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COMPARATIVE QUALITY EVALUATION OF PARACETAMOL TABLET MARKETED IN SOMALI REGION OF ETHIOPIA.

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ABSTRACT

The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable. The efficacy of pharmaceutical dosage forms generally depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary. The aim was to evaluate the quality of paracetamol tablet marketed in Somali region of Ethiopia. The study was exclusively experimental that used BP, USP and other standard books to check the in vitro quality of Paracetamol tablet using different analytical techniques and procedure. Test for weight variation, friability, disintegration time, identification test and assay were conducted. All of the brands under the study were within the specification for weight variation test. But from the contraband brands, two for friability, one for disintegration and all for percentage content paracetamol failed to satisfy the requirement though all of the products contain the wright active ingredients. The research has showed that the quality of contraband tablets were below the standard in contrast to the legal paracetamol tablet which is hazardous to the community. The regulatory body must work to stop illegal smuggling of medications .

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

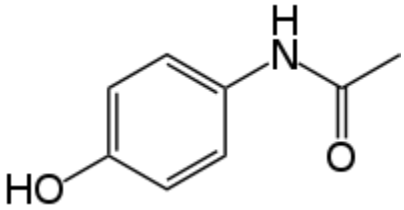

FIG. 1: CHEMICAL STRUCTURE OF PARACETAMOL

Paracetamol is used for the relief of pains associated with many parts of the body. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin in patients in whom excessive gastric acid secretion or prolongation of bleeding time may be a concern. Available without a prescription, it has in recent years increasingly become a common household drug [3].

It is classified as a non-steroidal anti-inflammatory drug (NSAID) by some sources, [4] and *not* as an NSAID by others, [5] while most sources implicitly distinguish them, for example by mentioning both NSAIDs and paracetamol in the same sentence [6-7]. Paracetamol has few anti-inflammatory effects in comparison to NSAIDs.

However, aspirin, paracetamol and other NSAIDs all act by the same mechanism (inhibition of prostaglandin synthesis by inhibiting cyclooxygenase (COX)) and all show varying levels of analgesic, anti-inflammatory, antipyretic and anti-platelet actions [8-9].

Regarding comparative efficacy, studies show conflicting results when compared to NSAIDs. A randomized controlled trial of chronic pain from osteoarthritis in adults found similar benefit from paracetamol and ibuprofen [10-11].

Paracetamol is generally safe for human use at recommended doses. But, overdoses of paracetamol can cause potentially fatal liver damage and in rare individuals, a normal dose can do the same [12].

The quality of pharmaceuticals is a global concern; counterfeit medicines are increasingly detected worldwide [13]. Counterfeiting is deceptive and immoral in any field. But in healthcare, it is criminal and simply unacceptable [14]. It is important to make a distinction between counterfeit medicines and other kinds of substandard medicines. All counterfeit medicines are substandard because they are manufactured and distributed outside of regulatory control and their composition is unpredictable. On the other hand, not all substandard medicines are counterfeit because not all of them have been 'deliberately and fraudulently mislabeled' [14-15].

According to WHO, Substandard medicines are genuine medicines produced by legitimate manufacturers that do not meet the quality specifications that the producer says they meet. Many cases of counterfeiting have been uncovered while investigating therapeutic failure or adverse events observed in patients. Such cases lead to a serious consequence i.e. the erosion of confidence in health-care systems. Counterfeit drugs particularly affect the most disadvantaged people in poor countries [13].

The quality of marketed drugs determines the quality of treatment patients receive, which in turn ensures their well-being. On the other hand, a patient's health can be put at risk by the use of spurious and substandard drugs. Constant screening of marketed drugs by the drug regulatory authority or a consumer organization, using pharmacopoeial methods, therefore enables consumers to be aware of the quality of drugs available to them. However, pharmacopoeial methods are not straightforward or inexpensive to carry out in most developing countries, and numerous small and medium-sized pharmaceutical companies do not analyze their drugs before they are marketed because of the considerable expense of maintaining a proper quality control laboratory [16].

The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable [1, 17]. The efficacy of pharmaceutical dosage forms generally depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary [18-19].

Poor quality medicines do not meet official standard for strength, quality, purity, packaging and labeling. Use of counterfeit and substandard drugs bears serious health implication; such as treatment failure, adverse reactions, drug resistance, increased morbidity and mortality. In combating such type of problem studies on quality assurance take the big share. This study focus on investigation of the quality of paracetamol tablet which is registered by drug regulatory body of Ethiopia, Drug Administrative and Control Authority of (DACA) and which are not registered but marketed in Somale region of Ethiopia comparatively.

