# BATCH AND FLOW INJECTION SPECTROPHOTOMETRIC METHODS FOR DETERMINATION OF PARACETAMOL IN PHARMACEUTICAL PREPARATIONS VIA OXIDATIVE COUPLING WITH 4-AMINOANTIPYRINE

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**Abstract**

A simple, rapid and sensitive batch and flow injection spectrophotometric methods have been developed for the determination of paracetamol in pure form and pharmaceutical preparations. The proposed methods are based on the oxidative coupling reaction of paracetamol with 4-aminoantipyrine in presence of ammonium persulfate in alkaline medium to produce an orange-reddish product that having absorptivity maximum at 461 nm. The optimum reaction conditions and other analytical parameters have been evaluated. Linearity was observed from 2-16 and 100-700 μg $mL^{-1}$ paracetamol by batch and flow injection procedures, respectively. Statistical analysis of the results and comparison with results by the British Pharmacopoeia method are also reported.

**Keywords:**Paracetamol; Spectrophotometric; Flow Injection; 4-Aminoantipyrine; Oxidative Coupling Reaction.

## Introduction

Paracetamol (N-acetyl-p-aminophenol) is well known as analgesic anti-pyretic drug. It is the active metabolite of phenacetine responsible for its analgesic effect. It is well tolerated, lacks many of the side effects of aspirin, So it's commonly used for the relief of fever, head ache and other minor aches and pains[1-3].

Various methods for paracetamol determination have been described, including chromatography[4,5], spectrophotometry[6-9], fluorimetry[10,11] and chemiluminescence[12].

The British Pharmacopoeia (BP) method describes a titrimetric procedure for paracetamol determination in pharmaceutical formulations using Ce (IV) in acidic media and 1, 10-phenanthroline-iron(II) complex (ferroin) to determine the end point. The titration is performed in ice[13].

Flow injection (FI) system are adequate procedures to use in routine analysis in pharmaceutical laboratories control due to their simplicity, high analytical frequency and capacity to reduce reagent consumption when compared with batch procedure[14,15].

Oxidative coupling organic reactions are recently used for spectrophotometric determination of several drugs such as phenylephrine hydrochloride[16], folic acid[17], salbutamol[18], amoxicillin[19] and catecholamine drugs[20].

In this paper, two batch and FI methods using spectrophotometric detection at 461 nm are described for the determination of paracetamol via oxidative coupling reaction. The method are depends on the formation of orange-reddish product between this drug and 4-aminoantipyrine in presence of ammonium persulfate in alkaline medium. The proposed methods have been successfully applied to the determination of paracetamol in pharmaceutical preparations.

## Experimental

### Apparatus

All spectral and absorbance measurements were performed on a Shimadzu UV - VIS 260 (Tokyo, Japan) digital double-beam recording spectrophotometer using 1 cm quartz cells.

The FI system comprised a peristaltic pump (Ismatec, Labortechink-Analytic, CH-8152, glatbrugg-zurich, Switzerland, six channels) with poly vinyl chloride flow tubes

of 0.8 mm i.d., an injection valve (Rheodyne, Altex 210, Supelco-USA), a 50 μL flow cells and Shimadzu UV-VIS 260 spectrophotometer (Tokyo, Japan) as the detector. Flexible Teflon tubes of 0.5 mm i.d. were used for reaction coils and to transport reagents solutions. T-link was also used to mix two streams of reagents.

**Reagents**

All chemicals were of analytical reagents grade.

1- Paracetamol stock standard solution (500 μg $mL^{-1}$) was prepared by dissolving 0.0500 g of pure paracetamol (SDI) in 20 mL of ethanol with carefully stir and made up to 100 mL volumetric flask with distilled water. Working standard solutions were prepared by suitable dilution of the stock standard solution.
2- 4-Aminoantipyrine (4-AAP) solution (for batch procedure $3 \times 10^{-2}$ M) was prepared by dissolving 0.6090 g of this reagent (Fluka) in 25 mL of distilled water with stir, and made up to 100 mL volumetric flask with distilled water.
3- 4-AAP solution (for FI procedure $6 \times 10^{-2}$ M) was prepared by dissolving 1.2180 g of 4-AAP in distilled water with stir, and made up to 100 mL volumetric flask with distilled water.
4- Sodium hydroxide solution (1 M) was prepared by dissolving 10 g of sodium hydroxide (Merck) in distilled water and diluting to the marked with the same solvent in 250 mL volumetric flask.
5- Ammonium persulfate solution ($1\times10^{-2}$ M) was prepared by dissolving 0.5705 g of ammonium persulfate (BDH) in distilled water and diluting to marked with the same solvent in 250 mL volumetric flask.
6- Oxidation solution (for FI procedure) was prepared by transfer 30 mL of ammonium persulfate solution ($1.5 \times 10^{-2}$ M) with 25 mL of sodium hydroxide solution ($6 \times 10^{-2}$ M) in 100 mL volumetric flask and the volume was completed with distilled water.

