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IN-VIVO EVALUATION OF DIFFERENT TYPES OF COMMERCIAL ASPIRIN TABLETS

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ABSTRACT

In-vivo evaluation of four different types of aspirin tablets namely effervescent, soluble,buffered and aluminium derivative of aspirin was assessed in six healthy subjects. The bioavailability parameters of the studied aspirin types were calculated. Effervescent aspirin showed the best results, while buffered aspirin showed the worst.

The pharmacokinetic parameters of the six subjects for the different types of aspirin tablets were also computed. Out of all the different types of aspirin tablets studied, effervescent aspirin exhibited the highest absorption rate constant, while aluminium derivative of aspirin showed the lowest absorption rate constant. Sex was found to greatly affect the

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To whom inquiries should be directed.

absorption of aspirin from the different types of tablets studied, where in all cases male subjects gave higher absorption rate constants and greater bioavailability parameters than females.

INTRODUCTION

Aspirin is the most frequently used nonprescription analgesic, and selection of an aspirin product should be based on formulation preference and proven efficacy (16). Although uncoated conventional aspirin preparations are inexpensive and relatively well absorbed, their usefulness may occasionally be limited by the development of gastric irriation. This irritation may occur after chronic administration of large doses or acute intermittant administration of smaller doses. To reduce such gastric irritation, aspirin could be administered in the form of aqueous solution (effervescent or soluble tablets), buffered tablets and its aluminium derivative.

Although bioavailability studies have been conducted on many dosage forms of aspirin (4,11), non of these studies were concerned with the bioavailability evaluation of the different types of aspirin tablets. Therefore, bioavailability evaluation of the different types of aspirin tablets seems to be of great importance.

In the present study, in-vivo evaluation of selected batches of four different types of commercial brands of aspirin tablets marketed in Egypt was performed.

EXPERIMENTAL

Materials

A single batch of four brands of different types of aspirin tablets were used in this study. The batch numbers of the studied brands are listed below:
Brand H (Trade name: Alexoprine forte, 300 mg aluminium acetylsalicylate, manufactured by Alexandria Co. for Pharmaceutical and Chemical Ind., Alexandria,Batch No. 604041); Brand I (Trade name: Alkaspirin, 300 mg aspirin, buffered aspirin tablet, manufactured by Kahira Pharmaceutical & Chemical Ind. Co., Cairo,Egypt, Batch No. 2723); Brand J (Trade name: Effervescent Aspo-Cid, 500 mg aspirin, manufactured by Chemical Industries Development, Giza, Egypt, Batch No.482133); and Brand K (Trade name: Dispirin, 300 mg aspirin, soluble aspirin, manufactured by Reckitt & Colman (Overseas), Ltd. Reckitt's (Ireland) Ltd., Bluebell, Dublin 12, Batch No. B01347).
Hydrochloric acid 32% (E.Merck,Darmstadt,West Germany); chloroform (Analytical reagent, Mallincrodt Inc., St. Louis, Missouri, U.S.A); Ferric ammonium sulphate (E. Merck, Darmstadt, West Germany), and sodium salicylate

Table 1. General Characteristics of Subjects.

Subject	Sex	Weight (kg)	Age (years)	Height (cm)
M.E	M	65	26	178
M.S	M	84	28	185
M.H	M	78	26	178
A.A	F	57	26	160
M.R	F	68	26	160
R.K	F	67	26	157

(Bayer, Leverkusen, West Germany) were also used in this study.

Apparatus

Centrifuge (Kokusan Ensinki Co., Ltd., Tokyo, Japan), Mechanical Shaker (Fisher, U.S.A), Screw top pyrex culture tubes (Fisher No. 14-932A, 125 x 16 mm, 16 ml size), and Unicam SP 1800 Spectrophotometer were used in this study.

Bioavailability study

Six healthy male and female subjects had no history of GI, liver or kidney disease were shared in

this study. Their general characteristics are shown in Table 1.

