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Conference Proceedign

PHARMACEUTICAL QUALITY AND STABILITY OF FUROSEMIDE TABLETS IN TROPICAL STORAGE CONDITIONS: AN IN-VITRO ANALYSIS

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ABSTRACT

Background:
Improper storage conditions can affect the pharmaceutical quality and stability of medicines.

Objective:
This study evaluated the *in vitro*pharmaceutical quality and stability of furosemide tablets under two different storage conditions.

Method:
Two generic and one branded furosemide 40 mg tablet formulations were collected from Karapitiya healthcare facilities. Samples were stored for 30 days in the same packaging material as dispensed. A time zero analysis (T_0) and stability analysis after one month (T_1) were carried out following BP/IP guidelines. Both recommended (T_{1R}) and home (T_{1H}) storage conditions were used to test the stability. T_{1R} mimicked the manufacturer's recommendation (20-25 °C, RH 57%-65%) while T_{1H} mimicked the environmental conditions in a tropical room (27-46 °C, RH 33%-88%).

Results:
All samples tested at T_0 and T_{1R} complied with official limits of quality parameters except the hardness test (<40 N). At T_{1H} analysis, all samples met the acceptance limits for weight variation (<7.5%), and disintegration (<15 min) tests except hardness (<40 N), friability (>1%), and assay (<95%). Only under home storage conditions, generic samples in polythene packages showed discoloration.

Conclusion:
Furosemide tablets stored under recommended storage conditions were within the defined quality specifications and remained stable for 30 days. However, home storage conditions can negatively impact the drugs' stability.

Keywords: Furosemide; Medicine stability; Post-market surveillance; Quality control; Sri Lanka; Storage conditions.

INTRODUCTION:

The presence of poor-quality medicines in the market is increasing, because of poor manufacturing practices, poor adherence to quality control standards, counterfeiting, or improper storage. The use of potentially dangerous, substandard, ineffective, and counterfeit pharmaceuticals can be threatened the health and well-being of the people and it is a waste of money from the government, the public, and patients. It also leads to build-up a lack of trust regarding the overall healthcare system (1,2).

Stability testing reveals how the quality of the product changes over time because of various environmental conditions. The shelf life of medicine is based on the assumption that it is kept in ideal storage conditions (3). However, most people do not keep their medicines in safe and recommended storage conditions. Since it is challenging to maintain the manufacturer's recommended storage conditions at home, especially in tropical countries like Sri Lanka due to high-temperature changes in most parts of the island. Therefore, medicines are exposed to various environmental conditions continually. For example, changes in temperature, humidity, exposure to direct sunlight, and loss of original package integrity can potentially affect the shelf life and physical and chemical changes to the pharmaceutical products. It leads to a decrease in the effectiveness of the medicines and can harm the patient's health. Stability testing assesses the impact of external influences on the quality of medicinal products (3). A study revealed that the physicochemical parameters of furosemide tablets changed by the changes in the climate while they were placed on a shelf for over a year (4). A group of researchers conducted a stability study in which Paracetamol tablets being stored outside or in a car trunk for 24 months harmed the pharmaceutical stability (5).

Many researchers have conducted physiochemical quality assessment studies on the various brands and generic formulations of furosemide tablets marketed in various countries. The quality control tests on some of the furosemide samples evaluated were passed according to the respective specifications, while some of the samples were deemed to be substandard (6). Some of the studies revealed that the generic product can be used instead of the brands of furosemide in clinical settings (2,7). In Sri Lanka, there were no previous in-vitro studies reported on the quality and stability of furosemide tablets. Therefore, this study was planned to evaluate the in-vitro pharmaceutical quality and stability of Furosemide tablets available in Sri Lanka.

