Formulating Veterinary Chewable Tablets

To improve and promote the palatability of solid oral dosage forms for companion animals.

Formulation of Veterinary Chewable Tablets to Achieve Different Dosage Strengths and Tablet Robustness

Background

Commercially manufactured veterinary medicinal products (VMP) are often designed using 'human' formulation strategies. Although in many instances, this works well, it doesn't address the specific needs for a chewable type of veterinary dosage form. Chewable tablets may lack effective taste-masking of the active ingredient, and not choosing the appropriate excipient can negatively impact palatability and voluntary acceptance.

Products for veterinary use require careful formulation to achieve a robust final dosage form; blend flowability, tablet hardness, and low friability are all vital attributes for successful product development and manufacture. In many cases, tablets and capsules dispensed to companion animals are given via a 'poke down' method or hidden in an attractive food. Ideally, the tablet or capsule would be voluntarily consumed from the pet parent's hand or the pet's bowl, which means veterinary pharmaceutical and health supplement companies strive to develop products with high palatability.[1,2]

With a chewable substrate, achieving desired tablet properties for companion animals with individual needs is essential. When developing a hard or chewable tablet, age and special needs should be considered.

Canine osteoarthritis (OA), which results in chronic pain and decreased physical activity, is often treated with NSAIDs, such as carprofen.[3]

This study investigated a formulation strategy using a starch-based excipient in a chewable veterinary carprofen (suitable for animal use only) formulation. In addition, manufacturing processes and resultant tablet properties were evaluated.

Formulation Strategy for Robust Performance

In this study, partially pregelatinized starch (Starch 1500® or StarTab®) was combined with microcrystalline cellulose (MCC) using a ratio of 1:2 at low, medium, and high drug loads to formulate and manufacture a carprofen tablet.

The combination of primary and secondary diluents in the formulation provides downstream flexibility for the formulation, as well as robust tablet properties (Table 1). The flexibility provided by the diluents accommodates changes in formulation for improved flow, better tablet properties, manufacturability, and stability without introducing new excipients.

Direct compression (DC) was chosen as the preferred simple and efficient manufacturing method. The tablet ingredients were blended using a twin-shell V-blender with an intensifier bar.

Table 1: Carprofen Tablet Formulation

Ingredients	Low Drug Load (5%)		Medium Drug Load (40%)		High Drug Load (60%)	
	L1	L2	M1	M2	H1	H2
	% (w/w)		% (w/w)		% (w/w)	
Carprofen, USP (Acura Labs PVT LTD.)	5.00	5.00	40.00	40.00	60.00	60.00
Avicel PH 102 (MCC, DuPont)	56.00	56.00	33.00	33.00	19.50	19.50
Starch 1500® (Colorcon)	28.00	-	16.00	-	9.50	-
StarTab® (Colorcon)	-	28.50	-	16.50	-	10.00
Artificial Powdered Beef Flavor (Pet Flavors, Inc)	10.00	10.00	10.00	10.00	10.00	10.00
Colloidal Silicon Dioxide (IMCD, US)	0.50	-	0.50	-	0.50	-
Magnesium Stearate (Peter Greven)	0.50	0.50	0.50	0.50	0.50	0.50
Total	100	100	100	100	100	100
Diluent Ratio	2 to 1	2 to 1	2 to 1	2 to 1	2 to 1	2 to 1
Tablet Weight (mg)	500	500	500	500	500	500
Drug Load (%)	5	5	40	40	60	60
Carprofen (mg) per Tablet	25	25	200	200	300	300

Powder Blend Property Testing

Powder flow properties of the carprofen API and formulation blends were characterized using a Hosokawa Powder Characteristics Tester PT-X (Hosokawa Micron Ltd.). Tests were the angle of repose, angle of fall, angle of difference, bulk/tapped density, and dispersibility. In addition, particle size distribution was measured using a Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments, USA).

Tablet Compression

After weighing and blending, each formula was compressed using a Piccola B/D rotary tablet press fitted with 10 mm round B-tooling. All tablets were compressed to a target weight of 500 mg with compression forces ranging from 2.5 to 15 kN to generate a compression profile. Gravity feed and a turret speed of 40 rpm were used for all compression trials. Tablet samples were collected at each compression force, then tested for hardness, friability, disintegration, and dissolution. Tablet ejection forces were also recorded as a measure of manufacturability.

