

Reviewer's Comments

Quality Assessment of Different Brands of Paracetamol Tablets in Yemeni Market

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Abstract

Background: Paracetamol or acetaminophen is active metabolites of phenacetin. It is a widely used over-the-counter analgesic and antipyretic. Chemically, it is 4-hydroxy acetanilide (acetaminophen). Paracetamol is approved for reducing fever in people of all ages. It is commonly used for the relief of headaches, other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. Many different brands and dosage forms of paracetamol are available in Yemeni market that places health practitioners in a dilemma of drug substitution in case of non-availability of a particular brand.

Aim/Objective: The aim of the present study was to evaluate the quality control of four brands of paracetamol tablets (500 mg) marketed and commonly prescribed in Yemeni market. The results and findings of the present study will be interpreted and discussed.

Materials and methods: Four brands of paracetamol tablets (500 mg) were purchased from the retail pharmacy outlets and their pharmaceutical quality were assessed by using *in-vitro* tests according to USP and BP standards and unofficial standards as recommended by the manufacturers. The assessment of tablets included the evaluation of uniformity of weight, hardness, friability, disintegration time, dissolution test as well as assay content by UV spectrophotometric method.

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Results: All brands passed USP and BP standards *in-vitro* quality control tests prescribed for the tablets except hardness test but all products were satisfactory for hardness.

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Conclusion: The results indicated that the overall quality of all tested paracetamol tablets brands was satisfactory as they met the requirements of the official and unofficial quality control tests.

Keywords: *Quality Control, Paracetamol, Dissolution, Disintegration, Hardness, Friability.*

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1. Introduction

Paracetamol or acetaminophen is active metabolites of phenacetin (figure 1). It is a widely used over-the-counter analgesic and antipyretic. Chemically, it is 4-hydroxy acetanilide (acetaminophen) [1].

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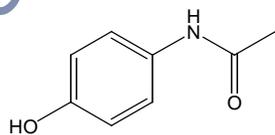


Figure 1. Chemical structure of Paracetamol

Paracetamol is approved for reducing fever in people of all ages. It is commonly used for the relief of headaches, other minor aches and pains, and is a major ingredient in numerous cold and flu remedies [2].

It is classified as a non-steroidal anti-inflammatory drug (NSAID) by some sources [3], and not as an NSAID by others [4], while most sources implicitly distinguish them, for example by mentioning both NSAIDs and paracetamol in the same sentence [5 - 6]. Paracetamol has few anti-inflammatory effects in comparison to NSAIDs.

Paracetamol is available in different dosage form: tablet, capsules, drops, elixirs, suspension and suppositories. Dosage form of paracetamol and its combinations with other drugs have been listed in various pharmacopoeias [7 - 8].

Quality of the drug according to the modern definition requires that the product contain the quantity of each active ingredient claimed on its label within the applicable limits of its specifications, contain the same quantity of active ingredient from one dosage unit to the next, be free from extraneous substances, maintain its potency, therapeutic availability and appearance until used, and upon administration release active ingredient for full biological availability [9].

Poor quality medicines do not meet official standard for strength, quality, purity, packaging and labeling [10].

Most researchers investigating stated content of paracetamol have utilized HPLC assay that was used as an accurate, simple, reproducible and sensitive method for the determination of paracetamol in tablet formulation [11].

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers [12].

In present study a quality control for a Paracetamol from different manufacturing sources in Yemeni market was investigated.

2. Materials and Methods

2.1. Material

This study is based on the comparison of available paracetamol 500 mg tablets brands in Yemeni market that are available for consumer use. Four brands of drug were taken that are coded accordingly as A, B, C, and D (table 1), and assessed using the quality control parameters of weight uniformity, hardness, friability, disintegration time, dissolution profile and active ingredient content. The labeled shelf life of all of the tablets was three years from the date of manufacturing and was taken for the evaluation before two years of the labeled expiry date. The evaluation was done according to USP and British pharmacopoeia (BP) standards.

Table 1. Different brands of Paracetamol tablets.

<i>Code</i>	<i>Dosage form</i>	<i>Country of origin</i>	<i>Batch no.</i>
A	tablet	Ireland	120979
B	tablet	Egypt	122378
C	tablet	U.A.E	1822
D	tablet	U.A.E	2909

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2. Methodology

Various analytical methods and tests are important for the development and manufacture of pharmaceutical formulations. The evaluation was done according to USP and BP standards.

2.1 Weight Variation

Tablets of each brand were weighed individually using a digital analytical balance Shimadzu. The percentage deviation of the individual tablets from the mean was determined according to USP.

