Comparative Evaluation of the Pharmaceutical and Chemical Equivalence of Some Commercial Brands of Acetaminophen Tablets

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Abstract: Acetaminophen (Paracetamol) tablets are popular OTC products among patients as analgesics and antipyretics. Acetaminophen is marketed by a lot of suppliers around the world. The aim of the present investigation was the comparison between many Acetaminophen tablets obtained from different suppliers (six brands produced by different pharmaceutical companies in Middle East countries, and Panadol® manufactured in Ireland). Evaluation of pharmaceutical and chemical equivalency of the six commercially available tablet brands of Acetaminophen and Panadol® tablets were performed through the determination of weight variation, hardness, friability, drug content, disintegration time and dissolution profile between the commercially available tablet brands of paracetamol according to USP standards. Additionally, the influence of different temperatures 4ºC, 25ºC and 40ºC at 75% relative humidity on the stability of the same brands in their original packaging during storage for two months has been evaluated. The results revealed that all Acetaminophen tablet brands complied with the official USP specifications (USP 30). In conclusion, all the tested brands are pharmaceutically and chemically equivalent. Standard quality control parameters always should be maintained not only for Acetaminophen tablets but also for all kinds of medicine for getting better drug products. Moreover, Acetaminophen tablets preferred to be stored at 25ºC.

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Keywords: Non official tests-hardness and friability; official tests –disintegration, dissolution, Acetaminophen and drug content.

1. Introduction

Acetaminophen (paracetamol) is a non-steroidal anti-inflammatory drug (NSAID) and is prescribed most frequently. It is widely used over-the-counter analgesic and antipyretic drug [1]. Generally it is used to treat headache, other minor aches, pain and as in cold and flu remedies. It could also be used in the management of more severe pain in cancer in combination with other drugs [2]. Generally, Acetaminophen is safe for human use at recommended doses [3]. It is used for the relief of pain 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 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 [4]. In addition, safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is reliable. Generally, the efficacy of pharmaceutical dosage forms depends on their formulation properties, and manufacturing methods, hence it is likely that the quality of dosage form may vary [5]. Dissolution test is one of the in vitro tests usually employed to assess the quality of oral pharmaceutical solid dosage forms such as tablets and capsules [6]. In vitro dissolution tests can be used to guide formulation developments, identify critical manufacturing variables, monitor formulation quality from batch to batch and also serve as a surrogate for bioavailability and bioequivalence [7].

Drug products that are chemically and pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile and should be in the same dosage form, for the same route of administration [7]. Any substantial variations in the dissolution rate among same generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution testing of drug products plays an important role as a quality control tool to monitor batch to batch consistency of drug release [9] and also for prediction of *in-vivo* bioavailability in most oral preparations [10-12]. To this extent, manufacturing methods, coupled with excipients used in the production processes, could contribute to the overall quality and release proficiency of medicament. Therefore, in order to ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product [12]. As such the need to ensure that the generic and branded drugs products

are pharmaceutically equivalent cannot be overemphasized and the necessity to select one product from several generic drug products of the same active ingredients during the course of therapy is always a cause for concern to healthcare practitioners [7, 8].

The present study was conducted to evaluate the pharmaceutically and chemical equivalency of different Acetaminophen brands marketed in the Middle East. The difference between the dissolution profiles was determined to identify the critical manufacturing variables and to predict the in vivo performances. Additionally, the stability of the tested brands by storage at temperatures 4ºC, 25ºC and 40ºC at 75% relative humidity over a period of two months was performed. Then the tablets were evaluated for their physical properties and their release kinetics. Statistical data analysis and study of the release kinetic were achieved by fitting the data to the release models; Zero order, first order, Hixon–crowel, Higuchi and Koresmeyer-Peppas. The order and the mechanism of drug release were investigated.

2. Experimental

2.1. Materials and reagents

Different brands of Acetaminophen tablets with a label strength of 500 mg (Table 1) were obtained from the Middle east market namely, Fevadol® 500**,** Panadrex® ,Paracetamol®, Pyral® , Revanin®**,** Panadol® and Panda® caplets. All tests were performed within product expiry dates. Acetaminophen powder was supplied by (laboratory chemical reagent, Market Harborough, UK).

