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The Influence of Temperature and Moisture on the Physical and Chemical Properties of Metformin Hydrochloride Tablets (850 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 metformin hydrochloride tablets (850 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 test and assay the content. High humidity and temperature (RH=75% & 40°C) decreased in hardness and content of metformin hydrochloride(less than 95%) and increased in friability (more than 1%) in all studied brands. The 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.

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 the drug stability such as [4-8]

(a) Temperature: high temperature accelerates oxidation, reduction and hydrolysis reaction which leads to drug degradation.

(b) pH: acidic and alkaline pH influence the rate of decomposition of most drugs.

(c) Moisture: Water catalysis 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 the presence of water.

(f) Concentration: the rate of drug degradation is constant for the solutions of the same drug with different concentration. So, the ratio of the degraded part to the total amount of drug in diluted solution is bigger than of the concentrated solution.

(g) Drug incompatibility: reactions between components of pharmaceutical dosage form 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) 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.

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 a costly product recall that the quality of 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 condition within the determined time period [9-13].

Metformin hydrochloride (MET) is chemically N, N-dimethyl imido dicarbonimidic diamide hydrochloride (1, 1-dimethyl biguanide hydrochloride) that acts by decreasing intestinal absorption of glucose, reducing hepatic glucose production, and increasing insulin sensitivity (Fig.1). Metformin is considered the first-line oral hypoglycemic agent in the treatment of type 2 diabetes mellitus. MET is the drug of choice in obese patients.1–3 Metformin activates adenosine monophosphate-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells.

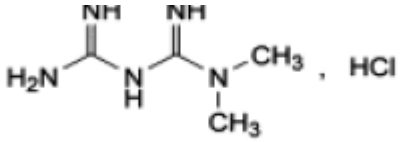

Figure.1. Structure of metformin hydrochloride

The present work is based on a study of the effect storage conditions (temperature and humidity) on the physiochemical stability of different brands of metformin hydrochloride (850mg) tablets marketed in Syria.

MATERIALS AND METHODS:

Three commercial brands (A, B, C,) of metformin hydrochloride were randomly selected. Metformin brands having label strength of 850 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 and freshly distilled water were used throughout the work.

Storage conditions:

Metformin hydrochloride 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:

a- **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 sufficient 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.

b- **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[14].

Chemical stability:

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

a- **Calibration curve of metformin hydrochloride in distilled water at 232 nm**: A standard curve was created for metformin hydrochloride using pure drug powder diluted to 5 known concentrations (range between 0.21 and 0.84 mg/100ml). These standard curves were established to verify accurate analysis of the drug.

b- 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 water. 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 232 nm. The drug content was quantified by calculating the concentration from the absorbance readings obtained through UV analysis. were calculated 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 than the average of the content percentage for 10 tablets was calculated. The average should be in the range of 95-105% for metformin hydrochloride (proxy USP specification for drug-content [15].

RESULTS AND DISCUSSION:

A-Calibration curve of metformin hydrochloride in distilled water at 232 nm: A linear relationship between the absorbance and the concentration of metformin hydrochloride in distilled water at 232 nm in the concentration range of 0.21-0.84mg/100ml is observed. The regression equation is Y= 0.9326X+0.039 and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9974.

B- Storage in (RH=75% & 40°C):

This study reviews the effect of moisture and temperature on metformin hydrochloride (850 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 for brand A after one month and after 2 months for brand B as shown in the table (2). Also, these conditions affected on the friability of tablets and the values of friability in all brands exceeded BP specifications 1% after 3 weeks for (A &B) brands and after 5 months for brand C.

