Predictive Modeling of Moisture Ingress in a pMDI

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Introduction & Motivations

- Pressurized metered dose inhalers (pMDIs) are critical for respiratory treatment for COPD and asthma.
- Stability testing for pMDIs requires up to 2 years of tests, incurring high cost and delaying patient access.
- Regulatory transitions toward low-GWP propellants require reformulation and re-testing.
- Moisture ingress impacts shelf life by degrading pMDI formulation and affecting dose delivery.
- This project develops a predictive diffusion-based model to simulate moisture ingress and estimate shelf life under various storage conditions.

$$M(t) = M_\infty - (M_\infty - M_0) \times \exp\left(\frac{-P_w a_0}{m_f M_\infty} t\right)$$

Background

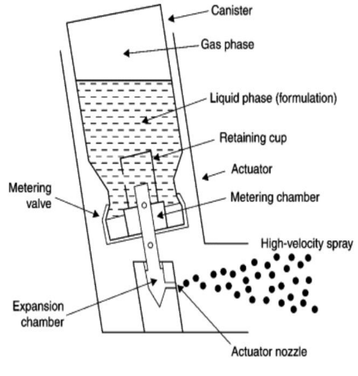

Fig 1. Diagram of pMDI Components

- pMDI stability is sensitive to moisture ingress through packaging components like valves and gaskets, impacting drug solubility and shelf life.
- A Fickian diffusion-based model was developed, incorporating formulation mass, RH, temperature, and experimentally derived permeability.
- This framework enables shelf-life prediction without the need for lengthy stability studies.

Methods

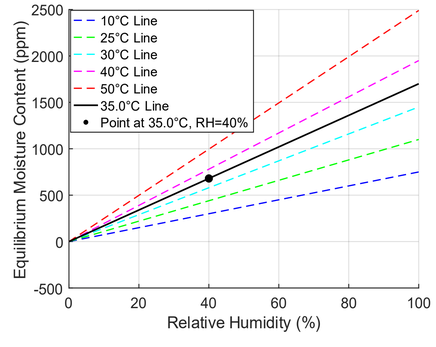

Fig 2. Moisture Equilibrium at Interpolated/Extrapolated Temperature

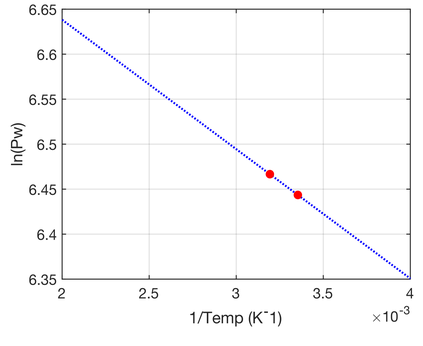

Fig 3. Linearized Arrhenius Equation at 25 and 40ºC

$$\ln(Pw) = -\frac{E_a}{R}\left(\frac{1}{T}\right) + \ln(A)$$

Cost-Benefit Analysis

Savings & Cost	Estimated Value
Net Benefit	$2.1 - $5.30 million
Implementation Costs	$970K
ROI	116 - 446%

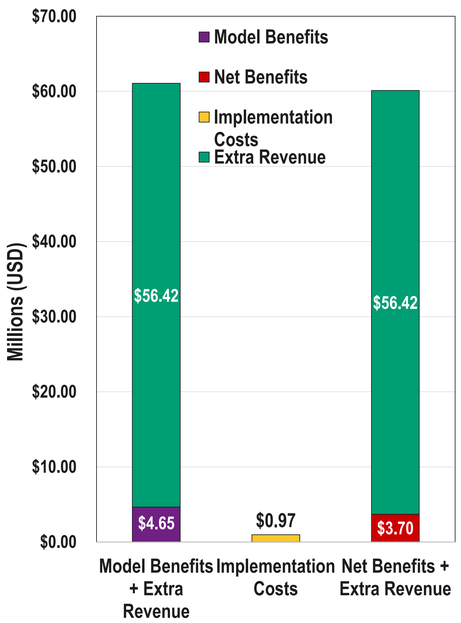

Fig 4. Savings and Cost Estimates from Model Implementation

Code Flowchart

SECTION 1.0: Get User Inputs
- Propellant Type (High GWP, Low GWP, or Custom)
- Uses Porous Particles?
- Temperature [1–50°C]
- Relative Humidity (RH) [0–100%]
- Initial Moisture (M0) [ppm]
- Storage Time [months]

