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Original Article

Comparative evaluation of the physicochemical properties of acetaminophen formulations

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ABSTRACT

The current study compared the physicochemical properties of 7 Acetaminophen (AAP) formulations from Thailand (3 formulations), the Philippines (3 formulations), and Japan (1 formulation). This study assessed the appearance of formulations from Thailand (T-A, -B, and -C), the Philippines (P-A, -B, and -C), and Japan (J). This study was subjected to a hardness test, uniformity of weight test, content uniformity test, and dissolution test in accordance with the Japanese Pharmacopoeia. Results of the hardness test indicated that all of the formulations had a hardness of 70 N or greater. All formulations showed within 97–02% by uniformity of weight test. Comparison of dissolution profiles indicated that the P-B formulation had dissolution of about 77% at 15 min, and this level of elution was lower than that from other formulations ($p<0.05$). Unlike the P-B formulation, the other 6 formulations had around 85% or more elution of AAP in 15 min. The physical and chemical properties of the T-A, -B and -C formulations that are used in the Thailand, the P-A and -C formulations that are used in the Philippines, and the J formulation that is used in Japan complied with the Japanese Pharmacopoeia. Thus, these formulations are assumed to be equivalent.

Keywords: acetaminophen, equivalent, Thailand, Philippines, dissolution profiles

INTRODUCTION

Acetaminophen (N-acetyl-p-aminophenol: AAP (paracetamol)) is a drug that has been widely used in clinical practice as an antipyretic/analgesic. Use of non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin in children is avoided over concerns about exacerbating influenza-associated encephalopathy. This is why AAP is commonly used as an antipyretic/analgesic for children. AAP and NSAIDs are non-opioid analgesics. The 3-step analgesic ladder of the World Health Organization (WHO) describes drugs to manage cancer pain, and the first step in that ladder is the use of AAP or an NSAID[1-2]. AAP is considered useful in various situations, but poisoning due to an overdose poses a problem. AAP can cause several problems, including elevated methemoglobin resulting in cyanosis, hemolysis resulting in anemia, renal dysfunction, and hepatic dysfunction[3-4]. Therefore, pharmaceutical equivalence is an important factor in terms of therapeutic effectiveness and safety. A dissolution test is commonly conducted in vitro in order to ensure the pharmaceutical equivalence of orally administered tablets and capsules. This is because there are differences between batches, and such testing facilitates the development of different dosage forms and it helps to ensure the quality of preparations. Predicting a preparation's bioequivalence and bioavailability in vitro is also crucial[5-6].

Over the past few years, an increasing number of countries allow AAP to be purchased without a prescription. In the Philippines, for example, customers can purchase AAP as an antipyretic once they explain their symptoms to a pharmacist at the counter of a pharmacy. In Thailand, AAP can be purchased at convenience stores in town. Although AAP must be purchased with an understanding of the effectiveness, efficacy, and safety of paracetamol and the characteristics of the preparation in question, information on the characteristics of that preparation may not be conveyed to the patient. In contrast, AAP is still a prescription drug in Japan. A patient may obtain AAP from a pharmacist pursuant to a prescription from his or her doctor. In February 2015, a 500-mg

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AAP formulation became available by prescription in Japan. This formulation, which is manufactured in accordance with the Japanese Pharmacopoeia, adheres to the same standards as formulations available overseas.

In the current study, the Japanese 500-mg AAP formulation was used as a reference standard to assess the physicochemical properties of 6 other formulations, 3 of which came from Thailand and 3 of which came from the Philippines. The appearance of the formulations and blister packs were assessed, and a hardness test and a uniformity of weight test were conducted to verify the properties of each formulation. As described here, a content uniformity test and a dissolution test were also conducted to assess the quality of the formulations.

