

Effect of moisture on solid state stability

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ABSTRACT

Water is omnipresent during pharmaceutical product manufacturing and may interact with the drug substance, excipients, and the drug product in either solvent or vapor form, resulting in several physico-chemical changes, ultimately affecting product performance. Therefore, understanding the mechanisms behind such moisture-induced changes is necessary at every stage of pharmaceutical development and manufacturing to obtain the target formulation.

Characterization tools, such as water sorption, spectroscopy, thermal analysis, diffraction, and more sophisticated approaches like simulations and PAT techniques, can help in the selection of the appropriate solid form, manufacturing method, excipients, and storage conditions, enabling the manufacturing of a stable drug product formulation.

Introduction

Water plays a critical role in the development, manufacturing, and storage of drugs. It influences the physicochemical and microbiological properties of the active drug substance, excipients, and the final drug product. The physical impacts of these interactions are: (i) changes in molecular properties, (ii) changes in bulk properties, and (iii) variations in final product performance. Additionally, water may contribute to changes in chemical stability, such as degradation and the formation of impurities. Consequently, all these factors can shorten the shelf life of pharmaceutical products. Therefore, it is absolutely necessary to under-

stand the fundamentals of such interactions, which is imperative for manufacturing a robust drug product [1].

Zografi and co-workers [2] have shown how different physical states of water in solids, ranging from sorbed water to bulk water, affect their physicochemical properties. Consequently, not all water molecules in the solid should be treated as equivalent, as they do not affect the physicochemical properties of the solid in the same manner, rate, and extent.

Figure 1 below summarizes the main potential interactions of water with APIs, excipients, and drug products [1].

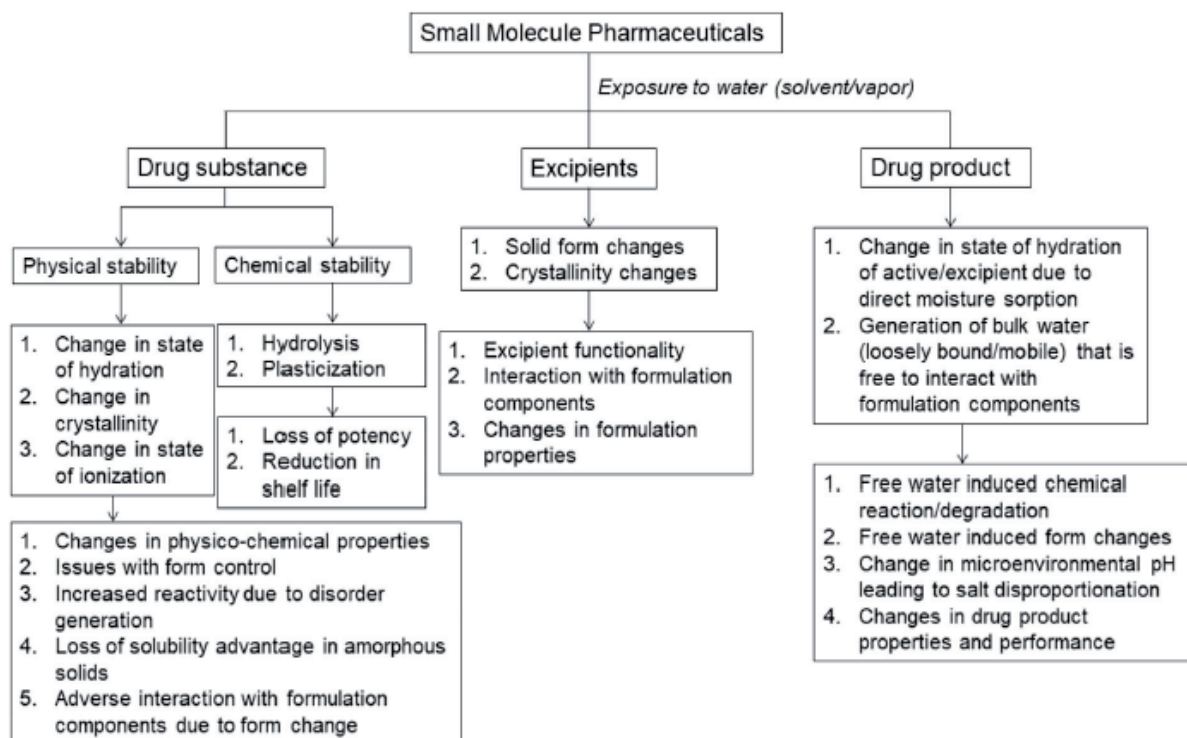


Figure 1. Water-solid interactions encountered during the drugs manufacturing [1].

