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# FORMULATION, BIOAVAILABILITY AND PHARMACOKINETIC PROPERTIES OF COMBINED PARACETAMOL / ORPHENADRINE IN TABLETS

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فى هذه الدراسة تمت مقارنة كل من الخواص المعملية والاتاحة الحيوية وكذلك الخواص الحركية لصيغتين مختلفتين من الأقراص تحتويان على خليط من الباراسيتامول والأورفينادرين.

كانت الصيغة الأولى (منتج أ) هو (نورجيسيك أقراص انتاج شركة ايبيكو- ج.م.ع) بينما كانت الصيغة الثانية (منتج ب) هو أقراص تمت صياغتها فى هذه الدراسة ولها نفس التركيب.

وقد أثبتت النتائج أن معدل الذوبان فى حالة المنتج (أ) كان أعلى منه فى حالة المنتج (ب). أما دراسة الاتاحة الحيوية فقد تمت على متطوعين ذكور أصحاء تناولوا جرعة واحدة من أى من الصيغتين تبعا لدراسة تبادلية. تم تجميع عينات الدم فى المتطوعين على فترة ثمانى ساعات عقب تناول الأقراص.

بعد ذلك تم إيجاد الخواص الحركية لكل الصيغتين مثل متوسط أعلى مستوى للدواء فى الدم والوقت اللازم لبلوغ أعلى تركيز للعقار فى الدم وفترة نصف العمر ومعدل الإخراج النهائى وكذلك المساحة تحت منحنى تركيز العقار فى البلازما.

وقد وجد أن متوسط أعلى مستوى للدواء فى الدم كان فى حالة الصيغة (أ) أعلى منها فى (ب). أما بالنسبة للوقت اللازم لبلوغ أعلى تركيز للعقار فى الدم وفترة نصف العمر ومعدل الإخراج النهائى فقد ثبت أنه لا يوجد اختلاف احصائى بين الصيغتين المستخدمتين.

بالاضافة إلى ذلك فقد تبين من الدراسة أنه لا يوجد اختلاف احصائى فى مدى الامتصاص الدوائى لكل من الصيغتين وذلك كما هو واضح من نتائج المساحة تحت منحنى تركيز العقار فى البلازما فى الحالتين.

وبناء على ما تم الحصول عليه من نتائج فإنه يمكن القول بأن كلا من الصيغتين اللتين تمت دراستهما قد وجدا متكافئتين حيويا وذلك من حيث الاتاحة الحيوية والخواص الحركية وذلك عند دراسة خواصهما على متطوعين آدميين.

*In this investigation, the in-vitro characters, the bioavailability, as well as the pharmacokinetic parameters of two different paracetamol/orphenadrine citrate tablet formulations were compared. The first formulation (product A) was Norgesic tablets (Manufactured by E.I.P.I.Co., A.R.E) while the other (product B) was formulated tablets of the same composition.*

*The in-vitro dissolution revealed faster dissolution rate in case of product A. Bioavailability study was conducted on healthy male subjects after receiving a single oral dose of either product A or B according to a 2-way crossover study. Blood samples were collected over an eight hour period and analyzed for their drug contents using HPLC.*

*Pharmacokinetic parameters were determined for both formulations including, mean maximum plasma concentration ($C_{max}$), time of maximum concentration ($T_{max}$), half-life ($t_{1/2}$), terminal rate of elemination ($K_e$) and area under serum concentration- time curve (AUC)*

*It was found that $C_{max}$ obtained with product A was higher than that with product B. Regarding $T_{max}$, $t_{1/2}$, and $K_e$, both products were found to be not statistically different.*

*Furthermore, the two products were not found significantly different in the extent of absorption as indicated by area under serum concentration-time curve.*

*These findings may indicate that the two products are bioequivalent in terms of bioavailability and pharmacokinetic properties determined in normal healthy male volunteers.*

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## INTRODUCTION

Orphenadrine citrate is one of the skeletal muscle relaxants whose action is suggested to be central (due to CNS depressant effect). Accordingly, it is used to treat skeletal muscle spasms associated with acute painful muscloskeletal conditions.[1] In combination with paracetamol, a synergestic effect occurs for the relief of pain.

It is readily absorbed from G.I.T. with peak plasma level of 2 hrs and duration of action 2-8 hrs.[1,2] The half-life is about 14 hrs for the parent compound.[1] The onset of action is within one hr and peak serum concentration is 110-210 ng for a dose of 100 mg.

Paracetamol [acetamide, N-(4-hydroxyphenyl)] is an analgesic agent whose mechanism of action is thought to be due to inhibition of prostaglandin synthesis and to a lesser extent due to peripheral blocking of pain impulses. On the other hand, its antipyretic effect is owed to its direct action on the heat regulating center in the hypothalamus. This action will lead to peripheral vasodiltation resulting in increased blood flow through skin, sweating and heat loss.[1,3] Its absorption from G.I.T. is rapid and almost complete but may decrease with high carbohydrate meals. The time required to peak concentration is 0.5-2 hrs, with a peak plasma concentration of 5-20 μg (dose 650 mg) and a duration of action of 3-4 hrs. Its half-life is about 1-4 hrs. Approximately, 90-95% of the dose is metabolized in the liver.[1-3]

Several investigations were carried out for the study of the bioequivalence of various formulations of paracetamol tablets,[4,5] while others reported significant differences in the absolute bioavailability of paracetamol tablets obtained from different manufacturers.[6,7]

In addition, the problems associated with the compression of paracetamol are also reported.[6] Accordingly, the work in this investigation was oriented towards the formulation of paracetamol combination tablets with orphenadrine for the purpose of assessment of a formula that will be bioequivalent to the standard formulations in addition to the trial to adjust formulation factors as well as *in-vitro* testing methodologies to make these methods, as possible, an alternative for *in-vivo* studies.

