Scale-up and Stability of Ibuprofen Tablets Containing StarTab®, Directly Compressible Starch

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Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used in high doses to treat pain and fever. It is a poorly compressible and poorly flowing material with a low melting point (~75°C) which can lead to punch sticking and picking issues during scale-up at high tableting speeds. Stability issues such as prolonged disintegration times and reduced dissolution rates may also arise. StarTab®, directly compressible starch, was used to mitigate these challenges. The purpose of this study was to investigate a simple direct compression formulation of ibuprofen using StarTab on small- and large-scale tablet compression machines, followed by film coating and stability study.

Methods

Immediate release tablets containing ibuprofen (Ibuprofen 70, BASF) were formulated at a 200 mg dose with StarTab as the filler excipient (Table 1). The materials were mixed in a twin-shell blender (O'Hara) for 15 minutes with an intensifier bar (I-bar), then lubricated with stearic acid (passed through 60# mesh screen) for an additional 3 minutes without the I-bar. The final blend was evaluated for powder flow properties using bulk and tapped density (Tap Density Tester, Varian), flow rate via Flodex (Hansen) and particle size distribution (Mastersizer 2000 Particle Size Analyzer, Malvern). Tablets, compressed at a target tablet weight of 400 mg, were prepared on both single station small (Piccola B/D 370, Riva) and large scale (Manesty TPR 200, Bosch) rotary tablet presses. Rotary tablet press parameters are listed in Table 2. All tablets were evaluated for physical properties and disintegration time. The large-scale trial batch was film coated using a 3% weight gain using Opadry® QX brown at standard coating parameters in a 24" pan O'Hara coater (Labcoat II). Dissolution testing of coated and uncoated tablets was performed using USP Apparatus II (paddles) at 50 rpm in 900 mL of phosphate buffer pH 7.2 at 37°C. The samples were analyzed spectrophotometrically at a UV wavelength of 223 nm. Uncoated and coated tablet samples were packaged into 75 cc HDPE bottles with induction sealing, then placed to accelerated storage conditions (40°C/75% RH) with properties evaluated through six months.

Table 1. Composition of Ibuprofen Immediate Release Tablets

Core Tablet Ingredients	% w/w	mg / tablet
Ibuprofen	50.0	200.0
StarTab	49.0	196.0
Stearic Acid	1.0	4.0
Final Core Tablet Weight	***100.0***	***400.0***

Table 2. Rotary Tablet Press Parameters

Parameter	Piccola B/D	Manesty TPR 200
Number of Stations	4	25
Feeder Type	Paddle	Paddle
Tooling Dimension (B-Tooling)	10 mm round flat-faced	10.5 mm std. round concave
Main Compression Force (kN)	9 -18	12kN*
Dwell time (mS)	24	7
Turret Speed (rpm)	50	92
Tablet Output (tablets/min)	200	2300
Tablet Output (tablets/h)	12000	138000
***Compressed with and without 2kN pre-compression force**		

Results

Ibuprofen is a poorly flowing material with a mean particle size of approximately 22 µm (Table 3). Conversely, StarTab has exceptional powder flow properties, demonstrated by powder flow through the 4 mm diameter orifice (smallest size available) and larger mean particle size (approximately 90 µm). The inclusion of StarTab produced a final formulation with acceptable powder flow and compression properties for both small- and large-scale tableting operations.

Table 3. Powder Properties of Bulk Materials and Final Core Tablet Blend

Property	Ibuprofen	StarTab	Formulation Blend
Bulk Density (g/mL)	0.49	0.57	0.58
Tapped Density (g/mL)	0.65	0.70	0.84
Hausner Ratio	1.33	1.22	1.44
Compressibility Index (%)	24.0	18.0	31.0
Particle Size d(0,1) (µm)	3.8	36.9	12.8
Particle Size d(0,5) (µm)	22.1	89.8	66.5
Particle Size d(0,9) (µm)	83.1	171.4	154.6
Flow Rate (g/min)	No Flow	37.6 (4 mm orifice)	19.3 (4 mm orifice)
Overall Flow	***Very Poor***	***Good***	***Good***

In the small-scale rotary compression trial, a compression profile was generated indicating that 12kN main compression force was suitable for scale-up (data not shown). Pre-compression is often used in high-speed tableting as an initial compaction step to prevent migration of material from the die cavity and avoid issues such as tablet capping and lamination. For the large-scale trial, a pre-compression force of 0 or 2kN was applied, followed by 12kN for the main compression.

