What is so special about excipients?

- All medicines depend on excipients to stabilize and deliver their active ingredients
- The quality and effectiveness of the medicine depends greatly on how the excipient performs
- Performance of active ingredients and excipients together determines healthcare benefits for the patient
A century long heritage
With roots in dairy producing companies

Our heritage

- 1900 – HMS (Dutch Milk Sugar Factory) founded
- 1926 – Six Dutch dairy producers form DMV
- 1946 – First lactose plant built in Kapuni NZ
- 1960 – DOMO starts producing pharmaceutical grade lactose
- 1985 – Start inhalation grade lactose by DOMO in Borculo
- 2003 – Superdisintegrants acquired from Avebe
- 2006 – DMV-Fonterra Excipients created from DMV & LNZ
- 2010 – DOMO-pharma integrated
- 2011 – Acquisition Brahmab cellulose India
- 2011 – Launch new corporate brand name DFE Pharma
- 2013 – Global launch of MCC by DFE Pharma

DFE Pharma – a joint venture between 2 leading global dairy cooperatives

50%

DFE Pharma

50%

Sales Marketing HR QA R&D F&A Operations
Our parent companies

- International dairy cooperative
- Registered head office in Auckland (New Zealand)
- Turnover NZ$ 19.8 billion
- Up to 17,300 employees
- Up to 10,600 share holders

- International dairy cooperative
- Registered head office in Amersfoort (the Netherlands)
- Turnover € 9.6 billion
- 19,000 employees
- 14,400 member dairy farms

Responsiveness with global presence

Offices, production facilities & global distributor network

- Sales Office US
- Production Germany
- Main Office Germany
- Global distributor network
- Production New Zealand
- Sales Office Singapore
- Sales Office India
- Sales Office Japan
**DFE Pharma Strategy**

**Our ambition**

- We want to grow from a lactose supplier to an excipient expert.

![Diagram showing progression from lactose supplier to wide range supplier to excipient expert](image)

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**The perfect fit of DFE Pharma Excipients**

- MCC
- Starch
- Lactose
- Inhalation
- Superdisintegrants

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**The pursuit of excipient excellence**
DFE Pharma excipientFest 2013

DFE Pharma production facilities

- Borculo
  The Netherlands
- Foxhol
  The Netherlands
- Kapuni
  New Zealand
- Nörten Hardenberg
  Germany
- Veghel
  The Netherlands
- Cuddalore
  India

Quality is guaranteed

Production:
- cGMP production standards
- ICH Q7A Guidelines (API)
- Pharmacopoeial standards: USP/NF, Ph. Eur., JPE
- Drug Master Files
- ISO 9001:2008 certified production facilities, FDA inspected

Shelf life guaranteed:
- MCC: 4 years
- Milled & sieved lactose: 3 years
- Direct compression lactose: 2-3 years (vary by grade)
- Starches: 2-4 years
- Superdisintegrants: 5 years
Directly Compressible Excipients

The pursuit of excipient excellence

DC Excipients for Tablet Production

Most important requirements for DC filler/binders

- Good flowability
- High compactability
- Good recompactability for dry granulation
- Good blending properties
- No (drug) segregation
- Physical and chemical stability
- Chemical compatibility
Choices for Excipients??

- DCP
- Lactose
- MCC
- Starch
- ...

Direct compression lactose
The best DC lactose for your application

Spray-dried lactose (SD)
- Excellent flow
- Improvement of compaction
- Low dose formulations
- Low tablet weight variation

Anhydrous lactose (AN)
- Roller compaction
- Moisture sensitive drugs
- High dose formulations

Granulated lactose (GR)
- Low dose applications
- Quick disintegration
- Capsule and sachet filing
Direct compression lactose
Summary of production routes

Crystals of pharmaceutical grade α-lactose monohydrate

Spray-drying
Roller drying
Granulated

Lactopress® Spray Dried 250 SuperTab® 11SD or 14 SD
Lactopress® Anhydrous 250 SuperTab® 21AN or 22 AN
Lactopress® Granulated SuperTab® 30GR

AN=anhydrous, GR=granulated, SD=Spray Dried

SuperTab® 24AN
“A New Generation of Directly Compressible Lactose”
SuperTab® 24AN
Overview

- Introduction SuperTab® 24AN
  - Description
  - Production process & product properties

- Application studies
  - Study 1: Mixing potential & Content Uniformity
  - Study 2: Quick disintegration with high compaction
  - Study 3: High speed tableting properties