## EXPERIMENTAL

### Materials

Orphenadrine citrate-paracetamol tablets [Norgesic®, EIPICo, ARE, under licence from 3M Health Care, England, B.N. 993980 and Exp. Date 8/02] was selected as reference (Product A).

Orphenadrine citrate (kindly donated by EIPICo, 10th of Ramadan city, A.R.E.), paracetamol and PVP (Mwt 40.000) (Sigma, St. Louis, MO, USA), phosphoric acid, diethyl ether, chloroform (HPLC grade), sodium lauryl sulphate and perchloric acid (B.D.H., poole, UK), trichloroacetic acid (Mallinckrodt, St louis, MO, USA), gelatin powder and potassium dihydrogen phosphate (E. Merck, Darmstadt, Germany), starch, talc and lactose (El-Nasr Pharm. Chem. Co., Abuzabal, ARE), avicel PH 101 and 102 (FMC, Philadelphia, USA), magnesium stearate (Fluka, Buchs, Switzerland).

### Equipment

High performance liquid chromatograph consisting of waters 610 pump, 486 spectrophotometric detector, 717 autosampler and equipped with millennium 2010 chromatography manager, using 30 cm x 3.9 mm (id.) μ bondapak C18 reversed phase column with an average particle size of 10 μm (Waters, division of Millipore corp., Milford, MA, USA). Centrifuge, MSE-minor 35 (MSE, Sussex, UK). Vernier caliber (Oct 166-80, USSR). Tablet press, Stokes 912-512.1 (Sharples-stokes division. Pennwalt corp., Warminister, Penna, USA). Hardness tester (Erweka, TB24), Roche Friabilator (Eerweka, TAP), Disintegration tester (Erweka, ZT3) and Dissolution tester (Erweka, DT) [Erweka App., Main, Germany].

### Methodology

#### 1. Preparation of tablets

Tablet formulations containing paracetamol and orphenadrine citrate were listed in Table (1). Formulations B and C were prepared by wet granulation while D and E were prepared by direct compression technique.

For wet granulation technique; each of the two drugs, lactose and half the amount of starch were mixed in a mortar and kneeded with either

**Table 1:** Composition of various formulated tablets

| Ingradients (in mg) | Formulation | | | |
|---|---|---|---|---|
| | B | C | D | E |
| Paracetamol | 450 | 450 | 450 | 450 |
| Orphenadrine citrate | 35 | 35 | 35 | 35 |
| Gelatin (5% solution) | -- | QS(≡20 mg) | -- | -- |
| Starch | 20 | 20 | 20 | 20 |
| Talc | 20 | 20 | 20 | 20 |
| Magnesium stearate | 5 | 5 | 5 | 5 |
| Lactose | 130 | 130 | -- | -- |
| PVP (10% solution) | QS(≡20 mg) | -- | -- | -- |
| Avicel PH 101 | -- | -- | 150 | -- |
| Avicel PH 102 | -- | -- | -- | 150 |

10% PVP solution (formulation B) or 5% gelatin solution (formulation C). The mix was passed through 2 mm sieve, dried at 60° for 12 hrs and mixed with the remaining powders in the formula. Then, the powder was compressed. For direct compression technique; all the tablet components were sieved, mixed and compressed.

Tablet compression was carried out at constant pressure using 12 mm diameter flat-faced punches.

**2. *In-vitro* evaluation of tablets**

All of the prepared tablet formulations (B,C,D and E) as well as the reference one (formulation A) were subjected to *in-vitro* testing 24 hrs after compression.[8] The tablet properties tested were; hardness, friability, dimensions, disintegration time, drug content, weight variation in addition to the dissolution kinetics.

Each of hardness, dimensions and drug content testing was carried out on ten tablets, while twenty tablets were used for each of weight variation and friability testing. Disintegration time testing was carried out according to USP 24[9] specifications.

Dissolution testing was done according to USP 24,[9] using USP 1 dissolution tester (Basket type). The dissolution medium composed of 900 ml of phosphate buffer[10] pH 6.8[11] adjusted at 37±0.5° and stirred at a rate of 100 rpm.

Samples were withdrawn at predetermined time intervals and assayed by HPLC for paracetamol contents at 254 nm[3] and for orphenadrine citrate contents at 264 nm[12] using conditions mentioned below under analytical techniques (Figs. 1,2).

