Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Pharmacy 233

Solid State Characterisation and Compaction Behaviour of Pharmaceutical Materials

BY

CHRISTINA GUSTAFSSON

ACTA UNIVERSITATIS UPSALIENSIS
UPPSALA 2000

Dissertation for the Degree of Doctor of Philosophy (Faculty of Pharmacy) in Pharmaceutics presented at Uppsala University in 2000

ABSTRACT

Gustafsson, C., 2000. Solid State Characterisation and Compaction Behaviour of Pharmaceutical Materials. Acta Universitatis Upsaliensis. *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy* 233. 64 pp. Uppsala.
ISBN 91-554-4813-5.

In this thesis, factors important in tableting operations and for tablet properties have been studied and characterised by different spectroscopic techniques as well as by some more conventionally used particle characterisation techniques. The spectroscopic techniques solid-state NMR, FT-IR and NIR spectroscopy, proved to be valuable tools in the estimation of particle and tablet properties, offering both specificity and sensitivity in the measurements. Because of the large amount of information obtained in a spectrum, multivariate data analysis was in some cases used in the processing of the spectral data. Correlations between the solid state structure measured by spectroscopy and the particle and tablet properties could be obtained including useful prediction models.

The surface area obtained using different principles has in this thesis been shown to reflect different properties and tableting behaviour of a collection of pharmaceutical materials. The particle shape and the external surface area of the powders measured by permeametry, were found to be important factors for the tensile strength of tablets made of hydroxypropyl methylcellulose. Furthermore, the external surface area could be used to access dominating interparticulate bonding mechanisms in compacts of different materials by normalising the tablet tensile strength for the tablet surface area. It was also shown that for materials prone to develop solid bridges, the actual surface area participating in the bonding was more important than the average interparticulate distance.

When studying the properties of microcrystalline cellulose and cellulose powder from the alga *Cladophora* sp., the cellulose fibril surface area estimated by solid-state NMR resulted in better correlations to the tableting behaviour and to tablet disintegration than the external permeametric surface area did. It was suggested that the difference in fibril surface area of the two celluloses was the primary factor responsible for properties like the crystallinity and the disintegration of the tablets.

Christina Gustafsson, Department of Pharmacy, Division of Pharmaceutics, Uppsala Biomedical Centre, Box, 580, SE-751 23 Uppsala, Sweden

ISSN 0282-7484
ISBN 91-554-4813-5

Printed in Sweden by University Printers, Uppsala 2000

Till min underbara familj

No matter how many levels of consciousness one reaches,
the problem always goes deeper.

Shulamith Firestone

Contents

Papers discussed

This thesis is based on the following papers which will be referred to by the corresponding Roman numerals in the text.

I Gustafsson, C., Lennholm, H., Iversen, T., Nyström, C., 1998. Comparison of solid-state NMR and isothermal microcalorimetry in the assessment of the amorphous component of lactose. Int. J. Pharm. 174, 243-252.

II Adolfsson, Å., Gustafsson, C., Nyström, C., 1999. Use of tablet strength adjusted for surface area and mean interparticulate distance to evaluate dominating bonding mechanisms. Drug Dev. Ind. Pharm. 25(6), 753-764.

III Gustafsson, C., Bonferoni, M. C., Caramella, C., Lennholm, H., Nyström, C., 1999. Characterisation of particle properties and compaction behaviour of hydroxypropyl methylcellulose with different degrees of methoxy/ hydroxypropyl substitution. Eur. J. Pharm. Sci. 9, 171-184.

IV Gustafsson C., Lennholm, H., Bonferoni, M. C., Caramella, C., and Nyström, C. Important characteristics of hydroxypropyl methylcellulose influencing compactibility and prediction of powder and tablet qualities by infrared spectroscopy. Submitted.

V Gustafsson, C., Lennholm, H., Ek, R., Iversen, T. and Nyström, C. Evaluation of surface and bulk characteristics of cellulose-1-powders in relation to compaction behaviour and tablet properties. In manuscript.

Reprints have been made with permission from the journals

Solid state properties of pharmaceutical materials

The vast majority of pharmaceutical products available today, are administered as solid dosage forms, which are in turn produced by the formulation and processing of powdered solids. Thus, a thorough comprehension of as many physical aspects as possible is of indubitable value and the monitoring of structural changes of the solids during processing, production and storage are important to ensure that the desired qualities of the formulation are obtained. In the following paragraphs some important solid state properties of pharmaceutical solids will be outlined and the processes associated with these change will be mentioned.

Crystal structure

The molecular structure of a pharmaceutical compound is important for several reasons. Well known structure-activity relationships (SARs) of pharmaceutical compounds correlating molecular structure with biological activity facilitate the research into new drug candidates. The structure and factors like charge, size and partitioning are then related to the biological activity of the compound (Wells and Aulton, 1988). However, in the production of pharmaceutical dosage forms, it is not only the active compound that is of interest, but also the excipients included in the dosage form. When it comes to solid dosage forms and particularly to tablets, the volume reduction behaviour, the tablet tensile strength and the disintegration may all be correlated to the molecular structure of the components included. For example, a relatively simple molecular structure is believed to be one of the prerequisites for the development of strong solid bridges in tablets (Führer, 1977). Another example is the cross-linking of carboxy methylcellulose sodium in, e.g., Ac-Di-Sol, resulting in a faster disintegration of tablets and capsules compared to ordinary carboxy methylcellulose sodium (Wade and Weller, 1994).

Depending on the conditions during crystallisation, the molecules may in some cases arrange themselves in more than one way in the crystal and different polymorphs of the compound will be obtained with different properties caused by their arrangement superimposed upon the molecular structure. In addition, rapid crystallisation or extensive processing of a material may result in a more or less disordered or amorphous structure. Both the existence of polymorphism and the degree of order (crystallinity) of the compound will significantly influence its properties (Hüttenrauch, 1978; York, 1983) and thus it is essential to characterise them.

A more disordered structure and a correspondingly higher energy state of the compound is generally connected with a faster dissolution rate (e.g. Florence et al., 1976; Burt and Michell, 1981; York, 1983) and may be utilised for sparingly soluble drugs (e.g. Florence et al., 1976; Mosharraf, 1999). However, the stability of these compounds will often be poor, since the materials tend to recrystallise into a more stable conformation even at low humidities. Further, it has been suggested that a disordered surface structure is a prerequisite for bond formation and compact strength increase during storage (Mitchell and Down, 1984) and for lactose, a disordered structure has been shown to deform more plastically than the corresponding crystalline form (Sebhatu et al., 1999).

