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Research Article

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Physico-chemical evaluation of four brands of Paracetamol 500mg tablets by using quality control techniques

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Abstract Paracetamol is common non-steroidal anti-inflammatory drug (NSAID) and it is over-the counter (OTC) drug, frequently used as analgesic, antipyretic and against different aches. The purpose of this research work is to assess the quality of four brands of Paracetamol tablets by using different test parameters Greater Noida, India. Four brands of Paracetamol 500mg tablets were analyzed by different Physico-chemical quality evaluation parameters as per Indian Pharmacopeia (IP) standard. Based on the result of the current study, all the brand samples passed hardness, thickness, weight uniformity and friability tests and they satisfy the IP standard limit. All test samples are disintegrated in distilled water within the range between 3.17 to 7.75 min. This indicates the disintegration rate of all the samples are less than 15min.Moreover the dissolution test confirmed that the percentage drug release of the three study brands of Paracetamol at 30 minutes were was over 80% in conformity with the Pharmacopeia specification limit and one brand sample fail to IP specification limit. The drug assay results of the test samples were determined by UV spectrophotometer analytic technique. The percentage drug content results of the samples by UV technique are ranged between 90.8% and 104.6%. It was observed that out of four brands samples, three samples (P1, P3 and P4) comply with Pharmacopeia specification limit (95-105%). In general, the results of this study show that most of the brand samples satisfy all quality control parameters with low standard deviations.

Keywords Over- the- counter, quality control parameter, Paracetamol, Pharmacopeia

Introduction

Paracetamol/Acetaminophen tablets are also called "aniline derivatives analgesic" and are considered as over -the-counter (OTC), non-steroidal anti-inflammatory drugs (NSAID), frequently used for treatment of different aches, pain and body fever caused by circulating microorganism [1-2]. The word paracetamol is from a chemical name for para-acetylaminophenol and it consists of a benzene ring center, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para (1, 4) pattern as indicated in figure (1) below [3].

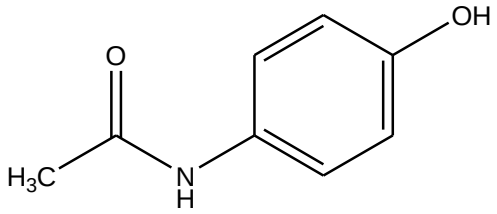

Figure 1: Chemical Structure of paracetamol ($C_8H_9NO_2$)

The analgesic and antipyretic action of Acetaminophen is through inhibiting the action cyclooxygenase (COX) enzyme and prostaglandins (PGs) [4]. Paracetamol selectively inhibits (COX-2 and COX-3) enzyme only in central nerve system (CNS) where the concentration of peroxides is low [5].

Paracetamol is mainly metabolized in the liver and changed to nontoxic sulfate glucuronide and other conjugates and approximately 90% of the metabolites are excreted in the urine. (Oscier& Milner;2009;, Vidhya and Bai; 2012).About 5-10% is oxidized by hepatic cytochrome CYP450 enzymes resulting in the formation of highly toxic N-acetyl-p-benzoquinoneimine (NAPQI) and this toxic by-product is generally inactivated by liver glutathione and excreted in the urine [6].

The efficacy and safety of pharmaceutical products are directly depending on the drug quality, drug content, dose, formulation properties and etc. The dose of the drug is important factors that affect the safety, efficacy and bioavailability of the products thus low dose can cause treatment failure and high dose causes potential toxicity [4].

Statement of the Problems

Most of the OTC drugs are low quality, fake and substandard form throughout the world [7]. The prevalence of poor quality and overdose utilization of OTC drugs are frequently reported in developing countries particularly in African and Asian countries, thus they are more harmful and results treatment failure, adverse drug event (ADE), organ damage, toxic effect, morbidity, disability, mortality and increase medication cost [8].

Paracetamol is common OTC drugs mostly purchased and dispensed without prescription and used without any knowledge about the drug in many developing countries. Even in developed countries Paracetamol being associated with many public health problems such as suicide and toxic effect to the liver and other organ [9]. Every year there was gradually increasing number of registered cases of Paracetamol-induced liver intoxication all over the world [2]. Acetaminophen is the common drug that causes liver-toxicity, renal, cardiactoxicity and acute liver failure especially among young people in the United States, UK and other European countries [10]. According to the report of Food and Drug administration (FDA), in the United States between 1998 and 2005, Paracetamol is common and ranked 5th among drugs suspected of causing adverse drug events and fatal adverse reactions [11].

