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HUMIDITY-INDUCED ALTERATIONS IN CRITICAL QUALITY ATTRIBUTES OF IMMEDIATE-RELEASE METFORMIN TABLETS: A LOW-COST EXPERIMENTAL STUDY

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ABSTRACT

Metformin hydrochloride is a widely prescribed first-line antihyperglycemic agent for the management of Type 2 Diabetes Mellitus. Due to its highly water-soluble and hygroscopic nature, exposure to elevated environmental humidity may significantly influence the physicochemical stability and performance of immediate-release (IR) tablet formulations. The present study aimed to evaluate the effect of high relative humidity (RH) on the Critical Quality Attributes (CQAs) of commercially available generic Metformin 500 mg immediate-release tablets using a low-cost and accessible experimental methodology suitable for small laboratories and community pharmacy settings. Three commercially available brands of Metformin IR tablets were subjected to controlled humidity exposure using a saturated sodium chloride solution capable of maintaining approximately 75% RH within a sealed desiccator chamber. Pre- and post-exposure analyses were conducted for weight variation, hardness, friability, disintegration time, and dissolution behavior using USP-recommended methods. The results demonstrated significant moisture-induced alterations in tablet performance, including increased tablet mass due to moisture uptake, reduction in hardness, elevated friability, prolonged disintegration times, and modified dissolution profiles. Similarity factor (f_2) analysis revealed measurable deviations between fresh and humidity-exposed tablets, indicating altered release characteristics after storage under humid conditions. These findings highlight the vulnerability of Metformin tablets to moisture-induced degradation in tropical and resource-limited environments. The study further emphasizes the importance of appropriate packaging systems and affordable stability assessment techniques for ensuring product quality and therapeutic efficacy.

KEYWORDS: Metformin hydrochloride, humidity stability, critical quality attributes, hygroscopicity, pharmaceutical stability, immediate-release tablets.

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) remains one of the most prevalent chronic metabolic disorders worldwide, with rapidly increasing incidence rates in both developed and developing countries. Among available oral antidiabetic agents, Metformin hydrochloride continues to serve as the primary first-line therapy because of its efficacy, safety profile, cardiovascular benefits, and affordability.[1] Immediate-release (IR) Metformin tablets are widely distributed across tropical and subtropical regions where elevated temperature and humidity conditions frequently challenge pharmaceutical stability.

Metformin hydrochloride is highly water-soluble and exhibits hygroscopic behavior, making it particularly susceptible to environmental moisture exposure.[2]

Hygroscopicity refers to the tendency of pharmaceutical materials to absorb moisture from the surrounding atmosphere, potentially altering physical and chemical characteristics of dosage forms.

Moisture uptake may influence tablet integrity, hardness, friability, disintegration behavior, dissolution kinetics, and ultimately bioavailability.[3]

Environmental humidity represents a major but often underestimated factor affecting pharmaceutical quality, especially in low- and middle-income countries where climate-controlled storage facilities may be unavailable. In tropical climates, relative humidity can exceed 70–80% for prolonged periods, potentially accelerating degradation processes in solid oral dosage forms.[4] Community pharmacies, rural healthcare centers, and household storage conditions may therefore expose medicines to suboptimal environmental conditions, increasing the risk of therapeutic inconsistency.

Critical Quality Attributes (CQAs) are physical, chemical, biological, or microbiological characteristics that must remain within predefined limits to ensure desired product quality and performance.[5] For immediate-release tablets, important CQAs include tablet hardness, friability, weight uniformity, disintegration time, and dissolution profile. Alterations in these attributes may compromise patient compliance and therapeutic efficacy.

