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COMPARATIVE IN VITRO QUALITY AND DISSOLUTION ASSESSMENT OF DIFFERENT BRANDS OF PARACETAMOL TABLETS MARKETED IN SUDAN: IMPLICATIONS FOR BIOWAIVER ELIGIBILITY

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ABSTRACT

Bioequivalence studies are the usually accepted methods to determine the therapeutic equivalence of two drug products or more. Because in-vivo bioequivalence studies are time consuming and expensive to conduct, major regulatory authorities have introduced biowaivers for some selected medicines belonging to BCS class I and III drugs. Comparative dissolution tests are used in biowaiver procedure to waiver the bioequivalence requirement. The objectives of this research were to determine the quality of three brands of Paracetamol (500 mg) tablets (B, C, and D) available in Sudanese market and to compare with the innovator brand drug product (A) through measurement of different physiochemical parameters under biowaiver condition. different tablets from each brand (A,B,C, and D) were taken from the market and were determined by the quality control parameters including weight variation, friability, hardness, disintegration test and dissolution test. The dissolution profiles were obtained in three different pH media (1.2, 4.5, and 6.8) for each brand. The percentage released of paracetamol in all dissolution media were determined by UV spectrophotometric method and the brand tablets were evaluated to check if they are complying with the specification of BP. **Result:** all brands were passed the test when compared with the specification and all brands B, C, and D released paracetamol with 90% and more within 30 min in all the three media. **Conclusion:** The tablets met with specification, they had the desired and optimum therapeutic efficacy.

INTRODUCTION

Biowaiver Study

Biowaivers are considered as the waivers of clinical bioequivalence studies.[1] The biowaiver can be defined as the acceptance for regulatory purposes of the replacement of in-vivo bioequivalence studies and bioavailability by in-vitro test.[2] According to the Food and Drug Administration (FDA) bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[3] Bioequivalence studies are as vital concern in drug development process, which are required for small changes in drug products that develop during drug development to ensure that the dosage forms prove to be safe and effective.[4] Moreover, bioequivalence has proven even more significant in case of drugs narrow therapeutic index (NTI). The bioequivalence studies are required for the finical development of new chemical entities (NCE), when the formation of the pharmaceutical dosage form has been changed. The in-vivo pharmacokinetic data can be used as an important constraint for in -vivo solubility and permeability data.[5]

As it is estimated that the in-vivo bioavailability and bioequivalence studies cost up to $250,000 each and require up to 2 months to complete, whereas, the in-vitro

laboratory tests are rather inexpensive and fast, in which dissolution studies, similarity factor (f2) profile calculations and report writing represent a large part of the laboratory work.[6]

Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms dissolution, solubility and intestinal permeability.[7]

According to the BCS, drug substances are classified as follows

- Class 1: High Solubility-High Permeability
- Class 2: Low Solubility - High Permeability
- Class 3: High Solubility-Low Permeability
- Class 4: Low Solubility-Low Permeability

The BCS has appeared as a supportive means in product development by evading to the in-vivo performance of the active substance.[8] The bio-relevance of the BCS properties and the invitro release are expressed through a correlation between in-vitro and in-vivo data. Recently, BCS has been executed for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance, which can be strategically deployed to save time and resources during generic drug development. Moreover, BCS has been developed to allow prediction of in-vivo pharmacokinetic performance of drug products from measurements of permeability and solubility. In addition, the BCS has been adopted as a useful tool for in vivo drug design and development worldwide, and thus, BCS-based biowaiver has become an important and cost-saving tool in generic drug approval process.[9]

Requirements for a BCS-Based Biowaiver Study

1. Dissolution test in 3 different media (in 900 ml and at 37°C) which are:[10]
- Buffer pH 1.2, simulated gastric fluid (SGF) without enzymes or 0.1 N HCl
- Buffer pH 4.5
- Buffer pH 6.8 or simulated intestinal fluid without enzymes

2. Samples should be collected at sufficient number of intervals to characterize the dissolution profile of the drug product (e.g. 5, 10, 15, 30 and 45 minutes).[10]
3. The profiles of the test and reference products must be similar in all three media.[10]
4. The products are similar if the similarity factor f2 ≥ 50 for both products.[10]

The similarity factor (f2) is a measurement of the similarity in the present dissolution between two dissolution curves. It is inversely proportional to the average squared difference between the two profiles. It is a logarithmic reciprocal square root transformation of the sum of squared error and is given by the formula:[11]

$$f2=50 \times \log \{[1+(1/n) \sum t=1 \times n (Rt-Tt)2]-0.5 \times 100\}$$

Where, n is the number of testing time points, Rt is the average dissolution value of the reference product units at time t and Tt is the average dissolution value of the test product units at time t.[11]

