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Paracetamol: A Simple Analgesic/ Antipyretic Underwent *In Vitro* Quality Evaluation Tests of Three Different Marketed Brands In Three Different Media

B. Haarika[1]*, Ch. Pushpasri[2], V. Bhagya Lakshmi[2]
[1]*Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, 12-5-31/32, Vijayapuri Colony, Tarnaka, Secunderabad, 500017, Telangana, India.
[2]Department of Pharm.D, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, 12-5-31/32, Vijayapuri Colony, Tarnaka, Secunderabad, 500017, Telangana, India.
For Correspondence: haarikabalusu09@gmail.com

ABSTRACT
The study is aimed to investigate the quality control tests of three different brands of paracetamol tablets, coded them as A, B and C.The tablet formulation of the drug can have a significant impact on quality parameters such as weight fluctuation, hardness, friability, disintegration time, percentage drug release, and content uniformity. Hence the study was to assess and compare quality control parameters between three brands of tablet formulations. The efficacy of tablet formulation depends upon the amount specified in the label and its accessibility to the human body. Quality control invitro comparative analysis was performed among commercially available three different brands of paracetamol. To evaluate the weight variation, hardness, friability, disintegration time, dissolution profile and content uniformity. Weight variation, diameter, thickness, hardness and friability of all the three different brands of paracetamol tablets were within the limits of the USP. All the three different brands of paracetamol tablets in three different media have passed the tests for disintegration time, dissolution and content uniformity. All brands of paracetamol tablets in three different media have qualified all quality control parameters of tablets and do not have any deviation according to standard values of USP.Even though, these three different brands of paracetamol tablets have shown different results in disintegration, content uniformity and percentage drug release upon using three different types of media such as 0.1NHCl, Phosphate buffer pH5.8 and pH 6.8. Although the results varied slightly, still, they are within the acceptable limits of USP..
Keywords: *Paracetamol, UV spectrophotometer, Comparative evaluation, Percent drug release, Different brands of paracetamol tablets.*

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INTRODUCTION

A common over-the-counter analgesic and antipyretic is paracetamol (INN) or acetaminophen (USAN). It's true. Fever, headaches, and other aches and pains can all be relieved with this drug. For various minor aches and pains, it's a big part of the recipe in a variety of cold and flu medicines [1].The efficacy of tablet formulation in clinical trials depends on at least two factors, such as the drug's efficacy and safety being present in the amount specified on the label, and its accessibility to the human body.

The drug's formulation can have a big impact on quality criteria including weight fluctuation, hardness, friability, disintegration time, percentage drug dissolution, content uniformity are the important factors to be considered. The physicochemical properties of the formulations are very important which includes properties related to excipients, active pharmaceutical ingredients as well as manufacturing processes. There are several procedures that must be followed for quality control measures, as well as for physical factors which are equally important. The study's goal was to compare quality control parameters between three brands of a formulation's tablets because standardized quality requirements are necessary for the superior quality of medicine [2- 3].

Because the efficacy of drugs is directly proportional to their quality, quality evaluations of medications at all stages of production and distribution are critical [4 - 5].

Paracetamol was first used clinically in 1893 and then avoided for more than 60 years due to concerns about paracetamol – induced methemoglobinemia [6]. In the United States, paracetamol was introduced. As an oral preparation, it was first introduced in 1950and is currently widely employed [7- 10]. In the United States, prescriptions are written on an annual basis, and non-prescriptions are written on an irregular basis. Over 25 billion dollars in prescription sales doses every year, making it the most widely and commonly prescribed medication [11].