The aim of the study was to investigate the *in vitro* quality of Paracetamol tablet marketed in Ethiopia**.** The study provide information about trend and characteristics of counterfeit and substandard paracetamol tablet, point out the relative variation of marketed paracetamol table in comparison with standard set by British Pharmacopeia (BP) [20] and United States Pharmacopeia (USP)[21] and the degree of adherence of marketed tablet to the standard set by regulatory body in Ethiopia.

MATERIAL AND METHODS:

Materials: Paracetamol tablet of legally registered brand namely Paradol, Paracetamol Tablet from Green Filed Pharmaceutical, Paracetamol Tablet from Ethiopian Pharmaceutical Manufacturing Company (EPHARM) and illegal brand namely Makmol, Cetamol and Paracetamol Tablet from Anuhi Well Come Company were used during the study. Paracetamol

working standard were obtained from kindly donation of EPHARM. Working standard, United State pharmacopeia & British pharmacopoeia were used as a reference for the experiment.

Chemicals and Reagents: Acetone (TECHNO PHARMACHEM®, 231295, India), Hydrochloric acid (MERCK 7464527, Germany), potassium dichromate (BDH AnalaR®, England), Sodium Hydroxide (LOBA CHEMIE PVT Co., Batch No 59265, India) all analytical grade reagent and distilled water.

Apparatus and Equipments: Single beam spectrophotometer (UV/Vis. JENWAY Ltd., 2304, UK), melting point apparatus (GRIFFIN and GEORGE Ltd. UK), analytical balance(ADAM AFP 110 L, India), tablet friability tester (PHARMA TEST, 10880, India), disintegration apparatus (JAINSONI, India), heater, beaker, cylinder, funnel, mortal, pestle, thermometer, sieve (FRITSCH, 03.802/2524, Germany), dish, micropipette, stop watch, Filter paper (grade 1) and capillary tube, drying oven.

Methods: The study used BP and other pharmacopeias to check the in vitro quality of Paracetamol tablet using different analytical techniques and procedure described in the analytical techniques and procedures described in the pharmacopeias. Physicochemical test was used to test physical and chemical parameter of Paracetamol tablets. Various instruments were used to measure content as well as qualities in general.

General Tests: Quality of Paracetamol tablet was assessed in compliance with BP specifications. General tests include weight variation, tablets friability and Disintegration time. Basic tests were used for the detection of substandard paracetamol tablets and to determine quality compliance in accordance with established, approved, validated techniques or methods in pharmacopeia monographs.

Weight Variation: Twenty tablets were powdered and weighed using analytical balance. The mean weight and deviation was calculated. According to USP for tablet weighing greater than 325mg there should not be more than two tablets deviating from the average by no more than 5 percent and none deviated by more twice of 5 percent (10 percent). Weight variation was used to show the uniformity of content of tablet.

Friability Testing: BP test was used to determine how well tablets will stand up to coating, packaging, shipping and other Processing conditions. Twenty tablets was de dusted and weighed on the analytical balance. The tablet was placed in the section one of the drum of the friability tester and rotated 100 times. Finally the tablets were de dusted and reweighed.

Disintegration Time: BP test was used to determine the time required for tablet to disintegrate. A 900 ml beaker was filled with water at $37\pm2^{o}C$, and then six tablets were placed in to the basket rack assembly and connected to the disintegration apparatus. The time required for the tablet to disintegrate was recorded.

Specific test for Paracetamol: To assure and differentiate counterfeit and substandard Paracetamol from quality product, the following specific tests were performed.

- **Identification test of Paracetamol:** Two identification tests were conducted in the compliance to the British pharmacopeias (BP).

- **Content Uniformity:** Test for uniformity of content is based on the assay of the individual contents of active ingredient of a number of single dose units. Test to weight variation is also used to show the uniformity of active ingredient (AI) and the excipients. According to BP the weight for tablet weighing greater than 325mg there should not be more than two tablets deviating from the average by no more than 5 percent and none deviated by more twice of 5 percent (10 percent). Tablets out of this specification are not uniform enough in terms API or excipient or both.

- **Assay:** Assay is a single test carried out for the purpose of estimating the potency of material preparation or pooled result of two or more such tests which pharmacopoeia depend. So in this research assay was performed in compliance to BP to assess percentage content of paracetamol. BP specifies the content of Paracetamol to be between 95 to 105% of the stated amount.

