Animal Health

Compression of Probiotics for Companion Animals

Introduction

Probiotics, defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host," are popular for their digestive benefits in the human health science industry. Numerous *in vitro* studies indicate the promising potential of probiotics for humans, as well as animals. Although *in vivo* studies in companion animals have been more difficult to prove [1], several publications illustrate the intestinal health benefits of probiotics for animals, especially dogs (Tab. 1). These *in vivo* studies focused particularly on Enterococcus and/or Lactobacillus for cats and dogs and Saccharomyces for horses.

Animal	Strain	Indication
Cat [2]	*E. faecium*	Diarrhea prevention
Dog [3]	*E. faecium* *B. coagulans* *L. acidophilus*	Diarrhea prevention
Dog [4]	*L. acidophilus* *L. johnsonii*	Diarrhea prevention
Dog [5]	*L. acidophilus*	Improved feces consistency
Dog [6] (puppies)	*E. faecium*	Immunostumilation
Dog [7] (puppies)	*L. rhamnosus*	Prevention of allergenic dermatitis
Dog [8]	*E. faecium*	Blood cholesterol regulation
Dog [9]	*L. farciminis* *P. acidilactici* *B. subtilis* *B. licheniformis* *L. acidophilus*	Reduced convalescence time in acute gastroenteritis
Dog [10]	*L. sakei*	Treatment of atopic dermatitis
Dog [11]	*L. plantarum* *L. bulgaricus* *L. casei* *L. acidophilus* *B. breve* *B. longum* *B. infantis* *S. thermophilus*	Treatment of inflammatory bowel diseases
Horse [12] (foals)	*L. salivarius* *L. reuteri* *L. crispatus* *L. johnsonii* *L. equi*	Diarrhea prevention Growth enhancement
Horse [13]	*L. casei* *L. acidophilus* *E. faecium*	Reduced incidence of Salmonella shedding
Horse [14]	*S. boulardii*	Decreased duration and severity of acute enterocolitis

Tab. 1: Overview of studies that indicated a beneficial effect of probiotics on the health of companion animals.

Normally, probiotics are filled into capsules; however, capsules are expensive to produce and usually have a high content of gelatin, putting the probiotic stability at risk. Additionally, when administering probiotics to animals, it is important to note that capsules have a neutral flavor, giving animals no positive incentive to ingest them. Because dogs and cats are prone to chewing capsules, the filling has the potential to be released from the capsule, necessitating a careful control on its palatability. An alternative to capsules, mixing dry probiotic powder into feed via sachets, requires an immediate and complete ingestion of the food to avoid irreversible damage to the microbial cells by exposure to moisture and oxygen. These factors make it worth considering direct compression of probiotics into tablets. It is important to note that the compression of live microorganisms can lead to their destruction due to heat and pressure sensitivity. This destruction can be avoided, however, by using high functionality excipients, such as silicified microcrystalline cellulose.

Formulation Objectives

Probiotics are very sensitive to pressure and their survival rate depends on compaction force. Most preferred excipients for direct compression of probiotics must be able to deliver both robust tablet hardness and less friability under already low compaction forces. A less abrasive surface of the binding particles and a less condensed tablet matrix is also beneficial. The goal of this study was to optimize the balance between tablet hardness and probiotic survival rate in the direct compression tableting process.

Formulation Results

Selected Excipients for Probiotic Tablets

Probiotic tablets were produced by direct compression (200 mg, 13 mm punch). The directly compressible excipients, silicified microcrystalline cellulose (**PROSOLV® SMCC** 90) and dextrates (**EMDEX®**), were selected as the binders for the formulation development.

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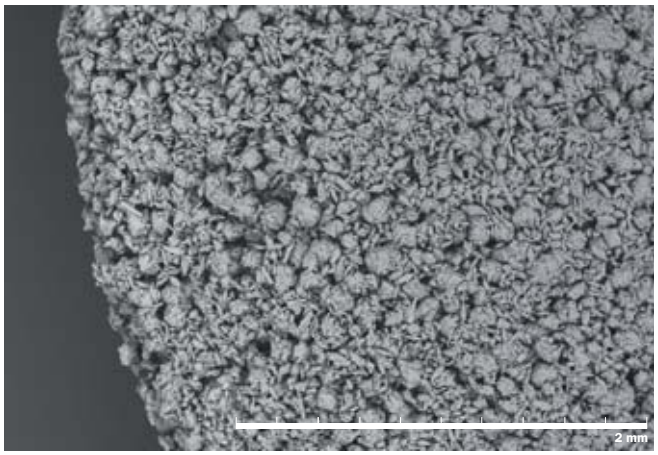
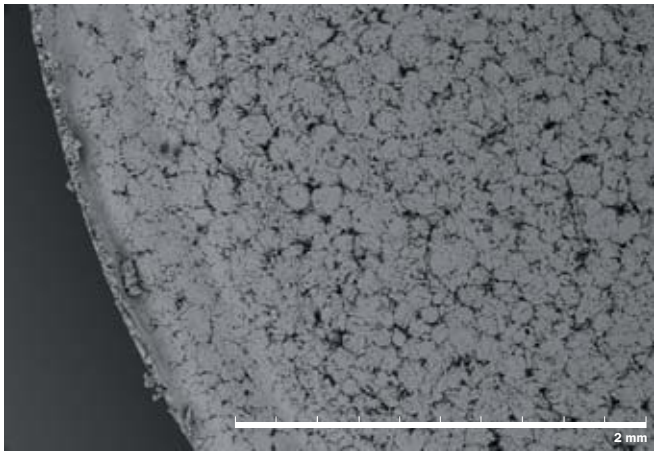
Silicified Microcrystalline Cellulose
Silicified microcrystalline cellulose is a high functionality excipient composed of a special co-processed combination of microcrystalline cellulose and colloidal silicone dioxide. JRS Pharma's **PROSOLV® SMCC** exhibits a five-fold increased specific surface area compared to microcrystalline cellulose and imparts superior flow and compaction capabilities.

