Quality Comparisons of Acetaminophen Tablets Commercially Available in Thailand
การศึกษาเปรียบเทียบคุณภาพของยาเม็ดอะเซตามิโนเฟน ที่มีจำหน่ายในประเทศไทย

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Abstract

Acetaminophen or paracetamol is one of the most widely used over-the-counter analgesic and antipyretic medications. Many different brands of acetaminophen tablets are available in Thailand market where people can easily access medicines. The aim of this present study was to compare the quality of three brands of acetaminophen tablets (500 mg/tablet) marketed in Thailand with various prices. The three brands of acetaminophen tablets were obtained from a retail pharmacy and their qualities were evaluated using criteria and methods according to USP 40 and BP 2017 together with CDER--Center for Drug Evaluation and Research guidance 1997. The quality of the acetaminophen tablets was compared based on uniformity of weight, tablet friability, tablet breaking force, dissolution test, assay procedure as well as uniformity of dosage unit. All brands conformed to USP and BP criteria. According to CDER guidance, dissolution profiles of two brands were considered to be equivalent, but they are slightly different from the other one. However, the overall quality of the three brands of acetaminophen tablets was satisfactory as they met the USP 40 and BP 2017 requirements.

Keywords: Acetaminophen tablet, quality control, dissolution test, assay, uniformity of dosage unit

บทคัดย่อ

อะเซตามิโนเฟนหรือพาราเซตามอลเป็นยาแก้ปวดลดไข้ตัวหนึ่งที่นิยมใช้กันอย่างแพร่หลายโดยไม่ต้องมีใบสั่งยา มีวางจำหน่ายในประเทศไทยในชื่อทางการค้าที่หลากหลาย ซึ่งผู้บริโภคสามารถเข้าถึงยาได้ง่าย งานวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาเปรียบเทียบคุณภาพของยาเม็ดอะเซตามิโนเฟน ขนาด 500 มิลลิกรัมต่อเม็ดของ 3 บริษัทที่มีวางจำหน่ายในประเทศไทยด้วยราคาจำหน่ายที่แตกต่างกัน โดยเลือกซื้อตัวอย่างยาเม็ดอะเซตามิโนเฟนจากร้านขายยาทั่วไป การประเมินคุณภาพของยาเม็ดอะเซตามิโนเฟนได้ใช้เกณฑ์และวิธีตาม USP 40, BP 2017 ร่วมกับคำแนะนำของ CDER หัวข้อที่ใช้ในการทดสอบและเปรียบเทียบคุณภาพของเม็ดยา ได้แก่ ความสม่ำเสมอของน้ำหนักเม็ดยา ความกร่อนของเม็ดยา แรงที่ทำให้เม็ดยาแตก การทดสอบการละลายของเม็ดยา การวิเคราะห์หาปริมาณตัวยาสำคัญในเม็ดยา และการทดสอบความสม่ำเสมอของปริมาณตัวยาสำคัญในยาแต่ละเม็ด จากการทดสอบ พบว่ายาเม็ดอะเซตามิโนเฟนของทั้ง 3 บริษัทมีความสอดคล้องกันตามเกณฑ์มาตรฐานที่ USP 40 และ BP 2017 กำหนด และจากคำแนะนำของ CDER พบว่ากราฟแสดงการละลายของเม็ดยาของ 2 บริษัทเท่าเทียมกัน แต่ต่างจากอีกบริษัทหนึ่ง อย่างไรก็ตาม คุณภาพโดยรวมของยาเม็ดอะเซตามิโนเฟนของทั้ง 3 บริษัทเป็นที่น่าพอใจ เนื่องจากเป็นไปตามเกณฑ์มาตรฐานของ USP 40 และ BP 2017

คำสำคัญ: ยาเม็ดอะเซตามิโนเฟน, การควบคุมคุณภาพ, การทดสอบการละลาย, การวิเคราะห์หาปริมาณตัวยาสำคัญ, การทดสอบความสม่ำเสมอของปริมาณตัวยาสำคัญในยาแต่ละเม็ด

Introduction

Acetaminophen, also known as paracetamol and APAP (N-acetyl-para-aminophenol) is one of the most widely used over-the-counter analgesic and antipyretic medication. It was first prepared by H. N. Morse in 1878. Although many studies on its use as an analgesic were performed, it was not marketed until 1950 under the name Triagesic. Today, its most common trade names are Tylenol and Panadol, but a large percentage of its sales are as generic drugs (American Chemical Society, 2014, September 15) which prices are typically 20% to 90% cheaper.

