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การศึกษาเปรียบเทียบการเอื้อประโยชน์ในร่างกายของ

ยาเม็ดไอบูโพรเฟนที่จำหน่ายในประเทศไทย

นางสาววรรณภา   ธรรมสุจริต

COMPARATIVE STUDIES OF BIOAVAILABILITY OF
IBUPROFEN TABLETS COMMERCIALLY AVAILABLE IN THAILAND

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                  Tablets Commercially Available in Thailand

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วรรณภา ธรรมสุจริต : การศึกษาเปรียบเทียบการเอื้อประโยชน์ในร่างกายของยาเม็ด ไอบูโพรเฟนที่จำหน่ายในประเทศไทย (COMPARATIVE STUDIES OF BIOAVAILABILITY OF IBUPROFEN TABLETS COMMERCIALLY AVAILABLE IN THAILAND) อ.ที่ปรึกษา : รศ.ดร.ดวงจิต พนมวัน ณ อยุธยา , ๑๙๖ หน้า

การวิจัยครั้งนี้มีจุดมุ่งหมาย เพื่อ เปรียบ เทียบถึงความสมมูลในร่างกายของยา เม็ด เคลือบน้ำตาล ไอบูโพรเฟน ๒๐๐ มิลลิกรัม ที่ผลิตภายในประเทศกับผลิตภัณฑ์ต้นแบบ (บรูเฟน) โดยจะมีการประเมินคุณภาพ ทั้งในหลอดทดลองและในร่างกาย

การศึกษาในห้องปฏิบัติการได้ทดลองทั้ง การแตกกระจายตัวและการละลาย เวลาในการแตก กระจายตัวของยา เม็ดไอบูโพรเฟน มีค่าตั้งแต่ ๔ นาที ถึงนานกว่า ๕ ชั่วโมง ในจำนวน ๑๕ ตำรับที่ทำการ ศึกษา มี ๑๓ ตำรับ ที่ยาเม็ดสามารถแตกกระจายตัวได้ภายใน ๑ ชั่วโมง ยาเม็ดของ ๑ ตำรับ มีช่วงเวลา ในการแตกกระจายตัวต่างกันมากระหว่าง เม็ด คือมีค่าตั้งแต่ ๑.๒๘ ถึง ๒.๔๒ ชั่วโมง ในขณะที่อีก ๑ ตำรับ ยาเม็ดยังไม่มีการแตกกระจายตัว แม้ว่าการทดลองจะผ่านไปนานเกิน ๕ ชั่วโมงแล้ว ยาเม็ดทั้ง ๑๕ ตำรับ มีค่าคงที่อัตราการละลายแตกต่างกัน โดยมีค่าตั้งแต่ ๐.๐๐๕ ถึง ๐.๓๓๐ ต่อนาที สำหรับปริมาณยาที่ ละลายออกมาภายใน ๓๐ นาที เมื่อเปรียบ เทียบกับมาตรฐานกำหนดของ เภสัชตำรับสหรัฐอเมริกา พบว่า มี ๕ ตำรับ ที่เข้ามาตรฐานกำหนด ๗ ตำรับ ไม่เข้ามาตรฐานกำหนด ส่วนอีก ๓ ตำรับ ต้องการการทดลอง เพิ่มเติมอีกจึงจะระบุได้แน่ชัดว่า เข้ามาตรฐานหรือไม่

ยาเม็ดไอบูโพรเฟน ๕ ตำรับ ซึ่งมีค่าคงที่อัตราการละลายต่าง ๆ กัน ได้ถูกเลือกมาเพื่อศึกษา ถึงความสมมูลในร่างกาย ทำการศึกษาในอาสาสมัครชายไทย ที่มีสุขภาพสมบูรณ์ อายุ ๒๑ - ๒๗ ปี จำนวน ๑๒ คน โดยรับประทานยาเม็ดไอบูโพรเฟน ๒๐๐ มิลลิกรัม ๒ เม็ด ครั้งเดียว หลังจากอดอาหารตลอดคืน แบบแผนการรับประทานยา เป็นแบบการทดลองข้าม เก็บตัวอย่าง เลือด เพื่อนำมาวิเคราะห์หาปริมาณไอบูโพร- เฟนในพลาสมาในช่วง เวลาต่าง ๆ หลังจากรับประทานยา ซึ่งวัดโดยวิธี เฉพาะด้วยไฮเพอร์ฟอร์แมนซ์ ลิควิด โครมาโตกราฟี ผลปรากฏว่าปริมาณยาที่ถูกดูดซึม เข้าร่างกายของยา เม็ดไอบูโพรเฟนที่นำมาศึกษาไม่แตกต่าง กันอย่างมีนัยสำคัญทางสถิติที่ระดับความ เชื่อมั่น ๙๕% (ยก เว้น ตำรับที่มี เวลาในการแตกกระจายตัวนานกว่า ๕ ชั่วโมง ซึ่งตรวจไม่พบปริมาณไอบูโพร เฟนในพลาสมา เลยไม่ว่าที่เวลาใด ๆ) ส่วนอัตรา เร็วการดูดซึมของ ยา เข้าร่างกายมีความแตกต่างกันระหว่างตำรับอย่างมีนัยสำคัญทางสถิติที่ระดับความ เชื่อมั่น ๙๕%

เมื่อ เปรียบ เทียบ เวลาการแตกกระจายตัว กับค่าคงที่อัตราการละลาย เวลาการแตกกระจายตัว กับ พารามิเตอร์ที่ เกี่ยวกับอัตรา เร็วการดูดซึมยาในร่างกาย พบว่ามีความสัมพันธ์ เชิง เส้นกันอย่างมีนัยสำคัญ ทางสถิติที่ระดับความ เชื่อมั่น ๙๕% แต่ไม่พบความสัมพันธ์ เชิง เส้นอย่างมีนัยสำคัญระหว่างค่าคงที่อัตราการ ละลายกับพารามิเตอร์ที่ เกี่ยวกับอัตรา เร็วการดูดซึมยาในร่างกายที่ระดับความ เชื่อมั่น ๙๕%

ในการทดลองครั้งนี้ หาค่า เฉลี่ยของระดับยาสูงสุดในพลาสมาได้ค่าอยู่ระหว่าง ๑๖.๘๐ ถึง ๔๒.๒๐ ไมโครกรัมต่อมิลลิลิตร ส่วน เวลาที่ระดับยาสูงสุดในร่างกาย มีค่าตั้งแต่ ๑.๒๔ ถึง ๔.๗๕ ชั่วโมง ค่ากึ่งชีพของยาไอบูโพรเฟนในคนไทย คือ ๒.๓๔ ชั่วโมง (๒.๐๗ ถึง ๒.๖๕ ชั่วโมง) ซึ่งค่าดังกล่าวนี้ใกล้ เคียงกับค่าที่มีรายงานไว้ในวารสารต่างประเทศ

ภาควิชา ....เภสัชกรรม............

สาขาวิชา ....เภสัชกรรม............

ปีการศึกษา ....๒๕๓๐............

ลายมือชื่อนิสิต ....

ลายมือชื่ออาจารย์ที่ปรึกษา ....

WANNAPA THAMASUCHARIT : COMPARATIVE STUDIES OF BIOAVAILABILITY OF IBUPROFEN TABLETS COMMERCIALLY AVAILABLE IN THAILAND. THESIS ADVISOR: ASSO. PROF. DUANGCHIT PANOMVANA NA AYUDHYA,Ph.D. 196 PP.

This investigation was to assess the bioequivalence of the local manufactured brands of 200 mg ibuprofen sugar coated tablets relative to the original brand, Brufen^R. These tablets were evaluated both in vitro and in vivo.

The in vitro studies included both disintegration time and dissolution rate. The disintegration times of ibuprofen tablets were ranged from nine minutes to more than five hours. Of the 15 brands studied,tablets of 13 brands were able to disintegrate within one hour, tablets of one brand had wide varied disintegration times ranged from 1.28 to 2.42 hours and tablets of one brand did not disintegrate evenafter they were placed in the medium for over five hours. The dissolution rate constants of these fifteen brands of ibuprofen tablets were ranged from 0.0035 to 0.3310 per minute. The amount of drug dissolved at 30 minutes indicated that five brands met the U.S.P. XXI specification for drug dissolution while seven brands failed to meet the specification and three brands required extra experiments before any conclusion could be made.

Five brands of ibuprofen tablets with difference in their dissolution rate constant were selected to study for their bioequivalence in 12 Thai healthy male volunteers ranging in age from 21 to 27 years using a crossover design. After an overnight fasted two tablets, each containing ibuprofen 200 mg, were administered orally. Plasma ibuprofen levels were determined by a specifically high-performance liquid chromatographic method. Individual plasma profile was analyzed using both compartmental and noncompartmental methods. No significant difference ($p > 0.05$) in the extent of absorption could be observed among the five brands of ibuprofen studied (except for the brand which its in vitro data showed no disintegration evenafter five hours, no ibuprofen was detected in the plasma of any subjects at any time). However, they differed significantly in terms of their absorption rate ($P < 0.05$).

There were statistically significant correlation between disintegration time and dissolution rate constant, between disintegration time and in vivo absorption rate ($p < 0.05$) but no significant linear relationship was observed between dissolution rate constant and in vivo absorption rate ($p > 0.05$).

In this study, the mean peak plasma ibuprofen concentration and the time required to reach the peak were ranged from 16.80 to 42.20 µg/ml and 1.29 to 4.75 hours respectively. The elimination half-life of ibuprofen in Thai male was 2.34 hours (2.17 - 2.65 hours). These results are quite similar to those previously reported in the foreign literatures.

ภาควิชา ......เภสัชกรรม...................... ลายมือชื่อนิสิต ....

สาขาวิชา ......เภสัชกรรม......................

ปีการศึกษา ......๒๕๓๐...................... ลายมือชื่ออาจารย์ที่ปรึกษา ....

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LIST OF ABBREVIATIONS

$^{\circ}$C	=	degree Celcius
g	=	gram
hr	=	hour
kg	=	kilogram
L	=	litre
mg	=	milligram
ml	=	millilitre
min	=	minute
rpm	=	revolutions per minute
%	=	percent
μg	=	microgram
AUC_0^{∞}	=	area under the plasma concentration -time curve
$AUMC_0^{\infty}$	=	area under the (first) moment curve
C_t	=	plasma concentration at time t
Cp_{max}	=	peak plasma concentration
F	=	fraction of an extravascular dose of drug absorbed
K_a	=	absorption rate constant
K_{el}	=	overall elimination rate constant
MRT	=	mean residence time
$t\frac{1}{2}$	=	half - life
t_o	=	lag time
T_{max}	=	time to peak plasma concentration
SGOT	=	serum glutamic oxaloacetic transaminase
SGPT	=	serum glutamic pyruvic transaminase
SEM	=	standard error of the mean

CHAPTER I

INTRODUCTION

Background and Rationale

        The group of non - steroidal anti - inflammatory drugs
(NSAIDs)   provide the first choice in drug therapy in patients with
active rheumatoid arthritis. · Ibuprofen is a widely prescribed nonste-
roidal agent with anti-inflammatory , analgesic and antipyretic actions
used in the treatment of rheumatoid arthritis and related conditions ,
and, mild to moderate pain from a variaty of sources including dysmenor-
rhea.

        Ibuprofen was introduced into the United Kingdom (UK) in 1967 ,
and in the United States (US) in 1974 (1). It was the first propionic
acid derivatives to be used in rheumatic diseases and was·developed
directly as a result of the problems associated with the use of corti-
costeroids in the treatment of rheumatoid arthritis and also because of
the gastrointestinal irritation and general intolerability of the
established NSAIDs , at that time. Ibuprofen was readily accepted
because, unlike the previous drugs , its therapeutic efficacy was easily
seen to outweigh the severity of its side effects (2)

        Since 1983, the new UK Medicines Act legislation has allowed
pharmacists to sell ibuprofen over the counter (OTC) and provided that
it was labelled with a maximum dose of 400 mg and a maximum daily dose
of 1200 mg (3). The US Food and Drug Administration (FDA) has also

approved ibuprofen for sale without a prescription in 1984 (4). In addition , it is one of the drugs in the National Essential Drug List of Thailand (5) , which must be used by generic in all governmental hospitals.

To my knowledge , at least 15 different brands of 200 mg ibuprofen tablets were currently marketed in Thailand. Meanwhile , it is well - documented that the manufacturing process and final formulation may markedly affect the bioavailability of the drug (6). Eventhough there appears to be some information about the bioavailability of ibuprofen tablets available in foreign countries (7-13) but none is about the products manufactured in Thailand. The question about the bioequivalence of the local products as compare to their innovator's is thus arisen.

Of particular importance is their in vivo performance in terms of the rate and extent of ibuprofen gastro-intestinal absorption from the solid oral dosage forms. Consequently , the present investigations were conducted to assess the bioavailability of the local products relative to their original product in healthy volunteers.

The purposes of this research were to :

1. compare the disintegration time of commercial ibuprofen tablets available in Thailand.

2. compare the dissolution rate of these ibuprofen tablets.

3. investigate the bioequivalence of the local manufactured brands of ibuprofen tablets as compare to their original brand.

4. correlate the in vivo parameters with the in vitro parameters obtained from disintegration and/or dissolution test.

5. investigate the pharmacokinetics of ibuprofen after single oral administration of ibuprofen tablet in Thai healthy volunteers.

Significances of the study :

1. This study should provide an information about the correlation between disintegration and/or dissolution of ibuprofen tablets and their bioavailability. It is assumed that if there is a relationship between in vitro test and in vivo bioavailability , the results obtained from in vitro testing can be used as a predictive tool in dosage form development.

2. This study will provide significantly an information about the bioavailability of ibuprofen tablets manufactured in Thailand which would enable the possibility to evaluate and select the effective and economical products to provide the same therapeutic efficacy.

3. The pharmacokinetic parameter of ibuprofen obtained from Thai volunteers will be compared with previously reported studies which were conducted in foreign countries. The effect of races and tribes on the pharmacokinetics of this drug could thus be notified. If any significant differences were detected , then a readjustment to a more appropriate dosage regimen of ibuprofen for Thai people could be recommended.

Review of Ibuprofen

In recent year , there has been an intensive search for new nonsteroidal antirheumatic agents that would provide some advantages over those currently available. Of the hundred of chemical compounds screened for analgesic and anti-inflammatory activities , a group of aryl acetic and propionic acid derivatives appears to be promising. One member of

of this group is ibuprofen , the first phenyl alkanoic propionic acid

A. <u>Physicochemical Properties</u> (14-17)
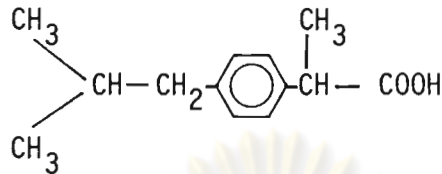
Figure 1   Structural Formula of Ibuprofen

Description   : White or almost white powder or

                          crytals with a characteristic odours.

Emperical formula   : $C_{13}H_{18}O_2$

Chemical name   : 2 - [4- isobutylphenyl] propionic acid

                          or p - isobutylhydratropic acid

                          or $\propto$ - methyl -4- [2 - methylpropyl]

                          benzeneacetic acid

Molecular weight   : 206.3

Melting point   : 75 - 77.5 $^{\circ}$C

Dissociation constant : pKa 4.4 , 5.2

Solubility   : Practically insoluble in water ;

                          soluble at 20°C in 1.5 parts of

                          ethanol (96 percent) , in 1 part of

                          chloroform, 2 parts of ether, 1.5 parts

                          of acetone ; also soluble in aqueous

                          solution of alkali hydroxides and

                          carbonates.

B. Mode of Action

Ibuprofen acts symptomatically by alleviating pain, reducing inflammation in joints and soft tissues , and reducing pyrexia. It can be classified as a nonsteroidal antiinflammatory agent also possessing analgesic and antipyretic action. As with other NSAIDs , its mechanism of action is uncertain.

Over the past decade , most researchers have espoused the idea that NSAIDs act by inhibiting cyclooxygenase , thereby removing prosta-glandins , which are thought to be responsible for pain and inflammation (1,2,18). Recent studies , however , have demonstrated that prostaglan-dins have important immunomodulating properties and that NSAIDs , actually provide partial correction of several immunoregulatory dysfunction in patients with rheumatoid arthritis. In addition , some NSAIDs inhibit migration along with other monocyte and polymorphonuclear leukocyte functions. Data suggest that these actions are not related to inhibition of cyclooxygenase (18).

C. Therapeutic Efficacy

1. Classical Rheumatism

Ibuprofen has been prescribed for the treatment of rheumatoid arthritis , including juvenile rheumatoid arthritis , ankylosing spondylitis , osteoarthrosis and other nonrheumatoid (serogerative) arthropathies (1,2,19,20). Its excellent tolerance has allowed the recommended daily dosage to be gradually increased so that patients with severe symptoms or those who do not respond to moderate doses of 800 - 1200 mg daily may be given up to 2400 mg (in UK) or 3200 mg (in USA) daily in divided doses (2).

mainly headaches , migraine , muscular rheumatism , period pains , toothache and cold / flu symptoms. It is particularly useful in the treatment of primary dysmenorrhea. The recommended dosage regimen for patients with dysmenorrhea is 400 to 800 mg as an initial dose , followed by 400 mg four times a day (22).

For treatment of other mild to moderate pain 200 mg of ibuprofen appears to be at least as effective as 650 mg of aspirin (4) and 400 mg of ibuprofen appears to be more effective than 650 mg of aspirin or 600 mg of acetaminophen in acute postsurgical dental pain (23). More recently ibuprofen has been used in combination with centrally - acting analgesics such as methadone and codiene for the relief of more severe or chronic cancer pain (2,24) such as that encounterd in bone cancer.

4. Antipyretic

Numerous controlled studies have demonstated ibuprofen's antipyretic properties in febrile children equipotent with aspirin and paracetamol (2).

D. Drug Interaction

Aspirin   : The concomitant use of aspirin may reduce plasma
               ibuprofen levels to less than half those observed
               with ibuprofen alone (25) ; however the clinical
               importance of the interaction has not been adequately
               evaluated.

Anticoagulants : Ibuprofen does not appear to affect significantly prothrombin times in patients taking anticoagulants such as warfarin (1,2,20). However , ibuprofen should be avoided in patients who are taking anticoagulants or who have pre-existing coagulation disorders , because of the possibility of gastrointestinal bleeding or an additive effect due to ibuprofen's reversible antiplatelet action (26).

Diuretics : Ibuprofen may cause fluid retention , resulting in a need to increase the dosage of the diuretic. Particular caution must be exercised in patients with impaired renal function who are taking potassium - conserving diuretics , because of the risk of hyperkalemia (26).

Alcohol : The consumption of alcoholic beverages while taking ibuprofen may increase the occurrence of gastrointestinal side effects (26).

Other drugs : Although ibuprofen binds to a significant extent to plasma proteins , interactions with other protein bound drugs occur uncommonly. Nevertheless , caution should be observed when other drugs also having a high affinity for protein binding sites are administered concurrently. Some observations have suggested a potential for ibuprofen to interact with digoxin , phenytoin , and lithium salts , although the mechanisms and significance of these occurrences are not currently known (26).

E. Toxicity

Acute toxicity studies in the mice have shown the LD_{50} of ibuprofen to be 320 mg/kg intraperitoneally and 800 mg/kg orally. It is interesting to note that irrespective of route , death in mice was a result of perforated gastric ulcers and in rats intestinal ulceration (19,27).

Chronic toxicity studies have been performed in dogs. No signs of clinical toxicity were noted when 16 mg/kg of ibuprofen were given daily for 30 days. However gastric ulceration and intestinal inflammation was found upon gross examination. These lesions were not seen at doses of 4 mg/kg given daily for the same period of time. Two dogs developed transient leukocytosis , the only hematological reaction noted (19,27).

From studies done with pregnant rabbits were shown that no teratogenic effects on the fetus were observed. The number of live fetuses per liter from rabbits receiving 60 mg/kg per day was , however, less than that of control animals indicating the possibility of reduced fertility (19).

Although toxicity studies can be performed experimentally , controlled studies of overdose in human subjects obviously are impossible.

Retrospective studies by Barry et al. (28) described that their highest reported overdose blood level (723.3 µg/ml) occurred in a 16- month-old child who ingested up to 35 tablets and still recovered. Other investigation showed that no death or permanent injury occurred in

children and there was a low chance of death or injury from ibuprofen overdose compared with that of aspirin or acetaminophen (29). Furthermore , there did not appear to be any significant chance of abnormality or loss of pregnancy after ibuprofen exposure in utero. However , avoidance of exposure during pregnancy , especially in last trimester , and breast - feeding is still advised. The use of ibuprofen during the last trimester may delay the onset of labor , cause complications during delivery and possibly could cause bleeding postpartum or in the newborn (4,19,26,30).

F. Tolerability

Clinical studies and case reports published since the introduction of ibuprofen indicated that its overall therapeutic benefit - to - risk ratio is equal to or better than those of other currently available NSAIDs (39). Much data concerning side effects have been gathered on the treatment of arthritis patients with ibuprofen.

Gastrointestinal side effects are experienced by 5 - 15% of patients taking ibuprofen ; epigastric pain , nausea , heartburn , abdominal discomfort and sensations of "fullness" in the gastrointestinal tract are the usual difficulties. However , the incidence of these side effects is less with ibuprofen than with aspirin or indomethacin (1,30,31, 32,33)

Other side effects of ibuprofen have been reported less frequently. They include thrombocytopenia , skin rashes , headache , dizziness and blurred vision , and in a few cases , toxic amblyopia , fluid retention , and edema. Patient who develop ocular disturbances should discontinue the use of ibuprofen (30,31,34). Concerning renal safety , Bonney et al.(35)

found a very low incidence of potentially serious adverse renal effects
in a large , carefully monitored group of arthritic patients in clinical
trials with ibuprofen.

G. Pharmacokinetic Studies

The pharmacokinetics of ibuprofen after oral administration
were reported by several investigators both in patients (36,37,38) and
in healthy volunteers (25,39-46).

Ibuprofen taken orally is rapidly absorbed from the upper
gastrointestinal tract , peak serum concentration occurred within 2
hours. The serum half - life of ibuprofen is approximately 2 hours
which does not increase significantly even with high doses and there is
little intersubject variability (2). Neither food nor antacid substan-
tially changes absorption. The bioavailability of ibuprofen is only
minimally altered by the presence of food(25) and antacid (39). It
does not seem to accumulate in tissues that are not in equilibrium with
the plasma. Therefore , an ibuprofen dosage schedule of 3 or 4 times
daily is unlikely to cause excessive accumulation of ibuprofen , even
in the elderly (40).

Wagner et al. (41) indicated that absorption profiles following
400 mg ibuprofen were S - shaped , while those following 800 , 1200 mg
had partial linear segments indicating zero order absorption. However,
Lockwood et al. (42) suggested that the efficiency of absorption of
ibuprofen is dose independent.

The drug is more than 99 percent bound to plasma protein and
saturation of binding sites can occur at clinical doses (42). The extent

of ibuprofen binding to plasma protein is unrelated to age or sex (40).
Aaron et al. (36) found that ibuprofen is more strongly bound to normal
plasma than to human serum albumin. Data in rats indicated that
saturation occurred in the binding of ibuprofen to tissue component (47).

Ibuprofen is biotranformed principally by oxidative mechanism.
Its metabolism occurs mainly in the liver , where the drug is hydroxy-
lated to 2 - [4-(2- methylpropyl) phenyl] propionic acid, carboxylated
to 2-[4-(2 - carboxypropyl) phenyl] propionic acid , and glucuronidated(32).

After metabolism , ibuprofen is excreted through the biliary
tract and kidneys. Ibuprofen was not excreted in saliva after ingestion
of a single 400 mg tablet (48) and concentration of ibuprofen in breast
milk was below detection level (1 μg/ml) at all times (25). Animal
studies indicated that 25 - 28 percent of intravenous ibuprofen is
excreted through the biliary tract , and no enterohepatic recirculation
is evident (43). Absolute urinary recovery of ibuprofen in normal human
subjects is about 80 percent(range 75.7 to 84.9) , with 99 percent
relative bioavailability when comparing the tablet to solution (42).
In human subjects , approximately 20 percent of the drug could possibly
be excreted through the biliary tract. and feces (49) , but neither
study has investigated an enterohepatic recirculation of ibuprofen.
Since 99 percent of ibuprofen excreted in the urine was investigated
to be metabolized , makes it likely that little unchanged drug could
get into the urine or feces (25). After administration of either dextro
or levo ibuprofen to man urinary metabolite (hydroxylated and carboxylated)
were dextrorotatory (43).

CHAPTER II

MATERIALS AND METHODS

Materials

A. Test Products

Fifteen commercial brands of ibuprofen , 200 mg sugar - coated tablets were obtained from usual commercial sources (mainly from different drug stores) without any attempt to procure or select lots. The letters (A,B,C,D,E,F,G,H,I,J,K,L,M,N, and O) were given to represent the brand names of products. Information of these products were accessible in Appendix A.

B. Reagents

1. Working standard ibuprofen powder , potency 99.7 % (Marsing Co., Ltd., Denmark) Lot No. 0284 - 2

2. Internal standard ; phenylbutazone powder , (Lab Dr ESTEVE) Lot No. 67.417

3. Acetonitrile HPLC grade (BDH , England) Lot No. 9610310 E

4. Methanol HPLC grade (BDH , England) Lot No. 4738090 G , (J.T. Baker , U.S.A.) Lot No. A11097

5. Chloroform AR (E.Merck , West Germany) Lot No. 644K3270245, 647K3391545 , 611K2083245

6. Phosphoric acid AR (E. Merck , West Germany) Lot No. 616K2327173

7. Sodium hydroxide AR (E.Merck , West Germany) Lot No.2717966

8. Monobasic potassium phosphate (E. Merck , West Germany) Lot No. 440A877573

9. Phenolphthalein (E. Merck , West Germany) Lot No. 522K4371433

10. Potassium hydrogen phthalate (BDH , England) Lot No.9227600D

11. Pepsin (E. Merck , West Germany) Lot No. 0148545

12. Pancreatin(E. Merck , West Germany) Lot No. 1195274

13. Heparin 5000 i.u/ml (David Bull Laboratories Proprietary Limited , Australia) Lot No. G043096

C. Apparatus

1. Analytical Balance (August Sauter KG D-7470 , West Germany)

2. Disintegration Tester (Model 64.700.136 , Hanson Research Corp., Northridge , CA., U.S.A.)

3. Dissolution Apparatus (72RL , Hanson Research Corp., Northridge , CA. , U.S.A.)

4. Spectrophotometer (Spectronic 2000, Bausch & Lomb , N.Y., U.S.A.)

5. High Performance Liquid Chromatography Apparatus ;
   Solvent Pump   Model 510 , 501

Variable Wavelength LC Spectrophotometer Model 481

Automated Gradient Controller

Automatic Sample Processor Model 712 WISP

Data Module Model 740

(Waters Assoc., Milford , MA., U.S.A.)

6. Automatic High Speed Refrigerated Centrifuge (Model 20 PR - 52 D , Hitachi Koki Co., Ltd., Tokyo , Japan)

7. Digital pH meter (PBS 730 , El - Hama Instruments , Isarel)

8. Vortex mixer (Vortex - Genie , Scientific Industries . Inc., Bohemia , N.Y., U.S.A.)

9. Waterbath (W-0 350 , Willi Memmert KG, West - Germany)

10. Digital Computer (IBM Compatible 16 Bit , Micro Source)

11. Micropipet (SOCOREX® , Switzerland)

12. Glassware

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Method

A. In Vitro Studies

Fifteen brands of ibuprofen, 200 mg sugar-coated tablets were evaluated using the official and non - official tests of U.S.P. and/or B.P. for sugar-coated tablets. The tests included :

1. Standard for Content of Active Ingredient in Tablets (50)

Twenty tablets were washed with distilled water to pale the colour and then, the amount of ibuprofen in tablets was determined according to the following procedure :

Twenty colourless tablets were weighed and powdered. A quantity of the powder equivalent to 500 mg of ibuprofen was then shaked with 20 ml of chloroform for 20 minutes. After filtration , the powder was washed with three quantities ,each of 15 ml of chloroform and filtered again. After the combined filtrates were evaporated to dryness using waterbath at 70°C , the residue was dissolved thus obtained in 100 ml of ethanol USP, previously neutralized to phenolphthalein solution. This alcoholic solution was titrated with 0.1 M sodium hydroxide VS using phenolphthalein solution as indicator.

Each ml of 0.1 M sodium hydroxide VS is equivalent to 20.63 mg of ibuprofen $C_{13}H_{18}O_2$.

2. Disintegration Test

The disintegration tests for fifteen brands of ibuprofen tablets were determined according to the USP XXI method for plain coated tablets (51).

Individual tablet was introduced into each of the six tubes of the basket. If the tablet has a soluble external coating, the basket was then immersed in water at room temperature for five minutes. A disk was thereafter added to each tube , and the apparatus was operated using simulated gastric fluid TS maintained at 37±2°C as the immersion fluid. After thirty minutes of operation in simulated gastric fluid TS, the basket was lifted from the fluid, and the tablets were observed. If the tablets had not disintegrated completely*, simulated intestinal fluid TS maintained at 37±2°C was then substituted as the immersion fluid. The test was continued for a total period of time, including previous exposure to simulated gastric fluid TS and water. The mean disintegration time of each brand was calculated.(Preparation of simulated gastric fluid TS and simulated intestinal fluid TS see Appendix B)

*Complete disintegration is defined as that state in which any residue of the unit , except fragments of insoluble coating , remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

3. Dissolution Test

According to USP XXI (52) , dissolution of ibuprofen tablets was established using the rotating basket method of the U.S.P. (51) and phosphate buffer pH 7.2 as dissolution media (Preparation of dissolution media see Appendix B)

Comparison of dissolution rates of ibuprofen tablets from fifteen commercial brands was carried out by the method as described :

Nine hundred millilitres of dissolution medium was placed in the vessel and equilibrated at 37 $\pm$ 0.5 °C. A tablet was placed in each basket and introduced into each of the six vessels, the apparatus was then immediately operated and maintained stirring speed at the rate of 150 $\pm$ 5 rpm. Five millilitres of samples were taken just prior to introducing the tablets and appropriate time intervals for each brand, filtered through stainless steel, and analyzed for drug content. The equivalent amount of temperature equilibrated phosphate buffer pH 7.2 was added immediately after each sampling to maintain a constant volume of dissolution medium during the course of the test. The amount of drug dissolved was determined using a UV spectrophotometer at 222 nm, and then calculated from a standard curve.

Standard Curve

About 75 mg, accurately weighed, of ibuprofen was dissolved in the dissolution medium and then adjusted to volume of 250 ml. Appropriate dilutions were made with the same solution to obtain standard solutions of known concentrations between 0 - 20 µg/ml. The UV absorbance at 222 nm of each concentration were determined using the dissolution medium as blank. Absorbances obtained versus known concentrations were fitted to a straight line using linear regression. (53)

The standard curves were constructed each time the new dissolution medium was prepared. The concentration of ibuprofen in unknown samples were determined using the standard curve obtained from the same medium. (The result of this standard curve was shown in Appendix D)

4. In Vitro Evaluation

The physical characteristics of all fifteen commercial brands of ibuprofen tablets were examined and evaluated , using general standard of U.S.P. and/or B.P. to determine which brand passed the requirement. Analysis of variance and student's t - test were performed using a computerized statistical program ABSTAT (54) to assess any differences in disintegration time and dissolution parameters between the original and local brands.

B In Vivo Studies

1. Test Products

Five commercial brands of ibuprofen tablets with differences in their in vitro characteristics : disintegration and/or dissolution were selected as described :

1. The original brand , assigned as the reference standard

2. The brand with maximum dissolution rate

3. The brand with moderate dissolution rate

4. The brand with minimum dissolution rate and longest disintegration time

5. The brand with minimum dissolution rate and moderate disintegration time

2. Subjects

Twelve healthy male volunteers with mean age 22.7 years
(range 21 - 27) , mean body weight 60.4 kilograms (range 48 - 73) ,
and mean height 171.5 centimetres (range 164 - 178) enrolled in this
study. A medical history , completely physical examination , routine
blood and urinalysis , and normal values for kidney and liver function
tests were performed for each individual subjects prior to the study.
(Appendix C) The method of the study was fully explained to all
subjects and all gave their written consents before entering the study.
They were permitted to take no medication for at least one week preceding
the study and refrained from all other medication during the entire course
of the study.

3. Drug Administration

Each subject received orally single dose of two tablets of
200 mg ibuprofen. The drug was administered with 100 - 200 ml of water.
The volunteers were required to fast for at least ten hours before and
two hours after drug administration. Apart from the dictates of early
frequent sampling , no undue restriction on physical activity were
imposed and the subjects were allowed to carry out normal routine duties.

4. Experimental Design

The study was performed as an open label in a randomized latin -
square crossover design in which each formulation preceded each other
formulation an equal number of times (55) , over the first four
formulations (Formulation A,C,K and O). Each subject received the
drug in a randomized order.

Formulation N was added in the last week because it seemed that the results of the first four treatment phases could not indicate whether the disintegration time or the dissolution rate was a better correlated parameter of the in vivo parameters. Treatment phases were seperated by a washout peroid of two weeks. Treatment schedule was presented in Table 1.

Table 1   Treatment Schedule

Showing a randomized latin-Square crossover design , except for treatment N[**]

Subject No	Week				
	1	3	5	7	9
1	A	C	K	O	N
2	C	O	A	K	N
3	K	A	O	C	N
4	O	K	C	A	N
5	A	C	K	O	N
6	C	O	A	K	N
7	K	A	O	C	N
8	O	K	C	A	N
9	A	C	K	O	N
10	C	O	A	K	N
11	K	A	O	C	N
12	O	K	C	A	N

[*] A,C,K,N and O represents the brand name of ibuprofen tablet

[**] See text for explanation

5. Sample Collection

Blood samples (5 ml) were drawn from a forearm vein by
individual venipuncture just prior to dosing and at 0.5, 1, 1.5, 2 ,
3,4,5,7,10 hours following drug administration. These blood samples
were placed into the heparinized tubes (one drop of 5000 units/ml of
heparin solution into the test tube). After centrifugation at 3000 rpm
for ten minutes , the plasma samples were collected and kept at -10°C
until subsequent analysis.

6. Determination of Ibuprofen in Plasma

The plasma samples were quantitatively analyzed for the
concentration of unchanged ibuprofen utilizing high performance liquid
chromatographic (HPLC) method which modified from those described by
LaLande et al. (56). The procedure was developed as follow :

An aliquot (1 ml) of heparinized plasma was acidified with two
drops of phosphoric acid (85 %). After brief mixing, 2.5 ml of
acetonitrile (containing phenylbutazone as an internal standard at a
concentration of 8 μg/ml) was added to precipitate the protein. The
tubes were then vortexed for 15 seconds before centrifugation at
4000 rpm for 15 minutes at 4°C. The supernatant was transfered to
the vials of the autosampler from which 20 μl were injected into the
HPLC using the automatic sample processor.

HPLC Conditions for Ibuprofen Analysis in Plasma

Apparatus : HPLC consisted of a Model 510,501 solvent pump, a
Model 481 variable wavelength LC spectrophotometer,
automated gradient controller, a Model 712 WISP
automatic sample processor , and a Model 740 data
module. (Waters Assoc., U.S.A.)

Column : μ - Bondapak C_{18} , 10 μm irregular , stainless steel
column , 30 cm x 3.9 mm i.d. (Waters Assoc., U.S.A.)

Mobile phase : 0.05 % phosphoric acid : Methanol = 28 : 72

Detector : 220 nm

Flow rate : 1.5 ml/min

Attenuation : 16

Pressure : 1700 - 1800 Psi

Temperature : ambient

Injected volume: 20 μl

Chart Speed : 5 mm/min

Retentime time : Internal standard (phenylbutazone) 4.933 minutes
Ibuprofen   7.025 minutes

The ibuprofen concentration in plasma samples were quantified employing the standard curve

7. Standard Curve

About 50 mg , accurately weighed , of ibuprofen was dissolved in methanol and then adjusted to the volume of 10 ml. Aliquots of this stock solution equivalent to 5,10,15,20,25,30,35,40,50,55,60 μg were pipetted respectively into a series of glass tubes. After the methanol was evaporated to dryness using waterbath at $70\,^{\circ}$C, 1 ml of pooled drug - free plasma and 2 drops of phosphoric acid (85%) were added to each tube. The capped tubes were placed on a vortex - mixer to allow dissolution of the drug in the acidified plasma. These samples were analysed following the same procedure as described previously. The ratios of ibuprofen peak areas to internal standard peak areas versus the known ibuprofen concentration were fitted to a straight line using linear regression (52).

The standard curves were constructed for each treatment phase which plasma samples were analyzed. The concentration of ibuprofen in the unknown samples were calculated from the standard curve which obtained from the same phase. (The result of this standard curve was shown in Appendix D)

8. Pharmacokinetic Analysis

Individual ibuprofen profile from each treatment was analyzed using both noncompartmental and compartmental method.