Water-solid interactions in active pharmaceutical ingredient (API)

2.1. Chemical stability

Moisture-mediated chemical reactions, leading to the decomposition, particularly of active ingredients, and subsequently shortening the shelf life, are among the primary concerns during drug product development. Water not only acts as a reactant but can also participate as a reaction medium, catalyst, or plasticizer by enhancing the molecular mobility of the compounds, making them more reactive. It is essential to note that only mobile water (high water activity, a_w), present during processing or released inside the formulation components, is responsible for degradation reactions [3].

In a study [4] assessing the chemical stability of Levothyroxine Sodium Pentahydrate (LSP) tablets under increased temperature and humidity conditions, it was observed that hygroscopic excipients (e.g., povidone, crospovidone) were not suitable. These excipients release the sorbed water, leading to extensive LSP degradation.

Highly soluble crystalline salts are susceptible to chemical instability caused by deliques-

cence, i.e., the transition from the solid to the liquid state when the ambient relative humidity (RH) exceeds a critical threshold value (RH_0). Such salts, e.g., ranitidine hydrochloride, exhibit higher degradation rates when stored at $RH > RH_0$. Furthermore, including deliquescent actives and/or excipients with low RH_0 in the formulation can lead to the condensation of water vapours during storage, initiating or accelerating the degradation of actives [5]. Acetylsalicylic acid (Aspirin) is another moisture-sensitive drug susceptible to hydrolysis from the free water released by some excipients, like microcrystalline cellulose or dibasic calcium phosphate dihydrate [6].

Physical changes

The interactions change in physical stability typically refers to a modification in the solid form:

- i) Change in the state of hydration: hydrate formation can affect solubility, dissolution rate, surface area and its energy, and mechanical properties. This may alter in-vivo exposure and bioavailability of APIs [7]. For example, it was shown that the formation of theophylline monohydrate upon storage led to the dissolution failure of tablets due to a lower dissolution rate of the hydrate [8].

ii) Change in crystallinity: in an effort to improve solubility and dissolution rate, and so the bio-availability, actives are increasingly prepared in the amorphous state. The essential property of this energetically higher state is to convert back to the more stable the crystalline and loss of all amorphous state benefits.

As an example, when amorphous (glassy) griseofulvin [9] gained only 0.75% of water via ad(ab)sorption, it transformed into the crystalline phase within 12 hours (**Figure 2**) [9].

iii) Change in the state of ionization: APIs exist either as weak acids or bases and are, however, often delivered as salts to improve solubility, dissolution, and physicochemical stability. In these salts is a risk of disproportionation, i.e. the conversion of the ionized form to the neutral form via proton transfer. This results in the loss of the ionized state benefits. Such conversions, can be triggered by small amount of water. Exposure to the moisture is possible during manufacturing, storage, and shipping and represents a concern for the quality of the drug product.

David A. Hirsh et al. [10] reported about such conversion with pioglitazone HCl (PiogHCl) in mixtures with metallic stearate excipients. ³⁵Cl solid-state nuclear magnetic resonance was used to detect the conversion's degree in formulations. Mixtures with Na-St and Mg-St, at 75% RH and 40 °C for 5 days only, produced the conversion of PiogHCl into Piog for about 7% and 15%, respectively [10, 11].

Water-solid interactions during the formulation process and in the formulation

During tableting, various defects may be present in the ejected tablets. To investigate the ability of formulations to consolidate under pressure, some equations, such as Heckel, have been developed. These equations are valuable for preparing optimal formulations; however, they do not provide insight into the phenomena occurring in the powder during compaction. To address this, simulation models based on the finite element method (FEM) have been developed to analyse the powder behaviour during compaction, allowing for a better understanding of the compression.

In the study [16], the authors investigated the sticking phenomena during the compaction of powder by simulating powder temperature and moisture behaviour/change. The simulation of 3D powder temperature distribution showed that, at the end of compaction, a similar temperature (36–40°C) was observed at the tablet's interfaces, but the core's temperature remained higher (about 46°C) [16]. Due to this temperature gradient, water migrates from the core to the tablet surfaces. The simulation of this is shown in **Figure 3**.