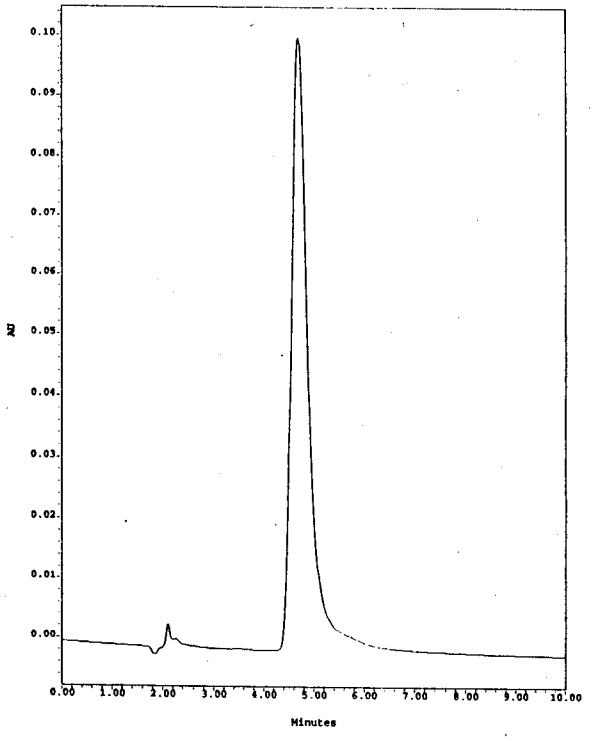


**Fig. 1:** Typical HPLC chromatogram of paracetamol.

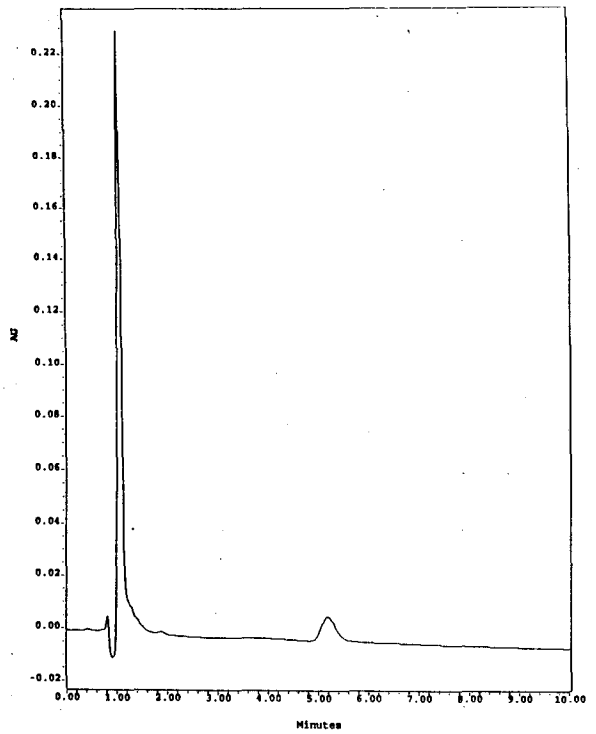


**Fig. 2:** Typical HPLC chromatogram of resolved paracetamol and orphenadrine.

### 3. *In-vivo* study

**Ethics and legal aspects**

The bioavailability study was performed according to the rules and recommendations of Helsinki.[13] All subjects were given detailed information on the goals and possible risks of the study and vocal consents were taken.

**Subjects**

The study was conducted in laboratories of Department of Pharmaceutical Technology, Tanta University. Fourteen healthy male adult volunteers participated in this study. Their mean (±SEM) age was 32±1.4 years with a range of 23-42 years, body weight of 68.3±1.8 kg with a range of 52-76 kg and height of 170.8±0.6 cm with a range of 159-178 cm. All subjects were selected on the basis of negative past medical history, no subject had a history or evidence of diabetes, cardiac, renal or G.I. diseases or drug allergy. The volunteers were asked to abstain from taking any drug for two weeks prior to the study. All subjects were fasted for twelve hrs before start of drug administration.

**Clinical study**

Each subject received the tested products (A and B) on two treatment days with a 7 day washout period. Each product was assigned to a treatment day in a single-dose, 2 way-crossover design. On the test day, each subject was asked to swallow the specified tablet with 250 ml of water. During the study period, every subject received one litre of fluids and two standardized medium fat meals[13] at two and eight hrs after the start of experiment.

Five ml blood samples were withdrown before drug administration (zero time), at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hrs following drug administration. Then, serum was separated by centrifugation at 3000 rpm for 10 minutes and immediately frozen at-20° till analyzed.

**Analytical techniques**

**- Determination of paracetamol in serum**

The HPLC method reported by Horwitz *et al.*[14] and modified by Fritz *et al.*[15] was selected for analysis of paracetamol in serum. Due to the presence of another drug (orphenadrine), calibration curve of paracetamol in serum was constructed in presence and absence of orphenadrine citrate.

The assay procedure involved sample thawing, deproteinization using trichloroacetic acid and extraction with 7 ml of diethyl ether. The residue left after evaporation using Rotavapour (Heidolph VV 2000), was dissolved in 10 ml of mobile phase consisting of 0.1% potassium dihydrogen phosphate in "acetonitrile/water 7:93 V/V adjusted to pH 2.4 with phosphoric acid". 50 µl of drug solution in mobile phase was injected into the HPLC at a flow rate of 1.2 ml/min. Paracetamol was detected at 254 nm.[3]

**- Determination of orphenadrine citrate in serum**

The HPLC method described by Shelkirk *et al.*[16] was selected with slight modification. Standard curve in presence and absence of paracetamol was constructed.

For analysis, samples were thawed, protein was precipitated (as above) and solutions were extracted with three portions of chloroform each of 5 ml. The residue left after evaporation (as mentioned before) was dissolved in 10 ml of mobile phase consisting of "acetonitrile/water 50:50 containing 50 mM potassium dihydrogen phosphate and 40 mM sodium lauryl sulphate and adjusted to pH 4 with phosphoric acid".

Fifty µl of drug solution was injected into the HPLC at a flow rate of 2 ml/min. Orphenadrine citrate was detected at 264 nm.

**- Pharmacokinetic analysis**[17]

Both the maximum drug concentrations ($C_{max}$) and corresponding peak times ($t_{max}$) were determined from the data and serum concentration-time curves. The elimination rate constant ($K_e$) was obtained from the least square fitted terminal log-linear portion of the serum concentration-time curve. The area under serum concentration curve ($AUC_{0-8}$) was obtained by the trapezoidal rule.

**- Statistical analysis**

Average serum levels as well as the standard error of the mean and the coefficient of variation were calculated for each product.

Two way analysis of variance (2-ANOVA) was performed on overall values to determine subject and product variations.

## RESULTS AND DISCUSSION

**1. *In-vitro* evaluation of tablets**

Table (2) shows the physical properties of various tablet formulations tested.

**a) Friability and weight variation**

All formulations were found to satisfy the USP requirements for uniformity of weight and friability.

**b) Hardness and disintegration time testing**

All the prepared tablets were subjected to these tests.

From Table (2), it is clear that formulations prepared using avicel (D and E) have hardness values about 6 kg/inch$^2$ while formulations B and C prepared with PVP and gelatin as binders had values of 7.75 and 7.92 respectively.

