TECHNICAL INFORMATION

The Use of **EMDEX®** in a Lactose-free Reformulation of Cetirizine Tablets

Abstract

Spray-dried lactose is widely used as filler and binder in the pharmaceutical industry, but many adults are not able to digest lactose. Therefore, it is indispensable to provide alternatives to lactose-containing drugs in order to make them suitable for lactose intolerant patients. **EMDEX®** is a promising substitute for spray-dried lactose as it has similar powder and tableting properties. The aim of this study was to test a lactose-free reformulation of cetirizine tablets. **EMDEX®** was used successfully as a lactose substitute in cetirizine tablets resulting in comparable tablet properties in terms of crushing strength, disintegration time and dissolution profile. Furthermore, the **EMDEX®** formulation was characterized by an excellent powder flow and low ejection forces during the tableting process.

Introduction

Cetirizine dihydrochloride belongs to the group of second-generation antihistamines and is used in the treatment of hay fever, allergies, angiodema and urticaria. As an H1 antagonist, cetirizine relieves the symptoms of allergical reactions by blocking the action of histamine at the H1 receptors temporarily.[1,2] Cetirizine is one of the most common H1 antihistamines, but many cetirizine tablets on the market contain lactose which makes them unsuitable for lactose intolerant patients.[3]

Approximately 33 % of the global population is affected by lactose intolerance, which is the inability to digest the milk sugar lactose. Lactose intolerance is caused by the shortage of the enzyme lactase, which splits lactose into glucose and galactose, leading to gastrointestinal symptoms, such as abdominal pain, bloating, diarrhea, gas and nausea. Whereas almost all infants produce the enzyme lactase in a sufficient quantity, about 75 % of adults have impaired lactase activity. Especially in large parts of Asia and Africa, lactose intolerance is prevalent. For this reason it is very important to provide alternative excipients for the development of lactose-free drugs.[4,5]

A potential substitute for spray-dried lactose is **EMDEX®**, a directly compressible, water-soluble tablet filler and binder. **EMDEX®** is composed of 95 % glucose monohydrate and 5 % oligosaccharides resulting from the enzymatic hydrolysis of starch. It is monographed as dextrates in the USP. Due to its comparable properties to spray-dried lactose in terms of powder characteristics and functional tablet parameters, **EMDEX®** is a promising substitute for lactose.

Study Design

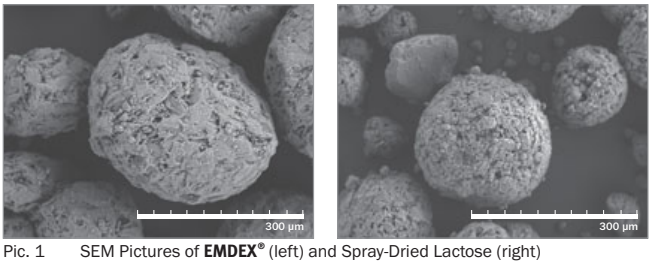
The aim of this study was the substitution of lactose in marketed cetirizine tablets (Reactine®) by **EMDEX®**. The cetirizine tablets were reformulated in both a lactose-based version to match the original formulation as closely as possible, and in a lactose-free version containing **EMDEX®** instead of spray-dried lactose. Both formulations were pressed into tablets of the same format and size as the original tablets, using compaction forces between 2 and 15 kN, and compared in terms of powder flow, ejection force and functional tablet characteristics, such as crushing strength and friability. Furthermore, coated tablets with the same crushing strength as the reference product were produced. Their disintegration time and dissolution profiles were analysed and compared with the original cetirizine tablets.

Powder Characteristics of **EMDEX®** and Spray-Dried Lactose

A comparison of **EMDEX®** and spray-dried lactose with regard to their powder characteristics demonstrates the similarity of the two materials (Table 1). Both are water-soluble, crystallized powders with a porous structure and a spherical particle shape (Picture 1). The particle shape in combination with the high bulk density leads to excellent powder flow of **EMDEX®** and spray-dried lactose. Furthermore, both excipients are appropriate for direct compression applications and deform mainly by brittle fracture.

Parameter	EMDEX®	Spray-Dried Lactose
Particle Size d_{50} (µm)	190 – 220	130 – 160
Bulk Density (g/L)	600 – 700	600 – 700
Tapped Density (g/L)	700 – 800	700 - 800
Flodex Index (mm)	4	4
Water Solubility (g/L)	1000	220

Tab. 1 Powder Characteristics of **EMDEX®** and Spray-Dried Lactose



Pic. 1 SEM Pictures of **EMDEX®** (left) and Spray-Dried Lactose (right)

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Selected Ingredients & Formulations

Reference Product

As reference product, we selected Reactine®. These are film-coated tablets containing 10 mg of cetirizine dihydrochloride. The tablets are white oblong tablets with breakline, 4 x 10 mm in size, with a weight of 120 mg and an average crushing strength of 79 N (Picture 2).
In addition to cetirizine dihydrochloride, Reactine® tablets contain microcrystalline cellulose (MCC) and lactose monohydrate as a filler-binder, silicon dioxide as a glidant, and magnesium stearate as a lubricant. The tablets are coated with Opadry Y-1-7000, which is composed of hypromellose, titanium dioxide and Macrogol 400.

