

Compressibility and compactibility of pectin powders

-A study of their potential as direct compression excipients in tablets



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A dissertation for the degree of Philosophiae Doctor

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Tromsø 2011

To Øystein

*Alt for å finne det sannes mysterium,
-det er den ekte forskers kriterium.*
From "Peer Gynt", Henrik Ibsen (1828-1906)

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ABSTRACT

This thesis is dedicated to direct compression studies of pectin, a natural polysaccharide with potential as a pharmaceutical excipient due to its ability to act as a carrier for colon-specific drug delivery as well as for sustained drug release purposes. The main objective of this thesis was to study the suitability of pectin as a matrix former in tablets. The compressibility and compactibility of pectin powders were studied as a function of various degree of methoxylation (DM) grades and different particle sizes.

Pectin powders with similar powder characteristics were compressed by direct compression on a compaction simulator and an instrumented tablet press, respectively. The results showed that pectin powders, irrespective of DM and particle size, were classified as class IIA powders, showing a low degree of particle rearrangement and a relatively low degree of fragmentation. The powders were relatively soft and resembled the deformation behaviour of pregelatinized starch, an elastically deforming material. The pectinic acids (DM \leq 10%) were slightly more viscoelastic than the other pectin grades. However, in general terms, it should be emphasized that the DM had a limited effect on the compression behaviour (i.e. compressibility) although an increased DM gave slightly softer and slightly less brittle particles. On the contrary, the compactibility was strongly dependent on both DM and initial particle size. The low-methoxylated (LM) pectin (DM < 50%) and especially pectinic acids (DM \leq 10%) produced mechanically strong tablets, whereas the high-methoxylated (HM) pectins did not produce coherent tablets. The tensile strength increased with decreasing initial particle size. Pectin also proved to have a high dilution potential as a binder/matrix former, as coherent tablets were produced even when 70% of an inert material was incorporated. To summarize, the results showed that pectins with DM \leq 40% have potential as direct compression excipients in tablets.

ABBREVIATIONS

API	Active pharmaceutical ingredient
DCPD	Dibasic calcium phosphate dihydrate
DM	Degree of methoxylation
DSC	Differential scanning calorimetry
ER	Elastic recovery
GalA	1,4-linked α -D-galacturonic acid
HG	Homogalacturonan
HM	High-methoxylated
HPMC	Hydroxypropyl methylcellulose
LM	Low-methoxylated
MCC	Microcrystalline cellulose
PGS	Pregelatinized starch
Ph.Eur	The European Pharmacopoeia
PXRD	Powder X-ray diffraction
RG-I	Rhamnogalacturonan I
RG-II	Rhamnogalacturonan II
RH	Relative humidity
SEM	Scanning electron microscopy
SRS	Strain rate sensitivity
$Sv_{(powder)}$	Volume-specific surface area of powder
$Sv_{(tablet)}$	Volume-specific surface area of tablet
WoC	Work of compaction
WoE	Work of immediate elastic recovery
YP	Yield pressure
YP, comp.	Yield pressure during the compression phase
YP, decomp.	Yield pressure during the decompression phase
α -LM	α -lactose monohydrate

SYMBOLS

A	Constant in the Heckel equation
a	Constant in the Kawakita equation
b	Constant in the Kawakita equation
C	Degree of volume reduction
D_{rel}	Relative density
d	Time plasticity
d	Tablet diameter
E	Porosity
E_0	Initial porosity
e	Pressure plasticity
F	Crushing strength
f	Constant in the Shapiro equation
H	Height of the compact at pressure P
H_0	Initial apparent height of the powder ($P = 0$)
h	Tablet height
$h_{at\ max.\ pressure}$	Tablet height at maximum pressure
h_x	Tablet height at time x
k	Constant in the Heckel equation
k	Constant in the Shapiro equation
P	Compaction pressure
p	Pressure
p_{max}	Maximum pressure
t	Normalized time
t_{max}	Normalized time at maximum pressure
V	Volume of the compact at pressure P
V_0	Initial apparent volume of the powder ($P = 0$)
$\rho_{rel, max}$	Maximum relative density
σ	Tensile strength
ω	Twisting angle at t_{max} , fast elastic decompression

LIST OF PAPERS

The present thesis is based on the following papers, which are referred to in the text by their Roman numerals*:

- I: Salbu, L., Bauer-Brandl, A., Tho, I. Direct compression behaviour of low- and high-methoxylated pectins, AAPS PharmSciTech 2010, 11 (1): 18-26

- II: Salbu, L., Bauer-Brandl, A., Alderborn, G., Tho, I. Effect of degree of methoxylation and particle size on compression properties and compactibility of pectin powders, Pharmaceutical Development and Technology, in press, early online: DOI: 10.3109/10837450.2010.535831

- III: Salbu, L., Picker-Freyer, K. M., Schmid, W., Bauer-Brandl, A., Tho, I. Is one tablet sufficient? –Application of 3-D modelling to the compression of pectin powders, manuscript

1 AIMS OF THE THESIS

The overall aim of this thesis was to study the compressibility and compactibility of pectin powders to evaluate their suitability as direct compression excipients for tableting.

More specific aims have been:

- To characterize the powder properties of the various pectin grades (paper I and II)
- To explore if coherent pectin tablets can be produced by direct compression employing zero dwell-time (paper I)
- To study the compressibility by different approaches involving
 - classical “in-die” Heckel analysis and elastic recovery measurements “in-die” and “out-of-die” (paper I)
 - the use of a classification system combined with sequential handling of the compression parameters (paper II)
 - a simultaneous evaluation of the variables force, time and displacement by the 3-D modelling technique (paper III)
- To study the effect of DM and particle size on compressibility and compactibility of pectin powders (paper I and II)
- To compare the compressibility and the compactibility of pectin powders with other pharmaceutical powders with well-known compression behaviour (paper I-III)
- To challenge the 3-D model by evaluating only one tablet (e.g. one relative density) in order to use small amounts of materials and examine how much information can be obtained (paper III)
- To examine the dilution potential of pectin as a binder/matrix former and to explore its compressibility at different levels of pectin and an inert material (thesis)

2 INTRODUCTION

2.1 General methodological considerations at the early stages in development of tablets produced by direct compression

A challenge at the early stages in development of tablets is the limited amount of drug available. Therefore, the order and type of experiments need to be planned thoroughly in order to keep the powder consumption low. In general, the term powder may represent active pharmaceutical ingredients (API's) and/or excipients as well as mixtures of these. From a formulation scientist's point of view, the optimum goal would be to obtain as much information as possible from as few experiments as possible in order to reduce time and costs (i.e. rational tablet development). In order to achieve a high-quality product, a systematic approach during the development phase is essential. For developing new tablets, the powder is firstly characterized, secondly, the compressibility is investigated, and finally, the tablets are characterized in terms of the powder's compactibility. The ultimate goal is to predict the final tablet properties (e.g. tensile strength, drug release properties etc.) from the powder and/or compression characteristics.

2.1.1 Suggestions on suitable powder characterization methods

Physical properties of a powder, such as particle size, size distribution, and shape as well as bulk, tapped and helium densities (the last-mentioned is also known as apparent true density (1)), degree of crystallinity and water content, are likely to influence the compactibility of the powder. Several methods are available for studying the physical properties, but as the amount of powder is limited in the early stages of development, no more than a few methods should be performed for each physical property. Firstly, non-destructive methods such as helium gas pycnometry, should be employed. Helium density is defined as the mass of the particles divided by the solid volume (2). Secondly, methods that have modest sample requirements (milligram quantities) should be performed. These include, for example, optical microscopy, scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), and differential scanning calorimetry (DSC). The microscopy methods provide information on particle shape and morphology. In some cases information on particle size can be obtained by measuring different particle diameters, for instance, Feret's diameter. PXRD is a useful tool in describing the degree of crystallinity, whereas DSC provides information on phase transitions (e.g. glass transition, melting, recrystallization). Thirdly, more powder consuming may be employed,

such as evaluation of powder flow characteristics. By determining the bulk and tapped volumes of a powder sample, the corresponding bulk and tapped densities can be calculated. The European Pharmacopoeia (Ph.Eur) 2.9.34 (method 1) (3) recommends using a 250 ml graduated cylinder and powder samples of 100 g and 220 ± 44 g for the bulk and tapped densities, respectively. These amounts are well above the sizes of the powder samples available in an early phase, hence, reductions may be needed. Klevan *et al.* has reduced the amount of powder to 15 – 58 g in a graduated 50 ml cylinder (4) and even further reduced the amount of powder to 3.5-10.3 g in a 10 ml graduated cylinder (5). The calculated bulk and tapped densities can be further combined to calculate the Hausner ratio and the Carr index (also known as the compressibility index), both of which are measures of the powder flowability (6, 7). Water may be present in a powder sample either as water of crystallization in the powder itself, as adsorbed water or in the headspace as relative humidity (RH) (8). A widely used method is determination of loss on drying (Ph.Eur. 2.2.32, (9)). For hygroscopic materials it might also be interesting to measure the equilibrium moisture sorption by plotting water sorption/desorption isotherms. These can be carried out either gravimetrically or volumetrically. Finally, the particle size distribution of the powder should be estimated. It is generally accepted that in the absence of electrostatic effects, it is easiest to produce homogeneously mixed powders if the individual components to be mixed are of similar particle size, particle density and spherical shape (10). The particle size distribution of dry powder samples can be estimated, for instance, by laser diffraction or analytical sieving. The latter represents a simple and widely used method and is performed according to Ph.Eur. 2.9.38 (11).

2.1.2 Examination of the compressibility

The compressibility of a powder is defined as its ability to deform under pressure (12). During powder compression in a confined space, the material is subjected to compressive forces resulting in a volume reduction. The volume is reduced by decreases in the intra- and interparticulate pore space. The compression is normally described as a sequence of processes involving various mechanisms as described by Alderborn (13). A short summary of these mechanisms is presented in Figure 2.1. At low pressures, the particles firstly undergo rearrangement, which results in a closer packing structure and reduced porosity. When a certain pressure is reached, the rearrangement will cease due to the reduced space and the increased interparticulate friction. The further volume reduction will then take place by changes in the dimensions of the particles. These can either fracture into smaller, discrete

particles or fragments (i.e. particle fragmentation), or the original particles can undergo either temporary (i.e. elastic deformation) or permanent (i.e. plastic deformation) changes in shape as the pressure is increased. The literature (13) also suggests that the smaller particles obtained during the fragmentation could further rearrange and at higher pressures again undergo deformation. Thus, one single particle may undergo this cycle of events several times during one compression event. The mechanisms described so far have in common that all are time-independent processes. However, the deformation can also be time-dependent, which means that the degree of deformation is related to both the applied stress and the time of loading. This deformation behaviour is referred to as the viscoelastic and viscous deformation of a material (13).

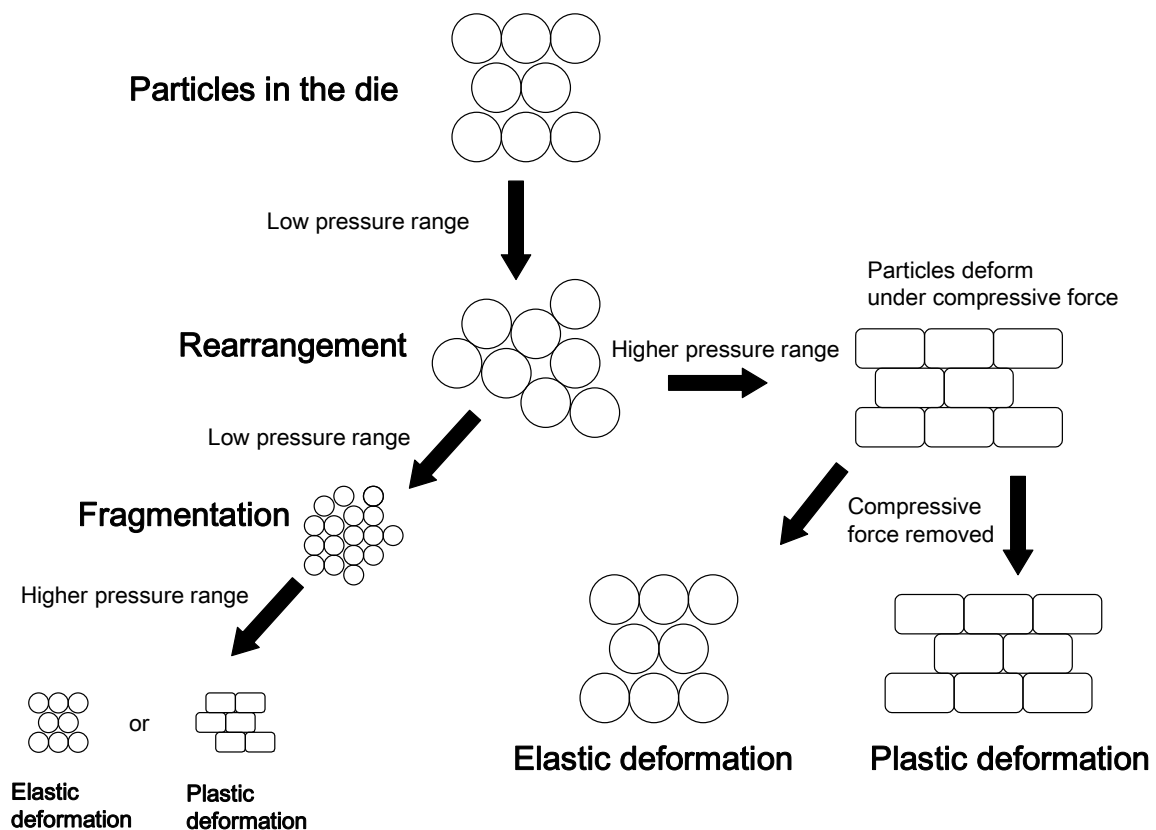


Figure 2.1: Schematic illustration of the mechanisms involved during compression of powder particles

Both fragmentation and plastic deformation are considered to be strength-producing compression mechanisms, whereas elastic deformation is considered to be a disruptive rather than bond-forming mechanism (13). Since fragmentation results in the formation of smaller particles that constitute the tablet, fragmentation is suggested to increase the strength by the

large number of contact sites between particles at which bonds can be formed. For plastic deformation, the increased bonding force is usually explained as an effect of increased contact area at the interparticulate contact sites (13).

As the pressure is increased and the powder particles in a die have undergone some of the mechanisms described, the particle surfaces are brought into close proximity to each other and the consolidation phase starts. Predominantly three bonding mechanisms are assumed to take place during compression of dry powders: intermolecular forces, solid bridges, and mechanical interlocking (13). Bonding by intermolecular forces, also known as adsorption bonding, is formed when two solid surfaces are brought into intimate contact and subsequently adsorb to each other. Solid bridges, also referred to as the diffusion theory of bonding, occurs when two solids are mixed at their interface and accordingly form a continuous solid phase. Mechanical interlocking is suggested to take place in particles that are atypical in shape, for instance needle-shaped or highly irregular and rough, by a strength-increasing-mechanism involving interparticulate hooking (13).

As the powder compression is a complex process and takes place in several stages, it seems challenging, and maybe even unrealistic, to develop one simple equation with few parameters covering the entire compression process. Therefore, a number of different equations exist in the literature (14) that are capable of covering either the initial or the final stage of the densification process. These equations usually have in common that they require accurate measurements of time-resolved force and displacement data. This is achieved by employing instrumented tablet presses (15, 16) or compaction simulators (5, 17-19). The collected force and displacement data is transformed to express, for instance, the relationship between applied pressure and porosity. Using different equations, different compression parameters can be derived. The goal is that these compression parameters could be employed in predicting the properties of the tablets, such as, for instance, the mechanical strength (20). Thus, it is important that the compression parameters actually express the correct physical properties.

The Heckel equation (21, 22) shown as equation 1 is one of the most frequently used equations for characterizing the compressibility. This is probably due to its simplicity.

$$\ln\left(\frac{1}{E}\right) = kP + A \quad (\text{eq. 1})$$

In this equation E represents the porosity of the compressed powder bed at applied pressure P , whereas k and A are constants. Heckel first claimed that it provided information on plastic deformation via curve fitting in the linear region in the compression phase (21, 22). Later, Paronen (23) suggested that information on fast elastic deformation could be obtained by curve fitting in the linear region in the decompression phase. The compression parameter obtained is denoted as the yield pressure, $YP = 1/k$, (either $YP, comp.$ or $YP, decomp.$) and is often referred to as either “apparent yield pressure” or “mean yield pressure” depending on whether the measurement is performed “in-die” (also denoted “at-pressure”) or “out-of-die” (also denoted “zero-pressure” or “ejected tablet”), respectively (24). The former is often preferred due to its reduced time and material consumption. Per definition $YP, comp.$ reflects the total deformation ability, i.e. both plastic and elastic deformation (25), even though it generally seems to be accepted to let $YP, comp.$ denote the plastic deformation only. The equation has some limitations in describing and quantifying what actually happens at low pressures displayed as an initial bending in the Heckel profile (non-linearity). Heckel (21) claimed that this is probably due to particle movement and rearrangement processes before interparticulate bonding becomes appreciable. It should be emphasized that Heckel studied metal powders only. As pharmaceutical powders are expected to have different properties compared to metal powders, Denny (26) proposed that the non-linearity is caused by densification by brittle fracture (i.e. fragmentation) or by the presence of agglomerates of primary particles.

