The Role of Water Activity in ICH Guidelines and QbD in the Pharmaceutical Market

Introduction

Establishing appropriate product quality programs with effective and validated methods during drug developmentcan be very challenging. The purpose of the InternationalConference on Harmonization (ICH) is to provide guidance in establishing quality testing and batch release programs (Hussong 2009). It emphasizes that quality testing programs should be risk-based and supported by science. Testing procedures and acceptance criteria for drug release programs are outlined in ICH Q6A. Instructions on best methods for determining microbiological attributes are found in Decision Trees #6 and #8. In both decision trees, the need for microbial limits testing is based on whether the product is inherently "dry" enough to not support microbial growth. The assumption in the pharmaceutical industry is that this dryness can be established using moisture content, or amount of water in a product, usually through a Karl Fischer analysis. However, since the work of Scott in the 1950's, it has been well established that it is water activity, or the energy of water, that actually determines whether or not microorganisms can access the water in a system Scott 1957). Therefore, the "dryness" referenced in the decision trees of ICH Q6A should be measured using water activity. Water activity should also be considered and utilized when constructing a stability protocol using ICH Q1A. An information pharmacopeia chapter, USP Chapter <1112>, provides further scientific evidence that water activity should necessarily be part of any risk-based drug release quality program to ensure microbial safety and product quality (See Decagon's Application Note, Understanding Water Activity for Reduced Microbial Testing Using USP Method <1112>.

The USDA's Quality by Design (QbD) initiative encourages manufacturers to define the most desired condition for a product and then identify the key parameters that will ensure that condition is maintained. Attributes critical to achieving the highest level of quality are identified as Critical Quality Attributes (CQA's) and the testing parameters that will be used to maintain CQA's are identified as Critical Process Parameters (CPP's). Water activity should be considered as a CPP to establish microbial safety as a CQA. Water activity as a CPP also influences other CQA's such as chemical degradation, stability of API, flow characteristics of excipient powders, and dissolution of solid dosages.

Not All Water Is Equal

Water in a system may be thought of as present in three general forms: bulk or "free", absorbed, and "bound" or monolayer water. Bulk or "free" water has the same energy and properties as pure water. Absorbed water is held less tightly than "bound" water, but still has reduced energy and different properties than pure water. "Bound" water has reduced energy as the result of direct physical binding of water to the matrix by hydrogen or ionic bonding. In reality, water molecules readily move between each of the forms and it is impossible to quantify the amount of water in any one form. Rather, the overall energy status of water is determined by the relative contributions of each of these water layers. A reduction in the energy of the water, (i.e. lower water activity), results in less available water for influencing biological and chemical reactions. Moisture content analysis can only measure the total amount of water in a product. It can't differentiate between the types of water.

Karl Fischer titrations are effective at quantifying even tightly "bound" water, and are often considered a better moisture analysis method than loss on drying for that reason. In fact, this extra water that is measured using Karl Fischer is often referred to as the "bound" water. But, while Karl Fischer analysis may provide a more complete determination of total water content, it still only measures the amount of water and not the energy

status of the water. Because it measures the energy or "availability" of water, water activity provides better correlations to biological and chemical reaction rates than Karl Fischer analysis.

What is Water Activity?

Water activity describes the thermodynamic energy status of the water in a system. Though not scientifically correct, it may help to picture water activity as the amount of "available" water in a system. It is not a measure of how much water is present in a product, but is an indicator of how much the water in the product resembles and behaves like pure water. Water activity values range from 0 (bone dry) to 1.0 (pure water). As water activity decreases, the water in a product decreases in energy and is less "available" for microbial growth, for chemical reactivity, for moisture migration, and to act as a solvent.

Scientifically, water activity is defined as the vapor pressure of water (p) over a sample divided by the vapor pressure of pure water (po) at a given temperature. By measuring this vapor pressure relative to the vapor pressure over pure water at the same temperature, it is possible to determine the energy of water in the sample. Water that is associated chemically or physically in a sample has lower energy and will not readily move into the vapor phase, thereby decreasing the vapor pressure above the sample.

Water activity in ICH

Water activity is the best index for microbial growth. A product may contain a relatively large percentage of moisture, but if the water is chemically "bound" to humectants or solutes, such as salts, sugars, or polyols, the water is biologically unavailable for microbial growth. The water activity concept has served microbiologists and food technologists for decades and is the most commonly used criterion for food safety and quality. Every microorganism has a limiting aw below which it cannot grow. No direct relationship exists for moisture content and microbial growth.

Consequently, the dry condition referenced in ICH Q6A that justifies reduced microbial testing can only be determined using water activity. In addition, ICH Q1A, which outlines stability testing programs for newly released drug products, requires that products be held at various humidity levels. This is essentially the same as requiring products to be held at various water activity levels, because water activity and equilibrium relative humidity are the same measurement (a_w = %ERH/100). Humidity is a critical part of these stability programs because water activity (or %RH) drastically influences product stability.

Water Activity in QbD

A drug manufacturer that decides to develop their nonsterile drug release program based on QbD principles needs to identify their CQA's. If they determine that microbial attributes are one of their CQA's, they will need to setup one or several CPP's that will describe the microbial safety of their product. Currently, most pharmaceutical companies will follow USP <61> and conduct microbial limits release testing. However, the purpose of both ICH and QbD is to develop risk-based, science backed programs. Minimum water activity limits for microbial growth are well established in the scientific literature as well as in USP <1112>. Consequently, especially for solid dosage products, water activity makes more sense as a CPP for establishing microbial safety than microbial testing because it is cheaper, faster, and scientifically sound. Furthermore, it is more reliable thanmicrobial testing since it establishes the safety of an entire batch while microbial testing only assures the integrity of the sample tested (Hussong 2009).

Water activity is not only useful as a microbial CPP, but also has merit as a CPP for other CQA's such as product integrity, API stability, and dissolution. Differences in water activity levels between components or a component and the environmental humidity is a driving force for moisture migration. If an API is combined with an excipient or coating system at different water activities, water can migrate to the API making it more susceptible to

degradation. Water leaving a coating due to water activity differences will cause cracking while water movement into the coating will make the coating sticky.

Many excipient/drug combinations are amorphous systems. As water activity increases, the plasticizing effect of water increases resulting in moisture induced phase changes. These phase changes are equivalent to a glass transition that can lead to crystallization, which changes dissolution and increases degradation of Active Pharmaceutical Ingredients (API) (Harmon et al. 2009). A critical water activity for the induction of glass transition can be established using a moisture sorption isotherm analysis. This critical water activity can then be used as a CPP for dissolution and API stability.

Conclusion

Pharmaceutical quality programs have been slow to adopt water activity as an effective tool. Factors may include insistence on using moisture content, lack of understanding of the water activity concept, and lack of general acceptance of water activity as a useful method. The guidance provided by ICH and new quality paradigms like QbD that are science based provide excellent opportunities to begin effectively using water activity in pharmaceutical quality programs. A new reference, Water Activity Applications in the Pharmaceutical Industry by Anthony Cundell and Anthony Fontana, is now available from Davis Healthcare Publishing. For additional information regarding the use of water activity in pharmaceutical products, please contact Decagon Devices.

Reference List

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