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Original Article

In-Vitro Comparative Quality Evaluation of Paracetamol Tablets Marketed in Iraq

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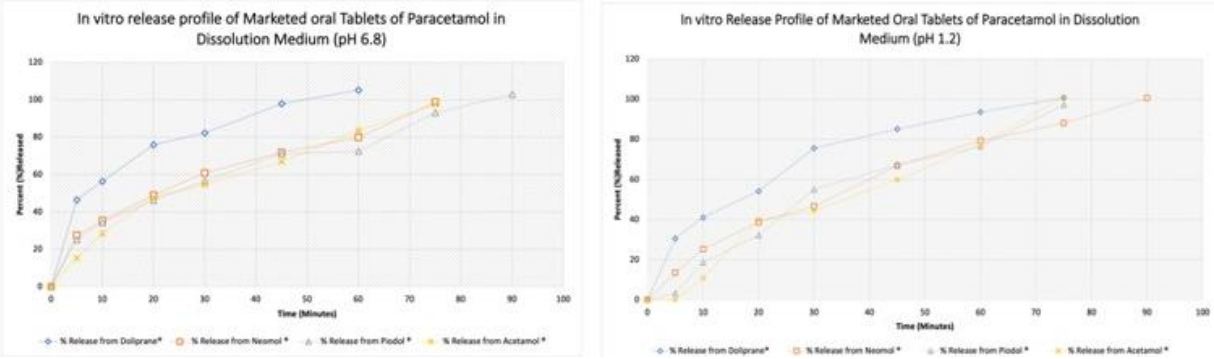
ABSTRACT

One of the crucial responsibilities of pharmacists is to provide Iraqi people with safe and effective medicines. Quality control tests have been performed to ensure that these medicines could meet acceptable standards of quality, efficacy, and safety. Paracetamol is an analgesic medication that is used very frequently; thus, this study aimed to quality evaluate different brands of paracetamol 500 mg tablets marketed in Iraq, four brands of paracetamol tablets were used in the study obtained from private pharmacies. Method: The selected paracetamol tablets were evaluated using standardized quality tests such as: weight variation, drug. Content uniformity, tablets hardness test, tablets friability, disintegration test, and dissolution test. Results: The tablets were assessed to check if they conform with the specifications of United States Pharmacopeia (USP). From the analysis of the results, it was observed that the weight variation showed an acceptable range. Drug content in all selected paracetamol tablets was found between96.8%-101.2%; it was within the specified 85%-115% standard range. Friability tests showed that all selected tablets were within USP's 1% mass loss limits. Doliprane and Neomol showed comparatively acceptable limits of hardness. All tablets disintegrated were within a time limit of less than 15 minutes. Additionally, an *in vitro* release study of the drug in 0.1 N HCl (pH 1.2) and phosphate buffer (Ph 6.8) exceeded 90% after 75 min. The FT-IR study showed that the main characteristic bands of FT-IR spectra for the active ingredient (paracetamol) were found in all-selected tablets and the FT- IR spectra of pure drug. This study concluded that all selected Paracetamol tablets were met pharmacopeial standards.

GRAPHICAL ABSTRACT



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Introduction

The healthcare status of the Iraqi people has become one of the most crucial concerns of the country. The quality control tests of medicines and pharmaceutical products have been performed to ensure that these medicines could meet acceptable standards of quality, efficacy, and safety [1]. The Food and Drug Administration (FDA) constrains pharmaceutical manufacturers to employ a fixed manufacturing process, with specifications that are essential not only in quality confirming of products but because it could be capable of identifying variances batch to batch that may possibly have therapeutic consequences [2]. In Iraq, the responsibility of pharmaceutical quality control is upon the National Center for Drug Control and Research (NCDCR), recognized as the National Drug Control Laboratory (NDQCL) too [3]. Recently, many educational institutions have employed their capabilities and resources to contribute to the pharmaceutical evaluation process and provide the national database with many valuable studies.

Paracetamol (N-acetyl-p-aminophenol) else, identified as (Acetaminophen), is the active pharmaceutical ingredient of many pharmaceutical formulations. Paracetamol-containing pharmaceutical products are increasingly dispensed with or without prescription to alleviate mild-moderate pain and reduce fever [4]. Paracetamol is available in the market in diverse dosage forms such as; injectable intravenous and intramuscular preparations, rectal suppository and oral (solid tablet, and capsule), and (liquid syrups and suspensions) [5]. The oral dosage forms are the most convenient route of drug administration due to easiness of administration, lesser cost of production, elevated patient compliance, and other beneficial characteristics in the formulation and stability [6].

