Assay of paracetamol tablets from different manufacturing sources in Sulaimani market in Iraq

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Abstract

Background: Paracetamol is a common analgesic and antipyretic drug that is marketed individually or as in combination with other drugs. Tablets produced by different manufacturers can have different physical and chemical properties due to the usage of different excipients and manufacturing methods.

Objective: This research was conducted to study ten different paracetamol brands commercially available in the city of Sulaimani to compare their content percentage, dissolution profile and friability.

Patients and Methods: The tablet content assay in this research was conducted using a method stated by the Indian pharmacopeia, while dissolution and friability test methods were derived from the United States Pharmacopeia. A total of ten brands of paracetamol (three local and seven international) were chosen for this study.

Results: All of the tested brands had their active ingredient content within the specified limits of 95%-105%. Regarding dissolution test, all the studied tablets showed a dissolution yield of more than 80% within 30 minutes with the tablets manufactured by GlaxoSmithKline showing the fastest dissolution rate. All the tablets had an acceptable weight loss of less than 1% after applying the friability test but the tablets manufactured by Samaraa have shown the highest friability of 0.34%.

Conclusion: It was concluded that all of the tested products which are available in Iraqi market/City of Sulaimani meet the requirements specified by United States Pharmacopeia in terms of content assay, dissolution rate and friability.

Key words: Paracetamol, content assay, dissolution test, friability test.

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Introduction

Paracetamol is a non-opiate analgesic agent that is considered to be the most popular over the counter painkiller and is frequently included in anti-flu remedies[1][2]. It is also used as a first choice treatment for mild to moderate Osteoarthritis [3]. Chemically, paracetamol (also known as acetaminophen) is a derivative of aniline and is named is 4-hydroxy acetanilide [4]. It exerts its action by inhibition of prostaglandin synthesis in the CNS through inhibition of cyclo-oxygenase (COX) enzyme which is responsible for converting arachidonic acid into prostaglandin [5][6].Consequently

Nerve endings will not be sensitized to histamine and bradykinin and there will be a reduction in pain sensation [7]. Inhibition of cyclo-oxygenase in the brain would lower body temperature by impeding prostaglandins synthesis and minimizing their effect on the anterior hypothalamic thermoregulatory center, this gives rise to paracetamol antipyretic properties [8].

Paracetamol offers major advantages over other analgesics as it neither cause gastric irritation as in NSAID's, nor it causes Respiratory depression as in opiates [9]. Even though it is considered to be safe in comparison to NSAID's; an overdose of paracetamol (more than 4g) can cause severe hepatitis [10]. This is believed to be caused by depletion of glutathione followed by formation of N-acetyl-p-benzoquinone imine (NAPQI) which reacts with sulfhydryl groups of hepatic proteins, forming covalent bonds and resulting in Hepatotoxicity [11][12].

Oral Administration is the most convenient route of drug delivery, with tablets and capsules being the mainstay of oral dosage forms [13][14].Different generic and brand forms of paractemol tablets are available worldwide. Despite the fact that these tablets are said contain the same amount of active ingredient; they can have different bioavailability and therapeutic profile[15]. This occurs mainly due to variation in manufacturing processes and the usage of different excipients [16]. Such differences in bioavailability can be evaluated by conducting dissolution tests which is considered to be one of the most important quality control tests [17]. Dissolution test can be achieved using: basket apparatus, paddle apparatus, reciprocating cylinder and flow-through apparatus [18].

Another important quality control test that can be applied to tablets is content assay. Variation in tablet content can occur due to failure in preparation techniques such as compression methods or due to defects in Machinery [19].Over the recent years, several methods have been developed to determine paracetamol concentration in different pharmaceutical preparation; these include titrimetry, chromatography and spectroscopy [20][21][22][23]. According to The United States pharmacopeia the tablet content assay is achieved by using high performance liquid chromatography (HPLC), while the Indian pharmacopeia describes a different method that involves utilizing UV-VISspectrophotometry [24][25]. On the other hand, the British pharmacopeia offers several methods that include: cerium sulphate titrimetry, high performance liquid chromatography and UV-VIS spectrophotometry [26].

Furthermore, Tablets can be tested for their friability which can be defined as the percentage of tablet weight that can be lost after sustaining mechanical stress throughout manufacturing, packaging and transportation [27].

