99	93.2 - 100.3	92.5 - 101.0	.
HALF-LIFE	2.108	1.903	10.79	0.0712	99.71	103.9 - 117.7	102.6 - 119.0	.
LCMAX	3.435	3.556	-3.40	0.0207*	99.96	83.4 - 94.1	82.4 - 95.2	88.6
LAUC	4.719	4.802	-1.74	0.0039*	99.99	89.0 - 95.1	88.4 - 95.7	92.0
LAUC-INF	4.761	4.826	-1.34	0.0273*	99.99	90.6 - 96.9	90.0 - 97.6	93.7

Statistical Comparison of Plasma Ibuprofen Pharmacokinetic Parameters

Treatment B versus Treatment C

Parameter	Treatment Means B	Treatment Means C	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Confidence Intervals (95% Confidence)	Mean Ratio
CMAX	33.675	35.474	-7.89	0.0635	99.99	87.1 - 97.1	86.1 - 98.1	.
TMAX	1.988	1.735	14.58	0.3463	42.92	96.2 - 132.9	92.6 - 136.6	.
AUC	116.178	125.183	-7.19	0.0036*	99.99	90.0 - 95.7	89.4 - 96.2	.
AUC-INF	122.606	128.705	-4.74	0.0458*	99.99	92.5 - 98.0	91.9 - 98.6	.
KEL	0.368	0.373	-1.31	0.6575	99.99	95.1 - 102.2	94.4 - 102.9	.
HALF-LIFE	2.062	1.903	8.36	0.1501	99.71	101.5 - 115.2	100.1 - 116.6	.
LCMAX	3.465	3.556	-2.56	0.0758	99.96	86.0 - 97.0	84.9 - 98.2	91.3
LAUC	4.730	4.802	-1.52	0.0102*	99.99	90.0 - 96.1	89.4 - 96.7	93.0
LAUC-INF	4.771	4.826	-1.13	0.0549	99.99	91.5 - 97.9	90.9 - 98.6	94.7

Treatment B versus Treatment A

Parameter	Treatment Means B	Treatment Means A	Pct Difference	PR>|T|	Power (%)	Confidence Intervals (90% Confidence)	Confidence Intervals (95% Confidence)	Mean Ratio
CMAX	33.675	32.006	2.09	0.6566	99.99	96.5 - 107.6	95.5 - 108.7	.
TMAX	1.988	1.772	12.19	0.4245	44.44	94.2 - 130.2	90.7 - 133.7	.
AUC	116.178	116.000	0.15	0.9530	99.99	97.1 - 103.2	96.5 - 103.8	.
AUC-INF	122.606	122.532	0.06	0.9808	99.99	97.1 - 103.0	96.6 - 103.6	.
KEL	0.368	0.361	2.00	0.5215	99.99	98.3 - 105.7	97.6 - 106.4	.
HALF-LIFE	2.062	2.108	-2.19	0.6804	99.94	91.6 - 104.0	90.4 - 105.2	.
LCMAX	3.465	3.435	0.88	0.5568	99.96	97.0 - 109.5	95.9 - 110.8	101.1
LAUC	4.730	4.719	0.23	0.7027	99.99	97.8 - 104.5	97.2 - 105.1	101.1
LAUC-INF	4.771	4.761	0.21	0.7263	99.99	97.7 - 104.5	97.0 - 105.2	101.0

Treatment B = 2 x Vicoprofen(R) tablets + 20 mL sorbitol suspension - test
Treatment A = 2 x Vicoprofen(R) tablets - reference

Values for Treatments B and A are the least-square means (LSMEANS) from the ANOVA
Parameters with the 'L' prefix are log-transformed parameters
. = value was not calculated

Pct Difference = difference between treatments (B - A) expressed as a percentage of Treatment A

PR>|T| = ANOVA test for significant differences between treatments
(* difference is statistically significant; p<0.05)

Power = power (%) to detect 20% differences between treatments (a=0.05)