Pic. 2 Reference product (Reactine®)

Reformulation of the Cetirizine Tablets

The quantitative composition of the lactose-based reformulation is shown in Table 2. The proportion between MCC and lactose monohydrate in the original tablets was assessed by separating water-soluble and insoluble components and weighing them out. In addition to the API, the water-soluble fraction contains mainly lactose monohydrate, whereas the water-insoluble fraction consists mainly of MCC, resulting in relative proportions of about 30 % MCC and 59.7 % lactose monohydrate. Furthermore, 1 % silicon dioxide and 1 % magnesium stearate were added to the formulation. In case of Formulation 2, the lactose monohydrate was substituted by **EMDEX®**.

Ingredient		Formulation 1 (Lactose) (%)	Formulation 2 (EMDEX®) (%)
Cetirizine Dihydrochloride		8.3	8.3
Microcrystalline Cellulose	**VIVAPUR®** 102	30.0	30.0
Lactose Monohydrate	Spray-Dried Lactose	59.7	-
Dextrates	**EMDEX®** non GMO	–	59.7
Silicon Dioxide	Aerosil® 300	1.0	1.0
Magnesium Stearate	Ligamed® MF-2-V	1.0	1.0
Opadry Y-1-7000	**VIVACOAT®** PC-1P-101	additional	additional
	Total:	100.0	100.0

Tab. 2 Formulations of the Reformulated Cetirizine Tablets (120 mg Total Weight)

Results and Discussion

Powder flow and tablet characteristics of uncoated tablet cores

The lactose and **EMDEX®** based formulations showed similar results in terms of powder flow, ejection force and compactibility (Figure 1). Both formulations were characterized by an excellent flowability resulting in a very low Flodex index of 8 mm. The ejection force of both formulations remained below 200 N, even at a high compaction force of 15 kN, and an appropriate tablet hardness was obtained. Both formulations resulted in tablets with a very low friabililty. Already at moderate compaction forces (≥ 7 kN) the friability decreased to below 0.1 % (Table 3).

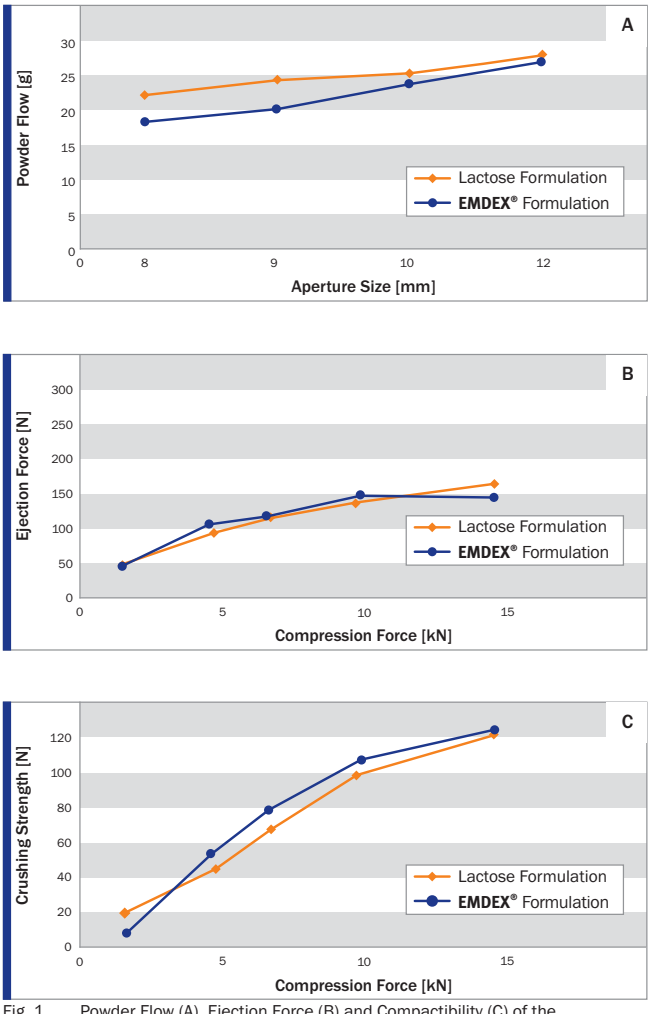

Fig. 1 Powder Flow (A), Ejection Force (B) and Compactibility (C) of the Lactose and **EMDEX®** Based Formulations

	Friability [%]		
	2 kN	5 kN	≥ 7 kN
EMDEX® Formulation	n.a.	0.06	< 0.1
Lactose Formulation	n.a.	0.26	< 0.1