The reagents used were sodium hydroxide, and potassium phosphate (BDH Chemicals, UK). Freshly deionized distilled water was used throughout the work.

Table 1: Acetaminophen Brands Under Test In This Study

Brand Name	Product Name
Fevadol®	Al-Gassim Pharmaceutical Plant Saudi (SPIMACO)
Panadrex®	Kuwait Saudi Pharmaceutical Industries Company (S.A.K)
Pyral®	Kahira Pharm. &Chem. Industry Company
Paracetamol®	The Arab Drug Company
Revanin®	The Arab Pharmaceutical Manufacturing Company
Panda®	Jordan Sweden Medical And Sterilization Company

Prepared Reagents

Phosphate buffer (pH 5.8) was prepared by dissolving 40 g of potassium dihydrogen phosphate in 2 L of deionized distilled water then 90 ml of 0.2M sodium hydroxide solution was added and diluted to volume in a 5-L volumetric flask according to the USP standards.

The evaluation was done according to USP standards.

2.2. Visual Inspection

The shape, size, and color of the different brands of tablets were examined visually.

2.3. Friability Test

Twenty tablets were weighed and subjected to abrasion using ERWEKA friabilator (Heusenstamm, Germany) for 4 min at 25 rpm. The values of <1% are considered to be highly satisfactory evaluation characteristics.

2.4. Hardness Test (non-official)

The crushing strength of the tablets was determined using ERWEKA hardness tester (Heusenstamm, Germany).

2.5. Weight uniformity

Tablets of each brand were weighed individually using a digital analytical balance. The percentage deviation of the individual tablets from the mean was determined.

2.6. Disintegration Test

Tablet disintegration was determined at 37 °C using ERWEKA disintegration testing apparatus (Heusenstamm, Germany).

2.7. Dissolution test

The in vitro drug release was determined using ERWEKA dissolution rate testing apparatus DT600 (Heusenstamm, Germany) using 900 ml of the medium at 37 ± 0.5 °C. The basket was rotated at 50 rpm. Five milliliters of sample was drawn at 5-min intervals for 30 minutes with 5 mL of fresh dissolution medium replaced after each withdrawal. The UV absorbance was measured at 243 nm using a UV/vis spectrophotometer (Shimadzu). The amount of acetaminophen in the samples was determined based on the calibration curve generated at a wavelength of 243 nm. According to USP specifications not less than 80% (Q) of the labeled amount of acetaminophen is dissolved within 30 minutes.

2.8. Drug content in Acetaminophen tablets

The assay was done to find out any difference between the actual amount of active ingredient and the labeled amount.

20 tablets from each brand weighed and finely powdered then an accurately weighed portion of powder equivalent to 150mg acetaminophen were transferred to a 200ml volumetric flask , 50 ml of 0.1M sodium hydroxide and 100ml of distilled water was added and shacked mechanically for

15minutes, then diluted to the volume and filtered. 10ml of the filtrate was transferred to100ml volumetric flask and further diluted to 100mlwith distilled water. Then 10ml of the filtered solution with 10ml 0.1M NaOH was transferred to another 100ml volumetric flask and the volume was completed with distilled water.

The absorbances of the assay preparation was determined against the $E_{1\%}$at λ_{max} 257nm with UV-3300PC Spectrophotometer using NaOH solution as a blank. The quantity in mg of acetaminophen in the portion of tablet was calculated. The accepted limit of drug content percentage is 90-110%[3].

3. Results and discussion

The results of the present study revealed that all the commercial brands met the USP requirements of the quality control tests. A total of 6 Acetaminophen tablets brands marketed in the Middle East countries were screened for weight variation, friability, disintegration time, identification and content uniformity. Table 2 shows the evaluated physicochemical parameters. The weight uniformity test for all the brands revealed values that complied with official specifications for weight uniformity as none of the brands deviated by up to ±5% from the mean value.

