



A PRELIMINARY COMPARATIVE QUALITY EVALUATION TESTING OF ACETAMINOPHEN TABLET MARKETED IN SAKAKA CITY, SAUDI ARABIA

Muhammad Masood Ahmad¹, Tanveer Ahmad Khan^{2*}, Muhammad Anwar Bashir³

¹Department of Pharmaceutics College of Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia.

²Faculty of Pharmacy, Riyadh Elm University, Riyadh, Kingdom of Saudi Arabia.

³ICI Pharmaceutical Hattar Industrial Estate, Haripur, Khyber Pakhtunkhwa, Pakistan.

*Corresponding author: ahmadtanveer2001@yahoo.com

ABSTRACT

Acetaminophen is an Over the Counter (OTC) medication used as an antipyretic and analgesic. Different dosage forms of acetaminophen are available acetaminophen tablet were opted for this study. The main stressing point of the current study is to evaluate and compare quality control of three brands of acetaminophen tablets available in Sakaka, Saudi Arabia. Each of the sample of having 500mg as an active constituent were assessed for their quality evaluation using *in-vitro* tests according to official monograph of US and BP. The parameter for quality evaluation included content uniformity, weight variations, thickness, hardness, friability, disintegration and dissolution assay according to the specification of monograph. The weight variation, friability and hardness values of each of the branded tablet were complied with specifications. In-vitro disintegration and dissolution analysis showed that the disintegration time of all three brands were within 15min and dissolution test results represented that more than 80% drug was released within 30min. The results represented overall finding of the quality control evaluation of all tested brands of acetaminophen tablets that are available were observed with the official requirement of USP and BP specifications.

Keywords: Acetaminophen, OTC, Quality evaluation, Content uniformity, Dissolution test

INTRODUCTION

Acetaminophen is a medication used to relieve mild to moderate pain [1] from headaches, muscle aches and to reduce fever. It is also known as *N*-acetyl-para-aminophenol (APAP). Acetaminophen is the

chief metabolite of both acetanilide and phenacetin [2]. It is available as over-the-counter (OTC) medication in pharmacies, and the recommended dose is generally safe for humans. Overdoses of acetaminophen that cause fatal liver damage and in rare individuals, with normal dose, can do the



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same [3]. It is used to relieve fever for all ages [4] and is available in the market in different pharmaceutical dosages forms [5] such as capsules, tablets, drops, elixir, suspension, solution, suppositories [6]. Acetaminophen is generally not considered a non-steroidal anti-inflammatory drug (NSAID) [7] because it has only minor anti-inflammatory activity. Pharmaceutical dosage form safety and efficacy depend upon the quality of the product [8]. For the tablet manufacturing process, the current good manufacturing (cGMP) practice is to ensure that the active ingredients are appropriate in each tablet and the entire ingredient is mixed properly [9]. Insufficient mixing of the tablet components is usually not obtained by simple processes of blending [10]. The material must be passed from the granulator before compression to confirm that equal distribution of active ingredient in the final tablet formulation [11]. According to the modern quality definition the active ingredient [12], is claimed on the label of the pharmaceutical product must meet to the pharmacopeia standards [13]. The main aim of this study was to evaluate the pharmaceutical quality of acetaminophen tablets that are sold in local pharmacies of Sakaka City, Saudi Arabia by comparative analysis [14].

MATERIALS AND METHODS

Study Desing

Comparative study and quality evaluation among the commercially available acetaminophen 500mg tablets brands in the

sales outlets of Sakaka, Saudi Arabia were selected for this purpose. In order to check the pharmaceutical quality evaluation of parameters such as weight variation test, hardness test, thickness, friability, disintegration, dissolution was performed and analyzed by UV-Visible spectrophotometry as specified in the USP and BP.

After analysis, the statistical assessment was made to establish any differences among the physico-chemical parameters of each sample products. For the collection of the sample, the three marketed brand samples of acetaminophen (40 tablets from each brand) were purchased from different local pharmacies in Sakaka, Saudi Arabia. At the time of purchase, the sample was checked properly by physical appearance, manufacturing company, manufacturing date, license number, expiry date, batch number.

Each tablet samples were labeled approximately one year from the date of manufacturing and expiry date. Tablet labeled claimed to contain 500mg of acetaminophen per tablet. Furthermore, all of the tablet samples were purchased in blister packing.

