SJIF Impact Factor 2022: 8.197| ISI I.F. Value: 1.241| Journal DOI: 10.36713/epra2016 ISSN: 2455-7838(Online)
EPRA International Journal of Research and Development (IJRD)
Volume: 7 | Issue: 12 | December 2022 - Peer Reviewed Journal

REVIEW ON MOISTURE CONTENT: A STABILITY PROBLEM IN PHARMACEUTICALS

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Article DOI: https://doi.org/10.36713/epra11911
DOI No: 10.36713/epra11911

ABSTRACT

Liquid water is associate in many different manufacturing processes including pharmaceutical processes. Moisture can affect the thixotropy of semi-solid dosage forms as well as the chemical stability, crystal structure, powder flow, compaction lubricity, dissolution rate, and polymer film permeability of solid dosage forms. While water content measures how much water is in a sample, moisture analysis tells us how wet or dry a sample is. It's crucial to measure this because substances other than water can make a sample moist. Additionally, it has an impact on unit operations that naturally depend on the quantity and quality of water present.

As a result, it is crucial to understand how moisture affects each component's unique qualities, including those of the active substances and excipients. In this article, the significance of moisture content in pharmaceuticals is highlighted. Moisture is measured using a variety of techniques, and changes caused by moisture are shown for a number of product and process attributes.

KEYWORDS: *Moisture Content, Pharmaceuticals, Determination of Moisture Content, Importance, Moisture Induced Changes.*

INTRODUCTION

In each of the three states, water is present in every natural setting (solid, liquid, and gaseous). Liquid water is participant in many different manufacturing processes including pharmaceutical processes. Water is almost always the base of liquid dosage forms, however it can also be found in semi-solid dosage forms as hydrophilic ointments. It is typically crucial to maintain a low water content in solid dosage forms since a high water content could adversely influence the product's physico-chemical, chemical, and microbiological stability.[1]

However, water is frequently used in manufacturing processes (such as wet granulation, spray-drying, coating processes, etc.), but the majority of them must be eliminated in subsequent manufacturing steps. The tablet is the most popular dosage form, and the majority of its weight is typically made up of various excipients.[1]

Manufacturing pharmaceutical tablets effectively and successfully depends on the characteristics and behaviour of the powder. A powder's water or moisture content is a crucial characteristic. A powder's "hygroscopicity" is a measurement of its capacity to absorb atmospheric water vapour. Different physical states of water can exist in powders:

(1) Monolayers or multilayers of adsorbed material on the particle surfaces,
(2) Water that has condensed on a particle's surface.
(3) The particle physically absorbed water, or
(4) Chemisorbed water.

Numerous aspects of the powder are impacted by the condition and distribution of the water, which are dependent on the powder and the volume of water absorbed via exposure to humid air. The link between the water content of a substance and the humidity of the contacting gas is displayed by moisture adsorption isotherms. Five categories were initially used to classify adsorption isotherms.[2]

There are many ways to analyse moisture, including using an oven or a chemical titration. Ovens can reach high temperatures, but they can also be cumbersome, inaccurate, and easily cause samples to burn. Chemical titration can be challenging with materials

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that have little moisture content to begin with, especially if the moisture is brought on by liquids other than water. A moisture analyzer is portable, evenly heated, and capable of measuring moisture contents precisely.

A pharmaceutical product's physical characteristics, which in turn affect the chemical reactivity and binding properties that determine the shelf-life of the product, can be negatively impacted by an excessive or inadequate moisture content. The moisture level is crucial for the crystallisation, agglomeration, and chemical form of these substances during the manufacture of tablets since pharmaceutical products may also contain substances that are dangerous when in touch with the skin or when inhaled. So, a standard quality check in the pharmaceutical sector involves moisture analysis.[3]

WHY IS THE MOISTURE CONTENT OF PHARMACEUTICALS SO IMPORTANT?

