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# IN-VIVO EVALUATION OF COMMERCIAL AND FORMULATED CONVENTIONAL ASPIRIN TABLETS

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## ABSTRACT

In-vivo evaluation of eight brands of conventional aspirin tablets (six commercial brands and two prepared formulae) was assessed in six healthy subjects. Measurements of urinary salicylate excretion were carried out using the method of Chiou and Onyemelukwe in which a proposed reagent was used instead of Trinder's reagent for the assay of total salicylate in urine. The bioavailability parameters of the studied brands were calculated. Out of all the studied commercial brands, brand A showed the best results while brand D showed the worst. A prepared formula (Y) was found to superior over all

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the commercial brands concerning their bioavailability. The inclusion of a surfactant in formula Y was found to be the main reason for absorption enhancement. The pharmacokinetic parameters of the six subjects for the different brands were also computed. A marked intersubject variation for bioavailability and pharmacokinetic parameters was observed.



## INTRODUCTION

The estimation of the bioavailability of a drug in a given dosage form is direct evidence of the efficiency with-which a dosage form performs its intended function (1).

Aspirin is the most frequently used nonprescription analgesic. Since some studies indicated bioavailabity inequivalence among aspirin products (2) and there is no information in the literature on the bioavailability of the aspirin tablets sold in Egypt, therefore, bioavailability evaluation of the various brands of aspirin tablets marketed in Egypt seems to be of utmost importance and is highly needed.

In the present study, in-vivo evaluation of six selected batches from six different brands of commercial conventional aspirin tablets was assessed. In

addition, the in-vivo evaluation of other two formulated conventional aspirin tablets was also done.

## EXPERIMENTAL

### Materials

A single batch of six commercial brands of conventional aspirin tablets and two formulated aspirin tablets were used in this study. The batch numbers of the studied brands are listed below :
Brand A (Trade name: Rivo, 320 mg aspirin, manufactured by the Arab Drug Co., Cairo, A.R.E., Batch No. 507049); Brand B (Trade name: Aspeol, 500 mg aspirin, manufactured by Kahira Pharmaceutical and Chemical Industries Co., Cairo, A.R.E., Batch No. 4349); Brand C (Trade name: Aspocid, 300 mg aspirin, manufactured by Chemical Industries Development, Giza, A.R.E., Batch No. 3169879); Brand D (Trade name: Aspo Nasr, 300 mg aspirin, manufactured by El Nasr Pharmaceutical Chemicals Co., Abu Zaabal, A.R.E., Batch No. 789601-122); Brand E (Trade name: Aspirin Bayer, 300 mg aspirin, manufactured by Bayer, Leverkusen, West Germany, Batch No. 2382B) and Brand F (Trade name: Aspro, 324 mg aspirin, manufactured by Nicholas Laboratories Limited, U.K., Batch No. 71116). The two used formulae

in this study were formula (X) which consists of 300 mg aspirin, 8 mg lactose, 80 mg maize starch and 12 mg talc and formula (Y) which consists of 300 mg aspirin, 7.2 mf lactose, 80 mg maize starch, 12 mg talc and 0.8 mg Aerosol-OT sprayed on powder.

Hydrochloric acid 32 % (E. Merck, Darmstadt, West Germany), Chloroform (Analytical reagent, Mallinckrodt INC. St. Louis, Missouri, U.S.A.), Ferric ammonium sulphate (E. Merck, Darmstadt, W. Germany) and Sodium salicylate (Bayer, Leverkusen,W. Germany) were also used in this study.

## Apparatus

Centrifuge, Kokusan Ensinki Co., L.T.D., Tokyo, Japan; Unicam SP 1800 U.V. Spectrophotometer; Mechanical shaker, Stuart flask shaker and screw top pyrex culture tubes, Fisher No. 14-932 A, 125 X 16 mm, 16 ml size were employed in this study.

## Subjects and Methods

Six healthy male and female subjects had no history of GI, liver or kidney disease were selected for this study. The general characteristics of these subjects are shown in Table 1.

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 |



## Urine collection

Each volunteer was instructed to abstain from all medication, alcohol and beverages 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 introduced to void his bladder and ingest 250 ml of water. In 1 hr the 0-hr urine sample was taken as a control, and 600 mg of aspirin was ingested with 250 ml of water. No food 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 uniform meal was served after the 4-hr sample.

The different commercial and formulated brands were given to each subject, using a random crossover design with 7 days between administrations.

## Urine analysis

The total amount of salicylate in the urine samples was measured using the procedure of Chiou and Onyemelukwe (3). Concentrated hydrochloric acid (2 ml) was added to 3 ml of urine samples in a screwtop pyrex culture tube. After sealing the tubes with plastic caps, they were incubated in an oven at 100°C for 17 hours.

After cooling to room temperature, 0.5 ml of approximately 5 N 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 mechanically for 10 minutes and

centrifuged for 5 minutes. Following centrifugation, 3 ml of the chloroform layer was then accurately transferred to another screw-top culture tube. Six milliliters of modified Trinder's reagent without mercuric chloride was added. The tubes were shaken for 10 minutes and centrifuged. After centrifugation, the absorbance of the aqueous layer was measured at 540 nm using SP 1800 U.V. Spectrophotometer. Modified Trinder's reagent without mercuric chloride was used for 100 % transmittance adjustment.

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 volunteers urine samples as a quality control check.

## Pharmacokinetic analysis

The pharmacokinetic parameters determined in this study were overall elimination rate constant, biolog-

ical 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 equation developed by Nelson (4), to calculate absorption rate constant ($K_a$) from the measurement of urinary excretion of the absorbed drug was used in this study.