Furthermore, among solid oral dosage forms, tablets are the most widely used due to their self-administration, ease of handling, transportation, stability, dosing precision, efficient manufacturing process, and good patient compliance [7]. Tablets could be manufactured by various methods, though they are mostly made by applying compression [8]; the formulation factors and inactive ingredients could predominantly affect the dissolution and disintegration profile and other quality parameters of tablets [9]. This study aimed to evaluate quality control considerations for commercial paracetamol tablets in Iraq. The different brands of paracetamol 500 mg tablets were obtained from private pharmacies. Four brands of paracetamol tablets were used in the study.

Martials and Methods

Pure paracetamol powder obtained from Shanghai pharmaceuticals technology Co., Ltd, China. Potassium di-hydrogen orthophosphate was purchased from BDH Laboratory supplies, U.K. Disodium hydrogen phosphate was purchased from CDH fine chemicals, India. HCl Hydrochloric acid was obtained from Thomas Baker, India.

Paracetamol tablets were selected from four different companies. The selected marketed paracetamol named Doliprane 500 mg (Sanofi®), Neomol 500 mg (Neopharma®), Piodol 500 mg (Pioneer®), and Acetamol 500 mg (Al-Fayhaa pharmaceutical industry®). Distilled water and other materials used were of analytical grade.

Characterization of paracetamol

Determination of paracetamol melting point

Melting point determination for pure raw paracetamol powder was conducted to recognize solid crystalline ingredients and to determine their purity; The melting point of paracetamol was determined by tapping a small amount of paracetamol powder into a capillary glass tube, which is was then placed inside a melting point apparatus (STUART SM20, U.K). The gradual uprising of temperature had been combined with closed observation to determine the point at which all powder particles converted into liquid. The melting point will be attained at the temperature at which the drug powder particles all transformed into liquid 10. The melting point obtained was then compared with the reference value (169-172 °C) [11].

Paracetamol UV-spectroscopy analysis

Preparation of buffer solutions

pH (6.8) phosphate buffer was prepared by mixing two solutions. Solution (A) was prepared by dissolving 9.073 g of potassium dihydrogen phosphate in sufficient distilled water to make one litter solution. Solution (B) was prepared by dissolving 11.87 g of disodium hydrogen phosphate (dihydrate) in an adequate quantity of distilled to make one litter solution.

The solution of phosphate buffer pH 6.8 was then prepared by mixing 534 mL from solution A with 466 mL from solution B, and the pH was checked by a pH meter.

A solution of 0.1 N HCl pH (1.2) was prepared by diluting the calculated volume of concentrated HCl with distilled water to the required volume [12].

Determination of paracetamol λ

Stock solution (100 µg/mL) was prepared by dissolving (10 mg) of paracetamol in 100 mL of each 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8). medium. Suitable dilutions were prepared from the stock solution to prepare a series of drug solutions in the investigated media. The prepared solutions were scanned in the ultraviolet wavelength region (200-400 nm) to determine the wavelength of maximum absorption (λ) of paracetamol in each medium [13].

Construction of standard calibration curves of paracetamol

Calibration curves of paracetamol in phosphate buffer of (pH 6.8), 0.1 N HCl (pH 1.2), and ethanol were made separately by preparing a serial of dilutions of different concentrations of paracetamol [1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (mg/mL)] for from a stock solution (100 µg/mL) of paracetamol in one of the above media. The absorbance was then measured at the λ_{max} of the drug. The measured absorbencies were plotted versus the consequent concentrations to get a calibration curve [14].

Evaluation tests for the chosen products

Weight variation test of paracetamol tablets

Twenty tablets were randomly selected from the marketed products. The selected tablets were weighed separately by an analytical balance (Model: adventure (AX324), (WTB 200)). The average weights were recorded. Then, the percentage and standard deviations from mean values were calculated. The individual tablets were compared with the upper and lower limits.

$$Upper\ limit = \text{Average weight} + \{\text{average weight} \times \%\ \text{error}\}$$
$$Lower\ limit = \text{Average weight} - \{\text{average weight} \times \%\ \text{error}\}$$

For a tablet to be accepted, not more than two tablets differ from the weight difference range, and no tablet differs by more than double the percent [15].