According to ASEAN harmonization product on pharmaceutical registration ASEAN Common Technical Requirements--ACTR, 2016), all registered medications in Thailand are tightly controlled by the Food and Drug Administration--Thai FDA; reassuringly, generic drugs and new drugs (original brand name drug) are equivalent in quality, safety and efficacy for interchangeability. Quality part is evaluated from quality assurance process in pharmaceutical industries whereas safety and efficacy are evaluated from clinical trials for new drugs or bioequivalence studies/dissolution tests for generic drugs (U.S. Department of Health and Human Services Food and Drug Administration, 2017). Acetaminophen products are exempted from a bioequivalence studies because it is categorized in the Biopharmaceutical Classification System--BCS Class I (World Health Organization, 2006).

Quality of drug products is mainly set according to the official pharmacopoeias such as the United States Pharmacopeia and the National Formulary-USP-NF. (The United States Pharmacopeia 40: National Formulary 35, 2016; Stippler, 2019, June 5) and the British Pharmacopoeia--BP (British Pharmacopoeia 2017, 2016). For the conventional

tablets, uniformity of weight (mass), tablet friability, tablet breaking force, dissolution, assay and uniformity of dosage units are required to perform to confirm the quality of tablets.

Uniformity of weight, also known as weight variation, is a test for ensuring that every tablet contains an amount of a drug substance intended with little variation among tablets within a batch. This test is applicable for uncoated and film coated tablets. Friability test is carried out to measure the mechanical strength of compressed and uncoated tablets. Tablet breaking force, commonly known as tablet hardness in the pharmaceutical literatures, is the force required to cause the tablets to break in a specific plane. Both friability test and tablet breaking force tests are carried out to test the strength and resistant force to withstand mechanical shock during production, packaging, distribution and storage. However, uniform of weight, friability and tablet breaking force are not present in the pharmacopoeial monograph. They are part of manufacturer's own product specifications especially for in-process quality control.

Dissolution testing measures the amount of drug that goes into solution at specific time point (dissolution test) or over a period of time (dissolution profile) under standardized conditions. The Center for Drug Evaluation and Research--CDER guidance (U.S. Department of Health and Human Services Food and Drug Administration, 1997) suggests that a comparative dissolution testing at three to four or more dissolution time points (other than zero and equally spaced) should be utilized for rapidly dissolving drugs. Dissolution plays a major role in the decision-making process, particularly in the development and approval of generic dosage forms, where unnecessary human studies e.g. bioequivalence study may be waived.

Assay is the quantitative determination of a drug substance in a drug product, expressed as the percentage of the labeled amount (%LA). Uniformity of dosage units is the test to ensure the consistency of dosage units. Each unit in a batch should have a drug substance content within a narrow range around the labeled amount. The uniformity of dosage units can be demonstrated by either content uniformity or weight variation.

In the present study, the quality of acetaminophen tablets commercially available in Thailand was compared.

Research Objective

Acetaminophen tablets are widely used OTC drug but there are many brands with various price available in Thailand market, making it difficult for consumer to decide to buy by themselves. Therefore, the aim of the present study was to compare the quality of acetaminophen tablets (500 mg/tablet) by selecting three different brands of pharmaceutical equivalence with the price ratio of 1.00: 0.80: 0.25 from the retail stores. Evaluation of the results base on USP 40 and BP 2017 together with CDER guidance 1997.

Materials and Methods

1. Materials

1.1 Chemicals and reagents

Acetaminophen powder BP (chromatographic purity: 99.7%) was obtained from Vidhyasom (Bangkok, Thailand). Methanol (HPLC grade) and water (HPLC grade) were purchased from RCI Labscan (Bangkok, Thailand). Other chemicals were analytical grade.