More dilute solutions were prepared by simple dilutions using distilled water.

**Pharmaceutical preparations of Paracetamol**

Pharmaceutical preparations were obtained from commercial sources.

1- Paracetamol tablets (Troge-Hamburg): 500 mg paracetamol for each tablet.
2- Paracetol tablets (SDI-Iraq): 500 mg paracetamol for each tablet.
3- Algesic tablets (SDI-Iraq): 350 mg paracetamol for each tablet.
4- Colden tablet (SDI-Iraq): 450 mg paracetamol, 5 mg promethazine hydrochloride, and 5 mg phenylphrine hydrochloride for each tablet.
5- Emidol tablets (Global Pharam- UAE): 500 mg paracetamol for each tablet.
6- Kanagesic tablets (Kanawati Medical products-Syria): 450 mg paracetamol and 45 mg orphenadrine citrate for each tablet.
7- Ultramol suppositories (Medico Labs. HOMS-Syria): 250 mg paracetamol for each suppository.
8- Hayamol injections (Ibn Hayyan Pharmaceutical HOMS-Syria): 375 mg paracetamol for each injection (5 mL).

**Procedure**

***1- General batch procedure***

In to a series of 25 mL volumetric flasks, added increase volumes of a liquid of sample containing 50 - 400 μg of paracetamol, 5 mL of ammonium persulfate solution ($1 \times 10^{-2}$ M), 2 mL of sodium hydroxide solution ($5\times10^{-2}$ M) and 1.5 mL of 4-aminoantipyrin solution ($3 \times 10^{-2}$ M). The mixture of solution was diluted with distilled water to mark and allow the reaction mixture to stand for 50 min at room temperature. Measure the absorbance at 461 nm against reagent blank.

***2- General FI procedure***

FI system is shown in Fig. (1).

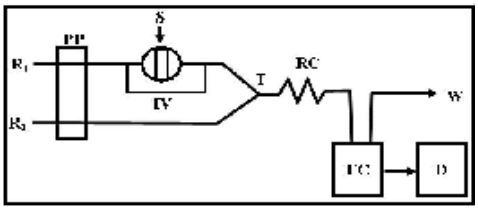



***Fig. (1): FI manifold for determination of paracetamol***

***($R_1$ = 4-AAP, $R_2$ = $(NH_4)_2S_2O_8$ + NaOH, PP = Peristaltic Pump, IV = Injection Valve, T = T-link, RC = Reaction Coil, FC = Flow Cell, D = Detector and W = Waste).***

150 µL aliquots of paracetamol solutions prepared at different concentrations (100 - 700 µg $mL^{-1}$) were injected into carrier stream of 4-AAP solution ($6 \times 10^{-2}$ M). The oxidation solution ($(NH_4)_2S_2O_8$ + NaOH) was mixed with the carrier stream at the down stream confluence point. Calibration graphs were prepared by plotting the absorbance of the peak maximum versus paracetamol concentration.

**Procedure for the assay of pharmaceutical preparations**

***1- Tablets solution (500 µg $mL^{-1}$)***

Weigh and finally powdered of 20 tablets, extract an accurately weighed portion of the powder equivalent to about 125 mg of paracetamol in 20 mL of ethanol and diluted with distilled water in 250 mL volumetric flask. The solution was filtered twice into a 250 mL volumetric flask.

***2- Suppositories solution (500 µg $mL^{-1}$)***

Weigh four suppositories mixed them well and dissolved an equivalent amount weighed of suppositories containing 125 mg of paracetamol in 10 mL of ethanol and little amount of boiling distilled water. Filter the solution twice into a 250 mL volumetric flask, the residue was washed with 10 mL of ethanol and boiling distilled water and made up to the mark with distilled water.

