Pharmaceutical equivalency of locally and regionally manufactured generic pharmaceutical products in UAE

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ABSTRACT

Generic drugs or generic medicines are pharmaceutical products manufactured to be equivalent to the brand/innovator drug products. They represent the majority of worldwide prescribed medicines; therefore, their quality is critical to maximize patients’ therapeutic outcomes. This study aimed to evaluate the pharmaceutical equivalency of locally and regionally manufactured generic pharmaceutical products being sold in the United Arab Emirates (UAE) market to enhance public confidence, promote their utilization, and reduce treatment costs. Three drugs (tadalafil, rosuvastatin, and acetaminophen) from three different pharmacological classes were selected from the UAE market as representatives for generic drugs. At least two generic products for each locally (L) and regionally (R) manufactured generic were evaluated according to the USP criteria in comparison to the brand (B) comparator product. All comparative tests were performed before storage and 3 and 6 months after storage during the accelerated stability study performed under the conditions for climatic zone IV (40 °C ± 2 °C (75% RH ± 5% RH)). Although results were statistically different from the comparators using ANOVA and Tukey’s Kremer post hoc tests, all tests were within the USP acceptance limits, except one, for friability, disintegration, content uniformity, and dissolution. Significant changes were observed following their storage over 6 months during accelerated stability studies, however, without failing the USP limits. Only one locally manufactured acetaminophen generic failed the USP dissolution tests before and after its storage and failed the disintegration test following its storage under accelerated conditions for zone IV. In conclusion, the majority of the locally and regionally manufactured generic products being sold in the UAE market were of good quality and performed similarly to their comparators. However, a continuous independent quality evaluation for the marketed generic drugs is essential to enhance public confidence.

Keywords: Acetaminophen, Generics, Pharmaceutical equivalency, Rosuvastatin, Tadalafil, United Arab Emirates

1. Introduction

Generic drugs are pharmaceutical products formulated and manufactured to be same as a marketed brand drug and result in same pharmacological and clinical responses. Generic drug should meet both the pharmaceutical (having same dosage form, route of administration, strength, quality, and performance characteristics) and therapeutic (having same safety and efficacy profile “bioequivalent”) equivalency of brand product to be approved by various regulatory agencies to be sold in the market where they are registered (U.S. FDA, 2021). Pharmacologically equivalent generic product having the same active pharmaceutical ingredient (API) and bioequivalent to the brand product is expected to share the same risks and benefits of the brand product, therefore interchangeable with the brand drug (U.S. FDA, 2020).

Generic drugs offer significant accessibility benefits for patients by reducing treatment cost and allow for price competition that stimulates therapeutic innovation and quality improvement that would impact the whole healthcare system. Generic pharmaceutical companies can afford to offer their generic drugs at a much more competitive prices, up to 85–95% lower, compared to brand products due to significant cost-savings resulting from avoiding registration requirements for conducting safety and efficacy clinical trials (U.S. FDA, 2018, 2019b). This price difference between brand and generic drugs would justify substituting brand products...
with generics by physicians and pharmacists (Masson and Steiner, 1985). This resulted in having 90% of the US filled prescriptions to be generic drugs (U.S. FDA, 2019b).

Furthermore, the introduction of generic competitors would motivate and drive the whole drug discovery and development field to innovate new treatments and develop novel medications and delivery systems. Existing and newly emerging research and development (R&D) pharmaceutical companies would then compete to offer more innovative and safer new or alternative drug products compared to off-patent drugs. Additionally, the larger the number of generic drugs in the local market, the more competitive the prices would be (U.S. FDA, 2019a), leading to the potential of reducing the prices of both locally manufactured and imported brand and generic drugs.

Recently, we reviewed the literature and found a limited number of independent studies evaluating the quality of generic products in the local market of UAE or even in the regional and international markets (Abdul Rasool et al., 2011; Hanafy, 2016; Mullaicharam et al., 2012; Otsuka et al., 2008). The number and the magnitude of the published studies that were conducted to evaluate the quality of generic products were minimal compared to the number of generic drugs being sold in the local, regional, and international markets. Additionally, not all the generic products that have been evaluated in the published studies were within the acceptable USP limits. Furthermore, these published studies were not performed regularly to ensure the continuity and maintenance of acceptable qualities of the existing generic products in the market. Therefore, we aimed in this study to evaluate the pharmaceutical equivalence of locally and regionally manufactured generic drugs that are being sold in the UAE market to provide more comprehensive assessment for the quality of the generic drugs being consumed by the citizens, residents, and tourists in UAE.