2.2 Hardness Test

A tablet was placed vertically on the Monsanto Hardness tester. The load was then applied along the radial axis of the tablet. The weight or load required for breaking the tablet was noted down.

Similarly it was done for 10 tablets.

2.3 Friability

It was performed using Roche Friabilator, 10 tablets were weighed and placed in apparatus. The apparatus was rotated at a speed of 25 rpm. The apparatus was made to rotate for 4 min. The tablets were then weighed and the weights were compared with the initial weights. The % friability was calculated using the formula.

$\% F = [1 - (W/W_0)] \times 100$ Where, % F = Friability in %, W_0 = Initial weight of tablets, W = Weight of the tablets after revolution.

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2.4 Tablet Disintegration

It was performed using Electro Lab disintegration apparatus, 6 tablets were placed in disintegration test apparatus. It was maintained at $37 \pm 0.2^\circ\text{C}$ containing simulated gastric fluid (0.1N HCl).

Noted down the time taken for tablets to disintegrate.

2.5 Dissolution Test

For this test USP Type-1 (Basket) 6 Paddle Apparatus was used. The tablets formed were immersed into 900 mL of dissolution medium, simulated gastric fluid (0.1N HCl). The temperature of the dissolution medium was maintained at $37 \pm 0.2^\circ\text{C}$. The basket was rotated at a speed of 150 rpm. After an interval of every 10 minutes, 2 mL of the medium was pipette out and replaced with fresh medium (0.1N HCl). This was continued all along for one hour. The pipetted out samples were then diluted to 10 mL with fresh dissolution medium and were then filtered. The absorbances of the filtered samples were determined using U.V. Spectroscopy at λ_{max} 222 nm. According to USP [13] specifications not less than 80% (Q) of the labeled amount of acetaminophen is dissolved within 30 minutes.

2.6. Assay Paracetamol

Weigh and powdered 20 tablets accurately a quantity of powder equivalent to 0.15 gms of paracetamol and 50 mL of 0.1M NaOH, diluted with 100 mL of water, shaken for 15 minutes and add sufficient water to produce 200 mL mixed and filtered and diluted 10 mL of filtrate to 100 mL with water. To 10 mL of resulting solution add 10 mL of 0.1 M NaOH dilute to 100 mL with water and measure the absorbance of the resulting solution at about 257 nm. Assay content for paracetamol was carried out by measuring the absorbance of the sample at 257 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard paracetamol in the same medium. An accurately weighed quantity of this powder was taken, suitably dissolved in pH 5.8 phosphate buffer, making dilution and analyzed and carried out in triplicate and mean was taken. The concentration of each sample was also determined using Beer Lambert's law according to BP [14].

2.7. Data processing and analysis

After the completion of all test procedures data for all the individual tablets were recorded and separated on a different sheets according to the manufacturer. Finally data were analyzed by using the above mentioned mathematical formula and MS-Excel®, 2007.

3. RESULTS AND DISCUSSION:

During this research standard books and procedure were used to conduct each test. Among the books BP [15] and USP [16] were widely used. The degree of tolerance was also taken from the two pharmacopeias. A total of 6 Paracetamol brand marketed in Somali region were screened for weight variation, friability, disintegration time, identification and content uniformity.

3.1 Average Weight and Weight Variation

The average weight and weight variation of the different brands of paracetamol tablets tested are shown in Tables 3.1 and Fig.3.1. It was found that the average weight of different four

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brands tablets of paracetamol ranged from 566.3 mg \pm 0.912 % to 668.38 mg \pm 0.944 %. According to official books, the specified limit on weight variation for tablets more than 324 mg is \pm 5 %. It was found that all the tablets passed the USP specifications for weight variation as none of the brands deviated by upto \pm 5% from the mean value. This indicates that the factors leading to weight variation were taken in consideration. Also, the very small %RSD values of weight variation prove the high homogeneity of the tablets produced and shown high efficiency of weight uniformity and weight distribution. Weight variation gives a rough idea of content uniformity, but not a confirmatory test. On the other hand, there were differences in the weight of tablet even though all tablets contain 500 mg active. A possible explanation for this might be that different excipients used for the manufacturing which are increasing or reducing the weight of the tablet [17].

Table 2. Average weight, % deviation from average weight, content uniformity, % deviation from content uniformity, hardness (kg/cm²) and % deviation from hardness of different brands of paracetamol tablets.

