

Predictive Shelf-life Moisture Control Computer Modelling for Ultra-reliable Pharmaceutical and Medical Device Packaging Solutions



The new computer model developed by Baltimore Innovations' R&D Director, Dr Mark Valentine, is a highly detailed evaluation of humidity and desiccant adsorption behaviour within a product's protective packaging to avoid decomposition, degradation or other forms of moisture damage.

The model uses 3D numerical techniques based on the interaction between fluids and desiccants to accurately understand the role of desiccants within pharmaceutical packaging and their effect on shelf-life. This new model can help companies supplying pharmaceuticals or medical devices to develop optimised, ultra-reliable packaging solutions, whatever the environmental and climatic conditions.

Vital Role of Desiccants

Scientific modelling of fluid mechanics systems or 'computational fluid dynamics' (CFD) is well established in many industries, from streamlining the flow of air over a car bonnet, to investigating the bubble behaviour in a membrane bioreactor. However, the application of these techniques to desiccant systems has been neglected. Desiccants play a vital role in the protection of moisture-sensitive drugs and products. By removing water vapour from the air, the desiccant prevents undesirable reactions between the product and the water molecules. These include degradation known as 'hydrolysis', the cleavage of chemical bonds by water. The desiccant and product are placed inside a protective barrier which will repel most of the external vapour from the interior. [See Figure (1) - Effervescent tablet degradation at 20°C and 80% RH.]

Limitations of Established Methods

The established practice in desiccant selection has been to determine the total moisture load for the required shelf-life of the product before being exposed for use by the consumer. This is a combination of the initial water vapour, and the vapour ingress through the boundary of the packaging. This mass of moisture is then fed into the desiccant's capacity to determine the total mass of desiccant required. This ensures the desiccant

remains active during the shelf-life.

However, this approach does not account for kinetic factors at play within the packaging. For example, as the desiccant reaches saturation, the rate at which it will pick up moisture will decrease. Therefore, even though the desiccant is still 'active', the humidity inside the package will increase. This increase in humidity places the product at greater risk of hydrolysis. A more advanced method will account for changes to both the rate of ingress of moisture, which will decrease as the internal humidity increases, and the rate of moisture adsorption of the desiccant. The balance between these factors gives the key picture.

New Predictive Modelling Approach

The analysis carried out to develop this new predictive modelling system for desiccants is based on sophisticated mathematical models. "Having previously worked on modelling gas-liquid-solid fluid systems at the University of Oxford Chemical Engineering group, it was clear there was substantial scope to develop new mathematical models specifically for the desiccant industry," commented Dr Mark Valentine.

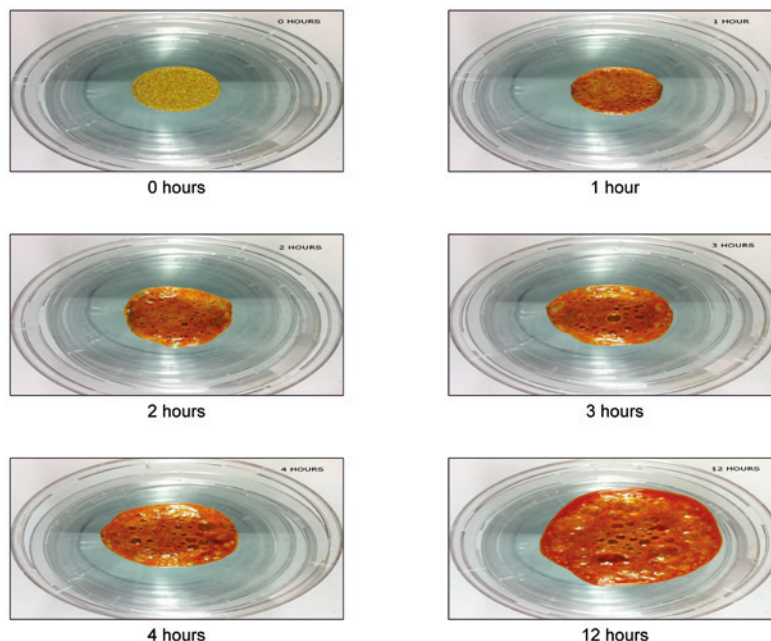


Figure (1) - Degradation of an effervescent tablet at 20°C and 80% RH. Failure occurs despite the absence of any liquid water.

Extensive research and experimental tests were undertaken to develop a comprehensive understanding of desiccant adsorption behaviour in a variety of storage environments and packaging. The storage environment is defined by the temperature and relative humidity (RH) of the air, which will give the absolute humidity. The packaging includes aluminium foils of different thickness, and vials that might be employed for pharmaceutical applications. The model can be applied to any desiccant-based packaging system used for applications such as the protection of pharmaceuticals, vitamins, diagnostics kits, medical devices and healthcare products, as well as large-scale 'work in progress' containers.