The main goal of this study is to test and compare paracetamol tablets available in Iraqi market that are produced by local and international manufacturers to determine whether or not they comply with standards set by the United States Pharmacopeia.

Patients and Methods

Chemicals and samples

All reagents and materials were provided by school of pharmacy/ University of Sulaimani where this study was conducted. The working standard was manufactured by Hebei Jiheng, China (batch No.1412001).Ten different brands of paracetamol were selected for this study that included three local Iraqi Manufacturers and 7 foreign manufacturers (table 1).

Table (1): A list of the brands studied and their manufacturing information.

Manufacturer	Country	Batch No.	Prod. date	Exp. Date
Samaraa	Iraq	-	1/5/2015	1/5/2018
Pioneer	Iraq	160015A	1/1/2016	1/1/2019
Awamedica	Iraq	PA1007	1/9/2014	1/8/2017
Julphar	UAE	333	1/9/2014	1/9/2017
Cipla	India	ACN4019	1/1/2014	1/1/2017
Trog	Germany	13829-04	1/5/2015	1/5/2019
Basi	Portugal	14039	1/12/2015	1/1/2018
GSK	UK	FK213	1/4/2015	1/4/2018
Wockhardt	UK	XQ10771	1/6/2015	1/5/2018
Bristol	UK	E6163099	1/7/2013	1/6/2018

Content assay

In this study content assay was achieved using the method stated by Indian pharmacopeia with modifications which involves using UV-Vis spectrometry.

Standard solution preparation

The standard solution was prepared by placing 150 mg of working standard material in a 100 ml volumetric flask then adding 25 ml of 0.1M NaOH and 50 ml of distilled water. The resulting solution was then shaken by mechanical means for 15 minutes and was made to the mark using distilled water. An aliquot of 10 ml of the resulting solution was diluted 10 folds, and another aliquot of 10 ml of the last solution was placed in a 100 ml volumetric flask; to which 10 ml of 0.1M NaOH was added and made up to the mark using distilled water.

Sample preparation

20 tablets were weighed and grinded into fine powder, then accurate amount of powder (equivalent to 75 mg) was placed in a 100 ml volumetric flask to which 25ml of 0.1M NaOH and 50 ml of distilled water was added and shaken by mechanical means for 15 minutes. The resulting solution was then filtered by passing it into a 0.5 um membrane Discarding the first 20 ml ,then an aliquot of 10 ml was diluted by 10 folds; and another aliquot of 10 ml of the last solution was placed in a 100 ml volumetric flask to which a 10 ml of 0.1M NaOH was added then made up to the mark using distilled water.

Spectrometry

The concentration of paracetamol in each sample was determined by using a UV-Vis spectrometer (UV 1650 pc Shimadzu, Japan) by measuring absorbance at 243 nm and using linear regression equation obtained from standard solutions.

Dissolution Test

This test was conducted by Placing 1 tablet in each vessel of the apparatus (paddle stirring module; Caleva dissolution tester, UK), while taking care to avoid formation of bubbles near the surface of the tablet and operating the instrument at 50 RPM for 30 min. The dissolution medium was 900 ml of distilled water (37° ± 0.5) with pH being adjusted at 5.8 using phosphate buffer. Then a specimen of 10 ml was withdrawn from the area between the surface of the Dissolution Medium and the rotating blades 1 cm away from the container walls every at 5,10,15,30,45,60 minutes . Each sample was filtered then diluted to 50 folds and the testing vessel was replenished with 10 ml of testing solution. This test was conducted for 6 tablets chosen randomly. Stock solution was prepared from working standards by dissolving 50 mg in a 1L volumetric flask

then preparing a series of dilutions having concentrations of 5,10,15,20 and 25 mg/ml. The percentage release of paracetamol was then assayed utilizing a UV-Vis spectrometer at the wave length of maximum absorbance which was 234 nm.

Friability Test

According to United States Pharmacopeia if the tablets weigh less than 650 mg, 10 tablets must be tested for friability. The tablets should be dedusted with a brush, weighed then placed in the apparatus drum (Caleva Model: FT 15/25, UK). The drum is then rotated at 25 RPM for 4 minutes which results in a total of 100 rotations.