Equipment Used in the Studies

For the determination of quality control analysis of acetaminophen tablets the following equipment was used for the analysis and quality evaluation were Weighing balance (GF-300, Germany), Disintegration Apparatus SOTAX Disi



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Test50 (Japan), Friability Apparatus (PHARMA TEST, China), Tablet Hardness Machine (PHARMA TEST, China), Dissolution Apparatus (COMPLEY SECINTIFIC) & Spectrophotometer GENESYS 10S UV-VIS (Thermofisher Scientific, USA)

Analytical Methods

For the study of quality control evaluation of the tablet sample acetaminophen tablets. The following test was performed as tablet Weight variation, thickness, hardness, diameter, friability, disintegration, dissolution and assay determination [15].

Weight Variation Test

For determination accurate weight of the drug, calibrated digital scale (AND GF-300) was used. This test was measured in routine tablet assessment to check the specified amount of drug present in the formulation. Standard procedure for weight variation test was made according to specification of USP [16]. The values of weight [17] are shown in Table 1.

The acceptance criteria of the weight variation test are that not more than two tablets should outside the percentage limit and no tablet deviates from the percentage limit twice according to the official monograph (USP).

Diameter Measurement

Test for diameter determination of acetaminophen was performed according to

the official monograph [16]. Took 3 tablets of acetaminophen of each brand and determine the diameter of each tablet individually with a screw gauge. After it, the average diameter of each brand tablet was calculated.

Thickness Measurement

Tablet thickness test was performed according to an official monograph of USP [18]. 3 tablets of acetaminophen were taken of each brand and calculate the thickness of each tablet by a micrometer used for determination of the average thickness of the tablet. Then the standard deviation was determined.

Friability Test

Friability tests of each tablet as a loss of percentage weight was performed using Roche Friabilator. The test was followed as per USP [19]. In this test 10 tablets of acetaminophen from the blister of each brand were taken and weighted. The drum of the friability was opened and place these tablets and press the start button by setting 25rpm for 4 minutes (total 100 revolutions). After completion of time took the tablet again, weigh it accurately, and calculate the percentage of weight loss must be less than 1% [17] and was calculated according to the given formula:

$$\% \text{ Friability} = \frac{[(\text{Initial weight (W1)} - \text{Final weight (W2)}) / \text{Initial weight (W1)}] \times 100}$$



Table -1: Values of weight variation specification.

Weight Variation Tolerances of Uncoated Tablets Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
130 or less	+/- 10
130-324	+/- 7.5
More than 324	+/- 5

Hardness Test

The hardness of the tablet may influence the other properties of the tablet such as friability, disintegration, and dissolution. A tablet hardness test was performed for quality evaluation of the tablet. Crushing strength or hardness of the tablet load is required to crush the tablet when placed on the edges of the tablet. This test was conducted according to official monographs (standard procedure of USP) using digital hardness tester. First of all, on the instrument was calibrated and then set the required units (N, Kg, K lb, Sc). Place the tablet between the metal jaws of the machine and load was gradually increased until the tablet fractured. The noted value of the load at that point is the hardness of the tablet. Repeat the procedure for 10 tablets. Calculate the average hardness and standard deviation of each batch of tablets.

Disintegration Test

The time of disintegration depends upon the quality of the product. Disintegration test was performed as per Official Monographs [20]. Determination procedure of

disintegration tests were performed according to standard procedure [21]. The instrument name DISI-50 was used for disintegration. simulated gastric media 900ml was prepared in a beaker. Set the temperature at $37 \pm 0.5^{\circ}\text{C}$, a number of the basket (3 or 6) place six tablets along with a disk, and positioned in the beaker containing medium. The disintegration time was observed, on the screen of the instrument and repeat this procedure triplicate. According to USP, within 30 minutes all acetaminophen tablets must disintegrate [22]. Test passes when 16/18 tablet disintegrated. If not repeat this procedure. After repeating, if the result did not comply with the official monograph; the test will be considered failed [20].

Dissolution Test

Dissolution study is the correlation between in vitro in vivo (IVIV) because we study the disintegration time of the tablet. When the tablet is broken and releases the active content in the stomach or intestine. The human body facilitates dissolution in the biological fluids before GI absorption



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followed by drug distribution, metabolism, and excretion [23], it is a general concept that if any tablet did not fulfill the criteria, it will presumably not be up to the mark of dissolution [19]. The dissolution study was performed according to the official monograph of USP using dissolution apparatus type (Dis-8000 of COPLEY Scientific Made by the UK). For these purposes six paddles USP-I (Basket Assembly) was used. Simulated gastric media was prepared with a concentration 0.1N HCl and tablet immersed in 900ml dissolution medium at $37 \pm 0.2^\circ\text{C}$. The speed of the basket was set at 50rpm, and after every 10 minutes a 2ml sample was withdrawn by replacing fresh media (0.1N HCl), then further continued this process for 60min. The sample absorbance was noted at 243nm by double beam spectrophotometer (Model 6800 JANEWAY) and estimated the quantity of acetaminophen dissolved in 60min. No less than 80% quantity of acetaminophen dissolved as given on labeled amount, according to the official specification of USP [20].

