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In Memoriam

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DuraLac® H: A new, alternative source of anhydrous lactose

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Introduction:

Anhydrous lactose was developed and patented in the United States of America in the early 1940s and this product quickly found its way into pharmaceutical applications. Most notably, the initial use of anhydrous lactose was preferentially focused in the Anglo-American hemisphere, perhaps due to academic, economic and political circumstances. Asia and Europe have traditionally favored α-lactose monohydrate grades.
Globalization has occurred in all industry categories. Fundamental changes have also been observed within the pharmaceutical landscape and consequently, this has had as well an impact on the excipient industry. Worldwide migration of production sites and their accompanied products, the development of new, diverse formulations, and a variety of manufacturing techniques has necessitated the constant supply of robust, ubiquitous and reliably sourced excipients. *Meggle* has accepted this challenge and introduced an alternative source for anhydrous lactose, DuraLac® H.

Material and methods:

Angle of repose, compressibility-related indices, Hausner ratio (rt/rb), and Carr's Index ([rt-rb]/rt x100) were evaluated by compendial methods. FlowRatex® operation was conducted per the manufacturer recommended protocols. Blends comprising 0.5 % lubricant (Mg-stearate, Merck; Germany) and a glidant (hydrophilic fumed silica, Aerosil® 200, Evonik; Germany) were mixed in a Turbula® mixer (Bachofen; Switzerland) at 45 rpm for 5 min. Compaction trials were performed on a STYL'One® tablet press (Medelpharm; France). ANALIS® software was utilized for documentation acquisition. Punch diameter was 11.28 mm, round, flat-faced, with 22 mm high die walls. Tablet hardness was evaluated, using an Erweka hardness tester, Type TBH® 30. Disintegration was handled by an Erweka ZT® 3-2 apparatus, according to compendial requirements (Ph.Eur. 2.9.1). For active pharmaceutical ingredients (APIs) Theophylline (anhydrous, BASF), Paracetamol (Salutas), and Diprophylline (fine powder, BASF) were selected for their solubility profiles (tablet hardness ca. 70 N). An USP 35 dissolution paddle apparatus was used for dissolution trials (Sotax; Switzerland). Hydrophilic fumed silica and Mg-stearate were preferred in a concentration of 1 %, and congruence of release profiles was analysed by similarity factor f2, according to Moore and Flanner. Particle size distribution (PSD) was investigated by Sympatec®/Helos & Rodos particle size analyzer. Scanning electron microscopy (SEM) was used to scan the material at a beam voltage of 5 kV (Ultra 55® FESEM, ZEISS).

Production process, regulatory and quality information:

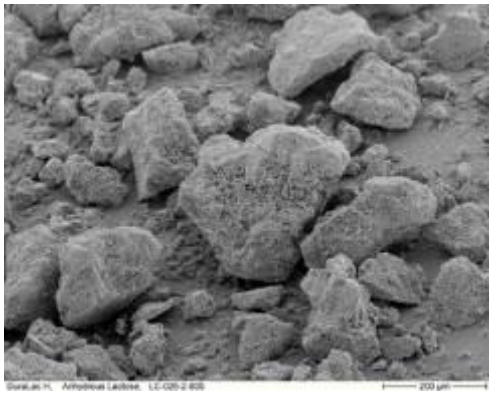
Meggle offers dual sourcing, and DuraLac® H is produced in Le Sueur, MN; USA. This state of the art, pharma-dedicated production site complies with cGMP-standards according to the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients and USP NF General Information Chapter <1078>. Starting material is an USP NF-compendial α-lactose monohydrate grade, dissolved in water and sprayed on two counter rotating drums at elevated temperatures. Anhydrous lactose spontaneously crystallizes on hot surfaces and is subsequently scraped off (picture 1).

Picture 1: Anhydrous lactose production: Scrape-off and fall into a chute of white DuraLac® H crystals from a rotating drum after spontaneous crystallization on the hot surface.

