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EFFECT OF TEMPERATURE AND MOISTURE ON THE PHYSICAL AND CHEMICAL PROPERTIES OF METFORMIN HYDROCHLORIDE TABLETS

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ABSTRACT

Stability is an essential factor of quality, safety, and efficacy of a drug product and drug substance. The objective of this study was to investigate the effect of moisture and temperature on metformin hydrochloride tablets (1000 mg) marketed in India. 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 six months and storage on shelf for 12 months. Changes in physicochemical properties of tablets were determined by hardness, friability test and drug assay. High humidity and temperature (RH=75% & 40°C) decreased in hardness and drug content of metformin hydrochloride and increased in friability (more than 1%) in all the three 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 drug content of tablets according to climatic conditions during the total year.

KEYWORDS: Moisture, temperature, metformin hydrochloride, physicochemical properties, 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] There are many factors affecting the drug stability such as

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.[2]

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. Stability assessment of drug products and drug substances are mandated by regulatory agencies across the globe. 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.[3]

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 II diabetes mellitus.[4]

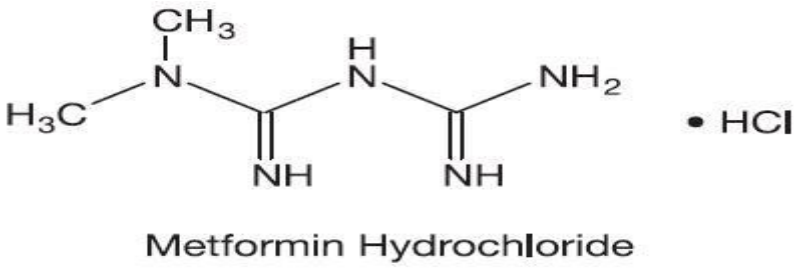

Fig-1: Structure of Metformin hydrochloride.

The present work is based on a study of the effect of storage conditions (temperature and humidity) on the physiochemical stability of different brands of metformin hydrochloride (1000 mg) tablets marketed in India.[5]

MATERIALS AND METHODS

Three commercial brands (A, B, C,) of metformin hydrochloride were randomly selected. Metformin brands having label strength of 1000 mg were purchased from registered pharmacies. 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.[6]

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 (^{0}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:

1. Hardness test: Ten tablets of each brand were taken, a tablet was placed between the spindle of the hardness tester machine and pressure was applied by turning the knot just sufficient to hold the tablet in position.[7] The pressure was then increased as uniformly as possible until the tablet was broken and the pressure required to break the tablet was then read off the machine and recorded.[8]

2. Friability test: Twenty tablets of each brand were weighed together before transferring them to the Roche friabilator. The friabilator was adjusted to 25 rpm for 4 minutes.[9] After that, the tablets were taken and cleaned from dust and weighed again. By using the formula percent of friability was calculated.

$$\text{Friability} = \frac{(W1 - W2)}{W1} \times 100$$

W1 = Initial weight of tablets, **W2 =** Final weight of tablets

Chemical stability

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

1. 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 five known concentrations (range between 0.21 and 0.84 mg/100ml). These standard curves were established to verify accurate analysis of the drug.[10]

2. Drug assay: Ten 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.[11] Then the samples were mixed well before filtration through a membrane filter. The samples of each solution were assayed for drug concentration using UV 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.[12] 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.[13]

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.

B- Storage in (RH=75% & 40°C)

This study reviews the effect of moisture and temperature on metformin hydrochloride (1000 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 excipients or additive.

High (relative humidity 75% and temperature 40°C) decrease in tablets hardness for all studied brands after six months of storage, then hardness reached to values less than 3 kilopascal for all brands (A,B,C) as shown in the table-2. Also, these conditions affected on the friability of tablets and after six months for all brands, the drug content of tablets in all studied brands was decreased and reached to values less than 95% after 3 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 for (A, B, C) brands in order at the end of storage period.

Table 2: Result of Tablets stored in (RH = 75% & 40^0 C) condition.

Time	Hardness(k p)			Friability (%)			Drug content (%)		
	A	B	C	A	B	C	A	B	C
0 days	5.50	6.12	4.52	0.81	0.79	0.01	99.45	98.61	97.21
1 week	5.33	6.01	4.65	0.85	0.81	0.03	95.31	94.38	93.21
3 weeks	4.31	5.24	3.96	0.96	0.92	0.05	94.25	88.34	92.29
1 month	3.96	4.85	3.86	1.01	1.03	0.26	91.56	86.24	89.31
3 months	2.52	3.21	3.01	1.81	1.79	0.49	65.38	67.58	70.24
6 months	1.15	1.21	2.71	3.41	3.24	1.31	32.45	22.54	21.64

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 kilopascal after six months as shown in the table-3. Also, this condition affected on the friability of tablets. The content of tablets in all studied brands was decreased

after 3 weeks from storage and reached to values less than 95% after 3 weeks for all three brands. This happened because of the degradation of metformin hydrochloride and the content reached to low values 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: Result of Tablets stored in (RH = 75% & 25^0 C) condition.

Time	Hardness(k p)			Friability (%)			Drug content (%)		
	A	B	C	A	B	C	A	B	C
0 days	5.51	6.21	4.45	0.82	0.79	0.02	99.35	98.54	97.68
1 week	5.21	6.01	3.96	0.79	0.76	0.03	97.12	96.57	96.25
3 weeks	4.58	5.88	3.52	0.81	0.79	0.05	94.54	93.21	94.36
1 month	4.06	5.61	3.12	0.92	0.84	0.07	92.18	91.27	93.57
3 months	3.58	4.88	2.98	1.21	1.11	0.29	71.25	72.54	73.29
6 months	1.86	2.95	1.58	2.15	1.89	0.84	34.52	29.58	28.45

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 5 kilopascal after six 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 1% while stayed less than 1% for brand C.

The drug content of tablets in all studied brands was decreased and reached to values less than 95% after three months for all brands. 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: Result of Tablets stored in (RH = 60% & 40^0 C) condition.

Time	Hardness(kp)			Friability (%)			Drug content (%)		
	A	B	C	A	B	C	A	B	C
0 days	5.62	6.25	4.16	0.86	0.78	0.02	99.57	97.25	96.34
1 week	5.54	6.14	4.02	0.94	0.81	0.03	98.25	96.37	95.24
3 weeks	5.21	5.98	3.97	0.96	0.84	0.05	96.58	95.27	94.27
1 month	4.97	5.84	3.64	0.99	0.87	0.11	95.24	93.57	92.25
3 months	3.95	5.02	3.52	1.02	0.98	0.21	74.28	71.29	70.24
6 months	3.05	4.58	3.01	1.21	1.14	0.56	60.54	58.21	54.28

E- Storage in (RH=60%&25°C)

This condition is the ideal for storage. Hardness was decreased at the end of the storage, but still it is above 3 kilopascal for all studied brands as shown in the table-5. Also, the values of friability in all brands did not exceed 1%. The drug content of metformin hydrochloride in tablets of all studied brands remained above 95% during all the storage period.

Table 5: Result of Tablets stored in (RH = 60% & 25^0 C) condition.

Time	Hardness(k p)			Friability (%)			Drug content (%)		
	A	B	C	A	B	C	A	B	C
0 days	5.41	6.34	4.26	0.85	0.79	0.01	99.58	98.21	99.54
1 week	5.14	6.25	4.15	0.87	0.84	0.02	99.25	97.56	98.34
3 weeks	4.95	5.94	4.05	0.89	0.89	0.02	98.34	97.19	97.12
1 month	4.12	5.26	3.91	0.97	0.94	0.03	97.24	96.36	96.89
3 months	3.95	4.97	3.11	0.98	0.96	0.05	96.39	96.16	96.29
6 months	3.69	4.81	3.05	0.99	0.98	0.06	96.14	95.29	96.17

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 3 kilopascal for all brands after 8 months as shown in the table-6. The friability of tablets in (A, B) brands exceeded 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% after 5 months for brand A and after 4 months for B and after 3 months for brand C.

Table-6: Result of Tablets stored in shelf condition.

Time	Hardness(k p)			Friability (%)			Drug content (%)		
	A	B	C	A	B	C	A	B	C
0 days	5.59	6.25	4.22	0.84	0.79	0.01	99.63	98.29	97.29
1 month	5.21	6.01	4.02	0.86	0.84	0.06	98.25	97.26	96.24
2 months	5.01	5.58	3.95	0.89	0.89	0.12	97.29	96.34	95.28
3 months	4.96	5.01	3.65	0.91	0.94	0.16	96.34	95.24	94.38
4 months	4.84	4.98	3.06	0.94	0.98	0.21	95.48	94.26	93.67
5 months	4.03	4.52	2.95	0.98	1.02	0.29	94.26	93.48	92.38
6 months	3.68	3.95	2.46	1.02	1.09	0.38	93.64	92.18	91.27
7 months	3.12	3.24	2.06	1.06	1.12	0.41	92.58	91.26	90.28
8 months	2.95	2.96	1.95	1.12	1.24	0.49	91.28	90.26	89.27
9 months	2.81	2.84	1.58	1.19	1.34	0.54	90.67	89.24	87.24
10 months	2.01	2.60	1.39	1.26	1.39	0.68	89.29	88.37	86.31
11 months	1.91	2.11	1.24	1.52	1.41	0.75	88.49	87.56	85.49
12 months	1.58	1.98	1.16	1.64	1.46	0.88	87.24	86.34	84.27

CONCLUSION

From this work, we can conclude that metformin hydrochloride tablets, when stored in an inappropriate storage condition that is usually in high humidity which can cause acceleration changes on the physical and chemical properties of the tablets that leads to a less effective drug.

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CONFLICT OF INTEREST

No conflict of interest was associated with this work.

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