Leveraging the Digital Tool HyperStart C2C® for the Development of Low Dose API Formulation and Comparative Analysis of Tablet Coatings

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Challenge

Formulating oral solid dosage forms can be a lengthy and complex process. HyperStart C2C® is a unique digital self-service platform designed to enhance the formulation development process for oral solid dosage forms. It offers interactive formulation development from the dosage Core to its outer Coating (C2C), providing significant value to customers by increasing R&D productivity, accelerating formulation development, and speeding up time to market.

This study explores the utilization of the algorithm-based digital tool HyperStart C2C to develop a formulation for the low dose (4 mg; 2.67%) crystalline active pharmaceutical ingredient (API) chlorpheniramine maleate (CPM) and determining the ideal coating agents and procedures for this dosage form.

Method

The digital tool HyperStart C2C was employed to generate formulation composition for the low dose API (Figure 3), along with a detailed procedure to prepare the tablets.

Blend Preparation:

The tablet blend included StarTab® (for its excellent flow and direct compression properties) and microcrystalline cellulose (MCC) as a diluent. CPM was first blended with half quantity of StarTab and bag blended, then passed through a 30-mesh (600 µm) screen to deagglomerate the API. The mixture was transferred to a twin-shell V-blender (Patterson Kelley, USA) with the remaining StarTab and MCC and blended for 10 minutes. Magnesium stearate, passed through a 40-mesh (425 µm) screen, was added and mixed for 2 minutes. Blend uniformity was assessed by CPM assay at various blender locations.

Tablet Preparation:

Tablets were prepared using a rotary tablet press (Piccola, Riva, Argentina) with 8 mm round standard concave tooling at various compaction pressures and 50 rpm turret speed, following HyperStart C2C guidelines.

Coating:

Coating was applied to 3% weight gain using Opadry® QX, and alternatively with Opadry Mineral Free (277U) in 12-inch perforated pan. Tablets were evaluated for tensile strength, friability, disintegration, and in-vitro dissolution (USP II, 500 mL 0.1N HCl).

Core Tablets

HyperStart C2C was utilized to generate the core formulation composition as given below.