Paracetamol Content Determination

Twenty tablets from each of the four brands, then ten tablets were weighed individually with an analytical balance (Model: adventure (AX324), (WTB 200)). Each tablet was transferred to a 100mL volumetric flask, and about 70 mL ethanol was added. An ultrasonic bath was used to disperse the tablet in ethanol. After that, the volume of dispersion in ethanol was completed to 100mL. Dispersion of tablet in ethanol was mixed, then centrifuged. A precisely measured volume of the clear supernatant with ethanol was analysed spectrophotometrically at the detected λ_{max} [16].

Hardness test of paracetamol tablets

Tablet hardness testers function on the principle that it yields a definite extent of force to break down a tablet. An automatic tablet hardness tester (ERWEKA Hardness Tester) was used to establish the destructive strength. The force required to crush each tablet was recorded for ten tablets from each company [15].

Friability test of paracetamol tablets

The friability test was completed using the ERWEKA friability tester. Twenty tablets were selected randomly and weighed, then placed together in the friabilator device. All tablets were subjected to the combined effect of abrasion and

shocks. The plastic chamber of the instrument was adjusted to revolve at a speed of 25 rpm for 4 minutes. The 20 tablets were collected, and the dust and remnant were removed by a brush and then weighed to obtain the final weight. Friability percent is obtained by the following equation: [15].

$$\%\ \text{of weight loss}\ (\%\text{Loss}) = 100 * \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \quad \text{Eq2}$$

Disintegration test of paracetamol tablets

The disintegration test apparatus (ERWEKA, Germany) was used to determine the disintegration time of the selected tablets. It normally contains a basket rack involving six open-ended tubes. Six tablets were placed in these six tubes and covered with a specific disk. a stainless-steel mesh screen basket was positioned in simulated gastric fluid (pH 1.2) at 37±2 °C. The tablets are placed in a basket that remains 2.5 cm below the surface of simulated gastric fluid on the upward movement and descend not closer than 2.5 cm from the bottom of the beaker. The motor-aid movement of the basket assembly holding the tablets up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. Accordingly, the time needed to finish the disappearance of the pill from the glass tube was documented [17].

Dissolution test of paracetamol tablets

Dissolution is essential in determining the bioavailability of a drug. The dissolution test method was developed and validated for paracetamol tablet dosage from quality control. In the present study, the *in vitro* dissolution study of paracetamol tablets was done in simulated gastric fluid pH 1.2 and simulated intestinal fluid pH6.8. Dissolution tests for paracetamol were performed using the USP paddle method (Apparatus II) at a speed of 50 rpm. The volume of the dissolution medium in each vessel was 900 mL. The medium was maintained at 37±0.5°C. In all the experiments, 5 mL of dissolution sample using a 5 mL syringe was taken at 5, 10, 20, 30, 45-, 60-, 75-, and 90-min. The sample volume should be substituted with an equal volume of fresh dissolution medium to maintain sink condition. Samples were filtered using a filter syringe and examined by UV-visible to determine the concentration [6].

Fourier-transform infrared spectroscopy (FT-IR)

The infrared light absorbance by the substance was measured, and the IR spectrum was represented by a graph presenting the intensity of absorbed spectra on the vertical axis and the frequency (wavelength) on the horizontal axis. Identification of the drug and compatibility with other constituents in the selected marketed tablets was tested. FTIR spectroscopy was performed at ambient temperature for pure drug powder and crushed mixtures from the selected tablets. The pure drug and each tablet dosage form were scanned separately with infrared (IR) and investigated from 4000-400 cm^{-1} [18, 19].

Results and Discussion

Characterization of paracetamol

Determination of paracetamol melting point

The melting point of paracetamol was determined by a digital SMP10 (UK) melting Point apparatus. The particular melting point identified from this test in triplicate was (169 °C) ± 1 S.D, which is in the same reported range in the approved sources. This indicates the purity of the drug powder used in this study [20].

Paracetamol UV-spectroscopy analysis

Determination of paracetamol λ_{max}

The UV spectrum of paracetamol of 10 mg/mL of drug in (0.1 N) HCl (pH 1.2) and phosphate buffer solution (pH 6.8) was obtained with a wavelength of maximum absorption (λ) at 243 nm in 0.1 N HCl and Ethanol 70%. In contrast, paracetamol wavelength of maximum absorption (λ) at 374nm in phosphate buffer (pH 6.8) comes in concours with what is mentioned in references [21–23].