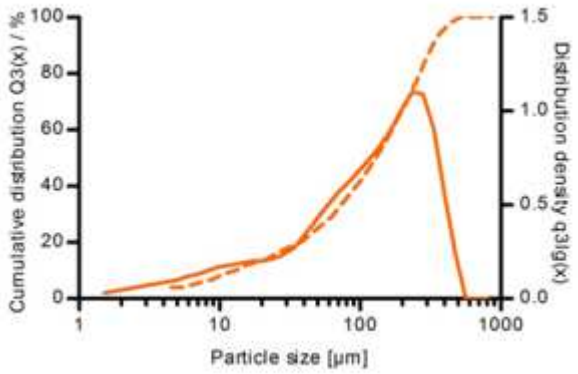
The white crystals fall into a chute and are transported by a screw-conveyor to a final milling and sieving step, assuring the defined PSD. Finally, pharmaceutical anhydrous lactose grade DuraLac® H is packed either into 25 kg carton boxes or 50 kg fiber drums, both containing aluminium laminated inliners. The shelf life is 24 months, according to ICH Q1A stability guidelines. Further detailed information on high batch-to-batch consistency, specifications and regulatory documents can be downloaded from www.meggle-pharma.com. DuraLac® H complies with lactose anhydrous monographs in JP, Ph.Eur., USP NF, and is GRAS listed.

Physico-chemical characterisitics:

Anhydrous lactose, appearing as a white to off-white, crystalline, odorless powder heap, has a slightly sweet taste. Morphology of anhydrous particles is different to monoclinic sphenoidal crystals of α-lactose monohydrate. Anhydrous lactose granules are remarkably dense, representing agglomerates of microcrystals exhibiting a wide irregularity in shape and breaking edges due to its production process (picture 2).



Picture 2: SEM of anhydrous lactose DuraLac® H crystals. The particles represent agglomerates of microcrystals and exhibit a wide irregularity in shape due to its production process.



Picture 3: Typical cumulative PSD and distribution density of Meggle's anhydrous lactose grade DuraLac® H. Analyzed by Sympatec® /Helos & Rodos particle size analyzer.

A typical laser diffraction PSD exhibits a d_{50} value of 135 µm (d_{10} 15 µm, d_{90} 310 µm; see picture 3), and a specific BET-surface area is found in the range between 0.3 and 0.4 m^2/g. Additional basic powder technological data may be taken from table 1.

DuraLac® H*

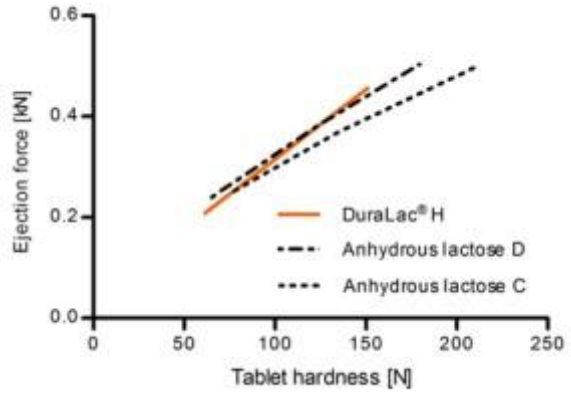
Parameter	Value	Unit
Water (KF)	0.6	[%]
Loss on drying	0.1	[%]
Bulk density	670	[g/ml]
Tapped density	880	[g/ml]
Carr-Index	1.31	[%]
Hausner-ratio	23.86	[1]
Angle of repose	42	[^{0}]

*typical values, only

Table 1: Typical powder technological parameters for anhydrous lactose grade DuraLac® H.

Lactose appears as α- and β-anomer, and in anhydrous lactose, a typical ratio of 20% α- and 80% ß-modification, containing no water of crystallization is evident. The ß-anomer exhibits higher water solubility, respectively.
DuraLac® H is largely moisture stable, showing very low hygroscopicity. It starts to absorb significant amounts of moisture not before a relative humidity of 70 % at 25°C, as indicated by differential vapor sorption (DVS). Passing through conditions of higher humidity anhydrous lactose demonstrates hysteresis behavior, caused by the conversion of lactose from anhydrous to monohydrate form.