The Heckel profile is often used to compare compression characteristics of different materials. In order to compare the derived compression parameters for different materials, the compression is either performed to the same maximum pressures (16, 18, 27) or to the same maximum relative densities ($\rho_{rel, max}$) of the tablets (28, 29). Figure 2.2 shows the Heckel profiles of four frequently used pharmaceutical excipients with different compression behaviour: Microcrystalline cellulose (a) is a predominantly plastically deforming material, pregelatinized starch (b) is a relatively elastically deforming material, α -lactose monohydrate

(c) is an intermediately fragmenting material, whereas dibasic calcium phosphate dihydrate (d) shows extensive fragmentation (18). Usually a formulation scientist aims at repeating the experiments in order to get a measure of the variation. However, with the aid of compaction simulators providing highly reproducible time-resolved force and displacement data, it is possible to achieve high repeatability, as shown by Haware *et al.* (18) who obtained almost identical Heckel profiles in triplicate (Figure 2.2). This shows that with highly reproducible time-resolved force displacement data, the same amount of information can be obtained independently of how many repetitions are made. Thus, reducing the number of experiments can be justified. This reduces the powder consumption, which again is advantageous in an early development phase with limited powder resources available.

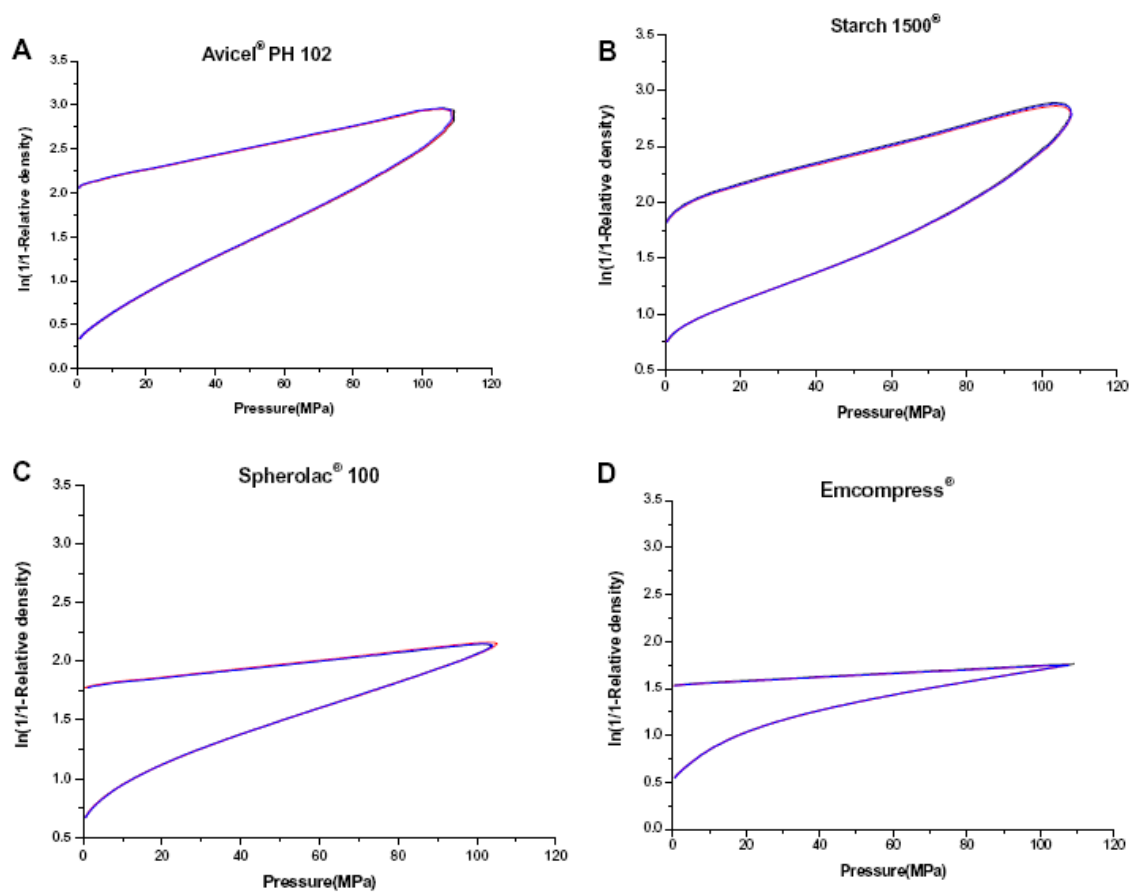


Figure 2.2: Heckel profiles in triplicate with high repeatability obtained from highly reproducible time-resolved force and displacement data collected on a compaction simulator for excipients with different compression behaviour (figure from Haware *et al.* (18))

The Kawakita equation (30) is another equation providing information on the compression behaviour of a powder. The linear form of the Kawakita equation is presented in equation 2:

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \quad (\text{eq. 2})$$

where

$$C = \frac{V_0 - V}{V_0} = \frac{H_0 - H}{H_0}, \quad (\text{eq. 3})$$

P is the applied pressure, and C is the degree of volume reduction (30, 31), which is equivalent to the engineering strain of the particle bed (32, 33), thus related to volume or bed height at applied pressure zero (V_0, H_0) and P (V, H). The slope of the linear part of the compression phase is represented as $1/a$ and by extrapolating the linear regression line, $1/ab$ is found as the intercept with the y-axis. From this procedure two compression parameters are derived: a and $1/b$. The former is commonly interpreted as a constant representing the initial porosity (E_0) (30, 31), which corresponds to the total degree of volume reduction for the bed of particles (34). The Kawakita b parameter is a constant inversely related to the yield strength of the particles (34), and $1/b$ is therefore comparable to $YP, comp.$ from the Heckel analysis, providing information on plastic deformation. It is generally accepted that the Kawakita equation is best used for low pressures and high porosities (26). The equation is applicable for a limited range of materials, predominantly those that produce Heckel profiles with a strong curvature at low pressures. As for the Heckel analysis, an amount of powder sufficient to produce one tablet would be satisfactory for the Kawakita analysis, if the prerequisite of highly repeatability data obtained from a compaction simulator is fulfilled (Figure 2.2).

The compressibility can also be studied by other more complex compaction equations such as the Cooper-Eaton equation (35), the log-exp-equation (also known as the Sonnergaard equation) (36) and the Shapiro equation (37, 38). The linear form of the last-named is shown in equation 4 (37, 38):

$$\ln(E) = \ln E_0 - kP - fP^{0.5} \quad (\text{eq. 4})$$

where E is the porosity, E_0 is the initial porosity, P is the applied pressure and k and f are constants. In a Shapiro profile the f parameter is a measure of the initial bending in the first region, whereas the k parameter reflects the linear part during the compression phase.

Another approach in examining the compressibility is to study the energy involved during the compaction cycle. This can be assessed via force-displacement profiles where various work descriptors can be calculated from different areas under the curve. The apparent work of compaction (WoC) represents the apparent net work used in the formation of the compact and the work needed to overcome die wall friction. Another work descriptor is the work of immediate elastic recovery (WoE), which describes the work, or energy, recovered during the decompression, i.e. the work of elastic recovery during decompression (39). The elastic recovery may continue even after ejection from the die and is observed as an increase in the tablet height.

The classical approach is to validate the results from one equation with results obtained via another equation (for instance the Heckel equation vs the Kawakita equation). As a next step, “out-of-die” measurements of the tablet height at different time intervals make it possible to calculate the elastic recovery (ER) over time according to equation 5:

$$ER(\%) = \frac{h_x - h_{at \text{ max. pressure}}}{h_{at \text{ max. pressure}}} * 100 \quad (\text{eq. 5})$$

where h_x is the tablet height at time x and $h_{at \text{ max. pressure}}$ is the tablet height at maximum pressure.

Recent studies indicate that the compression parameters should be handled sequentially in order to draw correct conclusions on the deformation mechanisms of powders (4, 5, 32). It has been shown statistically that the classification of a powder should be performed according to a series of steps (4), as illustrated in Figure 2.3.

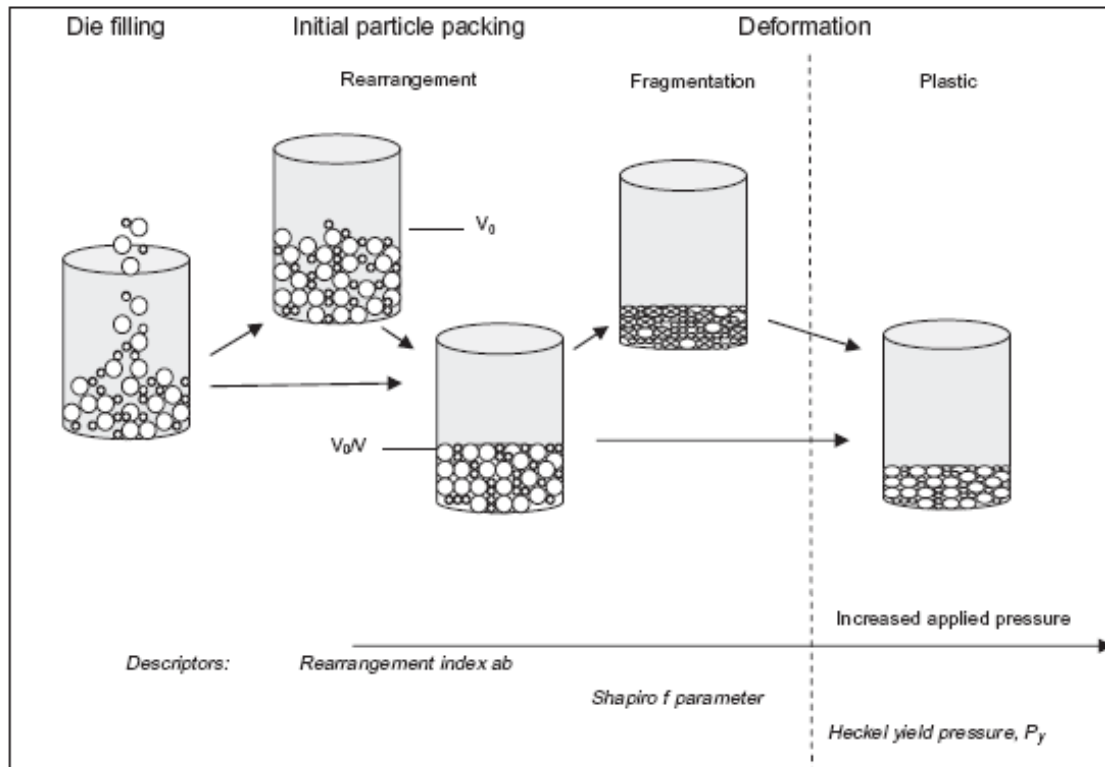


Figure 2.3: Schematic illustration of a new approach with sequential handling of the compression parameters proposed by Nordstöm et al. (32) and Klevan et al. (4, 5) (Figure from Klevan et al. (4))

Firstly, the particle rearrangement should be estimated, which can be done from the ab index derived from the Kawakita parameters a and $1/b$ (30, 32, 34). Materials with a high ab index possess high particle rearrangement and are classified as class I materials. Class II materials show limited particle rearrangement and hence low ab indices. Secondly, a sub-categorization of powder fragmentation propensity should be made, which can be performed using the Shapiro f parameter (5, 37, 38). The fragmentation propensity can also be investigated via determination of the difference in volume-specific surface area of tablets and powders; $Sv_{(tablet)} - Sv_{(powder)}$ (13). Materials with low fragmentation propensity and limited particle rearrangement are classified as class IIA materials, whereas class IIB materials are defined as highly fragmenting with limited particle rearrangement. Finally, the plastic deformation

should be identified. The yield pressure from the Heckel analysis describing the permanent deformation of the particles should be investigated independently of particle rearrangement and particle fragmentation (4). With this stepwise approach, the most important material properties are first determined, thus reducing the risk of misinterpretation. Since the indirect methods involved in determining the volume-specific surface area of powder and tablets do not include data from compaction simulators and as such are expected to have larger standard-deviations, these experiments require replicates, for instance, to be performed in triplicate.

Another approach for studying the compression behaviour of powders is to use the 3-D modelling technique introduced by Picker/Picker-Freyer (40, 41). The 3-D model is presented in equation 6:

$$z = \ln\left(\frac{1}{1 - D_{rel}}\right) = (t - t_{max}) \cdot (d + \omega \cdot (p_{max} - p)) + (e \cdot p) + (f + d \cdot t_{max}) \quad (\text{eq. 6})$$

where D_{rel} = relative density, t = normalized time, p = pressure,

$$d = \frac{\partial \ln\left(\frac{1}{1 - D_{rel}}\right)}{\partial t}, \quad e = \frac{\partial \ln\left(\frac{1}{1 - D_{rel}}\right)}{\partial p}, \quad f = \ln\left(\frac{1}{1 - D_{rel}}\right),$$

t_{max} = normalized time at maximum pressure, p_{max} = maximum pressure, and ω = twisting angle at t_{max} . This model allows a simultaneous evaluation of force, time and displacement. Three parameters are derived from the model: d , e and ω . Time plasticity (d) describes the plastic deformation with respect to time, pressure plasticity (e) describes the relationship between density and pressure, while the inverse angle of torsion (ω) is a measure of the materials' elastic recovery in-die (fast elastic decompression) (40, 41). Compared to Heckel and Kawakita analysis, the 3-D model is able to provide more detailed information on elastic behaviour of the materials since viscoelastic materials can be differentiated from materials that predominantly undergo elastic deformation.

2.1.3 Characterization of the tablets

A powder's compactibility is defined as its ability to form coherent strong compacts (12), whereas the mechanical strength of a tablet is associated with the resistance of the solid specimen towards attrition and fracturing (13). The intention with the attrition-resistance methods, also referred to as friability tests, is to mimic the kind of forces a tablet is subjected to all the way from production to administration. Such tests are performed according to Ph.Eur 2.9.7 (42). The fracture resistance is usually determined in terms of the force required to fracture a specimen across its diameter. The force determined in this diametral-compression test is denoted as the crushing strength. In order to allow comparisons of the results, the tablet dimensions have to be taken into consideration. This is achieved through the tensile strength (σ) according to equation 7 (43):

$$\sigma = \frac{2F}{\pi dh} \quad (\text{eq. 7})$$

where F is the crushing strength, d is the diameter and h is the tablet height.

The tensile strength should not be mixed-up with the term “hardness”, which may be defined as the resistance of a solid to local permanent deformation (44). Hardness is generally measured with static indentation methods. In general a tablet may fracture in five different ways. The ideal case is when a straight crack is dividing the tablet into two semi-circular parts. In cases where this is not obtained, a greater variability in the crushing strength measurements will be observed (45). Hence, Ph.Eur 2.9.8 (46) recommends measuring the crushing strength of ten tablets. This is easily achieved as an in-process control during manufacturing of tablets, but is challenging to redeem during the development phase. If possible, a minimum of three to five tablets should be tested.

2.2 Pectin

2.2.1 Structure

Pectin is a heterogeneous complex polysaccharide present in the cell wall of all higher plants. Commercial pectin is mainly extracted from apple pomace and citrus peel (47, 48). The principal component of pectin is 1,4-linked α -D-galacturonic acid (GalA) (Figure 2.4), which constitutes the backbone of homogalacturonan (HG), one of the three main building blocks of pectin (49-51). The HG molecule is linear and unbranched and is often referred to as the “smooth region” of the pectin structure.

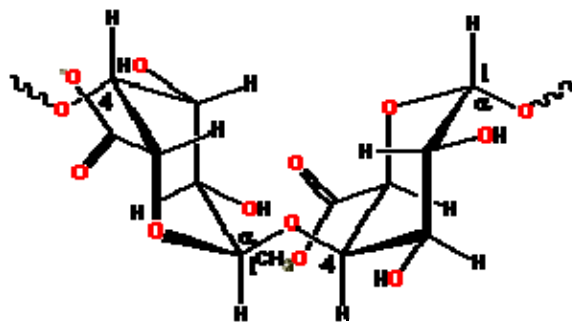


Figure 2.4: Schematic illustration of homogalacturonan (HG) which consists of poly- α -1,4 D-galacturonic acids residues (“smooth region”) (figure from (52))

Rhamnogalacturonan I (RG-I) and rhamnogalacturonan II (RG-II) represent the two other building blocks. Contrary to HG, RG-I is a highly branched polysaccharide. Therefore, this pectin region is often referred to as the “hairy” region. The backbone consists of the repeating disaccharide [\rightarrow 4)- α -D-GalA-(1 \rightarrow 2)- α -L-Rha-(1 \rightarrow] (50, 51, 53). Some of the rhamnose residues in RG-I are substituted at O-4 with side chains of neutral sugars, mainly arabinose and galactose. The branches can be composed of a single sugar unit, or of complex polymers such as arabinogalactan and arabinan (49-51, 53). RG-II on the contrary, has a highly conserved chemical structure. In spite of its name, the structure of RG-II differs strongly from that of RG-I. The backbone of RG-II is composed of approximately nine 1,4-linked α -D-GalA residues. This chain has four heteropolymeric side chains of known and consistent composition. These side chains contain 11 different monosaccharides, among them several rather uncommon sugars (49-51).

2.2.2 Classification

The GalA residues can be methyl esterified at C-6, and the degree of methoxylation (DM) represents the percentage of GalA residues that carries a methyl ester. When $DM \geq 50\%$, the pectins are classified as high-methoxylated (HM), whereas pectins with $DM < 50\%$ are denoted as low-methoxylated (LM) (54). The latter is further subcategorised as pectinic acids when $DM \leq 10\%$. Commercially available LM pectins are prepared by controlled de-esterification of HM pectins with acid in alcoholic medium.

2.2.3 Pharmaceutical applications

Pectin (55) has proven suitable as a thickening agent for stabilizing suspensions (56) and emulsions (57). It is frequently used for controlling drug release due to its ability to swell and form gels, which provide diffusion and/or erosion controlled release. The LM pectins form gels by addition of cross-linking agents, e.g. calcium ions, whereas the HM pectins form gels without addition of cross linkers (58). Pectin is also a potential excipient for colon-specific drug delivery due to its specific degradation by colonic enzymes (59-61). Gamma scintigraphic studies of pectin-based tablets (62) as well as pectin-based press-coated tablets (63) in humans, have shown that the tablets arrived essentially intact in the colon and were degraded locally by enzymes. Pectin could also be combined with other polymers as a film forming excipient to either protect drug substances in a core or to control drug release from the core (64-69). As a solid dosage form, pectin-based pellets have been produced successfully via the extrusion/spheronization method (70-74).

