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Quality Assessment on Generic Antipyretic Tablets and their Stability Withstanding Unfavourable Environments.

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Abstract
Paracetamol is an antipyretic drug that is commonly used to lower body temperature. It is classified as an over-the-counter medicine and safe to be consumed with proper guidance. Paracetamol comes in many dosage forms, most commonly in tablet form. In this research, a comparison of two different brands of generic paracetamol tablets with a significant difference in selling price difference was evaluated. Two brands were tested, namely brand A and brand B, which passed the quality tests set by British Pharmacopoeia and United State Pharmacopeia in terms of the weight variation, friability, hardness test, disintegration, uniformity of thickness and dissolution. It was suggested that the cheaper paracetamol tablets (brand A) exhibited better quality as per the required standard. A stability study on the cheaper tablets (brand A) was also performed by manipulating the storage temperature of the tablet for a period of 30 days. The study revealed there were no significant quality changes when there was a change in storage temperatures. Overall, the study suggested that cheaper medication especially in tablet dosage form possessed excellent quality and appeared stable in different storage conditions. The present finding indirectly debunks the stigma that expensive medications are far better in terms of quality than the cheaper ones. Simultaneously, this will help in reducing the economic burden of patients from low- or middle-class income in finding suitable medication.

Keywords: Tablet dosage form, paracetamol, quality control, pharmacy, pharmaceutical technology.

Introduction

Antipyretic drug is a medication that is prescribed for patients with fever. Paracetamol, the antipyretic agent can overcome high body temperature by inhibiting the prostaglandin that induces elevation of temperature. [1] This medication is easy to get as it is classified as an over-the-counter (OTC) medicine. The variety of medicine brands available in the market influences their selling price, as manufacturers use different excipients and formulation techniques during drug development. Hence, end-users, customers, or patients will seldomly get confused about selecting the best medicine options. It is often assumed that medicine with a higher price has better quality and efficacy as compared to the cheaper medicine option. This kind of stigma or perception is common among the citizens. A study carried out in Italy revealed that 50% of the test respondents were aware that the cheaper generic medicine is due to unneeded research and development (R&D), marketing, and promotion activities by the manufacturer company, as data can be readily obtained from the originator. However, another 50% of respondents believed that generic drug price fluctuation was due to the medicine's quality. [2]

Paracetamol is formulated in many types of dosage forms. The most common one is in a tablet form with the strength of 500 and 650 mg. The designation of paracetamol as an OTC medication opens the opportunity for pharmaceutical manufacturers to produce more generic paracetamol to be marketed under their specific brands. Besides, tablet is one of the dosages forms that require less expensive raw materials to be produced thus higher profits return is expected. In the effort of evaluating the quality of the marketed tablet, several relevant tests such as disintegration, dissolution, hardness, friability, and weight variation can be carried out. These specific tests allow the comparison to be made between the generic tablets marketed with different brands. Outcomes from the testing strictly adhere to standard requirements by United State Pharmacopeia (USP) and British Pharmacopeia (BP).

Methodology

The subsequence quality tests are conducted in accordance with requirements suggested by USP, BP and National Pharmaceutical Regulatory Agency (NPRA).

Sample preparation

Two brands of paracetamol tablets (namely A and B) were randomly selected and purchased from a random pharmacy located in Ipoh, Perak (Malaysia). In total, 96 units of the tablet were prepared to be used for quality control and stability testing. Tablet details such as price, dose strength, and expiry date were identified and recorded. The actual marketed brand name cannot be revealed due to product privacy in terms of marketing jeopardization.

Physical evaluation

Tablets from each brand were physically evaluated in terms of their colour, odour, and shape. Details of the evaluation were recorded.

Quality control test

Generic paracetamol tablets (500 mg) from two different brands were used for assessment of its quality control parameters such as weight variation, hardness test, friability, disintegration, dissolution, and uniformity content.

(A) Weight variation

Twenty paracetamol tablets from each brand were weighted, and the average weight was calculated for its percentage mean. The weight variation percentage was referred to the standard requirements set up by BP and USP guidelines.

(B) Hardness test

Ten paracetamol tablets from each brand were individually tested for their hardness test by using a hardness tester machine (SOTAX). A tablet was

placed vertically, and the force was applied to the tablet. The step was repeated on the remaining tablets from each brand and the force required was recorded.

