

Case Study 1: Pharmaceutical Development of EXUBERA[®]

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EXUBERA[®]



- Insulin human (rDNA origin) Inhalation Powder
- Re-usable Exubera[®] Inhaler
- 1 mg, 3 mg unit dose blisters
- Indications: Type 1 and Type 2 Diabetes Mellitus

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EXUBERA®



Clear chamber: designed to hold aerosolized insulin before inhalation

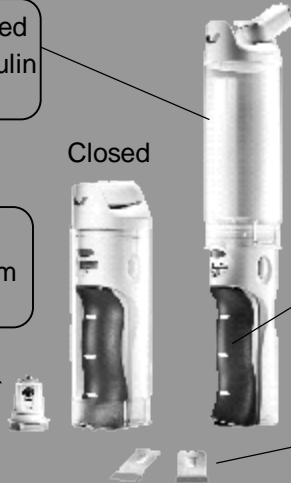
Extended

Base: device provides energy required for dispersion of EXUBERA powder via air pump mechanism in the device base (no batteries required)

Insulin release unit: disperses powder from blister into chamber

Closed

Blisters: available in 1-mg (green) and 3-mg (blue) doses



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Pharmaceutical Challenges in EXUBERA® Development



... relative to conventional inhalation products

... specific to insulin

Uniqueness presented challenges as well as opportunities!

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Challenges Relative to Conventional Inhalation Products



- Systemic Delivery
- Importance of Particle Size
- Standard PK/PD studies are possible
 - BE, Variability, Dose Response, IV / IVc, Interaction Studies, Special Populations, Other Biopharm
- Defining the Relevant Performance Attributes
- Labeling / Label Claim
 - Contained Dose vs Emitted Dose vs Respirable Dose

Fill Mass (mg powder)	Nominal Dose (mg insulin)	Emitted Dose (mg insulin)	Fine Particle Dose (mg insulin)
1.7	1.0	0.53	0.4
5.1	3.0	2.03	1.0

Source: EXUBERA® US Package Insert

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Challenges Specific to Insulin



- A new, non-invasive route of insulin administration
- Insulin dosing based on mg (not units)
 - Robust Education and Customer Care programs
- Performance benchmark against SC injection
 - Defining the unit doses
 - Performance comparisons *in vivo* and *in vitro*
- Biologic
- Stability
 - Opportunity for improvements over current insulin products
 - Refrigeration not required !

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Insulin Stabilization Challenge

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Insulin Formulation

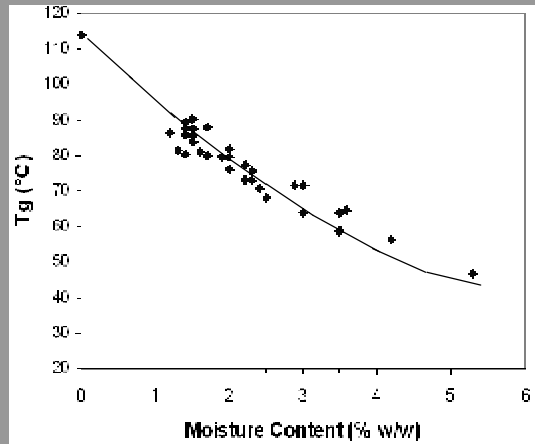


- Dry powder
- High drug load: 60% insulin in a buffered sugar-based matrix.
- Stabilization approach: Maintain insulin in glassy state
 - Excipients selected to provide a glass transition temperature well above pharmaceutically relevant storage temperatures.
 - Exhibits a single T_g (indicative of a single amorphous phase).
 - The high T_g is maintained over the shelf life of the product and across a range of moisture content.
- Moisture content and its affect on glass transition temperature (T_g) was a critical parameter impacting chemical stability.
- Moisture Control challenges throughout the manufacturing process and for packaging design

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Glass Transition Temperature

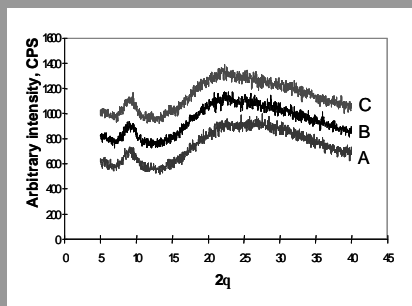


- T_g decreases with increasing water content
- Spray dried powder water content is ~2 % (w/w), consistent with a T_g ≈ 80°C.