Figure 1: Set Up a Project: CPM Core Formulation

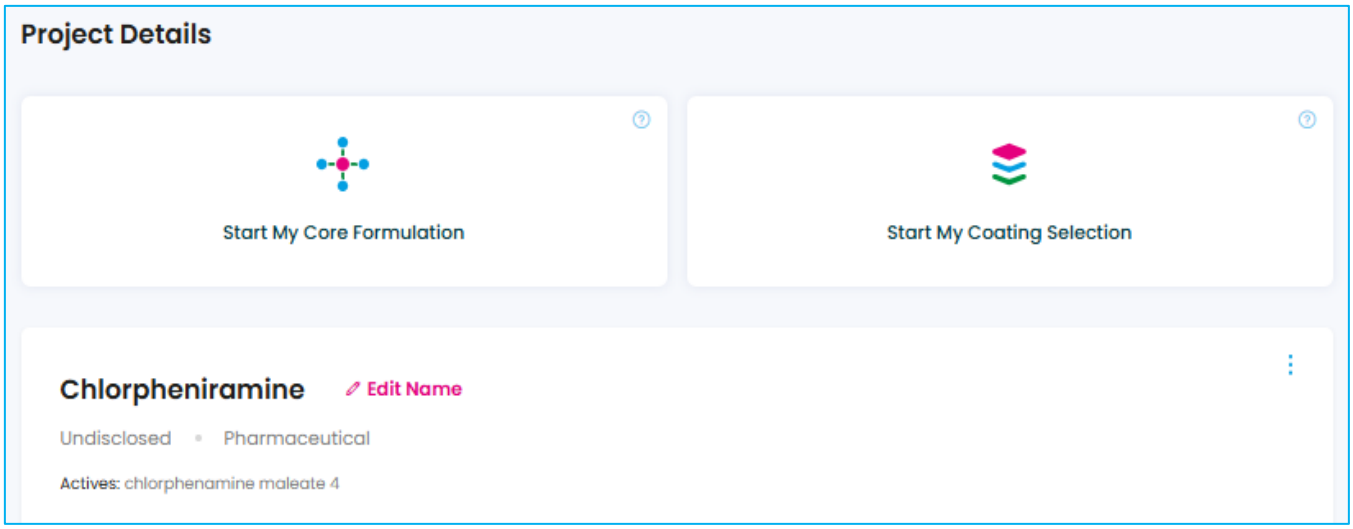