Physical properties of uncoated tablets compressed on the Piccola (tablet output 200 tablets/min) and Manesty TPR 200 (tablet output 2300 tablets/min) at 12kN were robust with quick disintegration times (Table 4). No manufacturing defects (i.e. punch sticking and picking) were observed during the compression trials. Tablet properties of the large-scale tablets compressed with and without pre-compression were comparable. The results indicated that the scale of manufacture and use of pre-

compression did not have an impact on tablet properties. Additionally, drug release profiles of uncoated tablets prepared on the large scale were consistent with the small-scale data (Figure 1).

Tablets were successfully coated to a 3% weight gain and free of visible defects (Figure 2). The application of the film coat increased tablet hardness and had no impact on disintegration time. Both coated and uncoated tablets were stored for six months in accelerated conditions at 40℃/75% RH. At all time points, tablets were robust and stable with dissolution results meeting the USP criteria for ibuprofen drug release (Figure 3). At six months, the tablets had no change in appearance and maintained good hardness (Table 5). There was a slight increase in disintegration time, however, this is still well under the USP limit.

Table 4. Physical Properties of Uncoated and Coated Ibuprofen Immediate Release Tablets

Property	Piccola B/D	Manesty TPR 200			
	12kN	12kN	12kN (Coated)	12kN + 2kN PC*	12kN + 2kN PC* (Coated)
Weight (mg)	412.3 ± 1.1	413.5 ± 14.1	419.9 ± 7.0	399.7 ± 5.6	410.2 ± 8.0
Thickness (mm)	4.69 ± 0.02	6.11 ± 0.06	6.15 ± 0.02	6.07 ± 0.01	6.14 ± 0.03
Hardness (kP)	8.2 ± 0.7	6.9 ± 2.4	11.1 ± 1.0	5.7 ± 0.8	9.2 ± 1.3
Friability (%)	0.76	0.53	-	0.50	-
Disintegration Time (sec)	93 ± 10	58 ± 19	68 ± 17	51 ± 40	65 ± 23
**** PC = Pre compression***					

Figure 1. Dissolution of Ibuprofen Tablets Manufactured at Small or Large Scale

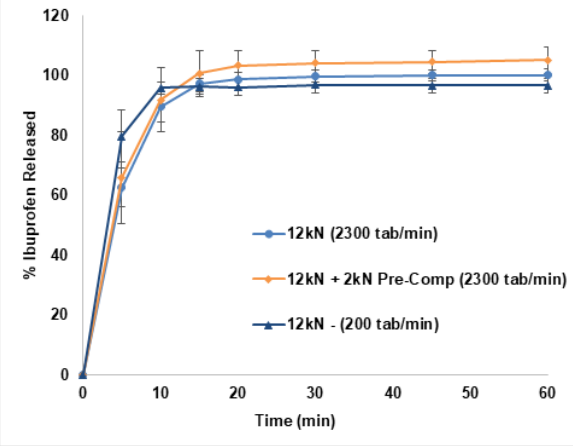


Figure 2. Opadry QX Coated Ibuprofen Immediate Release Tablets – (A) Tablet Core Compressed at 12kN and (B) Tablet Core Compressed at 12kN with 2kN Pre-Compression

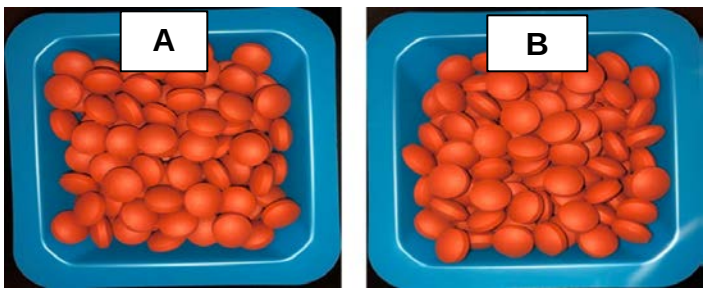
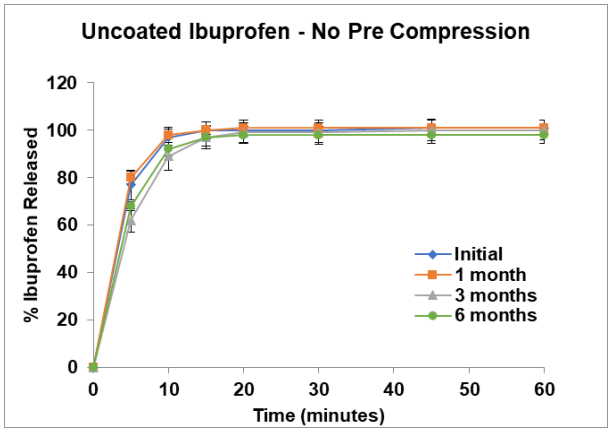
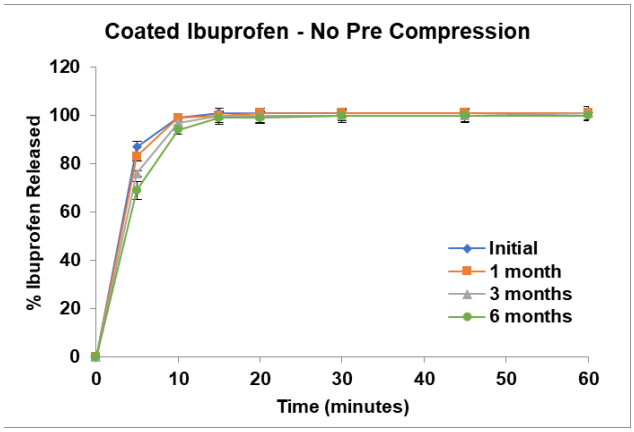