When mixing and granulating raw materials, such as Active Pharmaceutical Ingredients (APIs) and excipients, moisture content is a crucial consideration. The consistency of blended powders and overall flow characteristics are influenced by moisture content. Moisture content is one of the quality criteria for finished tablets and capsules that takes into account mechanical strength, solubility, and overall shelf-life stability.[4]

Numerous pharmaceutical goods' characteristics are impacted by moisture content, which has a direct impact on how tablets are manufactured. These include lubricity, dissolving rate, compaction, powder flow, chemical stability, crystal structure, and polymer film permeability.[3]

The consistency and stability of tablets are impacted by moisture. A tablet will crumble and get agglomerated with powder if there is too much moisture present; the opposite is true if there is not enough moisture. Excipients that are powdered may not flow properly if they are excessively wet, and excessive moisture may cause some active pharmaceutical ingredients (APIs) to crystallise or change their form. Numerous techniques, including as freeze drying, fluid bed drying, compaction, granulation, and extrusion, are used to create solid dosage forms. The quantity and quality of water present affects each of these processes. Individual active components and excipients' chemical and physical characteristics might also be impacted by moisture.[3]

The texture and binding abilities of a chemical are significantly influenced by moisture. For instance, effervescent medication must dissolve in a glass of water rather than between the user's fingers and must remain intact in the packaging. If the product is a powder, it shouldn't bunch up or it won't mix properly. For some people, a tablet may be too sticky or crumble into dust, and a syrup may be too thick to swallow (or too watery, in which case the patient must drink more to achieve the same effect).[5]

Due to the particular nature of the equipment and delivery methods, moisture is also crucial for manufacturing and distribution. For instance, syrup with excessive moisture may leave residue in machinery that may eventually clog it and cost money to repair. A pill with insufficient moisture risked crumbling before packaging.[5]

Every step of the process, including packaging, is tested because moisture analysis is so crucial. Since most people don't consume the entire contents of a bottle or may have a long-term prescription, it's important to ensure that medication will remain stable and resistant to water, dust, or humidity incursion while still packaged.[5]

Hydrophobic medications are frequently manufactured with hydrophilic polymers added to create miscible mixtures known as amorphous solid dispersions. From the standpoints of processing and stability, the interaction of moisture in these blends is a crucial factor. Moisture issues include:

- Due to the moisture content, the flow of the API and excipients was not as anticipated.
- Differences in the weight of batches of finished tablets or raw materials
- Clogging or caking in process equipment
- Moisture-permeable packing materials that maintain the content’s stability
- The undesirable effect of moisture on chemical stability (e.g. antibiotic hydrolysis) and physical stability (e.g. change of dissolution rate)
- Drugs having functional groups such as esters, amides, lactones, or lactams, as well as many polymers, undergo hydrolytic breakdown.
- A powder or granulate's angle of repose is not what is expected. Water can fill voids between particles, altering electrostatic attraction and ultimately affecting the characteristics of how powder flows.

Manufacturers must take into account both the finished product and the effect of moisture in bulk materials. Since moisture content varies from batch to batch, uniformity in formulation demands an accurate method for determining moisture content. Methods for determining moisture must be quick, reproducible, and accurate in order to be useful.[3]

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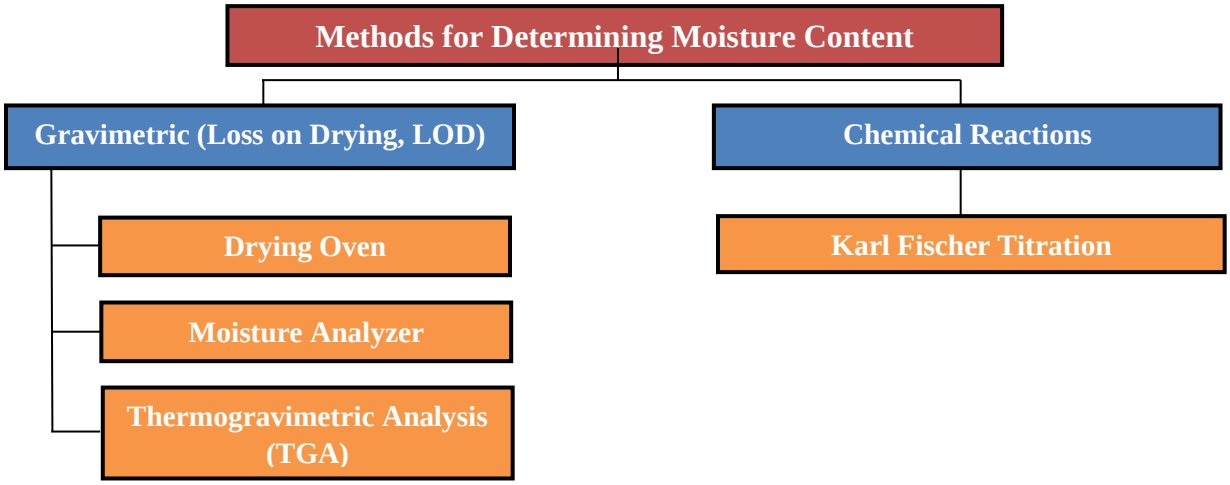
DETERMINATION OF MOISTURE CONTENT