METHODS

Sample collection

Three different products of furosemide 40 mg tablets were obtained from registered private and government healthcare facilities in the Karapitiya region of Sri Lanka. From each product, 350 tablets were obtained from the same batch number. The samples were coded as Generic 1 (Sample A), Brand 1 (Sample B), and Generic 2 (Sample C). Samples were stored in the same packaging material as they were dispensed by the pharmacy. The following information was recorded during sample collection Table

Table 1: Information on the sample collection

Information	Furosemide sample code		
	A (Generic 1)	B (Brand 1)	C (Generic 2)
Registration at NMRA*	Registered	Registered	Registered
Date of manufactured	May 2021	January 2020	March 2022
Date of expiry	August 2023	December 2022	March 2024
Primary packagingtype of dispensing	Polyethylene bag	Strip packaging	Polyethylene bag
Storageconditions (as per the label)	Below 30 °C	Below 30 °C	Below 30 °C
The temperature at the site of sample collection.	30 °C	24 °C	28 °C

*Product registration details were obtained from the National Medicine Regulatory Authority's (NMRA) public web interface.

Study design

The study was carried out in two steps; Step 1- Time zero analysis (T_0) at the time of sample collection, Step 2- After one month (T_1) of sample collection. All samples were tested to check their stability. The stability of furosemide samples was tested under two different environmental conditions; home (T_{1H}) and manufacturer's recommended (T_{1R}) storage conditions. T_{1H} simulated the temperature and humidity (27℃-46℃, RH 33%–88%) changes in a tropical room and T_{1R} simulated the manufacturer's recommendation for storage (20℃-25℃, RH 57%-65%). The quality control parameters were determined by uniformity of weight, hardness, friability, disintegration, and assay as per the pharmacopoeial standards claimed by the product; Generic 1 (Sample A) & Generic 2 (Sample C) as per British Pharmacopoeia (BP2020) and Brand 1 (Sample B) as per Indian Pharmacopoeia (IP 2018). Changes in the physicochemical characteristics of the tablets were assessed between the T_0 and T_1 analyses under both storage conditions.

Quality control tests

1. Weight variation test

From each sample, twenty pills were chosen at random and weighed one by one using an analytical balance (CITIZEN S. NO 1043174). Then the average weight and percentage deviation were calculated using the following formula:

Average weight = Total weight of 20 tablets/20

Percentage Deviation = [(Individual weight of tablet –Average weight)/Average weight]×100%

2. Hardness Test

The hardness tester (Biobase, China) was used. Ten tablets were randomly selected from each sample of furosemide and placed between the jaws of the hardness tester individually. The amount of Newton (N) needed to break for each tablet was recorded. The average crushing force was calculated for each sample.

3.Friability Test

The total weight of 6.5 g of tablets was randomly taken from each sample. The tablets were dedusted and accurately weighed. Then tablets were placed inside the drum of the Friability tester (LABINDIA FT1020, India) that was set to run 100 rotations. The dust of each tablet was removed and reweighed. The percentage of friability was calculated for each sample by using the initial (W1) and final weight (W2) of tablet samples.

Percentage of Friability = [(W1 −W2)/W1]×100%

4. Disintegration Test

The disintegration tester (LABINDIA DT1000, India) was assembled. Six tablets were selected randomly from each sample of the furosemide tablets. The distilled water of 900 mL was used as the disintegration medium and it was heated to 37± 2°C. The time that all particles had completely gone through the mesh and none were still on the mesh of the basket was determined as the disintegration time. The mean disintegration time for each product was determined.

5. Assay Test

The assay tests for the Generic 1 (sample A) and Generic 2 (sample C) were done in line with the specifications of BP (2020) and Brand 1 (sample B) was done in line with the specifications of IP (2018). According to BP (2020), twenty tablets were selected randomly from each sample and weighed together at once by analytical balance. All the tablets were ground into powder using a mortar and pestle. The powder of each sample (A and C) was measured as equivalent to 200 mg of furosemide. It was mixed with 300 mL of 0.1 M sodium hydroxide and shaken for 10 minutes, and then the solution was diluted to 500 mL using the 0.1 M sodium hydroxide solvent. The solution was filtered and 5 mL of sample was taken from it. It was diluted with 0.1 M sodium hydroxide up to 250 mL.