MATERIALS AND METHODS

Materials: Seven different AAP formulations were used in the present study. Three AAP formulations of 500-mg caplets were from Thailand: Paracap from Masa Lab Co. Ltd. (Lot No. 140320) was designated T-A, SaRa from Thai Nakorn Patana (Lot No. 0140414) was designated T-B, and Tylenol from Janssen-Cilag Ltd. (Lot No. 401245) was designated T-C. Three AAP formulations of 500-mg tablets were from the Philippines: Biogestic from United Lab (14038301) was designated P-A, Rapidol from Pasteur Pharma (Lot No. BC141M04) was designated P-B, and Paracetamol from JB Orchid Pharmaceuticals, Inc. (9634) was designated P-C. One formulation of 500-mg caplets was from Japan: Calonal from Showa Yakuhin Kako Co., Ltd. (Lot No. 4041V) was designated J (Table 1). In addition, a standard sample of AAP and other reagents were purchased from Wako Pure Chemical Industries Ltd., Japan.

Determination of appearance: Formulations were uncoated tablets or caplets. The diameter of the caplet/tablet was measured and stamping on its surface was noted. Labeling on the formulation's blister pack was also noted.

Hardness test: The hardness of 10 tablets/caplets of each formulation was measured in the direction of the diameter using a Monsanto tablet hardness tester (Minato Medical Co., Ltd.).

Uniformity of weight test: A uniformity of weight test was conducted with each formulation. The weight of 10 uncoated tablets/caplets was measured using an electronic balance (AUW220D, Shimadzu, Tokyo).

Disintegration test: A disintegration test was conducted with a disintegration tester (NT-2H, Toyama Sangyo) to measure the disintegration time for 5 tablets/caplets of each formulation.

Content uniformity test: A content uniformity test was conducted in accordance with the 16th edition of the Japanese Pharmacopoeia. A sample solution was prepared using 10 tablets/caplets of each formulation and a standard solution was prepared using a standard sample of AAP. For the standard solution, each tablet/caplet was placed in a 200-mL water:methanol (25:25) solution, and the solution was shaken for 60 min. After shaking, 10 mL of the sample solution was collected and filtered using a 0.2-μm membrane filter. Five mL of the filtrate was diluted to 50 mL with water:methanol (25:25). Afterwards, 5 mL of that sample solution was measured and diluted to 50 mL with water:methanol (25:25). Five mL of that sample solution was measured and diluted to 50 mL with water:methanol (25:25) to obtain the sample solution. High-performance liquid chromatography (HPLC) was used to calculate the AAP content in proportion to the indicated amount of AAP in the formulation. Content was ascertained by determining the acceptance value in accordance with the 16th edition of the Japanese Pharmacopoeia. The criterion for the acceptance value is 16% according to the Japanese Pharmacopeia. If the acceptance value did not exceed 15%, the formulation complied with the Japanese Pharmacopeia.

Dissolution test: A dissolution test was conducted in accordance with the paddle method in the 16th edition of the Japanese Pharmacopoeia and the Guidelines for Bioequivalence Testing of Generic Drugs[12] (hereafter denoted as the Guidelines). Dissolution testing of samples was performed using a dissolution apparatus (NTR-593, Toyama Sangyo) at 37 ± 0.5°C with 900 mL of distilled water that was stirred at 50 rpm using the paddle method. Ten mL of each sample solution was collected after 0, 5, 10, 15, 30, and 60 min and then filtered through a 0.20-μm membrane filter. Afterwards, 5 mL of the filtered sample was measured and diluted to 50 mL with water:methanol (20:25). Five mL of the diluted sample solution was diluted to 50 mL with water:methanol (25:25) to serve as the sample solution. The AAP content in each sample solution was determined using HPLC.

HPLC: HPLC was performed in accordance with a dissolution test for AAP tablets as specified in the 3rd section of the Japanese Pharmaceutical Codex (denoted here as the 3rd section of the JPC). Assays were done with a high-performance liquid

chromatograph (HPLC, SPD-20A Shimadzu, Kyoto). Assay conditions were a column of Inertsil ODS-3 (4.6×150 mm, 5 μm), a column temperature of 40°, a mobile phase consisting of a mixture of 0.05 mol/l potassium dihydrogen phosphate and methanol (4:1, pH 4.7), and a detection wavelength of 245 nm. AAP retention time was set so that the flow rate would be 5 min, and the sample injection volume was 40 μL.

