Pharmacokinetics And Bioavailability Of Ibuprofen Tablets Produced by AKRKHIN Company (Russia) In Comparison With Ibuprofen Tablets Produced by BOOTS Company (Brufen Tablets, England).

Jaefer Hashim Muhsin
Ministry of Sciences and Technology - Baghdad
jafferhashim@yahoo.com

Khawla Ahmed
Baghdad University - College of Medicine
Mohammed Khalil
Ministry of Sciences and Technology - Baghdad

Abstract: *Ten healthy male adult volunteers aged 20-40 years and of weight 55-75 kgm administered in empty stomach and in two occasions under same conditions 200 mg of ibuprofen tablets produced by AKRKHIN company (Russia) and 200 mg of ibuprofen tablets produced by BOOTS company (England). Statistical comparison of the pharmacokinetic parameters including the absorption half-life, the elimination half-life, the time to reach maximum concentration of the drug in serum and the maximum concentration of the drug in serum between the above companies indicated*

insignificant differences. Moreover it appeared that ibuprofen tablets produced by AKRKHIN company (Russia) is bioequivalent to the ibuprofen tablets produced by BOOTS company (England).

Introduction:

Ibuprofen, a propionic acid derivative, is a non-steroidal antiinflammatory drug. It is used in the management of mild to moderate pain, dental pain, musculo-skeletal and joint disorders such as ankylosing spondylitis , osteoarthritis and rheumatoid arthritis . the main adverse effects are gastrointeastinal disturbances, therefore if gastro-intestinal disturbances occur ibuprofen should be given with food or milk (10). Ibuprofen is absorbed from the gastro-intestinal tract and peak plasma concentration occur about 1-2 hours after ingestion .The drug has a plasma half-life of about 2hours (2,3,4,5,6,8,9,10) .The efficacy of ibuprofen is dependent upon achieving an adequate concentration of the drug in plasma. Therefore ,the measurement of blood or serum levels of ibuprofen and studying the rate and extent of drug bioavailability and clinical pharmacokinetics are important for insuring a safe and effective therapy especially when using this drug this drug for long time (10) . It is well known that formulation factors can influence the rate and extent of drug bioavailability and pharmacokinetics (12). Therefore the present work was carried out to establish the relative bioavailability (bioequivalence) of ibuprofen tablets 200 mg produced by AKRAKHIN company (Russia) in comparison with a reference (standard) product of ibuprofen tablets 200 mg produced by BOOTS company (England). Moreover, some important clinical pharmacokinetic informations were also introduced in the present work.

Materials and Methods

Clinical data:

Ten male adult healthy volunteers aged 20-40 years and weight of about 55-75kg with normal renal and liver functions and no contraindication to the use of the drug were selected for this study. The drug was not allowed to be taken by volunteers for one week prior the investigation and three days for other medications. The subjects were fasted overnight and during the first 4 hours after the drug intake. Five mls of blood was taken from each volunteer before drug intake, which was regarded as blank, or zero time. One tablet of ibuprofen 200mg produced by AKRKHIN company was administered directly to each volunteer with 20oml of water after the blank sample. Five mls of blood was withdrawn after 0.25, 0.5, 1, 2, 3, 6, 9 and 12 hours following drug intake.

One week later, the same procedures were repeated on the same volunteers and under the same conditions but using tablets of ibuprofen 200mg produced by BOOTS company (Brufen tablets).

Each blood sample was kept for 15 minutes to clot and then centrifuged for 10 minutes. The serum was then separated and kept in deep freeze until analysis carried out.

Samples Analysis:

The serum was analyzed using HPLC method in combination with UV detector with a detection limit of 0.1 microgram of ibuprofen in each ml of serum (1, 7, 11).

Data Analysis:

The concentrations of ibuprofen in serum versus time date (Tables 1 and 2) are plotted on demo-log graph papers (Fig. 1- Fig. 12). The kinetic parameters including the absorption rate constant (Ka), the absorption half-life ($T_{0.5abs}$), the elimination rate constant (K) and the elimination half-life ($T_{0.5elim}$) were calculated according to standard methods (12). The above pharmacokinetic parameters were measured by curve fitting method applying the method of Residuals and linear regression analysis (12). The area under the concentration of the drug in serum versus time curves (AUC) from

time zero to time 12 hours following drug intake were determined by Trapezoidal Rule (12). The AUC from time 12 hours to time infinity were measured as the concentration of the drug at 12 hours divided by the terminal elimination rate constant (K). The total AUC from time zero to time 12 hours and the AUC from time 12 hours to time infinity. The time to reach the maximum concentration of the drug in serum (C_{max}) and the time to reach this level (T_{max}) were estimated by visual inspection of the drug concentration in serum versus time curves (Table 1-4, Fig. 1-12).