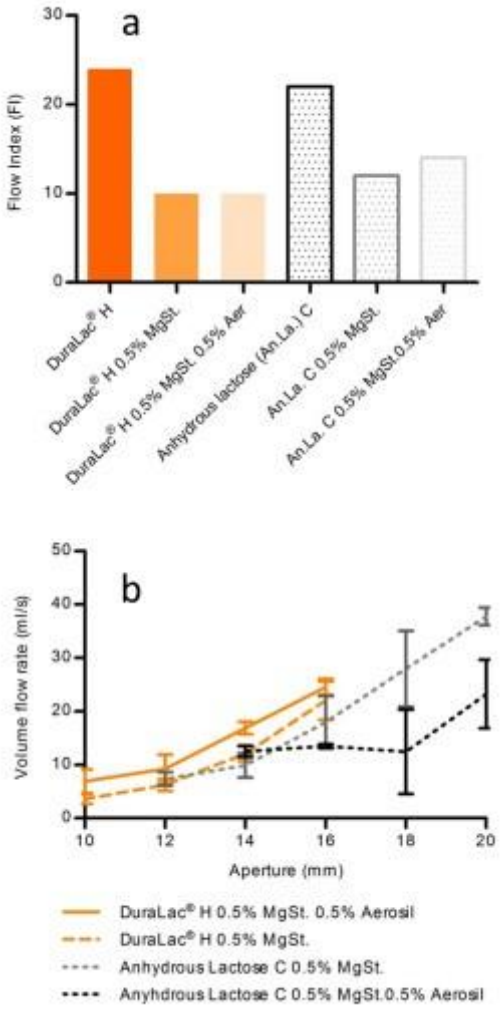
DuraLac® H demonstrates excellent compaction properties and low lubricant sensitivity, which may be attributed to the brittle nature of anhydrous lactose. This leads to large, new bonding surface during compaction. It also facilitates the necessary functionality required by direct compression processes to produce robust tablets at high speed, and defined granules in roller compaction. A typical tensile strength of 2.5 N/mm^2 for DuraLac® H placebos may be seen at a corresponding compaction pressure of 180 MPa. Ejection forces up to 400 N are common and may be observed at a tablet hardness of 130 N for neat anyhydrous lactose grades (see picture 4).



Picture 4: Typical ejection forces of various anhydrous lactose grades (DuraLac® H, Anhydrous Lactose C and D), showing similar PSD (1% Mg-stearate; STYL'One® tablet press (Medelpharm; France)).

Flowability is a result of various powder properties, and amongst them PSD and morphology seem to have the utmost impact. With its rough surface, neat anhydrous lactose is generally defined by modest flow due to particle structure prone to cohesive effects and an elevated fraction of fines. However, this reflects reality in limited common formulation practices as the strong majority of formulations is lubricated. Anhydrous lactose drastically enhances its flow properties upon lubrication.
With the introduction of lubricants and glidants, anhydrous lactose flowability was evaluated using a FlowRatex®, a robust and simple device to mimic a tableting or device filling process, allowing a substantial increase in flowability to be quantified.
Aperture diameters of 22 mm (equivalent to a Flowability Index (FI) of 22) and larger are required to insure consistent powder flow of two commercially available, neat anhydrous lactose grades (DuraLac® H and Anhydrous Lactose C).
Adding 0.5 % Mg-stearate to this system cuts the FI almost in half, indicating a dramatic improvement in flow properties. For DuraLac® H, the FI drops from 24 to 10. For the second investigated lactose grade (Anhydrous Lactose C) the FI changes from 22 to 12. In general a smaller FI stands for better flow.
An additional concentration of 0.5 % fumed silica to the system seems to have a positive impact on DuraLac® H only, as indicated by a subsequent increase in volume flow (see picture 5b, orange dotted versus orange continuous line), and the FI value of 10 for DuraLac® H does not change.

However, with the additional fumed silica, the FI for Anhydrous Lactose C increases from 12 to 14, and a decrease in volume flow is observed (see picture 5b, grey dotted versus black dotted line). This gives evidence that the further addition of a glidant may not be successful in all cases.

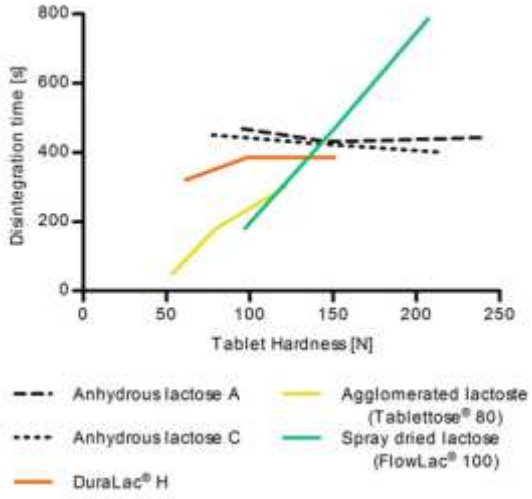


Pictures 5a, b: Powder flow of neat and lubricated anhydrous lactose compared by flow index (FI) and volume flow rate. Adding 0.5 % Mg-stearate to the system cuts numbers of FI almost in half, indicating a dramatic improve in flow properties (5a).

Extra lubrication by 0.5 % fumed silica seems to have an impact on DuraLac® H only, as indicated by an increase in volume flow rate (5b: compare orange dotted versus orange continuous line). FlowRatex® operation was conducted as per the manufacturer recommended protocols.

Disintegration of anhydrous lactose-based tablets is less hardness dependent compared to α-lactose monohydrate compacts, and at moderate to high compression forces disintegration is also faster. This phenomenon is due to the presence of ca. 80% ß-lactose anhydrous, which shows increased water solubility in comparison to α-anomer anhydrous and hydrous. α -lactose anhydrous is known to block water imbibition by its small pore diameter and precipitation of dissolved anhydrous α -lactose into hydrous α-lactose. At low compression force porosity seems to be the crucial factor.
If several commercially available anhydrous lactose grades are investigated, little difference may be seen (picture 6, dashed and dotted black lines, orange continuous line). Neat, anhydrous lactose grades comprising comparable PSD are roughly defined by disintegration times between 300 and 450 sec at a broad range of tablet hardness between 50 and 200 N. Hardness dependent disintegration performance may not be assumed.
On the contrary, α-lactose monohydrate-based grades, like agglomerated Tablettose® 80 or spray-dried FlowLac® 100 are highly hardness dependent (picture 6, yellow and green continuous lines). For spray-dried lactose, an increase in disintegration time is most distinct, from 200 to 800 sec at 100 to 200 N tablet hardness, respectively. Tablettose® 80 performs within the range of 50 to 300 sec disintegration time at 50 to 125 N tablet hardness.

Aside from the solubility exhibited by the α- and ß-anomers, a more plastic compaction process, leading to different pore forming may be taken into consideration with spray-dried lactose as well. Higher plasticity is a result of the presence of amorphous lactose.



Picture 6: Disintegration of anhydrous lactose-based tablets (DuraLac® H, Lactose A and C; orange continuous line, dashed and dotted black lines) is less hardness dependent compared to α-lactose monohydrate compacts (agglomerated Tablettose® 80, FlowLac® 100; yellow and green continuous lines) at moderate to high tablet hardness. Disintegration testing was performed by an Erweka ZT® 3-2 apparatus, according to compendial requirements.

