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Brief/Technical Note

On the Drug-Loading Capacity of Pectin Powder for Direct Compression

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KEY WORDS: 3-D modelling; colon cancer treatment; colon targeting; compaction behavior; Heckel equation; matrix tablets; mechanical properties.

INTRODUCTION

Pectin has lately gained much attention for colon cancer treatment (1–3): it reduces the severity of colon cancer (3), and it is selectively digested by colonic microflora, which can be exploited as a trigger for drug release. Therefore, a pectin matrix potentially serves dual purposes in treatment of colon cancer as drug carrier and/or therapeutic agent itself.

We have previously investigated how pectin powders alone behave in direct compression (DC) of tablets (4,5). Pectin is a soft material, which undergoes low degrees of particle rearrangement and fragmentation (5). The degree of methoxylation (DM) was found to have a limited effect on compressibility, but the mechanical strength of the tablets is strongly dependent on both DM and initial particle size. Pectins with DM ≤10 % produce mechanically strong tablets, whereas pectins with DM >50 % produce incoherent compacts.

In the present study, a suitable pectin quality is challenged as a matrix former: a model drug material, which will not deform and contribute to bonding and thus increased tablet tensile strength (*i.e.*, "inert"), is mixed in different ratios with pectin powder. Drugs and excipients usually contribute to the formation of tablets, but quartz (SiO_2) will not. If coherent tablets can be made of pectin and quartz powder by DC, pectin should also be promising for use as colon-targeting DC matrix tablets containing different drugs. The aim of the current study was to characterize the compaction behavior and mechanical properties of DC tablets made with different ratios of pectin DM 4 % with ultrafine quartz powder.

MATERIALS AND METHODS

Materials

Pectin of DM 4 % (Pectin classic AU-L 049/01) was donated by Herbstreith & Fox GmbH, Germany. Ultrafine quartz powder (Millisil® W12) was obtained from Quarzwerke, Germany.

Methods

Powders and tablets were handled at constant temperature (23±0.5°C) and humidity (43±2 % RH) throughout the study. Powder mixtures of pectin DM 4 % and Millisil® W12 were *stepwise mixed by hand* in the ratios 100:0, 70:30, 50:50, and 30:70 (*m*/*m*). Apparent particle densities were determined by helium pycnometry (AccuPyc 1330, Micromeritics, USA) as described in (6).

Tablets were produced at various maximum relative densities ($\rho_{rel,\ max}$ from 0.77 to 0.90) by varying the tablet height. Eleven-millimeter flat-faced punches (Ritter Pharma-Technik GmbH, Germany) were used on an instrumented tablet press (EK0/DMS, Korsch GmbH, Germany) at ten tablets per minute. Displacement was measured using an inductive transducer (W20 TK, Hottinger Baldwin Messtechnik, Germany) and corrected for elastic deformation. A mass of 450.0-mg powder was accurately weighed and manually filled into

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Table I. Powder Characteristics of the Raw Materials

Characteristic	Pectin DM 4 %	Millisil® W12[a]
Bulk density (g/cm^3)	0.54	0.90
Tapped density (g/cm^3)	0.69	1.33
Apparent particle density (g/cm^3)	1.661±0.003	2.65
Hausner ratio	1.28	1.48
Flowability (from Hausner ratio)	Poor	Very poor
LOD (%)	8.0	Not determined
Particle size (μm)		
D50	69.9±0.5	16
D90	141.0±1.4	50[b]

[a] Data provided by producer
[b] D95

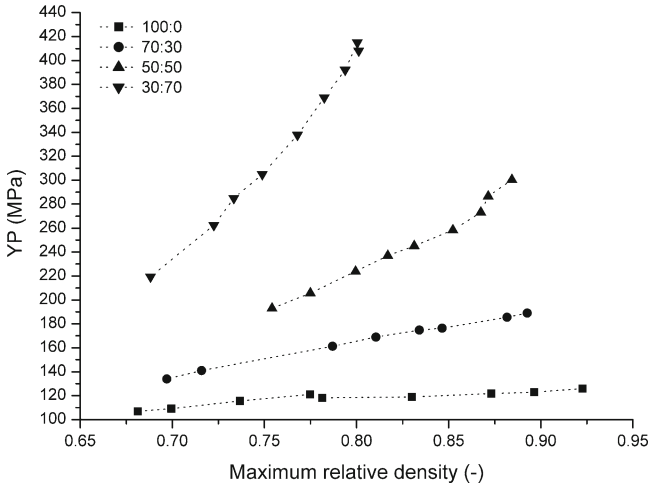

Fig. 1. Heckel yield pressure as function of maximum relative density ($\rho_{rel,\ max}$) for different ratios of pectin DM 4 % and Millisil® W12, $n=1$

the die and compressed without a lubricant. Force, time, and displacement data of the upper punch were recorded by DMC-plus (Hottinger Baldwin Messtechnik, Germany). For each compaction, the "in-die" yield pressure was derived from the linear part of the Heckel profile (7,8), which corresponded to 20–80 % of the maximum pressure.

