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Bioequivalence Study On Some Commercially Available Paracetamol Tablets With The Innovator Product: In Vitro Dissolution Study

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ABSTRACT

Dissolution testing is a crucial in vitro technique in the formulation and development of pharmaceutical dosage forms. Tablets, a common dosage form, consist of a mixture of active ingredient(s), usually in powder form, with or without excipients. Acetaminophen is one of the most widely used drugs in the world. Numerous brands of acetaminophen are available commercially which are widely considered bioequivalent. The aim of the current study was to conduct a dissolution test on various products of acetaminophen tablets to assess their bioequivalence. Five different generic formulations of 500 mg paracetamol tablets from different manufacturers were selected and tested for dissolution in a 5.8 pH phosphate buffer for 30 minutes. Results were compared to those obtained from the reference product using a USP Type II dissolution testing apparatus. The dissolution testing revealed that products A, B, C, D, and E have dissolution rates of 96%, 103%, 114%, 111% and 94%, respectively, in comparison to the brand Panadol, which dissolved at 99% within 30 minutes. All tested tablets were within the pharmacopoeia criteria.

KEYWORDS: Dissolution, Paracetamol, Dissolution Comparison.

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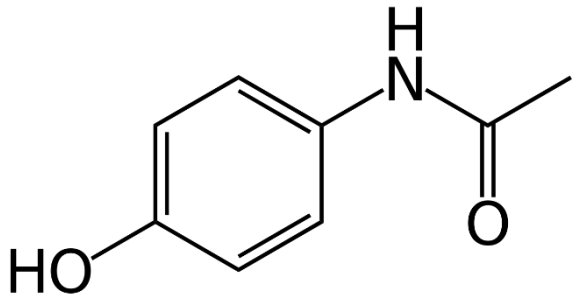
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1. Introduction

Paracetamol, also known as Acetaminophen, or APAP [4-hydroxyacetanilide], belongs to the aniline analgesics drug class, and is the only drug of this class still in use [1]. It has the molecular formula C8H9NO2, and it is soluble in alcohols. However, its solubility decreases with the increase in the length of the carbon chain in the n-alcohol series [2]. Paracetamol exhibits some pharmacological similarity with non-steroidal anti-inflammatory drugs (NSAIDs), but it is not classified as one of them due to lack of significant anti-inflammatory effects [3, 4]. This analgesic is one of the most widely available over-the-counter (OTC) medications which is used in the treatment of mild to moderate pain and pyrexia [5]. Paracetamol is generally safe at recommended doses but overdoses can cause severe liver damage. [6, 7] Currently, paracetamol toxicity is a leading cause of acute liver failure in both the United States and the United Kingdom. The therapeutic dose in adults is 0.5–1 g, with a maximum of 4 g/day and 10-15 mg/kg every 4-6 hours in children [8 - 10].



4−hydroxyacetanilide

The compressed tablet is the most widely used dosage form today, due to several advantages. Being a unit dosage form, tablets provide the greatest dose precision and the least content variability. Their lower cost compared to other dosage forms is a further advantage. In addition, their compact size and light weight contribute to their being easy and cheap to package and ship. Moreover, they enjoy simple and cheap product identification if an embossed or monogrammed punch face is used. Tablets also contribute to patient compliance as a result of ease of use. They are also the oral dosage form of choice for large-scale production. In addition, they enjoy great chemical, mechanical, and microbiological stability compared to other oral dosage forms .

Special release profile products can be also formulated in tablet form such as enteric coated tablets, delayed release, extended release and many others to provide a consistent release profile or faster onset of action [11]. The safety and efficacy of a pharmaceutical dosage form can be guaranteed when its quality is acceptable. The efficacy of a pharmaceutical dosage form generally depends on their formulation properties, and manufacturing methods. There are a number of tests that are used to evaluate the quality of a dosage form. In the case of tablets, one of the most widely used tests is dissolution test. This test is one of the in-vitro tests usually performed to

assess and test the quality of a solid dosage form such as capsules and tablets. In the pharmaceutical industry, a drug dissolution test is usually used to provide critical in vitro drug release profile for quality control purposes to assess batch-to-batch consistency of solid oral dosage forms such as tablets. [12] The end goal of a dissolution test is to measure the rate at which the active ingredient(s) is released from the solid dosage form and dissolves in a particular dissolution medium. It is important for such a test to be performed under well-defined conditions as to allow comparative studies of observed data. A variety of guidelines, protocols, and methods are used. These protocols tend to vary greatly between a drug product and another, and often the same product is tested under different conditions, depending on whether the test is performed for quality control (QC) purposes or to assess the performance of the drug product in the digestive tract. Dissolution paracetamol tablets members agreed that the quantification based on the respective assay methods should be evaluated for the paracetamol tablets monographs. [13] Members also agreed that a limit of 75% (Q) in 45 minutes should be included for stakeholder comment. [14] A key variable that should be considered when designing dissolution tests is the type of dissolution apparatus used. Although there are many types of dissolution apparatus available, the most commonly used are standardized dissolution apparatus. These are well-defined and robust dissolution testers described by pharmacopoeias [14].