## Estimation of % Bioavailability

% bioavailability 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 ($Ts_2$).

$$\% \text{ Bioavailability} = \frac{Ts_1}{Ts_2} \times 100$$

## RESULTS AND DISCUSSION

Measurements of urinary salicylate excretion have been used to study the bioavailability of salicylate such as aspirin and sodium salicylate from their dosage forms. Two analytical methods are most often emp-

loyed : (a) Trinder's reagent method (5), and (b) Levy's modification (6) of the method of Smith (7). Chiou and Onyemelukwe (3), in 1974, suggested a simple and modified colorimetric method for total salicylate assay in urine after salicylate administration.

In this study, a trial was made to prepare a new reagent in which we used simply a mixture of hydrochloric acid (12 ml of 1 N solution) and ferric ammonium sulphate (4.77 gm) to prepare 100 ml solution. The use of hydrochloric acid in this mixture was for the complete conversion of the assayed salicylate into salicylic acid. This formed salicylic acid would react with the available ferric ammonium sulphate to give a colored salicylic acid-ferric-ion complex. The absorbance of this new formed complex could be then assayed at 540 nm either colorimetrically or spectrophotometrically. Different standard solution of sodium salicylate were assayed using Trinder's reagent and the calibration curve is shown in Fig. 1. The same standard solutions were assayed using our proposed reagent and the calibration curve is shown in the same figure. The results showed straight line relationship in both cases which obeyed Beer's-Lambert's law. The results showed that the slope of the straight line produced by our proposed reagent had about

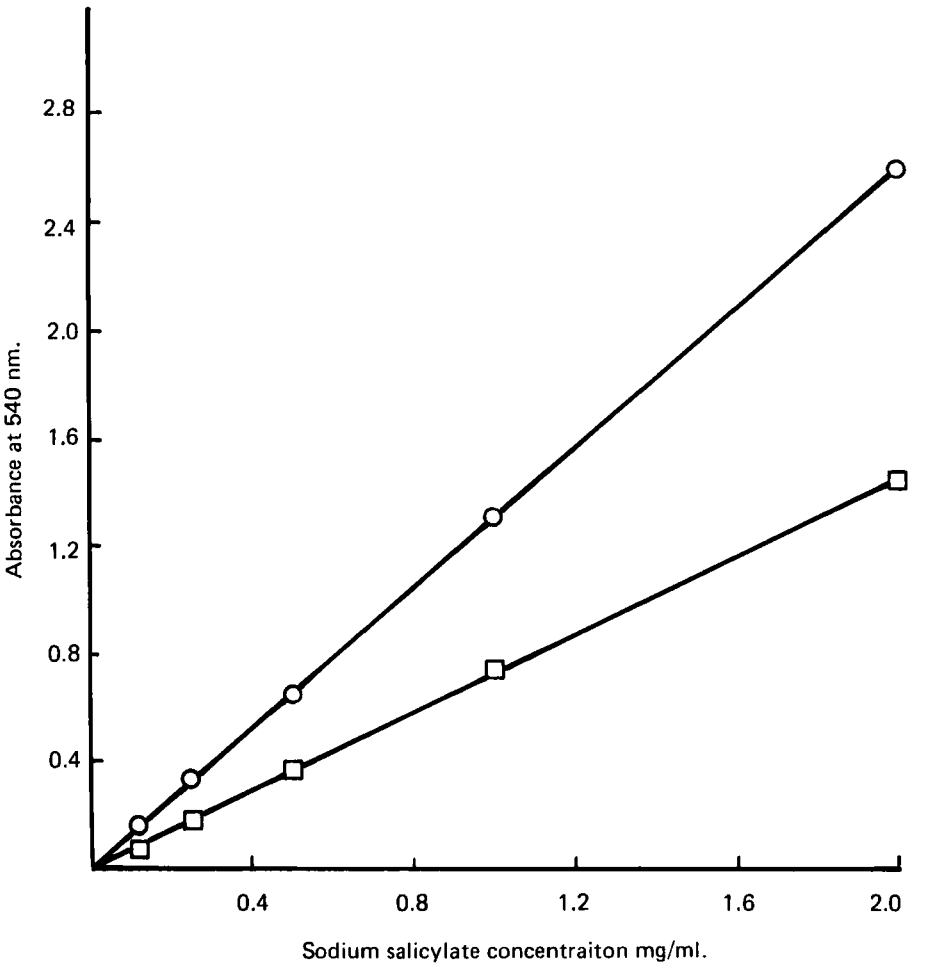


FIGURE 1. Standard curves of sodium salicylate solutions ○——○, Trinder's reagent: □——□, proposed reagent:

half the value of that slope obtained by Trinder's reagent for the same concentrations of salicylate standard solutions. Therefore, higher molar concentrations of ferric ammonium sulphate having the same pH were used for the measurements of these standard sol-

utions of sodium salicylate. The results obtained gave the same slope of the initial proposed concentration of ferric ammonium sulphate. This result indicated that, the salicylic acid-ferric-ion complex resulting from the reaction of salicylic acid with our proposed reagent was independent on the concentration of ferric ion over the initial proposed concentration. This result also proved that the low slope value of the standard curve obtained from our proposed reagent was mainly due to the lower absorbability of the salicylic acid-ferric-ion complex produced from ferric ammonium sulphate than that produced from ferric nitrate.

The reproducibility of the proposed reagent was checked several times for standard aqueous solutions of sodium salicylate and different spiked concentrations of urine samples and the slope was found to be constant in all cases.