- Summary

SuperTab® 24AN
Description

- Combines the key properties of granulated and anhydrous lactose
  - High powder flowability (granulation)
  - Quick disintegration time (granulation)
  - Excellent mixing properties (granulation)
  - High compactability (granulation of anhydrous material)
  - Low moisture content below 1.0 % H₂O (anhydrous material)

- Product is an anhydrous lactose according to Pharmacopeia
SuperTab® 24AN
Process flow

Patented: EP1851344 (B1), US2009/0081308

SuperTab® 24AN
Product properties

<table>
<thead>
<tr>
<th>Property</th>
<th>SuperTab® 24AN</th>
<th>SuperTab® 21AN</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O content – KF (%)</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>β/α ratio</td>
<td>75/25</td>
<td>80/20</td>
</tr>
<tr>
<td>Bulk density (g/cm³)</td>
<td>0.490</td>
<td>0.700</td>
</tr>
<tr>
<td>Tapped density (g/cm³)</td>
<td>0.600</td>
<td>0.870</td>
</tr>
<tr>
<td>Flodex (mm)</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>PSD* % &lt;75µm</td>
<td>~ 20 (nmt 30)</td>
<td>~ 19</td>
</tr>
<tr>
<td>PSD* % &lt;150µm</td>
<td>~ 65 (55-80)</td>
<td>~ 50</td>
</tr>
<tr>
<td>PSD* % &lt;250µm</td>
<td>~ 92 (nlt 80)</td>
<td>~ 83</td>
</tr>
</tbody>
</table>

* By Rotap sieve analysis
SuperTab® 24AN
Product Properties - visualization

Light Microscope

SEM

SuperTab® 24AN
Product Properties – PSD (laser diffraction)

\[ \begin{align*}
    x_{10} &= 34 \, \mu m \\
    x_{50} &= 128 \, \mu m \\
    x_{90} &= 273 \, \mu m
\end{align*} \]
SuperTab® 24AN
Product properties - flow

Flodex Results

AN=anhydrous, GR=granulated, SD=Spray Dried
Excellent flow: comparable to granulated/spray-dried lactose

< 0.7% of water uptake up to 90% RH when measured by Dynamic Vapour Sorption (DVS)
Application study 1:
Mixing potential & Content Uniformity

Goal: comparison of mixing properties/potential vs. regular anhydrous lactose

Formulation
- 2% Propranolol HCl, 97.5% Lactose, 0.5% Magnesium Stearate
- 500 g formulations

Experimental conditions:
- Mix API & Lactose for 2, 5, 8 minutes (Turbula 62 rpm)
- Add lubricant & mix for 2 min
- Compress on rotary Tablet Press (250 mg tablets, 9 mm, fbe tooling)
- Test tablets on content uniformity

SuperTab® 24AN
Study outline

- Goal: comparison of mixing properties/potential vs. regular anhydrous lactose
- Formulation
  - 2% Propranolol HCl, 97.5% Lactose, 0.5% Magnesium Stearate
  - 500 g formulations
- Experimental conditions:
  - Mix API & Lactose for 2, 5, 8 minutes (Turbula 62 rpm)
  - Add lubricant & mix for 2 min
  - Compress on rotary Tablet Press (250 mg tablets, 9 mm, fbe tooling)
  - Test tablets on content uniformity
SuperTab® 24AN gave excellent content uniformity (RSD ≤3%) after only 2 minutes; a similar result for regular anhydrous grade is obtained after only 8 minutes mixing time.

Goal: comparison of content uniformity over long tableting duration: SuperTab® 24AN vs. regular anhydrous lactose

Formulation
- 2% Paracetamol, 97.5% Lactose, 0.5% Magnesium Stearate

Experimental conditions:
- Premix API & 10% Lactose for 5 min, screen through 500μm sieve
- Add remaining lactose and mix for 10 min (Turbula 62 rpm)
- Add lubricant and mix for 2 min
- Compress on rotary Tablet Press (250 mg tablets, 9 mm, flat beveled tooling)
- Test tablets on content uniformity
SuperTab® 24AN gave excellent content uniformity over the entire tabletting duration.

