Influence of different directly compressible mannitol grades on dissolution of low soluble fenofibrate

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Objectives

- To investigate the influence of different commercially available DC (directly compressible) mannitol types on in vitro dissolution of fenofibrate tablets
- To find relationships between dissolution and granule or tablet properties

Introduction

Pharmaceutical excipients are important factors for the quality of final dosage forms, influencing stability, safety, galenical properties and bioavailability.

DC mannitol is an interesting tablet carrier with distinct advantages such as excellent compatibility, compactibility and higher intrinsic dissolution rate compared to other fillers (e.g. alpha-lactose-monohydrate). In this study dissolution profiles of mannitol tablets containing low soluble fenofibrate were investigated to determine the influence of different commercially available DC mannitol types on dissolution.

Fenofibrate is a BCS class II substance, showing high permeability leading to rapid and nearly complete absorption of appropriately formulated dosage forms. The very poor water solubility (< 1 mg/l), however, can cause severe bioavailability problems depending on the individual formulation.

Methods

DC Mannitol + Fenofibrate + Aerosil

1st Mixing step

+ Mg-stearate

2nd Mixing step

Tabletting

Figure 1: Diagram of manufacturing process

Tablets were produced by direct compression on an instrumented single punch press (EK0, Korsch, Germany). The composition and manufacture were identical except for the different DC mannitol grades used (four spray-dried and three granulated types).

Composition	Content in mg	Content in %
Fenofibrate (D_{50}5 µm)	100.0 mg	20.0%
DC Mannitol	387.5 mg	77.5%
Highly dispersed silicon dioxide	5.0 mg	1.0%
Magnesium stearate	7.5 mg	1.5%
Total weight:	500.0 mg	
Hardness:	80 ± 5 N	
Shape:	12 mm, round, biplanar, beveled	

Table 1: Composition of fenofibrate tablets

DC Mannitol	Manufacturing Process	Modification (XRD)	BET Surface (m^2/g)	Particle Size (µm)			
				D_{10}	D_{50}	D_{75}	D_{90}
A*	Sprayed	~100%β	1.91	40	96	144	211
B	Sprayed	~70%α, ~30%β	0.43	73	128	173	222
C**	Sprayed	~100%β	2.83	71	240	367	505
D	Sprayed	~90%α, ~10%β	0.26	93	169	225	283
E	Granulated	~100%β	0.55	52	325	385	442
F	Granulated	~100%β	0.46	232	515	715	930
G	Granulated	~100%β	0.35	277	613	870	1150

Table 2: Characterization of DC mannitol types used for tabletting

Characterization of Granules

- Particle size distribution (laser diffraction)
- Morphology (SEM)
- Modification (NIR, XRD)
- Surface area (BET method)

Characterization of Tablets

- Hardness (Erweka system)
- Thickness, weight and calculated density
- Disintegration time (USP apparatus)
- Dissolution (USP paddle)
- Porosity (mercury intrusion)
- Morphology (SEM)

Compaction forces were selected to obtain tablets with equal hardness of 80 ± 5 N for all formulations (TBH 30 MD, Erweka, Germany).

In vitro Dissolution:

- 1000 ml USP simulated gastric fluid without enzymes containing 2% sodium dodecyl sulfate (Roth, Germany)
- USP paddle dissolution tester (Erweka, Germany) directly connected to a computerized UV-system (Perkin Elmer, USA)
- Six tablets for each formulation were tested at 37 ± 0.5 °C and 75 rpm
- UV absorbance of fenofibrate was measured at 290 nm in a 2 mm flow-through cell

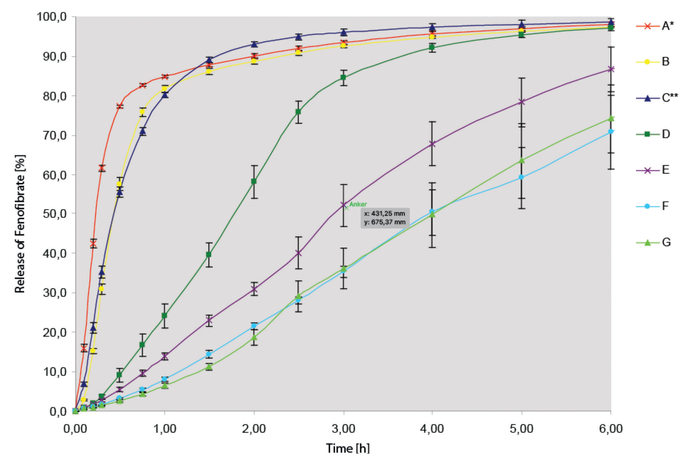

Figure 2: Dissolution of fenofibrate tablets with different DC mannitol grades

The $t_{50\%}$ dissolution values for the tablets ranged from 14 min up to 107 min for spray-dried DC mannitols and between 173 min and 241 min for granulated DC mannitols. The tablet total pore volumes measured by mercury intrusion varied from 148–253 mm^3/g (spray-dried mannitols) and from 119–146 mm^3/g (granulated mannitols). Particle sizes (D_{50}) of the DC granules ranged from 96–240 µm (spray-dried types) and from 325–613 µm (granulated types).