Figure 2: Product Requirements: Core Formulation

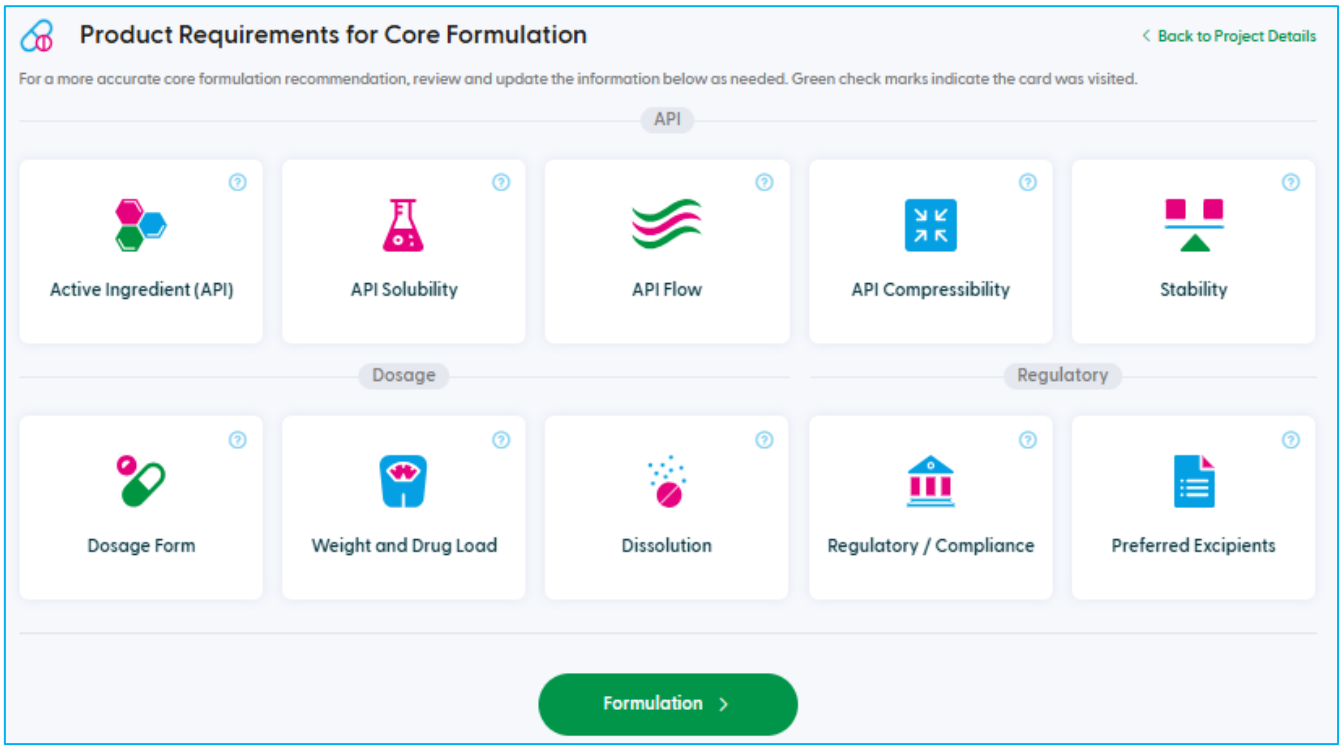


Figure 3: Recommended