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GMP Manufacturing of Oral Aspirin Spray Dry Dispersion and Encapsulation

Contract # MBI-2212A (v4)

05 Jan 2023

Agenda

- ❑ Safety
- ❑ Background information
- ❑ Analytical development
- ❑ Lab scale spray drying prototype
- ❑ SDD GMP manufacture and encapsulation

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1. Safety

- Compound OHC assessment to be provided.

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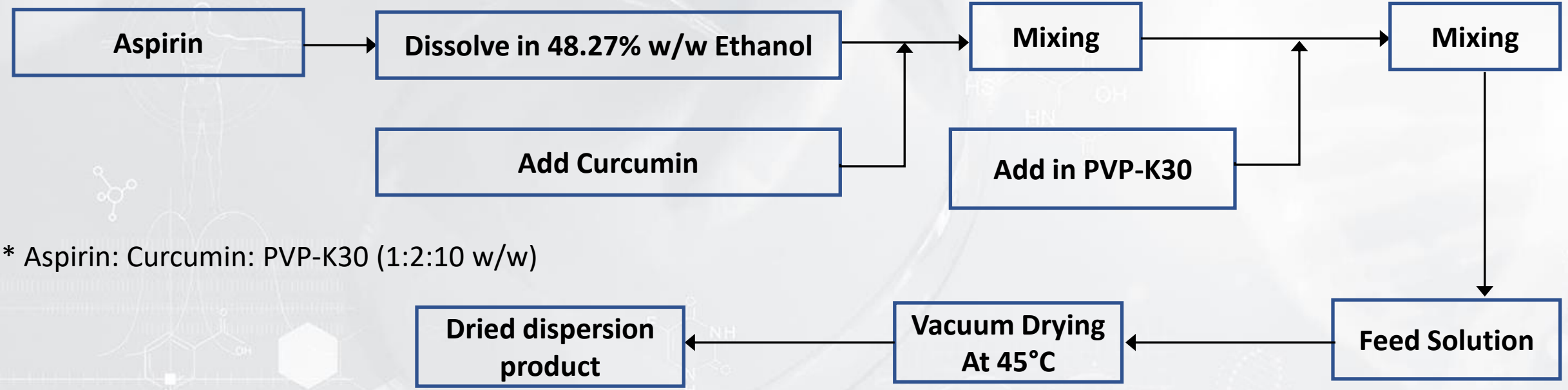
2. Background information

❑ Current technology in producing Aspirin-Curcumin-PVP dispersion



* Aspirin: Curcumin: PVP-K30 (1:2:10 w/w)

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3. Analytical

1. Assay and Impurities — Method Evaluation
• Evaluate USP method for Aspirin Tablets
• Verify chromatography—one run using existing API/reference standards and column

2. Assay and Impurities - Method Validation
• Generate Validation Protocol
• Evaluate specificity, linearity, accuracy and precision, LOD and LOQ; one analyst, one run
• Sample and Reference Standard Stability – up to 3 days
• Issue Analytical Test Method and Statement of Success
• (Optional) Method Validation Report

3. Water Content by Karl Fischer — Method Adaptation
• Optimize Sample Prep
• Evaluate the method per USP <921> Method 1c and BioDuro SOP

4. Residual solvent by GC — Method Adaptation
• Determine sample preparation and optimum GC conditions for analysis of residual solvents in per USP <467> or BioDuro method

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3. Analytical

5. Equipment Cleaning Verification — Method Development

- Evaluate API recovery from API contaminated and cleaned metal and glass coupons to determine limit of cleaning and recovery
- Determine LOD and LOQ
- Single API/impurity, existing HPLC or TOC method

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4. Process Development of Oral Aspirin Spray Dry Dispersion (SDD)

1. Generation of Process Development Protocol

2. Prepare SDD Prototypes on B-290 Spray Dryer

- Prepare up to 10 – 20 g SDD prototype
- Evaluation and optimization of process parameters using Client's formulation
- 1 process parameters