Each volunteer was instructed to abstain from all medication, alcohol and beverage or foods that might interfere with the drug for one week before each administration and also during the day of experiment.

Following an overnight fast, each subject was instructed to void his bladder and ingest 250 ml of water. In 1 hr, the 0-hr urine sample was taken as control, and 600 mg of aspirin was ingested with 250ml of water. The effervescent and soluble tablets were dissolved in 150 ml of water 3 minutes prior to dosing, and then the mixture was swallowed. The glass was rinsed with 100 ml of water and this rinsed solution was then swallowed. No foods or liquids other than water were permitted for 4 hours following ingestion of the dose. Cumulative urine samples were taken at 0,0.5,1,1.5,2,3,4,6,8,10,12 and 24 hr. The volume and pH of the collected urine samples were measured at each collection time and samples were refrigerated immediately. Each subject was instructed to drink 250 ml of water after each urine collection for the first 3 hr, and a simple uniform meal was served after the 4-hr sample.

The different types of aspirin tablets were given to

each subject using a random crossover design with 7 days between administration.

Urine analysis

The total amount of salicylate in the urine samples was measured using the procedure of Chiou and Onemelukwa (2). Concentrated hydrochloric acid (2 ml) was added to 3 ml of urine samples in a screw-top pyrex culture tube. After sealing the tubes with plastic caps, they were incubated in an oven at 100°C for 17 hr. After cooling to room temperature, 0.5 ml of approximately 5N hydrochloric acid (prepared by dilution of concentrated hydrochloric acid with an equal volume of distilled water) and 6 ml of chloroform were added. The tubes were shaken for 10 minutes and centrifuged for 5 minutes. Following centrifugation, 3ml of the chloroform layer was then accurately transfered to another screw-top pyrex culture tube. Six milliliters of our proposed reagent (6), without mercuric chloride was added. The tubes were shaken for 10 minutes and centrifuged. After centrifugation, the absorbance of the upper aqueous layer was measured at 540 nm using SP 1800 spectrophotometer.

The concentration of salicylate in the urine sample was determined from a standard curve prepared by measuring the absorbance of sodium salicylate solutions

of known concentrations after subjecting them to the described procedure. Each urine sample was analyzed in duplicate, and the average value was used to calculate the amount of total salicylate excreted during each collection interval. Urine blanks, urine standards spiked with known amounts of sodium salicylate and aqueous sodium salicylate standard solutions were assayed with each batch of the volunteer's urine samples as a quality control check.

Pharmacokinetic analysis

The pharmacokinetic parameters determined in this study were overall elimination rate constant, biological half-life of elimination, absorption rate constant and biological half-life of absorption.

The overall elimination rate constant was determined by the ARE (amount of drug remaining to be excreted) method. The last few (terminal) points of cumulative amounts of drug excreted, were substracted from the total amount excreted and are plotted on a semi-log paper versus time. The slope of the curve gave the overall elimination rate constant (K_{el}).

Methods for the calculation of absorption rates from blood or urine data are well established (13). However, these older methods, have been largely supplanted by a simplified approach, which allows the

calculation of percentage absorbed (of that amount eventually absorbed versus time values without requiring knowledge of the value of the apparent volume of distribution or the fraction of drug excreted unchanged (17). The equation developed by Nelson (8), to calculate absorption rate from the measurement of urinary excretion of the absorbed drug is

$$\frac{dA}{dt} = \frac{1}{f}\left(\frac{1}{K_{el}} \cdot \frac{d^2 Ae}{dt^2} + \frac{dAe}{dt}\right) \ldots\ldots \quad \text{Eq. 1}$$

where f is the fraction of the amount absorbed, dAe/dt is the excretion rate and $d^2 Ae/dt^2$ is the derivative of the excretion rate.

