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A COMPARATIVE STUDY FOR THE QUANTITATIVE DETERMINATION OF DIFFERENT BRANDS OF PARACETAMOL TABLET USING UV-VISIBLE SPECTROPHOTOMETRIC, POTENTIOMETRIC AND TRIMETRIC METHODS.

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ABSTRACT:
Paracetamol (acetaminophen) is a widely used over-the-counter analgesic, antipyretic and a mild anti inflammatory drug. In several developing countries some of pharmaceutical industries sale fake, counterfeit and substandard drugs which affect the health of people. The present study investigates the comparison for the quantitative determination of various brands of paracetamol tablet using UV-Visible spectrophotometric, potentiometric and trimetric methods. Four brands (Pacimol, Paracip, Parazest, and Crocin) of paracetamol tablets having 500 mg strength were purchased from various pharmacy shops within Pari chowk and Jagat market in Greater Noida, India. Weight variation test was performed before the assay of paracetamol samples. The result of tablets weight variation (Mean ± S.D) of Crocin, Parazest, Paracip and Pacimol brand was 0.66 ± 0.014**,** 0.64 ± 0.010, 0.58 ± 0.007 and 0.55 ± 0.009 respectively. All brands showed different mean weight which indicates the use of different excipients in the different brands. The ranges of the amount of paracetamol content (g/tab) for paracetamol samples analyzed using UV-Visible spectrophotometric, potentiometric and trimetric methods were from 0.49195-0.52010, 0.48300-0.52100 and 0.48106-0.50110 respectively. The results indicated that all four brands of paracetamol tablets have sufficient quantity and amount is approximately similar to the company's recommended or claimed value. Similarly, the ranges of percentage content (assay) of the analyzed samples using UV-Visible spectrophotometric, potentiometric and trimetric methods were from 98.69-104.20%, 96.60-104.20%, and 96.21-100.22% respectively. The assay results indicated that variation among all brands and this may show that different manufacturer formulates the different brands are under the IP specification. However, all of the brands of the tablets under the study were complied with the IP specification and passed for weight variation test and assay conducted on it. Hence, the drug control authority of the government should be continuously monitored the safety, quality, and efficacy of paracetamol tablet through post marketing surveillance practices, and the proper internal quality control of the pharmaceutical companies need to take further necessary steps to ensure the continuity in the establishment of the product quantity and quality.
Keywords: Assay, Brands, Comparative, Determination, Paracetamol, Tablets

INTRODUCTION

Analgesics, antipyretics and nonsteroidal anti inflammatory drugs (NSAIDs) are the most commonly prescribed medications worldwide[1-3]. They are commonly used for inflammatory disorders of the musculoskeletal system. They constitute a heterogeneous group of compounds with the common ability to inhibit cyclooxygenase, and thus, prostaglandin synthesis[4].

Analgesics refer to a group of drugs used to temporarily relieve pain. They are sometimes known as painkillers. They block pain signals by changing how the brain interprets the signals and slowing down the central nervous system. The common analgesics are acetaminophen or paracetamol, aspirin, and ibuprofen[5]. It has been revealed that a combination of analgesic drugs from different classes may provide addictive analgesic effects with fewer side effects than when a single therapeutic drug is used[6].

Paracetamol is a widely used over-the-counter analgesic (pain reliever), antipyretic (fever reducer) and a mild anti inflammatory drug[7-8], though its mechanism of action is not yet confirmed[9]. It has

been proposed that the analgesic mechanisms action of paracetamol which involves prostaglandins (PGs), has a controversial result of inhibiting the central cyclo-oxygenases (COX-1, COX-2, and COX-3)[10]. It is available in different dosage form: tablet, capsules, drops, elixirs, suspension, and suppositories. The dosage form of paracetamol and its combinations with other drugs have been listed in various pharmacopoeias[11-12].

The words acetaminophen ($C_8H_9NO_2$) and paracetamol both come from a chemical name for the compound para-acetyl aminophenol and para-acetyl aminophenol. In some contexts, it is simply abbreviated as APAP, for acetyl-para-aminophenol[13]. Paracetamol consists of a benzene ring core, substituted by one hydroxyl (OH) group and the nitrogen atom of an amide group in the para (1, 4) pattern (figure 1)[14].