Quality Control of Tablets

The tablets require passing not only weight variation test, friability test, hardness test, thickness & diameter test, disintegration test and dissolution test but a visual inspection must be made regarding uniformity of size, colour and shape.[12] Tablets should be smooth and undamaged; evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking and swelling.[13] In official books the following Quality control tests are recommended:

Weight Variation Test

Weight variation test is a very important quality control parameter because it is related with the content uniformity of a drug. According to USP, the weight variation test is run by weighing 20 tablets individually in an analytical balance, calculating the average weight and comparing the individual tablet weights to the average.[14]

The tablets meet the USP test if no more than 2 tablets are outside the percentage limit of 1% and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for uncoated tablets differ depending on average tablet weight. The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or essentially all (90 to 95%) active ingredient, or if the uniformity of the drug distribution in the granulation of powder from which the tablets were made were perfect. However, the weight variation test is clearly not sufficient to assume uniform potency of tablets of moderate or low-dose drugs, in which excipients make up the bulk of the tablet weight.[14]

Friability Test

Shock and frictional forces can cause the tablets to get damaged or break. With this test, it is possible to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping which is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test using a friability test apparatus is considered generally acceptable and any broken or smashed tablets are not picked up.[15]

Hardness Test

In order to withstand mechanical shocks of handling during its manufacture, packaging and transport, the tablet requires a certain amount of strength, or hardness. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer.

Adequate tablet hardness is a necessary requisite for consumer acceptance. Moreover, there is evidence that hardness may influence tablet disintegration and, perhaps more significantly, drug dissolution release rate. It may be especially important to carefully monitor tablet hardness for drug products that possess real or potential bioavailability problems or are sensitive to altered dissolution-release profiles as a function of the compressive force employed.[14]

Thickness & Diameter Test

Tablet thickness is an important quality control test for tablet packaging. Very thick tablet affects packaging either in blister or plastic container. Tablet thickness is determining by the diameter of the tablet. Tablet diameter is also an important test; tablet thickness can be measured by micrometer or by other device and should be controlled within a ± 5% variation of standard value.[16]

Disintegration Test

It is the time required for the tablet to break into particles, the disintegration test is measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through 10 mesh screen.[17] Disintegration time may vary considering to its disintegrator used. Higher the disintegration time required lower the dissolution rate and followed to pour absorption. So disintegration is the crucial part of a drug for therapeutic action. Uncoated USP tablets have disintegration time standards as low as 5 minutes, but the majority of the tablets have a maximum disintegration time of 30 minutes.[14]

Dissolution test

Dissolution is the process by which the solid enters a solution. The dissolution rate is the amount of drug substance that goes into solution per time under standardized conditions of liquid\ solid interface, temperature and solvent composition. Dissolution is one of the most quality control tests and consider as a tool for predicating bioavailability, in some cases replace clinical studies to determine bioequivalence, in face a direct relationship between invitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in-vitro-in-vivo correlation (IVIVC). A variety of designs of apparatus for dissolution testing is varying from simple beaker to complex system where an attempt is made to mimic the biological media. The choice of the apparatus to be used depends largely on the physicochemical properties of the dosage form.[17]

Method of analysis

UV/Visible spectrophotometer

UV/Visible spectrophotometer is an easy, cheap, robust and more precise method for quantitative analysis of drug in formulations. A routine method for determination of some physiochemical properties of drugs which need to be known for purposes of the drug formulation.[18]

Justification

It is necessary to carry out study on the quality control parameters of paracetamol tablets for the appropriate evaluation of quality, therapeutic efficacy, and safety of the generic tablets compared with the innovator. This is in order to accept or reject the generic brands for use instead of the originator.

Also biowaiver studies are less expensive to be conduct which may help in the further improvement of the products.

Drug Profile

Acetaminophen, also known as paracetamol is an active metabolite of phenacetin, is commonly used for its analgesic and antipyretic effects. Its therapeutic effects are similar to salicylates, but it lacks anti-inflammatory, antiplatelet, and gastric ulcerative effects.[1] It is one of the most commonly used 'over-the-counter' analgesics for headache, mild migraine, musculoskeletal pain, dysmenorrheal, etc. Paracetamol is generally safe for human use at recommended dose.[19]

Chemical name: N-(2,3,5,6-tetradeuterio-4-hydroxyphenyl) acetamide.[20]

The structure of Paracetamol was shown below in Figure. 1.