Significance of the Study

A quality control assessment test of pharmaceutical products covers all measures taken to ensure the starting materials, intermediate, packaging materials, finished pharmaceutical products, identify the strength, safety and purity of the product [12]. These evaluation test parameters includes tablets thickness, diameter, tablet weight variation, crushing strength, friability test, disintegration time, dissolution rate and chemical assay by UV spectrophotometer analytic techniques on selected brand samples based on pharmacopeia standard limits Therefore, the aim of these research work are to assess the physical and chemical quality of four brand of Paracetamol tablets produced in different manufacturers found in the study area and to evaluate the drug content the samples by using by using different quality control parameters.

Materials and Methods

Study Design

Comparative physico-chemical quality evaluation assessments of four brands of Paracetamol tablets available in the study area were conductedin School of Pharmacy, Sharda University. It was done by using different quality control techniques as per Pharmacopeia guidelines, from February, 2019 to July, 2019.

Study Area

The current quality evaluation assessment was conducted on the tablet samples collected from PariChowk and Jagat Farm Greater Noida, U.P., India. The analysis work was conducted in School of Pharmacy, Sharda University.

Paracetamol tablets physico-chemical Quality Evaluation test Parameters

Different drug quality evaluation test methods are performed to ensure the tablets quality, safety and efficacy. For the current study of quality assessment, there are different tablets quality control evaluation techniques are performed for all selected brands of tablets.

Tablets Thickness and Diameter Test

The tablet thickness and diameter is about the size and dimensional variable related to the compression process. Ten tablets for each test from each brand were measured by using Vernier caliper and the mean values were calculated. The test value should be controlled within the range of 5% deviation from the mean value [13].

Thickness = Main scale reading + (Vernial scale reading*least count reading) [14]

Tablets Hardness Test for Selected Brand Sample

Tablets Hardness test is assessing the ability of tablets in resistant to chipping, breakage, mechanical shocks during handling, manufacturing, shipping and etc. Ten tablets of each brand were subjected to Monsanto hardness tester and the crushing strength of the tablets was measured.

Tablets Weight Variation Test

Twenty tablets from each brand were weighed individually and the mean weight, standard deviation and percent of weight variation were calculated [13].

%weight variation=Individual weight _ average weight /average weight *100

The test tablets meet the IP specification limit, if % of the weight variation should not be greater than 5% deviation [15]

Tablets Friability Test

It is assessing about percentage weight loss of tablets due to removal of some fine particles from tablets surfaces when exposed to different physical stress condition and to assess the effect of rotating drum friction and shock which may often cause tablets to chip, cap or break [16]. Twenty tablets from each brand samples were weighed before and after friability test and calculate the percent of friability.

$$\% \text{ Friability} = [W_0 - (W_i/W_0)] \times 100.$$

The % friability value should be less than 1% for compressed tablet [13].

Tablets Disintegration Test

Disintegration is about tablets physical beak down and passes through the wire mesh of the tube in disintegration medium in specified time [13]. Six tablets from each brand were tested by 900ml distilled water at 37 ± 0.2^0C as medium and mean disintegration time was calculated. If all six tablets from each brand samples disintegrated within not more than 15 minute, the samples are comply IP standard limit.

Dissolution Test

Dissolution is defined as the tendency of a drug or tablets dissolved in the solution before absorption. It describes the general rate of the drug release process involved in the body system and it gives information about the drug absorption and bioavailability [17].

Phosphate buffer solution at pH 5.8 is used as dissolution medium at $37\pm0.5\ ^0$C

Preparation of solutions for Calibration curve

Stock solution 1: 100mg of pure drug dissolved in 100ml of phosphate buffer and mix for 15min

Stock solution 2: 10ml of the above solution is diluted to 100ml with same medium and filter. The serial dilutions are prepared from the filtrate by taking0.2ml, 0.4ml, 0.6ml, 0.8 ml; 1ml and 1.2mlthen make 10ml by the medium

which gives (2, 4, 6, 8, 10 and 12µg/ml drug concentration. The absorbances of these solutions were measured by UV spectrophotometer at 243nm and a calibration curve was plotted [17-18].

Dissolution test procedures (Basket type Apparatus)

Six tablets from each brand samples were assessed. A single tablet from each brand samples was placed in wire mesh basket and immersed in a dissolution medium and rotated at the speed of 50rpm. 5ml of samples were withdrawn at the time of 5, 10, 20, 30, 40 and 50 minutes and the same amount of fresh buffer solution were immediately replaced. The samples were filtered and 1ml sample was diluted 50ml buffer solution then measure the absorbance at 243nm [13].

