Co-Processed Lactose-based excipients for Direct Compression

Ulrich Marcher
Meggle GmbH & Co. KG, Germany
Co-processed Excipients

Definition:
“Combining two or more established excipients by an appropriate process”

Aim:
- Formation of excipients with superior properties compared to the simple physical mixtures of their components
- To obtain a product with added value related to the ratio of its functionality / price.
Co-processed Excipients

**Reasons for developing new direct compressible excipients:**

- High speed tablet press
- Poor compressibility of actives
- Avoid new chemical excipients
Co-processing: Technology

Pharma Spray Tower at Meggle: H 21.4 m; Dmax 9.41 m. D; V 700 m3; 1,500 kg/h Water evaporation
Co-processed Excipients

Tabletting

Direct Compression

Granulation

Cellactose®

Tablettose®

Granulac®

PrismaLac®

DuraLac®

Tablettose®

FlowLac®

MicroLac®

Cellactose® 80

PrismaLac® 40

Inhalac® 70

Inhalac® 400

Granulac® 140

Tablettose® 80

FlowLac® 90

DuraLac® H

MicroceLac® 100

CapSolLac® 60

Inhalac® 170

Granulac® 700

Tablettose® 100

FlowLac® 100

StarLac®

Sachelac® 80

Inhalac® 230

Granulac® 150

SorboLac® 400

Retalac®

SphereLac® 100

Inhalac® 250

Granulac® 230

Inhalac® 250

Granulac® 230

Inhalac® 250
Lactose in co-processed Excipients (DC)

Cellactose® 80

spray-dried

- 75% α-Lactose Monohydrate [Ph.Eur./USP-NF/JP]
- 25% Powdered Cellulose [Ph.Eur./USP-NF/JP]

\[d_{50} \approx 180 \, \mu m, \quad \text{Hausner ratio} = 1.24\]

| Ulrich Marcher | ©MEGGLE |
Cellactose 80: Compaction profile

- Cellactose 80
- 75% Tablettose 80 + 25% MCC 102
- Tablettose 80

Hardness [N] vs. Compaction Pressure [MPa]
Cellactose® 80:
High loaded Vitamin C tablets

Formulation:
Vitamin C 98% DC  69%
Cellactose 80  30%
Compritol 888  (1%)

Tablet press: comprex I
Tablet: d=12mm, w=500mg

![Graph showing the relationship between compression force and tablet hardness.](image-url)
Adherence Capacity

Micronized Glibenclamide

Different Excipients

Turbula mixer
30 min.

Separation of nonadhered particles by Air jet sieving

Assay

Schmidt and Rubensdörfer, 1994, Evaluation of Ludipress as a „Multipurpose Excipient” for DC Part I: Powder Characteristics and Tabletting Properties, Drug dev. ind. Pharm. 20(18); 2899-2925
Adherence Capacity: Results

Glibenclamide adhered [%]

Glibenclamide content before blending

Cellactose 80
Karion Instant
Ludipress
Avicel PH 200
Cellactose® 80: Disintegration properties

For very hard compressed Cellactose® 80 tablets, an addition of 2-3% superdisintegrant can reduce the disintegration time significantly.
Meggle Lactose – Cellactose® 80

- Ideal Diluent / Binder Combination
- Spherical form → Good Flowability
- High Adherence Capacity (micronized API)
- High Dosage Formulations (up to 75 % API)

**Application:**
- Chewable tablets (pleasant mouthfeel)
- Difficult to compress formulations (e.g. oblong tablets)
- Suitable alternative to undergo MCC/Lactose in patents
MicroceLac® 100

MicroceLac® 100 spray-dried

- 75% α-Lactose Monohydrate [Ph.Eur./USP-NF/JP]
- 25% Microcrystalline Cellulose [Ph.Eur./USP-NF/JP]

$\mu_{50}\text{ MicroceLac}^G = 150\,\mu\text{m}, \text{ Hausner ratio} = 1.22$
MicroceLac® 100: Compaction Profile

![Graph showing compaction profile for MicroceLac® 100, 75% Tablettose 80 + 25% MCC 102, and Tablettose 80.](image)