***3- Injection solution (500 µg $mL^{-1}$)***

A mixed content of five injections equivalent to 125 mg of paracetamol (1.7 mL) was shaken with 20 mL of ethanol and diluted to 250 mL with distilled water in a volumetric flask.

Working solutions were prepared by appropriate dilution of an aliquot of pharmaceutical preparations for batch and FI procedure using distilled water.

**Results and Discussion**

**Preliminary Studies**

When a very dilute aqueous solution of paracetamol was mixed with 4-AAP reagent and ammonium persulfate in sodium hydroxide medium, an intense orange-reddish product formed. This product has a maximum absorption at 461 nm [Fig. (2)]. In contrast to the reagent blank which shows no absorption at the same wavelength.

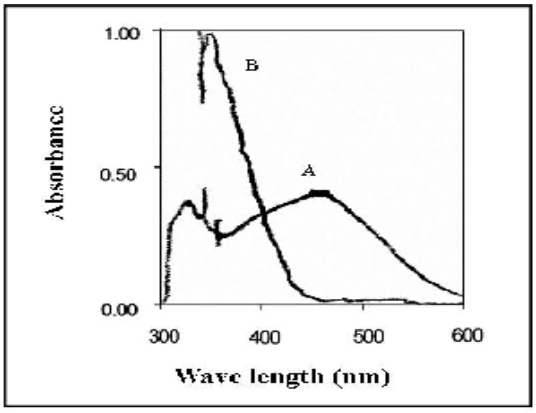



***Fig. (2): Absorption spectra of product against reagent blank (A) and reagent blank against distilled water (B).***

**Optimization of the experimental conditions**

The effects of various parameters on the absorption intensity of the formed product were optimized.

***1- Batch method***

In the subsequent experiments, 500µg $mL^{-1}$ of paracetamol was taken in 25 mL final volume and the absorbance of a series of solutions were measured by varying one and fixing the other parameters at 461 nm versus reagents blanks.

The effects of different volumes (0.5-4mL) of 4-AAP ($3 \times 10^{-2}$ M), (3-7 mL) of ammonium persulfate ($1 \times 10^{-2}$ M) and (1-4 mL) of sodium hydroxide ($5 \times 10^{-2}$ M) were examined on the maximum absorbance of the formed product. Fig. (3) shows that 1.5 mL of 4-AAP ($3 \times 10^{-2}$ M), 5 mL of ammonium presulfate ($1 \times 10^{-2}$ M) and 2 mL of sodium hydroxide ($5 \times 10^{-2}$ M) were enough to obtain the maximum absorbance.

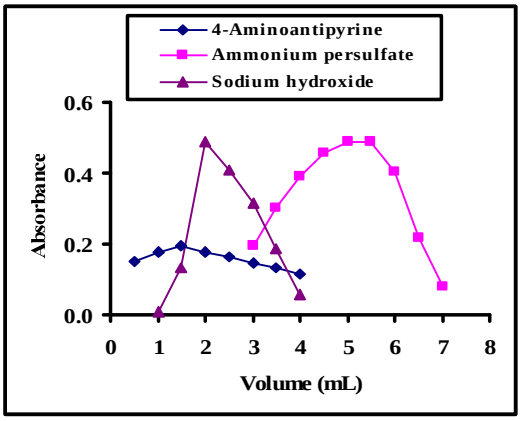



***Fig. (3): Optimum conditions of batch procedure for determination of paracetamol.***

The orange-reddish product was only formed in alkaline medium. Therefore, the effects of different alkaline solutions were studied such as sodium hydroxide, sodium carbonate, potassium hydroxide and ammonium hydroxide. It was found that sodium hydroxide the most suitable alkaline medium for a maximum absorbance and was used in all subsequent experiments.

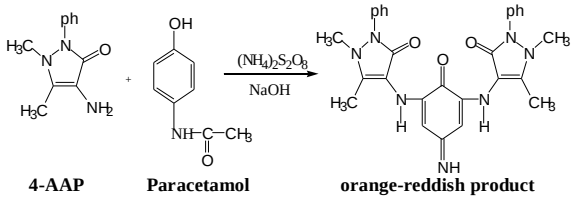
To obtain optimum results the order of addition of reagents should be followed as given under the procedure, otherwise a loss in color intensity and stability was observed.