Statistical Analysis:

Student's t test was applied to evaluate the differences on the pharmacokinetic parameters studied on the present investigation between ibuprofen produced by AKRKHIN company (Russia) and ibuprofen produced by BOOTS company (England).

Results and Discussions:

Pharmacokinetic data obtained from the administration of a single oral dose of ibuprofen 200mg tablets produced by AKRKHIN company to 10 healthy adult volunteers were summarized in Table 3.

Pharmacokinetic data obtained from the administration of a single oral dose of ibuprofen 200mg tablets produced by BOOTS company to 10 healthy adult volunteers were summarized in Table 4.

Statistical evaluation of the above data, Table 3 and Table 4 indicate that there are significant variations in the kinetic parameters between the individuals administered ibuprofen tablets produced by AKRKHIN company and ibuprofen tablets produced by BOOTS company and it seems that both products are bioequivalent. Table 5, Fig. 1 – Fig. 12.

Tables 3 and 4 show a relatively short elimination half-life of ibuprofen (about 2 hours). This explain the negligible contribution of the AUC_2 (measured from time 12 hours to time infinity) to the total AUC (measured from time zero to time infinity). Accordingly, 12 hours of ibuprofen sampling in serum after oral ingestion of

ibuprofen tablets is enough for reliable bioavailability and pharmacokinetic studies.

Tables 3 and 4 also exhibited clear individual variations on the pharmacokinetic parameters studied, ($T_{0.5abs}$, $T_{0.5elim}$, T_{max}, C_{max} and AUC). The pharmacokinetic parameters $T_{0.5elim}$, T_{max} and C_{max} are comply with the corresponding pharmacokinetic parameters introduced by previous studies (2, 3, 4, 5, 6, 8, 9, 10).

Conclusions:

In conclusion, it appeared that pharmacokinetic parameters obtained in the present work including $T_{0.5abs}$, $T_{0.5elim}$, T_{max}, and C_{max} are not significantly different after the administration of ibuprofen 200mg tablets produced by AKRKHIN company and ibuprofen produced by BOOTS company. Moreover, it seems that the two products are bioequivalent. The pharmacokinetic parameters found including $T_{0.5abs}$, $T_{0.5elim}$, C_{max}, T_{max} and AUC exhibited clear individual variations. The values of ($T_{0.5abs}$, $T_{0.5elim}$, C_{max} and T_{max}) are similar to the values presented by previous studies.

Table 1. Concentrations of Ibuprofen in serum (µg/ml) with time after the administration of 200mg Ibuprofen tablets, IBUPROFEN, AKRKHIN company, 10 healthy adult volunteers

Subject Number	Time (hour)								
	0	0.25	0.5	1	2	3	6	9	12
1	0	2.6	4.4	14.1	13.7	6.3	5.0	2.1	1.0
2	0	3.0	7.3	14.9	19.5	13.1	4.9	3.1	1.4
3	0	2.1	5.0	10.2	9.3	6.0	3.0	1.6	0.5
4	0	1.0	4.0	8.7	15.7	11.6	5.6	2.8	1.4
5	0	3.0	5.9	12.7	7.6	5.0	3.2	1.5	0.2
6	0	5.6	8.3	15.1	10.0	5.0	2.1	1.2	0.1
7	0	4.4	10.3	12.7	18.5	10.0	5.5	3.2	1.1
8	0	3.0	12.7	15.0	19.0	11.6	5.0	1.2	0.4
9	0	2.2	8.8	15.7	6.6	5.0	2.1	1.4	0.7
10	0	5.6	10.3	12.7	16.5	11.0	5.9	1.4	0.6
Mean	0	3.3	7.7	13.2	13.6	8.5	4.2	2.0	0.7
± SD	0	1.43	2.75	2.16	4.67	3.16	1.40	0.75	0.44
N	10	10	10	10	10	10	10	10	10

Table 2. Concentrations of Ibuprofen in serum (µg/ml) with time after the administration of 200mg Ibuprofen tablets, BRUFEN, BOOTS company, 10 healthy adult volunteers