According to the IP (2018), From sample B, 20 tablets were chosen at random and weighed all at once using an analytical balance. All the tablets were ground into powder using a mortar and pestle. The powder of sample B has measured as equivalent to 100 mg of furosemide. It was mixed with 150 mL of 0.1 M sodium hydroxide for 10 minutes and diluted up to 250 mL using the 0.1 M Sodium hydroxide.

The solution was filtered and 5 mL of filtrate was taken. It was diluted with 0.1 M sodium hydroxide up to 200 mL. The absorbance of the final solution of three furosemide samples was determined at 271 nm wavelength using a double-beam UV (Ultraviolet) -visible spectrophotometer (Model: UV-1800, Shımadzu Corporatıon, Japan). The mean absorbance and percentage of assay of each sample were calculated as per the pharmacopoeial specification (580 as the value of absorbance; [1%,1 cm] at the maximum at 271 nm).

Statistical Analysis

Data were statistically evaluated using Microsoft excel 2010 and IBM SPSS Statistics 25 software. Statistical significance was determined by $p<0.05$. The mean and standard deviation were used to express the results. Samples stored at different storage conditions were compared using an independent sample t-test.

RESULTS

The pharmaceutical quality and stability of three samples of furosemide 40 mg uncoated tablets were evaluated following the specifications outlined in the BP (2020) and IP (2018) standards. Tables 2 and 3 demonstrate the physicochemical parameters and physical appearance of the three furosemide 40 mg samples at Time zero analysis (T_0), and after one month under home (T_{1H}) and recommended (T_{1R}) storage conditions respectively.

Table 2: Results of physicochemical parameters of furosemide 40 mg tablet samples.

Description of analysis	Sample Code	Weight variation	Weight of tablets (M ± SD)	Hardness (N) (M ± SD)	Friability percentage (w/w)%	Disintegration time (min) (M ± SD)	Assay (w/w)% (M ± SD)
T_0 Analysis[a]	A_0	(CV%)	223.12±1.89	*16.64±1.32	0.391	2.82 ±0.08	97.70±0.33
	B_0	0.85	160.12±1.98	50.67±6.92	0.018	0.86 ±0.06	96.83±0.19
	C_0	1.24	204.93±2.29	*14.05±2.57	0.044	0.31 ±0.02	97.05±0.33
T_{1R} Analysis[b]	A_R	1.12	208.65±2.90	*22.48±1.48	0.467	2.75 ±0.06	98.39±0.29
	B_R	1.39	161.62±1.76	*37.43±7.39	0.797	1.00 ±0.05	96.58±0.27
	C_R	1.09	210.09±1.89	*17.39±2.71	0.301	0.26 ±0.04	98.20±0.45
T_{1H} Analysis[c]	A_H	0.90	208.75±2.60	*21.36±2.54	*1.252	0.16 ±0.08	*93.89±0.07
	B_H	1.25	162.17±2.59	*34.10±5.12	*2.198	0.2 ±0.02	*89.44±0.75
	C_H	1.59	210.49±2.89	*17.35±2.79	*1.314	0.18 ±0.03	*90.03±0.26

[a]T_0 – Time zero analysis. [Sample A_0; Generic 1, Sample B_0; Brand 1, Sample C_0; Generic 2]
[b]T_{1R} – After one month of analysis under recommended storage conditions. [Sample A_R; Generic 1, Sample B_R; Brand 1, Sample C_R; Generic 2]
[c]T_{1H} – After one month of analysis under home storage conditions. [sample A_H; Generic 1, sample B_H; Brand 1, sample C_H; Generic 2]
* Fail to meet BP/IP pharmacopoeial specification
M: Mean, SD: Standard Deviation

Table 3: Results of the physical appearance of the furosemide 40 mg tablet samples

Description of Analysis	Sample Code	Physical appearance
T_0 Analysis[a]	A_0	White-colored tablet. Round, odorless, and uniformly shaped.
	B_0	White-colored tablet. Round, odorless, and uniformly shaped.
	C_0	White-colored tablet. Round, odorless, and uniformly shaped.
T_{1R} Analysis[b]	A_R	White-colored tablet. Round, odorless, and uniformly shaped.
	B_R	White-colored tablet. Round, odorless, and uniformly shaped.
	C_R	White-colored tablet. Round, odorless, and uniformly shaped.
T_{1H} Analysis[c]	A_H	Yellow-colored discoloration. Round, odorless, and uniformly shaped.
	B_H	White-colored tablet. No discoloration. Round, odorless, and uniformly shaped.
	C_H	Yellow-colored discoloration. Round, odorless, and uniformly shaped.