The validity of the proposed reagent was assessed by determining the amount of salicylate recovered in urine following the administration of an aqueous solution of aspirin (prepared by dissolving 600 mg effervescent aspirin tablet in 250 ml water before administration). The amount of salicylate recovered in urine after 24 hr was about 95 % of the administered

dose. This result was in a close agreement with that reported by Chiou and Onyemelukwe (3) using Trinder's reagent prepared by ferric nitrate.

The absorbance of salicylic acid-ferric-ion complex resulting from the reaction of salicylic acid with ferric ammonium sulphate could vary markedly with the pH of the solution. Therefore, some precaution should be exercised in preparing our proposed reagent and standard curve should be established for each lot of the reagent prepared. The prepared reagent was found to be stable for several months when stored at room temperature in a light-resistant tight container.

In this paper, bioavailability study was carried out on six selected batches from the six different brands of commercial conventional aspirin tablets previously studied by the author (8). In addition, the bioavailability of two formulated conventional aspirin tablets was also studied. The choice of these batches and formulae was based on their in-vitro properties. The selected batches showed the highest dissolution profiles 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. Also formula X

showed the highest dissolution profile out of some studied formulae. Formula Y was involved in this evaluation to study the effect of surfactants on the bioavailability of aspirin as this formula was the best formula out of the formulae containing surface active agents in their in-vitro evaluation.

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 the studied eight brands of conventional aspirin tablets (six commercial brands and two prepared formulae).

It is well doccumented that the cumulative urinary excretion data describe the extent of bioavailability of drugs (9).

The cumulative mg salicylate excreted after 24 hours for the tested brands are presented in Table 2, and are shown graphically in Fig. 2.

The results showed that the cumulative mg salicylate excreted after 24 hr for all the tested brands ranged from 318.06 - 453.75 mg with an average of 379.35 mg. The studied brands gave different cumulative excreted amounts in the following order :

$$Y > X > A > F > C > E > B > D$$

Table 2. Cumulative mg Salicylate Excreted After 24 Hours Following Oral Administration of Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | Formulated Tablets | | Average | a | S.E* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | X | Y | | | |
| M.E | 470.73 | 383.35 | 492.01 | 310.41 | 339.89 | 328.53 | 430.30 | 500.06 | 406.91 | 67.80 | 27.06 |
| M.S | 499.22 | 346.66 | 433.23 | 455.21 | 469.21 | 410.75 | 461.35 | 405.01 | 435.08 | 72.50 | 16.73 |
| M.H | 386.28 | 346.12 | 387.45 | 356.21 | 401.02 | 437.82 | 473.93 | 589.82 | 422.33 | 70.40 | 28.05 |
| A.A | 472.34 | 273.05 | 301.73 | 299.20 | 360.42 | 321.07 | 459.44 | 413.23 | 362.56 | 60.40 | 27.19 |
| M.R | 434.83 | 349.09 | 360.94 | 225.85 | 261.12 | 557.43 | 414.05 | 508.16 | 388.93 | 64.80 | 40.21 |
| R.K | 243.45 | 289.90 | 187.19 | 261.50 | 277.34 | 237.46 | 279.37 | 306.24 | 260.30 | 43.38 | 33.98 |
| Average | 417.81 | 331.36 | 360.43 | 318.06 | 351.50 | 382.17 | 419.74 | 453.75 | 379.35 | 63.20 | 16.81 |
| b | 69.60 | 55.28 | 60.00 | 53.00 | 58.60 | 63.70 | 69.90 | 75.63 | | | |
| S.E* | 38.33 | 16.92 | 43.50 | 32.85 | 31.72 | 45.52 | 29.48 | 40.57 | | | |

a. The average per cent excreted after 24 hours per subject.

b. The average per cent excreted after 24 hours per brand.

*. Standard error of the mean.

