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Simplify the Manufacturing of Joint Health Tablets for Dogs: A Case Study with Green-Lipped Mussel Extract

Introduction

Joint health products are some of the best-selling products in the animal health supplement market. With a prevalence of 20 %, osteoarthritis, or degenerative joint disease, is the most common form of joint disease in dogs[1]. The disease's prevalence increases from 15 % to 67 % as dogs age[2]. Several studies provide evidence that arthritic-related symptoms can be alleviated in dogs[3,4,5,6,7,8], cats[9], and horses[10] by oral supplementation of green-lipped mussel powder (GLM) from *Perna canaliculus*. Although the mechanism of action is not yet fully understood, GLM powder is widely used for prevention and treatment of osteoarthritis and may reduce, or even eliminate, the need for conventional medical therapy[4] NSAID's (non-steroidal anti-inflammatory agents), in particular. GLM is known to contain anti-inflammatory omega-3 essential fatty acids, eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA), glycosaminoglycans (including chondroitin sulfate and hyaluronic acid), and other nutrients (vitamins, minerals, amino acids) that may have a beneficial effect on the joint health of animals[11,4]. Beneficial effects of GLM were reported for daily intakes of 10-75 mg per kg[3, 4, 5, 6, 10]. Based on the average daily intake of 42.5 mg/kg, a dose of 128-3400 mg per day would be necessary for dogs in a weight-range of 3-80 kg. Such amounts enable a controlled and convenient medication by tablets with 1-3 servings per day. However, the activity of GLM is considerably reduced by heat treatment[3], which necessitates a gentle processing of GLM. Direct compression of tablets eliminates the requirement of moisture and heat during the process. However, it requires a careful selection of excipients, specifically the binding agent, with regards to flowability, compactibility and avoidance of segregation. Moreover, palatants, in addition to high supplement loads, may further limit the quantity of binder, which may result in poor tablet hardness and friability. A solution for overcoming these challenges is **S**ilicified **M**icro**C**rystalline **C**ellulose (SMCC) instead of MCC. This high functionality binder exhibits outstanding binding properties even at moderate usage levels.

Formulation Objectives

The goal of this study was to evaluate formulations of palatable tablets with a 500 mg GLM content in regards to their compactibility in a simple direct compression process. A high functionality binder and a tailored palatant powder were selected to further simplify the process through the reduction of the number and content of excipients and thus, the maximum possible supplement load. The high functionality binders chosen were two different grades of co-processed **S**ilicified **M**icro**C**rystalline **C**ellulose (**PROSOLV® SMCC 50** and **PROSOLV® SMCC 90**). The two co-processed **S**ilicified **M**icro**C**rystalline **C**ellulose grades were compared with an equivalent physical mixture of microcrystalline cellulose and colloidal silicone dioxide. The quality of the powder mixture was evaluated in terms of flowability and dust formation; the tablets, with regards to friability and tablet hardness.

Selected Excipients

PC-0060 is a hypo-allergenic artificial powdered **meat flavor** for supplemental pet food tablets, made available by Pet flavor Inc., Melbourne, FL, USA. This product is composed of hydrolyzed vegetable non-GMO proteins and contains no ingredients from bovine or other animal origin. It is manufactured following Food and Drug Administration (FDA) regulations within a USDA/FDA inspected facility. The most common usage rates are between 10 % w/w to 15 % w/w.

VIVAPUR® Microcrystalline Cellulose (MCC) is widely used as a robust and inert binder to enhance compactibility. Commercially available grades are distinguished by particle size (15-250 μm), density (0.2-0.5 g/mL), and moisture level. For direct compression, the most commonly used standard grade of MCC, 102, with an average particle size of 130 μm, represents a compromise between flowability, which usually increases with increasing particle size, and binding properties, which, contrarily, increase with decreasing particle size. Powder flow is further adjusted by glidants, like silicon dioxide.

Animal Health

Silicified **M**icro**C**rystalline **C**ellulose **(PROSOLV® SMCC)** is an co-processed composite of MCC and colloidal silicon dioxide. The specific production process leads to a homogeneous distribution of the colloidal silicon dioxide particles. Silicification reduces the cohesiveness of the powder bed, which results in much better powder flowability than traditional MCC grades of the same particle size. Consequently, silicification eliminates the need for dicalcium phosphate for flow regulation or additional silicon dioxide, which is inconvenient to handle. Silicification further increases the surface area by more than 400 %[12], thus improving the outstanding binding properties of microcrystalline cellulose. A wide variety of SMCC (**PROSOLV® SMCC**) grades are available differing in particle size, bulk density, and moisture level. For this study, **PROSOLV® SMCC 90** and **PROSOLV® SMCC 50** were selected.