- **MicroceLac® 100**
- **75% Tablettose 80 + 25% MCC 102**
- **Tablettose 80**

*Hardness [N]* vs. *Compaction pressure [MPa]*
MicroceLac® 100: Improving Content Uniformity

Micronized Glibenclamide 5%

V-type mixer

Sample taken at prescribed (2, 5, 10, 15, 20 and 30 min.) time and defined points

Assay

By courtesy of Prof. Sunada, Meijo University, Nagoya
MicroceLac® 100: Improving Content Uniformity

**Formulation 1**
5% Glibencl. / **PHYSICAL ADMIXTURE**

- Glibenclamide 5,00 %
- Tablettose 80 71,25 %
- Avicel PH 101 23,75 %

**Formulation 2**
5% Glibencl. / **MicroceLac 100**

- Glibenclamide 5,00 %
- MicroceLac 100 95,00 %
Meggle Lactose – MicroceLac® 100

- Ideal Diluent / Binder Combination
- Spherical Form → Good Flowability
- High and Consistent Tablet Hardness
- Helps solving Content Uniformity problems
- Very Low to High Dose Formulations

**Application:**
- DC tableting
- Formulations with poorly flowable, micronized APIs
StarLac®

**StarLac®**

* spray-dried

- 85% α-Lactose Monohydrate [Ph.Eur./USP-NF/JP]
- 15% Corn Starch [Ph.Eur./USP-NF/JP]

$d_{50}$, StarLac = 180µm, Hausner Ratio = 1.19
Comparison: StarLac® vs. Physical Admixture

**Physical Admixture**
- 15% Corn Starch
- 85% spray dried Lactose

**StarLac®**
- 15% Corn Starch
- 85% α-Lactose monohydrate
StarLac®: Disintegration

16 mm tablets, flat, height 4 mm, Exacta 21 tablet press, 0.6 % Mg stearate
Comparison: StarLac® vs. Physical Admixture

Flowability:

Dissolution (30 % Vitamin C): up to 40% faster for tablets with StarLac®
StarLac®:
Compression-Hardness Profile

![Graph showing compression-hardness profile for StarLac and Tablettose 70](image-url)
StarLac®:
Influence of Mg-Stearate
# StarLac®:
## Orodispersable Formulation I

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>250.0 mg</td>
<td>20.83 %</td>
</tr>
<tr>
<td>StarLac</td>
<td>888.8 mg</td>
<td>74.07 %</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>36.0 mg</td>
<td>3.00 %</td>
</tr>
<tr>
<td>Orange flavour</td>
<td>12.0 mg</td>
<td>1.00 %</td>
</tr>
<tr>
<td>Aspartam</td>
<td>3.6 mg</td>
<td>0.30 %</td>
</tr>
<tr>
<td>Acesulfam K</td>
<td>3.6 mg</td>
<td>0.30 %</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>6.0 mg</td>
<td>0.50 %</td>
</tr>
</tbody>
</table>

Total: 1200.0 mg

- **Weight SD:** 0.14 %
- **Tablet thickness:** 3.52 mm
- **Tablet density:** 1.344
- **Tablet hardness:** 54.6 N
- **Hardness SD:** 14.37 %
- **Compression:** 30.6 kN
# StarLac®:
# Orodispersable Formulation II

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcysteine</td>
<td>200.0</td>
<td>16.67 %</td>
</tr>
<tr>
<td>StarLac</td>
<td>953.2</td>
<td>79.43 %</td>
</tr>
<tr>
<td>Orange flavour</td>
<td>24.0</td>
<td>2.00 %</td>
</tr>
<tr>
<td>Aspartame</td>
<td>7.2</td>
<td>0.60 %</td>
</tr>
<tr>
<td>Acesulfam K</td>
<td>7.2</td>
<td>0.60 %</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>8.4</td>
<td>0.70 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1200.0</strong></td>
<td><strong>100 %</strong></td>
</tr>
</tbody>
</table>