Statistical analysis: Results are presented as the mean ± standard deviation, and statistical significance was evaluated using the Tukey-Kramer test.

RESULTS

Hardness test: Results of the hardness test were 148.0±10.2 N for the T-A formulation, 137.0±13.2 N for the T-B formulation, 106.5±5.5 N for the T-C formulation, 215.9±11.6 N for the P-A formulation, 107.8±12.7 N for the P-B formulation, 71.5±10.6 N for the P-F formulation, and 91.7±2.4 N for the J formulation. All of the formulations had a hardness of 70 N or greater (Table 2). Significant differences between the T-A formulation and the T-B formulation and between the T-C formulation and the P-B formulation in terms of hardness were not noted. However, significant differences in hardness (p<0.05) were noted for other formulations.

Uniformity of weight test: The weight of the T-A formulation, the T-B formulation, the P-B formulation, and the J formulation was around 550 mg. However, the T-C formulation, the P-A formulation, and the P-C formulation had a weight of 600 mg or greater.

Content uniformity test: Results of the uniformity of weight test are shown in Table 2. The AAP content in individual formulations ranged from 97–102% of the labeled content. The acceptance value for the T-A formulation was 4.3, that for the T-B formulation was 8.5, that for the T-C formulation was 10.9, that for the P-A formulation was 5.1, that for the P-B formulation was 7.1, that for the P-C formulation was 8.9, and that for the J formulation was 3.9. Acceptance values for all of the formulations were 15% or less (the criterion in the 16th edition of the Japanese Pharmacopoeia), so requirements were met.

Disintegration test: Results of the disintegration test were 74.0±2.8 s for the T-A formulation, 128.5±19.9 s for the T-B formulation, 144.3±10.6 s for the T-C formulation, 192.2±11.7 s for the P-A formulation, 429.3±13.8 s for the P-B formulation, 121.8±22.9 s for the P-C formulation, and 169.7±21.2 s for the J formulation. The disintegration time was 300 sec or less for all of the formulations except the P-B formulation (Table 2). Significant differences between the P-B formulation and the T-A formulation, the T-B formulation, the T-C formulation, the P-A formulation, the P-C formulation, and the J formulation and between the T-A formulation and the P-A formulation in terms of the disintegration time were noted.

Dissolution test: The dissolution profiles for the Thai formulations (the T-A formulation, the T-B formulation, and the T-C formulation) are shown in Fig. 1-a. The T-B formulation was found to have a dissolution rate that was 15 slower than that of the T-A formulation. The dissolution profiles for the Filipino formulations (the P-A formulation, the P-B formulation, and the P-C formulation) are shown in Fig. 1-b. Differences in the dissolution profiles of the individual formulations were not noted.

Dissolution profiles for all of the formulations are shown in Fig. 2. As is apparent, the T-A formulation, the T-B formulation, the T-C formulation, the P-A formulation, the P-C formulation, and the J formulation had dissolution of 85% or greater prior to 15 min. However, the P-B formulation, did not have dissolution of 85% prior 15 min. All of the formulations were found to have dissolution of 85% or greater prior to 30. In addition, significant differences in dissolution at 15 min were not noted for the P-B formulation in comparison to dissolution at 15 min for other formulations (p<0.05).

Appearance: Diameters of individual formulations (long and short axes) are shown in Table 2. Thai formulations (the T-A formulation, the T-B formulation, and the T-C formulation) and the Japanese formulation were caplets. In contrast, Filipino formulations (the P-A formulation, the P-B, and the P-C formulation) were all tablets.

Oblong tablets had a long axis of 15.0–17.5 mm, a short axis of 7.0–8.0 mm, and a thickness of 5.5–6.0 mm. Round tablets had a diameter of 12.8–13.0 mm and a thickness of 3.7–4.5 mm. The name of the formulation was stamped on the surface of each tablet. The brand name was stamped on both sides of the T-A formulation. The T-B formulation and the T-C formulation had the specified content (500) and the brand name stamped on one side. The P-A formulation, the P-B formulation, and the P-C formulation had the specified content (500) and the brand name or the company logo stamped on one side (Fig. 3). In contrast, the J formulation only had an identification number stamped on one side. All of the P formulations were scored. A photo of the packaging of individual formulations is shown in

Fig. 4. The T-A formulation, the T-B formulation, and the T-C formulation featured the brand name in Thai and English on the packaging. The P-A formulation, the P-B formulation, and the P-C formulation featured the brand name in English. The expiration date was listed on the packaging of the T formulations and the P formulations. The brand name in Japanese and English was written on the J formulation.