Application study 2:
Quick disintegration combined with high compaction.
Goal: Comparison of placebo tablets on the tablet properties (disintegration & tablet crushing strength)

Formulation:
- 95.5% lactose, 4% Primellose® (Croscarmellose Sodium), 0.5% Magnesium Stearate
- 500 g formulations

Experimental conditions
- Mix Lactose & disintegrant for 8 minutes (Turbula, 62 rpm), add Lubricant and mix for further 2 minutes
- Compress on a R&D rotary tablet press (Rotab T, Luxner)
- 250 mg tablets, 9 mm, flat beveled tooling
- Test tablets on Tablet Crushing Strength (TCS), Disintegration Time (DT)

SuperTab® 24AN
25% more compactable vs. regular anhydrous lactose

24AN
22AN
21AN
11SD
30GR

AN=anhydrous, GR=granulated, SD=Spray Dried
250mg tablets, 9mm flat bevel edged tooling, RoTab rotary tablet machine
SuperTab® 24AN
Quicker disintegration at higher tablet hardness

Disintegration Time vs Tablet Crushing Strength

- 24AN
- 21AN
- 22AN
- 11SD
- 30GR

AN=anhydrous, GR=granulated, SD=Spray Dried
2% and 4% Primojel for 30GR and 11SD respectively
250mg tablets, 9mm flat bevel edged tooling, RoTab rotary tablet machine

Application study 3:
High speed tableting properties
SuperTab® 24AN

Study outline

- Goal: investigation tableting properties on a high speed tableting machine with a low dose formulation

- Formulation:
  - 0.1% APAP ($d_{50} = 19 \ \mu m$), 99.4% lactose, 0.5% Magnesium Stearate
  - 20 kg blends

- Experimental conditions:
  - Premix API & 10 % Lactose (2 min), Premix + Lactose (8 min), Lubrication (2 min) – drum mixer
  - Bosch Manesty Xpress 325*, 1300 tpm
  - 800 mg tablets, 12.6 mm concaved tooling (precomp. 1.8 kN, maincomp. 5.9 kN)

* Turret speed equal to XPress700 = 1.1 million tablets/h

SuperTab® 24AN

High speed tableting properties

- High consistency of tablet crushing strength & thickness during tablet run
SuperTab® 24AN
High speed tableting properties

- Consistent uniformity (range 108-116% label, RSD ~ 2.3%) >> no segregation during tablet run

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SuperTab® 24AN
Summary

- **Agglomerated anhydrous** lactose (complies with Pharmacopeia for anhydrous lactose)

- Combines the key properties of granulated and anhydrous lactose
  - High powder flow / excellent mixing properties
  - Superior compaction on high speed machine
  - Short disintegration time @ high tablet hardness
  - Low moisture content, below 1.0 % H2O (anhydrous material)

- May provide a solution for:
  - content uniformity issues in DC (incl. low dose drugs) & transfer WG formulations to DC (cost & time)
  - improving drug dissolution, due to quicker disintegration times
  - formulating hygroscopic drugs
  - roller compaction
  - Medium/high dose drugs
  - Bilayer tablets
Bilayer or Multi-layer FDC Tablets

- Major drivers: life cycle management
  - Improve patient compliance
  - Improve therapeutic outcomes
  - Decrease adverse reactions
  - Motivation by regulatory agencies

- Distinct layers of active formulations
  - Chemical incompatibility
  - Different release profile/rates
  - Core for osmotic pump

- More complicated than single layer tablets

Considerations guiding excipient selection for bilayer tablets

- Better flowing formulation is selected as first layer
  - First layer determines fill and weight control of second layer

- Select more re-compactable material as first layer
  - First layer undergoes 2 compressions

- Increase success in compression and layer adhesion
  - Layers with similar compaction/relaxation properties
  - Layers with similar expansion (thermal or moisture driven)

- Optimization of compaction pressure and tableting speed
  - Strength of interface adhesion
**Effect of materials on the strength of bilayer tablets**

![Graph showing the effect of materials on the strength of bilayer tablets.](image)

(Ex1=material in layer 1; Ex2=material in layer 2)

Total tablet weight 500 mg with each individual layer being 250 mg.

**Lactose is good for bilayer tablets**

- Bilayer tablets made with brittle materials (lactose) in both layers are strongest.
- For lactose–lactose tablets, an increase in adhesion between layers was observed, due to the formation of solid bridges upon storage.
- More significant fracture is induced when MCC is the bottom layer (MCC 1st) than when it is compressed as the top layer (lactose 1st).
- Interface was weakest for the compacts made with plastic materials (MCC) in both layers.
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