REVIEW OF LITERATURE

- A Comparative *in vitro* evaluation was done by Kumar et.al 2012 to evaluate the weight variation, hardness, assay, dissolution, and disintegration on two different brands of Paracetamol and the results of the above parameters of two different brands are within the acceptable limits [2].
- Comparative quality *invitro* evaluation test done by Ayenew et.al 2014 on eleven different brands of paracetamol from different sub-cities of Ethiopia. Results have shown that weight variation, friability, diameter and thickness results were in accordance with the British Pharmacopeia for all the samples. But Paracetamol tablet of Epharma doesn't comply with the British pharmacopeia limits. Except tablet Asmol remaining tablets passed the Assay test[4].
- A Comparative *Invitro* quality control test done by Md. Najeem Uddin et.al 2018 on seven different brands of Paracetamol found the weight variation, hardness, assay, friability, dissolution and disintegration of all the tablets are within the limits of USP[11].
- *Invitro* Comparative evaluation tests done by Abhishek S. Pujari et.al 2018 on five different brands of paracetamol. And results have shown that all the tablets have passed weight variation, hardness, friability, dissolution and disintegration are within the limits of BP and USP [12].
- Mahfuza Rahman et.al 2021 conducted an *in vitro* evaluation parameter to assess the quality of five brands of paracetamol tablets 500mg from various manufacturers. They reported weight variation, hardness, friability, disintegration time, dissolution profile and content uniformity were within the limits. They determined that practically all paracetamol tablets purchased from Bangladeshi retail shops are made and marketed in accordance with GMP[13].
- Reem Aiswayehayyins et.al 2021conducted an *in-vitro* quality control evaluation on nine different brands of 500mg paracetamol tablets. Weight variation of 5% from mean weight (because tablet weight was 250 mg); mean ASC between 90–110% of the label; 1% weight loss owing to friability; complete disintegration in water within 15 minutes; and release of 85% in phosphate buffer after 30 minutes (pH 5.8)[14].
- Omar Rwaiha, et.al 2020 performed an *invitro* comparative study among different brands of paracetamol tablets. The quality of five different paracetamol brands was evaluated, with most of the results meeting British Pharmacopeia quality guidelines. Brand 3 failed the friability test, with a deviation of twenty times the desired level (20.23 percent) Therefore, they concluded that it is evident from the study that most of the brands tested showed reliable results[15].

MATERIALS AND METHODS: [16 – 17]

High precision balance,Roche Friabilator, Monsanto hardness tester, Disintegration apparatus, USP dissolution apparatus II paddle, UV spectrophotometer, Potassium dihydrogen phosphate, Disodium hydrogen orthophosphate, Sodium phosphate dibasic heptahydrate, Sodium phosphate monobasic monohydrate.

Study design:

A quality control invitro comparative analysis was performed among commercially available three different brands of paracetamol. To evaluate the weight variation, hardness, friability, disintegration time, dissolution profile and content uniformity. The disintegration time, dissolution profile and content uniformity were performed in three different mediums such as 0.1 N HCl, Phosphate buffer pH 5.8 and phosphate buffer pH 6.8.

Sample collection:

This study was performed by collecting the paracetamol tablets from different manufacturers through the drug store. These three brands of paracetamol have a drug label claim of 500mg of paracetamol per tablet. The shelf life of all tablets was three years from the year of manufacture and evaluation was done before two years of expiry.

Sample identification:

The three different brands of paracetamol tablets were coded Calpol as A, Crocin as B and Paracip as C.

RESULTS AND DISCUSSION

For the manufacture and evaluation of pharmaceutical tablets, various formulating methods and various quality control tests are important. Following quality control tests were performed for different brands

ofparacetamol tablets in this study. All the data are stated as mean ± SD and $p < 0.05$ was measured to be statistically significant.

Weight variation:

weight variation parameter is the key controlling parameter for crushing strength and friability of the paracetamol tablets to be assessed.

The USP weight variation test is performed by individually weighing 20 tablets by using weighing balance Mettler Toledo.

$$\text{Percentage weight variation} = \frac{\text{Initial weight} - \text{Average weight}}{\text{Initial weight}} \times 100$$

According to USP standards, the maximum percentage deviation allowed is ±5%. If no more than two tablets depart from the average weight by more than ±5% and none tablet differs by more than double the percent. All the brands of the tablets were within ±5% deviation.

In this study, the three different coded (A, B, C) brands of 20 paracetamol tablets were weighed and all the three different brands have passed the weight variation test as per the limits of USP (Not exceed ±5% deviation).

Diameter:

The homogeneity of tablet diameter is critical for increasing patient compliance and preventing patients from becoming confused by variable tablet sizes. The patient may believe that the medications or tablets have different amounts of active substances due to the variation in sizes. In our study the diameter of three different brands of paracetamol tablets of code A was 3.1 ± 0.63, code B was 8.1 ± 0.67 and code C was 3.1 ± 0.78.

In our study, the diameter of all three different coded brands of paracetamol tablets was within the limits as per USP.