Method validation

Accuracy

Accuracy describes how close the results are to the true value which can be used to measure the recovery percentage during an analytical process eliminating the possibility of the results acquired being incorrect due to systemic errors. Accuracy of the method was validated using acetaminophen USP Reference Standard material (lot No.K2M244) to measure the recovery percentage using the same preparation procedure for the samples. Three different solutions were prepared having concentrations of 0.01, 0.02 and 0.04 mg/ml giving recovery yields of 99.37, 99.82 and 99.17 % respectively.

Precision

Precision describes how close the results are to each other which can be used to eliminate the possibility that the acquired values were obtained due to random errors. To measure the precision of the results, each sample was run in 3 replicates and the relative standard deviation was calculated (table 2).

Linearity

Linearity was tested by preparing 5 different standard solutions and plotting them. The calibration curve demonstrated linearity in the range of 1-20 µg/L with the slope being 0.0133, the intercept being 0.0002 and R2 being 0.9994 (Figure 1).

Results

Content assay

According to the Indian pharmacopeia the tablet content for each brand should contain not less than 90% and not more than 110% active ingredient. The active ingredient content of the tested brands is illustrated in Figure 2 and Table2.

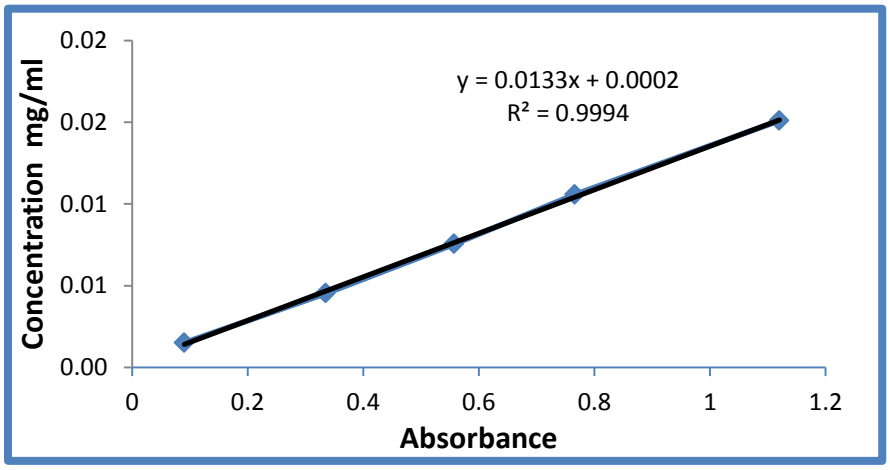

Figure (1): Content Assay calibration graph

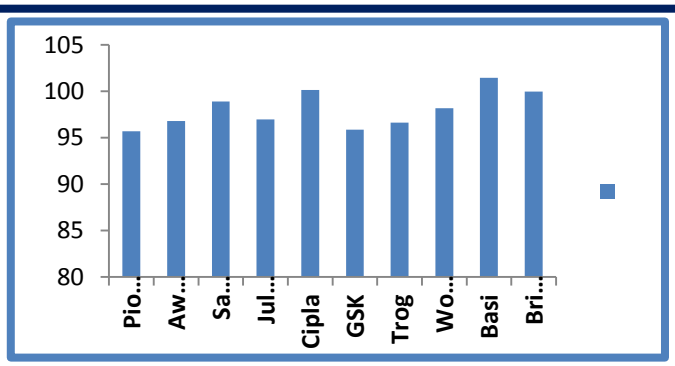

Figure (2): Content Assay recovery percentage.

Table (2): Content Assay results

Brand	Weight Mg	% Recovery	RSD*
Samaraa	478.443	95.689	1.132
Pionner	484.004	96.801	0.678
Awamedica	494.509	98.902	0.956
Julphar	484.805	96.961	1.095
Cipla	500.757	100.151	0.613
Trog	479.336	95.867	0.651
Basi	483.135	96.627	0.698
GSK	490.939	98.188	1.002
Wockhardt	507.304	101.461	1.381
Bristol	499.865	99.973	0.409

***RSD: Relative standard deviation.**

Dissolution Test

The release rate of paracetamol tablets was calculated using a calibration graph that showed linearity at 10-30 µg/L with the slope being 0.0282, the intercept being 0.0002 and R2 being 0.9994 (Figure 3). A release percentage of not less than 80% in 30 minutes is required for tablets to pass the dissolution test using apparatus II (paddle stirring apparatus).