(C) Friability

The initial weight of 10 tablets from each brand was recorded. Then the tablet friability was evaluated using a friabiliator machine (COPLEY) that was set to operate at 25 rpm for 4 minutes. All tablets were reweighted, and the total final tablet weights were recorded. The friability percentage loss was calculated according to the following formula. Limit loss stated by USP is not more than 1%.

$$\%F = \frac{\text{Wo} - \text{Wi}}{\text{Wo}} \times 100$$

%F = Percentage of friability
Wo = Initial total weight
Wi = Final total weight

(D) Disintegration test

Six tablets from each brand were subjected to disintegration testing. In this assessment, distilled water was used as a disintegration medium at a temperature of 37.0 ± 0.5°C. Time taken for each tablet to be fully disintegrated was recorded. For an uncoated tablet time requirement stated by BP is less than 15 minutes.

(E) Uniformity of thickness

Uniformity of thickness was measured using a SOTAX machine to find the mean thickness of the tablet. Exactly 5 tablets of each brand were individually measured, and the measurement data was recorded.

(F) Construction of standard graph

Exactly 100 mg of paracetamol powder was dissolved in 75 mL of 0.1 M phosphate buffer and 25 mL of methanol (1:3 v/v) in a volumetric flask to produce 1,000 µg/mL of paracetamol stock solution. Series of paracetamol concentration 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/mL were prepared through dilution technique using 0.2 M of sodium phosphate buffer as diluent. Paracetamol standard curve was constructed based on absorbance value obtained through an ultraviolet-visible (UV-Vis) spectrometry analysis at a wavelength of 243 nm.

(G) Dissolution test

Six tablets from each brand were subjected to dissolution test. According to USP, the preferable dissolution medium that can be used is 0.2 M sodium phosphate buffer at pH 6.8. The USP type-1 dissolution machine (Basket Apparatus) was used, the operation protocol was set at 50 rpm and the temperature of the medium was maintained at 37.0 ± 0.5°C. The specimen of the dissolution was withdrawn within the time interval of every 10 minutes until 1 hour. Exactly 1 mL of the sample was taken and was diluted into 10 mL of fresh 0.2 M sodium phosphate buffer, 37.0 ± 0.5°C. The same amount of dissolution medium was replaced in the dissolution vessel. The absorbance of the solution was measured by using UV-Vis spectrophotometer at a wavelength of 243 nm.

Stability testing

A total of 32 paracetamol tablets was placed in the refrigerator at a temperature of 4°C ±3°C to study its stability against a selected storage condition. All experimental protocols were in accordance with the standard guidelines prepared by NPRA. This experiment was conducted upon one selected brand, kept in selected storage condition for 30 days. The criteria for choosing a tablet brand are depending on data obtained from a comparison between two brands. According to NPRA, parameters such as tablet appearance, weight variation test, hardness test, friability, uniformity of thickness, and dissolution profile are necessary to study tablet stability against external factors.

Statistical analysis

The one-way analysis of variance (ANOVA) was used to analyze all collected data, with the significant difference between data means

determined by Duncan's multiple range test at a 95% confidence level (p<0.05) with a minimal number of replication (n=3) using SPSS 17.0 Statistic software. All graphs and standard curves were constructed by using GraphPad Prism 5 software.

Results and discussion

Sample preparation

Generic paracetamol tablets (500 mg) were purchased from a local pharmacy located in Ipoh, Perak (Malaysia). Since paracetamol is in the OTC group, a prescription was not required. Two generic brands of paracetamol tablets (namely brand A and brand B) were selected based on the significant price difference. Details on the tablet were listed in Table 1. Information on the manufacturer company for both tablets was classified, due to the nature of the study that focuses on the random commercial OTC medication. Brand A cost much cheaper compared to brand B. The pricing criterion is important to emphasize that a slightly cheaper medicine is also manufactured in good quality as compared to the expensive medicine.

Table 1. Details of generic paracetamol tablets from brand A and B.

	*Brand A	*Brand B
Price each strip (RM)	1.00	3.00
Quantity per strip	10	10
Lot number	PAI8M382	2002115
Expiry date	06/21	02/22

**Actual information on manufacturer for both tablet brands were classified*

Physical evaluation

Referring to Table 2, generic paracetamol tablets of brand A and brand B appeared in white colour and come with round and oval shapes, respectively. Both brands are manufactured in different shapes despite having a similar concentration of API. Every manufacturer uses a similar API for the same medicine production, which is the paracetamol (acetaminophen) with a variety of excipient formulations that is suitable with reasonable total production cost. Hence, the difference in shape is assumed that the manufacturer is using different types of excipient or formulation methods. [3] This also relatively explains the smoother surface texture of tablets from brand B as compared to brand A. As for colour, both tablet brands appeared in white. Tablet colour also indicates the preferable target consumers. The main production intention is for adult consumption as colouring tablets are usually for kid attraction. [4-5]

Table 2. Physical appearance of generic paracetamol tablets from brand A and brand B.