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Validate Inputs

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Section 1.1: Initial Setup & Data Loading

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All inputs valid → Proceed

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Section 2: Equilibrium Moisture Calculation

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Section 3: Permeability Calculation

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Section 4: Porous Particle Adjustment

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Section 5: Moisture Ingress & Shelf-Life Estimation

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Section 6: Output Results
- Equilibrium Moisture (M_inf_Final) [ppm]
- Permeability Coefficient (Pw_atUserTemp) [ug/month]
- Moisture Content at Storage Time (M(t)) [ppm]
- Shelf-Life (t_shelflife) [months]

Results

Table 1. Propellants with porous particles, M0 = 30 ppm

Conditions		Equilibrium Moisture Content (ppm)	Moisture Content @ 12 months (ppm)	Shelf-life Approximation (Months)		Equilibrium Moisture Content (ppm)	Moisture Content @ 12 months (ppm)	Shelf-life Approximation (Months)
25°C/60%RH	High GWP Propellant (HFA-134a)	1020	433	8.1	Low GWP Propellant	474	453	2.9
30°C/65%RH		1327	483	6.9		534	500	2.7
30°C/75%RH		1521	542	5.8		607	568	2.1
40°C/75%RH		1462	569	5.5		682	600	2.3

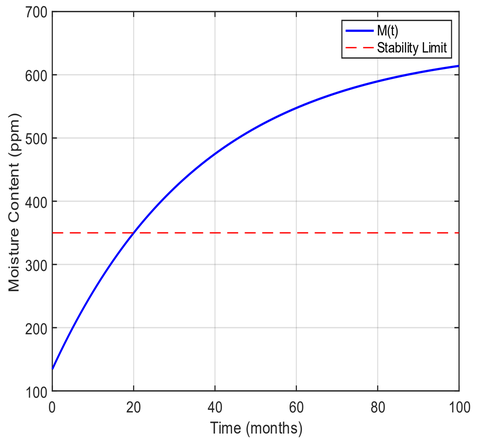

Fig 5. MATLAB Simulation of Moisture Content (ppm) over Time (months) and Associated Stability Limit

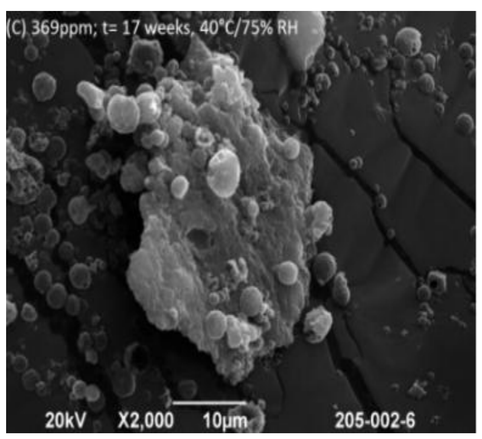

Fig 6. Porous Particle Phospholipids Excipient in Formulation at High Moisture Content

Conclusions

- Initial model development shows promise of developing a robust predictive moisture ingress model to determine shelf life.
- The predictive MATLAB model decreases waste in resources in pharmaceutical development and improves time-to-market for earlier patient access.
- Further development is needed to tune model predictions to match historical results and apply parameters for primary and secondary packaging components.
- New low-GWP propellant is not characterized well enough to gain accurate results.

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References: