

Designing Pharmaceutical Packaging Using Product-Packaging Stability Modeling

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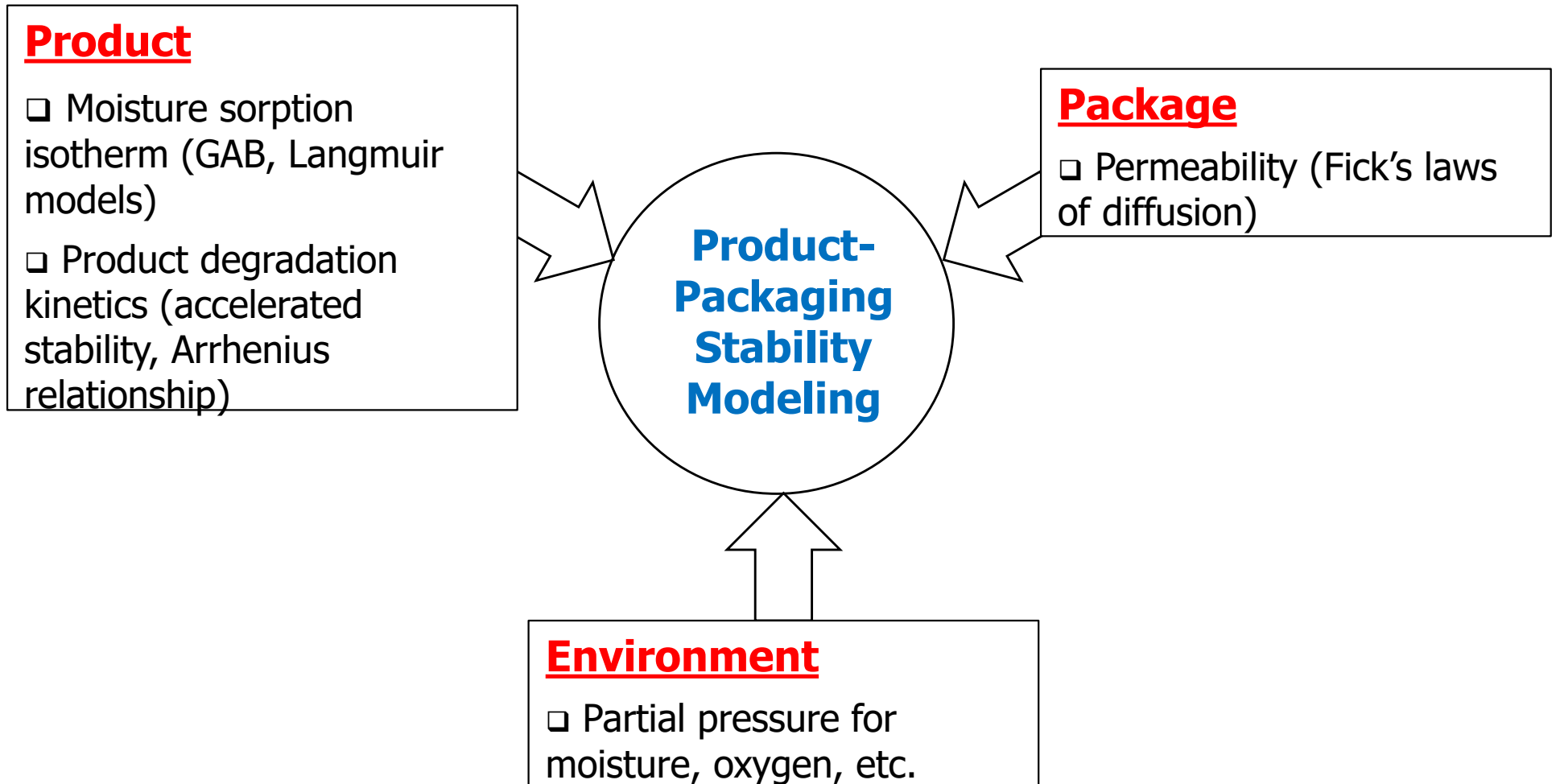
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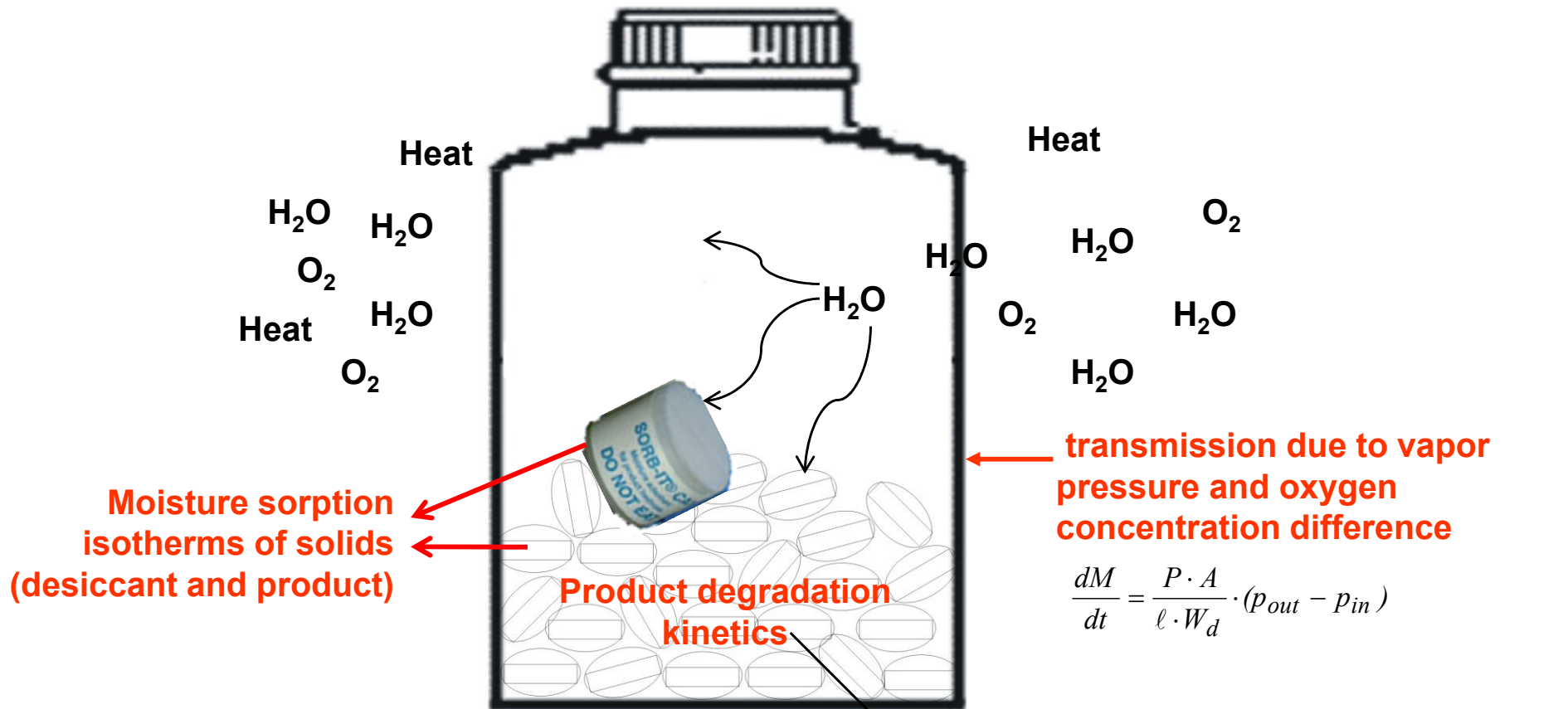
Introduction