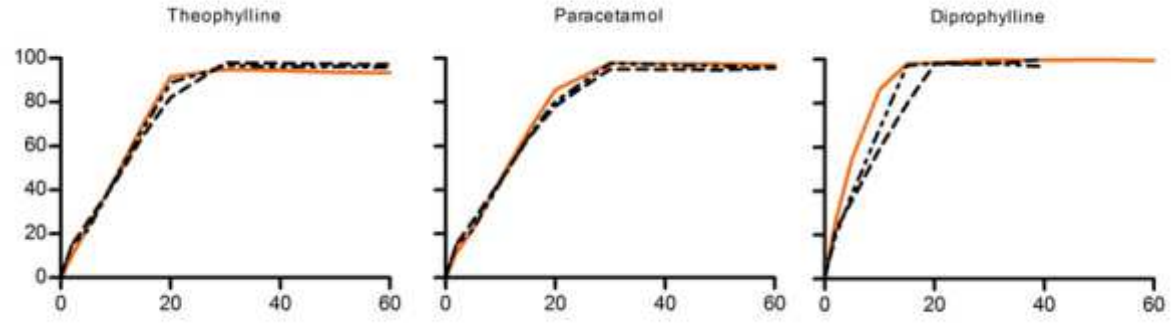
Drug dissolution and release profiles are routinely used to monitor product quality and even predict in vivo performance. Whereas drug dissolution may be seen as a relatively simple operation, drug release can involve quite complex steps as tablet disintegration is influenced by penetration of water, drug diffusion through pores or even change of the water-filled network by precipitation. As a result of good water solubility and surface wetting anhydrous lactose favors immediate release.
To prove robustness and exchangeability of various commercially available anhydrous lactose grades in a formulation, a rational approach was chosen by taking different solubilities of drug substances in water into account. Three diverse APIs, showing poor to excellent water solubility had been consulted as model systems: Theophylline (7.4 g/l), Paracetamol (14 g/l) and Diprophylline (330 g/l), defined by highest water solubility, at 25 °C in each case.

An overall low API load of 10 % was chosen to slow down drug release and observe the primary effects of the "lactose matrix" being present in a disproportionally high ratio. Subsequently, no disintegrants or superdisintegrants were applied. All investigated anhydrous lactose grades showed similar PSD, represented by a d_{50} of 139 ± 9 µm. Drug release profiles of a formulation using different lactose matrices had been compared quantitatively by using the similarity factor f2 according to Moore and Flanner[i], whereas values of f2 ≥ 50 -100 are indicating equivalence of two curves. The release kinetics of 3 different commercially available anhydrous lactose grades as a matrix were compared (DuraLac® H as reference, and Anhydrous Lactose grades A and B for comparison) by using the three selected APIs. In all cases, the results demonstrated similar factors of f2 ≥ 50, indicating product equivalence. Only in one example was a divergence investigated (table 2). These results give a strong indication that a simple mutual substitution of anhydrous lactose as an excipient matrix within a formulation may be achieved.

Conclusion:

DuraLac® H, disclosing complete regulatory documentation opens a new, alternative source for anhydrous lactose in pharmaceutical tableting operations and manufacture. Chemical-, physical-, and functionality related powder parameters are found within a range comparable to other commercially available anhydrous lactose grades. DuraLac® H is an equivalent alternative in anhydrous lactose formulations.

API		Theophyllin	Paracetamol	Diprophyllin	
Lactose	Anh. Lact. A - - - -	66,06	73,74	41,83	f2
	Anh. Lact. B - • • -	71,45	83,66	50,78	
	DuraLac®H - - - -	reference	reference	reference	



Drug release kinetics; x-axis: time (0 - 60 min) and y-axis: rel. drug release

Table 2: Comparison of drug release kinetics using 3 different commercially available anhydrous lactose grades (DuraLac® H as reference, Anhydrous Lactose A and B for comparison) in a formulation containing either Theophylline, Paracetamol or Diprophylline. By using similarity factor f2 ≥50 as an indicator of product equivalence a simple mutual substitution of anhydrous lactose within a formulation may be achieved.