Starch 1500®, partially pregelatinized maize starch, has been successfully used to increase acceptance in veterinary oral dosage forms. In this study, a formulation strategy using Starch 1500 in a chewable veterinary supplement was investigated evaluating suitability of both tablet properties and performance.

CASE STUDY

Formulating Veterinary Chewable Tablets to Improve Palatability and Acceptance

For veterinary medicinal products (VMP), compliance and convenience are critical to ensure the success of prevention, control, and treatment medication programs. There is a recognized need for highly palatable solid oral dosage forms for companion animals that are freely accepted from their feeding bowl or via the hand of the pet owner. Improving dosage forms to focus on the treatment regime, with convenience and compliance, represent a growing trend in companion animal formulations; this is especially true for medications administered for chronic conditions. Companies are also looking to meet marketing objectives such as product differentiation and customer loyalty.[1]

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 owner's hand or the pet's bowl, which means veterinary pharmaceutical companies strive to develop products with high palatability.[2,3]

The Problem: Poor Acceptance of a Drug Product or Ingredient by Companion Animals

According to the European Medicines Agency (EMA) palatability is defined as being acceptable to the mouth, "pleasant to the taste" or "acceptable to the taste". When applied to a VMP, this term suggests that the product is palatable enough to ensure voluntary uptake of the product from a feeding vessel, or via hand when offered as a treat by the animal owner.[4] In this instance palatability involves taste, smell, and mouthfeel such as texture, size, or chewiness.

Commercially manufactured 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 drug substance and excipient selection can negatively impact palatability and voluntary acceptance.

Colorcon's proven and trusted Starch 1500®, partially pregelatinized maize starch, has been successfully used as a key excipient in formulating veterinary oral dosage forms. In this study, a formulation strategy using Starch 1500 in a chewable veterinary supplement was investigated. Manufacturing processes and resultant tablet properties were evaluated.

Formulation Strategy for Improved Palatability and Performance

Many chewable tablet formulations intended for veterinary administration use a similar formulation approach with commonly used ingredients consisting of diluents, flavor, compressible sugars, flow aid, and lubricant. Other ingredients may include binders, animal / vegetable-sourced proteins, disintegrants, pigments, etc.

For this study, a partially pregelatinized maize starch (Starch 1500) was combined with microcrystalline cellulose (MCC), or MCC and lactose, at different ratios in a glucosamine tablet. To produce a chewable tablet of good hardness with low ejection force, low friability, and fast disintegration a ratio of Starch 1500 to MCC of 1:1 or 1:2 is recommended.

Ingredient	Formula 1 (%)	Formula 2 (%)	Formula 3 (%)
Glucosamine HCL	30	30	30
Starch 1500	**56**	**36**	**26**
MCC	0	20	20
Lactose	0	0	10
Flavor	12	12	12
Mag Stearate	1	1	1
SiO2	1	1	1
Total	100	100	100

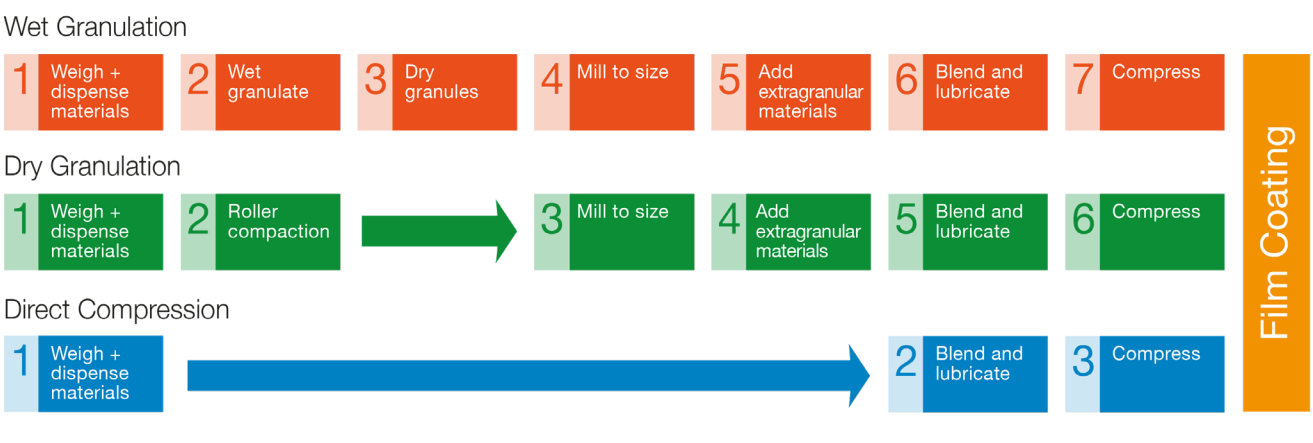
This strategy also provides manufacturing process flexibility without having to introduce new excipients to the formulation; enabling an easy move to granulation technologies like high shear and fluid bed.