Amount of drug release = Sample concentration*dilution factor* dissolution vol./1000

% drug release= Amount of drug release/label claim*100 [17].

Evaluation of paracetamol tablet by UV spectrophotometer (Drug assay)

The drug assay determines the concentration of the active Pharmaceutical ingredient (API) in the sample by using UV spectrophotometer techniques. It involves measuring the amount of ultraviolet and visible radiation absorbed by a substance in solution in the range of 180 to 780nm [19]. This analytic technique is simple, rapid, reproducible, specific and applicable to small quantities of compounds [13].

Assay procedures

Twenty tablets from each sample were weighed and average is calculated. The sample tablets were powdered and take the quantity of the powder equivalent to 0.15gram and transferred to 200ml volumetric flak. Add 50ml of 0.1M NaOH solution and 150ml of distilled water. The sample solutions mixed properly for 15 minute and filtered for assay. 10 of this filtrate were diluted in 100ml of distilled water. Again 10 ml of this dilute was mixed with 10 ml of 0.1M NaOH solution and make the volume 100ml with distilled water. The same procedure was repeated for the Acetaminophen standard drug using 0.15gram then measure the absorbance of both standard and sample solutions at 257nm by using 0.1M NaOH solution as a blank and each sample solutions were assayed [13].

Formula to calculate percent of drug content [20].

% drug content =

$$\frac{\text{Av. wttablets}}{\text{labelclaim.}} \text{X} \frac{\text{Wt of std taken}}{\text{Wt. of the sample taken}} \text{X} \frac{\text{abso. of sample}}{\text{Abs. of standard}} \text{X } 100$$

Results and Discussion

Table 1: The physical quality evaluation of test result of four brand samples

Sample	Thickness (mm) (mean ± SD (n=10)	Diameter (mm) (mean±SD (n=10)	Hardness (Kg/cm^2) (mean ± SD, n= 10)	Weight variation(mg) (mean ±SD, n=20)	% of friability (n=20)	Disintegration time (minute) (mean ±SD, n=6)
P1	3.48 ± 0.11	12.53 ± 0.04	7.55 ± 0.5503	596.150 ± 10.574	0.34	7.55 ± 0.010
P2	3.57 ± 0.46	12.54 ± 0.03	7.4 ± 0.4595	579.650 ± 9. 040	0.51	7.25 ± 0.013
P3	3.73 ± 0.06	12.59 ± 0.08	6.95 ± 0.4378	547.750 ± 11.111	0.72	3.17 ± 0.020
P4	4.17 ± 0.06	12.46 ± 0.08	8.05 ± 0.4972	629.500 ± 14.460	0.32	7.57 ± 0.035

Mean - average result of test tablets, SD- Standard deviation of test tablets, n- number of tablets from each sample, P1-Dolo, P2- PUC, P3- Asmol and P4- Calpol Paracetamol brands.

The tablets thickness and diameter are measured by using Vernial caliper having least count reading of 0.02mm. The thickness and diameter results of the paracetamol brand samples mentioned in the above table show that, all of test samples are comply with Indian Pharmacopeia specification limit.

Evaluation of tablets hardness is the most important physical feature of the tablets for assessing the capability of tablets to withstand chipping, abrasion, breakage and mechanical shocks during its handling, manufacturing, storage,

packaging and shipping. Thus, the tablet formulations require standard amount of crushing strength or hardness. The Pharmacopeia specification limit of hardness value of a tablet should be in the range of 4-10kg/cm^2 [14]. The result achieved from hardness test for four brand samples shows all the selected brands sample results are found in the range of (6.95 - 8.05 kg/cm^2) and comply with Pharmacopeia specification limit.

Weight variation test is a very important quality control parameter because it is an indication of the corresponding in drug content uniformity of tablets.

According to IP the acceptable limit tablets having the weight of 250mg and above weight, each tablets should not to deviate by more than ±5% limit of from individual weight of the tablets and if no more than 2 tablets from 20 tablets are outside the percentage limit of the test was acceptable [13]. The present weight uniformity assessment results of four brand samples shown in table 4 above, test samples are acceptable weight variation test and comply with pharmacopeia standard. It indicate that no brand sample deviate by more than ±5 percent of deviation from the average weight.