The effect of temperature on the color intensity of the product was studied. In practice, high absorbance was obtained when the color was developed at room temperature (25°C) that when the calibrated flasks were placed in ice bath (5°C) or in water bath (50°C).

The development of the color of the product from a mixture containing 10 μg $mL^{-1}$ of paracetamol with 4-AAP, ammonium persulfate in alkaline medium give evidence that the color after 50 min and remains stable for at least 2 h.

The stoicheiometry of the product was investigated using the mole ratio and continuous variation methods.

The results obtained Fig. (4) and Fig. (5) shows that a 1:2 complex was formed between paracetamol (D) and 4-AAP (R). Therefore, the formation of the product probably occurs:



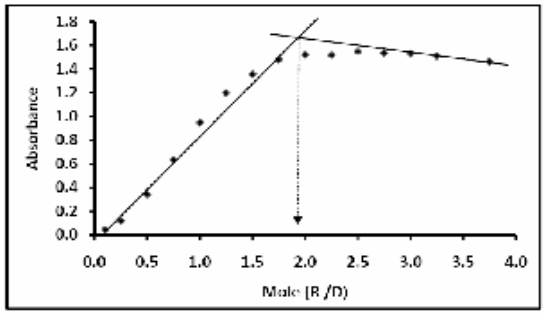




***Fig. (4): Mole ratio plot.***

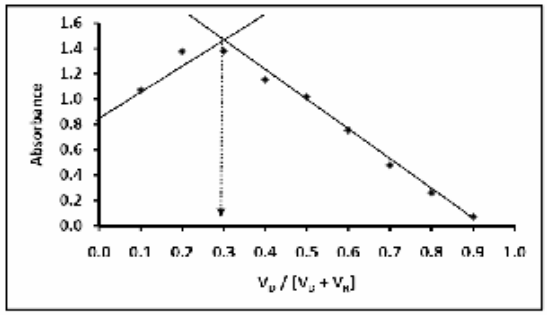



***Fig. (5): Continuous variation plot.***

The formed product is stable in water. The apparent stability constant was calculated by comparing the absorbance of a solution containing stoicheiometric amount of paracetamol and 4-AAP reagent. The stability constant of the product in water under the described experimental conditions was $1.146 \times 10^6$ $L^2$ $mol^{-2}$.

In order, assess the possible analytical applications of the proposed methods. The effects of some common excipients frequently found with paracetamol drugs in pharmaceutical formulations, such as lactose, starch, talc, magnesium stearate and poly vinyl pirrolidone (PVP) were studied by analyzing. Synthetic sample solutions containing 10 μg $mL^{-1}$ of paracetamol and excess amounts (10-fold excess) of each excipient, none of these substances interfered seriously [Table (1)].

***Table (1)***
***Determination of 10 μg $mL^{-1}$ of paracetamol in the presence of excipients.***

| Excipient (100μg $mL^{-1}$) | Concn. of paracetamol (μg $mL^{-1}$) | E**, % | Recovery, % |
|---|---|---|---|
| | Found* | | |
| Starch | 10.0424 | 0.424 | 100.424 |
| Lactose | 9.9154 | -0.846 | 99.154 |
| Talc | 9.9788 | -0.212 | 99.788 |
| Mg-stearate | 10.0213 | 0.213 | 100.213 |
| PVP | 10.0854 | 0.854 | 100.854 |

* *Average of five determination.*
** *E is relative error.*

### *2- FI method*

Batch method for the determination of paracetamol was adopted as a basis to develop FI procedure. The manifold used for the determination of paracetamol is shown in Fig. (1).

A two-channel FI system was applied, in which the sample was injected into the 4-AAP stream, which was then mixed with a stream of oxidation solution. The reagent and the oxidation solution streams were pumped at the same flow rate to achieve effective mixing of the sample and reagents solutions. Maximum absorbance intensity was obtained when the sample was injected into a stream of 4-AAP and was then combined with the stream of oxidation solution.

The parameters of flow in the determination of paracetamol were optimized by the univariated method with the purpose of maximizing the analytical frequency and reproducibility.

According to the results of preliminary spectrophotometric studies concerning the effect of alkaline medium on the absorbance of the product, sodium hydroxide was used for the FI method.

