TECHNICAL INFORMATION

Direct Compression of Probiotic Tablets with **PROSOLV® EASYtab Nutra**

Abstract

Although probiotics are mostly administered in the form of capsules, there are some advantages of tablets in terms of production effort, cost efficiency and stability of the probiotic bacteria. As probiotics are sensitive to high pressure and temperature, it is essential to select appropriate excipients for direct compression to ensure sufficient viability of the bacteria cells during production and storage. The aim of this study was to investigate the performance of the high functional excipient **PROSOLV® EASYtab Nutra** for direct compression of probiotic tablets. As **PROSOLV® EASYtab Nutra** is an all-in-one composite, only one mixing step is required before the compaction which makes the tableting process easy and comfortable. In order to evaluate the performance of **PROSOLV® EASYtab Nutra**, the survival rate of the bacteria and functional tablet properties were determined and compared to a lactose-based formulation. The study showed that **PROSOLV® EASYtab Nutra** is considerably better suited for direct compression of probiotic tablets because of the remarkable survival rate of 91.5 % of the bacteria cells as well as the quick disintegration within 18 seconds, which is almost 10 times faster compared to the lactose formulation. Furthermore **PROSOLV® EASYtab Nutra** is characterized by excellent compactibility and an extremely low friability.

Introduction

There is an increasing demand for probiotic products worldwide and this trend is expected to continue in the following years. The global probiotic market was amounted to more than 34 billion USD in 2015 and an annual growth rate of 8 % from 2015 to 2020 was forecasted. The major applications are probiotic dietary supplements, food and beverages and animal feed probiotics.[1,2,3,4]

Probiotics were redefined as “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host” by a FAO/WHO expert group in 2001. Probiotics provide a wide range of health benefits, including positive effects on immunological, digestive, and respiratory functions.[5] The most common microorganisms used in probiotic formulations are bacteria belonging to the genera of *Lactobacillus* and *Bifidobacterium*, but also yeasts such as *Saccharomyces boulardii* can be used as probiotics.[6,7]

As only living bacteria can have beneficial effects, it has to be ensured that the probiotic products contain viable bacteria in large enough numbers.[5] The typically used delivery systems in the nutraceutical field are tablets and capsules, which provide increased storage stability compared to liquid preparations due to their low moisture content, as well as their easy and convenient administration.[6] Additionally, tablets are less-expensive, easy to manufacture and allow the highest dosage due to the strong compaction.[8] However, the high compression forces and temperature increase during tablet production can destroy bacteria, leading to a reduced effectiveness of the probiotic products.[6,9] In order to overcome these challenges, particular excipients are required, which are suitable for direct compression of probiotic tablets.

Study Design

The aim of this study was to develop a direct compression formulation for probiotic tablets with a viable cell count of at least 10^9 cfu per dose unit. As a model probiotic we selected a strain of *Bifidobacteria*, which is widely used in dietary supplements due to its positive impact on intestinal health and immune system.
In order to reduce the mechanical stress for the sensitive probiotics and thus to improve the survival rate during manufacture, we chose **PROSOLV® EASYtab Nutra**, which is a high functional excipient especially for nutraceutical applications.
The performance of **PROSOLV® EASYtab Nutra** in probiotic tablets was compared to standard spray-dried lactose, which is also suitable for direct compression. Therefore, tablets with a crushing strength of 80 N were pressed and evaluated in terms of viability of the *Bifidobacteria*. Further tested parameters were the compactibility and water activity of the powder mixture, as well as functional tablet characteristics, such as friability and disintegration.

Ingredients and Compactibility

Selected Ingredients

The probiotic *Bifidobacterium* strain BB-12® (*Bifidobacterium animalis* subsp. *lactis*) was provided by Chr. Hansen (Hoersholm, Denmark). The BB-12® bacteria cells were preserved by lyophilization, resulting in reduced water activity and therefore improved stability and viability of the bacteria.[6] Numerous clinical studies and scientific publications have proven the beneficial effects of BB-12® on intestinal health and immune system, including a reduced risk of an upset stomach, improvement of the immune response, reduced respiratory tract infections, support of bowel function and alleviation of skin irritations.[10]

PROSOLV® EASYtab Nutra is an all-in-one excipient, specifically developed for the nutraceutical industry. It is composed of four components: microcrystalline cellulose as a binder, colloidal silicon dioxide as a glidant, crosscarmellose as a disintegrant, and saturated vegetable oil as a lubricant. The special co-processing leads to a homogeneous distribution of the four components and synergistic effects in terms of functional performance. Because of the excellent compaction properties of **PROSOLV® EASYtab Nutra** it is possible to manufacture mechanically robust tablets at low compression forces resulting in reduced mechanical stress for sensitive ingredients such as probiotic bacteria. As **PROSOLV® EASYtab Nutra** is a ready-to-use composite, only one mixing step with the active is required before the compression process leading to a convenient and cost-efficient tableting process.