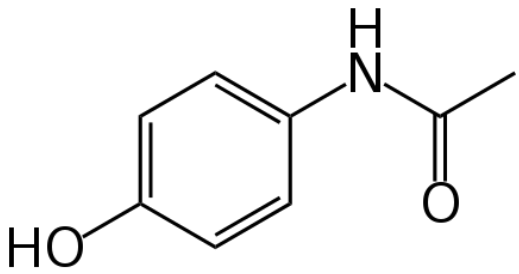

Figure 1: Chemical Structure of Paracetamol.[20]

Molecular formula: C8H9N02[20]
Dosage form: Paracetamol Tablets[20]
Generic name: Paracetamol 500mg[21]

History of Paracetamol

The history and discovery of Paracetamol is fascinating as it was discovered by accident when a similar molecule acetanilide was put to use as an analgesic and antipyretic medicine in the late 1800s.[22]

Physiochemical properties

Paracetamol is white odourless crystalline powder, large monoclinic prisms from water. It's melting point is 169-170.5°C.[23]

Regarding its solubility, it is Soluble in water (1:70, 1:20 at 100°C), ethanol (1:7), acetone (1:13), chloroform (1:50), glycerol (1:40), methanol (1:10), propylene glycol (1:9) and solutions of alkali hydroxides; insoluble in diethyl ether. A saturated aqueous solution has a pH of 6. 139.

Stability Dry, pure paracetamol is stable to 45°C. Contamination with traces of Para-aminophenol, and humid conditions that cause hydrolysis to para-aminophenol, result in further degradation and discoloration. Slightly light-sensitive in solution, and degradation is catalysed by acids or bases.[23]

Mechanism of action

It is surprising that after more than 100 years, the exact mechanism of action of paracetamol remains to be determined. There is evidence for a number of central mechanisms, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide (NO), and cannabinoid pathways, and it is likely that a combination of interrelated pathways are in fact involved.[24]

The mechanism of action of paracetamol is not completely understood. Unlike NSAIDs such as aspirin, paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system, and this appears to be the reason why it is not useful as an anti-inflammatory. It does appear to selectively inhibit COX activities in the brain, which may contribute to its ability to treat fever and pain. This activity does not appear to be direct inhibition by blocking an active site, but rather by reducing COX, which must be oxidized in order to function.[25]

Clinical uses

Paracetamol 500 mg Tablet is used to temporarily relieve fever and mild to moderate pain such as muscle ache, headache, toothache, arthritis, and backache.[26]

Paracetamol has following usage[26]

- Used as Antipyretic, analgesic agent. It has negligible anti-inflammatory action.
- It is suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/ risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti inflammatory action of NSAIDs.
- It is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).
- Paracetamol is one of the most commonly used 'over-the-counter 'analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea etc, but is relatively ineffective when inflammation is prominent.
- It is recommended as first choice analgesic for osteoarthritis by many professional bodies.
- It is one of the best drugs to be used as antipyretic, especially in children (no risk of Reye's syndrome).[26]

MATERIALS AND METHODS

Materials

Samples

All brands of paracetamol tablets were selected from pharmacies, the three generics paracetamol 500 mg tablets were coded as B,C,D and the innovator brand (panadol® 500 mg) was used as a reference sample, it was coded as A. The four different brands of paracetamol 500 mg tablets were tabulated in table 1.

Table 1: History of Selected Brands of Paracetamol 500mg Tablets.

Brand Code	Brand Name	Manufacturers	Origin
Brand (A)	Panadol 500 mg	Glaxosmithkline	United Kingdom
Brand (B)	Amidol 500 mg	Amipharma Laboratories Ltd	Sudan
Brand (C)	Nabidol 500 mg	Dr.Nabil Pharmaceutical &Chemical Laboratories	Sudan
Brand (D)	Nilodol 500 mg	Blue Nile Pharmaceuticals Factory	Sudan

Reagents

All reagents were of analytical reagent grade and distilled water was for the preparation of all solution. The source the reagents is demonstrated in table 2.

Table 2: Chemical Reagents Used Throughout the Study.

Reagent Name	Company	Origin
Sodium Hydroxide	Carlo Erba Reagents	United kindom
Potassium Dihydrogen Phosphate	Carlo Erba Reagents	United kindom
Hydrochloric Acid	Carlo Erba Reagents	United kindom
Sodium chloride	Carlo Erba Reagents	United kindom
Acetic Acid	SDFCL	India
Sodium Acetate Anhydrous	Elnasr Pharmaceuticals Chemicals Company	Egypt
Purified Water	Dr. Nabil Pharmaceutical & Chemical Laboratories	Sudan

Instruments and Equipments
All the instruments used throughout the study were mentioned in table 3.

Table 3: instruments used throughout the study.