Formulation Composition

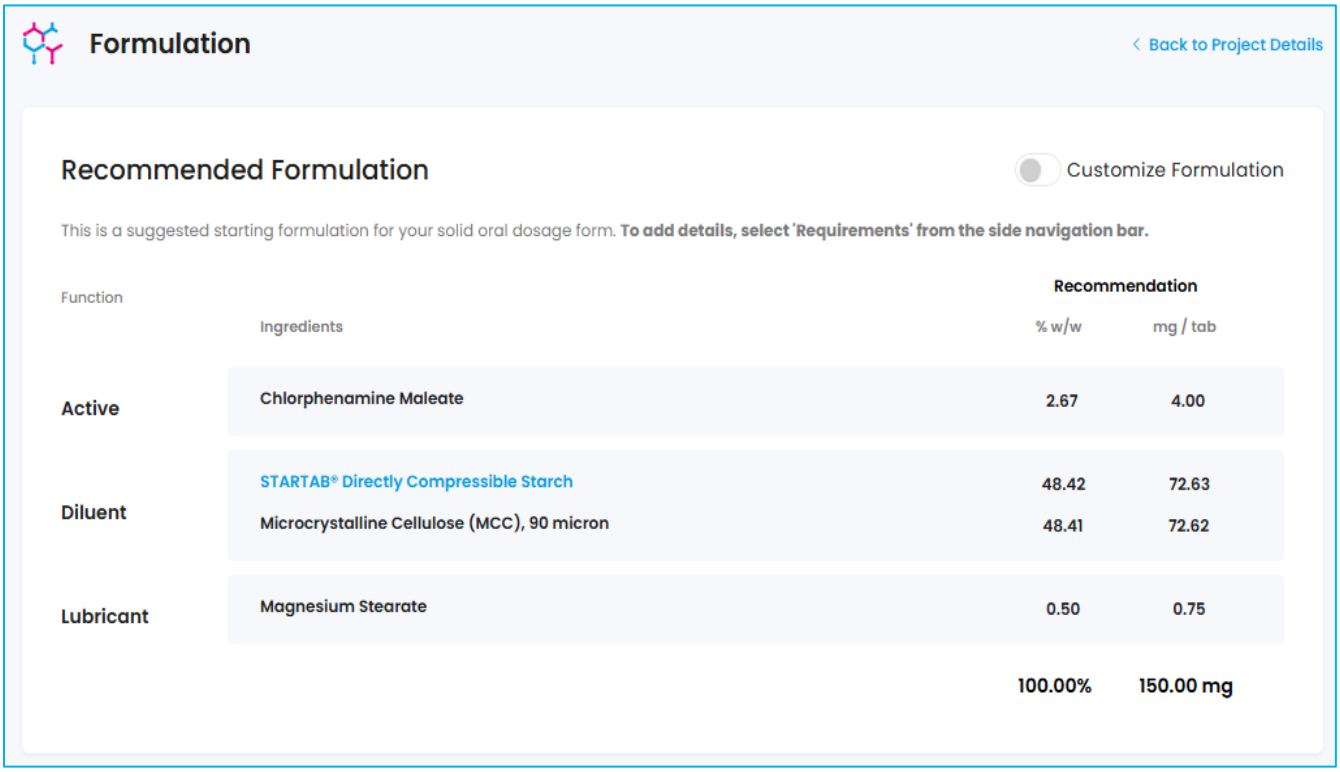
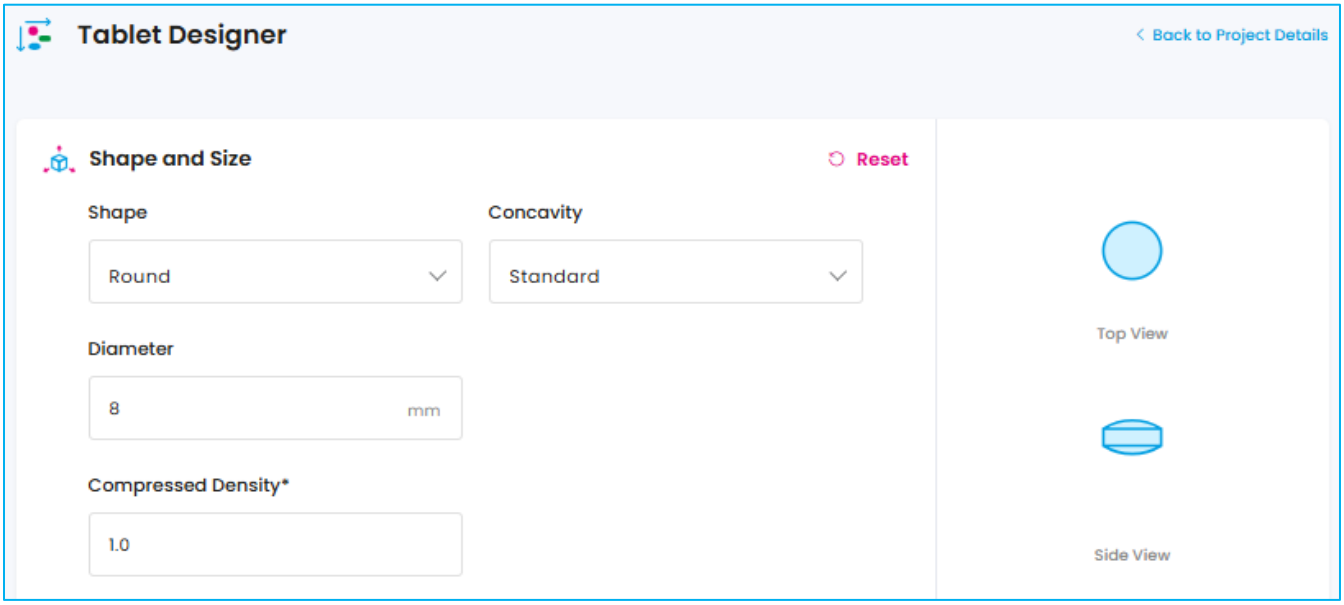