1.2 Samples

Three brands of commercially available uncoated acetaminophen tablets were taken and coded accordingly as A, B and C. Detailed information of the different brands of acetaminophen tablets are summarized in Table 1. The labeled shelf life of all tablets is five years from the manufacturing date. The tablets were taken for evaluation before four and a half years of the labeled expiry date. All three brands have the same labeled amount of acetaminophen (500 mg/tablet) and the relative prices for 100-tablet package of brand A, B and C are 1.00:0.80:0.25. However, there is no detailed information about their excipients.

Table 1

Acetaminophen tablets used in the tests

Brand	Appearance	Manufacturing Date	Expiry Date	Relative Price
A	White uncoated caplet (oblong tablet) with name on one side and dose on the other side	10/09/18	10/09/23	1.00
B	White uncoated caplet with name on one side and dose on the other side	12/09/18	12/09/23	0.80
C	White, circular uncoated tablet with name on one side and distributor name on the other side	10/08/18	10/08/23	0.25

2. Methods

All test methods were carried out as stated in USP40 NF35 except uniformity of weight (mass) and dissolution profile comparisons which were carried out as stated in BP2017 and the CDER guidance, respectively.

2.1 Uniformity of Weight (Mass)

Twenty tablets of each sample were randomly taken and weighed individually using an analytical balance (Sartorius, ENTRIS 224i-1S). Percent deviations of individual mass from the average mass were calculated as follows: % mass deviation=[(individual mass-average mass)/average mass]x100

2.2 Tablet Friability

For tablets with a unit weight equal to or less than 650 mg, a sample of whole tablets corresponding as near as possible to 6.5 g is taken. Therefore, 11 tablets from brand A, 12 tablets from brand B and 13 tablets from brand C were weighed and placed in drums (Erweka Friabilator) separately. The drums were rotated at 25±1 rpm for 4 minutes. Dust from the tablets was removed and the tablets were reweighed. Tablet friability was expressed as % friability calculated using following equation.

% friability = (lost weight/initial weight) x 100

2.3 Tablet Breaking Force

Ten tablets of each sample were inserted individually into a tablet breaking machine (Erweka Hardness Tester) lined up in the center of the plate. When the device was turned on, the plate gradually applied force onto the tablets until the

tablets were split. Then, the force at which this event occurred was recorded. Tablet breaking force was expressed as mean with %RSD.

2.4 Dissolution

2.4.1 Dissolution Test

Dissolution test of each sample was carried out using USP Apparatus 2 (paddle) at a speed of 50 rpm in 900 mL of dissolution medium (phosphate buffer pH 5.8) maintained at 37±0.5 °C and controlled by a water bath fitted with a variable speed stirrer and heater (Vankel, VK 7010). Samples (5±0.1 mL) were taken at 30 minutes. Each sample was filtered, diluted, measured for the absorbance at 243 nm using a UV-Visible spectrophotometer (Shimadzu, UV 1800). Concentrations of acetaminophen in the samples were determined from a calibration curve generated by plotting the absorbance against six different concentrations (0.2, 0.5, 0.8, 1.0, 1.2 and 1.4 mg/100 mL) of standard acetaminophen solution (n=3). The coefficient of determination, y-intercept and slope of the regression line were determined by linear regression analysis.

2.4.2 Dissolution Profile

Dissolution profiles were carried out under the same conditions as in the dissolution test except the sampling times. The profiles presented as the cumulative percentages of the amount of drug released at each sampling interval. Each profile is an average of twelve individual tablets. Samples (5±0.1 mL) were taken at a predetermined time interval (1, 3, 5, 10, 15, 30, 45 and 60 minutes) and replaced with an equal volume of fresh medium to maintain a constant dissolution volume. Each sample was filtered, diluted, measured for the absorbance at 243 nm. Concentrations of acetaminophen in the samples were determined against the calibration curve as indicated in section 2.4.1. Similarity factors (f2) were determined for dissolution profile comparison.

$$f2 = 50 \times \log\{[1+(1/n) \sum(R-T)^2]^{-0.5} \times 100\}$$

R - mean percentage of dissolution from reference brand

T - mean percentage of dissolution from test brand

2.5 Assay

Standard solution (0.01 mg/mL)

An accurately weighed quantity of acetaminophen powder BP equivalent to 25 mg of acetaminophen was transferred to a 50-mL volumetric flask and made up to the volume with mobile phase. A 5 mL of the resulting solution was transferred to a 250-mL volumetric flask and made up to the volume with mobile phase.