Lactose is widely used as a filler and diluent in solid dosage forms such as tablets and capsules[11]. For this study, we used spray-dried lactose, which is characterized by its exceptional compactibility compared to other lactose grades. Therefore, it is particularly suitable for direct compression applications.

Results and Discussion

Correlation between compaction force and viability

As outlined before, probiotics are sensitive to pressure, to which the microorganisms are exposed during tablet manufacture. High compaction forces may damage the bacteria cells and therefore decrease their viability drastically depending on the robustness of the strain. Fig. 1 shows the correlation between the compaction force and the viability of the probiotic strain BB-12®. Already at a moderate compression force of 10 kN only 63 % of the probiotic survived the tableting process. In order to maintain the viability of the probiotics at the best possible rate, an excipient with excellent compactibility is required, which enables sufficient tablet hardness at low compression forces.

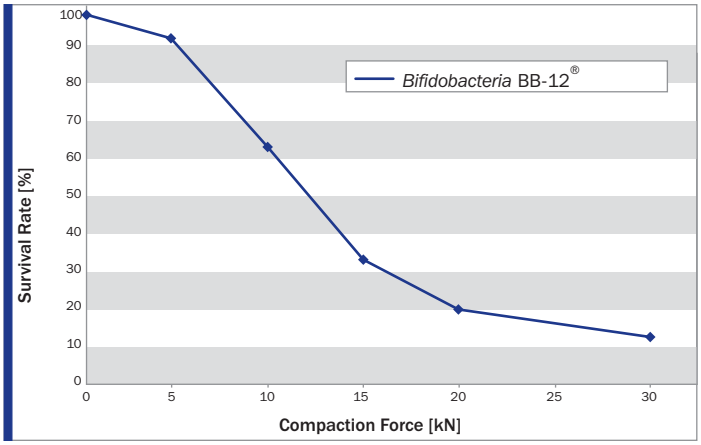


Fig. 1 Correlation between Compression Force and Viability of Bacteria Cells in Directly Compressed Probiotic Tablets Containing 20 % of the *Bifidobacteria* Strain BB-12®.

Compactibility of Single Ingredients

The compactibility of each ingredient was evaluated by manufacturing placebo tablets at different compaction forces (500 mg, 13 mm). The BB-12® itself was characterized by good flowability, but poor compactibility. At a compaction force of 13 kN, the pure probiotic tablets showed insufficient crushing strength of 35 N. Furthermore, the BB-12® powder is slightly sticky and therefore not suitable for direct compression in its pure form.

A comparison of the selected excipients showed that **PROSOLV® EASYtab Nutra** provides considerably better compactibility than the spray-dried lactose (Fig. 2). In order to produce tablets with a crushing strength of 80 N, a compaction force of about 4 kN was necessary in case of **PROSOLV® EASYtab Nutra** . However, in the case of spray-dried lactose, a compaction force of about 19 kN was required, which is nearly fivefold the mechanical stress compared to the **PROSOLV® EASYtab Nutra** formulation. This indicates that probiotic tablets, produced with **PROSOLV® EASYtab Nutra**, may provide a higher survival rate of the bacteria cells than lactose-based tablets with the same crushing strength. The results of the study, which are shown below, confirm this hypothesis.

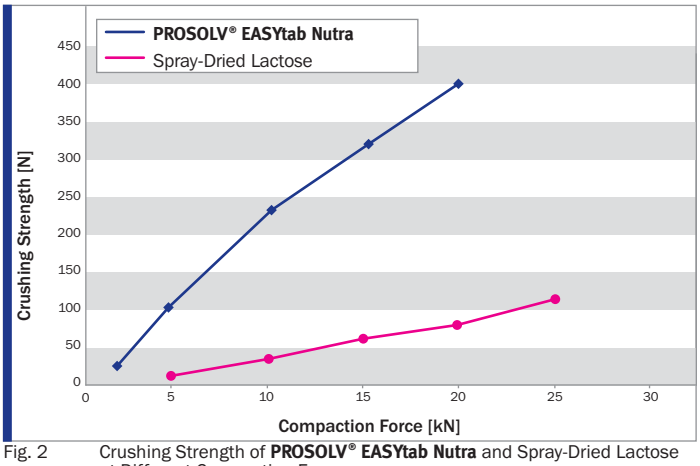


Fig. 2 Crushing Strength of **PROSOLV® EASYtab Nutra** and Spray-Dried Lactose at Different Compaction Forces.