We hypothesized that regular, continuous, and random independent but comprehensive evaluation for the quality of locally and regionally manufactured and sold generic pharmaceutical products, which represent a large percentage of the consumed medicines, is essential to ensure the continuous production of high-quality generic products. Such studies would complement the mission of regulatory agencies, enhance public confidence and awareness about the quality of generic products and potential treatment savings due to increased generic drugs utilization.

2. Materials and methods

2.1. Materials

The generic and brand pharmaceutical products tested in this study along with their corresponding APIs used for their manufacturing were generously donated by their local manufacturing companies or agents in the UAE. Additional packages were purchased from local community pharmacies when necessary.

Trifluoroacetic acid (TFA), glacial acetic acid (GAA), sodium dodecyl sulfate (SDS), phosphate buffer (PB), and sodium citrate dehydrate (SCD) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Methanol and acetonitrile were purchased from Honeywell (MI, USA). Phosphoric acid (PA) was purchased from VWR International (Fontenay-sous-Bois, France) and anhydrous citric acid was purchased from CDH (Daryaganj, New Delhi, India). All purchased chemicals were high-performance liquid chromatography (HPLC) grade and the water used was deionized water.

2.2. Methods

2.2.1. Selection of generic drugs

The research design for the evaluation of the quality of generic drugs in the UAE market was based on the selection of APIs that belongs to three different pharmacological classes. The selection criteria for the sampled generic and brand drug products from the three pharmacological classes required their availability in the same dosage form and strength in the UAE market. The generic products to be selected should be available as well as locally (L) and regionally (R) manufactured generic products in the UAE market. For regionally marketed generic products, the search was limited to the Kingdom of Saudi Arabia, Oman, Kuwait, and Jordan.

Following obtaining the required permissions, the database of the Ministry of Health and Prevention (MOHAP) was accessed to screen for the products that fit the previously mentioned study selection criteria for the pharmaceutical equivalence evaluation.

A minimum of two generic products were selected from each of the three pharmacological classes that are manufactured and sold by two different local pharmaceutical companies (L) in the UAE market to be evaluated according to the quality control tests described hereafter. Additionally, a minimum of two generic products of the same pharmacological classes that are manufactured by two different regional manufacturers (R) and sold in the UAE market were also selected to be evaluated. The selected four locally and regionally manufactured generic products were coded L1, L2, R1 and R2 for the three APIs tadalafil, rosuvastatin and acetaminophen. The same pattern of coding was used to code any additional products that were tested from the three APIs.

The selected comparator brand products available in the UAE market were Cialis®, Crestor® and Panadol®. The dosage form and strength of the selected brand and generic products for each pharmacological class were the same. The comparators were coded B for the three actives.

2.2.2. Evaluation of selected products

The selected drug products and their comparators were tested for their pharmaceutical quality in accordance with the United States Pharmacopeia (USP) methods and criteria. Quality testing of the tablets included dimensions, hardness, friability, disintegration, content uniformity, dissolution, and accelerated stability testing for 6 months. All the USP tests were performed from the same batch for each product at room ambient temperature before storage (0 month) and at 40 °C ± 2 °C /75% RH ± 5% RH (Zone IV) after storage for 3 and 6 months.

The obtained generic and brand drug products for each pharmacological class were divided into three groups. The products in the first group were tested and analyzed for their quality immediately after their collection to represent the initial sampling time point (0 months) before their storage for accelerated stability testing. The other two groups were placed in their original manufacturer packaging in a stability chamber Climacell (MMM Medcenter Einrichtungen GmbH, München, Germany) to test for changes in their quality over 3 and 6 months of storage at 40 °C ± 2 °C /75% RH ± 5% RH (Zone IV). These changes included physical changes and changes in the API content and dissolution.

2.2.2.1. Appearance and color changes. All tested tablets (n = 6) were visually inspected for appearance and color changes after storage for 3 and 6 months in the stability chamber at 40 °C ± 2 °C /75% RH ± 5% RH (Zone IV).