Construction of standard calibration curves of paracetamol

Calibration curves of paracetamol in phosphate buffer of (pH 6.8), 0.1 N HCl (pH 1.2) and ethanol

were made separately by preparing a serial of dilutions of different concentrations of paracetamol [1, 2, 3, 4, 5, 6, 7, 8, 9, 10 (mcg/mL)] for from a stock solutions (100 µg/mL) of paracetamol [23].

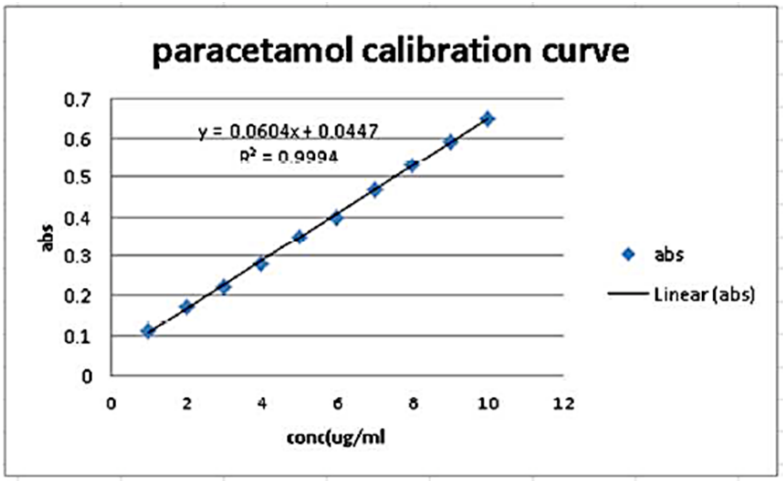

Figure 1: Calibration curve of pure paracetamol in pH 1.2

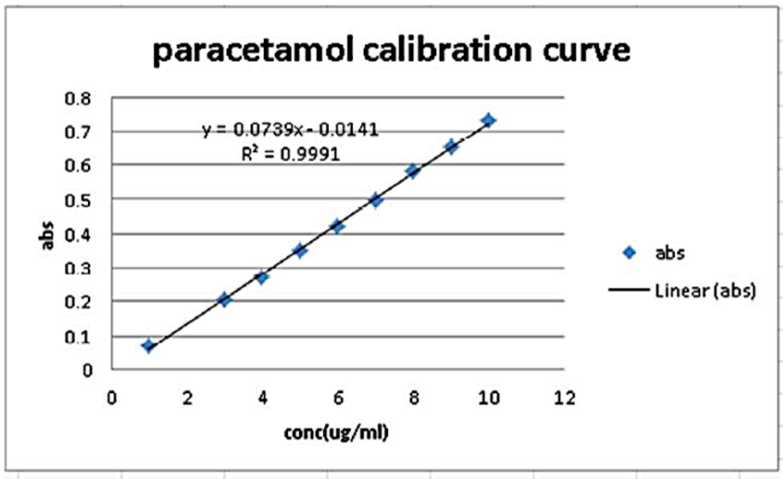

Figure 2: Calibration curve of pure paracetamol in phosphate buffer pH 6.8

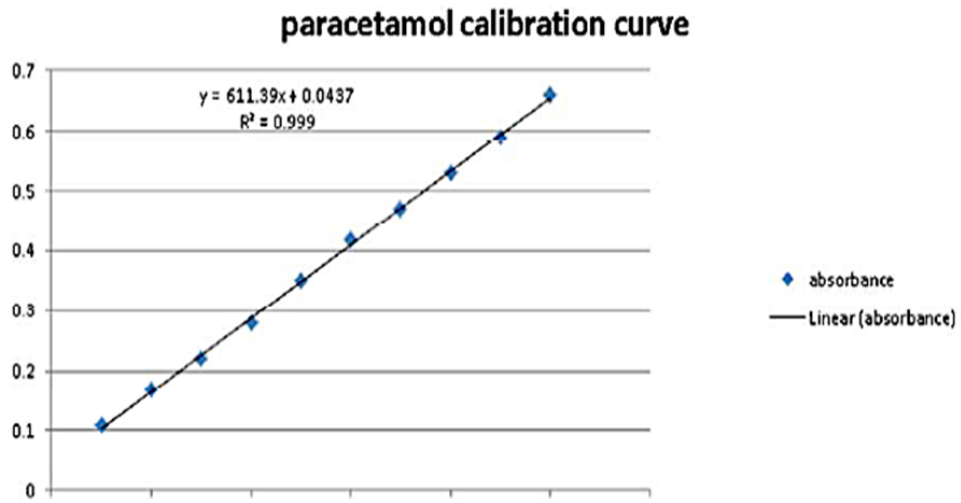

Figure 3: Calibration curve of pure paracetamol in ethanol 70% conc (ng/mL)

Paracetamol calibration curves in 0.1 N HCl, phosphate buffer pH6.8 and ethanol 70% was presented in the following: Figure 1, Figure 2, and Figure 3, respectively; these figures were obtained by plotting UV absorbance of paracetamol in each medium versus the concentration used. A straight line was achieved in each curve with high regression (R^2), revealing that the obtained calibration curve of paracetamol in each medium obeys Beers-Lambert law within the concentration of paracetamol used [24].

Evaluation tests for the chosen products

Weight variation test of paracetamol tablets

All results for the weight variation test of the four marketed products from different companies are documented in Table 1. The weight variation test of the tablet is used to confirm that the prepared tablet has the accurate amount of active drug in which no more than two tablets are outside the percentage limit. The results indicate a weight uniformity in the selected tablets and all tablets within the usual range, and no one exceeds the allowed percent [25].

Paracetamol Content Determination (Content Uniformity)

Percentages of content uniformity tests for selected paracetamol tablets where are shown in Table 2. The percentage range for all selected marketed tablets was found to be between 96.8% and 101.2%. In content uniformity testing for selected tablets, each individual content was within the limits range of the average content; therefore, all the selected tablets passed the uniformity of content test [15].