DISCUSSION

The purposes of this study were to compare quality standards for 7 seven AAP formulations available in Thailand, the Philippines, and Japan and to assess those standards. Comparison was done using physical and chemical parameters for AAP tablets (500 mg). Physical and chemical properties such as hardness, weight variation, content uniformity, dissolution, and preparation appearance (shape, stamping, and packaging) were compared. Tests yielded results specific to certain formulations. These results reflected differences in the physical properties of individual formulations.

The weight variation test revealed differences in the weight of individual formulations. These results indicate differences in the amount and types of additives in individual formulations. The P-C formulation had a weight of 609.2±9.6 mg, and the standard deviation in that weight tended to be greater than that of other formulations.

Hardness ranged from 70 N to 220 N. Differences in hardness were attributed to types of additives and tableting process used to produce individual formulations. A study has reported that a tablet with a diameter of 6–8 mm and a hardness of 50 N or greater or a tablet with a diameter of 9–10 mm and a hardness of 70 N or greater will typically not be damaged during manufacture or transport[7]. In addition, a high level of hardness causes the capping of tablets and can potentially cause tablet damage. The current findings indicated differences in the weight of individual formulations, and properties of additives in powder form, and tablet shape and size. However, tablets were presumably not hard enough to affect drug quality. A dissolution test is an important index with which to assess the pharmaceutical equivalence of tablets. Such an approach is used to compare brand-name and generic drugs. Japanese guidelines for generics stipulate 85% or more elution of AAP in 15 min. However, comparison of dissolution profiles indicated that the P-B formulation had elution of about 77% at 15 min, and this level of elution was lower than that from other formulations ($p<0.05$). The P-B formulation was found to have variations in weight and content. This means that its physical properties would differ from those of other formulations. Unlike the P-B formulation, the other 6 formulations had around 85% or more elution of AAP in 15 min. Thus, these 6 formulations were generally equivalent. In contrast, the P-A formulation had a hardness of 215.9 N, which was greater than that of the other formulations. If tablets contain the same additives, their disintegration time is known to typically lag in proportion to their hardness [8]. However, the dissolution profile for the P-A formulation was similar to that for the other Thai formulations (T), the Filipino formulations (P) (except for the P-B formulation), and the J formulation. Pharmaceutical information regarding the additives in individual formulations was unavailable, but based on the profiles for the formulations the additives in the P-A formulation contributed to the disintegration of those tablets. Looking specifically at hardness, the T-C formulation had a hardness of around 70 N, which was lower than that of the other formulations. This formulation is an OTC pharmaceutical that is available at convenience stores, so care with regard to damage is required when this formulation is commercially distributed. The T formulations and the P formulations featured the brand name or generic name on the surface of tablets/caplets. In Thailand, a prescription is not necessary when purchasing drugs in a convenience store, so drug packaging features a bar code. Depending on the country, there are differences in ways in which AAP formulations are handled despite the fact that those preparations contain AAP.

This study conducted physical and chemical testing to compare different AAP formulations in accordance with the Japanese Pharmacopoeia. The tested formulations were the T-A formulation, the T-B formulation, and the T-C formulation that are sold in Thailand, the P-A formation and the P-B formulation that are sold in the Philippines, and the J formulation that is sold in Japan. These formulations were assumed to be equivalent. The Thai formulations and the Filipino formulations conformed to the US Pharmacopoeia while the J formulation was formulated based on the Japanese Pharmacopoeia. Assessing pharmaceutical equivalence or similarity is a crucial component in terms of harmonizing drugs in Thailand, the Philippines, and Japan, as the current results have indicated. In this study, adequate numbers of tablets of the T formulations and the P formulations could not be obtained to test tablet friability and perform a disintegration test and long-term stability test. Temperature and humidity levels vary more in Japan as seasons change (high temperatures and humidity in the summer and low temperatures and dryness in the winter) than they do in Thailand and the Philippines. A stability test that takes these

seasonal variations into account needs to be performed in the future.