Gravimetric Methods

A sample is weighed before being dried using a suitable temperature programme until the sample mass reaches a "constant" value in a gravimetric method. This measurement approach seems straightforward and trustworthy at first glance. However, the following significant issues surface:[6]

- Release of water and other volatiles can also contribute to mass loss (gravimetric methods are not specific with respect to water). In addition, the material may degrade while drying and emit breakdown byproducts. Therefore, one can only use gravimetric methods to estimate the water content if one can make the assumption that decomposition processes do not occur and that other volatiles are absent. Therefore, only the loss on drying (content of moisture and volatiles) may be assessed using gravimetric methods, and even then, only if the sample doesn't break down while drying.[6]
- The drying process is influenced by the drying conditions, including temperature, ambient pressure, and ambient humidity. In theory, it takes a long time for a substance to dry completely. Therefore, a drying criterion is established in practise (for instance, with the halogen moisture analyzers). This is done by setting a maximum value for the mass loss, Δm_{max} that occurs in a certain time interval, Δt. If the mass loss rate $\Delta m/\Delta t$ is higher than $\Delta m_{max}/\Delta t$ after a certain time, the material is not dry, below this value it is considered to be “dry” (see Figure).[6]

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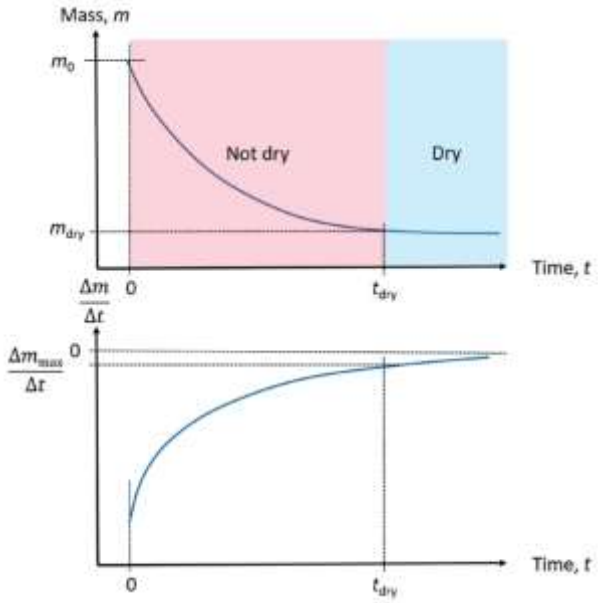

- The amount of moisture or water is often expressed as a percentage of the sample mass. Concerning the reference mass, the following question arises: Does the reference mass relate to the dried product's mass or the mass of the sample before drying? The "dry mass" is referred to as the reference mass in the latter scenario. But after drying, is the sample indeed "dry"? The mass of the sample before drying is frequently chosen as the reference mass due to practical considerations. This is presuming that the sample's moisture content does not alter throughout sample preparation, such as by water evaporation or adsorption, which would have an impact on the sample preparation process.[6]

Drying Oven

Using a drying oven is the traditional method for calculating the moisture content (also known as loss on drying). By using heated (and ideally dry) air in an oven set at a specific temperature, one (or more) samples are dried (sometimes also under reduced pressure). After drying, the difference between the beginning mass and the finished mass is used to compute the moisture content. USP 40 [1] contains a comprehensive description of the process. It takes a lot of time (usually 2 to 3 hours) and effort to determine the moisture content using a drying oven (the weighing process is done manually). However, the most crucial approach for determining moisture content or loss during drying is still the usage of drying ovens.[6]

Moisture Analyzer

The moisture content (also known as loss on drying) of a material can be ascertained in 5 to 15 minutes if halogen moisture analyzers are employed. The sample is heated to the drying temperature (usually 105 °C) using halogen heating technology in a halogen moisture analyzer like the METTLER TOLEDO HX204. The mass of the sample is continually measured throughout the heating phase and the ensuing isothermal phase, and the sample's drying curve is presented. The corresponding moisture content is determined when the drying criterion specified in the measurement method is attained.[6]