[a] T_0 – Time zero analysis. [Sample A_0; Generic 1, Sample B_0; Brand 1, Sample C_0; Generic 2]
[b] T_{1R} – After one month of analysis under recommended storage conditions. [Sample A_R; Generic 1, Sample B_R; Brand 1, Sample C_R; Generic 2]
[c] T_{1H} – After one month of analysis under home storage conditions. [sample A_H; Generic 1, sample B_H; Brand 1, sample C_H; Generic 2]

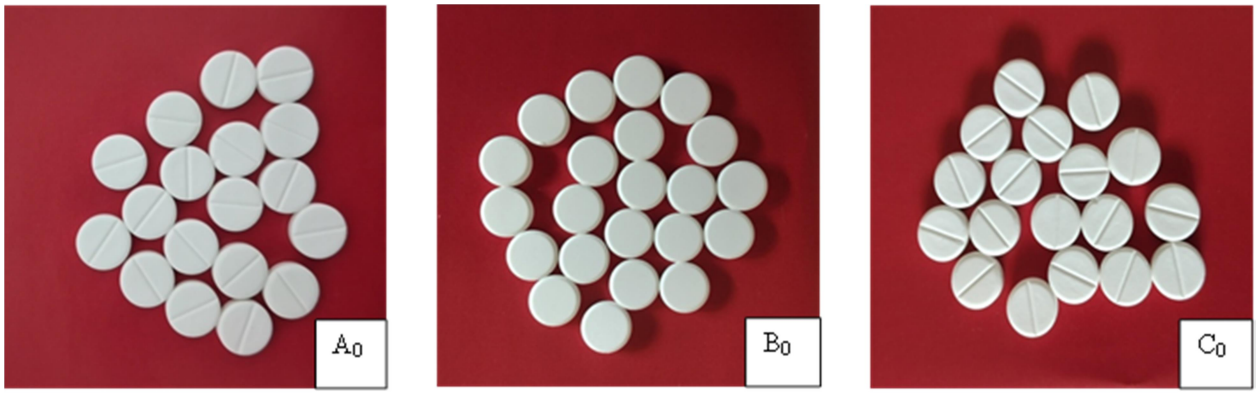

Figure 1: Physical appearance of furosemide tablet samples at T_0[a]analysis
[a]T_0 – Time zero analysis. [Sample A_0; Generic 1, Sample B_0; Brand 1, Sample C_0; Generic 2]