Thickness:

Due to differences in granulation density, pressure applied and speed during tablet compression, the thickness can vary with changes in filled weight. According to USP, a ± 5% is the allowable limit, depending on the size of tablets. From this study on three different brands of paracetamol tablets, the thickness of code A was 4.5 ± 0.75, code B was 5.5 ± 0.63 and code C was 4 ± 0.73.

The tablet's thickness is within the limits (± 5%) and no deviation was found as per USP.

Hardness:

The Monsanto hardness tester was used to evaluate tablet hardness,it is one of the first testers for this test. The fracture force is measured in kilograms.

It is the second most important parameter to assess the hardness of the tablets. According to the USP, the limits of the hardness of the tablets are as follows; the hardness of the oral tablets is 4 to 10kg but chewable and hypodermic tablets have a hardness of 3kg and sustained released tablets have about 10 to 20 kg. In our study it was found that all the three brands of paracetamol tablets of code A are4.5 ± 0.31, code B is 4.3 ± 0.34 and code C is 4.2 ± 0.38 have passed the crushing strength or hardness. Three of these brands have an average acceptable crushing strength of 4 kg/ cm^2 to 10 kg/cm^2. And has no deviation as per USP.

Friability:

The Roche friabilator of Analab can be used to test the friability of a tablet in the lab. Twenty (20) tablets are weighed and placed in the friabilator, which is then spun at 25 rpm for four minutes, Afterthe tablets are taken away and weighed. Then disparity between the two weightsis noted andfriability is calculated using the formula

$F = 100 X (1 – W/ W_0)$

W_0 denotes the weight of tablets before friability and W denotes the weight of the tablets after friability. According to the USP, typically compressed tablets that lose not more than 1 % of their weight (after 100 rotations) are normally regarded appropriate. Three of these different paracetamol brands have shown impressive results in our study the friability values of these brands ranges from 0.22 ± 0.35, 0.33 ± 0.45 and 0.36 ± 0.4 for code A, B and C respectively.

In three of these formulations the percent of friability was less than 1% this ensures three of these are mechanically stable.

Disintegration test:

TheLab-Line USP disintegration test apparatus consists of six 3-inch-long glass tubes that are open at the top and held against a 10-mesh screen at the basket rack assemblies at the bottom end. One tablet is placed in each tube and the basket rack is positioned in the prescribed medium at 37 ± 2°C such that the tablet remains 2.5 cm below the surface of the liquid on its upward journey and descends not closer than 2.5 cm from the bottom of the beaker to test. In basket assembly housing the tablets are moved up and down by a typical motor-driven device at a frequency of 28 to 32 cycles per minute over 5 to 6 cm. This test can also

be done with perforated plastic discs. These are placed on the tops of tablets to give them an abrasive effect. The discs may or may not be significant or add sensitivity to the test, however, they are helpful for floating tablets. Operate the equipment for time specified (15 minutes for uncoated tablet unless otherwise justified and authorized). In this study, the disintegration test was performed on six tablets. According to USP the disintegration time for uncoated paracetamol tablets should not exceed 30 minutes. Our study has shown the disintegration time of three different paracetamol brands in three different media the results were found to be in between the range of 7 minutes to 9 minutes. Three of these different brands of paracetamol tablets have shown satisfactory results as per USP.

Dissolution:

The USP dissolution apparatus II (paddles) DS8000 is used to perform the dissolution test.During the test, the water bath or heating device keeps the temperature within the vessel at 37 ± 5°C while keeping the bath fluid in a steady, smooth motion. Assemble the device and bring the dissolving media to a temperature of 37 ± 5°C. Place each tablet in each six cylindrical baskets. According to USP, the dissolution test was done on six tablets which must meet the specific requirements if one or two tablets failed, should repeat the test on six additional tablets[18].And the percentage of drug release should not be less than 70% of the quantity contained in the tablet after 45 min and after 2hrs its should not be more than 115% of drug release. Three of these different brands in three different media have shown the different percentages of drug release at different time intervals. The percentage drug release of code A after 45 min is 97.85% ± 5% in 0.1 N HCl, 87.94% ± 5% in phosphate buffer pH 5.8 and 96.85% ± 5% in phosphate buffer pH 6.8. The percentage drug release of code B after 45 min is 97.85% ± 5% in 0.1 N HCl, 91.03% ± 5% in pH 5.8 phosphate buffer and 94,23% ± 5% in pH 6.8 phosphate buffer. The percentage drug release of code C after 45 min is 99.43% ± 5% in 0.1 N HCl, 87.09 % ± 5% in phosphate buffer pH 5.8 and 95.43% ± 5%in phosphate buffer pH 6.8. The percentage drug release of tablet A after 120 min is 100.10% ± 5% in 0.1 N HCl, 87.94% ± 5% in phosphate buffer pH 5.8 and 96.85% ± 5% in phosphate buffer pH 6.8. The percentage drug release of tablet B after 120 min is 102.27% ± 5% in 0.1 N HCl, 98.05% ± 5% in phosphate buffer pH 5.8 and 101.27% ± 5% in phosphate buffer pH 6.8. The percentage drug release of tablet C after 120 min is 104.84% ± 5% in 0.1 N HCl, 98.32% ± 5% in phosphate buffer pH 5.8 and 96.84% ± 5% in phosphate buffer pH 6.8. All three brands of paracetamol tablets in three different media have passed the percentage drug release as per USP. They showed a slight variation in the percentage of drug release for all brands in three different media at different time points, even though all the results were within the limits.

Content uniformity:

30 tablets of code A, B and C tablets were selected randomly. Among them,10 tablets of each code were used for testing content uniformity. Powder the selected 10 tablets of each code and amount of powder is equivalent to 0.15gms of paracetamol was weighed exactly and dissolved in 15 ml of 0.1 N NaOH. Shake it for fifteen minutes, dilute up to 100 ml with the same. Shake it for a few minutes and keep aside for a few minutes of all three volumetric flasks of code A, B and C. Filter this primary stock solution. From thisprimary stock solution required dilutions were done in 0.1 N HCl, phosphate buffer Ph 5.8 and pH 6.8 for three codes of A, B and C paracetamol tablets. Measure the absorbance of the drug in 0.1 N HCl, phosphate buffer Ph 5.8 and phosphate buffer pH 6.8 for three codes of paracetamol tablets at 257nm[19]. According to USP the drug labelled content should not be less than 85% and not more than 115% (± 15%). If the above 10 tablets fail the test repeat the test with the other 20 tablets and none should deviate ± 25%.In this, the study content uniformity of three different codes of paracetamol was found to be 100% ± 5%. The content uniformity of code A was 100.10% ± 5% in 0.1 N HCl, 92.03% ± 5% in phosphate buffer pH 5.8 and 98.10% ± 5% in phosphate buffer pH 6.8. The content uniformity of code B was 99.48 % ± 5% in 0.1 N HCl, 95.48% ± 5% in pH 5.8 phosphate buffer and 97.48% ± 5% in pH 6.8 phosphate buffer. content uniformity of code c was 101.02% ± 5% in 0.1 NHCl, 97.02 % ± 5% in phosphate buffer pH5.8 and 102.02% ± 5% in phosphate buffer pH 6.8. USP specifications for content uniformity of paracetamol should not be less than 85% and should not be more than 115%.In this, the study content uniformity of three different codes of paracetamol was found to be 100% ± 5%. The content uniformity of all the three different codes of paracetamol tablets is within the limits as per USP.

Table 1: Post compression evaluation parameters.

Formulation code	Weight variation (mg) (n = 20) mean ±SD	Diameter (mm) (n = 20) mean ±SD	Thickness (mm) (n = 20) mean ±SD	Hardness (kg/cm²) (n = 5) mean ±SD	Friability (%) (n = 20) mean ±SD
A	106 ± 0.53	3.1 ± 0.63	4.5 ± 0.75	4.5 ± 0.31	0.22 ± 0.35
B	104 ± 0.23	8.1 ± 0.67	5.5 ± 0.63	4.3 ± 0.34	0.33 ± 0.45
C	102 ± 0.57	3.1 ± 0.78	4 ± 0.73	4.2 ± 0.38	0.36 ± 0.4

Statistical significance (p< 0.05)

Table 2: Evaluation of disintegration, content uniformity and percentage drug release in different media.