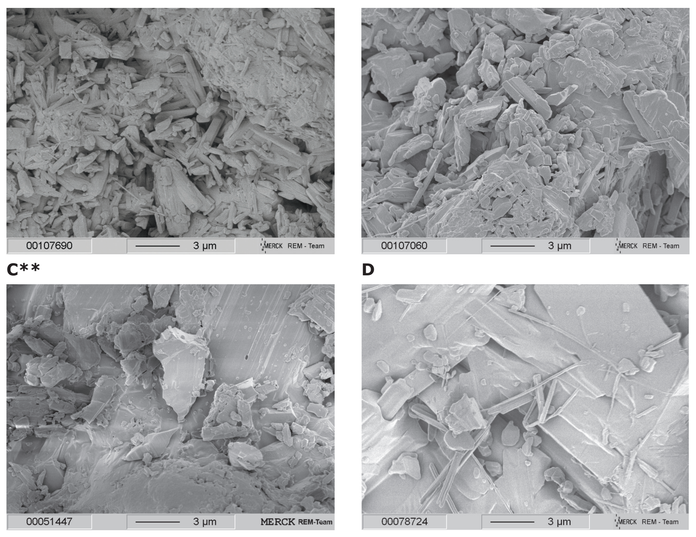

Figure 3: SEM of DC mannitol granules (5000x)

SEM pictures show clear morphological differences not only between the DC mannitols but also for the resulting tablets.

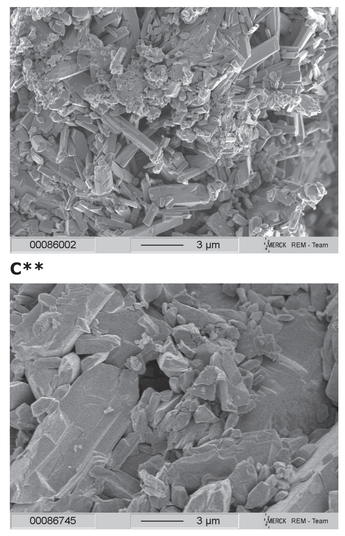

Figure 4: SEM of tablets breaking surfaces (5000x)

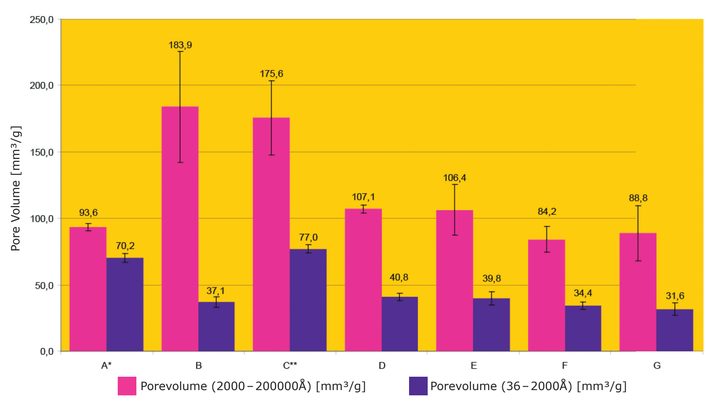

Figure 5: Mercury intrusion of fenofibrate tablets based on different DC mannitols

For sprayed DC materials with comparable particle size (A*/B and C**/D) an influence of mesopore (36–2,000 Å) pore volume on dissolution can be observed whereas dissolution of tablets based on granulated mannitol is mainly influenced by DC material particle size distribution.

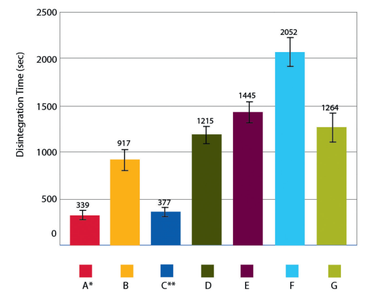

Figure 6: Disintegration time of fenofibrate tablets

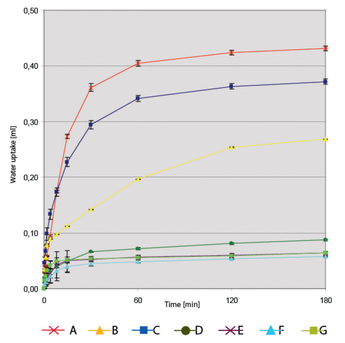

Figure 7: Water uptake of fenofibrate tablets vs. time (Enslin method)

Conclusions

Large differences in dissolution rates of the fenofibrate tablets were observed depending on the DC mannitol used. Generally, an accelerated dissolution was observed for tablets based on spray-dried materials compared to those containing granulated DC mannitols. The dissolution profiles correlate with particle sizes of the DC granules, tablet porosities and morphology. A correlation between tablet water uptake and disintegration time could be observed, but hardly correlation of those two parameters with dissolution.

KEY
* Parteck® M 100 excipients
** Parteck® M 200 excipients

Acknowledgements
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