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EFFECT OF MOISTURE ON THE PHYSICAL AND DISSOLUTION PROPERTIES OF IBUPROFEN TABLETS: A NARRATIVE REVIEW

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ABSTRACT

Ibuprofen is poorly water-soluble, and its tablets are sensitive to storage humidity, making them a useful model for studying moisture-related instability. This narrative review examines how moisture affects the physical and dissolution properties of ibuprofen tablets: how water is taken up, how it changes hardness, disintegration and dissolution, and how coating and packaging influence these outcomes, along with key analytical and regulatory considerations. Moisture is not simply harmful. Small amounts (up to ~2.5%) can strengthen tablets by improving particle bonding, whereas levels above ~3.5% tend to weaken them, and storage at ≥75% relative humidity usually causes measurable hardness loss. The main effects occur through hygroscopic excipients such as microcrystalline cellulose, starch and disintegrants, which absorb water, soften the tablet matrix and slow disintegration, often reducing drug release. Coating and packaging strongly modulate these effects. In the studies reviewed, some sugar-coated tablets lost dissolution performance under humid conditions, while film-coated tablets did not, and appropriate packaging offered additional protection. Thus, controlling moisture uptake is as much a formulation and packaging challenge as a stability one. Key gaps remain, including real-time imaging of moisture within tablets, models that distinguish temporary softening from permanent damage, understanding moisture behavior in amorphous dispersions, and developing in-line monitoring for continuous manufacturing.

Keywords: Ibuprofen, Moisture Uptake, Tablet Hardness, Dissolution, Film Coating, Packaging, Stability Testing

1 INTRODUCTION

Ibuprofen tablets are a useful model for studying moisture-driven instability because ibuprofen is poorly water soluble, dissolution varies substantially across products and test conditions, and storage humidity can alter both mechanical performance and drug release. **[1],[2]** In ibuprofen products specifically, moisture exposure has been linked to changes in compact strength, disintegration, and in some cases profound dissolution failure, making control of water uptake a formulation and packaging problem as much as a stability problem. **[3]**

For tablets broadly, water sorption can change crushing strength, disintegration, and dissolution through a small set of physical mechanisms: surface diffusion and capillary condensation, viscous flow in amorphous regions, and stress on interparticle bonds from moisture-induced expansion. **[4]** Recent storage studies also show that many of these changes occur in stages, with rapid early moisture uptake driving swelling and strength loss, followed by slower changes in wettability, liquid penetration, and disintegration performance. **[5]**

In ibuprofen compacts, the effect of moisture is nonlinear rather than uniformly harmful. Increasing moisture up to about 2.5% increased tablet strength, likely because a bound moisture film improved force transmission and interparticle bonding, whereas moisture above about 3.5% reduced strength by increasing hydrostatic resistance and reducing effective particle contact.

2 MECHANISM OF MOISTURE UPTAKE

Moisture uptake in solid materials proceeds through a sequence of thermodynamic and transport stages driven by vapor pressure differences and chemical potential gradients.

The process initiates with localized monolayer surface chemisorption or hydrogen bonding, transitions into multilayer clustering and bound-water diffusion, and culminates in capillary condensation and structural swelling. **[6]**

Table 1: Physical Mechanisms Across Moisture Regimes

Moisture Mechanism	Governing Driving Force	Structural Locus	Reference
Monolayer Physisorption	Hydrogen bonding and electrostatic attraction to polar sites	Functional groups in polymers and frameworks	[7]
Bound-Water Diffusion	Chemical potential and concentration gradients	Amorphous networks and interconnected fibrils	[8]
Capillary Condensation	Meniscus curvature described by the Kelvin relationship	Nanoscale and microscale voids or cell lumina	[7]
Polymer Swelling & Relaxation	Free-volume expansion and chain plasticization	Glassy or cross-linked macromolecular networks	[8]
Deliquescent Absorption	Vapor pressure depression from solute dissolution	Hygroscopic salts and confined electrolytes	[9]