Table 1: Weight variation test of selected paracetamol tablets

Tablet	Doliprane Weight (mg)	Neomol Weight (mg)	Piodol Weight (mg)	Acetamol Weight(mg)
1	545	619	545	632
2	549	611	549	643
3	547	623	547	648
4	546	616	546	631
1	545	619	545	632
2	549	611	549	643
3	547	623	547	648
4	546	616	546	631
5	545	619	545	632
6	549	611	549	643
7	547	623	547	648
8	546	616	546	631
9	545	619	545	632
10	549	611	549	643
11	547	623	547	648
12	546	616	546	631
13	545	619	545	632
14	549	611	549	643
15	547	623	547	648
16	546	616	546	631
Average ±SD	545.5±0.05	618±0.05	549.6±0.05	638±0.05

Table 2: Content uniformity of selected paracetamol tablets

	Doliprane (500 mg)		Neomol (500 mg)		Piodol (500 mg)		Acetamol (500 mg)	
	Drug Content (mg)	Percentages of Drug	Drug Content (mg)	Percentages of Drug	Drug Content (mg)	Percentages of Drug	Drug Content (mg)	Percentages of Drug
1	502	100.4	499	99.8	505	101	492	98.4
2	499	99.8	500.9	100.18	498	99.6	484	96.8
3	504	100.8	497	99.4	506	101.2	499	99.8
4	500	100	496	99.2	502	100.4	496	99.2
5	497	99.4	494	98.8	497	99.4	502	100.4
6	502	100.4	499	99.8	504	100.8	504	100.8
7	504	100.8	487	97.4	498	99.6	492	98.4
8	499	99.8	497	99.4	506	101.2	486	97.2
9	500.9	100.18	492	98.4	489	97.8	489	97.8
10	502	100.4	500.9	100.18	502	100.4	502	100.4
x_m	500.99 mg		496.28 mg		500.7 mg		494.6 mg	
S.D	±2.260998		±4.323527		±5.313505		±7.0742	
RSD	0.451306		0.871187		1.061215		1.43028	

Hardness test of paracetamol tablets

Sufficient tablet hardness is essential to ensure destruction resistance to endure mechanical shocks during production, packaging, and transportation. In addition, tablets should be able to tolerate reasonable mishandling by the consumer. The harness test results tabulated in Table 3 show that most paracetamol brands exhibited hardness within the objectionable range. Sanofi® and Neopharma ® products showed a comparatively acceptable standard deviation of their hardness (86.7 and 154.7, respectively). However, using different excipients or the same excipients in different ratios might be one of the reasons for the observed differences in hardness value among the samples; however, the deviation between tablet to tablet in the same brand was unexpected and needed more investigation [26].