The friability was carried out for all the brands. It was less than 1% for all the brands except Revanin® tablets that were more fragile (1.9%), which may be due to the nature of the binders and additives used in the manufacturing procedures. All the brands failed the non-official hardness test, Paracetamol® had the highest crushing strength of all the six brands with hardness of 18 kg.

Table 2: Evaluation parameters of acetaminophen tablets

Brand Name	Weight Uniformity (Gm)	Friability%	Disintegration Time (Min.)	Hardness Kg	Drug Content %
Fevadol®	0.568±0.007	0.17	6	16	103
Panadrex®	0.548±0.006	0.18	5.3	10	104.8
Pyral®	0.587±0.014	0.34	2	11	107
Paracetamol®	0.617±0.013	0.48	2.5	18	108
Revanin®	0.550±0.011	1.9	3.4	9	104
Panda®	0.560±0.01	0.36	18	13	104

The results showed that all the brands passed the disintegration test according to USP, which specifies 30 minutes as disintegration time. The USP specifications for assay are that the drug content should be less than 90 % and not more than 110 %. Assay values of all brands were within the range of 90% to 110% of stated amount of acetaminophen. Therefore, the assay results ascertain the presence and compendial quality of the drug in all products. The differences of the values may be due to different additives and manufacturing mechanism used in different factories.

The *in vitro* dissolution profiles were varied for each tablet, but within the prescribed limit [13].

Since the analgesic and antipyretic medications containing Acetaminophen are used by patients to relief pain within short time to give the onset of action which depends mainly on the release of the drug. Therefore, the fast drug release is preferred in order to relief the pain and decrease the fever within short time. The Panadrex® tablets are preferred than the other acetaminophen products for faster relief of pain and fever (Figure 1).

In the present investigation, the stability was studied by storage of the Acetaminophen tablets under test for two months at different temperatures 4ºC, 25ºC and 40ºC at 75% relative humidity. Furthermore the tablets were evaluated after this stability period for their disintegration and release compared to Panadol® manufactured in Ireland (originator Acetaminophen brand). In addition, the order and the mechanism of the drug release were investigated (Figures 2-7). The study of the release kinetics showed that the higher values of correlation coefficient R^2 (Table 3) obtained from release profile of the acetaminophen products were in accordance with Higuchi Model at 4ºC (average R^2= 0.9816) and 25ºC (average R^2= 0.947). While, the release obeyed the zero order at 40ºC. The mechanism of reaction was confirmed with Korsmeyer-peppas model (Table 4). The model indicated that the drug release followed the fickian diffusion in case of tablets stored at 25ºC. The average n value was less than 0.45 (average n value =0.260) for the tested products. According to the n value in which the average was above 0.89 (average n value =1.87 and 0.952) for the tested products which indicate case -2 relaxation or super case transport-2 at 4ºC and 40ºC, respectively.

At different temperatures, the drug release was more than 80% after 30 minutes for all brands. In contrast, the release was lower than 80 % at 40ºC for Pyral®, Revanin® and Panadol® tablets. Moreover, the drug release in case of Panda® caplets did not comply with official tests at 4ºC, and 40ºC. Additionally , after storage at 40ºC the disintegration time of these brands was within 30 minutes , but for the Paracetamol® and Panda®

tablets stored at 40ºC , the disintegration was more than 30 minutes. At 4ºC, all brands tablets disintegrated within 30 minutes.