At low relative humidity, water molecules initially bind directly to specific polar or ionic functional groups via strong intermolecular interactions. In metal-organic systems and hydrogels, metal-centered coordination environments and hydroxyl or carboxyl groups serve as primary early hydration motifs. Similarly, in cellulosic matrices, water sorbs into amorphous domains by forming hydrogen bonds with accessible hydroxyl groups on biopolymer chains. **[7]**

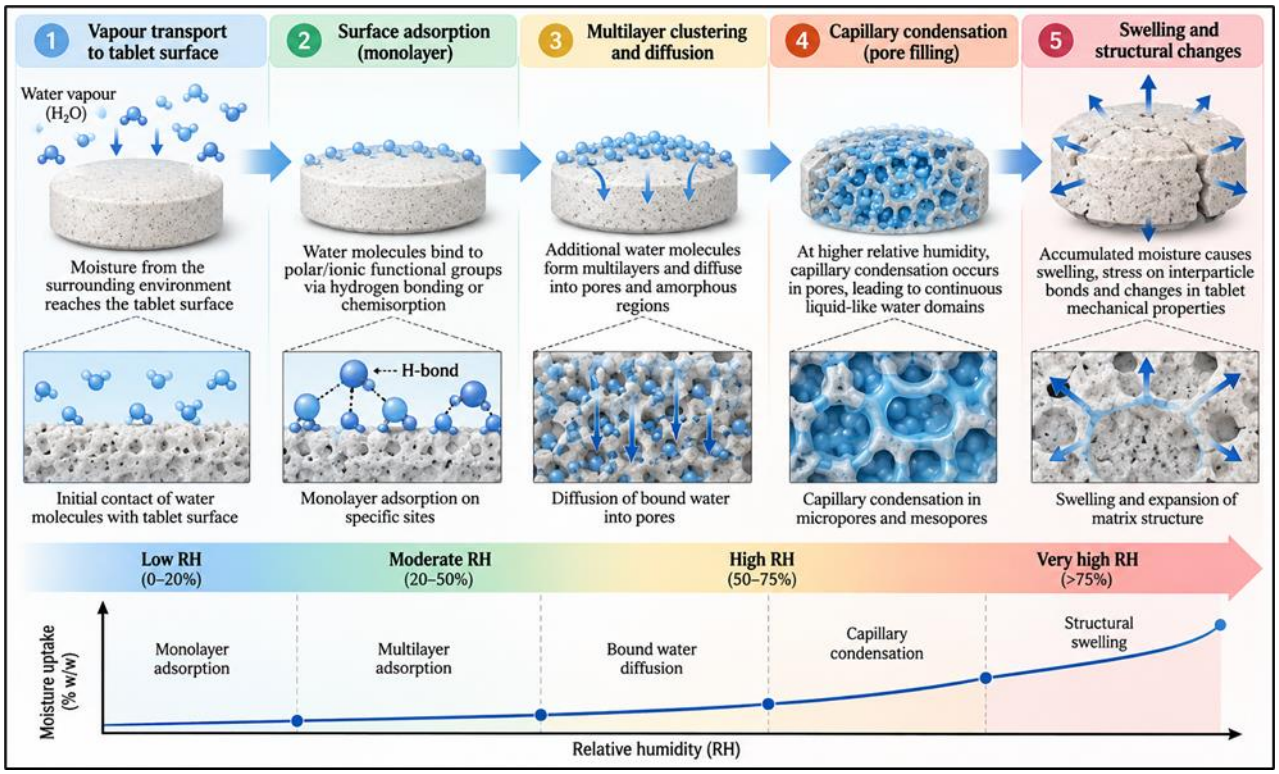


Figure 1: Moisture Uptake in Ibuprofen Tablets

3 EFFECT OF HUMIDITY ON TABLET HARDNESS

Humidity significantly influences tablet mechanical strength by altering interparticle bonding, moisture-induced plasticization, and internal structural porosity.