Tab. 3 Friability of the Lactose and **EMDEX®** Based Tablets

Coated tablets

In order to obtain a final tablet hardness of about 80 N, as measured for the marketed product Reactine®, tablet cores with a crushing strength of 50 N were produced and subsequently coated with a weight gain of 4 %. For both formulations only low compaction forces of 5.75 and 4.15 kN were required to form tablet cores with an adequate tablet hardness (Table 4). After the coating process, a crushing strength of 76 and 80 N was determined in the lactose and **EMDEX®** based formulations, respectively. The coated tablets disintegrated within 3 min and exhibited a comparable tablet weight and height as the original cetirizine tablets.
The dissolution profiles of the lactose and **EMDEX®** based tablets (as well as Reactine®) showed a high degree of similarity (Figure 2). Only during the first few minutes, slight fluctuations between the different formulations could be observed, but already after 10 min the total cetirizine amount was released in all formulations.

Parameter	Reactine®	Formulation 1 (Lactose)	Formulation 2 (EMDEX®)
Crushing Strength (N)	79	76	80
Compaction Force (kN)	–	5.75	4.15
Disintegration Time (s)	< 3min	< 3 min	< 3 min
Tablet Weight (mg)	120	128	126
Tablet Height (mm)	3.2	3.4	3.5

Tab. 4 Tablet Characteristics of the Lactose and **EMDEX®** Based Tablets Compared to the Reference Product Reactine®

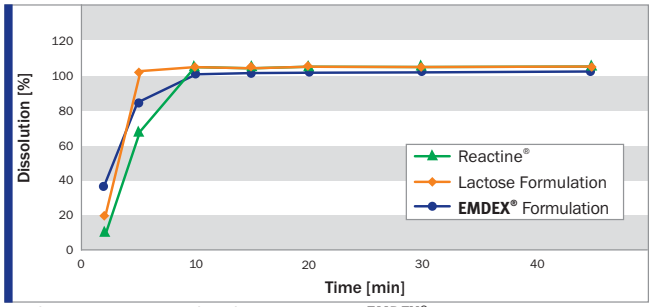

Fig. 2 Dissolution Profile of the Lactose and **EMDEX®** Based Tablets Compared to the Reference Product Reactine®.

Conclusion

Like spray-dried lactose, **EMDEX®** is a water-soluble filler-binder with brittle fracture as the main binding mechanism. **EMDEX®** and spray-dried lactose show great similarity in terms of particle morphology, bulk density and flowability. **EMDEX®** was therefore ideally suited as a substitute for spray-dried lactose in reformulating cetirizine tablets in order to make them suitable for lactose intolerant people. The **EMDEX®** based formulation was fully equivalent to the lactose-based tablets and the marketed product Reactine® regarding powder characteristics and tablet parameters, such as compactibility, disintegration time and dissolution profiles.

Reference:

1 Bopp, A. & Herbst, V. (2010) Handbuch Medikamente: vom Arzt verordnet: für Sie bewertet, 8. Auflage, Berlin: Stiftung Warentest.

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4 Mattar, R. et al. (2012) Lactose intolerance: diagnosis, genetic, and clinical factors. Clinical and Experimental Gastroenterology, 2012:5 113–121.

5 Deng, Y. et al. (2015) Lactose Intolerance in Adults: Biological Mechanism and Dietary Management. Nutrients, 2015, 7, 8820-8835.

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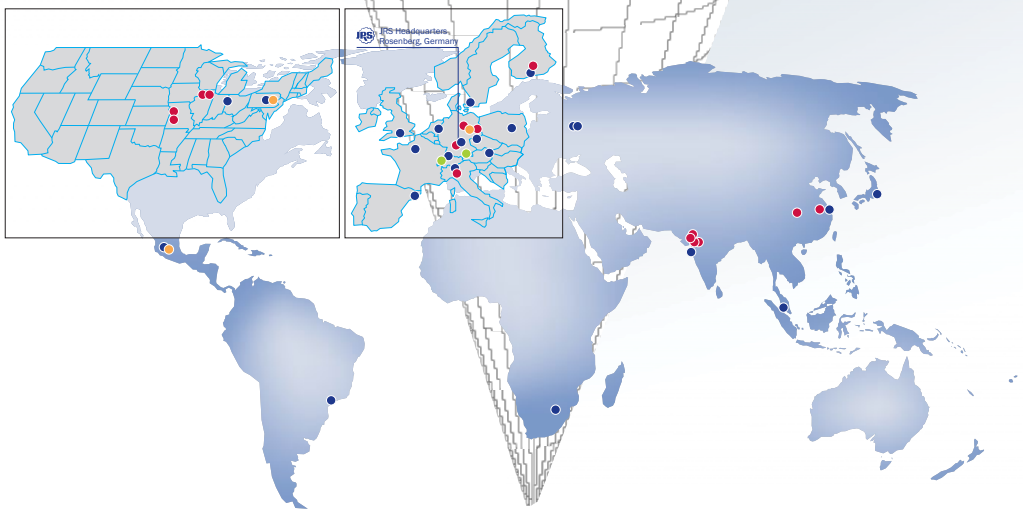

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