GSK tablets showed faster dissolution rate in comparison to other manufacturers. Despite the fact that paracetamol tablets produced by other manufacturers showed slower rate of dissolution , all of them passed the test and achieved more than 80% drug release within 30 minutes (Figures 4A and 4B).

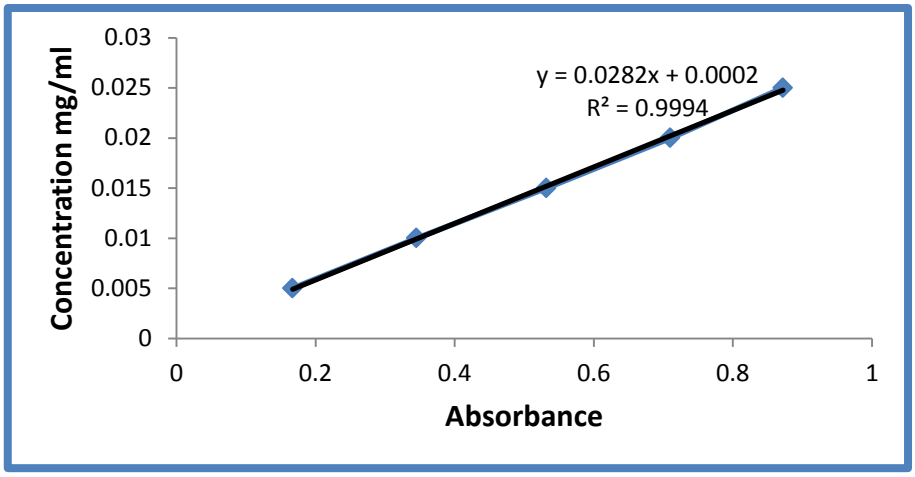

Figure (3): Dissolution Test calibration graph.

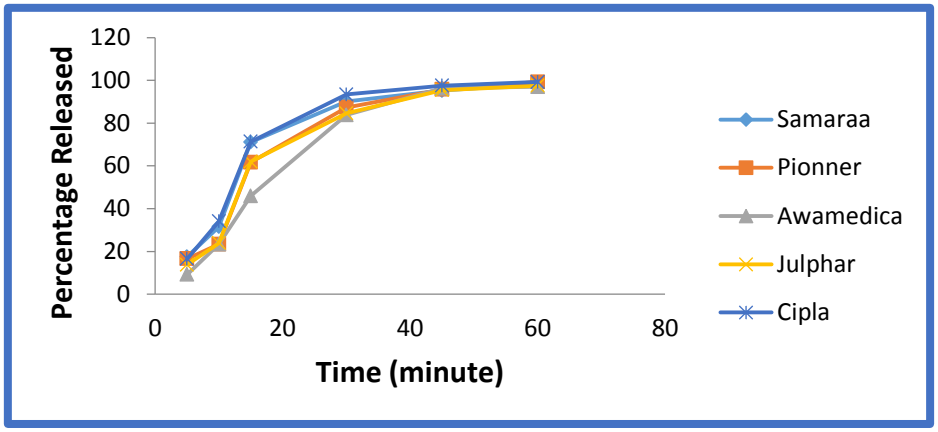

Figure (4A): Dissolution profiles of paracetamol tablets.

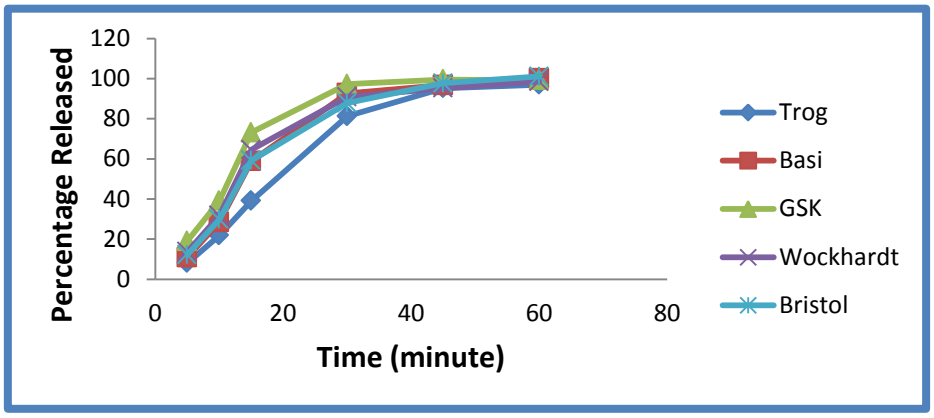

Figure (4B): Dissolution profiles of paracetamol tablets.