While elevated relative humidity (RH) typically causes tablet softening through matrix swelling or deliquescence, moderate moisture can sometimes enhance tensile strength via capillary bonding or recrystallization bridging. [10]

Exposure to high relative humidity typically causes a marked decrease in tablet breaking force and tensile strength across diverse formulations. Moderate moisture exposure can increase tablet strength in certain soluble or amorphous matrices by promoting solid bridging, recrystallization, or plastic flow. **[11]**

Microcrystalline cellulose and swellable excipients undergo premature expansion and softening during initial storage stages under humid conditions.

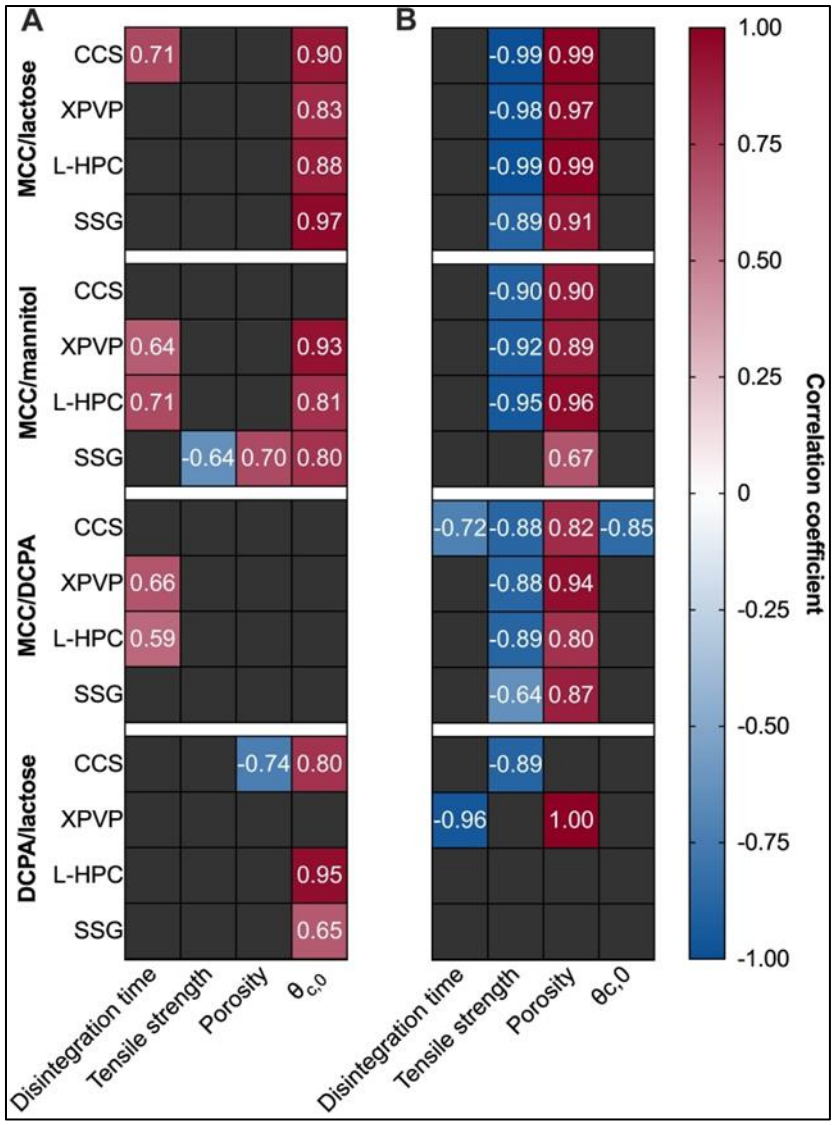


Figure 2: Pearson correlation coefficient between (A) storage temperature and (B) storage humidity with physical tablet properties. Only significant correlations ($p<0.05$) are shown.