Sample stock solution (0.5 mg/mL)

For each sample, 20 tablets were accurately weighed and ground to fine powder. A quantity of powder equivalent to 100 mg of acetaminophen was transferred to a 200-mL volumetric flask followed by a 100 mL of mobile phase. The flask mechanical shaken for 10 minutes, sonicated for 5 minutes and made up to the volume with mobile phase.

Sample solution (0.01 mg/mL)

A 5 mL of the sample stock solution was transferred to a 250-mL volumetric flask and made up to the volume with mobile phase. A portion of this solution was passed through a 0.45-μm filter. The first 10 mL of the filtrate was discarded. The clear filtrate was used.

Chromatographic condition

High performance liquid chromatography (Shimadzu, LC 10AD) was carried out at ambient

temperature, using a C18 column (4.6x250 mm, 5 μm). An isocratic mobile phase of methanol and water (25:75 v/v) was used at a flow rate of 1.5 mL/min. The injection volume was 10 μL and the total run time for each sample was 5.0 min. The sampling needle was washed with mobile phase between each injection.

System suitability

Chromatographic parameters were determined from five replicate injections of standard solution. Theoretical plate was not less than 1000, tailing factor was not more than 2 and relative standard deviation was not more than 2.0%.

Analysis

Triplicate independent determination for each sample was performed. The percentage of the labeled amount of acetaminophen in the sample tablets taken (%LA) was calculated and expressed in mean with %RSD.

$$\%LA = (PAU/PAS) \times (CS/CU) \times 100$$

PAU - average peak area from two replicate injections of the sample solution

PAS - average peak area from two replicate injections of the standard solution

CU - concentration of acetaminophen in the sample solution (mg/mL)

CS - nominal concentration of acetaminophen in the and standard solution (mg/mL)

2.6 Uniformity of Dosage Units

The uniformity of dosage units was determined by weight variation due to high content of acetaminophen (≥25 mg and ≥25%). Ten tablets were individually weighed and determined the content from the assay result. The Acceptance Value--AV was calculated. If the value was not accepted, twenty more tablets were tested. The AVs from the content of overall thirty tablets were recalculated.

Result and Discussion

1. Uniformity of Weight (mass)

Uniformity of weight was carried out according to BP instead of USP because only weight variation of dietary supplements (not for drug products) is available in USP. The results of uniformity of weight (Table 2) showed that all three brands conformed to the BP acceptance criteria which is not more than 2 of the individual masses deviate from the average mass by more than 5 percent and none deviates by more than 10 percent. Brand A had the highest average weight and the narrowest range of the percentage of mass deviation (630.7 mg, -1.2% to 1.5%) following by Brand B (575.8 mg, -2.0% to 2.2%) and Brand C (526.0 mg, -2.3% to 2.0%).

Table 2

Uniformity of weight, friability, table breaking force, dissolution, assay and uniformity of dosage unit results from three brands of acetaminophen tablets

Test	Brand A	Brand B	Brand C
Uniformity of weight (mean in mg, %deviation)	630.7, -1.2 to 1.5	575.8, -2.0 to 2.2	526.0 -2.3 to 2.0
Friability (%)	0.16	0.19	0.40
Table breaking force (mean in Kp, %RSD)	24.91, 5.9	29.29, 10.9	30.19, 11.3
Dissolution (mean in %dissolution, %RSD)	95.2, 4.8	96.0, 5.4	96.3, 5.6
Assay (mean in %LA, %RSD)	99.3, 0.2	102.5, 1.1	101.8, 3.6
Uniformity of dosage unit (mean in %LA, AV)	99.2, 1.7	102.1, 3.0	100.6, 3.1

2. Tablet Friability

The results of tablet friability (Table 2) showed that all three brands conformed to the USP acceptance criteria which friability is not more than 1 percent and no cracked, cleaved, or broken tablets were observed. However, Brand C had the highest percentage of friability (0.40%) following by Brand B (0.19%) and Brand A (0.16%).

