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Quality Control Study on Ten Brands of Paracetamol Tablet Available on the Palestinian Drug Market

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ABSTRACT: Post-Marketing monitoring of medicines has been performed to evaluate the quality of marketed pharmaceutical brands. The objective of the this study is to assess the quality of ten brands of paracetamol tablets marketed in Palestine. The quality of paracetamol tablets was assessed through evaluation of identification, diameter and thickness, uniformity of weight, friability, hardness, disintegration, dissolution as well as assay of content of active ingredient. All brands of paracetamol tablets passed the British Pharmacopoeia 2018 standards for identification, uniformity of weight, friability, disintegration, dissolution tests and assay of content of active ingredient.

KEYWORDS: In vitro, Palestine, Quality control, Paracetamol.

I. INTRODUCTION

Paracetamol or acetaminophen is a widely used over-the-counter analgesic and antipyretic drug. It has both analgesic and antipyretic properties and is used for the treatment of mild and moderate pain. Although the precise mechanism of paracetamol has not been established, data suggests that central prostaglandin synthetase inhibition plays a large role. Unlike NSAIDs, paracetamol does not inhibit the peripheral generation of prostaglandins and exhibit a clinical anti-inflammatory effect. Paracetamol does not alter the generation of prostaglandins in gastric mucosa and, therefore, it is particularly suitable for patients with a history of GI disease or on concomitant medication where peripheral prostaglandin inhibition would be undesirable. (1)

The necessary components of any health care system are health services, qualified staff, and drugs. Of these components, drugs must have special concern as they have curative and preventive roles. Furthermore, they are costly and might be dangerous, therefore they must be managed and used rationally (2).

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 (3).

The marketing of multisource drug products registered by national drug agencies in developing countries, with the view of improving health care delivery through competitive pricing, has its attendant problem of ascertaining their quality and interchangeability(4).

Increasing economic activities in many parts of the world has led to proliferation of pharmaceutical manufacturing industries with attendant introduction of many brands of the same drug into the drug market (5).

The increase in the number of generic drug products from different multiple sources has placed people and prescribers in a position of selecting one from among several seemingly equivalent products (6). Many of these products are inexpensive and affordable, but with uncertainly about their quality (5). Variable clinical responses to drugs presented as generics and batch-to-batch inconsistencies have been reported (7).

Preliminary physicochemical assessment of the products is very important and in vitro dissolution testing can be a valuable prediction of the in vivo bioavailability and bioequivalence of oral solid dosage forms (6). In fact, the dissolution test of solid dosage forms has been appeared as an

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important quality control test to interpret the in-vivo behavior of the drug product(8). Drugs in-vitro dissolution test can differentiate between the formulations of the same generics(9).Therefore, this in-vitro test can be used to determine batch consistency of drug formulations from the same manufacturer as well as in assessing the drug product quality from various manufacturers for comparing. Similarly, drug products disintegration test for compressed tablets, which is already enclosed in all official publication(pharmacopoeias), is another standard quality control tool to show not only the time needed for the breakdown of a tablet but also to check batch to batch consistency and quality(10).

There is an increase of generic drug products from different multiple sources in Palestine, and the physicians have noticed that some medicines which have the same active pharmaceutical ingredient from different companies differ in its effectiveness. So this study is covering the quality control tests of some brands of one of essential drugs that are available on Palestinian market.

II. MATERIALS AND METHODS

2.1 Materials used

Paracetamol powder (Merck, Germany), Paracetamol tablets (500 mg): ten brands "seven brands uncoated and three brands film coated".

2.2 Instruments used

Analytical balance (YMC, Japan), Disintegration apparatus (Toyama sangyo, Japan), Dissolution test apparatus (Apparatus II "Paddle apparatus"), Electric-heating distilling apparatus, Friabilator (Toyama sangyo, Japan), Magnetic stirrer (Heidolph, Germany), Micrometer (Mitutoyo, Japan), Micropipette (Nichiryo, Japan), Tablet Hardness tester (Jyoti, India), UV-visible spectrophotometer (equipped with 1cm Shimadzu, 1601, matched quartz cells).