Figure 4: Recommended Tablet Size and Shape



HyperStart C2C was utilized to generate coating formulation as given below.

Figure 5: Recommended Coating Formulation

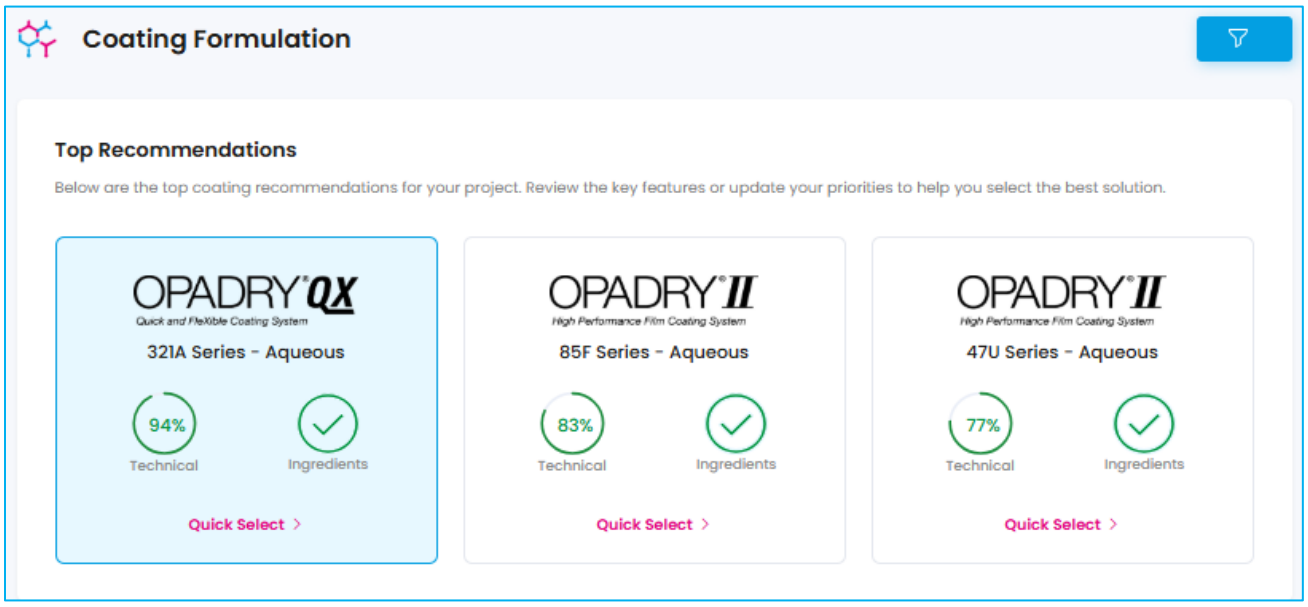


Figure 6: Recommended Coating Formulation: When Opting to Avoid Titanium Dioxide.

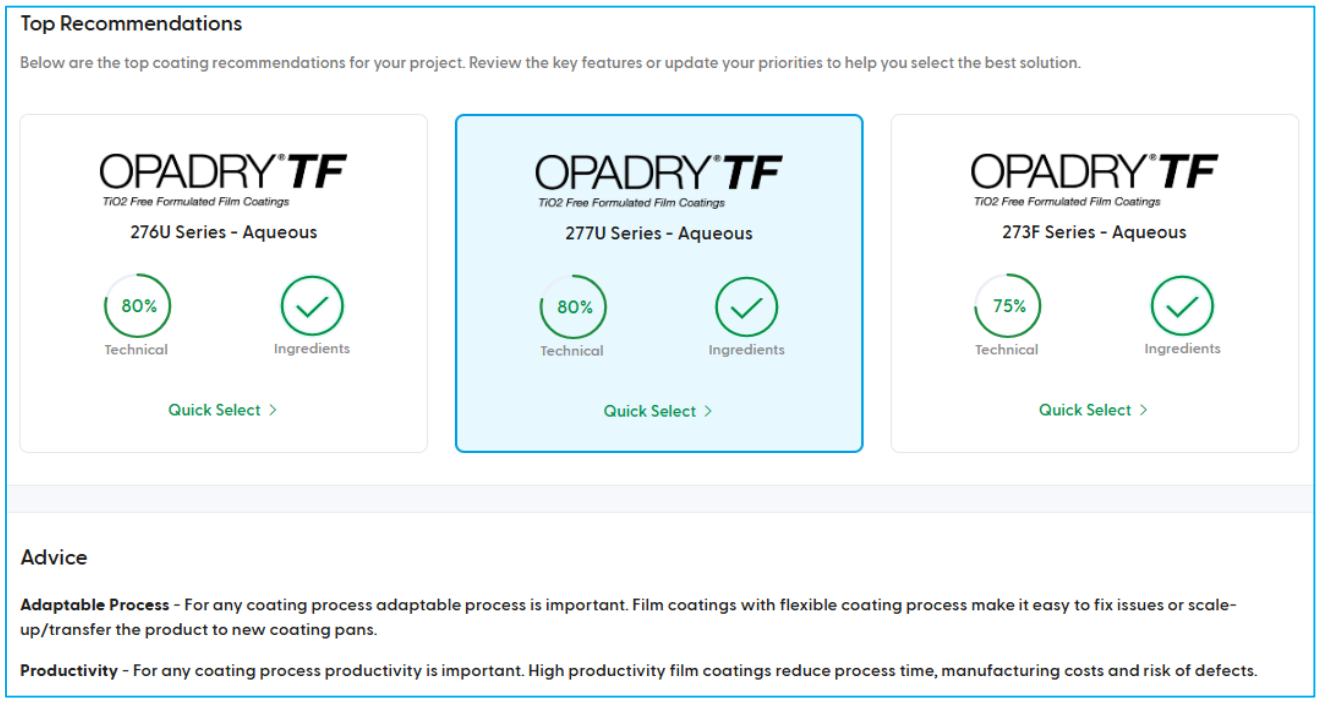


Table 1: Starting Process Parameter Recommendations for Coating CPM Tablets

Process Parameter	Opadry QX	Opadry TF
Solvent	Aqueous	Aqueous
Dispersion Solid (%)	30	20
Weight Gain (%)	3	3
Batch Size (kg)	1.1	1.1
Pan Speed (rpm)	16	16
Drying Air Volume (cu.ft/min)	125	125
Inlet Temperature (°C)	60-70	60-70
Product Temperature (°C)	46	43
Exhaust Temperature (°C)	48	45
Spray Rate (g/min)	10	10
Gun to Bed Distance (inch)	4	4