Subject Number	Time (hour)								
	0	0.25	0.5	1	2	3	6	9	12
1	0	3.0	5.1	15.9	15.1	7.0	5.2	2.0	0.9
2	0	2.7	6.5	13.0	17.6	12.0	4.1	2.5	1.1
3	0	2.5	6.0	11.5	10.5	7.0	3.5	2.0	0.7
4	0	1.2	5.0	9.2	17.0	12.5	6.0	3.2	1.0
5	0	3.3	6.5	14.0	7.0	6.1	4.5	2.0	0.3
6	0	6.0	9.2	15.9	9.5	6.0	3.2	0.9	0.2
7	0	4.0	11.2	13.9	17.0	13.0	8.0	2.2	0.5
8	0	2.0	10.0	13.5	16.1	10.1	3.9	2.0	0.5
9	0	3.6	6.9	15.2	7.2	5.9	3.6	1.9	0.8
10	0	4.4	8.1	11.5	15.1	10.5	5.0	2.1	1.0
Mean	0	3.3	7.4	13.4	13.2	9.0	4.7	2.1	0.7
± SD	0	1.28	2.00	2.03	4.00	2.75	1.37	0.54	0.30
N	10	10	10	10	10	10	10	10	10

Table 3. Pharmacokinetic data of Ibuprofen after the administration of 200 mg Ibuprofen tablets, IBUPROFEN, AKRKHIN company, to 10 healthy adult volunteers.

Subject Number	Ka hr^{-1}	$T_{0.5abs}$ hr	K_{elim} hr^{-1}	$T_{0.5elim}$ hr	C_{max} µg/ml	T_{max} hr	AUC_1 (µg/ml) hr	AUC_2 (µg/ml) hr	$AUC_{(total)}$ (µg/ml) hr
1	0.885	0.783	0.238	2.912	14.1	1	62.1	4.2	66.3
2	1.407	0.493	0.255	2.718	22.5	2	86.3	5.5	91.8
3	1.252	0.533	0.244	2.840	10.2	1	46.1	2.0	48.1
4	0.874	0.793	0.239	2.900	15.7	2	74.6	5.9	80.5
5	1.363	0.508	0.332	2.087	12.7	1	44.7	0.6	45.3
6	1.590	0.436	0.409	1.694	15.1	1	45.8	0.2	46.0
7	1.242	0.558	0.257	2.696	18.5	2	86.7	4.3	91.0
8	1.203	0.576	0.384	1.805	19.0	2	78.2	1.0	79.2
9	1.356	0.511	0.254	2.728	15.7	1	44.0	2.8	46.8
10	1.076	0.644	0.338	2.050	16.5	2	77.5	1.8	78.3
Mean	1.225	0.584	0.295	2.443	16.0	1.5	64.5	2.83	65.33
± SD	0.22	0.11	0.062	0.453	3.27	0.5	17.13	1.94	19.07
N	10	10	10	10	10	10	10	10	10

Ka: Absorption Rate Constant

$T_{0.5abs}$: Absorption half-life

K_{elim} : Elimination Rate constant.

$T_{0.5\ elim}$: Elimination half-life.

C_{max} : Maximum concentration of drug in serum.

T_{max} : Time to maximum cincentration of drug in serum.

AUC_1 : Area under drug concentration in serum versus time curves measured by Trapezoidal Rule from time 0 to time 12 hours.

AUC_2 : Area under drug concentration in serum versus time curves measured from time 12 hours to time infinity which is equal to concentration of drug in serum at 12 hours divided by the terminal elimination rate constant (K).

$AUC_{(total)}$: Total area under drug concentration in serum versus time curves measured from time zero to time infinity which is equal to $AUC_1 + AUC_2$.

Table 4. Pharmacokinetic data of Ibuprofen after the administration of BOOTS company, to 10 healthy adult volunteers.

Subject Number	Ka hr^{-1}	$T_{0.5abs}$ Hr	$K_{0.5elim}$ hr	$T_{0.5elim}$ hr	C_{max} µg/ml	T_{max} hr	AUC_1 (µg/ml) hr	AUC_2 (µg/ml) hr	$AUC_{(total)}$ (µg/ml) hr
1	0.910	0.762	0.259	2.676	15.9	1	66.8	3.5	70.3
2	1.311	0.529	0.271	2.557	17.6	2	76.0	4.1	80.1
3	1.361	0.509	0.250	2.772	11.5	1	53.8	2.8	56.6
4	0.811	0.855	0.271	2.557	17.0	2	80.4	3.7	84.1
5	1.409	0.492	0.298	2.326	14.0	1	53.0	1.0	54.0
6	1.749	0.396	0.375	1.848	15.9	1	51.2	0.5	51.7
7	1.057	0.656	0.345	2.009	17.0	2	90.1	1.4	91.5
8	1.385	0.500	0.328	2.113	16.1	2	69.3	1.5	70.8
9	1.751	0.396	0.237	2.924	15.2	1	51.8	3.4	55.2
10	1.214	0.571	0.270	2.567	15.1	2	71.9	3.7	75.6
Mean	1.300	0.567	0.290	2.435	15.5	1.5	66.4	2.6	70.0
± SD	0.298	0.142	0.043	0.332	1.676	0.5	12.93	1.256	13.32
N	10	10	10	10	10	10	10	10	10