Disintegration time testing revealed that formulations D and E showed disintegration time less than two minutes while formulation A was disintegrated after 4 minutes. On the other hand, formulations B and C were found to have disintegration time values of 6.5 and 14.8 minutes respectively. These results are coinciding with those of hardness and with the reported data.[18] Also, the results of hardness were found to confirm those of friability as previously reported.[19]

In addition, formulations D and E showed lower thickness, higher diameter values and lower hardness values compared to other ones. So, those tablets will be expected to have higher porosity. This in addition to the presence of Avicel may conclude for the rapid disintegration in this case compared to other formulations.

**c) Dissolution study**

The dissolution medium was composed of 900 ml of phosphate buffer pH 6.8. Figures (3 and 4) show dissolution profiles of various tablet formulations. The figures show that significant differences in the dissolution profiles between various formulations prepared by wet granulation and those prepared by direct compression were observed.

From Figure (3), it is clear that formulations D and E showed higher initial drug release for both drugs than those of B and C. The amount of drug released after 90 minutes was 58 and 76% in case of formulations D and E respectively.

In addition, from Figures (5 and 6), it is clear that the highest rate of drug release was achieved in case of formulations A and B which scored nearly the same rate followed in a descending order by formulations C and E while formulation D showed the lowest drug release rate.

These results may be explained on the basis that the presence of cellulose derivatives (avicel PH 101 and 102) in formulations D and E might increase the holding capacity of the tablet matrix towards the drug. This may explain the reduced total amount of drug released from these formulations.

***2. In-vivo evaluation of tablets***

Products A and B were subjected to this study. These products were selected in view of their *in-vitro* release characteristics.

The mean serum concentrations at specified time intervals are presented in Figures (7 and 8). In addition, the mean pharmacokinetic parameters for tested products were deduced and illustrated in Tables (3-6). These tables show some intersubjects as well as intersubject variabilities which are consistent with what have been reported.[20]

**Table 2:** Physical properties of various tablet formulations

| Tablet properties | Formulation type | | | | |
|---|---|---|---|---|---|
| | A | B | C | D | E |
| Hardness (kg/inch$^2$) | 10.5(±1.0) | 7.75(±0.75) | 7.92(±0.37) | 6.37(±1.1) | 5.9(±1.0) |
| Friability | 0.21% | 0.19% | 0.18% | 0.52% | 0.64% |
| Dimensions. | | | | | |
| a) Diameter (mm) | 12.85(±0.05) | 12.15(±0.05) | 12.1(±0.1) | 12.0(±0.0) | 12.0(±0.0) |
| b) Thickness (mm) | 6.2(±0.0) | 6.9(±0.05) | 6.8(±0.1) | 7.6(±0.1) | 7.5(±0.3) |
| Disintegration Time (minutes) | 4.0(±0.2) | 6.5(±0.18) | 14.8(±0.91) | 1.7(±0.30) | 1.2(±0.16) |
| Weight variation (mg) (uniformity of weight) | 700.5(±4.5) | 663.5(±3.5) | 648.5(±8.5) | 670.5(±4.5) | 683(±5.2) |
| Drug content (content uniformity) | | | | | |
| a) Paracetamol | 99.6% | 99.8% | 98.5% | 100.9% | 101.7% |
| b) Orphenadrine citrate | 100.3% | 100.6% | 97.9% | 101.3% | 102.6% |
| Dissolution parameters | | | | | |
| a) $t_{50}$ (minutes) | 6.3 | 9.1 | 16.5 | 32.4 | 16.5 |
| b) Dissolution rate constant (K) (min$^{-1}$) | | | | | |
| i- Paracetamol | $7.37\times10^{-2}$ | $4.44\times10^{-2}$ | $3.54\times10^{-2}$ | $0.71\times10^{-2}$ | $1.40\times10^{-2}$ |
| ii- Orphenadrine citrate | $3.56\times10^{-2}$ | $3.43\times10^{-2}$ | $3.75\times10^{-2}$ | $0.87\times10^{-2}$ | $1.46\times10^{-2}$ |