- **Weight SD:** 0.11 %
- **Tablet thickness:** 4.91 mm
- **Tablet density:** 1.216
- **Tablet hardness:** 51.6 N
- **Hardness SD:** 14.22 %
- **Compression:** 16.5 kN
Meggle Lactose – StarLac®

- Spherical form → excellent flowability
- Fast, hardness-independent disintegration
- Minimal influence of hydrophobic lubricant (Mg-stearate)
- Low to mid-dose dosage formulation (up to 20%)

**Application:**
- DC Tableting with fast release
- ODT` s
Product Functionality

- Tablettose 70/80
- Tablettose 100
- FlowLac 100
- FlowLac 90
- StarLac
- Cellactose 80
- MicroceLac 100
RetaLac®:
A new DC excipient for SR formulations
Common oral extended-release Systems

Reservoir systems

- Membrane controlled (constant or non-constant activity)
- Membrane –matrix combination

  Common dosage form: Multi unit-coated beads, Multi-unit coated minitablet, Monolithic coated tablet

Osmotic pump systems

- Elementary osmotic pump
- Microporous osmotic pump
- Layered osmotic pump (e.g. Push-Pull®, Push-Stick®)

  Common dosage form: Coated monolithic tablet, Coated layered tablet

Matrix systems

- Hydrophilic (erosion/diffusion or swelling/erosion controlled)
- Hydrophobic Homogenous (dissolved drugs)

  Heterogenous (dispersed drugs)

  Common dosage form: Monolithic tablet, Multi-unit minitablets, Layered tablet,
  Compression coated tablet
API Release Mechanisms

Two competing dissolution mechanisms:

- API diffusion
  - Fickian diffusional API release
API Release Mechanisms

Two competing dissolution mechanism:

- API diffusion
  - Fickian diffusional API release
  - **Tablet erosion**
Hydrophilic matrix system: API release

1. Administration of SR tablet
2. Hydrating, formation of gel layer, water penetration, Expansion of gel layer
   - API release controlled by diffusion
3. Completed hydration, API release controlled by Erosion
4. Erosion of tablet
RetaLac®

**RetaLac® spray-agglomerated**

- 50% α-Lactose Monohydrate [Ph.Eur./USP-NF/JP]
- 50% HPMC, Type 2208, 4000 mPas (2% w/v at 20 °C); [Ph.Eur./USP-NF/JP]
RetaLac – Functional performance - Flowability

Flowability
RetaLac versus an
Admixture Comprising Tablettose 80 & HPMC K4M DC

- RetaLac
- Admixture 1
- Admixture 2
- Admixture 3

Flow rate [ml/s]

Aperture [mm]
RetaLac – Functional performance

Tensile Strength as a Function of Compression Pressure
RetaLac versus an Admixture Comprising Tablettose 80 & Hypromellose K4

- RetaLac lot L1004 A4020
- RetaLac lot L1021 A4020
- RetaLac lot L1033 A4020
- Physical admixture 1
- Physical admixture 2
- Physical admixture 3

[Graph showing the tensile strength vs. compaction pressure for different samples and admixtures.]
## Wetgranulation vs. Direct Compression

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Direct compression</th>
<th>Wet granulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>mg</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>50</td>
<td>500</td>
</tr>
<tr>
<td>RetaLac</td>
<td>49.5</td>
<td>495</td>
</tr>
<tr>
<td>Lactose monohydrate, 200 mesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypromellose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>1000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Direct compression</th>
<th>Wet granulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compaction force (kN)</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Tablet hardness (N)</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>Dissolution profile</td>
<td>See graph</td>
<td></td>
</tr>
</tbody>
</table>
Wet Granulation vs. Direct Compression

Metformin Dissolved as a Function of Time
Dissolution in 0.05 M pH 6.8 Phosphate Buffer