Content Uniformity Test

For acetaminophen assay calculated the weight of 20 tablets and then grounded in pestle and mortar. Took 150mg of acetaminophen tablet powder accurately weighed and added 50ml solution of 0.1M NaOH, diluted it with 100ml distilled water in 1st volumetric flask. Agitated for 15min and make up the distilled water up to 200ml dilution. Filtered the solution and took 10ml

of filtered solution in a volumetric flask and diluted it up to 100ml distilled water in the 2nd volumetric flask. Took 10ml from 2nd volumetric flask, added 10ml NaOH (0.1M), and diluted with distilled water up to 100ml in 3rd volumetric flask. Measure the absorbance by double beam spectrophotometer (Model 6800 JANEWAY) at 243nm and prepare the calibration curve of standards acetaminophen in the same medium for comparison of the contents. Acetaminophen powder was accurately weighed, dissolved in phosphate buffer pH- 5.8, prepared the dilution, analyzed in triplicate, and taken average value. By using Beer Lambert's law according to the official monograph of BP [24] and determine the concentration of each sample.

RESULTS

For determination of quality analysis of acetaminophen tablet, standard operating procedures (SOPs) and official books were used for performing all tests during research. The main emphasis on official books BP and USP and degree of variation follow from the respective monograph of pharmacopeias.

According to results physicochemical analysis of three acetaminophen tablet brands showed the following results and their morphological characteristics with code is presented as tablet Sample Fevadol (FDA), Panadrex (PND) and Panadol (PAD), in the Table 2. Different marketed brands of acetaminophen tablet weight



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variation tests are shown in Table 3 and Figure 1. It was noted the range of weight of three brand acetaminophen tablets was from 553mg to 672mg. According to the official monograph of USP specification, the limit of weight variation for more than 324mg is $\pm 5\%$. It was found from the tablet weight variation result from all brands of acetaminophen tablet pass the USP official monograph and the mean value did not deviate in any selected brand of acetaminophen tablet up to $\pm 5\%$ and consideration of weight variation of the tablet [25]. The uniformity and homogeneity of the selected brands of acetaminophen tablets are proven by very small values indicated in the percentage of deviation. All the brands have active ingredient content of 500mg but the ratio excipient increase or decreases the weight of the tablet. The content uniformity is roughly estimated but not the confirmation.

The parameter of hardness testing concerning tablet manufacturing in the pharmaceutical industry. The tablet must bear the weight during cargo. The average result of selected brands of acetaminophen tablet hardness is present in Table 3 and Figure 2, which fall in the range of 129.8 N to 158.7N. All the brands were above the normal range which is 39.2N to 98.06N according to the official monograph [4, 26]. The hardness increased due to an increase in the force of compression during manufacturing and high crushing strength. The parameter of the tablet hardness is not a

key quality control parameter. The determination of active ingredient in the tablet was confirmed by assay of the tablet content and content uniformity (Assay) of the tablet according to the official monograph. Table 3 and Figure 3 represent the values of average chemical content in acetaminophen tablets. The active content of acetaminophen tablets' values falls between 98.20% to 99.55 and comply with the official monograph value of USP, which is the range of 90% to 110% [27]. The brand PND achieved the highest value of drug content is 99.95%. These results of different brands of acetaminophen tablets showed the statistically insignificant difference and all different brands of tables comply with the USP specification.

In pharmaceutical solid dosage form, the factor of tablet disintegration is considered as an official test because on the base of disintegration the tablet disintegrates into smaller particles. In drug absorption for the dissolution of tablets, it important is to disintegrate at the proper time. The average disintegration values are shown in Table 4 and Figure 4. All brands of acetaminophen tablets disintegrate in between 1-5 minutes and the minimum level achieved by PND. The disintegration result of all brands of acetaminophen tablet falls within the limits of USP and BP.

The parameter of friability is related to tablet strength. The tablet friability average values are shown in Table 4 and Figure 5. The USP specification of friability is not more



Table -2: Different acetaminophen tablet marketed brands.

Brand Name	Code no.	Country	Batch no.	Active Qty.(mg)	Tablet Shape
Fevadol Tablet	FAD	Saudi Arabia	9-212-92	500	Round
Panadrex Tablet	PND	Kuwait	JT631	500	Capsule
Panadol Tablet	PAD	Ireland	MV2U	500	Oval

Table -3: Weight variation, Thickness, Hardness, Diameter and Content Uniformity of acetaminophen tablet.