2.2.2.2. Tablets dimensions. The tablets’ dimensions for each tested product (n = 6) were measured using a digital caliper (Vernier electronic digital caliper, Vinca, China) to ensure consistency within the tablet batch. The dimensions measured included the thickness and diameter for round tablets and the thickness, length, and width for caplets. The tablets’ dimensions were measured again for the same products following their storage for 3 and 6 months to detect any changes in their dimensions.
2.2.2.3. Hardness. The mechanical strength of the tablets must withstand the different processing stages starting from the manufacturing, packaging, and shipping until they are administered by patients. The mechanical strength of the tablets \((n = 6)\) was measured using Benchesaver tablet hardness tester (Varian, Toronto, ON, Canada) to ensure appropriate hardness and consistency within the tablet batch and to detect changes over 3 and 6 months of storage at zone IV (USP/NF, 2020d).

2.2.2.4. Friability. Friability test was performed using a Friability Tester (ElectroLab, India) to measure the physical strength of the compressed tablets and their ability to withstand shipping and handling. This test will be helpful to ensure that the different generic products being sold in the UAE market maintain the required physical strength during shipping and storage and, therefore, their physical quality over 3 and 6 months of storage at zone IV.

For products with a tablet weight of >650 mg, a sample of ten tablets was carefully dedusted and accurately weighed. When the tablet weight was equal to or less than 650 mg, the number of sampled tablets was increased to reach as near as possible to 6.5 g. Tablets were placed in the drum of the friability rotator and rotated 100 times at a speed of 25 ± 1 rpm., then removed and accurately weighed after the removal of any loose dust from the tablets (USP/NF, 2020e). The procedure was repeated for the tablets stored for 3 and 6 months at zone IV to detect changes in the friability of the tablets.

Usually, the test is performed once, unless the difference in weight loss is >1%, then the test should be repeated twice, and the mean of the three tests should not exceed 1% to pass the USP criteria. If any cracked, cleaved, or broken tablets are detected after tumbling, the batch fails the USP test.

2.2.2.5. Disintegration. The disintegration test was performed using a disintegration tester (ElectroLab, India) to ensure complete tablets disintegration within the prescribed time (15 min), consistency within the tablet batch, and to detect changes in disintegration time over 3 and 6 months of storage at zone IV. The test was performed by placing one tablet in each of the six tubes of the basket-rack assembly and operating the apparatus in an immersion fluid of distilled water at a temperature of 37 ± 2 °C. At the end of the time, the basket-rack assembly is lifted from the immersion fluid, and the tablets are observed for any remaining tablet residues. If one or two tablets fail to disintegrate completely, the test should be repeated using additional twelve tablets. According to the USP disintegration criteria, all the tested six tablets should disintegrate entirely, and if sixteen tablets were tested, no less than sixteen tablets should disintegrate completely within 15 min of operating the apparatus (USP/NF, 2020a). The disintegration test was repeated again for tablets stored for 3 and 6 months to detect disintegration changes over time due to storage under zone IV conditions.

2.2.2.6. Content uniformity. The content uniformity test aims to confirm that the distribution of the drug substance between the dosage units within the batch is uniform and API content in the sampled tablets meet the USP product monograph criteria. According to the USP criteria, ten tablets were randomly selected and individually assayed for their API content to calculate the USP acceptance value \((AV)\) of ≤15 using the following equation (USP/NF, 2020c):

\[
AV = |M - X| + ks
\]

where \(AV\) is the acceptance value, \(M\) is the reference value depending on the target content per dosage unit, \(X\) is the mean of individual contents, \(k\) is the acceptability constant, and \(s\) is the sample standard deviation.

The content uniformity test was performed by vortexing one tablet from each product for 15 min \((n = 10)\) in a calculated volume of the diluent to obtain a final solution concentration of 0.1 mg/mL for tadafalil and rosuvastatin and 0.01 mg/mL for acetaminophen. The obtained solutions were then filtered through 0.2 μm pore-size Whatman filters (GE Healthcare Life Science, Little Chalfont, UK) using a vacuum pump filtration system (WVR international, Leuven, Belgium). Filtrates were frozen at −20 °C until analyzed within two weeks of their storage using HPLC system as described hereafter. The diluents used for tadafalil contained acetonitrile and water at a ratio of 1:1 (USP/NF, 2020h) and 25:75 for rosuvastatin (USP/NF, 2020g). For the analysis of acetaminophen, the diluent used was methanol and water at a ratio of 10:90 (USP/NF, 2020f).

The same procedure was repeated for each product following their 3 and 6 months storage under zone IV conditions to detect changes in their API content.