What makes silicified microcrystalline cellulose the perfect binder for probiotic tablets ?
Silicified microcrystalline cellulose provides sufficient tablet hardness at already low compression forces. The lower the compression force, the less dense the tablet matrix. The influence of the compression force on the porosity of the tablet can be seen in Pictures 1 and 2, which show the porosity of a 400 mg placebo tablet made with **PROSOLV® SMCC** 90, compressed with forces of 1.5 kN, and 9.5 kN, respectively.
PROSOLV® SMCC 90 compressed with 9.5 kN resulted in a placebo tablet with a high crushing strength of 200 N, which is sufficient for tablet coating and packaging. Despite its high crushing strength, this tablet exhibited still cavities that protect the strains from compression stress. In comparison to a placebo tablet composed of microcrystalline cellulose type 102 or spray dried lactose, 25 %, and even 200 %, higher compression forces would be required for the same tablet hardness, respectively, which would decrease the survival rate dramatically. For highly moisture sensitive probiotic strains **PROSOLV® SMCC** 90 LM with a moisture content (<3 %) is recommended.



Pic. 1: SEM image of a tablet surface, compressed with **PROSOLV® SMCC** 90, 13 mm punch, 400 mg, compaction force 1.5 kN, crushing strength 20 N.



Pic. 2: SEM image of a tablet surface, compressed with **PROSOLV® SMCC** 90, 13 mm punch, 400 mg, compaction force 9.5 kN, crushing strength 200 N.

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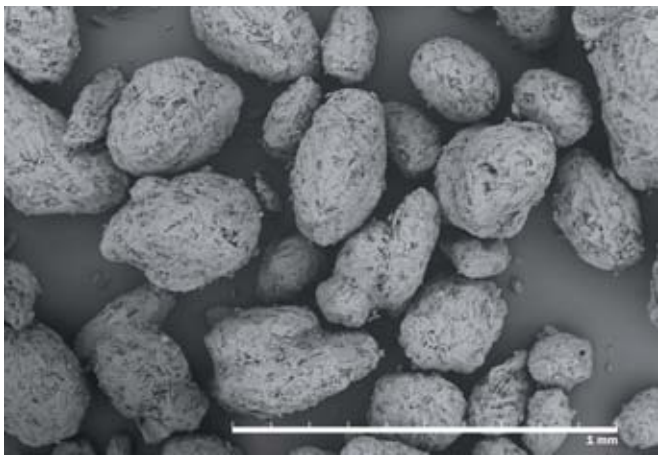
Dextrates

Dextrates are a unique combination of glucose monohydrate and different polysaccharides derived from starch. This water soluble tablet binder is often used for veterinary tablets due to its palatable sweet taste. The spherical shape of JRS Pharma's dextrates product, **EMDEX®**, ensures excellent flowability (Pic. 3).



Pic. 3: SEM picture of JRS Pharma's **EMDEX®** dextrates.

Ingredients	Dosage [mg]
Formulation 1	
Lactobacillus bulgaricus	20
PROSOLV® SMCC 90 (Silicified Microcrystalline Cellulose)	178
PRUV® (Sodium Stearyl Fumarate)	2
Formulation 2	
Lactobacillus bulgaricus	20
PROSOLV® SMCC 90 (Silicified Microcrystalline Cellulose)	89
EMDEX® (Dextrates)	89
PRUV® (Sodium Stearyl Fumarate)	2

Tab. 2: Formulations of a *L. bulgaricus* probiotic tablets (200 mg). Compaction force 8 kN.

	Crushing strength [N]	Survival rate [%]	
		24 h	6 months
Formulation 1	120	84 %	72 %
Formulation 2	100	93 %	88 %

Tab. 3: Crushing strength and survival rate of tablets containing *L. bulgaricus*

Improving Probiotic Survival Rate

The survival rates of probiotics after compression were tested after 24 hours and 6 months. *Lactobacillus bulgaricus* was used as a model strain for the probiotic tablets. The survival rate of probiotics compressed with silicified microcrystalline cellulose (Formulation 1, Tab. 2) was 84 % after 24 hours and was significantly higher than in tablets compressed under the same conditions with microcrystalline cellulose grade 102 (survival rate 60 %). The survival rate of lactobacillus can be improved even more by adding dextrates into the formulation (Formulation 2, Tab. 2). A 1 to 1 ratio of silicified microcrystalline cellulose to dextrates resulted in the best outcome of a survival rate of 93 % after 24 hours.

Conclusion

A formulation with a 1 to 1 ratio of the high functionality binder, silicified microcrystalline cellulose, and dextrates resulted in a survival rate of >90 % for *Lactobacillus bulgaricus* probiotics in a direct compression tablet. It also resulted in sufficient tablet hardness (100 N at 8 kN compaction force). Both binders are permitted for use in pharmaceuticals, nutraceuticals, and animal feed products. Furthermore, the sweet taste of dextrates increases the palatability of the tablet.

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