	Brand A	Brand B
Size	Large	Large
Colour	White	White
Shape	Round	Oval
Surface textures	Rough	Smooth

Quality control evaluation

Quality control testing is important to ensure the quality of the tablet is safe, effective, and efficient. [6] There are several quality tests that are mandatory to be run for a medicine prior to its being marketed. As for tablet dosage form, weight variation, hardness test, friability, disintegration, uniformity of thickness, and dissolution assessment are the common tests carried out as per BP and USP.

(A) Weight variation

A weight variation test is required to test the homogeneity of a tablet in each production batch. [7] Failure to comply with the requirement set by BP or USP indicates that the drug content in each tablet does not reflect the labeled API strength. In this evaluation, both brands of generic paracetamol tablets with a strength of 500 mg passed the weight variation test (Table 3). According to BP, tablets that weigh more than 250 mg should not exceed ± 5% fluctuation of weight variation. [8] Weight variations of tablets

from both brands A were within the range set by BP, which was ± 5% of the mean weight of 543.50 to 600.71 mg and 538.93 to 595.65 mg, respectively. The variety of weight variations among different brands of paracetamol tablets exist due to the type of excipients used in the formulation. Every manufacturer may or may not use the same type of excipients. [8] The percentage of relative standard deviation (%RSD) value can be used as an indicator to determine the reproducibility and homogeneity of manufactured tablets. Data analysis showed that tablets from both brands have no significant difference (p<0.05) in terms of the weight means, suggesting that tablets from both brands appeared in excellent quality.

Table 3. Weight variation of generic paracetamol tablets from brand A and brand B.

	Brand A	Brand B
Average tablet weight (mg)	572.10 ± 6.754[a]	567.29 ± 8.218[a]
Tablet weight (mg)	564.80 – 585.90	552.00 – 579.90
*Weight variation limit (%)	5.0	5.0
*Weight variation limit (mg)	543.50 – 600.71	538.93 – 595.65
**RSD (%)	1.18	1.45
Quality status	Passed	Passed

*Data on average tablet weight was presented as mean ± SD (n=20). Superscripted letter (a) indicates no significant difference at p<0.05. *Limit variation is accordance to BP guideline for a tablet below 250 mg. **%RSD was calculated based on standard applied formula.*

(B) Hardness test

A hardness test was performed to determine the minimum force applied to break the tablet. A high degree of hardness strength can avoid chipping or breakage during the handling of the tablet. [9] The hardness test requirement as set by BP is more than 40 N. [10] Hence, a tablet that can withstand at least 50 N is considered as in good quality. [8] Referring to Table 4, the hardness of tablets from brand A was determined as 170.9 ± 8.399 N, while the hardness of tablets from brand B was determined as 176.3 ± 16.159 N. During the manufacturing process, the hardness of the tablets can be improved by compressing the tablet at higher force, increase the binder concentration and increase the total volume of granulating fluid. [11] However, over hard tablet may affect the disintegration time, whereby the tablet will disintegrate at a slower rate. [9] Data analysis shows no significant difference (p<0.05) in terms of the hardness and suggested that both brands passed the quality requirement for standard tablet production.

Table 4. Hardness assessment of generic paracetamol tablets from brand A and brand B.

	Brand A	Brand B
Average tablet hardness (N)	170.9 ± 8.399[a]	176.3 ± 16.159[a]
Tablet hardness range (N)	152 – 179	147 – 197
*Hardness variation limit (N)	> 40 N	> 40 N
Quality status	Passed	Passed

*Data on average tablet hardness were presented as mean ± SD (n=10). Superscripted letter (a) indicates no significant difference at p<0.05. *Limit variation is accordance to BP guideline.*

(C) Friability

Friability test is a test to demonstrate and predict the possible weight loss during transportation. [9] In this study, 10 tablets from each brand were randomly selected and subjected to friability test using Roche friabilator tester. Failure of friability test indicates a problem in formulation especially concentration of binder. [12] The total final weight of the tablets was recorded, and the percentage of weight loss was calculated. Referring to Table 5,

tablets from both brands have passed the friability test, indicating compliance to the USP guideline, in which the percentage of loss is less than 1%. Tablets from brand A and brand B exhibited the percentage loss of 0.61% and 0.33%, respectively. Tablets from brand B seems to possess better durability against external force. However, both tablet brands still considered fulfilling standard requirement of not losing more than 1% weight loss against external force. Friability study is one of the indicators used to determine the ability of tablets to withstand undesirable physical force during transportation and distribution after manufacturing. If friability is more than 1%, it can affect the content of the active ingredients, which may reduce the therapeutic efficacy.