3. Tablet Breaking Force

The results of tablet breaking force (Table 2) showed that Brand C had the highest breaking force (30.19 Kp) following by Brand B (29.29 Kp) and Brand A 24.91 (Kp). In addition, Brand C had the highest percentage of relative standard deviation (11.3) following by Brand B (10.9) and Brand A (5.9).

It is impossible to directly compare the breaking force among tablets from these three brands because they have different dimension and geometry. Moreover, their tablet orientations in the tester were also different: the width (parallel to the longest axis) of caplets for brand A and B, the diameter of round tablet for brand C.

4. Dissolution

4.1 Dissolution Test

The mean regression equation for the calibration curve of acetaminophen was y=0.5516x + 0.0153 and the mean coefficients of determination (R2) was 0.9992. Concentrations of acetaminophen in each tablet determined from the regression equation were shown in term of percentage of dissolution (Table 2). All three brands conformed to the USP acceptance criteria at first stage (S1) which the number of tests was 6 tablets and the percentage of dissolution of each tablet was not less than Q + 5% (Q=80). Brand C had the highest mean percentage of dissolution and the highest percentage of relative standard deviation (96.3%, 5.6%) following by Brand B (96.0%, 5.4%), and Brand A (95.2%, 4.8%) respectively. There was no significant difference among the different manufacturer's products although their tablet breaking forces were quite different.

4.2 Dissolution Profile

The results of dissolution profiles are shown in Figure 2. According to the regulatory interest focusing on how similar the two curves,

the f2 comparison has been the focus and used to make decision (Moore and Flanner, 1996; Shah et al., 1998). From f2 equation if summation of two curve difference is equal to 10%, the value of f2 will approximately be 50. Generally, f2 values greater than 50 (50-100) ensure equivalence of the two curves (difference <10%).

Only three data points at 3, 5 and 10 minutes from each brand were accepted for f2 calculation according to the CDER guidance. From the calculated f2, dissolution profiles of Brand B and Brand C were considered to be equivalent, but they are slightly different from Brand A.