3. In-Process Testing of Process Development SDD Sample

- Number of samples: 1
- List of tests: Residual Solvents (GC), PSD, Bulk Density and Tap Density

4. Analytical Testing of Process Development SDD Sample

- Number of samples: 1
- List of tests: Assay/impurity

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5. GMP Manufacture

1. Generation and Approval of Specifications

2. Release Testing of Raw Materials and API

3. Generation & Approval of 2 Master Batch Records -Manufacturing

4. Manufacture of GMP SDD

- Manufacture SDD on MS-35 for GMP Batch
- Process: Compounding, Spray Drying, Secondary Drying
- Batch size: up to 3 kg of SDD

5. In-Process Testing of SDD

- List of tests: Residual Solvents (GC), PSD, Tap and Bulk Density, Calculation of Flowability (Carr's Index)

6. Manufacture of Active Capsules

- Process: Encapsulation using Profill
- Number of Dosage Units: 3,000 capsules
- Bulk Package Final Product

7. In-process Testing of GMP Active Capsules

- Final Blend Sieve Particle Size
- Final Blend Uniformity

8. Analytical/Release Testing of SDD and Capsules

- List of tests: Assay/Impurities (HPLC), Water Content by Karl Fischer, MLT

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Questions/Comments

1. **Specific supplier for Aspirin and Curcumin ?**

2. **In the current formulation is Curcumin fully soluble in Ethanol ? Acetone as alternative ?**

3. **Solid content will be adjusted for spray drying (10-20% solids).**

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01 Mar 2023

Buchi B290 Prototype

Ingredient	%w/w Solids	%w/w Solution
Aspirin	7.7	1.0
Curcumin	15.4	2.0
PVP K30 (Kollidon 30)	77.0	10.0
Tetrahydrofuran (THF)		71.1
Ethanol		15.9
Total weight	100.0	100.00

Ingredient	Theoretical Quantity (g)
Aspirin	7.0
Curcumin	14.0
PVP K30 (Kollidon 30)	70.0
THF	497.7
Ethanol	111.3
Total weight (g)	700.0

In-process parameters

Parameter	Set point
Inlet temperature	69-73 °C
Outlet Temperature	53 °C
Feed Rate*	5.6-6.0 g/min
Aspirator	100%
Nozzle Assembly	0.7 mm nozzle
Drying air flow	1744 L/h
Feed Solution Batch Size	700.0 g

- Wet yield of ~82% (~72g powder collected).
- Secondary drying completed at 40C under vacuum for 24 hours.
- Powder has poor flowability with electrostatic charge (expected from spray dried powders).