Desiccant-CFD Modelling

The data sets from experimentation are used to develop a sophisticated desiccant 'behaviour' model. This is in the form of a set of differential equations that are flexible to accept all relevant variables, size and type of package, storage conditions, and type of desiccant. These are solved using normal

numerical techniques. Once the desiccant behaviour is known, this can be coupled with existing fluid mechanics knowledge, creating a desiccant-CFD model for the water molecules inside the package.

The relevant fluid mechanisms to consider are 'advection' and 'diffusion' of water molecules. Advection refers to motion resulting from a flow of air, as driven by pressure differences. However, for most packaging and storage environments the product is sealed and stationary in a uniform temperature field. As such, convection can typically be ignored.

Diffusion is the motion of molecules from high concentration to low concentration. This is an important mechanism when considering the interplay between desiccants and their environments. As the desiccant adsorbs moisture it creates a low water vapour concentration around it. This draws in molecules throughout the package by diffusion.

The convection and diffusion of water molecules is well understood; the original work in the model lies in the characterisation of the desiccant adsorption properties. Desiccants have a very large surface area to mass ratio. This surface area possesses many adsorption sites to which water molecules can stick. They adhere to the surface, hence adsorption. Further adsorption also occurs in layers away from the desiccant by $H_2O - H_2O$ bonding.

As the desiccant adsorbs moisture, the number of adsorption sites will decrease, hence the probability of a water molecule being adsorbed at any given time will decrease at a given relative humidity. This is an important consideration as it determines the rate at which the desiccant picks up moisture. As the desiccant approaches saturation the rate of moisture adsorption will become much slower. Eventually a tipping point will be reached where the partially-saturated desiccant will not be able to keep up with the moisture entering the package. At this stage the humidity will start to rise, even though the desiccant is still 'active'. [See Figure (2) - Average humidity inside a foil pouch for the active lifetime of the desiccant.]

Mapping the Humidity

The interior of the package in the desiccant-CFD model is represented as a Cartesian or cylindrical grid depending

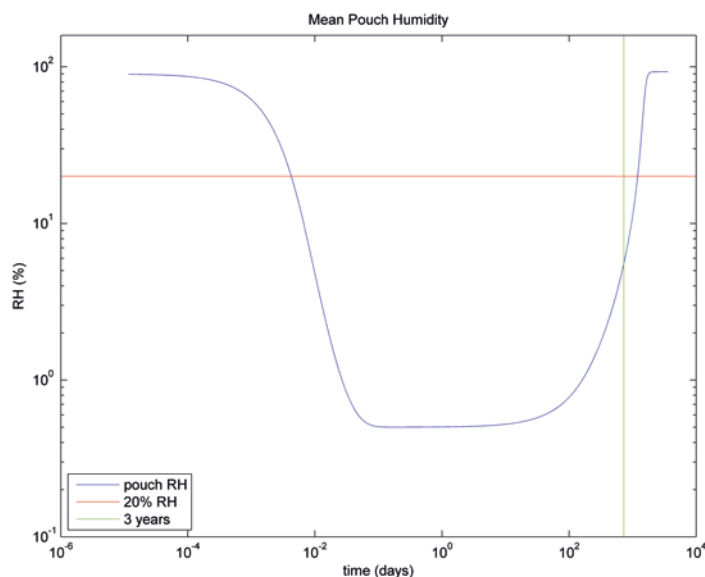


Figure (2) - Modelling of average humidity inside a foil pouch for the active lifetime of the desiccant (logarithmic scales used for better illustration). Design lines of three-year shelf-life and below 20% RH are supplied by the customer. There is a brief initial moisture pick-up region, followed by a long, slow increase in RH as the desiccant adsorption rate falls below the moisture ingress rate.

on its geometry. The ingress-diffusion-adsorption equations are solved over the grid points, giving a 2D or 3D view of the humidity inside the package. These are progressed over each time step for the required shelf-life of the product. Thus the humidity for any given point inside the package can be determined for any time throughout its shelf-life. This knowledge is especially powerful to minimise the work and costs associated with getting a product to market. [See Figure (3) - Humidity map inside a foil pouch with desiccant.]

Accelerated Stability Trials

In order to establish that the desiccant does its job in protecting the product, stability trials are undertaken. To help speed up new product launches, accelerated tests can be carried out. This is where the packaging containing product and desiccant is subject to a very high humidity, using the principle that if the test is done at five times the actual storage humidity then one month under test conditions equates to five months in storage. This is an effective and