A commonly used excipient in the direct compression of tablets is microcrystalline cellulose. It is a biopolymer of glucose units and the commercially available microcrystalline cellulose is produced from wood pulp. Its excellent compaction properties have been studied thoroughly over the years and been attributed to e.g. the relatively high particle surface area (Nyström et al., 1993) and its ability to undergo plastic deformation (Sixsmith, 1976). It has also been suggested that the composition of crystalline and disordered structures of microcrystalline cellulose is of importance (Doelker et al., 1987). However, the primary reason for its behaviour and properties has not yet been fully explained. The original source of the microcrystalline cellulose determines the width of the cellulose fibrils making up the cellulose particles (Wickholm et al., 1998). This will affect the surface on this level and thereby also the exposure to the environment. Thus, if one is to explain the properties of microcrystalline cellulose, the effect that the size and surface area of cellulose fibrils have on a macroscopic level will be of interest.

Particle dimensions

Particle size and powder surface area

Changes in the particle size are generally believed to also change the functional behaviour of most particle processes. Hulett (1901) already showed examples of the effect of particle size on solubility at the beginning of the last century. In the pharmaceutical industry, processes like micronisation of sparingly soluble drugs, such as griseofulvin has, for example, been utilised to improve the dissolution rate of the formulation (Atkinson et al., 1962). The relation between the particle size and the powder surface area is crucial here since a reduced particle size increases the surface area available for solvent interaction.

The importance of particle size with regard to compaction has been studied in a range of papers over the years (e.g. Alderborn and Nyström, 1982; McKenna and McCafferty, 1982; Vromans et al., 1986). The tensile strength of tablets has generally been found to increase when the particle size of the material being compacted is decreased (Shotton and Ganderton, 1961; Alderborn and Nyström, 1982; McKenna and McCafferty, 1982) and has been explained in terms of an increased potential bonding surface area. However the opposite has also been reported, especially for sodium chloride (Alderborn and Nyström, 1982) where the concentration of the applied stress on a few contact points facilitates the development of strong interparticulate bonds like solid bridges. Depending on the volume reduction mechanism of a material, the effect of particle size on the mechanical strength may be more or less evident. The mechanical strength will be less affected by a change in particle size when the material undergoes volume reduction predominantly by fragmentation rather than by plastic deformation (Alderborn and Nyström, 1982). In addition, at a specific critical particle size a material may also change its volume reduction behaviour from a mainly fragmenting behaviour to plastic deformation (Roberts and Rowe, 1987). Considering the above mentioned effects of particle size and thereby powder surface area, it is obviously important to measure and control these factors if one is to control the product and process behaviour.

Particle shape and surface morphology

From a technological point of view, the crystal habit, i.e., the geometrical form of the crystals of a material, is of importance. It may influence the ease of compression of a tablet and the flow properties of the powder. For example, plate-like crystals of tolbutamide have been shown to cause capping problems during tableting (Florence and Attwood, 1998). The crystal habit obtained depends on the crystallisation conditions, e.g., the solvent used, the temperature and the concentration and presence of impurities. However, during processing in pharmaceutical production or because of the environmental conditions, the particle may not only break, but may also recrystallise and aggregate into new shapes.

It has been suggested that the irregular particle shape and rough surface texture of microcrystalline cellulose contribute to the high tablet tensile strength of this material, it is possible that mechanical interlocking of particles in the powder occurs (Karehill and Nyström, 1990; Nyström et al., 1993). In addition, it has been suggested that the fibrous fractions of cellulose derivatives might be partially responsible for the rapidly created rigid gel-layer in extended release matrices (Bonferoni et al., 1996).

The effect of activation and deactivation in relation to processing

During the processing of pharmaceutical materials such as drying (Hüttenrauch and Fricke, 1981), grinding (Buckton et al., 1988; Elamin et al., 1994) and compaction (Ek et al., 1995), the solid-state properties of a material will be altered. The particle size and shape may change, but more fundamentally, energy transmitted to the material will also create disordered regions, that can be manifested throughout the entire crystal, at the particle surface or at localised regions of that surface called frictional hot spots (Hersey and Krycer, 1980).

Activation of a material has both advantages and disadvantages. The activated regions will probably affect the volume reduction behaviour since the deformability of the surface layer of the particles may increase and thereby increase the strength of the tablets produced (Hüttenrauch, 1977). Another consequence of disordered regions may be an increased dissolution rate and a change in the apparent solubility (Mosharraf, 1999). However, one disadvantage of a disordered structure is that its higher energy level than its crystalline counterpart tends to make it less stable than the crystalline form. Thus, the disordered structures are prone to recrystallise to obtain a lower energy level. Surface recrystallisation is facilitated by environmental moisture uptake and the amount of moisture absorbed has been shown to be proportional to the degree of disorder (Ahlneck and Zografi, 1990). Since recrystallisation of a partly amorphous compound can take place even at low humidities and thereby cause deactivation, the storage of the activated material is critical and often associated with problems. Even small unnoticed changes may cause significant differences in the properties of a compound compared to the starting material and it is important to monitor and control these changes.

Characterisation of solid state structure

As the factors already mentioned influence the properties of drug substances, excipients and formulated products, it is obviously important to characterise them with suitable techniques. The methodologies used in the characterisation of the solid state structure of the materials in this thesis, will be reviewed here together with other commonly used techniques in the pharmaceutical field.

Spectroscopy in pharmaceutical analysis

With the exception of X-ray diffraction, the application of spectroscopic techniques has, been rather limited in the pharmaceutical field until recently. However, the use of rapid techniques like near infrared spectroscopy (NIR) is increasing, and this is especially true of the development of on-line production control, such as mixing processes (Hailey et al., 1996)and moisture analysis (Rantanen et al., 1998).

Spectroscopic techniques use the interaction between electromagnetic radiation and the sample to monitor properties of interest of the compound. The electromagnetic spectrum covers a wide frequency or wavelength range and thereby also a broad range of investigative energies. The different spectroscopic techniques operate over different frequency ranges, depending on the process and magnitudes of the energy changes involved when radiating samples. Thus by choosing an appropriate technique, the crystallinity, the molecular structures and processes can be studied. Some interesting spectroscopic techniques in the characterisation of the solid state structure of pharmaceuticals are presented below. It should be noted that in this discussion, the techniques and their applications are discussed from a pharmaceutical perspective only. Thus, although the benefits to be gained may be similar in other fields, neither these, nor their applications outside the field of pharmaceutics are considered.