For more details of the table see Table 3.

Table 5. The relative bioavailability (in percent) of Ibuprofen 200mg of AKRKHIN company (test product) to BOOTS company (standard product) after the administration of Ibuprofen 200 mg tablets to 10 healthy adult volunteers in two occasions under the same conditions.

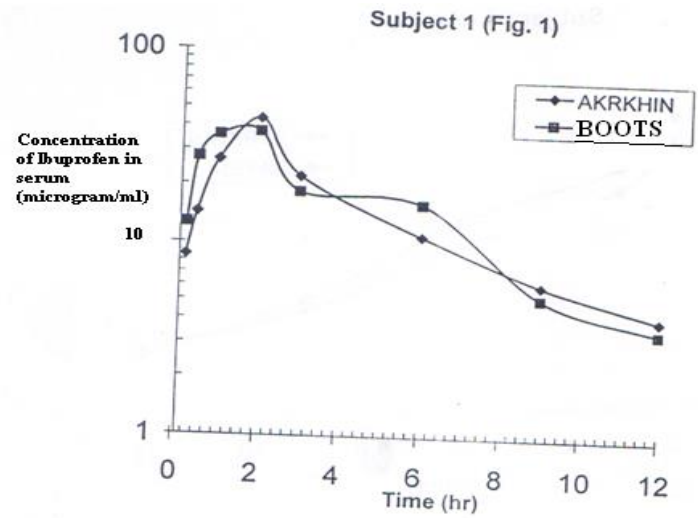
Subject Number	Relative Bioavailability
1	94.3
2	114.6
3	85.0
4	95.7
5	83.9
6	96.7
7	99.5
8	111.9
9	84.8
10	104.9
Mean	97.1
± SD	10.36
N	10

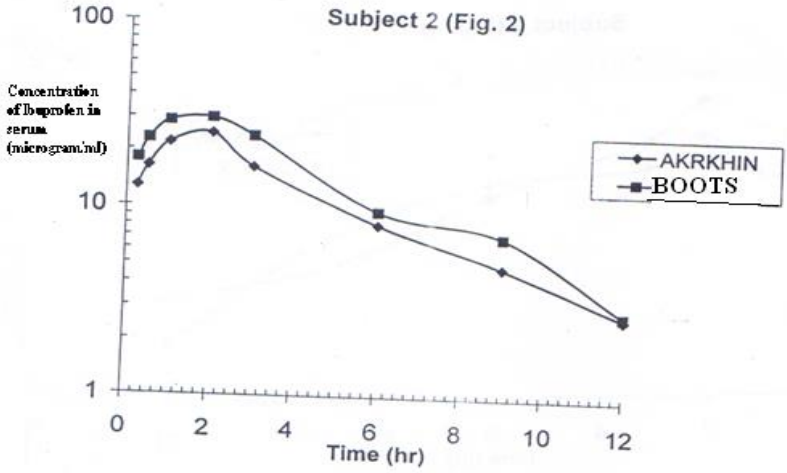
Relative Bioavailability= $(AUC_{(total)test} / AUC_{(total)standard})$ (Bioequivalence) $\times (Dose_{standard} / Dose_{test})$.