The content of tablets in all studied brands was decreased after 3 days from storage and reached to values less than 95% (USP specifications for drug content) after 2 weeks for A & C brands and after one week for brand B. This happened because of the degradation of metformin hydrochloride and the content reached to low values (26.56, 18.13, 23.41) for (A, B, C) brands in order 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	5.56	6.22	44.12	0.81	0.76	0.01	99.13	98.09	97.67
3 days	5.34	6.19	44.09	0.83	0.79	0.01	98.32	97.88	97.11
1 week	5.01	5.98	42.21	0.87	0.82	0.02	96.32	95.11	96.32
2 weeks	4.44	5.34	40.09	0.91	0.87	0.04	95.44	93.89	95.98
3 weeks	4.12	5.08	38.32	0.98	0.93	0.08	94.89	88.71	94.12
1 month	3.91	4.78	33.21	1.05	1.03	0.22	91.22	85.12	90.76
2 months	2.55	3.22	29.12	1.44	1.35	0.35	83.09	78.35	81.07
3 months	2.01	2.65	23.98	1.84	1.78	0.53	69.76	65.32	70.91
4 months	1.32	1.94	21.09	2.78	2.56	0.65	55.54	49.15	53.13
5 months	0.87	1.01	15.90	2.98	2.98	0.95	40.06	33.91	37.08
6 months	0.15	0.21	12.78	3.51	3.09	1.3	26.56	18.13	23.41

C- Storage in (RH=75%&25°C):

In this condition, the relative humidity is high while the temperature is normal. The high humidity also decreases in tablets hardness for all studied brands and hardness reached to values less than 3 kp for brand A after 4 months and after 5 months for brand B as shown in the 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 2 months for (A &B) brands, while stayed less than 1% for brand C.

The content of tablets in all studied brands was decreased after 2weeks from storage and reached to values less than 95% (USP specifications for drug content) after 3 weeks for A & C brands and after 2 weeks for brand B. This happened because of the degradation of metformin hydrochloride and the content reached to low values (30.06, 27.55, 31.89) for (A, B, C) brands in order at the end of storage period. The effect of this condition is low compared 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	5.56	6.22	44.12	0.81	0.76	0.01	99.13	98.09	97.67
3 days	5.32	6.21	44.09	0.82	0.76	0.01	98.95	97.95	97.35
1 week	5.21	6.09	43.88	0.83	0.79	0.02	97.94	96.81	97.02
2 weeks	4.95	5.89	41.98	0.85	0.82	0.03	96.75	95.09	96.18
3 week	4.54	5.55	40.77	0.88	0.87	0.05	96.09	90.23	95.33
1 month	4.02	5.24	37.82	0.91	0.93	0.17	93.01	88.95	92.89
2 months	3.75	4.97	33.41	0.98	0.97	0.21	86.23	79.41	83.56
3 months	3.62	4.11	28.90	1.03	1.01	0.49	70.08	69.04	74.32
4 months	3.08	3.54	26.09	1.33	1.34	0.57	59.65	64.11	69.69
5 months	2.65	3.08	23.76	1.97	1.77	0.79	45.75	40.08	44.67
6 months	1.88	2.11	20.98	2.23	1.96	0.89	33.06	27.55	31.89

D- Storage in (RH=60%&40°C):

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

The content of tablets in all studied brands was decreased and reached to values less than 95% (USP specifications for drug content) after 2months for A & C brands and after one month for brand B. This happened because of the degradation of metformin hydrochloride. The effect of this condition is low compared with the above condition (RH=75%&25°C), so we can say that the effect of humidity on metformin hydrochloride 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	5.56	6.22	44.12	0.81	0.76	0.01	99.13	98.09	97.67
3 days	5.55	6.22	44.11	0.81	0.76	0.01	98.91	97.87	97.59
1 week	5.52	6.18	44.09	0.82	0.77	0.01	98.14	97.22	97.43
2 weeks	5.34	6.09	43.96	0.84	0.81	0.02	97.96	97.02	97.38
3 weeks	5.09	5.93	43.77	0.86	0.83	0.03	97.56	96.66	97.12
1 month	4.86	5.84	43.09	0.89	0.86	0.06	97.32	95.11	96.91
2 months	4.12	5.21	40.89	0.92	0.90	0.11	95.53	93.22	95.09
3 months	3.98	4.85	36.78	0.97	0.92	0.32	86.42	83.13	85.89
4 months	3.09	4.09	34.56	1.02	0.97	0.44	82.08	78.89	80.07
5 months	2.91	3.76	30.96	1.54	1.08	0.61	77.90	71.07	74.65
6 months	2.08	3.02	27.09	1.98	1.12	0.75	63.23	58.54	60.06

