ABSTRACT
Six brands of paracetamol (acetaminophen) 500 mg tablets have been evaluated using specific quality control tests for uniformity of weight, hardness, friability, content, disintegration and dissolution with the aim to assess its bioequivalence. The results obtained have been discussed in details using monographs in United States Pharmacopeia and British Pharmacopoeia. In conclusion, despite some apparent minor differences in tablet hardness and disintegration time profiles, the dissolution characteristics of various paracetamol tablets appears to be similar and not significantly different from various manufacturers.

KEYWORDS: Quality control tests; paracetamol; dissolution; dissolution efficiency; weight variation; disintegration.

Introduction
Post-market evaluation involves all activities undertaken to obtain more data and information about a product after it has been granted marketing authorization and made available for public use. The obtained quantitative and qualitative data could be employed for product development and improvement of the standard of the product as per the regulations. Regulatory agencies rely on limited information obtained during clinical trials and, to some extent, scientific literature as guides to granting marketing authorization of medicines for public use. The post-market evaluation is imperative to monitor the approved medicines in order to adequately assess the quality, therapeutic effectiveness and safety of medicines for the end user. Post-market evaluation should be a continuous event throughout the life of a drug product. Activities of post market evaluation of a drug have been identified to include: evaluation and investigation of reported drug complaints and procedures for production and review of product claims and labeling; public access to information taken and reported to the regulatory agencies; and in vitro testing of products for compliance to standards (Hennessy, 1998).

In vitro testing or quality control of drugs is a set of studies undertaken during production. Routine laboratory testing of drugs in the market is crucial to protect public health especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. Counterfeit and substandard medicines are a major cause of morbidity, mortality, and diminished public confidence in drugs and health structures (Kasim et al., 2004; Cockburn et al., 2005).

China and India are known as the leading countries in counterfeit drug production (Khan and Ghilzai, 2003) Other countries are Pakistan, Egypt and Indonesia (Rafu, 2003; Ngweluka et al., 2006; Oschekpe et al., 2006). To reduce the cost of medicines especially for the low income group of developing countries, the World Health Organization (WHO) has continuously advocated the use of generic brands (WHO, 2004), but this approach has not provided sufficient evidence for the substitution of one brand for another. The difference in cost between a branded and generic medicine may be as high as 90%. To assist in substitution of branded with generic drugs for affordability and at the same time achieve therapeutic efficacy, bioequivalence studies become chief concern.

Bioequivalence has been described as the absence of a significant difference in the rate and extent to which the active ingredient or excipients in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action, when they are administered at the same molar dose under similar conditions in an appropriately designed study (FDA, 1997; 2000; 2003).

Two pharmaceutical products are considered to be equivalent when their bioavailability factors are so similar that they are unlikely to produce clinically relevant differences in therapeutic and adverse effects (Polli et al., 1997; Chen et al., 2001; Meredith, 2003). Generic substitution could be considered when a generic copy of a reference drug contains an identical value of the same active ingredient in the same dose formulation
and route of administration, as well as meet standards for strength, purity, quality, and identity. However, evidences over the years indicate that marketed products with the same amount of active ingredient exhibit marked differences in their therapeutic responses (Rani, 2007). This may be due to the extent of absorption being dissimilar or perhaps due to different excipients employed.

Bioequivalence studies focus on the release of the drug from the formulation and subsequent absorption into the systemic circulation. However, with the introduction of the biopharmaceutical classification system (BCS), in vivo bioequivalence studies could be waived for immediate release solid oral dosage forms for class I (high solubility and permeability) and class III drugs (high solubility and low permeability) (Wu et al., 2005; Polli, 2008). Hence, only in vitro testing may be used to determine bioequivalence for highly soluble and highly permeable drugs. Dissolution testing, a substitute for bioequivalence testing, is certainly a practical and economic approach in developing countries where technology and resources are limited for in vivo studies. One of the values of the dissolution test is that it can be used to define characteristics of bioavailability problems and assess the need for in vivo bioavailability. The release of the active pharmaceutical ingredient from drug product, the dissolution of the drug under physiological conditions and the permeability across the gastrointestinal tract determines the drug absorption. Based on this, in vitro dissolution may be vital in assessing in vivo performance. Dissolution testing also serves as a tool to distinguish between acceptable and unacceptable drug products (Anderson et al., 1998; Shah et al., 1998; Shah, 2001).