Equation 1 may be integrated between the limits of t= 0 and t= T to obtain

$$A_T\,(f) = \frac{1}{K_{el}} \cdot \frac{dAe}{dt} + Ae\ (mg) \ldots\ldots \quad \text{Eq. 2}$$

where Ae is the cumulative amount excreted in the urine to time T, i.e., upon multiplication of the excretion rate, dAe/dt, for each sampling period by the reciprocal value of the elimination rate constant, K_{el}, and adding to the cumulative amount excreted, Ae, up to that sampling time one obtaine the amount of drug absorbed up to that time A (f).

As soon as all of the drug is absorbed, successive values will stay more or less constant. The average of the asymptotic values gives the total amount absorbed

A_T (f) As. Per cent drug absorbed up to a particular sampling time is calculated according to the following equation

$$\text{Per cent of Drug Absorbed} = \frac{A_T\ (f)}{A_T\ (f)\ As} \times 100 \quad \ldots \text{ Eq. } 3$$

However, it should be pointed out that per cent of drug absorbed is not that percentage of drug absorbed from a given amount of drug, but the percentage of drug absorbed of the amount of drug ultimately absorbed. The slope of a plot of $\log \left(1 - \frac{A_T\ (f)}{A_T(f)\ As} \right)$ versus time equal to the absorption rate constant, K_a.

The physiological availability of aspirin from a particular formulation can be calculated by comparing the "total salicylate" recovered in the urine after administration of the tested tablets (Ts_1) with that recovered after an equivalent dose of aspirin administered in aqueous solution (Ts_2)

$$\% \text{ bioavailability} = \frac{Ts_1}{Ts_2} \times 100 \quad \ldots\ldots \quad \text{Eq. } 4$$

RESULTS AND DISCUSSION

In this paper, bioavailability study was carried out on four selected batches from the different four types of commercial brands of aspirin tablets previously studied (7). The choice of these batches was based on their in-vitro properties.

The selected batches showed the highest dissolution profile comparing to the other batches of the same brands and also gave the best results for the other official and non official tests involved in the in-vitro evaluation of these tablets.

The cumulative mg of salicylate excreted after 24 hours, the urinary peak height (mg/hr), the time to reach that peak (hr) and the per cent bioavailability were used as the bioavailability parameters to evaluate and compare between these studied brands of aspirin tablets.

It is well deccumented that the cumulative urinary excretion data describe the extent of bioavailability of drugs (15).

The cumulative mg salicylate excreted after 24 hours for the tested types are presented in Table 2 and the average cumulative amounts excreted of the six subjects for each brand are shown graphically in figure 1. The results showed that the cumulative mg salicylate excreted after 24 hr for all the tested types ranged from 350.72 - 512.00 with an average value of 433.47. The different types of aspirin tablets gave a different cumulative amounts excreted in the following descending order J - H - K - I. Out of all the studied types, type J showed the highest cumulative

Table 2. Cumulative mg Salicylate Excreted after 24 hr Following Oral Administration of Different Types of Aspirin Tablets.

Subjects	Brands						
	H	I	J	K	Average	a	S.E[x]
M.E	-	345.17	569.62	538.75	484.50	80.75	70.32
M.S	432.14	-	526.15	500.00	486.09	81.02	28.05
M.H	492.50	-	519.50	493.61	501.87	83.65	8.83
A.A	-	-	465.81	377.27	421.54	70.26	44.40
M.R	486.59	401.14	432.92	352.98	418.41	69.73	28.05
R.K	369.74	305.84	557.97	292.94	381.62	63.60	61.13
Average	445.24	350.72	512.00	425.93	433.47	72.25	33.17
b	74.21	58.45	85.33	70.98			
S.E[x]	28.60	27.68	21.66	40.06			

a. The average percent excreted after 24 hours per subject.
b. The average percent excreted after 24 hours per brand.
x. Standard error of the mean.