2.2.4 Pectin tablets

Little attention has been given to the tableability of pectin, despite the fact that tablets are the most popular solid dosage form. Sriamornsak *et al.* (75) have produced pectin tablets by direct compression for swelling studies, but applied a prolonged dwell-time of 20 seconds. In a study from Kim *et al.* (76) on the compactibility of two grades of granular pectin (DM 30-37% and DM 65-72%), it was concluded that pectin was hard, rigid and poorly compactible. However, to our knowledge there exist no systematic studies on the influence of DM of pectin with respect to compressibility and compactibility. Therefore, pectin should not be excluded as a possible tableting excipient based on the results from Kim *et al.* (76). More thorough

studies on the compressibility and compactibility of pectin are required in order to draw conclusions on its suitability as a potential tableting excipient.

3 SUMMARY OF PAPERS

3.1 Paper I

This is the first systematic study on the DM of pectin with respect to its compression behaviour and suitability as a direct compression excipient. Pectin was classified as a predominantly elastically deforming material as elastic recovery measurements were of the same order of magnitude as pregelatinized starch. An initial curvature of the Heckel profile indicated a certain degree of fragmentation. The compression behaviour was principally affected by the DM and to a minor degree by the particle size. Tablets with adequate tensile strengths were produced successfully with zero dwell-time. Both the DM and the particle size affected the compactibility; a correlation relating low DM grade with increasing compact strength was observed, and decreased particle size resulted in increased mechanical strength. The HM pectins did not produce coherent compacts, despite the fact that they exhibited the greatest degree of plastic deformation. In general the results from this paper indicated that the LM pectins and pectinic acids had potential as pharmaceutical excipients for direct compression of tablets.

3.2 Paper II

As the results from paper 1 showed that coherent pectin tablets were obtainable, the focus in the next paper was to perform a thorough examination of particle fragmentation and plastic deformation, as these compression mechanisms often are described as facilitating interparticulate bond formation. Recent research has shown that in order to extract information about the compression mechanism from powder compression data, it is important to interpret the phenomena in an appropriate sequential order. Therefore, the chosen approach in this paper was to employ a sequential handling of the “in-die” derived compression parameters in order to study the effect of DM and particle size on the compactibility of pectin powders. According to this powder classification system all pectin powders irrespective of DM and particle size were classified as class IIA powders, showing low degrees of particle rearrangement and relatively low degrees of fragmentation. Pectin particles were found to be relatively soft, with a tendency towards softer particles for pectins of higher DM. The overall variation in fragmentation and deformation behaviour was limited for the various pectin grades tested. Both DM and initial particle size affected the tensile strengths of the pectin tablets. The difference in surface hydrophobicity caused by the DM, was suggested as being

responsible for the variation in the mechanical strengths. The suitability of LM pectins and pectinic acids as potential direct compression excipients was once more confirmed, as these powders consisted of soft particles with high compactibility.

3.3 Paper III

In this paper rational tablet development was in focus as the 3-D modelling technique was challenged in a development set-up using as few tablets as possible to study the compression behaviour of pectin powders. Compared to the evaluations performed in paper I and II, the 3-D model provided additional information on time plasticity and elasticity. Results from one compression showed that the 3-D model was able to distinguish different compression behaviours by separating the pectin powders into three clusters: pectinic acids ($DM \leq 10\%$), LM and HM pectins. The LM pectins exhibited the highest degrees of plastic deformation and fast elastic deformation, whereas the pectinic acids were found to possess a certain degree of fragmentation. The HM pectins were more easily deformable than the pectinic acids. When compacts with various maximum relative densities ($\rho_{rel, max}$) were added to the classical equations (Heckel and Kawakita), no additional information was provided. However, with this set-up the 3-D model gave more detailed information on the elasticity as the shape of the density profile differentiated viscoelastic (pectinic acids, $DM \leq 10\%$) and elastically deforming pectins (those with a $DM \geq 25\%$). In general the results from paper I, II and III have shown that for a first classification of tableting materials, it is suggested to use a single tablet and sequential handling of Kawakita, Shapiro, Heckel and the 3-D model. If the 3-D model is employed alone, or if the material is found to be viscoelastic, it is recommended to use several tablets in order to achieve the model's full potential.

4 EXPERIMENTAL CONSIDERATIONS

4.1 Materials

Table 4.1: An overview of the different pectin grades and excipients used in the study.

Material	Batch no.	Composition	Short name	Supplier	Paper
Pectin classic AU-L 049/01	0106214, 4%	Pectin (of apple pomace origin)	DM 4%	Herbstreith & Fox, Germany	III
Pectin DM 5%	130807DM5, 4.1%		DM 5%		I, II, III
Pectin DM 10%	200807DM10, 8.0%		DM 10%		I, II, III
Pectin DM 25% ^a	310707DM25, 26.1%		DM 25%		I, II, III
Pectin classic CU 701	0903185, 35%		DM 35%		II
Pectin DM 35% ^a	310707DM35, 34.8%	Pectin (from citrus sources)	DM 35%	Herbstreith & Fox, Germany	I, II, III
Pectin DM 40% ^a	310707DM40, 41.7%		DM 40%		I, II, III
Pectin DM 50% ^a	310707DM50, 51.0%		DM 50%		I, II, III
Pectin DM 60% ^a	310707DM60, 61.6%		DM 60%		I, II, III
Pectin classic CU 202	0810679, 72%		DM 72%		II, III
Emcompress [®]	905003	Dibasic calcium phosphate dihydrate	DCPD	JRS Pharma, Germany	I, II, III
Spherolac [®] 100	907012	α -lactose monohydrate	α -LM	Meggle Pharma, Germany	I, II, III
Avicel [®] PH 102	907014	Microcrystalline cellulose	MCC	FMC Biopolymer, Belgium	I, III
Starch 1500 [®]	IN 509959	Pregelatinized starch	PGS	Colorcon, United Kingdom	I, II, III
Millisil [®] W12	-	Quartz sand	-	Quartzwerke, Germany	Thesis
Magnesium stearate	MF19/70089	Magnesium stearate	-	NMD, Norway	I, II, III
Aceton	-	Propanone	-	VWR International, Norway	I, II, III

^afrom same batch origin

4.2 Features of the compaction simulator employed in this study

Compaction simulators are computer-controlled devices designed to mimic the exact cycle of any tableting process in real time with subsequent recording of all important parameters during the cycle (77). The instrumented eccentric presses use sinus-functions as the displacement function, whereas for the studies in the current thesis a saw-tooth displacement profile was employed in the compaction simulator. The compaction simulator employed in the current study is composed of two independent modules; an electromechanical precision press (module 1; Figure 4.1 a-c) and a powder compression device (module 2; Figure 4.2 a-b) (78).

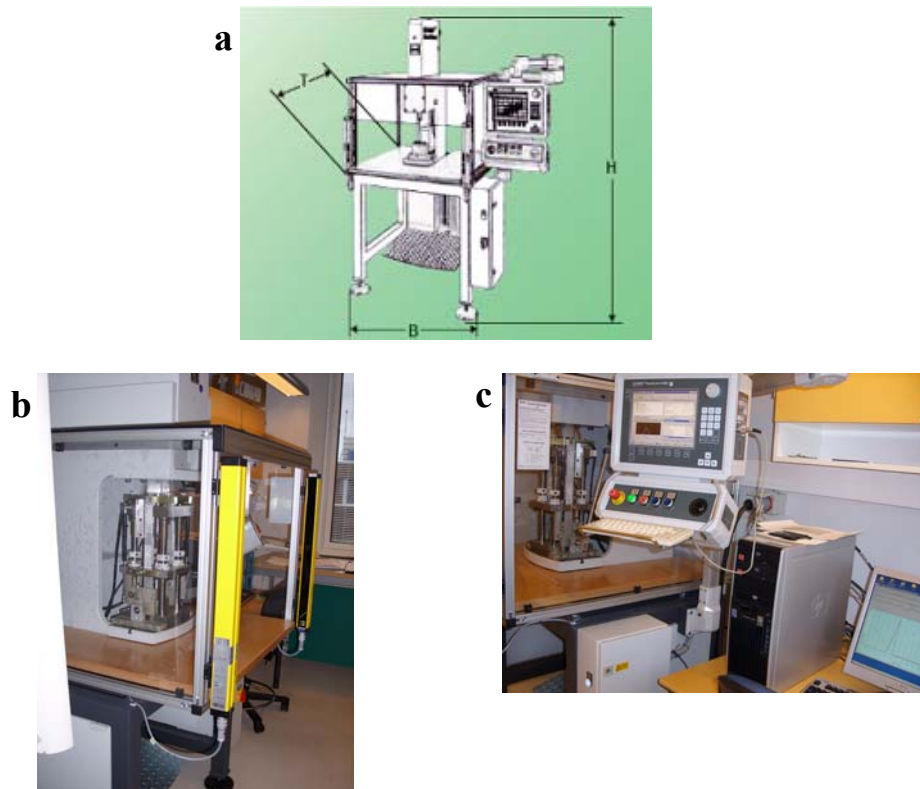


Figure 4.1: *The electromechanical precision press (Schmidt® Servopress 450, Schmidt Technology GmbH, Germany; H: 2.5 m, B: 1.1 m, and T: 1.2 m); module 1 where a shows a schematic illustration (Schmidt Technology GmbH, reproduced with permission), and b and c are original photos.*

Module 1 (Figure 4.1 a-c) is a commercially available precision press with a control unit that drives module 2. Force, position and speed can be set through the number of intermediate stages during one compression cycle. This allows a free definition of the operating profile. It is possible to obtain a maximum force of 50 kN, and a maximum punch speed of 200 mm/s. Module 2 (Figure 4.2 a-b) is a custom-made powder compression device instrumented with sensors that measure time-resolved force and displacement (Figure 4.3 a-d).

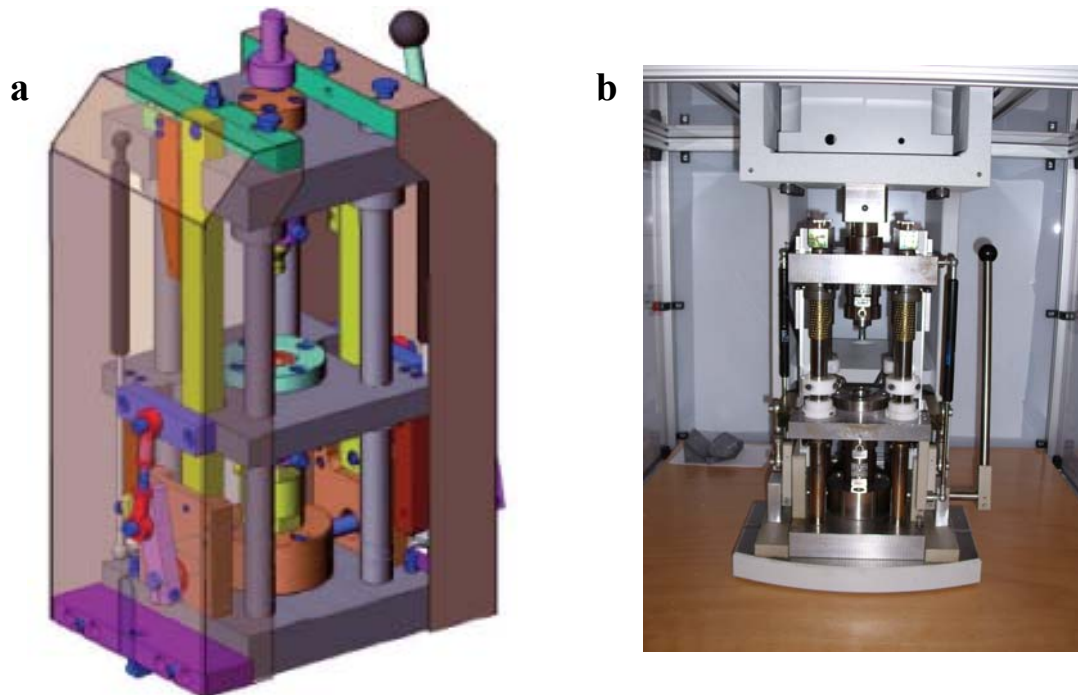


Figure 4.2: *The custom-made powder compression device; module 2 where **a** shows a schematic illustration (IBR Reichenbach, Waldkirch, reproduced with permission) and **b** is an original photo.*

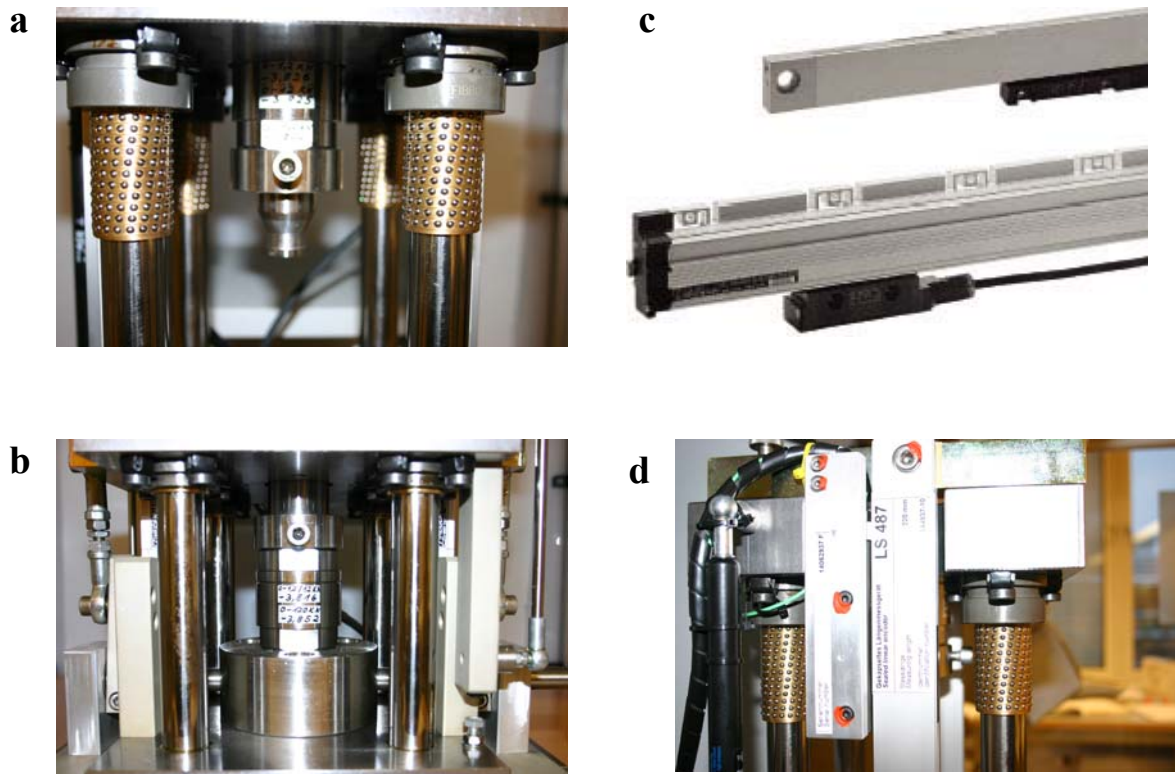


Figure 4.3: *Sensors on module 2: Piezoelectric press force sensor at **a** the upper punch holder and **b** the lower punch holder. **c** and **d**: Sealed optical linear encoders for time-resolved displacement readings (a, b, d: Original photos from (79), c: Heidenhain GmbH).*

Piezoelectric press force sensors (Kistler AG, Switzerland) are mounted on the upper and lower punch holders (Figure 4.3 a-b). These are supplied calibrated and are therefore ready to be used. The time-resolved displacement data of the upper punch is measured by two sealed optical linear encoders (Heidenhain GmbH, Germany, Figure 4.3 c) mounted on each side of the module (Figure 4.3 d). These are guaranteed to have a resolution of $0.1 \mu\text{m}$ and an accuracy of $\pm 0.2 \mu\text{m}$. Tests performed by Haware (80) have shown that the displacement sensors are able to measure distances less than $1 \mu\text{m}$. Both static and dynamic calibration was performed for the displacement sensors. The former was executed by measuring the displacement of blocks of known sizes, whereas the latter was performed by compressing both the upper and the lower punches against each other (punch-to-punch) at 10 mm/s (the upper punch speed employed in this study). In general the dynamic calibration gives information on the deformation of the punches and other machine parts (e.g. punch holders). The raw displacement data were corrected for both the static and dynamic calibrations. The acquisition of the time-resolved force displacement data is performed employing

custom-made software based on C++ and Microsoft Excel.

5 RESULTS AND DISCUSSION

5.1 Powder characterization

Table 5.1 summarizes the powder properties of both unsieved and sieved (90-125 μm) qualities of pectins with DM ranging from 5 to 60% and 5 to 72%, respectively, and reference materials (dibasic calcium phosphate dihydrate (DCPD), α -LM (α -lactose monohydrate), microcrystalline cellulose (MCC), and pregelatinized starch (PGS)). The pectin sample with DM 25% was fractionated into six different size fractions (180-250 μm , 125-180 μm , 90-125 μm , 63-90 μm , 45-63 μm and <45 μm) (Table 5.1). In general, the basic powder properties were all rather similar, except for the particle size expressed as D_{90} of the unsieved samples, which was approximately 220 μm for DM 25%-DM 60% and approximately 90 μm and 125 μm for DM 5% and DM 10%, respectively. The powder flowability was generally poor as illustrated by Hausner ratios above 1.35, except for some samples where it was either passable (Hausner ratio 1.26 – 1.34) or fair (Hausner ratio 1.19 – 1.25) (6, 7). Among the reference materials, DCPD and α -LM exhibited fair powder flow. An effect of the particle size on the flowability of pectin powders was also observed; the flowability became poorer with decreased particle size, except for the smallest size fraction as illustrated in the fractionated sample. In general, the cohesive forces are expected to increase with decreasing particle size, thus reducing the powder flowability. In order to improve the flowability, addition of a glidant should be considered. Possible glidants could be colloidal silica, talc or magnesium stearate, each employed in low concentrations (i.e. <1% by weight) (13).