Literature data are reviewed on the properties of paracetamol (acetaminophen) related to the BCS. According to the current BCS criteria, acetaminophen is a BCS Class III compound. Differences in composition seldom, if ever, have an effect on the extent of absorption. However, some studies show differences in rate of absorption between brands and formulations. In particular, sodium bicarbonate, present in some drug products, was reported to give an increase in the rate of absorption, probably caused by an effect on gastric emptying. In view of Marketing Authorizations (MAs) given in a number of countries to acetaminophen drug products with rapid onset of action, it is concluded that the differences in rate of absorption were considered therapeutically not relevant by the Health Authorities. Moreover, in view of its therapeutic use, its wide therapeutic index and its uncomplicated pharmacokinetic properties, in vitro dissolution data collected according to the relevant guidance can be safely used for declaring bioequivalence (BE) of two acetaminophen formulations. Therefore, accepting a biowaiver for immediate-release (IR) acetaminophen solid oral drug products is scientifically justified if the test product contains only those excipients reported in this paper in their usual amounts and the test product is rapidly dissolving, as well as the test product fulfills the criterion of similarity of dissolution profiles to the reference product (Yu et al., 2002).

The present study was undertaken to evaluate the efficacy and justification of the generic substitution of paracetamol in the Malaysian market. Paracetamol (acetaminophen) is a widely used over-the-counter (OTC) analgesic and antipyretic agent.

The ultimate objective of dissolution testing may be described as ensuring adequate and reproducible bioavailability without recourse to routine in vivo testing. Drug release in the human body can be measured in vivo by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official in vitro tests, which are now rigorously and comprehensively defined in the respective Pharmacopoeia.

Chemistry of Paracetamol. Chemical structure and properties of paracetamol are listed below.

- **IUPAC Name**: N-(4-hydroxyphenyl)acetamide
- **Chemical Formula**: C₈H₉NO₂
- **Molecular Weight**: 151.17

**Synonyms**: 4’-hydroxyacetanilide; TYLENOL; Paracetamol; Paracetamolo; Paracetamole; P-acetamido-Phenol; 4’-hydroxyacetanilide; n- (p- Hydroxyphenyl)-Acetamide; N-(4-hydroxyphenyl)-Acetamide; P-acetamidophenol; 4-Acetamidophenol; Acetaminofen; Acetaminophen; P-Acetaminophen; N-acetyl-p-aminophenol; P-Acetylamino Phenol; P-hydroxyacetanilide; Paracetamol; 4-hydroxy Acetanilide; 4-hydroxamylid Kyseliny Octove; N-(4- hydroxyphenyl) Acetamide

**Physical Properties:**

(a) Physical state: white crystalline powder
(b) Melting point: 169 – 172 °C
(c) Solubility in water: sparingly soluble
(d) pH: 5.5 – 6.5
(e) Stability: stable in normal condition

**Materials and Methods**

**Materials.** Standard paracetamol >99% was obtained as a gift from a research colleague. Six different brands of paracetamol tablets as shown in Table 1 were purchased from retail pharmacies in Malaysia.

Standard materials from standard sources were used. To perform dissolution testing, an Electrolab instrument was used. A Monsanto hardness tester was used to test the hardness. A UV-visible spectrophotometer from GBC Cintralol was used. A disintegration tester from Electrolab was used (Allen et al., 2004).
Determination of Weight Uniformity. Twenty tablets from each of the six brands were weighed individually with an analytical weighing balance (Kern). The average weight for each brand as well as the percentage deviation from the mean value was calculated.

Hardness Test. The crushing strength was determined with a tablet hardness tester (Monsanto). Four tablets were randomly selected from each brand for this test.

Friability Test. Ten tablets of each brand were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev/min for 4 minutes. The tablets were then weighed and compared, with their initial weights and percentage friability being obtained.

Disintegration Test. Tablet disintegration was determined in the tablet disintegration tester (Es Eagle Scientific Limited, Nottingham). Six tablets from each brand were employed for the test in distilled water at 37°C using the Educational Sciences Disintegration Apparatus (Es Eagle Scientific Limited, Nottingham). The disintegration time was taken to be the time no particle remained on the basket of the system.

Dissolution Test. The dissolution test was undertaken using USP apparatus I (basket method) in 6 replicates for each brand. Preparation of Phosphate Buffer, pH 5.8: The rpm was set to 50.

Ten ml of the samples were withdrawn from dissolution basket at various time intervals such as 0, 10, 20, 30, 45 and 60 min using a graduated pipette and replaced with equal volume to maintain sink condition. The samples were filtered and diluted 10 by 10 times and the absorbance was measured at 243 nm. The concentration of each sample was determined from a calibration curve obtained from pure samples of paracetamol.

Results and Discussion

The research study has highly demonstrated the formulation and in vitro equivalency evaluation of paracetamol tablets. Six different brands of paracetamol tablets were studied for their dissolution, disintegration, weight variation and hardness. The six different brands of paracetamol tablets are named accordingly by alphabetical order as products A-F.

