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THE EFFECT OF TEMPERATURE AND MOISTURE ON THE PHYSICAL AND CHEMICAL STABILITY OF FUROSEMIDE TABLETS (40 MG) MARKETED IN SYRIA

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ABSTRACT

Stability is an essential factor of quality, safety and efficacy of a drug product. The objective of this study was to investigate the effect of moisture and temperature on furosemide tablets (40 mg) marketed in Syria. Three commercial brands (A, B, C) were examined. Tablets were exposed to different storage conditions (RH=75% & 40°C), (RH=75% & 25°C), (RH=60% & 40°C), (RH=60% & 25°C) for 6 months and storage on shelf for 12 months. Changes in physicochemical properties of tablets were determined by hardness, friability tests and assay the content. High humidity and temperature (RH=75% & 40°C) decreased in hardness and content of furosemide tablets(less than 90%) and increased in friability (more than 1%) in all studied brands. Second condition also caused the same results, but less than the first condition because of normal temperature. The effect of temperature on stability is less than moisture as we saw in the third condition (RH=60% & 40°C). Physicochemical properties of tablets remained without changes when stored in (RH=60% & 25°C) condition. The storage of tablets on shelf caused changes in hardness, friability, and content of tablets according to climatic changes during the year.

KEYWORDS: Moisture, temperature, furosemide, physicochemical properties, storage, stability.

INTRODUCTION

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient.[1-3] There are many factors affecting on the drug stability such as[4-8]

a) Temperature: high temperature accelerates oxidation, reduction and hydrolysis reaction which lead to drug degradation.
b) pH: acidic and alkaline pH influence the rate of decomposition of most drugs.
c) Moisture: Water catalyses chemical reactions as oxidation, hydrolysis and reduction reaction and promotes microbial growth.
d) Light: affects drug stability through its energy or thermal effect which lead to oxidation
e) Pharmaceutical dosage forms: solid dosage forms are more stable than liquid dosage forms for presence of water.
f) Concentration: rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution.
g) Drug incompatibility: reactions between components of pharmaceutical dosage forms itself or between these components and cover of the container.
h) Oxygen: exposure of drug formulations to oxygen affects their stability.

The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability is an essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of sufficient stability, can result in changes in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formation of high risk decomposition substances).

The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic byproducts that are harmful to the patient. Microbiological instability of a sterile drug.

Product could also be hazardous. Stability evaluation of drug substance or drug product is the key to drug quality as it determines the efficacy of any drug or dosage form. Stability assessment of drug products and drug substances are mandated by regulatory agencies across the globe. In fact, stability-testing issues are responsible for a number of audit findings by regulatory agencies. Stability testing problems are regularly cited in warning letters and

sometimes results in costly product recall. Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature, relative humidity etc. The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the drug product packed in it specified packaging material and stored in the established storage condition within the determined time period.[9-13]

Furosemide (figure 1) is a potent diuretic with a rapid action. Like the other loop or high-ceiling diuretics it is used in the treatment of edema associated with heart failure including pulmonary edema, and with renal and hepatic disorders and may be effective in patients unresponsive to thiazide diuretics. It is also used in high doses in the management of oliguria due to renal failure or insufficiency. Furosemide is also used in the treatment of hypertension either alone or with other anti-hypertensive Furosemide inhibits the reabsorption of electrolytes primarily in the thick ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium, and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase.[14-15] Furosemide is fairly rapidly absorbed from the gastro intestinal tract; bioavailability has been reported to be about 60 to 70% but absorption is variable and erratic. The half-life of furosemide is up to about 2 hours although it is prolonged in neonates and in patients with renal and hepatic impairment. Furosemide is up to99% bound to plasma albumin, and is mainly excreted in the urine, largely unchanged. There is also some excretion via the bile and non-renal elimination is considerably increased in renal impairment. Furosemide crosses the placental barrier and is distributed into breast milk.[16]

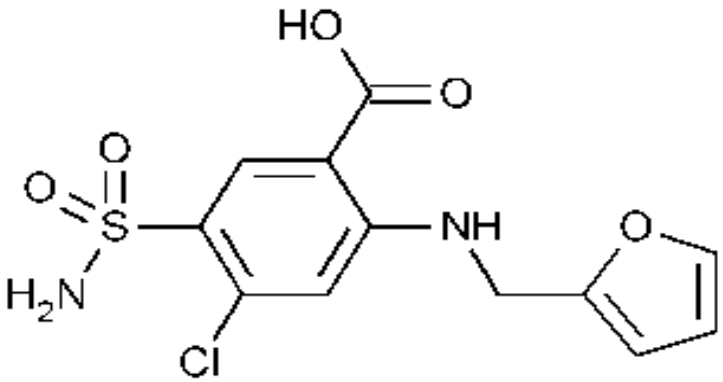

Figure 1: structure of furosemide.