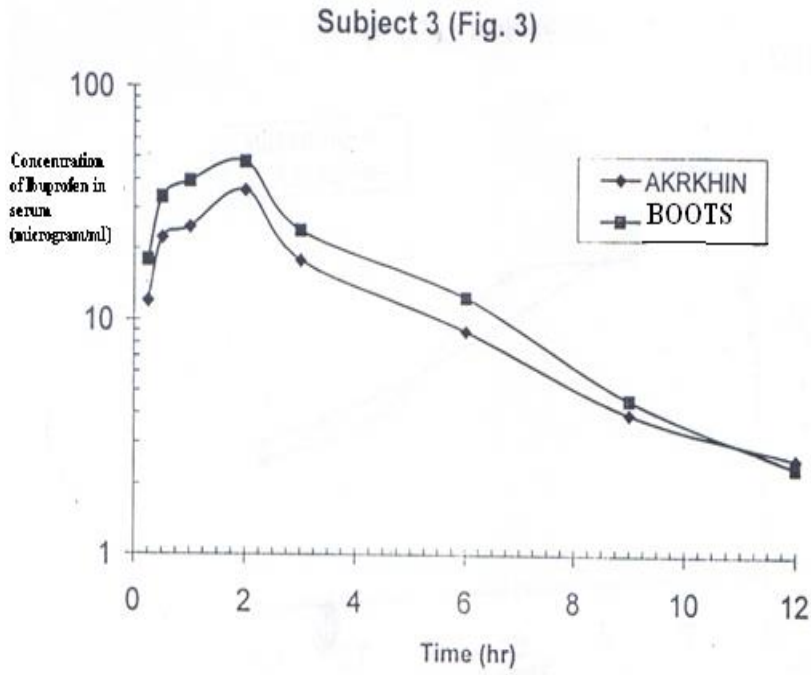
References:

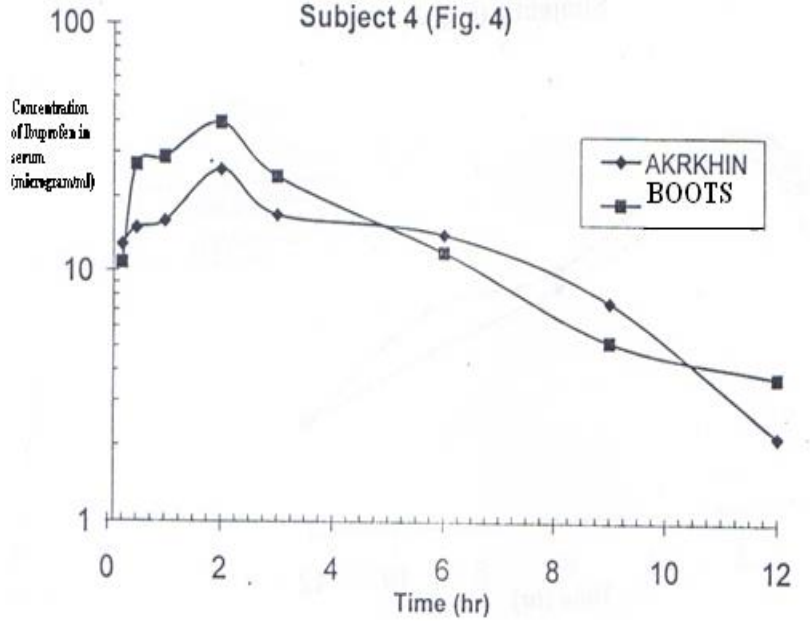
1. A. Ali, S. Kazmi and F. M. Plakogiannis, J. Pharm. Sci., 1981, 70, 944-945.
2. A. J. Hultt and J. Cald-Well, Clin. Pharmacokinet., 1984, 9, 371.
3. A. M. Evans, et al. Biopharam Drug Dipos., 1990, 11: 507-18.
4. D. G. Kaiser and G. J. Vangiessen, J. Pharm. Sci., 1974, 63, 219.
5. D. G. Kaiser, J. Pharm. Sci. 1975, 64, 798.
6. D. G. Kaiser et al., J. Pharm. Sci. 1976, 65, 798.
7. D. Pitre and M. Grandi, J. of Chromatogr., 1979, 170, 278-81.
8. E. J. D. Lee et al., Br. J. Clin. Pharmacol., 1985, 19, 669.
9. G. Geisslinger et al., Eur. J. Clin. Pharmacol., 1990, 38: 493-7.

