Book of Abstracts
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Effect of the Microstructure of Paracetamol Granules on Tablet Properties

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1. Summary

Paracetamol Tablets are based on Paracetamol granules mixed with excipients. The production process of these granules effects on the final tablet properties too. Most common is the granulation of Paracetamol in a fluidized bed. An alternative is a production process in a high-shear mixer. Research on the compressibility, the microstructure and the distribution of the binder was done using granules out of these production processes. The microstructure of a granule produced in a high shear process shows a much more dense packing and a more homogeneous distribution of the binder (starch). The difference of the microstructure is confirmed by X-ray micro-tomography. The effect of the granule structure on tablet strength was investigated using granules produced in a fluidized bed and in a high-shear mixing process. Plotting the strength of the tablets versus the compression force shows a significant higher strength of the tablets for granules produced in a high-shear process. As a result it can be stated that the production process of Paracetamol granules effects on the resulting microstructure and the final properties of the tablets. Whether these findings can be transferred to other pharmaceutical products is subject to further research.

Keywords: Microstructure, Paracetamol, Granule, Product Design

2. Extended Abstract

Introduction

Tablets containing Paracetamol are based on Paracetamol granules mixed with excipients. Typically the Paracetamol granules contain 90-96% Paracetamol and a binder, e.g. starch. The effects of starches on the mechanical properties of Paracetamol tablet formulations are described by *[Alebiowu]*. The production process

of these granules effects on the final tablet properties too. Most common is the granulation of Paracetamol in a fluidized bed. An alternative is a high shear production process *[Pietsch]*. Granules out of these production processes were used for the experiments.
Research on the compressibility, the microstructure and the distribution of the binder was done using granules with an identical composition (96% Paracetamol, 4% starch).

Experimental methods

Analysis of the microstructure

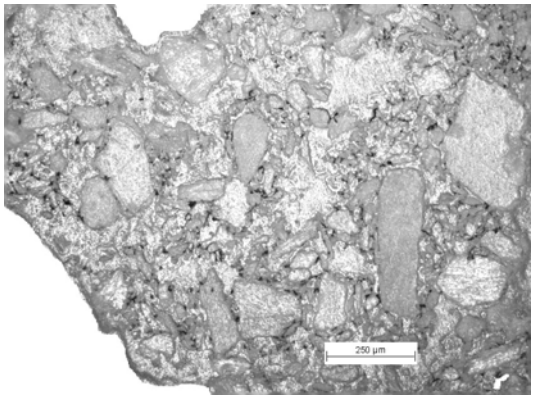
An analysis of the microstructure of the granules is based on several preparation steps. First granules in the size region of 1 mm must be fixed in a resin. This improves the handling properties and ensures that there is no effect on the microstructure due to the following preparations steps. In the next preparation step the fixed granules were abraded and polished. Using the iodine-starch reaction on the polished surface of the embedded granules offers the opportunity to distinguish between starch and Paracetamol / resin. An image analysis gives a size and density distribution of the starch within the granules.

Compressibility

The compressibility of the Paracetamol granules was tested using an eccentric press, Type EK0, Korsch Company. Tablets of 630 mg with a diameter of 12mm were produced. The strength of these tablets was determined using a fully automated tablet testing system type WHT1, Pharmatest Company.

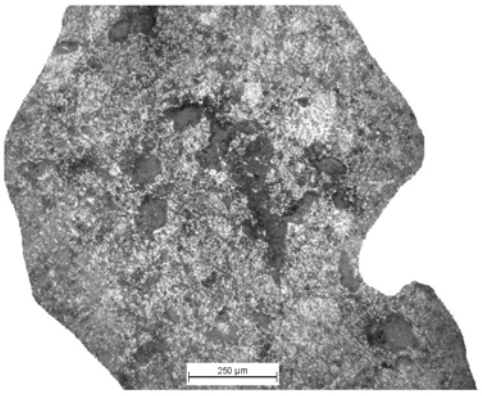
Results and discussion

The typical microstructure of a fluidised bed granule after the preparation steps can be seen in Picture 1. The black dots represent the location of the starch.



Picture 1. Microstructure of a fluidised bed granule

Picture 2 shows the microstructure of a granule produced in a high shear process. Due to the energy input a much more homogeneous distribution of the starch can be seen. Additionally the Paracetamol crystals are reduced in size, thus the energy input is high enough to support grinding.



Picture 2. Microstructure of a granule produced in a high shear process

The surface area of the starch was determined using image analysis. The surface area increases from 2.5% (Picture 1) up to 13% (Picture2).

In Figure 1 the strength of the tablets is plotted versus the compression force. For all compression forces the granules produced in a high shear process are inducing a significant higher strength of the tablets.

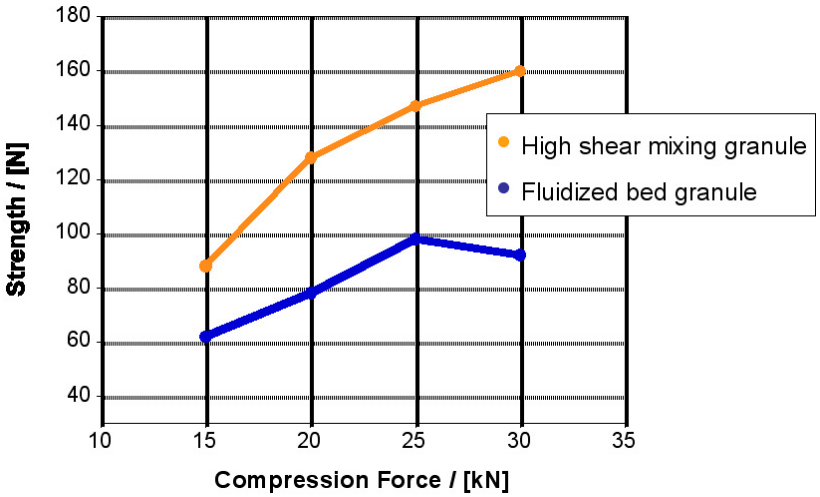


Figure 1. Effect of granule structure on tablet strength

Conclusion

It can be stated that the production process of Paracetamol granules effects on the resulting microstructure. A clear correlation between microstructure and tablet strength can be stated. It is to be expected that these findings could be transferred to other pharmaceutical products.

References

Alebiowu G., Itiola O. A., Acta Pharm. 53 (2003)
Pietsch, W., Agglomeration in Industry, Wiley–VCH–Verlag, Weinheim, 85-166 (2005)