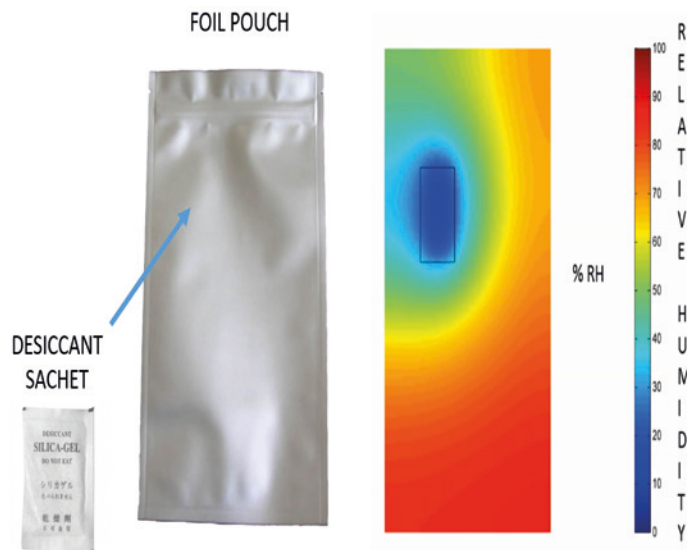


Figure (3) - Shows the humidity map inside a foil pouch with desiccant during the initial moisture pickup stage. Cooler colours indicate lower relative humidity, hotter colours show higher humidity. The presence of the desiccant is clearly seen.

established test method of more rapidly determining product efficacy.

However, it is not without its limitations. The timescales make it important to minimise the number of trials undertaken. Even at an accelerated rate, a two-year shelf-life evaluation can still take six months to complete. Also, there is the risk of over-desiccation, as during an accelerated trial the ingress through the packaging will place a greater burden on the desiccant adsorption rate, resulting in a higher internal humidity than would be present under non-accelerated conditions.

Desiccant Selection Quality

The quality of the desiccant selection in a packaging specification is vital. An inaccurate initial desiccant quantity can also lead to stability failures and insufficient shelf-life performance, adding months to a product's development time and delays in getting new products in the market. Additionally, any extra unnecessary desiccant used builds in additional cost for the entire line.

Performance in Practice

A snapshot of the result of modelling the humidity inside a typical effervescent tablet vial can be obtained. [See Figure (4) - humidity gradient from top to bottom of tablet tube.] Here the desiccant is in the lid at the top of the vial. As such, the desiccant will remove moisture from the top first as illustrated in the graphic. In practice, vials can be repeatedly opened and closed over a significant amount of time as the consumer removes each tablet one at a time.

This raises the question: What effect will repeated opening and closing have on the actual product shelf-life? A product may be designed to perform satisfactorily whilst closed in terms of shelf-life, but may fail if repeatedly opened in a humid bathroom; when opened, the desiccant in the lid will be exposed and the vial headspace filled with humid air. The flexibility of the 3D model allows the effects of regular opening and closing of the package to be considered. This will ensure the quality of the product remains until the last tablet is removed.

Ultra-reliable Optimised Packaging

By including all critical variables, the desiccant-CFD model can help companies supplying pharmaceuticals and medical devices to optimise existing desiccant

packaging specifications, or to develop ultra-reliable packaging solutions with predictable humidity ranges; the mathematical model significantly improves accuracy in desiccant specification, to a high confidence level in the shelf-life and storage performance of a packaging system, whatever the environment and climatic conditions.

By obtaining a full understanding of a product's thermo-fluidic environment, companies can achieve both the optimal quantity and ideal placement of desiccant within packaging. This helps to maintain the ideal humidity, and ensures stated shelf-life and storage requirements.

Dr Valentine explains: *"The major advantage of the 3D modelling system is that one is able to get an in-depth mathematical analysis of moisture loading and desiccant requirements, tailored for specific atmospheric conditions from tropical to temperate. This ensures that the correct packaging and amount of desiccant materials are used to safeguard product stability."*

Additional Cost Benefits

Using the 3D modelling techniques developed by Baltimore Innovations offers significant benefits to companies, especially smaller companies (SMEs) who often don't have in-house packaging expertise. These benefits include: lowering desiccant costs by eliminating excess usage; improving shelf-life and

performance by better desiccant selection and placement; and reducing packaging bulk volume and weight for lower packing and transport costs.

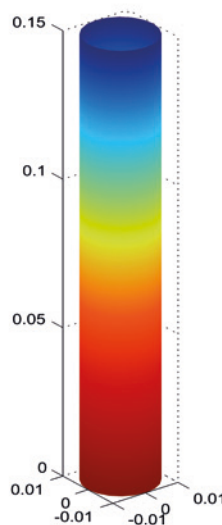


Figure (4) - Graphic showing a snapshot of the humidity inside a desiccated effervescent tablet tube. The desiccant is in the lid at the top as shown by the humidity gradient from top to bottom.



Dr Mark Valentine joined Baltimore Innovations Ltd. after completing his PhD at Oxford University, where he worked in the Chemical Engineering Group in the field of 'Fluid Mechanics and

Multiphase Flow'.

In his current role as R&D Director, he works closely with the in-house business development team, strategic manufacturers and key supply partners to develop new moisture control related packaging products, as well as providing desiccant consultancy advice and technical support to customers within the pharmaceutical, medical device and food packaging industries.

Email: mark.valentine@baltimoreinnovations.co.uk