1.3 Methods

1.3.1 Identification test of active substance

Paracetamol tablets

20 tablets from each brand were weighed then powdered by mortar and pistil. A quantity of the powdered tablets from each brand containing 0.25g of paracetamol was extracted with 10ml of acetone, and filtered, then the filtrate was evaporated to dryness. After that 0.1 g of dried powder was boiled with 1 ml of concentrated HClfor 3 minutes, and 1 ml of distilled water was added and cooled, then 0.05 ml of 0.0167 M potassium dichromate was added (BP 2018).

Paracetamol pure powder

0.1g of paracetamol pure powder was boiled with 1ml of concentrated HCl for 3minutes, and 1ml of distilled water was added and cooled, then 0.05ml of 0.0167 M potassium dichromate was added (BP 2018).

1.3.2 Diameterand thicknessmeasurement

The measurement of the diameter and the thickness was done for uncoated brands of paracetamol tablets (P1, P2, P3, P4, P5, P6 and P7).10 tablets were taken from different brands, the diameter and thickness of the tablets were measured using micrometers to determine the average thickness and diameter(11).The mean, percentage deviation from the mean and Standard Deviation (SD) were calculated.

1.3.3 Uniformity of weight determination

20 tablets from each brand were taken at random and brushed from dust using soft brush then were weighed individually using analytical balance. The average weight, percentage deviation from the average weight and SD were calculated (BP2018).

1.3.4 Friability test

This test was done for uncoated brands of paracetamol tablets (P1, P2, P3, P4, P5, P6 and P7).For tablets weighing up to 0.65 g each, a sample of 20 tablets was taken, but for tablets weighing more than 0.65 g each, a sample of 10 tablets was taken.So according that 20 tablets were taken from all brands except for brand (P2) 10 tablets were taken.Any loose dust with the aid of soft brush was removed, then the tablets were weighed and placed in the friabilator**.**The weight loss was determined as percentage of the initial weight (BP 2018).

% weight loss = {(initial weight – final weight)/initial weight}× 100

Determination was done in triplicate, and then the mean of percentage andSD were calculated. Coated tablets don't undergo friability test(12).

1.3.5 Hardness test

This test was done for uncoated brands of paracetamol tablets (P1, P2, P3, P4, P5, P6 and P7).10 tablets from each brand were taken and the

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hardness was determined using tablet hardness tester.The mean and SD were calculated.

1.3.6 Disintegration test

This test was done for paracetamol tablets. Disintegration time of six units per brand was determined in distilled water at 37 ± 1°C using disintegration apparatus (BP 2018).Determination was done in triplicate, and then the mean and SD were calculated.

1.3.7 Dissolution test

According to official monograph, the dissolution was performed for paracetamol tablets according BP 2018. The dissolution rate was determined by using dissolution apparatus II,and900 ml ofphosphate buffer (PH = 5.8) was used as the dissolution medium. Six units were used from each brand.The dissolution medium was maintained at 37 ± 0.5°C, and the paddle was rotated at 50 rpm.Samples (10 ml) were withdrawn at different time intervals (10, 20, 30, 45, and 60 minutes).The samples were filtered and diluted appropriately with 0.1 M sodium hydroxide.The absorbance was measured using UV-visible spectrophotometerat 257 nm. The content of paracetamol tablets was determined using A (1 %, 1 cm) = 715.

1.3.8 Assay of content of active ingredient

20 tablets were weighed and powdered.A quantity of the powder containing 75 mg of paracetamol was added to 25 ml of 0.1 M sodium hydroxide, diluted with 50 ml of distilled water, shaken for 15 minutes and sufficient distilled water was added to produce 100 ml.The resulting solution was mixed, filtered and 10 ml of the filtrate was diluted to 100 ml with distilled water. 10 ml of the resulting solution was added to 10 ml of 0.1 M sodium hydroxide, and diluted to 100 ml with distilled water.The absorbance of the resulting solution was measured at the maximum at 257nm using UV-visible spectrophotometer.The content was calculated taking 715 as the value of A (1 %, 1 cm) (BP 2018).Determination was done in triplicate, and then the mean of percentage content and the SD were calculated.

III. RESULTS

3.1 Identification test of paracetamol

The identification test of the standard (pure paracetamol) and the various brands resulted as the following:No precipitate was developed after adding distilled water, and violet color was produced slowly in standard and in all brands after adding potassium dichromate.

The results of the physicochemical properties of the various brands of paracetamol tablets are presented in Table 1 and Table 2.

3.2 Diameterand thicknessmeasurement

Results showed that the uncoated brands were examined had the diameter within range of 12.05 - 13.1 mm, while the thickness within range of 3.595 – 5.075 mm(Table 1).All brands showed acceptable thickness as none of the uncoated brands deviated by up to ± 5.0 % from the mean value as stipulated by the reference (13).

3.3Uniformity of weight determination

All brands showed acceptable uniformity of weight as none of the brands deviated by up to ± 5.0 % from the mean value as stipulated by BP 2018 (Table 1 andTable 2).

3.4 Friability test

All uncoated brands had mean of the percentage loss in weight of less than 1.0 % and no tablet cracked, split or broken in the course of the test. So all brands showed compliance with BP 2018 specification (Table 1).

3.5 Hardness test

The results showed that the mean value of the hardness of uncoated brands within range of 14.0 - 15.2 Kg (Table 1).The recommended value for tablet hardness is 4.0 – 6.0 kg (14), thus all of them have high value.

3.6 Disintegration test

The disintegration time mean of seven uncoated brands was less than 15 minutes as BP 2018 specification for uncoated tablets (Table 1).The disintegration time mean of three coated brands was less than 30 minutes as BP 2018 specification for film coated tablets (Table 2).There is wide range of disintegration time values between coated brands that the brands (P8, P9 and P10) have disintegration time of 2.277, 8.443 and 15.493 minutes respectively (Table2**).**

3.7 Dissolution test

The BP 2018 stipulated that at 45 minutes, all tablets should have released into the dissolution medium an amount not less than 70.0 % of the labeled amount of paracetamol

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Table 1: Physicochemical properties of seven brands of paracetamoluncoatedtablets

Brand	Diameter (mm)	Thickness (mm) Mean ± SD	Weight uniformity (g) Mean ± SD	Friability (%) Mean ± SD	Hardness (Kg) Mean ± SD	Disintegration time (minutes) Mean ± SD	Dissolution at 45 minutes (%) Mean ± SD	Assay (%) Mean ± SD
P1	13.05	5.075 ± 0.026	0.634 ± 0.004	0.163 ± 0.004	14.900 ± 0.316	3.153 ± 0.040	99.009 ± 0.657	102.564 ± 0.388
P2	13.10	4.560 ± 0.052	0.712 ± 0.010	0.145 ± 0.029	14.700 ± 0.473	0.757 ± 0.023	98.476 ± 1.275	101.570 ± 0.655
P3	13.05	3.875 ± 0.035	0.577 ± 0.005	0.049 ± 0.027	15.200 ± 0.416	1.927 ± 0.093	96.261 ± 1.408	100.699 ± 0.323
P4	13.05	3.595 ± 0.028	0.523 ± 0.007	0.174 ± 0.026	14.000 ± 0.000	1.977 ± 0.068	99.058 ± 1.702	102.378 ± 0.646
P5	12.55	4.275 ± 0.026	0.604 ± 0.005	0.207 ± 0.008	14.000 ± 0.000	0.890 ± 0.079	99.763 ± 1.627	99.456 ± 0.215
P6	12.05	4.205 ± 0.028	0.549 ± 0.007	0.222 ± 0.028	14.000 ± 0.000	5.250 ± 0.477	97.939 ± 1.164	100.326 ± 0.559
P7	12.75	4.025 ± 0.035	0.587 ± 0.005	0.257 ± 0.050	14.000 ± 0.000	1.757 ± 0.160	100.057 ±2.124	102.564 ± 0.559

Table 2: Physicochemical properties of three brands of paracetamol film coated tablets.

Brand	Weight uniformity (g) Mean ± SD	Disintegration time (minutes) Mean ± SD	Dissolution at 45 minutes (%) Mean ± SD	Assay (%) Mean ± SD
P8	0.680 ± 0.006	2.277 ± 0.025	99.193 ± 0.644	99.953 ± 0.672
P9	0.545 ± 0.005	8.443 ± 0.356	97.701 ± 1.351	102.440 ± 0.469
P10	0.599 ± 0.005	15.493 ± 1.294	100.763 ± 2.326	100.425 ± 1.749

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The percentage mean of the amount released at 45 minutes which are represented in Table 1 and Table 2 showed that all brands passed the dissolution test, that all brands released more than 70.0 % of their content within 45 minutes.

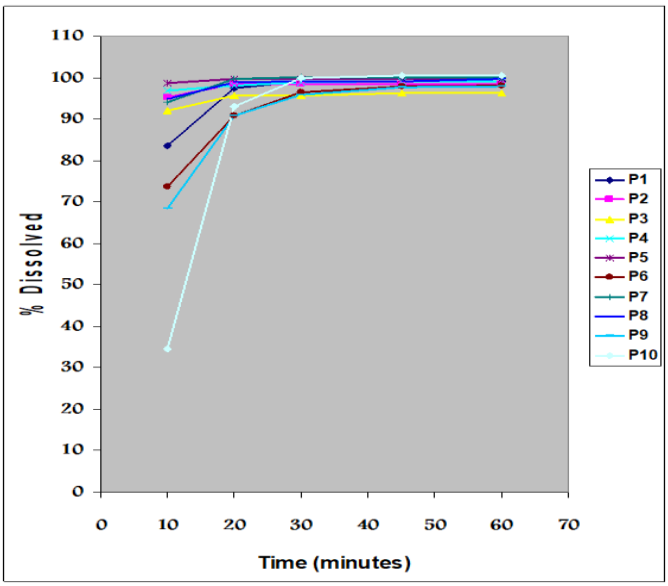

Figure 1: Dissolution profile of the ten different brands of paracetamol tablets in phosphate buffer PH = 5.8

The obtained dissolution profile shown in Figure1 revealed that:

Within 10 minutes brands (P2, P3, P4, P5, P7 and P8) released more than 90.0 % while the release of brand (P1) in range of 80.0 – 90.0 %, brand (P6) in range of 70.0 – 80.0 %, brand (P9) in range of 60.0 – 70.0 %, and brand (P10) in minimum range of 30.0 – 40.0 %.Within 20 minutes, 30 minutes, 45 minutes and 60 minutes all brands released more than 90 % of active ingredient. So all brands passed the dissolution test as BP 2018 limits, (which stipulated that at 45 minutes all tablets should have released into the dissolution medium an amount not less than 70.0 %).The above results shows that all brands rapidly dissolved except brands (P10 and P9) slowly dissolved than other brands within 10 minutes, but after that all brands rapidly dissolved.

3.8Assay of content of paracetamol

The results showed that all brands had values range (99.456 - 102.564 % w/w), thus it lies within BP 2018acceptable range (95.0 – 105.0 % w/w) (Table 1 and Table 2).

IV. DISCUSSION

4.1 Identification test of active substance

From the results of each of paracetamol tablets it was observed that all brands contain the needed active substance by comparing the result with that of standard pure active substance.

The reaction mechanism of the resulted color

The violet color which resulted as shown in section 3.1 was contributed to the following:Paracetamol (1) is an N-arylamide and thus is sensitive to hydrolysis giving 4-aminophenol (2) and acetic acid (3), then this step is followed by oxidation with potassium dichromate giving violet color which attributable to the formation of the merocyanine (5) resulting from (4) and (2) as shown in Figure 2 (15).

