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In-Vitro Evaluation of Marketed Brands of Paracetamol Tablets in India Using Quality Control Tests

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S. S. Dahiwal*, S. G. Bhokare

Department of pharmaceutics, Rajesh Bhaiyya Tope College of Pharmacy Nipani- Bhalgaon, Aurangabad, Maharashtra, India

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ABSTRACT

Paracetamol tablets are popular over the counter (OTC) products among the patients as a good analgesics and the objective of this study was to compare the quality of the paracetamol tablet formulations those are locally available in India pharmaceutical market manufactured by various pharmaceutical companies with pharmacopeia standards. The four popular brands (A, B, C, D) of paracetamol conventional tablet of 500 mg strength were chosen. The paracetamol tablets were obtained from government hospital pharmacies as well as from local private pharmacies. To compare the quality of tablet formulations of different brands various official parameters like friability, weight variation, disintegration time, dissolution and drug assay tests were performed as per the pharmacopeia. The result of all these parameters of different brands was in the pharmacopoeial limits so it could be concluded that marketed pharmaceutical tablets of paracetamol of these brands are safe, effective and efficacious as well as satisfy quality control limits of pharmacopeia.

INTRODUCTION

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

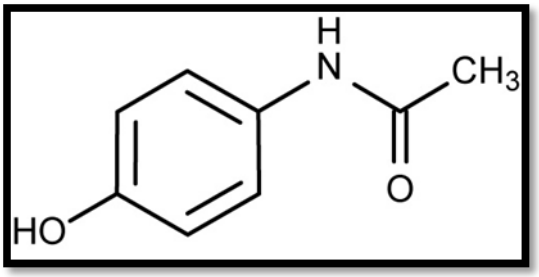

Fig. 1: Chemical Structure of Paracetamol

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 a 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 antiplatelet 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. However, 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. However, 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 sub standard 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 the 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 the investigation of the quality of paracetamol tablet which is registered by drug regulatory body of India, Drug Administrative and Control Authority of (DACA) and which are not registered but marketed in Somale region of India comparatively. The aim of the study was to investigate the *in-vitro* quality of

Paracetamol tablet marketed in India**.** The study provides 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,] United States Pharmacopeia (USP)[21] and Indian Pharmacopeia(IP)[22]& the degree of adherence of marketed tablet to the standard set by regulatory body in India.

MATERIALS AND METHODS:[2, 5]

TABLE 1: LIST OF EQUIPMENT USED

EQUIPMENT NAME	MAKER
High Precision Balance	Globus
Roche Friabilator	UTS
Monsanto Hardness Tester	Zineo Scientific Instruments
Dissolution Apparatus (6 Paddle)	Model no.- TDT-68L Elecrolab
U.V. Spectrophotometer	Model no. – U.V.1650 Shimadzu

TABLE 2: LIST OF CHEMICAL USED

SR. NO.	CHEMICAL NAME
1.	0.1M Sodium Hydroxide
2.	0.1N Hydrochloric Acid
3.	Distilled Water

STUDY DESIGN: Comparative *in-vitro* quality control parameters between the commercially available tablet brands of paracetamol were studied through the evaluation of weight variation, hardness, friability, disintegration time, dissolution profile and pharmacopoeial assay. The study was done by performing various test procedures associated to assess the quality of tablets.

SAMPLE COLLECTION: To perform the study paracetamol tablets from two different manufacturers were purchased from the drug store. Both the tablet brands of paracetamol were labeled to contain 600 mg of paracetamol per tablet. The labeled shelf life of all of the tablets was three years from the date of manufacturing and was taken for the evaluation before two years of the labeled expiry date.

SAMPLE IDENTIFICATION: After purchasing, tablets of both the brands were coded as A and B for paracetamol tablets of two different manufacturers. Finally, the coded samples were separated as the same manufacturer and taken for evaluation.

PROCEDURE OF EVALUATION: Various analytical methods and tests are important for the development and manufacture of pharmaceutical formulations. For the evaluation, following quality control tests were performed for both the tablet brands in the study.

1. WEIGHT VARIATION: 10 tablets were taken and were weighed using globus high precision weighing machine. Their average weight and standard deviation were noted down.

a) Then each tablet was weight and their % difference from the average weight was determined.

2. HARDNESS TEST:

a) A tablet was placed vertically on the Monsanto hardness tester.

b) The load was then applied along the radial axis of the tablet.

c) The weight or load required for breaking the tablet was noted down.

d) Similarly, it was done for 10 tablets.