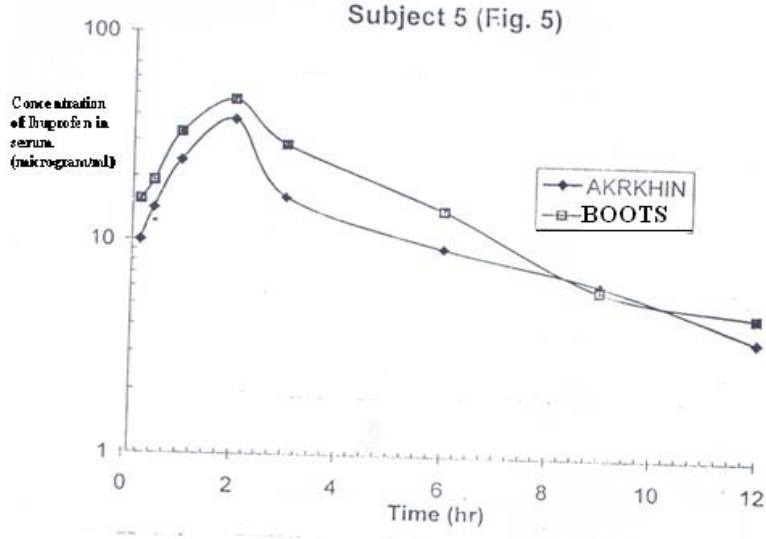
10. Matindale, the extra pharmacopoeia, thirty-first edition, 1996.
11. P. E. Minkler and C. L. Hoppel, J. of Chromatogr., 1988, 428, 388-394.
12. R. Malcolm and T. Tomas, Clinical Pharmacokinetics, Concepts and applications, Second Edition, 1989.

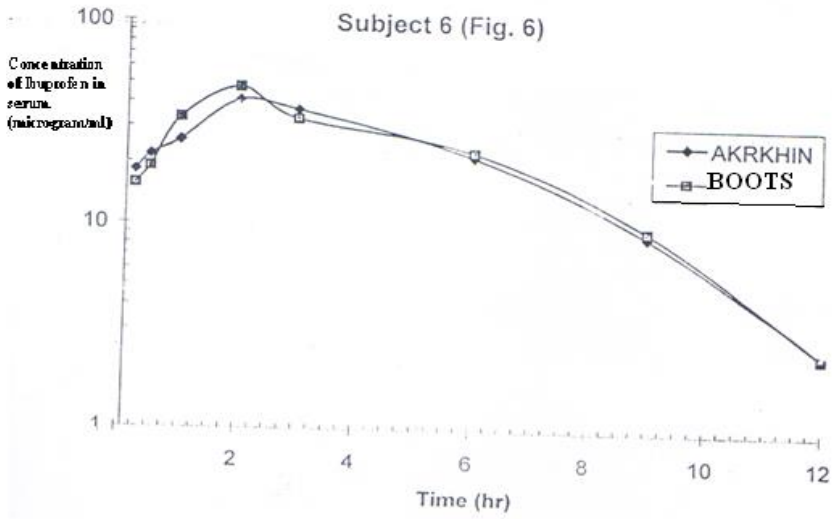

Subject 1 (Fig. 1)
100
Concentration of Ibuprofen in serum (microgram/ml)
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)

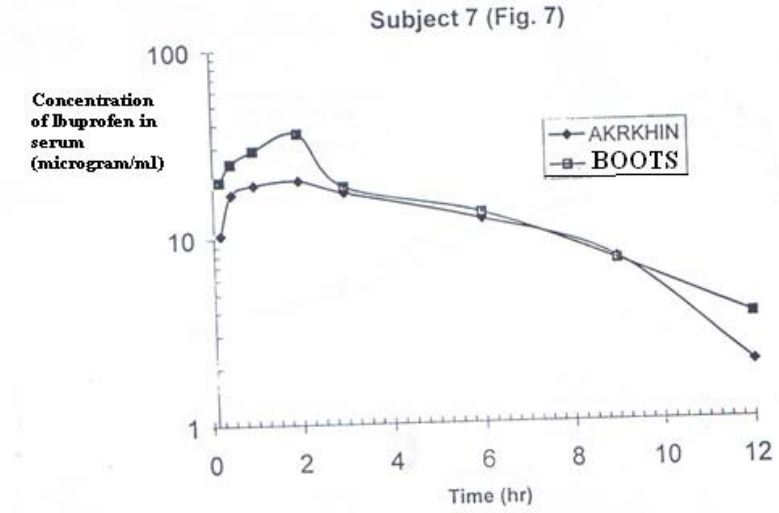

Subject 2 (Fig. 2)
100
Concentration of Ibuprofen in serum (microgram/ml)
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)

