Co-processed Compound Based on Lactose and Starch Compared to Physical Mixtures: Tablet Formation and Disintegration at Different Maxium Relative Densities

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INTRODUCTION

- Direct compression is a major formulation process in Pharmaceutical Technology. StarLac® is a new direct compression excipient, produced by spray-drying of - lactose-monohydrate and maize starch.
- The aim of this study is to study the tablet formation of a compound based on lactose and starch (85:15 w/w) compared to the pure substances and graded physical mixtures. Pressure-time-profiles, pressure-porositypro-files and compactibility-plots help to evaluate the tableting properties.
- Second aim is to study in detail the disintegration and drug release from tablets of StarLac® compared to those of the physical mixture and this especially at higher maximum relative densities.

MATERIALS & METHODS

StarLac®, a spray-dried compound of lactose and maize starch (Meggle GmbH, Wasserburg, Germany); FlowLac® 100, spray-dried lactose (Meggle GmbH, Wasserburg, Germany); maize starch (Roquette Freres, Lestrem, France); theophylline monohydrate (Carl Roth GmbH, Karlsruhe, Germany) and magnesium stearate (Caelo GmbH, Hilden, Germany) were used.
A mixture containg FlowLac® 100: Maize starch / 85:15 similar to StarLac® will be called in this context physical mixture.
Tablets were produced on an instrumented eccentric tableting machine (Korsch EK0, Berlin, Germany). The mass for each tablet was calculated for each maximum relative density used (0.750 - 0.975). Each tablet was manually filled in and produced with an accuracy of ± 0,001 at maximum relative density. 0,5 % magnesium stearate were used as lubricant.
For mathematical analysis of the data the 3D-model (Picker 2000 and 2002) was primarily used because only this method includes all the three parameters time, porosity and pressure simultaneously:

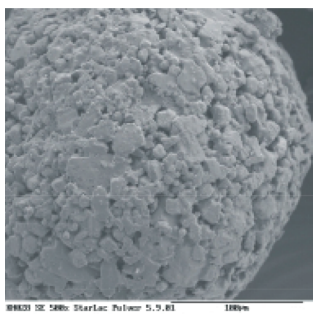
$$z = \ln \frac{1}{1 - D}$$
$$= ((t - t_{max}) * (d + \omega * (P_{max} - P))) + (e * P) + (f + d * t_{max})$$

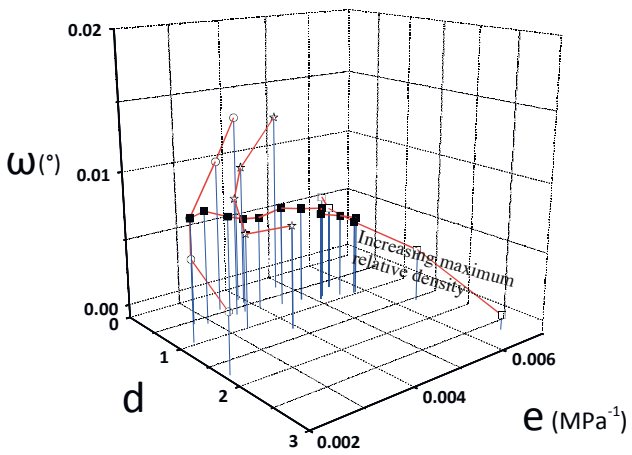
with t = time, p = pressure, ω = angle of torsion, D = relative density, d = time plasticity, e = pressure plasticity , f = intersection.

Pressure plasticity e correlates with the micro-hardness of the final tablets, the angle of torsion ω with the Young's modul and time plasticity d is influenced by tableting speed (Picker 2002).
Elastic recovery was tested using a micrometer screw (Mitutoyo, Tokyo, Japan), crushing strength was analyzed (Erweka, Heusenstamm, Germany) and disintegration was performed (Erweka, Heusenstamm, Germany).

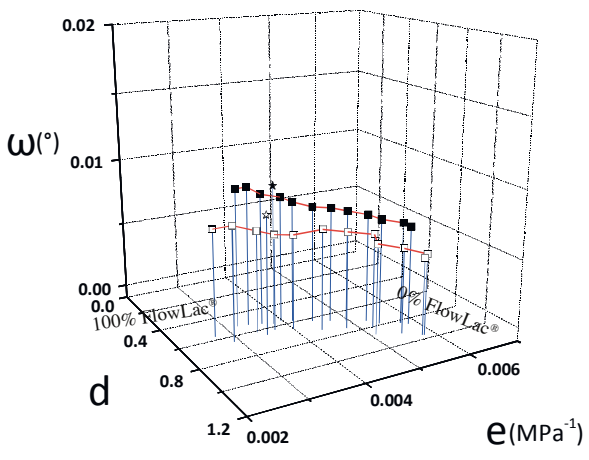
RESULTS & DISCUSSION

StarLac® - Co-processed Compound Based on Lactose and Starch





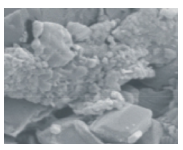
StarLac® (✋), FlowLac® (○), maize starch (□), binary mixtures (■)



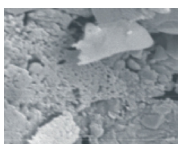
Binary mixture [□], ternary mixtures with theophylline [■], StarLac® [✋],mixture of StarLac® with theophylline [✋]

Tablet Formation Compared to Mixtures

Analysis by three-dimensional modeling indicates that the tableting behavior of StarLac® at a maximum relative density from 0.75 to 0.90 is similar to that of FlowLac®.
The influence of maize starch becomes visible at a maximum relative density from 0.90 to 0.95 as well by the pressure plasticity of the 3D-Model as by the slope of the Heckel function. Maize starch shows a higher percentage of elastic deformation in comparison to StarLac® and FlowLac®.