Table 1:
Glucosamine Tablet Formulation

Demonstrating Process Flexibility

To demonstrate the flexibility of a chewable tablet formulation strategy using Starch 1500 and MCC, processing methods commonly used in the VMP industry were studied: top spray fluid bed granulation (FB), high shear granulation (HS), direct compression (DC), and roller compaction (RC). The simplest manufacturing process being direct compression (DC), while wet granulation (FB and HS) are more complex multi-step methods.

Figure 1:
Comparison of Tablet Manufacturing Methods



Batch Manufacturing Process

For each trial, a 3 kg batch size of the formulation was prepared. Fluid bed (FB) trials were conducted in a Freund-Vector VFC-3 multi-fluid bed system with a 12 L container. The amount of water added and the spray rate was kept consistent across the formulations.

High shear granulation (HS) was completed in a Freund-Vector GMX-B 10 L bowl. Power consumption (KW) was used as an endpoint determination for each trial batch.

Following granulation, each batch was wet-milled using a Quadro Co-Mil with a 0.5" square hole screen, and the resulting granules dried in a VFC-3 fluid bed, with a 12 L drying container. Roller compaction (RC) was completed using a Freund-Vector TFC-220 with standard serrated rolls. The resulting ribbons were milled using an in-line oscillating screen granulator with a 12-mesh screen.

For consistency through the test formulations and process technology, Starch 1500 was added to the dry blend. Excipients not critical to the granulation process (such as the flavor and lubricants) were excluded from the granulation process then added via a V-Blender post-granulation. The DC blends were all blended using a V-Blender with an intensifier bar for 3 minutes.

Tablet Compression

Following the granulation and blending steps, each blend was compressed utilizing a Piccola B/D rotary tablet press fitted with 17 mm round concave D-tooling. Tablets were compressed to a target weight of 1000 mg with compression forces ranging from 25 to 45 kN to generate a compression profile. A paddle feeder was used on the turret and 50 rpm turret speed was used for all compression trials. Tablet samples were collected at each compression force and resulting tablets were tested for hardness, tensile strength, friability, disintegration, assay, and dissolution.

The Results:

Granulation

All formulations performed well in the two wet granulation processes (FB and HS), with each resulting in similar performance. As expected the HS granulations were more dense and larger than the FB granulations in particle size, with HS granulations being largely influenced by the post-granulation milling process.

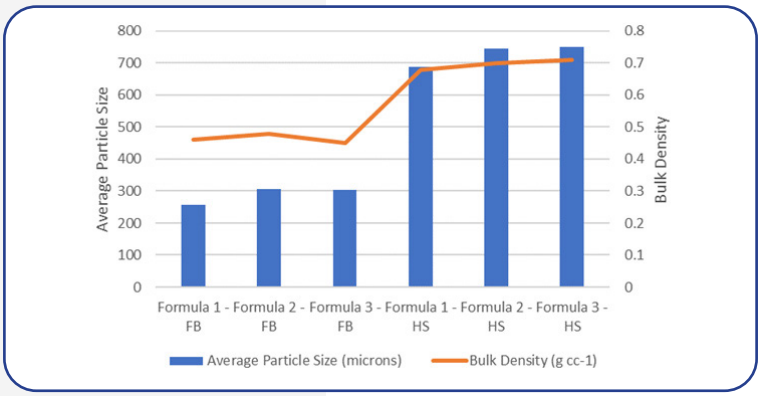


Figure 2:
Comparison of Particle Size and Bulk Density for the Formulations Using Fluid Bed (FB) and High Shear (HS) Processing

Tablet Properties

The formulation had a large influence on the resulting hardness of the tablets, with those produced using a Starch 1500: MCC blend resulting in the range of 6-8 KP, across the manufacturing technologies. All formulations exibited adequate lubricity resulting in acceptable tablet ejection forces. As expected, the highest ejection forces were seen with formulations containing lactose. All tablets exhibited low friability when compressed at moderate to high compression forces; making them suitable for subsequent film coating, packaging, and handling. The tablets also demonstrated fast disintegration times of <5 minutes facilitating good dissolution of the active.