The effects of the concentration of sodium hydroxide in oxidation solution were studied in the range (4-8) $\times 10^{-2}$ M with fixed paracetamol concentration of 500 μg $mL^{-1}$. As, can observed from Fig. (6), the absorbance was increased as the concentration of sodium hydroxide increased up to $6 \times 10^{-2}$ M. The effects of various concentration ($2.5 \times 10^{-3}$ – $2.5 \times 10^{-2}$ M) of ammonium persulfate in oxidation mixture were similarly studied. A concentration of $1.5 \times 10^{-2}$ M gave the best results [Fig. (6)].

It was found that the reaction between paracetamol and 4-AAP in sodium hydroxide medium in presence of ammonium persulfate depends on the 4-AAP concentration. Therefore, the effect of different concentration of 4-AAP ($3 \times 10^{-2}$ – $8 \times 10^{-2}$ M) was studied [Fig. (6)]. The results obtained indicated, that the absorbance increased with the increasing concentration of 4-AAP up to $6 \times 10^{-2}$ M, which gave the maximum absorbance and was chosen for further use.

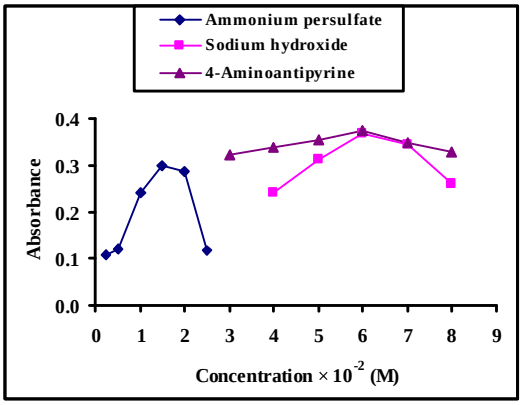



***Fig. (6): Chemical conditions of FI procedure for the determination of paracetamol.***

The variable studies under the optimized reagent concentrations were the flow rate, the injected sample volume and the reaction coil length [Fig. (7)].

The effects of flow rate in the analytical response were studied over the range 0.8-3.36 mL $min^{-1}$. Fig. (7) shows that the absorbance increased up to 1.5 mL $min^{-1}$. Therefore, this rate was selected.

The reactor length is an essential parameter that effected on the sensitivity of the colored reaction product and was investigated in the range 25-250 cm. The result obtained showed that a coil length of 200 cm gave the highest absorbance as shown in Fig. (7) and was used all subsequent experiment.

The volume samples injected in the range 50-250 μL was evaluated by changing the length of sample loop in the injection valve, while other variable remained fixed. The absorbance increased with increasing volume of sample injected up to 150 μL [Fig. (7)], which was chosen.

The flow system selected provided a sampling rate of 20 samples $h^{-1}$.

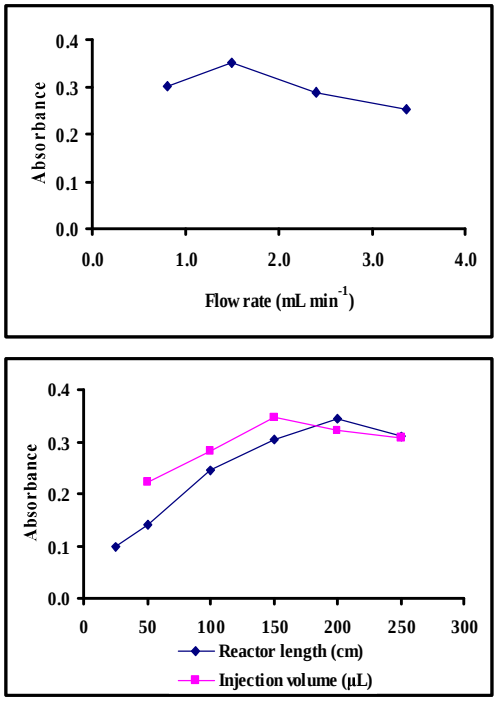



***Fig. (7): Physical conditions of FI procedure for determination of paracetamol.***

**Analytical characteristics of the batch and spectrophotometric methods**

For batch and FI methods, the calibration graphs were obtained by the procedures described previous and a series of standard solutions was analyzed in triplicate to test the linearity. The slope (a), the intercept (b), the correction coefficient (r) and correlation of determination ($r^2$) were evaluated by a least squares regression analysis and are included in Table (2).

Statistical evaluation[21] of the regression line gave the values of standard deviations for residuals ($S_{y/x}$), slope ($S_a$) and intercept ($S_b$) at 95% confidence are shown in the same table. These small figures point out to the high precision of the proposed methods.