1. Product-packaging stability modeling is a good example of QbD paradigm.
2. Concept of product-packaging stability modeling has been developed in early 1990's in literature.
3. This modeling has been applied to pharmaceutical products for more than 10 yrs.
4. Product stability studies with packages at different storage conditions are a time consuming, costly and difficult process. Studies can't cover all various situations.
5. Product-packaging stability modeling becomes more and more useful tool and is being well accepted by pharmaceutical researchers.

Theories



Theories (graphical representation)



$$\frac{dM}{dt} = \frac{P \cdot A}{\ell \cdot W_d} \cdot (p_{out} - p_{in})$$

$$m_T = W_{dA} \left\{ \frac{W_{mA} C_{gA} K_A (p/p_s)}{[1 - K_A (p/p_s)] \times [1 - K_A (p/p_s) + C_{gA} K_A (p/p_s)]} \right\} + W_{dB} \left\{ \frac{W_{mB} C_{LB} (p/p_s)}{[1 + C_{LB} (p/p_s)]} \right\} + \frac{p_s \cdot V \cdot (p/p_s) \times 18}{R \cdot T}$$

$$\ln(k) = A \cdot \text{moisture} + B \cdot \text{oxygen} + C \cdot \text{temperature} + D$$

Critical modeling inputs/outputs

Modeling utilizes:

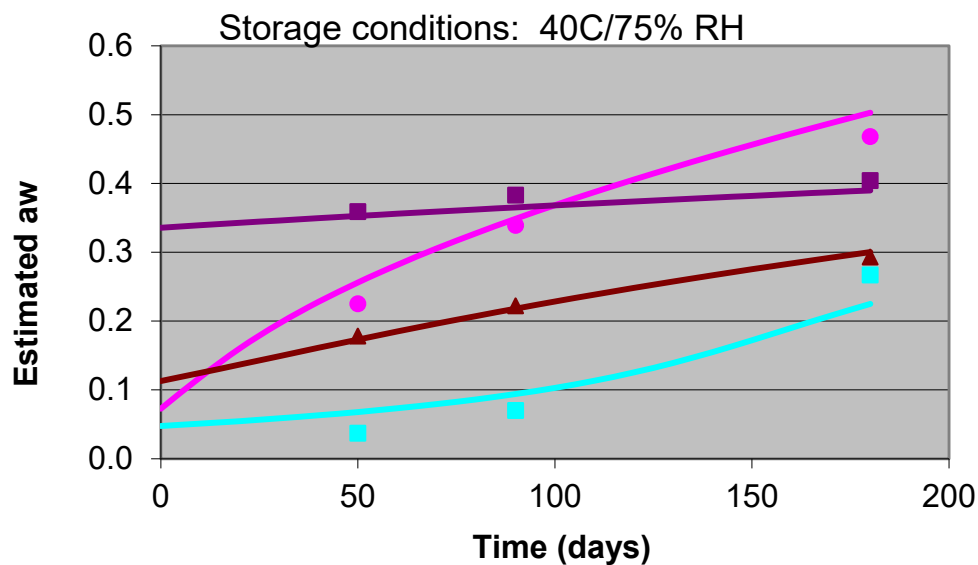
- **Experimentally Determined Inputs (material properties)**

- Packaging – moisture (and oxygen) permeability
- Product – initial moisture content and moisture sorption isotherm for solids, product degradation rate constants
- Environment – any desired conditions

To provide:

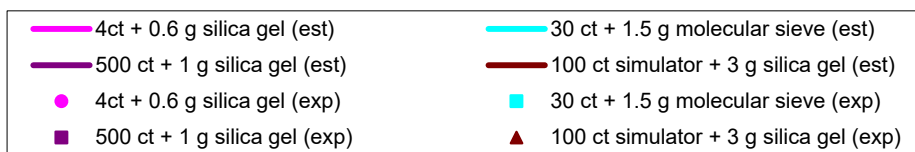
- **Theoretically Estimated Outputs:** A_w (water activity) and moisture contents of solids, impurity, etc
- **The Product-Packaging model provides scientific estimates based upon material properties and first principles.**

Modeling results verification



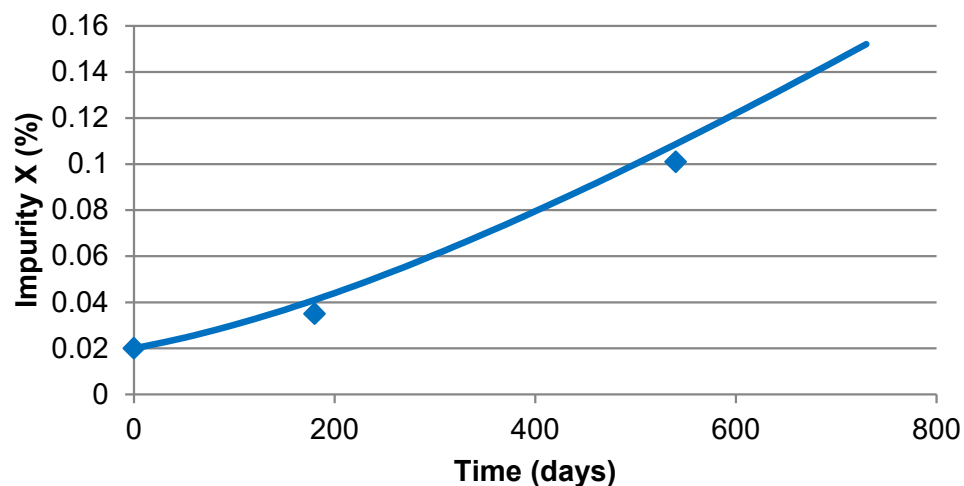
← water activity (a_w) estimation

Lines (-) – model estimate
Dots (♦) – experimental



impurity estimation →

tablet in 2 mil Aclar blister at 30C/65% RH



Applications

1. Packaging design for new products
 - a. Packaging material selection
 - b. Determine the amount of desiccant and type of desiccants
 - c. Justification of initial aw, oxygen concentration , etc.
2. Support for manufacturing deviations
3. Post approval changes
 - a. Packaging material changes
 - b. Bottle count change
 - c. Sealing method change (e.g., heat seal vs. cable tie)

Case Study I – packaging design for new products

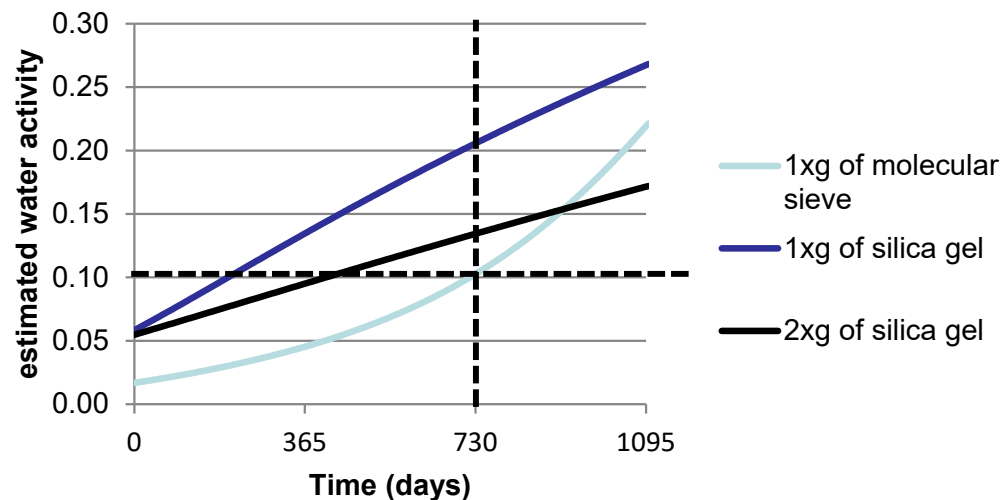
Situations: moisture and oxygen sensitive tablets, 2 years shelf life at 30°C/65% RH

- ❑ Product degradation kinetic study
 - Combinations of different temperatures, RHs and oxygen concentrations
 - Design criteria: maintain A_w below 0.1 and oxygen concentration below 5%
- ❑ Packaging design
 - Container closure system: permeation for moisture and oxygen
 - Desiccant: type and amount
 - Process control for moisture and oxygen

Case Study I – packaging design for new products (cont'd)

- Packaging Design: 1xg of molecular sieve desiccant + oxygen barrier bottle + N₂ purged packaging headspace
- Can maintain the initial O₂ concentration for the entire shelf life
- Silica gel and molecular sieve have a different moisture sorption capacity at low RH regions.

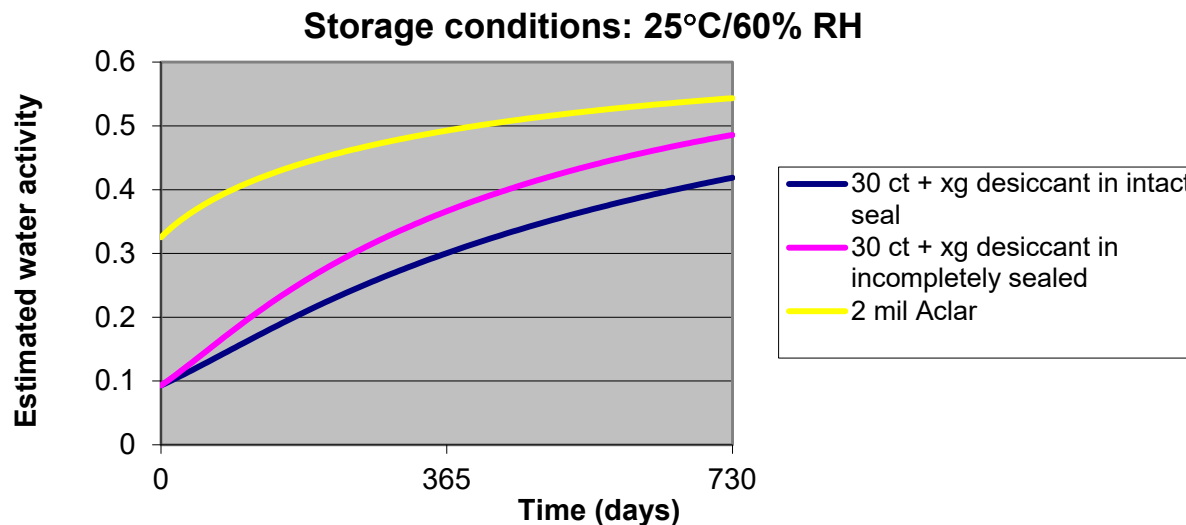
30 count bottles at 30°C/65% RH



Molecular sieve is a better choice for this particular situation.

Case Study II – support for manufacturing deviations

- ❑ Prepare for unexpected situations
 - a. Product degradation kinetic information
 - b. Packaging permeability with a variety of simulated defects
- ❑ An example for incompletely sealed bottles



Stability data from 2 mil Aclar can support the stability of products in incompletely sealed bottles.

Conclusions

1. Product-packaging stability modeling is a good example of QbD paradigm.
2. Minimize trial and error approach – package screening study should not be a tool to select packages but to confirm QbD approach.
3. This modeling can minimize unnecessary work but maximize necessary work. Overall, reduce cycle time for package design and ensure cost effective packages.
4. Powerful QbD tool to explain product stability in a variety of situations.
5. High confidence in new packaging design and acceptable product stability.