Figure 3:
Tablet Hardness (KP) vs Compression Force (kN)

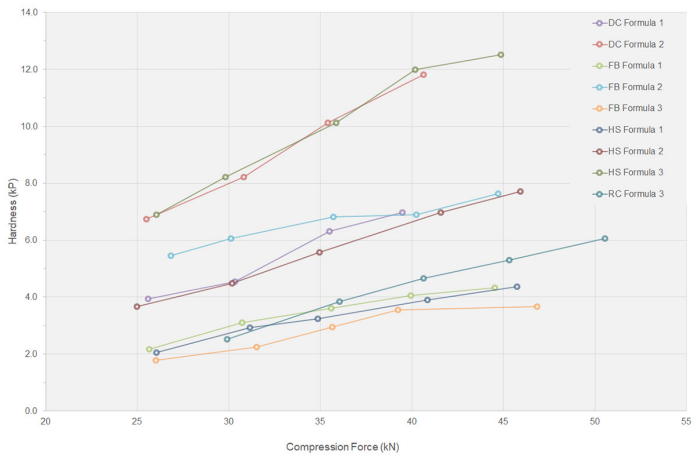


Figure 4:
Ejection Force (kP) vs Compression Force (kN)

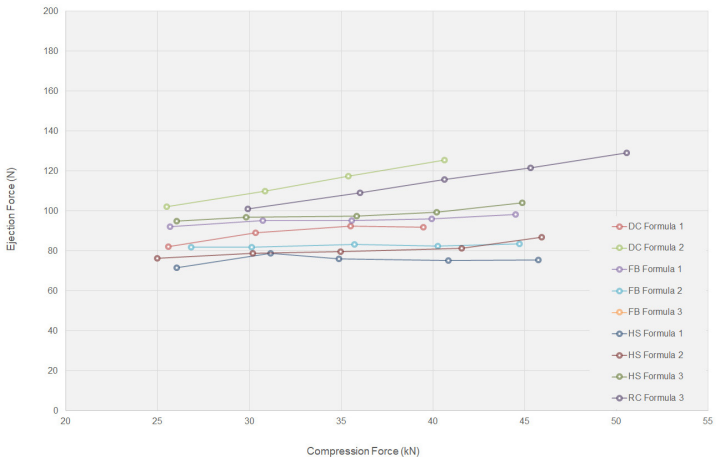


Figure 5:
Friability (%) vs Compression Force (kN)

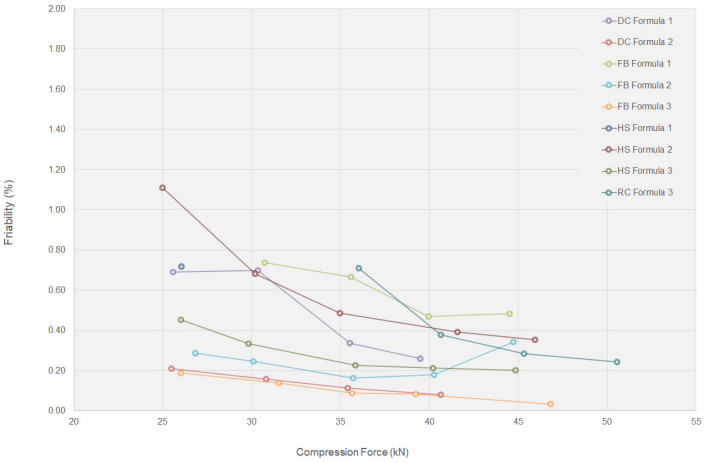
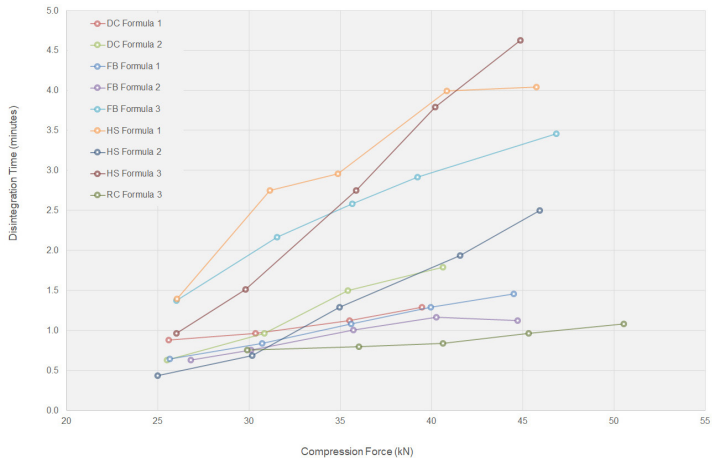