Before



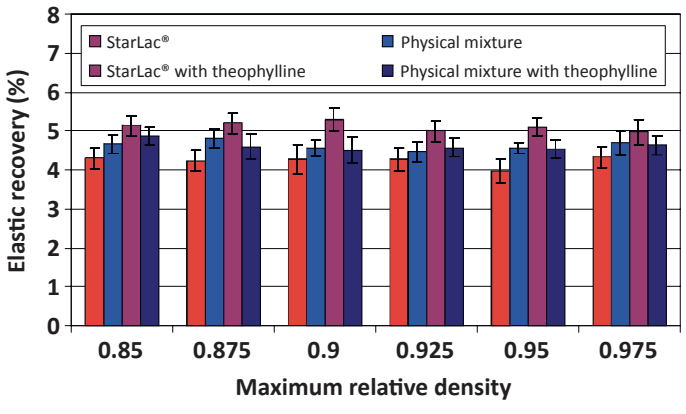
After

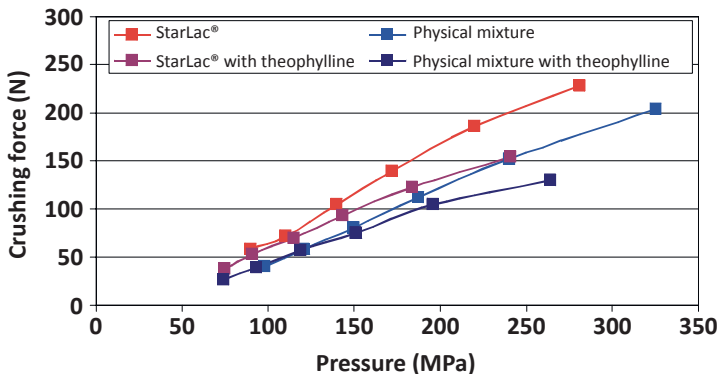
Tableting

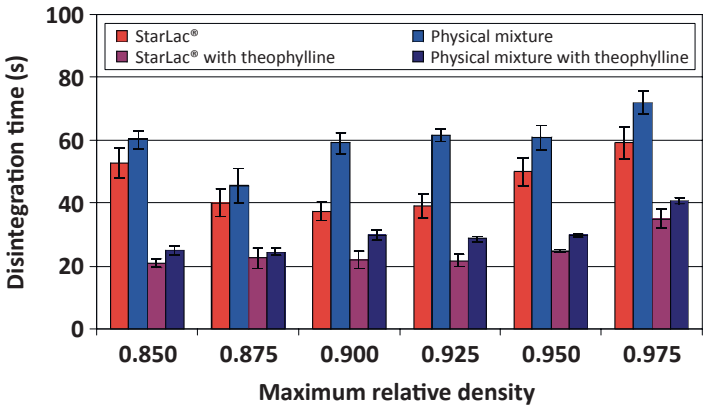
SEMs show a difference before and after tabletting of StarLac®. After deformation the crystals of lactose are smaller and the particles of starch create a fine net work. A reason can be the viscoelastic flow of starch at high pressure, since that can only be detected at a maximum relative density of 0.95.

Tablet Formation at Higher Maximum Relative Densities

Since the study of mixtures indicates an influence at higher maximum relative densities, tablets of StarLac® and the physical mixture without and with theophylline were produced at higher maxium relative densities.
At higher maximum relative densities elastic reovery was lower and compactibility higher for tablets containing StarLac® compared to the physical mixture for tablets with as well as without theophylline.
This shows that the spray dying process improves compactibility.
In this context it is important that the pressure to produce the same maximum relative density is lower for tablets containg StarLac®. With theophyllline monohydrate elastic recovery increased and compactibility decreased.







Disintegration

All tablets fulfilled the condition of Ph.Eur. (15 minutes (900 seconds) for tablets). All tablets disintegrated rapidly. Disintegration time increased with increasing maximum relative density respectively maximum pressure.
It did not correlate with elastic recovery and compactibility.
Even when elastic recovery of StarLac® is lower and its compactibility higher disintegration time was higher. This is in accordance with results from Schroeder et al. (2001) and Schwarz et al. (2001).
Especially, starting at a maximum relative density of 0.900 a clear difference can be seen between tablets made with StarLac® and those made with the physical mixture. This means that the difference in disintegration time exists mainly at higher pressures when the materials are highly deformed.
Thus the disintegration is influenced by the tablet formation process. When the maize starch is included in the particles as it is only the case at higher maximum relative densities (SEMs) it disintegration is enahnced. Most probably a disintegrating force inside the particles is created.
Summarizing, the compound shows improved disintegration by improved plastic deformation.

CONCLUSION

- Tableting properties indicate, that StarLac® is a useful new excipient for direct compression.
- Its advantage compared to FlowLac® is the higher plastic deformability. The better compactibility is superior to the physical mixure. The improvement compared to the physical mixtures can be derived from the deformation properties.
- At higher maximum relative densities, there is a higher compactibility for StarLac® and at the same time a faster disintegration of the tablets. The difference in disintegration is significant mainly at higher maximum relative densities.

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