2.2.2.7. Dissolution. According to the USP, the dissolution test is used to analyze the amount of API released and dissolved from the tested dosage unit to ensure compliance with the specifications described in the USP product monograph. The test was performed using an automated USP dissolution paddle apparatus (ERWEKA DTS820 Dissolution Apparatus, ERWEKA GmbH, Germany) by placing one tablet in each of the six apparatus’s vessels containing a dissolution medium specified in the USP product monograph and maintained at a constant temperature of 37 ± 0.2 °C. Multiple samples are withdrawn from the vessel at different time intervals according to the drug USP product monograph. All withdrawn samples were automatically filtered through 0.2 μm pore-size Whatman filters and a fresh dissolution medium was used to replenish withdrawn volumes by the dissolution apparatus (USP/NF, 2020b).

The dissolution test for tadafalil was performed in 1000 mL distilled water (DW) containing 0.5% sodium dodecyl sulfate (SDS) as a dissolution medium. The paddles were rotated at a speed of 50 rpm. Samples \((n = 6)\) were withdrawn at two-time intervals, 10 min and 30 min. The USP criteria for tadafalil dissolution is not less than 40% of the labeled amount dissolved in 10 min and not less than 80% of the labeled amount dissolved in 30 min (Table 1) (USP/NF, 2020h).

For rosuvastatin, the dissolution medium used was 900 mL of citrate buffer (CB) prepared at pH 6.6. The rotation speed was set at 50 rpm and only one sample \((n = 6)\), as required by the USP product monograph, to be withdrawn at 30 min with not less than 75% of the labeled amount dissolved (Table 1) (USP/NF, 2020g).

For the dissolution of acetaminophen, a 900 mL of phosphate buffer (PB) prepared at pH 5.8 was used as the dissolution medium. The dissolution test was performed at a rotation speed of 50 rpm and one sample \((n = 6)\) was withdrawn at 30 min. The USP product monograph criteria for passing the test require not less than 80% of the labeled amount dissolved (Table 1) (USP/NF, 2020f).

Collected dissolution samples were frozen at −20 °C until analyzed within two weeks by HPLC as described hereafter. The dissolution test for each product was repeated after 3 and 6 months of storage under zone IV conditions to detect changes in their API dissolution.

2.2.3. HPLC analysis

All the frozen samples from content uniformity and dissolution tests were thawed at room temperature before their analysis by HPLC.

For the HPLC analysis, a reversed-phase C18 column (4 μm particles size) (Waters Nova-Pak C18, Framingham, MA, USA) and alli-
Table 1

| Dissolution medium | Rotation speed (rpm) | Sampling time (min) | USP acceptance criteria |
|--------------------|---------------------|---------------------|------------------------|
| Tadalafil          | DW (1000 mL) + SDS (0.5%) | 50                  | 10 and 30              | Not less than 40% of the labeled amount dissolved in 10 min and not less than 80% dissolved in 30 min |
| Rosuvastatin       | CB (900 mL; pH 6.6) | 50                  | 30                     | Not less than 75% of the labeled amount dissolved |
| Acetaminophen      | PB (900 mL, pH 5.8) | 50                  | 30                     | Not less than 80% of the labeled amount dissolved |

DW: deionized water; SDS: sodium dodecyl sulfate; CB: sodium citrate dehydrate; PB: phosphate buffer.

Table 2

| USP Test                  | Diluent                        | MP                  | FR (ml/min) | IV (µL) | PDA WL (nm) | Standard CC (n = 5) |
|---------------------------|--------------------------------|---------------------|-------------|---------|-------------|--------------------|
| Tadalafil Content uniformity | Acetonitrile +DW (1:1)          | acetonitrile + DW + TFA (35:65:0.1) methanol + DW (50:50) | 1.0         | 10      | 285         | Linear (R² = 1) |
| Tadalafil Dissolution     | DW + SDS (0.5%)                 |                     | 1.3         | 20      | 225         | Linear (R² ≥ 0.99) |
| Rosuvastatin Content uniformity & dissolution | Acetonitrile +DW (25:75)       | acetonitrile + DW + PA (400:600:1) | 1.0         | 20      | 242         | Linear (R² = 1) |
| Rosuvastatin Content dissolution | Acetonitrile +DW (25:75)       |                     | 1.3         | 20      | 225         | Linear (R² ≥ 0.99) |
| Acetaminophen Content uniformity & dissolution | Methanol +DW (10:90)            | Solution A: GAA (1%) + DW q.s. Solution B: methanol | 0.8         | 10      | 243         | Linear (R² ≥ 0.999) |

MP: mobile phase; FR: flow rate; IV: injection volume; PDA WL: photodiode-array wave length; CC: calibration curve.
significantly decreased after 3 months of storage. Storing the tablets for additional 3 months restored their hardness and that increase in the tablet hardness was significant for B, L1, and R2.