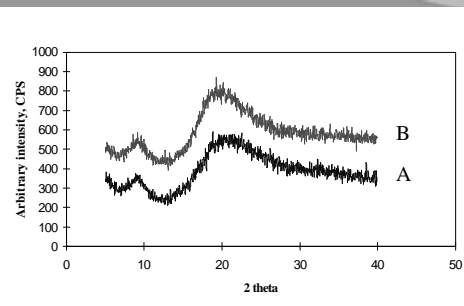
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Physical Form Stability



XRPD patterns after up to 88% RH for (A) 22.5, (B) 26, and (C) 28 hours



XRPD patterns before (A) and after (B) exposure to 150°C for 15 minutes

- No evidence of crystallization in insulin powder for inhalation upon moisture or thermal challenge

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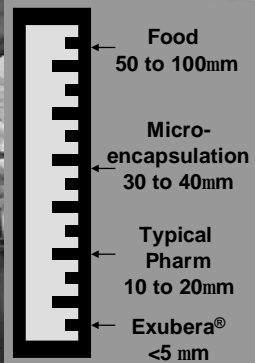
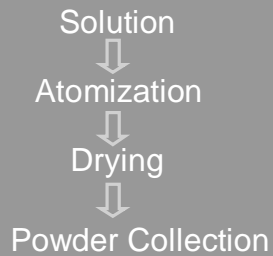
Manufacturing Challenges

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Spray Drying



Spray Drying enables production of homogenous particles of controlled size with:

- Low moisture
- High drug purity
- Small particle size (<5 mm)
- Non-critical excipient physical form

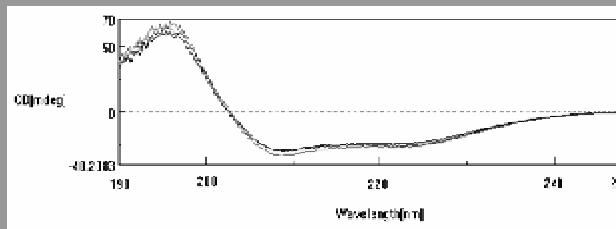
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Maintenance of Insulin Molecular Structure



- The spray-drying process does not affect the secondary structure of insulin, assuring pharmacological activity
- Techniques included Circular Dichroism, FTIR
- Quaternary/Oligomeric Structure: Insulin Monomer (HP-SEC, SDS-PAGE, DLS)

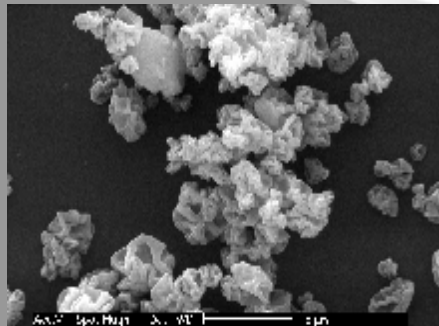
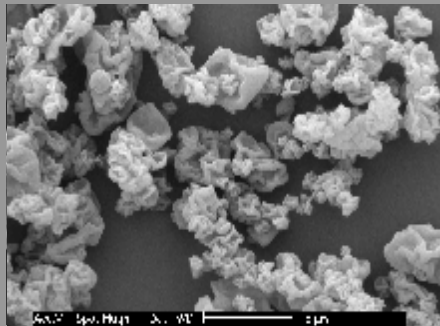


CD spectra for insulin in the formulation matrix before (blue), and after (green) spray drying, compared with ingoing insulin API (red).