In actuality, the sample temperature can vary from the set drying temperature by a few degrees. The samples are heated by the absorption of the radiation generated from the halogen lamp, which is primarily in the IR range. This is owing to the various absorption capabilities of the materials to be studied. The photo of METTLER TOLEDO HX204 Halogen Moisture Analyzer can be seen in Figure.[6]

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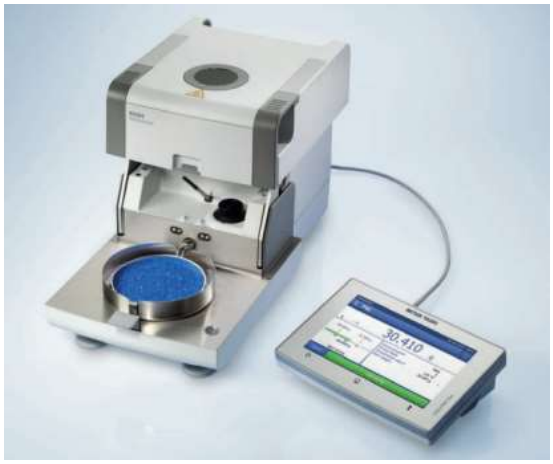

The halogen light is used to heat the sample to the proper drying temperature, and it is subsequently dried for, typically, 10 minutes. There is constant measurement of the sample mass. The drying standard that the user has chosen determines the moisture content.

Thermogravimetric Analysis

Thermogravimetric analysis can also be used to measure moisture contents (TGA). TGA measurements can be made using significantly smaller samples than drying ovens and halogen moisture analyzers. Additionally, it is also possible to take measurements while the pressure is lowered. Water can be discriminated from other volatile chemicals or from decomposition products if the TGA is connected to an evolved gas analysis instrument, such as a mass spectrometer MS or a Micro GC/MS. In this situation, the TGA approach is unique to water. [6]

CHEMICAL REACTIONS

Karl Fischer Titration

Titration is a technique used in analysis to determine the concentration of a certain component in a solution (the sample solution). In a chemical reaction, the substance in question in the sample solution is titrated with a standard solution (the titrant) of known composition. On the basis of the stoichiometry of the reaction with the standard solution, the volume of the standard solution consumed is measured, and the unknown concentration of the chemical in the sample solution is determined. The reaction equation states that water can be found using the so-called Karl Fischer titration (KFT):

$$ROH + SO2 + 3\ RN + I2 + H2O \rightarrow (RNH)\cdot SO4R + 2\ (RNH)I$$

where RN is a base (often imidazole) and ROH is an alcohol (typically methanol)[16]. The Karl Fisher titration can be used as a technique to selectively determine water content if the sample doesn't contain any other compounds besides water that react either directly or indirectly with the Karl Fischer reagent.[6]

HOW DOES MOISTURE AFFECT THE STABILITY OF MEDICINE?

A product could decompose after a week or two on the shelves due to too much moisture. This could be disastrous for medicine delivered to distant places because too much moisture can result in germs or fungus.[5]

Additionally, too much water may result in hydrolysis, a chemical reaction in which water dissolves a substance's bonds. For instance, paediatric penicillin medicines are crucial and must be stocked in children's hospitals, yet they are unstable in water. This means that before administering the solution to patients, doctors and nurses must mix a stable form they have on their shelves with water.[5]

Doctors can better learn how to administer various substances to patients by seeing how they respond to moisture and water. A medicine is not a good fit for something like an IV bag if it degrades more quickly in water.

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Through the magic of chemistry, substances that could be dangerous or toxic alone can be combined to produce advantageous results (for example, common aspirin has compounds that can cause gastric bleeding if not mixed with other chemicals). But that depends on the combination properly keeping together. That link might be broken by insufficient or excessive moisture, which would cause compounds to separate or mix in the wrong amounts and cause undesirable reactions.

