TECHNICAL INFORMATION

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

Abstract

Due to the high prevalence of lactose intolerance, lactase supplements increasingly gain popularity as they are known to improve the lactose digestion and reduce gastrointestinal symptoms. The aim of this study was to develop lactase tablets by a simple and robust direct compression process, which enables tableting of the moisture sensitive enzymes without the addition of water. Additionally, this study aimed to simplify the formulation by using a two-component blend composed of API and only one ready-to-use excipient, **PROSOLV® EASYtab Nutra CM**. The pure lactase powder was shown to be unsuitable for direct compression leading to tablets with insufficient tensile strength and high friability. Furthermore, the compression of pure lactase powder led to a significant loss of lactase activity by 20 – 40 %, depending on the compaction force. The addition of only 30 % of the high functionality excipient **PROSOLV® EASYtab Nutra CM** dramatically improved the tensile strength by almost tenfold. Furthermore, **PROSOLV® EASYtab Nutra CM** had positive effects on disintegration leading to a reduction of disintegration time of more than 50 %. Due to the excellent compactability of **PROSOLV® EASYtab Nutra CM**, only a low compaction pressure of 5.75 kN was required to produce mechanically robust tablets which showed only 2.8 % loss of enzyme activity during tableting. Additionally, a comparison with marketed lactase tablets showed once again that **PROSOLV® EASYtab Nutra CM** is perfectly suited to produce lactase tablets with comparable or even better functional tablet properties. In contrast to the complex formulation of the marketed lactase tablets, the number of components in the **PROSOLV® EASYtab** based formulation could be reduced considerably to only two components, namely lactase powder and **PROSOLV® EASYtab Nutra CM.**

Introduction

Approximately 75 % of the global population is affected by lactose malabsorption or lactose intolerance which is the inability to digest the milk sugar lactose caused by inadequate amount of the enzyme lactase.[1] Lactose is a disaccharide composed of glucose and galactose that is found in milk and other dairy products.
The enzyme lactase, which is located in the brush border of the small intestine, breaks lactose into its monosaccharides in order to enable the transport across the cell membrane (Figure 1). In the case of lactase deficiency, unabsorbed lactose passes into the colon where it is fermented by bacteria. Thereby, gas and acids are produced leading to gastrointestinal symptoms, such as abdominal pain, bloating, diarrhea, gas and nausea.[2] In addition to dietary management, the administration of exogenous lactase in the form of tablets or capsules can improve the lactose digestion and tolerance, as shown in numerous studies.[3,4,5]

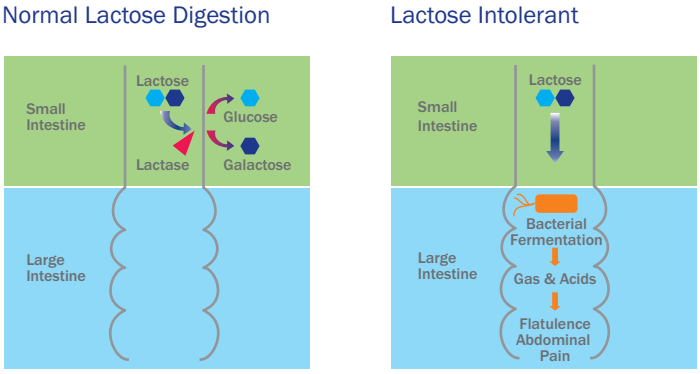

Fig. 1 Schematic Illustration of Lactose Digestion in Persons Suffering from Lactose Intolerance Compared to Usual Lactose Digestion.

Study Design

The aim of this study was the development of lactase tablets that can be produced by direct compression. In order to avoid stability problems of the enzyme lactose, caused by high temperature and moisture, direct compression is the most suitable tableting process. The performance of pure lactase powder in terms of lactase activity, ejection force during compression as well as functional tablet characteristics was investigated and compared to a blend of lactase powder and 30 % of the high functionality excipient **PROSOLV® EASYtab Nutra CM**. Furthermore, the performance of the **PROSOLV® EASYtab** based formulation was compared to marketed lactase tablets.