The present work is based on a study of the effect storage conditions (temperature and humidity) on the physiochemical stability of different brands of furosemide tablets (40 mg) marketed in Syria.

MATERIAL AND METHODS

Three commercial brands (A, B, C,) of furosemide were randomly selected. Furosemide tablets brands having label strength of 40 mg were purchased from registered pharmacies in Lattakia, Syria. All tests were performed within product expiration dates. The reagents used were sodium chloride, sodium bromide, sodium hydroxide and Freshly distilled water was used throughout the work.

Storage conditions

Furosemide tablets to be tested were subjected to storage conditions as shown in table(1). samples were withdrawn within periods of time and evaluated for physical and chemical stability.

Table 1: Storage conditions.

Storage conditions		Storage period
Moisture (RH%)	Temperature(°C)	
75±5	40±2	6 months
75±5	25±2	6 months
60±5	40±2	6 months
60±5	25±2	6 months
Storage on shelf		12 months

Physical stability

Physical stability was evaluated through hardness, friability, and weight variation tests:

Hardness test: Sample tablets (10) of each brand were taken, a tablet was placed between the spindle of the Erwerka hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet in position. The pressure was then increased as uniformly as possible until the tablet broke and the pressure required to break the tablet was then read off the machine and recorded.

Friability test: Sample tablets (20) of each brand were weighed together before transferring them to the Roche friabilator. The friabilator was adjusted to 25 rpm for 4 minutes. After that, the tablets were taken and cleaned from dust and weighed again. By using this formula % of

Friability = [(Wi – Wf)/ Wi] x 100 was calculated. The loss should be less than 1% according to BP.[17]

Chemical stability

Chemical stability was evaluated through assay the content of the stored tablets:

Calibration curve of furosemide in sodium hydroxide 0.1N at 271 nm: A standard curve was created for furosemide using pure drug powder diluted to 5 known concentrations (range between 0.40 and 2.04 mg/100ml). These standard curves were established to verify accurate analysis of the drug.

Assay the content: 10 tablets were taken from each brand. Each tablet was crushed and dissolved separately using a combination of manual agitation and sonication techniques in 100 ml of distilled sodium hydroxide. Then the samples were mixed well before filtration through a membrane filter. The samples of each solution were assayed for drug concentration using spectrophotometer at 271 nm. The drug content was quantified by calculating the concentrations from the absorbance readings obtained through UV analysis. Several measures were calculated in order to assess the amount and acceptability of variations in drug content. The measured drug content expressed as a percent of label claim was calculated for each tablet then the average of the content percentage for 10 tablets was calculated. The average should be in the range of 90-110% for furosemide (proxy USP specification for drug content.[18]

RESULTS AND DISCUSSION

Calibration curve of furosemide in sodium hydroxide 0.1N at 257 nm

A linear relationship between the absorbance and the concentration of furosemide in sodium hydroxide at 271 nm in the concentration range of 0.40 – 2.04mg/100ml is observed. The regression equation is Y= 0.4132X+0.0234 and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9999.

Storage in (RH=75% & 40°C)

This study reviews the effect of moisture and temperature on furosemide (40 mg) tablets. It was stated that the amount of moisture adsorbed by drugs or excipients and increased in temperature influences hardness, friability and content. These changes may alter bioavailability, and therapeutic efficacy, even though the drug potency. The influence of

relative humidity and temperature depends on its chemical affinity for tablet and nature of excipient or additive.

High (relative humidity 75% and temperature 40°C) decrease in tablets hardness for all studied brands after 3 days of storage and hardness reached to values less than 3 kp after (four, three, one) months for brands(A, B, C) respectively, as shown in table (2). Also these conditions affected on the friability of tablets and the values of friability in all brands exceeded BP specifications 1% after two month for (A &B) brands and after one week for brand C.