Results

Core Tablets

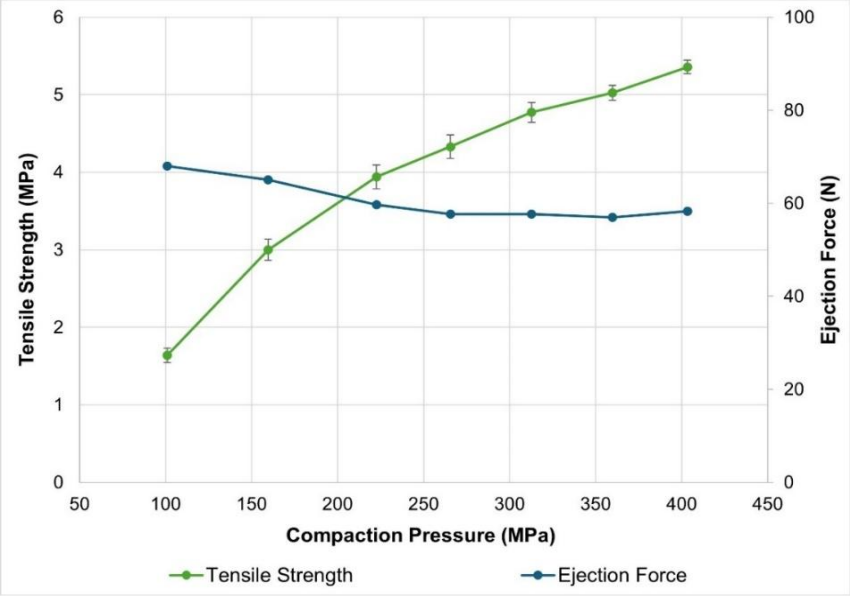
Figure 7: Powder and Tablet Properties: Starting Parameter vs. Actual Results

Powder Properties		
Powder Flow Properties	**Starting Parameters**	**Actual Results**
Compressibility or Carr's index (%) (USP)	<25	19.4 ± 1.4
Hausner Ratio	<1.34	1.24 ± 0.0
Angle of Repose (°) (USP)	<45	25.64
Minimum Orifice Diameter (mm)	<10	6
Bulk Density (g/mL)	>0.3	0.43 ± 0.0
Particle Size D50 (micron)	>80	102
Tablet Properties		
Core Tablet Properties	**Starting Parameters**	**Actual Results at 250 MPa**
Tablet weight (mg)	150	152.3 ± 0.5
Tablet thickness (mm)	~4-6	3.2 ± 0.0
Tablet hardness (kp)	8-20	13.0 ± 0.4
Tablet tensile strength (MPa)	~0.8 - 2	4.3 ± 0.2
Tablet friability (%)	<1	0.13
Disintegration time (in water 37C) with disks (s)	30	108.9 ± 2.7

Table 2: Blend Uniformity Results of CPM Blend (n=3)

Location	% Drug Content
Top Right	101.1 ± 5.3
Bottom Right	101.6 ± 0.8
Top Left	99.8 ± 6.0
Bottom Left	100.1 ± 5.6