PROSOLV® SMCC 90 is recommended for formulas in which a balance of flow and compaction is required.

PROSOLV® SMCC 50 is a perfect option for formulas in which optimal compaction and decent flow is required.

Formulation Results

Characterization of Single Ingredients

Flowability of each ingredient was determined using a Flodex apparatus* and was expressed as flowability index. The lower the index, the better the flowability.

*(Hanson Research Corp., USA)

Compactibility of each ingredient was evaluated by compacting each pure ingredient powder into placebo tablets (500 mg, 13 mm diameter, 10 kN compaction force).

The commercially available GLM powder was characterized by good flowability, but poor compactibility. At a compaction force of 10 kN, the pure GLM tablet exhibited a low crushing strength of 35 N. It was not possible to compress the pure meat flavor without lubrication, and care has to be taken in regards to moisture due to high hygroscopicity. However, the powder showed an extraordinary flowability (Tab. 1).

Tablet hardness of **PROSOLV® SMCC 90** and **PROSOLV® SMCC 50** placebo tablets was about 63 % and 92 % higher than the physical mixture of MCC and silicon dioxide, respectively. In terms of flowability, **PROSOLV® SMCC 90** was clearly superior against the physical mixture with a comparable particle size and **PROSOLV® SMCC 50** with a lower particle size (Tab.1).

Evaluation of 50 % GLM Powder Blend and Tablets

Three different formulations with a GLM content of 50 % and differing in type of binder were compared (Tab. 2). Formulation I contained a physical mixture with a common microcrystalline cellulose (**VIVAPUR® 102**) and colloidal silicon dioxide as glidant. In formulations II and III, co-processed **S**ilicified **M**icro**C**rystalline **C**ellulose **PROSOLV® SMCC 90** and **PROSOLV® SMCC 50** were used, respectively, replacing the physical mixture of microcrystalline cellulose and colloidal silicon dioxide of formulation I.

Tab.1: Characterization of Single Ingredients

Ingredient		Brand Name	Manufacturer	Hardness[a] [N]	Flowability Index [mm]	Bulk Density [g/mL]	Average Particle Size [µm]
Supplement	Green-Lipped Mussel extract	–	–	35	16	0.40	–
Physical Blend of Binder and Glidant	98 % MCC + 2 % Colloidal silicon dioxide	**VIVAPUR® 102** +Aerosil 200	JRS Evonik	228	18	0.28 – 0.33	130
High Functionality Binder	Silicified MCC	**PROSOLV® SMCC 90**	JRS	372	12	0.25 – 0.37	125
High Funtionality Binder	Silicified MCC	**PROSOLV® SMCC 50**	JRS	437	22	0.25 – 0.37	65
Palatant	Meat Flavor	PC-0060	Pet Flavor Inc.	n.d.	9	–	–

[a] 500 mg tablets (13 mm) compressed at 10 kN

Tab. 2: Formulations of 500 mg GLM Tablets (1 g total weight).

Ingredient		Formulation 1 – Physical Mixture	Formulation 2	Formulation 3
Supplement	Green-Lipped Mussel extract	50.0	50.0	50.0
Binder	MCC (**VIVAPUR® 102**)	33.3	–	–
High Functionality Binder	Silicified MCC (**PROSOLV® SMCC 90**)	–	34.0	–
High Functionality Binder	Silicified MCC (**PROSOLV® SMCC 50**)	–	–	34.0
Palatant	Meat Flavor PC-0060 (Pet Flavor Inc.)	15.0	15.0	15.0
Lubricant	Magnesium Stearate	1.0	1.0	1.0
Glidant	Colloidal Silicon Dioxide (Aerosil A 200)	0.68	–	–

The flow characteristic of the binder crucially dominated the flowability of the blend, although the content of binder was moderate (34 %). Formulation 2, with **PROSOLV® SMCC 90,** was, with regards to flowability, clearly superior over the physical mixture and fine grade of **S**ilicified **M**icro**C**rystalline **C**ellulose (**PROSOLV® SMCC 50**) (Tab. 3). Segregation was not observed during processing which was favored by the equal density of GLM powder and binder (Tab. 1). The use of **SMCC** markedly reduced dust formation of the blend, eliminating the need for additional colloidal silicon dioxide. Consequently, excipients could be reduced to palatant, lubricant and **SMCC**.