Instrument	Source(supplier Name)	Origin
UV/Visible spectrophotometer	Shimadzu model:U.V-1800 240V, serial no:A11454806532	Japan
Dissolution Apparatus	ERWEKA DT 820, serial no:125289 09ce	Germany
Disintegration Tester	ERWEKA ZT122, serial no:125327 09ce	Germany
Friability Tester	ERWEKA TA 220, serial no:125322 09ce	Germany
Hardness Tester	ERWEKA TBH 225 D, serial no:125270 09ce	Germany
Thickness Tester	ERWEKA TBH 225 D, serial no:125270 09ce	Germany
Sensitive Balance	Sartorius CPA225D	Germany
Magnetic Stirrer	DAIHAN LABTECH model:LMS-1001	Korea

Apparatus
Class A glassware was used and all the apparatus used throughout the study were mentioned:
Beaker, Test tube, Mortar and Pestle, Volumetric flask (50, 100, 200, 1000 ml), Measuring cylinder 1000 ml, Glass rod, Spatula, Syringe 10ml, Filter paper size 45 µm, Pipette (1,2,5,10 ml) and Funnel.

Quality control Tests (Methods)
Uniformity of weight (weight variation)
Twenty intact tablets of each brand were weighed individually using sensitive balance and each tablet was weighed individually then the average weight was calculated and the percentage deviation of each tablet from the mean was then calculated which was expressed in percentage by the following formula:
Average weight=sum of tablets/ number of tablets
Deviation percentage (%) = (Iw-Aw) / Awx 100%
Where:
Iw = Individual weight of tablet
Aw=Average weight of tablet
According to BP the allowed percentage deviation is ±5 when the average weight of the tablet is More than 324 mg.

Friability test
Twenty tablets of each brand were weighed on the sensitive balance. The tablet was placed in the section one of the drum of the friability tester and rotated 100 rpm (i.e. 25 rpm for 4 minutes). Any loose dust was removed from the tablets and then they were reweighed. The difference in weight was taken and percentage friability was calculated by the following formula:
Friability = [(Initial weight - Final weight)/ Initial weight] x 100
According to BP the total weight loss should not be more than 1% and no tablet should show any type of break or crack.

Hardness test
Ten tablets of each brand were selected randomly to perform this test using Hardness tester. The tablet was placed vertically between two anvils of the tester and the digital scale was adjusted to zero. The force was applied to the anvils and the crushing strength that just cause the tablet to break was recorded. A mean hardness and standard deviation were calculated for each brand. Hardness is not an official test so there is no such a specified limit for hardness but a crushing strength of between 4 kg/cm2 to 10 kg/cm2 is considered minimum requirement for a satisfactory tablet.

Thickness test
This test was performed using thickness and diameter tester for ten tablets and average thickness and standard deviation were recorded. ± 5 is allowed depending on the size of the tablet.

Diameter test
This test was performed using thickness and diameter tester for ten tablets and the average and standard deviation were recorded.

Disintegration test
Six tablets of each brand were placed in disintegration apparatus, where the volume of disintegration medium was 900 ml of water maintained at 37±5°C. The time taken to break each tablet into small particles and pass through the mesh was recorded and average time was calculated.
According to BP 2018 for most uncoated tablets the period is not more than 15 minutes.

Dissolution test
The dissolution profiles for each brand were performed using dissolution apparatus I at 50 revolutions per minute (rpm) using automated equipment with different dissolution media prepared according to the British Pharmacopeia to show the drug dissolution through the stomach and intestine. Phosphate buffer solution pH 5.8, hydrochloric acid media pH 1.2, acetate buffer pH 4.5 and phosphate buffer solution pH 6.8 were used and prepared as the following:
Phosphate buffer solution pH 5.8: 250 ml of 0.2M of potassium dihydrogen phosphate was mixed with 112 ml of 0.2 M sodium hydroxide and the volume was completed to 1000 ml of water.

Hydrochloric acid media pH 1.2: 250 ml of 0.2M sodium chloride and 425 ml of 0.2 M hydrochloric acid were added and the volume was completed to 1000 ml water.

Acetate buffer solution pH 4.5: 2.99 g of sodium acetate was dissolved in 100ml of water. 14 ml of 2M acetic acid was added and the volume was completed to 1000 ml water.

Phosphate buffer solution pH 6.8: 250 ml of 0.2M of potassium dihydrogen phosphate was mixed with 112 ml of 0.2 M sodium hydroxide and dilute to 1000 ml of water.

One tablet was put in a vessel containing 900 ml of dissolution media at 37+0.5℃ (equilibrate by thermometer). Six vessels were used for each brand. The apparatus was operated at 50 rpm (Basket form). 10 ml was withdrawn in a manual manner by syringe from the zone midway between the surface of dissolution media and the top of the blade (not less than lem from the walls of vessel). A multiple sampling times (10, 15, 30, 45, 60 minutes) were taken and the withdrawal volume was replaced with the same volume of dissolution media. All samples were filtered through 0.45 µm filter paper. The first few milliliters of the filtered samples were used to wash the test tubes which were already cleaned with soap and tap water and then washed three times with distilled water.