S. No.	Code no.	Weight Variation (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)	Assay Content (%)
1	FAD	553±0.471	4.45±0.029	158.7±2.04	13.1±0.009	98.60±1.736
2	PND	561±1.247	4.85±0.004	129.8±5.52	17.67±0.021	99.55±0.673
3	PAD	672±0.942	6.38±0.004	147.1±1.07	17.16±0.009	98.20±0.506

Table -4: Disintegration, Friability, and dissolution of acetaminophen tablets.

S. No.	Code no.	Disintegration Time (min.)	Friability (%)	Dissolution (min)
1	FAD	5.10	0.19	97.95±0.081
2	PND	1.53	0.19	100.02±0.108

Table -5: Cumulative results of acetaminophen tablet different brands evaluation.

S. No.	Code no.	Weight Variation (mg)	Hardness (N)	Assay Content (%)	Disintegration Time(min.)	Friability (%)	Dissolution (min)
1	FAD	553±0.471	158.7±2.04	98.60±1.736	5.10	0.19	97.95±0.081
2	PND	561±1.247	129.8±5.52	99.55±0.673	1.53	0.19	100.02±0.108
3	PAD	672±0.942	147.1±1.07	98.20±0.506	3.11	0.04	98.25±0.763

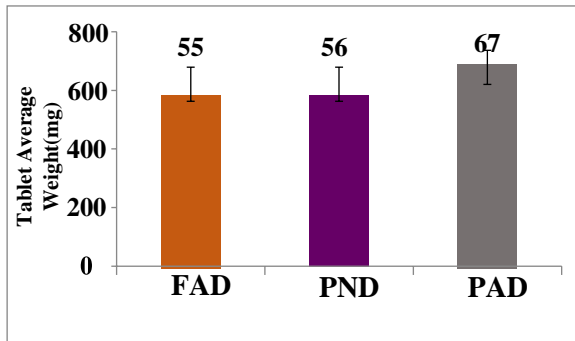


Figure -1: Weight variation of different brands of acetaminophen tablet

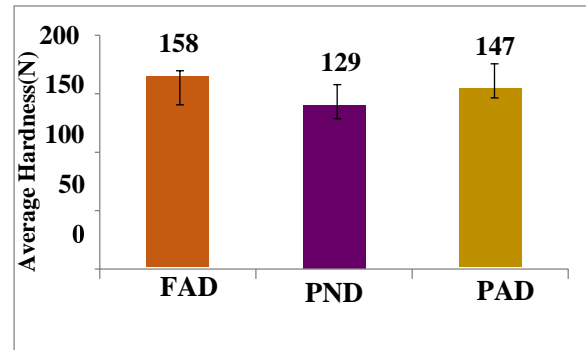


Figure -2: Hardness testing of different brands of acetaminophen tablet

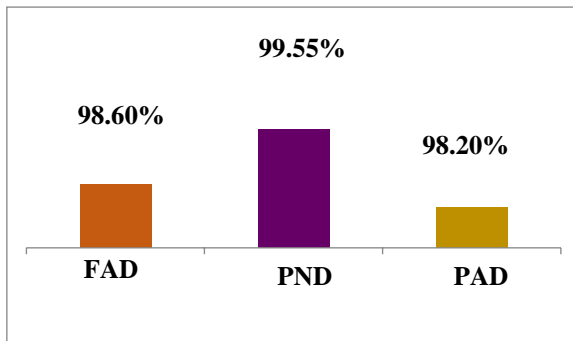


Figure -3: Content Uniformity (Assay) %age different brand of acetaminophen tablet