Friability test of paracetamol tablets

Tablets must resist corrosion when subjected to tensions from collision and tablet slip towards one another and other solid bodies, which can result in removing small pieces from the tablet surface. It is usually measured by a friability tester. In the friability test, the friability values for paracetamol tablet brands ranged from 0.194 to 0.781%. All four brands of paracetamol have passed the friability test and met the USP specification, which specifies that any brand must not lose more than 1% of its initial weight [15] (presented in Table 4 below). The result may further suggest the resistance of the tablets to external forces from manufacturing, distributing, and shipping. At the same time, high tablet strength should not interfere with the disintegration than the dissolution of the drug in the stomach [15].

Table 3: Hardness test of selected paracetamol tablets

	Thickness (mm)	Diameter (mm)	Hardness (Newton N)
Doliprane	6.44	11.3	87
	6.41	11.4	90
	6.39	11.2	79
	6.45	11.5	85
	6.44	11.2	75
	6.42	11.1	88
	6.41	11.4	95
	6.45	11.5	101
	6.38	11.3	85
	6.42	11.4	82
Avarge±S.D	6.421 ± 0.0242	11.33 ± 0.1337	86.7 ±7.5284
Neomol	5.22	8.61	155
	5.25	8.55	158
	5.31	8.58	147
	5.21	8.62	153
	5.29	8.53	143
	5.32	8.49	156
	5.19	8.55	163
	5.22	8.52	169
	5.23	8.53	153
	5.28	8.58	150
Avarge±S.D	5.252±0.0451	8.556±0.0411	154.7±7.5284
Piodol	5.52	8.03	More than 250
	5.55	7.97	248
	5.61	8.01	More than 250
	5.51	8.04	239
	5.59	7.95	More than 250
	5.62	7.91	More than 250
	5.49	7.97	245
	5.52	7.94	246
	5.53	7.95	More than 250
	5.58	8.01	238
Avarge±S.D	5.552 ±0.0451	7.978 ±0.0426	243.2
Acetamol	5.74	9.02	More than 250
	5.77	8.96	More than 250
	5.83	9.01	248
	5.73	9.03	More than 250
	5.81	8.94	More than 250
	5.84	8.9	246
	5.71	8.96	More than 250
	5.74	8.93	249
	5.75	8.94	More than 250
	5.81	9.01	248
Avarge±S.D	5.773±0.0459	8.97 ±0.0445	247.75

Table 4: Friability test of selected paracetamol tablet

Paracetamol Tablet Product	% Weight loss
Doliprane	0.194%
Neomol	0.162%
Piodol	0.544%
Acetamol	0.781%

Disintegration test of paracetamol tablets

Disintegration test of paracetamol tablets is the devastation process of the tablet into smaller particles when it becomes in contact with body fluid and is the first step towards the dissolution process; this test simulates the disintegration time of the medication in the human body. The official requirement in the USP disintegration test is that uncoated tablets should disintegrate in less than 30 minutes [15]. As shown in Table 5, the disintegration time ranges from 1.31 to 6.15 minutes. Hence, all samples comply with the USP requirements. Literature supports the direct relationship between hardness and disintegration time, which was observed in this study [27].

FT-IR (Fourier-transform infrared spectroscopy)

Infrared spectroscopy is one of the essential means for the identification of the chemical compound. It is often used to identify the drug in most pharmaceutical preparations [27]. The spectrum of pure paracetamol powder and paracetamol tablets from each company has been represented below (Figure 4, Figure 5). The assignment of the IR absorption band to the corresponding functional group is represented in the following (Table 6) [28, 29].