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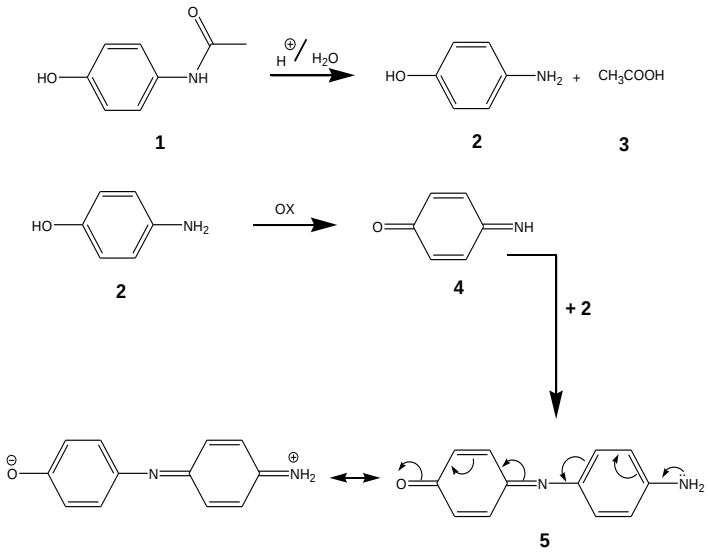

Figure 2: Reaction mechanism of paracetamol with potassium dichromate in acidic media(Roth et al., 1990).

4.2 Diameter and thickness measurement

Diameter and thickness of the tablets during the manufacturing process are critical as potential problems associated with tablet weight and content uniformity can be detected at an early stage. The uniformity of the diameter to be accepted for each tablet with a diameter of more than 12.5mm, the standard deviation should not exceed ±3%, while for a tablet with diameter less than 12.5mm the standard deviation should not exceed ±5% (11).

From the results in section 3.2 it was noticed that there is no wide difference in values of diameter among uncoated brands of paracetamol tablets. So the consumer should not doubt about potency.If the tablets manufactured by different companies and contained the same amount and differ in size then consumer may doubt whether these tablets have same potency. So diameter standard of the same active ingredient tablets can assist to remove this doubt.Also from the results in section 4.2 it was noticed that all uncoated brands of paracetamol tablets had thickness variation of mean value within ± 5.0 % as stipulated by reference (13), this revealed that the factors affecting thickness were taken in the consideration. Tablet thickness is important for tablet packaging. The thickness of the tablet can affect the therapeutic effect as with increasing thickness, there is a decrease in hardness due to compression force, on the other hand with decreasing thickness there is an increase in hardness (16).

4.3 Uniformity of weight determination

Weight variation is important to ensure good manufacturing practices (GMP) sustained by the manufacturers and the content uniformity of the formulation (17). From results it was noticed that the uniformity of weight determination for all the brands showed compliance with the BP 2018 specification, as none of the brands deviated by up to ± 5.0 % from their mean values. This indicates that the factors leading to weight variation were taken in consideration.Factors that affect tablet weight includes tooling of the compression machine, head pressure, machine speed and flow properties of the powder(18).

4.4 Friability test

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets may produce chipping, capping and lamination problems. Therefore another measure of tablet strength i.e. friability is often measured, i.e. the friability A friability test is performed to determine the ability of tablets to withstand abrasion during packaging, handling, and shipping processes (19).

It was noticed that all the uncoated brands of paracetamol tablets complied with BP 2018 specification that percentage loss in weight is less than 1.0 %, and no tablet caps, laminates or breaks up in the course of the test. This showed that all the brands could withstand abrasion without loss of tablet integrity, and the causes of high friability were taken in consideration during manufacturing the tablet.

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4.5 Hardness test

Tablet hardness test used by the pharmaceutical industry to determine the breaking point and structural integrity of a tablet and find out how it changes "under conditions of storage, transportation, packaging and handling before usage" The breaking point of a tablet is based on its shape (17).Hardness has an impact on disintegration. If the tablet is hard then it cannot disintegrate within the specified time and if the tablet is soft then it becomes hard to withstand the handling during coating or packaging. Therefore, adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. Oral tablets normally have a hardness of 4 to 8 or 10kg (20).