The content of tablets in all studied brands was decreased after 3 days from storage and reached to values less than 90% (USP specifications for drug content) after (four, two) months for A & B brands and after one week for brand C. This happened because of the degradation of furosemide and the content reached to low values (77.23, 65.43, 55.15) for (A, B, C) brands, respectively, at the end of storage period.

Table 2: The results of storage in (RH=75% & 40°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
3days	7.09	6.34	4.03	0.48	0.71	0.95	98.03	94.22	90.22
1 week	6.92	6.08	3.87	0.54	0.75	0.99	97.87	93.76	90.09
2weeks	6.86	5.87	3.34	0.66	0.80	1.34	97.03	93.11	90.01
3 weeks	5.72	5.31	3.13	0.78	0.84	1.78	96.32	92.77	87.31
1 month	5.13	5.06	3.04	0.89	0.92	2.04	95.34	91.04	85.12
2 months	4.56	4.34	2.45	0.95	0.99	3.01	93.11	90.02	80.46
3 months	4.08	3.04	2.12	1.12	1.13	3.98	91.05	84.13	72.77
4months	3.11	2.51	1.45	2.12	2.32	4.35	90.11	79.65	66.21
5months	2.15	2.01	1.05	2.97	3.08	4.78	85.32	73.12	60.35
6 months	1.07	0.87	0.43	3.98	4.21	5.45	77.23	65.43	55.15

Storage in (RH=75% & 25°C)

In this condition the relative humidity is high while the temperature is normal. The high humidity also decrease in tablets hardness for all studied brands and hardness reached to values less than 3 kp after (five, four, two) months for brands(A, B, C) respectively, as shown in table (3). Also this condition affected on the friability of tablets and the values of friability in (A, B) brands exceeded BP specifications 1% after (three, two) months for brands (A, B) brands, respectively, and after one week for brand C.

The content of tablets in all studied brands was decreased after 2weeks from storage and reached to values less than 90% (USP specifications for drug content) after (four, three, one) months for (A, B, C) brands, respectively. This happened because of the degradation of furosemide and the content reached to low values (79.11, 72.98, 60.11) for (A, B, C) brands, respectively, at the end of storage period. The effect of this condition is low comparison with the above condition because of normal temperature in this condition.

Table 3: The results of storage in (RH=75% & 25°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
3days	7.11	6.73	4.07	0.49	0.71	0.94	98.32	94.19	90.60
1 week	6.96	6.23	4.02	0.55	0.76	0.98	98.05	94.02	90.55
2weeks	6.90	6.11	3.87	0.61	0.83	1.22	97.11	93.93	90.42
3 week	6.77	5.87	3.66	0.65	0.88	1.45	96.74	93.78	90.31
1 month	6.41	5.21	3.22	0.78	0.92	1.89	96.09	93.22	90.01
2 months	5.34	4.33	3.01	0.89	0.99	2.43	95.22	91.36	84.90
3 months	4.65	3.87	2.12	0.98	1.54	2.97	93.09	90.05	80.12
4months	3.95	3.02	1.62	1.61	2.12	3.67	90.05	84.15	72.15
5months	3.01	1.95	0.93	2.09	3.02	4.02	85.44	80.98	65.98
6 months	1.65	0.98	0.33	3.66	3.98	4.87	79.11	72.98	60.11

Storage in (RH=60% & 40°C)

In this condition, the temperature is high while the relative humidity is normal. The high temperature also decrease in tablets hardness for all studied brands and hardness reached to values less than 3 kp after (five, five, three) months for brands(A, B, C) respectively as shown in table (4). Also this condition affected on the friability of tablets and the values of friability friability in all brands exceeded BP specifications 1% after (four, three) months for (A &B) brands, respectively, and after two weeks for brand C.

The content of tablets in all studied brands was decreased and reached to values less than 90% (USP specifications for drug content) after(5, 4, 2) months for (A, B, C) brands, respectively. This happened because of the degradation of furosemide. The effect of this condition is low comparison with the above condition (RH=75%&25°C), so we can say that the effect of humidity on furosemide tablets stability is larger than temperature.