Evaluation of Probiotic Powder Mixture and Tablets

Two different formulations with 20 % of probiotic powder BB-12® were compacted into 500 mg tablets, corresponding to a theoretical bacterial count of about 10^{10} cfu per tablet. Formulation 1 contained spray-dried lactose as a binder, **VIVASOL® GF LM** (crosscarmellose, food grade, E 468) as a disintegrant, and magnesium stearate as a lubricant (Tab. 1). In formulation 2 the high functional excipient **PROSOLV® EASYtab Nutra** was used, which makes the use of further excipients unnecessary as **PROSOLV® EASYtab Nutra** itself includes a disintegrant and a lubricant. The water activity (a_w) of both formulations showed appropriate values of 0.26 (**PROSOLV® EASYtab Nutra**) and 0.13 (spray-dried lactose) (Tab. 2). At higher a_w values, the probiotics may be damaged due to undesired enzymatic processes; a too low a_w below 0.1 may also cause irreversible damage to the bacteria cells.[12]

Ingredient		Formulation 1	Formulation 2
Probio-Tec® BB-12®	Probiotic strain	20 %	20 %
Spray-Dried Lactose	Filler-binder	77 %	-
PROSOLV® EASYtab Nutra	High functional binder	-	80 %
VIVASOL® GF LM (Crosscarmellose sodium)	Disintegrant	2 %	-
Ligamed MF-2-V (Magnesium stearate)	Lubricant	1 %	-

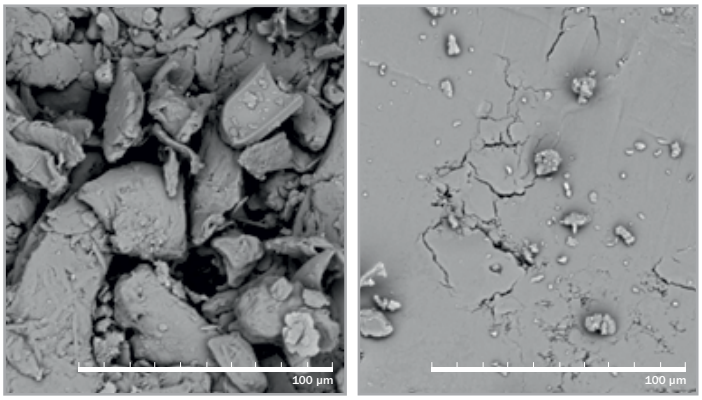
Tab. 1 Formulations of Probiotic Tablets (500 mg Total Weight)

The **PROSOLV® EASYtab Nutra** formulation resulted in a considerably higher survival rate of 91.5 % compared to the lactose formulation, which had a viable cell count of 58.4 % after compaction (Tab. 2). This may be caused by the much better compactibility of the **PROSOLV® EASYtab Nutra** formulation. In order to achieve a crushing strength of 80 N, a compression force of 9.8 kN was required in case of the **PROSOLV® EASYtab Nutra** formulation. Because of the lower compression force, the **PROSOLV® EASYtab Nutra** tablets had a more porous structure, leading to sufficient space for the microorganisms to survive (Pic. 1, left). In contrast, in the case of the lactose formulation, a compression force of 30.5 kN was necessary to press tablets with a crushing strength of 80 N, resulting in a very dense and compact structure without much space for the probiotic bacteria (Pic. 1, right). An additional advantage of the porous structure is the much quicker tablet disintegration. The **PROSOLV® EASYtab Nutra** tablets disintegrate within 18 seconds and thus, almost 10 times faster than the lactose-based tablets. Furthermore, the **PROSOLV® EASYtab Nutra** tablets had a lower friability compared to the lactose tablets demonstrating the high robustness of **PROSOLV® EASYtab Nutra** (Tab. 2).

Parameter	Formulation 1 (Spray-dried Lactose)	Formulation 2 (**PROSOLV® EASYtab Nutra**)
Survival rate [%]	58.4	91.5
Compression force*[kN]	30.5	9.8
Disintegration time [s]	172	18
Friability [%]	0.31	0.25
Water activity [-]	0.13	0.26

Tab. 2 Characteristics of the Probiotic Powder Blends and Tablets

* Required for Tablets with 80 N Crushing Strength



Pic. 1 Tablet Surface of Probiotic Tablets with a Crushing Strength of 80 N Containing **PROSOLV® EASYtab Nutra** (left) and Spray-dried Lactose (right), Respectively.