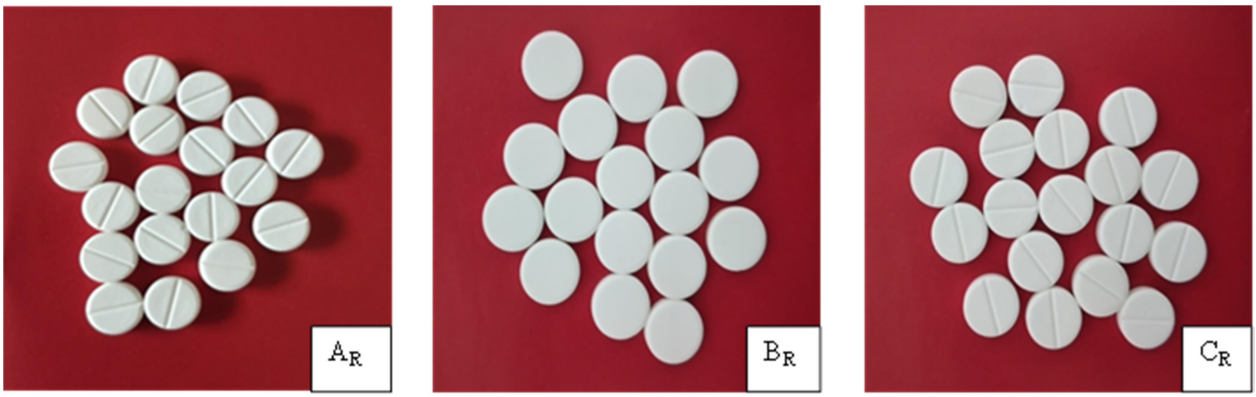

Figure 2: Physical appearance of furosemide tablet samples at T_{1R}[b]analysis
[b]T_{1R} - After one month of analysis under recommended storage conditions. [Sample A_R; Generic 1, Sample B_R; Brand 1, Sample C_R; Generic 2]

Figure 3: Physical appearance of furosemide tablets at T_{1H}[c] analysis [c]T_{1H} - After one month of analysis under home storage conditions. [Sample A_H; Generic 1, sample B_H;Brand 1, sample C_H; Generic 2]

DISCUSSION

Each tablet was visually examined for color, shape, and the presence of any spots or broken edges. These characteristics are necessary for consumer compliance and batch-to-batch uniformity (8). The aliquots of sample A_H (Generic 1) and sample C_H (Generic 2) furosemide 40 mg tablets stored in polyethylene packages, under home storage conditions for one month, showed signs of yellow discoloration. The yellow color appearance is probably due to sunlight. However, even after experiencing environmental fluctuations under home storage conditions, sample B_H (Brand 1) in the strip package remained white-colored throughout the study period. Any surface flaws or color alterations in tablets would be a sign of issues with the production processes or chemical or physical instability and also the package integrity affects the quality and stability characteristics of the tablets and also impacts patient compliance (5,7). In this study, researchers did not change the packaging of the product taken for the study. The study was conducted keeping the tablets in the same pack as they were dispensed from the pharmacy. There can be an effect of polythene pack used in the repacking causing the discoloration of tablets.

Weight variation provides a general indication of content uniformity. Inadequate therapeutic medication levels or toxicity may result from high dosage variability (2). All samples of furosemide 40 mg tablets were screened for the weight variation test and had an average weight between 80 – 250 mg and according to the specification, tablets can be accepted within 7.5% deviation (9,10). Weight variation test findings show that none of the samples had a percentage deviation in weight greater than 7.5% at T_0 analysis, and T_1 analysis was stored under both storage conditions. This indicates that the active pharmaceutical ingredient and excipients would be distributed fairly or with little fluctuation in each tablet (11). Comparison of study results of the weight variation test after one month under home ($p<0.008$) and recommended ($p<0.015$) storage conditions (T_{1H} and T_{1R}) separately with T_0 analysis, each sample showed a statistically significant variation. Comparing the weight between two storage conditions after one-month analysis, each furosemide sample experienced no significant difference between the two storage conditions ($p>0.221$).

The hardness test demonstrates the potential of oral tablets to withstand pressure or stress during handling, packing, and shipping. The minimum requirement of hardness value for tablets is 40 N (8). Furosemide sample A_0 and sample C_0 failed to satisfy the acceptance criteria except for sample B_0 at T_0 analysis. According to the hardness results of furosemide tablets samples after one month of analysis (T_1) under both storage conditions, failed to satisfy the acceptance criteria for hardness. If the hardness of the tablet is very low, tablets will easily break down during handling, shipping, and packaging. Friability and disintegration are both influenced by hardness. The friability and rate of disintegration of tablets increase as their hardness decreases. A tablet's hardness that is too hard prolongs the time it takes for it to dissolve, which eventually reduces its bioavailability (2). There was a significant difference ($p<0.01$) in the hardness values for each sample under both storage conditions following one month when compared with the baseline value at T_0. Comparing hardness between two storage conditions after one-month analysis, each furosemide sample experienced no significant difference between the two storage conditions ($p>0.244$).