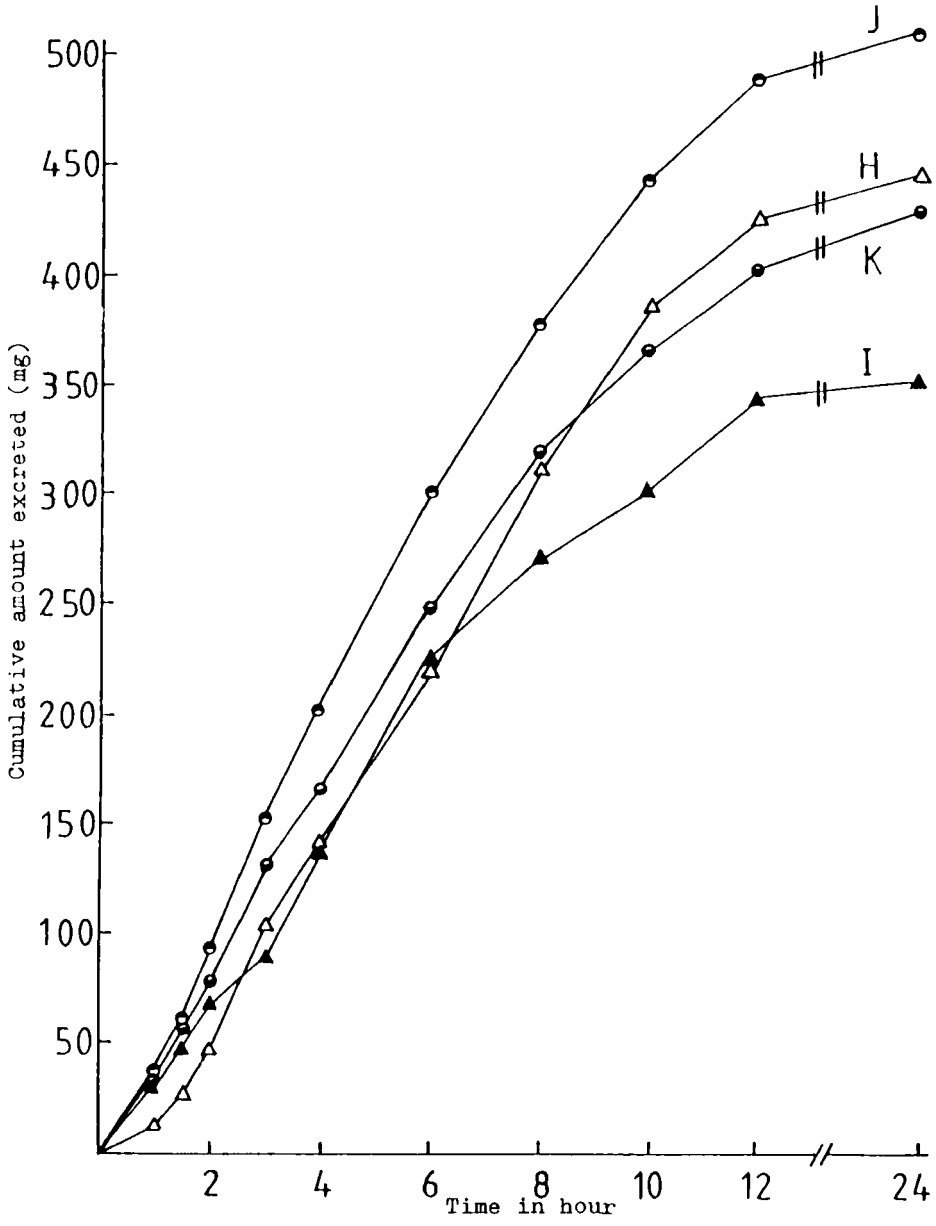

FIGURE 1. Average cumulative apparent salicylate excreted following oral administration of 4 types of aspirin tablets to 6 subjects.

amount excreted, i.e., the greatest extent of bioavailability, while type I showed the lowest cumulative amount excreted, i.e., the lowest extent of bioavailability. In addition, subject M.H. showed the highest cumulative amount of salicylate excreted, while subject R.K. showed the lowest cumulative amount of salicylate excreted among the subjects.