All tablets revealed an acceptable tablet hardness of >120 N at a compaction force of 20 kN (Fig. 1).

PROSOLV® SMCC 90 and **PROSOLV® SMCC 50** were more compactible than the formulation with the physical mixture, providing 16 % and 29 % harder tablets and less friability at the same compaction force (Tab. 3, Fig. 1).

PROSOLV® SMCC accommodated the poorly compactible GLM and delivered superior compactibility for a high supplement load of 50 % GLM. Flowability and tablet hardness may be further balanced by a custom mixture of **PROSOLV® SMCC 90** and **PROSOLV® SMCC 50**.

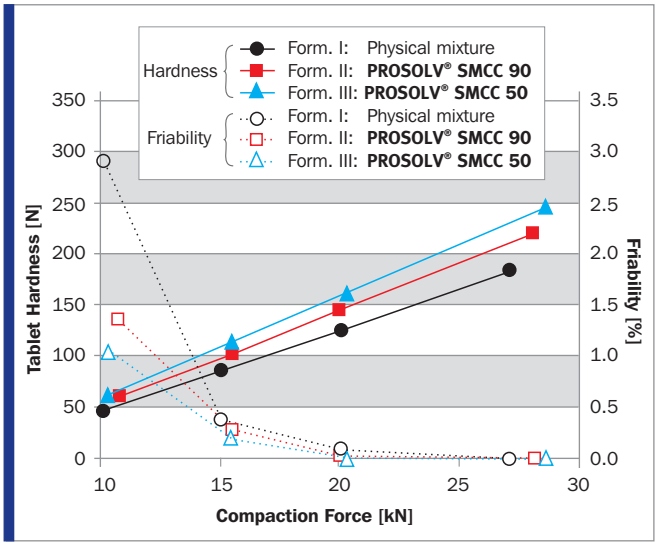

Fig. 1: Tablet Hardness and Friability Versus Compaction Force of 1 g Tablets with 50 % GLM Content Differing in the Binder used. Formulations are given in Tab. 2.

Tab. 3 Characteristics of the 50 % GLM Powder Blends and Tablets. Formulations are shown in Tab. 2.

Ingredient	Powder Blend		Tablet[a]	
	Flowability Index [mm]	Dust Number[b]	Hardness at 20 kN	Friability [%]
Formulation 1 (Physical Mixture)	**18**	**71**	**126**	0.10
Formulation 2 (**PROSOLV® SMCC 90**)	**16**	**24**	**146**	0.03
Formulation 3 (**PROSOLV® SMCC 50**)	**22**	**43**	**162**	0.00

[a] 1 g Tablets (16 mm) Compressed at 15 kN; [b] Measured with a Dust View System, Palas GmbH, Germany

Animal Health

The use of pet flavor required a higher level of lubrication (Tab. 1). However, lubricants like magnesium stearate are well known to reduce the interparticle bonding, especially of plastically deforming compounds. The negative effect of magnesium stearate on the tensile strength of microcrystalline cellulose is deemed to be less pronounced with SMCC than with pure MCC[12, 13]. Odeniji (2008)[14] even reported some inherent lubricating qualities of SMCC which allow an enhanced lubrication efficiency.

Conclusion

Both, **S**ilicified **M**icro**C**rystalline **C**ellulose (**PROSOLV® SMCC**) and a physical mixture comprising microcrystalline cellulose and colloidal silicone dioxide enabled direct compression of green-lipped mussel tablets and counterbalanced the poor compactibility of GLM powder. However, the high functionality binder **PROSOLV® SMCC** provided tremendous advantages against a physical mixture:

- Increased tablet hardness by 16 - 30 %
- Reduced friability by more than 30 %
- Decreased compaction force by 25 % to generate same tablet hardness, enabling a reduction of energy costs and improved tooling life
- Improved workers‘ safety and handling due to dust reduction
- Eliminated the need for separate addition of colloidal silicone dioxide
- **PROSOLV® SMCC 90** proved to be the most suitable grade with 33 % better flowability and 70 % less dust formation compared to a simple physical mixture.

In conclusion, **S**ilicified **M**icro**C**rystalline **C**ellulose is clearly preferable for direct compression, if high supplement and palatant load restrict the quantity of binder.

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