Protection Beyond the Packaging

There are many factors to be considered in the quest for drug quality assurance – including environmental moisture, stability and packaging solutions. If all of these aspects are addressed throughout the manufacturing and storage processes, the product can be protected from all possible threats to quality and efficacy

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Exposure to environmental moisture can lead to degradation of sensitive active pharmaceutical ingredients, severely impacting stability and efficacy of the drug product. Traditionally, these types of products have been packaged using low permeability moisture barrier materials, or else packaged with moisture-scavenging desiccants. While these solutions can certainly be effective, they are associated with higher costs. These expense contributions can be significant when dealing with lower margin products, such as generic pharmaceuticals or over-the-counter products. Careful consideration of product design and composition can incorporate multiple layers of moisture protection, without adding significant costs (see Figure 1).

Maintaining Integrity

Understanding product stability requires knowledge and consideration from multiple perspectives. Long-term stability testing has been a pillar of pharmaceutical product development, with clearly defined environmental conditions for accelerated and real time studies.

The EMA, in recently published guidance on in-use stability testing of human medicinal products, aims to consider what happens once the medicine reaches the patient (1). This guideline refers to medicinal products in multi-dose containers that may expose the product to unwanted environmental hazards and other agents which can contribute to degradation. The testing requires simulation of use in practice, with sampling under normal environmental conditions, removing doses at specified intervals and analysed for efficacy.

Product quality must also consider temperature and humidity excursions that may occur prior to, or after, removal from primary packaging, including bulk storage, transport or repackaging. There is often limited consideration given to storage conditions when the dosage form has been dispensed by the pharmacist, caregiver or patient. It is not unusual for patient medication to be transferred into a pill sorter, or for a patient to simply place their medication into any convenient container – or even a clothing pocket.

Maintaining the integrity of solid oral dosage forms once they have left the

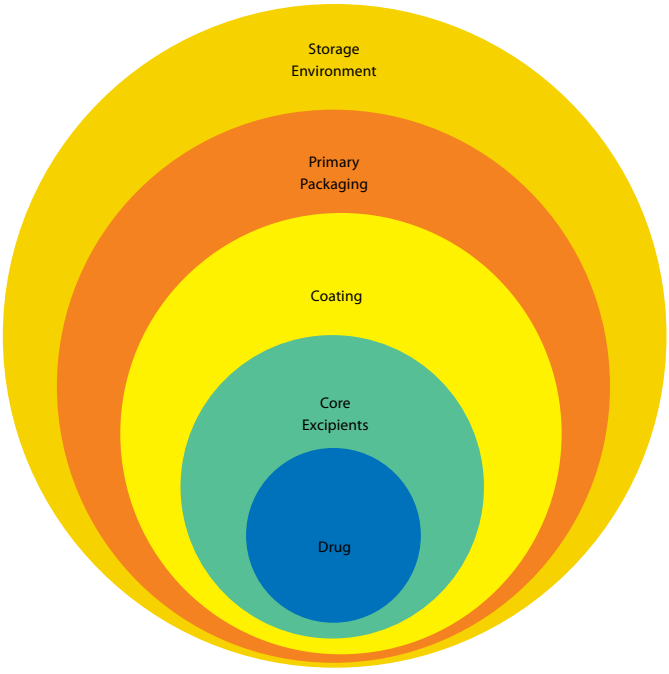

Figure 1: Levels of formulation development and product design that impact moisture protection

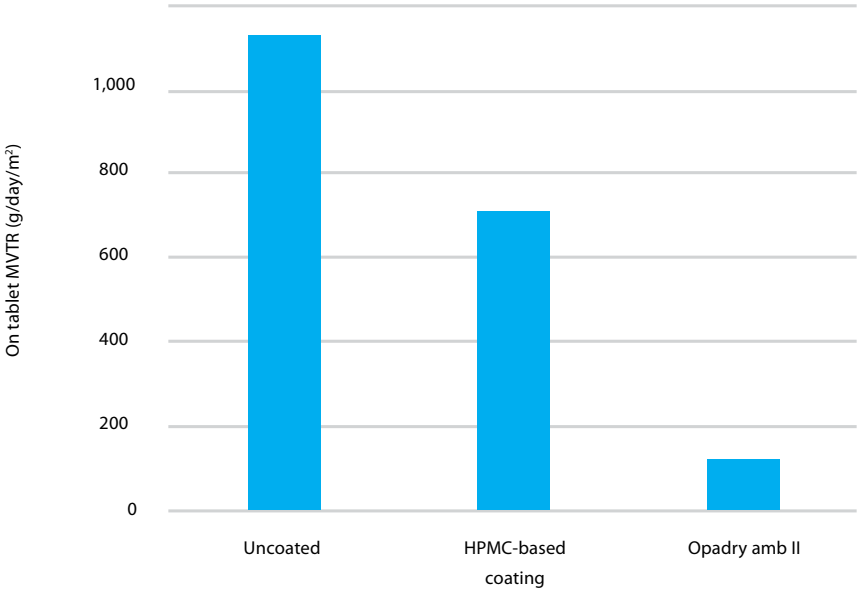

Figure 2: Comparison of MVTR (for placebo tablets) shows reduction with the application of Opadry amb II aqueous moisture barrier coating, compared to uncoated or HPMC-based coating

primary package remains a priority to ensure product efficacy; therefore, primary packaging alone should not be considered as the only protection for moisture-sensitive dosage forms.