On using the student t test to compare between the extent of bioavailability of the different types of aspirin tablets with that of the best bioavailable conventional aspirin tablets in a previous study (6), no significant differences in the extent of bioavailability as judged from urinary recovery of total salicylate were observed. This result was in a good accordance with some reported results (3,5).

The peak height of the urinary excretion rate curve, as well as the time to reach the peak, could be used as suitable parameters to describe the rate and extent of aspirin absorption. The individual and the average data for the peak height and time necessary to reach the peak are summarizes in Tables 3 & 4 respectively. The average urinary excretion rates of the tested types are shown graphically in Fig. 2.
The results indicated that the urinary peak height for all the tested types ranged from 39.22 - 61.46 mg/hr with an average value of 49.23 mg/hr. The studied

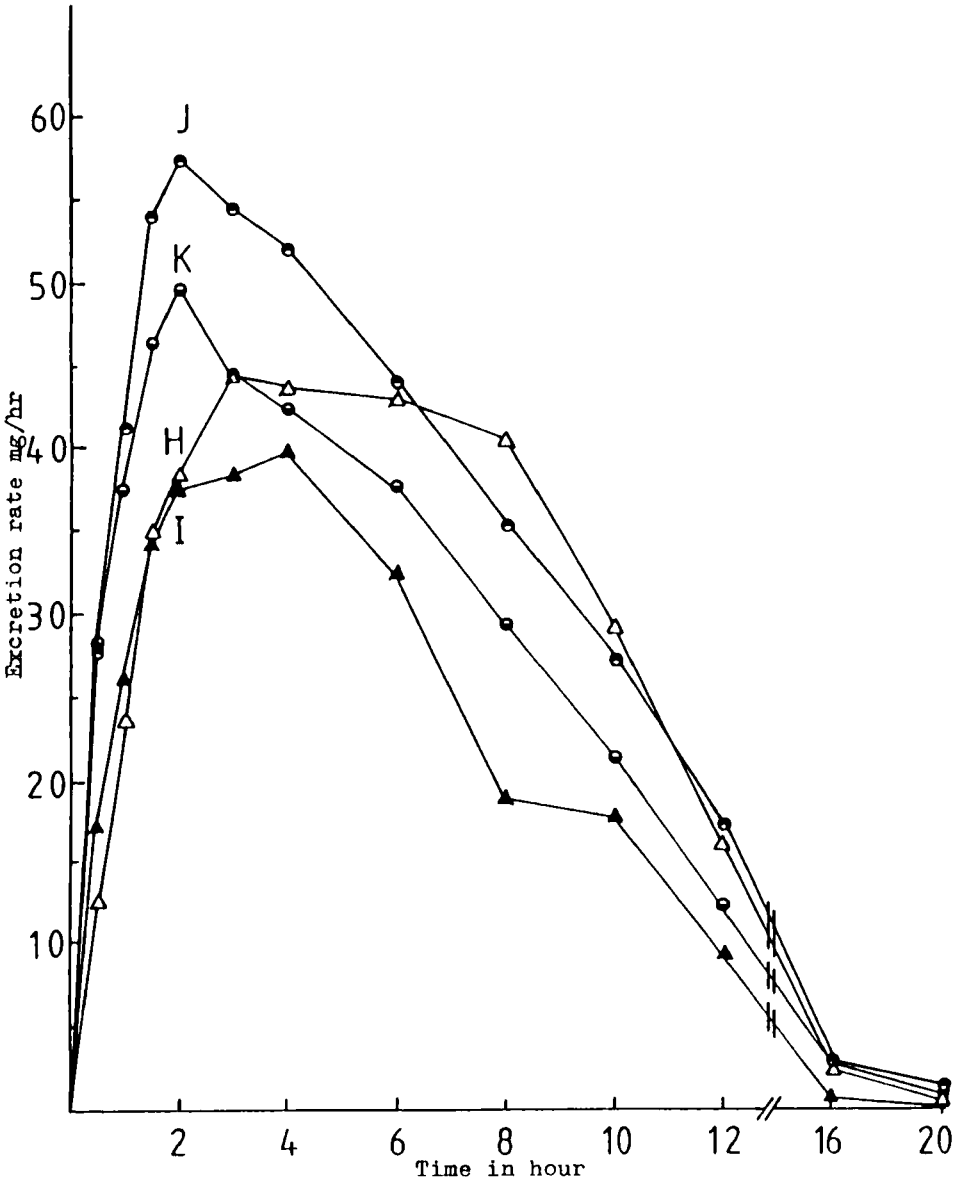

FIGURE 2. Average excretion rate mg/hr for 4 types of aspirin tablets.