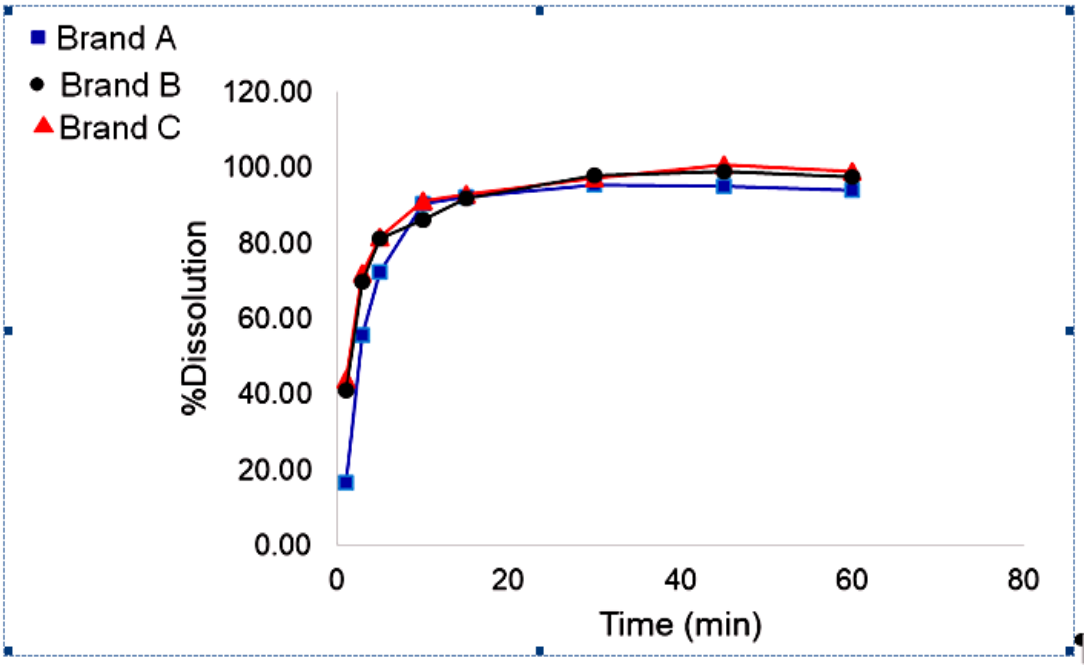

Figure 2 Dissolution profiles of three brands of acetaminophen tablets in phosphate buffer pH 5.8 ($f_{2,A-B}$ = 47.97, $f_{2,A-C}$ = 49.79, $f_{2,B-C}$ = 74.05)

5. Assay

According to the USP method, the concentration of acetaminophen in the samples were determined by HPLC using single point external standard. Acetaminophen showed a well- defined chromatographic separation within a run time of 5 minutes (Figure 3). The retention time of acetaminophen was 3.493 minute, 0.383% (mean, %RSD, n=5).

The contents of acetaminophen in the tablets from all three brands (Table 2) conformed to the USP acceptance criteria which %LA is 90.0 to 100.0. However, the contents of acetaminophen in Brand C were spread out over the largest range of values (%RSD=3.6).

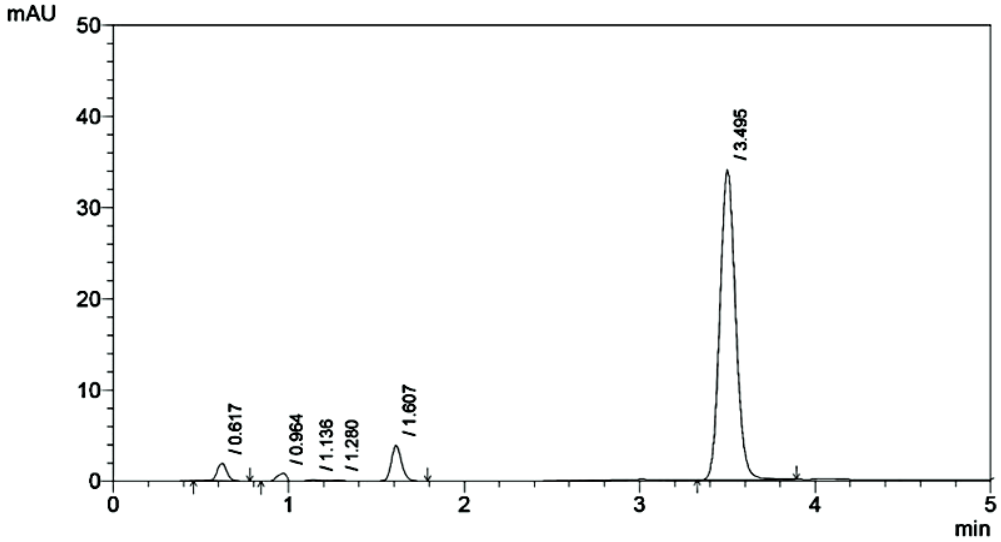

Figure 3 Typical chromatogram of acetaminophen (0.01 mg/mL in 25%v/v methanol)

6. Uniformity of Dosage Units

All three brands conformed to the USP acceptance criteria at first level (L1) which number of tests was 10 tablets and the AV was not more than 15. Brand C had the highest AV (3.1) following by Brand B (3.0) and Brand A (1.7).

Conclusion

This study clearly demonstrated that all three brands of acetaminophen tablet comply with USP 40 and BP 2017 criteria for the tests of uniformity of weight, friability, dissolution test, assay as well as uniformity of dosage unit except the test of tablet breaking force due to no available pharmacopoeial acceptance criteria. It was also found that the distribution of the results from lower price brand were slightly wider than the more expensive brand. According to CDER guidance, dissolution profiles of two brands were considered to be equivalent, but they are slightly different from the other one. However, the overall quality of the three brands of acetaminophen tablets was satisfactory as they met the USP 40 and BP 2017 requirements. It seems that the price has no effect on the acetaminophen tablet quality according to pharmacopoeial standards.

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