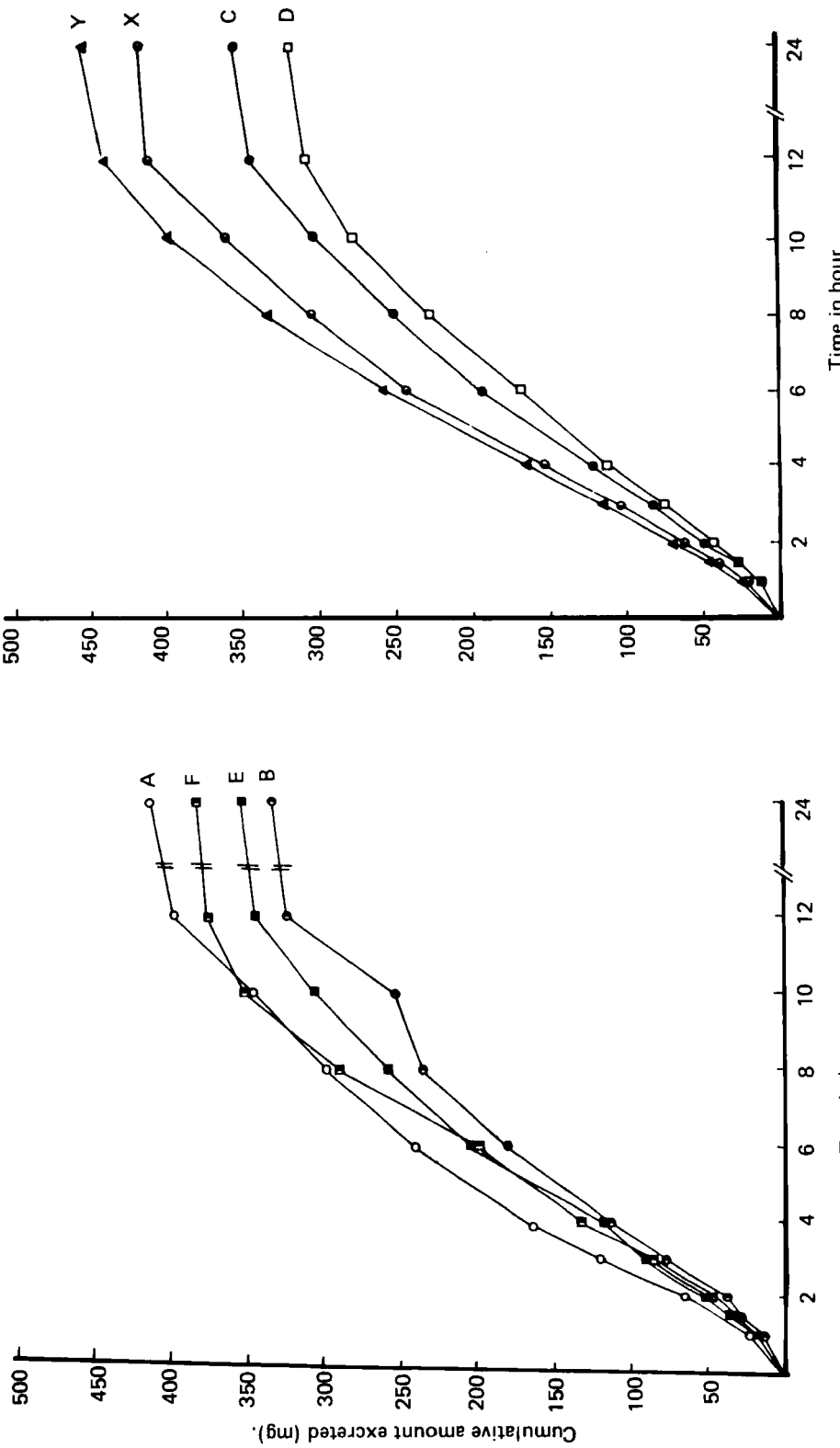


FIGURE 2. (A&B). Average cumulative apparent salicylate excreted following oral administration of 8 brands of conventional aspirin tablets to 6 subjects.

Analysis of variance of these data is summarized in Table 3. The data showed statistically significant difference between the various brands tested at the five per cent level of confidence and a significant inter-subject variation at the one per cent level of confidence was also observed.

This means that the different brands of conventional aspirin tablets had different extent of bioavailability as there was a significant difference between brands relative to the cumulative amount of salicylate excreted after 24 hr. However, the inter-subject variation was more significant as indicated by its significance at the lower level of confidence.

Out of all the studied brands, brand Y showed the highest cumulative amount excreted, i.e. the greatest extent of bioavailability, while brand D showed the lowest extent of bioavailability. In addition, subject R.K. showed the lowest cumulative amount of salicylate excreted among the subjects.

Chiou and Onyemelukwe (10), reported that there were no significant differences in the percentage of the dose ultimately excreted in the urine after 24 hours from five aspirin tablets. However, the results obtained in our study indicated a great variation between

Table 3. Analysis of Variance For The Cumulative mg Excreted After 24 Hours.

| Source of variance | Sum of squares | Degrees of freedom | Mean of squares | F ratio |
|---|---|---|---|---|
| Between brands | 95076.83 | 7 | 13582.4 | 3.22(S)[a] |
| Between subjects | 162076.96 | 5 | 32415.4 | 7.68(S)[a] |
| Error | 147634.31 | 35 | 4218.1 | — |

a. Significant.

Tabular F (7,35) = 2.33 at p= 0.05

Tabular F (5,35) = 3.70 at p= 0.01

brands in the amount of salicylate excreted after 24 hours.

The peak serum concentration was suggested to be a function of both the rate and extent of drug absorption, while the time necessary to reach that peak is only a function of the rate of drug absorption (9). Similarly, in the present study, the peak height of the urinary excretion curve, as well as the time to reach that peak, could also be used as suitable para-

meters 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 summarized in Tables 4 & 5. The average urinary excretion rate curves of the tested brands are shown graphically in Fig. 3. The results from Table 4 indicated that the urinary peak height for all the tested brands was ranged from 35.42 - 50.90 mg/hr with an average value of 43.72 mg/hr. The studied brands gave different peak height in the following order :

$$Y > A > X > F > C > E > B > D$$

Subject M.S. showed the highest peak height while subject R.K. showed the lowest one. Out of all the studied brands, brand Y gave the highest peak height, while brand D showed the lowest one.

Results of analysis of variance of the peak height are shown in Table 5. No statistically significant differences between brands were observed from peak height data at $p = 0.05$. However, a very significant intersubject variation was observed at $p = 0.01$.

Table 6 shows that the time taken to reach the peak urinary concentration of the tested aspirin brands ranged from 2.08 - 3.33 hours with an average value of 2.75 hours. From the average values of the

Table 4. Urinary Peak Height (mg/hr) Following Oral Administration Of Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | Formulated Tablets | | Average | S.E* |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | X | Y | | |
| M.E | 57.80 | 55.12 | 63.61 | 36.26 | 38.98 | 41.12 | 48.64 | 56.39 | 49.74 | 3.54 |
| M.S | 67.45 | 45.16 | 49.57 | 52.93 | 62.20 | 54.44 | 64.25 | 42.74 | 54.84 | 3.20 |
| M.H | 49.72 | 38.29 | 39.92 | 38.16 | 46.97 | 51.13 | 73.81 | 91.45 | 53.68 | 6.76 |
| A.A | 39.73 | 24.50 | 30.75 | 31.76 | 29.35 | 38.33 | 36.01 | 37.99 | 33.55 | 1.87 |
| M.R | 68.50 | 47.47 | 55.99 | 33.90 | 38.83 | 49.47 | 40.55 | 52.10 | 48.35 | 3.87 |
| R.K | 17.25 | 23.65 | 15.90 | 19.49 | 20.85 | 28.82 | 26.69 | 24.73 | 22.17 | 1.86 |
| Average | 50.07 | 39.03 | 42.62 | 35.42 | 39.53 | 43.88 | 48.33 | 50.90 | 43.72 | 1.99 |
| S.E* | 7.93 | 5.21 | 7.14 | 4.41 | 5.84 | 3.92 | 7.26 | 9.29 | | |

* Standard error of the mean.