X-ray diffraction

The main ways in which X-rays can be used are diffraction, emission and absorption and X-ray diffraction is the most commonly used spectroscopic technique. In this technique, the wavelengths of the electromagnetic radiation is around 1 Å. The technique is particularly suited to the identification of different polymorphic forms and the solvated and anhydrous forms of a compound (Suryanarayanan, 1995). It has been widely used to measure the degree of crystallinity (e.g. Klug and Alexander, 1974; Black and Lovering, 1977; Munoz-Ruiz et al., 1996), where the peak heights or the integrated intensities of the peaks compared to an internal standard usually are used as a measure of the crystallinity. However, the relative sensitivity of the X-ray in this application has been reported to be lower than to e.g. that of IR spectroscopy (Nail et al., 1975). X-ray diffraction has also been used to quantitatively determine the amounts of the active ingredient in multicomponent tablet formulations (Suryanarayanan and Herman, 1991a; 1991b).

Solid-state nuclear magnetic resonance

The combination of magic angle spinning and cross polarisation techniques has made it possible to use nuclear magnetic resonance (NMR) not only for solution-phase studies but also in studies of the solid state of compounds. The application of solid-state NMR in the pharmaceutical field is, however, still very limited and up to now has mainly been used in the area of polymorphism at the qualitative and quantitative level (Byrn, 1982; Fletton et al., 1987; Harris et al., 1989; Harris et al., 1990). In a few studies solid-state NMR has also been used in the assessment of the degree of crystallinity (Ek et al., 1995; Mosharraf 1999). Further, in the studies by Sekizaki et al. (1995) and Nerdal et al. (2000), solid-state NMR was utilised for investigation of interactions between drug and polyvinylpyrrolidone and drug and liposomes respectively.

The radiation used in the NMR technique is in the radiofrequency range and the amount of absorption of the irradiation by a sample placed in a strong magnetic field is detected. Solid-state NMR is a nondestructive, multinuclear technique that has the ability to probe the chemical environment of a number of atom nuclei which can be chosen to best suit the sample to be investigated. For pharmaceutical purposes, the most common isotope used is ^{13}C (Bugay, 1995). Further, solid-state NMR is a bulk technique that need not consider particle size effects on the intensity of the measured signal. This may be an advantage when the purpose is only to study the polymorphic conversion under various processing techniques, but in the case where the differences in particle size are an important property to be studied alongside the structural changes, other techniques such as NIR should be used in combination with solid-state NMR. There are a number of studies where solid-state NMR has been used in conjuction with other techniques to characterise polymorphic systems, e.g. X-ray diffraction, differential scanning calorimetry, infrared spectroscopy, and microscopy (Doherty and York, 1988; Brittain et al., 1991; Gerber et al., 1991; Brittain et al., 1993; Raghavan et al., 1993).

Vibrational spectroscopy

When using the infrared (IR) methods, the vibrational modes of a molecule are used to deduce structural information. There are three different spectral intervals commonly identified, namely, the far-IR (100-400 cm^{-1}), mid-IR (400-4000 cm^{-1}) and near-IR also written NIR (4000-14 000 cm^{-1}). The most important use of IR has been for the identification of organic compounds, their mid-IR spectra are generally very complex and may be taken as a fingerprint of the compound and is used to identify it. The diffuse reflectance method in the mid-IR range is the preferred method for application to powders. In the literature, the qualitative differentiations of different polymorphs are dominating (see e.g., Chao and Vail, 1987; Lin, 1992; Neville et al., 1992; Brittain et al., 1993; Raghavan et al., 1994; Martiez-Ohárriz et al., 1994). Quantitative measurements of polymorphs have also been performed (e.g., Hartauer et al., 1992; Roston et al., 1993), but they need homogenous calibration and careful evaluation of the samples and a consistant particle size for all components in order to avoid prediction errors. Another disadvantage with mid-IR spectroscopy is that the sample often has to be prepared in a suitable way, e.g. it might need to be diluted before the measurement.

There is a variety of possible applications for NIR spectroscopy, but the broad and less distinct spectra obtained in comparison with mid-IR spectra make it less suitable for

direct identification purposes (Ryan et al., 1991). However, using some kind of multivariate data analysis software, the NIR technique has been used successfully for tablet assays (Morisseau and Rhodes, 1997) and blending validation (MacDonald and Prebble, 1993; Hailey et al., 1996; Ciurczak, 1991). Furthermore, it is a suitable technique for the quantitative determinations of water content and the active compound within a formulated tablet (Jensen et al., 1988; Lonardi et al., 1989; Corti et al., 1990). The advantages of rapid evaluation of the sample without any need for sample preparation, make NIR into the ideal form of analysis in a quality control, or on-line, process analysis environment (Bugay and Williams, 1995).

Raman spectroscopy is a vibrational spectroscopy technique where the spectra are obtained by irradiating a sample with a powerful laser source. As for the above mentioned IR-techniques, Raman spectroscopy has also been used to study polymorphic forms of pharmaceuticals (e.g. Bellows et al., 1977; Bolton and Prasad, 1984; Deeley et al., 1991; Tudor et al., 1993). Other applications are, e.g., simultaneous multicomponent determinations of dosage forms (King et al., 1985; Hameau et al., 1988) determinations of crystallinity (e.g. Quin and Kean, 1998; Taylor and Zografi, 1998) and drug interaction studies (Bolton and Prasad, 1984; Taylor and Zografi, 1997). The peaks in a Raman spectrum are sharp and selective, as they for the mid-IR spectrum, however complex mixtures containing large molecules will result in complex and overlapping peaks which may need multivariate analysis methods for the evaluation of the results. A main advantage of Raman spectra over mid-IR techniques is that water does not cause interference so that both solids and aqueous solutions can be analysed. In addition, Raman spectroscopy analysis is non-destructive, rapid and does not need any sample preparation procedures, which make it suitable for processing analytical applications (Svensson, 1999).

Calorimetry in pharmaceutical analysis

In one way or another most solids are “thermally active” and can therefore be profitably studied by calorimetry. The heat evolved or absorbed in different processes is then measured and can be related to both physical and chemical properties of compounds. Calorimeters can be divided according to whether the calorimeter works at constant or changing temperature (Angberg, 1992) and some of the most commonly used will be addressed here.

Thermal analysis instruments

Thermal analysis instruments are calorimeters for which the temperature is changed during the analysis. Differential thermal analysis (DTA) measures the difference in temperature between a sample and an inert reference material as a function of temperature and thereby detects changes in heat content. DTA is normally not used for quantitative work, but instead to deduce temperatures associated with thermal events (Brittain, 1995). Nevertheless, the technique has successfully been used for compatibility studies (Jacobson and Reier, 1969) and in studies of polymorphism (Yang and Guillory, 1972; Lee and Hercey, 1977; Van Aerde et al., 1984; Matsuda et al., 1984).

A related technique is differential scanning calorimetry (DSC), which is designed to allow quantitative measurements to be made of enthalpy changes. Integration of the peaks in a DSC spectra, yields the heat of reaction since the area under the peaks is directly proportional to the heat absorbed or evolved by the thermal event. DSC is the most widely used method of thermal analysis and can be used for determination of absolute purity (Beyrich et al., 1997; Rustichelli et al., 1999), crystallisation and glass transition temperature (Elamin et al., 1995) and is particularly useful in the study of compound polymorphism (e.g. Kuhnert-Brandstätter and Ulmer, 1973; Agafonov et al., 1991; Craig and Newton, 1991).

Thermogravimetry (TG) records the mass of a sample as a function of temperature or time, and is most commonly used to study desolvation processes and compound decomposition (McCauley and Brittain, 1995). It is often advantageous to combine TG analysis with DTA or DSC analysis (Ertel and Carstensen, 1988; Kitamura et al., 1994).

Isothermal microcalorimetry

In contrast to the thermal analysis instruments, isothermal microcalorimetry relies upon maintaining a constant temperature. In the isothermal heat conduction calorimeter a reaction vessel is connected to a thermostat via heat-conduction material. The technique involves monitoring the heat conduction into or out of a measuring cell from or to the heat sink. A heat signal of 10^{-6} °C can be detected by the microcalorimeter and is monitored as the heat flow (dq/dt). The heat flow is proportional to the reaction in the sample vessel (Buckton and Beezer, 1988; Angberg, 1992).

In the literature, there are examples of various applications of microcalorimetry in the pharmaceutical field. Studies have been made on, e.g., stability (Angberg, 1992), adsorption of water vapour onto surfaces of hydrophobic powders (Buckton and Beezer, 1988), interaction of water vapour sorption with excipients (Blair et al., 1990) and crystallinity (Sebhatu et al., 1994; Mosharraf, 1999). The crystallinity of a compound can be obtained from the heat flow during the crystallisation of the amorphous portion of the compound and several studies have shown the great sensitivity of this technique compared to, e.g., DSC or X-ray techniques (Sebhatu et al., 1994; Buckton et al., 1995; Giron et al., 1997). To induce crystallisation at room temperature, moisture can be used as a medium for water soluble compounds and organic vapour for hydrophobic compounds (Ahmed et al., 1996).

Water sorption

The presence of moisture is important for the physical and chemical properties of pharmaceutical solids. Properties such as flow, compaction, disintegration, dissolution, hardness and chemical stability are all influenced by moisture. The amount of water present, where it is located and in what state it is associated with the solid are all important issues to address to be able to predict and control the behaviour of a solid powder during processing. Water sorption can be measured both by gravimetric methods and by volumetric methods (Kontny and Zografi, 1995).

Microscopy

Microscopy studies can provide information about the solid state of a material since crystalline solids often possess a characteristic crystal habit (Segal, 1985). As well as the shape, the crystal habit can also reflect internal structural changes, e.g., polymorphs and solvates, as well as revealing the presence of impurities (Florence and Attwood, 1998). Not surprisingly, in contrast to crystalline particles, amorphous particles often possess a less distinct shape and in the case of spray dried amorphous lactose and sucrose particles, the shape has been shown to be spherical or rounded respectively (Elamin et al., 1995). From visual studies of particles, it may be possible to predict the flow properties of the powder to a certain extent and to deduce how the particles will behave during compression (Florence and Attwood, 1998). Nowadays the use of computerised image analysis has facilitated particle characterisation by microscopy.

Density measurements

Depending on the packing of the molecules into crystals and particles, the density of the materials will differ. By measuring the apparent particle density, e.g. by helium pycnometry, an indication can be obtained of changes in the degree of crystallinity or polymorph composition (Hüttenrauch et al., 1985; Suryananen and Mitchell, 1985; Duncan-Hewitt and Grant, 1986). It has been reported that the compression of some materials results in apparently negative porosities and an increase in the true density of the materials (e.g. Blattner et al., 1986; Pedersen and Kristensen, 1994; Adolfsson and Nyström, 1996). Pedersen and Kristensen (1994) reported that the volume of the unit cell of acetylsalicylic acid was to some extent irreversibly changed under pressure. In the study by Adolfsson and Nyström (1996), the increase in the density of polyethylene glycol was accompanied by an increase in the melting point and the heat of fusion. Thus, the compaction procedure may affect the solid state properties of a material and measurement of the apparent density would reveal this.

Characterisation of specific surface area and inter/intra particulate pores

As has been mentioned earlier (p. 10), the surface area of a powder is related to the particle size. However, the term “surface area” may be defined in a variety of ways. Armstrong (1996) suggested that firstly, a visible or outer surface area may be obtained, e.g., by image analysis of particles. Secondly, the external surface, i.e., the sum of the surface areas of all the particles where they are considered to be nonporous units may be measured by permeametry or light extinction. Thirdly, the total surface area including fine structure and pores within the particles may be sought. Depending on the pore size distribution of the particles and the penetration capacity of the technique used, the total surface area may differ and must be specified. The techniques used most commonly for measurements of the total surface area are gas adsorption and mercury porosimetry.

Permeametry

Permeametry techniques consider the air flowing through a powder bed under the influence of a pressure drop. The surface of the particles constitutes the principal resistance to airflow and the permeability of the powder bed is an inverse function of its surface area. The Kozeny-Carman equation is the basis of most permeablility methods (Kaye, 1967). For very fine powders the rate of gas flow is greater than predicted by this equation and a correction for this slip flow is also made. Several different kinds of permeametry apparatus are available, either utilising a constant pressure on the powder bed measuring the pressure drop over the powder bed (e.g. Fisher apparatus), or measuring the time for a constant volume of air to pass through the powder bed (e.g. the Blaine and Friedrich permeameters). The use of the Kozeny-Carman equation in connection with tablets has been criticised (Selkirk, 1985), but nevertheless, this approach is frequently adopted (e.g. Alderborn et al., 1985a; 1985b; Nyström and Karehill, 1986; Wong and Pilpel, 1990; Sebhatu and Alderborn, 1999).