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CONFLICTS OF INTEREST

This study was conducted fairly and impartially and ethical considerations were taken into account. The authors have no relationships with any companies or other commercial entities mentioned in this paper.

Table 1 Tablets and caplets

Country	Brand Name	Serial No.	Lot No.
Thailand	PARACAP	T-A	140320
Thailand	SaRa	T-B	0140414
Thailand	Tylenol	T-C	401245
Philippines	BIOGESTIC	P-A	14038301
Philippines	Rapidol	P-B	BC141M04
Philippines	PARASETAMOL	P-C	9634
Japan	CALONAL	J	4041V

Table 2 Comparison of the physical properties of each AAP formulation

Serial No.	T-A	T-B	T-C	P-A	P-B	P-C	J
Content Uniformity (%) (n=10)	102.1 ±1.0	101.4 ±2.2	97.1 ±3.6	102.2 ±1.3	101.7 ±2.5	100.0 ±4.0	100.4 ±1.6
Weight Variation (mg) (n=10)	564.0 ±2.8	564.3 ±5.2	629.7 ±1.7	644.5 ±4.8	549.8 ±8.4	609.2 ±9.6	559.4 ±0.7
Hardness (N) (n=10)	148.0 ±10.2 [a]	137.0 ±13.2 [b]	106.5 ±5.5 [c]	215.9 ±11.6 [d]	107.8 ±12.7 [e]	71.5 ±10.6 [f]	91.7 ±2.4
Degradation (sec) (n=5)	74.0 ±2.8 *	128.5 ±19.9	144.3 ±10.6	192.2 ±11.7	429.3 ±13.8 [#]	121.8 ±22.9	169.7 ±21.2
Shape major-axis×minor-axis ×thick	Couplet 15.0×8.0 ×6.0	Couplet 17.5×7.0 ×5.5	Couplet 17.5×7.0 ×6.0	Tablet 12.8×4.3	Tablet 12.8×2.8	Tablet 13.0×4.5	Couplet 17.5×7.5 ×5.2

a : $p < 0.05$ T-A vs. P-C, P-A, P-B, P-C, J ; b : $p < 0.05$ T-B vs. P-C, P-A, P-B, P-C, J
c : $p < 0.05$ T-C vs. P-A, P-C, J ; d : $p < 0.05$ P-A vs. P-B, P-C, J
e : $p < 0.05$ P-B vs. P-C, J ; f : $p < 0.05$ P-C vs. J
: $p < 0.05$ P-B vs. T-A, T-B, T-C, P-A, P-C, J ; * : $p < 0.05$ T-A vs. P-A
Presented as mean ± SD. All statistical analyses were done using the Tukey-Kramer test

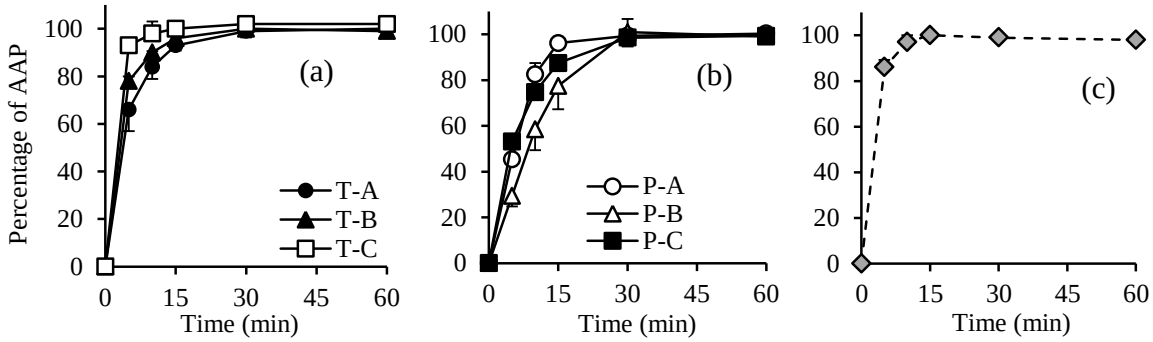

Figure 1 Dissolution profile of different AAP formulations
(a) Thai formulations T-A, -B, and -C, (b) Filipino formulations P-A, -B, and -C, (c) Japanese formulation J