Table 5. Analysis of Variance For The Peak Height (mg/hr).

| Source of variance | Sum of squares | Degrees of freedom | Mean of squares | F ratio |
|---|---|---|---|---|
| Between brands | 1336.86 | 7 | 190.98 | 1.81(N.S)[a] |
| Between subjects | 6786.96 | 5 | 1357.39 | 12.87 (S)[b] |
| Error | 3689.69 | 35 | 105.42 | |

a. Not significant.

b. Significant.

Tabular F (7,35) = 2.33 at p= 0.05

Tabular F (5,35) = 3.7 at p= 0.01

time taken to reach the peak, the tested brands can be arranged in the following order :

$$Y > A > X > E > F > D > C > B$$

Analysis of variance for the time to reach the peak is shown in Table 7. No statistically significant differences between brands were observed at p = 0.05. However, a significant intersubject variation was observed at p = 0.05.

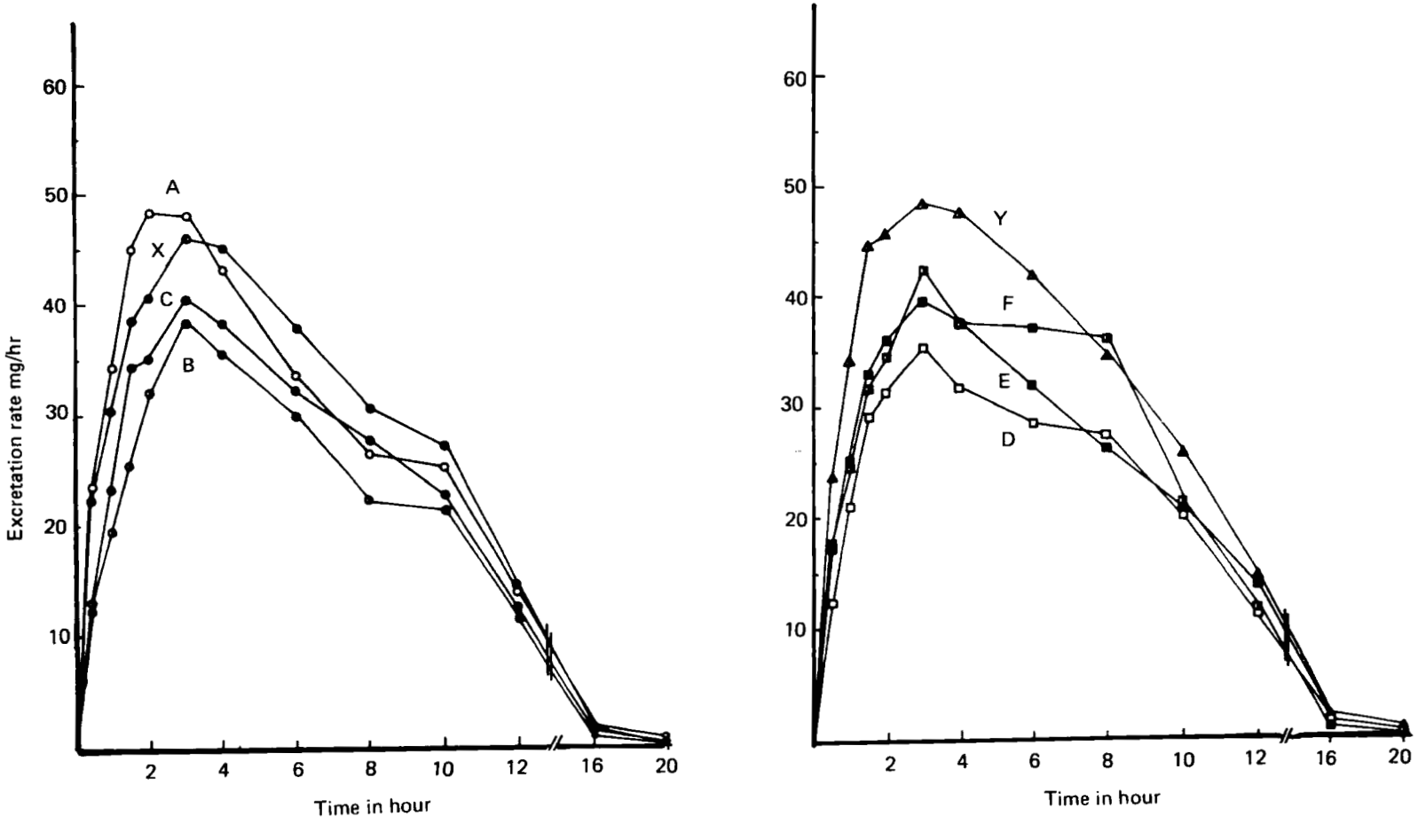


FIGURE 3. (A&B). Average excretion rate mg/hr for 8 brands of conventional aspirin tablets.