Moisture and hydrolysis can slow down the drug's metabolism in addition to preventing the medicine from degrading before it is consumed. Anesthetics typically consider hydrolysis; the less prone a drug is to hydrolysis, the longer it can stay stable. On the other hand, inactive compounds may take longer to degrade and be disposed of if a chemical takes too long to reach hydrolysis.[5]

Chemicals can change in a variety of ways through different reactions, some of which may have unfavourable effects. Pharmaceutical labs offer very detailed instructions regarding the ingredients of their products, including the amount of water and moisture. It appears on a quality control checklist along with many other things. To get quick, accurate, and reproducible results, a good moisture analysis process is necessary, as is the use of the appropriate equipment.[5]

WATER CONTENT LIMIT IN PHARMACEUTICALS

Limits on water and moisture content vary depending on the medication type, delivery method (such as syrup, tablet, or powder), and how it will be combined. Specific guidelines and limitations governing acceptable moisture and water content in their products should be provided to the manufacturer and quality testing laboratories. A generic prescription drug or a comparable product made for children rather than adults may have a slightly different formulation, so it's crucial to double-check everything. Laboratories should establish and maintain their own databases because information on medication stability isn't usually shared or generally accessible.

Formulation is made simpler by the common use of percentages to describe water and moisture contents. Additionally, since the formulation of the same product should be proportional, percentages guarantee that the numbers stay the same regardless of how much is tested.[5]

MOISTURE-INDUCED CHANGES

A research done by Carstensen and Van Scoik has shown that moisture can have a significant impact on a substance's physical characteristics[7]. Lyophilization, which creates an amorphous, highly porous solid cake, was used to create amorphous sucrose spheres. In the first several days of the investigation, its moisture content rises significantly.

However, the moisture absorbed by the porous amorphous sucrose phase eventually led to the collapse of the structure and a corresponding decrease in moisture content because of the dramatically reduced amount of surface that could convert to the crystalline form at a rate that was dependent on relative humidity. In addition to the physical change from a loose to a denser amorphous form, the amorphous sucrose was also demonstrated to be humid. This illustration is in line with the increased focus on solid state changes brought on by sorption.

Dealing with variations in surface area as a continuous variable is one of the challenges posed by a thermodynamic approach of solids. Copeland and Young offered an early thermodynamic solution to this issue in 1961.[8] These authors provided a foundation for understanding the thermodynamic properties of powder systems as continuous functions by interpreting a change in the number of moles of adsorbent as the addition or removal of particles with the same specific surface area.

This method was utilised by Wu and Copeland to characterise barium sulphate. They emphasised that although thermodynamic variables of adsorbents are typically fewer than those for adsorbates, this can be misleading and found convincing evidence to refute the "inert" adsorbent idea.[9] Adsorbents' characteristics are those of the corresponding component on average. This approximation is appropriate if the adsorbed moisture is evenly distributed throughout the solid. The thermodynamic changes would be much increased if the process were adsorption and only the top few layers of the adsorbent were affected. The analysis of the thermodynamic characteristics of the adsorbent, which is a promising field for further study, is almost seldom done in medicinal studies.

Zografi talks about the need to address changes in adsorbent. He notices that water can function as a plasticizer and lower the glass transition temperature when it is incorporated into the bulk structure of a solid. The mobility of molecules or portions of molecules in the system increases above the glass transition point.[10] The collapse and subsequent crystallisation of lyophilized cakes, direct compaction properties, powder caking, permeability of coatings and packaging materials, and solid state chemical stability are just a few physical chemical processes that can be explained by the transition from the "glassy state" to the "rubbery state" and are of interest to the pharmaceutical industry.[9] The single most significant recent development in creating a framework for comprehending and forecasting the impact of moisture is the recognition of this reality.

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Incorporating the degree of crystallinity into the experimentally obtained monolayer capacities of microcrystalline cellulose, Zografi and Kontny discovered values that were largely consistent. This outcome confirmed the theory that water is restricted to the noncrystalline portions of microcrystalline cellulose.[10]

CONCLUSION

It is crucial to describe how moisture affects the unique features of active substances and excipients. Moisture can and does affect these properties. Gravimetric measurements always reveal the entire volatile content (including water) of samples and are LOD techniques. KFT or physical procedures, on the other hand, are unique for water and determine the water content of samples.

The method, as well as the measurement and evaluation criteria, are what determine the moisture content's (or water content's) outcome (temperature program, drying criterion, etc.). In addition, the release of moisture and decomposition frequently coincide, making it more challenging to determine the true moisture level. As a result, Moisture content should be determined at each level in the pharmaceutical industry to obtained a product of predetermined specification.

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