***Table (2)***
***Data for calibration graphs for paracetamol using the proposed methods.***

| Parameter | Value | |
|---|---|---|
| | Batch method | FI method |
| Linearity range (µg $mL^{-1}$) | 2 - 16 | 100 - 700 |
| r | 0.9978 | 0.9964 |
| $r^2$ | 0.9957 | 0.9929 |
| a (mL $\mu g^{-1}$) | 0.0495 | 0.0003 |
| b | 0.0436 | 0.1866 |
| $S_{y/x}$ | $1.8815 \times 10^{-2}$ | $6.6038 \times 10^{-3}$ |
| $S_a$ | $1.4565 \times 10^{-3}$ | $1.2063 \times 10^{-5}$ |
| $S_b$ | $1.4731 \times 10^{-2}$ | $5.5649 \times 10^{-3}$ |
| E%* | -0.305** | -0.549*** |
| RSD%* | 1.0975 | 0.5041 |

**Average of five determination.*
***For 4 µg $mL^{-1}$ of paracetamol.*
****For 500 µg $mL^{-1}$ of paracetmol.*

**Accuracy and precision of the batch and FI spectrophotometric methods**

The accuracy and precision of the two methods were tested by analyzing five replicate samples of paracetamol by batch and FI spectrophotometric methods. The low values of percentage errors (E%) summarized in Table (2). The percentage relative standard deviation (RSD%) was found to be less. These values indicated the high accuracy and precision of the two methods.

**Pharmaceutical applications**

The two proposed methods were applied successfully to analysis of different pharmaceutical formulations containing paracetamol and the results are summarized in Table (3). For all formulations examined, the assay results of both methods were in good agreement with the declared content.

The results obtained by two proposed methods were compared with BP method[22] [Table (4)] by applying the F-test and t-test at 95% confidence level. The calculated values for F and t for batch and FI methods (1.053, 0.7614 and 1.1107, 0.2437 respectively) did not exceed the critical values of $F_{9,9}$ = 4.033 and t = 2.101 ($n_1+n_2-2$ =18). These confirming

that there are no significant differences between the two proposed methods with BP method with respect to precision and accuracy in the determination of paracetamol in pharmaceutical preparations.

## Conclusions

Two simple, accurate and sensitive batch FI spectrophotometric methods have been developed for determination of paracetamol in pharmaceutical preparations. The developed procedures based on oxidative coupling reaction with 4-AAP reagent in presence of ammonium persulfate in alkaline medium. The proposed methods require neither temperature control nor solvent extraction step. The methods were successfully applied to a different pharmaceutical preparation samples.