Gas adsorption

The total surface area of a solid can be measured by gas adsorption methods. The adsorbate is usually nitrogen, helium or krypton gas and any internal structure to which the adsorbate has access will be included in the results of the analysis. The amount of adsorbent required to cover all the available surface with a single molecular layer of gas can be determined, and related to the surface area of the solid powder or tablet by the Langmuir isotherm (Langmuir, 1918). Brunauer, Emmet and Teller (1938), derived the so-called B.E.T. equation, which is based on the Langmuir isotherm in order to calculate the surface area of solids. However, other adsorption isotherms defining the relationship between the amount adsorbed gas and the pressure surrounding the gas also exist. In addition to the surface area of a solid, the pore size and pore size distribution may also be obtained from gas adsorption analysis and a number of alternative equations are available for this purpose (Allen, 1997). Nitrogen is the most commonly used adsorbent in gas adsorption analysis of solids (e.g. Hardman and Lilley, 1973; Nakai et al., 1977; Stanley-Wood and Johansson, 1978) but other adsorbents may also be used, e.g., argon, carbon dioxide and krypton. Especially the latter is utilised for small surface areas, e.g., coarse particulate systems of tablets (Hardman and Lilley, 1973; Alderborn et al., 1985; Nyström and Karehill, 1986: Nyström et al., 1993), due to its lower saturation pressure.

Mercury porosimetry

Mercury porosimetry is most commonly used for the characterisation of pore and void structure (Allen, 1997), but may also be used for surface area determinations (e.g. Vromans et al., 1985; Westermark, 1998). Compared to gas adsorption, the range of pore radii covered by mercury porosimetry is much wider making it supplementary to the other techniques available because of its ability to estimate large pores, whereas gas adsorption must be used for pores less than 20 Å (Allen, 1997). In mercury porosimetry the intrusion of mercury into the pores of a powder bed or a tablet is gradually increased

by the applying pressure and this is followed by extrusion as the pressure is lowered. Assuming cylindrical parallel pores, the surface area can be calculated easily. However, the real nature of most porous media is much more complicated and by using the simplified pore model, the results will only be comparative, not absolute. Furthermore, pores of ink-bottle shape, together with pores within the particles which are not accessible to the filling media introduce further problems. The latter problem may also be of interest in gas adsorption measurements. Finally, in the determination of pore size distribution, it may sometimes be difficult to separate the intraparticulate pores from the interparticulate ones.

CP/MAS ^{13}C-NMR

CP/MAS ^{13}C-NMR has been used in this thesis (paper V) to evaluate the surface area of cellulose fibrils. It is not a technique commonly used for surface area determination in the pharmaceutical field, however in the area of cellulose chemistry, several studies have been performed to evaluate and determine accessible and non-accessible surface areas of cellulose fibrils (e.g., Wickholm et al., 1998; Larsson et al., 1999). The technique is based on spectral fitting and the relative signal intensities of the NMR-peaks (Larsson et al., 1999).

Other techniques for the determination of surface area

Apart from the methods mentioned above, surface areas may also be calculated from size distribution data. Light extinction, and X-ray-, light- and electron scattering are examples of methods available for this purpose (Allen, 1997). Different adsorption techniques, including adsorption from solution are also used for surface area determinations. Depending on whether the material is hydrophilic or hydrophobic, water or organic solvents may be used. Calculating the surface area based on water vapour sorption data was shown to result in very high values compared to, e.g., gas adsorption measurements (Zografi et al., 1984; Zografi and Kontny, 1986). However, since the moisture sorption has been shown to be proportional to the degree of amorphicity, it was suggested that the values obtained by water vapour sorption might be artifactual surface areas (Zografi et al., 1984).

Compactability of pharmaceutical powders

The most commonly used pharmaceutical dosage forms today are tablets of different kinds. During production and handling, tablets have many advantages over other dosage forms, in addition to which they are convenient for the patient to use. The compaction of a powder into a coherent compact involves a series of steps leading to bond formation. The particles are rearranged and subjected to fragmentation and deformation (Train, 1956). The energy adsorbed by the particle surfaces during compression will be released and will form interparticulate bonds when the particles are brought into close proximity with each other, thereby creating a coherent compact (Hüttenrauch, 1977; CoffinBeach and Hollenbeck, 1983; Rowlings et al., 1995).

The compaction of powders has been the subject of research for many years, yet the process is not fully understood. There is still a need for additional knowledge concerning factors influencing the tableting process and the resulting compacts, for a more rational approach to tablet formulation to be adopted.

Factors affecting the mechanical strength of pharmaceutical compacts

The mechanical strength of pharmaceutical compacts is of great importance since there is a need to ensure that the tablets produced are sufficiently strong to withstand handling and yet it must still be possible for the drug substance to be released from the tablets. In the field of fracture mechanics, the compact strength is regarded as being related to the occurrence of defects and flaws in the compact (Mullier et al., 1987; Kendall, 1988). The review regarding solid state properties of pharmaceutical compounds so far in this thesis, has already dealt with some factors which may influence the development of disturbances (e.g. polymorphism, particle shape and size), thereby also influencing the mechanical strength of compacts. However, some additional factors will be discussed here since, it has been common for the pharmaceutical literature to interpret the strength of tablets in terms of interparticulate bonding mechanisms and bonding surface area (Rumpf, 1962).

Bonding mechanisms in pharmaceutical materials

The dominating bond types adhering the particles in a compact are often divided into three main types: distance forces, solid bridges and mechanical interlocking (Führer, 1977; de Boer et al., 1978).

In this thesis, the term *distance forces* is used as a collective term for all bonding forces that act between surfaces separated by a distance and will thus include van der Waals forces, electrostatic forces and hydrogen bonding. It is believed that van der Waals forces are the most important bonding mechanism for pharmaceutical materials (Leuenberger et al., 1989; Luangtana-Anan and Fell, 1990; Karehill and Nyström, 1993). The strength of the van der Waals forces is dependent on the distance between the particles or ions (up to 100-1000 Å), the medium surrounding and the nature of the attracting particles or ions (Israelachvili, 1992a). Through electrostatic interaction, hydrogen bonds may develop within and/or between molecules containing electronegative atoms (e.g., O, N, F, and Cl) and hydrogen atoms. In all kinds of cellulose, e.g., microcrystalline cellulose, the extended intraparticulate hydrogen bonding is largely responsible for the interparticulate strength (Heiner and Teleman, 1997). Electrostatic forces may arise during processing of materials where the highly charged surfaces obtained interact over quite large distances (Führer, 1977). However, these forces are likely to be neutralised rather quickly by electrostatic discharging and are probably of minor importance for the strength of tablets stored at ambient conditions (Nyström and Karehill, 1996).