The noncompartment (model independent) estimating program was used to calculate the following parameters :

(a) The area under the concentration - time curve , AUC_o^∞ (by linear trazepoidal rule with extrapolation to infinite time , see Appendix G)

(b) The elimination rate constant , K_{el}

(c) The mean residence time after oral administration ,MRT_{oral} (Calculation see Appendix G)

For compartmental method , the CSTRIP program (57) was used to estimate the initial polyexponential parameters. Then PCNONLIN nonlinear estimating program by iteration (58) was applied utilizing the initial parameter obtained from the CSTRIP program. Whether the plasma concentration - time result was fitted to one or two compartment depends upon the percentage improvement in R squared (r^2) calculated from each equation which the model is based upon. (see Appendix H)

In compartmental analysis it is reasonable to use the fewest number of compartments which are necessary to adequately describe the experimental data.

9. Bioavailability and Statistical Analysis

The comparative bioavailability of the five brands of ibuprofen tablets was evaluated using the following parameters :

a) The area under the plasma concentration time curve , AUC_o^∞

b) The peak plasma concentration , Cp_{max}

c) The time to the peak plasma concentration , T_{max}

A one-way analysis of variance (ANOVA) was performed to test the hypothesis of no difference among the five treatment group. If the ANOVA result showed significant difference then Student's test were performed to investigate pairwise difference between treatments.

C. In Vitro - In Vivo Correlation Study

The relationship between in vitro and in vivo parameters was analyzed and the correlation coefficient was obtained. Student's t - statistics were then performed to test whether this correlation was significant. The in vitro parameters of interested included both disintegration time and dissolution rate while the in vivo parameters included were those pharmacokinetic parameters which related to the absorption rate of the drug, i.e., the absorption rate constant (K_a) , the time to peak plasma concentration (T_{max}) , and the mean residence time after oral administration (MRT_{oral}).

CHAPTER   III

RESULTS

In Vitro Studies

        The fifteen commercial brands of 200 mg ibuprofen tablets were
first assayed for the content of active ingredient. The ibuprofen
content of each product was shown in Table 2 . Results indicated that
each brand was within the 90 - 110% limit which met existing standard
in the United State Pharmacopeia monograph. These data supported the
assumption that all various brands were chemically equivalent.

        Neither USPXXI nor BP 1980 contains a disintegration time
specification for ibuprofen tablets. However, disintegration time
requirement is currently official for general plain coated tablet. As
reported in Table 3 , most of the local manufactured brands of ibuprofen
tablets can disintegrate within one hour , except for tablets from
brand K which the disintegration time was ranged from 77 to 145 minutes,
and brand O remained none disintegrate evenafter they were placed in
the medium for over five hours. Rank order of fifteen brands in terms
of mean disintegration time were brand L < B < D < C < F < A < G < E
< N < M < I < J < H < K < O.   Statistical comparison of disintegration
time among fifteen brands of ibuprofen tablets were reported in Table 4-6.
Table 4 showed analysis of variance , Table 5 showed the t - value of
the comparison between treatments , and Table 6 showed statistically
significant difference between treatments.

Table 2   Percent Labelled Amount of Fifteen Commercial Brands of
          200 mg Ibuprofen Tablets

Experiment No Brand	Percentage Content				
	1	2	3	Mean	SEM
A	99.23	99.01	99.62	99.29	0.18
B	99.29	99.93	98.76	99.33	0.34
C	100.21	101.26	100.82	100.76	0.30
D	97.00	97.68	96.02	96.90	0.48
E	100.14	100.00	101.37	100.51	0.43
F	100.27	100.40	100.98	100.55	0.22
G	98.11	98.89	98.58	98.52	0.23
H	97.14	97.85	97.83	97.61	0.23
I	99.48	99.35	99.63	99.49	0.08
J	98.83	98.33	97.21	98.12	0.48
K	94.42	94.82	94.20	94.48	0.18
L	104.26	104.71	103.75	104.24	0.28
M	99.84	99.82	100.32	99.99	0.16
N	99.13	99.51	99.37	99.34	0.11
O	99.53	99.81	100.31	99.88	0.23

Table 3 Disintegration Time of Fifteen Commercial Brands of Ibuprofen Tablets

Tablet No. Brand	Disintegration Time (minutes)								
	1	2	3	4	5	6	MEAN	SEM	% CV
A	13.00	13.50	14.50	15.00	15.17	15.33	14.42	0.39	6.65
B	9.00	10.00	10.33	10.58	10.67	11.00	10.26	0.29	6.86
C	11.50	12.00	12.17	12.50	12.67	17.00	12.97	0.82	15.53
D	10.00	10.00	10.83	11.00	12.00	12.83	11.11	0.46	10.11
E	14.00	15.00	15.67	18.50	18.75	19.00	16.82	0.89	13.00
F	8.00	12.00	12.50	13.00	13.50	24.00	13.83	2.19	38.71
G	10.00	14.67	15.83	16.00	16.30	17.00	14.97	1.04	17.03
H	42.00	43.00	44.00	47.00	52.00	61.00	48.17	2.96	15.05
I	33.00	34.00	34.50	35.00	38.00	40.00	35.75	1.09	7.49
J	36.00	37.00	40.00	42.00	47.00	48.00	41.67	2.04	12.02
K	77.00	80.00	85.00	95.00	100.00	145.00	97.00	10.25	25.88
L	9.00	9.50	9.67	9.82	10.00	10.00	9.67	0.16	3.93
M	27.00	30.00	32.00	33.00	34.00	35.00	31.83	1.19	9.19
N	23.00	25.00	27.00	35.00	37.00	40.00	31.17	2.88	22.63
O	>5 hr	>5 hr	>5 hr	>5 hr	>5 hr	>5 hr	>5 hr		

Table 4   Analysis of Variance for Disintegration Time among Fifteen

Brands of Ibuprofen Tablets.

Source of variance	d.f.	S.S.	M.S.	F
Among treatments	14	661567.0	47254.8	864.452
Within replication	75	4099.8	54.7	
Total	89	665666.8		

$$F_{0.05\ (14,75)} = 1.8708$$

d.f.	=	degree of freedom
S.S.	=	sum of square
M.S.	=	mean square
F	=	variation ratio

Table 5 Pairwise Statistical Comparison of Disintegration Time among Fifteen Brands of Ibuprofen Tablets by Student's t - test.

Brand	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
A															
B	7.8063														
C	1.4473	2.8375													
D	5.0038	-1.4286	1.8040												
E	-2.2508	-6.3829	-2.8935	-5.1932											
F	0.2398	1.4780	-0.3365	-1.1127	1.1546										
G	-0.4516	-3.9765	-1.3725	-3.0949	1.2330	-0.4274									
H	-10.3190	-11.6349	-10.4580	-11.2935	-9.2562	-8.5179	-9.6596								
I	-16.7668	-20.5767	-15.1952	-18.9668	-12.2432	-8.1859	-12.5682	3.5921							
J	-11.9531	-13.8885	-11.8887	-13.3155	-10.1700	-8.4904	-10.6267	1.6496	-2.3300						
K	-7.3518	-7.7240	-7.6439	-7.6439	-7.1161	-7.2461	-7.2707	-4.1795	-5.4258	-4.8343					
L	10.2977	1.6691	3.6049	2.7226	7.2084	1.7358	4.5984	11.8575	21.5581	14.2508	7.7794				
M	-12.6446	16.0216	-11.8687	-14.7795	-9.1899	-6.5162	-9.7172	4.6711	2.2074	3.7814	5.7664	-16.7938			
N	-5.2608	-6.5928	-5.5453	-6.2779	-4.3438	-4.3764	-4.8293	3.7577	1.3582	2.7141	5.6461	-6.8050	0.1952		
O	-805.8980	-1110.86	-385.109	-694.241	-351.034	-144.571	-302.670	-96.1728	-270.679	-142.174	-23.4299	-2061.34	-250.711	-104.230	

$t_{(0.05,10)}$ = 2.2281

$t_{(0.01,10)}$ = 3.1693

Table 6   Statistically Significant Pairwise Differences of Disintegration Time among Fifteen Brands
of Ibuprofen Tablets.

Brand	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
A															
B	**														
C		*													
D	**														
E	*	**	*	**											
F															
G		**		*											
H	**	**	**	**	**	**	**								
I	**	**	**	**	**	**	**	**							
J	**	**	**	**	**	**	**		*						
K	**	**	**	**	**	**	**	**	**	**					
L	**		*	*	**		**	**	**	**	**				
M	**	**	**	**	**	**	**	**		**	**	**			
N	**	**	**	**	**	**	**	**	*	**	**				
O	**	**	**	**	**	**	**	**	**	**	**	**	**	**	

*   Significant level at   p < 0.05

** Significant level at   p < 0.01

According to the United State Pharmacopoeia XXI, the amount of ibuprofen dissolved from the tablets at 30 minutes should not less than 55 % of the labelled amount. The results of this study (Table 7) demonstrated that only 5 brands (brand A,B,C,D,and E) met the United State Pharmacopoeia specifications for drug dissolution while 7 brands (brand G,I,J,K,M,N, and O) failed to meet the specifications and 3 brands(brand F,H,and L) required extra experiments before any conclusion could be made.

Figure 2 illustrated the dissolution profiles of all fifteen brands of ibuprofen tablets in phosphate buffer pH 7.2. Numerous differences were observed for the rate and extent of dissolution of different drug products. Dissolution data of ibuprofen tablets from brand A to brand O were presented in Table 8 - 22 respectively.

The dissolution rate constants (K) were calculated from the slope of the first order plot between the amount of ibuprofen to be dissolved ($B_\infty - B_t$) versus time in semi - logarithmic scale (Appendix E)and the corresponding values were reported in Table 23. Rank order of fifteen brands in terms of mean dissolution rate constant were brand C > A > B > D > E > F > G > L > J > K > I > H > M > N > O. Comparison of the dissolution rate constants by analysis of variance and Student's t - test were presented in Table 24,25 respectively.Table 26 demonstrated statistically significant pairwise difference between treatments.

From dissolution profile in Figure 2 and statistical comparison of dissolution rate constant , these fifteen commercial brands of ibuprofen tablets can be classified into three groups as follow :-

1) The brand with high dissolution rate included brand A,B,C,and D.

2) The brand with moderate dissolution rate included brand E,F, G,H,I,J,K, and L.

3) The brand with low dissolution rate included brand M,N,and O.

Due to the numerous local manufactured brands of ibuprofen tablets, a representative from each group was chosen to assess bioavailability of these local products relative to the original product.   The brands chosen were :

1. Brand A (original brand)

2. Brand C (high dissolution rate)

3. Brand K (moderate dissolution rate)

4. Brand O (low dissolution rate , and no disintegration)

5. Brand N (low dissolution rate , but having ability to
             disintegrate within 30 minutes)

Brand C has maximum dissolution rate , brand O has minimum dissolution rate and the dissolution rate constant of brand C was ten times higher than brand K while the dissolution rate of brand K was ten times higher than brand O. Brand N was chosen to verify whether the disintegration time or the dissolution rate could correlate better with the in vivo parameter since its dissolution rate was lower than brand K while its disintegration time was shorter.

Table 7   The Amount of Ibuprofen Dissolved at 30 Minutes of Fifteen Commercial Brands of
Ibuprofen Tablets

Tablet No. Brand	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
A	96.05	96.54	99.15	91.06	96.11	94.57	95.58	1.09
B	96.42	96.89	96.13	91.67	95.55	93.75	95.07	0.81
C	95.34	99.03	101.98	97.70	101.40	97.86	98.89	1.02
D	99.35	96.62	95.40	95.36	99.90	99.81	97.74	0.89
E	82.44	78.13	86.93	88.08	82.93	87.95	84.41	1.61
F	92.52	46.27	12.38	40.43	7.07	87.84	47.75	14.80
G	0.31	0.40	0.36	0.35	0.35	0.52	0.38	0.03
H	85.40	90.57	0.63	90.67	76.08	85.42	71.46	14.33
I	0.21	0.49	1.42	0.53	1.64	0.63	0.82	0.23
J	0.11	0.19	0.22	0.34	0.33	0.17	0.23	0.04
K	1.81	2.58	2.19	2.26	1.59	0.61	1.84	0.28
L	90.58	84.39	1.09	89.35	88.15	92.82	74.40	14.71
M	0.60	0.56	9.43	0.76	0.57	0.67	2.10	1.47
N	0.53	0.51	0.49	0.46	0.49	0.52	0.50	0.01
O	0.55	0.46	0.48	0.37	0.49	0.41	0.46	0.03
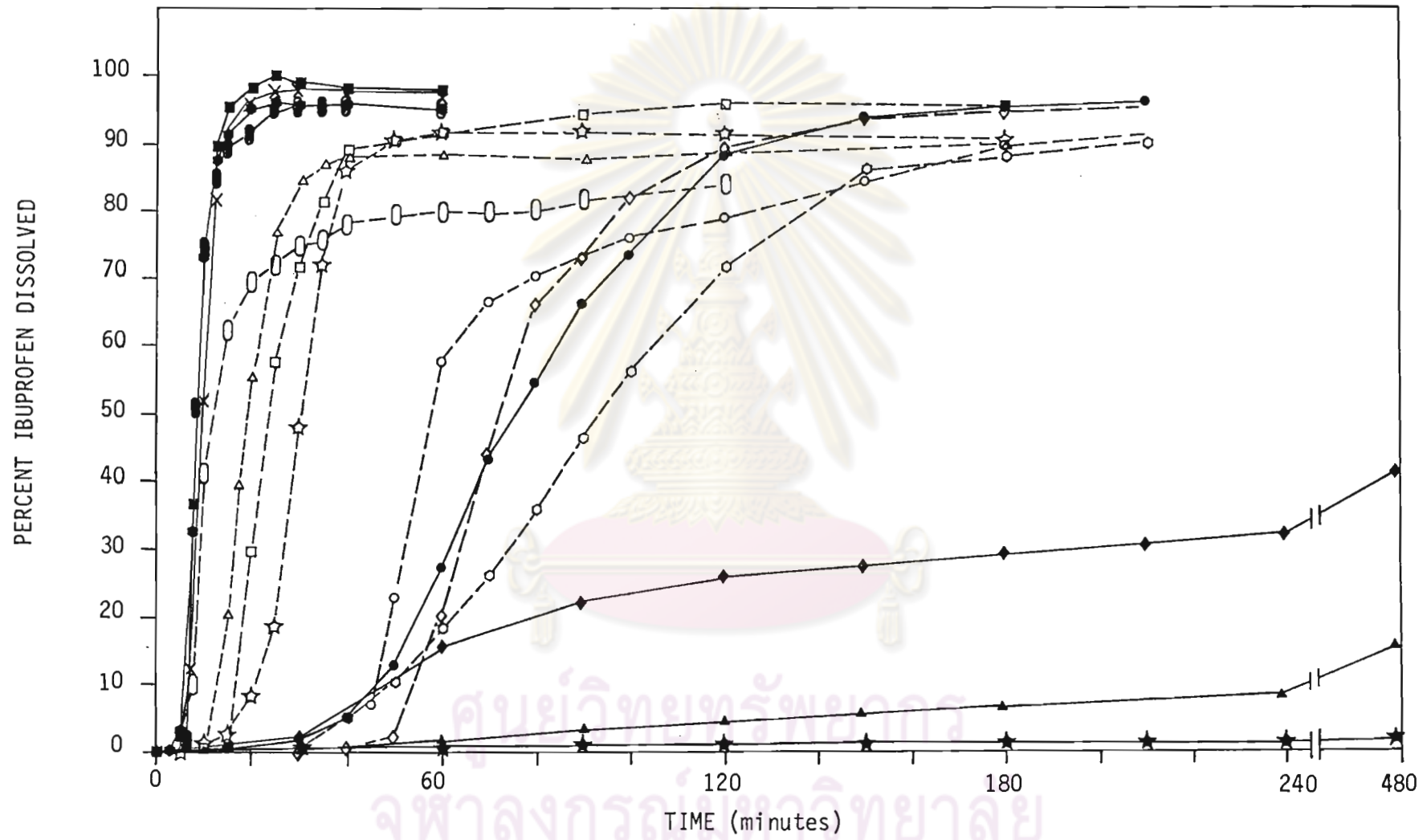
Figure 2 Dissolution profile of fifteen commercial brands of ibuprofen tablets in phosphate buffer pH 7.2

Key : Brand A (●) , Brand B (◖) , Brand C (■) , Brand D (✕) , Brand E (△) , Brand F (☆),
Brand G (○) , Brand H (□) , Brand I (○) , Brand J (◇) , Brand K (●) , Brand L (◖),
Brand M (◆) , Brand N (▲) , Brand O (★)

Table 8   Dissolution Data of Brand A Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2.5	0.00	0.01	0.02	0.00	0.01	0.01	0.01	0.00
5.0	1.67	2.07	0.28	13.36	0.42	0.45	3.04	2.09
7.5	26.81	43.46	19.79	65.43	27.17	12.12	32.46	7.84
10.0	72.84	77.59	72.65	82.75	70.60	63.50	73.32	2.66
12.5	87.77	87.55	89.50	89.77	85.16	85.43	87.53	0.80
15.0	91.25	91.08	92.60	89.97	91.52	89.98	91.07	0.41
20.0	94.74	93.70	100.25	93.03	93.70	93.91	94.89	1.10
25.0	96.05	96.32	100.90	91.93	96.11	94.57	95.98	1.19
30.0	96.05	96.54	99.15	91.06	96.11	94.57	95.58	1.09
40.0	96.71	95.89	98.94	90.40	96.32	96.75	95.84	1.17
60.0	95.84	95.23	96.53	89.97	95.23	96.31	94.85	1.00
90.0	95.40	95.23	96.53	89.31	92.83	96.10	94.23	1.12
120.0	94.96	95.45	96.53	89.53	91.30	94.78	93.76	1.11

Table 9   Dissolution Data of Brand B Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.14	5.21	0.74	0.17	0.10	4.17	1.76	0.94
7.5	25.51	72.38	69.34	0.41	63.49	75.31	51.08	12.58
10.0	74.07	84.78	84.01	33.81	86.39	86.75	74.97	8.45
12.5	82.42	97.16	88.86	62.59	92.59	88.90	85.42	4.98
15.0	89.69	96.89	92.09	72.82	94.20	91.59	89.55	3.49
20.0	91.30	97.16	95.05	77.13	94.47	91.59	91.12	2.94
25.0	97.76	97.16	96.13	87.90	98.51	92.13	94.93	1.68
30.0	96.42	96.89	96.13	91.67	95.55	93.75	95.07	0.81
35.0	96.42	97.16	95.59	93.01	96.36	92.67	95.20	0.78
40.0	95.81	96.09	95.59	95.16	96.89	92.13	95.29	0.67
60.0	94.26	95.28	96.94	96.63	95.28	92.67	94.84	0.57
90.0	94.26	96.09	95.59	94.36	95.01	92.40	94.62	0.53
120.0	89.69	95.55	96.67	94.36	95.28	92.67	94.03	1.03

Table 10   Dissolution Data of Brand C Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
Tablet No.	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.25	0.76	11.29	0.12	0.85	0.69	2.33	1.80
7.5	13.22	38.25	58.66	22.50	52.71	33.94	36.55	7.07
10.0	47.66	77.83	91.37	66.31	89.13	72.28	74.10	6.59
12.5	74.17	88.79	97.92	87.10	97.80	90.53	89.39	3.57
15.0	88.15	95.15	101.24	93.19	99.60	94.68	95.34	1.91
20.0	93.93	97.23	100.80	96.24	103.49	97.17	98.14	1.40
25.0	97.66	99.86	101.34	99.45	102.37	99.94	100.10	0.66
30.0	95.34	99.03	101.98	97.70	101.40	97.86	98.88	1.02
40.0	94.37	98.20	100.27	96.52	101.68	97.73	98.13	1.07
60.0	94.65	97.78	99.19	96.79	100.16	97.58	97.69	0.78
90.0	94.51	97.92	98.54	96.38	99.87	97.45	97.44	0.75
120.0	94.24	97.09	98.37	97.04	100.69	97.73	97.53	0.86
180.0	93.13	97.23	98.37	97.37	100.53	96.76	97.23	0.99

Table 11   Dissolution Data of Brand D Ibuprofen Tablets in phosphate Buffer pH 7.2

Tablet No. Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.37	0.38	0.99	0.22	0.27	0.30	0.42	0.11
7.5	0.93	46.07	24.54	2.29	0.57	1.59	12.66	7.68
10.0	22.32	79.13	70.29	65.44	13.22	63.44	52.31	11.20
12.5	77.05	87.99	82.59	83.84	76.00	84.41	81.98	1.87
15.0	91.15	92.45	87.92	90.61	90.54	92.90	90.92	0.72
20.0	97.05	94.89	95.54	94.49	96.87	97.94	96.13	0.55
25.0	101.08	96.05	95.83	94.92	99.32	98.22	97.57	0.96
30.0	99.35	96.62	95.40	95.36	99.89	99.81	97.74	0.89
40.0	99.21	96.05	94.68	96.22	100.32	98.51	97.50	0.88
60.0	98.78	96.19	94.68	96.08	99.17	98.37	97.21	0.73
90.0	98.63	95.76	93.38	95.64	99.03	97.07	96.59	0.86
120.0	98.63	94.47	93.38	95.50	98.60	96.64	96.20	0.88
180.0	97.91	94.18	92.52	95.64	97.01	97.07	95.72	0.83

Table 12   Dissolution Data of Brand E Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	\ Tablet No.							
	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	.SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.07	0.00	0.04	0.12	0.10	0.00	0.05	0.02
10.0	0.26	0.22	0.21	1.27	0.23	0.38	0.43	0.17
15.0	2.13	1.74	12.94	52.24	19.26	33.10	20.24	7.98
17.5	2.79	14.88	34.82	74.19	53.28	57.40	39.56	11.08
20.0	24.77	46.63	50.47	75.31	63.51	71.71	55.40	7.67
25.0	67.54	67.21	78.94	86.75	77.61	84.22	77.04	3.34
30.0	82.44	78.12	86.92	88.08	82.93	87.94	84.41	1.61
35.0	87.49	79.72	87.98	91.00	85.59	89.54	86.89	1.61
40.0	89.62	82.11	90.91	90.21	84.26	90.60	87.95	1.54
60.0	90.15	85.04	89.05	89.94	86.65	89.54	88.40	0.84
90.0	89.09	86.10	88.25	88.08	86.65	87.68	87.64	0.44
120.0	92.28	86.63	89.58	88.34	86.65	88.21	88.62	0.86
180.0	90.42	86.37	87.98	89.41	92.77	89.54	89.42	0.88
240.0	89.36	86.90	83.73	86.21	84.26	85.28	85.96	0.83

Table 13   Dissolution Data of Brand F Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.20	0.12	0.15	0.10	0.11	0.09	0.13	0.01
10.0	5.59	0.23	0.24	0.20	0.23	0.16	1.11	0.89
15.0	16.08	0.30	0.31	0.22	0.31	0.24	2.91	2.63
20.0	48.46	0.40	0.30	0.34	0.31	0.37	8.37	8.01
25.0	93.04	2.15	0.37	3.68	0.47	12.24	18.66	14.98
30.0	92.51	46.27	12.37	40.43	7.06	87.84	47.75	14.80
35.0	91.98	80.49	50.69	63.48	53.16	91.98	71.96	7.64
40.0	91.71	86.34	89.78	78.38	77.10	91.71	85.84	2.68
50.0	92.25	89.27	96.16	85.02	86.41	93.58	90.45	1.75
60.0	91.98	92.73	95.90	85.82	90.13	92.78	91.56	1.37
90.0	91.18	95.65	94.04	87.42	89.06	91.98	91.56	1.24
120.0	89.32	93.79	93.77	89.01	88.53	92.78	91.20	1.02
180.0	88.52	94.59	90.58	85.82	88.27	92.51	90.05	1.29

Table 14   Dissolution Data of Brand G Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprefen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30.0	0.30	0.40	0.36	0.34	0.34	0.51	0.38	0.03
45.0	1.64	11.44	4.43	11.12	1.53	10.34	6.75	1.93
50.0	4.80	46.62	16.68	31.79	9.85	25.71	22.57	6.28
60.0	36.50	74.40	46.53	60.94	58.07	68.60	57.51	5.72
70.0	59.71	81.73	52.22	65.75	62.27	75.94	66.27	4.43
80.0	65.41	85.11	55.60	69.13	65.41	80.25	70.15	4.41
90.0	69.09	88.01	58.39	70.86	67.42	84.14	72.99	4.52
100.0	72.43	90.01	61.28	74.64	71.87	85.48	75.95	4.22
120.0	77.29	90.52	63.78	77.83	72.22	90.99	78.77	4.31
150.0	85.00	91.07	71.76	85.26	76.07	94.84	84.00	3.57
180.0	89.77	94.46	81.73	92.42	82.09	95.70	89.36	2.49
240.0	94.74	95.57	82.62	94.86	90.31	98.37	92.69	2.27
300.0	97.77	96.68	86.40	96.64	94.31	98.37	95.03	1.81

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Table 15   Dissolution Data of Brand H Ibuprofen Tablets in Phosphate Buffer pH 7.2

Tablet No. / Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10.0	0.30	0.24	0.37	0.40	0.43	0.34	0.35	0.02
15.0	0.44	0.36	0.37	0.34	0.45	0.35	0.39	0.01
20.0	0.53	79.91	0.45	55.89	0.49	38.68	29.33	13.96
25.0	76.80	90.51	0.55	86.23	8.62	81.45	57.36	16.82
30.0	85.40	90.56	0.62	90.67	76.07	85.42	71.46	14.33
35.0	86.50	92.33	43.55	93.97	82.46	87.84	81.11	7.69
40.0	87.60	93.87	73.04	98.16	88.63	91.58	88.81	3.51
50.0	87.79	94.05	78.01	99.26	90.17	90.70	90.00	2.89
60.0	88.04	94.31	80.09	100.58	91.49	92.24	91.12	2.78
90.0	91.78	97.61	86.48	100.36	93.91	94.00	94.02	1.95
120.0	91.56	97.39	89.34	100.80	97.21	95.99	95.38	1.71
180.0	91.78	95.63	90.88	97.72	96.55	96.65	94.87	1.15
240.0	92.44	95.63	91.76	96.39	96.11	95.99	94.72	0.83

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Table 16 Dissolution Data of Brand I Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	\ Tablet No.							
	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30.0	0.20	0.48	1.41	0.52	1.64	0.63	0.81	0.23
40.0	0.22	4.34	12.33	1.62	8.18	4.20	5.15	1.81
50.0	0.38	10.69	25.51	4.49	15.34	6.08	10.42	3.68
60.0	1.19	15.84	35.56	10.39	32.70	13.31	18.17	5.45
70.0	6.23	22.60	51.84	16.29	41.50	17.96	26.07	6.99
80.0	13.31	35.99	65.14	24.44	54.12	21.12	35.69	8.26
90.0	22.46	51.23	78.22	33.33	67.43	26.33	46.50	9.35
100.0	30.24	74.20	81.35	45.50	69.92	37.02	56.37	8.75
120.0	54.80	86.26	89.14	56.87	83.89	58.40	71.56	6.70
150.0	97.31	90.29	89.14	67.56	89.27	81.83	85.90	4.18
180.0	97.73	90.29	87.80	76.39	90.61	83.85	87.78	2.93
210.0	97.73	92.44	88.34	85.26	91.15	84.39	89.89	2.03
240.0	96.39	92.17	90.22	90.63	93.03	86.00	91.41	1.40
300.0	96.12	92.17	89.95	92.78	91.69	86.81	91.59	1.26

Table 17　Dissolution Data of Brand J Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
Tablet No.	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30.0	0.10	0.19	0.22	0.33	0.32	0.16	0.22	0.03
40.0	0.33	0.43	0.46	0.55	0.56	0.34	0.45	0.04
50.0	0.47	1.49	1.69	0.87	5.58	2.01	2.02	0.74
60.0	0.63	33.25	16.48	28.04	22.55	20.35	20.22	4.59
70.0	8.10	51.28	45.73	50.46	61.81	48.12	44.25	7.57
80.0	21.85	59.77	85.93	63.00	87.45	77.62	65.94	9.98
90.0	35.55	64.65	92.41	70.31	88.56	86.04	72.92	8.69
100.0	68.13	70.92	94.73	77.11	89.99	89.97	81.81	4.57
120.0	90.89	79.76	96.57	84.28	90.92	92.22	89.11	2.46
150.0	100.17	85.06	97.90	90.70	92.46	93.99	93.38	2.19
180.0	102.16	87.50	98.12	90.70	94.01	93.99	94.41	2.12
240.0	102.16	90.59	98.12	92.69	96.44	94.21	95.70	1.68
300.0	102.38	92.80	97.45	92.46	95.56	93.99	95.78	1.52

Table 18   Dissolution Data of Brand K Ibuprofen Tablets in phosphate buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
Tablet No.	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15.0	0.42	0.82	0.47	0.49	0.14	0.10	0.41	0.10
30.0	1.80	2.58	2.18	2.26	1.58	0.61	1.84	0.28
40.0	4.69	5.29	4.96	6.86	7.91	1.14	5.14	0.94
50.0	13.16	8.86	13.35	17.77	20.91	3.77	12.97	2.50
60.0	27.68	15.93	31.90	35.14	42.81	10.13	27.27	4.99
70.0	41.07	22.30	51.53	66.33	60.64	19.55	43.57	7.97
80.0	55.91	32.35	60.77	75.68	74.70	28.67	54.68	8.27
90.0	69.08	44.80	78.44	83.80	82.55	39.05	66.29	8.02
100.0	74.14	64.46	83.45	85.54	86.57	47.32	73.58	6.27
120.0	96.49	87.95	90.25	87.81	90.81	76.76	88.34	2.65
150.0	98.48	97.57	92.51	89.51	91.10	93.72	93.81	1.45
180.0	99.89	98.42	96.19	92.62	91.38	93.89	95.40	1.36
210.0	101.02	97.29	95.62	92.90	92.51	96.72	96.01	1.28
240.0	101.87	96.44	94.21	92.34	91.38	98.14	95.73	1.60
270.0	100.46	96.44	91.94	91.20	90.81	96.16	94.50	1.56
300.0	97.34	95.31	90.81	86.11	90.25	90.21	91.67	1.64

Table 19   Dissolution Data of Brand L Ibuprofen Tablets in Phosphate in Phosphate Buffer pH 7.2

Tablet No. Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5.0	0.08	0.09	0.07	0.00	0.09	0.29	0.11	0.04
7.5	6.48	0.22	0.22	36.83	3.48	9.11	9.39	5.67
10.0	53.16	0.23	0.23	78.07	53.19	59.21	40.68	13.32
15.0	74.93	53.35	0.35	81.90	77.12	82.81	61.74	13.03
20.0	88.01	70.79	0.59	87.80	83.02	83.32	68.92	13.90
25.0	87.75	81.82	0.82	88.32	84.30	87.94	71.83	14.23
30.0	90.58	84.39	1.08	89.34	88.15	92.82	74.39	14.70
35.0	91.35	86.19	1.26	90.37	89.43	93.07	75.08	14.83
40.0	98.53	88.75	1.46	90.88	91.23	95.64	77.75	15.32
50.0	97.76	91.06	1.81	91.39	94.56	97.69	79.05	15.49
60.0	95.96	92.34	4.90	91.91	94.82	98.46	79.73	14.99
70.0	94.94	91.83	11.04	91.65	92.00	95.64	79.51	13.71
80.0	91.60	90.55	18.56	91.14	92.51	94.61	79.83	12.26
90.0	92.37	90.29	26.68	90.37	93.79	94.87	81.40	10.96
120.0	91.60	90.03	41.32	92.16	92.25	94.10	83.58	8.46

Table 20   Dissolution Data of Brand M Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min) \ Tablet No.	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30.0	0.59	0.55	9.43	0.76	0.56	0.66	2.09	1.46
60.0	2.32	2.09	20.41	62.35	2.48	2.71	15.40	9.84
90.0	3.70	3.50	42.56	73.55	4.20	5.12	22.11	12.05
120.0	4.93	4.80	51.85	79.60	5.34	6.79	25.55	13.20
150.0	6.30	6.33	55.31	80.68	6.61	8.26	27.25	13.29
180.0	7.42	7.65	60.06	81.33	7.73	9.58	28.96	13.48
210.0	9.11	9.95	60.28	82.84	8.91	10.88	30.33	13.36
240.0	9.93	10.86	66.32	83.49	9.90	12.44	32.16	13.70
270.0	11.29	12.13	67.62	85.43	11.42	14.66	33.76	13.72
300.0	12.93	13.82	69.13	83.92	12.49	15.16	34.58	13.40
330.0	14.00	15.30	69.78	83.92	13.93	16.76	35.62	13.17
360.0	15.48	17.15	71.07	85.00	16.03	18.08	37.14	13.06
420.0	17.71	20.24	73.45	84.57	22.16	20.09	39.70	12.52
480.0	19.76	23.28	73.45	85.65	24.05	22.31	41.42	12.17

Table 21   Dissolution Data of Brand N Ibuprofen Tablets in Phosphate Buffer pH 7.2

Time (min)	Percent Ibuprofen Dissolved							
	1	2	3	4	5	6	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30.0	0.53	0.51	0.48	0.45	0.48	0.52	0.49	0.01
60.0	1.76	2.09	1.93	1.79	1.75	2.09	1.90	0.06
90.0	3.08	3.65	3.39	3.33	3.02	3.57	3.34	0.10
120.0	4.20	4.96	4.64	4.63	4.09	4.87	4.57	0.14
150.0	5.21	6.14	5.76	5.80	5.09	6.00	5.66	0.17
180.0	6.15	7.16	6.70	6.83	5.93	7.09	6.64	0.20
240.0	7.96	9.19	8.51	8.79	7.55	9.22	8.54	0.27
300.0	9.33	10.77	10.13	10.60	9.40	11.07	10.22	0.29
360.0	11.12	12.64	11.67	12.39	10.65	12.90	11.89	0.36
420.0	12.58	15.01	13.33	14.51	12.57	15.02	13.84	0.47
500.0	15.20	16.80	15.54	16.51	14.52	17.10	15.94	0.41

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Table 23 Dissolution Rate Constant of Fifteen Commercial Brands of Ibuprofen Tablets.

Tablet No. Brand	Dissolution Rate Constant (min^{-1})								
	1	2	3	4	5	6	MEAN	SEM	% CV
A (5-15 min)[*]	0.3108	0.2990	0.2781	0.3463	0.3124	0.2928	0.3065	0.0095	7.56
B (5-15 min)	0.2614	0.4010[a]	0.2882	0.1585	0.3214	0.3830	0.3022	0.0361	29.29
C (5-15 min)	0.2373	0.3124	0.4793	0.2944	0.3494	0.3129	0.3310	0.0332	24.56
D (5-20 min)	0.2421	0.2774	0.3762	0.2926	0.2519	0.2868	0.2878	0.0194	16.53
E (10-30 min)	0.1192	0.1244	0.1649	0.1771	0.1200	0.1857	0.1485	0.0126	20.73
F (20-40 min)	0.0465[b]	0.1294	0.1233	0.1090	0.0950	0.2352	0.1231	0.0255	50.68
G (15-50 min)	0.0972	0.0820	0.0619	0.2029	0.0912	0.0847	0.1033	0.0205	48.64
H (45-180 min)	0.0177	0.0224	0.0175	0.0186	0.0127	0.0345	0.0206	0.0031	36.44
I (40-120 min)	0.0097	0.0321	0.0509	0.0120	0.0274	0.0121	0.0240	0.0066	66.99
J (50-150 min)	0.0398	0.0239	0.0637	0.0371	0.0328	0.0619	0.0432	0.0066	37.27
K (40-150 min)	0.0334	0.0403	0.0327	0.0330	0.0428	0.0266	0.0348	0.0024	16.81
L (7.5-35 min)	0.0881	0.1082	0.0010	0.1066	0.0937	0.0939	0.0819	0.0165	49.35
M (30-240 min)	0.0032	0.0029	0.0099	0.0157	0.0024	0.0036	0.0063	0.0022	85.72
N (0-420 min)	0.0040	0.0048	0.0044	0.0046	0.0044	0.0046	0.0045	0.0001	5.83
O (0-360 min)	0.0034	0.0037	0.0034	0.0031	0.0042	0.0033	0.0035	0.0002	10.60

[*] (The number in parenthesis indicated the time interval for the rate constant calculation).

(a) The rate constant was calculated from the time range 5 - 10 minutes.

(b) The rate constant was calculated from the time range 5 - 20 minutes.