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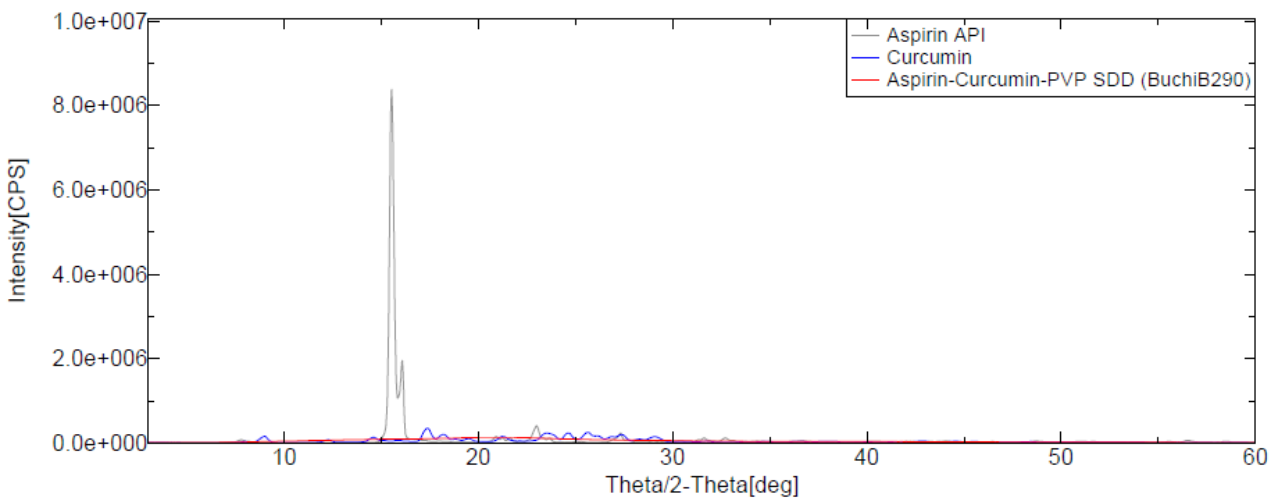
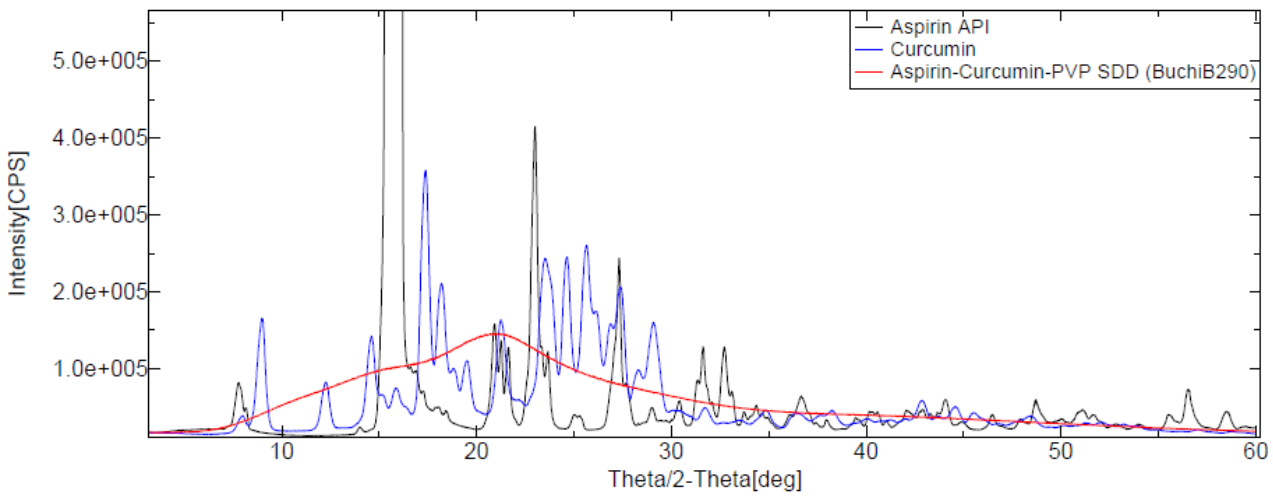
Buchi B290 Prototype- Testing (pXRD)





- pXRD diffractogram of the spray dried dispersion material shows no residual crystalline peaks indicative of amorphous nature of the components in the formulation