Solid bridges may develop between particles when there is an interaction between the surfaces at the atomic level and the molecules or ions in the solid bridge are then

arranged and bonded in the same manner as those inside each particle. A continuous phase is created between the particles in the tablets, making these tablets stronger than those where only distance forces occur. It has been suggested that solid bridges develop through partial melting and advanced interparticulate diffusion of molecules and ions, and thus their formation requires a special chemical and physical structure and mechanical behaviour of the materials (Führer, 1977; Führer, 1996; Adolfsson et al., 1997). It has also been purported that the presence of moisture is important for the development of solid bridges (Ahlneck and Alderborn, 1989; Eriksson and Alderborn, 1994).

Mechanical interlocking could be a contributing factor for the tablet tensile strength of compacts made of microcrystalline cellulose (Karehill and Nyström, 1990). The term is used to describe the hooking onto and twisting together of fibrous or irregular particles in a compact (Goetzel, 1949; Führer, 1977). Smooth spherical particles will have little tendency to interlock.

The concept of bonding surface area

Through the characterisation of the tablet particles and/or the tablet pores, a considerably amount of information about the internal structure of the tablets be may revealed. As already mentioned, the surface area of solids may be obtained by several different techniques. However, it is more difficult to estimate the actual fraction of the tablet surface area that participates in interparticulate bonding, i.e., the bonding surface area. In some studies, the surface area of the starting material has been compared with the surface area of the compacted material (Armstrong and Haines-Nutt, 1970; Hardman and Lilley, 1973; Stanley-Wood and Johansson, 1978; Nyström and Karehill, 1986). and in others, a comparison has been made of surface areas of tablets with the surface areas of deaggregated tablets (Alderborn and Glazer, 1990). Both of these approaches suggest that the surface area involved in bonding is minute in comparison with the total measured surface area. Several studies of lactose have shown a direct relationship between tensile strength and tablet surface area (e.g. Vromans et al., 1985; Vromans et al., 1987; de Boer et al, 1986) however, these findings could not be confirmed by others (Eriksson and Alderborn, 1995; Juppo, 1996).

Different values of the surface area will be obtained depending which technique is adopted to determine the surface area. For the purpose of estimating the bonding surface area, the permeametry technique, measuring the external surface area of the particles, is thought to be probably the most appropriate technique to use (Alderborn et al., 1985). By other techniques, the intraparticulate surface area not participating in interparticulate bonding may substantially influence the surface area of the tablets. However, other factors than the surface area participating in bonding are also of importance for the interparticulate interactions. For example, the strength of a powder and a tablet made of the same powder will differ considerably, although the two may have the same surface area. Thus, the distance between the particles will influence the mechanical strength of a powder bed (Israelachvili, 1992a). Both the distance and the bonding surface area will in turn be affected by the volume reduction behaviour of the particles and their protrusions. Extensive elastic recovery of the tablets may, for example, cause a pronounced decrease in tablet strength through breakage of interparticulate bonds,

thereby reducing the bonding surface area (Duberg and Nyström, 1986). Readily deformable protrusions on the particle surfaces on the other hand may result in small distances (often expressed as low porosity) between the surface areas of the particles, thereby favouring particle interactions (Olsson and Nyström, 2000b; Nyström and Karehill, 1986).

Methods for characterising mechanical strength and bonding mechanisms

The mechanical strength of pharmaceutical compacts can be determined by a number of different methods. The most common method is the diametral compression test, where the radial tensile strength is calculated from the diametral breaking force, which makes this an indirect test method (Fell and Newton, 1970). The diametral compression test was developed to enable one to measure the tensile strength of brittle materials like concrete, coal and gypsum (Davies and Newton, 1996) and, when applied on tablets, requires a tensile failure of the tablet. To ensure this, the compressive strength needs to be at least three times the tensile strength, which may not always be the case for pharmaceutical compacts. However, by increasing the rate at which the load is applied to the tablet, the failure may change from ductile to brittle however this will also affect the values obtained for the tensile strength (Davies and Newton, 1996). Generally, it is considered that the diametral compression test reflects the average strength of the compact since the location of the fracture is predetermined. In contrast, direct tensile strength measurements, like the determination of the axial tensile strength will reflect the weakest plane in the tablet (Nyström et al., 1978). Here, the location of the fracture is not predetermined, but may occur anywhere in the tablet perpendicular to the direction of compaction. Very low values of the axial tensile strength compared to the radial tensile strength may indicate capping tendencies in the tablets.

Different ways of estimating the dominating bonding mechanisms in tablets have been the purposed. For example, the surface specific tablet strength was calculated by Karehill et al. (1993) and resulted in high values for materials bonding with contribution from solid bridges and low values for materials bonding through distance forces alone. Using lubricant films of magnesium stearate Karehill and Nyström (1990) were also able to filter out distance forces within the compacts, leaving only the solid bridges. When removing the lubricant, the strength of the compacts increased, showing that the effect of the filtering lubricant was reversible and that the distance forces constitute the dominating bonding mechanism for the investigated materials. Bonding through the contributions from solid bridges was only found in tablets made of sodium chloride. The compaction of tablets in liquids with differing dielectric constants has also been found to be useful in distinguishing between different bond types (Karehill and Nyström, 1990; Olsson et al., 1996; Adolfsson et al., 1997). As in the case of lubricant films, the weak distance forces were filtered out and this was best achieved when the liquid compaction medium had a dielectric constant of 18. The remaining tensile strength was then attributed to solid bridges and, again, the weak distance forces were found to be the dominating bonding mechanism for most pharmaceutical materials.

Multivariate data analysis to identify the presence of correlations

Multivariate data analysis, MVDA, has been widely used in the fields of pharmaceutics, chemistry, biology and engineering during the last years and a number of different computer software programs are available on the market (Marten and Naess, 1989; Eriksson et al., 1999). With MVDA, it is possible to extract information from data with many variables, using them all simultaneously. Furthermore, it is possible to model the factors and responses and find relationships between all the factors and all the responses. MVDA deals with the problem of dimensionality, it can separate regularities from noise, cope with missing data and can handle many variables and few observations, as well as few variables and many observations.

One MVDA technique, principal component analysis, PCA, involves observations (measured properties) and the variables (e.g. spectral data), being transformed into a new co-ordinate system that is defined by the principal components (Jackson, 1991; Wold et al., 1984). The direction in the total data with the largest variation is occupied by the first PC, whilst the second PC occupies the direction with the largest variation orthogonal to the first PC. Most of the variation is covered by the first two principal components, but it is possible to compute new principal components in this way until no variations are left. From this, score and loading plots are obtained. A score plot shows the location of the objects (samples) relative to each other and a loading plot shows how important the variables are for different directions in the score plot. Objects in the score plot having similar properties will for example be situated close to each other.