Dosage Design and Product Stability

Although the primary packaging and desiccants are considered a dosage form's key defence from the environment, the design and composition of the drug product itself can also affect the moisture sensitivity of the finished product.

Film coating systems are employed for a variety of reasons, including aesthetics, taste-masking, light and environmental protection, as well as serving as physical barriers for moisture when applied to tablets. The right film coating formulation can provide a functional barrier to improve stability of moisture-sensitive compounds by reducing the moisture vapour transmission rate (MVTR), as shown in Figure 2. While conventional hypromellose (HPMC) based coatings do impede the uptake of moisture compared to an uncoated tablet, coatings that utilise polyvinyl alcohol (PVA) as the film-forming polymer show significantly less transmission of moisture (2). Opadry amb II PVA-based film coating has been specifically developed as a high productivity, polyethylene glycol-free moisture barrier to address this concern.

Case Study

A case study examined the effects of film coating on amoxicillin/clavulanic acid tablets for both long-term accelerated and in-use stability conditions. Due to the well-known moisture sensitivity of clavulanic acid, this combination was selected to investigate the moisture protection properties of an innovative versus traditional system. Commercially marketed versions of this combination product are typically coated with an HPMC-based film coating, and in this study the stability of the drug components was monitored for uncoated, HPMC-coated and Opadry amb II-coated tablets.

For long-term accelerated stability studies (40°C/75% relative humidity

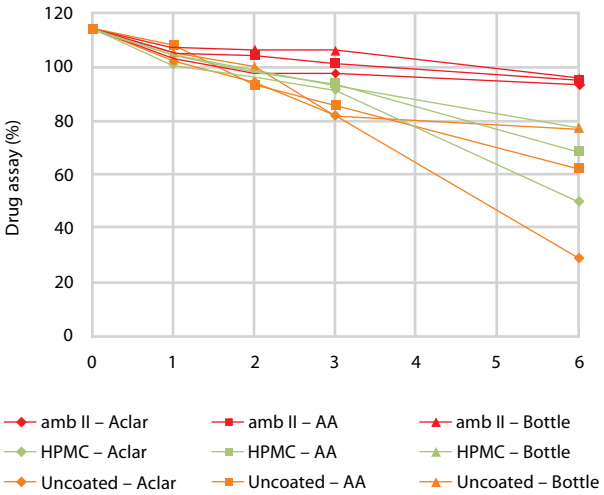

Figure 3: Long-term accelerated stability of clavulanic acid. Packaged tablets stored at 40ºC/75% RH for six months

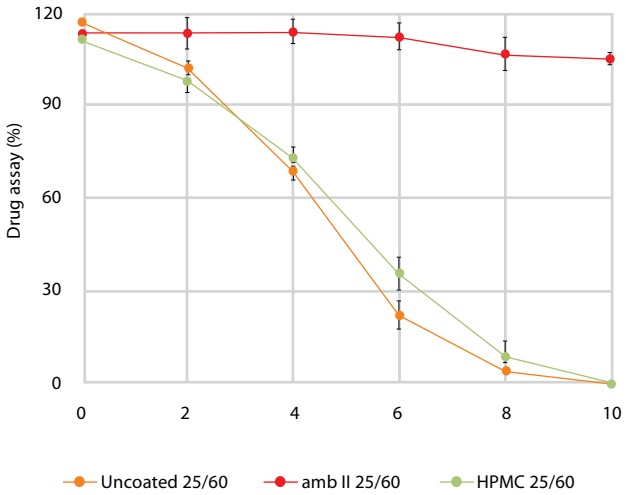

Figure 4: In-use stability of clavulanic acid. Tablets placed in a pill sorter and stored at 25ºC/60% RH for 10 days. Tablets coated with Opadry amb II remained stabled for the duration of the drug regimen