Table 5: Disintegration time of 6 tablets for each company

Tablet	Doliprane Disintegration time (Minutes)	Neomol Disintegration time (Minutes)	Piodol Disintegration time (Minutes)	Acetamol Disintegration time (Minutes)
1	1.32	3.61	6.15	5.42
2	1.33	3.57	6.13	5.43
3	1.29	3.55	6.20	5.41
4	1.32	3.60	6.17	5.46
5	1.30	3.54	6.12	5.60
6	1.31	3.62	6.15	5.59
Average	1.31	3.58	6.15	5.48

Table 6: The assignment of the IR absorption band to the corresponding functional group of pure paracetamol powder and paracetamol tablets from each company

Band	Pure Paracetamol	Doliprane	Neomol	Piodol	Acetamol
O- H Vibrational	3317 cm^{-1}	3317cm^{-1}	3318cm^{-1}	3318cm^{-1}	3318cm^{-1}
C-H Stretching (CH_3)	3107 cm^{-1} 3049 cm^{-1}	3154cm^{-1} 3050cm^{-1}	3154cm^{-1} 3050 cm^{-1}	3154cm^{-1} 3050cm^{-1}	3154cm^{-1} 3050cm^{-1}
C=O Stretching	1647 cm^{-1}	1647cm^{-1}	1648cm^{-1}	1648cm^{-1}	1648cm^{-1}
C=C Stretching	1609 cm^{-1}	1609 cm^{-1}	1609 cm^{-1}	1609 cm^{-1}	1610 cm^{-1}
N- H Bending (amide II)	1557 cm^{-1}	1558 cm^{-1}	1558 cm^{-1}	1558 cm^{-1}	1558 cm^{-1}
C-H Asymmetrical bending	1502 cm^{-1}	1503 cm^{-1}	1503 cm^{-1}	1503 cm^{-1}	1503 cm^{-1}
C-C Stretching	1432 cm^{-1}	1433 cm^{-1}	1433 cm^{-1}	1433 cm^{-1}	1433 cm^{-1}
C-H Stretching(aryl)	1367cm^{-1} 1321cm^{-1}	1368 cm^{-1} 1322cm^{-1}	1368cm^{-1} 1323cm^{-1}	1369 cm^{-1} 1323cm^{-1}	1369 cm^{-1} 1323cm^{-1}
C-N Stretching(aryl)	1242cm^{-1}	1225 cm^{-1}	1226 cm^{-1}	1226 cm^{-1}	1226 cm^{-1}
C-O Stretching	1108cm^{-1}	1108 cm^{-1}	1107cm^{-1}	1108 cm^{-1}	1107cm^{-1}
C-N Stretching(amide)	965 cm^{-1}	967 cm^{-1}	967 cm^{-1}	965 cm^{-1}	967 cm^{-1}
Para-disubstituted aromatic ring Vibrational	836 cm^{-1}	837cm^{-1}	837cm^{-1}	837cm^{-1}	837cm^{-1}

Dissolution test of paracetamol tablets

Dissolution was an important quality control concern directly associated with the drug absorption and bioavailability [30]. The percentages of drug release after one hour in 0.1 N HCl (pH 1.2) were 93.6%,79.3%, 76.5% and 77.4% from Doliprane 500 mg (Sanofi®), Neomol 500 mg (Neopharma ®), Piodol 500 mg (Pioneer®) and Acetamol 500 mg (Al fayhaa Pharmaceutical industry ®) respectively. From drug release profiles, it was found that Doliprane 500 mg (Sanofi®) showed the highest drug release compared to others. The results of the test are shown in Figure 4. The study showed that the release rate of the drug from Doliprane 500 mg at different time intervals was better. The same results were observed in phosphate buffer pH 6.8 since they exhibited 105.1%, 79.8%, 72.5%, and 83.5 of drug release after one hour from Doliprane500mg (Sanofi®), Neomol 500mg (Neopharma ®), Piodol 500 mg (Pioneer®) and Acetamol 500 mg (Al fayhaa Pharmaceutical industry ®) respectively as seen in Figure 5.