Conclusion

The high functional excipient **PROSOLV® EASYtab Nutra** is ideally suited for the manufacture of probiotic tablets containing the bacteria strain BB-12® because of its superiority over the lactose formulation in terms of survival rate of the probiotics, compactibility and further tablet characteristics, such as disintegration time and friability. In particular, the **PROSOLV® EASYtab Nutra** tablets are characterized by:

- Exceptionally high survival rate of over 90 %
- Excellent compactibility, resulting in good tablet hardness at moderate compression forces
- Fast disintegration
- Low friability
- Appropriate water activity for usage in probiotic applications

Further advantages are the simple processing of **PROSOLV® EASYtab Nutra** with only one mixing step before the tablet compaction and the reduction of energy costs and tooling abrasion, as only moderate compression forces are necessary in order to form mechanically stable tablets.
In conclusion, **PROSOLV® EASYtab Nutra** is extremely well suited for direct compression of probiotic tablets because of the very high survival rate of bacteria cells during compaction and the excellent functional tablet parameters.

Regulatory Information

PROSOLV® EASYtab Nutra in its standard form complies with food regulations in most countries, including the USA and EU. For countries with deviating regulations, special grades of **PROSOLV® EASYtab Nutra** are available on request.

To learn more, visit www.jrspharma.com

Disclaimer:
The information provided in this brochure is based on thorough research and is believed to be completely reliable. Application suggestions are given to assist our customers, but are for guidance only. Circumstances in which our material is used vary and are beyond our control. Therefore, we cannot assume any responsibility for risks or liabilities, which may result from the use of this technical advice.

Reference:

1 Kumar, A. (2016) The Probiotic Market: Ingredients, Supplements, Foods. Market Research Reports, BBC Research.
2 Global Marek Insights Inc. (2016) Probiotics Market Size to Exceed USD 64 Billion by 2023. PRNewswire. Available at: http://www.prnewswire.com/news-releases/probiotics-market-size-to-exceed-usd-64-billion-by-2023-global-market-insights-inc-578769201.html
3 Grebow, J. (2017) Ingredient Trends to Watch for Food, Drinks, and Dietary Supplements: Probiotics. Nutritional Outlook. Vol. 20 No. 1.
4 Grand View Research (2016) Probiotics Market Analysis.
5 FAO/WHO (2001) Health and Nutritional Properties of probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. Report of a Joint FAO/WHO Expert Consultation.
6 Govender, M. et al (2014) A Review of the Advancements in Probiotic Delivery: Conventional vs. Non-conventional Formulations for Intestinal Flora Supplementation. AAPS PharmSciTech. Vol. 15, No. 1, pp. 29-43.
7 National Center for Complementary and Integrative Health (2017) Probiotics: In Depth. Available at: https://nccih.nih.gov/health/probiotics/introduction.htm
8 AllStarHealth (2008) Sorting Out Supplements: Tablets vs. Capsules vs. Liquids vs. Powders vs. Chewables. Available at: http://www.allstarhealth.com/blog/products-and-ingredients/tablets-capsules-liquids-powders-chewables/
9 Chan, E.S. & Zhang, Z. (2002) Encapsulation of probiotic bacteria Lactobacillus acidophilus by direct compression. Transl Chem. Vol. 80, Part C, pp. 78-82.
10 Chr. Hansen Holding A/S (2017) Facts about Bifidobacterium (BB-12®). Available at: http://www.chrhansen.com/en/probiotic-supplements-and-infant-formula/cards/product-cards/bifidobacterium-animalis-subsp-lactis-bb-12
11 Rowe, R.C., Sheskey, P.J. & Quinn, M.E. (2009) Handbook of Pharmaceutical Excipients. Sixth edition. Pharmaceutical Press.
12 Novasina (2017) Der Einfluss der Wasseraktivität bei der Entwicklung von Probiotika. Available at: http://www.easyfairs.com/uploads/tx_ef/Pressetext_aw_Probiotika_0805.pdf

www.jrspharma.com
JRS PHARMA GMBH & CO. KG
Business Unit Excipients
73494 Rosenberg (Germany)
Phone: +49 7967 152-312
ExcipientsService@JRSPharma.de

PH004_V1_GB_2.01709KE