For acetaminophen, the tablet hardness for the five products are shown in (Fig. 2c) and were in the range of 14–31 kN. The tablet hardness of L2 and R1 were significantly higher than B before storage. Storing tablets under zone IV conditions over 6 months resulted in an increase in their hardness, except for L2, and this increase was significant for B, L1, and R1 tablets.

3.4. Friability

There were differences in the friability between the generic products and their comparator product and also over the 6 months of storage at zone 4 (Fig. 3); however, all tablets from the five different products of the three pharmacological classes were within the USP accepted range for friability (<1%).

3.5. Disintegration

The disintegration of the generic products of tadalafil was significantly higher than B before their storage under zone IV conditions, except for L1, but all tablets disintegrated in less than 5 min which is within the USP limit of 15 min (Fig. 4a). Storing the tablets for 3 months resulted in significantly faster tablet disintegration for L1, L2, and R2 then followed by an increase in their disintegration time after 6 months of storage, which was significant for L1 and R2. On the other hand, B and R1 tablet disintegration was not affected by their storage (Fig. 4a).

Before storage, the tablet disintegration time of rosuvastatin generic products was significantly different from B, however, all tablets disintegrated in less than 3 min (Fig. 4b). Also, all the tablets resulted in a significantly faster disintegration time following their storage for 3 and 6 months under zone IV conditions (Fig. 4b).

The disintegration of acetaminophen generic tablets before storage was significantly higher than B except for R2, but all the tablets passed the USP disintegration test (Fig. 4c). Storing acetaminophen tablets resulted in a significant increase in their disintegration time, except for R2 tablets which showed a significant decrease in their disintegration time after 6 months of storage. However, the significant increase in the disintegrating of only L2 tablets following their storage for 3 months resulted in failing the USP test even after repeating the test for additional 12 tablets according to the USP method (Fig. 4c). Therefore, two additional locally manufactured generic products for acetaminophen (L3, and L4) were selected to increase the number of locally manufactured acetaminophen products evaluated to four different products instead of two. Both L3 and L4 for acetaminophen generic products passed the USP disintegration test and disintegrated in less than 15 min despite the increase in their disintegration time following their storage at zone IV as previously observed for the other acetaminophen tested products (Fig. 4c).

3.6. Content uniformity

The USP acceptance value (AV) for the content uniformity test ranged between 3.2 and 10.8 for tadalafil products, 2.6 and 11.6 for rosuvastatin products, and 4.8 and 13.4 for acetaminophen products (Table 4). Storing the tablets from the different products under zone IV conditions for up to 6 months did not affect their API content (Fig. 5) and the AV of their USP content uniformity test performed at 3 and 6 months was less than 15, which is the maximum accepted value to pass the USP content uniformity test.

3.7. Dissolution

The dissolution of the tablets from all tested products from the three pharmacological classes was within the accepted limits described in their corresponding USP product monograph for dissolution testing at zone IV before and after storage for 3 and 6 months, except for one of the tested locally manufactured (L2) acetaminophen generic products (Fig. 6) despite passing the content uniformity test (Table 3). L2, which previously failed the disintegration test, failed as well to release and dissolve the prescribed acenaminophen percentage (80%) for stage 1 (S1) (USP/NF, 2020f). Repeating the test for stage 2 and 3 (S2 and S3) using additional 18 tablets according to the USP dissolution testing criteria (USP/
NF, 2020b) did not result in passing the USP dissolution tests before and after the storage under accelerated conditions for zone IV (Fig. 7). Therefore, two additional locally manufactured generic products for acetaminophen (L3, and L4) were selected to increase the number of evaluated locally manufactured acetaminophen products to four different products. Both L3 and L4 acetaminophen generic products passed the USP dissolution test and released >80% after 30 min of the test before and after the storage under accelerated conditions for zone IV (Fig. 6c).