Table 5. Friability testing on generic paracetamol tablets from brand A and brand B.

	Brand A	Brand B
Initial total tablet weight (mg)	5741.2	5656.7
Final total tablet weight (mg)	5706.3	5637.6
*Weight loss (%)	0.61	0.33
**Limit of weight loss (%)	1.0	1.0
Quality status	Passed	Passed

*Number of tablets for each brand is 10 (n=10). *Percentage of weight loss was calculate based on a standard formula. **Limit variation is in accordance with BP and UPS guidelines for a tablet above 250 mg.*

(D) Disintegration

Disintegration test was carried out to determine the time taken for a tablet to fully disintegrate or break down into small particles and release into a medium. [13] Time taken for tablets to disintegrate was recorded. According to USP, uncoated tablet disintegration time must be less than 15 minutes. Table 6 shows that all tested tablets achieved to meet the specification required by USP as tablets from brand A disintegrated at an average of 1 minute, while brand B disintegrated at an average of 59 seconds. Data analysis showed that there is no significant difference in terms of the disintegration rate for both tablet brands. The disintegration procedure is considered completed if there are no tablet residues or traces that remain visible on the apparatus screen or at the bottom surface of the disc. [3] Disintegration profile can be affected by the hardness of the tablet. A tablet that is intended to be fast acting commonly possesses lower hardness. [14] The disintegration rate can be manipulated during tablet formulation. For example, the use of a super disintegrant such as crospovidone can improve the time taken for tablet to be disintegrated. This formulation is perfect for a fast-release type of tablet. [14] Disintegration is one of the important qualities to be controlled as small changes in formulation could affect the drug release property in the body system, relatively affecting both kinetics and dynamics of the API. [3]

Table 6. Disintegration time for generic paracetamol tablets from brand A and B.

	Brand A	Brand B
Disintegration time (mins)	1.04 ± 0.03^a	0.52 ± 0.05^a
*Disintegration time limit (mins)	< 15	< 15
Quality status	Passed	Passed

*Data presented was mean ± SD (n=20). Superscripted letter (a) indicates no significant difference at p<0.05. *Limit disintegration time is in accordance with USP guidelines for uncoated tablet.*

(E) Uniformity of thickness

The thickness of a tablet is a part of unofficial tests. However, the table thickness relates to the quality of a manufactured tablet. Commonly, a manufacturer has the standard size for packaging. Variations in thickness can affect the packaging of the tablet. [12] According to Table 7, all tablets were produced with appropriate thickness. Although the thickness of the tablet is not an important criterion highlighted by BP or USP, however, it is crucial to monitor the thickness of the tablet to ensure there is no variation in thickness as it can affect the acceptance of consumers. [12] Statistical analysis shows that there is a significant difference in terms of the thickness of tablets between brand A and brand B.

This can be explained that both tablet brands have different shape, whereas brand A comes in round-shaped and brand B come in an oval shape. Every manufacturer has a different excipient and method used in the preparation of tablets. These differences can also affect the differences in tapped density or particle size, which can affect the difference in thickness of the tablet. [12]

Table 7. Thickness of generic paracetamol tablets from brand A and B.

	Brand A	Brand B
Average tablet thickness (mm)	4.10 ± 0.06^{a}	6.05 ± 0.04^{b}

Data presented was mean ± SD (n=10).
Superscripted letters (a-b) indicate the significant difference at $p<0.05$.