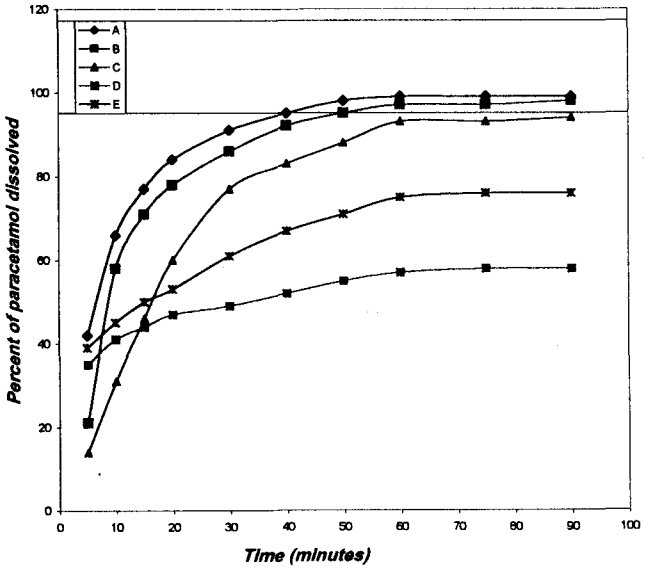


**Fig. 3:** Release of paracetamol from various tablet formulations.

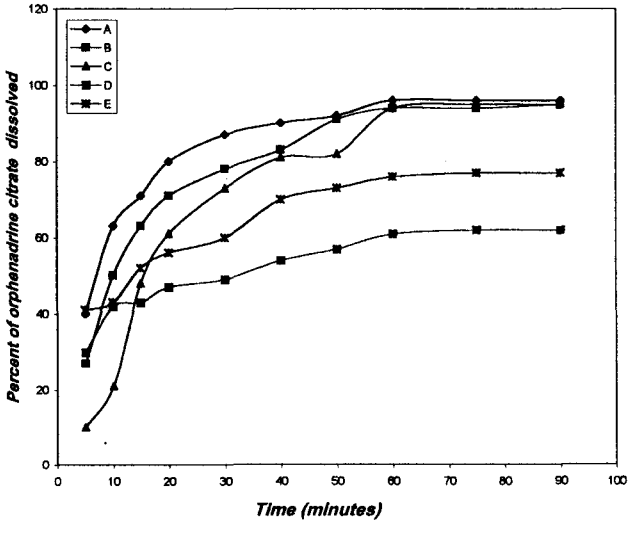


**Fig. 4:** Release of orphenadrine citrate from various tablet formulations.

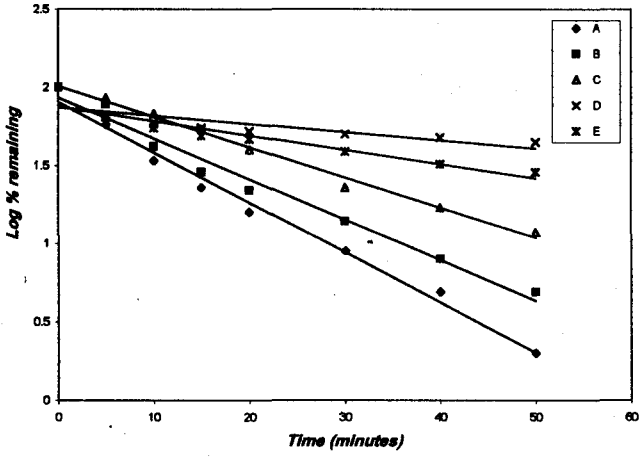


**Fig. 5:** First order kinetics for paracetamol release from various tablet formulations.

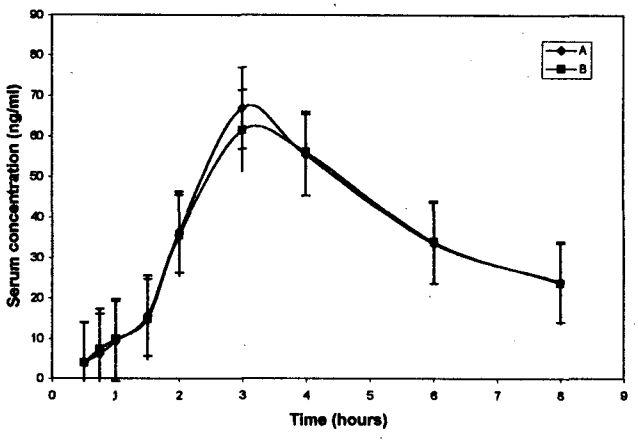


**Fig. 7:** Mean serum orphenadrine citrate concentrations following oral administration of products A and B.

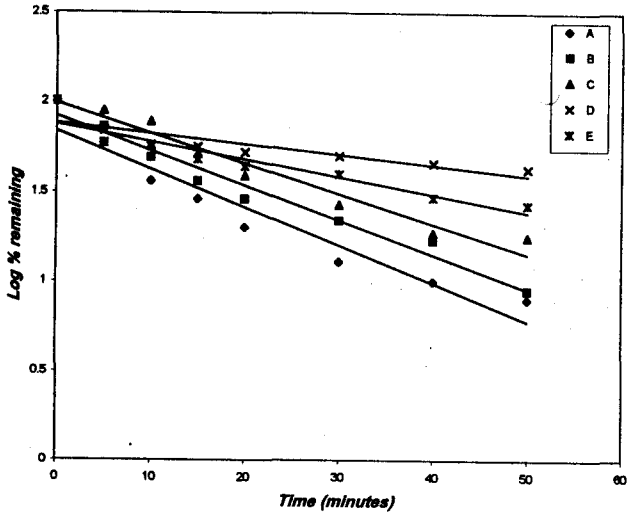


**Fig. 6:** First order kinetics for orphenadrine citrate release from various tablet formulations.

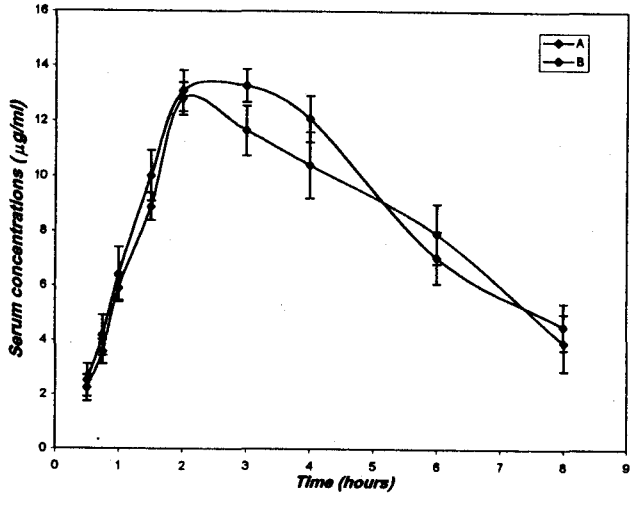


**Fig. 8:** Mean serum paracetamol concentrations following oral administration of products A and B.

**Table 3:** Individual serum orphenadrine citrate concentrations (ng/ml), $t_{1/2}$, $K_e$, $C_{max}$, $T_{max}$ and AUC after administration of a single dose of product A.