Table 24   Analysis of Variance for Dissolution Rate Constant among
                 Fifteen Brands of Ibuprofen Tablets

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	14	1.2919	0.0923	51.4697
Within replications	75	0.1345	0.0018	
Total	89	1.4264		

$$F_{0.05\ (14,75)} \quad = \quad 1.8708$$

d.f. = degree of freedom

S.S. = sum of square

M.S. = mean square

F   = variation ratio

Table 25 Pairwise Statistical Comparison of Dissolution Rate Constants among Fifteen Brands of Ibuprofen Tablets by Student's t -test

Brand	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
A															
B	0.1057														
C	-0.6443	-0.5339													
D	-0.7921	0.3209	1.0231												
E	9.1741	3.6675	4.6878	5.4973											
F	6.1675	3.7005	4.5339	4.6971	0.8200										
G	8.2137	4.3704	5.3219	5.9627	1.7173	0.5512									
H	26.2404	7.0897	8.4910	12.4070	9.0396	3.6177	3.6415								
I	22.3867	6.9150	8.2724	11.7452	8.0230	3.4381	3.3607	-0.4332							
J	20.8604	6.4380	7.7551	10.8900	6.7857	2.7719	2.5473	-2.8480	-1.8847						
K	25.4102	6.7410	8.1151	11.8025	8.1243	3.1500	3.0281	-3.3454	-1.4014	1.0957					
L	10.7809	5.0631	6.1282	7.3756	2.9341	1.2379	0.7422	-3.3358	-2.9755	-1.9891	-2.5787				
M	28.2046	7.4623	8.9000	13.1447	10.1882	4.1708	4.2932	3.4603	2.3366	4.8611	8.0177	4.1466			
N	29.1311	7.5223	8.9698	13.3176	10.4763	4.2519	4.3993	4.8046	2.7184	5.3798	11.5905	4.2845	0.7591		
O	29.2197	7.5460	8.9955	13.3615	10.5441	4.2855	4.4410	5.0810	2.8484	5.5093	11.9364	4.3364	1.1466	4.6191	

$t_{(0.05,10)}$ = 2.2281

$t_{(0.01,10)}$ = 3.1693

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Table 26 Statistically Significant Pairwise Differences of Dissolution Rate Constant among Fifteen Brands of Ibuprofen Tablets.

Brand	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
A															
B															
C															
D															
E	**	**	**	**											
F	**	**	**	**											
G	**	**	**	**											
H	**	**	**	**	**	**	**								
I	**	**	**	**	**	**	**								
J	**	**	**	**	**	*	*	*							
K	**	**	**	**	**	*	*	**							
L	**	**	**	**	*			**	*		*				
M	**	**	**	**	**	**	**	**	**	**	**	**			
N	**	**	**	**	**	**	**	**	*	**	**	**			
O	**	**	**	**	**	**	**	**	*	**	**	**		**	

* Significant at α = 0.05
** Significant at α = 0.01

In Vivo Studies

A. Analysis of Ibuprofen in Plasma Samples

Plasma ibuprofen concentrations were analyzed by high performance liquid chromatography. Typical chromatograms of ibuprofen and internal standard were illustrated in Figure 3. Retention times for ibuprofen and internal standard were 7.025 and 4.933 minutes , respectively. The analytical procedure was specific and reproducible. Analytical recoveries of ibuprofen and internal standard were about 99%. The sensitivity of detection for ibuprofen in plasma was 0.5 μg/ml.

B. Clinical Observations

No side effects and/or any indication of intoxications were observed after the administration of ibuprofen tablets.

C. Plasma Ibuprofen Level

Plasma ibuprofen concentrations at each sampling time ranging from 0 to 10 hours after administration of brand A,C,K and N ibuprofen tablets are reported in Table 27 - 30 respectively while plasma ibuprofen level was undetectable at all time for all subjects receiving brand O. The mean plasma concentration profile for each product were shown graphically in Figure 4.

D. Pharmacokinetics of Ibuprofen Tablets

The in vivo result was analyzed by both noncompartmental and compartmental method.
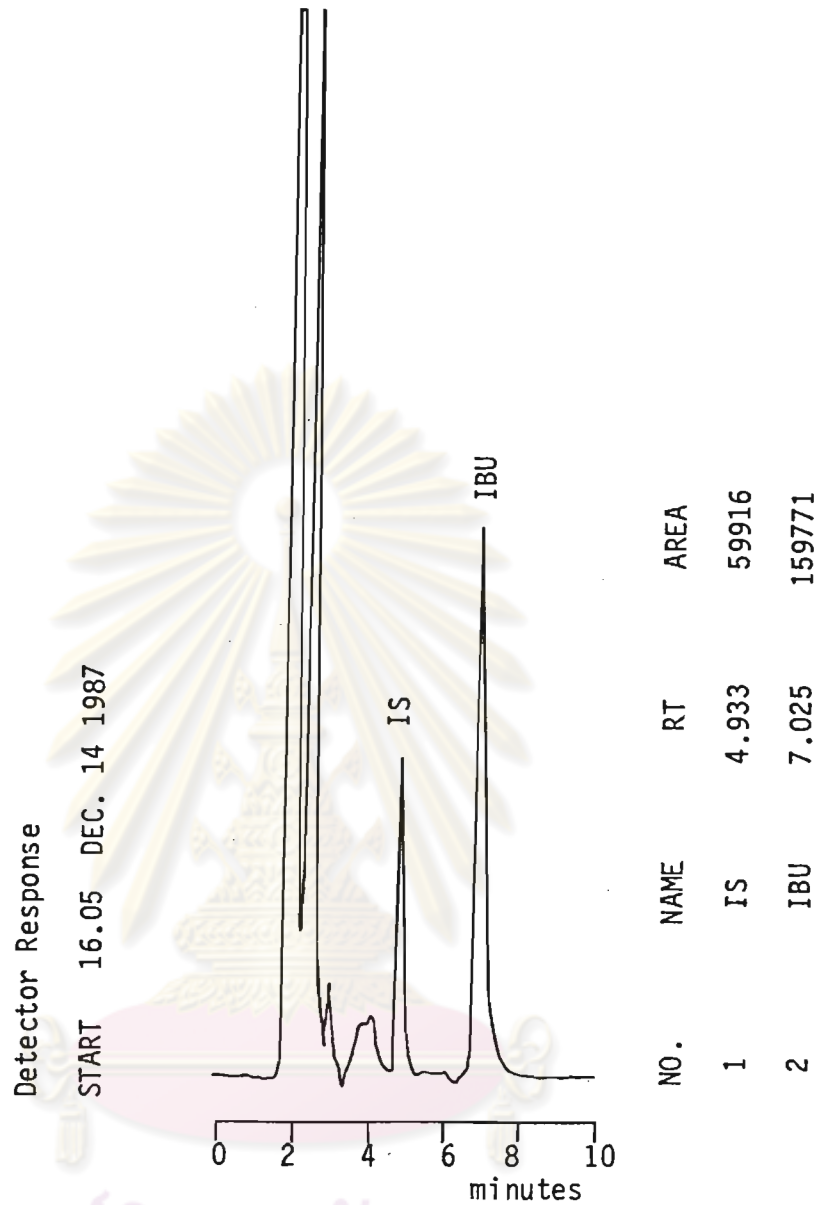
Figure 3 High performance liquid chromatogram[a] of
ibuprofen (IBU) and internal standard (IS)

a Obtained from HPLC analysis of human plasma containing
   60.60 μg/ml of ibuprofen and 8 μg/ml of internal
   standard.

Table 27   Plasma Ibuprofen Concentration at Various Times Following Oral Administration of Two 200 mg Ibuprofen Tablets , Brand A ,

to 12 Subjects.

Time (hr)	Plasma Ibuprofen Concentration (µg/ml)													
Subject No.	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	41.60	19.32	30.42	29.01	2.61	43.60	3.38	21.84	37.77	20.42	3.66	44.76	24.87	4.52
1.0	60.60	31.36	36.50	30.90	17.53	35.96	16.63	56.22	40.57	31.16	7.81	46.02	34.27	4.50
1.5	51.87	33.60	24.25	32.09	45.76	27.98	25.71	53.15	37.76	31.63	8.31	42.84	34.58	3.67
2.0	41.52	32.38	19.92	27.78	42.85	21.75	37.39	45.08	32.51	26.31	42.41	35.80	33.81	2.45
3.0	26.42	20.80	15.26	22.23	29.37	16.60	24.34	34.30	22.79	16.92	25.58	20.96	22.97	1.59
4.0	16.85	12.55	9.79	18.38	18.85	10.43	18.51	25.00	15.24	11.50	17.00	15.58	15.81	1.24
5.0	13.44	8.85	7.10	13.63	12.59	8.25	13.18	17.59	11.44	6.70	11.26	10.76	11.23	0.90
7.0	9.52	3.80	3.26	8.58	8.29	4.20	7.91	10.88	4.88	2.72	5.35	5.32	6.23	0.77
10.0	1.96	1.37	2.20	5.54	2.47	2.07	4.41	4.08	1.13	1.27	2.00	3.08	2.63	0.39

Table 28   Plasma Ibuprofen Concentration at Various Times Following Oral Administration of Two 200 mg Ibuprofen Tablets , Brand C ,

to 12 Subjects.

Subject No. / Time (hr)	Plasma Ibuprofen Concentration (µg/ml)													
	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	29.25	14.79	20.63	11.86	24.51	13.92	4.65	0.00	9.42	5.00	1.24	19.48	12.89	2.69
1.0	32.24	20.86	40.20	24.70	32.50	44.32	16.50	3.75	20.19	8.22	2.69	36.65	23.57	4.05
1.5	38.91	26.47	36.55	29.33	35.05	38.37	32.50	20.64	26.64	13.32	30.49	42.86	30.93	2.41
2.0	41.41	35.53	27.50	31.00	31.11	33.11	34.71	26.60	30.07	19.06	39.16	41.02	32.52	1.86
3.0	25.05	42.73	22.15	22.38	26.05	20.76	32.35	40.69	23.56	40.36	31.29	27.96	29.61	2.27
4.0	17.14	22.78	15.33	15.51	17.36	14.83	22.91	27.20	13.27	21.15	18.42	18.98	18.74	1.17
5.0	12.83	17.23	9.11	10.83	12.06	10.60	18.68	17.87	8.91	15.19	13.31	14.45	13.42	0.96
7.0	6.35	9.38	4.43	5.40	7.03	6.61	10.62	10.32	3.73	6.00	6.82	8.24	7.08	0.63
10.0	2.27	2.82	1.93	2.35	3.02	2.89	5.71	4.95	1.37	2.03	4.43	4.05	3.15	0.38

Table 29 Plasma Ibuprofen Concentration at Various Times Following Oral Administration of Two 200 mg Ibuprofen Tablets , Brand K ,

to 12 Subjects.

Time (hr)	Plasma Ibuprofen Concentration (μg/ml)													
Subject No.	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.00	0.00	0.58	0.00	0.00	0.00	0.00	0.00	0.00	0.57	0.00	0.31	0.12	0.06
1.0	0.00	0.00	1.09	0.03	0.00	0.00	0.00	0.00	0.00	0.81	0.00	0.35	0.19	0.10
1.5	0.00	2.62	1.46	2.46	2.20	1.12	0.78	0.00	0.00	2.19	0.00	0.57	1.11	0.30
2.0	0.00	8.97	4.01	5.36	7.36	2.37	3.51	0.00	1.23	6.83	1.73	1.27	3.55	0.86
3.0	9.46	13.52	11.82	17.16	11.89	6.60	11.41	6.89	10.09	9.88	2.00	6.32	9.75	1.13
4.0	14.68	22.19	14.60	18.70	18.64	6.95	19.38	14.31	19.16	10.25	2.59	11.67	14.43	1.66
5.0	13.48	14.95	14.08	17.60	16.00	7.18	18.50	25.86	14.35	12.93	4.16	14.24	14.44	1.56
7.0	10.99	13.25	12.88	9.55	7.36	8.39	17.59	23.49	8.46	7.19	12.80	13.35	12.11	1.36
10.0	9.51	9.39	11.12	4.92	3.95	7.92	7.78	10.97	5.86	3.41	10.75	12.33	8.16	0.87

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Table 30 Plasma Ibuprofen Concentration at Various Times Following Oral Administration of Two 200 mg Ibuprofen Tablets , Brand N ,

to 12 Subjects.

Time (hr)	Plasma Ibuprofen Concentration (μg/ml)													
Subject No.	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SEM
0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.99	3.97	0.00	0.00	0.00	0.41	0.33
1.0	20.10	5.94	7.58	13.08	8.61	11.13	0.80	8.91	6.79	5.29	0.00	3.63	7.66	1.58
1.5	23.36	13.69	17.32	18.17	20.35	38.73	3.99	16.71	8.67	14.90	21.40	6.23	16.96	2.63
2.0	28.95	14.70	16.39	22.28	20.98	36.14	14.95	29.18	12.47	16.23	33.10	10.27	21.30	2.48
3.0	22.49	14.28	15.26	29.60	24.17	23.80	25.49	42.28	18.61	22.84	27.44	29.78	24.67	2.15
4.0	17.75	19.87	19.46	24.99	17.80	15.09	23.01	32.07	22.60	19.15	24.09	21.84	21.48	1.27
5.0	13.15	13.03	13.02	18.53	12.08	10.47	17.03	23.92	19.15	12.13	14.76	18.41	15.47	1.13
7.0	5.81	8.80	7.45	10.08	6.19	6.18	9.32	17.40	10.33	5.47	7.83	11.94	8.90	0.97
10.0	2.33	5.28	3.12	6.05	3.00	3.06	4.30	7.85	5.42	1.84	3.18	8.59	4.50	0.62
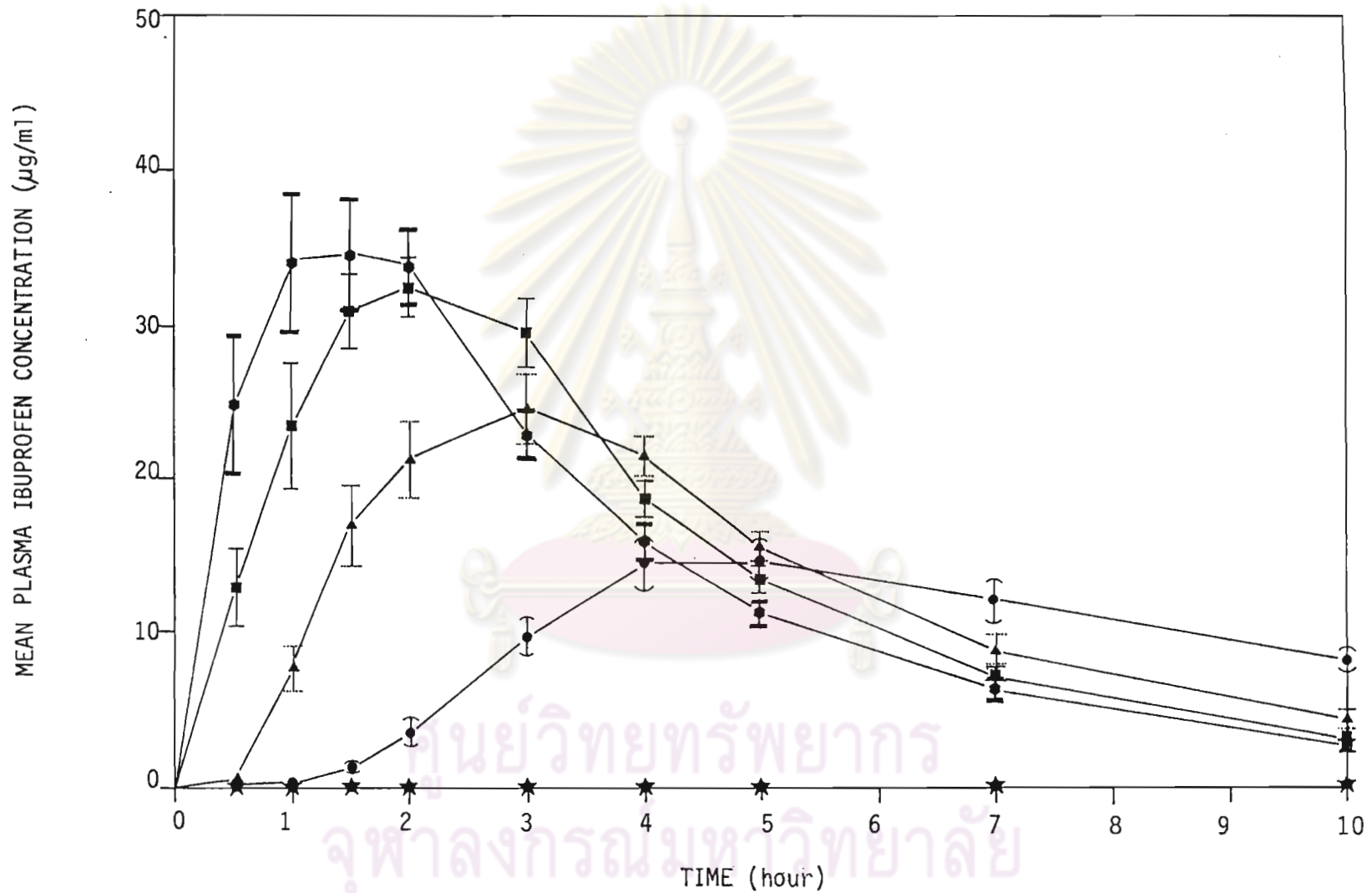
Figure 4 Comparison of the mean plasma ibuprofen concentration profile of five different brands following oral administration of two 200 mg ibuprofen tablets to 12 subjects.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲), Brand O (★)
(Vertical lines indicated standard error of the mean values)

1. <u>Noncompartmental Method</u>

The derived pharmacokinetic parameters based on noncompartmental analysis of the plasma concentration -time data were presented in Table 31 - 44. The area under plasma concentration -time curve , AUC_0^∞ calculated from individual plasma data was reported in Table 31. As shown in Table 32 , there were no statistically significant difference among AUC_0^∞ from four commercial brands. However , the AUC during the entire ten hours of sample collection differed significantly as seen in Table 33,34 . Rank order in terms of AUC_0^t were brand A,C > brand N > brand K (at $p < 0.05$).

The mean residence time after oral administration (MRT_{oral}) was shown in Table 35. Statistical analysis of difference among these values in Table 36 indicated that there were significant differences observed among four treatments, ie, brand A < brand C < brand N < brand K

The peak plasma ibuprofen concentration (Cp_{max}) as shown in Table 37 was read directly from the plasma concentration -time curve of each individual. The mean peak plasma concentration was 42.20 ± 2.63 , 38.55 ± 1.36, 16.80 ± 1.37 , and 28.08 ± 2.07 μg/ml for brand A,C,K, and N , respectively. The results of the statistical analysis was presented in Table 38. The order ranking from the highest to the lowerst was brand A,C > brand N > brand K (at $p < 0.05$).

The time to peak plasma level (T_{max}) as presented in Table 39 was also point out directly from the plasma concentration -time curve of each individual. The mean T_{max} for brand A , brand C , brand K , and brand N was 1.29 ± 0.13 , 2.00 ± 0.20 , 4.75 ± 0.33 , and 2.96 ± 0.23 hours respectively. Statistical result seen in Table 40 demonstrated

Table 31   Area under the Plasma Concentration-Time Curve (AUC_0^∞)
            of Ibuprofen Calculated by Noncompartmental Method
            Following the Administration of Two 200 mg Ibuprofen
            Tablets of Five Different Brands to 12 Subjects

Brand Subject No.	AUC_0^∞ (μg.hr.ml^{-1})				
	A	C	K	O	N
1	203.83	168.45	216.22	-	128.29
2	128.13	184.89	212.75	-	133.84
3	114.71	140.00	344.06	-	112.80
4	183.98	134.61	118.35	-	174.65
5	163.87	163.23	99.91	-	120.28
6	130.09	154.99	476.38	-	136.79
7	156.76	194.58	160.25	-	132.89
8	232.36	176.86	178.47	-	234.38
9	154.40	115.76	111.58	-	145.15
10	111.77	134.83	82.47	-	103.69
11	122.93	156.26	244.90	-	143.25
12	173.99	190.55	524.20	-	183.89
MEAN	156.40	159.58	230.80	-	145.82
SEM	10.83	7.17	42.07	-	10.43
C.V.	23.99	15.57	63.15	-	24.77

Table 32   Analysis of Variance and Pairwise Statistical Comparison of AUC_0^∞ of Ibuprofen Calculated by Noncompartmental Method[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	54410.8	18136.9	2.9523 *
Within subjects	44	270294.0	6143.1	
Total	47	324704.8		

$F_{0.05\,(3,44)} = 2.82$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	0.2893	0.0000		
K	1.6605	1.7664	0.0000	
N	- 1.3877	- 1.2645	- 2.0299	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable

*   Significant level at P <0.05

Table 33   Area under the Plasma Concentration-Time Curve (AUC_0^t) of Ibuprofen Calculated by Noncompartmental Method Following the Administration of Two 200 mg Ibuprofen Tablets of Five Different Brands to 12 Subjects

Brand / Subject No.	AUC_0^t $(\mu g.hr.ml^{-1})$				
	A	C	K	0	N
1	198.39	162.01	86.14	-	121.47
2	124.64	176.80	113.43	-	104.48
3	107.70	134.49	101.04	-	102.34
4	157.70	127.38	98.83	-	149.03
5	156.65	153.00	85.50	-	110.32
6	123.13	145.53	59.55	-	126.72
7	139.96	171.30	117.25	-	117.46
8	218.48	160.10	135.21	-	200.73
9	151.56	112.30	81.68	-	123.01
10	108.55	129.97	69.56	-	98.92
11	117.60	140.00	60.31	-	133.59
12	164.32	175.61	92.84	-	134.64
MEAN	147.39	149.04	91.78	-	126.89
SEM	10.03	6.01	6.65	-	7.95
C.V.	23.58	13.97	25.10	-	21.70

Table 34   Analysis of Variance and Pairwise Statistical Comparison
of AUC_0^t of Ibuprofen Calculated by Noncompartmental
Method [a]

One way analysis of variance

Source of variance	df	S.S	M.S.	F
Among treatment	3	25555.5	8518.51	11.6297 [*]
Within subjects	44	32229.0	732.48	
Total	47	57784.6		

$$F_{0.05\ (3,44)} = 2.62$$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	0.1651	0.0000		
K	- 6.2435 [*]	- 8.7640 [*]	0.0000	
N	- 2.9414 [*]	- 2.3218 [*]	4.4654 [*]	0.0000

$$t_{0.05,11} = 2.2010$$

a   The result of four brands only was used, brand O was excluded
since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

Table 35   Mean Residence Time after Oral Administration (MRT_{oral})
            of Ibuprofen Calculated by Noncompartmental Method
            Following the Administration of Two 200 mg Ibuprofen
            Tablets of Five Different Brands to 12 Subjects

Brand / Subject No.	MRT_{oral} (hour)				
	A	C	K	O	N
1	3.213	3.459	16.663	-	4.155
2	3.155	4.039	12.563	-	7.064
3	3.441	3.340	24.234	-	5.138
4	5.173	3.852	6.608	-	5.801
5	3.914	3.914	6.283	-	4.752
6	3.333	3.806	55.535	-	4.292
7	4.894	5.211	8.416	-	5.716
8	3.932	5.097	8.130	-	5.968
9	2.979	3.434	8.102	-	6.156
10	3.025	4.150	6.488	-	4.414
11	4.028	4.857	22.254	-	4.649
12	3.405	4.171	38.139	-	7.882
MEAN	3.708	4.111	17.785	-	5.499
SEM	0.206	0.183	4.429	-	0.335
C.V.	19.24	15.43	86.26	-	21.07

Table 36   Analysis of Variance and Pairwise Statistical Comparison of MRT_{oral} of Ibuprofen Calculated by Noncompartmental Method [a].

One way analysis of variance

Source of variance	df.	S.S.	M.S.	F
Among treatment	3	1624.1	541.36	9.1138[*]
Within subjects	44	2630.8	59.40	
Total	47	4237.9		

$F_{0.05(3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	2.0559	0.0000		
K	3.1338[*]	3.0621[*]	0.0000	
N	4,6208[*]	3.8920[*]	- 2.7606[*]	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

*   Significant level at P<0.05

Table   37   Peak Plasma Concentration (Cp_{max}) of Ibuprofen Reading Directly from the Plasma Concentration Time Curve of Each Individual Following the Administration of Two 200 mg Ibuprofen Tablets of Five Different Brands

Brand Subject No.	Cp_{max} (µg/ml)				
	A	C	K	O	N
1	60.60	41.41	14.69	-	28.95
2	33.60	42.74	22.20	-	19.87
3	36.50	40.21	14.61	-	19.46
4	32.09	31.00	18.71	-	29.61
5	45.76	35.06	18.64	-	24.17
6	43.61	44,33	8.39	-	38.73
7	37.40	34.71	19.39	-	25.50
8	56.23	40.69	25.86	-	42.29
9	40.57	30.08	19.16	-	22.61
10	31.64	40.37	12.93	-	22.84
11	42.42	39.16	12.81	-	33.11
12	46.02	42.87	14.24	-	29.79
MEAN	42.20	38.55	16.80	-	28.08
SEM	2.63	1.36	1.37	-	2.07
C.V.	21.56	12.23	28.26	-	25.58

Table 38   Analysis of Variance and Pairwise Statistical Comparison
of Cp_{max} of Ibuprofen Obtained from Directly Reading the
Plasma - Concentration Time Curve of each individual [a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	4703.65	1567.88	35.0051 *
Within subjects	44	1970.55	44.79	
Total	47	6674.20		

$$F_{0.05(3,44)} = 2.62$$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 1.4163	0.0000		
K	- 8.9166 *	9.6718	0.0000	
N	- 6.2784 *	- 4.9066 *	4.4483 *	0.0000

$$t_{0.05,11} = 2.2010$$

a   The result of four brands only was used, brand 0 was excluded
    since its bioavailability was undetectable.

*   Significant level at P < 0.05

Table 39   Time to Peak Plasma Level (T_{max}) of Ibuprofen Reading
Directly from the Plasma Concentration Time Curve of Each
Individual Following the Administration of Two 200 mg
Ibuprofen Tablet of Five Different Brands.

Brand Subject No.	T_{max}(hour)				
	A	C	K	O	N
1	1.0	2.0	4.0	-	2.0
2	1.5	3.0	4.0	-	4.0
3	1.0	1.0	4.0	-	4.0
4	1.5	2.0	4.0	-	3.0
5	1.5	1.5	4.0	-	3.0
6	0.5	1.0	7.0	-	1.5
7	2.0	2.0	4.0	-	3.0
8	1.0	3.0	5.0	-	3.0
9	1.0	2.0	4.0	-	4.0
10	1.5	3.0	5.0	-	3.0
11	2.0	2.0	7.0	-	2.0
12	1.0	1.5	5.0	-	3.0
MEAN	1.29	2.00	4.75	-	2.96
SEM	0.13	0.20	0.33	-	0.23
C.V.	34.85	35.36	23.96	-	27.40

Table   40   Analysis of Variance and Pairwise Statistical Comparison
of T_{max} of Ibuprofen Obtained from Directly Reading the
Plasma Concentration Time Curve of Each Individual[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	80.7917	26.9306	40.5740*
Within subjects	44	29.2083	0.6638	
Total	47	110.0000		

$F_{0.05}(3,44) = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	3.5588*	0.0000		
K	9.4365*	6.6241*	0.0000	
N	6.5044*	3.5299*	- 3.4438*	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

that there were significant difference in T_{max} among four treatment groups.

The apparent elimination rate constant (K_{el}) was determined from a least - square linear regression fit of the terminal region of the semilogarithmic plasma concentration -time curves. The values of the apparent elimination rate constant of each individual were presented in Table 41 and the statistical analysis which was reported in Table 42 indicated that there were significant difference among four treatments and most pairs except between brand A and brand C. The order ranking from the highest to the lowest was brand A, C > brand N > brand K.

The plasma half-life calculated from noncompartmental method was shown in Table 43. The values of this parameter were 2.17 , 2.19 10.21 , and 2.65 hour for brand A , brand C , brand K , and brand N respectively. Statistical comparison as seen in Table 44 indicated that the plasma half-life of drug differed significantly from each other except between brand A and C , brand A and N (at $p < 0.05$)

2. Compartmental Method

The plasma - concentration time data was first analyzed using the CSTRIP program , results obtained demonstrated that most data were fitted to a one compartment model with or without a lag time. Therefore one compartment model was used to describe all individual plasma data in compartmental analysis and the following pharmacokinetic parameters were estimated using CSTRIP program :- (a) the absorption rate constant, K_a (b) the elimination rate constant , K_{el} (c) the plasma half-life, $t_{\frac{1}{2}}$ and (d) the lag time, t_o.

Table 41   Elimination rate constant (K_{el}) of Ibuprofen Calculated
             by Noncompartmental Method Following the Administration of
             Two 200 mg Ibuprofen Tablets of Five Different Brands to
             12 Subjects.

Brand / Subject No.	K_{el} (hour^{-1})				
	A	C	K	O	N
1	0.362	0.354	0.073	-	0.343
2	0.395	0.349	0.095	-	0.180
3	0.314	0.351	0.046	-	0.299
4	0.211	0.326	0.252	-	0.236
5	0.343	0.295	0.274	-	0.302
6	0.298	0.307	0.019	-	0.304
7	0.263	0.245	0.181	-	0.279
8	0.295	0.296	0.254	-	0.233
9	0.398	0.398	0.196	-	0.245
10	0.394	0.419	0.265	-	0.387
11	0.377	0.273	0.058	-	0.329
12	0.319	0.271	0.029	-	0.175
MEAN	0.331	0.324	0.145	-	0.276
SEM	0.017	0.015	0.029	-	0.019
C.V.	17.668	16.176	69.758	-	23.312

Table 42   Analysis of Variance and Pairwise Statistical Comparison of K_{el} of Ibuprofen Calculated by Noncompartment Method[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.2662	0.0887	17.3922[*]
Within subjects	44	0.2259	0.0051	
Total	47	0.4921		

$F_{0.05 (3,44)}$ = 2.62

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 0.4549	0.0000		
K	- 5.1958[*]	- 5.9701[*]	0.0000	
N	- 2.4842[*]	- 2.3445[*]	3.9776[*]	0.0000

$t_{0.05,11}$ =2.2010

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

*   Significant level at P <0.05

Table 43   Plasma Half-life($t_{\frac{1}{2}}$) of Ibuprofen Calculated by
Noncompartmental Method Following the Administration of
Two 200 mg Ibuprofen Tablets of Five Different Brands to
12 Subjects

Brand / Subject No.	$t_{\frac{1}{2}}$ (hour)				
	A	C	K	O	N
1	1.91	1.96	9.48	-	2.02
2	1.76	1.99	7.33	-	3.85
3	2.20	1.98	15.13	-	2.32
4	3.28	2.12	2.75	-	2.93
5	2.02	2.35	2.53	-	2.30
6	2.32	2.26	36.47	-	2.28
7	2.64	2.82	3.83	-	2.48
8	2.35	2.34	2.73	-	2.97
9	1.74	1.74	3.53	-	2.83
10	1.76	1.66	2.62	-	1.79
11	1.84	2.54	11.89	-	2.11
12	2.17	2.56	24.23	-	3.97
MEAN	2.17	2.19	10.21	-	2.65
SEM	0.13	0.10	3.06	-	0.20
C.V.	20.78	15.88	103.80	-	25.96

Table 44   Analysis of Variance and Pairwise Statistical Comparison of
t ½ of Ibuprofen Calculated by Noncompartmental Method[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	559.55	186.52	6.5955[*]
Within subjects	44	1244.31	28.28	
Total	47	1803.86		

$F_{0.05(3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	0.2112	0.0000		
K	2.6257[*]	2.6371[*]	0.0000	
N	2.1761	2.2414[*]	- 2.4803[*]	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
since its bioavailability was undetectable.

*   Significant level at P <0.05

The first order absorption rate constant obtained from individual plasma data of 12 subjects was presented in Table 45. Statistical analysis of this parameter as shown in Table 46 indicated that all treatments differed significantly from each other. The order of absorption rate constant ranking from the fastest to the slowest was brand A > brand C > brand N > brand K (at $p < 0.05$).

The elimination rate constants estimated from CSTRIP program and their statistical results were reported in Table 47,48 respectively. There were no significant difference between brand A and C , A and N. But the elimination rate constant of brand A , C, and N was significantly more than that of brand K.

The plasma half-life and its statistical comparison were shown in Table 49 and 50. The half - life of ibuprofen after administration of brand K was significantly higher than those obtained after administration of brand A , C, and N while the half-life of ibuprofen obtained after oral administration of brand A , C and N were not statistically significant different.

The last pharmacokinetic parameter obtained from CSTRIP program was the lag time. As shown in Table 51 , the mean lag time was 0.057, 0.134 , 0.704 , and 0.353 hour for brand A , C , K , and N respectively. Statistical results , seen in Table 52 , indicated that the lag time of all products differed significantly from each other, except between brand A and C.

Not only the CSTRIP program was used to analyze the pharmaco-kinetic parameters , but the PCNONLIN program was also applied to estimate and calculate these parameters by iteration method.

Table 45   Absorption Rate Constant (K_a) of Ibuprofen Calculated by
            Compartmental Method, CSTRIP Program, Following the
            Administration of Two 200 mg Ibuprofen Tablets of Five
            Different Brands to 12 Subjects.

Brand / Subject No.	K_a (hour^{-1})				
	A	C	K	O	N
1	2.131	1.589	0.401	-	1.196
2	2.094	0.910	0.595	-	0.815
3	5.361	2.211	0.491	-	1.040
4	3.345	1.516	0.581	-	0.709
5	1.376	1.756	0.609	-	0.912
6	2.030	0.985	0.434	-	0.647
7	1.066	1.205	0.523	-	0.890
8	1.564	0.701	0.302	-	0.630
9	2.473	1.226	0.508	-	0.565
10	2.181	0.712	0.545	-	0.693
11	0.579	1.108	0.125	-	1.136
12	4.355	1.563	0.393	-	0.452
MEAN	2.380	1.290	0.459	-	0.807
SEM	0.396	0.130	0.040	-	0.067
C.V.	57.61	34.99	30.46	-	28.86

Table 46   Analysis of Variance and Pairwise Statistical Comparison
of K_a of Ibuprofen Calculated by Compartmental Method,
CSTRIP Program[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	25.1851	8.3950	15.5694*
Within subjects	44	23.7263	0.5392	
Total	47	48.9114		

$$F_{0.05(3,44)} = 2.62$$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 3.2861*	0.0000		
K	- 4.9600*	- 6.4785*	0.0000	
N	- 3.7769*	- 3.9367*	4.0506*	0.0000

$$t_{0.05,11} = 2.2010$$

a   The result of four brands only was used, brand O was excluded
since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

Table 47   Elimination Rate Constant (K_{el}) of Ibuprofen Calculated
by Compartmental Method, CSTRIP Program, Following the
Administration of Two 200 mg Ibuprofen Tablets of Five
Different Brands to 12 Subjects.

Brand / Subject No.	$K_{el}(hour^{-1})$				
	A	C	K	O	N
1	0.362	0.354	0.048	-	0.343
2	0.395	0.365	0.115	-	0.172
3	0.314	0.351	0.046	-	0.290
4	0.207	0.326	0.234	-	0.236
5	0.332	0.295	0.208	-	0.302
6	0.307	0.307	0.019	-	0.284
7	0.263	0.237	0.181	-	0.279
8	0.295	0.296	0.178	-	0.233
9	0.398	0.398	0.122	-	0.245
10	0.394	0.361	0.248	-	0.372
11	0.279	0.285	0.058	-	0.319
12	0.319	0.286	0.029	-	0.110
MEAN	0.322	0.322	0.124	-	0.265
SEM	0.017	0.013	0.024	-	0.021
C.V.	18.17	14.05	67.60	-	27.39

Table 48 Analysis of Variance and Pairwise Statistical Comparison of K_{el} of Ibuprofen Calculated by Compartmental Method, CSTRIP Program[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.3145	0.1048	23.8182*
Within subjects	44	0.1952	0.0044	
Total	47	0.5097		

$F_{0.05(3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 0.0252	0.0000		
K	- 6.3741*	- 7.1412*	0.0000	
N	- 2.1861	- 2.3828*	4.9982*	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

Table 49   Plasma half-life ($t_{\frac{1}{2}}$) of Ibuprofen Calculated by
            Compartmental Method, CSTRIP Program, Following the
            Administration of Two 200 mg Ibuprofen Tablets of Five
            Different Brands to 12 Subjects

Brand Subject No.	$t_{\frac{1}{2}}$ (hour)				
	A	C	K	O	N
1	1.91	1.96	14.44	-	2.02
2	1.75	1.90	6.03	-	4.03
3	2.21	1.97	15.07	-	2.39
4	3.35	2.13	2.96	-	2.94
5	2.09	2.35	3.33	-	2.29
6	2.26	2.26	36.47	-	2.44
7	2.63	2.92	3.83	-	2.48
8	2.35	2.34	3.89	-	2.97
9	1.74	1.74	5.68	-	2.83
10	1.76	1.92	2.79	-	1.86
11	2.48	2.43	11.95	-	2.17
12	2.17	2.43	23.90	-	6.30
MEAN	2.23	2.20	10.86	-	2.89
SEM	0.13	0.09	3.00	-	0.35
C.V.	20.59	14.82	95.76	-	42.02

Table 50   Analysis of Variance and Pairwise Statistical Comparison
of t ½ of Ibuprofen Calculated by Compartmental Method,
CSTRIP Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	642.35	214.12	7.7862*
Within subjects	44	1209.77	27.50	
Total	47	1852.12		

$F_{0.05(3,44)}$ = 2.62

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 0.2492	0.0000		
K	2.8646*	2.8906*	0.0000	
N	1.7671	1.9790	- 2.7195*	0.0000

$t_{0.05,11}$ = 2.2010

a   The result of four brands only was used, brand 0 was excluded
since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

Table 51   Lag time (t_0) of Ibuprofen Calculated by Compartmental
Method, CSTRIP Program, Following the Administration of
Two 200 mg Ibuprofen Tablets of Five Different Brands to
12 Subjects

Brand / Subject No.	Lag time (hour)				
	A	C	K	O	N
1	0	0	0.747	-	0.280
2	0.125	0.217	0.697	-	0.278
3	0	0	0.602	-	0.626
4	0	0.128	0.662	-	0.243
5	0.325	0	0.600	-	0.290
6	0	0	0.619	-	0.164
7	0.197	0.226	0.829	-	0.642
8	0	0.356	0.870	-	0.330
9	0	0.140	0.726	-	0.360
10	0	0.225	0.610	-	0.300
11	0.040	0.310	0.680	-	0.424
12	0	0	0.805	-	0.300
MEAN	0.057	0.134	0.704	-	0.353
SEM	0.030	0.038	0.027	-	0.042
C.V.	184.20	99.41	13.23	-	41.13

Table 52   Analysis of Variance and Pairwise Statistical Comparison
            of Lag Time Calculated by Compartmental Method, CSTRIP
            Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	3.0246	1.0082	69.0548[*]
Within subjects	44	0.6435	0.0146	
Total	47	3.6681		

$F_{0.05(3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	1.5218	0.0000		
K	15.1777[*]	15.4910[*]	0.0000	
N	6.2618[*]	4.2621[*]	- 7.7132[*]	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand 0 was excluded
     since its bioavailability was undetectable.