4. Discussion

The pharmaceutical industry in the Gulf and Middle East region relies mostly on manufacturing generic pharmaceutical products or licensed products of international pharma. The number of local manufacturers in UAE has significantly increased from 4 manufacturers in 2010 to 23 manufacturers in 2021, 14 of which are for manufacturing pharmaceutical products (ADQ FWD, 2022). The sales of generic pharmaceutical products represented 19% of the total UAE pharmaceutical sales in 2020, which is much lower than the international utilization of generic products that reaches up to 90% of the prescriptions (Nagraj, 2022).
In order to increase the utilization and prescription of locally manufactured and imported generic pharmaceutical products, UAE adapted in 2018 an interchangeable policy for the brand pharmaceutical products with their alternative and pharmaceutically equivalent generics in the market. The lower-priced generics offer a cost-saving that can reach up to 60% of the brand products and can better meet the increasing population demands (Nagraj, 2022).

However, there is still the need for increasing the public confidence in the quality of manufactured generics that still prefer the brand products over the generics (Nagraj, 2022). Enhancing public awareness about the benefits of utilizing generic products and conducting more independent studies that evaluate the quality of generics being sold in the local market can contribute to increase the public confidence in the quality of generic products. Therefore, we aimed in this study to evaluate the quality of four different generic products from three different pharmacological classes as representative samples for generic tablet dosage form to provide more comprehensive assessment for the quality of locally marketed generic products in UAE to increase confidence and awareness of the public and promote generic drugs utilization.

The selection of the evaluated products was mainly based on their availability in the local market as brand, locally manufactured and regionally manufactured generics. Most of the selected generic products resulted in significantly different thickness, hardness, friability, and disintegration than their comparator brand product before storage (Figs. 2–4). Therefore, comparing the generics’ physical characteristics with the brand’s characteristics before and after storage was not feasible. Thus, we statistically compared the results from the after storage tests for each product with its own initial tests’ results before storage using custom comparison (\( -2 \)) one-way ANOVA and Tukey's Kremer post hoc tests by designating “-2” weight for before the storage data and “1” for the 3 and 6 months of storage. This design allowed us to determine the effect of storage on the physical characteristics of the stored tablets during the performed accelerated stability studies.

The storage conditions selected to perform the accelerated stability studies and evaluate the effect of storage on tablets characteristics were according the testing settings described in the ICH Q1A(R2) for zone IV (ICH Expert Working Group, 2003). Also, the selection of zone IV conditions (40 °C ± 2 °C /75% RH ± 5% RH) to perform the accelerated stability studies was based on the climate of UAE (hot and humid climate) that matches zone IVA conditions according to ICH Q1F guidelines (U.S. FDA, 2003).

The consistency of the tablets dimensions, especially the thickness and shape, provides the assurance for the reproducibility of tablet manufacturing. The effect of elevated temperature and humidity during the stability studies on the tablet color was minimal and resulted in no visually observed changes with the exception for acetaminophen products. Acetaminophen brand, L1 and L2 showed a light yellowish discoloration after storage for 3 months and progressed in intensity after 6 months of storage at zone IV conditions (Fig. 1).
It has been previously reported that acetaminophen is susceptible to degradation due to heat that accelerates its oxidation over time and causes the yellowish discoloration of the stored tablets (Mochizuki and Takayama, 2016). Humidity can also impact its stability, however, it was reported that low-vapor transmission packaging can reduce the potential of drug degradation over time due to increased humidity (Ahmad and Shaikh, 2003).

In order to further evaluate the significance of this issue, we reviewed the expiration dates for the donated acetaminophen samples and they were Dec 2022, Oct 2022, and Dec 2021 for B, L1, and L2 respectively. These expiry dates revealed that the tested products were about to expire or had one year before their expiry at the time of our evaluation. Exposing these samples to additional 6 months of accelerated stability testing, which is equivalent to a 2-years of shelf-life, close to their expiry date may have contributed to the observed color change. Therefore, we tested two additional locally manufactured acetaminophen generic products to examine the magnitude of the issue for the locally manufactured products and both products resulted in no tablet discoloration over the 6 months storage under zone IV accelerated conditions. Even though, based on our findings along with the support from the previous reports regarding the susceptibility of acetaminophen tablets to degradation upon exposure to elevated temperatures resembling the UAE climate require in-depth analysis for their stability and the levels of their degradants.