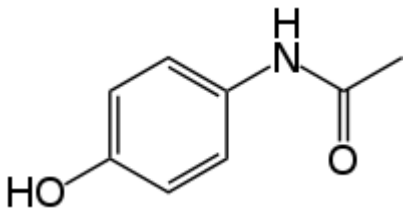

Figure 1: Chemical structure of Paracetamol.

Paracetamol is safe for human use at the recommended dose. But overdoses of paracetamol can cause potentially fatal liver damage and in rare individual, a normal dose can do the same. The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable[15]. The efficacy of a pharmaceutical dosage form generally depends on their formulation properties and manufacturing methods, hence the quality of dosage form may vary [16].

In several developing and low income countries, drug quality is a source of concern. It has been estimated that up to 15 % of all medicines sold across the world are fake especially in developing countries mainly in Africa and Asia about 70 % of counterfeit medicines were reported. The cause and expansion of the fake, counterfeit and substandard drugs are due to weakness and lack of effective regulatory bodies on quality control of medicines in the pharmaceutical manufacturing sector which makes entrepreneurs by considering the pharmaceutical market as an easy means of making profits and also perceives it as an ordinary commodity market[17].

Quantitative analysis is one of the analytical chemistry used for the analysis of drugs. It gives the amount of one or more components present in the sample in numerical terms[18]. The motto behind this quantitative estimation is to ensure that whether a particular drug contains the same amount of drugs as mentioned because if the dose given will be high then it will cause over dosage side effects and if is less then the patient will not get the required dose[19]. Many literature surveys revealed the estimation of paracetamol in pharmaceutical formulations by various techniques. The present study investigates the comparison for the quantitative determination of four brands of paracetamol tablet using UV-Visible spectrophotometric, potentiometric and trimetric methods.

MATERIALS AND METHODS

Chemicals and reagents: All the reagents and chemicals used for the experiment were analytical grade and were obtained from the School of Pharmacy, Sharda University. The chemicals and reagents include: Sodium hydroxide (NaOH), Hydrochloric acids (HCl), Sulphuric acid (H_2SO_4), Ceric ammonium sulphate, Ferroin solution (Redox indicator), 70% Perchloric acid ($HClO_4$), Glacial acetic acid, Dioxane, Paracetamol reference standard, Paracetamol tablets (500 mg) and etc.

Equipment and apparatus: Single beam UV-Visible spectrophotometer (Manufactured by Labrotnics, India) with a pair of 10 mm matched quartz cells, potentiometer/ pH meter, weighing balance, mortar and pestle, burette (50 ml) with burette stand, and etc.

Study design:

The four different brands of uncoated paracetamol tablets having label strength of 500 mg for the test sample were randomly purchased from various pharmacy shops within Pari chowk and Jagat market in Greater Noida, India. Paracetamol reference standard was supplied as a gift from Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, India.

Practical laboratory work was conducted at the School of Pharmacy laboratory, and Biotechnology laboratory (Department of Life Sciences), School of

Basic Science and Research, Sharda University. The methods for this study for the determination of acetaminophen contents of paracetamol tablets are the UV visible spectrophotometric, potentiometric and manual assay/trimetric methods. As stated in the Indian pharmacopoeia, paracetamol tablets contain not less than 95% and not more than 105% of the stated amount of paracetamol ($C_8H_9NO_2$) 500 mg strengths was assayed[20]. Weight variation test was conducted for paracetamol tablets before undergo further quantitative analysis.

Weight variation test: Twenty tablets were selected randomly from each four brands, weighed individually using an analytical balance and their average (mean) weight of the tablets was calculated. Then % of weight variation was calculated by using the following formula:

$$\% \text{ of Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Not more than two tablets should deviate from the average weight by a greater percentage as illustrated below A deviation of ±10% is permissible for an average tablet weighing less than 80mg. On the other hand, a tablet having a percentage deviation of ±7.5% for a tablet having an average mass of 80mg to 250mg is permissible. And finally, an average mass of tablets containing over 250mg of active ingredient should have a percentage deviation of ±5%[20].

UV Visible spectrophotometric assay method:

Procedure for preparation of paracetamol standard solution: Weigh accurately a quantity of the powder about 0.15 g of paracetamol, add 50 ml of 0.1N NaOH, dilute with 100 ml water. Shake for 15 minutes and add sufficient water to produce 200 ml. Mixed, filter and dilute to 10 ml of the filtrate to 100 ml with water. Add 10 ml of the resulting solution to 10 ml of 0.1N NaOH, dilute to 100 ml with water and mixed. Measure the extinction of 1cm layer of the resulting solution at the maximum about 257 nm, appendix 5.15A. Calculate the content of $C_8H_9NO_2$, taking 715 as the value of E (1%, 1cm) at the maximum about 257nm[21].