(F) Dissolution test

Dissolution test is an *in vitro* test to predict the percentage quantity of drug in a tablet dosage form to be dissolved in a solution that resembles the biological environment. The percentage amount of drug released was calculated based on constructed paracetamol standard curve. Referring to both dissolution profiles (Figure 1), tablets of brand A and brand B managed to release their content of around 85.22% and 96.27% within 30 minutes, respectively. Tablets from both brands can be considered to pass the quality check as the standard guideline (USP) requires the tablet to release their content of at least 80% within 30 minutes of consumption. [11] The dissolution rate data are correspondent to disintegration data (Table 6) as tablets from brand B disintegrated and dissolute at a higher rate as compared to tablets from brand A. Dissolution has a direct relationship with the bioavailability of the drug and affects the kinetic behavior of the drugs in the body system. [14] Hence, the study on dissolution quality of the finished tablets is crucial as it affects drugs absorption and bioavailability. [11] A documented comparison study revealed that the addition of crospovidone in formulation, instead of the other disintegrants such as sodium starch glycolate, croscarmellose sodium was proven to exert a higher dissolution percentage within 30 minutes with a very short difference in disintegration. [14] However, the formulation containing crospovidone also has a similar time of disintegration to croscarmellose sodium, but their dissolution percentage release is not the same, which is slightly lower as compared with the crospovidone formulation. Hence it is safe to say that dissolution profile is a complex mechanism and not just only can be affected by hardness, but the type of excipients used in the formulation. Data analysis showed that tablets from brand B were significantly ($p<0.05$) released at a much higher rate as compared to brand A. Nevertheless, all tablets had passed the dissolution requirement as set by USP.

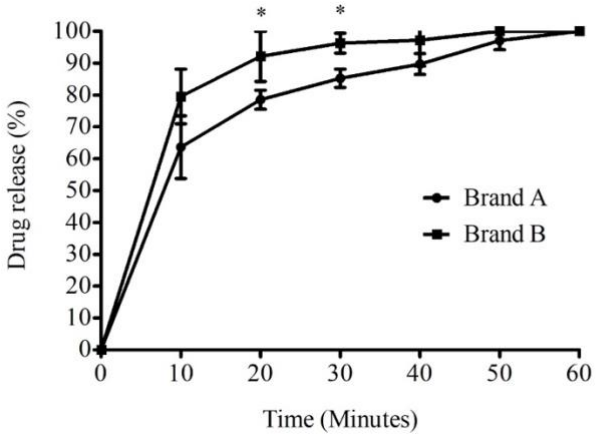

Figure 1. Dissolution profiles of generic paracetamol tablets. Asterisk signs (*) indicate significant differences of percentage drug release for brand A as compared to Brand B tablets at $p<0.05$ ($n=6$).

Stability study

The physical parameter of each tablet seems to pass the test. A guideline from NPRA emphasizes that the physical parameters such as colour and odour must be evaluated. The cheapest tablet brand yet possessed the equivalent quality was selected for stability assessment against storage conditions. Tablets were stored at room temperature and in the refrigerator. After 30 days of storage, a further quality test on weight variation, friability, hardness, and thickness was

conducted and it was found that all tablets passed the basal requirements for distribution (Table 8). Weight variation of room temperature was supposed in between 545.33 to 602.73 mg. The room temperature tablet minimum weight was 559.7 mg whereas the maximum weight was 597 mg. Hence, it passes the weight variation. As for weight variation of tablets in refrigerator, it was supposed to be in the range between of 542.90 to 600.05 mg. The minimum weight variation of tablets in refrigerator was 559.2 mg, whereas the maximum weight was 589.2 mg. Both tablets fall in desired weight hence they passed the test. SPSS statistical analysis shows that weight variation has no significant difference between both brands. Friability testing shows they both pass the quality test. The tablet stored in room temperature lost 0.42% whereas tablets stored in refrigerator weight lost was 0.31% of their average weight. To be considered passed, the weight loss of friability should not be more than 1% of its average weight. Hardness test of room temperature tablet mean are 162.60 ± 10.63 N whereas for tablet in the refrigerator are 189.10 ± 8.94 N. As discussed, hardness of tablet can be considered excellent quality if it is able to stand more than 50 N physical force. Statistical analysis between both tablets showed there is a significant difference in terms of their hardness. Documented research revealed that the storage of tablets at 4°C for more than 30 days may increase the hardness of the tablet. [15] However, the tablet's hardness started to degrade after 5 months. This is probably due to the increase moisture of the tablet at around 4–5%, where long exposure causes water to absorb in the tablet, disrupting the attraction forces between particles. [15] It was suggested that significantly deteriorate in tablet hardness can be observed if the study period is extended for more than 5 months in refrigerator. Tablet thickness is recorded as 4.17 ± 0.08 mm for room temperature and 4.16 ± 0.11 mm for refrigerator, respectively. The result pattern is expected as the tablet is manufactured using a similar formulation protocol. [12] The disintegration of the tablet is a complex quality assessment. There is a correlation between tablet hardness and the disintegration rate. [8] Tablets that are desired to possess a prolonged release property such as buccal dosage form are more favoured with a higher hardness so the tablet disintegration will take a longer time. However, it depends on the type of excipient used in the formulation. Since the tablet was manufactured using the similar formulation, the result showed there is no significant difference in terms of the disintegration rate (Table 9). Dissolution profiles of tablets stored at room temperature and refrigerator showed to pass the quality requirement set by USP and BP (Figure 2). For paracetamol to be considered as passed they need to release at least 80% of its active ingredient in 30 minutes. Tablets at room temperature manages to release 85.22% and for refrigerator release 84.72% of its content within 30 minutes. As for mean comparison, data showed no significant difference in terms of both dissolution profiles. Through the findings, it was suggested that 30 days of storage in a refrigerator is not affecting the quality of the tablet in terms of their dissolution.