*   Significant level at $P < 0.05$

As aforementioned , most individual data were fitted to one compartment model with or without a lag time. Consequently, all data were assumed to follow the classical one-compartment model with or without a lag time in the PCNONLIN program. The pharmacokinetic parameters obtained from this program were : (a) the area under the concentration -time curve , AUC_0^∞ (b) the absorption rate constant, K_a (c) the time to peak plasma level , T_{max} (d) the peak plasma concentration , Cp_{max} (e) the apparent volume of distribution (f) the elimination rate constant , K_{el} (g) the plasma half life , $t_{\frac{1}{2}}$ and (h) the lag time.

The AUC_0^∞ of four commercial products and their statistical comparison were shown in Table 53,54 respectively. No significant differences among these values were observed.

The first order absorption rate constant was reported in Table 55 , while their statistical results was shown in Table 56. The result demonstrated that the absorption rate constants of brand A,C > brand N > brand K.

The mean time to peak plasma level (T_{max}) for brand A , C , K and N was 1.21 , 1.85 , 4.71 and 2.70 hours respectively as shown in Table 57, they were statistically significant different from each other as seen in Table 58.

Similar results were observed for the peak plasma ibuprofen concentration (Cp_{max}) , as seen in Table 59,60. The mean values of this parameter were 40.02 , 34.27   , 16.05 , and 25.75 $\mu g/ml$ for brand A , C , K , and N respectively and there were statistically significant

Table 53   Area under the Plasma Concentration-Time Curve (AUC_0^∞)
of Ibuprofen Calculated by Compartmental Method,
PCNONLIN Program, Following the Administration of Two
200 mg Ibuprofen Tablets of Five Different Brands to
12 Subjects

Brand / Subject No.	AUC_0^∞ ($\mu g.hr.ml^{-1}$)				
	A	C	K	O	N
1	190.53	160.88	205.34	–	127.75
2	120.51	185.65	167.08	–	125.78
3	107.04	134.23	289.03	–	113.65
4	180.20	126.12	111.97	–	163.12
5	153.22	157.94	102.10	–	113.58
6	129.38	138.04	1022.08*	–	124.60
7	139.31	178.92	156.61	–	125.26
8	217.06	163.52	186.06	–	214.96
9	158.07	110.39	101.23	–	159.61
10	106.19	137.84	82.72	–	105.12
11	111.36	136.49	–**	–	142.80
12	165.98	172.03	197.85	–	159.51
MEAN	148.24	150.17	160.00		139.65
SEM	10.30	6.64	19.99		8.85
C.V.	24.08	15.31	39.51		21.96

*   This value was excluded when calculated the mean , SEM and CV
of brand K

**   This parameter was unobtainable for this individual due to
an erroneous mathematics.

Table 54　Analysis of Variance and Pairwise Statistical Comparison of AUC_0^∞ of Ibuprofen Calculated by Compartmental Method, PCNONLIN Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	1924.2	641.4	0.3639
Within subjects	36	63455.4	1762.7	
Total	39	65379.6		

$F_{0.05\ 3,36} = 2.872$

Student's t - statistics

Brand	A	C	K	N
A	0.0000 9[b]			
C	0.1692 11	0.0000 10		
K	0.2667 9	0.3735 9	0.0000 8	
N	- 1.2489 11	- 0.9412 11	- 0.8594 9	0.0000 10

$t_{0.05,9} = 2.2622$

$t_{0.05,11} = 2.2010$

a　The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

b　Degree of freedom appears under coefficient.

*　Significant level at $P < 0.05$

Table 55   Absorption Rate Constant (K_a) of Ibuprofen Calculated by
            Compartmental Method, PCNONLIN Program, Following the
            Administration of Two 200 mg Ibuprofen Tablets of Five
            Different Brands to 12 Subjects

Brand Subject No.	K_a $(hour^{-1})$				
	A	C	K	O	N
1	1.815	1.073	8.641*	–	1.218
2	1.288	0.503	0.624	–	0.637
3	3.330	1.198	1.100	–	0.646
4	2.822	1.156	0.739	–	2.023
5	3.899	1.338	0.421	–	0.926
6	4.109	4.251	0.702	–	3.009
7	1.697	0.858	0.329	–	0.805
8	0.986	0.569	0.351	–	0.448
9	2.549	0.689	9.387*	–	0.909
10	0.959	1.888	0.375	–	0.542
11	0.727	3.100	0.203	–	2.346
12	2.771	0.762	0.313	–	0.894
MEAN	2.246	1.449	0.516	–	1.200
SEM	0.337	0.327	0.086	–	0.235
C.V.	52.050	78.268	52.802	–	7.847

* These values were excluded when calculated the mean,
  SEM and C .V. of brand K.

Table 56   Analysis of Variance and Pairwise Statistical Comparison of K_a of Ibuprofen Calculated by Compartmental Method, PCNONLIN Program[a]

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	15.7518	5.2506	5.2627[*]
Within subjects	36	35.9180	0.9977	
Total	39	51.6698		

$$F_{0.05(3,36)} = 2.872$$

Student's t - statistics

Brand	A	C	K	N
A	0.0000 9[b]			
C	-1.9395 11	0.0000 10		
K	-4.7725[*] 9	-2.6635[*] 9	0.0000 8	
N	-3.0379[*] 11	-1.3409 11	-2.4564[*] 9	0.0000 10

$$t_{0.05,9} = 2.2622$$

$$t_{0.05,11} = 2.2010$$

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

b   Degree of freedom appears under coefficient.

*   Significant level at P <0.05

Table 57   Time to peak Plasma level (T_{max}) of Ibuprofen Calculated
            by Compartmental Method, PCNONLIN Program, Following the
            Administration of Two 200 mg Ibuprofen Tablets of Five
            Different Brands to 12 Subjects

Subject No.	A	C	K	O	N
1	1.01	1.39	3.44	-	1.93
2	1.37	2.21	4.20	-	3.03
3	0.71	1.27	4.57	-	2.68
4	0.98	1.65	3.76	-	2.82
5	1.57	1.36	3.80	-	2.36
6	0.20	1.39	7.75	-	1.55
7	1.93	2.22	4.87	-	3.16
8	1.48	2.71	5.60	-	3.06
9	0.89	1.77	3.34	-	3.63
10	1.25	2.71	3.95	-	2.67
11	2.30	1.96	-*	-	2.19
12	0.81	1.58	6.57	-	3.36
MEAN	1.21	1.85	4.71	-	2.70
SEM	0.16	0.15	0.42	-	0.18
C.V.	47.09	27.68	29.70	-	22.46

T_{max}(hours)

* This Parameter was unobtainable for this individual due
to an erroneous mathematics.

Table 58   Analysis of Variance and Pairwise Statistical Comparison of T_{max} of Ibuprofen Calculated by Compartmental Method, PCNONLIN Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	80.2547	26.7516	37.6253*
Within subjects	40	28.4393	0.7110	
Total	43	108.6940		

$F_{0.05\ (3,40)} = 2.84$

Student's t - statistics

Brand	A	C	K	N
A	0.0000 10[b]			
C	4.0453* 11	0.0000 10		
K	7.1970* 10	6.2237* 10	0.0000 9	
N	6.7173* 11	4.7112* 11	3.9290* 10	0.0000 10

$t_{0.05,10} = 2.2281$

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
    since its bioavailability was undetectable.

b Degree of freedom appears under coefficient.

* Significant level at P <0.05

Table 59   Peak Plasma Concentration (Cp_{max}) of Ibuprofen Calculated
            by Compartmental Method, PCNONLIN Program, Following the
            Administration of Two 200 mg Ibuprofen Tablets of Five
            Different Brands to 12 Subjects

Brand / Subject No.	Cp_{max} (µg/ml)				
	A	C	K	O	N
1	54.92	38.79	15.00	-	27.18
2	33.97	34.26	17.75	-	17.13
3	33.22	35.29	14.33	-	18.56
4	32.45	29.90	19.05	-	26.54
5	46.08	34.29	15.81	-	23.78
6	47.50	36.55	8.07	-	39.01
7	31.95	33.45	18.97	-	24.49
8	49.83	34.13	23.93	-	35.68
9	41.75	27.99	21.12	-	18.27
10	30.64	27.82	11.43	-	20.97
11	29.82	39.35	-*	-	33.32
12	48.16	39.46	14.29	-	24.12
MEAN	40.02	34.27	16.05	-	25.75
SEM	2.58	1.17	1.26	-	2.04
C.V.	22.32	11.81	27.29	-	27.39

* This parameter was unobtainable for this individual
  due to an erroneous mathematics.

Table 60   Analysis of Variance and Pairwise Statistical Comparison of Cp_{max} of Ibuprofen Calculated by Compartmental Method, PCNONLIN Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	3758.9	1253.0	31.3250[*]
Within subjects	40	1600.2	40.0	
Total	43	5359.1		

$F_{0.05 (3,40)}$ = 2.84

Student's t - statistics

Brand	A	C	K	N
A	0.0000 10[b]			
C	- 2.4196[*] 11	0.0000 10		
K	- 8.2355[*] 10	- 8.6023[*] 10	0.0000 9	
N	- 5.4074[*] 11	- 4.5614[*] 11	3.2974[*] 10	0.0000 10

$t_{0.05,10}$ = 2.2281

$t_{0.05,11}$ = 2.2010

a   The result of four brands only was used, brand O was excluded since its bioavailability was undetectable.

b   Degree of freedom appears under coefficient.

*   Significant level at $P < 0.05$

differences among four products.

The apparent volume of distribution (Vd) as shown in Table 61 for brand A , C, K and N was 0.1111 , 0.0942 , 0.3099 , and 0.1404 L/kg respectively. Table 62 showed that the Vd for brand K was significant different from those obtained for brand A , C , and N ; the value obtained for brand C differed significantly from that obtained for brand N but the value for brand A did not differ significantly from those obtained for brand C and N.

The elimination rate constant (K_{el}) was presented in Table 63 Statistical results as seen in Table 64 were similar to those obtained for the apparent volume of distribution.

The plasma half-life obtained was 1.69 , 1.47 , 4.26 and 1.97 hours for brand A , C, K and N respectively. Table 66 indicated that only the $t_{\frac{1}{2}}$ of ibuprofen obtained after administration of brand C was significantly different from those obtained for brand K and N while the rest were not significantly different.

The last parameter obtained from PCNONLIN program was the lag time. The mean values for this parameter was 0.23 , 0.35 , 1.92 and 0.83 hours for brand A , C , K and N respectively , and all treatments differed significantly from each other except for those between brand A and brand C , as shown in Table 67 , 68.

Table 61   Apparent Volume of Distribution (Vd) of Ibuprofen
             Calculated by Compartmental Method, PCNONLIN Program,
             Following the Administration of Two 200 mg Ibuprofen
             Tablets of Five Different Brands to 12 Subjects

Brand / Subject No.	Vd (L/kg)				
	A	C	K	O	N
1	0.0953	0.1145	0.5327	-	0.1850
2	0.1097	0.0742	0.2370	-	0.2205
3	0.1225	0.0838	0.3246	-	0.1466
4	0.1651	0.1247	0.1839	-	0.0927
5	0.0961	0.1037	0.1329	-	0.1276
6	0.1297	0.0706	0.7830	-	0.1338
7	0.1368	0.1062	0.1272	-	0.1363
8	0.0855	0.0882	0.1261	-	0.0836
9	0.1306	0.0992	0.3256	-	0.1522
10	0.0925	0.0850	0.2075	-	0.1132
11	0.0684	0.1049	0.4893	-	0.1218
12	0.1014	0.0754	0.2486	-	0.1720
MEAN	0.1111	0.0942	0.3099	-	0.1404
SEM	0.0321	0.0272	0.0895	-	0.0405
C.V.	24.004	18.262	64.546	-	27.488

Table 62   Analysis of Variance and Pairwise Statistical Comparison of
            Vd of Ibuprofen Calculated by Compartmental Method,PCNONLIN
            Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.3540	0.1180	11.1321[*]
Within subjects	44	0.4675	0.0106	
Total	47	0.8215		

$F_{0.05(3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	- 2.0666	0.0000		
K	3.3859[*]	3.6573[*]	0.0000	
N	2.1053	3.4014[*]	- 3.0037[*]	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
     since its bioavailability was undetectable.

*   Significant level at P <0.05

Table 63   Elimination Rate Constant (K_{el}) of Ibuprofen Calculated
by Compartmental Method, PCNONLIN Program, Following
the Administration of Two 200 mg Ibuprofen Tablets of
Five Different Brands to 12 Subjects

Subject No.	K_{el} (hour^{-1})				
	A	C	K	O	N
1	0.459	0.453	0.077	-	0.353
2	0.522	0.501	0.174	-	0.249
3	0.418	0.487	0.058	-	0.329
4	0.224	0.424	0.324	-	0.441
5	0.388	0.349	0.421	-	0.394
6	0.397	0.684	0.008	-	0.400
7	0.344	0.345	0.329	-	0.384
8	0.440	0.566	0.348	-	0.454
9	0.366	0.689	0.229	-	0.311
10	0.657	0.551	0.376	-	0.542
11	0.729	0.388	- *	-	0.329
12	0.403	0.523	0.138	-	0.247
MEAN	0.446	0.497	0.226	-	0.369
SEM	0.039	0.033	0.043	-	0.025
C.V.	30.650	23.084	63.258	-	23.164

* This Parameter was unobtainable for this individual due
to an erroneous mathematics.

Table 64   Analysis of Variance and Pairwise Statistical Comparison of
            K_{e1} of Ibuprofen Calculated by Compartmental Method,
            PCNONLIN Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	0.4555	0.1518	11.4135*
Within subjects	40	0.5317	0.0133	
Total	43	0.9872		

$F_{0.05 (3,40)} = 2.84$

Student's t - statistics

Brand	A	C	K	N
A	0.0000 10[b]			
C	0.9767 11	0.0000 10		
K	- 3.5949* 10	- 4.2743* 10	0.0000 9	
N	- 1.6721 11	- 3.0843* 11	4.0721* 10	0.0000

$t_{0.05,10} = 2.2281$

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
     since its bioavailability was undetectable.

b   Degree of freedom appears under coefficient

*   Significant level at $P < 0.05$

Table 65 Plasma Half-life (t $_{\frac{1}{2}}$) of Ibuprofen Calculated by Compartmental Method, PCNONLIN Program, Following the Administration of Two 200 mg Ibuprofen Tablets of Five Different Brands to Subjects

Brand / Subject No.	$t_{\frac{1}{2}}$ (hours)				
	A	C	K	O	N
1	1.51	1.53	9.01	-	1.97
2	1.33	1.38	3.98	-	2.79
3	1.66	1.42	11.87	-	2.11
4	3.09	1.64	2.14	-	1.57
5	1.79	1.99	1.65	-	1.76
6	1.75	1.01	83.49*	-	1.73
7	2.01	2.01	2.11	-	1.80
8	1.58	1.22	1.99	-	1.53
9	1.90	1.01	3.03	-	2.23
10	1.05	1.26	1.83	-	1.28
11	0.95	1.79	-**	-	2.11
12	1.72	1.33	5.03	-	2.81
MEAN	1.69	1.47	4.26	-	1.97
SEM	0.16	0.10	1.10	-	0.14
C.V.	32.11	22.98	81.86	-	23.85

* This value was excluded when calculated MEAN, SEM and C.V. of brand K.

** This parameter was unobtainable for this individual due to an erroneous mathematics.

Table 66   Analysis of Variance and Pairwise Statistical Comparison of
t ½ of Ibuprofen Calculated by Compartmental Method,PCNONLIN
Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	49.00	16.33	5.0872*
Within subjects	36	115.59	3.21	
Total	39	164.59		

$$F_{0.05(3,36)} = 2.872$$

Student's t - statistics

Brand	A	C	K	N
A	0.0000 9[b]			
C	- 1.3263 11	0.0000 10		
K	2.1747 9	2.4827* 9	0.0000 10	
N	1.2412 11	2.9031* 11	2.1543 9	0.0000 8

$$t_{0.05,9} = 2.2622$$

$$t_{0.05,11} = 2.2010$$

a The result of four brands only was used, brand O was excluded
  since its bioavailability was undetectable.

b Degree of freedom appears under coefficient.

* Significant level at $P < 0.05$

Table 67   Lag time (t_0) of Ibuprofen Calculated by Compartmental
            Method PCNONLIN Program, Following the Administration of
            Two 200 mg Ibuprofen Tablets of Five Different Brands
            to 12 Subjects

Brand / Subject No.	Lag Time (hour)				
	A	C	K	O	N
1	0	0	2.89	-	0.50
2	0.19	0.22	1.36	-	0.61
3	0	0	1.75	-	0.55
4	0	0.28	1.78	-	0.55
5	0.91	0	1.43	-	0.75
6	0	0	1.35	-	0.94
7	0.75	0.44	1.83	-	1.40
8	0	0.95	2.73	-	0.84
9	0	0.32	2.94	-	0.42
10	0	0.89	1.29	-	0.82
11	0.93	1.19	1.79	-	1.21
12	0	0	1.89	-	1.37
MEAN	0.23	0.36	1.92	-	0.83
SEM	0.11	0.12	0.17	-	0.10
C.V.	167.18	119.52	31.38	-	40.91

Table 68   Analysis of Variance and Pairwise Statistical Comparison
            of Lag Time of Ibuprofen Calculated by Compartmental
            Method, PCNONLIN Program[a].

One way analysis of variance

Source of variance	d.f.	S.S.	M.S.	F
Among treatment	3	21.2348	7.0783	34.9718[*]
Within subjects	44	8.9057	0.2024	
Total	47	30.1405		

$F_{0.05 (3,44)} = 2.62$

Student's t - statistics

Brand	A	C	K	N
A	0.0000			
C	0.8825	0.0000		
K	7.2721[*]	7.5720[*]	0.0000	
N	5.4723[*]	3.5453[*]	- 4.8674[*]	0.0000

$t_{0.05,11} = 2.2010$

a   The result of four brands only was used, brand O was excluded
     since its bioavailability was undetectable.

*   Significant level at P <0.05

3. Comparison among Different Method Used for Pharmacokinetic Analysis

The mean values of all pharmacokinetic parameters of ibuprofen obtained for each brand of ibuprofen tablets used in this study was summarized in Table 69 - 71. Table 69 showed the parameters obtained from noncompartmental method, Table 70 reported the results obtained from the compartmental method using CSTRIP program, and Table 71 presented the outcome of the compartmental method using PCNONLIN program. Statistical comparison of the parameters obtained for different brands of ibuprofen tablets revealed a few unlike conclusions when different method or program was used to calculate these parameters.

In Vitro -In Vivo Correlation

The bioavailability of a drug from tablet dosage forms depends on both the rate and extent of drug absorption into the general circula-tion. Since the statistical comparison revealed no significant difference in AUC_0^∞ using either noncompartmental or compartmental method (Table 69 , 71 respectively) indicated that the extent of drug absorption from the local manufactured brands did not differ significantly from each other and their original brand. On the contrary, the rate of drug absorption as measured by the time to peak plasma level, the first order absorption rate constant and the mean residence time indicated that the absorption rate for the local manufactured brands were significantly slower than that of their original brand , as shown in Table 69 , 70 and 71. Therefore the mean residence time (MRT_{oral}) , the time to peak plasma level , and the absorption rate constant were the three in vivo pharmacokinetic parameters chosen to test for their correlation with the in vitro measurements , i.e. the disintegration time and the

Table 69 The Mean Values of Some Pharmacokinetic Parameters for Ibuprofen Obtaind from Non Compartmental Method. Following Oral Administration of Two 200 mg Tablets of Five Different Brands to 12 Subjects. (The number in parenthesis indicated the SEM)

Parameter	Brand					Statistical Significance [a]
	A	C	K	O	N	
Area under the plasma concentration - time curve , AUC_0^∞ (μg.hr.ml^{-1})	156.401 (10.833)	159.583 (7.171)	230.795 (42.074)	ﬞ	145.824 (10.426)	NS
The mean residence time, MRT_{oral} (hr)	3.708 (0.206)	4.111 (0.183)	17.785 (4.429)	-	5.499 (0.335)	A , C < N < K
Peak plasma concentration, Cp_{max}(μg/ml)	42.204 (2.626)	38.552 (1.361)	16.804 (1.371)	-	28.077 (2.074)	A , C > N > K
Time to peak concentration , T_{max} (hr)	.1.29 (0.13)	2.00 (0.20)	4.75 (0.33)	-	2.96 (0.23)	A < C < N < K
Overall elimination rate constant, K_{el}(hr^{-1})	0.331 (0.017)	0.324 (0.015)	0.145 (0.029)	-	0.276 (0.019)	A , C > N > K
Plasma half - life , $t_{\frac{1}{2}}$ (hr)	2.17 (0.13)	2.19 (0.10)	10.21 (3.06)	-	2.65 (0.20)	A , C , N < K

a = significant level at p < 0.05

NS = no significant difference at p < 0.05

Table 70 The Mean Values of Some Pharmacokinetic Parameters for Ibuprofen Obtained from Compartmental Method , CSTRIP

Program , Following Oral Administration of Two 200 mg Tablets of Five Different Brands to 12 Subjects

(The number in parenthesis indicated the SEM)

Parameter	Brand					Statistical Significance [a]
	A	C	K	O	N	
Absorption rate constant , K_a (hr^{-1})	2.380 (0.396)	1.290 (0.130)	0.459 (0.040)	-	0.807 (0.067)	A > C > N > K
Elimination rate Constant , K_{el} (hr^{-1})	0.322 (0.017)	0.322 (0.013)	0.124 (0.024)	-	0.265 (0.021)	A , C , N > K
Plasma half-life , $t_{\frac{1}{2}}$ (hr)	2.23 (0.13)	2.20 (0.09)	10.86 (3.00)	-	2.89 (0.35)	A , C , N < K
Lag time , t_o (hr)	0.057 (0.030)	0.134 (0.038)	0.704 (0.027)	-	0.353 (0.043)	A , C < N < K

a = significant level at $p < 0.05$

Table 71 The Mean Values of Some Pharmacokinetic Parameters for Ibuprofen Obtained from Compartmental Method , PCNONLIN

Program , Following Oral Administration of Two 200 mg Tablets of Five Different Brands to 12 Subjects

(The number in parenthesis indicated the SEM)

Parameter	Brand					Statistical significance[a]
	A	C	K	O	N	
Area under the plasma concentration -time curve, AUC_0^∞ (μg.hr.ml^{-1})	147.68 (10.27)	151.72 (6.69)	150.72 (18.83)	-	138.76 (8.80)	NS
Absorption rate constant, K_a (hr^{-1})	2.246 (0.337)	1.449 (0.327)	1.932 (0.959)	-	1.200 (0.235)	A > C > N > K
Time to peak concentration , T_{max} (hr)	1.21 (0.16)	1.85 (0.15)	4.91 (0.43)	-	2.70 (0.18)	A < C < N < K
Peak plasma concentration , Cp_{max} (μg/ml)	40.023 (2.578)	34.273 (1.169)	16.046 (1.264)	-	25.753 (2.036)	A > C > N > K
Apparent volume of distribution, Vd (L/Kg)	0.1111 (0.0321)	0.0942 (0.0272)	0.3099 (0.0895)	-	0.1404 (0.0405)	A , C , N < K
Elimination rate constant , K_{el} (hr^{-1})	0.446 (0.039)	0.497 (0.033)	0.226 (0.043)	-	0.369 (0.025)	A , C > N > K
Plasma half-life , $t_{\frac{1}{2}}$ (hr)	1.69 (0.16)	1.47 (0.10)	11.46 (7.27)	-	1.97 (0.14)	NS
Lag time , t_0 (hr)	0.2312 (0.1116)	0.3566 (0.1230)	1.9195 (.1739)	-	0.8310 (0.0981)	A , C < N < K

a = significant   level at $p < 0.05$

NS = no significant difference at $p < 0.05$

dissolution rate.

Table 72 exhibited the linear relationship between disintegration time and dissolution rate of all fifteen brands of ibuprofen tablet. Statistical results indicated that there were significant correlation between disintegration time and dissolution rate constant. This relationship could also be observed graphically in Figure 5.

The correlations between disintegration time and mean residence time after oral administration (MRT_{oral}) , time to peak plasma level (T_{max}) , absorption rate constant (K_a) , and a reciprocal of absorption rate constant ($1/K_a$) were presented in Table 73 and Figure 6, Table 74 and Figure 7 , Table 75 and Figure 8 , and Table 76 and Figure 9 respectively. Evidences of significant linear correlation between disintegration time and MRT_{oral} , T_{max} , $1/K_a$ were found but there was no statistically significant linear relationship between disintegration time and K_a ($p > 0.05$)

On the other hand , the dissolution rate constants of ibuprofen tablets did not show significant linear correlation with their in vivo rate of bioavailability ($p > 0.05$), as shown in Table 77 , 78 , 79 , 80 and illustrated in Figure 10 , 11 , 12 and 13.

Table 72   Linear Correlation Between Disintegration . Time and
            Dissolution Rate Constant of Fifteen Brands of Ibuprofen
            Tablets.

Brand	Disintegration time (minutes)	Dissolution rate constant (minute^{-1})
A	14.42	0.3066
B	10.26	0.3022
C	12.97	0.3310
D	11.11	0.2878
E	16.82	0.1485
F	13.83	0.1231
G	14.97	0.1033
H	48.17	0.0201
I	35.75	0.0240
G	41.67	0.0432
K	97.00	0.0348
L	9.67	0.0819
M	31.83	0.0063
N	31.17	0.0045
O^a	> 5 hr	0.0035

r^2 = 0.3221

t - value = 2.3877

$t_{(0.05,12)}$ = 2.1788

a   Brand O was excluded from correlation since its exact
    disintegration time was not observed.
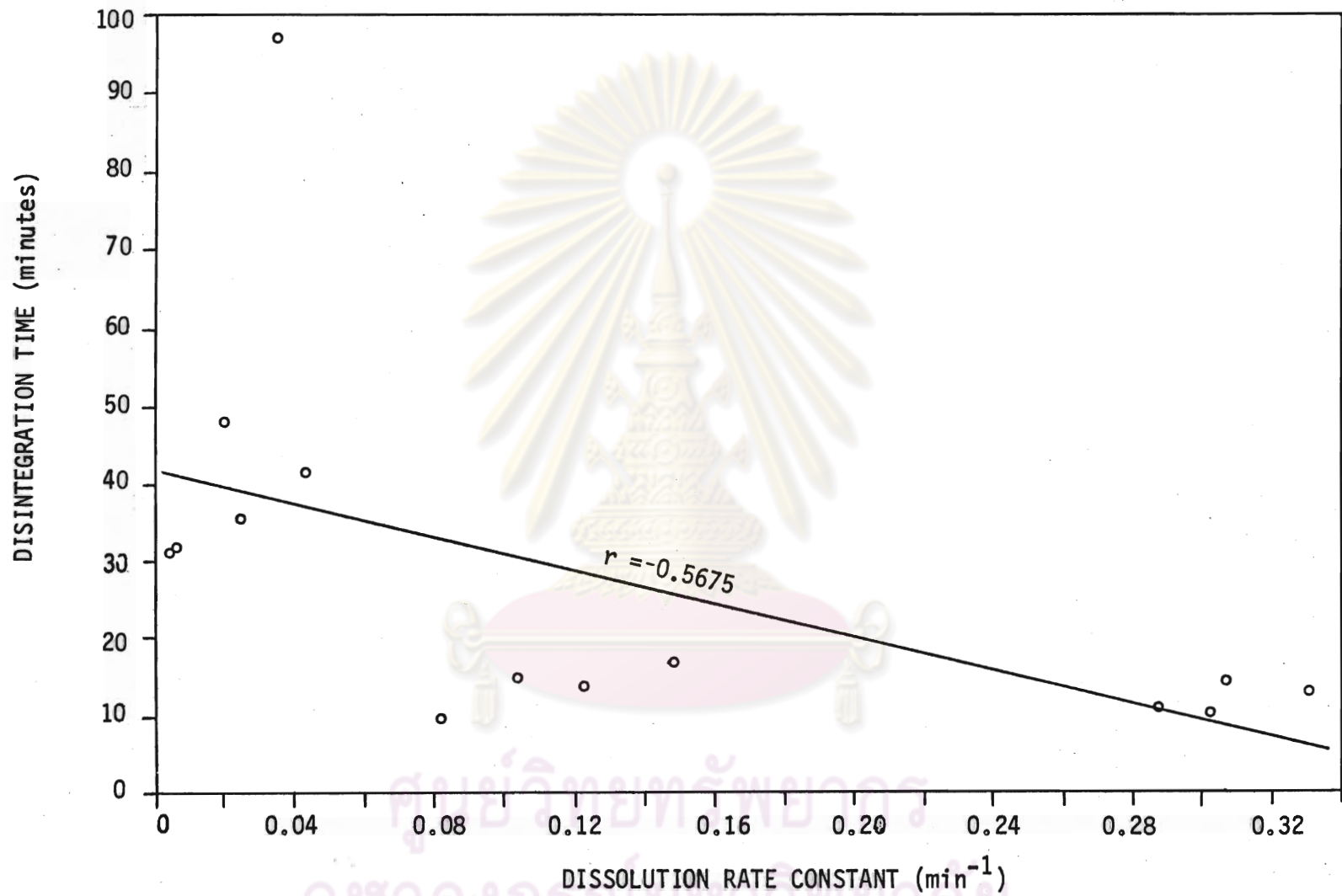
Figure 5   Correlation between disintegration time and dissolution rate constant of fourteen brands of ibuprofen tablets

Table 73   Correlation between Disintegration Time and the Mean
Residence Time after Oral Administration (MRT_{oral}) of
Ibuprofen Tablets.[a]

Brand	Disintegration time (min)	MRT_{oral} (hour)
A	14.42	3.71
C	12.97	4.11
K	97.00	17.78
N	31.17	5.50

Correlation coefficient   =   0.9945

t -value   =   13.4098

$t_{(0.05,2)}$ =   4.3027

a The result of four brands only was used , brand O was excluded
since its bioavailability was undetectable.
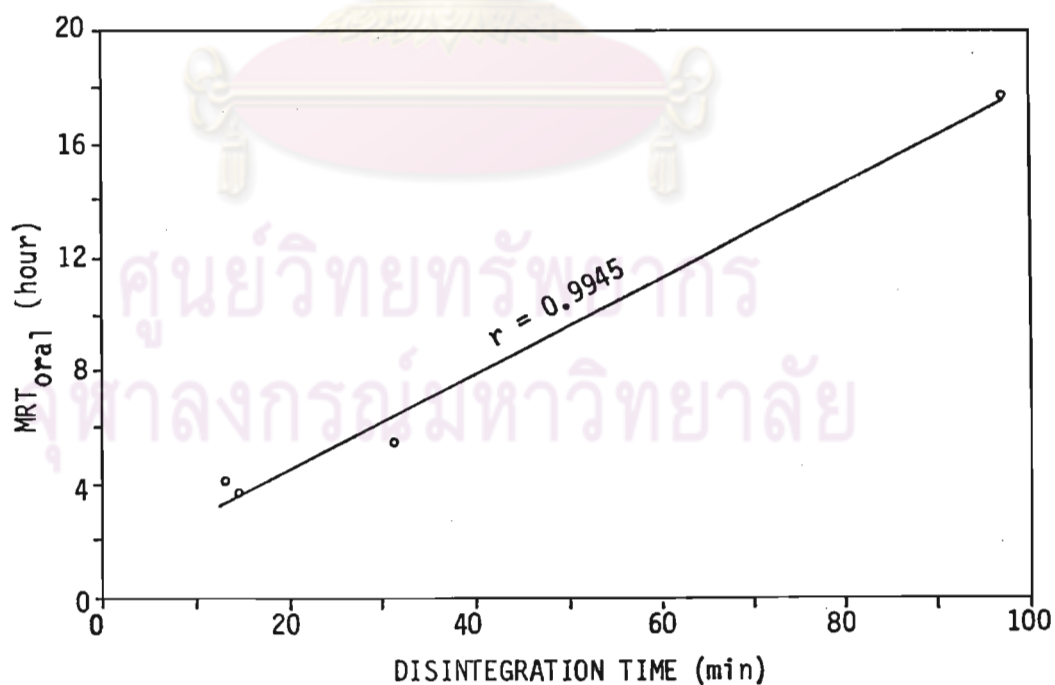
Figure 6   Correlation between disintegration Time and the mean
residence time , MRT_{oral}.

Table 74   Correlation between Disintegration Time and the Time to Peak
Plasma Level (T_{max}) of Ibuprofen Tablets.[a]

Brand	Disintegration time (min)	T_{max} (hour)
A	14.42	1.29
C	12.97	2.00
K	97.00	4.75
N	31.17	2.96

Correlation coefficient   =   0.9535

t -value   =   4.4725

$t_{0.05,2}$ =   4.3027

a The result of four brands only was used , brand O was excluded
since its bioavailability was undetectable.
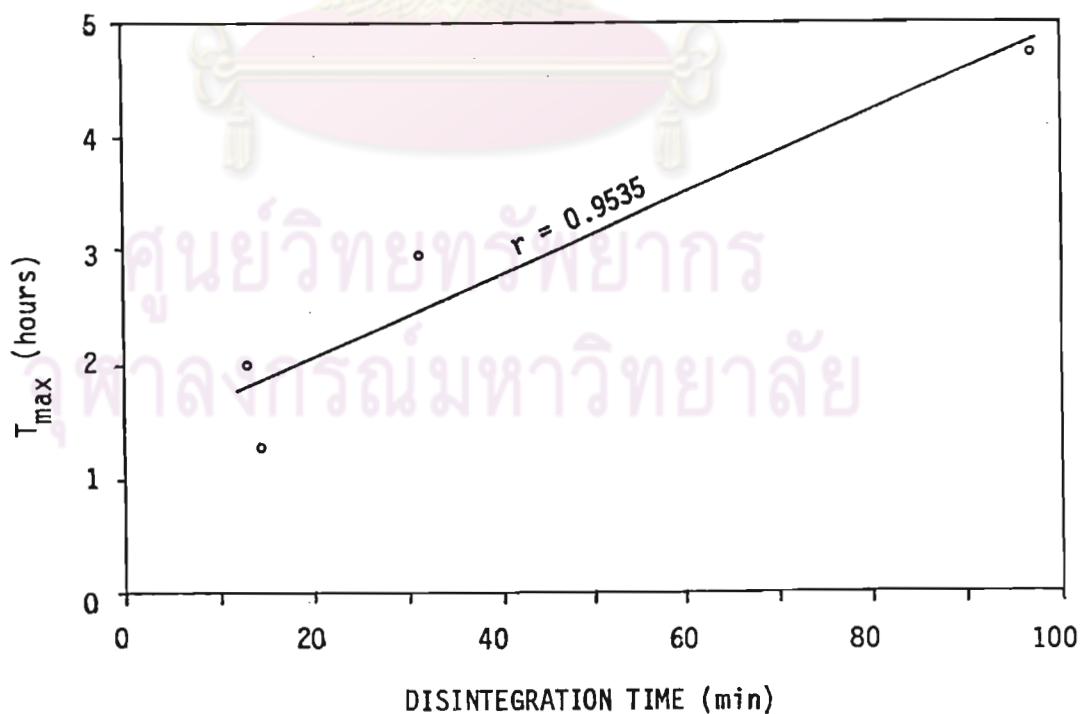
Figure 7 Correlation between disintegration time and time to peak
plasma level , T_{max}.