3.1 Optimal Moisture Range (Initial Effect)

Increasing moisture content up to about 2.5% progressively increases compact strength, likely due to hydrodynamic lubrication effects of moisture promoting better transmission and utilization of compaction force, plus formation of a moisture film around the drug that facilitates inter-particle hydrogen bonding and increases van der Waals forces. [12]

3.2 Excessive Moisture (Degradation)

At higher moisture contents beyond 3.5% w/w, tablet strength decreases, attributed to hydrostatic resistance of excess moisture in void spaces, which impedes force transmission. [12]

3.3 Storage Humidity Effects

All tablet samples showed deterioration in hardness at 75% relative humidity typically 5-10% loss at 25°C and 10-39% loss at 45°C, with little additional difference in hardness deterioration at 100% relative humidity. This deterioration occurs because tablets absorb moisture at high humidity levels. [13]

3.4 Equilibrium Moisture Content

As humidity increases (but remains below the critical deliquescent point), tablet hardness changes until the compact attains its equilibrium moisture content, after which hardness typically remains constant. [14[

4 EFFECT ON DISINTEGRATION AND DISSOLUTION.

Disintegration is the mechanical failure of the tablet matrix, and it is the rate-determining step for the release of poorly soluble drug.

4.1 This process is initiated by liquid penetration and driven by several theoretical mechanisms.

- **Wicking (Capillary Action)**: This is the primary mechanism for many disintegrants. The tablet's porous structure acts as a network of capillaries that draw water into the matrix. This water uptake is a prerequisite for other mechanisms but does not, by itself, generate the pressure to break the tablet apart. [15]
- **Swelling**: This is the most widely accepted mechanism. Disintegrant particles absorb water and swell, creating internal pressure that overcomes the tablet's tensile strength and causes it to fragment. The efficiency of swelling depends on optimal tablet porosity if voids are too large, the swelling action can be suppressed.
- **Shape Recovery (Deformation)**: During compression, disintegrant particles can undergo elastic deformation. Upon contact with water, they recover their original shape, causing a unidirectional expansion that disrupts the tablet matrix. This is the dominant mechanism for disintegrants like **crospovidone**.
- **Particle Repulsion**: A less common theory, this proposes that certain non-swelling particles can cause disintegration through electrostatic repulsion.

Moisture effects therefore come mainly from excipients such as microcrystalline cellulose, starch, and disintegrants. Water acts as a plasticizer: it lowers the glass transition temperature and weakens the hydrogen bonds and solid bridges between particles, which reduces tablet strength (Ahlneck & Zografi, 1990; Hancock & Zografi, 1994). [16]

Moisture content is measured first. Karl Fischer titration is the reference method, based on the 1:1 reaction of iodine with water in the presence of sulfur dioxide, a base, and an alcohol. Loss on drying and thermogravimetric analysis measure mass loss on heating, but because ibuprofen melts at about 75 °C and sublimes, drying at 105 °C overestimates moisture, so low-temperature vacuum drying or controlled TGA is preferred. Dynamic vapor sorption records mass change as relative humidity is stepped from 0 to 90%, giving a sorption isotherm and the critical relative humidity. [17]

Dissolution (USP <711>) follows the Noyes-Whitney equation, $dC/dt = DA(Cs - C)/hV$ (Noyes & Whitney, 1897). Moisture can reduce the exposed surface area (A) through slower disintegration, or thicken the diffusion layer (h) through gel formation, so dissolution slows. Because ibuprofen solubility rises sharply above pH 6, testing uses a phosphate buffer at about pH 7.2 to maintain sink conditions. [18]

5 EFFECT OF COATING AND PACKAGING

Film coating can modify the physicochemical and release characteristics of ibuprofen tablets by forming an additional barrier around the tablet core. Published studies have shown that the type and characteristics of the coating can influence disintegration and drug dissolution. In particular, the behaviour of the coating under moisture and storage conditions is important because changes in the coating and tablet core can markedly affect ibuprofen release. [19],[20]

Saville investigated the effect of storage conditions and packaging on different ibuprofen tablets, including sugar-coated and film-coated products. Tablets were exposed to different temperatures and relative humidities and were stored either unpacked or in moisture-protective containers, tablet vials, and unit-dose packs. Significant deterioration in dissolution was observed for some sugar-coated ibuprofen tablets under high-moisture conditions, whereas the film-coated tablets investigated were not significantly affected. The study also demonstrated that suitable packaging provided protection against storage-related changes. [21]