Procedure for preparation of test solution: Weigh and powdered 20 tablets, weigh accurately a quantity of the powder equivalent to about 0.15 g of paracetamol, add 50 ml of 0.1N NaOH, dilute with 100 ml water. Shake for 15 minutes and add sufficient water to produce 200 ml. Mixed, filter and dilute to 10 ml of filtrate to 100 ml with water. Add 10 ml of the resulting solution to 10 ml of 0.1N NaOH, dilute to 100 ml with water and mixed. Measure the extinction of 1cm layer of the resulting solution at the maximum about 257 nm, appendix 5.15A. Calculate the content of $C_8H_9NO_2$, taking 715 as the value of E (1%, 1cm) at the maximum about 257 nm [21]. The % content of paracetamol in the tablet was calculated by using the following formula.

$$\% \text{ Content of paracetamol} = \frac{\text{Avg.wt.of.tab}}{\text{Label claim}} \times \frac{\text{wt.of.std.taken}}{\text{wt.of sample taken}} \times \frac{\text{Abs.of sample}}{\text{Abs.of std}} \times 100$$

Manual assay or trimetric method: Accurately weighted equivalent to about 0.3 g of sample (from previously weighed and powdered of 20 paracetamol tablets) was dissolved in a mixture of 10 ml of water and 50 ml of 2N Sulphuric acid. The sample was boiled under a reflux condenser for 1hour cooled and diluted to100 ml with water. To 20 ml of solution, 40 ml of water in the form of ice was added. 15 ml of 2N hydrochloric acid and 0.1 ml of ferroin solution was added and the solution was titrated with 0.1 N ceric ammonium sulphate until a yellow colour appeared. A blank determination was also performed to make the necessary correction. Each ml of 0.1 M ceric ammonium sulphate is equivalent to 0.00756 g of $C_8H_9NO_2$ [22].

Preparation of solutions: (1) 0.1 N Standard Solution of Ceric Ammonium Sulphate (CAS) - 65 g CAS was dissolved in 30 ml H_2SO_4 and 500 ml of water was added into it and boiled then the solution was cooled and made it up to 1000 ml. (**2**) N Sulphuric Acid Solution- 55.0 ml of conc. H_2SO_4 was added into a 1 L volumetric flask and made it up to the mark. (**3**) 2 N Hydrochloric Acid- 181 ml of 11N HCl was added into 1000 ml by demineralised (D.M) water.

Calculation: - % of Paracetamol = $\frac{\mathbf{F} \times \mathbf{X}}{\mathbf{Y}} \times \mathbf{100}$

(1) Amount of CAS consumed by unknown sample = **X** ml

(2) Weight of sample taken = **Y** g

(3) Factor = **F** (0.00756g)

Potentiometric assay method: The pH-titrations were carried out with pH-meter in conjunction with Glass and calomel electrodes. The potentiometric measurement is performed at room temperature (25°C). The titration procedures performed following Gupta SNR method[23].

Acid-base titration of paracetamol in non aqueous solvents was done by taking equivalent to about 0.2 g of paracetamol tablet powder (from previously weighed and powdered of 20 paracetamol tablets) in a 250 ml beaker and was dissolved in 25 ml of glacial acetic acid. A bright platinum wire electrode was dipped; the solution was connected to a calomel electrode via the salt bridge and titrated with 0.1N perchloric acid in acetic acid. Titration of paracetamol tablet using platinum-calomel as well as glass-calomel electrode system. The titrant (0.1 N $HClO_4$) was added from a burette and content was stirred using a glass rod for 30 seconds. The equivalence point was located as accurately as possible by a differential graph of ΔE/ΔV versus Volume (V), and Potential (mV) against (Volume) V is shown in figure 2-5. The amount of paracetamol per tablet was computed using the following formula. Note: Amount of Paracetamol per tablet (g).

$$g = \frac{\text{Equivalence Point} \times \text{Mol. wt. of Paracetamol} \times \text{Normality of Titrant}}{1000 \times 1} \times \frac{\text{Av. Weight of Tablets}}{\text{Weight of Sample taken}}$$

Data processing and analysis: After the completion of all test procedures data for all the individual tablets were recorded and separated on a different sheet of Microsoft excel database system according to the manufacturer. Finally, data were analyzed by using the above mentioned mathematical formula and MS-Excel®, 2007.