Conventional pharmaceutical stability studies often require expensive environmental chambers and sophisticated analytical infrastructure, limiting their feasibility in small laboratories and educational institutions. Consequently, there is increasing interest in developing simplified and cost-effective experimental methodologies capable of assessing stability-related quality changes under simulated environmental stress conditions.[6]

The present study was designed to evaluate humidity-induced changes in selected CQAs of commercially available Metformin IR tablets using a low-cost experimental setup based on saturated salt solutions. The study also aimed to compare dissolution behavior before and after humidity exposure using similarity factor (f_2) analysis and to highlight the practical implications of improper storage conditions on pharmaceutical quality in tropical environments.

2. MATERIALS AND METHODS

2.1 Materials

Three commercially available brands of Metformin hydrochloride immediate-release tablets (500 mg) were procured from retail pharmacies. To maintain confidentiality and avoid commercial bias, the formulations were coded as Brand A, Brand B, and Brand C.

The following reagents and materials were used

Sodium chloride (analytical grade) Distilled water
Hydrochloric acid buffer medium (pH 1.2) Phosphate buffer solution (pH 6.8)
USP dissolution apparatus II (paddle type) Monsanto hardness tester
Roche friabilator
USP disintegration apparatus Analytical balance
UV-visible spectrophotometer
All reagents employed during experimentation were of pharmaceutical or analytical grade

2.2 Experimental Design

The study compared by freshly obtained tablets with tablets exposed to controlled high-humidity conditions. The experimental workflow included:

1. Initial characterization of fresh tablets
2. Controlled humidity exposure
3. Re-evaluation of CQAs after humidity exposure
4. Comparative dissolution profile analysis

2.3 Preparation of Low-Cost Humidity Chamber

A low-cost humidity chamber was constructed using a sealed glass desicator containing a saturated sodium chloride solution at the bottom compartment. Saturated NaCl solution is known to maintain approximately 75% relative humidity at room temperature.[7]

The setup included

Airtight desiccator chamber Saturated NaCl solution reservoir Perforated tray for tablet placement
Digital hygrometer for RH monitoring
Tablets were exposed to approximately 75% RH at room temperature (25 ± 2°C) for 14 days.

2.4 Evaluation of Critical Quality Attributes

2.4.1 Weight Variation Test

Twenty tablets from each brand were individually weighed before and after humidity exposure using an analytical balance. Mean weight and percentage deviation were calculated according to USP guidelines.

2.4.2 Hardness Test

Tablet crushing strength was determined using a Monsanto hardness tester. Ten tablets from each brand were tested, and average hardness values were recorded in kg/cm².

2.4.3 Friability Test

Friability testing was performed using a Roche friabilator operating at 25 rpm for 4 minutes (100 revolutions). Tablets were dedusted and reweighed after testing. Percentage friability was calculated using:

%Friability = initial weight – final weight / initial weight X 100

A friability value below 1% was considered acceptable according to pharmacopeial standards.

2.4.4 Disintegration Test

Disintegration testing was conducted using USP disintegration apparatus containing distilled water maintained at 37 ± 0.5°C. Six tablets from each batch were evaluated, and mean disintegration time was recorded.

2.4.5 Dissolution Study

In vitro dissolution studies were performed using USP Apparatus II (paddle method) at 50 rpm in 900 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically at 233 nm.

Drug release percentages were compared between fresh and humidity-exposed tablets.

2.4.6 Similarity Factor (f_2) Analysis

Dissolution profile comparison was performed using the similarity factor (f_2), calculated using the following equation:

$$F_2 = 50 \log \{[1 + 1/n \Sigma^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where:

R_t = dissolution value of reference at time t T_t = dissolution value of test at time t

n = number of dissolution time points

An f_2 value between 50 and 100 indicates similarity between dissolution profiles.

3. RESULTS AND DISCUSSION

3.1 Weight Variation Analysis

All tablet brands complied with pharmacopeial limits before and after humidity exposure. However, a slight increase in average tablet weight was observed after storage at 75% RH for 14 days, indicating moisture uptake.

Table 1: Weight Variation Before and After Humidity Exposure.

