Excipient Science in Protecting Moisture Sensitive Drugs

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Colorcon®

The Need for Stable Drug Formulations

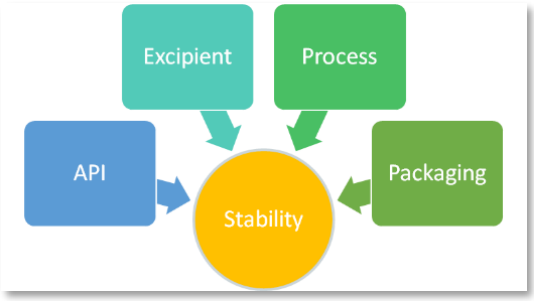
Stability is an essential quality attribute for pharmaceutical drug products. Unstable formulations may lead to loss of active ingredient, making the medicine ineffective for the purpose prescribed, and in some cases, this can lead to the formation of toxic degradation products. Changes in color and physical appearance on stability can also reduce patient acceptability.

Moisture content is known to be the main cause of the degradation of medicinal products, leading to impurities in solid dose formulations. Many drugs are highly sensitive to moisture and in 2018, a study of 300 drugs showed that 49% were classed as moisture-sensitive.[1] Moisture promotes chemical reactions, and the presence of free water has long been recognized as a critical factor in determining product safety and stability.

With heightened scrutiny of the potential presence of impurities in medicinal products by regulators and patient advocacy groups, it is imperative for manufacturers to actively manage moisture and understand how excipient science can help protect moisture-sensitive drugs. Primary packaging is essential for stability and shelf-life a product and it's now recognized that in-use stability should be explored, as patients and caregivers increasingly remove drugs from the original packaging and use pill holders as reminders and convenience for regimen adherence for chronic treatment. This is particularly pertinent in the case of older people.

Recently, there has been an increasing trend in drug recalls, which can negatively affect companies' sales, brand trust, and value, and may even result in liability issues. Of the US FDA recalls in 2018 and 2019, out of specification (OOS) and impurity related recalls could be the result of stability failure of the formulations.[2] The presence of an impurity (unclassified) detected during a product's shelf-life can lead to potentially serious side effects.

Factors Affecting the Stability of Formulations



Achieving stability for pharmaceutical formulations during shelf-life and in-use is a complex process and is influenced by several factors, including the active pharmaceutical ingredient (API), excipients, manufacturing process and packaging.

Many drugs are sensitive to environmental conditions and prone to degradation when exposed to moisture and oxygen. The choice of excipients can impact the stability or degradation of the drug. Any ingredient with a high affinity to absorb water moisture can lead to extensive degradation if the moisture becomes available as free water for chemical reactions. Therefore, the core composition is critical in terms of the compatibility of the API with other ingredients, and how they interact in the presence of moisture.

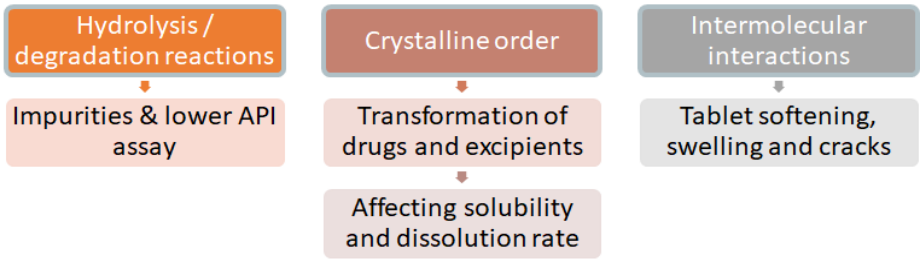
Controlling both process and relative humidity during manufacture is important to manage core stability. Multi-step processes, such as wet granulation, when water is added then removed using heat for drying, can impact and reduce stability. Whereas, dry granulation and direct compression methods which exclude water, help to manage the stability of moisture-sensitive drugs.