Table 3. Urinary Peak Height (mg/hr) Following Oral Administration of Different Types of Aspirin Tablets.

Subjects	Brands					
	H	I	J	K	Average	S.E*
M.E	-	47.78	56.45	68.05	57.43	5.88
M.S	35.06	-	65.62	75.97	58.88	12.30
M.H	57.60	-	63.70	64.96	62.08	2.27
A.A	-	-	75.43	32.03	53.73	21.76
M.R	56.12	37.71	58.67	36.06	47.14	5.95
R.K	32.78	32.18	48.90	27.93	35.45	4.61
Average	45.39	39.22	61.46	50.83	49.23	4.72
S.E*	6.65	4.57	3.68	8.61		

* Standard error of the mean.

types gave peak heights in the following order J > K > H > I (Table 3). Subject M.H., again showed the highest peak height while subjects R.K. showed the lowest one. Out of all the studied types, type J gave the highest peak height while type I showed the lowest one. Table 4 shows that the time taken to reach the peak urinary concentration of the tested aspirin types ran-

Table 4. Time to Reach the Urinary Excretion Peak (hr) After Oral Administration of Different Types of Aspirin Tablets.

Subjects	Brands					
	H	I	J	K	Average	S.E*
M.E	-	2.0	2.0	2.0	2.00	0.00
M.S	1.5	-	2.0	2.0	1.83	0.17
M.H	4.0	-	1.5	2.0	2.50	0.76
A.A	-	-	1.5	1.5	1.50	0.00
M.R	3.0	3.0	3.0	3.0	3.00	0.00
R.K	4.0	4.0	4.0	4.0	4.00	0.00
Average	3.13	3.00	2.33	2.42	2.72	0.21
S.E*	0.59	0.58	0.40	0.37		

* Standard error of the mean.

ged from 2.33 - 3.13 hours with an average value of 2.75 hours. From the average values of the time to reach the peak, the tested types can be arranged in the following order: J > K > I > H. Subject R.K. showed a longer time of peaking for all the studied types of aspirin tablets among subjects. Out of all the studied types of aspirin tablets, type J showed the shortest time of peaking, while type H showed the longest one.

Table 5. Percent Bioavailability Values for Different Types of Aspirin Tablets.

Subjects	Brands					
	H	I	J	K	Average	S.E*
M.E	-	60.60	100.00	94.58	85.06	12.34
M.S	82.13	-	100.00	95.00	92.38	5.33
M.H	94.80	-	100.00	95.02	96.60	1.70
A.A	-	-	100.00	80.99	90.49	9.53
M.R	112.40	92.66	100.00	81.54	96.65	6.48
R.K	66.27	54.81	100.00	52.50	68.39	10.96
Average	88.90	69.36	100.00	83.27	85.38	6.37
S.E*	9.77	11.78	00.00	6.73		

* Standard error of the mean.

The bioavailability of the oral dose of the different types of aspirin tablets was estimated. Table 5 summarizes the obtained results. The results indicated that physiological availability decreased significantly in the order of J, H, K and I. Aqueous solution of aspirin (600 mg/250 ml) was used as standard (100% bioavailability) for determining the physiological availability of the different types of aspirin tablets.

It should be noted that the average bioavailability parameters calculated in this study were considerably lowered by the data from subject R.K. This subject excreted small amounts of salicylate after the administration of all types of aspirin tablets except type J, in the presence of apparently normal renal function. Results from this subject illustrate the importance of intersubject variation in salicylate absorption as previously demonstrated (6).