Table 4: The results of storage in (RH=60% & 40°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
3days	7.12	6.77	4.08	0.47	0.72	0.93	98.61	94.66	90.62
1 week	6.99	6.71	4.03	0.51	0.75	0.95	98.13	94.23	90.56
2weeks	6.95	6.65	3.98	0.56	0.79	0.98	97.04	93.11	90.35
3 weeks	6.81	6.09	3.78	0.72	0.82	1.43	96.88	93.09	90.21
1 month	6.74	5.87	3.55	0.79	0.86	1.98	96.76	92.89	90.17
2 months	5.78	5.03	3.23	0.85	0.92	2.55	95.11	92.31	90.01
3 months	4.33	4.13	3.01	0.93	0.99	3.21	93.01	91.67	85.89
4months	4.03	3.93	2.23	0.98	1.15	3.98	92.05	90.01	80.91
5months	3.13	3.01	1.14	1.23	2.08	4.34	90.41	87.43	75.87
6 months	1.25	1.13	0.67	2.08	3.11	4.55	82.12	76.55	70.12

Storage in (RH=60% & 25°C)

This condition is the idealism condition for storage. Hardness was decreased at the end of the storage, but still above 3 kp for all studied brands as shown in table (5). Also the values of friability in all brands didn't exceed BP specifications 1%. The content of furosemide in tablets of all studied brands remained above 90% (USP specifications for drug content) during all the storage period.

Table 5: The results of storage in (RH=60% & 25°C) condition.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
3 days	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
1 week	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
2 weeks	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
3 weeks	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
1 month	7.31	6.98	4.07	0.43	0.68	0.92	98.65	94.76	90.65
2 months	7.31	6.98	4.07	0.43	0.68	0.92	98.65	94.76	90.64
3 months	7.31	6.98	4.06	0.43	0.68	0.92	98.65	94.73	90.64
4 months	7.29	6.96	4.06	0.43	0.68	0.94	98.65	94.71	90.63
5 months	7.29	6.96	4.05	0.41	0.67	0.94	98.63	94.70	90.61
6 months	7.29	6.95	4.05	0.41	0.67	0.94	98.62	94.70	90.61

Storage on shelf

In this condition the tablets exposed to different values of relative humidity and temperature according to climatic conditions across 12 months. Hardness of tablets was decreased in all studied brands and reached to values less than 3 kp after (11, 10, 5) months as shown in table

(6). The friability of tablets in (A, B) brands exceeded BP specifications 1% after (10, 10, 2) months for (A, B,C) brands, respectively.

The content of tablets in all studied brands was decreased to values less than 90% (USP specifications for drug content) after (11, 9, 5) months for (A, B,C) brands, respectively.

Table 6: The results of storage on shelf.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	7.31	6.98	4.09	0.43	0.68	0.92	98.65	94.76	90.65
1month	7.09	6.85	4.06	0.47	0.70	0.97	98.56	94.25	90.60
2 months	6.45	6.45	4.02	0.51	0.73	0.99	98.47	94.92	90.51
3 months	6.14	6.09	3.67	0.57	0.79	1.34	97.37	93.95	90.35
4 months	5.56	5.96	3.45	0.62	0.83	1.55	96.09	93.55	90.12
5 months	5.07	5.32	3.11	0.69	0.88	1.79	95.34	93.12	90.03
6 months	4.76	5.09	2.54	0.77	0.91	1.99	95.06	92.76	85.41
7 months	4.13	4.44	2.31	0.87	0.93	2.76	94.44	92.07	82.23
8months	3.87	3.98	2.15	0.92	0.96	2.98	93.12	91.01	76.78
9months	3.44	3.23	2.01	0.95	0.98	3.43	92.05	90.07	72.89
10 months	3.12	3.01	1.34	0.99	0.99	3.67	91.11	85.98	68.98
11months	3.03	2.77	1.03	1.23	1.31	4.08	90.02	79.89	65.44
12months	2.57	2.02	0.98	1.98	1.72	4.85	86.11	76.11	60.12

CONCLUSION

From this work we can report that furosemide tablets, when stored in inappropriate storage condition especially in coastal area weather of Syria that usually is in high humidity which cause acceleration changes on the physical and chemical properties leading to less effective drug.

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