Table 75   Correlation between Disintegration Time and Absorption Rate
            Constant (K_a) of Ibuprofen Tablets[a]

Brand	Disintegration time (min)	K_a (hour^{-1})
A	14.42	2.380
C	12.97	1.290
K	97.00	0.459
N	31.17	0.807

Correlation coefficient =   -0.7167

t -value   =   1.4533

$t_{0.05,2}$ =   4.3027

a The result of four brands only was used , brand O was excluded
   since its bioavailability was undetectable.
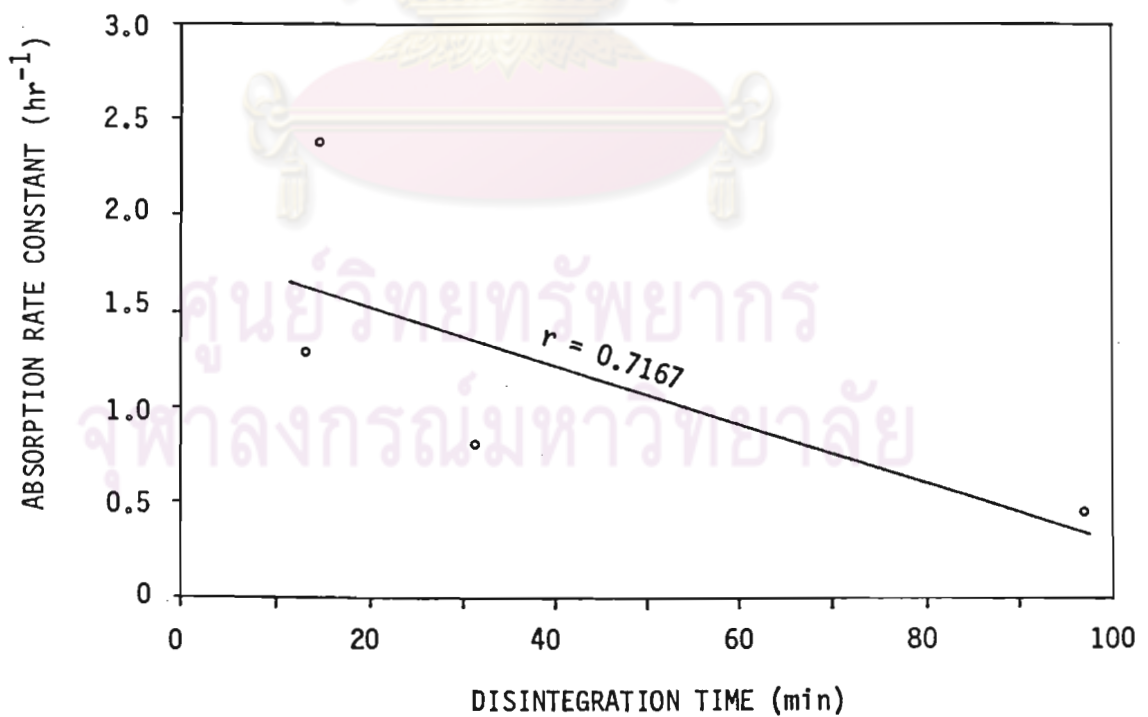
Figure 8   Correlation between disintegratime time and absorption rate
             constant , K_a.

Table 76   Correlation between Disintegration Time and Reciprocal of
            Absorption Rate Constant ($1/K_a$) of Ibuprofen Tablets[a]

Brand	Disintegration time (min)	$1/K_a$ (hour)
A	14.42	0.420
C	12.97	0.775
K	97.00	2.179
N	31.17	1.239

Correlation coefficient   =   0.9578

t -value   =   4.7131

$t_{0.05,2}$ =   4.3027

a   The result of four brands only was used , brand 0 was excluded
    since its bioavailability was undetectable.
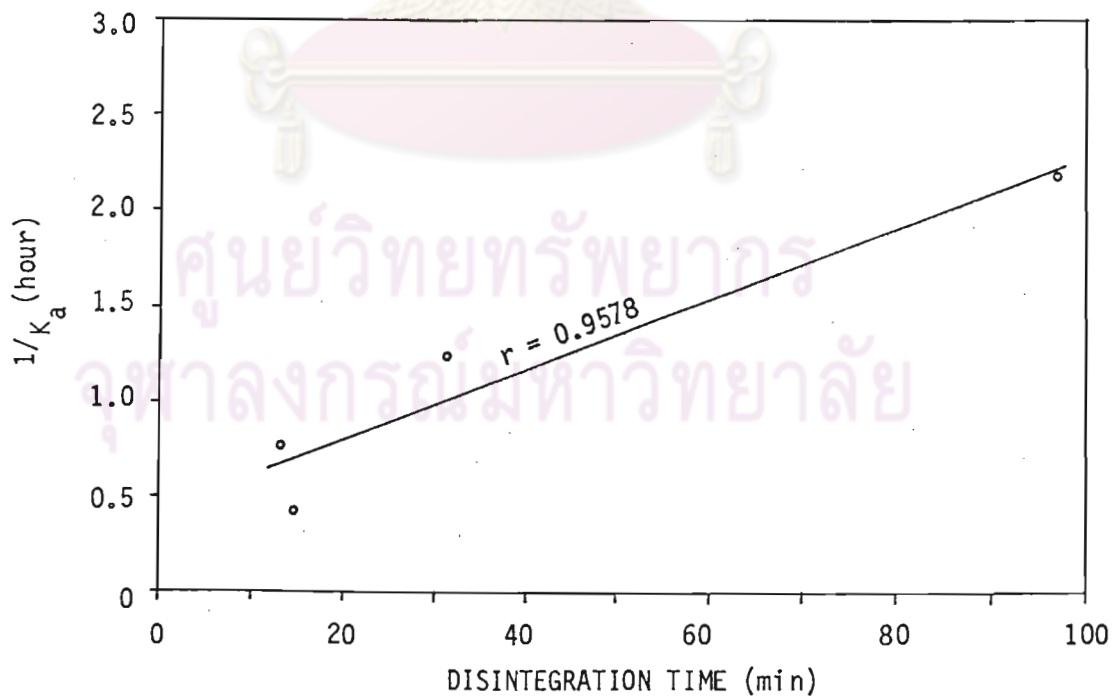
Figure 9   Correlation between disintegration time and reciprocal of
            absorption rate constant , $1/K_a$.

Table 77   Correlation between Dissolution Rate Constant and Mean

Residence Time (MRT_{oral}) of Ibuprofen Tablets[a]

Brand	Dissolution rate constant (min^{-1})	MRT_{oral} (hour)
A	0.3066	3.71
C	0.3310	4.11
K	0.0348	17.78
N	0.0045	5.50

Correlation coefficient   =   -0.6072

t -value   =   1.0808

$t_{0.05,2}$ =   4.3027

a The result of four brands only was used , brand O was excluded

since its bioavailability was undetectable.
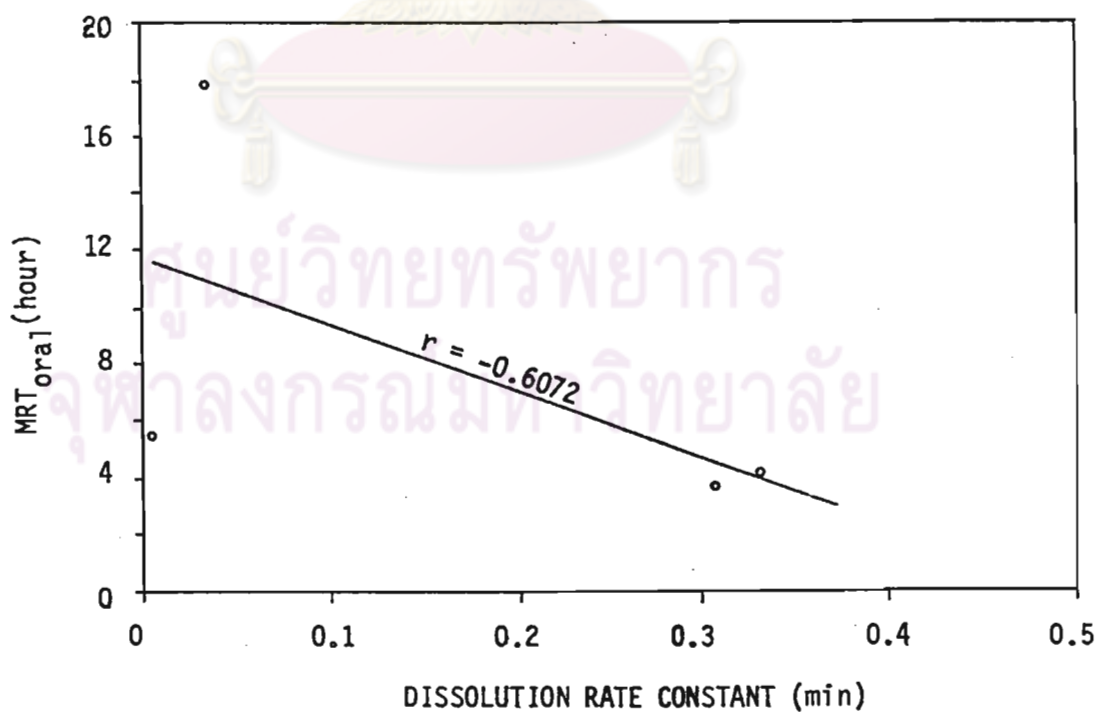
Figure 10 Correlation between dissolution rate constant and mean

residence time , MRT_{oral}.

Table 78   Correlation between Dissolution Rate Constant and Time to

Peak Plasma Level (T_{max}) of Ibuprofen Tablets[a]

Brand	Dissolution rate constant (min^{-1})	T_{max}(hour)
A	0.3066	1.29
C	0.3310	2.00
K	0.0348	4.75
N	0.0045	2.96

Correlation coefficient   =   -0.8016

t -value   =   1.8962

$t_{0.05,2}$ =   4.3027

a   The result of four brands only was used , brand O was excluded

since its bioavailability was undetectable.
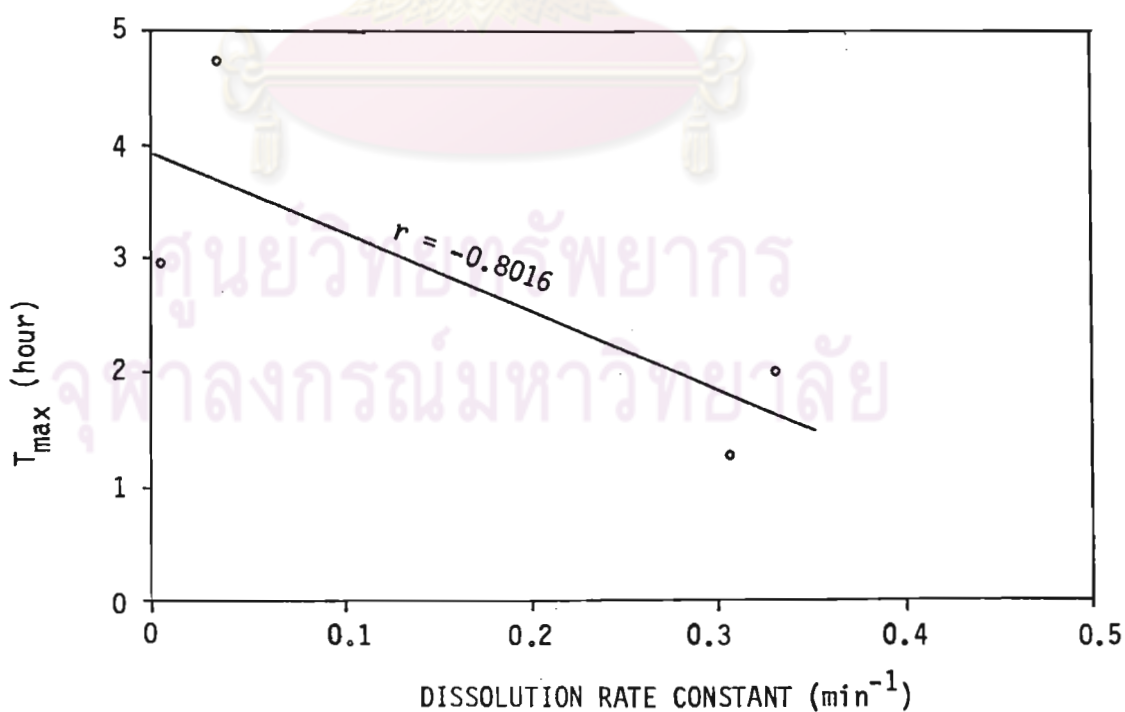
Figure   11   Correlation between dissolution rate constant and time to

peak plasma level , T_{max}.

Table 79   Correlation between Dissolution Rate Constant and Absorption

Rate Constant (K_a) of Ibuprofen Tablets.[a]

Brand	Dissolution rate constant (min^{-1})	K_a $(hour^{-1})$
A	0.3066	2.3796
C	0.3310	1.2901
K	0.0348	0.4590
N	0.0045	0.8069

Correlation coefficient   =   0.7835

t -value   =   1.7832

$t_{0.05,2}$ =   4.3027

a   The result of four brands only was used , brand O was excluded

since its bioavailability was undetectable.
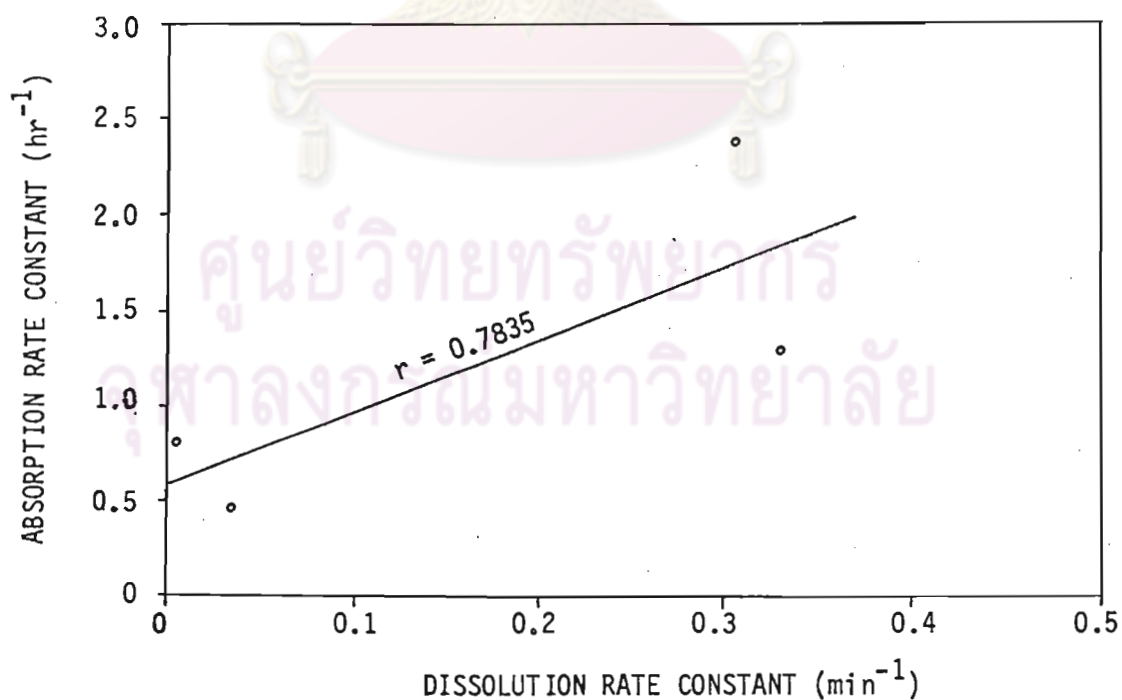
Figure 12 Correlation between dissolution rate constant and absorption

rate constant K_a.

Table 80 Correlation between Dissolution Rate Constant and Reciprocal

of Absorption Rate Constant ($1/K_a$) of Ibuprofen Tablets.[a]

Brand	Dissolution rate constant (min^{-1})	$1/K_a$ (hour)
A	0.3066	0.4202
C	0.3310	0.7751
K	0.0348	2.1786
N	0.0045	1.2393

Correlation coefficient = -0.7923

t -value = 1.8364

$t_{0.05,2}$ = 4.3027

a The result of four brands only was used , brand O was excluded

since its bioavailability was undetectable.
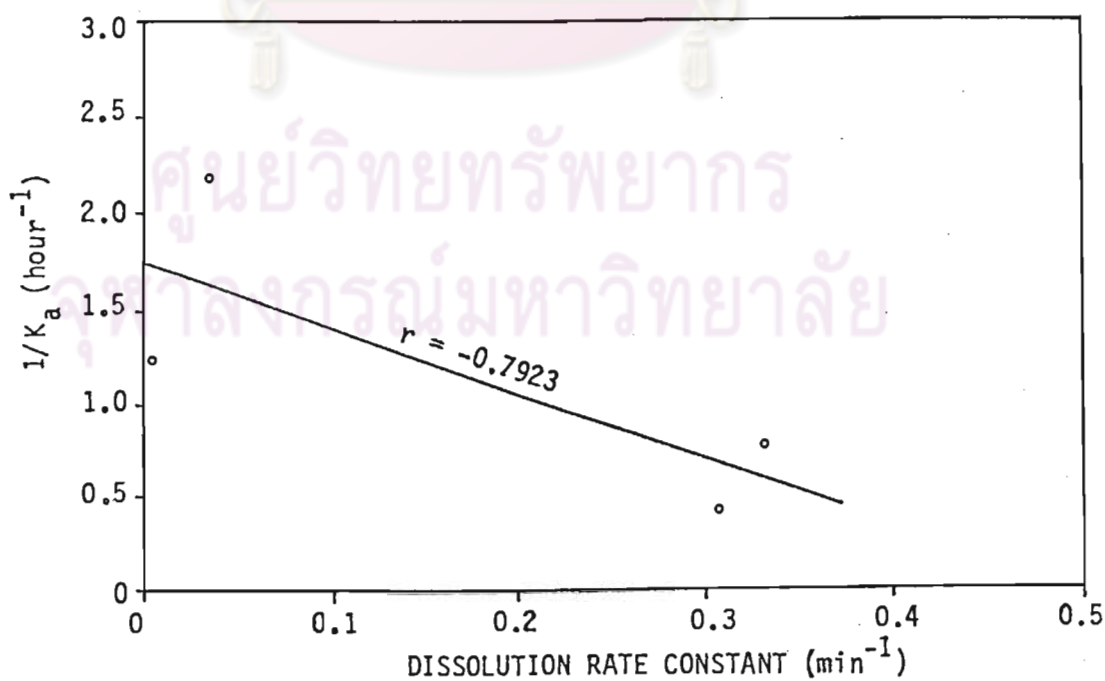
Figrue 13 Correlation between dissolution rate constant and

reciprocal of absorption rate constant , $1/K_a$

CHAPTER IV

DISCUSSION

In Vitro Studies

The active ingredient content of all fifteen commercial brands
of ibuprofen tablets as reported in Table 2 indicated that each brand
met existing standard in the United State Pharmacopoeia monograph.
These data supported the assumption that all various brands studied
were chemically equivalent.

Most of these ibuprofen tablets disintegrated completely within
one hour except for tablets of brand K and brand O , as seen in Table 3.
The long and widely varied disintegration time of brand K ranging from
77 to 145 minutes was not due to the inability of the tablet to
disintegrate but due to the inability of the aggregated granules to
pass through the sieve of the apparatus. This may caused by the type
and amount of the excipient , i.e. disintegrant , binder , and lubricant
used and/or manufaturing process. On the other hand , tablets of brand O
did not disintegrate evenafter they were placed in the medium for over
five hours because the coating of the tablet could not rupture in the
medium. This phenomenon might affect by the type and quantity of coating
material , and the coating process.

The rank order in terms of mean disintegration time was
brand L < B < D < C < F < A < G < E < N < M < I < J < H < K < O. Delay
of the sugar coated tablet to disintegrate may significantly impede the

process of drug dissolution. This is due to limited surface area to expose to dissolution medium.

Table 7 demonstrated that only 5 brands (brand A,B,C,D and E) met the United State Pharmacopoeia specification for drug dissolution while 7 brands (brand G,I,J,K,M,N, and O) failed to meet the specification and 3 brands (brand F,H,and L) required extra experiment before any conclusion could be made. In practice, the brand with wide variation in dissolution would not include in the bioavailability study.

Owing to difference in lag time of dissolution among brands of ibuprofen tablets as shown in Figure 2 , the dissolution rate constant was not calculated at the same time interval but it was calculated according to the appropriate time interval for each particular brand and the result was reported in Table 23. The reason that brand N and brand O showed poor dissolution data might be owing to the inability of the tablet to rupture or the insolubility of the coating material in dissolution medium , phosphate buffer pH 7.2. However , while performing disintegration test brand N was able to disintegrate in the simulated gastric fluid medium within 30 minutes.

The wide variation in dissolution rate among tablets of the same brand for ibuprofen tablet brand F,G,I,L, and M as indicated by the high coefficient of variation (C.V.) value shown in Table 23 was due in part to the composition and methods of manufacture as well as aging of the tablets while the slower release rate in phosphate buffer pH 7.2 for brand G,I,J,K,M,N as illustrated in Figure 2 was believed to cause by the poor solubility of sugar coating material in this medium.

For the same reason as mentioned in the disintegration test, since the coating of brand O could not rupture in the dissolution medium, its calculated dissolution rate was minimum. In fact , no ibuprofen could release from the tablet , as observed from the characteristics of the tablet at the end of eight hours of dissolution test. The tablet was looked exactly the same as that before testing. Tablets of brand M,N which was also classified as the brand with poor dissolution rate showed partially eroded on the surface of the tablets at the end of dissolution test.

In Vivo Studies

In accordance with the dissolution rate constant , fifteen commercial brands of ibuprofen tablets used in this study were divided into three groups. A representative from each group was chosen to assess bioavailability of these ibuprofen tablets.

. The mean plasma ibuprofen concentrations for each brand were illustrated in Figure 4. When brand O was administered to any subjects, and plasma samples were collected at various time intervals for ten hours neither one sample contains a detectable amount of ibuprofen ; therefore, the pharmacokinetic parameter of ibuprofen for this brand could not be calculated. Consequently , brand O were excluded from all statistical comparison.

In this study , both compartmental and noncompartmental methods were used to analyze each individual plasma data.

In compartmental method , the CSTRIP and the PCNONLIN programs were applied to estimate the pharmacokinetic parameters. From the

CSTRIP program , the plasma ibuprofen concentration versus time data
of most subjects were well described by a biexponential equation which
indicated that the pharmacokinetics of ibuprofen in Thai volunteers
could be explained in terms of a one compartment open model except for
the tenth subject which the percentage improvement in R squared cited
that a two compartment model might fit the data better than a one
compartment model. However , a one compartment model was also chosen
to describe the data of this subject in order to get the pharmacokinetic
parameters which could be compared with those obtained from other
subjects and the average value of these pharmacokinetic parameters could
be obtained. When the PCNONLIN program was applied, all plasma data were
assumed to follow the classical one compartment model with or without
a lag time.

The pharmacokinetic parameters obtained from this study were
described as follows :-

The mean AUC_0^∞ of each formulation obtained from both
noncompartmental and compartmental methods as shown in Table 31 and 53
did not differ significantly from each other indicating the equivalent
amount of ibuprofen absorption from each brand since the area under the
concentration time curve is related to the extent of drug absorbed
systemically. The reason that the mean AUC_0^∞ of brand K was higher
than the other brands while its bioavailability observed from the
graph (Figure 4) was less than the other brands might be due to an
error in the terminal slope determination resulted from the inadequate
number of data points in the elimination phase which could be observed
in several data sets ; the first, the second , the third , the sixth ,
the eleventh , and the twelfth subjects receiving brand K as illustrated

in Figure 17,18,19,22,27 and 28 (Appendix F). An erroneous terminal slope would in turn affect the calculation of the area under the curve extrapolated to infinited time ($AUC_{t_{last}}^{\infty}$) in noncompartmental analysis. The area under the curve from t_{last} to infinite time is equal the plasma ibuprofen concentration at last sampling time divided by the terminal slope. In compartmental analysis the terminal slope was also used as the initial parameter for the calculation of several other pharmacokinetic parameters. Consequently the parameter which would describe the pharmacokinetics of ibuprofen in Thai volunteers , i.e., the elimination rate constant and its half-life were averaged using the data obtained from three brands ; A , C and N only.

Previous reports (9,39) indicated that the mean peak plasma concentrations achieved following oral administration of 400 mg ibuprofen varied widely. Palva ,et al (9) reported a peak plasma ibuprofen level ranging from 34 to 39 μg/ml in volunteers. Gontarz, et al. (39) reported a peak plasma ibuprofen level ranging from 27.9 to 37.9 μg/ml. In the present study , the mean peak levels for each of the four brands of ibuprofen tablets obtained by reading directly from the individual peak level of 12 subjects was ranged from 16.8 to 42.2 μg/ml as presented in Table 37. The rank order for peak plasma ibuprofen was brand A , C > N > K (at $p < 0.05$). Since no significant difference was observed in the extent of absorption among four products studied (brand A , C , K and N) , the relatively lower peak concentrations resulting from formulation were an indicative of the slower rate of absorption and evidence of significant difference in the rate of ibuprofen absorption was found. The PCNONLIN program was also used to estimate Cp_{max} value of each individual data. However for the data

obtained from the first , the eighth , and the eleventh subjects receiving brand A , the Cp_{max} values estimated by the PCNONLIN program were much varied from the observed values. The observed value of the peak plasma concentration is thus concluded to be more reliable than the estimated value from PCNONLIN program.

The mean time to peak plasma ibuprofen level obtained from both noncompartmental and compartmental methods showed that the rank order for peak time was brand $A < C < N < K$. Both methods showed close similarity as recorded in Table 39 and 57 , i.e. 1.29 VS 1.21 , 2.00 VS 1.85 , 4.75 VS 4.71 , and 2.96 VS 2.70 hours for brand A , C , K and N respectively. This parameter was slightly different from those reported previously for ibuprofen by other investigation. Stead , et al (8) reported the time to peak plasma ibuprofen ranging from 2.07 to 2.48 hours. In report of Palva , et al (9) the time to peak plasma level was ranged from 1.81 to 2.84 hours.

The absorption rate constant obtained from compartmental analysis , both CSTRIP and PCNONLIN programs as seen in Table 45 , 55 showed the same conclusion as those obtained from the time to peak plasma level , i.e., the order ranking from the fastest to the slowest was brand $A > C > N > K$.

In contrast to the absorption rate, the value of the elimination rate constant showed close similarity among formulations which was as expected , except for brand K , as presented in Table 41,47 and 63. The mean values for brand A , brand C and brand N were 0.331 , 0.324, and 0.276 $hour^{-1}$ with noncompartmental method , were 0.322, 0.322 and 0.265 $hour^{-1}$ with CSTRIP program , and , were 0.446 , 0.497 and

0.369 hour^{-1} with PCNONLIN program respectively , these values were in good agreement with the mean values in volunteers found by other investigators. Stead et al (8) showed the value of ibuprofen elimination rate constant being 0.33 hour^{-1} and Lockwood , et al. (42) reported the elimination rate constant of ibuprofen ranging from 0.273 to 0.370 hour^{-1}. However, Wagner ,et al (41) found that the elimination rate constant of ibuprofen in their study was 0.579 hour^{-1}.

The plasma half-life of ibuprofen in Thai volunteers from this study as shown in Table 43, 49 and 65 for brand A , brand C and brand N was 2.17 , 2.19 and 2.65 hours with noncompartmental method, was 2.23, 2.20 and 2.89 hours with CSTRIP program , and , was 1.69, 1.47 and 1.97 hours with PCNONLIN program respectively. Similar results were found by other investigators , as example , Benvenuti , et al (12) reported plasma half-life of ibuprofen ranging from 1.81 to 2.99 hours, Greenblatt , et al.(40) reported this parameter being 2.2 hours and Collier, et al. (44) showed this parameter ranging from 1.43 to 2.52 hours. All of above mentioned was the plasma half-life in healthy volunteers, while Gallo , et al (37) reported the plasma half-life of ibuprofen in arthritis patients and its value was ranged from 1.66 to 2.02 hours.

The mean residence time represents the time for 63.2% of the administered dose to be eliminated irrespective of the distribution of drug (64). In this study , only the mean residence time after oral tablet administration (MRT_{oral}) could be calculated. This value was 3.71 , 4.11 , 5.50 and 17.79 hours for brand A , C , N and K respectively. The MRT_{oral} reported by Albert , et al (46) was 3.58 hours for elderly , and 3.84 hours for young volunteers. The mean

residence time after oral tablet administration is a mixed function of the mean residence time after intravenous administration (MRT_{iv}) , mean absorption time (MAT), mean dissolution time (MDT), and mean disintegration time. The difference in MRT_{oral} among four treatments might be due to any steps of the aforementioned parameters. However , the MRT_{iv} for any given drug should be constant.

The pharmacokinetic parameters obtained from this study were slightly different from those reported by other investigators. The factors possibly responsible to the differences were the formulation used, the subjects participated in the studies , the differences in their races, ages, weight and normal habits , the mathematics model applied and assumptions used to interpret the data.

In the present study, it was found that some data was not suitable to describe by compartmental method , for example, with the data obtained from the sixth subject receiving brand K and from the eleventh subjects receiving brand C , and K , the percent deviation of the estimiated concentration from the observed concentration of some data points in the absorption phase was higher than 100 percent. The outcome from the PCNONLIN program showed some erroneous calculation, for example , when the program was applied to estimate the pharmacokinetic parameter of ibuprofen from the eleventh subject receiving brand K , this program was unable to estimate several pharmacokinetic parameters such as AUC , T_{max}, Cp_{max} and K_{el} as seen in Table 53,57,59 and 63 respectively. With the data obtained from the sixth subject receiving brand K , the calculated AUC_0^∞ was 1022 $\mu g.hr.ml^{-1}$ which was unagreeable

when compared to the other values. In addition some parameters obtained from this program contained a minus value indicating that it was not an authentic value.

In Vitro - In Vivo Correlation

The relationship between disintegration time and dissolution rate constant as presented in Table 72 and Figure 5 indicated that the disintegration time might be the rate limiting step of ibuprofen tablets dissolution. Significant correlations were observed between disintegration time and in vivo parameters ; MRT , T_{max} , $1/_{K_a}$ with correlation coefficient of 0.9945 , 0.9535 and 0.9578 respectively. The disintegration time correlating to the reciprocal of absorption rate constant better than the absorption rate constant itself brought to a conclusion that the disintegration time did affect the rate of drug absorption but not in a linear relationship.

In contrast to the disintegration time, the dissolution rate constant was not related significantly to the in vivo pharmacokinetic parameter although there were some relationship between disintegration time and dissolution rate, and , between disintegration time and in vivo parameter. This might be due to the nonlinear correlation between dissolution rate constant and disintegration time as illustrated in Figure 5. In addition, the medium used in disintegration and dissolution tests was not the same , simulated gastric fluid and simulated intestinal fluid being used in the disintegration test while phosphate buffer pH 7.2 being used in the dissolution test.

These results indicated that the bioavailability of ibuprofen tablets was disintegration - controlled , i.e. once the tablet had disintegrated, the drug was then dissolved and absorbed into the general circulation.

This study seems contrary to the popular thinking that the dissolution of the drug which is slightly soluble in water would be a rate limiting step for in vivo bioavailability. However, bioavailability of ibuprofen tablet is quite different. All ibuprofen tablets studied were sugar coated tablets and it took time for the coating to rupture before the tablets were disintegrated and then dissolved in the medium. If the disintegration process , coating rupture and tablet disintegration, was the slowest process indicated that it was the rate limit step for in vivo bioavailability.

CHAPTER V

CONCLUSION

1. All fifteen commercial brands of 200 mg ibuprofen tablets
used in this study met the United State Pharmacopoeia XXI monograph
for percent labelled amount, i.e. the content of the active ingredient
was within 90 - 110%.

2. The disintegration times for each product were performed
in water for 5 minutes; simulated gastric fluid for 30 minutes, or
until tablets disintegrated completely; and simulated intestinal fluid
until the tablet disintegrated completely. The disintegration time for
these fifteen brands of ibuprofen tablets were ranging from 9.7 minutes
to more than five hours. The rank order in terms of mean disintegration
time was brand L< B < D < C < F < A < G < E < N < M < I < J < H < K < O.
The first thirteen brands were able to disintegrate within one hour.
Tablets of brand K varied widely in their disintegration time ranging
from 77 to 145 minutes while brand O could not disintegrate evenafter
they were placed in the medium for over five hours.

3. Dissolution profiles were determined for each product in
phosphate buffer pH 7.2. Studies were performed using the U.S.P.
Dissolution Apparatus Type I maintained at 150 rpm and a temperature
of 37 ± 0.5°C. Major differences were observed for the rate and
extent of dissolution among brands. Brand A,B,C,D and E met the United
State Pharmacopeia XXI for drug dissolution while brand G,I,J,K,M,N,and
O failed to meet the specifications and brand F,H,and L required extra

experiment before any conclusion could be made. The rank order in terms of the dissolution rate constant was brand $C > A > B > D > E > F > G > L > J > K > I > H > M > N > O$.

4. There was significant correlation between disintegration times and dissolution rate constants indicating that the disintegration time of tablets might be a rate-limiting step of the dissolution rate of ibuprofen tablets.

5. The comparative bioavailability of five brands (A,C,K,N and O) of ibuprofen tablets, with differences in their in vitro characteristics, was studied in normal subjects. Single dose of two 200 mg ibuprofen tablets was administered to 12 subjects. The plasma ibuprofen concentrations were determined by a high performance liquid chromatographic method. Individual plasma profile was analyzed according to compartmental and noncompartmental methods. Statistically significant differences ($p < 0.05$) were observed regarding to specific parameters among drug product formulations.

6. The pharmacokinetics of ibuprofen tablets after oral administration of two 200 mg tablet to Thai healthy volunteers showed that the mean individual peak plasma concentration reading directly from each data ranged from 16.80 to 42.20 μg/ml and statistical result revealed that the rank order was brand $A,C > N > K$ (at $p < 0.05$) while those obtained from the PCNONLIN program was ranged from 16.05 to 40.02 μg/ml and the rank order was brand $A > C > N > K$ (at $p < 0.05$)

The mean time required to reach the peak level reading directly from each data was ranged from 1.29 to 4.75 hours while those obtained

from the PCNONLIN program was ranged from 1.21 to 4.79 hours and the rank order from both methods was brand $A < C < N < K$ (at $p < 0.05$).

The absorption rate constants for brand A,C,N,and K obtained from the CSTRIP program were 2.380 , 1.290 , 0.807 , 0.459 $hour^{-1}$, while those obtained from PCNONLIN program were 2.246 , 1.449 , 1.200 ,0.516 $hour^{-1}$ respectively. These results showed the same conclusion as the time to peak plasma level in terms of the rate of absorption, i.e. the rank order of the absorption rate constant was brand $A > C > N > K$ (at $p < 0.05$).

The biological half-life of ibuprofen excluded brand K was 2.34 (2.17 - 2.65) hours with noncompartmental method , while those obtained from compartmental method, CSTRIP program, was 2.44 (2.33 - 2.89) hours and from PCNONLIN program was 1.71(1.69 - 1.97) hours. These results are in good agreement with those previously published data.

7. Correlation of the in vitro and in vivo data for the four different brands of ibuprofen tablet were made. Results showed that the disintegration time was significantly related to the rate of ibuprofen absorption while the dissolution rate constant was not. Therefore the disintegration time might be used to predict the absorption rate of ibuprofen tablets.

8. The bioavailability of brand O was undetectable. The AUC_0^{∞} of other brands studied (brand A,C,K and N) was ranged from 145.82 to 230.80 $\mu g.hr.ml^{-1}$ with noncompartmental method and those obtained from compartmental method was ranged from 139.65 to 160.00 $\mu g.hr.ml^{-1}$.

Statistical result indicated that these four brands were equivalent with respect to the amount of drug absorped from the dosage form. However, they differed markedly in terms of absorption rate , as indicated by T_{max} and absorption rate constant, i.e. the absorption rate of brand A >C > N > K. Since bioequivalence has been defined as equivalence in both extent and rate of drug absorption , it was thus concluded that brand C,K and N were bioinequivalent to the innovater's product due to their slower absorption rates.

Eventhough conclusion from this study could not be used as an absolute indication of clinical inequivalence among brands of ibuprofen tablets, slower absorption rate usually results in slower onset of the drug, it would thus be hypothesized that difference in clinical efficacy might be observed when different brand of ibuprofen tablet is administered as single dose for the relief of mild to moderate pain.