Another MVDA technique, partial least squares, abbreviated to PLS, also identifies relationships between observations and variables (Marten and Naess, 1989; Wold et al., 1984). In addition, quantitative prediction models may be obtained. Spectral data from IR-techniques (Svensson, 1999) or solid-state NMR (Lennholm, 1994), for example may be used to create predictive models to anticipate measured properties. From these models, the properties of new samples may be predicted from the spectral data for the samples alone. However, as with many analysis techniques, one drawback is the need for a calibration standard, which may be tedious to obtain.

In this thesis, PCA and PLS have been used to correlate powder characteristics, compaction behaviour and spectral data in Papers- I and IV. In addition, prediction models have also been developed for particle and tablet properties.

Aims of the thesis

The aim in conducting the work for this thesis was to

- Evaluate the applicability of various spectroscopic techniques in the assessment of particle and tablet properties (Papers I and III-V).
- Evaluate the importance of surface area (Papers II, III and V) and mean interparticulate distance for the mechanical strength of tablets and in the evaluation of dominating bonding mechanisms (Paper II).
- Identify important characteristics of microcrystalline cellulose and cellulose derivatives for the compaction behaviour and tablet properties (Papers III-V).

Materials and Methods

Choice of test materials

In Paper I, lactose was used as a model substance for several reasons: Firstly, it is a well known excipient that has been studied thoroughly, secondly, it has a relatively uncomplicated crystal structure comprising a limited number of well defined polymorphs. Last, but not least, lactose is ideal because samples that are totally crystalline or totally amorphous can be produced readily.

In Paper II, a range of different model substances were studied with the intention of better understanding the importance of the tablet surface area and mean interparticulate distance for different types of pharmaceutical powders in tablets.

In Papers III-V, cellulose derivatives, microcrystalline cellulose and cellulose from the alga *Cladophora* sp. were studied. It has been shown that cellulose in different forms has excellent compaction and tablet properties, however, the reasons for its suitability as a tablet excipient have not yet been completely delineated and the differences in its performance have yet to be fully explained.

Preparation of materials

The test materials of commercial grades used in the studies were lactose, sodium bicarbonate, sodium chloride, sucrose, microcrystalline cellulose (Avicel PH101) and hydroxypropyl methylcellulose of different degrees of substitution (Methocel and Metholose). In addition, amorphous lactose was produced by spraydrying (Niro Atomizer, Anhydro, Denmark) a lactose solution. A cellulose powder of the alga *Cladophora* sp. was also produced by spray drying (Niro Atomizer, Anhydro, Denmark) subsequent to hydrolysis, bleaching (described by Ek et al., 1998) and milling (Alpine 160 Z, Alpine AG, Germany).

Generally the coarse particulate size fractions (>90 μm) were obtained by dry sieving through laboratory test sieves (Retsch, Germany) and the fine particulate fractions

(<90 μm) were obtained by air classification (Alpine 100 MZR, Alpine AG, Germany) of either the raw material or of the material after milling in a pin disc mill (Alpine 63C, Alpine AG, Germany). All test materials were stored in desiccators over saturated chrome trioxide (40% RH) (Nyqvist, 1983), prior to powder characterisation and compaction. The moisture content of the powders in Papers III and V, was determined gravimetrically. In Paper III the Mettler P163 balance was used equipped with an infrared source (Mettler LP12, USA) and in Paper V the Halogen Moisture Analyser (HR73, Mettler Toledo, USA).

Characterisation of materials

Specific surface area measurement and particle size analysis

The external specific surface area associated with non porous particles was in paper II-V measured using a Blaine permeameter for the fine particulate size fractions (< 90 μm), and a Friedrich permeameter for the coarse size fractions (>90 μm) (Eriksson et al., 1990).

The total specific surface area (Paper V) including cracks and pores was obtained using nitrogen and krypton gas adsorption (ASAP 2000, Micromeritics, USA) in conjuction with the BET-equation. The micropore area was also extracted from these measurements.

An estimation of the surface area at the fibril level (30-50 nm) was obtained by solid-state NMR in Paper V (Wickholm et al., 1998). In addition, particle size analysis was performed by Laser diffraction (LS 230, Coulter, USA) using cyclohexane as the suspending agent (Extra pure, Merck, Germany).

Particle shape analysis

To obtain a qualitative analysis of the particles, SEM microphotographs were taken of the particles and of the fracture surfaces of the tablets (Papers III and V). Quantitative values in terms of the Heywood surface to volume shape factor (Heywood, 1954) were obtained from particle size measurements (Coulter Multisize, Coulter Electronics Ltd, Luton UK and LS 230, Coulter, USA) and permeametric surface area measurements.

Solid state structure analysis

In all papers the apparent particle density (B.S. 2955, 1958) of the materials was measured by helium pycnometry (Accu Pyc 1330, Micromeretics, USA), (n = 3). In Paper V, the bulk density of the powders was obtained by pouring powder into a 25 ml cylinder and weighing it (n = 3). Furthermore, the tapped density was given by tapping the cylinder 1000 times (n = 3) in a tap volumeter (Eberhard Bauer D7300, Germany) and the Hausner ratio was calculated from the values of the tapped and bulk density.

Isothermal microcalorimetry (2277, Thermal Active Monitor, Thermometric, Sweden) was used in Paper I to assess the degree of disorder in lactose mixtures. The mini

humidity chamber technique (Angberg et al., 1992) was used to induce the crystallisation process and the enthalpy values of disorder were obtained by calculating the heat generated during crystallisation.

CP/MAS ^{13}C-NMR spectra were recorded for the powder materials discussed in Papers I, III and V and for the tablets investigated in Paper V (Bruker AMX-300, Germany). The spectrometer operated at 75.47 MHz using a double air bearing probe and ZrO_2 rotors. In these investigations the spinning rate was 5 kHz, the contact time was 0.8 ms, the acquistion time was 37 ms, the sweep width was 368 ppm and the delay between the pulses was 2.5 s. The spectra were obtained by accumulating between 2000 and 650000 transients with 2048 data points zero filled to 4096 data points. The spectra were referenced to the carbonyl in external glycine (δ=176.03 ppm). In paper V, calculation of the so called crystallinity index (I_{CR}) was performed based on the integration of the surface area under on the bulk (86-93 ppm) and surface (80-86 ppm) expression of carbon 4 in the spectra (Ek et al., 1995).

Near infrared (NIR) spectra were acquired on a Bruker IFS 55 spectrometer equipped with an MCT-detector in Paper IV. Two spectra were recorded for each sample by pressing a fibre probe accessory against a plastic bag containing the dry powders. A total of 32 scans were acquired.