Figure 6:
Disintegration Time (min.) vs Compression Force (kN)



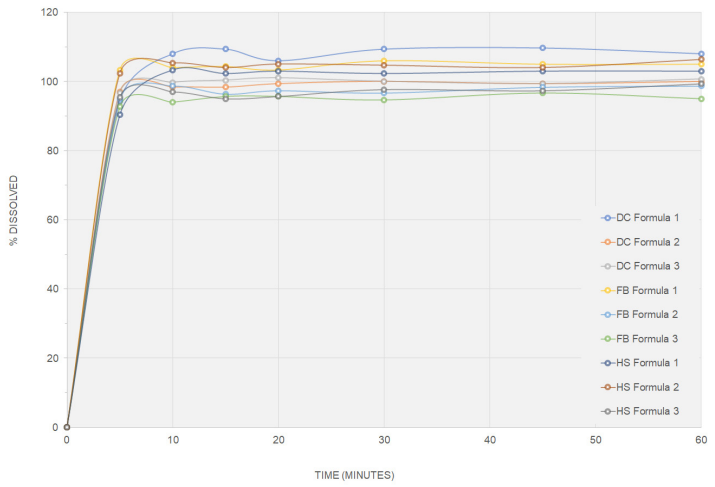
Dissolution Performance

Mobile Phase Flow		0.5 mL/minute
Column Temperature		30°C
Injection Volume		0.5 µL
Runtime		3 minutes
Detector Settings	Temperature	35°C
	Power Settings	1.0
	Data Collection Rate	5
	Filter Constant	10

Dissolution testing was performed in 900 mL of DI water at 37°C using USP Apparatus II (paddles) at 75 rpm for 60 minutes, with samples taken at 5, 10, 15, 20, 30, 45, and 60 minute intervals.

Table 2:
Glucosamine Assay and Dissolution Instrumental Conditions

Figure 7:
Dissolution Performance



Glucosamine assay and dissolution samples were analyzed on a Thermo Vanquish UHPLC system with charged aerosol detection. The chromatography was performed by HILIC separation using a Waters Acquity UPLC BEH, 50 mm x 2.1 mm, 1.7 µm column.

The mobile phase consisted of acetonitrile and 200 mM formate buffer, pH 3.65 in the ratio of 80:20 metered by the binary pump. The remaining instrument conditions are represented in Table 2.

Dissolution performance was similar for all formulas and all processing technologies, with the formulations releasing >90% of the glucosamine HCl in <5 minutes.

Benefits of a Formulation Strategy Including Starch 1500

Robust tablets were made for all formulations using different processing technologies, which offers maximum flexibility to formulators and manufacturers. Combining Starch 1500 with MCC in the formulation resulted in tablets with good hardness, low ejection force and friability, along with excellent disintegration properties and dissolution performance. This formulation strategy offers improved palatability and acceptance of a drug product or supplement for companion animals leading to better compliance and therapy outcomes.

When direct compression is not viable and formulators need to use wet granulation, specifically for active ingredients with low density and poor flow, the binding properties of Starch 1500 provide a distinct advantage in terms of quality, flowable granulations without the use of any polymer binders. The use of Starch 1500 provides formulation and process flexibility by enabling in-use ratio changes without the addition of new excipients, avoiding costly delays in late-stage development.

The Solution:

This formulation approach reduces manufacturing risk, eliminates the need for additional stability studies while resolving late-stage, post-field study formulation issues. As a naturally sourced excipient from identity-preserved non-GM corn and manufactured in dedicated GMP facilities, the use of Starch 1500 in veterinary dosage forms like chewable tablets and soft chews provides unique benefits for manufacturers:

- The manufacturing process used to produce Starch 1500 is a physical modification of maize starch. No chemical additives or surfactants are used in the process thereby giving Starch 1500 a neutral taste with good palatability.
- Starch 1500 exhibits good thermal stability to about 121° C, ideal for veterinary soft chew manufacture.
- Starch 1500 imparts plasticity (ductility) to the dosage form and helps maintain these properties over the shelf-life of the product.
- No animal products or by-products are used in the manufacture of Starch 1500.

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4. Committee for Medicinal Products for Veterinary Use (CVMP) (2014) Guideline on the Demonstration of Palatability of Veterinary Medicinal Products. European Medicines Agency, London, 1-7

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