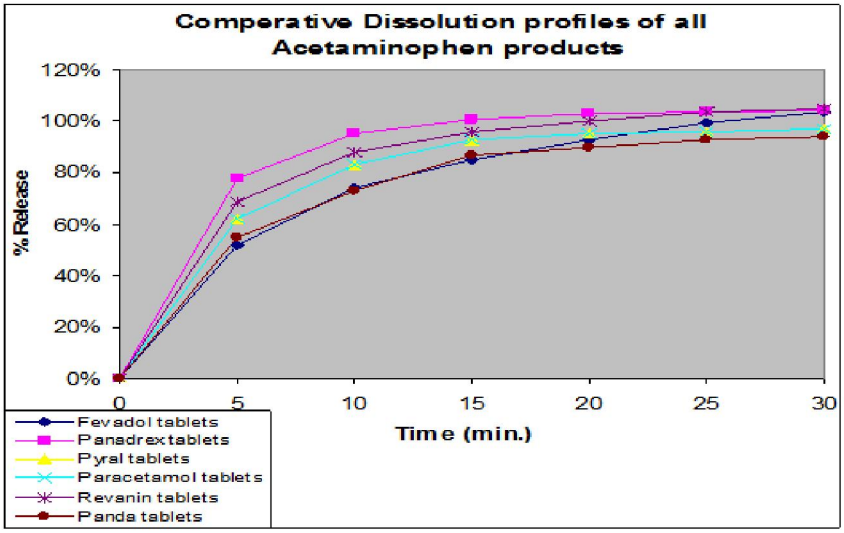

Figure 1: Comparative dissolution profiles of six acetaminophen brands products

Table 3: Comparative values of r2 from the release data of tested acetaminophen tablet brands which stored two months at different temperatures

Brand name	Zero order			First order			Higuchi model			Korsmeyer-peppasmodel		
	4°C	25°C	40°C	4°C	25°C	40°C	4°C	25°C	40°C	4°C	25°C	40°C
Fevadol®	0.981	0.9587	0.9972	0.8929	0.9265	0.9269	0.9961	0.9862	0.9916	0.9754	0.9403	0.9901
Panadrex®	0.9921	0.8446	0.9684	0.9293	0.8304	0.8855	0.9966	0.9034	0.9915	0.9902	0.9111	0.9676
Pyral®	0.9951	0.9053	0.9965	0.9555	0.8863	0.9409	0.9966	0.9501	0.9875	0.9982	0.912	0.9934
Revanin®	0.9406	0.9033	0.9844	0.8764	0.8810	0.9254	0.9752	0.9491	0.99939	0.9693	0.948	0.9861
Panda®	0.8815	0.9134	0.9972	0.8405	0.8904	0.965	0.9328	0.9561	0.9837	0.9491	0.9301	0.9861
Paracetamol®	0.963	0.8514	0.9967	0.8967	0.8292	0.9143	0.9809	0.9091	0.987	0.974	0.9222	0.9864
Panadol®	0.992	0.9662	0.994	0.8699	0.9295	0.9725	0.9935	0.9765	0.9791	0.9975	0.965	0.9954

Table 4: Estimated N values according to korsmeyer-peppas equation for acetaminophen tablet brands after storage for two months at different temperatures

Brand name	4°C	25°C	40°C
Fevadol®	0.830	0.354	0.658
Panadrex®	0.940	0.382	1.488
Pyral®	1.162	0.159	0811
Revanin®	1.201	0.261	1.32
Panda®	2.021	0.246	1.04
Paracetamol®	1.119	0.305	0.607
Panadol®	1.048	0.234	0.744