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Particle Morphology (SEM)



- Uniform, rugose morphology
- No effect on particle morphology before (left) and after (right) exposure to high humidity (75% RH, 25°C for 36 hours)

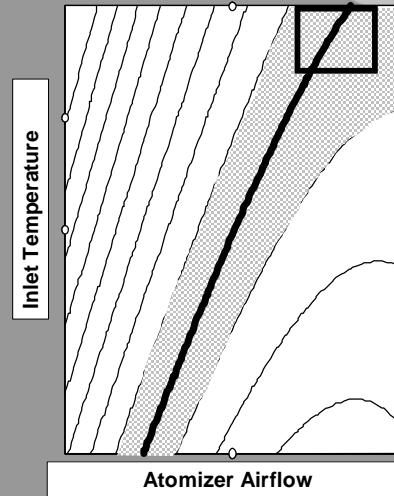
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Process Scale-Up / Optimization



- DOE on process parameters to map knowledge space
- Design space / control space based on aerosol performance
- Each contour line represents a constant predicted value for FPD



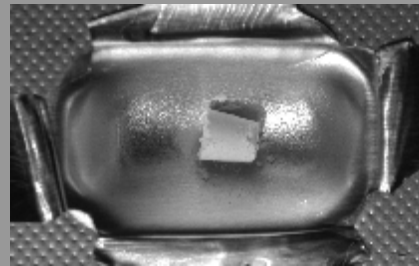
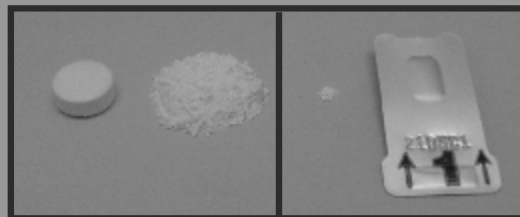
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Powder Filling



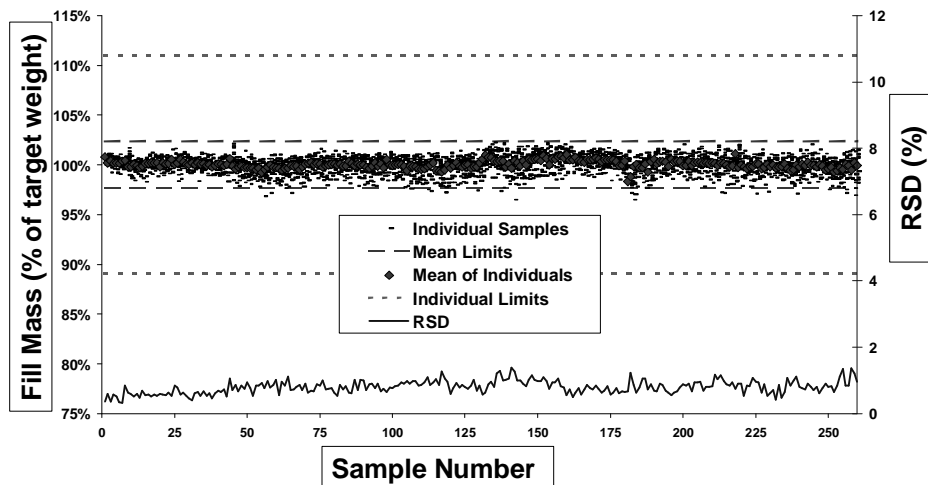
- Beyond capability of existing technology
- Design Challenges
 - Low density powders
 - Micro fill weights (1.7 mg and 5.1 mg)
 - High speed (>1500 fills/min)
 - Accuracy (~2% RSD)
 - Consistency



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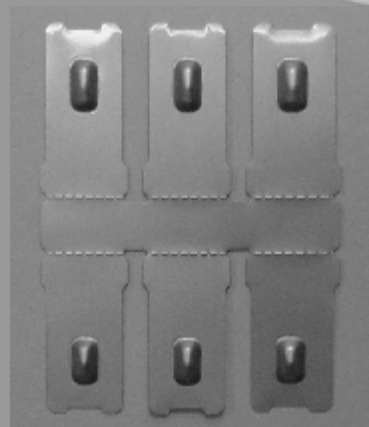
Fill Weight Control