Results

Powder Blend Properties

Blend particle size and bulk density were increased for all formulations compared to carprofen alone (Figure 1). An increase in particle size and bulk density was most significant for the low drug load (5%) formulations.

Increases in particle size and bulk density for the Starch 1500 and StarTab blends were similar regardless of drug load.

Blend flow was improved for all formulations over the carprofen active alone, which shows poor flow (Figure 2). The low drug load formulations containing Starch 1500 and StarTab showed the highest increases in flow, with >80% reported in Flow Index (results not shown). High and medium drug load formulations containing Starch 1500 and StarTab showed an increase in blend flow between 50-70%.

Figure 1. Comparison of Particle Size and Bulk Density for Dry Powder Blends (40% drug load)

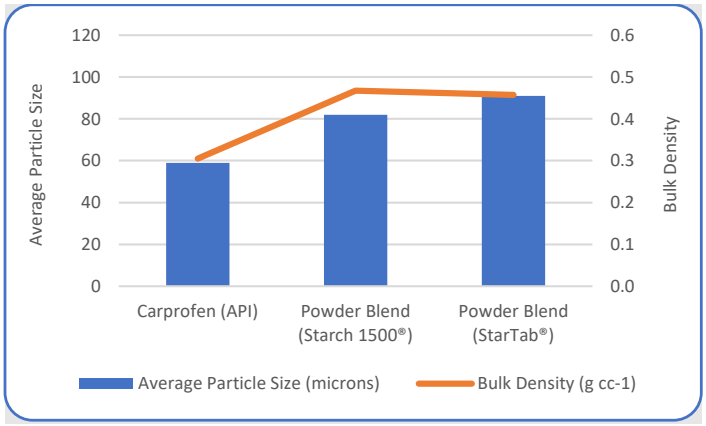
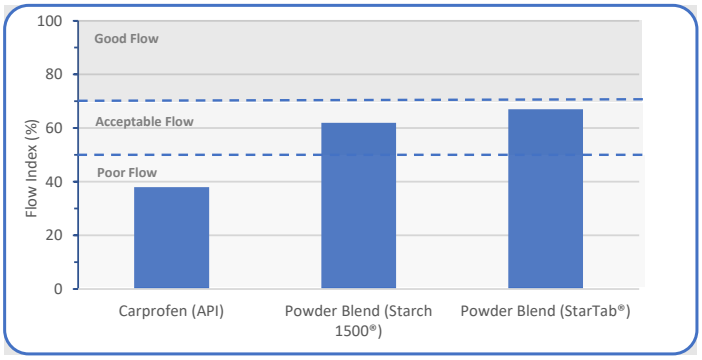


Figure 2. Comparison of Flow Index for Formulation of Dry Powder Blends (40% drug load)



Tablet Properties

Robust tablets were made for all formulations using direct compression, avoiding time-consuming and costly granulation and milling steps.

Both formulation and drug load influenced the resulting tablet properties. A broad range of tablet tensile strength values (0.4-2.9 MPa) with low friability (<0.5%) were achievable at compression forces of 5kN and greater, based on drug load (Figures 3 through 5). This range demonstrates the flexibility of Starch 1500 or StarTab formulations to achieve desirable properties for either hard or chewable tablets for companion animals.

Low tablet friability supports subsequent film coating, packaging, and handling. While the tablet disintegration time increased with increasing compression force for all formulations and drug loads, most demonstrated fast disintegration of less than 5 minutes. Only at higher compression forces and high drug loads did disintegration time exceed 5 minutes.