Friability Test

The Friability Test is conducted to measure the physical strength of tablets and their endurance to mechanical stress. As stated in United States Pharmacopeia, no more than 1% of weight loss should occur after testing in order for the tablets to pass the test. Tablets manufactured by GSK showed minimum friability amongst all brands with 0% weight loss after the end of the test. Tablets manufactured by Samaraa showed maximum friability of 0.34% followed by Cipla 0.19% and Julphar 0.12%. However, all the brands were within the acceptable limits and passed the test (Figure 5).

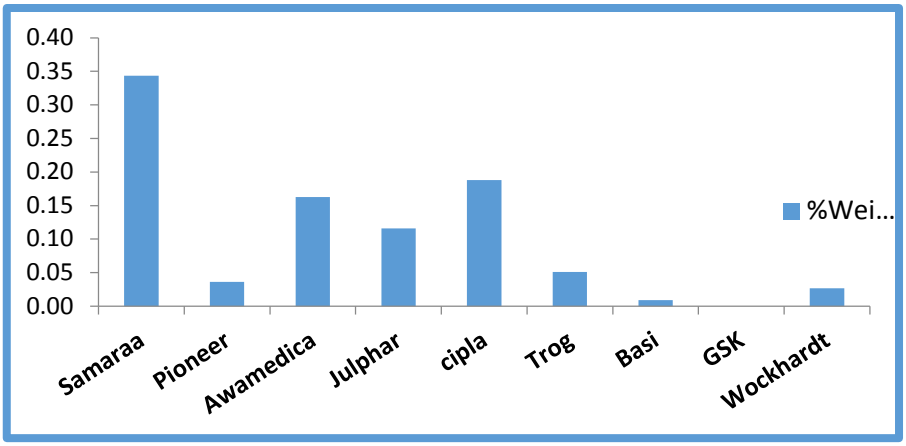

Figure (5): Percentage of weight loss after friability test.

Discussion

Drug products are considered to be pharmaceutically equivalent if they contain the same active ingredient, the same dosage form, identical strength and the same route of administration. This can be achieved if the tested drugs comply similarly with the compendial requirements as in the United States Pharmacopeia or Indian Pharmacopeia quality control tests [28].

The used method for content assay that has been derived from Indian Pharmacopeia proved to be accurate, precise and Cost effective as it requires analytical grade reagents, in comparison to other methods such as HPLC which requires using HPLC grade 99% pure reagents that are expensive. The content assay results showed that paracetamol tablets produced by all manufacturers, including local Iraqi manufacturers, in this study satisfied the minimum requirements stated by the United States Pharmacopeia which is 90-110% of the labeled amount [29].

The onset of action of any oral dosage form depends significantly on how fast the drug can achieve dissolution in order to be available for absorption. The release profile and dissolution rate of tablets manufactured by GSK proved to be the best amongst all the tested samples. It was formulated using Optizorb technology to obtain faster tablet disintegration and consequent dissolution which can be attributed to the excipients it contains that can result in faster analgesic effect compared to other brands [30]. Nevertheless, tablets produced by other manufacturers are still considered to be within the acceptable limits of dissolution which is not less than 80% drug release within 30 minutes of starting the test according to the United States Pharmacopeia[31].

Immune system plays an important role, not only in the defense against microbial infections but also in controlling and surveillance of malignant tumors. Immune system cells can scan the tissues in order to remove newly formed malignant or transformed cells before they can turn into fully formed malignancy [23].

Defects related to tablet manufacturing process can result in products suffering from low durability which causes a high percentage of powder to come out of them while being packed or transferred. This reduces the actual amount of the drug reaching the absorption site upon administration. .Even though they are within the approved range, tablets manufactured by Samaraa are highly friable (0.34%) in comparison to other manufacturers. This high level of friability can be related to insufficient amount of binding agents, the low compressibility of fillers or active

ingredients used and the compression method applied to produce the tablets[32].

In conclusion, tablets produced by Iraqi manufacturers Samaraa, Pioneer and Awamedica have proven to be of high quality that can be considered as pharmaceutically equivalent to other international manufacturers products.

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Conflict of Interest

The authors disclose that they have no conflict of interest in this study.

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