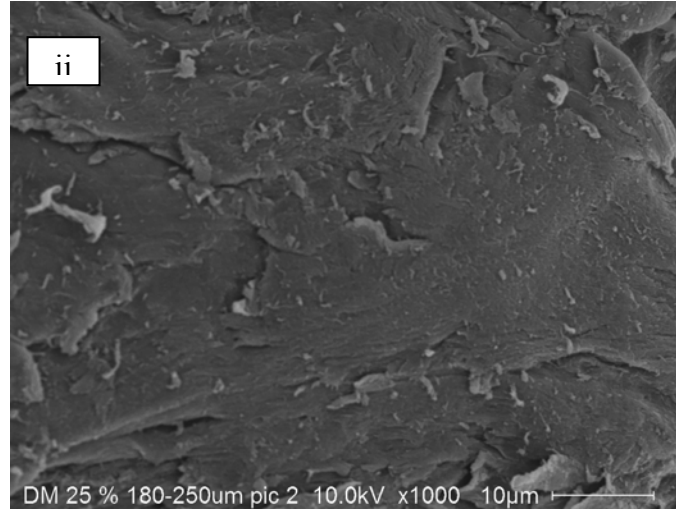
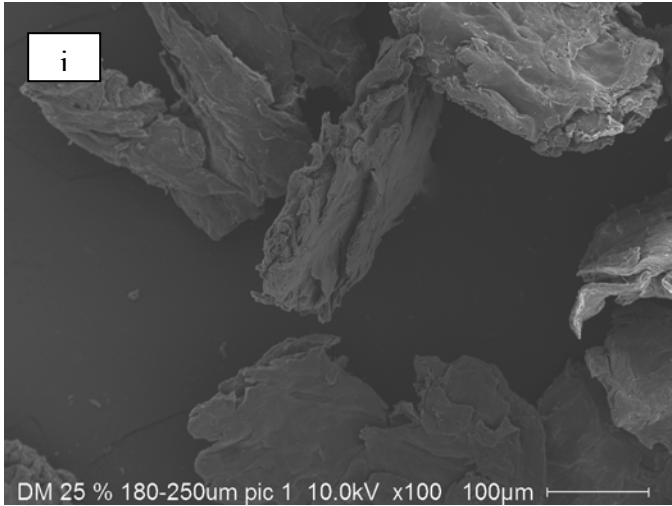
Table 5.1: Powder properties of unsieved and sieved qualities of pectins and reference materials (mean and in parenthesis relative standard deviation (%), n=3)

<i>Unsieved powder samples</i>							
Comment	Pectin grade, DM (%)	Particle size (µm)		Helium density ^a (g/cm ³)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Hausner ratio (-)
		D50	D90				
<i>Batches of different origin</i>	5	53.2	86.7	1.573 (0.05)	0.48 (0.32)	0.63 (0.32)	1.32 (0.00)
	10	65.1	124.9	1.595 (0.04)	0.48 (0.32)	0.63 (0.32)	1.32 (0.00)
<i>Batches of same origin</i>	25	131.6	220.1	1.540 (0.10)	0.37 (1.19)	0.53 (1.14)	1.44 (0.83)
	35	136.4	224.1	1.519 (0.07)	0.38 (0.30)	0.54 (0.30)	1.43 (0.00)
	40	135.7	223.4	1.515 (0.23)	0.37 (0.27)	0.54 (0.27)	1.47 (0.00)
	50	136.4	219.7	1.543 (0.06)	0.42 (0.27)	0.57 (0.27)	1.35 (0.00)
	60	135.4	220.4	1.506 (0.04)	0.43 (0.00)	0.56 (0.00)	1.28 (0.00)
<i>Reference materials</i>	DCPD	171.0	250.2	2.369 (0.05)	0.95 (1.58)	1.14 (0.52)	1.21 (2.07)
	α-LM	117.9	203.0	1.541 (0.03)	0.68 (3.07)	0.84 (3.11)	1.22 (2.21)
	MCC	84.5	177.3	1.558 (0.07)	0.36 (0.83)	0.47 (1.48)	1.31 (2.06)
	PGS	81.1	138.7	1.499 (0.17)	0.64 (5.33)	0.82 (1.47)	1.28 (1.01)
<i>Sieved powder samples</i>							
		Size fraction (µm)					
<i>Batches of different origin</i>	5	90-125		1.573 (0.05)	0.49 (2.08)	0.59 (0.67)	1.21 (1.49)
	10			1.595 (0.04)	0.51 (0.39)	0.64 (1.82)	1.26 (1.47)
	35			1.631 (0.02)	0.38 (0.31)	0.52 (1.27)	1.38 (1.57)
	72			1.537 (0.03)	0.34 (1.48)	0.49 (1.48)	1.44 (0.00)
<i>Batches of same origin</i>	25	90-125		1.540 (0.10)	0.35 (0.50)	0.50 (0.50)	1.43 (0.00)
	35			1.519 (0.07)	0.36 (1.05)	0.50 (0.60)	1.40 (1.63)
	40			1.515 (0.23)	0.34 (0.78)	0.49 (0.92)	1.44 (1.68)
	50			1.543 (0.06)	0.40 (0.38)	0.50 (0.38)	1.25 (0.00)
	60			1.506 (0.04)	0.39 (1.76)	0.48 (0.48)	1.24 (1.42)
<i>One batch, different size fractions</i>	25	180-250		1.540 (0.10)	0.37 (2.00)	0.49 (1.09)	1.30 (1.49)
		125-180			0.37 (1.03)	0.51 (1.03)	1.39 (0.00)
		90-125			0.35 (0.50)	0.50 (0.50)	1.43 (0.00)
		63-90			0.31 (0.00)	0.48 (0.00)	1.56 (0.00)
		45-63			0.28 (1.02)	0.44 (0.54)	1.57 (0.67)
		<45			0.27 (1.33)	0.36 (1.33)	1.33 (0.00)

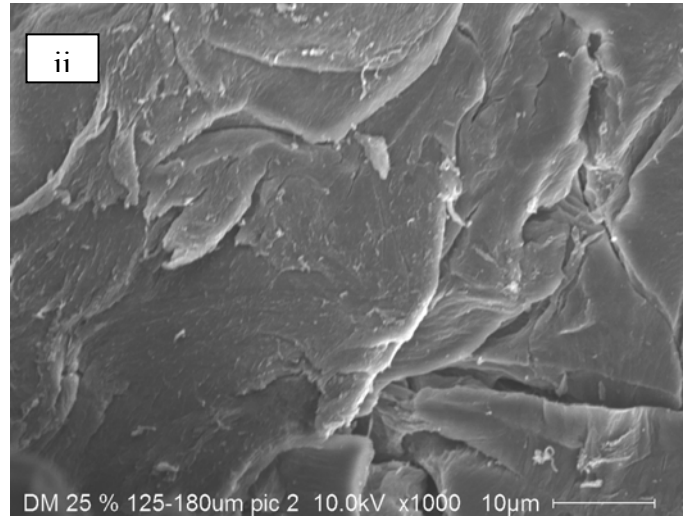
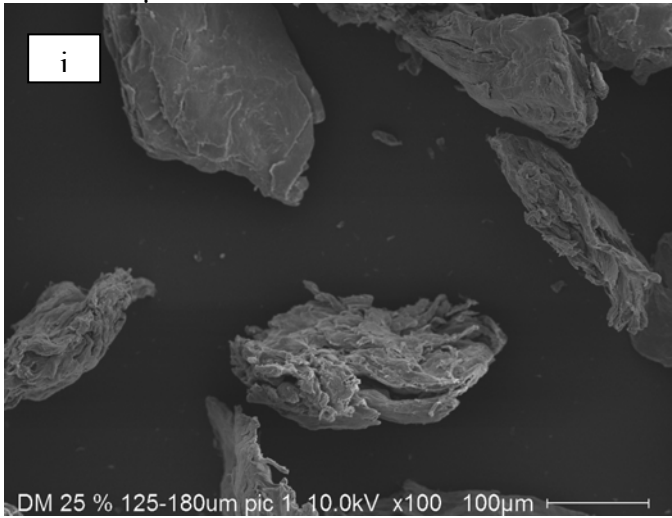
^ameasured for the unsieved powder samples only and values employed for the sieved samples as well

Scanning electron micrographs (SEM) of various size fractions of DM 25% are presented in Figure 5.1. In general the particles were fibrous and irregular in shape (Figure 5.1). This was applicable for all pectin samples irrespective of DM (paper I). At higher magnification (ii), rather rough particle surfaces were observed (Figure 5.1).

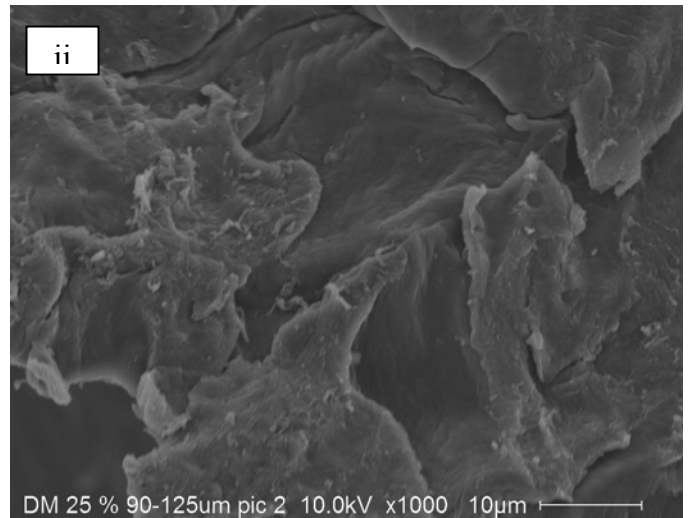
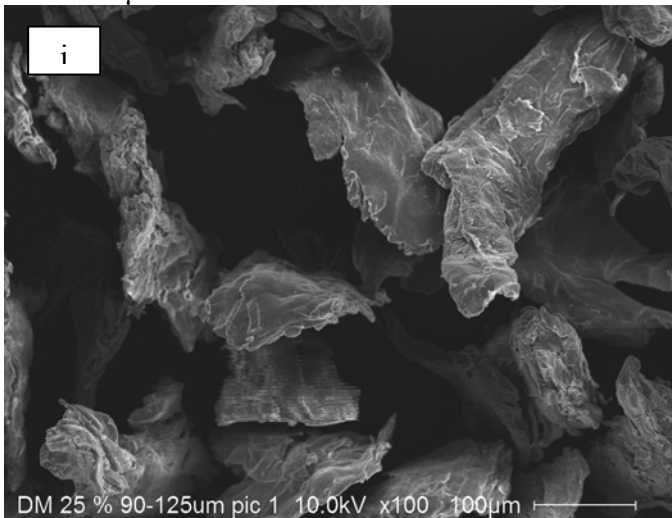
a 180-250 μm



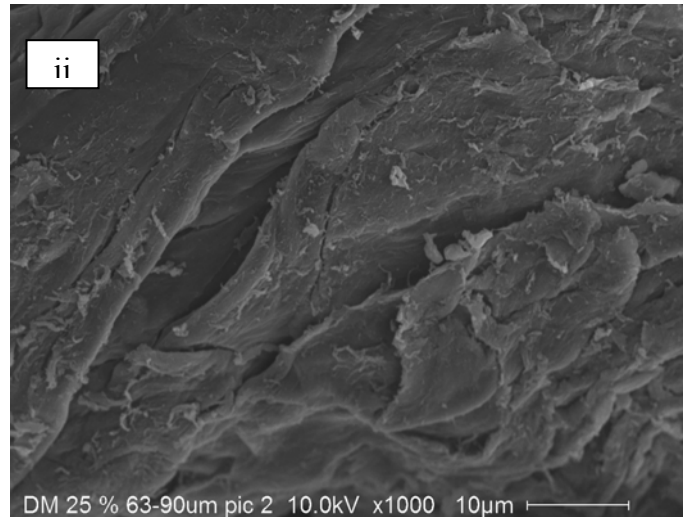
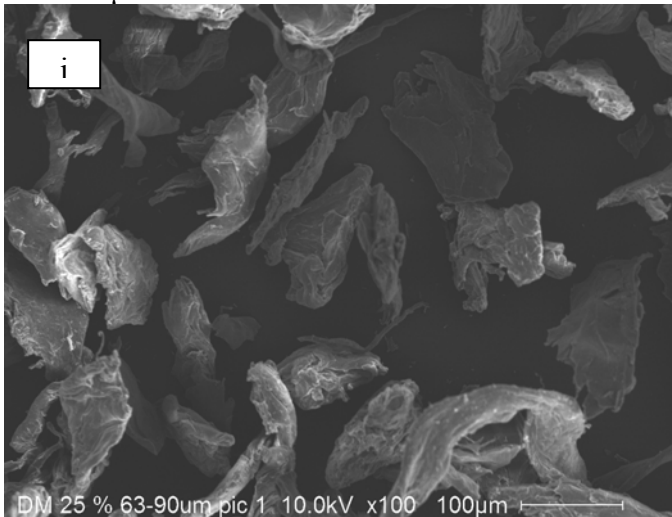
b 125-180 μm



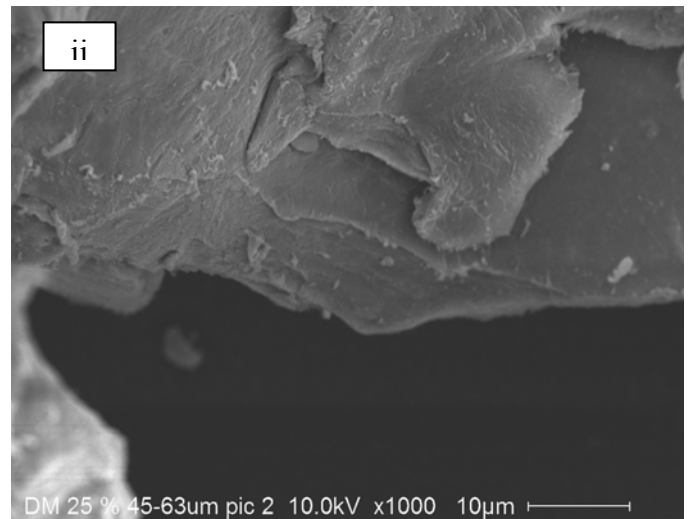
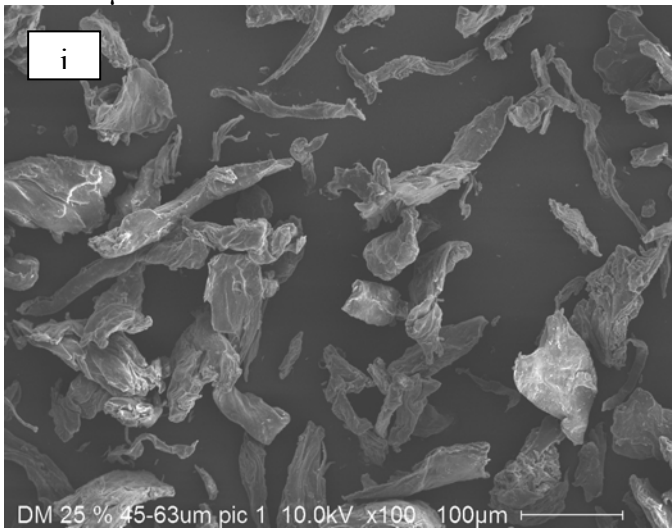
c 90-125 μm



d 63-90 μm



e 45-63 μm



f <45 μm

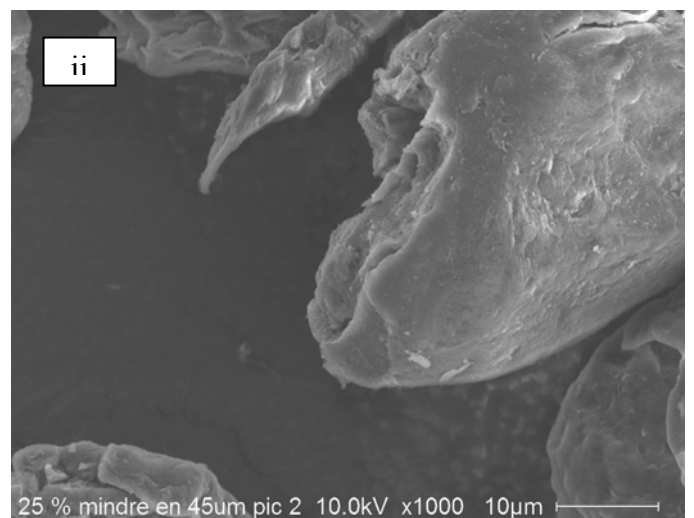
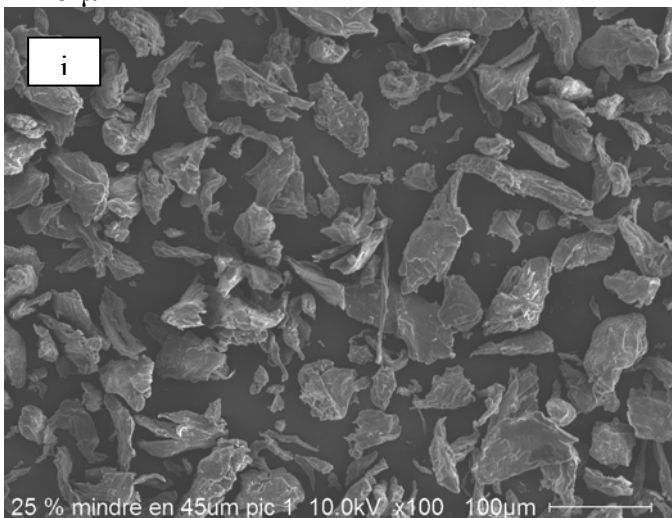


Figure 5.1: SEM micrographs of different size fractions of DM 25% at two different magnifications (i: 10.0 kV x 100, ii: 10.0 kV x 1000): a 180-250 μm , b 125-180 μm , c 90-125 μm , d 63-90 μm , e 45-63 μm , and f <45 μm

In order to study the degree of crystallinity, a powder X-ray diffraction (PXRD) analysis was performed on the unsieved samples (Figure 5.2). Two reflection angles were observed; one between 10 and 15° 2θ and a weaker one between 25 and 30° 2θ. As only marginal differences were observed in the PXRD patterns, a similar degree of crystallinity can be assumed to be present in the pectin samples with various DM.

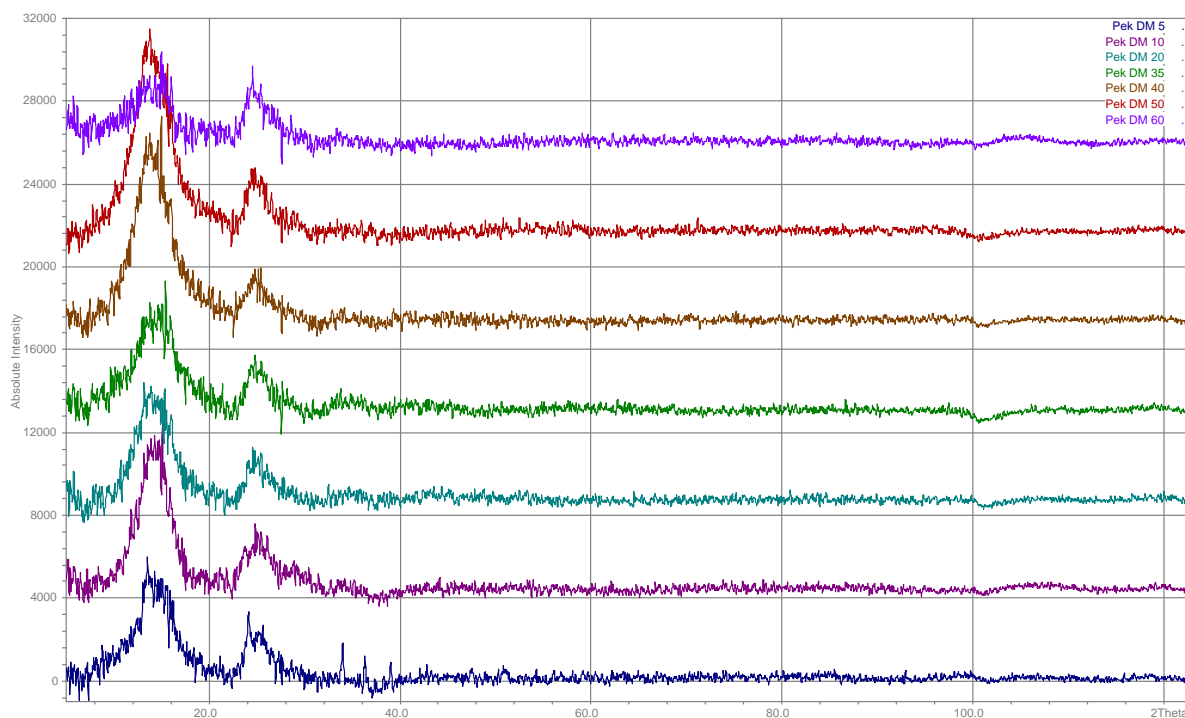


Figure 5.2: X-ray powder diffraction pattern of pectin grades with various degree of methoxylation (DM)

The sorption isotherms of pectin grades with various DM are presented in Figure 5.3. In general, all pectin samples increased their water content with the relative humidity (RH). At 32% RH the water content varied from 7 to 10%. This is of the same order of magnitude as reported for the two hydrophilic polysaccharides chitosan (81) and carrageenan (82), as well as for pregelatinized (83) and acid modified starch (84) under similar experimental conditions. In contrast, the water sorption of microcrystalline cellulose (MCC) at 32% RH has been reported to be lower; approximately 5% (82, 85). It can be hypothesized that the difference in water sorption of pectin and MCC is due to the different molecular structures. In MCC strong hydrogen bonds are suggested to hold the molecules tightly together (86). For pectin, the methoxy substituents both reduce the number of possible hydrogen bonds and

create a larger distance between the polymer chains, thus making them more susceptible for water molecules. This hypothesis seems to be confirmed by the differences in water sorption related to DM; the HM pectins (DM 50% and DM 60%) showed higher water sorption compared to the pectinic acid (e.g. DM 5%) (Figure 5.3). To summarize, the water sorption may be expected to be higher in pectin compared to MCC, and the water sorption was mainly found to increase with increasing DM.

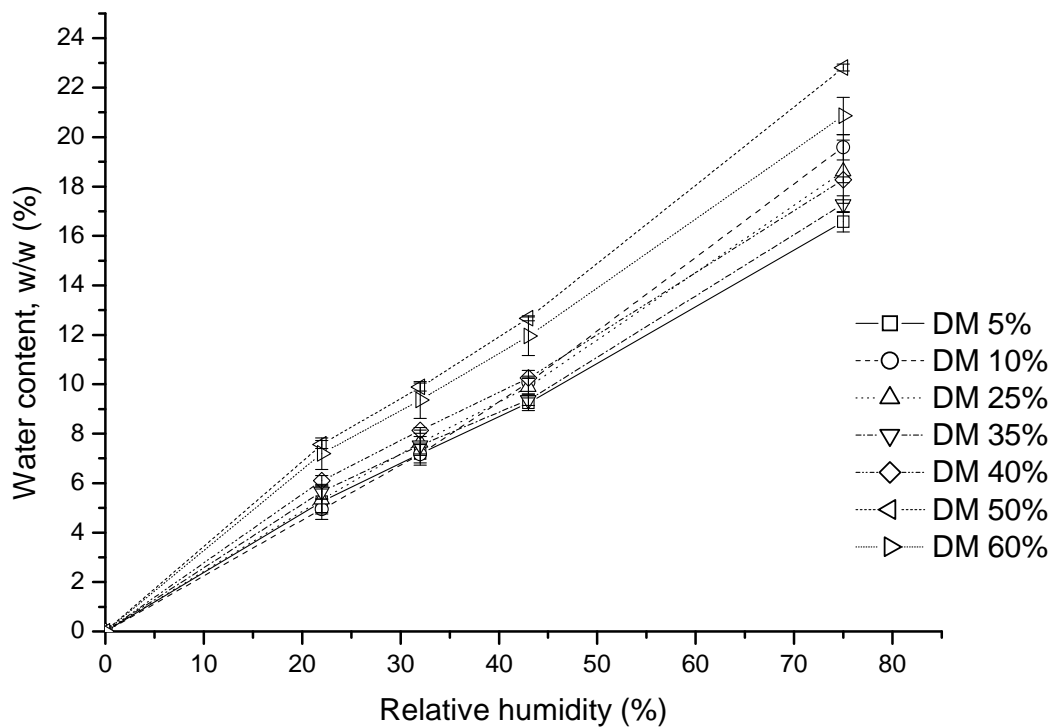


Figure 5.3: Sorption isotherms of various pectin grades at different relative humidities (RH)

The results from the powder characterization have not pointed to any major specific differences in the powder characteristics among the various DM grades tested. Hence, the various pectin grades are not expected to behave differently based on their powder characteristics.

5.2 Compressibility of pectin powders

5.2.1 Classical approach

The different compression parameters obtained through various analyses for pectin and reference materials with well-known compressibility, are summarized in Table 5.2. For both unsieved and sieved qualities of pectin powders, the classical approach with Heckel analysis suggested a slight increase in plasticity with increasing DM. Hence, the particles became softer with increased DM. The 3-D model divided the pectin samples into three groups in the 3-D parameter plot (Figure 5.4): the pectinic acids (DM 4%, DM 5% and DM 10%), the low-methoxylated (LM) pectins (DM 25%, DM 35% and DM 40%), and the high-methoxylated (HM) pectins (DM 50%, DM 60% and DM 72%).

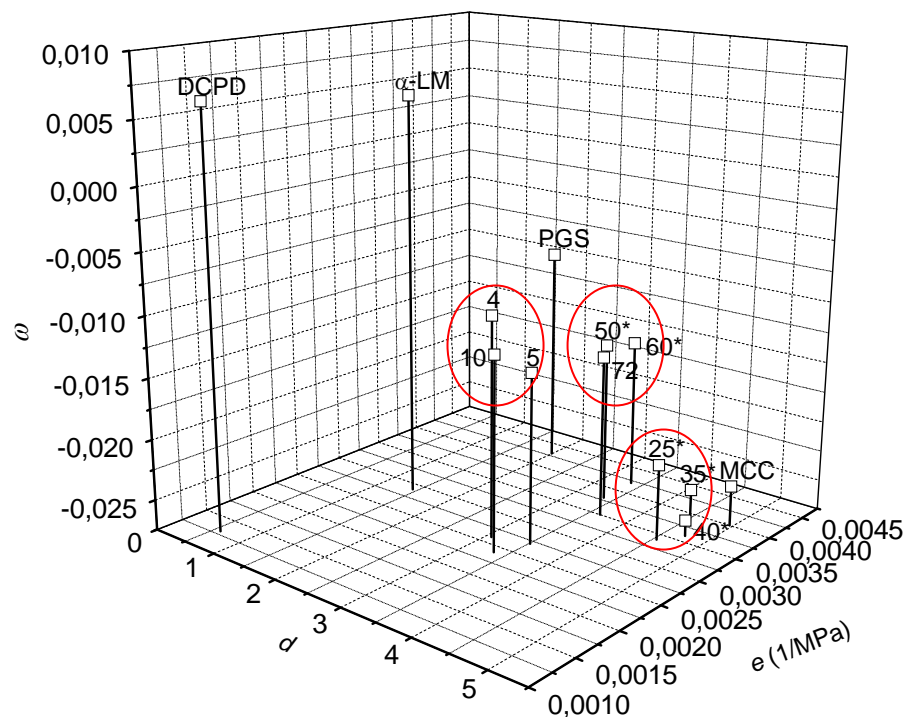


Figure 5.4: 3-D parameter plot of various pectin grades and reference materials at a maximum relative density ($\rho_{rel, max}$) of 0.85. The numbers represent the degree of methoxylation (DM) of each pectin sample, and the reference materials are referred to with the following abbreviations: DCPD: Dibasic calcium phosphate dihydrate, MCC: Microcrystalline cellulose, α -LM: α -lactose monohydrate, and PGS: Pregelatinized starch.

*: From same origin

The LM pectins were suggested to be most deformable (highest d values), whereas the pectinic acids could be suggested to exhibit some fragmentation propensity (slightly lower e values and slightly higher ω values).

Table 5.2: Compression parameters of different pectin samples and reference materials (dibasic calcium phosphate dihydrate (DCPD), α -lactose monohydrate (α -LM), microcrystalline cellulose (MCC), pregelatinized starch (PGS)) of both unsieved ($n = 1$) and sieved ($n = 3$, mean and in parenthesis relative standard deviation (%)) qualities

<i>Unsieved powder samples</i>										
Comment	Pectin DM (%)	YP, comp. (MPa)	YP, decomp. (MPa)	d (-)	e (1/MPa)	ω (-)				
<i>Batches of different origin</i>	5	104.6	645.2	3.5146	0.0027	-0.0136				
	10	114.7	689.7	3.3443	0.0024	-0.0117				
<i>Batches of same origin</i>	25	81.2	471.7	4.5417	0.0034	-0.0213				
	35	71.8	442.5	4.6084	0.0038	-0.0245				
	40	74.0	458.7	4.7321	0.0036	-0.0262				
	50	83.7	463.0	3.6397	0.0035	-0.0142				
	60	70.4	444.4	3.3539	0.0042	-0.0151				
<i>Reference materials</i>	DCPD	249.4	2188.6	0.5985	0.0013	0.0064				
	α -LM	98.3	1479.7	1.4331	0.0029	0.0056				
	MCC	61.7	591.7	4.9609	0.0040	-0.0242				
	PGS	83.6	398.4	1.9923	0.0043	-0.0093				
<i>Sieved powder samples</i>										
Comment	Pectin DM (%)	Size fraction (μm)	RH (%)	Compaction pressure for $E = 0.15$ (MPa) ^a	YP, comp. (MPa) ^b	a (-) ^b	$1/b$ (MPa) ^b	ab (1/MPa)	Δd (μm)	f (-)
<i>Batches of different origin</i>	5	90-125	21.8	118.7 (0.18)	97.5 (0.25)	0.64 (0.19)	20.5 (0.79)	0.03 (0.97)	19.5 (10.44)	0.08 (0.59)
	10		24.2	113.6 (2.05)	91.2 (0.33)	0.64 (0.21)	21.2 (0.99)	0.03 (0.85)	22.0 (9.35)	0.07 (0.60)
	35		20.1	113.6 (1.43)	90.6 (0.43)	0.67 (0.12)	13.7 (1.12)	0.05 (1.07)	16.8 (2.83)	0.11 (0.41)
	72 ^c		21.8	99.1 (-)	81.0 (-)	0.64 (-)	13.9 (-)	0.05 (-)	11.4 (14.04)	0.11 (-)
<i>Batches of same origin</i>	25	90-125	20.2	103.9 (0.64)	80.2 (0.20)	0.68 (0.03)	13.2 (1.27)	0.05 (1.28)	19.4 (13.50)	0.10 (0.57)
	35		21.4	95.0 (2.65)	72.2 (0.98)	0.70 (0.29)	13.1 (2.36)	0.05 (2.32)	17.0 (3.64)	0.08 (1.44)
	40		20.6	96.9 (1.22)	72.4 (0.21)	0.70 (0.22)	13.6 (2.38)	0.05 (2.55)	21.2 (11.94)	0.08 (1.94)
	50		20.1	102.5 (2.25)	83.2 (1.50)	0.65 (0.12)	13.6 (2.62)	0.05 (2.77)	16.9 (6.17)	0.10 (1.55)
	60		25.0	67.0 (1.76)	56.2 (1.34)	0.62 (0.44)	10.4 (1.10)	0.06 (1.44)	12.1 (2.86)	0.13 (2.74)
<i>One batch different size fractions</i>	25	180-250	38.6	86.9 (1.65)	69.8 (0.30)	0.66 (0.16)	11.3 (1.66)	0.06 (1.65)	23.7 (10.46)	0.11 (0.46)
		125-180	43.7	87.1 (2.88)	67.2 (1.23)	0.67 (0.04)	11.4 (4.49)	0.06 (4.43)	25.6 (13.02) ^f	0.11 (2.81)
		90-125	45.0	90.4 (1.32)	69.9 (0.31)	0.68 (0.15)	12.0 (1.21)	0.06 (1.35)	19.4 (13.50)	0.10 (0.91)
		63-90	41.0	88.2 (1.09)	68.2 (0.10)	0.69 (0.12)	11.4 (0.88)	0.06 (0.84)	14.3 (6.73)	0.10 (1.00)
		45-63 ^d	41.0	88.3 (-)	70.2 (-)	0.70 (-)	10.9 (-)	0.06 (-)	6.2 (8.05)	0.10 (-)
<45 ^e	39.8	87.2 (-)	68.3 (-)	0.68 (-)	12.6 (-)	0.05 (-)	3.4 (-)	0.10 (-)		
<i>Reference materials</i>	PGS	90-125	22.2	78.6 (0.35)	79.8 (0.67)	0.49 (0.20)	23.4 (2.24)	0.02 (2.02)	7.0 (24.20)	0.08 (1.55)
	α -LM		21.9	97.1 (0.84)	97.2 (1.49)	0.48 (0.09)	14.6 (1.47)	0.03 (1.54)	52.1 (5.67)	0.10 (0.23)
	DCPD		21.4	223.5 (0.27)	263.9 (0.26)	0.52 (0.06)	14.1 (0.47)	0.04 (0.45)	37.0 (6.06)	0.12 (1.20)

^aCorresponds to an “in-die”-porosity of 0.150 ± 0.005 (exception: 0.159 for fraction 45-63 μm DM 25%), ^bCalculated by linear regression from 20-80% of the maximum compaction pressure, ^c $n=1$ except for Δd where $n=3$, ^d $n=1$ except for Δd where $n=2$, ^e $n=1$, ^f $n=2$

Comparing the Heckel profiles of a representative pectin grade (DM 25%) with reference materials (Figure 5.5), showed that pectin and PGS displayed the most similar curve progression. This was further confirmed via 3-D modelling (Figure 5.6).

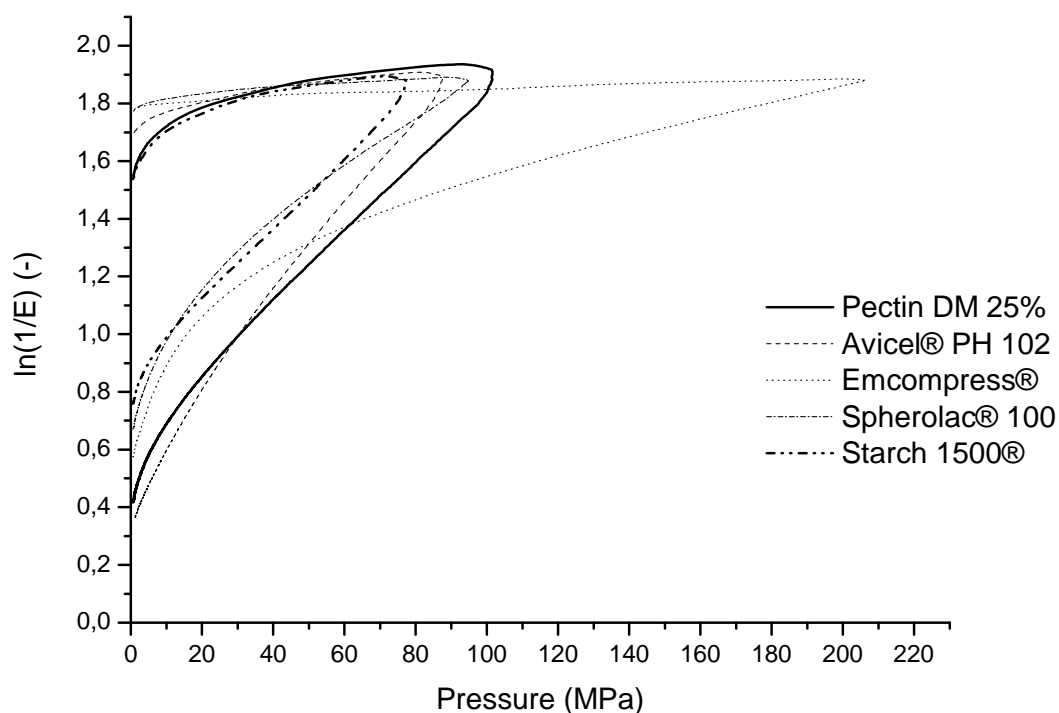


Figure 5.5: Heckel profiles of unsieved powders of pectin DM 25%, microcrystalline cellulose (MCC, Avicel[®] PH 102), dibasic calcium phosphate dihydrate (DCPD, Emcompress[®]), α -lactose monohydrate (α -LM, Spherolac[®] 100) and pregelatinized starch (PGS, Starch 1500[®]) at an “in-die” porosity of 0.150 ± 0.005 (equivalent to a maximum relative density of 0.850 ± 0.005)

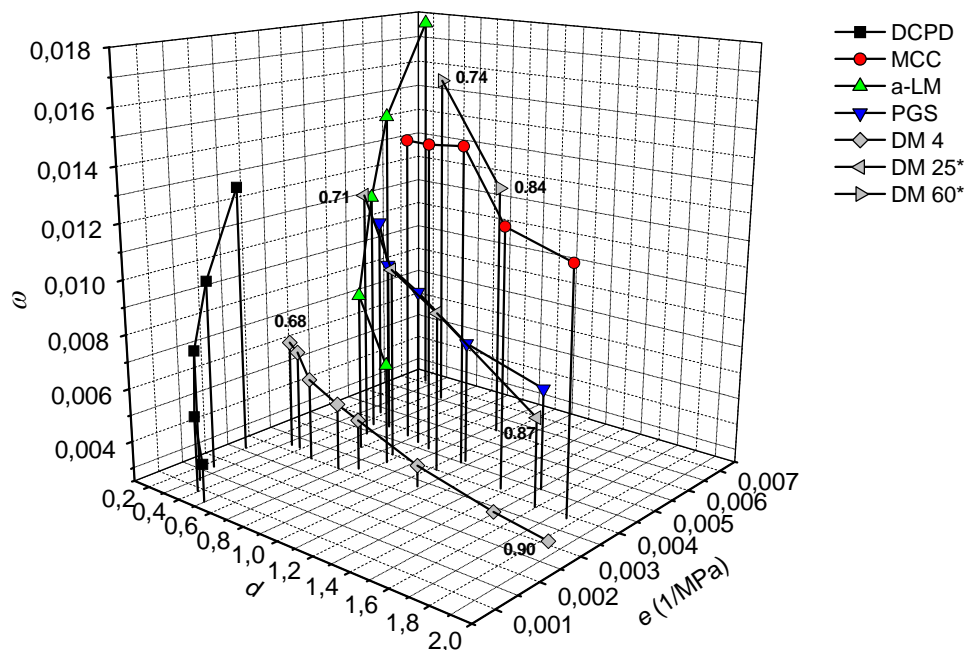


Figure 5.6: 3-D parameter plot of three selected unsieved pectin grades (DM 4%, DM 25% and DM 60%) and reference materials (dibasic calcium phosphate dihydrate (DCPD), microcrystalline cellulose (MCC), α -lactose monohydrate (α -LM), and pregelatinized starch (PGS)) published by Picker (28). For each pectin sample the maximum relative density ($\rho_{rel, max}$) intervals are given. *: From same origin

The 3-D modelling (Figure 5.6) also revealed the pectinic acids (DM \leq 10%) to possess slightly more viscoelastic behaviour compared to pectins of higher DM. As the pressure plasticity (e) increased with increased DM, this indicated a need of higher compaction pressures in order to deform pectin particles of higher DM. The fact that pectin and PGS showed similar compression behaviour might be due to their structural similarities, both being polysaccharides with a backbone of monomers (D-galacturonic acid (54, 87) and α -(D)-glucose (88), the latter being a monomer in amylose and amylopectin; the two components of starch) joined in chains by 1,4-glycosidic linkages.

The next step with the classical approach was to evaluate the elasticity, both “in-die” and “out-of-die”. Figure 5.7a and 5.7b show the axial tablet expansion at different time intervals of low-methoxylated (LM) pectins compared to PGS, and high-methoxylated (HM) pectins and PGS, respectively.

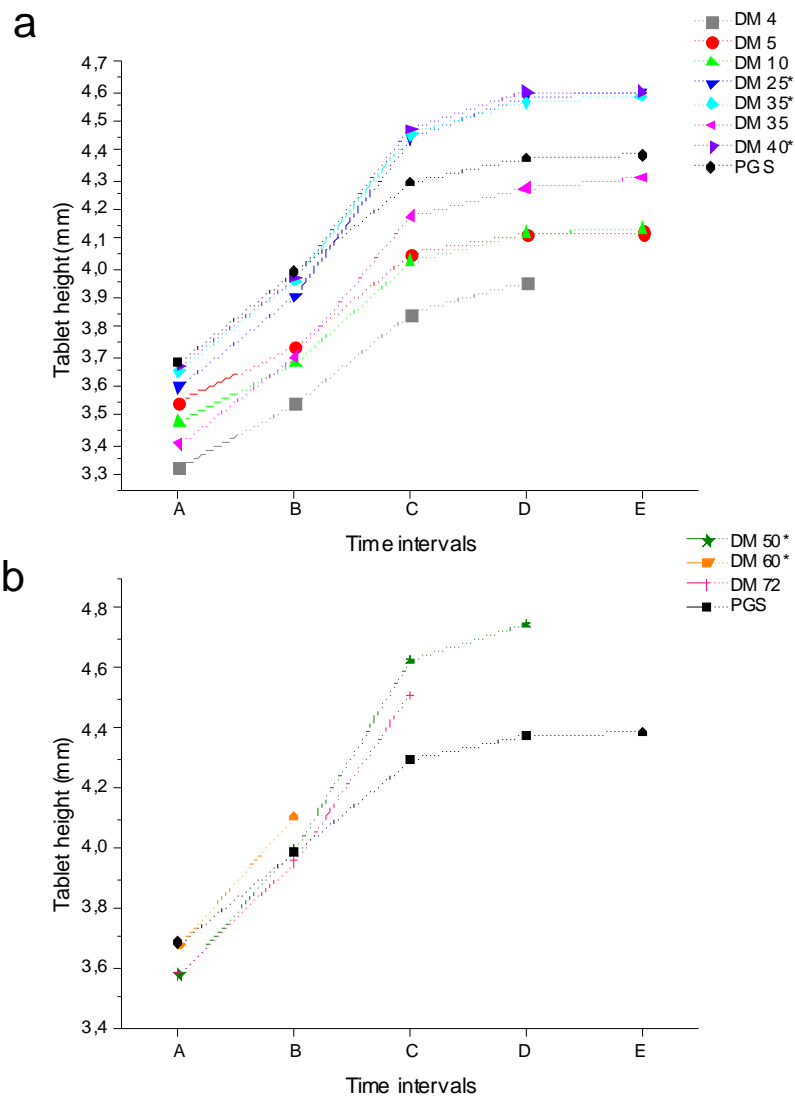


Figure 5.7: Tablet height at different time intervals (A: Under maximum compression, B: At the end of the decompression phase, C: Immediately after ejection from the die, D: After 24 hours, and E: After one week) for **a** the low-methoxylated pectins and pregelatinized starch (PGS) and **b** the high-methoxylated pectins and PGS

Maximum axial tablet expansion took place during the decompression phase until the tablet was ejected from the die (i.e. “in-die”). Slight changes in tablet heights were observed within 24 hours of storage, and even less expansion occurred during one week. Among the pectins, the pectinic acids (DM \leq 10%) displayed the lowest axial tablet expansion. This is consistent with the somewhat higher yield pressure values in the decompression phase (*YP*, decomp.) for these grades of pectin (Table 5.2). Pectins with DM ranging from 25% to 40% (except DM 35% from batches of different origin) showed higher “out-of-die” axial tablet expansion compared to PGS. For DM 60% the axial tablet expansion was so large that the tablets ruptured “in-die” (DM 60%). Pectin with DM 50% and DM 72% gave mechanically weak tablets such that it was possible to measure the tablet heights either immediately after ejection from the die or after 24 hours, but it was not possible to measure the diameters as that procedure ruptured the tablets. It might be speculated that the high number of methoxyl groups, which are larger in size than the hydroxyl groups, lead to a larger degree of steric hindrance, possibly resulting in less strong bonds between polymeric chains, thus promoting higher elastic recoveries with increased DM. Another hypothesis is that the particle surface becomes more hydrophobic as the DM increases, thus reducing the strength of the interparticular bonds formed between the particles in the tablet. The corresponding “in-die” elastic recovery values ranged from 8.2% to 11.7% for DM 25% - DM 60%, whereas DM 5% and DM 10% showed values of 5.4% and 5.7%, respectively. These values are of the same order of magnitude as those reported for carrageenan; 8.3% (82). In another study on carrageenan the elastic recovery was reported to be approximately 30% after 10 days storage (89). This is somewhat higher than the elastic recovery values obtained for pectin (paper I, Table II), and suggests that pectin has better tableting properties than carrageenan.

5.2.2 Sequential approach

Following the sequential handling of the compression parameters, introduced by Nordström *et al.* (32) and Klevan *et al.* (4, 5), pectin powders were classified as class IIA powders, showing a low degree of particle rearrangement (low *ab* indices, Table 5.2) and a relatively low degree of fragmentation. The latter was firstly evaluated via “in-die” Shapiro analysis of the initial part of the Heckel profile (Figure 5.8).

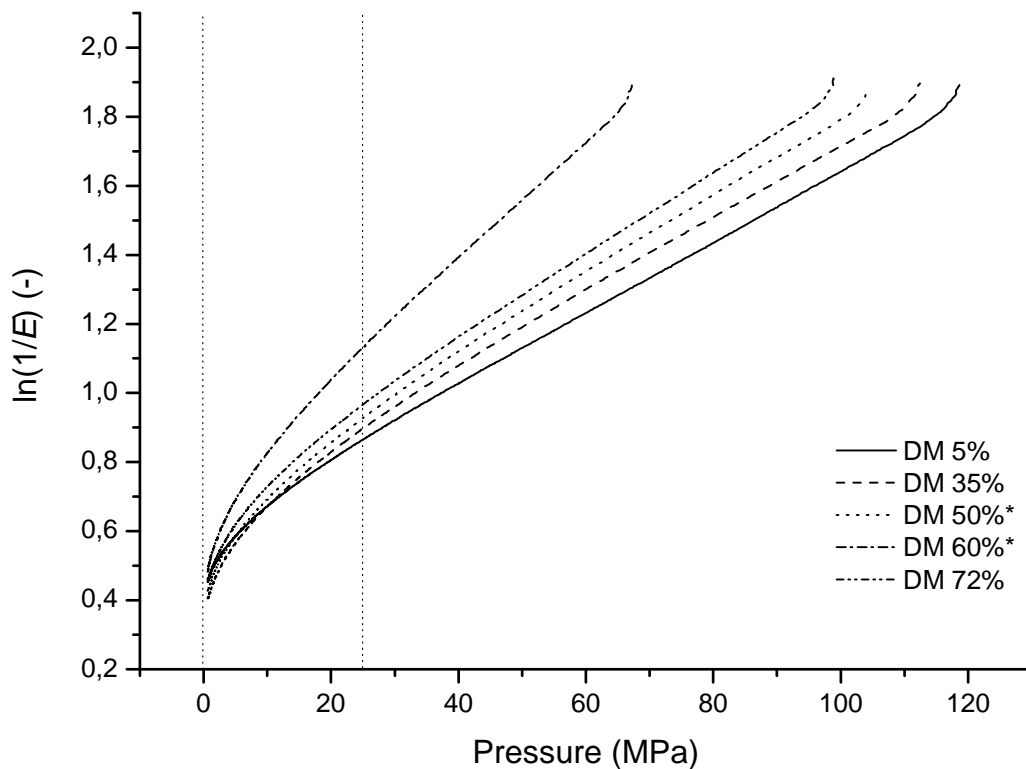


Figure 5.8: Heckel profiles (compression phase) of some pectin grades of size fraction 90-125 μm . *: From same origin. The dotted vertical lines show region I; 0-25 MPa

However, this method did not succeed in estimating the degree of bending in the initial phase of the Heckel profiles (Figure 5.8), as visual observations did not coincide with the calculated *f* parameters (Table 5.2). This was most probably caused by higher tableting speed and the way the initial powder bed height was determined in the current studies compared to the original method. Therefore, another method involving estimation of the difference in volume-specific surface area of tablets and powders ($Sv_{(tablet)} - Sv_{(powder)}$) was added in order to provide information on fragmentation propensity (Figure 5.9).

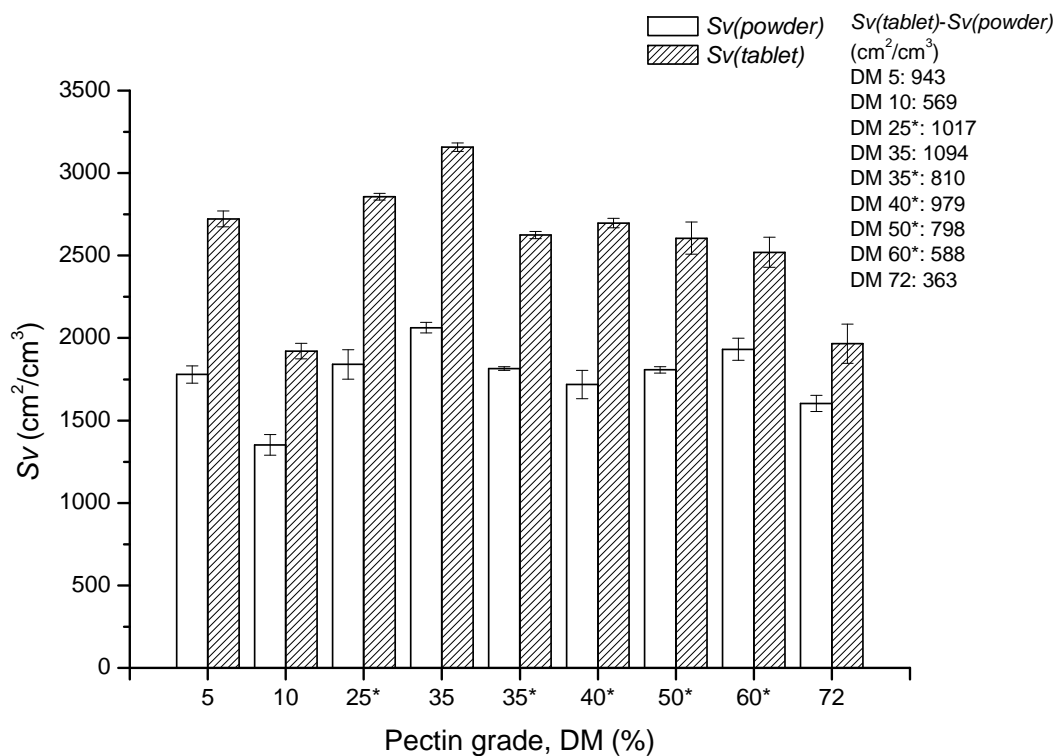


Figure 5.9: Volume-specific surface areas (S_v) of powders (white bars) and tablets (shaded bars) for different pectin grades of size fraction 90-125 μm . *: From same origin. Standard deviations are presented by error bars, $n = 3$

In general, an increased DM gave slightly less brittle particles (Figure 5.9) and somewhat softer particles (*YP* for sieved powder samples, Table 5.2). This was to some extent revealed during the classical approach with Heckel analysis and the 3-D modelling already discussed. It seems that the change in molecular structure caused by the methoxy substitution has a small effect on the mechanical properties of pectin particles. This is probably related to the interaction between the polymer chains forming the amorphous solid, and an increased DM will reduce the bonding (larger spatial arrangement and less hydrogen bonds) and thus facilitate relative motion of the polymer chains of the solid while subjected to an applied stress. This increased propensity to respond to an applied stress by deformation (flow), will reduce the tendency of the particles to fragment. However, in general terms, it should be emphasized and concluded that the DM had a small influence on the compression properties of pectin.