- **Quality Assurance:** In this study, standard laboratory procedures of BP and USP, high quality analytical grade chemicals and reagents were used.

Standard Paracetamol was used as control agent to compare, standard paracetamol result with the result of the tablets for identification test and assay

- **Data Analysis:** Simple statistical analysis was utilized for content uniformity of weight, uniformity of diameter and uniformity of thickness while dissolution efficiency (DE) was used for the *in vitro* dissolution studies.

RESULTS AND DISCUSION: During this research standard books and procedure were used to conduct each test. Among the books BP [20] and USP [21] 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. The entire brand of paracetamol tablets both legally registered by regulatory body of Ethiopia, DACA and those of tablets which are contraband were screened for all tests. From the conducted testes; those drugs having legal accreditation were compliant to the specification despite paracetamol tablet of GREEN FILED Pharmaceutical was at the border for the friability test. In contrast to the legal Paracetamol tablet, illegal Paracetamol tablets quality were substandard, implies it is below the specified standard.

Weight Variation: Weight variation being showing the relative variation of content of Active Pharmaceutical Ingredients (API) & excipient, it is used to show the content uniformity of drugs especially that of large dose pharmaceuticals such as tablet having weight greater than 325mg.

In this study, all of the contraband & illegal drugs were expected not to deviate more than 10 percent of the average and there should not be more than two tablets deviating from the average by more than 5 percent. Accordingly, weight variation studies were carried out for both legal & illegal Paracetamol tablets as per the BP specification to assure quality with the use of analytical balance. Fortunately, there were no drug deviating more than 5 percent of the average from both legal and illegal paracetamol tablets; implying the content uniformity although weight variation is not confirmatory test (**Table 1**).

TABLE 1: WEIGHT VARIATION OF DIFFERENT PARACETAMOL BRAND TABLETS

Brand	Average weight (mg)	Expected interval to adhere (mg)	Actual interval of the tablet weight (mg)
Paracetamol (EPHARM)	*636.9*	599.8mg-663	618mg-651
PARADOL	545.8	518.5mg-573.1	534mg-555
Paracetamol (Green filed pharmaceutical)	576.0	547.2mg-604.8	556mg-602
Paracetamol (Anuhi well come company)	572.9	544.3mg-601.5	560mg-596
Makmol	585.7	556.4mg-615.0	572mg-601
Cetamol	579.5	550.5mg-608.5	570mg-586

Friability: To evaluate how well the tablets stands up to coating, packing, shipping and other processing; friability test were conducted. From each brand of legal and illegal products, 20 tablets were taken and de dusted before weighing, after weighing the tablet were placed in drum of friability tester of which each tablet rotated 100 times. Finally 20 tablets of each brand were de dusted and reweighed and their percentage losses of weight were calculated.

According to BP [20] & USP [21] the total weight loss should not be more than one percent and no tablet should show any type of break or crack. From the three illegal drugs Makmol and paracetamol tablet from Anuhi well come company failed to comply with friability test. Although cetamol were in the specification the percentage loss of mass was 0.9484% meaning it is at the border. The drug will be destroyed (becomes powder rather than tablet) when it reaches to the patient after passing all process from production to patients. So, the patient faces difficulty of administration which reduces patient compliance or adherence to the medications. In contrast to the illegal drugs; all legal paracetamol tablets has complied with the specifications set by BP [20] and USP [21] (**Table 2**).

Disintegration Time: Test to disintegration time is performed to estimate the time required to disintegrate in gastric environment. It also shows the release profile of the drugs though it does not confirm. Paracetamol tablet being conventional tablet it were expected to disintegrate within 15minute.

According to BP [20]; a 900ml biker were filed with 37±2°C water then six tablet were placed in the basket rack assembly and connected to the disintegration apparatus. In this study all of Paracetamol tablets both legal or illegal has passed the test except Paracetamol tablet of Anuhi well come company which has left core mass after 15 minute of treatment within the disintegration apparatus containing 900 ml of water at 37±°C temperature. From the test, the time required to disintegrate were shown in **table 3**. Tablets of different form have different type of procedure and specification (**Table 4**).