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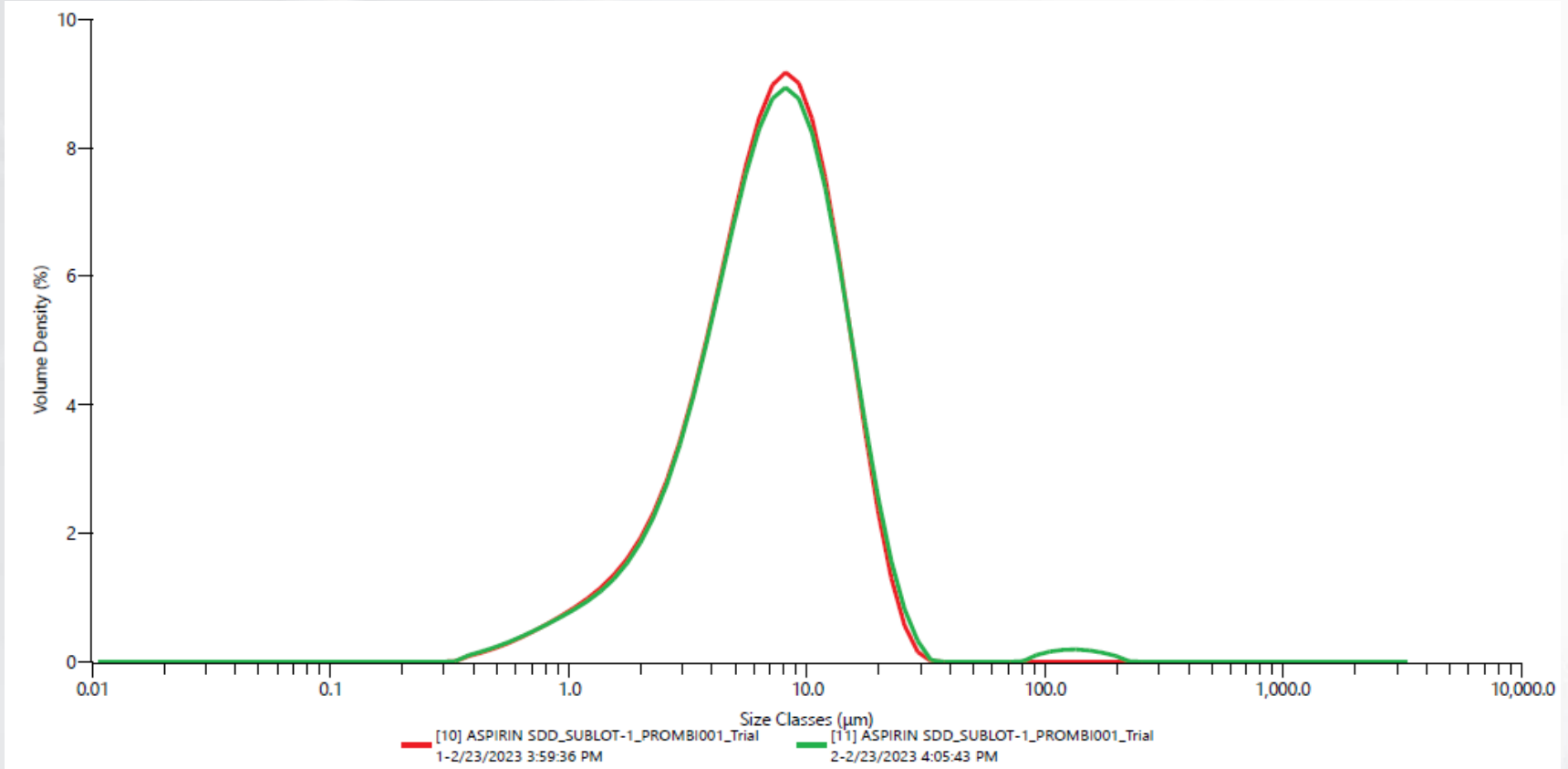
Buchi B290 Prototype- Testing (PSD and density)

- Bulk density of SDD was measured to be 0.22g/mL.
- Tapped density measured to be 0.42g/mL.



Trend

	Record Number	Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
	10	ASPIRIN SDD_SUBLOT-1_PROMBI001_Trial 1	2.28	6.97	14.8
	11	ASPIRIN SDD_SUBLOT-1_PROMBI001_Trial 2	2.32	7.08	15.6
Mean			**2.30**	**7.03**	**15.2**
1xStd Dev			**0.0277**	**0.0780**	**0.592**
1xRSD (%)			**1.20**	**1.11**	**3.89**

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Next Steps

1. **Lab scale assess/feasibility of SDD filling into capsules using Size 00 Profiller**
2. **Analytical testing of SDD material**

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