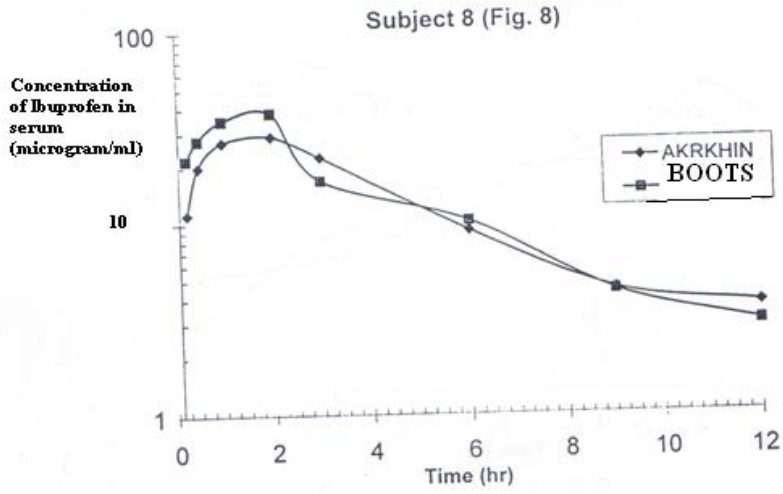

Subject 3 (Fig. 3)
100
10
1
Concentration of Ibuprofen in serum (microgram/ml)
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)

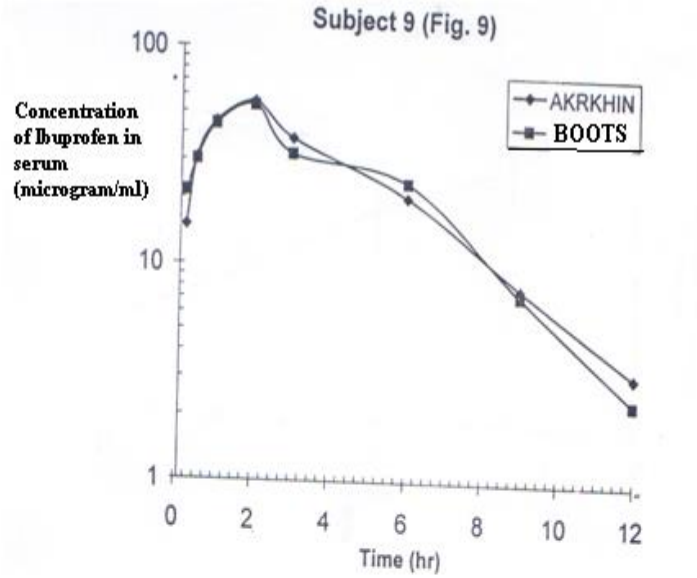

Subject 4 (Fig. 4)
100
10
1
Concentration of Ibuprofen in serum (microgram/ml)
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)

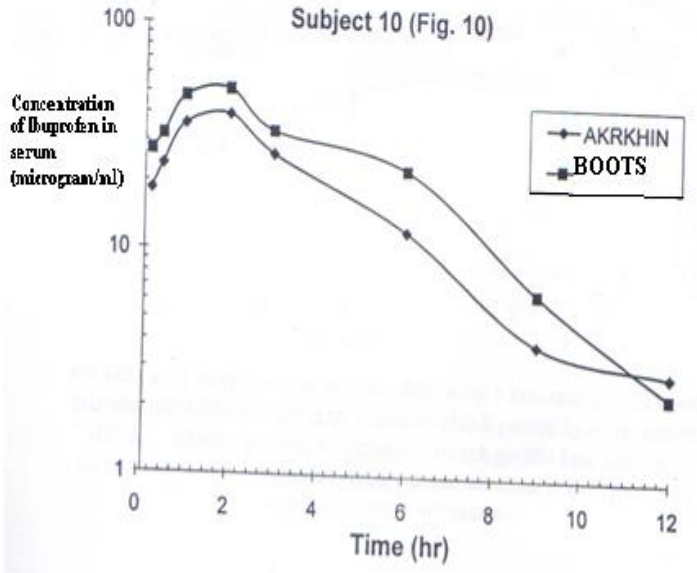

Subject 5 (Fig. 5)
100
10
1
Concentration of Ibuprofen in serum. (microgram/ml)
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)