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APPENDICES

APPENDIX A

TEST PRODUCTS

Brand name	Manufacturers	Mfg.date	Batch no.
Amxen	Amourkierti Trading L.P.	13- 8-1986	8608113
Borafen	Sriprasit Pharma Co.,Ltd.	10- 3-1986	T86061
Brufen*	The Boots Company PLC, England	-3-1987	74L
Buprofen	Nida Pharma Inc. Ltd.	-2-1987	874013
Busofen	Chemephand Medical	20-10-1986	67AU
Busofen	H.K. Pharmaceutical	11- 9-1986	6546
Cox-Fen	Cox Laboratories (Thailand) L.P.	9- 3-1987	259/0019
Hafen	Utopian Co., Ltd.	18- 3-1987	346057
Ibufen	Siam Bheasach Co.,Ltd.	11- 9-1986	21P120
Iburen 200	B.L. Hua & Co., Ltd.	16-10-1986	25-002
Profen	Pond's Chemical (Thailand)	7- 8-1985	808-320
Profensic	A.N.H. Products Ltd., Part	12-11-1985	851104
Rheumanox	Charoen Bhaesaj Lab Co.,Ltd.	31-10-1985	851001
Rumatifen	Chew Brothers & Co.,Ltd. Partnership	6-10-1986	T610301
Setora	Putchuban Dispensary Co.,Ltd.	26- 9-1986	005

*   Repacked by Boots Co., (Thailand) Ltd.

APPENDIX B

PREPARATION OF MEDIUM

Phosphate Buffer pH 7.2 (59,60)

6.805 gm. of monobasic potassium phosphate was dissolved in
250 ml of water and 173.5 ml of 0.2 M sodium hydroxide was added.
Then sufficient water was added to make 1000 ml. This resulting
solution was adjusted with 0.2 M hydrochloric acid or 0.2 M sodium
hydroxide to a pH of 7.2 ± 0.05.

Simulated Gastric Fluid TS (61)

2.0 gm of sodium chloride and 3.2 gm of pepsin were dissolved
in 7.0 ml of hydrochloric acid. Sufficient water was added to make
1000 ml. This test solution had a pH of about 1.2.

Simulated Intestinal Fluid TS (61)

6.8 gm of monobasic potassium phosphate was dissolved in
250 ml of water , then mixed. 190 ml of 0.2 N sodium hydroxide and
400 ml of water were added. 10.0 gm of pancreatin was later added and
mixed. The resulting solution was adjusted with 0.2 N sodium hydroxide
to a pH of 7.5 ± 0.1 , and diluted with water to 1000 ml.

APPENDIX C

SUBJECTS

Table 81 Physiological Characteristics of the Subjects

Subject No.	Age (yr)	Height (cm)	Weight (kg)	Surface area[a] (m^2)
1	22	164.0	48	1.49
2	21	176.0	58	1.71
3	22	176.0	73	1.88
4	21	167.5	60	1.67
5	21	172.5	70	1.82
6	22	178.0	60	1.75
7	26	166.0	61	1.67
8	27	176.0	49	1.59
9	24	164.5	53	1.56
10	22	174.0	62	1.74
11	22	174.0	72	1.85
12	22	170.0	59	1.68
RANGE	21 - 27	164 - 178	48 - 73	1.49 - 1.88
MEAN	22.67	171.54	60.42	1.70
SD	1.97	4.96	8.17	0.12

a Nomogram for calculating the body surface area of adults (62)

Table 82   Biochemical Laboratory Results

Test	Normal value	Subject											
		1	2	3	4	5	6	7	8	9	10	11	12
Glucose	65 - 100 mg/dl	97	101	93	80	82	94	89	77	100	82	84	148
Creatinine	0.5 - 2.0 mg/dl	0.6	0.9	0.7	0.8	0.9	0.8	0.9	0.7	1.0	0.9	0.7	0.9
Uric acid	3.5 - 8.0 mg/dl	6.1	5.9	7.6	6.8	6.1	8.0	5.9	4.5	7.4	5.9	8.5	6.5
Total bilirubin	0.3 - 1.2 mg/dl	1.1	1.0	0.3	2.0	0.3	1.4	0.8	0.8	1.0	0.6	0.8	0.3
Direct bilirubin	0 - 0.4 mg/dl	0.2	0.2	0.15	0.15	0.15	0.2	0.2	0.05	0.05	0.05	0.15	0.05
Alk. phosphatase	9 - 35 U/L	26.5	22.5	20.5	11.5	21.5	22.5	14.5	16.5	15.5	18.5	29.5	34
SGOT	up to 38 U/L	17	23	17	14	16	18	15	48	30	28	35	19
SGPT	up to 38 U/L	13	9	10	7	10	9	5	48	11	16	44	15
Total cholesterol	150 - 250 mg/dl	196	163	188	185	160	146	201	217	177	165	214	175
Triglycerides	40 - 155 mg/dl	124	80	83	42	107	72	258	81	52	91	164	69
Total protein	5 - 8 gm%	7.3	7.65	7.3	6.85	7.1	6.7	6.85	6.85	6.85	7.1	7.1	6.2

Table 83   Hematological Laboratory Results

Test	Normal value	Subject											
		1	2	3	4	5	6	7	8	9	10	11	12
Hemoglobin	14 - 18 gm%	15.4	15.8	16.6	15.2	13.7	17.3	14.8	14.8	15.9	16.0	16.6	16
Hematocrit	40 - 54 gm%	43	44	45	43	39	49	45	44	44	43	46	41
W.B.C.	4500-11000 cell/mm^3	5700	9000	6900	6500	5700	6800	10700	6000	4700	8900	6900	5000
Neutrophils	40 - 60 %	60	38	70	61	46	64	64	48	50	60	65	67
Eosinophils	1 - 3 %	2	-	-	-	6	1	13	7	2	2	-	1
Basophils	0-1 %								1	-	-	-	-
Lymphocytes	20 - 40 %	38	62	30	39	48	35	23	39	48	38	35	32
Monocytes	4-8 %	-	-	-	-	-	-	-	5	-	-	-	-

Table 84   Urinalysis Results

Test		Subject											
		1	2	3	4	5	6	7	8	9	10	11	12
Microscopic	R.B.C.	0	0	0	0	0	0	0-1	0	2	0	0	0
	W.B.C.	0	0	2-3	0	1-2	0-1	1-3	0-1	1-2	0	0	0
	Epithelium	1-2	1-2	0-1	0	2-3	0	1-2	1-2	1-2	1-2	0	1-2
	Casts	-	-	-	-	-	-	-	-	-	-	-	-
	Crystals	-	-	Amorphous 1+	-	-	-	-	-	-	-	Amorphous 2+	-
	Organisms	bact 1+	-	-	bact 1+	-	bact 1+	-	-	-	bact 1+	-	-
	Others	-	-	mucous 1+	mucous 1+	-	-	-	-	mucous 1+	mucous 1+	-	-
Chemistry	Albumin	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	+ve	-ve	-ve	-ve
	Sugar	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	Occult blood	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve

Note : -ve = negative , +ve = positive

APPENDIX   D

STANDARD CURVE DETERMINATION

The typical standard curve and data for ibuprofen concentration
in phosphate buffer pH 7.2 and human plasma are presented in Table 85 ,
Figure 86   and   Table 84,Figure 15 , respectively. The correlation
coefficients of the fit to the straight line were highly significant
(r^2 = .999 and .998 respectively).

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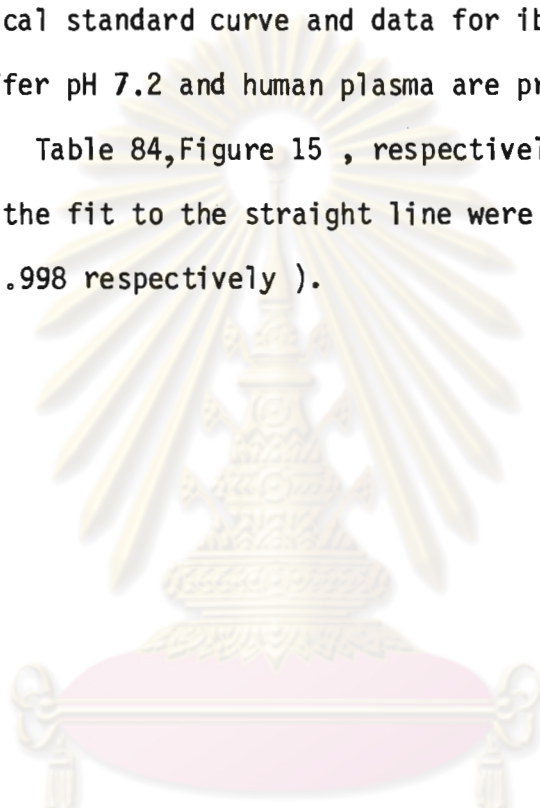
Table 85   Typical Standard Curve Data for Ibuprofen Concentration in Phosphate Buffer
pH 7.2 Estimated using Linear Regression [1]

Standard No.	Concentration (μg/ml)	Absorbance[a] at 222 nm	Inversely estimated[2] concentration(μg/ml)	% Theory[3]
1	3.0	0.138	3.051	101.70
2	4.5	0.201	4.497	99.94
3	6.0	0.269	6.058	100.97
4	7.5	0.328	7.413	98.83
5	9.0	0.395	8.951	99.45
6	10.5	0.461	10.466	99.67
7	12.0	0.527	11.981	99.84
8	13.5	0.592	13.473	99.80
9	15.0	0.664	15.126	100.84
10	16.5	0.725	16.526	100.16
11	18.0	0.788	17.972	99.85
12	19.5	0.854	19.487	99.94
			MEAN	100.08
			SD	0.76
			C.V.[4]	0.76%

1. r^2 = 0.999 , A = 0.00510 , B = 0.04356 (y = A + Bx)
2. Inversely estimated concentration = (Absorbance - 0.0051) / 0.04356
3. % Theory = $\dfrac{\text{Inversely estimated concentration}}{\text{Known concentration}}$ x 100
4. Coefficient of variation = $\dfrac{SD}{MEAN}$ x 100
a. Each value represents the average of triplicate samples.
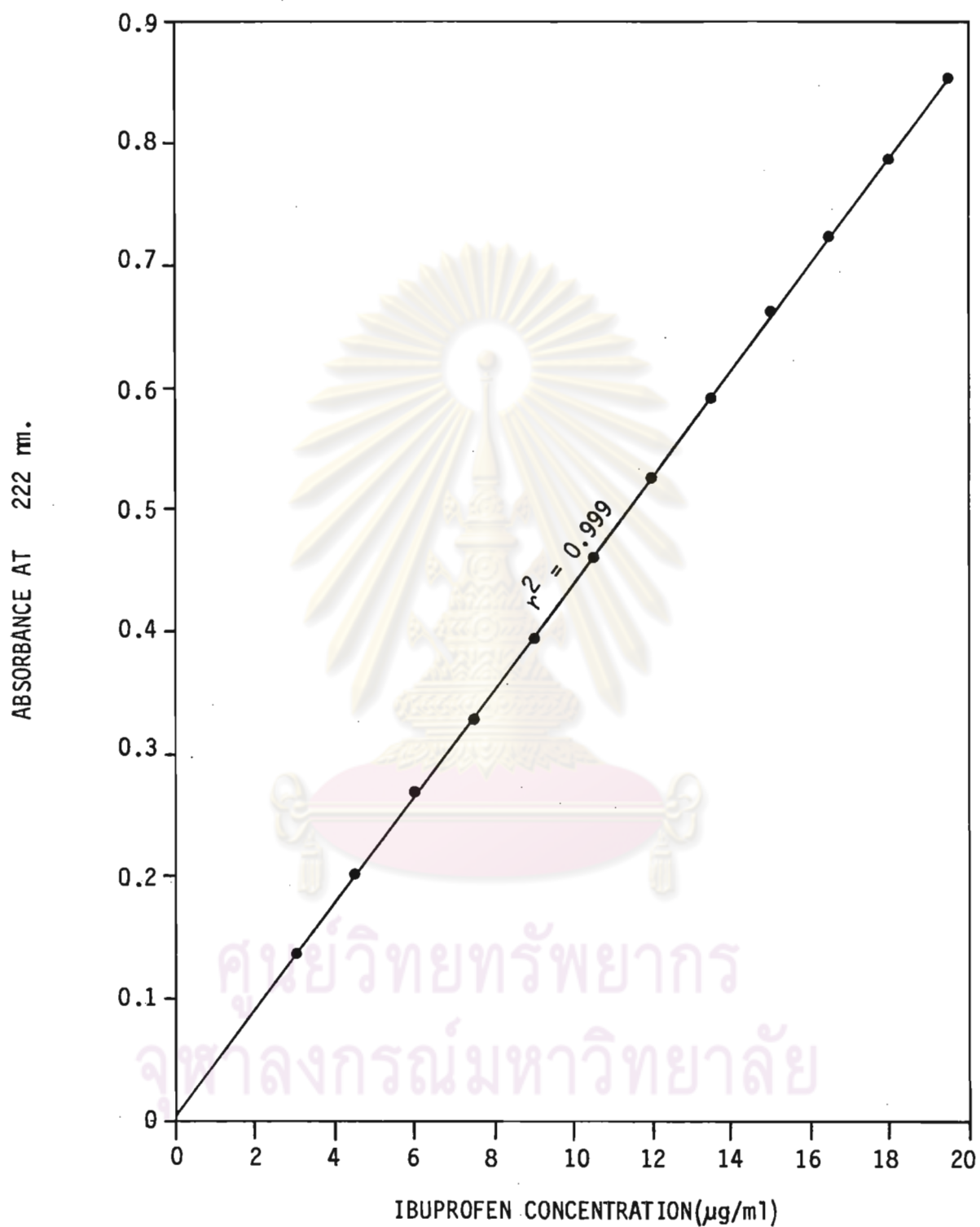
Figure 14 Typical standard curve for ibuprofen concentration in phosphate buffer pH 7.2

Table 86 Typical Standard Curve Data for Ibuprofen Concentrations in Human Plasma Estimated using Linear Regression[1]

Standard No.	Concentration (μg/ml)	Area Ratio IBU[*]/IS[**]	Inversely estimated[2] concentration(μg/ml)	% Theory
1	5	0.254	4.99	99.89
2	10	0.553	10.90	109.01
3	15	0.786	15.49	103.27
4	20	1.042	20.53	102.66
5	25	1.263	24.89	99.55
6	30	1.484	29.24	97.48
7	35	1.761	34.69	99.12
8	40	1.990	39.21	98.02
9	45	2.196	43.26	96.12
10	50	2.581	50.86	101.71
11	55	2.850	56.41	102.07
12	60	3.057	60.23	100.39
			MEAN	100.78
			SD	3.38
			C.V.	3.35%

1. r^2 = 0.998 , A = 0 , B = 0.05076 (y = A + Bx)

2. Inversely estimated concentration = Area Ratio / 0.05076

   * Ibuprofen

   ** Internal Standard
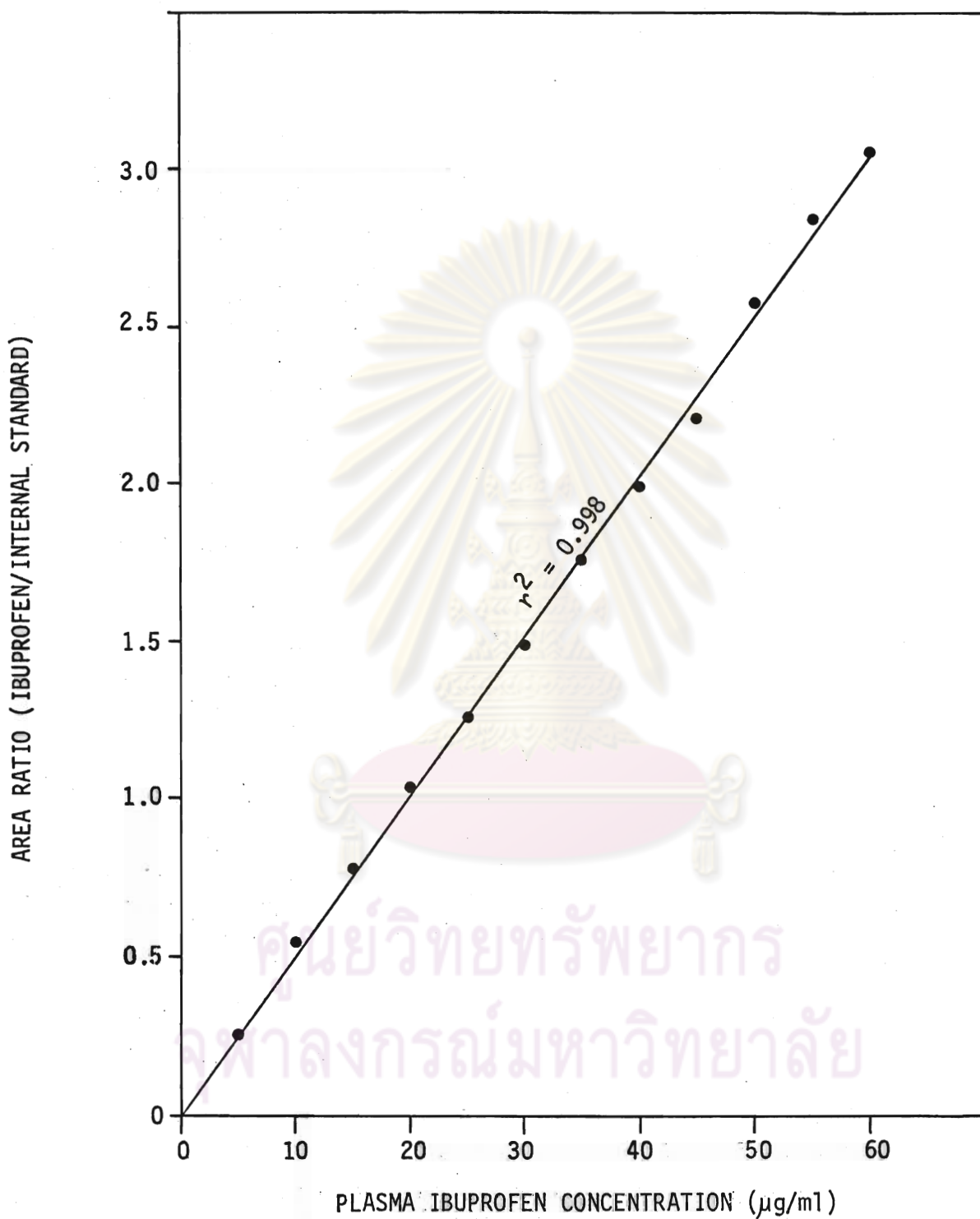
Figure 15 Typical standard curve for ibuprofen concentration in human plasma.

APPENDIX E

DETERMINATION OF DISSOLUTION RATE CONSTANT

In calculation of dissolution rate constant , it is assumed that the dissolution process is the first order process (63), then

$$\ln (B_{\infty} - B_t) = \ln B_{\infty} - kt \qquad (1)$$

where B_t = the amount of drug dissolved at time t.

B_{∞} = the maximum amount of drug dissolved from the tablet.

A plot of the natural logarithm of the variable Y where Y is (B_{∞} - B_t) versus time , as shown in Figure 16 , should be linear with the slope K. The rate constant may be calculated using linear regression.

The dissolution rate constants as presented in Table 23 were calculated using the maximum amount of ibuprofen dissolved from each tablet as B_{∞} . Since ibuprofen sugar coated tablets have different lag time for dissolution , an appropriate time interval for each brand was determined to calculate the rate constant.

As seen in Figure 16.the lag time for dissolution was approximately 5 minutes , the dissolution rate constant was therefore calculated from the time range 5 - 15 minutes and the slope obtained from linear regression was 0.342 with r^2 (0.9778).

Table 87   Example for Dissolution Rate Constant Calculation using
the data of the fourth tablet of brand A.

Time (min)	B_t (Percent dissolved)	$B_\infty - B_t$	$\ln (B_\infty - B_t)$
0.0	0.00	93.03	4.533
2.5	0.00	93.03	4.533
5.0	13.36	76.67	4.340
7.5	65.43	27.60	3.318
10.0	82.75	10.28	2.330
12.5	89.77	3.26	1.212
15.0	89.97	3.06	1.118
20.0	93.03*	0.00	
25.0	91.93		
30.0	91.06		

* B_∞ =   93.03 %
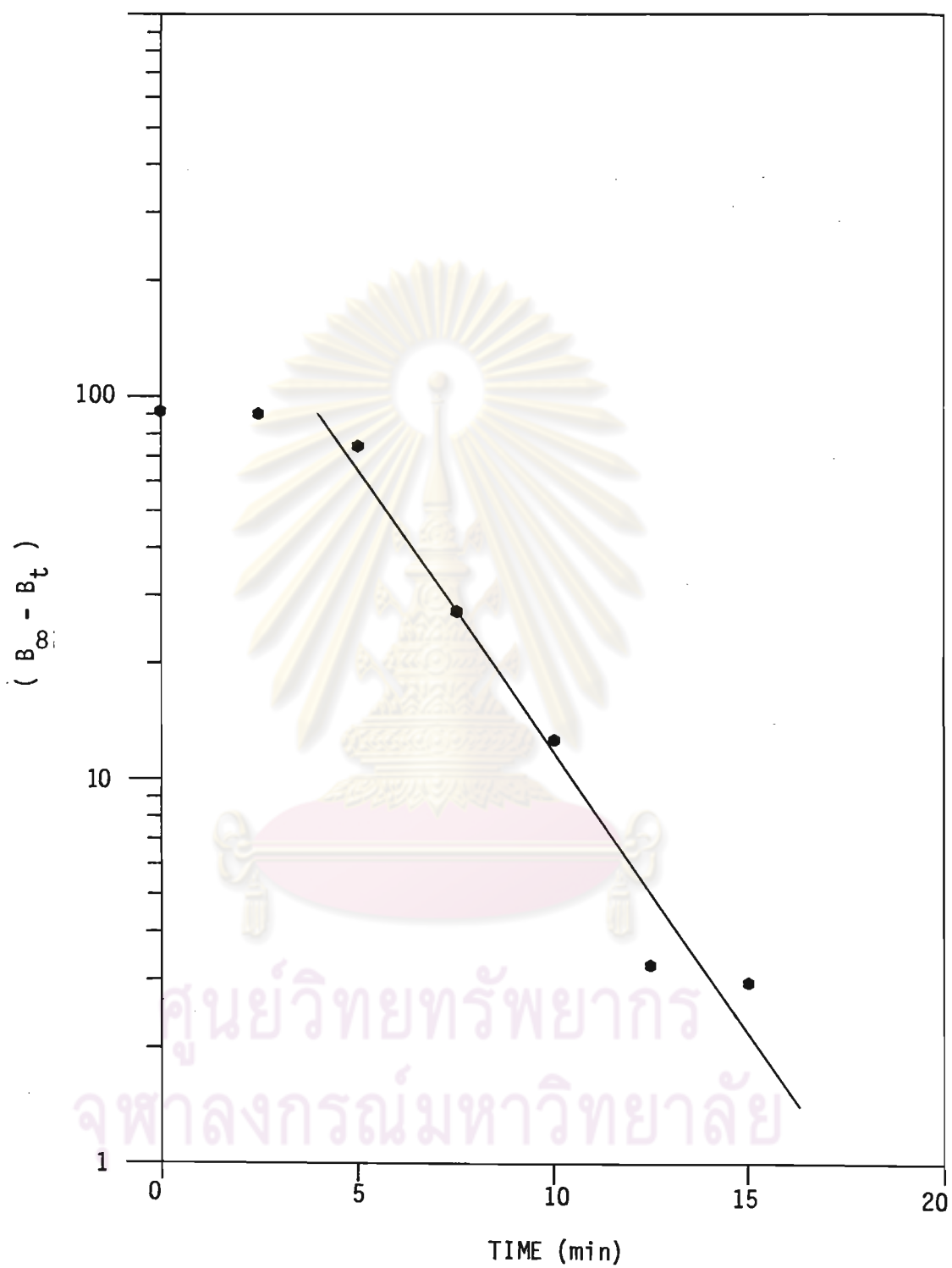
Figure 16   First order plot for dissolution of ibuprofen using the
data of the fourth tablet of brand A.

APPENDIX F

ADDITIONAL EXPERIMENTAL DATA

Comparisons of plasma ibuprofen concentration – time profiles among five different brands of each subject following oral administration of two 200 mg ibuprofen tablet were illustrated in Figure 17-28 respectively.

Figure 17 Plasma ibuprofen concentration -time profiles of the first subject following oral
administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

Figure 18 Plasma ibuprofen comcentration -time profiles of the second subject following oral
administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

Figure 19 Plasma ibuprofen concentration -time profiles of the third subject following oral administration of two 200 mg ibuprofen tablets of five different brands

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

Figure 20 Plasma ibuprofen concentration -time profiles of the fourth subject following oral administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

Figure 21 Plasma ibuprofen concentration -time profiles of the fifth subject following oral
administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

Figure 22 Plasma ibuprofen concentration -time profiles of the sixth subject following oral administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
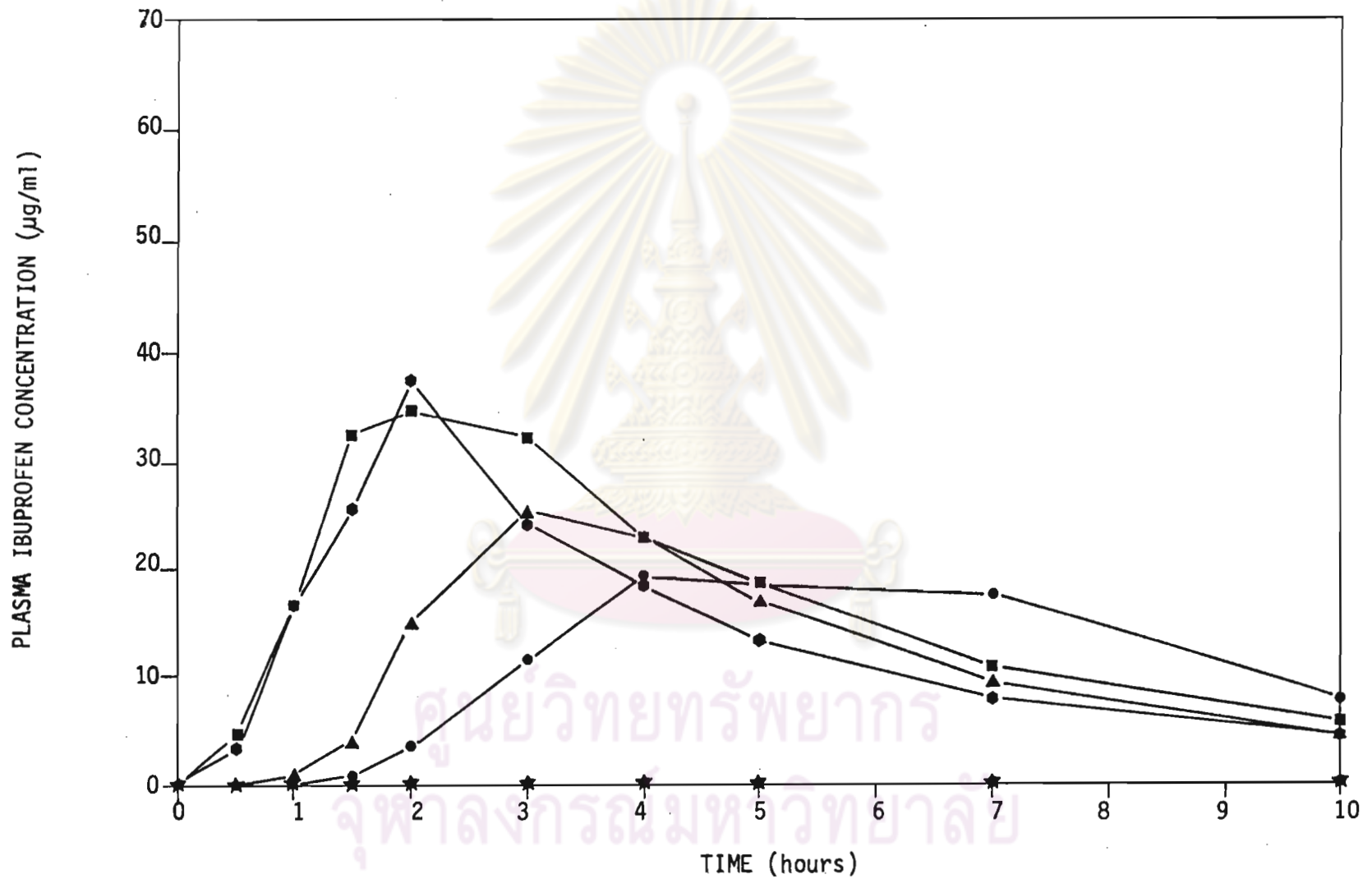
Figure 23 Plasma ibuprofen concentration -time profiles of the seventh subject following oral
administration of two 200 mg ibuprofen tablets of five different brands

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
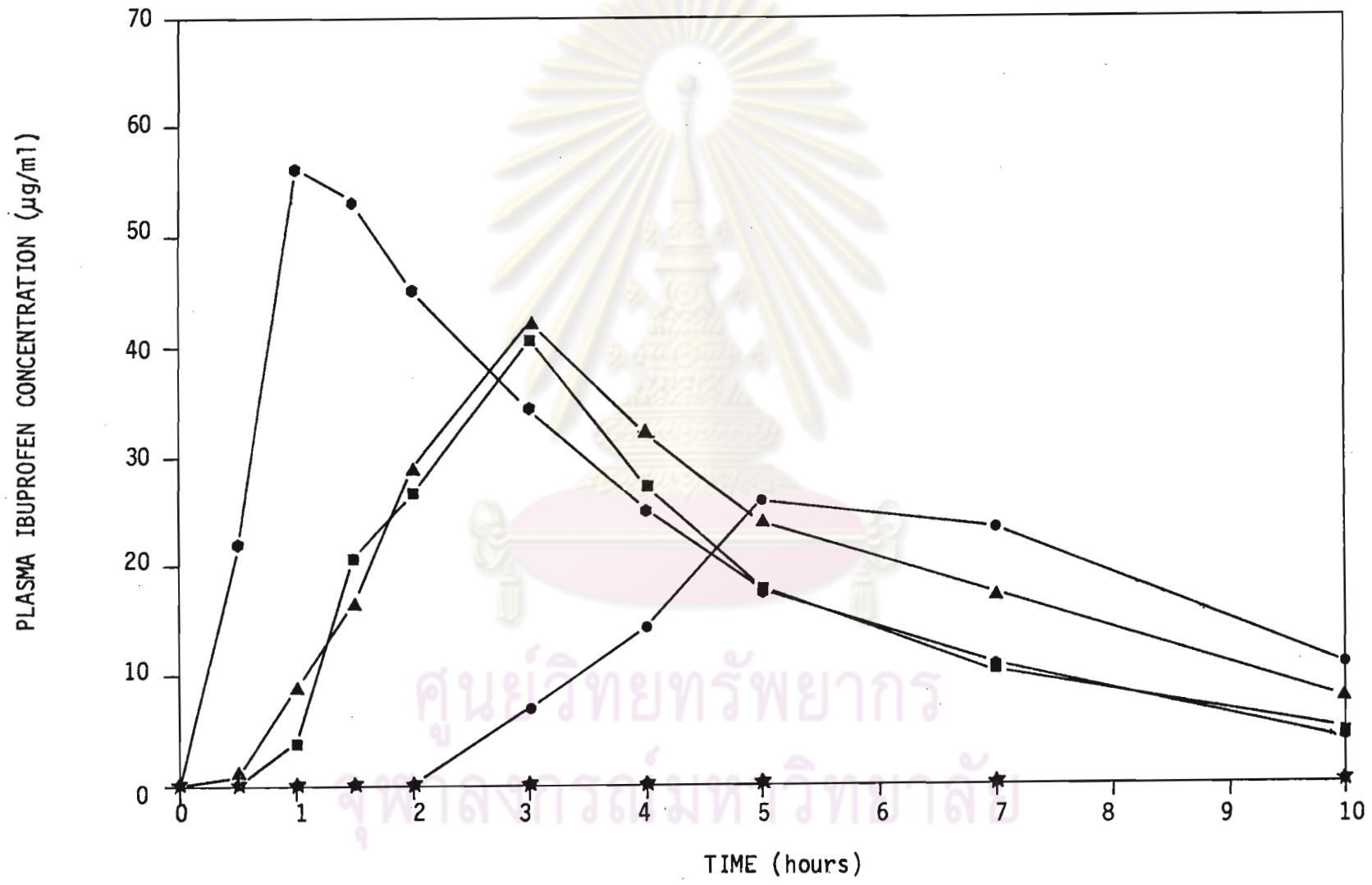
Figure 24 Plasma ibuprofen concentration -time profiles of the eighth subject following oral administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
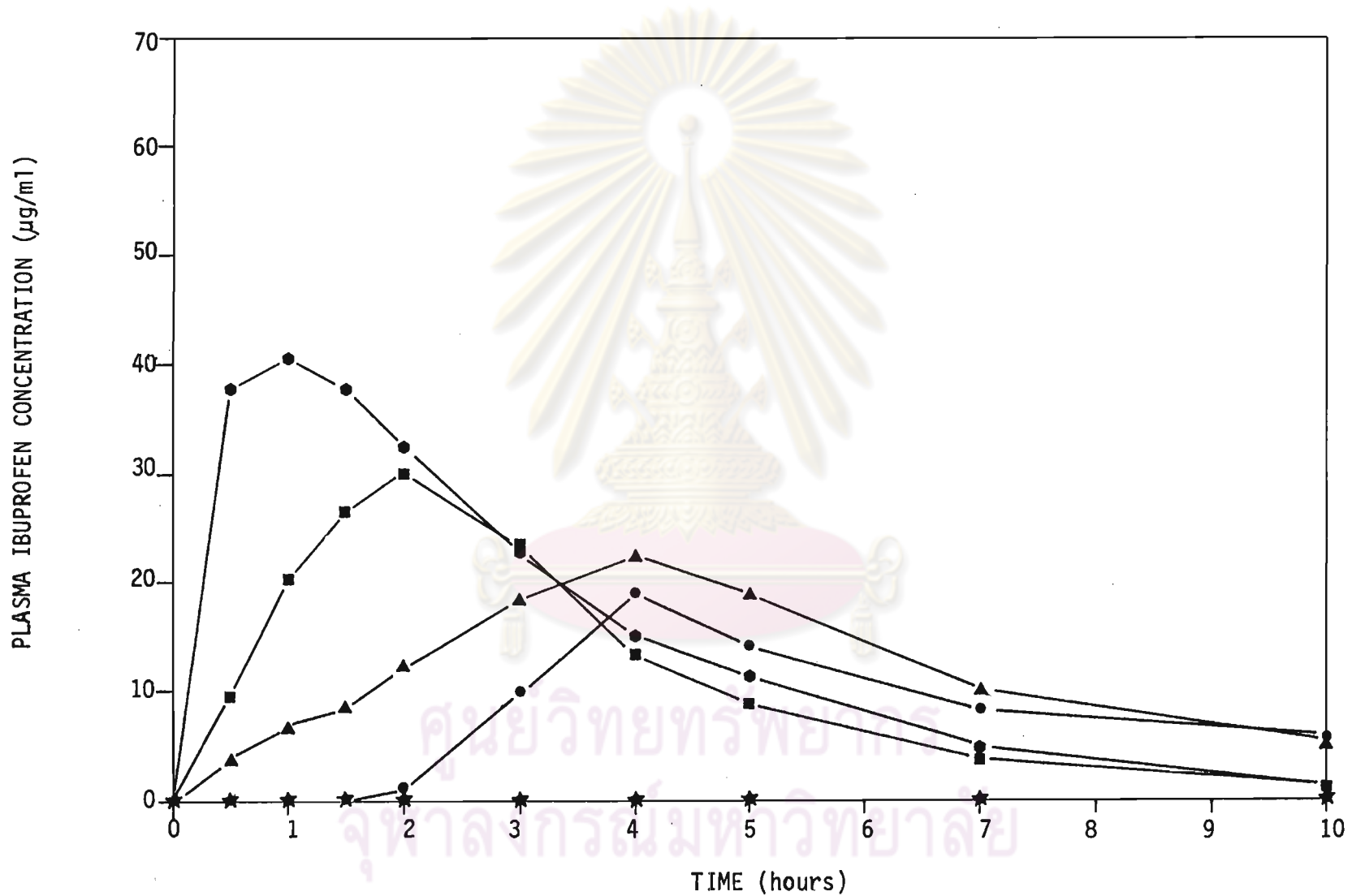
Figure 25 Plasma ibuprofen concentration -time profiles of the ninth subject following oral
administration of two 200 mg ibuprofen tablets of five different brands.