Brands	Average weight (mg) , % RSD	Content uniformity (%), % RSD	Hardness (kg/cm ²) , % RSD
A	668.38 \pm 0.944	98.3 % \pm 2.52	13.67 \pm 2.44
B	613 \pm 0.498	97.25 % \pm 1.26	26.075 \pm 13.33393
C	640.79 \pm 0.616	98.2 % \pm 0.44	19.57 \pm 2.348
D	566.3 \pm 0.912	99.15 % \pm 0.966	15.765 \pm 8.506

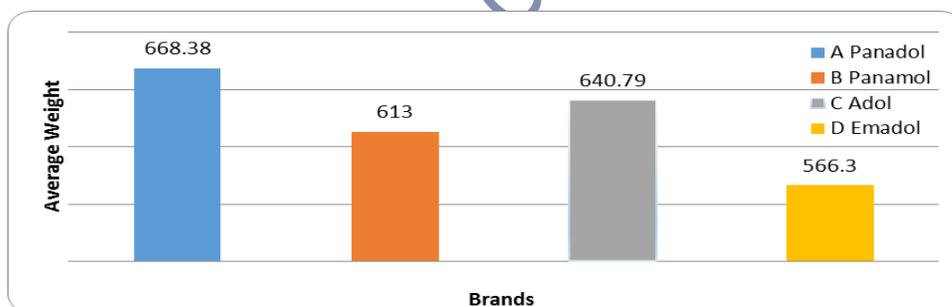


Figure 2. Comparison of different brands weight variation of different brands of paracetamol tablets.

3.2. Content Uniformity (Assay)

Test for percentage of content is based on the assay of the individual content of active ingredient of a number of single dose units. The average chemical content (assay) values of the different brands of paracetamol tablets tested are shown in table 2 and Figure3. The results of the assay of chemical content of paracetamol tablets showed that the active content of all the brands were between 97.25 % (B brand) and 99.15 % (D brand) of the labeled amount specified for paracetamol. According to the United State Pharmacopoeia [18], a paracetamol tablet should contain not less than 90% (450 mg) and not more than 110 % (550 mg) of paracetamol. The results indicated that although different manufacturer formulates the different brands are under the BP/USP specification [19]. The results indicated that although different manufacturer formulates the different brands are under the BP/USP specification [19]. There was no statistically significant difference between the different brands of the paracetamol tablets. Furthermore, all the brands of the tablets passed the test for the content of paracetamol.

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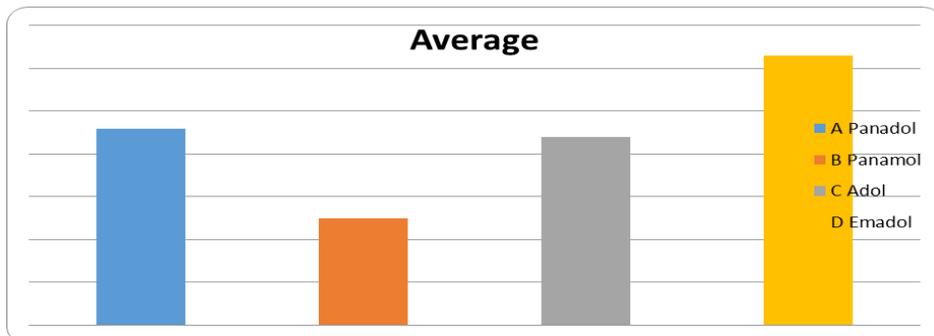


Fig.3. Comparison of assay content (Percent %) of different brands of paracetamol tablet.

3.3 Hardness

In the pharmaceutical industry, hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. The average values of hardness of the different brands of paracetamol tablets tested are shown in table 2 and figure 4. The results indicated that, the average values of hardness of the different brands of paracetamol tablets tested were in the range 13.67 kg/cm² – 26.075 kg/cm². In the study, all brands of paracetamol tablets were above the limit range of between 4 to 10 kg/cm² stated [20, 21]. High crushing strength is attributed to a high compression force, high binder concentration or excess volume of granulating fluid [22]. This related to one or combined factors affect on hardness. Although all uncoated brands of Paracetamol tablets have very high hardness, they still exhibited very good quality control parameters such as dissolution profile, disintegration time and chemical content determination. This indicates that hardness test is not a critical quality control parameter [23].