| Sub-ject | Time after dosing (hr) | | | | | | | | | $t_{1/2}$ (hr) | $K_e$ ($hr^{-1}$) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) | $AUC_{(0-8)}$ (ng/ml.hr) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | | | | | |
| 1 | 5.0 | 10 | 13.5 | 20.5 | 50 | 80 | 42.3 | 23.2 | 12.7 | 14.22 | 0.0487 | 80.00 | 3.12 | 262.75 |
| 2 | 4.2 | 6.3 | 9.5 | 15.2 | 35.2 | 59.5 | 62.3 | 40.3 | 30.2 | 14.10 | 0.0491 | 62.30 | 3.92 | 309.02 |
| 3 | 5.1 | 6.9 | 10.2 | 16.9 | 36.5 | 66.2 | 52.3 | 31.7 | 21.2 | 13.68 | 0.0506 | 66.20 | 3.19 | 275.11 |
| 4 | 3.3 | 5.3 | 8.5 | 15.7 | 37.2 | 63.2 | 49.3 | 29.3 | 18.2 | 13.22 | 0.0524 | 63.20 | 3.00 | 263.25 |
| 5 | 2.5 | 4.2 | 7.0 | 12.0 | 25 | 49 | 63.2 | 41.7 | 28.3 | 14.47 | 0.0478 | 63.20 | 4.06 | 281.26 |
| 6 | 2.1 | 4.0 | 7.2 | 13.7 | 36.2 | 61.2 | 52.1 | 30.2 | 20.7 | 13.52 | 0.0512 | 61.20 | 3.90 | 263.20 |
| 7 | 6.2 | 8.3 | 11.2 | 17.5 | 37.5 | 62.7 | 50.2 | 32.3 | 21.7 | 14.83 | 0.0467 | 62.70 | 3.06 | 272.85 |
| 8 | 3.3 | 5.2 | 8.5 | 14.5 | 24.5 | 47.7 | 61.2 | 39.5 | 28.7 | 13.15 | 0.0526 | 61.20 | 4.07 | 282.40 |
| 9 | 4.1 | 6.3 | 9.5 | 15.7 | 35.2 | 59.3 | 60.3 | 37.2 | 24.2 | 14.16 | 0.0489 | 60.30 | 4.00 | 295.65 |
| 10 | 5.1 | 6.9 | 10.1 | 16.0 | 37.2 | 61.2 | 58.2 | 35.1 | 24.1 | 13.22 | 0.0524 | 61.20 | 3.16 | 291.40 |
| 11 | 8.2 | 9.3 | 12.0 | 18.2 | 40.0 | 64.3 | 54.2 | 33.2 | 21.1 | 14.25 | 0.0486 | 64.30 | 3.08 | 283.65 |
| 12 | 2.0 | 4.2 | 8.0 | 14.5 | 42.2 | 67.2 | 56.2 | 37.7 | 26.3 | 13.80 | 0.0502 | 67.20 | 3.00 | 302.45 |
| 13 | 3.0 | 5.1 | 8.3 | 16.2 | 36.3 | 66.7 | 51.2 | 29.2 | 18.9 | 14.25 | 0.0486 | 66.70 | 3.08 | 267.65 |
| 14 | 1.8 | 3.0 | 6.2 | 12.3 | 35.3 | 58.8 | 62.3 | 30.7 | 20.3 | 14.10 | 0.0491 | 62.30 | 4.09 | 274.61 |
| Mean | 3.99 | 6.07 | 9.26 | 15.6 | 36.3 | 66.91 | 55.37 | 33.66 | 24.06 | 13.926 | 0.0497 | 64.428 | 3.481 | 280.375 |
| ±SEM | 0.14 | 0.33 | 0.42 | 0.29 | 0.27 | 0.20 | 0.11 | 0.19 | 0.12 | 0.508 | $1.83x10^{3}$ | 4.976 | 0.478 | 14.823 |

**Table 4:** Individual serum orphenadrine citrate concentrations (ng/ml), $t_{1/2}$, $K_e$, $C_{max}$, $T_{max}$ and AUC after administration of a single dose of product B.

| Sub-ject | Time after dosing (hr) | | | | | | | | | $t_{1/2}$ (hr) | $K_e$ ($hr^{-1}$) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) | $AUC_{(0-8)}$ (ng/ml.hr) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | | | | | |
| 1 | 4.8 | 7.7 | 10.5 | 15.2 | 34.7 | 67.2 | 57.2 | 36.7 | 24.7 | 13.62 | 0.0508 | 67.20 | 3.06 | 296.95 |
| 2 | 3.9 | 7.0 | 9.8 | 13.9 | 32.5 | 60.2 | 50.1 | 29.7 | 22.1 | 14.11 | 0.0491 | 60.20 | 3.10 | 263.44 |
| 3 | 4.9 | 7.8 | 10.5 | 15.5 | 37.5 | 68.3 | 58.3 | 37.8 | 26.3 | 13.80 | 0.0502 | 68.30 | 3.00 | 311.91 |
| 4 | 3.0 | 6.2 | 9.0 | 14.2 | 36.2 | 62.7 | 52.1 | 31.2 | 24.3 | 13.90 | 0.0499 | 62.70 | 3.02 | 277.82 |
| 5 | 2.1 | 5.5 | 8.6 | 13.9 | 33.2 | 60.2 | 50.3 | 28.3 | 20.5 | 14.22 | 0.0487 | 60.20 | 3.07 | 262.89 |
| 6 | 1.9 | 5.0 | 8.3 | 13.5 | 35.3 | 65.2 | 53.7 | 31.7 | 26.3 | 14.03 | 0.0493 | 65.20 | 3.01 | 283.29 |
| 7 | 7.0 | 9.8 | 12.2 | 17.2 | 39.4 | 60.2 | 49.5 | 28.2 | 18.1 | 14.60 | 0.0474 | 60.20 | 3.00 | 274.19 |
| 8 | 2.9 | 5.8 | 9.0 | 14.2 | 36.2 | 59.5 | 48.3 | 25.3 | 18.5 | 13.92 | 0.0497 | 59.50 | 3.00 | 254.22 |
| 9 | 3.8 | 6.8 | 9.5 | 14.9 | 37.2 | 62.1 | 58.2 | 37.2 | 27.2 | 13.82 | 0.0497 | 62.10 | 3.08 | 303.30 |
| 10 | 5.6 | 8.4 | 11.0 | 16.0 | 40.2 | 69.2 | 60.7 | 31.7 | 20.1 | 13.92 | 0.0499 | 69.20 | 3.10 | 302.70 |
| 11 | 7.8 | 10.2 | 12.9 | 17.8 | 36.2 | 62.1 | 57.2 | 38.2 | 21.3 | 14.60 | 0.0468 | 62.10 | 2.90 | 303.00 |
| 12 | 1.8 | 5.4 | 8.8 | 13.6 | 32.3 | 57.2 | 63.2 | 40.2 | 28.3 | 14.60 | 0.0474 | 63.20 | 4.08 | 307.60 |
| 13 | 2.9 | 5.9 | 8.9 | 13.9 | 33.7 | 55.2 | 65.3 | 40.3 | 28.5 | 14.61 | 0.0474 | 65.30 | 4.10 | 312.00 |
| 14 | 1.7 | 5.4 | 8.1 | 13.2 | 32.7 | 50.2 | 60.5 | 39.5 | 28.3 | 14.82 | 0.0467 | 60.50 | 4.00 | 295.90 |
| Mean | 3.86 | 7.3 | 9.79 | 14.7 | 35.5 | 61.39 | 56.04 | 34.0 | 23.7 | 14.197 | 0.0487 | 63.279 | 3.251 | 289.229 |
| ±SEM | 0.16 | 0.18 | 0.33 | 0.44 | 0.39 | 0.6 | 0.29 | 0.41 | 0.39 | 0.407 | $1.376x10^{3}$ | 3.246 | 0.442 | 19.650 |