5.2.3 Overall discussion

The results have shown that pectin was predominantly deformed by elastic deformation to a similar extent as modified starch for direct compression. However, the pectinic acids (DM \leq 10%) seemed to undergo a more time-dependent deformation, i.e. viscoelastic deformation in combination with a slight fragmentation propensity. The results also suggested that the particles became softer with increased DM. According to the study performed by Kim *et al.* (76) on one LM pectin (DM 30-37%) and one HM pectin (DM 65-72%), pectin was suggested to consolidate predominantly by fragmentation with little plastic deformation. These conclusions were drawn as similar *YP* values (200 MPa and 213 MPa) were obtained at two different punch speeds: 50 mm/s and 250 mm/s, respectively. This was further supported by a low strain rate sensitivity value (SRS = 6.1%) for the HM pectin. The compacts also underwent a substantial elastic recovery during decompression and ejection. For the present studies a rather low punch speed of 10 mm/s was employed for compression of pectin (paper I-III). At higher punch speeds, plastically deforming materials such as MCC have been reported to decrease their apparent density and increase their fragmentation propensity, whereas fragmenting materials such as α -LM seem unaffected (90-92). As fragmentation and elastic deformation seem to dominate over plastic deformation in pectin, it may be assumed that these compaction mechanisms will still dominate also at higher punch speeds. In general, tableting troubles such as loss of hardness, sticking, lamination and capping can occur as the punch speed is increased (92). As the tablet tensile strength has been reported to only affect plastically deforming materials at higher punch speeds (93, 94), the tablet tensile strength of pectin may be assumed to not be affected by the punch speed to a large extent.

As few studies exist on the compressibility of pectin powders, it is interesting to compare pectin's compression behaviour with that of other natural polysaccharides. Alginates are a natural polysaccharide extracted from brown seaweed. They exist either as alginic acid or as salts of alginic acid. The polysaccharide is composed of D-mannuronic and L-guluronic acid (95). Alginate's compression behaviour seems to resemble that of pectin, as it predominantly consolidates by elastic deformation (96). The LM pectins seem to display similar viscoelastic deformation behaviour as carrageenan (89), a natural polysaccharide extracted from algae of the class Rhodophyceae. They consist of sulfate esters of galactose and 3,6-anhydrogalactose copolymers, linked via α -(1,3) and β -(1,4) in the polymer (82). Another polysaccharide is chitin, which is composed of β -(1,4) linked *N*-acetyl-D-glucosamine units (97). Its deacetylated form, chitosan, is produced from the shells of crab, shrimps and lobster, which

are waste products from the food industry (98, 99). Chitosan seems to differ from pectin by exhibiting a more pronounced plastic deformation (81, 97). However, a high elastic recovery is reported for chitosan compacts after ejection from the die (81, 97), as is also seen for pectin compacts (paper I). Chitosans are reported to be more plastic and elastic than DCPD (97), an extensively fragmenting material, and less plastic and more elastic than MCC (81, 97), known as an outstanding binder due to its plastic deformation. Compared to MCC, pectin was less plastically deforming, as the elastic component was most prominent.

However, studies on another cellulose derivative, hydroxypropyl methylcellulose (HPMC), have shown relatively high elastic recovery values (27) comparable to pectin (paper I). HPMC is a widely used tablet excipient.

5.2.4 Effect of particle size on the compressibility of pectin powders

Pectin DM 25% was chosen as a most typical and representative pectin grade and fractionated into six different size fractions. The compressibility was evaluated with the approach introduced by Nordström *et al.* (32) and Klevan *et al.* (4, 5). No differences were observed with respect to initial particle size and the *ab* index (Table 5.2) for the size fractions. Heckel profiles for the different size fractions are shown in Figure 5.10.

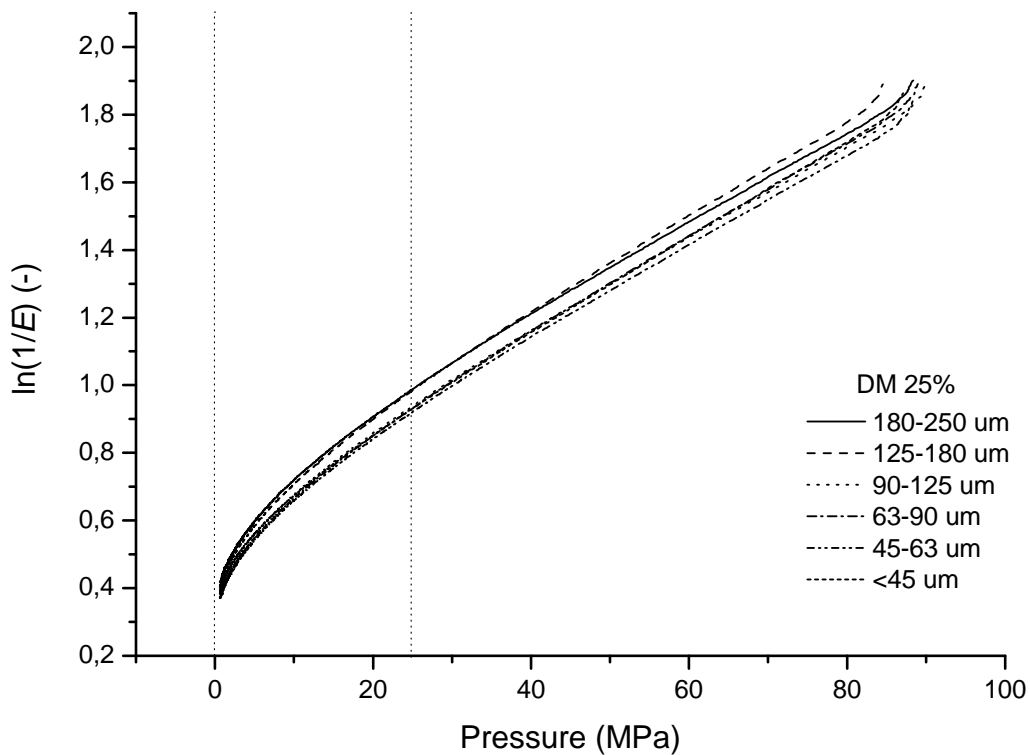


Figure 5.10: Heckel profiles (compression phase) of six different particle size fractions of pectin DM 25%. The dotted vertical lines show region I; 0-25 MPa

Visual inspection revealed no differences in the initial bending, and constant *f* parameter values were obtained (Table 5.2).

The difference $Sv_{(tablet)} - Sv_{(powder)}$, which also describes the fragmentation propensity, increased with decreasing initial particle size (Figure 5.11).

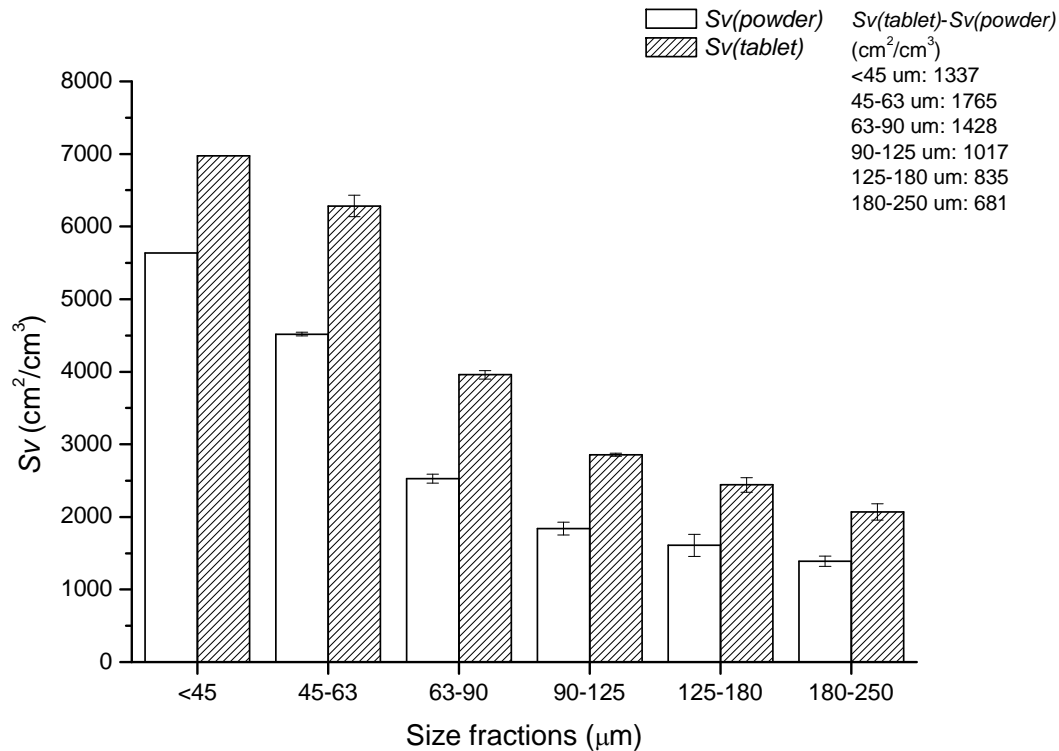


Figure 5.11: Volume-specific surface areas (Sv) of powders (white bars) and tablets (shaded bars) for six different particle size fractions of pectin DM 25%. Standard deviations are presented by error bars ($n = 3$, except for size fraction $<45 \mu\text{m}$ where $n = 1$)

This is consistent with reported results for materials that undergo deformation (5, 100), and also shows that a large powder surface area corresponds to a larger increase in surface area during compression. Compared to changes in surface area of extensively fragmenting materials (5, 100), the $Sv_{(tablet)} - Sv_{(powder)}$ for pectins were rather small, which are indicative of particles of relatively low fragmentation propensity. No differences in softness were observed for the different particle size fractions (YP and $1/b$, Table 5.2). Therefore, it can be concluded that the compressibility of pectin powders seems to be independent of the particle size in the investigated size range.

5.3 Resulting pectin tablets

The tensile strengths of the various pectin tablets with “in-die” porosities of 0.15 are summarized in Figure 5.12. In general, tablets possessing adequate tensile strengths were only obtained from pectin grades with $DM \leq 40\%$, i.e. LM pectins (Figure 5.12a and Figure 5.12b). Hence, the HM pectins ($DM \geq 50\%$) did not form coherent tablets. Among the LM pectins, the pectinic acids ($DM \leq 10\%$) displayed the mechanically strongest tablets. These results suggest that DM influenced the tensile strength. It can be hypothesized that the particle surfaces become more hydrophobic as the DM increases, thus reducing the strength of the inter-particulate bonds formed between the particles in the tablet. DM seemed to dominate over other parameters that are assumed to influence the tensile strength (e.g. compaction pressure required to obtain an “in-die” porosity of 0.15, Table 5.2). Only minor differences in tablet tensile strengths were observed between tablets of unsieved (Figure 5.12a) and sieved (Figure 5.12b) qualities.

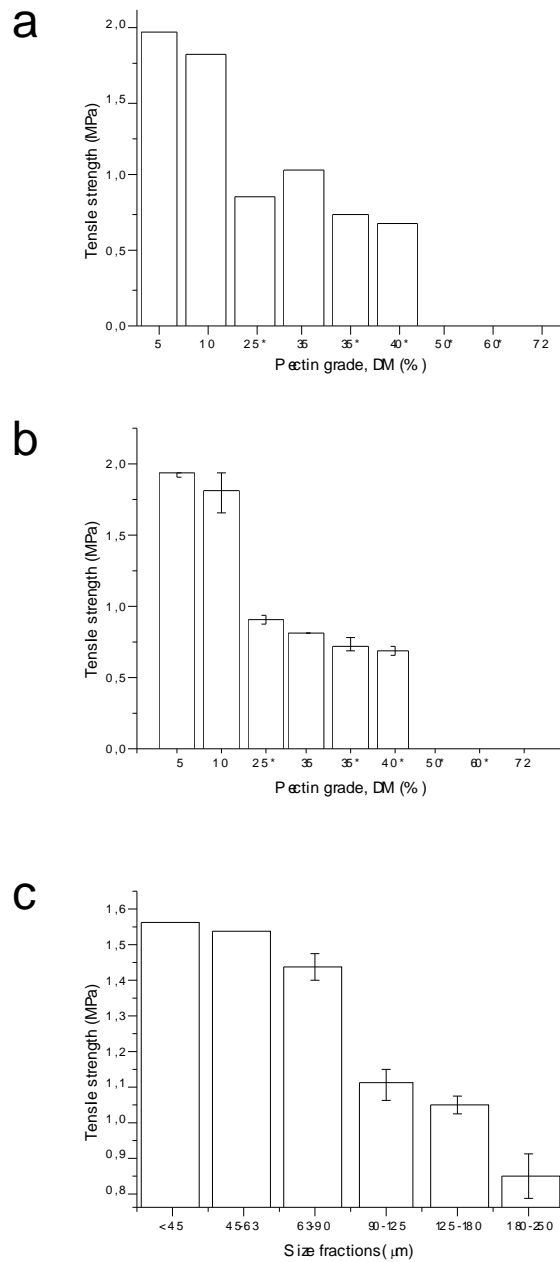


Figure 5.12: Tensile strengths of pectin tablets made from **a** unsieved pectin powders with different degrees of methoxylation (DM) ($n = 1$), **b** pectin powders with different DM and constant particle size (90-125 μm) ($n = 3$), and **c** six different particle size fractions of pectin DM 25% ($n = 3$, except for the size fractions <45 μm and 45-63 μm where $n = 1$). *: From same batch. Standard deviations are presented by error bars

Compared to MCC, which is known to be one of the most compressible and compactible direct compression excipients (101), pectins with the best compactibilities (DM 5% and DM 10%) are only capable of obtaining approximately 1/3 of MCC's tensile strength (paper I). Despite this, the LM pectins seem to be suitable direct compression excipients, as the tensile strength values are comparable to DCPD and α -LM, two materials with different fragmentation propensity, and higher than PGS (an elastically deforming material, paper I). The pectinic acids (DM \leq 10%) seem especially promising as tablet excipients whose tensile strengths are comparable to carrageenan and alginate, two materials that have proven suitable as tablet excipients (82, 89, 96). HPMC has been reported to produce slightly stronger compacts than the pectinic acids; approximately 2-3 MPa for various HPMC grades at a compaction pressure of 100 MPa (27). Even stronger compacts can be expected for chitosan (81), which has shown tensile strengths of the same order of magnitude as MCC (paper I) approximately 6 MPa at a compaction pressure of 100 MPa.

For pectin with DM 25%, a decreased initial particle size increased the powder compactibility, and thus increased the mechanical strength of the tablets (Figure 5.12c). A possible explanation is that the number of inter-particulate contact sites per cross sectional area of tablet increased with a decreased particle size.

To summarize, it can be concluded that the mechanical strength of pectin tablets is strongly dependent on both DM and initial particle size.

5.4 Can pectin incorporate an inert component in a matrix?

Since the results have shown that the pectinic acids (DM \leq 10%) are suitable as direct compression excipients in tableting, they should be further examined with respect to their possible use as functional matrix. Therefore, DM 4% was chosen in the next study. In order for pectin to be successful as a binder/matrix former, its drug-loading capacity (or dilution potential) should be characterized. This was studied by including an inert (i.e. non-compressible) component like quartz sand (Millisil[®] W12) in the matrix. The following pectin and quartz sand mixtures (pectin:quartz sand) were compressed on an instrumented excenter press (the same experimental set-up as in paper III): 100:0, 70:30, 50:50, and 30:70. The corresponding maximum relative density ($\rho_{rel, max}$) intervals were: 0.77-0.90, 0.79-0.89, 0.77-0.88, and 0.78-0.80, respectively. For comparison purposes, one specific $\rho_{rel, max}$ of 0.83 was chosen. This value was close to the $\rho_{rel, max}$ used in previous studies (0.85). However, the ratio

30:70 was an exception as the highest $\rho_{rel, max}$ was 0.80. The tensile strengths of pectin/quartz tablets in different ratios are presented in Figure 5.13.

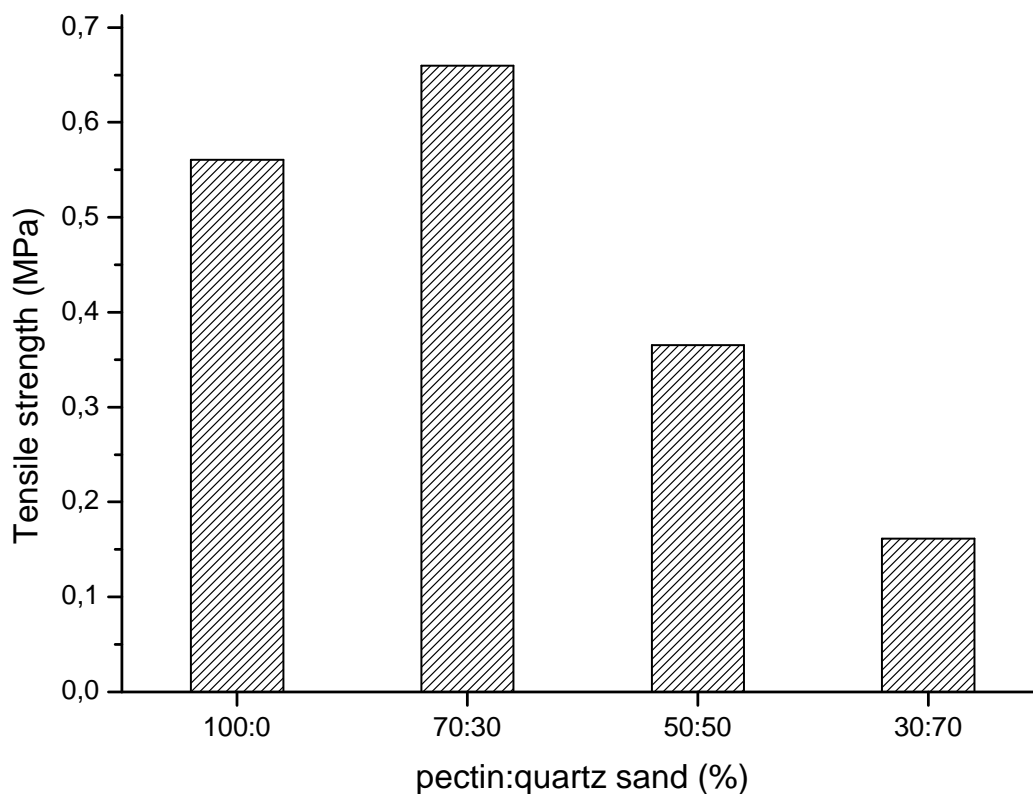


Figure 5.13: Tensile strengths of tablets made from different ratios of pectin DM 4% and quartz sand. Maximum relative density ($\rho_{rel, max}$): 0.83 (exception: $\rho_{rel, max} = 0.80$ for 30:70), $n = 1$

Firstly, the results showed that pectin was able to produce coherent tablets, though weak, even when only 30% pectin was present in the matrix. This implies that pectin had a high dilution potential as a binder/matrix former, i.e. the drug-loading capacity was high. It should be emphasized that the tensile strength is low, but still coherent tablets resulted. Secondly, there seems to be a general trend of decreasing tensile strengths with decreasing amounts of pectin powder (exception: 70:30). The tensile strengths of pure pectin tablets were lower compared to the tensile strengths of tablets produced from pectinic acid ($DM \leq 10\%$) on the compaction simulator (Figure 5.12). This is probably caused by a combination of different tableting machines used and the slightly lower $\rho_{rel, max}$.