Figure 8: Tabletability Profile of CPM Tablets



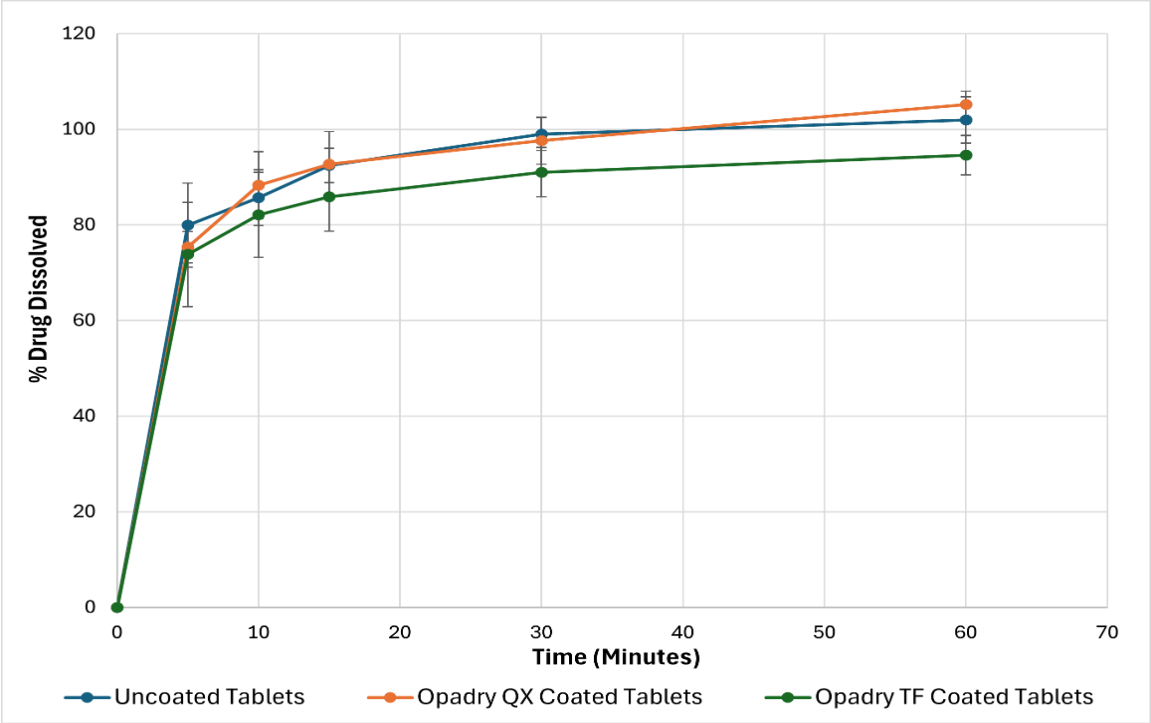
Excellent blend properties were observed in terms of flowability, bulk density, and particle size. Blend uniformity was achieved even at this low drug loading (2.67%) using a simple blending process without the need for granulation. Excellent tabletability profile and dissolution was observed for CPM tablets prepared using recommended formulation. Prepared tablets were coated with the recommended Opadry® QX formulation, and with the suggested Opadry Mineral Free (277U) as an alternative coating agent when opting to avoid minerals.

Coated Tablets

Table 3: Results of Coated CPM tablets in comparison to uncoated CPM tablets, Compressed at 250 MPa Compaction pressure

Batch	Tensile strength (MPa)	Friability (%)	Disintegration time (min.)
CPM tablets	4.33 ± 0.2	0.13	1.81 ± 0.0
CPM with Opadry QX	4.64 ± 0.3	0.00	2.44 ± 0.0
CPM with Opadry Mineral Free	4.66 ± 0.2	0.00	2.22 ± 0.1

Figure 9: Dissolution Profile of CPM Tablets: Compressed at 250 MPa Compaction Pressure



Excellent tabletability of coated tablets was observed with 0% friability. Similar in-vitro dissolution profiles were observed for both coated and core tablets with >80% drug dissolved in 10 minutes.

Conclusion

The integration of the digital tool HyperStart C2C in the formulation development process for low dose APIs like CPM offers significant advantages.

The use of StarTab and MCC in combination enhances R&D productivity, accelerates formulation development and ensures the production of high-quality tablets with optimal properties.

Opadry QX provides quick and flexible film coating that enhances tablet appearance and reduces coating time. The use of alternative coating agents like Opadry Mineral Free (277U) provides additional flexibility in formulation design, catering to specific regulatory and market requirements.

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