The tablet edges appear moister because of the higher powder density, which slows down the diffusion of water molecules into the surrounding area. Additionally, at the gaps between the compression tools and the tablet, capillary conden-

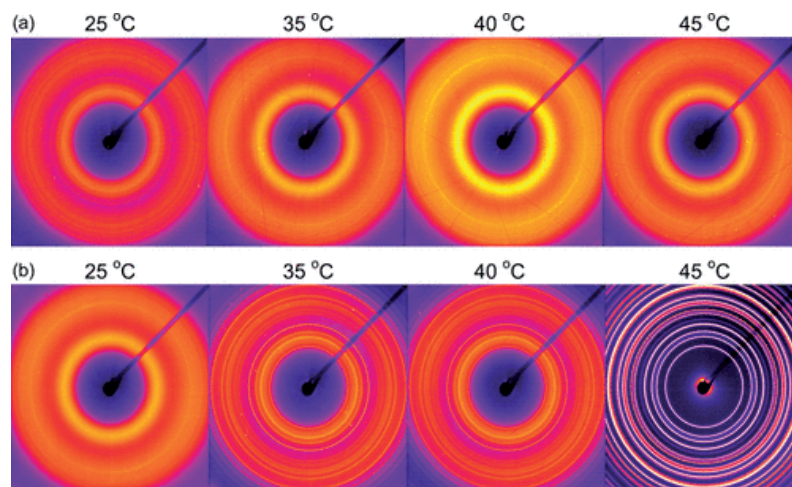


Figure 2. Synchrotron XRD patterns of amorphous griseofulvin after 12 h of storage at the indicated temperature. (a) Dry powder and (b) sample containing only 0.75% w/w water [9].

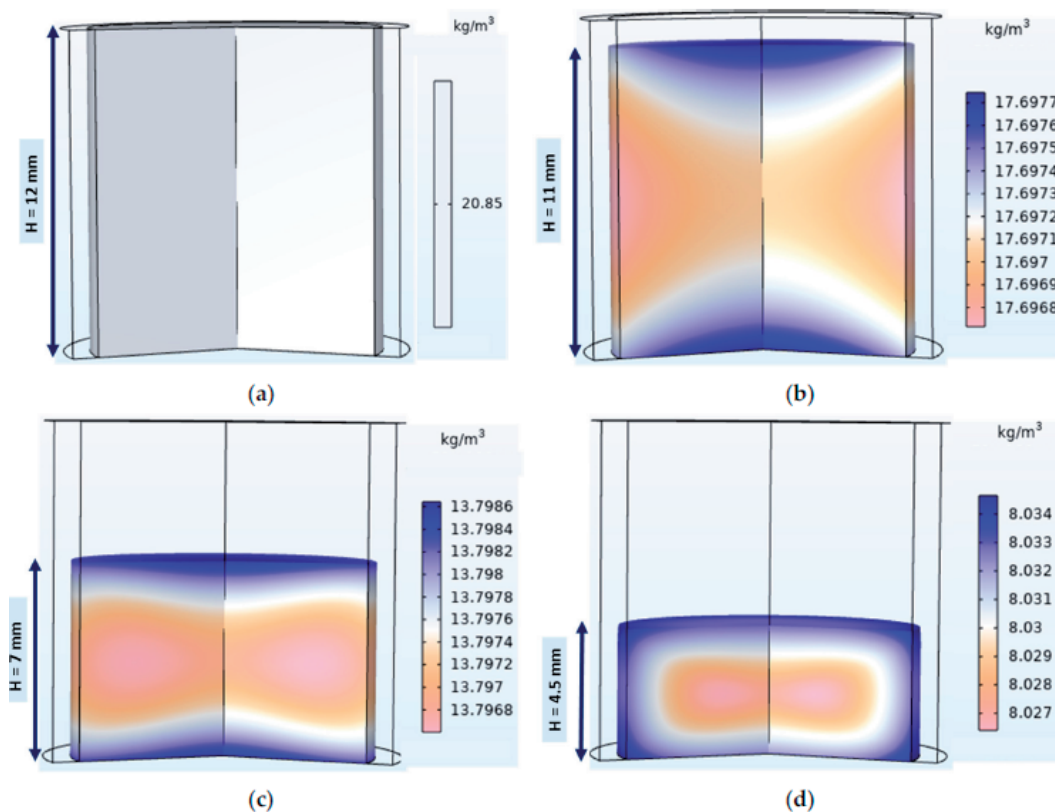


Figure 3. 3D view of the simulated moisture distribution during compaction of model powder (MCC VIVAPUR PH101) with flat-faced punches. The compaction process progresses from (a-d) [16].

sation occurs. All of these factors might be the source of serious problems: sticking, chipping, cracking, and capping [16].

The simulation results were validated using a thermal infrared camera (to monitor temperature evolution) and NIR sensors (for water distribution) [16].

Conclusion

Water molecules, either as a liquid or vapor, interact with solids in many ways, affecting their physico-chemical properties. Many of these interactions are often unknown and unpredictable; however, they are important for the drug product quality.

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Conflict of interest statement

The authors declare no conflict of interest.

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