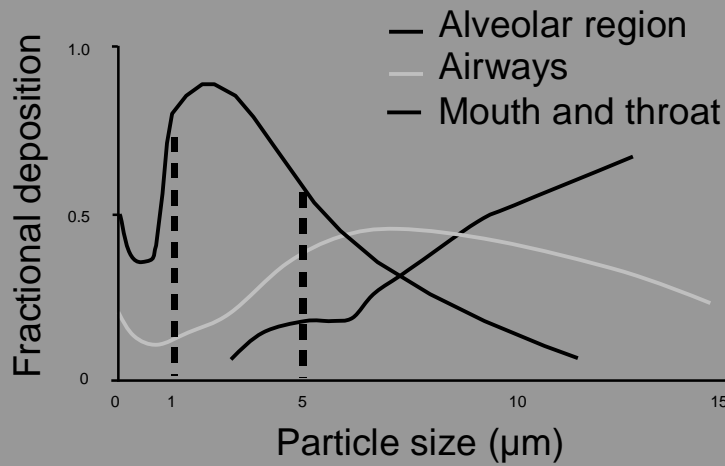
Packaging Design



- Compact Package
 - Patient handling
 - Device interface
- Foil Forming, Filling, Sealing
 - Blister cavity design
 - Tooling and manufacturing scale up
 - Operation in ultra-low humidity environment
- Drug Product Protection
 - High moisture barrier



Particle size: The optimal window for deposition

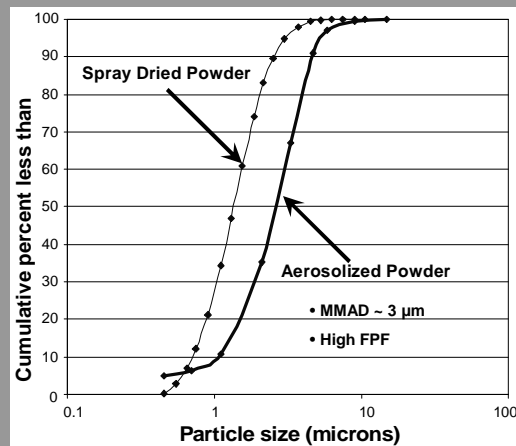


Byron PR. *J Pharm Sci.* 1986;75:433-438.

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Powder / Aerosol Particle Size Distribution



§ High dispersibility

§ Aerosol particle size broadly in line with spray dried powder.

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Inhaler Challenges

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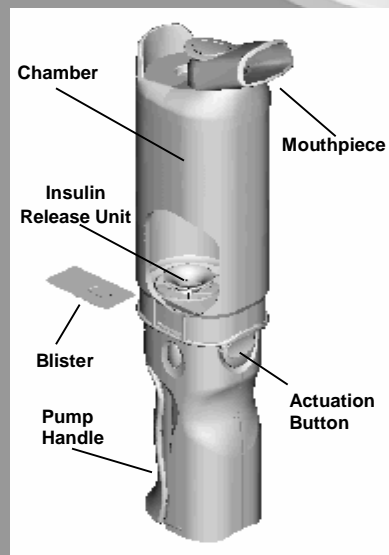


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Inhaler Design



- Reproducible powder extraction, deagglomeration and dispersion.
- Patient generated compressed air provides energy source
- Capable of aerosolizing relatively cohesive powders
- Suitable for delivering small powder masses (1-10 mg)
- Separate breathing maneuver from aerosol generation
- Chamber allows for patient feedback and dose delivery
- Designed for long-term repeated use



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Drug + Inhaler System Challenges



- Elaborate performance characterization programs
 - Risk based approach: comprehensive FMEA's
 - Inhaler Design Verification Testing
 - Testing to failure
 - Clinical experience
 - Use-Life simulations
 - FDA Draft MDI/DPI Guidance (...and beyond)
- Output contributed to:
 - Comprehensive product understanding
 - Assessment of impact on safety/efficacy
 - Instructions in labeling/medication guide; Customer Care

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Performance Characterization

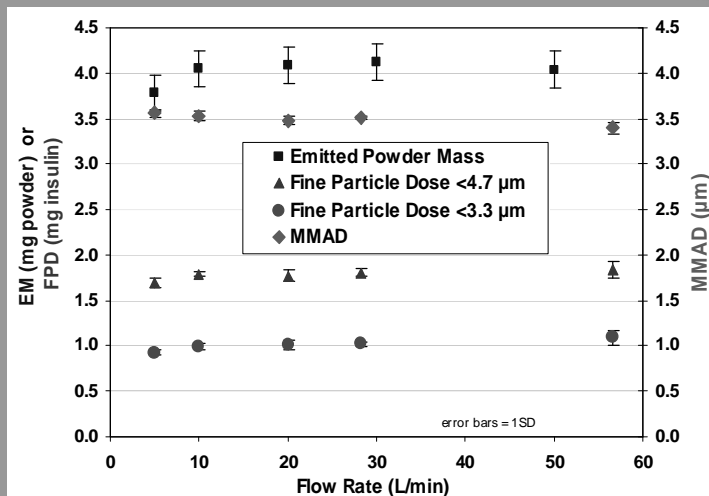


- Robust performance (aerosol dose delivery and mechanical integrity) demonstrated over a range of patient usage scenarios
- Environmental (temperature, humidity, altitude)
- Usage reproducibility
 - Independence from inhalation flow rate (10-60 lpm) and volume (400-1400 ml)
 - No priming effect
 - Independence of usage angle
 - Rugged performance with long term use