Brand	Initial Weight (mg)	Exposed Weight (mg)	% weight gain
A	612 ± 3.2	625 ± 4.1	2.12
B	598 ± 2.8	616 ± 3.9	3.01
C	605 ± 3.5	620 ± 4.0	2.47

The highest moisture uptake was observed in Brand B, suggesting greater hygroscopic susceptibility or less moisture-resistant excipient composition.

3.2 Hardness Evaluation

A significant reduction in tablet hardness occurred after humidity exposure due to moisture penetration into the tablet matrix.

Table 2: Tablet Hardness Before and After Humidity Exposure.

Brand	Initial Hardness (kg/cm²)	Exposed Hardness (kg/cm²)	% Reduction
A	7.1 ± 0.2	5.8 ± 0.3	18.3
B	6.8 ± 0.4	4.9 ± 0.2	27.9
C	7.3 ± 0.3	6.0 ± 0.2	17.8

Brand B demonstrated the greatest hardness reduction, indicating weaker resistance toward humidity stress conditions.

3.3 Friability Results

Humidity exposure increased friability values in all brands.

Table 3: Friability Comparison.

Brand	Initial Friability %	Exposed Friability %
A	0.32	0.71
B	0.41	0.96
C	0.29	0.68

Although all brands remained within USP acceptable limits (<1%), Brand B approached the upper specification limit after exposure.

3.4 Disintegration Time

Humidity exposure prolonged tablet disintegration time.

Table 4: Disintegration Time Analysis.

Brand	Initial DT (min)	Exposed DT (min)
A	5.2 ± 0.4	7.8 ± 0.5
B	4.9 ± 0.3	8.5 ± 0.6
C	5.4 ± 0.5	7.1 ± 0.4

The increase may be attributed to binder hydration and reduced tablet porosity caused by absorbed moisture.

3.5 Dissolution Profile Study

Fresh tablets showed rapid drug release, whereas humidity-exposed tablets exhibited slower dissolution.

Table 5: Percentage Drug Release at 45 Minutes.

Brand	Fresh Tablets (%)	Exposed Tablets (%)
A	98.4	91.2
B	97.8	86.5
C	99.1	92.7

3.6 Similarity Factor (f_2) Analysis

Table 6: Dissolution Similarity Comparison.

Brand	f_2 Value	Interpretation
A	58	Similar
B	42	Dissimilar
C	61	Similar

An f_2 value below 50 for Brand B indicated a significant alteration in dissolution behavior after humidity exposure.

Overall Interpretation

The results clearly demonstrate that prolonged exposure to high humidity adversely affected the critical quality attributes of Metformin immediate-release tablets. The major observations included:

Increased moisture uptake Reduced mechanical strength Higher friability.

Delayed disintegration Slower dissolution behavior
These findings support the hypothesis that hygroscopic drug formulations are vulnerable under tropical storage conditions and require enhanced packaging protection such as Alu-Alu blister systems.

4. CONCLUSION

This study demonstrated that exposure of immediate-release Metformin tablets to elevated relative humidity significantly alters multiple Critical Quality Attributes, including hardness, friability, disintegration behavior, and dissolution profile. Moisture uptake compromised tablet integrity and modified release kinetics, potentially affecting therapeutic performance and patient outcomes.

The findings emphasize the importance of proper storage and moisture-protective packaging systems for hygroscopic pharmaceutical products, especially in tropical and high-humidity environments. Compared with conventional PVC blister packaging, Alu-Alu blister systems provide superior moisture barrier protection and may help preserve product stability throughout shelf life.

Furthermore, the low-cost humidity chamber model used in this study offers a practical and accessible approach for conducting preliminary pharmaceutical stability evaluations in educational institutions and small laboratories lacking advanced infrastructure.

Future investigations may include accelerated stability studies, spectroscopic characterization, excipient interaction analysis, and real-time environmental monitoring to further understand moisture-induced pharmaceutical degradation mechanisms.

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