Figure 3: Tablet Properties: Hardness, Disintegration, and Friability (Low Drug Load)

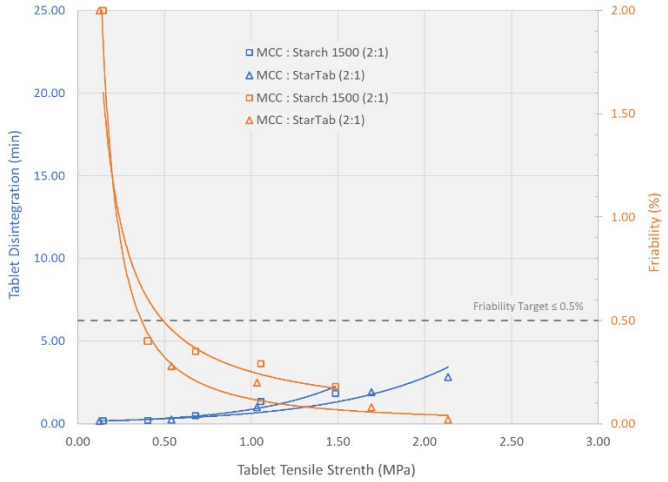


Figure 4: Tablet Properties: Hardness, Disintegration, and Friability (Medium Drug Load)

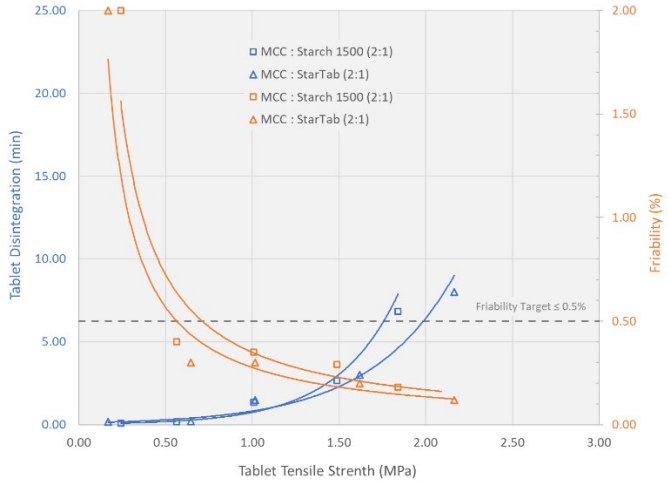
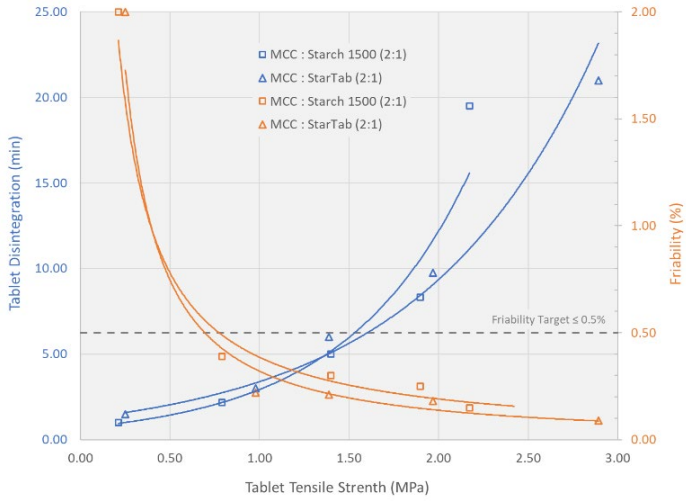
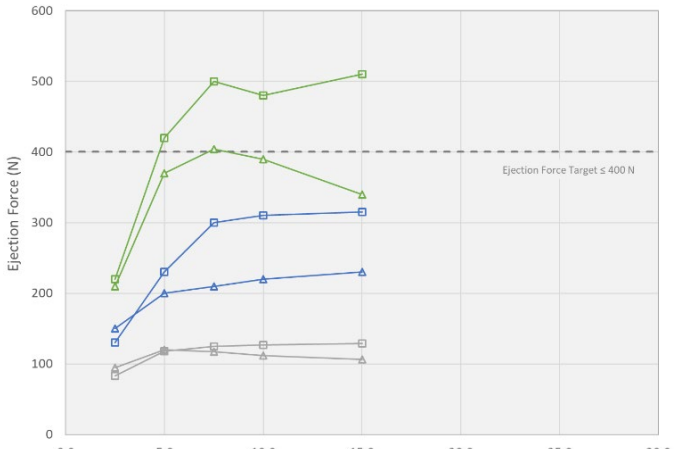


Figure 5: Tablet Properties: Hardness, Disintegration, and Friability (High Drug Load)



All formulations exhibited suitable lubricity resulting in acceptable tablet ejection forces. As expected, the higher drug loads saw the highest ejection forces (Figure 6).