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Inhaler Flow Rate: Little Impact on Aerosol Performance



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Characterization Studies (FDA MDI / DPI Draft Guidance)



Section IVB Recommendation	Studies Conducted/Relevant Data
Determination of Appropriate Storage Condition	Stability Studies DVT studies
Stability of Primary (Unprotected) Package	Stability Studies
Effect of Varying Flow Rates	Square Wave flow rate study Pediatric inhalation profile study
Effect of Storage on Particle Size Distribution	Stability Studies
Dose Build-Up and Flow Resistance	Use-life studies Cleaning frequency Mass Distribution
Effect of Orientation	Dosing orientation Drop and vibration testing
<i>In-Vitro</i> Dose Proportionality	Biopharmaceutics studies
Effect of Patient Use	Planned Returns Product Investigation Process
Effect of Moisture	Excursion studies Use life studies
Photostability	Stability study
Profiling of Doses Near Device Exhaustion	Not applicable since this product is not a DPI reservoir product
Fill Weight	
Priming	Priming
Device Ruggedness	Planned Returns Design Verification Testing Accelerated Patient Use Simulation Product Investigation Process
Cleaning Instructions	Cleaning Frequency Cleaning Effectiveness Cleaning Detergents Microbial Inoculation Study

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Drug + Inhaler System Challenges

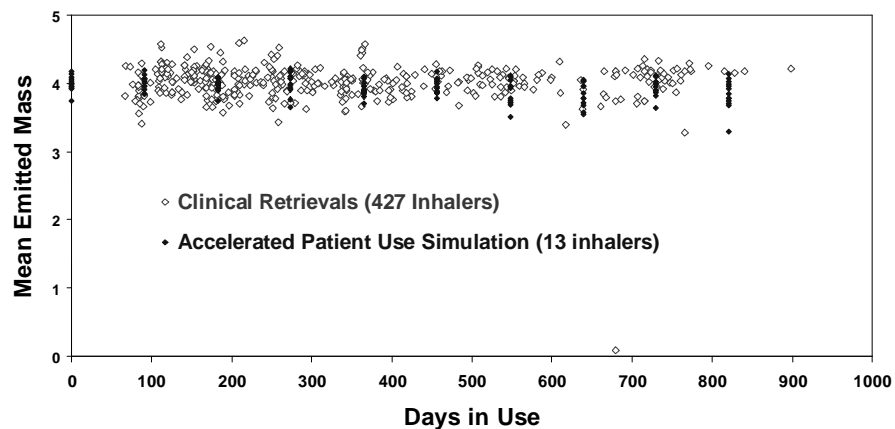


- **Extended-use inhaler: high bar for durability**
 - Unique patient-use simulations
 - Extensive patient-use evaluation
- **Findings from clinical experience enabled:**
 - Early input for robustness improvements
 - Optimization and “validation” in vitro tests

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Inhaler Robustness to Long-Term Use



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Additional CMC Challenges



- **Release Approach**
 - Blisters; Inhalers
 - What are the reference standards?
 - (FDA helped to define)
- **Controls and Acceptance Criteria**
 - Deep Product and Process understanding was critical
 - QbD, Design Space concepts (many variables, interactions)
 - Clinical experience
 - Test methods
 - (FDA helped to define)

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EXUBERA® (insulin human [rDNA origin]) Inhalation Powder



- Insulin naturally absorbed by the lungs without enhancers
- Dry powder insulin stable at room temperature
- Ideal particle size for systemic absorption via the lung
- Packaging system protects formulation from moisture
- Robust delivery device enables dosing as reliable as injections

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Acknowledgements



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*Current affiliation Epic
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