Mean Ratio = 100*exp(test - reference) for log transformed parameters only

VP-27 Subjects Plasma Ibuprofen Concentrations from Ibuprofen 400mg

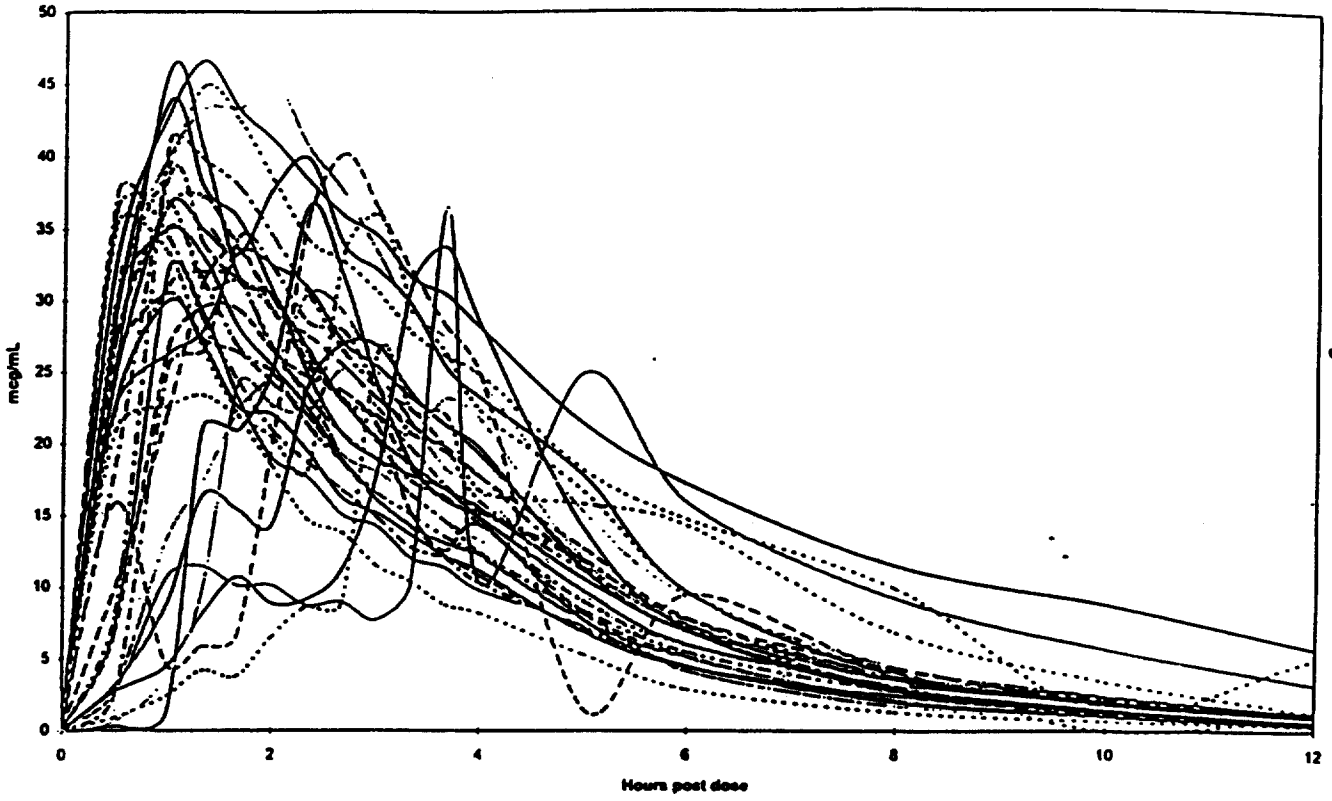