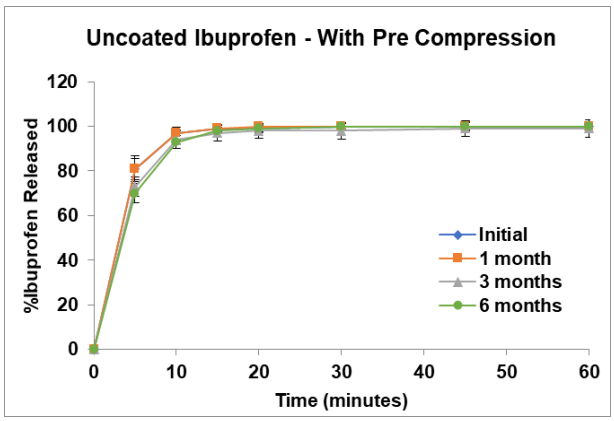
Table 5. Physical Properties of Uncoated and Opadry QX Coated Ibuprofen Immediate Release Tablets At 6 Months in Accelerated Stability (40°C/75% RH)

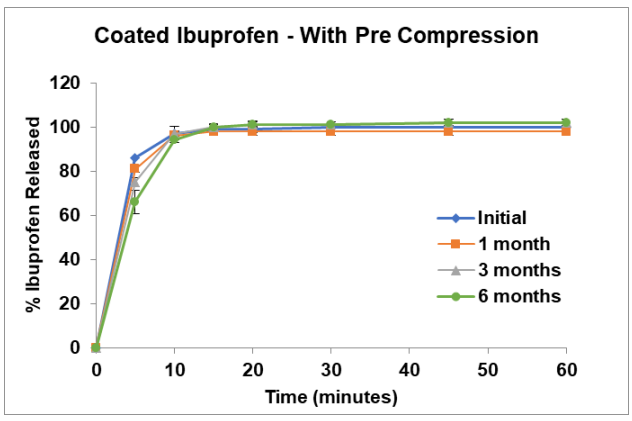
Property	Uncoated Ibu 12kN	Uncoated Ibu 12kN + 2kN PC	Coated Ibu 12kN	Coated Ibu 12kN + 2kN PC
Weight (mg)	399.4 ± 14.7	401.2 ± 5.5	419.4 ± 20.7	408.8 ± 7.1
Thickness (mm)	6.10 ± 0.03	6.12 ± 0.02	6.21 ± 0.09	6.20 ± 0.02
Hardness (kP)	10.4 ± 1.7	10.6 ± 0.9	11.8 ± 1.4	9.6 ± 1.4
Friability (%)	0.61	0.57	-	-
Disintegration Time (sec)	208 ± 55	106 ± 35	159 ± 50	168 ± 52

Figure 3. Dissolution Profiles of Uncoated and Opadry QX Coated Ibuprofen Tablets in Accelerated Stability (40°C/75% RH)









Conclusions

A simple immediate release ibuprofen formulation was successfully developed using a single tableting excipient with the desired performance attributes. The use of StarTab improved powder flow and eliminated the need for superdisintegrant or glidant in the formulation. The resulting tablets were robust with fast disintegration times and were subsequently film coated without any defects. Ibuprofen tablets were stable through six months of accelerated conditions with no change in their physical properties or drug release profiles.

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