Table 6. Time To Reach The Urinary Excretion Peak (hr) After Oral Administration of Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | Formulated Tablets | | Average | S.E* |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | X | Y | | |
| M.E | 1.50 | 3.00 | 2.00 | 3.00 | 1.50 | 3.00 | 2.00 | 1.50 | 2.18 | 0.25 |
| M.S | 2.00 | 3.00 | 4.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 0.19 |
| M.H | 3.00 | 4.00 | 3.00 | 3.00 | 4.00 | 3.00 | 3.00 | 3.00 | 3.25 | 0.16 |
| A.A | 3.00 | 4.00 | 6.00 | 3.00 | 3.00 | 3.00 | 1.50 | 2.00 | 3.19 | 0.48 |
| M.R | 2.00 | 3.00 | 1.50 | 3.00 | 3.00 | 3.00 | 4.00 | 1.50 | 2.63 | 0.31 |
| R.K | 2.00 | 3.00 | 3.00 | 3.00 | 2.00 | 2.00 | 1.50 | 1.50 | 2.25 | 0.23 |
| Average | 2.25 | 3.33 | 3.25 | 3.00 | 2.75 | 2.83 | 2.50 | 2.08 | 2.75 | 0.16 |
| S.E* | 0.25 | 0.21 | 0.65 | 0.00 | 0.36 | 0.16 | 0.41 | 0.30 | | |

* Standard error of the mean.

Table 7. Analysis of Variance For The Time to Reach The Peak (hr).

| Source of variance | Sum of squares | Degrees of freedom | Mean of squares | F ratio |
|---|---|---|---|---|
| Between brands | 8.53 | 7 | 1.22 | 2.17(N.S)[a] |
| Between subjects | 8.80 | 5 | 1.76 | 3.14 (S)[b] |
| Error | 19.75 | 35 | 0.56 | |

a. Not significant.

b. Significant.

Tabular F (7,35) = 2.33 at p= 0.05

Tabular F (5,35) = 2.35 at p= 0.05

**The bioavailability of the oral dose of 600 mg aspirin in the various tablet formulations (6 commercial brands and 2 formulated) was estimated. Table 8 summarizes the results obtained.**

**The results indicated that, physiological availability decreased significantly in the order Y, X, A, F, C, E, B and D.**

Table 8. Per cent Bioavailability Values For Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | Formulated Tablets | | Average | S.E* |
|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | X | Y | | |
| M.E | 82.64 | 67.30 | 86.38 | 54.50 | 59.67 | 57.68 | 75.54 | 87.79 | 71.44 | 4.78 |
| M.S | 94.88 | 65.89 | 82.34 | 86.52 | 89.19 | 78.07 | 87.69 | 76.98 | 82.69 | 3.18 |
| M.H | 74.36 | 66.63 | 74.58 | 68.57 | 77.19 | 84.27 | 91.29 | 113.54 | 81.30 | 5.40 |
| A.A | 101.40 | 58.62 | 64.77 | 64.23 | 77.37 | 68.93 | 98.63 | 88.70 | 77.83 | 5.84 |
| M.R | 100.44 | 80.64 | 83.37 | 52.17 | 60.32 | 128.76 | 95.75 | 117.38 | 89.85 | 9.29 |
| R.K | 43.63 | 51.96 | 33.59 | 46.87 | 49.71 | 42.56 | 50.07 | 54.89 | 40.67 | 5.22 |
| Average | 82.89 | 65.17 | 70.84 | 62.14 | 68.91 | 76.71 | 83.16 | 89.88 | 73.96 | 7.09 |
| S.E* | 8.96 | 3.93 | 8.10 | 5.86 | 5.99 | 12.05 | 7.38 | 9.51 | | |

* S.E: Standard error of the mean.

It should be noted that, the average results of cumulative salicylate excreted, peak height and per cent bioavailability observed in this study were considerably lowered by the data from one subject (R.K.). This subject excreted small amounts of salicylate after the administration of all products, in the presence of apparently normal renal function. Results from this subject demonstrate the importance of intersubject variation in salicylate absorption, especially in view of our findings of statistically significant intersubject differences.

Generally, on the basis of the calculated bioavailability parameters for the different studied brands of conventional aspirin tablets, brand Y showed the best results, while brand D showed the worst, i.e. brand Y had the highest values of the cumulative per cent excreted, peak height, per cent bioavailability and the shortest time of peaking (Table 13). Out of the studied six commercial brands of conventional aspirin, brand A had the best bioavailability parameters.

Comparing the in-vivo results obtained in this study with the in-vitro results of the same brands previously obtained by the author (8), brand A had a

better in-vitro results than brand D as brand A showed a higher dissolution rate, shorted disintegration time and excellent results for hardness, thickness, friability and hardness-friability ratio than brand D. This indicated that an excellent correlation exists between both in-vitro and in-vivo data of these brands of aspirin tablets. Although brand F showed a better in-vitro dissolution rate than brand A, brand A had a superior bioavailability parameters than brand F. This may be due to the formation of a coarse agglomerate of particles arised from the very fine powder which resulted from the disintegration of tablets of brand F in the gut as these coarse agglomerates would present a small effective surface area and so absorption of aspirin will be decreased. This decrease in aspirin absorption would affect its bioavailability parameters.

Concerning the bioavailability parameters of the two studied formulated aspirin tablets (X & Y), it was found that formula Y showed a higher per cent availability, higher peak height, greater per cent excreted after 24 hours and a shorter time of peaking than formula X. This in-vivo results was opposite to the in-vitro results obtained from these two formulae. This proved that, although the incorporation of the

surfactant in formula Y decreased the dissolution rate of its tablets (11), the surfactant markedly increased aspirin absorption rate and hence improved the bioavailability parameters of such formula. The enhancement in aspirin absorption in the presence of the surface active agent may be due to that surfactants directly alter membrane permeability of the GI tract (12). Although the mechanism of this "hyperabsorptive state" is unknown, most investigators believe that the surfactant disrupts the integrity of the epithelial membrane in a reversible fashion. The removal of proteins (13) and phospholipids (14), from the membrane by surfactants may alter permeability. "Plasticization" of the membrane by the action of surfactant molecules in the lipoidal epithelium has also been suggested as a possible mechanism for altered permeability (12).