Similarity Factor f2 = 90%
RetaLac®

Formulation studies
## Materials and Methods

<table>
<thead>
<tr>
<th>API</th>
<th>Solubility (25°C)</th>
<th>Absorbance (nm)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>7.4 mg/L</td>
<td>271</td>
<td><img src="image1" alt="Theophylline Structure" /></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>14.0 g/L</td>
<td>244</td>
<td><img src="image2" alt="Acetaminophen Structure" /></td>
</tr>
<tr>
<td>(Paracetamol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diprophylline</td>
<td>330 g/L</td>
<td>274</td>
<td><img src="image3" alt="Diprophylline Structure" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>API [%]</th>
<th>5.0</th>
<th>10.0</th>
<th>20.0</th>
<th>30.0</th>
<th>40.0</th>
<th>50.0</th>
<th>60.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>RetaLac [%]</td>
<td>84.5</td>
<td>89.5</td>
<td>79.5</td>
<td>69.5</td>
<td>59.5</td>
<td>49.5</td>
<td>39.5</td>
</tr>
<tr>
<td>Mg stearate [%]</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
RetaLac®

Release Profiles
Drug Release: Theophylline

0.1 M HCl

Phosphate pH 7.4

MEGGLE

Retalac®
Absolute Drug Release: Paracetamol

0.1 M HCl

- 60 % Paracetamol
- 50 %
- 40 %
- 30 %
- 20 %
- 10 %

Phosphate pH 7.4

- 60 % Paracetamol
- 50 %
- 40 %
- 30 %
- 20 %
- 10 %

Time [h]

Drug released, mg
Absolute Drug Release: Diprophylline

0.1 M HCl

Phosphate pH 7.4

Time [h]
RetaLac®

Influence of device design parameters
Tablet Surface Area, Height

Cylinder

Area of the top is $\pi r^2$
Area of the bottom is $\pi r^2$
Area of the side is $2\pi rh$
Surface area = $2\pi r^2 + 2\pi rh$
Volume $V = \pi r^2 h$

<table>
<thead>
<tr>
<th>Height (h) (r=1)</th>
<th>Volume (V)</th>
<th>Surface area (A)</th>
<th>A/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\pi$</td>
<td>$4\pi$</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>10$\pi$</td>
<td>$22\pi$</td>
<td>2.2</td>
</tr>
<tr>
<td>100</td>
<td>100$\pi$</td>
<td>202$\pi$</td>
<td>2.02</td>
</tr>
</tbody>
</table>

Ratio Surface area vs. Volume is smaller for a larger Tablet Height (h)
Tablet Height

Effects of the initial tablet height (indicated in the diagrams) on theophylline release from RetaLac®-based tablets in different buffer systems (drug loading: 50%, initial tablet diameter: 11.3mm).
Effects of the initial tablet diameter (indicated in the diagrams) on theophylline release from RetaLac®-based tablets in different buffer systems (drug loading: 10%, initial tablet height: 2.4mm).
Wettability of HPMC vs. RetaLac®

Agitation in cold water

50% HPMC 4000mPas & 50% Lactose monohydrate

Physical admixture

Co-processed RetaLac®

No dispersion after 10 min.  Immediate dispersion

(see also: http://www.meggle-pharma.de/de/produkte-und-leistungen/produkte/produktuebersicht/retalac-coprocessed-/)
RetaLac®: Characteristics

- Enables direct compression of sustained release formulations
- Superior compressibility to physical mixture, minimizes friability
- Structured surface, good flowability
- Defined and adjustable release profiles
- Reduced process steps (two-in-one system)
- Improves wettability of HPMC

**Applications:**
- Direct compression of modified release formulations (up to 60% API)
- Facilitates preparation of dispersions containing HPMC/Lactose
Starting materials (α–Lactose Monohydrate and Powdered Cellulose, MCC, Starch, HPMC) are monographed according to Ph.Eur, USP-NF, JP.

For US a Drug Master File is required and existing.

For Europe the formulation is registered according to the individual excipients.
## Meggle Contacts

**www.meggle-pharma.com**

**Sales Contact:** Ruth Leinenbach  
E-mail: ruth.leinenbach@meggle.com  
Tel.: +55 11 2893 4831  
Fax: +55 11 991 464 850

**Technical Contact:** Ulrich Marcher  
E-Mail: ulrich.marcher@meggle.de  
Tel.: +49 80 71 73 480  
Fax: +49 80 71 73 320
Questions?

Muh?