Generally, on the basis of the calculated bioavailability parameters for the different types of aspirin tablets studied, type J showed the best results while type I showed the worst results, i.e., type J had the highest values of the cumulative mg salicylate excreted after 24 hr, peak height, per cent bioavailability and the shortest time of peaking. Type J which gave the best results was an effervescent aspirin tablet. Effervescent aspirin preparations represent an optimal form of oral dosing, as the drug is ingested in solution. Several reports (1,5), also indicated that greater rates of absorption are seen after ingestion of an effervescent aspirin solution compared to non effervescent solutions. The greater absorption rate exhibited by effervescent tablets may be due to that, the total amount of alkali in such preparations is suffecient to effect a substantial increase in gastric pH. Aspirin

is more soluble at higher pH. At this higher pH, the concentration of unionized acetylsalicylic acid will, however, be decreased and for this reason the rate of aspirin absorption from stomach will tend to be decreased. This effect may well be counterbalanced by rapid gastric emptying and rapid absorption of the drug from intestine.

Comparing the in-vivo results obtained from type I in this study with its in-vitro properties previously obtained (7), a good correlation seems to be exist. Type I showed a poor dissolution profile, a prolonged disintegration time and a low tablet content, these were reflected by its low bioavailability parameters. The type and concentration of buffering agent used in this buffered aspirin may be the reason for its poor dissolution rate and in-vivo performance.

In order to make this in-vivo evaluation of the different types of aspirin tablets of more biological significance, some pharmacokinetic parameters were computed. These parameters were computed for each brand and each subject, assuming first-order elimination from a single compartment (11).

The values of elimination rate constant and elimination half-life are shown in Table 6. The half-life for all the tested types of aspirin tablets was found to be

Table 6. Values of Elimination Rate Constant (hr^{-1}), Kel, and Biological Half-life of Elimination (hr), $t_{1/2}$ el, for Different Types of Aspirin Tablets.

Subjects	Brands											
	H		I		J		K		Average		S.E*	
	Kel	$t_{1/2}$	Kel	$t_{1/2}$	Kel	$t_{1/2}$	Kel	$t_{1/2}$	Kel	$t_{1/2}$	Kel	$t_{1/2}$
M.E	-	-	0.267	2.60	0.270	2.56	0.263	2.63	0.267	2.60	0.002	0.02
M.S	0.240	2.88	-	-	0.200	3.60	0.201	3.45	0.214	3.20	0.013	0.22
M.H	0.200	3.46	-	-	0.101	6.86	0.226	3.06	0.176	3.90	0.038	1.21
A.A	-	-	-	-	0.200	3.46	0.256	2.70	0.228	3.04	0.028	0.38
M.R	0.236	2.94	0.251	2.76	0.208	3.33	0.230	3.01	0.231	3.00	0.009	0.12
R.K	0.251	2.76	0.233	2.97	0.230	3.01	0.280	2.47	0.250	2.77	0.011	0.12
Average	0.232	2.98	0.250	2.77	0.202	3.43	0.243	2.85	0.232	2.98	0.011	0.15
S.E*	0.011	0.15	0.009	0.11	0.022	0.63	0.012	0.15				

* Standard error of the mean.

ranged from 2.77 - 3.43 hr with an average value of 2.98 hr, which corresponded to an elimination rate constant of 0.231 hr^{-1}. This result was in a good accordance with that reported by Levy (10) and Cumming and Martin (4). The different types of aspirin tablets studied showed close values of elimination half-life. Also all the subjects shared in this study showed a very close values of elimination half-life.

The values of absorption rate constant and the absorption half-life are shown in Table 7. The rate constant for absorption ranged from 0.284 - 0.539 hr^{-1}, with an average value of 0.431 hr^{-1} which correspond to a half-life of 1.61 hr.