In this study five local tablet dosage forms each containing 500 mg paracetamol were studied for dissolution profile and the results were compared to those of the brand product. The study was performed according to Britch Pharmacopoeia 2020. [14] There are some other research studies that have used different methods to measure paracetamol dissolution rate [15 - 24].

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2. Materials and Methods

2.1. Apparatus and software

PG instruments, T60 UV-Visible spectrophotometer equipped with 1 cm quartz cells and connected to a computer, the computer was equipped with UV win software v6.0.0.

Rc-3 Dissolution Tester

The equipment used in this research was prepared in the Drug Control Laboratory at the Faculty of Pharmacy, AL-Wataniya Private University.

2.2. Materials

The five tested generic paracetamol tablet formulations (500 mg strength) included Cetamol (Thameco), Paracetamol Barakat (Barakat), Ultramol (Medicao Labs), Paramol (MPI), and Hayamol (Ibn Hayyan), with Panadol® (GSK) used as the reference product. Generic forms were coded A, B, C, D, and F respectively for anonymity.

Sodium Hydroxide pellets (Sigma-Aldrich, St. Louis, MO, USA), were kindly obtained from the Drug Control Laboratory at the Faculty of Pharmacy/AL-Wataniya Private University.
Potassium dihydrogen orthophosphate (Sigma-Aldrich, St. Louis, MO, USA), was also kindly obtained from the Drug Control Laboratory at the Faculty of Pharmacy/Al- Wataniya Private University.

2.3. Phosphate Buffer Preparation

A 5.8 pH phosphate buffer was prepared according to USP by mixing 50 mL of 0.2 M potassium dihydrogen orthophosphate with 3.7 mL of 0.2 M sodium hydroxide and diluting to 200 mL with water.

2.4. Dissolution test

The dissolution test was conducted in compliance with the British Pharmacopoeia. Six tablets from each product were tested for dissolution using Apparatus 2. The medium used was 900 mL of phosphate buffer at pH 5.8 and 37 C°, with the paddle rotated at 50 rpm. 1-mL. Samples of the medium were withdrawn at specified time intervals and replaced with fresh dissolution medium. Each sample was filtered and diluted with 0.1M sodium hydroxide before measuring the absorbance at 257 nm [14].

3. Results and Discussion

A dissolution test reflects the amount of drug dissolved to become available for absorption from the GIT. Drug products with poor dissolution will not reach the body system or target tissues at a rate fast enough to exceed the minimum effective concentration (MEC) and thus, won't elicit a therapeutic effect. Evaluation of the dissolution results showed that, all products met the pharmacopeial requirements. However, each type exhibited significant differences in disintegration and dissolution times, which were attributed to variations in formulation and manufacturing processes. Figures 1-6 present the dissolution profiles of the reference and the tested products. Panadol® and Tablet A show similar dissolution rates. Figures 1-6 show the dissolution profile test results in phosphate buffers at pH 5.8