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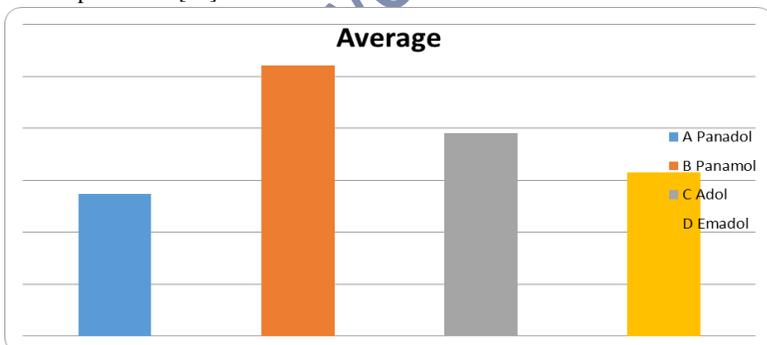


Figure 4. Comparison of hardness of different brands of paracetamol tablet.

3.4. Friability Test:

Friability is another important parameter that is related to hardness, disintegration and dissolution. The average values of friability of the different brands of paracetamol tablets tested are shown in Table 3 and Figure 5. The results indicated that all of the tablet samples tested showed impressive friability values ranging from 0.063 % (A brand) to 0.22 % (D brand). According to the USP [18] the allowed limit of friability is not more than 1.0 % of weight Loss. In all formulations

the percent (%) friability was less than 1% and as such all the brands of paracetamol had passed this friability specification. This indicated that all the tablets of each brand were mechanically stable [24].

Table 3. Friability percent (%), disintegration time (min), dissolution (30 min), % deviation from dissolution of different brands of paracetamol tablet

Brands	Friability (%)	Disintegration time (min)	Dissolution (min), % RSD
A	0.063	2.00	101.58 % ± 1.21
B	0.18	14.1	95.5 % ± 0.980
C	0.153	3.00	98.18 % ± 0.798
D	0.22	3.35	100.52 % ± 2.863

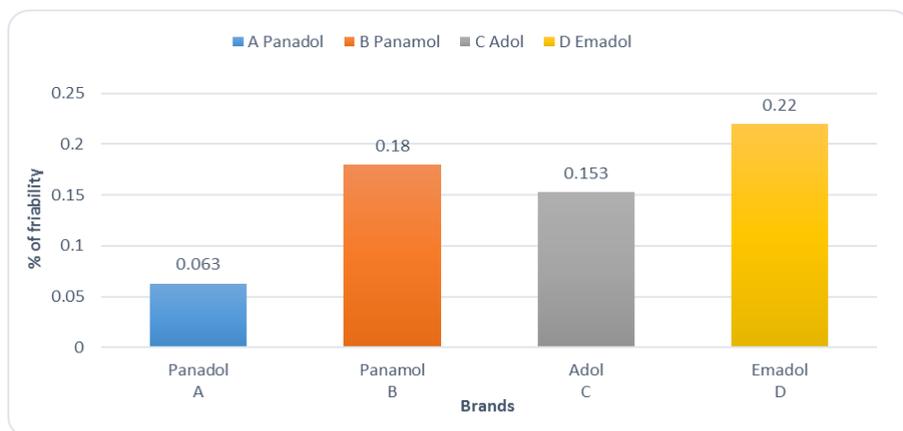


Figure 5. Comparison of friability percent (%) of different brands of paracetamol tablet.

3.5. Disintegration Time:

Tablet disintegration time is one of the very important physicochemical properties in solid dosage forms. The disintegration test measures the time required for tablets to disintegrate into particles. This is a necessary condition for dissolution and could be the rate-determining step in the process of drug absorption. The average values of disintegration of the different brands of paracetamol tablets tested are shown in table 3 and figure 6. The highest disintegration time (14.10 min) was observed for B brand, while the lowest disintegration time (2.00 min) was observed for A brand. That is, a brand quickly disintegrated compared to other brands, with disintegration time of 2.00 min. The result showed that disintegration time of all the selected tablets was found to be within specified limits of USP and BP. According to BP [25], which specifies 15 minutes as disintegration time whereas uncoated USP tablets have disintegration time standards as low as 5 minutes. All brands met the requirements for disintegration test.

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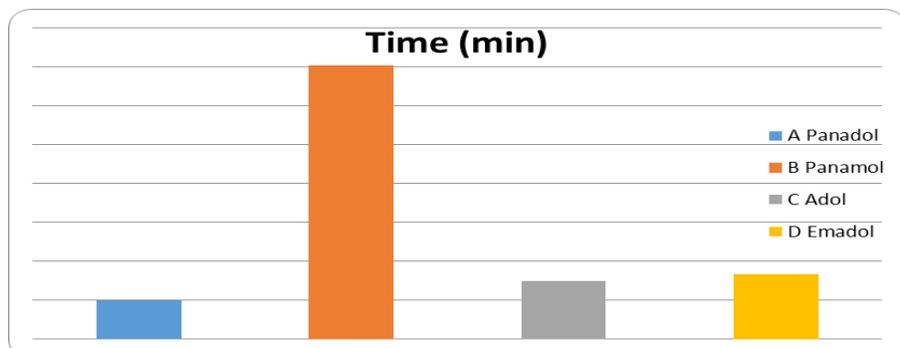


Figure 6. Comparison of disintegration time (min) of different brands of paracetamol tablet.