The inclusion of on-dose moisture barriers, film coatings with low moisture permeability, is the first defense against environmental factors and can be key to maintaining stability. High-density polyethylene (HDPE), glass bottles with desiccants or aluminum blister packs are widely used to help improve the stability of drugs but there is a cost impact. It is also important to consider how the product will be stored during shipping, before dispensing and then finally in the patients' hand: will it always remain in the original packaging; will it be stored in the home; or will it end up in a daily pill pack?

The Science of Excipient Selection to Enhance Product Stability

To reduce the negative impact of moisture and enhance the stability of formulations, it is important to select the best excipients for the tablet core and coating. Excipients in a drug formulation are generally assumed to be inert, which means they will have no impact on the final formulation; however, some ingredients interact with drugs or other excipients.

Moisture is present in all solid oral dosage forms. It is absorbed to varying extents on the surface of powders and carried into the core. Excess free moisture in a tablet core typically causes stability issues as it may facilitate hydrolysis/degradation reactions, disrupt the crystalline order and cause intermolecular interactions.

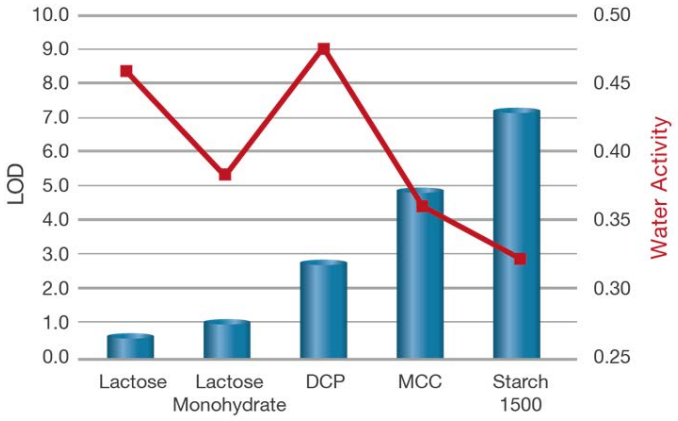


Excipient Selection for Tablet Core Formulation

Core Ingredients typically include API, filler, binder, disintegrant and other enablers or process improvers. Excipients may lose or take up moisture within the core formulation, so it is important to understand the microenvironment surrounding the API and whether the moisture is bound or free. Free water can lead to chemical or physical reactions.

A commonly used indicator for the state of water in food and pharma industries is water activity (a_w), which measures the thermodynamic energy, or availability, of water in a system. Water activity is defined as the thermodynamic activity of the available water associated with a solid powder. It may be calculated as the ratio of the vapor pressure of water in the substance to the vapor pressure of pure water at the same temperature; values range from $a_w = 0$ (completely dry) to $a_w = 1.0$ (distilled water). Water migrates from areas of high a_w to areas of low a_w, resulting in strongly bound water which is, therefore, not available to react with API or facilitate any reaction.

Comparison of Water Activity vs Loss on Drying (LOD)



Loss on drying (LOD), which is not the same as water activity, shows the amount of water that is held inherently by an ingredient. Compared to other commonly used fillers, partially pregelatinized starch (Starch 1500®) has a higher LOD; however, it has the lowest water activity which means it has the highest capacity for binding moisture, so not allowing it to interact with the API.

Studies have shown that formulations with partially pregelatinized starch may enhance drug product stability by preferentially binding to free moisture and decreasing the rate at which the relative humidity reaches equilibrium with the environment.

Fundamental Studies of the Water Binding Capability of Starch 1500®

It is important to understand why Starch 1500®, partially pregelatinized starch, binds with water and how this positively impacts stability. Starch $(C_6H_{10}O_5)_n$ is a polysaccharide comprising glucose monomers joined in α 1,4 linkages in different forms (amylose is the simplest form and is a linear polymer; amylopectin is a highly branched form of starch with many linkages). The glucose units which make starch have very hydrophilic hydroxyl groups. Water molecules bind to anhydro-glucose units within the amorphous regions of the modified starch; water has a strong affinity for starch due to the abundance of hydroxyl groups. Such materials, with a high capacity for binding water, equilibrate more slowly to higher levels of mobile water and consequently show greater chemical compatibility with moisture-sensitive drugs than materials with lower binding capacities for water.