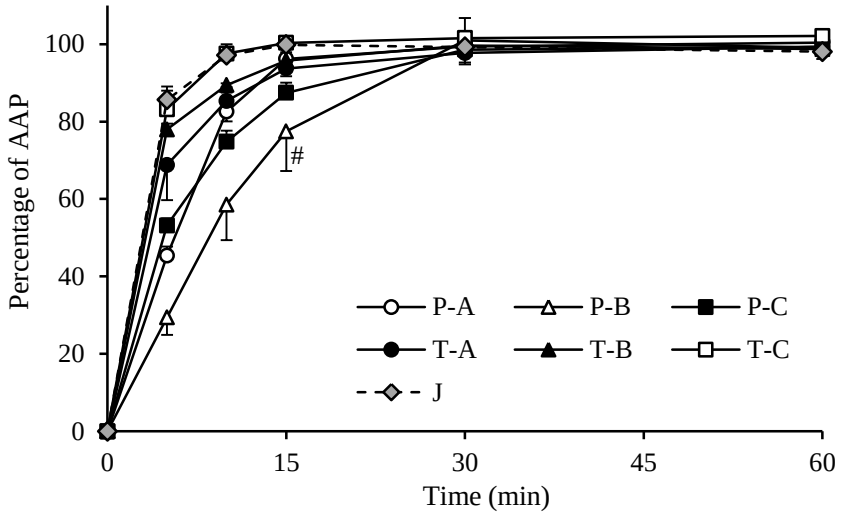

Figure 2 Dissolution profile of seven different AAP formulations
: $p < 0.05$ P-B vs. T-A, T-B, T-C, P-A, P-C, J