Figure 18

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg + Placebo Suspension

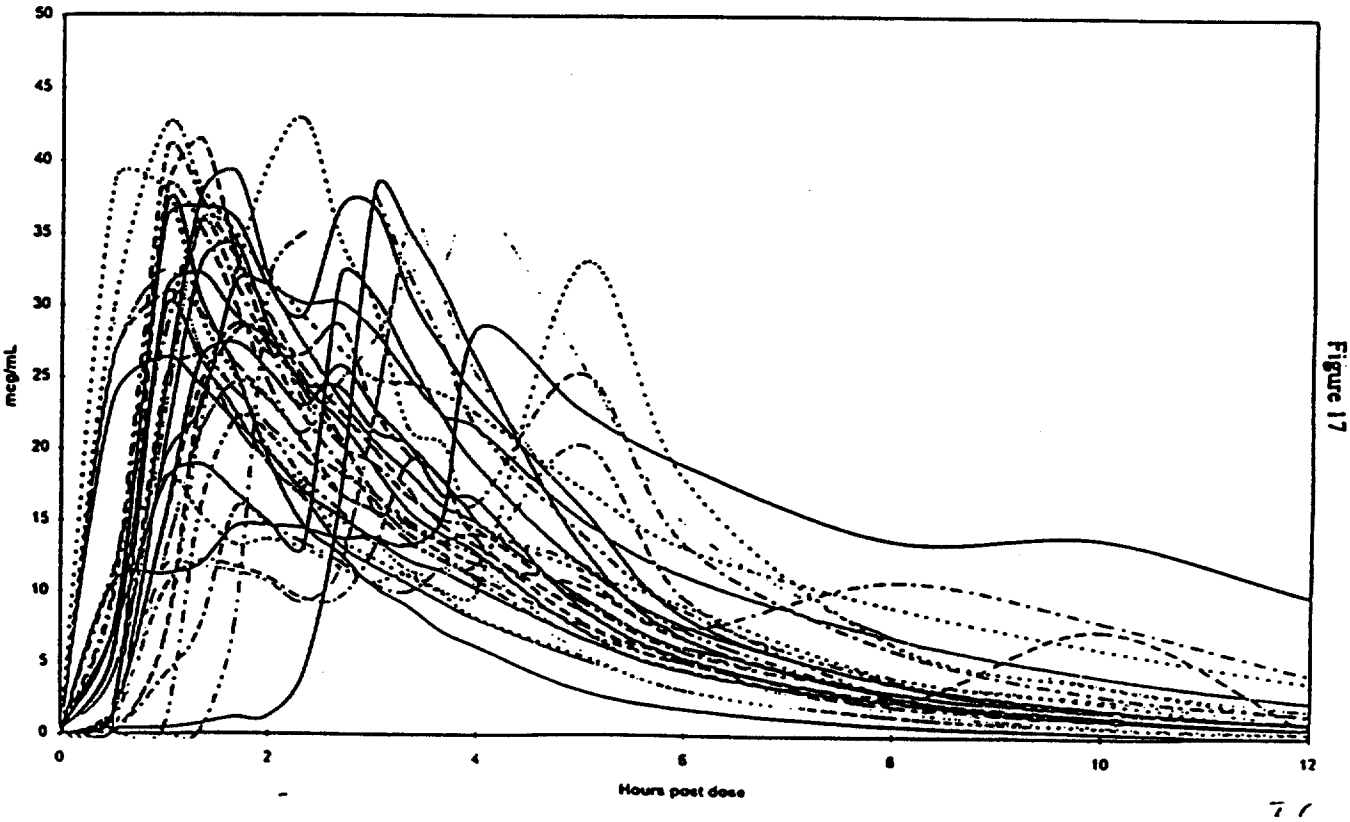


Figure 17