Used Ingredients

In this study, a yellow to slightly brownish lactase powder with a lactase activity of 85,000 FCC per gram was used as active ingredient (Figure 2). At optimal conditions, a lactase activity of 1000 FCC enables the digestion of up to 5 g lactose. At *in vivo* conditions, usually higher quantities are required. The containing lactase is of fungal origin and is produced by the fungus *Aspergillus oryzae*.
PROSOLV® EASYtab Nutra is a co-processed all-in-one excipient, which was specifically developed for nutraceutical applications. It is composed of microcrystalline cellulose as a binder, colloidal silicon dioxide as a glidant, as well as a disintegrant and a lubricant and thereby covers all necessary tableting functionalities. In the current study **PROSOLV® EASYtab Nutra CM** was used which includes croscarmellose sodium as a disintegrant and magnesium stearate as a lubricant. The special co-processing ensures a homogeneous distribution of the single ingredients and results in synergistical effect in terms of functional performance.

Due to the excellent compaction properties of **PROSOLV® EASYtab Nutra** only low compression forces are required to manufacture mechanically robust tablets; leading to less mechanical stress for sensitive materials such as enzymes or living microorganisms. As **PROSOLV® EASYtab Nutra** is a ready-to-use composite, only one mixing step with the active is required before the compression process, making the tableting process convenient and cost-efficient. In order to fulfill the regulatory requirements in various countries, different grades of **PROSOLV® EASYtab Nutra** with varying disintegrants and lubricants are available, which all show equivalent powder and tableting properties. Details about the different grades can be found in the JRS brochure about **PROSOLV® EASYtab**.[6]

Fig. 2 Pure Lactase Powder Characterized by Good Flowability, but Poor Compactibility, and **PROSOLV® EASYtab** Based Lactase Tablets.

Tabletability of Pure Lactase Powder

The compaction of pure lactase powder causes high ejection forces during the tableting process leading to defects of the tablets such as cracking of the tablet surface. Therefore, the lactase powder was lubricated with 1 % of magnesium stearate and compacted at compression forces between 5 and 30 kN. As shown in Figure 3, the compaction of pure lactase powder resulted in tablets with an insufficient maximum tensile strength of 1.1 MPa (equivalent to 45 N tablet hardness). Despite the high compaction pressure the tablets showed a high friability between 0.3 and 5.0 %, depending on the compaction force used. At low compression pressure, below 7 kN, the tablet hardness was not even measurable and the friability test resulted in broken tablets.
Furthermore, increasing compaction force caused a reduction of lactase activity in the final tablets (Figure 3). Depending on the compaction force, the lactase activity decreased by 22 % at 10 kN up to 40 % at 30 kN compared to the initial lactase activity of the powder blend before the tableting process.

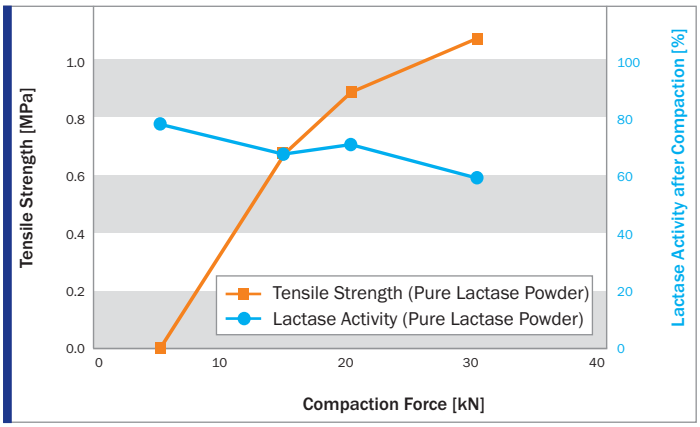

Fig. 3 Effect of Compaction Force on Tensile Strength and Lactase Activity of Tablets of Pure Lactase Powder Containing 1 % Magnesium Stearate as a Lubricant.