E- 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 the table (5). Also, the values of friability in all brands didn't exceed BP specifications 1%. The content of metformin hydrochloride in tablets of all studied brands remained above 95% (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	5.56	6.22	44.12	0.81	0.76	0.01	99.13	98.09	97.67
3 days	5.56	6.22	44.12	0.81	0.76	0.01	99.09	98.08	97.65
1 week	5.56	6.22	44.12	0.81	0.76	0.01	99.08	98.08	97.62
2 weeks	5.33	6.18	44.09	0.82	0.77	0.01	99.08	98.06	97.62
3 weeks	5.13	6.09	44.09	0.83	0.79	0.01	99.07	98.06	97.61
1 month	5.08	6.08	44.01	0.86	0.80	0.01	99.06	98.03	97.61
2 months	4.97	5.94	43.95	0.87	0.82	0.02	99.03	97.97	97.56
3 months	4.46	5.87	43.21	0.88	0.84	0.03	98.98	97.93	97.32
4 months	4.13	5.71	43.09	0.91	0.85	0.05	98.95	97.87	97.29
5 months	3.96	5.11	42.98	0.92	0.87	0.06	98.86	97.53	97.19
6 months	3.70	4.82	42.87	0.94	0.90	0.07	98.76	97.21	96.98

f- Storage on a shelf:

In this condition, the tablets exposed to different values of relative humidity and temperature according to climatic conditions across 12 months. A hardness of tablets was decreased in all studied brands and reached to values less than 3kp for brand A after 9 months and at the end of study for brand B as shown in the table (6). The friability of tablets in (A, B) brands exceeded BP specifications 1% after (6, 7) months for (A & B) brands in order, while stayed less than 1% for brand C.

The content of tablets in all studied brands was decreased to values less than 95% (USP specifications for drug content) after 9 months for brand A and after 8months for B &C brands.

Table 6: The results of storage on the shelf.

Time	Hardness (kp)			Friability (%)			Content (%)		
	A	B	C	A	B	C	A	B	C
Fresh	5.56	6.22	44.12	0.81	0.76	0.01	99.13	98.09	97.67
1 month	5.54	6.13	44.09	0.82	0.77	0.02	99.05	98.02	97.65
2 months	5.51	6.08	43.98	0.84	0.81	0.03	98.89	97.95	97.33
3 months	5.13	6.04	42.12	0.88	0.85	0.09	98.45	97.77	97.09
4 months	4.78	5.85	41.89	0.90	0.89	0.12	98.13	97.09	96.89
5 months	4.31	5.61	40.08	0.93	0.92	0.29	97.78	96.33	96.33
6 months	4.08	5.52	38.77	0.98	0.97	0.33	97.08	96.22	96.09
7 months	3.91	5.09	37.02	1.05	0.99	0.45	96.55	95.19	95.98
8 months	3.65	4.34	35.09	1.13	1.05	0.56	96.21	95.02	95.09
9 months	3.11	4.08	34.88	1.21	1.06	0.61	95.06	93.32	93.12
10 months	2.86	3.23	33.90	1.42	1.09	0.65	93.81	90.44	92.66
11 months	2.12	3.07	32.98	1.61	1.11	0.78	91.08	89.08	90.89
12 months	1.88	2.98	31.13	1.76	1.23	0.91	89.22	87.32	88.15

CONCLUSION

From this work, we can report that metformin hydrochloride 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 a less effective drug.

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