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg

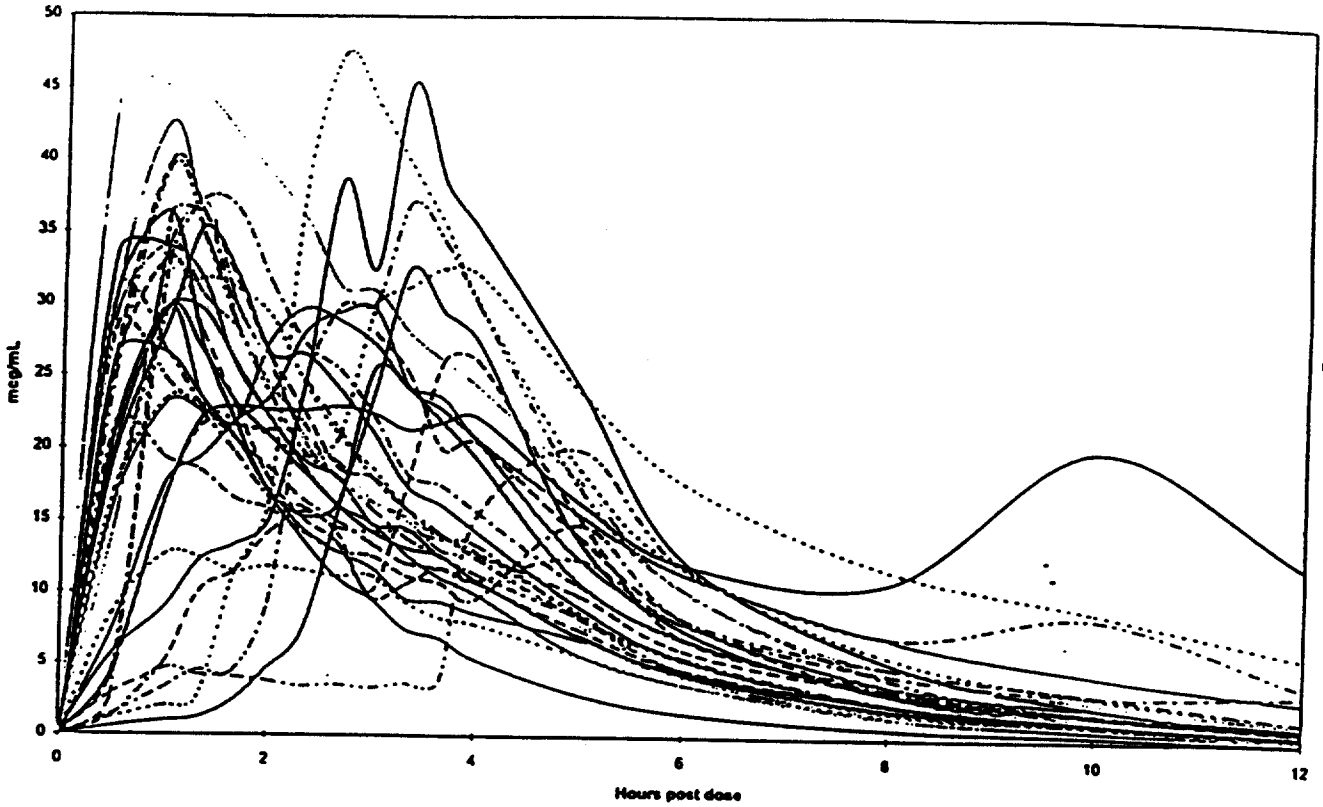


Figure 16

VP-27 Subjects Plasma Ibuprofen Concentrations from Vicoprofen 400/15mg + Placebo Suspension

