REVIEW

Package Selection for Moisture Protection for Solid, Oral Drug Products

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ABSTRACT: This review describes how best to select the appropriate packaging options for solid, oral drug products based on both chemical and physical stability, with respect to moisture protection. This process combines an accounting for the initial moisture content of dosage form components, moisture transfer into (out of) packaging based on a moisture vapor transfer rate (MVTR), and equilibration between drug products and desiccants based on their moisture sorption isotherms to provide an estimate of the instantaneous relative humidity (RH) within the packaging. This time-based RH is calculationally combined with a moisture-sensitive Arrhenius equation (determined using the accelerated stability assessment program, ASAP) to predict the drug product's chemical stability over time as a function of storage conditions and packaging options. While physical stability of dosage forms with respect to moisture has been less well documented, a process is recommended based on the threshold RH at which changes (e.g., dosage form dissolution, tablet hardness, drug form) become problematic. The overall process described allows packaging to be determined for a drug product scientifically, with the effect of any changes to storage conditions or packaging to be explicitly accounted for. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:4437–4452, 2010
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INTRODUCTION

In this review, the science associated with stabilization of solid, oral drug products by packaging is discussed. This review aims to lay out a rational process for package selection based on predicting drug product shelf-life in different packaging configurations. While many aspects of packaging selection have been developed and published previously,[1–4] this review attempts to provide a focus on moisture sensitivity and how packaging can be chosen to provide adequate product shelf-life while balancing cost and marketing needs.

Drug product shelf-life is determined based on the time a product remains within specifications agreed upon with regulatory agencies. In general, these specifications can be divided into two aspects of stability: chemical and physical. Chemical stability, with regard to expiration dating, involves how long a drug product, in its packaging, continues to have adequate potency (typically $100 \pm 5\%$ of the label claim, but the specification can sometimes be broadened with justification) and sufficiently low levels of any degradation product to assure safety. Degradants have specification limits agreed upon with regulatory agencies. These limits depend on whether the degradant is identified structurally, whether there is any indication of potential toxicity, and on the total daily dose of the active pharmaceutical ingredient, API, as described, for example, in the International Conference for Harmonization (ICH) guidelines.[5,6] Physical instability is associated with any change to the drug product performance (e.g., dissolution, hardness) or appearance. Specifications for such performance criteria often involve a range agreed upon with regulatory authorities, rather than a limit, for acceptable performance. Such changes can in some cases limit the shelf-life of a product.

One of the major stabilizing influences of packaging is protection from moisture. In this review, the influence of moisture on a product's chemical and physical stability is first discussed. This is followed by a discussion of the role of packaging in limiting moisture exposure. A drug product's moisture sensitivity and the protection afforded packaging are combined to allow package selection with regard to moisture.

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MOISTURE'S EFFECTS ON PRODUCT STABILITY

Water Activity and Psychrometry

Water activity in air, at a given temperature, is defined as the ratio of the fugacity of the water in the air to that of pure water.[7] This is generally approximated as equal to the ratio of the actual partial pressure of water vapor in the air to that of the air above pure water: the water activity of air above pure water (closed system) is defined as 1.0 at any temperature. While the water activity above pure water remains 1.0 independent of temperature, the amount of water in the air (mg/L) varies widely: warmer air can hold much more water than cold air. The relationship between the amount of water held in the air, at a water activity of 1.0, as a function of temperature can be seen in so-called psychrometry graphs, such as shown in Figure 1.[8] Relative humidity, RH, is essentially the same as water activity expressed as a percent; that is, a water activity of 1.0 corresponds to an RH of 100%. RH will be used in this review to refer to the air relative humidity, while water activity will be used to refer to water molecules in solids and solution. It should be understood that this is simply convention, and that the terms are effectively interchangeable.

The water activity value of a solid can be determined by measuring the RH of air above the solid when the sample is at equilibrium. This is essentially the ratio of the concentration of water in the air over a sample to the concentration of water vapor over pure water. At equilibrium, the RH in a closed system must be the same throughout; that is, the water activity of the solid must equal the RH of air in equilibrium with it. This is true independent of the physical state of the water associated with the solid. In other words, at equilibrium, the water activity of crystalline hydrates, adsorbed water molecules, and dissolved water molecules equals the RH of the vapor phase.

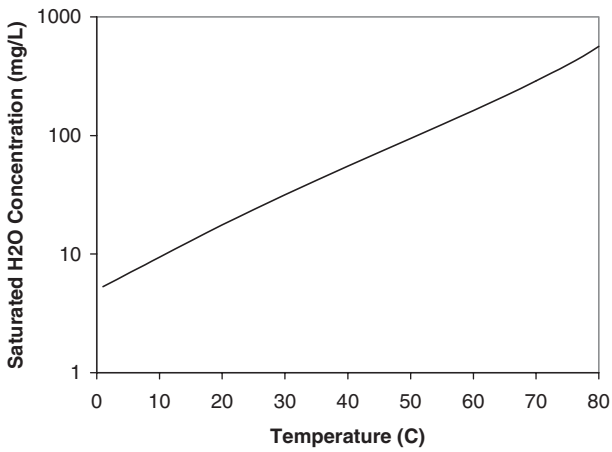

Figure 1. Psychrometry graph showing the saturated moisture content of air as a function of temperature.[8]

Critical Relative Humidity and Deliquescence

Some chemicals, when dissolved in water, lower the activity of the water proportionately to the solute concentration (as a colligative property). When the water activity of a concentrated solution of a material is lower than the storage condition RH, the higher air RH will cause water to condense. Condensation will continue until the water activity of the solution matches the RH of the air. In a similar way, if a solid has a lower water activity (for its corresponding saturated solution) than its surroundings, a process called deliquescence occurs, in which moisture condenses on the solid.[9] The liquid condensate will dissolve the material, and deliquescence will continue until the water activity of the dissolved material matches that of the surrounding air. For a solid, the RH of the air when deliquescence first occurs is known as the critical relative humidity (CRH).[10] When a sample is stored below its CRH, it will adsorb water as a function of the storage RH and stop adsorbing at a relatively low level when equilibrium is reached. This behavior is discussed in the Moisture Sorption/Desorption Isotherms Section. When a sample is stored above its CRH, it will deliquesce. A slurry (saturated solution) of a material, that is, a solution containing both liquid and undissolved solid, will reach equilibrium in a closed container at the CRH.

For most solid dosage forms, deliquescence to any significant extent will result in a physical or chemical change (e.g., appearance, dissolution, degradation) that effectively results in a product failing in one of its specifications. Consequently, one of the roles of packaging is to protect a product that can deliquesce from exposure to RH conditions where such deliquescence can occur. Table 1 shows the CRH of a number of excipients. As can be seen, some of the excipients have CRH values that vary with temperature, which can usually be related to changes in solubility with temperature.[12] It is also important to note that some combinations of APIs and excipients can show CRH values that are synergistically depressed; that is, when these materials are present in the same dosage form, they can deliquesce at a lower RH than when the materials are alone.[13]

Chemical Stability

Drug product chemical stability is generally affected by the RH that the sample experiences. Waterman and coworkers[14–16] describe an accelerated stability assessment program (ASAP) that combines an isoconversion paradigm, a moisture-corrected Arrhenius equation and statistical design and analysis. The isoconversion paradigm was developed to compensate