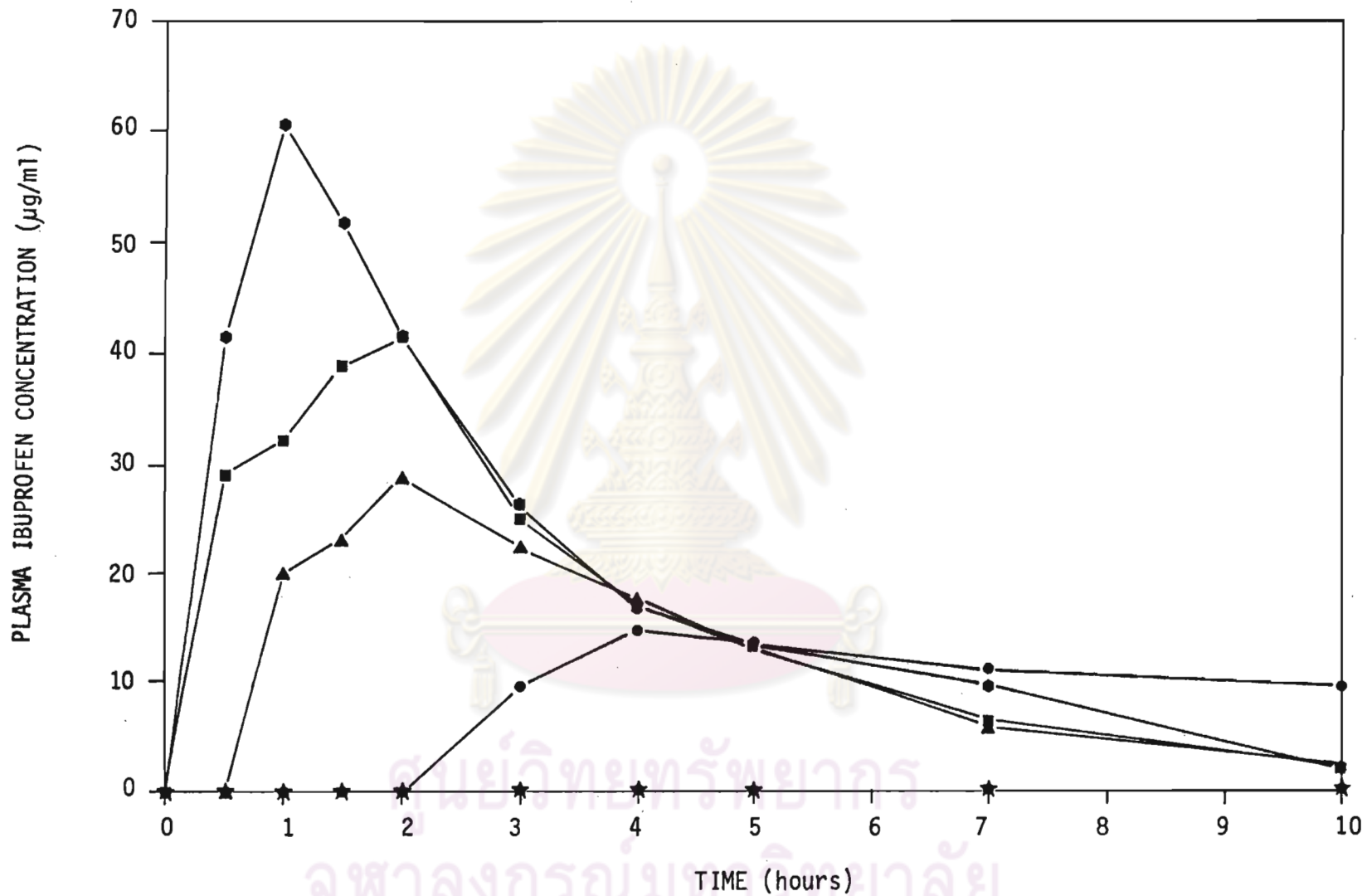Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
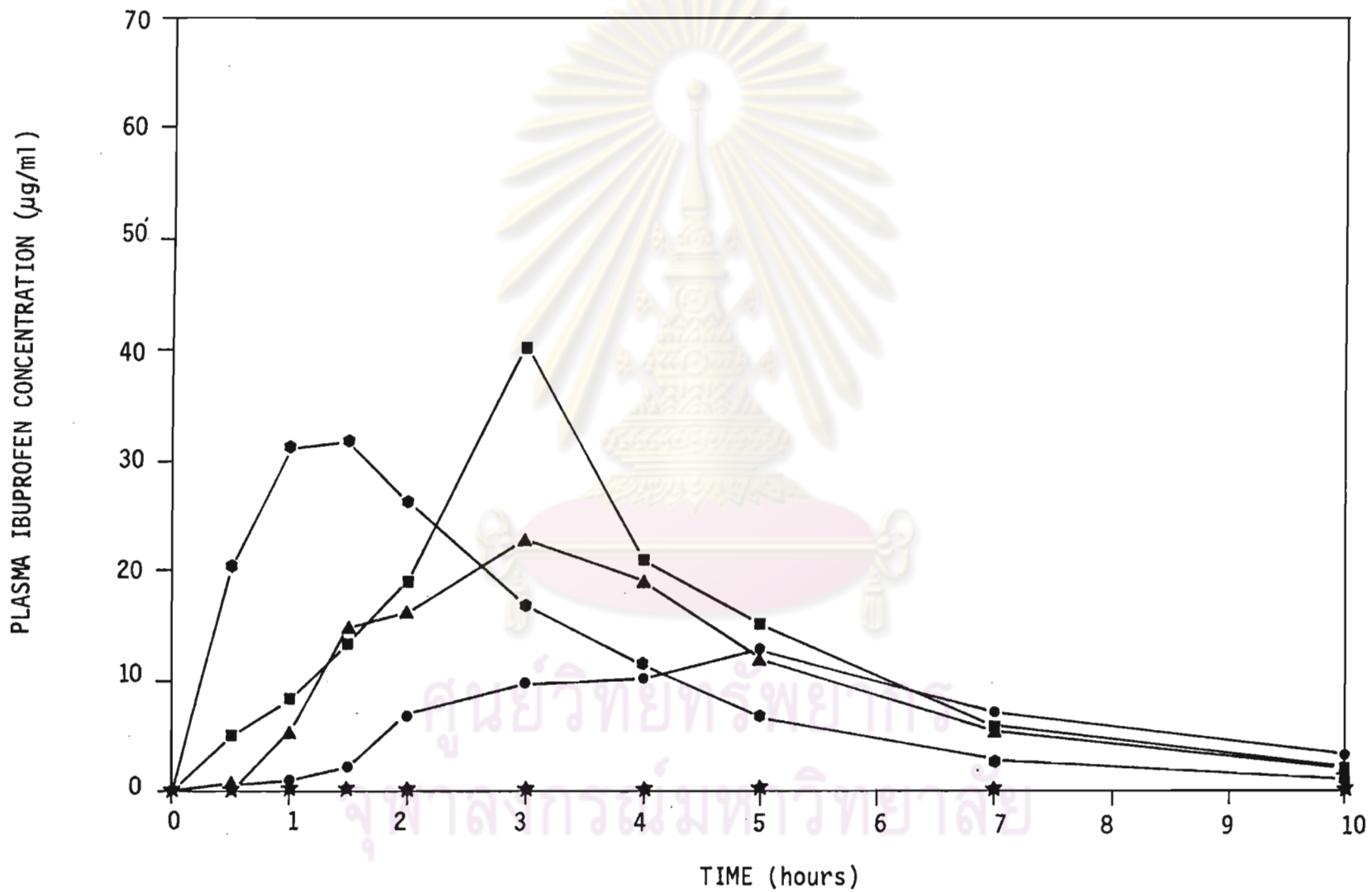
Figure 26 Plasma ibuprofen concentration -time profiles of the tenth subject following and administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
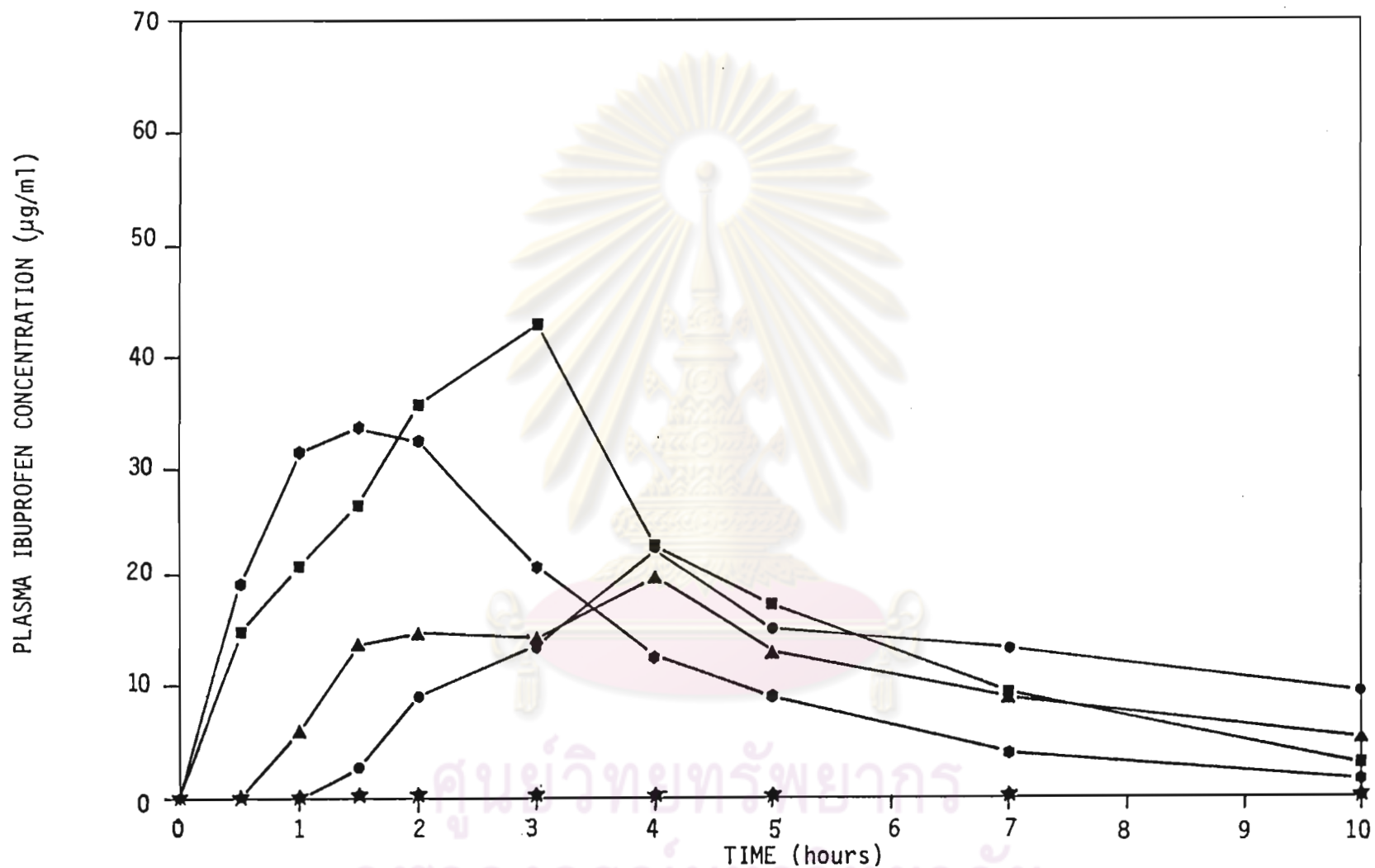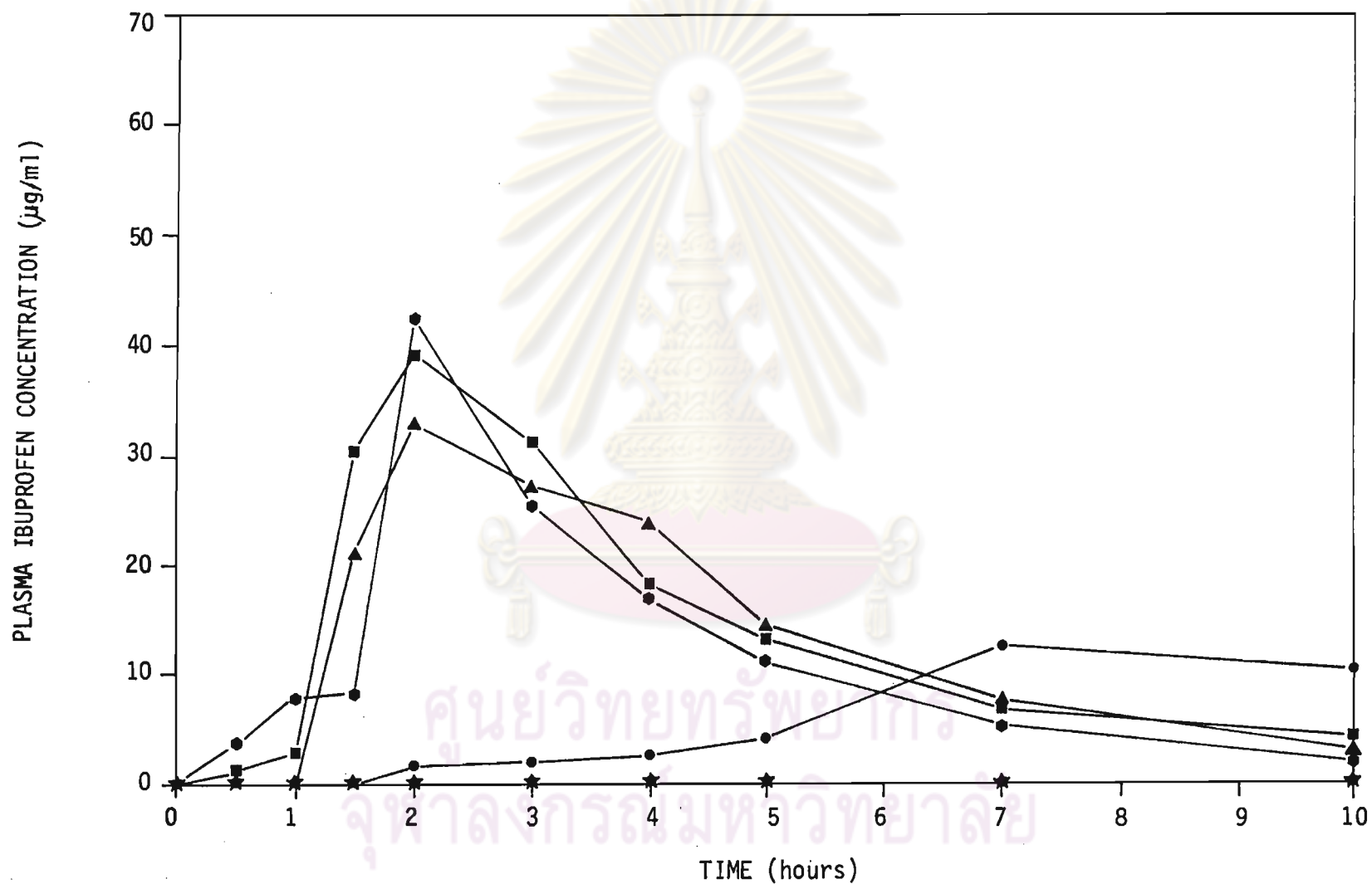
Figure 27 Plasma ibuprofen concentration -time profiles of the eleventh subject following oral administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)
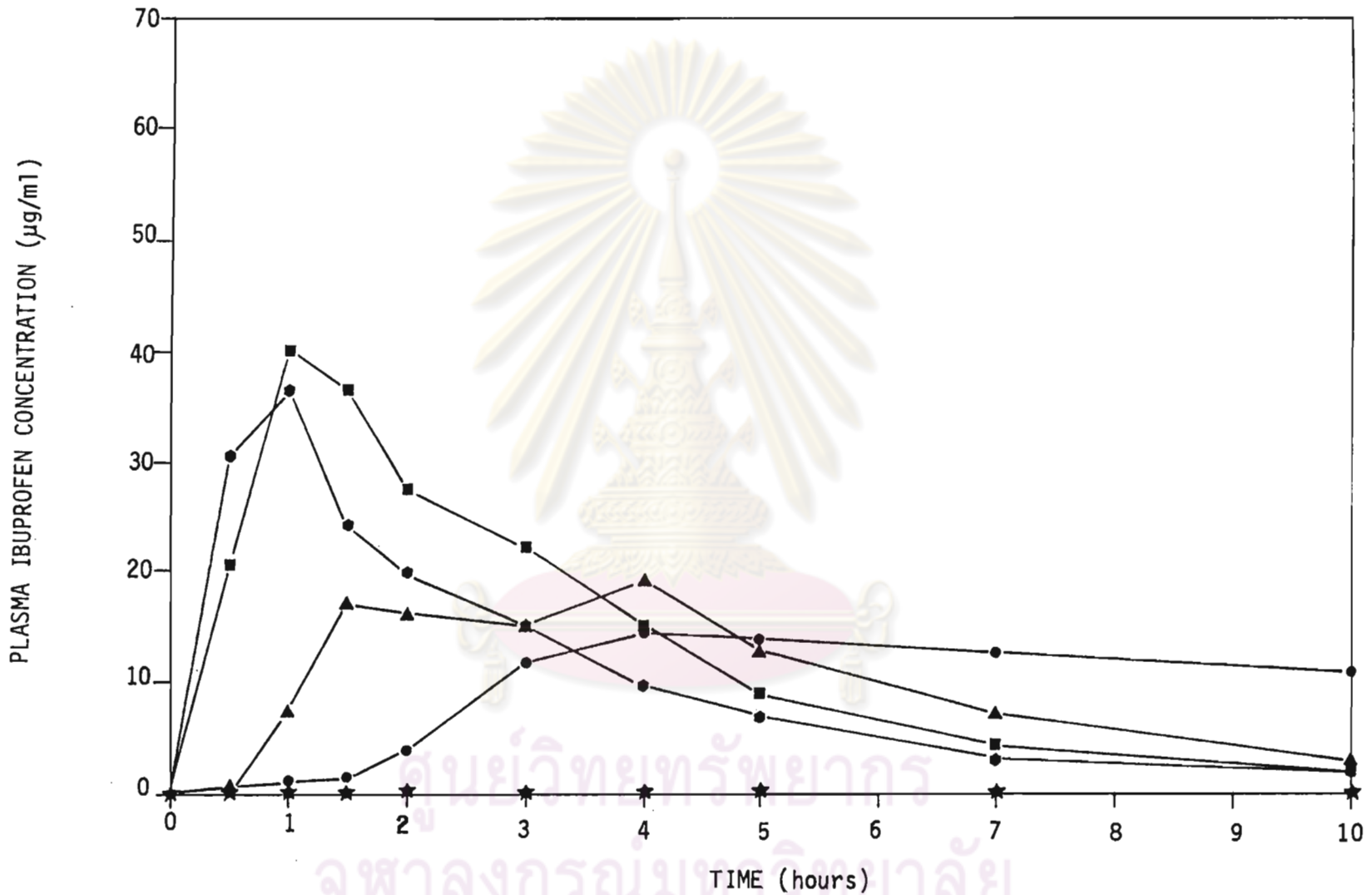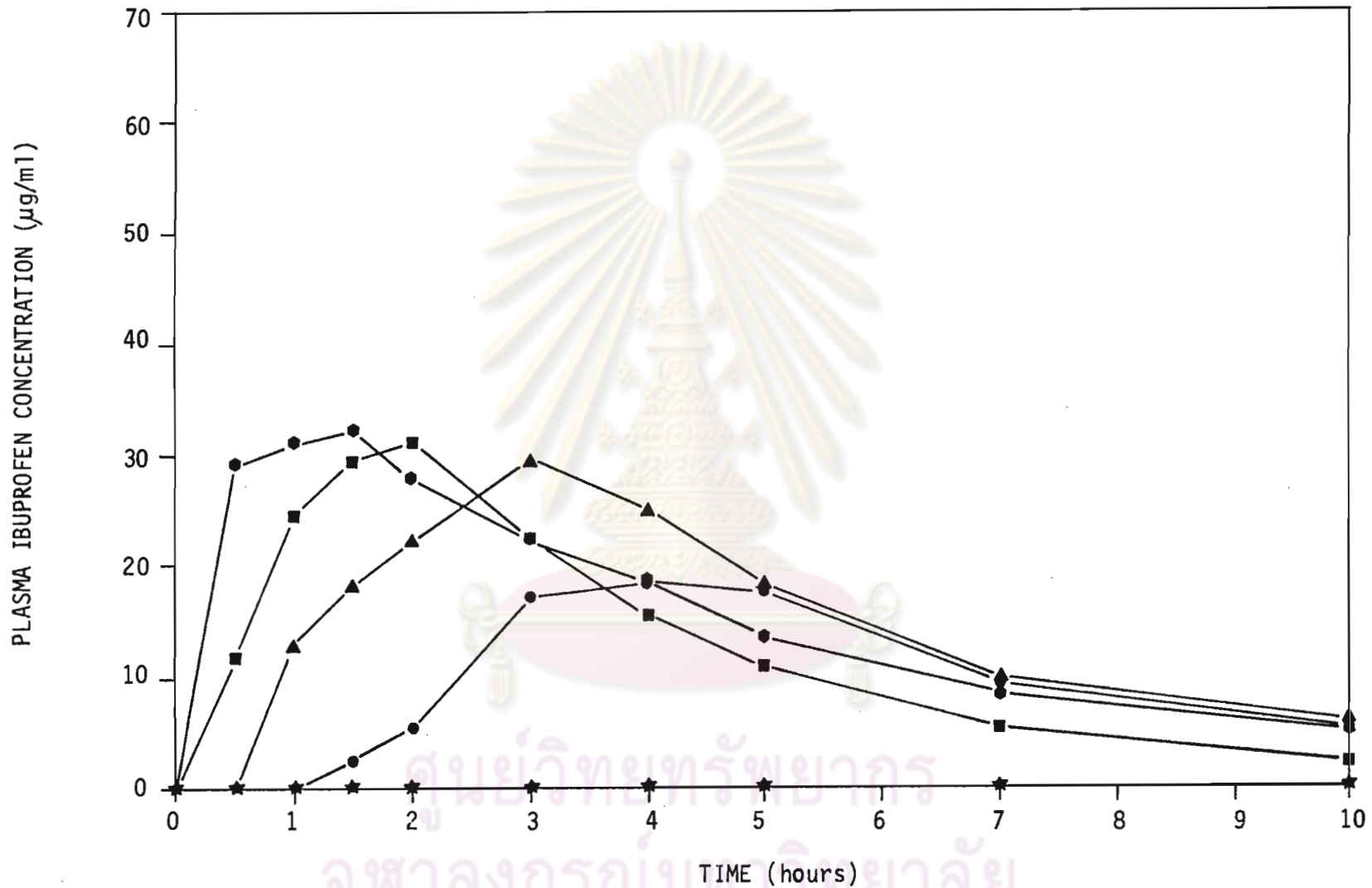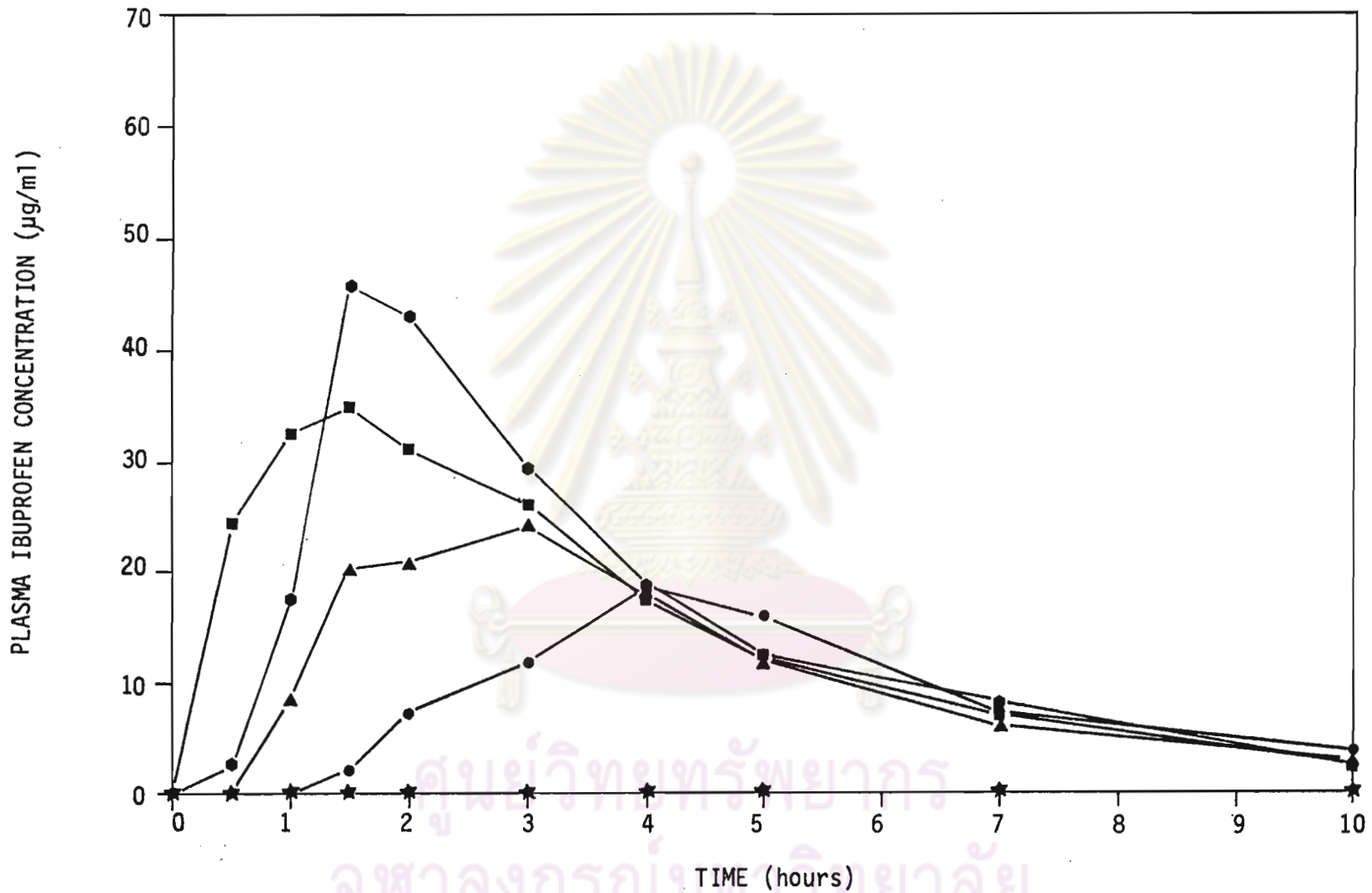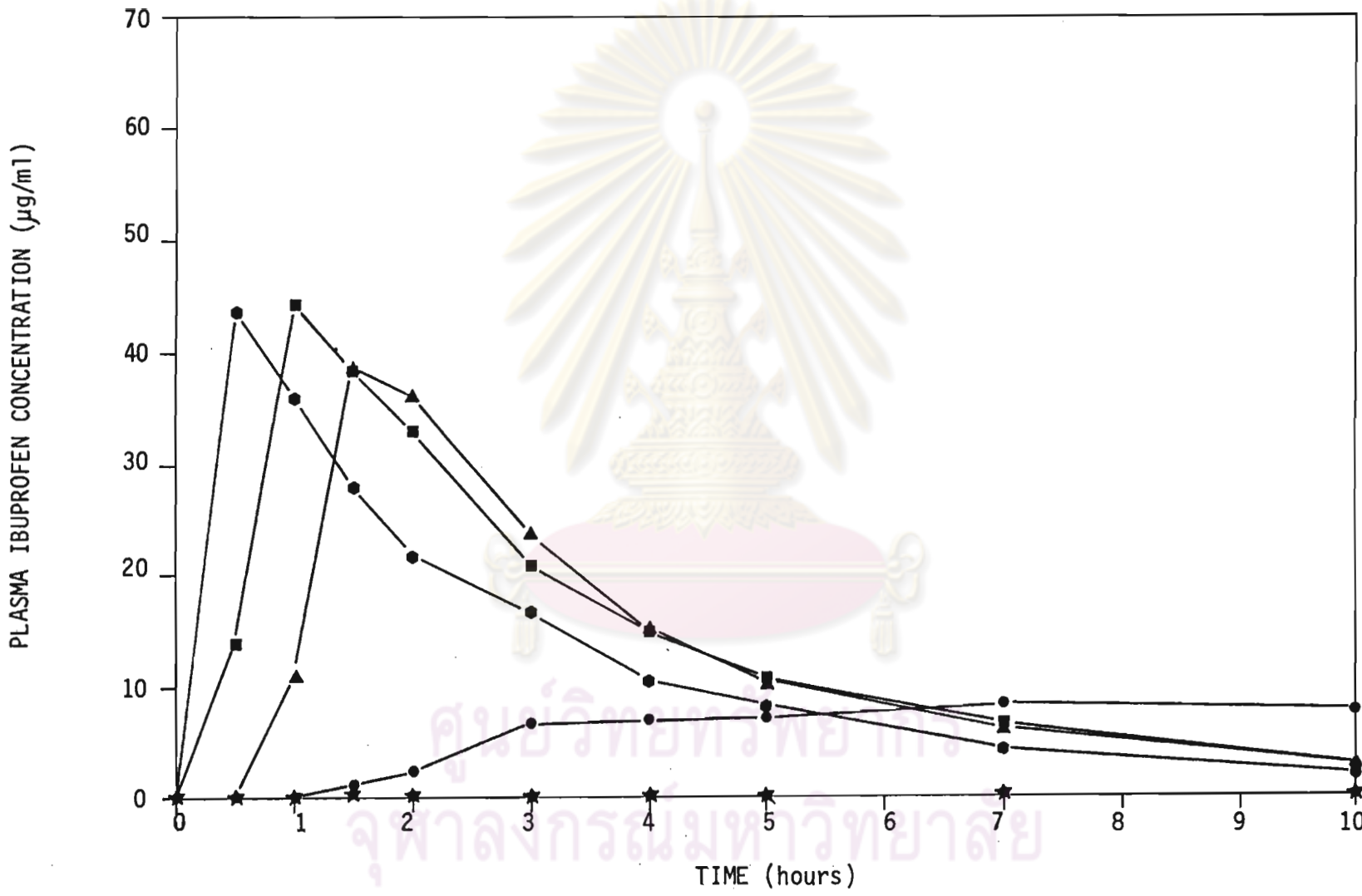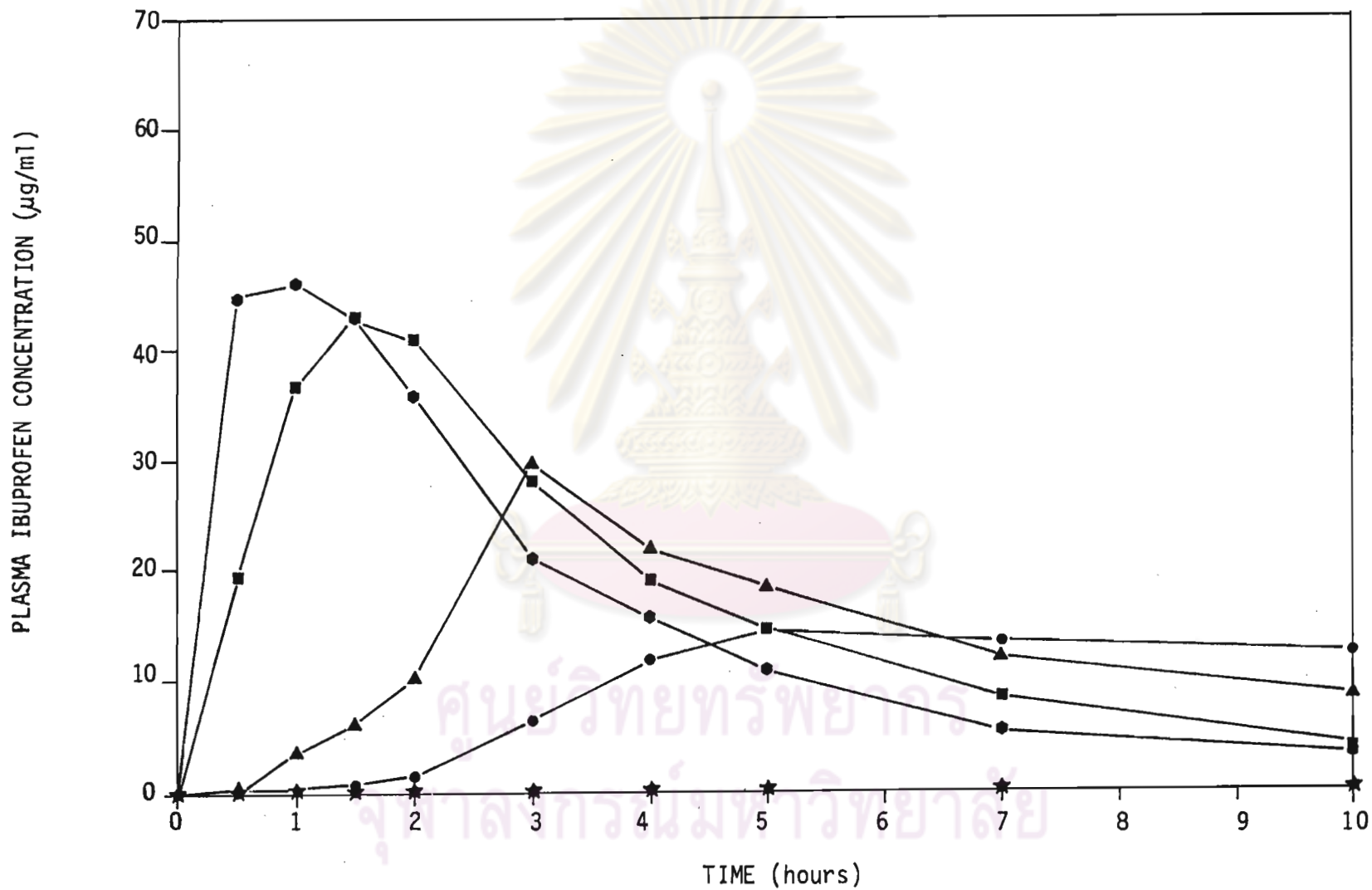
Figure 28 Plasma ibuprofen concentration -time profiles of the twelfth subject following oral administration of two 200 mg ibuprofen tablets of five different brands.

Key : Brand A (●) , Brand C (■) , Brand K (●) , Brand N (▲) , and Brand O (★)

NONCOMPARTMENTAL ANALYSIS

Noncompartmental methods (64) for the estimation of certain pharmacokinetic parameters are usually based on the estimation of the area under a plot of drug concentration versus time. Noncompartmental methods have been used to estimate bioavailability , clearance , apparent volume of distribution , and the fraction of a dose of a drug that is converted to a specific metabolite , based on data following single doses of drug and metabolite. These methods do not require the assumption of a specific compartmental model for either drug or metabolite. In fact , these methods can be applied to virtually any compartmental model, provided that we can assume linear pharmacokinetics.

Statistical Moments.

The application of statistical methods to pharmacokinetics was reported in 1979 by Yamaoka et al. (65) and Cutler (66). In 1980 , Riegelman and Collier (67) applied statistical moment theory to the evaluation of drug absorption.

The time course of drug in plasma can usually be regarded as a statistical distribution curve. Irrespective of the route of administration , the zero and the first moment are defined as follows :

$$AUC = \int_{0}^{\infty} Cdt \qquad (2)$$

$$MRT = \frac{\int_{0}^{\infty} tCdt}{\int_{0}^{\infty} Cdt} = \frac{AUMC}{AUC} \qquad (3)$$

Where MRT is the mean residence time of a drug in the body. AUC and MRT are termed the zero and first moment , respectively , of the drug concentration -time curve. The area under the curve of a plot of the product of concentration and time versus time from zero time to infinity is oftened refered to as the area under the (first) moment curve , AUMC. The moments defined above can be calculated by numerical integration using the trapezoidal rule from concentration -time data following drug administration.

In the usual single - dose pharmacokinetic study , blood sampling is stopped at some time t^* when drug concentration , C^* is measurable. Hence , estimation of the area under the blood level - time curve from zero time to infinity , AUC , must be carried out in two steps. The area under the curve from zero time to t^* is calculated by means of the trapezoidal rule. To this partial area we must add the area under the curve from t^* to infinity , which is usually estimated as follows :

$$\int_{t^*}^{\infty} C\,dt = \frac{C^*}{\lambda_n} \qquad (4)$$

where λ_n is 2.303 times the slope of the terminal exponential phase of a plot of log drug concentration versus time. The sum of the two partial areas is AUC.

The same approach must be used to estimated total AUMC. The area under the first moment curve from t^* to infinity is estimated as follows :

$$\int_{t^*}^{\infty} t\,C\,dt = \frac{t^* C^*}{\lambda_n} + \frac{C^*}{\lambda_n^2} \qquad (5)$$

Estimation of Areas

The estimation of areas under blood level - time curves is often required for pharmacokinetic analysis. These areas are usually estimated by employing an approximate integration formula. The trapezoidal rule is one such formula. This particular method involves the description of a given plasma concentration - time curve by a function that depicts the curve as a series of straight lines, thereby enabling the area under the curve to be divided into a number of trapezoids. The area of each trapezoid is easily calculated. In the linear trapezoidal method the area is given as follows :

$$\text{AUC} \Big|_{t_1}^{t_2} = \frac{(t_2 - t_1)(C_1 + C_2)}{2} \tag{6}$$

The sum of all the areas of all the trapezoids yield an estimate of the true area under the curve.