**Table 5:** Individual serum paracetamol concentrations (μg/ml), $t_{1/2}$, $K_e$, $C_{max}$, $T_{max}$ and AUC after administration of a single dose of product A.

| Sub-ject | Time after dosing (hr) | | | | | | | | | $t_{1/2}$ (hr) | $K_e$ ($hr^{-1}$) | $C_{max}$ (μg/ml) | $T_{max}$ (hr) | $AUC_{(0-8)}$ (μg/ml.hr) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | | | | | |
| 1 | 1.5 | 3.1 | 4.5 | 8.0 | 11.3 | 13.9 | 10.2 | 9.0 | 6.1 | 2.23 | 0.310 | 13.90 | 2.70 | 69.40 |
| 2 | 2.6 | 4.2 | 6.5 | 10.2 | 13.3 | 13.8 | 12.7 | 7.7 | 5.2 | 2.13 | 0.325 | 13.80 | 2.90 | 72.90 |
| 3 | 3.1 | 4.5 | 6.8 | 10.5 | 13.6 | 13.9 | 12.8 | 7.8 | 5.4 | 2.63 | 0.263 | 13.90 | 2.80 | 74.65 |
| 4 | 1.7 | 3.4 | 5.7 | 9.2 | 11.7 | 12.5 | 13.7 | 5.0 | 2.7 | 2.40 | 0.288 | 12.50 | 2.90 | 63.80 |
| 5 | 3.5 | 6.1 | 9.0 | 12.1 | 13.7 | 12.0 | 11.2 | 6.3 | 3.8 | 2.60 | 0.266 | 13.70 | 1.90 | 68.85 |
| 6 | 2.9 | 4.5 | 6.8 | 10.3 | 13.8 | 12.7 | 11.3 | 6.4 | 4.0 | 2.53 | 0.273 | 13.80 | 1.90 | 68.45 |
| 7 | 2.7 | 4.3 | 6.7 | 10.2 | 13.2 | 12.8 | 11.7 | 6.4 | 4.1 | 2.22 | 0.312 | 13.20 | 2.10 | 68.80 |
| 8 | 2.1 | 3.4 | 5.5 | 9.2 | 12.7 | 13.2 | 12.0 | 7.0 | 4.4 | 2.60 | 0.266 | 13.20 | 2.60 | 68.15 |
| 9 | 3.0 | 4.3 | 6.6 | 10.3 | 12.9 | 13.4 | 12.1 | 7.5 | 4.2 | 2.23 | 0.311 | 13.40 | 2.80 | 70.40 |
| 10 | 1.9 | 3.7 | 5.8 | 9.6 | 13.6 | 13.7 | 12.3 | 7.8 | 5.4 | 2.52 | 0.275 | 13.70 | 2.90 | 70.25 |
| 11 | 1.8 | 3.6 | 5.8 | 9.5 | 13.4 | 13.2 | 12.0 | 7.2 | 4.8 | 2.33 | 0.297 | 13.40 | 2.06 | 68.20 |
| 12 | 2.9 | 4.5 | 6.9 | 10.6 | 13.6 | 13.7 | 12.3 | 7.5 | 5.1 | 2.41 | 0.287 | 13.70 | 2.90 | 65.13 |
| 13 | 2.8 | 4.2 | 6.4 | 10.1 | 13.1 | 13.1 | 11.9 | 6.5 | 4.0 | 2.52 | 0.275 | 13.10 | 2.78 | 68.22 |
| 14 | 2.7 | 4.6 | 6.5 | 10.2 | 13.2 | 13.8 | 12.8 | 6.7 | 4.3 | 2.29 | 0.306 | 13.80 | 3.00 | 70.02 |
| Mean | 2.5 | 4.17 | 6.39 | 10.0 | 13.07 | 13.26 | 12.07 | 7.05 | 4.54 | 2.403 | 0.289 | 13.51 | 2.59 | 69.087 |
| ±SEM | 0.604 | 0.711 | 1.00 | 0.920 | 0.741 | 0.590 | 0.843 | 0.953 | 0.861 | 0.166 | 0.021 | 0.398 | 0.408 | 2.719 |