After filtration was performed, dilution was carried out as the following:

1. 10 ml was taking from the filtrate and the volume was completed to 100 ml with 0.1 sodium hydroxide.
2. 15 ml was taking from the first diluted solution and the volume was completed to 100 ml with 0.1 sodium hydroxide.

Then UV/visible spectrophotometer was used and the absorbance was measured at 254 am using 1 cm cell to perform the analysis of samples. The Paracetamol percentage released in each time interval was calculated using the following equation:

Average readings (absorbance) = sum of all readings/ number of readings

Release percentage = absorbance *100/715* 0.00075

Where:

715= was taken as the value of A (1%, 1cm)

0.00075=weight/volume x dilution factors=[0.5/1000] x [15/100] x [10]

Dissolution test result comply with the requirement of British Pharmacopeia when not less than 80% of active ingredient release within 45 minutes (BP, 2018).

Assay of content

Twenty tablets were weighed by sensitive balance and grinded by mortar and pestle. Accurately weighed portion of the powder equivalent to about 0.15g (150 mg) of Paracetamol for each brand were added to 50 ml 0.1M Sodium Hydroxide, then was diluted with 100 ml water, the solution was shaken for 15 minutes and a sufficient water was added to produce 200 ml water which was mixed & filtered and 10 ml of filtrate was diluted with 100 ml with water. 10 ml of resulting solution were added to 10 ml 0.1M Sodium Hydroxide and finally it was diluted to 100 ml with water, then the absorbance of the resulting solution was measured at 257 nm and the content percentage of Paracetamol was calculated by using the following equation:

Release percentage=absorbance* 100/715* 0.00075

Where:

715= was taken as the value of A (1%, 1cm)

0.00075-weight/volume x dilution factor=[0.15/200] x [10] x [10]/100

Data Analysis

Microsoft excel 2016 was used to analyse the data.

RESULT AND DISCUSSION

Physical Appearance

The four brands were inspected visually to demonstrate any evidence of physical instability. In table 4 below there was no change in physical appearance of tablets which indicate a good physical stability.

Table 4: Physical Appearance of Different Brands.

Brand	Colour	Shape
(A) Panadol	White	Caplet
(B) Amidol	White	Round
(C) Nabidol	White	Round
(D) Nilodol	White	Round

Weight Variation Test

The weight variation test was carried out by weighing 20 tablets using sensitive balance. According to limit test described in British Pharmacopeia[19] the allowed percentage deviation is 5% for tablets with average mass more than 324 mg. The results of weight variation are shown in Table 5 and all samples met British pharmacopeia requirement, thus all the brands possessed good uniformity of weight.

Table 5: weight Variation Measurement.

Brand	(A)	(B)	(C)	(D)
Total W.t of 20 Tablets	11.8455	11.1108	12.0116	12.0344
Average weight	0.5923	0.5555	0.6006	0.6017
Average Deviation	±0.1236	±0.0093	±0.0513	±0.0558
STD Deviation	0.007089	0.00574	0.00755	0.00486

Friability Test

This test was carried out using friability tester. 20tablets were weighed and recorded the weight and were placed in the tester, then were weighed again and the difference in weight was calculated as shown in Table 6. The innovator panadol shows the best friability compared with the other three brands. All tablets were passed the friability test since all results are found to be less than 1%according to Bp.

Table 6: Friability Measurement of Brand (A), (B), (C), (D).

Brand	Initial weight	Final weight	Friability%
A	11.8464	11.8464	0
B	11.1132	11.0812	0.29
C	12.0149	12.0005	0.12
D	12.0170	12.0066	0.09

Hardness Test

Hardness of the tablets is an important parameter because pharmaceutical tablets must have sufficient ability to survive the handling forces during packaging and shipping. However, if the hardness exceeds a certain limit, it increases the disintegration time, which ultimately affects the dissolution. This test was performed for ten tablets of A, B, C and D brands of paracetamol by hardness tester as shown in the table 7. The average hardness of the innovator A and other brands B, C, D of paracetamol was obtained.

Table 7: Hardness Measurement of 10 tablets.

Brand	(A)	(B)	(C)	(D)
Average	282.10 N	109.90 N	158.80 N	184.10 N
STD Deviation	53.16 N	10.17 N	13.32 N	23.53 N
Deviation Percentage	18.84%	9.25 %	8.39%	12.78 %

Thickness & Diameter test

This test was performed for ten tablets of A, B, C and D brands of paracetamol by thickness tester as shown in table 8,9,10 and 11 below. The average thickness & diameter of the innovator A and other brands B,C,D of paracetamol was obtained.

Table 8: Thickness & Diameter Measurement of Brand (A).