TABLE 2: FRIABILITY TEST RESULT

Brand of product	Weight before the test (g)	Weight after the test (g)	Percentage weight loss
Paracetamol (EPHARM)	12.632	12.577	0.4354%
Paradol	10.921	10.869	0.47615%
Paracetamol (Green filed pharmaceutical)	11.522	11.414	0.93734%
Makmol	11.477	11.182	2.5704%
Paracetamol (Anuhi well come company)	11.718	11.474	2.0823%
Cetamol	11.598	11.488	0.94844%

TABLE 3: DISINTEGRATION TIME TEST OF DIFFERENT PARACETAMOL BRANDS

Brand	Time required to disintegrate min sec
Paracetamol I (EPHARM)	5:30
Paradol	4:39
Paracetamol (Green Filed Pharmaceutical)	5:54
Paracetamol (Anuhi Well Come Company)	Failed to disintegrate within 15 minuet
Makmol	7:40
Cetamol	1.38
Disintegration time of conventional tablet	15:00

TABLE 4: TABLE SHOWING PROCEDURE AND SPECIFICATION OF DIFFERENT TYPE OF TABLET

Type of tablet	Media	Specified time
Uncoated	900 ml of water	15min
Enteric and sugar coated	a. 900 ml water*	120min
	b. 900 ml 0.1 hydrochloric acid solution	60min
Film coated	a. 900 ml water	60min
	b. 900 ml 0.1 hydrochloric acid solution	30min
Effervescent tablet	200 ml water at 15 °C -25 °C	5 min
Soluble tablet	200 ml water at 15 °C -25 °C	3min
Gastro retentive	a. 900 ml 0.1 hydrochloric acid solution	120min
	b. Phosphate buffer at pH 6.8	60 min

*For tablets having an alternative media, the second media (labeled as b) and specification is used, if an only if the tablet failed to disintegrate in first media (labeled as a)

Identification Test: According to BP [20] there are 3 tests to screen the authenticity of the active ingredient. To test the authenticity of the active ingredient; two identification test were carried out in this study, 0.5g of Paracetamol were extracted with 20 ml of acetone, filtered and evaporated. The filtrate was dried at 105°C with drying oven.

For the first test, 0.1g of the dried residue boiled with 1ml of Hydrochloric acid for 3 minute and 10ml of water were added and cooled. It was observed whether it formed a precipitate or not. Then, 0.05ml of 0.0167 m of potassium dichromate was added with micropipette to see the appearance of violet color which does not turn to red. Positive result was obtained, meaning there was no formation of precipitate and there were formation of violet color with addition of potassium dichromate.

The second test four identification tests was melting point. British pharmacopeia puts the melting point to be 169°C. Other standard books also accepts melting point between 168-171°C to be acceptable limit. In this study, the dried residues were melted along with standard Paracetamol after it was inserted in to capillary tube. All of the tablets were melted between 169°C and 170°C.

Percentage Content of Paracetamol: Test for percentage of content is based on the assay of the individual content of active ingredient of a number of single dose units. According to British pharmacopeia [20], 20 tables were weighted and the average weight of the powder containing 0.15g was calculated. The calculated amount of powder containing 0.15g of Paracetamol was dissolved with50ml of 0.1m Sodium Hydroxide and diluted with 100ml of water.

After dilution, the solution was shaken for 15 min and sufficient quantity of water was added to produce 200 ml of mixture. Filtering the mixture and 10ml of filtrate were taken and diluted with water to produce 100ml of the solution. From 100ml of the solution, 10 ml were taken and added to 10ml of 0.1 m sodium Hydroxide solution. Finally, sufficient quantity of water was added to produce 100 ml of the mixture. Sample from the last solution were taken and the absorbance was measured at 257 nm. And the following result was obtained (**Table 5**).

TABLE 5: SHOWING RESULT TO PERCENTAGE CONTENT OF PARACETAMOL

Brand	Absorbance	Content in %
Paracetamol (EPHARM)	0.520	96.97%
Paradol	0.811	95.347%
Paracetamol (Green filed pharmaceutical)	0.510	95.12%
Makmol	0.484	90.253%
Paracetamol (Anuhi well come company)	0.440	82.053%
Cetamol	0.464	86.533%

CONCLUSIONS: The finding showed that the quality of Paracetamol tablet which were not registered by DACA are substandard. Though the drugs contain the write API, it is below the percentage requirement set by standard books. Each illegal drug was failed to comply at list to one test out of five. The regional health bureau together with regulatory body must take action to stop illegal smuggling of medication in Somali regional states.

On the other hand, all of legally registered Paracetamol tablet test results were within the specification set by British pharmacopeia and United State pharmacopeia to each test.

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