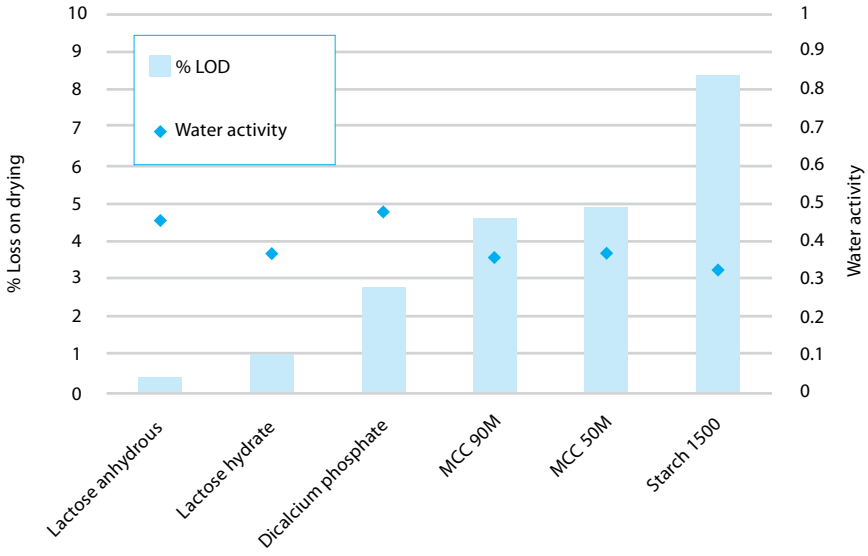

Figure 5: Moisture content and water activity of common tableting excipients. Moisture content encompasses all water present, while water activity discerns free and bound water. Only free water is available for reaction, while bound water is not readily available for chemical reactions (7)

(RH)), three different packaging configurations were assessed: Aclar blisters, aluminium foil-foil (AA) blisters and high density polyethylene bottles with dessicant (see Figure 3, page 42). HPMC-coated and uncoated tablets exhibited marked degradation of clavulanic acid, while tablets coated with Opadry amb II showed superior stability in all packaging formats. Interestingly, stability trends were more aligned with film coating than with packaging. These results affirm that film coating greatly enhances product stability in combination with the package.

To mimic patient use, coated and uncoated tablets were placed in a typical weekly pill sorter and stored at room temperature (25°C/60% RH) for 10 days (the typical length of the antibiotic regimen). After four days, the clavulanic acid already exhibited extensive degradation when uncoated or coated with HPMC-based coating; at the end of the 10-day period, no clavulanic acid was detected (see Figure 4, page 42). In contrast, tablets coated with Opadry amb II remained stable for the duration of the regimen, preserving the full spectrum of antibiotic action. Therefore, application of the moisture barrier coating resulted in improved tablet stability, even when removed from the primary packaging.

> “Many scientists believe that moisture content directly impacts moisture-induced degradation; however, water activity, not absolute moisture content, is the trigger for unwanted reactions”

Activity, Not Content

Excipient selection and core formulation certainly influence the stability of moisture-sensitive compounds. One common misconception surrounding choice of materials is the importance of excipient moisture content. Many scientists believe that moisture content directly impacts moisture-induced degradation; however, water activity, not absolute moisture content, is the trigger for unwanted reactions.

Water can be present as a free and mobile form which is available for chemical reactions with other materials, or in a bound form that is not free to react. For instance, Starch 1500® – partially pregelatinised maize starch – has a relatively high moisture content ranging from 6-14%, as measured by loss on drying (LOD). However, its water activity is equal to or lower than other excipients of lower moisture content (see Figure 5). Multiple studies have been performed showing that the low water activity of Starch 1500 improves product stability and reduces formation of degradants on actives including aspirin, hydrochlorothiazide and famotidine (3-6). It is thought that the excipient acts as a moisture scavenger, sequestering free water that may be present in the formulation (7).

Superdisintegrants, by their nature, are designed to quickly attract water to break apart a tablet. However, this hygroscopic action can be detrimental to a moisture-sensitive tablet formulation, accelerating moisture-induced degradation. Inclusion of disintegrants such as Starch 1500 can reduce and/or eliminate detrimental effects presented by hygroscopic superdisintegrants, while still meeting disintegration specifications (3-6).

Moisture Management

When working with a moisture-sensitive active, it is important to implement

several layers of protection to ensure product stability and consistent quality. Rather than thinking of moisture protection as being only applied at the packaging level, formulators should consider moisture management from the inside-out of the formulation – including low water activity excipients, a proven moisture barrier film coating and, finally, a low permeability packaging material.

References

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About the author

Elizabeth Shen PhD is Technical Marketing Manager at Colorcon, a world leader in film coatings and pharmaceutical excipients. Having begun her career as a formulator for GlaxoSmithKline, Elizabeth brings with her a broad vision and in-depth understanding of the pharmaceutical product development experience. She has been a member of Colorcon's expert technical services team for a number of years, working with innovator, generic and dietary supplement customers. Elizabeth earned her doctorate in Chemical and Biochemical Engineering from Rutgers, the State University of New Jersey, specialising in polymers for controlled drug release.

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