3.6. Dissolution Test

Dissolution was another studied important quality control parameters directly related to the absorption and bioavailability of drug. Also, dissolution behaviour of a drug has a significant effect on their pharmacological activity. In fact, a direct relationship between *in vitro* dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as *in vitro – in vivo* correlation [26]. Drugs with poor dissolution profile will not be available in the body system or target organ/tissue to elicit therapeutic effect. The average values of dissolution of the different brands of paracetamol tablets tested are shown in table 3 and figure 7. Tablet dissolution in 30 minutes ranged from 95.5 % to 101.58 %. All brands of showed more than 90 % drug release after 30 minutes. Dissolution of the all the selected brands of paracetamol tablets was found to be within the specified limits of not less than 80 % in 30 min (USP) [18] and not less than 70% (BP) [14]. All brands of paracetamol tablets achieved this standard. This might be as a result of strict adherence to good manufacturing practice in the process of manufacturing these tablets.

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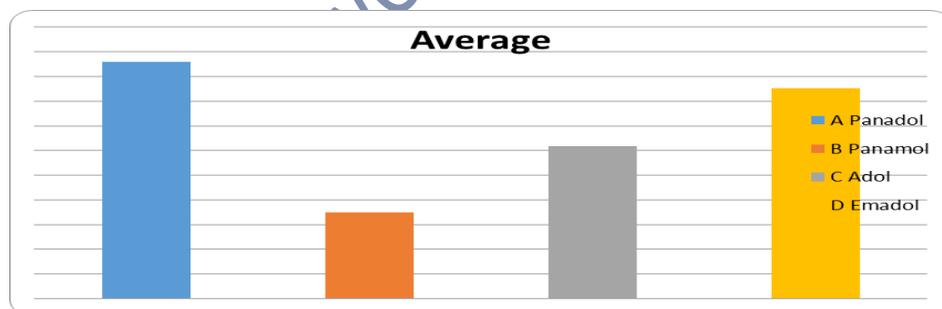


Figure 7. Comparison of dissolution test of different brands of paracetamol tablet.

Table 4. Summary evaluation test of different brands of paracetamol tablets

Brands	Weight uniformity (mg), %RSD	Assay content, %, %RSD	Hardness, kg/cm ² , %RSD	friability (%)	Disintegration (min)	Dissolution, % (30 min)
A	668.38 (±0.944)	98.3 (±2.52)	13.67 (±2.44)	0.063	2.00	101.58 (±1.21)
B	613 (±0.498)	97.25 (±1.258)	26.075 (±13.334)	0.18	14.1	95.5 (±0.980)
C	640.8 (±0.6157)	98.2 (±0.44)	19.57 (±2.348)	0.153	3.00	98.18 (±0.798)
D	566.3 (±0.912)	99.15 (±0.966)	15.765 (±8.506)	0.22	3.35	100.52 (±2.863)

CONCLUSION

The *in-vitro* physical and chemical evaluation of selected commercial brands of paracetamol available in Yemeni market proved the quality and efficacy according to the standards of USP and BP requirements. Paracetamol is a prescription drug, Hence, it is essential that it is manufactured following Good Manufacturing Practice (GMP). In this study, it was observed that all the formulation complied with the specification. It is also important that the tablets meet all the parameters because all are essential. All four brands of the paracetamol tablet comply with BP and USP specifications for *in vitro* quality control tests of uniformity of weight, uniformity of content, friability, disintegration time, and dissolution except hardens test (see table 3.3). The USP and BP specification of maximum hardens value of 10 kg/cm², where the lower value of hardens is 13.67 kg/cm² and the value is 26.075 kg/cm². But Hardness is referred to as non-compendial test.

If the hardness is increased, then the disintegration rate will increase and this will affect the dissolution profile. It is also necessary that the drugs disintegrate properly because this will influence the dissolution profile. Pharmaceutical equivalence can also be determined from these tests. According to my knowledge, not much work has been done to determine the quality control parameters of generic paracetamol tablet available in market. So further study needs to be conducted regarding the quality control parameters because paracetamol is widely used by people and it is necessary that the product is of good and acceptable quality.

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Reviewer's Comments