A summary of the results of uniformity of weight, hardness test, friability and disintegration are as shown in Table 2. Uniformity of weight, disintegration and dissolution are compendial standards to assess the quality of tablets while hardness and friability are referred to as non-compendial standards although friability is now included in the USP, 1995. Uniformity of weight does serve as a pointer to good manufacturing practices (GMP) as well as the amount of the active pharmaceutical ingredient (API) paracetamol contained in the formulation. All of the brands complied with the USP specification.

The hardness or crushing strength assessed the ability of tablets to withstand handling without fracturing or chipping. It can also influence friability and disintegration, as can be seen from Table 2. The harder a tablet, the less friable and the more time it takes to disintegrate. A force of about 4 kg is the minimum requirement for a satisfactory tablet (Allen et al., 2004). Hence, the tablets of all brands were satisfactory for hardness.

TABLE 1
Sample of paracetamol.

<table>
<thead>
<tr>
<th>Code</th>
<th>Brand Name</th>
<th>Dosage form</th>
<th>Country of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Tempol</td>
<td>Tablets</td>
<td>Malaysia</td>
</tr>
<tr>
<td>B</td>
<td>Dhamol</td>
<td>Tablets</td>
<td>Malaysia</td>
</tr>
<tr>
<td>C</td>
<td>Panadol</td>
<td>Tablets</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>D</td>
<td>Paracetamol</td>
<td>Tablets</td>
<td>India</td>
</tr>
<tr>
<td>E</td>
<td>Poro</td>
<td>Tablets</td>
<td>Malaysia</td>
</tr>
<tr>
<td>F</td>
<td>Ulphamol</td>
<td>Tablets</td>
<td>Malaysia</td>
</tr>
</tbody>
</table>

The compendia specification for friability is 1%. Friability for all brands was below 1%. The friability test was used to evaluate the tablets resistance to abrasion.

Disintegration could be directly related to dissolution and subsequent bioavailability of a drug (FDA, 2009abcd). A drug incorporated in a tablet is released rapidly as the tablet disintegrates; a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine (Costa et al., 2000; Gohel et al., 2005). All brands complied with the compendial specifications for disintegration. It was found that the results obtained from the disintegration test for tablet product A was relatively slower than the rest of the tablets products. Thus, tablet products D, E, F were being readily available in the solution when compared with tablet product A.

Weight Variation Test. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight. As per pharmacopeia, for tablets weight more than 250 mg, percentage deviation is 5%. Paracetamol tablets of
product A-I were of 500 mg and the weight variation fall between the ranges.

The tablet meets the USP requirements if no more than 2 tablets are outside the percentage limit and no tablet differs by more than double the percentage limit. Therefore, all of the tablets passed the test.

**Hardness Test.** The six different brands of paracetamol tablets are tested for their hardness as well. The standard for the hardness test is a 4 kg/square inch gauge; it is considered minimum for a satisfactory tablet. All products conformed to the standard of hard test. The hardness test reviewed the results as below:

According to USP specification, paracetamol tablets should release more than 80% of drug at 30 min. From the research carried out, we have found that product A showed 96.23%, product B showed 88.03%, product C showed 95.26%, product D showed 97.49%, product E showed 93.75% and product F showed 96.41% of the drug released at 30 min (Table 3). The results complied with the USP specification.

**TABLE 3**

Release studies of paracetamol.

<table>
<thead>
<tr>
<th>Time Interval (min)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>80.355</td>
<td>78.380</td>
<td>80.997</td>
<td>87.418</td>
<td>87.995</td>
<td>77.246</td>
</tr>
<tr>
<td>20</td>
<td>95.445</td>
<td>86.344</td>
<td>88.672</td>
<td>93.516</td>
<td>91.648</td>
<td>95.299</td>
</tr>
<tr>
<td>30</td>
<td>96.226</td>
<td>88.029</td>
<td>95.264</td>
<td>97.493</td>
<td>93.751</td>
<td>96.407</td>
</tr>
<tr>
<td>45</td>
<td>97.748</td>
<td>92.096</td>
<td>98.883</td>
<td>98.809</td>
<td>98.750</td>
<td>97.837</td>
</tr>
</tbody>
</table>

In disintegration testing, time taken for disintegration of product A was relatively longer than other products. Thus, product B, C, D, E and F were more readily available in the solution. The high rate of disintegration of a tablet indicates faster breakdown of a tablet into smaller particles and thus, enhanced the dissolution of the medicaments into the blood circulation, increasing the bioavailability.

**Conclusion**

Based on the finding from this study, it is concluded that, despite some apparent minor differences in tablet hardness and disintegration time profiles, the dissolution characteristics of various paracetamol tablets appears to be similar and not significantly different from various manufacturers.

**References**


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