3. FRIABILITY:

a) It was performed using Roche friabilator.

b) 5 tablets were weighed and placed in apparatus.

c) The apparatus was rotated at a speed of 25 rpm.

d) The apparatus was made to rotate for 4 min.

e) The tablets were then weighed and the weights were compared with the initial weights.

f) The % age friability was calculated using the formula.

$$\% F = [1 - (W/Wo)] \times 100$$

Where**,** % F = Friability in % age, Wo = Initial weight of tablets, W = Weight of the tablets after revolution.

4. TABLET DISINTEGRATION:

a) It was performed using USP disintegration device.

b) 6 tablets were placed in disintegration test apparatus.

c) It was maintained at 37± 0.2^{0}C containing simulated gastric fluid (0.1N HCl).

d) Noted down the time taken for tablets to disintegrate.

5. TABLET DISSOLUTION: For this test U.S.P. Type- 1 (Basket), 6 Paddle Apparatus was used. Gastric Fluid as Dissolution Medium: The tablets formed were immersed into 900 ml. of Dissolution medium, simulated gastric fluid (0.1N HCl). The temperature of the dissolution medium was maintained at 37 ± 0.2^{o}C. The basket was rotated at a speed of 150 rpm. After an interval of every 15 minutes, 2 ml. of the medium was Pipette out and replaced with fresh medium (0.1N HCl). This was continued all along for 2 hours. The pipetted out samples were then diluted to 10 ml. with fresh dissolution medium and were then filtered. The absorbance of the filtered samples was determined using U.V. Spectroscopy at λmax 222 nm.

6. PHARMACOPOEIAL ASSAY (I.P.): Weigh & powdered 20 tablets. Then weighed accurately a quantity of powder equivalent to about 0.15 gm of paracetamol. Then add 50 ml 0.1M NaOH& 100 ml. of distilled water. Shake the contents for 15 minutes & then add sufficient water to produced 200 ml. Then filtered & diluted 10 ml of filtrate to 100 ml. with water. Then again to 10 ml of resulting solution, add 10ml. of 0.1M NaOH& again diluted to 100 ml with water & mix thoroughly. Then note down the absorbance of resulting mixture at the maximum at 257nm & calculate the contents by taking A (1%, 1cm) as 715 at the maximum 257 nm.

7. DISSOLUTION: Dissolution was another studied important quality control parameters directly related to the absorption and bioavailability of the drug. The study revealed that at different time intervals drug release rate was better.

RESULT AND DISCUSSIONS

WEIGHT VARIATION: During the study, at first the weight variation, which is the key to controlling the crushing strength and friability of tablet, was assessed. The test stated that the samples of paracetamol coded A, B, C & D have passed the weight variation uniformity test as specified in the Indian Pharmacopoeia (not exceed 5% deviation) (Indian Pharmacopoeia, 2007).

TABLE 3: WEIGHT VARIATION OF DIFFERENT PARACETAMOL BRAND TABLETS

BRAND	AVERAGE WEIGHT (MG)	ACTUAL INTERVAL OF THE TABLET WEIGHT (MG)
A	*636.9*	618mg-651
B	545.8	534mg-555
C	576.0	556mg-602
D	572.9	560mg-596

Hardness: Hardness is the second most important physical feature for assessing tablet. In the study, it was found that A, B, C & D brands of paracetamol passed the test of tablet crushing strength or hardness. These brands have the acceptable crushing strength of between 4 kg/cm2 to 10 kg/cm2.

Friability: In the friability test, the friability values for paracetamol tablet brands were ranged from 0.43 to 0.94%. In formulations the percent, (%) friability was less than 1% which ensures that all the tablets of four brands of the formulation were mechanically stable and Shown in **Table 4.**

TABLE 4: FRIABILITY TEST RESULT

BRAND OF PRODUCT	WEIGHT BEFORE THE TEST (G)	WEIGHT AFTER THE TEST (G)	PERCENTAGE WEIGHT LOSS
A	12.632	12.577	0.4354%
B	10.921	10.869	0.47615%
C	11.522	11.414	0.93734%
D	11.477	11.380	0.84516%