Total of 10 tablets	Thickness (mm)	Diameter (mm)
Average	5.22 mm	7.43 mm
STD Deviation	0.07 mm	0.09 mm
Deviation Percentage	1.26%	1.20%

Table 9: Thickness & Diameter Measurement of Brand (B)

Total of 10 tablets	Thickness (mm)	Diameter (mm)
Average	3.74 mm	13.08 mm
STD Deviation	0.03 mm	0.02 mm
Deviation Percentage	0.68%	0.12%

Table 10: Thickness & Diameter Measurement of Brand (C)

Total of 10 tablets	Thickness (mm)	Diameter (mm)
Average	4.32 mm	12.45 mm
STD Deviation	0.05 mm	0.04 mm
Deviation Percentage	1.18%	0.32%

Table 11 : Thickness & Diameter Measurement of Brand (D)

Total of 10 tablets	Thickness (mm)	Diameter (mm)
Average	4.08 mm	13.10 mm
STD Deviation	0.02 mm	0.15 mm
Deviation Percentage	0.53%	1.18 %

Disintegration test

The disintegration time was measured by disintegration tester. Water was used as disintegration media at 37oC with 30 cycles per minute. The average disintegration time of tablet brands of paracetamol A, B, C & D were satisfactory as uncoated BP tablets have disintegration time not more than 15 minutes as shown in table 12.

Table 12: Disintegration Time of Brand (A), (B), (C), and (D).

Brand	Average disintegration time Time (minutes :seconds)
A	8:58
B	0:44
C	0:24
D	1:06

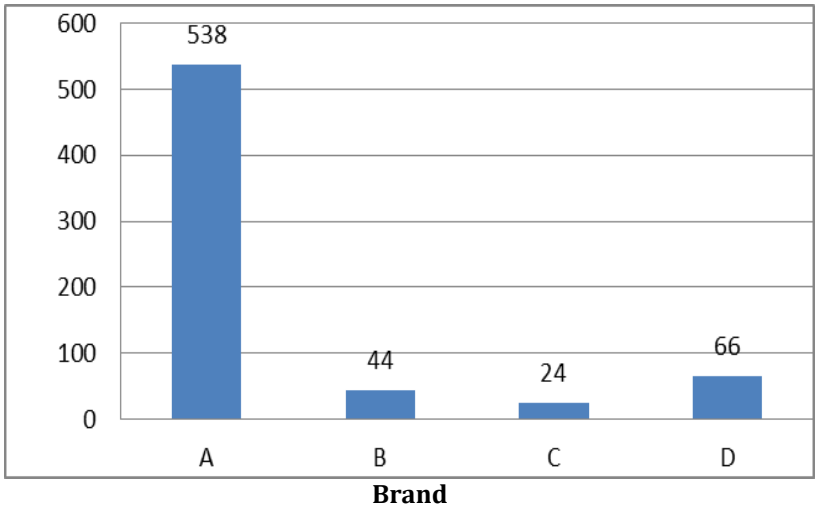

Figure 2 disintegration time of Panadol, Amidol, Nabidol, Nilodol.

Dissolution Test

The dissolution profile of four brands A, B, C and D in three different dissolution media with different pH values were shown in tables below and figure 3. The absorbance & percentage release were obtained in different time intervals (10, 15, 30, 45 & 60 minutes).

Dissolution results at pH 5.8

Table 13: Absorbance and drug release % of brand (A), (B), (C) and (D) in phosphate buffer media (pH 5.8).

Brand	Absorbance	Released %
(A) Panadol	0.519	96.8
(B) Amidol	0.524	97.7
(C) Nabidol	0.523	97.4
(D) Nilodol	0.512	95.5

Dissolution results at pH 1.2

The result showed in table 14 and figure 3 that the brands are complied with specification.

Table 14: Absorbance and drug release % in 0.2 M HCL Media (pH 1.2).

Brand	Sample	1	2	3	4	5	6
	Time	0	10	15	30	45	60
A	**Absorbance**	0.000	0.482	0.485	0.502	0.508	0.504
	Release	0.00	90.0	90.4	94.0	94.8	94.0
B	**Absorbance**	0.000	0.489	0.505	0.523	0.511	0.506
	Release	0.00	91.2	94.2	97.5	95.4	94.4
C	**Absorbance**	0.000	0.489	0.492	0.512	0.507	0.503
	Release	0.00	91.2	91.7	95.5	94.5	93.8
D	**Absorbance**	0.000	0.455	0.482	0.517	0.501	0.469
	Release	0.00	84.8	89.9	96.4	93.4	87.5