From results in section 3.5 it was noticed that all uncoated brands of paracetamol tablets have high value of hardness (14.0 - 15.2 kg), as hardness standard, 4.0 kg is considered suitable for handling the tablets and 6.0 kg or more will produce tablets of high compact nature (14).

4.6 Disintegration test

Disintegration is the breakdown process of a tablet into smaller particles and is the first step towards dissolution. It could be directly related to dissolution and subsequent bioavailability of a drug. A drug in corroborated in a tablet is released rapidly as the tablet disintegrates a critical step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine (1). It was observed that all brands of paracetamol tabletspassed BP 2018 specification of disintegration test, as the disintegration time of uncoated brands of paracetamol tablets was less than 15 minutes and of film coated brands of paracetamol tablets. This leads to achieve the aim that formulations will be broken down to facilitate release of content in the gastrointestinal tract.There is wide range in the disintegration time of the coated brands of paracetamol tablets, where brands (P8, P9 and P10) had disintegration time of 2.277, 8.443 and 15.493 minutes respectively. This is related to one or combined factors affected on the disintegration. Two factors of them are the thickness and physicochemical nature of the coating layer. As the type of coating in the brands is film coat, then the thickness of coat do not play an important role because it is not thicker than the page of this paper and are usually in range of 0.002 to 0.01 inch in thickness (21).

The physicochemical nature may effect on the disintegration time. The film coating with water–soluble polymer should have no significanteffect on the rate of disintegration and subsequent drug dissolution. But in case offilm coating with hydrophobic water–insoluble film coating material, lead tofilm coats acts as a barrier which delays and/or reduces the rate ofdrug release. Thus these types of film coating materials form barrierswhichcan produce a significant influence on drug absorption (22). However, it was not possible to determine the exact cause of these differences in disintegrating time from the coating composition or/and from other factors, as the composition of most formulations was not known.

4.7 Dissolution test

The dissolution test is the measurement of the proportion of drug dissolving in a stated time under standardized conditions in vitro (23). The importance of the test is to ensure the availability of the drug for absorption and to predict in vivo bioavailability (5).It was observed that all brands meet pharmacopoeia specification of dissolution test as BP 2018 specifies that not less than 70.0% of labeled content should dissolve at 45 minutes. The results revealed that all brands exhibit good release of the drug to the site of absorption and may have good bioavailability. It is interesting to note that several authors have previously disagreed on the correlation between disintegration time and dissolution time. Some authors mention that disintegration and dissolution times are correlated, while others continue to disagree (5). From results, it seems to be a high correlation between the two variables in case of paracetamol tablets. For example the brands (P10 andP9) which have the highest disintegration time, showed to have the lowest percentage release within 10 minutes for brands (P10 and P9). Dissolution of drugs can be influenced by the physicochemical proper ties of the drug substance, the dosage form design, the manufacturing process, and the testing conditions(24).

4.8 Assay of content of active ingredient

Assay of pharmaceutical products is a critical quality parameter required to confirm that the labeled amount of drug is available in a given dosage form and failure to meet the standard will result in poor quality medicines. Inadequate amounts of API will result in under-dosed medication, leading to poor treatment outcomes while excessive amounts of API cause over-dosage

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of medication, leading to increased adverse drug reactions and treatment failure (25). It was observed that all the brands of paracetamol tablets had chemical content percentage within BP 2018 specification range (95.0 – 105.0 % w/w).

V. CONCLUSION

The present study showed that all brands of paracetamol tablets, meet the quality specification of pharmacopoeia. Results showed that the high hardness of paracetamol tablets has no influence on the disintegration and the dissolution properties.Also, results indicated that there is direct relation between the disintegration time and the dissolution profile. In spite of presence some differences in the dissolution profile especially in first time of the dissolution, it seems that all brands have good dissolution character which predict good bioavailability. However, there is a special need to carry out in vivo studies to further substantiate the in vitro predictions. Thus in the absence of bioavailability data, there is no good reason apart from cost to prefer one brand to another.

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