RESULTS

Four different brands of uncoated paracetamol tablets having label strength of 500 mg for the test samples are shown in table 1.

Table 1: Paracetamol brands used in the study.

Sr. No	Brand Name	Manufacturer	Strength (mg)	Manufacturing date	Expire date	Batch No
1	Pacimol	IPCA Laboratories Pvt-Ltd, India	500	03/2019	02/2022	GR269025AZ
2	Parazest	Zee Laboratories Ltd, India	500	10/2018	09/2021	416-2009
3	Crocin	Remidex Pharma Pvt.Ltd, Bengaluru, India	500	11/2018	10/2020	R18278
4	Paracip	HSN International (Haridwar) India.	500	03/2018	02/2020	GS8794

Table 2: Weight Variation test of different brands of paracetamol.

Sr. No.	Brand Name	Total weight (g)	Weight variation (Mean ± S.D)	Range of % weight variation	R.S.D	Remark
1	Pacimol	11	0.55 ± 0.009	-1.81 to 3.63	1.63	Passed
2	Parazest	12.8	0.64 ± 0.010	-3.12 to 3.12	1.56	Passed
3	Crocin	13.2	0.66 ± 0.014	-3.03 to 4.54	2.12	Passed
4	Paracip	11.6	0.58 ± 0.007	-3.44 to 1.72	1.20	Passed

Three different assay methods were used for quantitative analysis. Accuracy and precision of the methods were confirmed by 3 replicate determinations and then S.D was calculated.

UV Visible spectrophotometric assay method:

Table 3: The percent content (assay) of four brands of paracetamol tablets obtained by UV-Visible spectrophotometric method.

Sr. No	Sample Name	Weight of sample taken (g)	Actual content of paracetamol (g)	Mean Absorbance at 257 nm	Assay ± S.D (n=3)	Remark
1	Pacimol	0.165	0.49195	0.542	98.69% ± 0.19	Passed
2	Parazest	0.192	0.51780	0.569	103.56%± 0.36	Passed
3	Crocin	0.198	0.52010	0.572	104.20% ±0.09	Passed
4	Paracip	0.174	0.51245	0.563	102.49% ±0.49	Passed

Manual assay or trimetric method:

Table 4: Comparison of manual assay of different brands of paracetamol tablets.

Sr.No	Brand Name	Actual content of Paracetamol per tablet (g)	Label claim (g)	Assay ± S.D	Remark
1	Pacimol	0.48106	0.5	96.21% ± 0.71	Passed
2	Paracip	0.49970	0.5	99.94% ± 0.90	Passed
3	Crocin	0.50110	0.5	100.22% ± 0.80	Passed
4	Parazest	0.48725	0.5	97.45% ± 1.15	Passed

Potentiometric assay method:

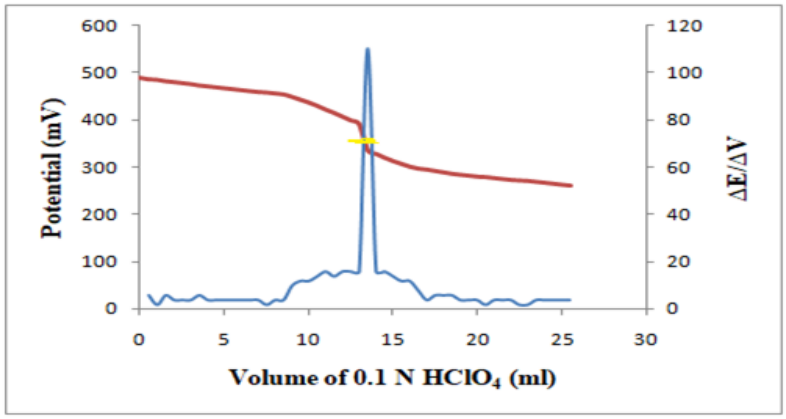

Figure 2: Potentiometric titration curve for Crocin in glacial acetic acid with 0.1 N $HClO_4$.