The tendency of a tablet to break into powder can have an impact on its aesthetic quality, consumer acceptance, and weight fluctuation or content consistency issues (2). The standard specification for the friability of uncoated tablets states as not more than 1% to pass the test (9,10). The friability percentages of all three furosemide 40 mg samples were less than 1% at T_0 analysis, and T_{1R} analysis (after one month under recommended storage conditions). It demonstrated that all furosemide samples could be transported and kept in good condition under any vibratory conditions (11). However, none of the furosemide samples passed the friability test at T_{1H} analysis (under home storage conditions) since the weight loss percentage

of all three samples of furosemide was greater than 1%. Tablets may break due to the temperature changes due to sunlight, which will weaken the mechanical strength of tablets as a result of material porosity. This might account for enhanced friability and decreased hardness (5). Comparing the friability percentage between two storage conditions after a one-month analysis, each furosemide sample showed a significant difference between the two storage conditions (p<0.05).

The prediction of drug behavior after ingestion is helped by in vitro tablet disintegration and dissolving, however, there is no obvious association between in vitro and in vivo performance (12). The uncoated tablet should be disintegrated within 15 minutes to pass the test (9,10). All three furosemide samples were disintegrated within 15 minutes at T_0 and after one month under home (T_{1H}) and recommended (T_{1R}) environmental conditions. All three samples demonstrated significant variations (p<0.043) in disintegration time between time zero analysis (T_0) and one-month analysis under home storage conditions (T_{1H}). When comparing disintegration time results at T_0 with after one-month storage under the recommended storage condition at T_{1R}, the statistical analysis showed that all furosemide samples experienced no significant change (p>0.100) in the disintegration time. After a one-month analysis comparing the disintegration times under the two storage condition, sample A (Generic 1) and sample B (Brand 1) both had p values less than 0.011. Therefore, a substantial difference between the two storage conditions was evident in both samples. However, sample C's (generic 2) p value of 0.130 indicated that there was no significant difference between the two storage conditions.

The assay determines the active pharmaceutical ingredient (API) concentration in a sample; following both BP (2020) and IP (2018), the concentration of furosemide that falls between 95 - 105% is considered acceptable. All three samples of furosemide 40 mg tablets tested at T_0 analysis and the T_{1R} analysis stored under the recommended storage conditions had furosemide API concentrations complied with standards. Consequently, all of the samples of furosemide tablets were of defined quality. All three samples of furosemide tablets stored under home storage conditions had assay results ranging from 88.62- 93.96% and failed to satisfy the pharmacopoeial specification at T_{1H} analysis. For optimum therapeutic action and less toxicity, tablets should contain the appropriate dosage of the medication. Inadequate API will result in unsatisfactory treatment outcomes (2). When assay test findings were compared with T_0, after one month of analysis under home storage conditions (T_{1H}), in each of the three samples, there were notable variations (p=0.001). Under recommended storage conditions (T_{1R}), each sample did not exhibit any significant differences (p>0.054). The content of the furosemide API could be reduced due to chemical degradation in changing environmental conditions (4). Comparing assay results between two storage conditions after one-month analysis, each furosemide sample (p<0.001) showed a significant difference between the two storage conditions.

This study revealed that the furosemide 40 mg tablet samples tested at T_0 analysis were in good condition and within the defined quality specifications mentioned in relevant pharmacopeias. Furosemide samples were stable after one month of storage under the recommended storage conditions (as mentioned on the label). However, the samples stored in home had been impacted by the changing temperature and humidity under the home storage conditions.

CONCLUSION

As the conclusion of this study, changes in the environmental conditions during one month of storage had an impact on the quality and stability of furosemide 40 mg tablets. Since Sri Lanka is a tropical country with a high temperature in most parts of the island, home storage conditions can negatively impact the stability of the drug. The stability testing of drugs in tropical environment conditions should be considered by the manufacturers, and storage advice should be given to patients in home settings for safe and effective drug

use. Further studies on the stability of furosemide tablets in different packaging can support designing a viable and protective packing material for furosemide tablets.

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