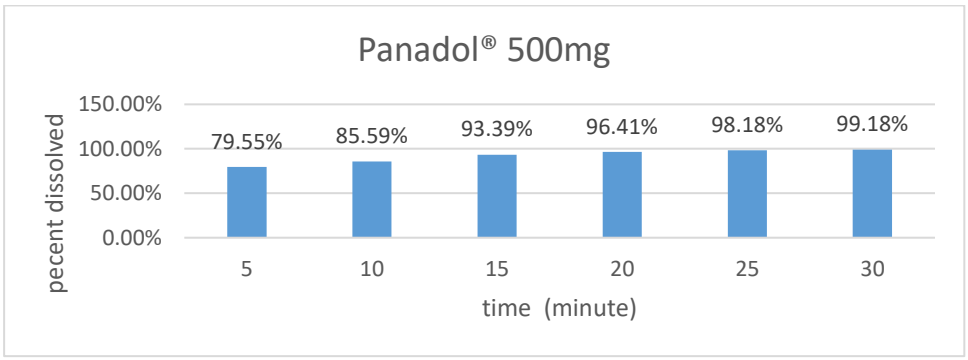


Figure (1): Panadol® (standard) values

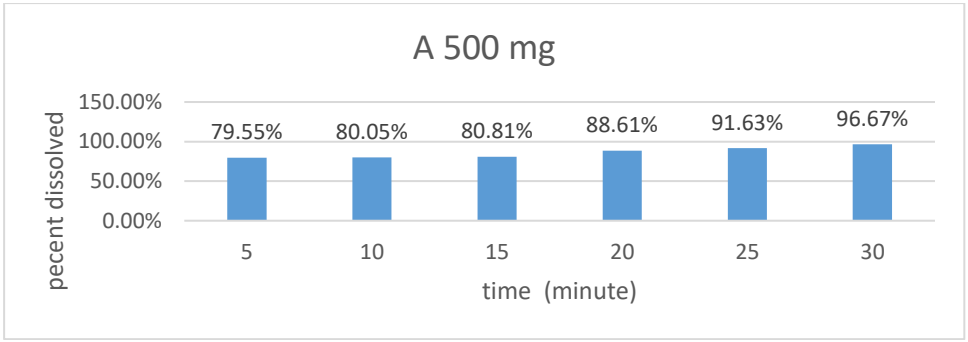


Figure (2): (A 500 MG) values

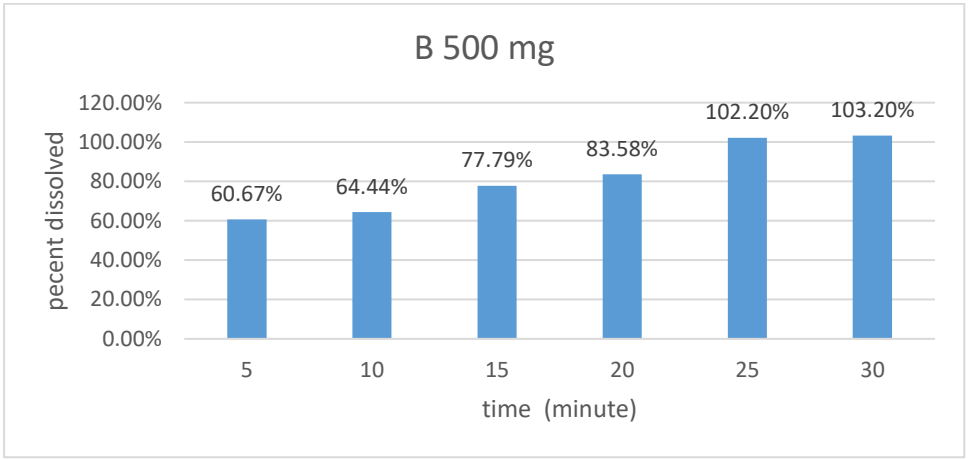


Figure (3): (B 500 MG) values

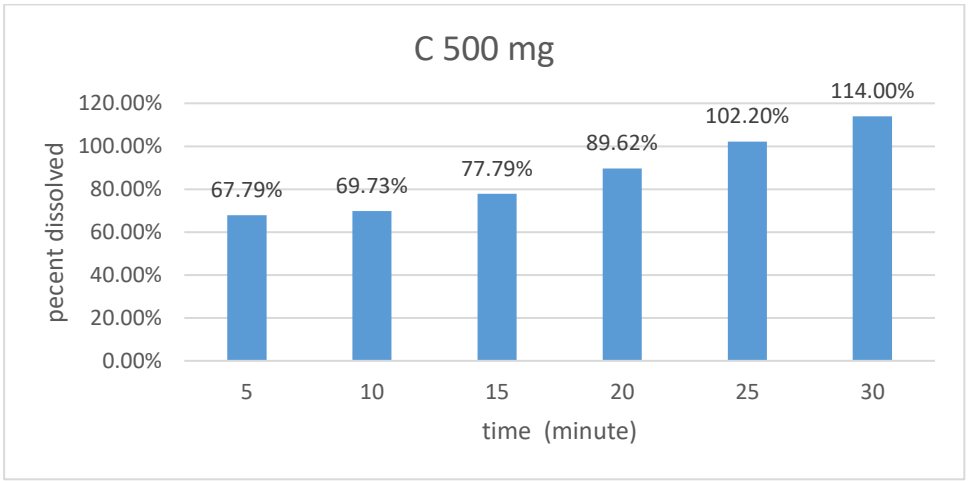


Figure (4): (C 500 MG) values

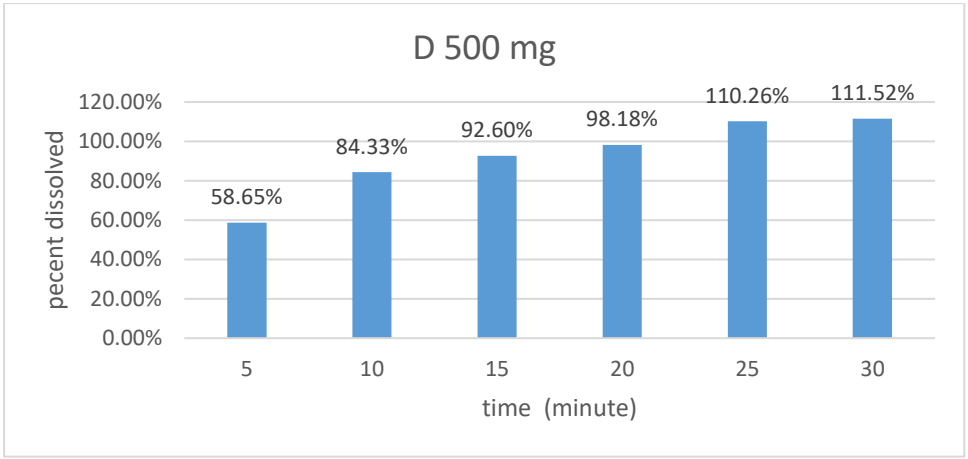


Figure (5): (D 500 MG) values

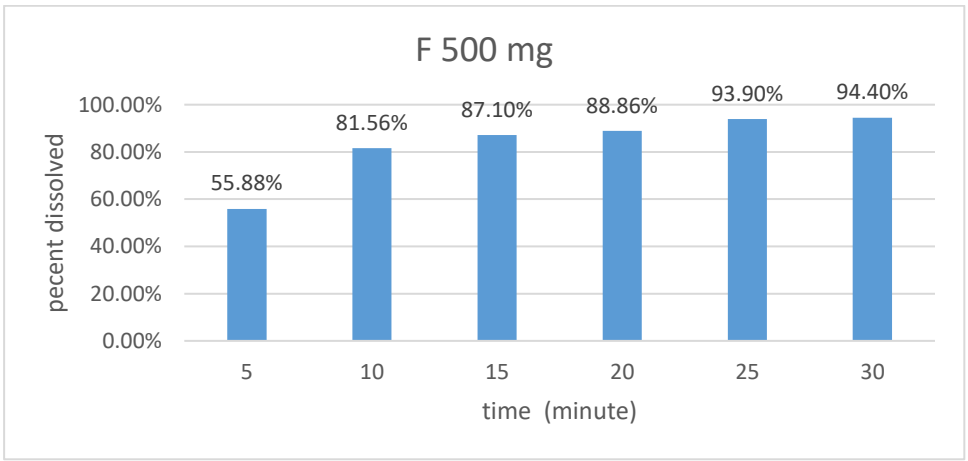


Figure (6): (D 500 MG) values

The bioequivalence comparison between Panadol® as brand and five local drugs goes as follows. The product is said to be acceptably dissolving when not less than 85% of the labeled API dissolves within 30 minutes. [23] As can be noted from results reported in tables, the products tested can be considered acceptably dissolving according to USP pharmacopeia. The dissolution rate of all drugs dissolved between 80% and 100% within 30 min, and hence, the products tested can be said to have a convergent dissolution model. This proves that the locally available brands of paracetamol tablets are of acceptable quality, compared with Panadol®. The reported data is considered as good evidence that the products B,C,D,F of paracetamol are dissimilar to the brand (Panadol®) only (A) having a similar dissolution profile. The in vitro dissolution profiles were found to be different for each tablet but all products were within the acceptance according to USP criteria

4. Conclusion

Our study discusses the comparative dissolutions for multi-sourced paracetamol products with the reference ones. It was concluded that, that the five local products

are similar to the reference drug, but there were simple differences between these products, due to their having different formulations and physical characteristics. We suggest that they must be subjected to in-vivo clinical study to give accurate details about bioavailability.

The results of this study indicate that differences in release characteristics between multi-source paracetamol tablets suggest potential effects on the bioavailability of the active ingredient. However, further guidance will be needed to determine whether observed in vitro differences are of clinical significance. Therefore, comparative in vitro dissolution studies have been considered as guidance studies to determine the comparative dissolution of multiple source drugs of different formulations and strengths versus reference drugs, and can be used as an alternative to in vivo studies under specific and well-defined conditions.

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