Formulation code	Disintegration time (min) (n = 6) mean ± SD			Content uniformity (%) (n = 10) mean ± SD			Percent drug release (%) (n = 6) mean ± SD		
	0.1 N HCl	pH 5.8	pH 6.8	0.1 N HCl	pH 5.8	pH 6.8	0.1 N HCl	pH 5.8	pH 6.8
A	8.5 ± 0.85	6.5 ±0.47	8.5 ±0. 57	100.10 ±0.87	92.03 ± 0.87	98.10 ± 0.65	101.20 ±0.87	95.98 ±0. 75	99.92 ±0.87
B	8.2 ± 0.86	8.6 ±0.57	7.6 ±0.87	99.48 ±0.78	95.48 ± 0.75	97.48 ± 0.76	102.27 ±0.78	98.05 ± 0.84	101.27 ± 0.76
C	8.7 ± 0.90	8.6 ±0.87	8.2 ±0.87	101.02 ±0.85	97.02 ± 0.78	102.02 ±0.86	103.84 ±0.76	98.32 ± 0.79	96.84 ±0.87

Statistical significance (p< 0.05)

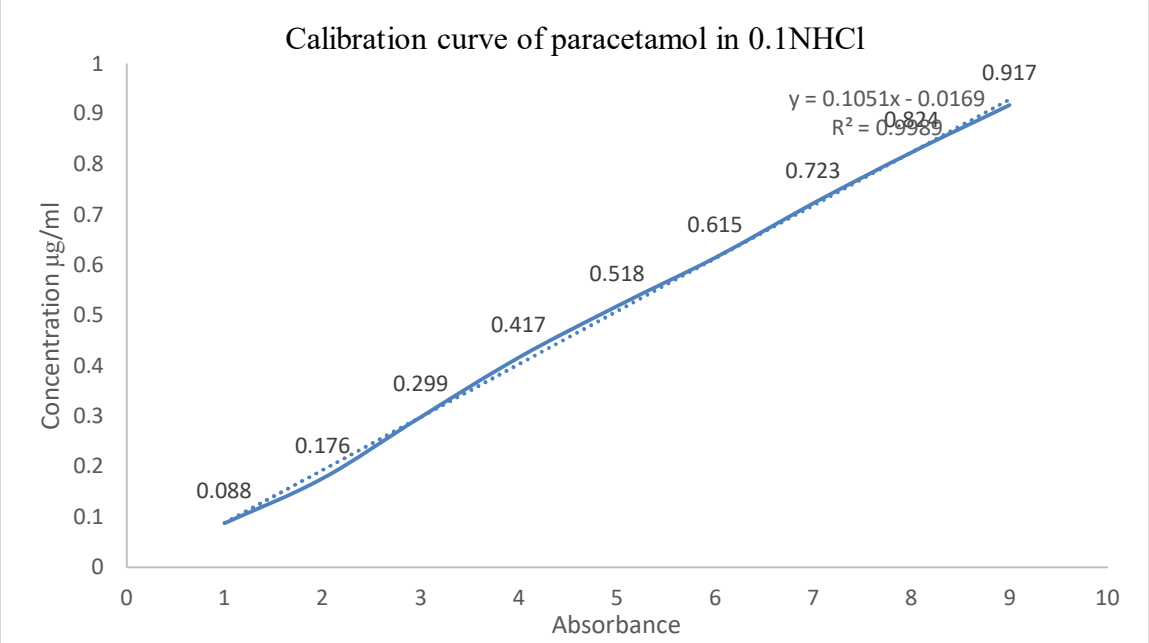

Figure1: Calibration Curve of Paracetamol in 0.1NHCl