Comparing the bioavailability parameters obtained from the formulated tablets (X & Y) with that showed by all the studied commercial brands of conventional aspirin tablets, it was found that formula Y showed the highest per cent bioavailability, the greatest per cent salicylate excreted after 24 hr, the highest peak height and the shortest time of peaking, while formula X had only greater per cent bioavailability and per

cent salicylate excreted after 24 hr than all the studied commercial brands of aspirin tablets.

In order to make this in-vivo evaluation of the different brands of conventional aspirin tablets of more biological significance, some pharmacokinetic parameters were computed. These parameters were computed for each brand for each subject, assuming first-order elimination from a single compartment (15).

In the present study, we have utilized measurements of total salicylate concentration to describe aspirin kinetics. The use of total salicylate data in the calculation of apparent absorption rate constants has been discussed by Levy (16) and Rowland, et al., (17). Rapid absorption of aspirin, its partial hydrolysis in the gastrointestinal tract by nonspecific esterases, and extensive first-pass hepatic clearence to salicylic acid are the major factors which substantiate the use of total salicylate concentration in the kinetic analysis. The rapid in-vivo hydrolysis of aspirin also prevents a significant change in the apparent volume of distribution during the time of absorption (16).

The values of elimination rate constant (Kel) and elimination half-life are shown in Table 9. The half-life for all the tested brands was found to be ranged

Table 9. Values of Elimination Rate Constant, ($hr^{-1}$), Kel and Biological Half-life of Elimination (hr), $t_{½}$ el, for Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | | | | | | | Formulated Tablets | | | | Average | | S.E* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | B | | C | | D | | E | | F | | X | | Y | | | | | |
| | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ | Kel | $t_{½}$ |
| M.E | 0.211 | 3.30 | 0.200 | 3.40 | 0.264 | 2.60 | 0.220 | 3.15 | 0.290 | 2.40 | 0.162 | 4.30 | 0.210 | 3.30 | 0.24 | 2.88 | 0.225 | 3.08 | 0.01 | 0.21 |
| M.S | 0.200 | 3.40 | 0.245 | 2.80 | 0.231 | 3.00 | 0.220 | 3.15 | 0.252 | 2.75 | 0.258 | 2.68 | 0.250 | 2.77 | 0.21 | 3.20 | 0.234 | 2.96 | 0.01 | 0.09 |
| M.H | 0.232 | 2.99 | 0.220 | 3.15 | 0.221 | 3.10 | 0.210 | 3.30 | 0.237 | 2.90 | 0.140 | 4.95 | 0.170 | 4.00 | 0.20 | 3.46 | 0.204 | 3.39 | 0.01 | 0.24 |
| A.A | 0.206 | 3.36 | 0.280 | 2.50 | 0.232 | 2.98 | 0.205 | 3.40 | 0.230 | 3.01 | 0.242 | 2.80 | 0.260 | 2.66 | 0.21 | 3.36 | 0.233 | 2.97 | 0.01 | 0.12 |
| M.R | 0.203 | 3.40 | 0.253 | 2.74 | 0.246 | 2.82 | 0.233 | 2.97 | 0.228 | 3.04 | 0.213 | 3.25 | 0.255 | 2.72 | 0.25 | 2.76 | 0.235 | 2.95 | 0.01 | 0.09 |
| R.K | 0.250 | 2.77 | 0.223 | 3.10 | 0.270 | 2.57 | 0.260 | 2.66 | 0.260 | 2.66 | 0.243 | 2.85 | 0.285 | 2.43 | 0.26 | 2.63 | 0.257 | 2.69 | 0.01 | 0.07 |
| Average | 0.217 | 3.19 | 0.237 | 2.92 | 0.244 | 2.84 | 0.225 | 3.08 | 0.250 | 2.77 | 0.210 | 3.30 | 0.238 | 2.91 | 0.23 | 3.01 | 0.231 | 3.00 | 0.01 | 0.06 |
| S.E* | 0.008 | 0.11 | 0.011 | 0.13 | 0.008 | 0.09 | 0.008 | 0.11 | 0.009 | 0.10 | 0.020 | 0.38 | 0.017 | 0.24 | 0.01 | 0.14 | | | | |

* S.E: Standard error of the mean.

Table 10. Values of Absorption Rate Constant ($hr^{-1}$), Ka, and Biological Half-Life of Absorption (hr), $t_{½}$ abs, For Different Commercial And Formulated Conventional Aspirin Tablets.