Half - life

The first moment of the blood level - time curve, mean residence time, is the statistical moment analogy of half - life. In effect, the MRT represents the time for 63.2% of the administered dose to be eliminated.

$$t_{\frac{1}{2}} = 0.693 \, \text{MRT}_{iv} \tag{7}$$

$$\text{and} \quad \text{MRT}_{iv} = \frac{1}{K_{el}} \tag{8}$$

APPENDIX H

COMPARTMENTAL ANALYSIS

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments , even though these compartments usually have no physiologic or anatomic reality , and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first - order or linear kinetics.

Kinetic linearity (68) may be defined as direct proportionally of transfer rates to concentrations or concentration differences. An important consequence of a linear system in pharmacokinetics is that the total area under blood (plasma or serum) concentration , time curve, following intravenous administration , is a linear function of the dose administered.

A compartmentalized system is only an approximation of a biological system , because variation in physical distribution , nonhomogeneity of the media and diffusion processes are all interrelated with chemical changes. Thus , a "compartment" is really an "average" rather than an exact state , and is really a reflected characteristic of a system rather than an absolute one. It is essential to remember that pharmacokinetic models are not the system itself , but rather an abstraction of it that emphasizes those aspects which the investigators feels to be important. The major contribution of a suitable model is that it allows the investigator to apply mathematical techniques.

The model is actually the equation , or sets of equations , which describe the proposed system. The solution of the differential equations of linear compartmental systems all turn out to be polyexponential in form. That is , the integrated equations can be generalized as follows :-

$$C = \sum_{i=1}^{n} C_i e^{-\lambda t} \qquad (9)$$

In this equation , C , for example , may represent the blood concentration at time t , C_i is the ith coefficient , which may be positive or negative , and λ_i is the exponent of the ith exponential term.

In order to determine whether a given set of data may be described by such a polyexponential equation the usual procedure is to perform an operation called by " stripping " or " method of residuals " This method , (a) determines whether the data may be adequately described by a polyexponential equation ; and (b) provides estimates of the coefficients (C_i values) and exponents (λ_i values).

In this study the CSTRIP (57), a Fortran IV computer program, was used to estimate the initial polyexponential parameters by stripping method. An example of calculation from data sets in the fourth subject receiving brand C was illustrated in figure 29 and table 88 . We plotted C_t versus t on a semilogarithmic graph paper and use the method of residual to determine K_a and K_{el}. The lag time (t_o) is the time at the point of intersection of the two residual lines on the x axis. For the CSTRIP program , the lag time is determined by trial and error solution of
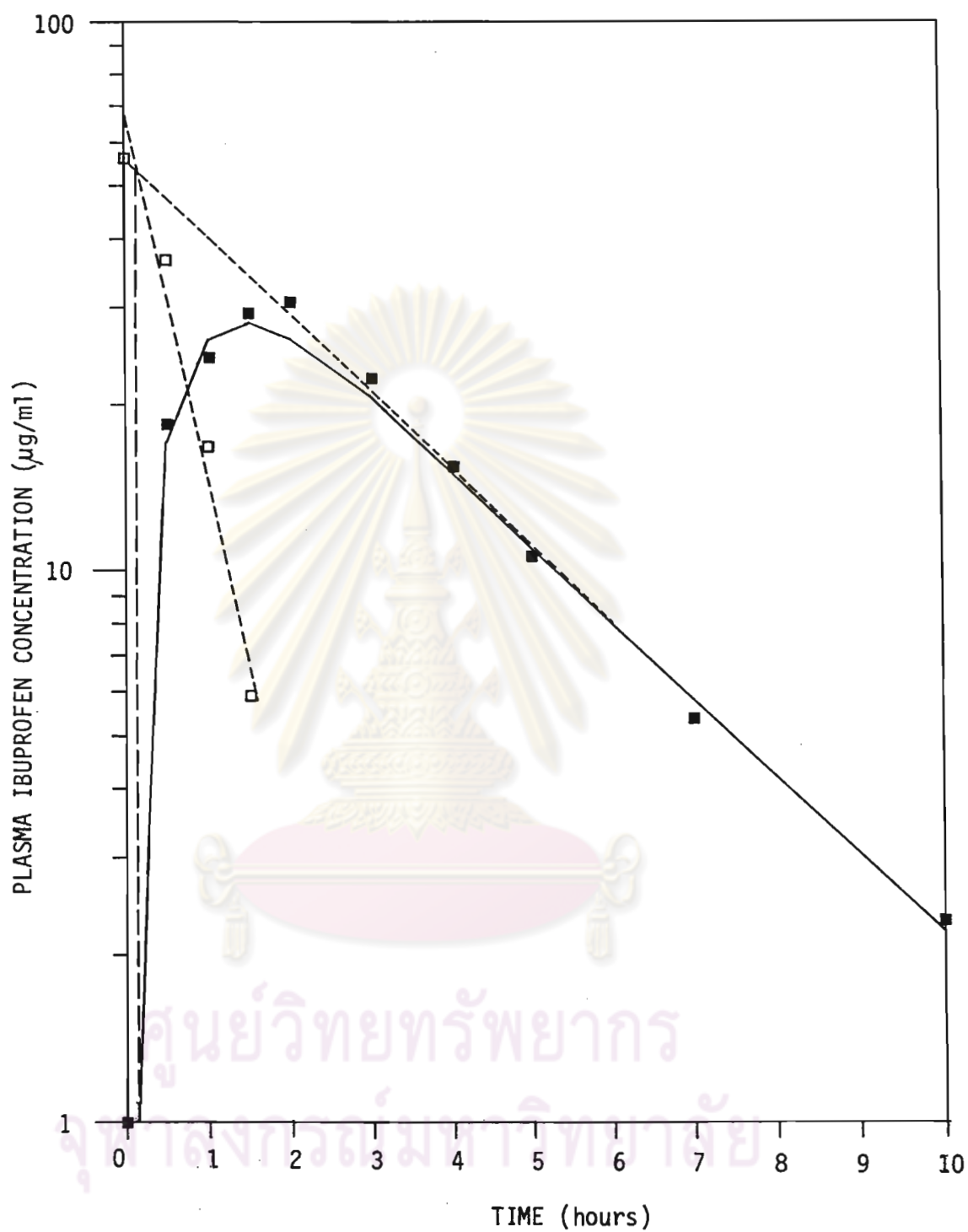
Figure 29 Graphical technique of calculating estimated pharmacokinetic parameters in the plasma ibuprofen concentration -time curve by the method of residuals.

Table 88   Stripping Biexponential from Set of the Plasma Ibuprofen
Concentration in the Fourth Subject Following a Single Oral
Dose of Two Tablets of Brand C

Time (hours)	C_{obs} (µg/ml)	$\hat{C}_t = 57.57e^{-0.326t}$	$R_1 = C_{obs} - \hat{C}_t$	C_{est}	$\dfrac{C_{est}}{C_{obs}} \times 100$
0	0	57.57	-57.57	-9.58	-
0.5	11.86	48.91	-37.05	17.46	147.22
1.0	24.70	41.55	-16.85	26.82	108.58
1.5	29.33	35.30	-5.97	28.40	96.83
2.0	31.00			26.76	86.32
3.0	22.38			20.94	93.57
4.0	15.51			15.47	99.74
5.0	10.83			11.24	103.79
7.0	5.40			5.87	108.70
10.0	2.36			2.21	93.64
				MEAN	104.27
				SD	17.71
				CV =	16.98 %

1. $\ln \hat{C}_t = 4.053 - 0.326t$ (r = -.9983) ; $\hat{C}_t = 57.57\,e^{-0.326t}$

2. $\ln |R_1| = 4.207 - 1.517t$ (r = -.9848) ; $\hat{R}_1 = 67.15^{-1.517t}$

Hence , $C_{est} = 57.57e^{-0.326t} - 67.15^{-1.517t}$

$$\sum_{i=1}^{m} C_i e^{-\lambda_i t_o} = 0 \qquad\qquad (10)$$

In this example the lag time was 0.128 hour. This program also calculated the R square of the estimate equation fitted to the data. The percent improvement in R squared was calculated to decide whether the plasma concentration - time result was fitted to one or two compartment.

The output of the data from the fourth subject receiving brand C as shown in Figure 31 indicated that

r^2 for two exponentials was 0.9487

r^2 for three exponentials was 0.9548

therefore the percent improvement $=\ \dfrac{0.9548 - 0.9487}{0.9487}\ $ x 100

$=\quad 0.64$

Compare this value with the value in the following table :

Table 89   Table to Decide Whether or Not You Should Choose One More Exponential Term.

r^2 of polyexponential of " m " terms	% improvement in r^2 with (m+1) terms
$r^2 \leqslant 0.75$	10
$0.75 < r^2 < 0.90$	5
$0.90 < r^2 \leqslant 0.95$	2.5
$0.95 < r^2$	1.5

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The value 0.64 was less than 2.5 , therefore it was enough to use two exponentials to describe the data. This indicated that the pharmacokinetic of ibuprofen tablet in the fourth subject could be explained in terms of a one compartment open model. Consequently , this data was assumed to follow the one compartment model with first - order absorption , first order elimination and the lag time (as shown in Figure 30 and Equation 11) in the PCNONLIN program , model 4 (58).
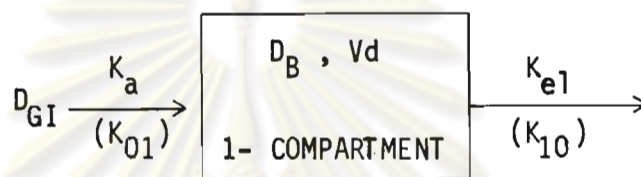
Figure 30 Diagram of One - Compartment Open Model with First - Order Absorption , First - Order Elimination and the Lag Time

$$C_t = \frac{K_a\ FD}{Vd\ (K_a-K_{el})} \left[e^{-K_{el}(t-t_o)} - e^{-K_a(t-t_o)} \right] \quad (11)$$

Where C_t is the plasma concentration at time t, F is the fraction of dose ,D, to be absorbed , Vd is the drug distribution volume in body , K_a and K_{el} are the first - order rate constants for absorption and elimination respectively , and t_o is the lag time (69, 70).

The initial estimates of the parameters (Vd , K_a, K_{el}, t_o) used with the PCNONLIN nonlinear estimation program were obtained from the CSTRIP program

As seen from the output of CSTRIP program in Figure 31

$$K_a \quad = \quad 1.516 \quad \text{hour}^{-1}$$

$$K_{el} \quad = \quad 0.326 \quad \text{hour}^{-1}$$

$$t_o \quad = \quad 0.128 \quad \text{hour}$$

Vd is calculated with the following equation

$$Vd \quad = \quad \frac{K_a \ FD}{(K_a - K_{el}) \times \text{Intercept}} \qquad (12)$$

$$= \quad \frac{1.516 \times 1 \times 400}{(1.516 - 0.326) \times 55.28}$$

$$= \quad 9.2 \qquad L$$

The final estimation of the parameters were obtained by repeatedly entering the computed parameter values as initial estimation until the values were the best fit to the data.   Results obtained from the computer analysis of the estimated pharmacokinetic parameters were showed in Figure 32.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

```
..........CURVE STRIPPING..........


**••••••••••••••••••••••••••••••••
CATA SET NUMBER


THE NUMBER OF EXPONENTIALS = 2
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER CF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST)
     L1=    6
     L2=    4


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
 A1= 0.552412E+02     B1= 0.326182E+00
 A2=-0.552875E+02     B2= 0.151594E+01
 F= 0.571052E+02




A LAG TIME WAS NEEDED TO DESCRIBE THESE DATA

THE LAG TIME =   0.128

R SQUARE(2) =   0.94871


    NO.         TIME        C(OBS)        C(EST)        % DEV
     1         0.0000        0.0000        0.0000        0.00
     2         0.5000       11.8648       17.4563      -47.13
     3         1.0000       24.7015       26.8202       -8.58
     4         1.5000       29.3302       28.4035        3.16
     5         2.0000       31.0043       26.7622       13.68
     6         3.0000       22.3441       20.9401        6.45
     7         4.0000       15.5109       15.4691        0.27
     8         5.0000       10.8346       11.2421       -3.76
     9         7.0000        5.3998        5.8712       -8.73
    10        10.0000        2.3560        2.2074        6.31


THE NUMBER CF EXPONENTIALS = 3
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER CF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST)
     L1=    4
     L2=    2
     L3=    4


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE
 A1= 0.502651E+02     B1= 0.313593E+00
 A2= 0.715582E+01     B2= 0.441801E+00
 A3=-0.574686E+02     B3= 0.142183E+01
 F= 0.503625E+02




A LAG TIME WAS NEEDED TO DESCRIBE THESE DATA

THE LAG TIME =   0.121

R SQUARE(3) =   0.95477


    NO.         TIME        C(OBS)        C(EST)        % DEV
     1         0.0000        0.0000        0.0000        0.00
     2         0.5000       11.8648       17.1574      -44.61
     3         1.0000       24.7015       26.5396       -7.44
     4         1.5000       29.3302       26.4198        3.10
     5         2.0000       31.0043       27.0309       12.82
     6         3.0000       22.3441       21.4254        4.28
     7         4.0000       15.5109       15.9510       -2.84
     8         5.0000       10.8346       11.6571       -7.59
     9         7.0000        5.3998        6.1524      -13.94
    10        10.0000        2.3560        2.3600       -0.17


THE NUMBER CF EXPONENTIALS = 4
SUMMARY OF EXPONENTIAL STRIPPING

THIS SET OF DATA CAN NOT BE DESCRIBED BY THE SUM OF 4 EXPONENTIALS
```

Figure   31   The output of the CSTRIP program from the data of
               the fourth subject receiving brand C ibuprofen tablets

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM VO1-E

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FOR INFORMATION CONTACT - STATISTICAL CONSULTANTS INC.
                          1-606-252-3890


       LISTING OF INPUT COMMANDS

       model 4,'nlin.lib'
       MODEL 4
       REMARK  ONE COMPARTMENT MODEL - FIRST ORDER INPUT AND OUTPUT
       REMARK  INCLUDES A TIME LAG
       REMA
       REMA   NO.   PARAMETER      CONSTANT      SECONDARY PARM.
       REMA   ---   ---------      --------      ---------------
       REMA    1     VOLUME         DOSE             AUC
       REMA    2     KO1                         KO1 HALF LIFE
       REMA    3     K10                         K10 HALF LIFE
       REMA    4     TLAG                            TMAX
       REMA    5                                     CMAX
       REMA*********************************************************
       REMA          I-----------------I
       REMA          I                 I
       REMA   KO1 --> I   COMPARTMENT  1   I  ---> K10
       REMA          I                 I
       REMA          I-----------------I
       REMA*********************************************************
       COMM
       NPARM 4
       NCON 1
       NSEC 5
       PNAMES 'VOLUME', 'KO1', 'K10', 'TLAG'
       SNAMES 'AUC', 'KO1-HL', 'K10-HL', 'TMAX', 'CMAX'
       END
       TEMP
       D=CON(1)
       V=P(1)
       KO1=P(2)
       K10=P(3)
       TLAG=P(4)
       COEF=D*KO1/(V*(KO1-K10))
       T=X-TLAG
       END
       FUNC1
       F=MAX(0,COEF*(DEXP(-K10*T)-DEXP(-KO1*T)))
       END
       SECO
       S(1)=D/V/K10
       S(2)=-DLOG(.5)/KO1
       S(3)=-DLOG(.5)/K10
       TMAX=(DLOG(KO1/K10)/(KO1-K10))+ TLAG
       S(4)=TMAX
       S(5)= (D/V)*DEXP(-K10*(TMAX-TLAG))
       END
       EOM
       cons 400
       init 9.2, 1.52, .33, .128
       nobs10
       data
       begin
```

Figure 32   The output of the PCNONLIN program from the data of the

             fourth subject receiving Brand C ibuprofen tablets.

PCNONLIN NONLINEAR ESTIMATION PROGRAM

ITERATION	WEIGHTED SS	VOLUME	K01	K10	TLAG
0	59.3064	9.200	1.520	.3300	.1280
1	10.6952	8.807	1.499	.3474	.3054
2	7.31983	7.860	1.236	.3918	.2812
3	6.68637	7.507	1.157	.4214	.2768
4	6.67682	7.496	1.159	.4230	.2776

CONVERGENCE ACHIEVED
RELATIVE CHANGE IN WEIGHTED SUM OF SQUARES LESS THAN   .000100

| 4 | 6.67649 | 7.482 | 1.156 | .4239 | .2772 |

PCNONLIN NONLINEAR ESTIMATION PROGRAM

PARAMETER	ESTIMATE	STANDARD ERROR	95% CONFIDENCE LIMITS		
VOLUME	7.482245	.918090	5.235758	9.728732	UNIVARIATE
			3.504769	11.459721	PLANAR
K01	1.155577	.244365	.557636	1.753517	UNIVARIATE
			.096903	2.214250	PLANAR
K10	.423897	.064215	.266768	.581026	UNIVARIATE
			.145695	.702099	PLANAR
TLAG	.277205	.037617	.185161	.369250	UNIVARIATE
			.114238	.440173	PLANAR

PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** CORRELATION MATRIX OF THE ESTIMATES ***

```
1.00000
 .95881  1.00000
-.97998  -.92841  1.00000
 .56722   .70352  -.51527  1.00000
```

*** EIGENVALUES OF (A TRANSPOSE A) MATRIX ***

NUMBER	EIGENVALUE
1	7381.
2	2382.
3	221.8
4	1.233

Figure 32 (cont) : The output of the PCNONLIN program

PCNONLIN NONLINEAR ESTIMATION PROGRAM

*** SUMMARY OF NONLINEAR ESTIMATION ***

FUNCTION   1

X	OBSERVED Y	CALCULATED Y	RESIDUAL	WEIGHT	SD-YHAT	STANDARIZED RESIDUAL
.0000	.0000	.0000	.0000	1.000	.0000	.0000
.5000	11.86	11.56	.3090	1.000	1.038	.2930
1.000	24.70	25.53	-.8248	1.000	.7975	-.7819
1.500	29.33	29.73	-.3986	1.000	.6646	-.3779
2.000	31.00	29.14	1.860	1.000	.6367	1.763
3.000	22.38	22.99	-.6073	1.000	.6992	-.5757
4.000	15.51	16.28	-.7700	1.000	.5947	-.7299
5.000	10.83	11.04	-.2094	1.000	.6180	-.1985
7.000	5.400	4.849	.5505	1.000	.6903	.5219
10.00	2.356	1.368	.9876	1.000	.4343	.9362

CORRECTED SUM OF SQUARED OBSERVATIONS = 1113.47
WEIGHTED CORRECTED SUM OF SQUARED OBSERVATIONS = 1113.47
SUM OF SQUARED RESIDUALS =   6.67649
SUM OF WEIGHTED SQUARED RESIDUALS = 6.67649
S = 1.05487   WITH   6 DEGREES OF FREEDOM
CORRELATION (Y,YHAT) = .997

PCNONLIN NONLINEAR ESTIMATION PROGRAM

SUMMARY OF ESTIMATED SECONDARY PARAMETERS

PARAMETER	ESTIMATE	STANDARD ERROR
AUC	126.115264	4.996378
K01-HL	.599828	.126717
K10-HL	1.635178	.247462
TMAX	1.647838	.068238
CMAX	29.901970	.633603

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION   1
PLOT OF X VS. OBSERVED Y AND CALCULATED Y

*** ARE CALCULATED POINTS, OOO ARE OBSERVED POINTS

```
    55.00    I
    50.00    I
    45.00    I
    40.00    I
    35.00    I                    O
    30.00    I                *O***
    25.00    I                O    O*
    20.00    I                *    *O*
    15.00    I                O      *O*
    10.00    I                *       ***O
    5.000    I                *        ******O
    .0000    I                O*
   -5.000    I
  -10.00     I
  -15.00     I
  -20.00     I
             -----+---------+---------+---------+---------+---------+-----
                -7.00     -2.00     3.00      8.00      13.0      18.0
                                     X
```
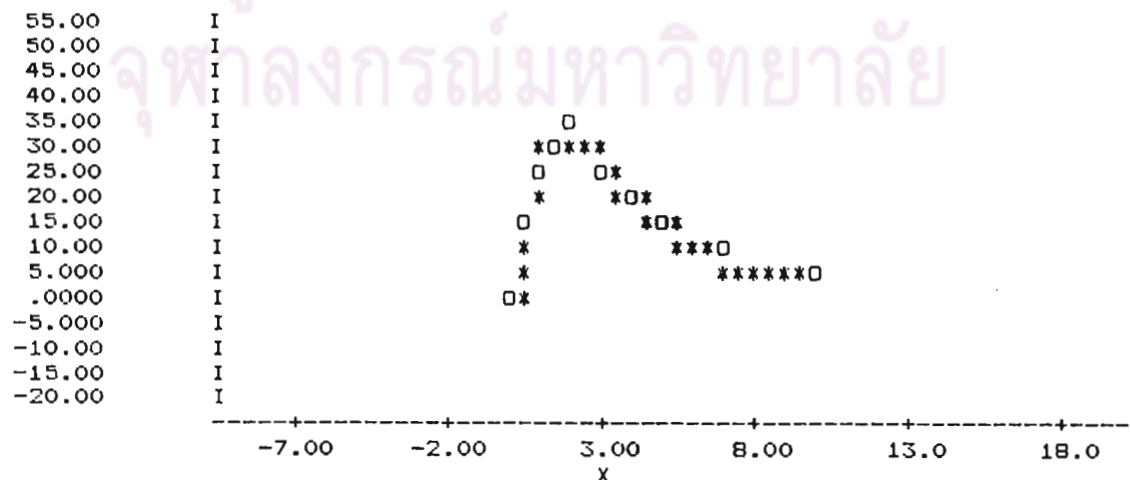
Figure 32   (cont) : The output of the PCNONLIN program

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF OBSERVED Y VS. CALCULATED Y

```
CALCULATED Y
    30.00     I                                                     *  *
    28.00     I
    26.00     I                                              *
    24.00     I                                          *
    22.00     I
    20.00     I
    18.00     I                                   *
    16.00     I
    14.00     I
    12.00     I                            **
    10.00     I
    8.000     I
    6.000     I                      *
    4.000     I
    2.000     I                *
    .0000     I          *
              ----+---------+---------+---------+---------+---------+-----
              -9.00      1.00      11.0      21.0      31.0      41.0
                                        OBSERVED Y
```

PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION 1
PLOT OF CALCULATED Y VS. RESIDUAL

```
RESIDUAL
    2.000     I                                            *
    1.800     I
    1.600     I
    1.400     I
    1.200     I
    1.000     I                      *
    .8000     I
    .6000     I                  *
    .4000     I                      *
    .2000     I
    .0000     I---------*----------------------------------------
   -.2000     I                        *                *
   -.4000     I
   -.6000     I                    *       *
   -.8000     I                            *
   -1.000     I
              ----+---------+---------+---------+---------+---------+-----
              -9.00      1.00      11.0      21.0      31.0      41.0
                                        CALCULATED Y
```
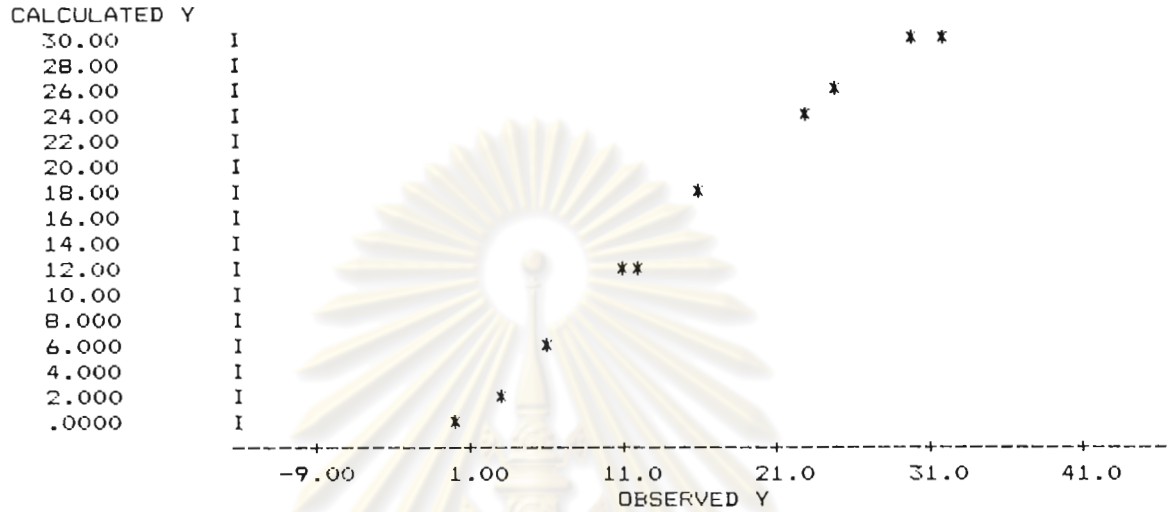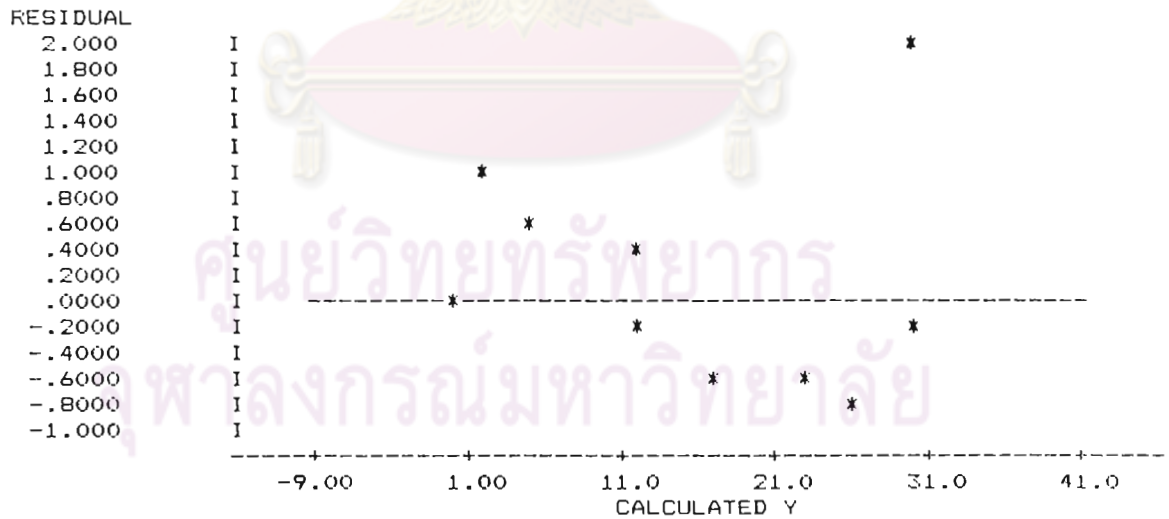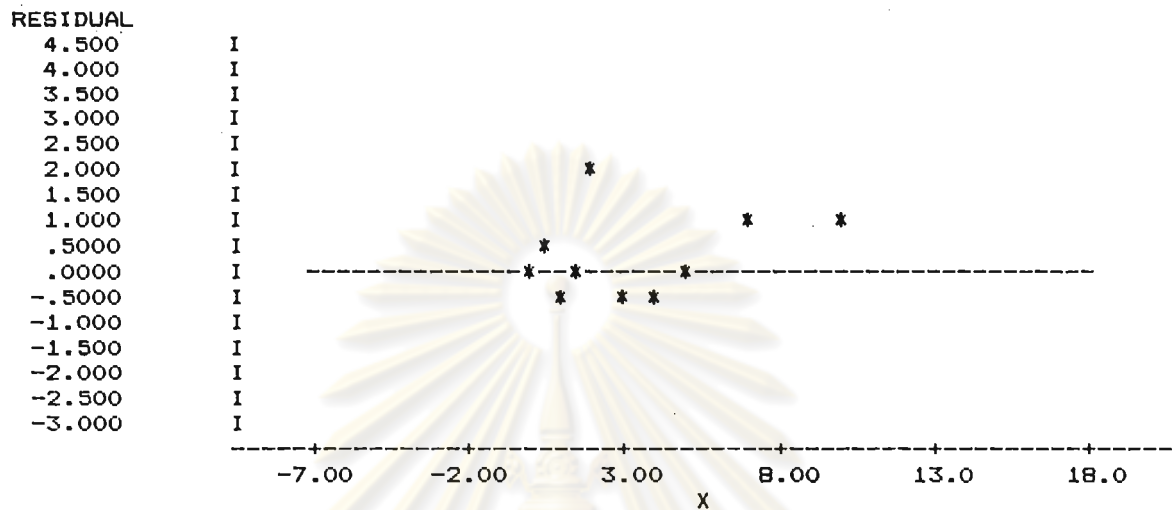
Figure 32 (cont) : The output of the PCNONLIN program

```
PCNONLIN NONLINEAR ESTIMATION PROGRAM

FUNCTION  1
PLOT OF X VS. RESIDUAL Y


RESIDUAL
   4.500        I
   4.000        I
   3.500        I
   3.000        I
   2.500        I
   2.000        I                                   *
   1.500        I
   1.000        I                              *         *
    .5000       I                         *
    .0000       I  ----------------*--*------*----------------------------
   -.5000       I                     *    * *
  -1.000        I
  -1.500        I
  -2.000        I
  -2.500        I
  -3.000        I
              ----+---------+---------+---------+---------+---------+------
               -7.00      -2.00      3.00      8.00      13.0      18.0
                                          X
```

PCNONLIN NONLINEAR ESTIMATION PROGRAM V01-E

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LISTING OF INPUT COMMANDS

 finish

NORMAL ENDING

Figure 32   (cont) : The output of the PCNONLIN program

APPENDIX I

STATISTICS

1. <u>Mean</u> ($\bar{X}$)

$$\bar{X} = \frac{\sum x}{N}$$

2. <u>Standard Deviation</u> (S.D.)

$$S.D. = \sqrt{\frac{\sum (x-\bar{x})^2}{N-1}}$$

3. <u>Standard Error of the Mean</u> (SEM)

$$SEM = \frac{S.D.}{\sqrt{N}}$$

4. <u>Coefficient of Variation</u>   (CV)

$$CV = \frac{S.D.}{\bar{X}} \times 100$$

5. <u>Testing Concerning the Difference of Two Means</u> , by Student's t-test

(71) (This test was performed in the in vitro evaluation)

Let $\mu_1 . \mu_2$ =   Population means

X_1 , X_2 =   Sample means

σ_1^2 , σ_2^2 =   Population variances

S_1 , S_2 =   Sample standard deviation

N_1 , N_2 =   Sample size

The null hypothesis H_o : $\mu_1 = \mu_2$

The alternative hypothesis H_a : $\mu_1 \neq \mu_2$

The statistic t was given as t $= \dfrac{(\bar{X}_1 - \bar{X}_2) - (\mu_1 - \mu_2)}{Sp}$

First homogeneity of variance is tested for using the F test , which is defined as follow:

$$F = \dfrac{(S_1)^2}{(S_2)^2}$$

where $(S_1)^2$ = the larger of the two sample variances

$(S_2)^2$ = the smaller of the two sample variances

With this test we are evaluating the null hypothesis of no difference between the two population variances. If the F is not significant , the null hypothesis stands.

5.1 If $\sigma_1^2 \neq \sigma_1^2$

The statistic t was given as

$$t = \dfrac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where S_p^2 was the pooled variance

$$S_p^2 = \dfrac{(S_1)^2}{N_1} + \dfrac{(S_2)^2}{N_2}$$

With degree of freedom

$$df = \dfrac{\left(\dfrac{S_1^2}{N_1} + \dfrac{S_1^2}{N_2}\right)^2}{\dfrac{\left(\dfrac{S_1^2}{N_1}\right)^2}{N_1 - 1} + \dfrac{\left(\dfrac{S_2^2}{N_2}\right)^2}{N_2 - 1}}$$

5.2 If $\delta_1^2 = \delta_2^2$

The test statistic for this case was

$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_p}$$

Where the pooled variance

$$S_p^2 = \left(\frac{1}{N_1} + \frac{1}{N_2}\right)\left(\frac{(N_1-1)\, S_1^2 + (N_2-1)\, S_2^2}{N_1 + N_2 - 2}\right)$$

And degree of freedom

$$df = N_1 + N_2 - 2$$

Comparing this t value with $t_{(Tab)}$ for $\frac{\alpha}{2}$ that is obtained from the table.

6. <u>Testing Concerning the Differences between Related Pairs</u> , by Student's t - test (71)

(This test was performed in the in vivo evaluation).

Let D_i =   differences in the individual pairs

$\bar{D}$ =   sample mean difference

μ_D =   average difference of the two treatments over the population

δ_D =   standard deviation of the population of differences

S_D = standard deviation of the sample of differences

n = the number of pairs

In the analysis , the deviations $D_i - \mu_D$ are assumed to be normally and independently distributed with population mean zero. When these assumptions hold , the sample mean difference $\bar{D}$ is normally distributed about μ_D with standard deviation or standard error $\sigma_D/\sqrt{n}$. The value of σ_D is seldom known , but the sample furnished an estimate :

$$S_D = \sqrt{\frac{\sum (D_i-\bar{D})^2}{n-1}} = \sqrt{\frac{\sum D^2 - (\sum D_i)^2/n}{n-1}}$$

Hence , $S_{\bar{D}} = S_D/\sqrt{n}$ is an estimate of σ_D , based on $(n-1)$df.

The important consequence of these results is that the quantity

$$t = \frac{(\bar{D} - \mu_D)}{S_{\bar{D}}}$$

follows student's t distribution with $(n-1)$ df. The t distribution was used to test the null hypothesis that $\mu_D = 0$

Comparing this t -value with $t_{(Tab)}$ for $\alpha/2$ that is obtained from the table.

7. Analysis of Variance(ANOVA) (72)

Table 90   Analysis of Variance for Completely Randomized Design.

Source of Variation	Sum of Squares	df.	Mean Square	Variation Ratio
Among-groups (Treatment)	$\sum\limits_{j=1}^{k} n_j (\bar{X}_{.j} - \bar{X}_{..})^2$	$k-1$	$\dfrac{SS_{among}}{k-1}$	$V.R. = \dfrac{MS_{among}}{MS_{within}}$
Within-group (Error)	$\sum\limits_{j=1}^{k} \sum\limits_{i=1}^{n_j} (X_{ij} - \bar{X}_{.j})^2$	$N-k$	$\dfrac{SS_{within}}{N-k}$	
Total	$\sum\limits_{j=1}^{k} \sum\limits_{i=1}^{n_j} (X_{ij} - \bar{X}_{..})^2$	$N-1$		

Where

X_{ij} = Observed value i at Treatment j

i = 1, 2, ..., n

j = 1, 2, ..., k

$T_{.j} = \sum\limits_{i=1}^{n} X_{ij}$

$\bar{X}_{.j} = \dfrac{T_{.j}}{n_j}$

$T_{..} = \sum\limits_{j=1}^{k} T_{.j}$

$\bar{X}_{..} = \dfrac{T_{..}}{N}$

$N = \sum\limits_{j=1}^{k} n_j$

Comparing the V.R. value with the critical value F obtained from table at degree of freedom (k-1) and (N-k).

If $F > F_{(Tab)}$, we reject the null hypothesis that $\mu_1 = \mu_2 = \mu_3 = \ldots = \mu_k$ and accept the alternative hypothesis.

If F is not significant, the null hypothesis stands.

8. <u>Correlation and Test of Significant</u> (73)

Correlation is a procedure commonly used to characterize quantitatively the relationship between variables. It is always used the correlation coefficient (r) to measure the degree of correlation

$$r = \frac{N \cdot \Sigma xy - \Sigma x \cdot \Sigma y}{\sqrt{[N \cdot \Sigma x^2 - (\Sigma x)^2] [n \cdot \Sigma y^2 - (\Sigma y)^2]}}$$

When   x is the data of the first group

   y is the data of the second group

   n is the pairs of data sets

It is of interest to test an observed correlation coefficient, r, versus a hypothetical value of 0. This test is based on an assumption that y is a normal variable.. The test is a t test with (N-2) degrees of freedom , as follows :

$$H_o \quad : \quad \rho = 0$$
$$H_a \quad : \quad \rho \neq 0$$

where ρ is the true correlation coefficient , estimated by r.

$$t_{N-2} = \frac{|r \sqrt{N-2}|}{\sqrt{1-r^2}}$$

The value of t is referred to a t distribution with (N-2) df.

If t-value $> t_{(Tab)}$, we reject the null hypothesis and accept the alternative hypothesis , i.e., there is a significant correlation between these two variables.

VITAE

Miss Wannapa Thamasucharit was born on December 12, 1960 in Bangkok. A scholarship to the Federal Republic of Germany was awarded to her by the German Educational Exchange Service (PAD) in 1978. She obtained her Bachelor Degree of Science in Pharmacy with Honors in 1984 from the Faculty of Pharmacy , Mahidol University , Bangkok , Thailand.