The influence of coating level on ibuprofen release has also been demonstrated in coated multiparticulate systems. Increasing the coating level can alter the drug-release rate because the polymeric coating acts as a diffusion barrier. Studies using Eudragit-based coatings have shown that coating composition and polymer characteristics can influence the release behaviour and physical stability of ibuprofen-containing systems. [22]

Packaging is therefore particularly important for coated ibuprofen tablets because moisture exposure can influence both the coating layer and the tablet core. A published study on enteric-coated ibuprofen tablets used **PVC–aluminium blister packaging** and evaluated assay and dissolution during long-term and accelerated stability studies. The tablets were stored at **30 ± 2 °C/65 ± 5% RH** for long-term testing and **40 ± 2 °C/75 ± 5% RH** for accelerated testing, with assay and dissolution used as stability-indicating parameters. [23]

6 ANALYTICAL METHODS

The ibuprofen content of the prepared tablets was determined using a validated analytical method. For assay determination, an accurately weighed quantity of powdered tablets equivalent to the required amount of ibuprofen was transferred into a volumetric flask and extracted using an appropriate solvent. The solution was sonicated to facilitate complete extraction of ibuprofen, followed by filtration and suitable dilution before analysis. The absorbance of the resulting solution was measured using a UV–visible spectrophotometer at the selected analytical wavelength. UV spectrophotometric determination of ibuprofen in film-coated tablets has previously been reported, although the relatively low specific absorbance of ibuprofen and potential interference from excipients should be considered. [24]

Alternatively, reverse-phase HPLC (RP-HPLC) can be employed as a more selective method for quantitative determination. Published comparative work on commercial ibuprofen tablets has demonstrated the use of both UV spectrophotometry and HPLC for assay determination, with HPLC providing reliable quantification in the presence of formulation excipients.

6.1 The percentage drug content was calculated using:

$$\text{Drug content (\%)} = \frac{\text{Amount of ibuprofen determined}}{\text{Label claim of ibuprofen}} \times \mathbf{100}$$

The results were expressed as mean ± standard deviation (SD), and the percentage relative standard deviation (%RSD) was calculated to assess analytical precision.

6.1.1 Dissolution Analysis

The dissolution behaviour of ibuprofen tablets was evaluated using a suitable USP dissolution apparatus under predefined experimental conditions. Samples were withdrawn at predetermined time intervals, filtered and appropriately diluted before quantitative determination of ibuprofen. UV–visible spectrophotometry or HPLC can be used for analysis of dissolution samples. Published ibuprofen dissolution studies have used UV/visible spectrophotometry following validation, while HPLC-UV methods have also been developed specifically for dissolution testing of ibuprofen immediate-release tablets. [25]

The cumulative percentage of ibuprofen released was calculated from the measured concentration of each dissolution sample, with appropriate correction for sampling and replacement of dissolution medium where applicable.

6.1.2 Analytical Method Validation

The analytical procedure should be validated for specificity, linearity, accuracy, precision, range, limit of detection (LOD), limit of quantification (LOQ), and robustness, where applicable. Published analytical studies have demonstrated validated UV methods for ibuprofen with good accuracy and precision, while HPLC methods have been reported to provide selective and reproducible determination. [24],[26]

7 REGULATORY REQUIREMENTS

The development and evaluation of coated ibuprofen tablets should comply with applicable pharmacopoeia requirements and internationally recognized regulatory guidelines concerning pharmaceutical quality, stability, analytical procedures, dissolution, and manufacturing processes. For coated and uncoated tablets, critical quality attributes should include appearance, identification, assay, dosage-unit uniformity, disintegration, dissolution, and appropriate physical characteristics. ICH Q6A specifically identifies dissolution as an important specification for solid oral dosage forms and indicates that the testing conditions and acceptance criteria should be appropriately justified for the dosage form. [27]

7.1 Drug Content and Specifications

The assay and dosage-unit uniformity of ibuprofen tablets should be established using a validated analytical procedure. Acceptance criteria should be scientifically justified and capable of ensuring consistent drug strength and product quality. ICH Q6A provides a framework for establishing specifications and test procedures for drug products, including coated and uncoated tablets.