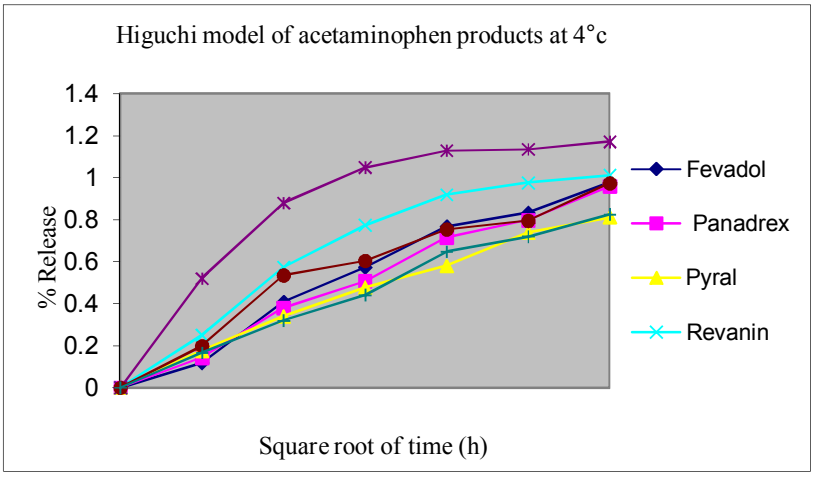

Figure 2: Higuchi model profile of acetaminophen products at 4ºC

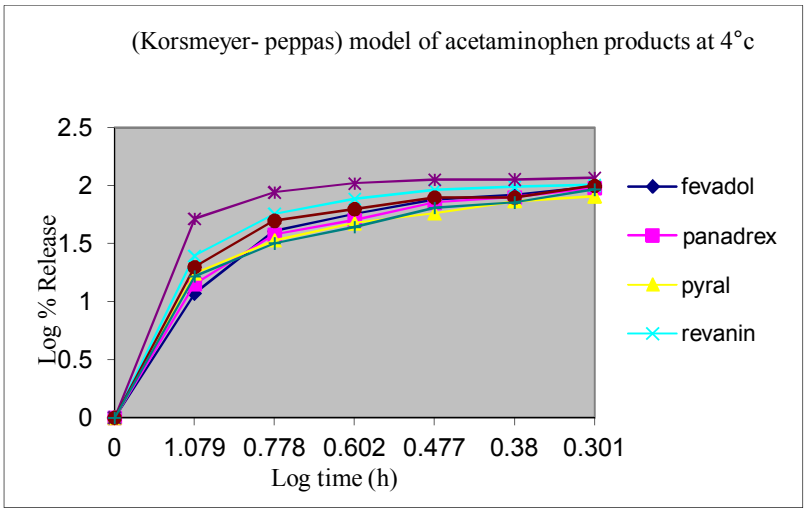

Figure 3: Korsmeyer–peppas profile of acetaminophen products at 4ºC

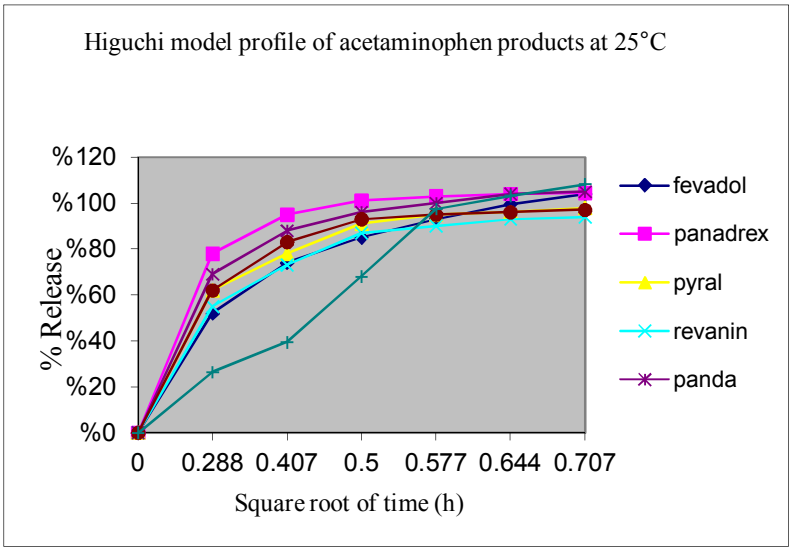

Figure 4: Higuchi model profile of acetaminophen products at 25ºC

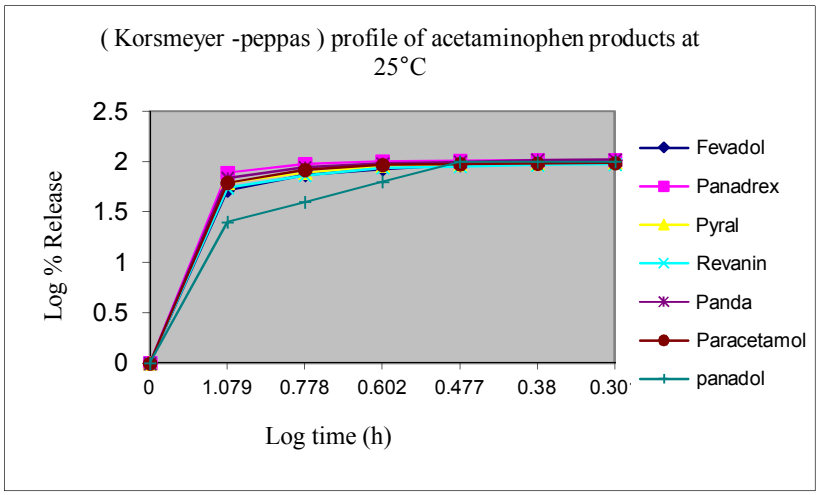

Figure 5: Korsmeyer–Peppas Profile of Acetaminophen Products at 25ºC

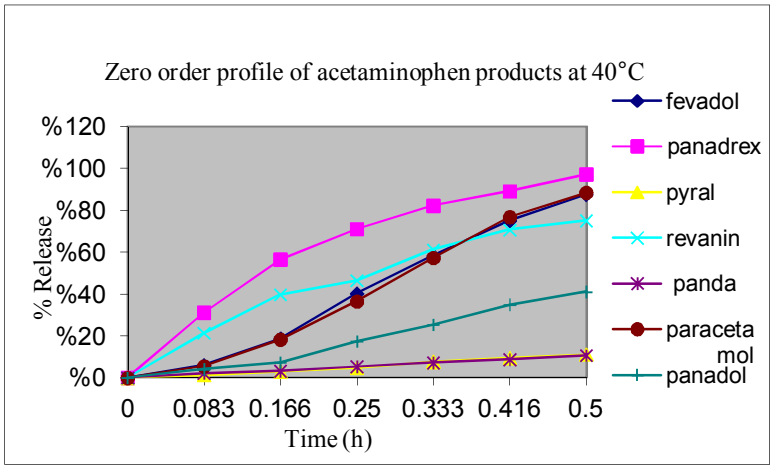

Figure 6: Zero Order Profile of Acetaminophen Products At 40ºC

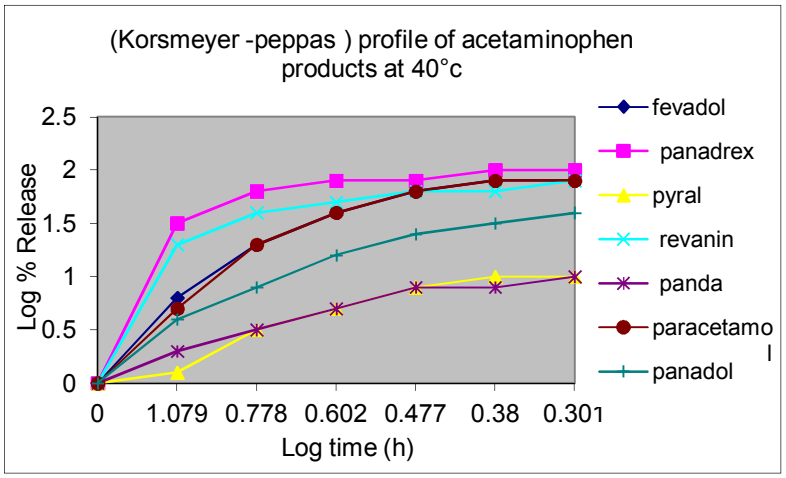

Figure 7: Korsmeyer–Peppas Profile of Acetaminophen Products At 40ºC

4. Conclusion

In the present study, the six commercial products of Acetaminophen manufactured in the Middle East were physically and chemically equivalent to each other with some exceptions. The presented quality control method is useful in monitoring the production consistency of batch-to-batch product release of each brand of acetaminophen and in comparing the quality characteristics of different marketed brands. The therapeutic equivalence of the drugs must also be investigated by comparison of their dissolution profiles. The fast drug release will improve the absorption of the drug. Furthermore, the antipyretic and analgesic effects will be very fast to relief the pain. In conclusion, all the brands tested in this study were physically and chemically equivalent and it is preferred to be stored at 25ºC.

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