Another parameter that was monitored and evaluated during the accelerated stability studies for the effect of storage conditions at zone IV was the tablet hardness. In this study, we demonstrated that the storage of tablets overtime had mixed effect on their hardness but with more tendency for an increase in the tablet hardness as observed with almost all acetaminophen products that had a significantly higher initial tablet hardness (Fig. 2) when compared with the other products, tadalafil and rosuvastatin. The changes in the tablet hardness might be mainly due to the elevated storage temperature/humidity that may have altered tablet moisture content and affected the strength of the inter-particulate bonding and therefore the tablet hardness. It has been previously reported that slight elevation of the humidity to 31% at 40 °C resulted in an increase in the stored tablet hardness, while the increase in temperature caused slight increase in tablets hardness ( Hosny, 1999).

Despite the significant differences in the tablet hardness after storage, these differences were yet very small due to the previously reported limited effect of temperature on tablet hardness ( Hosny, 1999). On the contrary, high humidity was reported to negatively impact tablet hardness ( Ahmad and Shaikh, 1994; Hosny, 1999).

However, the effect of elevated humidity of zone IV on the stored tablets in their original packaging was very limited in our studies and had no impact on tablet hardness due to the low vapor transmission rate of the used sealed packaging ( Ahmad and Shaikh, 2003).

Friability was also one of the parameters that was tested to evaluate the effect of storage conditions of zone IV on tablet friability. An increase in the tablet friability was observed with the increase in their storage time, however, all the products were within the USP limits of less than 1% weight loss (Fig. 3). A previous study reported a significant increase in the friability of tablets stored at elevated humidity of 75% at 25 °C when the packaging used did not provide efficient sealing properties (Gbenga and Taiwo, 2015), which indirectly indicates the high sealing efficiency of the packaging used for the products tested in this study, thus minimizing the negative effect of prolonged tablet exposure to high temperature and humidity.

Tablet disintegration is essential for drug dissolution and absorption. During the storage of the different tablets under zone IV conditions over 6 months, we observed a decrease in the tablet disintegration time for most of the tested products (Fig. 4), except for acetaminophen tablets. These results are in accordance with the results obtained for acetaminophen tablet hardness. The increase in the tablet hardness due to storage conditions resulted in an increase in the time required for complete tablet disintegration to the extent it resulted in L2 failing the USP disintegration test after storage. Since there is a direct relationship between tablet hardness and its disintegration, which was observed in this study as well (Fig. 2c and Fig. 4c), thus a significant change in the hardness would result in altering the disintegration time of the tablet.

Results from content uniformity tests for all tested products demonstrated tablets’ drug content within USP limits and was not affected by storage conditions of zone IV over 3 and 6 months. Passing the USP content uniformity test is an indication for the efficiency of the packaging materials used by the manufacturer (Table 3) in maintaining drug stability during storage by preventing moisture penetration into the tablets under the elevated humidity levels of zone IV.

Although thickness, hardness, friability, and disintegration can be Critical Quality Attributes and are commonly used to perform quality control testing, however, their variability from the comparator brand is not critical as long as they are not negatively impacting tablet dissolution and still passing the USP limits for tablets’ friability, disintegration, and content uniformity.

Finally, the effect of the accelerated storage conditions on the dissolution of the tested tablets was not that significant to the extent it can affect the USP acceptance criteria except for the acetaminophen L2 (Fig. 6) where drug dissolution was significantly decreased. This can be explained due to L2 failing the tablet disintegration test as previously reported which could have negatively affected drug release and dissolution.

Testing additional two locally manufactured acetaminophen generic products (L3 and L4) for their tablet disintegration and dissolution, in addition to the color change, helped confirming that L2 failing the USP disintegration and dissolution tests was an isolated case that requires internal investigation within the manufacturing facility and further monitoring by the local regulatory agency. Also, provided assurance for the high quality of the locally manufactured acetaminophen generic products.

5. Conclusion

The majority of the locally and regionally manufactured generic products being sold in the UAE market were of good quality and performed similarly to their comparator. However, one locally manufactured generic product was negatively affected by its storage over time at high temperature and humidity, indicating the importance of performing independent quality evaluation continuously for the marketed generic drug products in UAE.

This study was mainly focusing on the pharmaceutical equivalency of generic products. Future studies will focus on expanding the number of evaluated pharmacological classes, types of tested dosage forms, and more in-depth analysis for the percentage of chemical degradants after storage according to the USP limitations.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