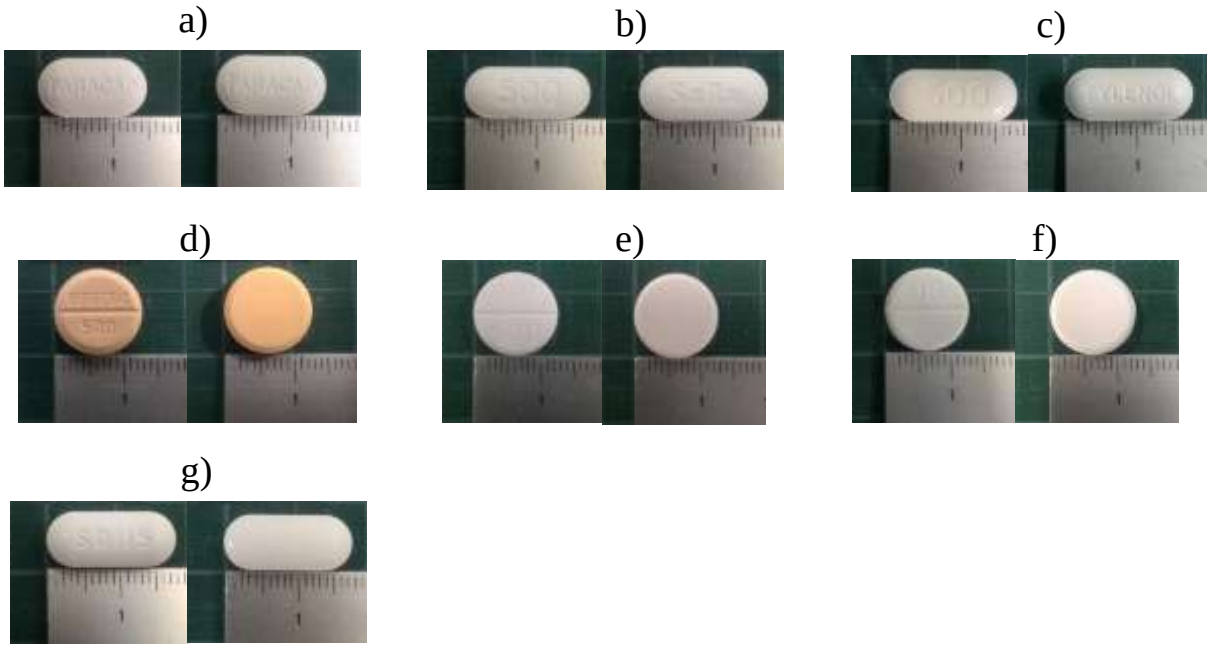

Figure 3 Appearance of formulations and stamping
a) T-A, b) T-B, c) T-C, d) P-A, e) P-B, f) P-C, g) J

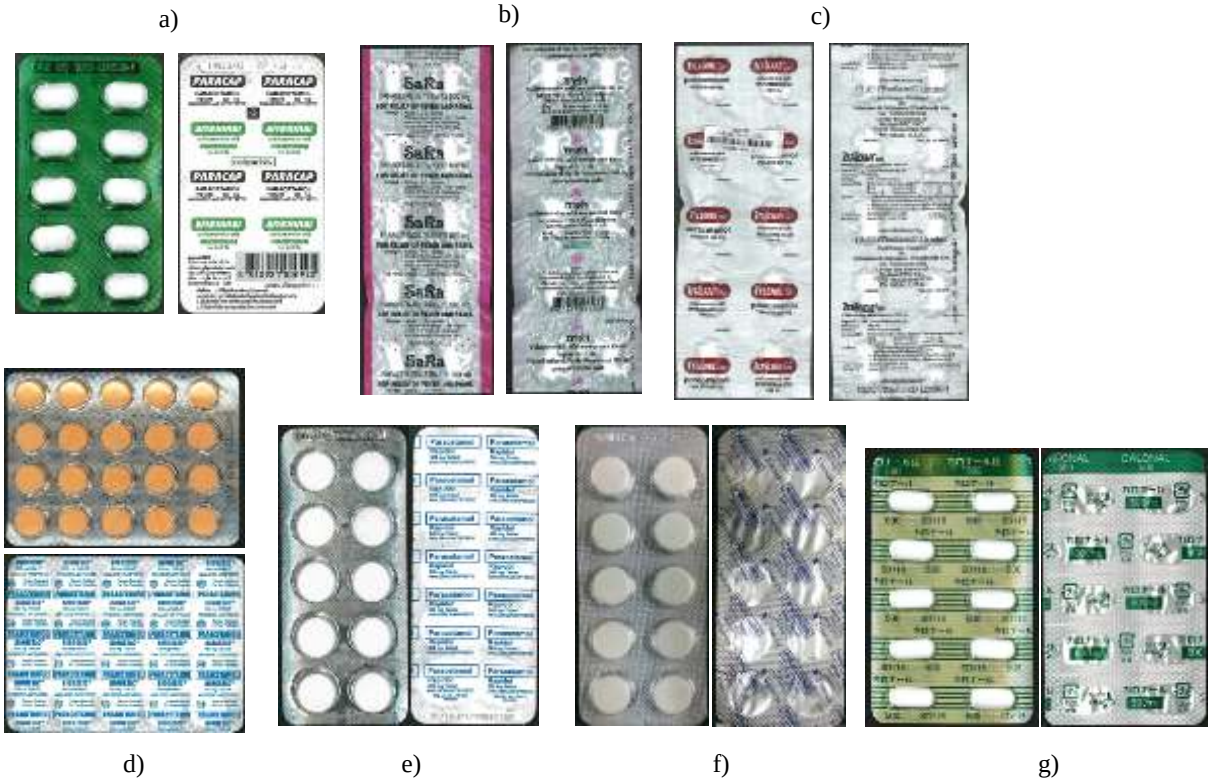

Figure 4 Photograph of the blister pack
a) T-A, b) T-B, c) T-C, d) P-A, e) P-B, f) P-C, g) J

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