Disintegration Time: The disintegration time of tablet brands of paracetamol A, B, C, and D was satisfactory as uncoated USP tablets have disintegration time standards as low as 5 minutes. The overall disintegration time for paracetamol tablet brands was in the ranged from 24 seconds to 4 minutes 52 seconds. After 10 minutes, the release rate of tablet brands of paracetamol was 43.96 to 45.60%. Finally, after 120 minutes, 85-95% drug release was observed in A, B, C and D for paracetamol brands. The outcome of the test has been shown in **Table 5.**

TABLE 5: DISINTEGRATION TIME TEST OF DIFFERENT PARACETAMOL BRANDS

BRAND	TIME REQUIRED TO DISINTEGRATE MIN SEC
A	5:30
B	4:39
C	5:54
D	7:40

TABLE 6: 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* b. 900 ml 0.1 hydrochloric acid solution	120min 60min
Film coated	a. 900 ml water b. 900 ml 0.1 hydrochloric acid solution	60min 30min
Effervescent tablet	200 ml water at 15°C -25°C	5 min
Soluble tablet	200 ml water at 15°C -25°C	3 min
Gastro retentive	a. 900 ml 0.1 hydrochloric acid solution b. Phosphate buffer at pH 6.8	120min 60 min

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

DISSOLUTION: Dissolution was another studied important quality control parameters directly related to the absorption and bioavailability of the drug. The study revealed that at different time intervals drug release rate was better. After 10 minutes, the release rates of tablet brands of paracetamol were 43.96 to 45.60%. Finally, after 120 minutes, 85-95% drug release was observed in for paracetamol brands. The outcome of the test has been shown in table 7& fig 2**.**

TABLE 7: EVALUATION OF DISSOLUTION PROFILE OF PARACETAMOL TABLETS

Concentration(µg/ml)	Absorbance
0	0
10	0.23
20	0.363
30	0.456
40	0.541
50	0.619
60	0.745
70	0.841

SAMPLE (TABLET BRANDS)	% DRUG CONTENT RELEASE (5 MIN)	% DRUG CONTENT RELEASE (10 MIN)	% DRUG CONTENT RELEASE (20 MIN)	% DRUG CONTENT RELEASE (40 MIN)	% DRUG CONTENT RELEASE (80 MIN)	% DRUG CONTENT RELEASE (120 MIN)
A	20.24	43.96	54.93	65.89	71.95	93.06
B	36.60	45.60	54.93	70.96	77.51	85.69
C	28.46	38.95	54.93	67.85	78.67	92.25
D	23.73	42.86	54.93	69.15	79.05	94.75

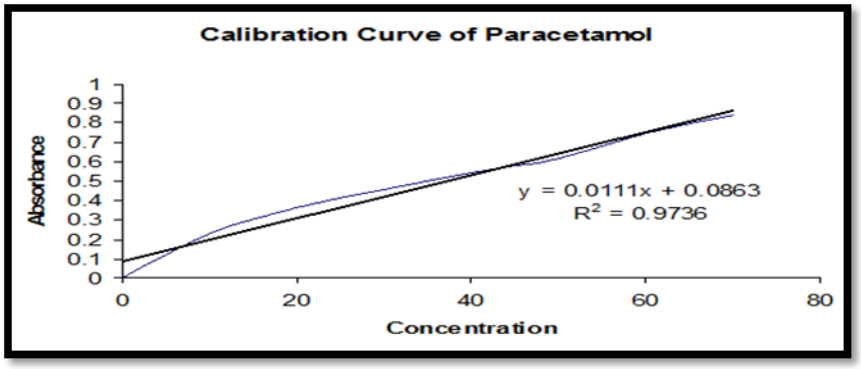

FIG. 2: CALIBRATION CURVE DATA OF PARACETAMOL

ASSAY OF PARACETAMOL: 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 British Pharmacopeia[20], 20 tables were weighed 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 was taken and the absorbance was measured at 257 nm. The following result was obtained.

TABLE 8: SHOWING RESULT TO PERCENTAGE CONTENT OF PARACETAMOL

BRAND	ABSORBANCE	CONTENT IN %
A	0.520	96.97%
B	0.811	95.347%
C	0.510	95.12%
D	0.484	90.253%

CONCLUSION

The quality control evaluations of four different brands of paracetamol tablets those are available in the pharmaceutical market of India were assessed by this study. The values were compared with the standards. This study showed that all four brands (A, B, C, D) of

paracetamol tablets meet the pharmacopeia specification of different parameters. The results of various quality control parameters for tablets like weight variation, friability, disintegration time, drug assay and dissolution study all are in the pharmacopeia limits.

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