Out of all the studied types, type J showed the highest absorption rate. This proved that effervescent aspirin tablets had the highest rate and extent of absorption comparing to the all types of aspirin used in this study. On the other hand, type H showed the lowest absorption rate constant among the different studied types. This result was in a good accordance with that reported by Levy and Shali (9). This result was also supported by the dissolution rate results of type H (7) which showed that aspirin of alexoprin dissolved appreciably more slowly in acid solution than aspirin and thus would be expected to dissolve less readily in

Table 7. Values of Absorption Rate Constant (hr^{-1}), Ka, and Biological Half-life of Absorption (hr), $t_{1/2}$ abs, for Different Types of Aspirin Tablets.

Subjects	Brands											
	H		I		J		K		Average		S.E*	
	Ka	$t_{1/2}$	Ka	$t_{1/2}$	Ka	$t_{1/2}$	Ka	$t_{1/2}$	Ka	$t_{1/2}$	Ka	$t_{1/2}$
M.E	-	-	0.498	1.390	0.340	2.04	0.571	1.210	0.469	1.48	0.07	0.250
M.S	0.256	2.710	-	-	0.490	1.41	0.945	0.730	0.564	1.23	0.20	0.580
M.H	0.357	1.940	-	-	0.660	1.05	0.450	1.540	0.489	1.42	0.09	0.260
A.A	-	-	-	-	0.820	0.845	0.310	2.230	0.565	1.23	0.25	0.690
M.R	0.288	2.410	0.384	1.80	0.591	1.170	0.338	2.050	0.400	1.73	0.07	0.260
R.K	0.235	2.950	0.371	1.860	0.335	2.07	0.295	2.350	0.310	2.24	0.03	0.240
Average	0.284	2.440	0.418	1.66	0.539	1.28	0.484	1.430	0.431	1.61	0.05	0.260
S.E*	0.030	0.220	0.040	0.147	0.077	0.211	0.101	0.260				

* Standard error of the mean.

Table 8. Average Bioavailability and Pharmacokinetic Parameters Obtained From the Male and Female Subjects.

Parameters	Males	Females
Cumulative % excreted after 24 hr	81.81	67.86
Peak height (mg/hr)	59.46	45.44
Time of peaking (hr)	2.11	2.83
% availability	91.35	85.17
Absorption rate constant (hr^{-1})	0.507	0.425
Half-life of absorption(hr)	1.37	1.73
Elimination rate constant (hr^{-1})	0.220	0.236
Half-life of elimination(hr)	3.20	2.94

gastric fluid. It has been previously reported that the rate of absorption of aspirin from the gastrointestinal tract was rate limited by its rate of solution (8,12).

The effect of sex on the bioavailability parameters of the different types of aspirin was shown in

Table 9. Average Bioavailability and Pharmacokinetic Parameters for Different Types of Aspirin Tablets.

Brand	Cumulative mg excreted after 24 hrs	Peak height (mg/hr)	Time of peaking (hr)	% Bioavailability	Absorption rate constant (hr^{-1})	Half life of absorption (hr)	Elimination rate constant (hr^{-1})	Half-life of elimination (hr)
H**	445.24	45.39	3.13	88.90	0.284	2.44	0.232	2.98
I*	350.72	39.22	3.00	69.36	0.418	1.66	0.250	2.77
J	512.00	61.46	2.33	100.00	0.539	1.28	0.202	3.43
K	425.93	50.83	2.42	83.27	0.484	1.43	0.243	2.85

** Average of four subjects;

* Average of three subjects.

Table 8. The results showed that male subjects gave higher cumulative per cent salicylate excreted, peak height and per cent bioavailability than females. The effect of sex on the absorption rate constant of aspirin from the different types of aspirin tablets was also studied (Table 8). The results illustrated that the average absorption rate constant obtained from the male subjects (0.507 hr^{-1}) was higher than that obtained from females (0.425 hr^{-1}).

Generally, the average bioavailability and pharmacokinetic parameters for the different types of aspirin tablets are summarized in Table 9.

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