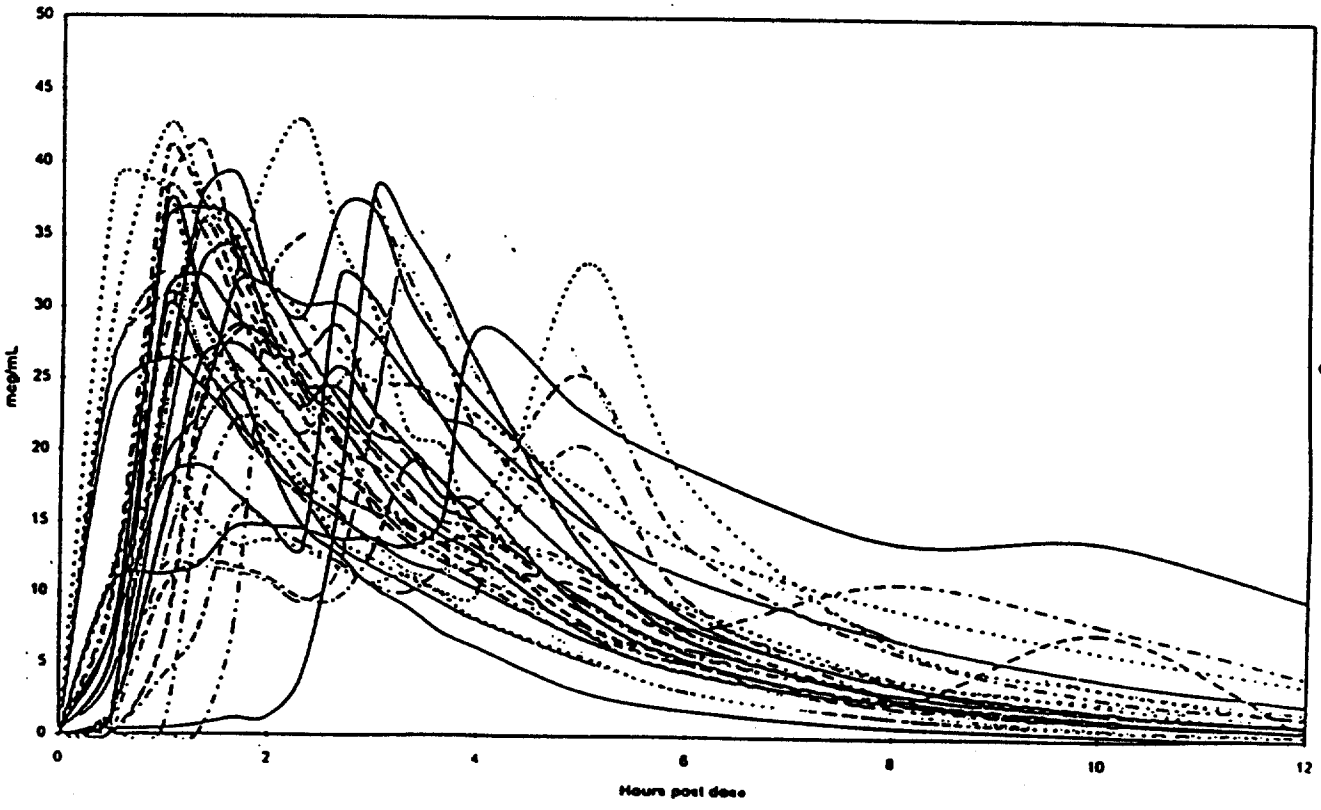


Figure 17

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

in which C is the concentration, in mg per mL, of 4-isobutylacetophenone in the *4-Isobutylacetophenone standard solution*, W is the weight, in mg, of Ibuprofen taken to prepare the *Assay preparation*, and R_U and R_S are the ratios of the 4-isobutylacetophenone peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 0.1% is found.■

Change to read:

Assay—

Mobile phase—Dissolve 4.0 g of chloroacetic acid in 400 mL of water, and adjust with ammonium hydroxide to a pH of 3.0. Add 600 mL of acetonitrile, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of valerophenone in *Mobile phase* having a concentration of about 0.35 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ibuprofen RS in *Internal standard solution* to obtain a solution having a known concentration of about 12 mg per mL.

