Pharmaceutical Applications for Water Activity

Knowledge of the water activity of pharmaceutical solids (proteins, drugs, and excipients) is essential to obtain a solid dosage form with optimal chemical, physical, microbial and shelf-life properties. Water activity (a_w) influences the chemical stability, microbial stability, flow properties, compaction, hardness, and dissolution rate of dosage forms of pharmaceuticals, proteins, biopharmaceuticals, nutraceuticals and phytochemicals. The importance of the measurement of water activity has been long recognized by the food industry. Although the measurement of water activity is traditionally less common to the pharmaceutical industry, the equipment used is suitable for pharmaceutical products.

Water activity (a_w), or equilibrium relative humidity (ERH) is a measure of the free water in a pharmaceutical dosage form. It is defined as the ratio of the water vapor pressure of the substance (p) to the vapor pressure of pure water (p_o) at the same temperature; $a_w = p/p_o$. Equilibrium relative humidity is water activity expressed as a percentage; ERH = a_w x 100. Water associated with a substance is classified as either free or bound. Free water (sometimes called mobile or unbound) is loosely adsorbed on the surface of the substance and has properties of bulk water. Bound water is directly or tightly associated with a material and is not readily available for chemical interaction with other species. Additionally, some water is less tightly bound, with properties reflecting a much higher level of structure than bulk water but less than that of tightly bound water. Thus, the amount of free water rather than the amount of total water is critical to the chemical and physical stability of a drug substance that is moisture sensitive.

At equilibrium, the water activity of a material is equal to the relative humidity (RH) of the atmosphere in which it is stored. Knowledge of whether water will absorb or desorb from a particular component is essential to prevent degradation, especially if one of the substances is moisture sensitive. For example, two separate materials (initially at different water contents and a_w's) stored at 25% RH will reach a water activity of 0.25, although the final water content of the two materials will be different. If the materials are moved to a higher or lower RH then the water will increase or decrease, respectively until equilibrium is reached. Likewise, if two materials of differing water activities and the same water content are mixed together, then the water will adjust between the materials until an equilibrium water activity is obtained. Therefore, water activity over water content provides useful information for formulation design, manufacturing conditions and packaging requirements.

The relationship between water content and water activity is complex. An increase in a_w is almost always accompanied by an increase in the water content, but in a nonlinear fashion. These curves are determined experimentally. Many disciplines use water content calculations to regulate product quality, however, water content measurement can be inaccurate and time-consuming, especially for pharmaceuticals. For example, a particular compound has a water content of 0.05% and measuring water content in this range is difficult and requires a precision balance. For this compound, changes as small as 0.02% in water content corresponded with a 0.2 change in a_w. Clearly, the a_w measurement permits much tighter control of the product's specifications.

Microbial Growth

Water activity is a better index for microbial growth than water content. The water activity concept has served the microbiologist and food technologist for decades and is the most commonly used criterion for safety and quality. Microorganisms have a limiting a_w below which they cannot grow. Knowledge of the behavior of microorganisms in pharmaceutical products at different a_w levels is important in meeting Federal Food, Drug and Cosmetic Laws.

Component Compatibility

The importance of water activity as opposed to total water is used in preformulation compatibility studies involving moisture-sensitive drugs. Hygroscopic excipients (starch, cellulose and magaldrate) have successfully been formulated for use with moisture sensitive drugs. The excipients may preferentially bind moisture and make the dosage form less susceptible to changes in relative humidity during manufacture, shipment, storage or patient use, thus extending shelf-life. This is also applicable to other polymer systems of pharmaceutical interest, such as proteins (gelatin, keratin) and various synthetic hydrogels.

Stability

Protein, enzyme and biopharmaceutical stability is influenced significantly by water activity due to their relatively fragile nature. Great care must be taken to prevent aggregation under pharmaceutically relevant conditions. Most proteins, enzymes and biopharmaceuticals also must maintain integrity to remain active. Maintaining critical water activity levels to prevent dissolution, aggregation and conformational changes from occurring is important to deliver the correct dosage.

Additional Applications

Water activity of powders effects the flow, caking, compaction and strength properties of solid dosage forms. Additionally, a_w is used in the study of shelf-life, aging and packaging requirements of pharmaceuticals. Water activity also has uses in design and development of coating technology. Understanding the response of solid dosage forms to changing environments aids in determination of formulation and packaging requirements. When tablets are in the process of equilibrating to a higher or lower value, or the tablets have a coating, the tablets should be crushed in order to obtain an accurate free moisture level for the entire tablet.

Above lists only a few of the many applications water activity measurement has to offer to the pharmaceutical industry. For rapid and accurate measurement of a_w of pharmaceuticals the AquaLab is well suited. The AquaLab is a research grade instrument that is successfully used throughout the food industry for its accuracy, speed and ease of use. Manufactured by Decagon Devices, Inc., the AquaLab uses a chilled mirror sensor to measure water activity. Less than five minutes are necessary to reach equilibrium relative humidity conditions in the AquaLab. An infrared thermometer measures sample temperature independently. AquaLab can then compute a_w from first principles without making assumptions about sample temperature. The AquaLab makes readings over a wider range (from 0.030 to 1.000 ± 0.003 a_w) than other water activity sensors. AquaLab provides rapid water activity measurement of powders, granulations, creams, fluids or tablets.

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