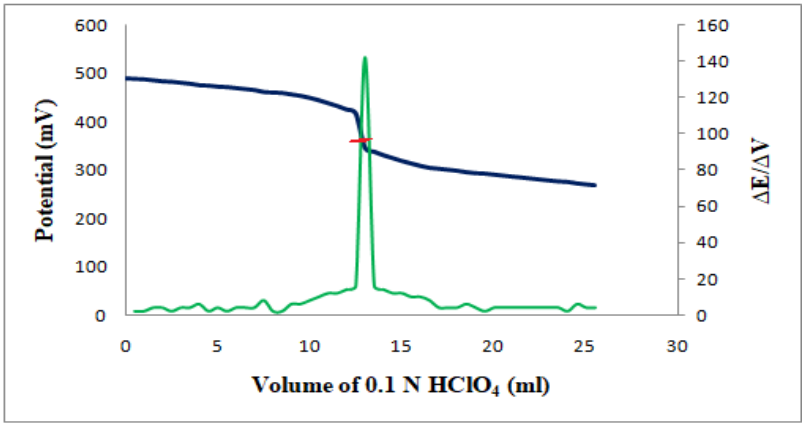

Figure 3: Potentiometric titration curve for Paracip in glacial acetic acid with 0.1 N $HClO_4$.

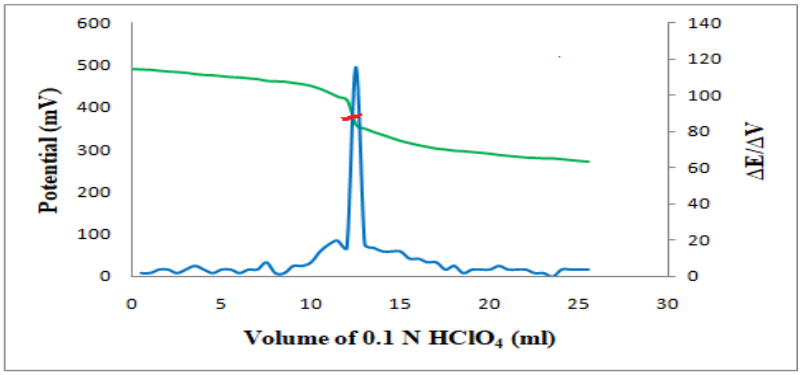

Figure 4: Potentiometric titration curve for Pacimol in glacial acetic acid with 0.1 N $HClO_4$.

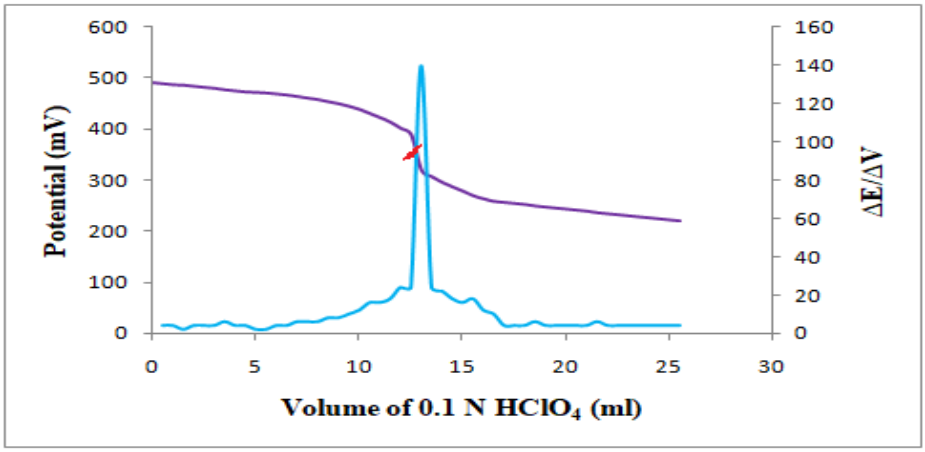

Figure 5: Potentiometric titration curve for Parazest in glacial acetic acid with 0.1 N $HClO_4$.

Table 5: Potentiometric assay of four brands of paracetamol tablets.