■*4-Isobutylacetophenone standard solution*—Quantitatively dissolve an accurately weighed quantity of 4-isobutylacetophenone in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to 100.0 mL of *Internal standard solution*, and mix to obtain a solution having a known concentration of about 0.012 mg of 4-isobutylacetophenone per mL.■

Assay preparation—Transfer about 1200 mg of Ibuprofen, accurately weighed, to a container, add 100.0 mL of *Internal standard solution*, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the resolution, R, between the ■ibuprofen■ and internal standard peaks is not less than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%. ■Chromatograph the *4-Isobutylacetophenone standard solution*, and record the peak responses as directed under *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for 4-isobutylacetophenone, the tailing factors for the individual peaks are not more than 2.5, the resolution, R, between the valerophenone peak and the 4-isobutylacetophenone peak is not less than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%.■

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation*, ■the *Assay preparation*, and the *4-Isobutylacetophenone standard solution*■ into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 1.4 for the internal standard and 1.0 for ibuprofen. Calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in the portion of Ibuprofen taken by the formula:

$$100C(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation*, and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation*, respectively.

* *

Ibuprofen Tablets

Add the following:

■Labeling—Where the Tablets are gelatin-coated, the label so states.■

Change to read:

Dissolution ⟨711⟩—

Medium: pH 7.2 phosphate buffer (see under *Buffers* in the section *Reagents, Indicators, and Solutions*); 900 mL.

■*Apparatus 2:* 50 rpm.■

Time: ■60■ minutes.

Procedure—Determine the amount of $C_{13}H_{18}O_2$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 221 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Ibuprofen RS in the same medium. ■[NOTE—Where the Tablets are labeled as gelatin-coated, determine the amount of $C_{13}H_{18}O_2$ dissolved from the ultraviolet absorbance at the wavelength of maximum absorbance at about 266 nm from which is subtracted the absorbance at 280 nm, in comparison with the Standard solution similarly measured.]■

Tolerances—Not less than ■80%■ (Q) of the labeled amount of $C_{13}H_{18}O_2$ is dissolved in ■60■ minutes.

Change to read:

Water, *Method I* ⟨921⟩: not more than 5.0%, ■except that Tablets labeled as gelatin-coated are exempt from this requirement.■

Add the following:

■Limit of 4-isobutylacetophenone—Using the chromatograms of the *Assay preparation* and the *4-Isobutylacetophenone standard solution* obtained as directed in the *Assay*, calculate the percentage of 4-isobutylacetophenone ($C_{12}H_{16}O$) in the Tablets taken by the formula:

$$10{,}000C(A/WI)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of 4-isobutylacetophenone in the *4-Isobutylacetophenone standard solution*, A is the average weight, in mg, of a Tablet, W is the weight of Tablet powder taken to prepare the *Assay preparation*, I is the quantity, in mg, of ibuprofen per Tablet as obtained in the *Assay*, and R_U and R_S are the ratios of the 4-isobutylacetophenone peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 0.1% is found per Tablet.■

Change to read:

Assay—

Mobile phase, Internal standard solution, ■and■ *Standard preparation* ■—Prepare as directed in the *Assay* under *Ibuprofen.*

■*4-Isobutylacetophenone standard solution*—Quantitatively dissolve an accurately weighed quantity of 4-isobutylacetophenone in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to 100.0 mL of *Internal standard solution*, and mix to obtain a solution having a known concentration of about 0.012 mg of 4-isobutylacetophenone per mL.■

Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1200 mg of ibuprofen, to a suitable container, add 100.0 mL of *Internal standard solution*, and shake for 10 minutes. ■[NOTE—Where the Tablets are coated, place an accurately counted number of Tablets, equivalent to not less than 1200 mg of ibuprofen, in a container, add an accurately measured volume of *Internal standard solution*, sufficient to obtain an *Assay preparation* containing about 12 mg of ibuprofen per mL, and about 15 glass beads, and shake until the Tablets are completely disintegrated.]■ Centrifuge a portion of the suspension so obtained and use the clear supernatant solution as the *Assay preparation.*

■*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative retention times are about 0.75 for ibuprofen and 1.0 for valerophenone, the tailing factors for the individual peaks are not more than 2.5, the resolution, R, between the ibuprofen peak and the valerophenone peak is not less than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *4-Isobutylacetophenone standard solution*, and record the peak responses as directed under *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for 4-isobutylacetophenone, the tailing fac-