Tableting Performance of **PROSOLV® EASYtab** in Lactase Tablets

In order to improve the tabletability, the lactase powder was mixed with 30 % of the high functionality excipient **PROSOLV® EASYtab Nutra CM**, compacted into tablets and compared with the tablets of pure lactase powder (Table 1, Figure 2). The addition of **PROSOLV® EASYtab Nutra CM** led to a significantly increased tensile strength of up to 6 MPa at a compaction force of 15 kN, which is almost 10 times the tensile strength of the pure lactase powder (Figure 4). Furthermore, **PROSOLV® EASYtab Nutra CM** had a positive effect on the disintegration time of the lactase tablets (Figure 5). Despite the weak tablet hardness, the pure lactase tablets had a disintegration time of up to 34 min at the highest tensile strength of 1.1 MPa. By adding 30 % of **PROSOLV® EASYtab Nutra CM** the disintegration time could be considerably reduced to less than 15 min at the same tensile strength.

Ingredient		Pure Lactase Powder (%)	EASYtab® Formulation (%)
Lactase Powder (85,000 FCC)	Active ingredient	99.0	70.0
PROSOLV® EASYtab Nutra CM	All-in-one excipient	–	30.0
Magnesium Stearate	Lubricant	1.0	–

Tab. 1 Formulation of Lactase Tablets (100 mg Total Weight).

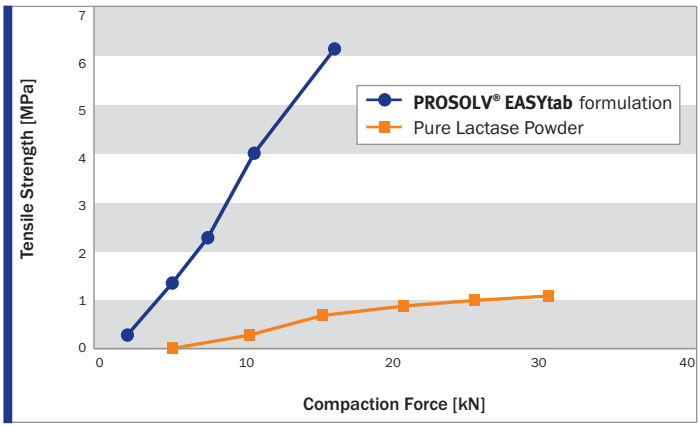

Fig. 4 Comparison of Tensile Strength of Lactase Tablets (200 mg) Composed of either Pure Lactase Powder Containing 1 % Magnesium Stearate as Lubricant or a Blend of Lactase Powder with 30 % of **PROSOLV® EASYtab Nutra CM**.

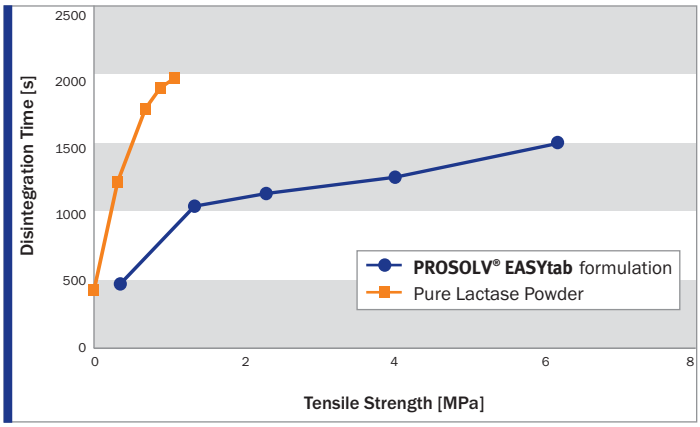

Fig. 5 Comparison of Disintegration Time of Lactase Tablets (200 mg) Composed of either Pure Lactase Powder Containing 1 % Magnesium Stearate as Lubricant or a Blend of Lactase Powder with 30 % of **PROSOLV® EASYtab Nutra CM**.

In addition, **PROSOLV® EASYtab Nutra CM** significantly improved the robustness of the tablets. Already at a low compaction force of 5 kN, the friability dropped to an excellent value of 0.8 %. Furthermore, in case of the **PROSOLV® EASYtab Nutra CM**, there is no need for additional lubrication.