The compaction behavior was also evaluated by 3-D modelling (9,10). In brief, a twisted plane is fitted to three parameters (normalized time, pressure, and ln (1/1-D_{rel})) above 50 % of the maximum pressure by the least-squares method of Levenberg–Marquardt (Matlab). Derived parameters are time plasticity (*d*), pressure plasticity (*e*), and fast elastic decompression, *i.e.*, the inverse of ω, which are plotted in the 3-D parameter plot (9, 10).

The axial tablet expansion was measured "in-die", *i.e.*, under maximum compression and at the end of the decompression phase (milliseconds after compression), and "out-of-die" immediately after ejection (seconds after compression), after 24 h and finally after 10 days. The percentage increase of tablet height related to the minimum tablet height was calculated. The crushing strength of the tablets was analyzed (TBH 30, Erweka GmbH, Germany), and tensile strength calculated (11).

RESULTS

Powder characteristics of pectin and quartz powder are summarized in Table I. The apparent particle density of quartz powder is significantly higher compared to pectin, and for the powder mixtures, almost the theoretical values were found (Table II).

Tableting Behavior

Quartz powder itself does not deform and will not form coherent tablets under the applied conditions. The tableting behavior of the pectin quartz powder mixtures changes proportionally to the fraction of non-compressible ("inert") component.

The Heckel yield pressures (Fig. 1 and Table II) increased with increasing fraction of quartz powder in the mixtures, meaning that the plasticity of the powder decreased as expected. 3-D parameters (Fig. 2) time plasticity (*d*) and pressure plasticity (*e*) increased with increased fractions of pectin. This was expected and supports the findings from the Heckel analysis. In addition, the 3-D model provides information on elastic properties of the powder mixtures. The fast elastic decompression, *i.e.*, inverse of ω, was highest for pure pectin powders and decreased with increasing fractions of quartz powder.

The elastic behavior of the powder mixtures was also evaluated by measuring the axial tablet expansion. Generally,

Table II. Characteristics of Powder Mixtures and Tablets

Pectin DM 4 %	Millisil® W12	Apparent particle density (g/cm^3)	Apparent particle density (theoretical value) (g/cm^3)	Compression to $\rho_{rel,\ max}$ 0.83	
				Yield pressure (MPa)[b]	Tensile strength (MPa)[b]
100	0	–[a]	–[a]	119	0.56
70	30	1.876±0.002	1.871	175	0.66
50	50	2.051±0.004	2.041	245	0.37
30	70	2.271±0.003	2.248	408[c]	0.16[c]

[a] given in Table I
[b] $n=1$
[c] $\rho_{rel,\ max}$ 0.80

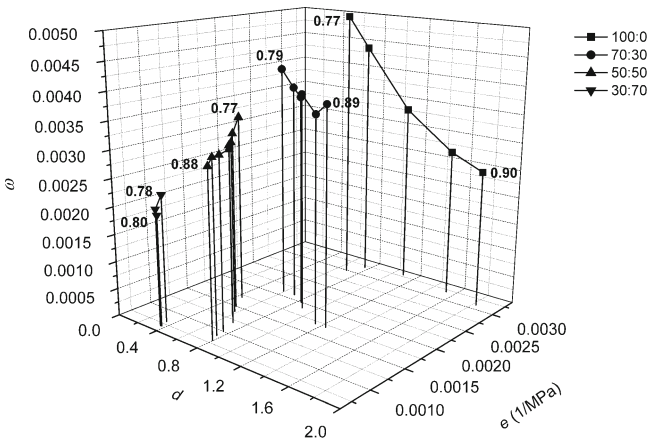

Fig. 2. 3-D parameter plot of different ratios of pectin DM 4 % and Millisil® W12. For each combination of pectin DM 4 % and Millisil® W12, the maximum relative density ($\rho_{rel,\ max}$) intervals are given, $n=1$

the increase of tablet height was most prominent "in-die" [(b) and (c) of Fig. 3] and decreased with increased fractions of quartz powder. It is known from previous studies that tablet relaxation of pectin tablets does not further increase after 7 days; hence, measurement after 10 days represents the endpoint.