In order to study the tablets produced from the powder mixture 70:30 in more detail, the tensile strengths at various $\rho_{rel, max}$ were determined (Figure 5.14).

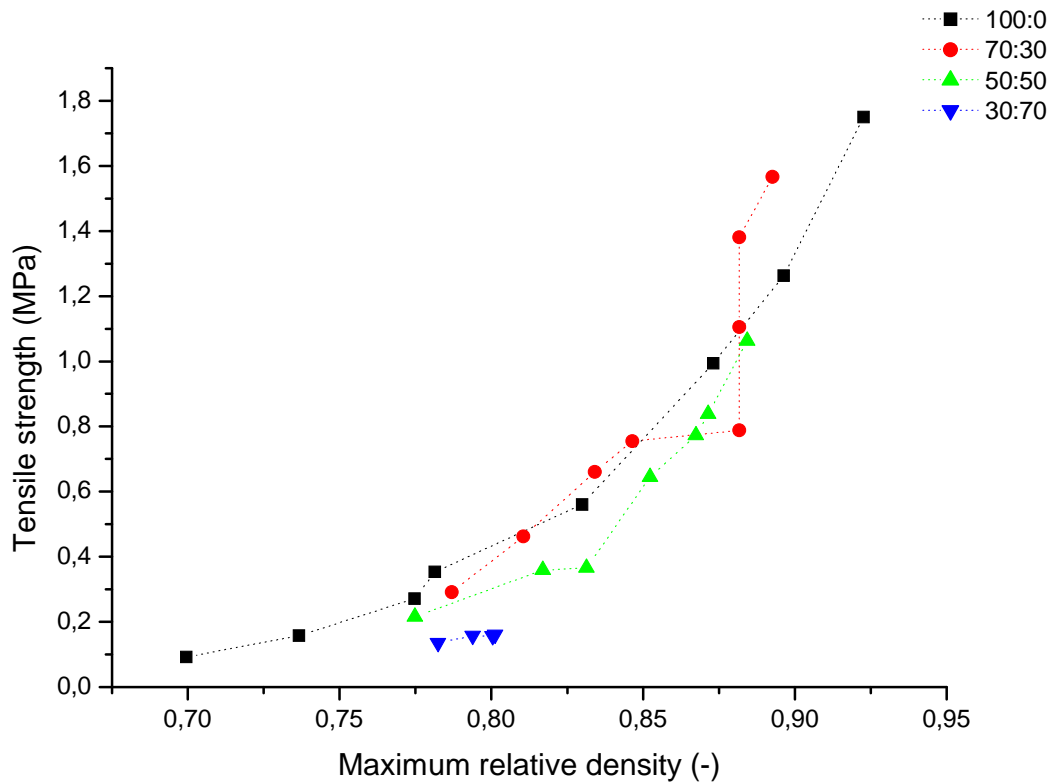


Figure 5.14: Tensile strengths of tablets made from different ratios of pectin DM 4% and quartz sand at different maximum relative densities ($\rho_{rel, max}$), $n = 1$

In general, the tensile strengths increased with increased values of $\rho_{rel, max}$, as expected, and no plateau or decrease occurred which would indicate elastic deformation. However, it should be kept in mind that the tensile strength was calculated for one tablet only, which may explain the somewhat different curve progression for tablets from the ratio 70:30. At $\rho_{rel, max}$ between 0.81 and 0.88, these tablets possessed higher tensile strengths than pure pectin tablets, and at similar $\rho_{rel, max}$, tablets with different tensile strengths were produced. This shows that the calculated tensile strengths (Figure 5.13 and Figure 5.14) for the different tablets should be considered to represent trends rather than accurate values. In order to calculate accurate tensile strength values, the crushing strength should be measured for several tablets, while maintaining a balance of material consumption and benefit.

An “in-die” Heckel analysis was performed to measure how the plastic properties changed by addition of quartz sand in the matrix. The *YP* for the different tablet formulations is shown in Figure 5.15.

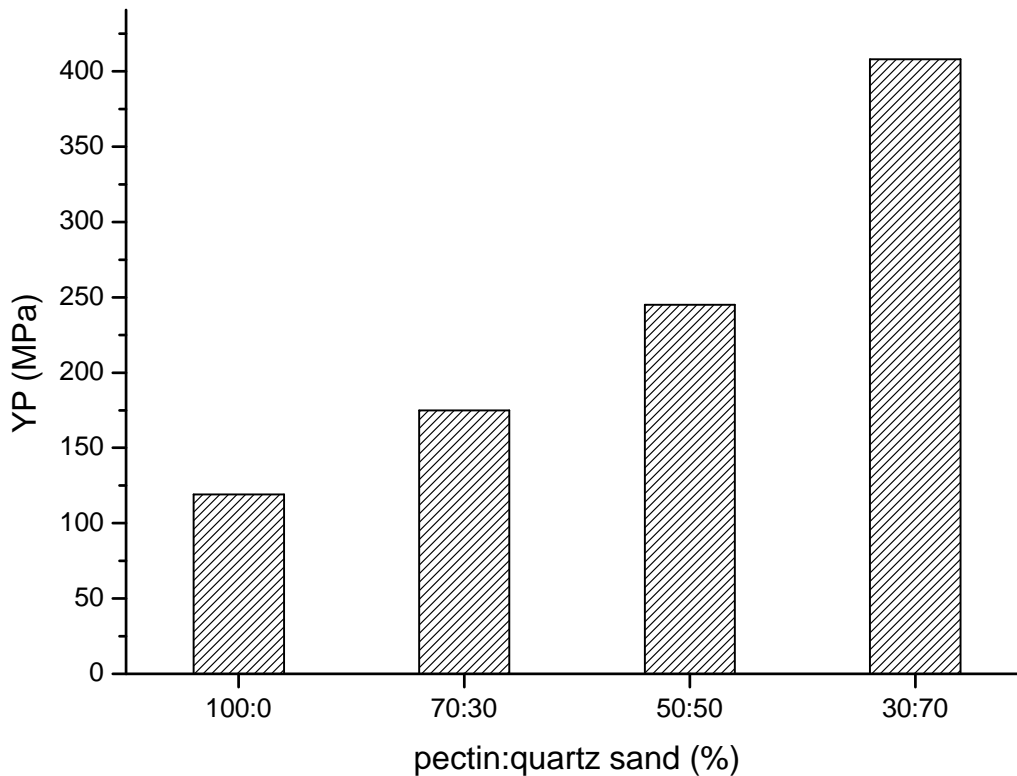


Figure 5.15: Yield pressure values at different ratios of pectin DM 4% and quartz sand, $n = 1$

In general, low YP values indicate high degree of plastic deformation and vice versa. Hence, the plasticity gradually increased by decreased levels of quartz sand, as expected. As plastically deforming particles in general are expected to form strong coherent tablets, this is more or less consistent with the calculated tensile strengths (Figure 5.13).

In order to get more information on the compressibility of pectin/quartz sand, the 3-D model was employed. The 3-D parameter plot is presented in Figure 5.16.

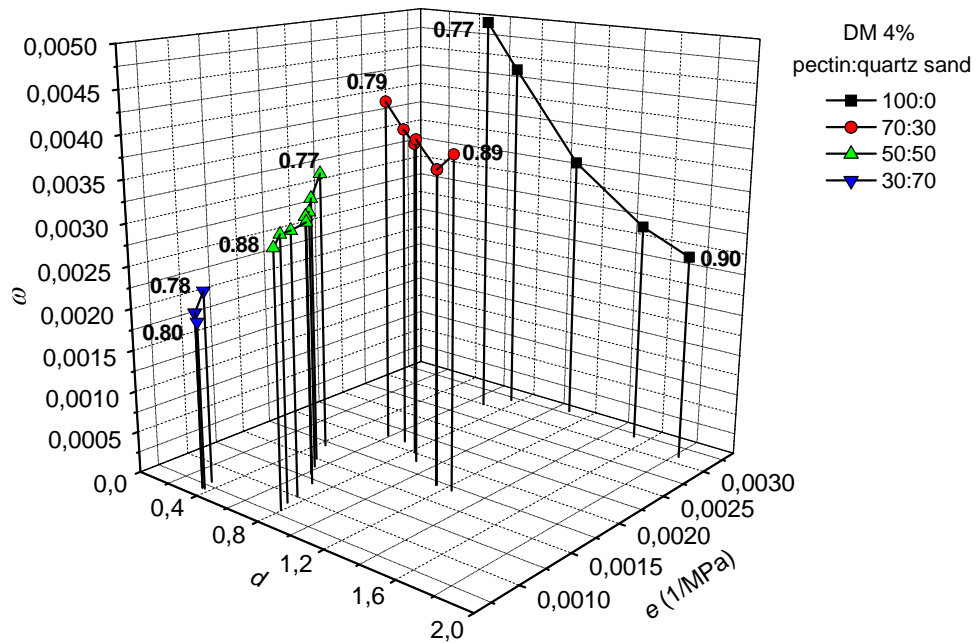


Figure 5.16: 3-D parameter plot of different ratios of pectin DM 4% and quartz sand. For each combination of pectin DM 4% and quartz sand the maximum relative density ($\rho_{rel, max}$) intervals are given

The time plasticity (d) increased with increased levels of pectin in the powder. Hence, pure pectin powder was faster deforming than powder mixtures with pectin and increased levels of quartz sand. In addition, the pressure plasticity (e) increased with increasing amounts of pectin. This suggests the pure pectin powder to be more easily deforming at low pressures compared to the powder mixtures of pectin and quartz sand. This was as expected as higher pressures are required to compress a powder mixture containing a non-compressible component. These results confirm the results from the Heckel analysis (Figure 5.15). In addition, the 3-D modelling technique is able to provide information on the elastic properties of a material. The largest decrease in ω values was observed for pure pectin powder, subsequently followed by powder mixtures with decreased levels of quartz sand. This indicates that the elasticity was highest for pure pectin powders and decreased when the

amount of quartz sand increased, i.e. the properties of the rigid quartz particles became more prominent as the level of quartz increased.

For validation purposes, the elasticity was also evaluated by measuring the axial tablet expansion, both “in-die” and “out-of-die”. The measured tablet heights are presented in Figure 5.17.

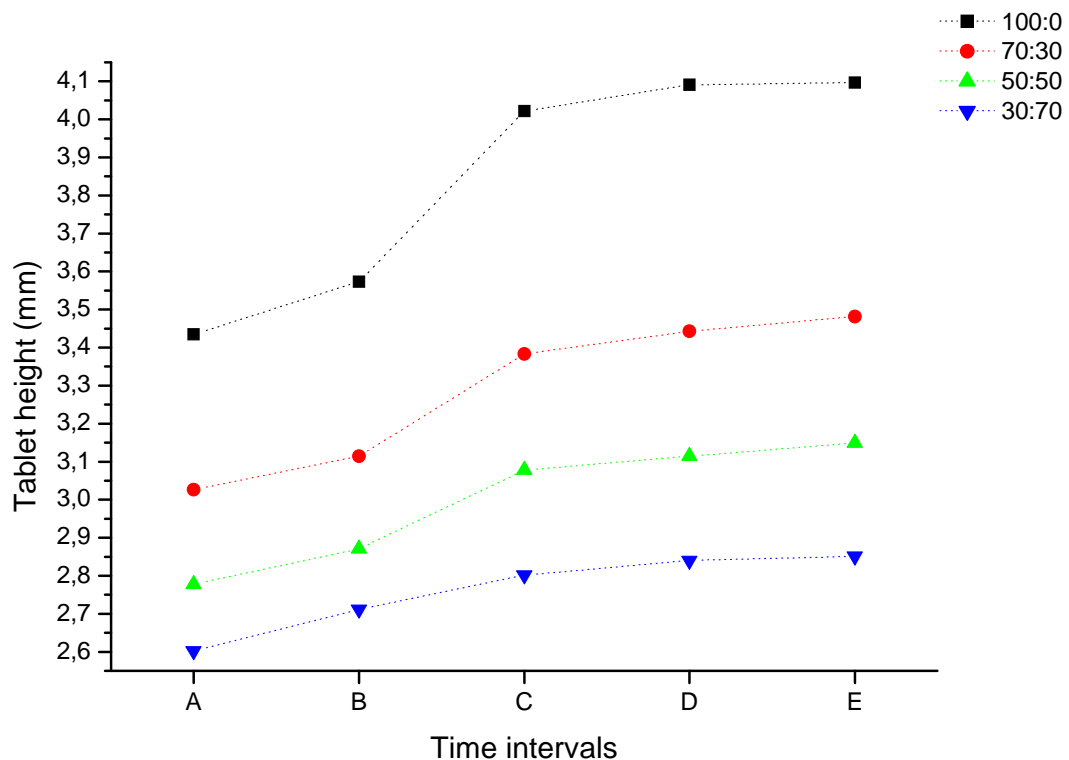


Figure 5.17: Tablet height at different time intervals (A: Under maximum compression, B: At the end of the decompression phase, C: Immediately after ejection from the die, D: After 24 hours, and E: After one week) for different ratios of pectin DM 4% and quartz sand

Several results are observed: Firstly, the axial tablet expansion (i.e. the elasticity) decreased with increased levels of quartz sand. This confirmed the results from the 3-model (Figure 5.16). Secondly, the largest axial tablet expansion took place during the ejection from the die (B-C). “In-die” from when the maximum pressure was obtained until the end of decompression was reached (A-B), the axial tablet expansion was at the same level for the different ratios of pectin and quartz sand. “Out-of-die” only minor changes in tablet height

were observed. It is thus concluded that the elasticity was most prominent “in-die”, and increased with increased levels of pectin.

To summarize, pectin has shown to have a high drug-loading capacity and the tablet tensile strength decreased with decreased amounts of pectin, even though the crushing strength should be tested on more than one tablet in order to calculate accurate tensile strength values. Both the Heckel analysis and the 3-D model showed that the plasticity increased with decreased levels of quartz sand. In addition, the 3-D model confirmed that the elasticity was highest for pure pectin powder, as expected. Moreover, the elasticity was most prominent “in-die”.

6 CONCLUSIONS

The present work shows that the low-methoxylated (LM) pectins, i.e. pectins with degrees of methoxylation (DM) < 50%, and especially the pectinic acids (i.e. DM ≤ 10%) are potential direct compression excipients consisting of soft particles with high compactibility. The pectinic acids produced coherent tablets with higher tensile strengths than pregelatinized starch (PGS) and α -lactose monohydrate (α -LM).

The powder characterization revealed no major differences in powder properties among the various pectin grades. This implies that differences in compression behaviour cannot be expected to be dependent on the powder characteristics.

Characterization of the compressibility by the classical approach employing “in-die” Heckel analysis followed by elastic recovery measurements both “in-die” and “out-of-die” showed that the pectin was elastically deforming and resembled PGS in terms of similar Heckel profiles. Following the sequential handling of the compression parameters, the pectin powders were classified as class IIA powders. Hence, the pectin powders could be expected to exhibit low particle rearrangement and relatively low fragmentation propensity. In general, the pectin particles were relatively soft. Neither DM nor initial particle size had a major effect on the compressibility of pectin powders, although an increased DM gave slightly softer and slightly less brittle particles. With the 3-D model, the pectinic acids were found to be slightly more viscoelastically deforming compared to the other pectin grades, which consolidated predominantly by elastic deformation. The latter was consistent with the results obtained via the classical Heckel approach and the newer approach including sequential handling of the compression parameters. Employing one tablet in the 3-D model set-up gave a certain degree of information on the compression behaviour of the pectins. However, in order to take full advantage of the 3-D model and to be able to differentiate elastic and viscoelastic deformation, addition of tablets with various maximum relative densities was necessary as the shape of the density profile gave this extra information.

The LM pectins also proved to have a high dilution potential, as coherent tablets were produced when 70% pectin was replaced by quartz sand, an inert material. As expected, the plasticity of the particles in the powder blend decreased with increased amount of the quartz sand. Likewise, the elastic recovery decreased with increased amount of the inert material.

Characterization of the compactibility revealed that the tensile strength was strongly dependent on both the DM and the initial particle size. The tensile strength increased with increased DM and decreased particle size, respectively. It was concluded that the effect of

DM on powder compactibility was related to a change in surface hydrophobicity of the pectin particles, rather than to particle compression properties. The studies showed that coherent pectin tablets were successfully produced for $DM \leq 40\%$ by direct compression employing zero dwell-time, whereas the high-methoxylated (HM) pectins ($DM \geq 50\%$) did not produce coherent tablets. The HM pectins are therefore not suitable as direct compression excipients. However, the poor flowability of pectins in general and the fact that the present study used a rather low upper punch speed (10 mm/s), are factors that should be further investigated in order to optimize pectin as a direct compression excipient. In general, it can be concluded that pectin represents an excipient whose compactibility could be modulated by changing the DM with only a minor effect on the compression properties of the particles.

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Paper 1

Paper 2

Paper 3



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