Comparison with a Marketed Product

Reference product

For the reference product, commercially available lactase tablets (6000 FCC units) were selected (Figure 6). These white to slightly yellow colored mini tablets are film-coated round tablets with a diameter of 6 mm and a weight of 100 mg. According to the packaging leaflet the reference product has a minimum lactase activity of 6000 FCC units per tablet which enables the digestion of up to 30 g lactose at optimal conditions.

Fig. 6 Reference Product

The mini tablets are based on a complex formulation, which is composed of lactase, maltodextrin, calcium phosphate, cellulose, hydroxypropylmethyl cellulose, fatty acid, silicon dioxide, magnesium salts of fatty acids, mono- and diglycerides of fatty acids, and fully hydrogenated palm oil.

Tableting process

In order to obtain the same lactase activity as in the marketed lactase tablets (6000 FCC per tablet), a quantity of 70 mg of the lactase powder per tablet was required. Therefore, the two-component formulation based on **PROSOLV® EASYtab** (Table 1), is compacted into 100 mg tablets. The same tablet format as for the original tablets was used and the tablet hardness was adjusted to about 100 N in order to allow a direct comparison of further tablet characteristics.

Lactase activity and functional tablet characteristics

Only a low compression pressure of 5.75 kN was necessary in order to compact the **PROSOLV® EASYtab** based formulation into tablets with a hardness of 100 N, as measured for the commercial product (Table 2). Both formulations, have a lactase activity of more than 6600 FCC per tablet and therefore, the minimum value of 6000 FCC per tablet was clearly exceeded.

A comparison with the lactase activity of the **PROSOLV® EASYtab** based blend demonstrated that the initial lactase activity was only reduced by 2.8 % due to the compaction process which is significantly less than in the pure lactase formulation (Figure 3). Moreover, the **PROSOLV® EASYtab** based lactase tablets disintegrated more than twice as fast as the reference tablets.

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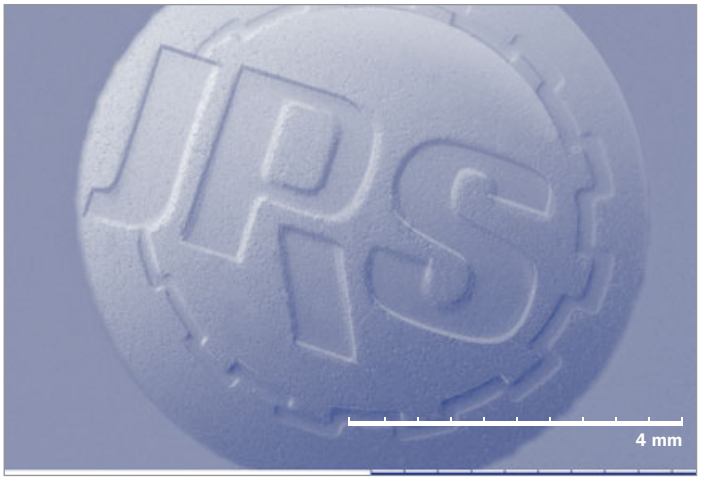
Parameter	PROSOLV® EASYtab Formulation	Reference Tablets (6000 FCC units) Lactase 6000
Lactase Activity (FCC/Tablet)	6670	6632
Loss of Lactase Activity During Compaction (%)	2.8	–
Tablet Hardness (N)	101.9	98.1
Compaction Force (kN)*	5.75	–
Disintegration Time (min)	13.9	35.2
Tablet Weight (mg)	100.1	97.1
Tablet Height (mm)	3.07	3.01
Number of Components	2	7 (according to packaging leaflet)

*Required compaction force in order to obtain a tablet hardness of 100 N.

Tab. 2 Characteristics of the **PROSOLV® EASYtab** Based Lactase Formulation Compared to the Reference Product.



PROSOLV® EASYtab also produced smoother tablet surfaces which lead to better film coating adhesion and a more pronounced logo embossing. (Additional technical information available).

References:

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6 Brochure: **PROSOLV® EASYtab.** JRS PHARMA GmbH & Co KG.

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