Tensile Strength of Tablets

The tensile strengths of the tablets increased with increasing values of $\rho_{rel,\ max}$ (Fig. 4). In general, the higher fraction of quartz powder, the weaker became the tablets. Even at 70 % quartz powder coherent tablets could be made. Small deviations from these trends (*i.e.*, some tablets containing 30 % of quartz powder at $\rho_{rel,\ max}$ 0.87 to 0.89) are supposed to be artifacts due to the single measurement approach.

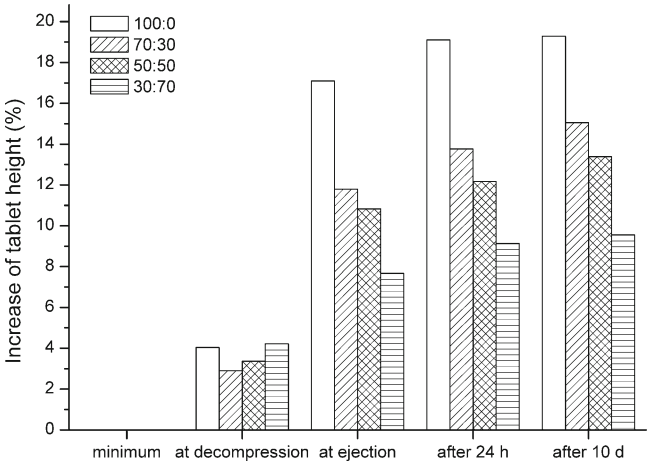

Fig. 3. Increase of tablet height at different time points as a result of tablet relaxation (a) under maximum compression "in die," (b) at the end of the decompression phase (after milliseconds), (c) immediately after ejection of the tablet from the die (after seconds), (d) after 24 h, and (e) after 10 days for different ratios of pectin DM 4 % and Millisil® W12. $\rho_{rel,\ max}=0.83$ for all except 30:70 where $\rho_{rel,\ max}=0.80$, $n=1$

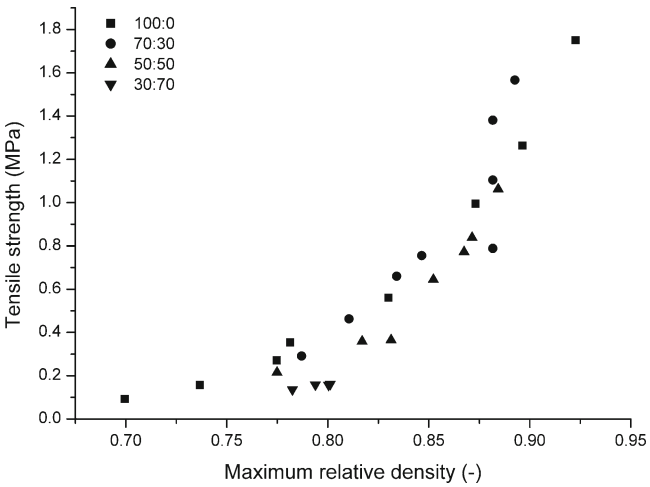

Fig. 4. Tensile strengths of tablets made from different ratios of pectin DM 4 % and Millisil® W12 at different maximum relative densities ($\rho_{rel,\ max}$), $n=1$

DISCUSSION

Quartz powder itself does not deform nor form tablets under the applied conditions. Adding quartz powder as an "inert" non-compressible component does not change the typical behavior of pectin, but reduces the extent of soft and ductile behavior of the mixtures proportional to the added fraction. The values of the derived parameters change accordingly: yield pressures increase, time plasticity (d) and pressure plasticity (e) decrease. The elastic component was reduced as observed by the inverse of ω and axial tablet expansion as a result of the reduced fraction of pectin. Higher pressures were required to compress the powder mixtures containing quartz powder compared to pure pectin.

Amounts larger than 50 % of the "inert" non-compressible component interrupt the pectin–pectin bonding and thereby reduce the mechanical strength of the tablets. Nevertheless, coherent tablets could be made with only 30 % pectin. This suggests a high drug-loading capacity of pectin.

CONCLUSION

The deformation parameters (Heckel, 3-D model) and axial tablet expansion of blends between an "inert" non-compressible model substance and pectin DM 4 % change systematically with the pectin fraction. The results indicate a high drug-loading capacity and suggest that pectin has a potential as a dry binder for colon DC tablets.

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