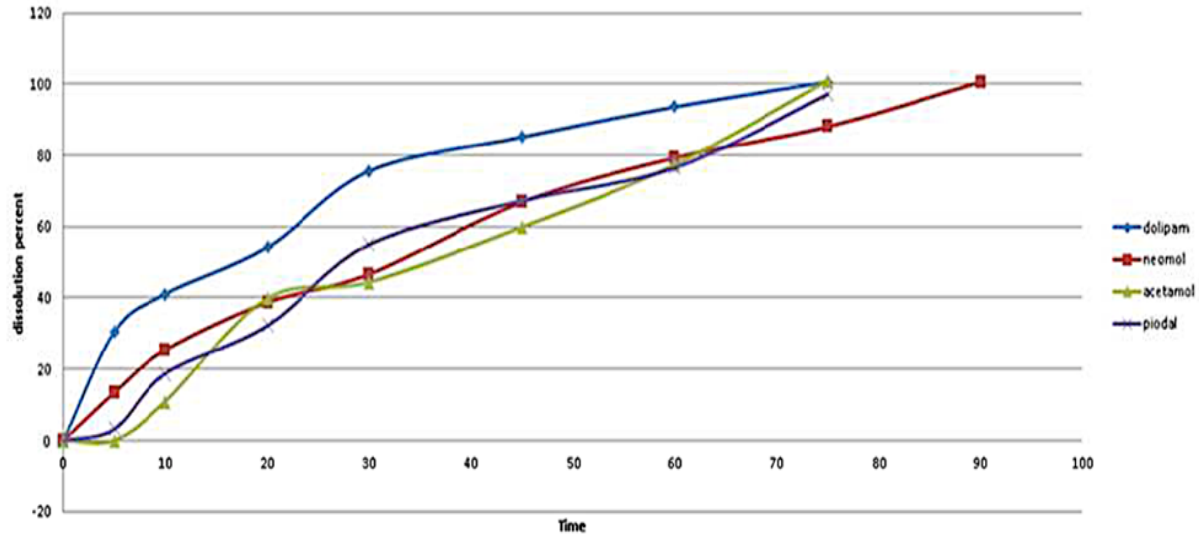

Figure 4: In vitro Release Profile of Marketed Oral Tablets of Paracetamol in Dissolution Medium (pH 1.2)

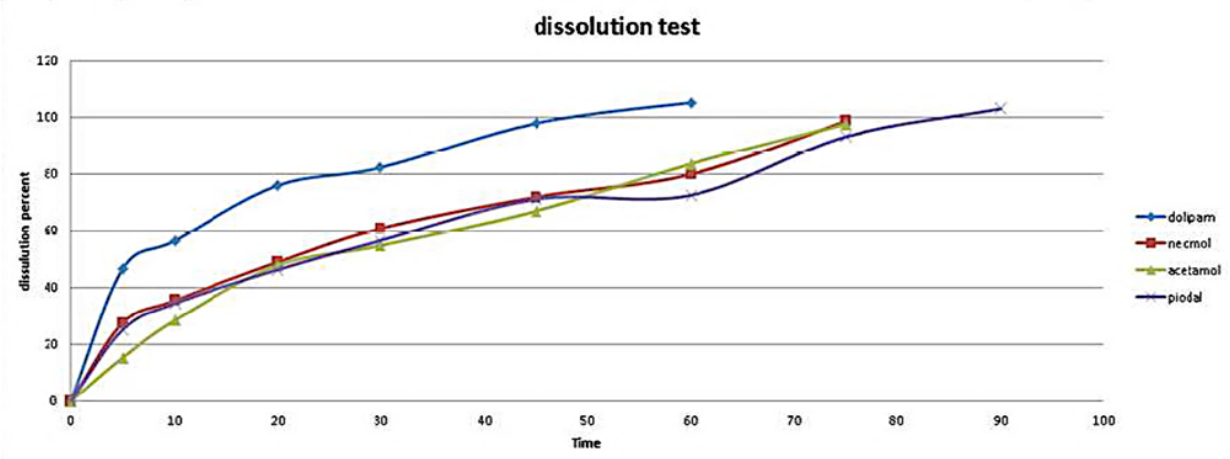

Figure 5: In vitro release profile of Marketed oral Tablets of Paracetamol in Dissolution Medium (pH 6.8)

Conclusion

The results of this study showed that all brands of paracetamol 500 mg oral tablets conformed to the official specification of standard pharmacopeia. All tablets disintegrated within a time limit of less than 15 minutes. An *in vitro* release study of the drug in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) exceeded 90% after 75 min. The FT-IR study showed that the main characteristic bands of FTIR spectra for the active ingredient (paracetamol) were found in

all-selected tablets and in the FT- IR spectra of pure drugs. According to the outcomes of this study, there were no deviations from pharmacopeia standards.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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Supporting Information

Copies of FT-IR spectra of Pure Paracetamol, Doliprane (Sanofi®), Neomol (Neopharma®), Acetamol (Al-fayhaa pharmaceutical), Piodol (Pioneer®) [PDF].

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