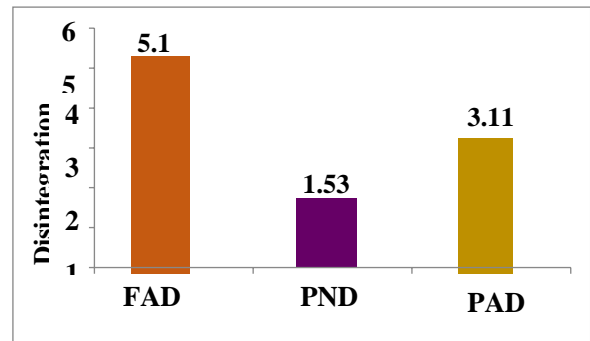


Figure -4: Disintegration time different brands of acetaminophen tablet

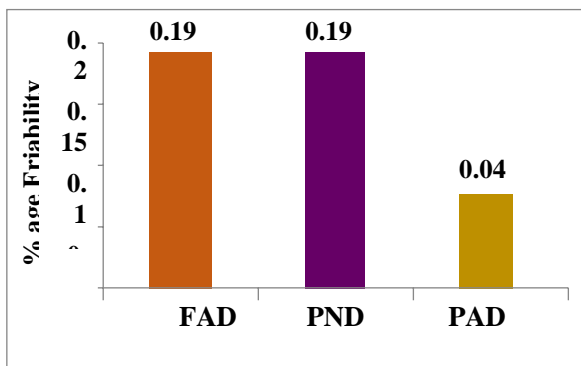


Figure -5: Friability test different brands of acetaminophen tablet

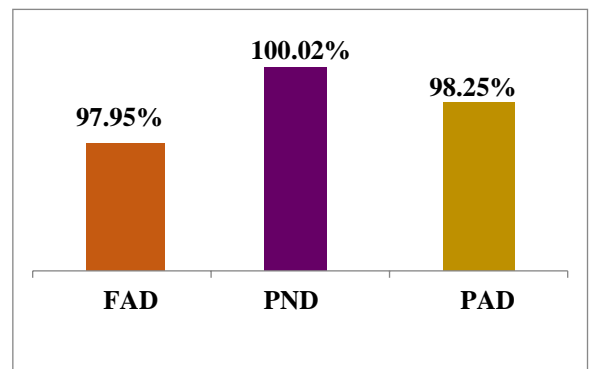


Figure -6: Dissolution study different brands of acetaminophen tablet



than 1% of tablet weight loss from the actual weight [27]. The result falls in between 0.04% to 0, 19% of weight loss. In the light of average results, all the brands of the acetaminophen tablets pass the friability test. For the determination of bioavailability of the drug, the key parameter is dissolution, which acts as a direct relationship between in-vivo & in-vitro correlation. Dissolution parameters directly link to drug absorption. Due to that factor dissolution studies take a key role in drug absorption assessment in the body. The average dissolution values of acetaminophen tablets are shown in Table 5 and Figure 6. The dissolution ranges from 97.95% to 100.02% within 30 minutes attained by all brands of acetaminophen tablets. The peak dissolution value was achieved by PND and after 30 minutes all the brands of the acetaminophen attained more than 90% of drug release. According to the USP specification within 30 minutes not less than 80% and BP specification within 30 minutes not less than 70% drug release from the product [28]. The result indicated that all the acetaminophen brands meet the official monograph limits. It is seemed to be that these pharmaceuticals follow good manufacturing practices. The cumulative results of all brands of acetaminophen are represented in Table 6. The factor of dissolution indicated the behavior of the drug product when the pharmaceutical dosage form was taken by a specified route of drug administration. Dissolution study also called

IVIVC (predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response) and important quality evolution tool which is used to verify manufacturing and product consistency.

DISCUSSION

Since the main focus of this study was to compare the quality control standard evaluation of the locally available three brands of acetaminophen tablet that was available in pharmacies in Sakaka, Saudi Arabia. The quality control evaluation of physical and chemical parameters comparative analysis of acetaminophen tablet that contains 500mg active constituent. The test performed like weight variation, thickness, hardness, friability, disintegration, and in-vitro analysis by dissolution study of acetaminophen tablet. Regarding the official monograph of B.P, the three brands of acetaminophen tablets were estimated not more than $\pm 5\%$ deviation from the average weight of the tablet. By careful observation, the weight variation test of three brands was passed because no tablet of each three brands deviates from the specified limit are shown in Table 6. The friability testing according to the official monograph of BP/USP is not more than 1% and PDA has lesser friability value as compared to the two brands and all three were under the specified limit. According to the official quality standard of B.P, the core tablet disintegration time is less than 15min.



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and PND disintegrates in less than 2min.to disintegrate and FAD and PAD disintegrate within 5min. which was in the range of official monographs areshown in Table 6.

The thickness values analysis has no official limit but results show that PAD was thicker as compared to the FAD and PND but it was in limit according to the registration item standard. The hardness of the three brands analysis showed that PND was less hard than the other two brands are shown in Table 5. All of the selected brands for the in-vitro dissolution analysis study did not cross the time. According to the official monograph of U.S.P limits for acetaminophen tablets dissolved amount should not be less than 80% quantity of the labeled amount in 30min. and our dissolution results were under the specified limit.

CONCLUSION

The official monography According to the United States Pharmacopoeia 2018 (USP 41), and Acetaminophen tablet should contain not less than 90% (450 mg) and not more than 110% (550 mg) of acetaminophen and our assay results of all these brands were in the range of official specified limits are shown above.

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