Sr. No.	Brand Name	Equivalence point	Weight of sample taken (g)	Amount of paracetamol per tablet (g)	Assay ± S.D	Remarks
1	Pacimol	12.8	0.220	0.48300	96.60% ± 0.23	Passed
2	Parazest	13	0.256	0.49100	98.20% ± 0.44	Passed
3	Crocin	13.8	0.264	0.52100	104.20% ± 0.61	Passed
4	Paracip	13.2	0.232	0.49800	99.60% ± 0.57	Passed

DISCUSSIONS

A comparative study for the quantitative determination of different brands of paracetamol tablet using UV-visible spectrophotometric, potentiometric and trimetric methods was carried out in this study. A tablet is designed to contain a specific amount of drug in a specific amount of tablet formulation so it is necessary to measure that the drug contains the appropriate amount. The weight variation (Mean ± S.D) of Crocin, Parazest, Paracip and Pacimol brand was 0.66 ± 0.014**,** 0.64 **±** 0.010, 0.58 **±** 0.007 and 0.55 **±** 0.009 respectively. All brands showed different mean weight which indicates the use of different excipients in the different brands[24]. Paracip and Pacimol brands had the least standard deviation value which shows the best uniformity of weight variation. However, Crocin and Paarazest brands had comparatively the highest S.D values which indicated a high dispersion of tablet weight from the mean weight and this contributed to making the tablet weights least uniform. RSD (%) indicates the accuracy of weight variation test for uniformity of weight in the investigated paracetamol tablets.

UV Visible spectrophotometric assay method: The actual content of paracetamol per tablet was 0.49195 g, 0.51780 g, 0.52010 g and 0.51245 g for Pacimol, Parazest, Crocin and Paracip brand respectively. This indicates that all these values are approximately similar to label claim of paracetamol tablet (0.5 g) and so could not be judged as counterfeits.

The assay of the tablets was found to be 98.86%, 103.56%, 104.20% and 102.49% for Pacimol, Parazest, Crocin, and Paracip brand respectively. The results ascertain the presence and compendia quantity of paracetamol in all the brands and all brands are passed as compared to the specified limit in the IP because they fall within the limit. However, the % content of paracetamol of Crocin brand is relatively high when compared to other brands. This may be due to the effect of interference i.e. the excipients used in the formulation.

Manual assay or trimetric method: The measured quantity (actual content) of paracetamol found in Pacimol, Paracip, Crocin, and Parazest (g/tab) was 0.48106, 0.49970, 0.50110 and 0.48725 respectively. The results revealed that the actual content of paracetamol per tablet was approximately similar to the label claim of a paracetamol tablet.

The results of the trimetric assay of the chemical content of paracetamol tablets showed that the active content of Pacimol, Paracip, Crocin and Parazest brand was 96.21%, 99.94%, 100.22%, and 97.45% respectively. The results indicated that variation among all brands and this may show that different manufacturer formulates the different brands are under the IP specification. But, all the brands of the tablets passed the test for the content of paracetamol. This revealed that there is good manufacturing for accepted brands.

Potentiometric assay method: The amount of paracetamol (g/tab) was found to be 0.48300, 0.49100, 0.52100 and 0.49800 for Pacimol, Parazest, Crocin, and Paracip brand respectively. The results revealed that the actual content of paracetamol per tablet of all brands is different. But, the values of content of paracetamol per tablets of all brands are nearly the same with the label claim of paracetamol tablet.

The potentiometric assay of the tablet was found to be 96.60%, 98.20%, 104.02% and 99.60% for Pacimol, Parazest, Crocin, and Paracip brand respectively. The result shows that the assay value of all brands is different. But, all the brands of the tablets passed the test because the values of the assay are within the limit of the monograph of IP specification for assay of paracetamol.

CONCLUSIONS

The present study has made to estimate a comparative study for the quantitative determination of various brands of paracetamol tablet using three different assay methods. The ranges of percentage content (assay) of the analyzed samples using UV-Visible spectrophotometric, potentiometric and trimetric methods were from 98.69-104.20%, 96.60-104.20%, and 96.21-100.22% respectively. The obtained results from this research indicate that all four brands of paracetamol tablets have sufficient quantity and amount is approximately similar to the company's recommended or claimed value. Furthermore, all the brands of the tablets complied with the IP specification for weight variation and assay.

The range of standard deviation (S.D) calculated for the three methods were from 0.09-0.49, 0.71-1.15 and 0.23-0.61 for UV-Visible spectrophotometric, trimetric and potentiometric methods respectively. The results indicated that the UV-Visible spectrophotometric method is more suitable, accurate and sensitive for assay of paracetamol tablets than other two methods.

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