7.2 Dissolution Requirements

Dissolution testing is particularly important when evaluating the effect of a film coating because the coating can modify the rate and extent of drug release. FDA guidance recommends scientifically justified dissolution conditions, including appropriate apparatus, medium, agitation speed, temperature, sampling time points, and acceptance criteria. For immediate-release solid oral dosage forms, USP Apparatus I (basket) and Apparatus II (paddle) are commonly used. Dissolution testing should generally be performed at **37 ± 0.5 °C**, with the selected medium and conditions justified according to the drug and formulation characteristics.[28] The dissolution method should also be sufficiently discriminatory to detect meaningful changes resulting from formulation or manufacturing variables, including coating conditions. FDA recommends appropriate method validation and evaluation of analytical performance for the quantification of drug released during dissolution testing. [29]

7.3 Stability and Packaging Requirements

Packaging should provide adequate protection of the finished dosage form against environmental factors that could adversely affect product quality. Stability studies should evaluate whether the selected formulation and packaging system maintain critical quality attributes throughout the proposed storage period. Parameters such as **ibuprofen assay, dissolution, appearance, moisture uptake, and physical properties** can be monitored during stability testing.

7.4 Process Validation and Coating Process Control

The coating process should be controlled and reproducible with respect to critical process parameters such as coating-solution concentration, spray rate, inlet/outlet temperature, atomization conditions, pan speed, drying conditions, and target coating weight gain. FDA's process-validation guidance describes a lifecycle-based approach intended to demonstrate that manufacturing processes consistently produce products meeting predefined quality requirements. [30]

7.5 Post-Approval Changes

If coating composition, manufacturing scale, manufacturing site, equipment, or other manufacturing parameters are changed after approval, the regulatory impact of the change should be assessed. FDA's **SUPAC-IR** guidance addresses changes to components/composition, manufacturing site, scale, and manufacturing processes for immediate-release solid oral dosage forms and describes the associated CMC, dissolution, and, where applicable, bioequivalence considerations. [31]

7.6 RESEARCH GAPS

- Micro/Nano-Mechanical Mapping: Lack of real-time spatial imaging (e.g., nanoindentation + Terahertz/Raman) to visualize local soft spots and internal moisture diffusion within the tablet core. [32]
- Eutectic & Thermal Interactions: Limited understanding of how moisture combined with low-melting-point ibuprofen ($\sim 75^{\circ}C$) and polymers (like PEG) depresses local glass transition temperature (T_g) in multi-component matrices. [33]
- Reversible vs. Irreversible Models: Absence of quantitative mathematical models distinguishing temporary moisture softening (plasticization) from permanent damage (solid-bridge recrystallization upon drying). [34]
- Amorphous Solid Dispersions (ASDs): Insufficient data on moisture-induced phase separation and recrystallization kinetics in novel amorphous or co-processed ibuprofen formulations. [35]
- Real-Time In-Line PAT: Minimal integration of Process Analytical Technology (like in-line NIR) to monitor moisture, matrix porosity, and tablet hardness simultaneously during continuous manufacturing. [36]

8 CONCLUSION

Moisture does not affect ibuprofen tablets in one simple way. A little water, up to roughly 2.5%, actually makes a tablet stronger, but past about 3.5% it gets weaker, and storing tablets in humid conditions wears down their hardness, slows how quickly they break apart, and can cut the amount of drug released. Much of this comes from the excipients, which soften and swell as they take up water. The best protection comes from a good film coating and proper moisture-resistant packaging, backed up by reliable testing and stability studies, and in the studies reviewed, film-coated tablets and well-packed products held up better than unprotected or sugar-coated ones. There is still work to do, though. We can't yet watch moisture move through a tablet as it happens, we lack good models for telling temporary softening from permanent damage, and we know little about how moisture behaves in amorphous ibuprofen formulations or how to track it during continuous manufacturing.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflict of interest regarding this manuscript.

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