Release%

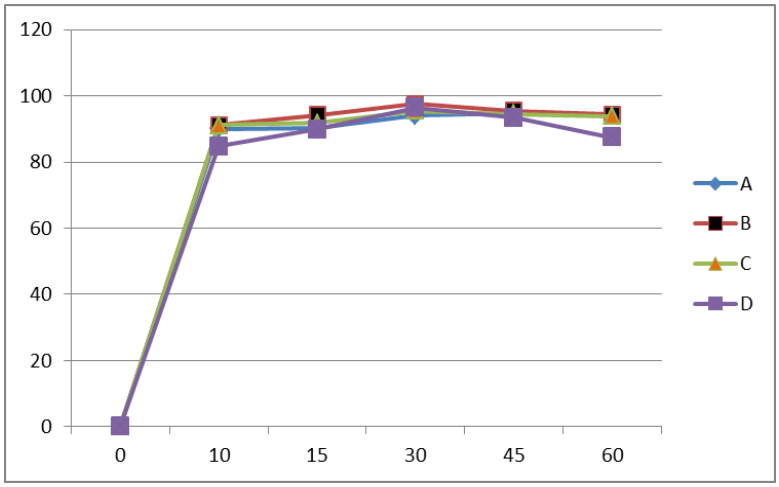

Figure 3: Comparative dissolution profile of four brands by using hydrochloric acid solution at pH 1.2.

Dissolution results at pH 4.5

The result showed in table 15 and figure 4 that the brands are complied with specification of BP. And Nilodol showed the highest release percentage.

Table 15: Absorbance and drug release % of brands in acetate buffer (pH 4.5).

Brand	Sample	1	2	3	4	5	6
	Time	0	10	15	30	45	60
A	**Absorbance**	0.000	0.402	0.430	0.496	0.502	0.514
	Release	0.00	75.0	80.2	92.5	93.6	95.9
B	**Absorbance**	0.000	0.456	0.488	0.495	0.490	0.483
	Release	0.00	85.0	91.0	92.3	91.4	90.1
C	**Absorbance**	0.000	0.476	0.493	0.514	0.508	0.507
	Release	0.00	88.8	92.0	95.9	94.7	94.5
D	**Absorbance**	0.000	0.500	0.507	0.533	0.527	0.510
	Release	0.00	93.2	94.5	99.4	98.3	95.1

Release%

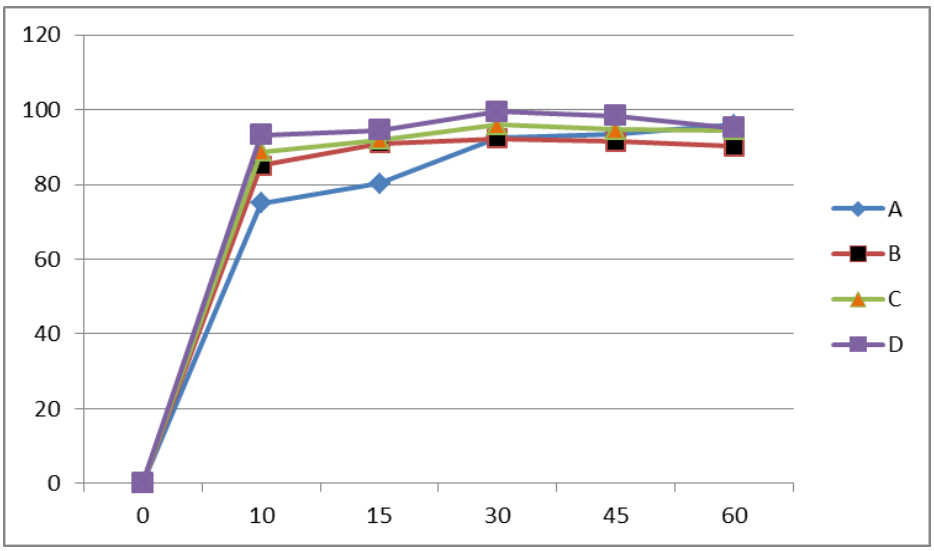

Figure 4 : Comparative dissolution profile of four brands by using acetate buffer at pH 4.5.

Dissolution results at pH 6.8

The result showed in table 16 and figure 5 that the brands are complied with specification especially Nabidol showed the highest release.

Table 16: Absorbance and drug release % of brands in phosphate buffer media (pH 6.8).

Brand	Sample	1	2	3	4	5	6
	Time	0	10	15	30	45	60
A	Absorbance	0.000	0.477	0.482	0.513	0.503	0.487
	Release	0.00	89.0	89.9	95.7	93.8	90.6
B	Absorbance	0.000	0.553	0.483	0.510	0.512	0.507
	Release	0.00	84.4	90.1	95.2	95.4	94.5
C	Absorbance	0.000	0.507	0.520	0.544	0.530	0.528
	Release	0.00	94.5	96.9	101.4	98.8	98.5
D	Absorbance	0.000	0.512	0.512	0.515	0.515	0.502
	Release	0.00	95.5	95.5	96.0	96.0	93.6