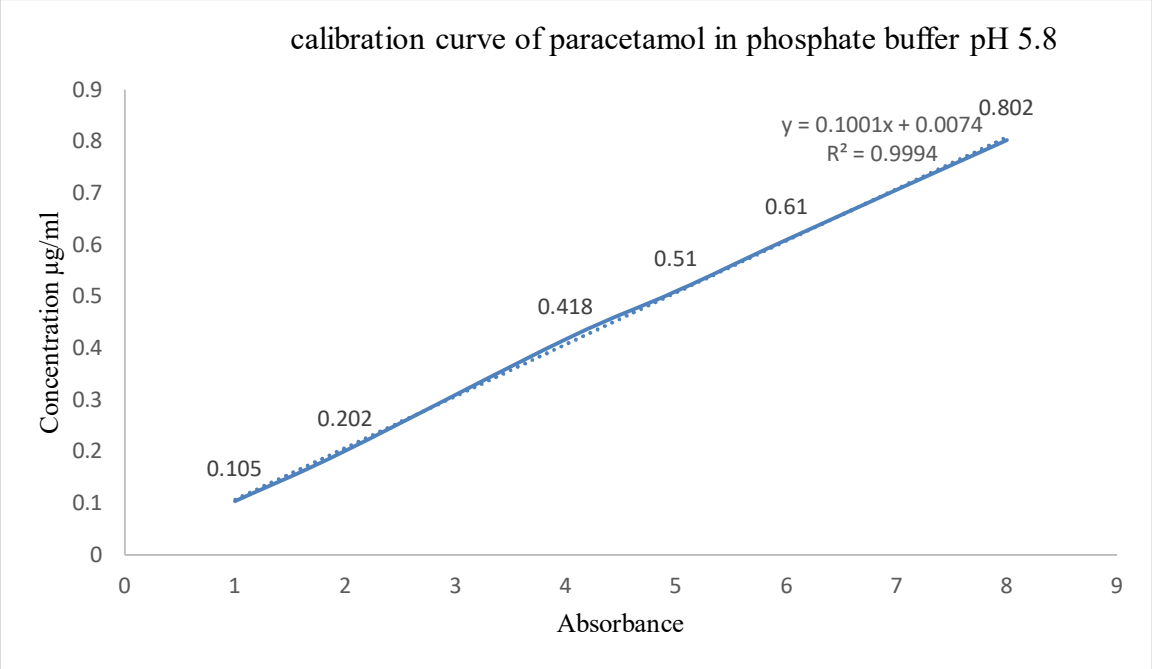

Figure2: Calibration Curve of Paracetamol in phosphate buffer pH 5.8

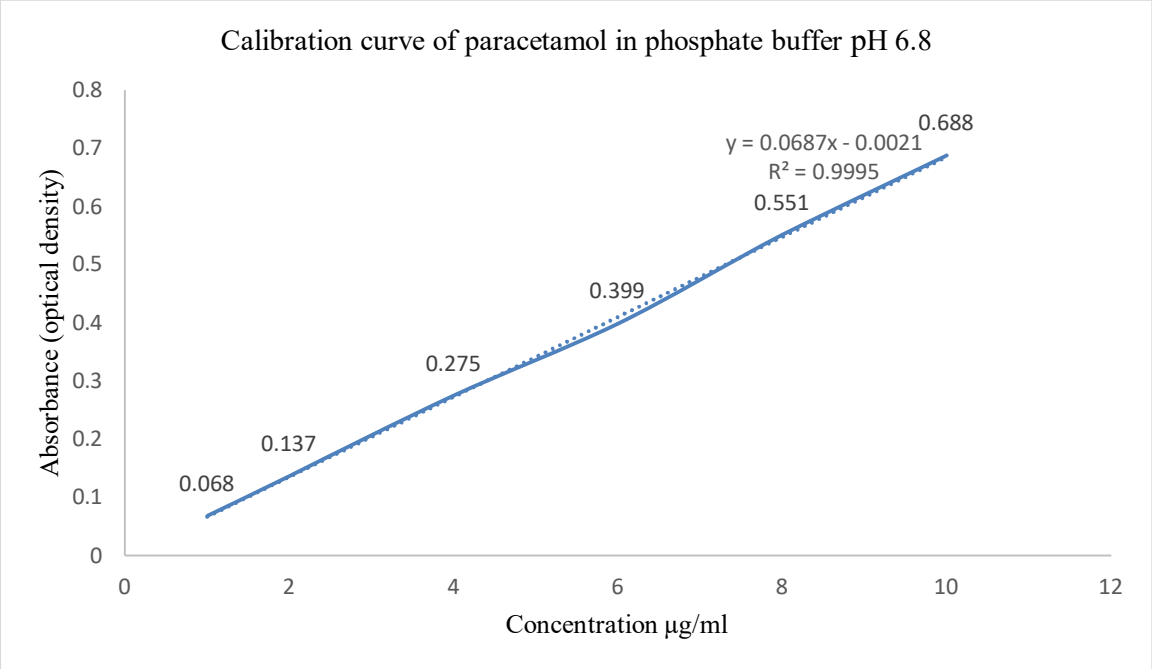

Figure3: Calibration Curve of Paracetamol in phosphate buffer pH 6.8

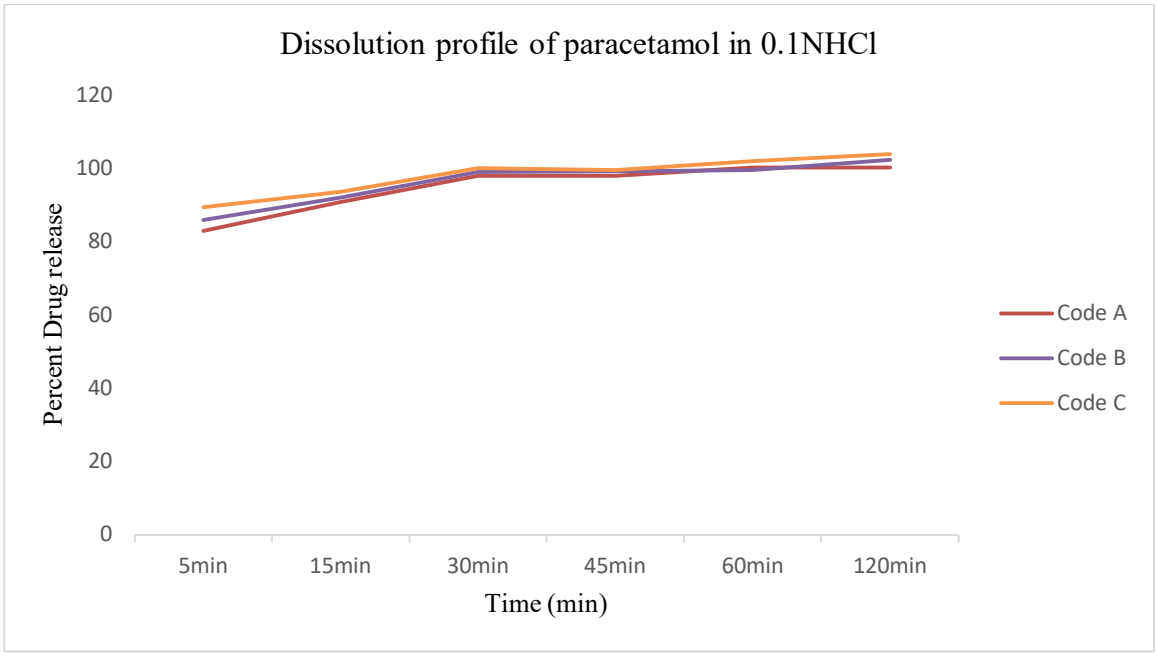

Figure 4: Dissolution profile of three different codes of paracetamol in 0.1NHCl.