***Table (3)***
***Pharmaceutical applications for paracetamol using the proposed methods.***

| Method | Pharmaceutical preparation | Concn. of paracetamol (μg $mL^{-1}$) | | E, % | Recovery, % | RSD, % |
|---|---|---|---|---|---|---|
| | | Presence | Found* | | | |
| Batch | Paracetamol tablets | 10.0000 | 10.0572 | 0.5720 | 100.5725 | 0.8899 |
| | | 16.0000 | 16.3715 | 2.3218 | 102.3218 | 0.9345 |
| | Paracetol tablets | 10.0000 | 9.9224 | -0.7760 | 99.2240 | 0.6476 |
| | | 16.0000 | 16.0000 | 0.0000 | 100.0000 | 0.5356 |
| | Algesic tablets | 10.0000 | 10.0195 | 0.1950 | 100.1950 | 0.7463 |
| | | 16.0000 | 16.0000 | 0.0000 | 100.0000 | 0.3472 |
| | Emidol tablets | 10.0000 | 10.0836 | 0.8360 | 100.8360 | 0.2532 |
| | | 16.0000 | 16.1088 | 0.6800 | 100.6800 | 0.1592 |
| | Coldin tablets | 10.0000 | 9.9166 | -0.8340 | 99.1660 | 0.6652 |
| | | 16.0000 | 16.0000 | 0.0000 | 100.0000 | 0.3520 |
| | Kanagesic tablets | 10.0000 | 9.9664 | -0.3360 | 99.6640 | 0.2915 |
| | | 16.0000 | 15.9637 | -0.2268 | 99.7773 | 0.2451 |
| | Panatol tablets | 10.0000 | 9.9647 | -0.3530 | 99.6470 | 0.2698 |
| | | 16.0000 | 16.0187 | 0.1168 | 100.1168 | 0.3018 |
| | Ultramol Suppositories | 10.0000 | 10.0000 | 0.0000 | 100.000 | 0.3769 |
| | | 16.0000 | 16.2607 | 1.6293 | 101.6293 | 0.5412 |
| | Hayamol injections | 10.0000 | 10.0695 | 0.6950 | 100.6950 | 0.7461 |
| | | 16.0000 | 16.0000 | 0.0000 | 100.0000 | 0.4307 |
| FI | Paracetamol tablets | 250.000 | 250.000 | 0.000 | 100.000 | 0.544 |
| | | 500.000 | 509.859 | 1.971 | 101.971 | 0.478 |
| | Paracetol tablets | 250.000 | 248.333 | 0.666 | 99.333 | 0.474 |
| | | 500.000 | 5.8.403 | 1.680 | 101.680 | 0.672 |
| | Algesic tablets | 250.000 | 245.000 | -2.000 | 98.000 | 0.707 |
| | | 500.000 | 518.207 | 3.641 | 103.641 | 0.382 |
| | Emidol tablets | 250.000 | 250.000 | 0.000 | 100.000 | 0.431 |
| | | 500.000 | 500.000 | 0.000 | 100.000 | 1.482 |
| | Coldin tablets | 250.000 | 249.166 | -0.333 | 99.666 | 0.841 |
| | | 500.000 | 495.824 | -0.835 | 99.164 | 1.404 |
| | Kanagesic tablets | 250.000 | 251.672 | 0.668 | 100.668 | 1.179 |
| | | 500.000 | 497.206 | -0.558 | 99.441 | 1.298 |
| | Panatol tablets | 250.000 | 248.322 | -0.671 | 99.328 | 0.515 |
| | | 500.000 | 491.596 | -0.1680 | 98.319 | 1.091 |
| | Ultramol Suppositories | 250.000 | 250.841 | 0.336 | 100.336 | 0.724 |
| | | 500.000 | 502.816 | 0.563 | 100.563 | 1.426 |
| | Hayamol injections | 250.000 | 250.847 | 0.338 | 100.338 | 0.276 |
| | | 500.000 | 504.225 | 0.845 | 100.845 | 1.872 |

*Table (4)*
*Comparison of the two methods with BP method for determination of pharmaceutical preparations.*

| Pharmaceutical preparation | Recovery*, % | | |
|---|---|---|---|
| | Batch method | FI method | BP method |
| Pure Paracetamol | 100.140 | 100.285 | 100.000 |
| Paracetamol tablets | 101.447 | 100.986 | 99.627 |
| Paracetol tablets | 99.612 | 100.507 | 100.192 |
| Algesic tablets | 100.097 | 100.821 | 100.777 |
| Emidol tablets | 100.758 | 100.000 | 100.813 |
| Coldin tablets | 99.583 | 99.415 | 98.978 |
| Kanagesic tablets | 99.718 | 100.055 | 100.000 |
| Panatol tablets | 99.882 | 98.824 | 100.000 |
| Ultramol Suppositories | 100.815 | 100.449 | 100.186 |
| Hayamol injections | 100.348 | 100.592 | 101.128 |

**Average of five determination.*

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**الخلاصة**

طورت طريقتا الدفعة و الحقن الجرياني للتقدير البسيط والسريع والحساس للباراسيتامول بصورته النقية وفي المستحضرات الصيدلانية. اعتمدت الطريقتان على تفاعل الازدواج التأكسدي للباراسيتامول مع كاشف 4- امينوانتي بايرين بوجود بيركبريتات الامونيوم و في الوسط القاعدي. إذ يتكون ناتج برتقالي- محمر يعطي أقصى امتصاصية عند طول موجي 461 نانومتراً. تم دراسة وتثبيت المتغيرات الكيميائية والفيزيائية للطريقتين. كان المدى الخطي للتراكيز الذي يطيع قانون بير ضمن المدى 2 - 16 و 100 - 700 مايكروغرام مل$^{-1}$ لطريقتي الدفعة والحقن الحرياني على التوالي. طبقت الطريقتان بنجاح في تقدير الباراسيتامول في المستحضرات الصيدلانية وتم مقارنة النتائج المستحصلة مع الطريقة القياسية المعتمدة في دستور الأدوية البريطاني.