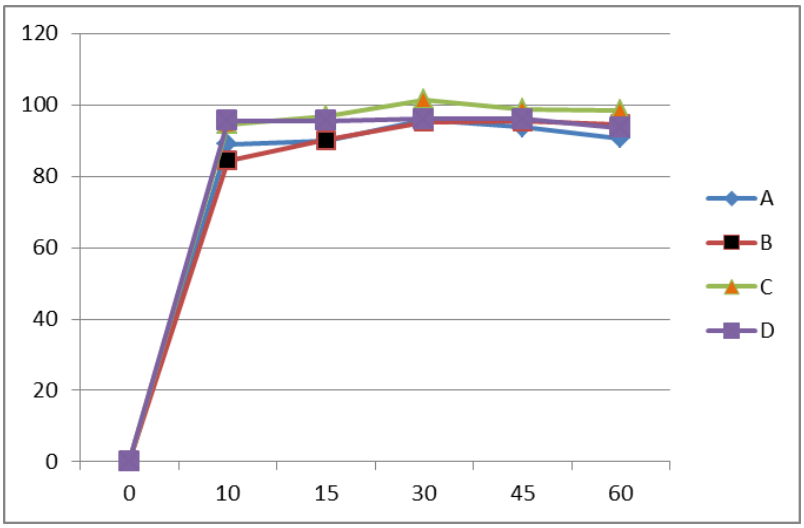

Figure 5: Comparative dissolution profile of four brands by using phosphate buffer at pH 6.8.

Assay

Test for a percentage of content is based on the assay of the individual content of active ingredient of a number of single dose units. According to the results shown in table 3.29 the content of paracetamol was determined by UV spectrophotometer at 257 nm. 0.1M sodium hydroxide was used as a solvent. All tablets complied with the specification of uniformity of weight. The British pharmacopeia limit for paracetamol content 80-110 % of tablet. The API assay limits for the innovator Paracetamol was 99.8% while it was 98% for Amidol, 101.4% for Nabidol and 101%for Nilodol. All the generic brands were complied with the British Pharmacopria assay limits for paracetamol, the result was clarified as following:

Table 17: Content percentage % of brand (A),(B),(C),(D).

Brand	Content%
Panadol	99.8
Amidol	98
Nabidol	101.4
Nilodol	101

DISSCUSION

Acetaminophen, also known as paracetamol is an active metabolite of phenacetin, is commonly used for its analgesic and antipyretic effects. Its therapeutic effects are similar to salicylates, but it lacks anti-inflammatory, antiplatelet, and gastric ulcerative effects. It is one of the most commonly used 'over-the-counter' analgesics for headache, mild migraine, musculoskeletal pain, dysmenorrheal, etc. Paracetamol is generally safe for human use at recommended dose. In this study four brands of paracetamol 500 mg tablets were studied to collect information on bioequivalence, and possible interchangeability of different generics. paracetamol tablet brands were studied by using simple and cost effective in vitro dissolution method (Biowaiver).

In the present study the samples of three generic brands and innovator of paracetamol 500mg tablets were collected randomly from the market, the three generic brands (B),(C)and (D)are locally manufactured, the four brands were within their expiry dates and their physicochemical properties and content percent were studied. all the brands studied fulfill the compendial specification for diameter, thickness, hardness, disintegration. The four brands also pass the assay test. This means that the four brands are pharmaceutically equivalents. Dissolution test was carried out for four brand products to establish bioequivalence between different brands. The test was carried out in three different buffer

media (pH1.2, pH4.5 and pH6.8) to cover the whole GIT environment of different pH, and the percentage release in each point was calculated.

All brands show very rapid dissolution (90% or more of API is released in 30 min) in the three pH different buffer media.

According to WHO requirements brand (B), brand (C) and brand (D) are bioequivalent and can be safely interchanged with innovator.

CONCLUSION AND RECOMMENDATIONS

Conclusion

- The four brands passed the weight variation test according to the BP (2018) requirement, the allowed deviation percentage were not more than 10% and the four brand deviation percentages fall within this range.
- All the brands disintegrated within the limit (15 minutes) of BP (2018) and pass the disintegration test.
- In the assay test brand (C) Nabidol showed the best release among the others brands including the innovator.
- The dissolution test was performed by using different dissolution media prepared according to BP (2018) methods and apparatus (1) the basket form and the amount of the drug released was determined in different time interval and the results show that all the brands pass the dissolution test specification according to the BP (2018).

RECOMMENDATIONS

- The three generic paracetamol brands Amidol, Nabidol and Nilodol passed the dissolution test according to biowaiver conditions compared to the innovator reference product Panadol and can be approved on the basis of biowaiver procedure and considered to be equivalent to innovator Panadol without in-vivo evaluation.
- A stability study is recommended for paracetamol tablets in order to justify the differences in the dissolution behaviour of different brands in different dissolution media.
- More brands should be tested in future in order to obtain various results.

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