Friability test measure the resistance of the tablets to abrasion or removal of particles by tumbling or rubbing them in a rotating drum. Percent of friability is about percentage weight loss of tablets due to removal of fine particles from its surfaces when exposed to different stress conditions. Test is performed to assess the effect of friction and shock which may often cause tablets to chip, cap or break [16]. The maximum percent of friability should not be more than 1% and any broken or smashed tablets are not acceptable [13]. The friability test results are ranges from 0.32% to 0.72% thus there is no more than 1% weight loss in all test sample. This may indicate the test sample are resistant to any mechanical pressure. Disintegration test is the first step of solid drug dissolution and important to assess drug absorption, bioavailability, quality, efficacy and better therapeutic action. The efficacy of the pharmaceutical product is related to its disintegration time [21]. The tablets were first broken into small pieces and discharged into the body fluids for dissolution. For better absorption and to bring better therapeutic outcome, tablets must sufficiently disintegrated within the standard time limit [22]. The according to India Pharmacopeia (IP) standard; disintegration time of uncoated Paracetamol tablets should be less than 15min in liquid medium. The current test result showed in table 4, disintegration time of all test brand tablets ranges from 3.17 ±0.020 min (P3) to7.57±0.035 min (P4) and all samples complies IP specification limit.

Calibration Curve and Dissolution Test Result

The effectiveness and bioavailability of the tablets relies on the drug dissolved in the body fluid.

Table 2: Absorbance profile of pure drug for calibration curve at 243nm using PBS

Drug concentration (µg/ml)	**0**	**2**	**4**	**6**	**8**	**10**	**12**
Absorbance at 243 nm	0	0.212	0.403	0.581	0.776	0.981	1.191

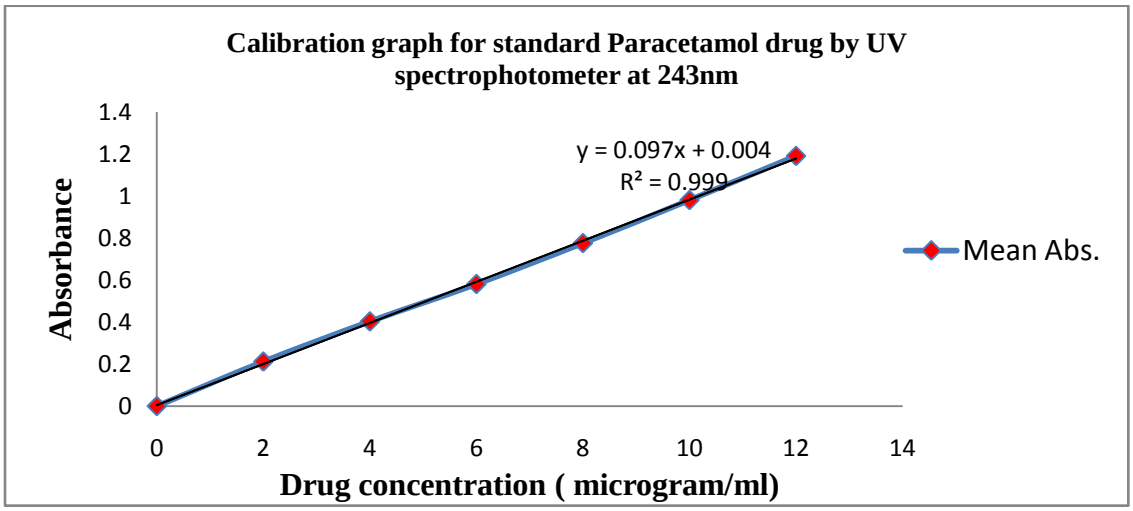

Figure 2: Calibration curve of standard Paracetamol drug in Phosphate buffer pH 5.8

Table 3: Percentage drug release result four brands of Paracetamol by dissolution test

Time interval (min)	% of Drug Release of Paracetamol Tablets			
	P1 Brand	**P2 Brand**	**P3 Brand**	**P4 Brand**
0	0.00	0.00	0.00	0.00
5	29.71±0.66	30.70±0.91	30.05±0.26	26.80±0.53
10	50.03±0.36	57.18±0.50	58.93±0.27	53.51±0.83
20	62.77±0.27	69.94±0.61	78.94±4.99	72.54±1.06
30	78.99±0.85	85.48±0.41	84.66±0.82	80.29±0.72
40	85.14±0.28	88.25±0.43	89.83±0.18	88.21±0.57
50	87.66±0.45	92.01±0.17	91.28±0.28	89.52±0.40