| Subjects | Commercial Tablets | | | | | | | | | | | | Formulated Tablets | | | | Average | | S.E* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | B | | C | | D | | E | | F | | X | | Y | | | | | |
| | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ | Ka | $t_{½}$ |
| M.E | 0.640 | 1.08 | 0.72 | 0.96 | 0.45 | 1.54 | 0.385 | 1.80 | 0.341 | 2.03 | 0.530 | 1.31 | 0.411 | 1.68 | 0.496 | 1.39 | 0.497 | 1.39 | 0.05 | 0.13 |
| M.S | 0.915 | 0.76 | 0.54 | 1.28 | 0.35 | 1.98 | 0.366 | 1.89 | 0.427 | 1.62 | 0.471 | 1.47 | 0.354 | 1.96 | 0.314 | 2.21 | 0.467 | 1.48 | 0.07 | 0.17 |
| M.H | 0.370 | 1.87 | 0.26 | 2.66 | 0.33 | 2.10 | 0.430 | 1.61 | 0.268 | 2.60 | 0.440 | 1.57 | 0.510 | 1.36 | .516 | 1.34 | 0.391 | 1.77 | 0.04 | 0.18 |
| A.A | 0.174 | 3.98 | 0.18 | 3.85 | 0.25 | 2.77 | 0.330 | 2.10 | 0.245 | 2.83 | 0.271 | 2.55 | 0.255 | 2.72 | 0.301 | 2.30 | 0.251 | 2.76 | 0.02 | 0.24 |
| M.R | 0.590 | 1.17 | 0.28 | 2.48 | 0.54 | 1.28 | 0.517 | 1.34 | 0.494 | 1.40 | 0.244 | 2.80 | 0.300 | 2.31 | 0.320 | 2.16 | 0.411 | 1.67 | 0.05 | 0.21 |
| R.K | 0.240 | 2.88 | 0.24 | 2.89 | 0.20 | 3.46 | 0.175 | 3.96 | 0.330 | 2.10 | 0.320 | 2.16 | 0.311 | 2.23 | 0.255 | 2.72 | 0.259 | 2.67 | 0.02 | 0.23 |
| Average | 0.488 | 1.42 | 0.37 | 1.87 | 0.35 | 1.98 | 0.367 | 1.89 | 0.351 | 1.97 | 0.379 | 1.83 | 0.357 | 1.94 | 0.367 | 1.89 | 0.379 | 1.83 | 0.04 | 0.06 |
| S.E* | 0.110 | 0.51 | 0.09 | 0.44 | 0.05 | 0.33 | 0.046 | 0.38 | 0.039 | 0.22 | 0.045 | 0.25 | 0.040 | 0.19 | 0.045 | 0.22 | | | | |

* S.E: Standard error of the mean.

Table 11. Analysis of Variance For The Absorption Rate Constant ($hr^{-1}$).

| Source of variance | Sum of squares | Degrees of freedom | Mean of squares | F ratio |
|---|---|---|---|---|
| Between brands | 0.078 | 7 | 0.011 | 0.68(N.S)[a] |
| Between subjects | 0.424 | 5 | 0.085 | 5.31 (S)[b] |
| Error | 0.549 | 35 | 0.016 | |

a. Not significant.

b. Significant.

Tabular F (35,7) = 3.38 at p= 0.05

Tabular F (5,35) = 3.70 at p= 0.01

from 2.69 - 3.39 hr with a mean value of 3 hr, which corresponded to an elimination rate constant of 0.231 $hr^{-1}$.

All the studied brands showed very close values of elimination half-life. Also, all the subjects shared in this study showed very close values of elimination half-life.

Table 12. Average Bioavailability and Pharmacokinetic Parameters Obtained from the Male and Female Subjects.

| Parameter | Male | Female |
|---|---|---|
| Cumulative % excreted after 24 hr | 70.23 | 56.19 |
| Peak height (mg/hr) | 52.75 | 34.69 |
| Time of peaking (hr) | 2.81 | 2.69 |
| % availability | 78.47 | 71.45 |
| Absorption rate constant ($hr^{-1}$) | 0.451 | 0.307 |
| Half-life of absorption (hr) | 1.54 | 2.26 |
| Elimination rate constant ($hr^{-1}$) | 0.221 | 0.42 |
| Half-life of elimination (hr) | 3.14 | 2.86 |

The values of absorption rate constant (Ka) and the absorption half-life are shown in Table 10. The rate constant for absorption ranged from 0.251 - 0.497 $hr^{-1}$, with an average value of 0.379 $hr^{-1}$ which corresponded to a half-life of 1.83 hr.

Analysis of variance on the values of absorption rate constant was performed. Table 11 shows no statis-

Table 13. Average Bioavailability And Pharmacokinetic Parameters For Different Commercial And Formulated Conventional Aspirin Tablets.

| Brand or formula | Cumulative % 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) |
|---|---|---|---|---|---|---|---|---|
| A | 69.60 | 50.07 | 2.25 | 82.89 | 0.488 | 1.420 | 0.217 | 3.190 |
| B | 55.20 | 39.03 | 3.33 | 65.17 | 0.370 | 1.870 | 0.237 | 2.920 |
| C | 60.00 | 42.62 | 3.25 | 70.84 | 0.350 | 1.980 | 0.244 | 2.840 |
| D | 53.00 | 35.42 | 3.00 | 62.14 | 0.367 | 1.890 | 0.225 | 3.080 |
| E | 58.60 | 39.53 | 2.75 | 68.91 | 0.351 | 1.970 | 0.250 | 2.770 |
| F | 63.70 | 43.88 | 2.83 | 76.71 | 0.379 | 1.830 | 0.210 | 3.300 |
| X | 69.90 | 48.33 | 2.50 | 83.16 | 0.357 | 1.940 | 0.238 | 2.910 |
| Y | 75.63 | 50.90 | 2.08 | 89.88 | 0.367 | 1.890 | 0.230 | 3.010 |

tically significant differences between the various brands tested. However, significant inter-subject variation at the one per cent level of confidence was observed. This indicated by the vast difference in the average absorption rate constant between subject M.E. (0.497 $hr^{-1}$) and subject A.A. (0.251 $hr^{-1}$).

On studying the effect of sex, Table 12 illustrated that males have markedly higher average cumulative per cent salicylate excreted, average peak height and absorption rate constant of aspirin than females.

Generally, the average bioavailability and pharmacokinetic parameters for the eight studied brands of conventional aspirin tablets are summarized in Table 13.

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