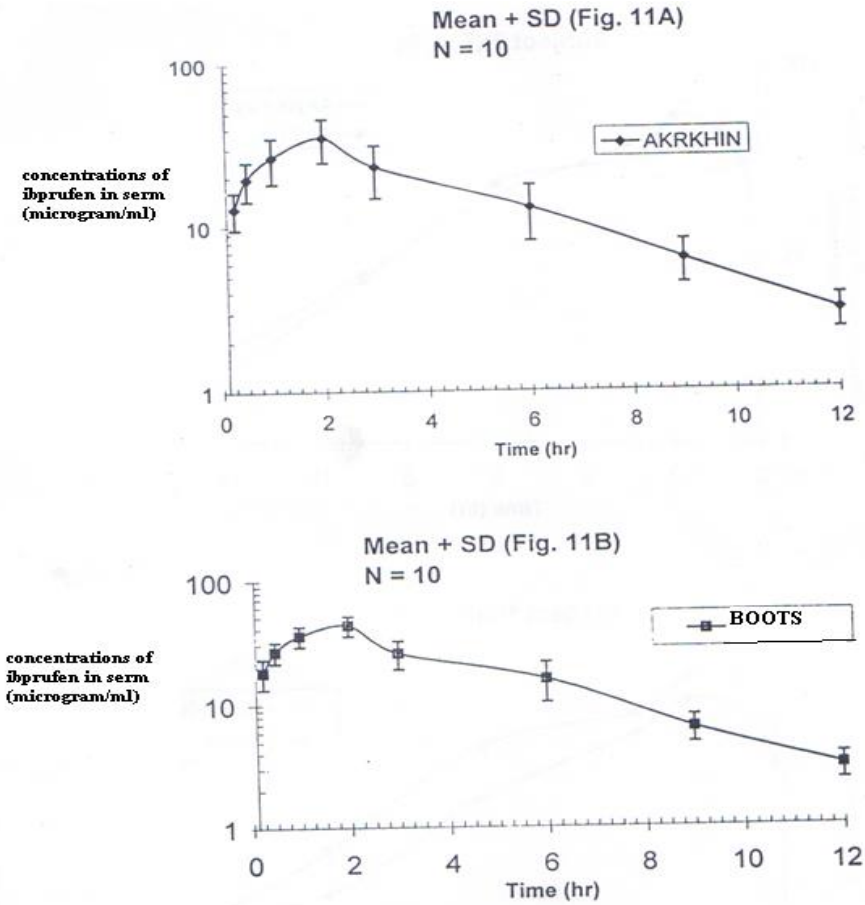

Subject 6 (Fig. 6)
100
10
1
Concentration of Ibuprofen in serum. (microgram/ml)
AKRKHIN
BOOTS
2
4
6
8
10
12
Time (hr)


Subject 7 (Fig. 7)
Concentration of Ibuprofen in serum (microgram/ml)
100
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)


Subject 8 (Fig. 8)
Concentration of Ibuprofen in serum (microgram/ml)
100
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)


Subject 9 (Fig. 9)
Concentration of Ibuprofen in serum (microgram/ml)
100
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)


Subject 10 (Fig. 10)
Concentration of Ibuprofen in serum (microgram/ml)
100
10
1
AKRKHIN
BOOTS
0
2
4
6
8
10
12
Time (hr)



Mean concentrations +SD of Ibprufen tablets in serum versus time after administration of 200mg of Ibprufen tablets AKRKHIN company, Fig 11A and 200mg of Ibprufen tablets BOOTS company. Fig 11B to 10 healthy adult volunteers in two occasions under the same conditions

المقارنة بين حركية الدواء والتوافر الحيوي لاقراص البروفين المنتجة من شركة اكارخين الروسية وشركة بوتس الانكليزية

جعفر هاشم محسن
وزارة العلوم والتكنولوجيا
jafferhashim@yahoo.com

خولة أحمد
جامعة بغداد – كلية الطب

محمد خليل
وزارة العلوم والتكنولوجيا

المستخلص:

عشرة من المتبرعين الذكور الاصحاء الذين تتراوح اعمارهم بين (20-40) سنة واوزانهم بين (55-75) كغم تعاطوا على معدة فارغة وبمجموعتين وتحت نفس الظروف، (200) ملغم من حبوب البروفين المنتجة من شركة اكارخين الروسية و(200) ملغم من حبوب البروفين المنتجة من شركة (بوتس) الانكليزية كل مجموعة على حدة. أظهرت المقارنة الاحصائية للمتغيرات الحركية الصيدلانية والمتضمنة عمر النصف للامتصاص، عمر النطف للطرح، الزمن اللازم للوصول الى اعلى تركيز للدواء في مصل الدم بين الشركتين عدم وجود اختلافات ملحوظة.

علاوة على ذلك فقد ظهر ان البروفين المنتج من شركة اكارخين الروسية يكافئ بايولوجيا للبروفين المنتج من شركة بوتس الانكليزية. تمت جميع القياسات باستخدام تقنية كروماتوغرافيا السائل عالي الاداء بعد تثبيت ظروف القياس والوصل الى الظروف المثلى واعلى حساسية.