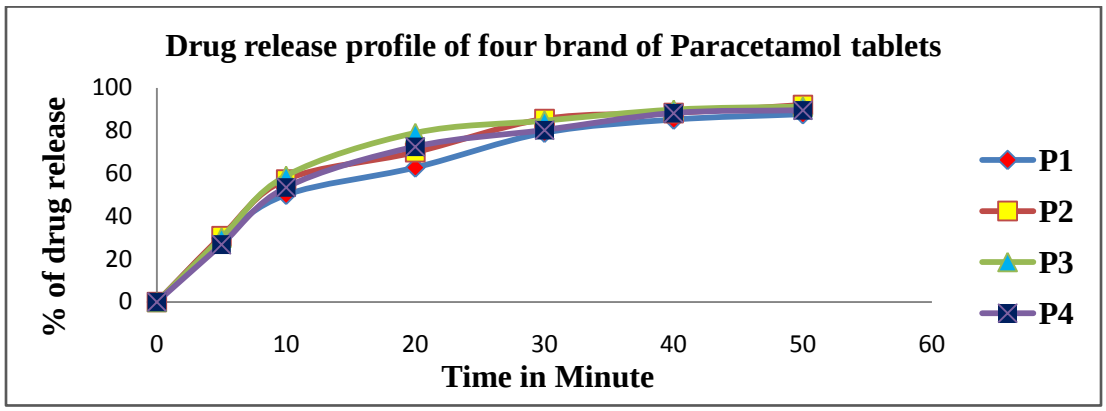

Figure 3: Dissolution profile of four brands of Paracetamol tablets, 500mg

Dissolution test result

It measures of the amount of the drug released into the dissolution medium within the specified time limit [23]. The percentage of drug release was determined based on the absorbance and concentration of the samples taken within specific time intervals of dissolution process. Calibration graph is plotted by using different concentration of pure drug and its UV absorbance at 243nm and also important to calculate of percent of drug release. According to IP specification limit the percentage of drug release of paracetamol tablets should not less than 80% within 30 minutes dissolution process.

The current study results showed in table 6 and figure 3; the highest percentage drug release in30 min is found in the sample (P2), 85.48% and the lowest percentage release at 30min was found in sample (P1), 78.99%. The three brands samples (P2, P3 and P4) comply with the pharmacopeia standard means more than 80% of the drugs released at 30min but P1 fail to the standard of pharmacopeia.

Assay result of test sample by UV visible spectrophotometer

UV spectrophotometer is one of the most routinely used techniques for analysis of pharmaceutical products and it involves measuring the amount of ultraviolet radiation absorbed by a substance in solution. It is important for quantitative as well as quality analysis of different pharmaceutical products. Spectrophotometer analytic technique is simple, rapid, reproducible and applicable to small quantities of compounds [13].

Table 4: Drug assay of four brand samples by UV spectrophotometer

No-	Sample	Absorbance (Mean± SD, n=3)	Amt. of sample taken	Average weight (n=20)	Assay result (%)
1	Standard	0.477±0.001	150mg		
2	P1	0.499±0.001	178.815mg	596..05mg	104.6
3	P2	0.433±0.001	176.37mg	587.9mg	90.8
4	P3	0.474±0.001	166.53mg	555.1mg	99.4
5	P4	0.481±0.001	190.35mg	634.50mg	100.8

n-is number of tests for absorbance and n- is number tablets for average weight.

Drug assay is important to determine the concentration of API in drug samples. According to IP the concentration of acetaminophen is accepted if it is within the range of 95%-105%. In the current study, percentage drug content result of each samples are analyzed and the result of four brands of paracetamol tablet samples using UV spectrophotometer method ranges from 90.8% -104.6%.This drug assay results are determined based on the Indian Pharmacopeia standard and from four test brand samples, the result of one brand sample PUC (P2) Paracetamol table sample is 90.8% and the concentration of API in the sample is below the standard limit. The assay result of the three brand samples P1, P3 and P4 contain more than 95% of active drug contents and pass the quality control evaluation techniques. Based on this analytic result, it can be said that, the three brands of paracetamol 500mg tablet samples are maintain the quality standard, safe and effective for use.

Conclusion and Recommendations

Paracetamol is the most common NSAID, analgesic and antipyretic drugs. The standard quality assessment of pharmaceutical products is important to ensure their safety and efficacy. Based on the current study result, all brand samples analyzed passed all physical quality control test parameters. Out of four test brands, three brand samples pass the dissolution test and drug assay test and comply with the Pharmacopeia limit while the dissolution result of one sample (P1) fails to pharmacopeia standard limit specification limit in 30 minute. Therefore the overall quality evaluation test results of the current study shows that most of the test samples satisfies Pharmacopeia standard limit. Therefore it is important to carry out rapid, frequent and sensitive quality control evaluation test of the paracetamol tablets to ensure its safety, efficacy and bioavailability of the drug products.

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