**Table 6:** Individual serum paracetamol concentrations (μg/ml), $t_{1/2}$, $K_e$, $C_{max}$, $T_{max}$ and AUC after administration of a single dose of product B.

| Sub-ject | Time after dosing (hr) | | | | | | | | | $t_{1/2}$ (hr) | $K_e$ ($hr^{-1}$) | $C_{max}$ (μg/ml) | $T_{max}$ (hr) | $AUC_{(0-8)}$ (μg/ml.hr) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | | | | | |
| 1 | 1.4 | 2.8 | 5.3 | 8.6 | 12.6 | 13.1 | 11.9 | 8.8 | 5.2 | 2.20 | 0.315 | 13.10 | 2.86 | 69.23 |
| 2 | 2.4 | 3.6 | 6.0 | 9.1 | 13.1 | 12.3 | 11.0 | 8.1 | 4.8 | 2.32 | 0.298 | 13.10 | 1.90 | 72.82 |
| 3 | 2.9 | 4.1 | 6.7 | 9.8 | 13.7 | 12.5 | 11.2 | 8.2 | 4.7 | 2.20 | 0.315 | 13.70 | 1.90 | 73.69 |
| 4 | 1.8 | 3.2 | 5.6 | 8.7 | 12.5 | 13.0 | 12.5 | 9.4 | 5.0 | 2.30 | 0.301 | 13.00 | 2.75 | 74.96 |
| 5 | 2.9 | 4.2 | 6.6 | 9.8 | 13.6 | 12.1 | 11.7 | 10.2 | 4.8 | 2.41 | 0.287 | 13.60 | 1.86 | 73.23 |
| 6 | 2.5 | 3.7 | 6.0 | 9.2 | 13.5 | 12.0 | 11.0 | 8.9 | 5.8 | 2.19 | 0.316 | 13.50 | 1.92 | 74.18 |
| 7 | 1.8 | 3.2 | 5.5 | 8.5 | 12.2 | 11.5 | 10.2 | 7.5 | 3.0 | 2.22 | 0.312 | 12.20 | 1.90 | 73.26 |
| 8 | 1.9 | 3.3 | 5.6 | 8.4 | 12.0 | 11.2 | 10.2 | 7.2 | 3.0 | 2.36 | 0.293 | 12.00 | 1.86 | 71.17 |
| 9 | 1.5 | 2.9 | 5.2 | 8.2 | 12.1 | 10.5 | 9.5 | 6.3 | 2.7 | 2.26 | 0.306 | 12.10 | 1.82 | 73.86 |
| 10 | 2.5 | 3.9 | 6.2 | 9.2 | 13.0 | 11.2 | 10.2 | 7.2 | 3.2 | 2.70 | 0.256 | 13.00 | 1.96 | 69.90 |
| 11 | 1.9 | 3.3 | 5.7 | 8.6 | 12.7 | 11.3 | 10.3 | 7.1 | 3.0 | 2.10 | 0.330 | 12.70 | 1.76 | 69.70 |
| 12 | 2.5 | 4.0 | 6.2 | 8.3 | 12.0 | 10.0 | 8.5 | 7.0 | 2.8 | 2.16 | 0.321 | 12.00 | 1.83 | 68.62 |
| 13 | 2.7 | 3.9 | 6.1 | 8.9 | 13.1 | 11.5 | 9.9 | 8.2 | 4.2 | 2.17 | 0.319 | 13.10 | 1.92 | 74.63 |
| 14 | 2.5 | 3.9 | 6.0 | 9.0 | 13.2 | 10.9 | 8.3 | 7.0 | 3.2 | 2.22 | 0.312 | 13.20 | 2.08 | 72.12 |
| Mean | 2.23 | 3.57 | 5.90 | 8.87 | 12.8 | 11.64 | 10.4 | 7.9 | 3.95 | 2.271 | 0.306 | 12.87 | 2.023 | 72.241 |
| ±SEM | 0.499 | 0.453 | 0.448 | 0.506 | 0.594 | 0.902 | 1.20 | 1.091 | 1.054 | 0.149 | 0.0184 | 0.588 | 0.340 | 2.134 |

Upon taking orphenadrine citrate levels, for product A, $C_{max}$ values ranged between 61.2 to 80 ng. $ml^{-1}$ with a mean of 64.428±4.976 ng.$ml^{-1}$ and the corresponding values for product B ranged between 59.5 and 69.2 ng.$ml^{-1}$ with a mean of 63.279±3.246 ng. $ml^{-1}$. The $t_{max}$ values (3.481±0.478 hr and 3.251±0.442 hr for A and B respectively) showed no significant differences. Furthermore, no significant differences were observed in the $AUC_{0-8}$ values (280.375±14.823 and 289.229±19.650 ng. hr. $ml^{-1}$) and the elemination half life was 0.0497 and 0.0487 $hr^{-1}$ for A and B respectively.

Accordingly, lack of significant differences in AUC values, $C_{max}$ and $t_{max}$ between the two tested products may indicate that the two formulations are closely similar in terms of rate and extent of absorption. This suggests that the *in-vivo* dissolution and absorption are close for these two formulations. In addition, these *in-vivo* findings are consistent with the *in-vitro* release pattern showed in Figures (3 and 4). From the results obtained it could be concluded that formulation variables have a pronounced effect on the *in-vitro* characteristics of the formulated tablets. These effects will be, in its turn, reflected on the bioavailability. Accordingly, the *in-vitro* testing may be used as a measure which can be utilized for the study especially when the drug has a formulation problem or a difficulty to conduct a biological study.

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