When Starch 1500 is initially exposed to water, the water molecules start sticking to the surface of the particles in a monolayer due to van der Waals forces, hydrogen bonding and ion-dipole forces. As the proportion of water increases, it starts to produce a multi-layer and finally water is adsorbed on the surface in the pore regions. The structure of Starch 1500 is very porous with lots of crevices, giving a large surface area which leads to physical entrapment of water molecules.

To better explain the science, Colorcon collaborated with Prof A. Nokhodchi at the University of Sussex, UK to investigate the water vapor sorption mechanism of starch-based pharmaceutical excipients. Results from the study are published in *Carbohydrate Polymers* in 2020.[3] The key findings are:

- Partial or full gelatinization of Starch 1500 does not affect the type of sorption isotherms
- The degree of gelatinization may influence the rate of water sorption; fully gelatinized starch may have slower water uptake. Fully gelatinized starch products are used as binders and not as fillers.
- The study recommends the utilization of Starch 1500 in the development of stable formulations for moisture-sensitive drug molecules.

To complement this study, Colorcon carried out three fundamental investigations on the interaction of Starch 1500 with water, using thermogravimetric analysis, differential scanning calorimetry, and dynamic vapor sorption. The first two studies clearly show that as only free water freezes on cooling and then melts on heating, only a small proportion of water molecules in unmodified Starch 1500 is free, the remaining water molecules are very tightly bound. Dynamic Vapor Sorption (DVS), a gravimetric sorption technique, is commonly used in the pharmaceutical industry for monitoring the moisture sorption properties of drugs, excipients and packaging to determine stability and storage conditions. It measures uptake or loss of moisture (both rate of change and total mass of water taken up or lost) by flowing a carrier gas at a specified relative humidity over a sample. Because not all the sorbed water molecules can dissociate during desorption or drying, a hysteresis loop will be formed, which is a fingerprint for a specific powder, i.e. the shape of the loop and the position at which the gap starts, and ends is a unique feature for the powder. Details of these studies are published separately. The area within the hysteresis loop for Starch 1500 is larger than other typical excipients, indicating its ability to strongly bind to water, which will not be freely available in a formulation to cause stability issues.

Impact of Moisture Barrier Film Coating

Film coatings provide a barrier that prevents or restricts water uptake, enhancing the stability of a product. A study, showing how application of a moisture barrier coating, Opadry® amb II, high performance moisture barrier film coating, positively impacts the stability of amoxicillin and clavulanic formulations (key ingredients in the antibiotic co-amoxiclav) during an in-use study, where samples were put in pill packs and monitored over time. This study showed the moisture barrier coating to be extremely effective in reducing the degradation of both active ingredients upon removal from the primary packaging.[4]

Conclusions

For effective drug formulation, it is crucial to consider not only the interaction of excipients with the API but also the interaction of excipients with moisture. This is particularly true for moisture sensitive drugs, which may account for half of those currently on the market.

In several studies, Starch 1500 has been shown to improve the stability of formulations by binding tightly to the water moisture in the formulation or within the microenvironment, thereby reducing the amount of free water that causes API degradation. The status of the water interacting with Starch 1500 will vary, but in all cases, Starch 1500 can retain a large amount of water in a bound form.

To determine the amount of Starch 1500 that should be included in a formulation, various aspects of the dosage form need to be considered starting with the drug itself and the final dosage form; then flow, compressibility, disintegration and stability requirements. In most cases, drug properties are critical and determine the choice of excipient to balance these parameters.

Benefits of including Starch 1500 in formulations have been observed with levels as low as 10% w/w. Starch 1500 can be used in combination with other tableting excipients to enhance the performance of the formulation. Starch 1500 will also have a moisture scavenging effect in capsules and has been used in several marketed products.

In addition to the selection of core excipients, the use of specialized film coatings (including Opadry amb II, moisture barrier film coating), environmental control during manufacturing and primary packaging all contribute

to managing moisture. With the increasing use of multi-dose pillboxes for elderly patients, guidance is now being provided on acceptable parameters, not only during the product shelf-life but also during the predicted in-use life of the product, reflecting how the patient is likely to remove the drug product from its primary packaging.

References

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