Figure 6: Tablet Ejection Force vs. Compression Force



Dissolution Performance

Dissolution testing was performed in 900 mL of 0.05N sodium phosphate buffer, pH 7.5 at 37°C using USP Apparatus II (paddles) at 50 rpm for 60 minutes, with samples taken at 10, 20, 30, 45, and 60-minute intervals. Carprofen is a white crystalline powder, freely soluble in ether, acetone, ethyl acetate, and sodium hydroxide TS or sodium carbonate TS; practically insoluble in water.[4]

Carprofen assay samples were analyzed on an HPLC system with ultraviolet (UV) detection. The chromatography was performed by reverse phase separation using an Xterra RP8 4.6 × 150 mm (C8) column. The mobile phase consisted of acetonitrile, water, and phosphoric acid in the ratio of 50:50:1. The remaining instrument conditions were as follows.

Table 2: Carprofen Assay Instrumental Conditions

Column	Xterra RP8 4.6 × 150 mm (C8)
Flow	1.0 mL/minute
Column Temperature	25°C
Injection Volume	20 µL
Runtime	9 minutes
Detector	UV – 240 nm

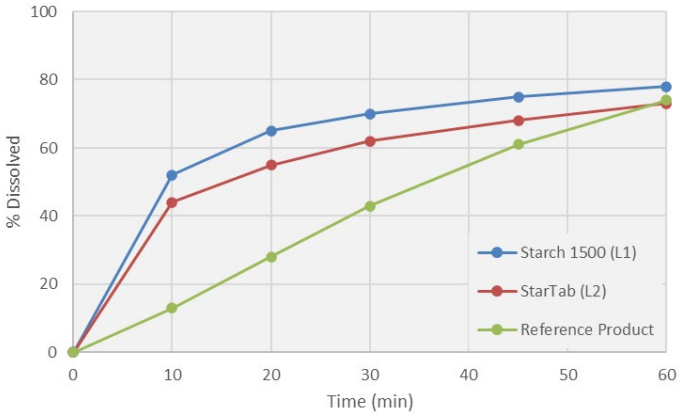
Carprofen dissolution samples were analyzed directly on UV after sampling from the dissolution bath. Samples were protected from light for all analyses as carprofen is sensitive to light.

Compared to a reference product of similar hardness, the tablets tested for disintegration and dissolution were compressed to 15kP hardness.

Formulations containing Starch 1500 or StarTab, along with the reference product, all met the USP assay specification of not less than 90.0 % and not more than 110.0% of the labeled amount of carprofen (data not shown).

Dissolution performance for formulations containing Starch 1500 or StarTab followed a similar trend, releasing faster than the reference product. The differences may be due to carprofen's properties, such as active particle size and morphology.

Figure 7: Dissolution Performance (low drug load)



Benefits of a Formulation Strategy Including Starch 1500 or StarTab

Combining a starch-based excipient such as Starch 1500 or StarTab with MCC resulted in tablets with good hardness, low ejection force, and friability, along with excellent disintegration performance. This formulation strategy improves palatability, as starch has no unacceptable flavor or odor, and the resulting tablet has better mouthfeel properties. The acceptance of a drug product or supplement for companion animals leads to better compliance and therapy outcomes. In addition, using a starch-based excipient provides formulation and process flexibility by enabling in-use ratio changes without adding new excipients, avoiding costly delays in late-stage development.

The Solution

As a naturally sourced excipient from identity-preserved non-GM corn which is manufactured in dedicated GMP facilities, the use of Colorcon's starch-based excipients in veterinary dosage forms like chewable tablets and soft chews provides unique benefits for manufacturers:

- The unique particle size and shape of StarTab provide excellent flow and high compressibility, especially at medium and high drug loads in DC formulations.
- Starch 1500 exhibits good thermal stability, ideal for veterinary soft chew manufacture.
- Starch 1500 imparts plasticity (ductility) to chewable dosage forms and helps maintain these properties over the product's shelf-life.
- No animal products or by-products are used to manufacture Starch 1500 or StarTab.
- No chemical additives or surfactants are used in the process, giving a neutral taste and good palatability for pet acceptance.

References

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4. USP Monographs, Carprofen Tablets. USP-NF. Rockville, MD

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