Table 8. Physical quality evaluation of generic paracetamol tablets of brand A at selected different temperature storage.

Quality test	Room temperature	$^{+}$Refrigerator
Weight variation (mg)	574.03 ± 9.28^{a}	571.48 ± 9.63^{a}
Hardness (N)	162.6 ± 10.63^{a}	189.1 ± 8.94^{b}
Friability (%)	0.42	0.31
Thickness uniformity (mm)	4.17 ± 0.08	4.16 ± 0.11

Data presented were mean ± SD, after 30 days of stability assessment. Superscripted letters across column (a–b) indicate significant difference at $p<0.05$.
$^{+}$Refrigerator temperature was set at 4 ± 3°C

Table 9. Disintegration time for generic paracetamol tablets of brand A at selected different temperature storage.

	Room temperature	+Refrigerator
Disintegration time (mins)	2.00 ± 0.34[a]	1.51 ± 0.24[a]
*Disintegration time limit (mins)	< 15	< 15
Quality status	Passed	Passed

*Data presented were mean ± SD (n=6). Superscripted letter (a) indicates no significant difference at p<0.05. *Limit disintegration time is in accordance with USP guideline for uncoated tablet. +Refrigerator temperature was set at 4 ± 3°C.*

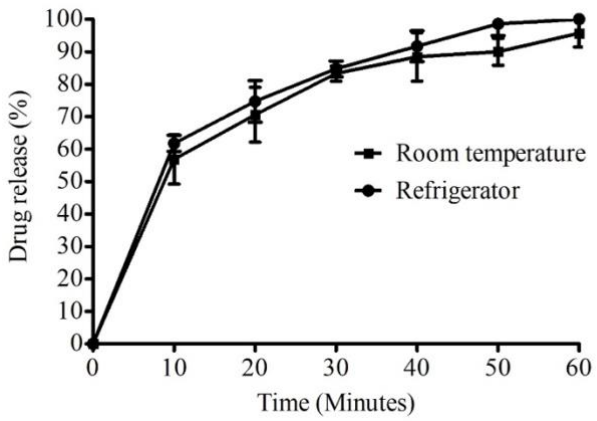

Figure 2. Dissolution profiles of generic paracetamol tablets (brand A) after being stored in different temperature for 30 days. Refrigerator temperature was set at 4 ± 3°C.

Conclusion

Referring to collected data, tablets from brand A and brand B have passed all the quality testing. As for the stability study, the selected cheapest tablets (brand A) that were stored at both storage temperatures managed to pass all the quality tests as well. The present study suggests that the difference in terms of selling price does not correlate with the quality of a tablet. The finished products must comply with a standard quality assessment prior to being marketed. The tablet from brand B indeed to possess remarkable standard quality, but with a slightly higher selling price. Consumers do have their preferences when it comes to medication selection. It brings to a fact that not all expensive medications are better than the cheaper option, thus cheaper medication may provide an alternative selection for people from the low-income category. In terms of drug stability, this study provides information that storage temperatures do not deteriorate tablet quality over time. However, the present stability study is limited to 30 days of storage period. Further study can be performed to evaluate the actual stability of the tablets if were stored for a much longer period. It can be concluded that medication in tablet dosage form does not require special storage conditions, such as low-temperature ambiance to prolong its shelf-life.

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Conflict of interest

Authors wish to confirm that there is no conflict of interest associated with this publication. Authors have read the manuscript and agreed to be subjected for publication.

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