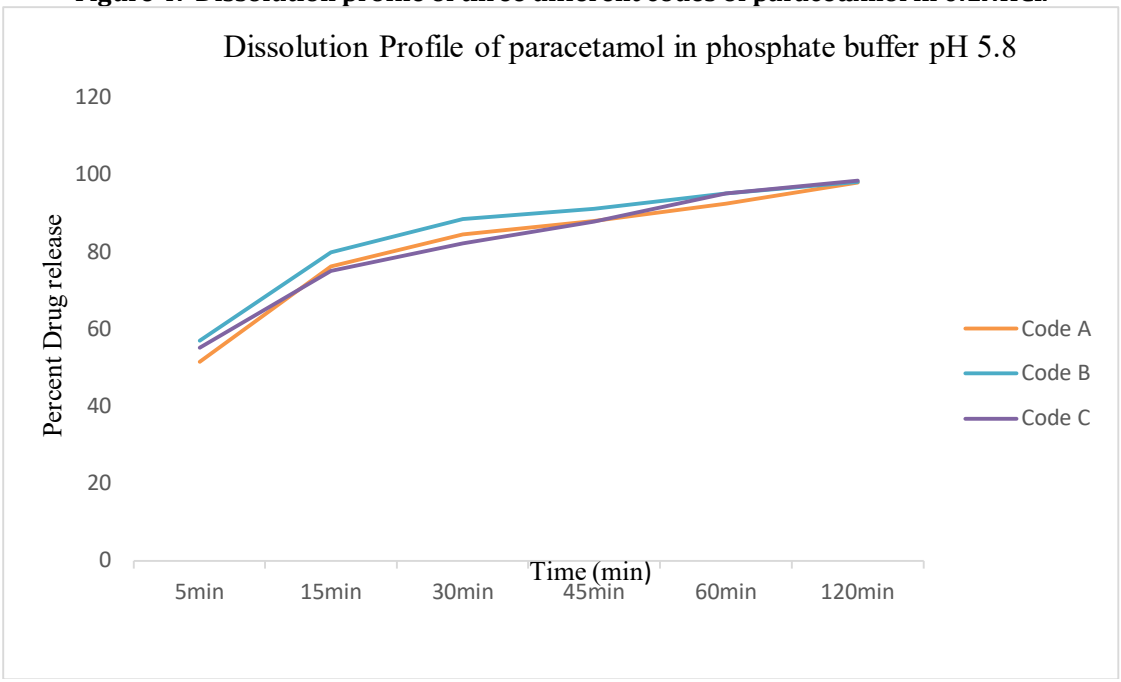

Figure 5: Dissolution profile of three different codes of paracetamol in phosphate buffer pH 5.8.

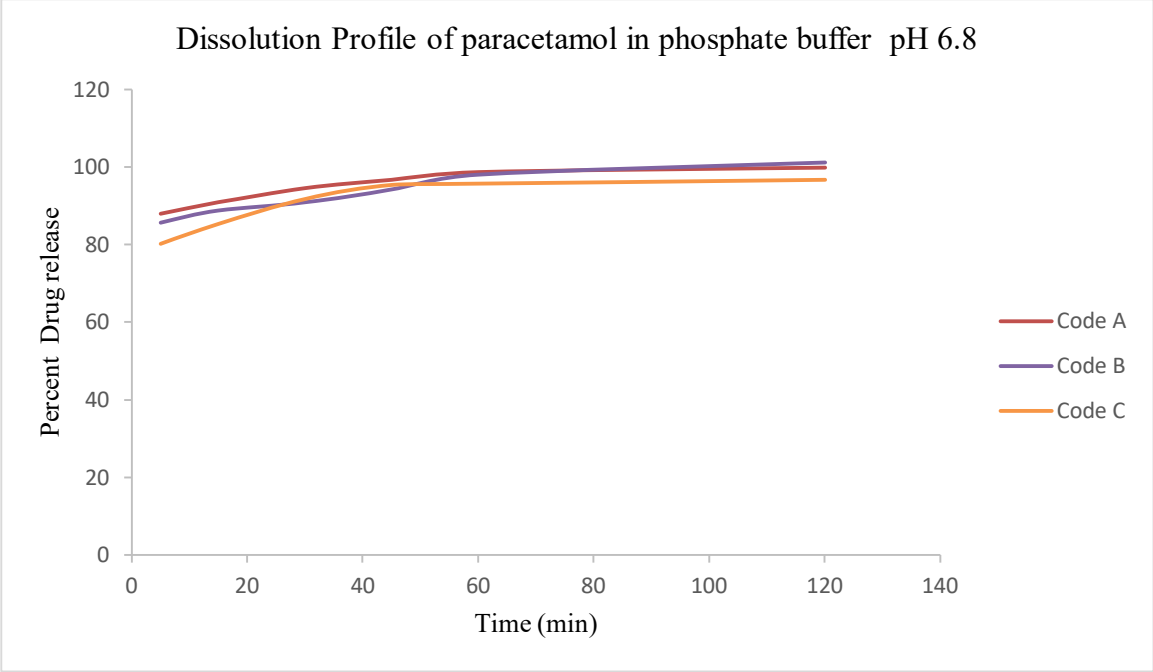

Figure 6: Dissolution profile of three different codes of paracetamol in phosphate buffer pH 6.8

CONCLUSION

Paracetamol is a proven analgesic and antipyretic drug. The therapeutic response of any type of formulation depends on the therapeutic response of a drug. From our study, we identified that all three different brands (codes A, B and C) of paracetamol tablets in three different types of media have qualified all quality control parameters of tablets and do not have any deviation according to standard values of USP. Anyway, these three different brands of paracetamol tablets coded as A, B and C have shown different results in disintegration, content uniformity and percentage drug release upon using three different types of media such as 0.1NHCl, Phosphate buffer pH5.8 and pH 6.8.Although the results varied slightly, still, they are within the acceptable limits of USP. For all the three codes of paracetamol, formulations had sufficient weight variation, diameter, thickness, hardness, friability as per USP.

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