In Paper IV, Fourier transform infrared (FT-IR) spectra were acquired on a Bruker IFS 55 spectrometer using a DTGS-detector. Spectra were recorded on two KBr tablets made from dry powders of the two components, using approximately 2 mg HPMC per 100 mg KBr. A total of 32 scans was acquired with a spectral resolution of 8 cm^{-1}.

Compaction of tablets

Compaction was performed using an instrumented single punch press (Korsch EK 0, Germany) equipped with 11.3 mm (Papers II-IV) or 5.47 mm (Paper V) flat punch faces. When using the larger punches, the die and punch faces were lubricated with magnesium stearate powder and the material was for each tablet weighed and poured by hand into the die. The distance between the punches in the lowest position of the upper punch was 3 mm for all these tablets at zero pressure; different compaction loads were obtained by varying the amount of material in the die.

To be able to run solid-state NMR analysis on intact tablets in paper V and to obtain compaction loads up to 1200 MPa a smaller punch diameter (5.47 mm) was used. No lubrication was used and a constant amount of 60 mg of material was weighted and compacted into tablets. The different loads were obtained by varying the position of the upper punch.

The maximum upper punch pressure during compression was recorded for each tablet and, depending on the series of experiments, a deviation from the desired compaction load not exceeding 3 (Papers II-IV) or 5% (Paper V) was acceptable. After compaction, the tablets were stored at 40% relative humidity and room temperature for at least 48 hours before any characterisation was made.

Characterisation of compaction behaviour

Deformability

The deformability of the powders in Papers III-V was characterised using the Heckel equation (Heckel, 1961a;b). The materials were either compressed at 100 MPa (paper III-IV) or 150 MPa (Paper V) and the thickness of the tablets was recorded every millisecond during the compression cycle (n = 2-3). The tablet porosity during the compression cycle was calculated from the thickness of the tablets and was used in the Heckel equation. The apparent yield pressure of the materials was calculated from the reciprocal of the linear part of the Heckel plot, which in this case corresponded to a pressure range of 20-80 MPa (Papers III-IV) and 60-120 MPa (Paper V).

Fragmentation propensity

The fragmentation propensity (Papers IV and V)was obtained from the gradient of the slope obtained when the specific surface area measured by permeametry was plotted against the compaction pressure (Alderborn et al., 1985b).

Elastic recovery

The elastic recovery was calculated as the difference between the minimum tablet thickness (at the maximum compaction load in the Heckel analysis; 100 or 150 MPa, depending on the experiment) and the maximum tablet thickness after 48 hours of storage (Armstrong and Haines-Nutt, 1972).

Characterisation of tablet properties

Mechanical strength

The radial tablet tensile strength was calculated using the diametral compression test (Fell and Newton, 1970). This was carried out using a Holland C50 (Great Britain).

The axial tablet tensile strength was calculated as described by Nyström et al. (1978) after using a material tester (M30K, Lloyd Instruments, England).

Tablet porosity

The tablet porosity was calculated from the apparent particle density (B.S. 2955, 1958) of the powder materials (Papers II-IV) or of the tableted materials (Paper V) and the dimensions and weight of the tablets.

Tablet surface area

The external volume (Papers II and III) and weight specific (Paper V) surface area of tablets obatined using different compaction loads were measured using a Blaine permeameter (Alderborn et al., 1985a) where the surface area was calculated according to Kozeny Carman and was corrected for slip-flow.

In Paper V the total specific surface area of the compacts was measured by Kr gas adsorption (ASAP 2000, Micromeritics, USA) on 2-20 tablets fom each compaction load (10-1200 MPa). In addition, a qualitative measurement of the surface area was performed on the fibril level by solid-state NMR by studying the area of the spectra corresponding to 80-86 ppm (Wickholm et al., 1998).

Mean interparticulate distance and micropore area in tablets
The mean pore radius within the compacts was estimated in Papers II-IV from the volume specific surface area obtained from permeametry measurements (Alderborn et al., 1985a) and the calculated porosity (Allen, 1997). In Paper V, the micropore area was obtained from Kr gas adsorption measurements (ASAP 2000, Micromeritics, USA).

Tablet disintegration

The disintegration of tablets in Paper V was performed on six tablets from each load in 37°C deionized water (Pharma Test PTZ 1E, Germany) during a maximum time of 60 minutes.

Solid state properties

The tablets compacted at 1200 MPa were characterised using CP/MAS ^{13}C-NMR with the same settings as for the powders. In addition, the values of the apparent particle density of the tablets obtained for each compaction load were used for the evaluation of structural changes.

Correlation among and predictions of the measured properties

In Papers I and IV, the results from particle characterisation, NMR, NIR and FT-IR analysis and characterisation of the compression process and final tablets were analysed using the software SIMCA 5.0 and 7.1 (Umetrics, Umeå, Sweden). The spectral data from the NMR, NIR or FT-IR analysis of the samples were used as X-matrix, and the measured particle, compaction and compact properties (Paper IV) or mixture compositions (Paper I) were used as Y-matrix.

Principal Component Analysis

Principal Component Analysis (PCA) models were constructed for the Y-matrix only and for the X- and Y-matrix in combination in Paper IV.

Partial Least Squares Analysis

In Paper I the composition data and NMR spectra of the lactose mixtures were correlated using partial least squares (PLS) and in Paper IV, one PLS model for each measured property was constructed using orthogonal signal correction (OSC) (Sjöblom et al., 1998).

Comparison between solid-state NMR and isothermal microcalorimetry in the assessment of small quantities of disordered structure

In Paper I, the techniques isothermal microcalorimetry and CP/MAS ^{13}C-NMR were assessed by measuring the amorphous content in lactose mixtures, containing spray dried amorphous lactose and crystalline α-lactose monohydrate in different proportions.

Microcalorimetry

A typical microcalorimetric profile of a lactose mixture reflecting the crystallisation of the amorphous portion, is shown in Fig. 1. In agreement with earlier studies on lactose (Sebhatu et al., 1994; Briggner et al., 1994; Buckton et al., 1995), isothermal microcalorimetry could detect the existence of very small amounts of amorphous material in the lactose samples (Fig. 2). However, the variations in the experimental results were larger than previously reported (Sebhatu et al., 1994; Briggner et al., 1994). The sampling procedure and heterogeneity of the powder mixtures are probably the largest source of variation. The variations obtained may also partly be explained by the mixing procedure of the crystalline and amorphous lactose powders, where a turbula mixer and glass beads were used in a manner comparable to industrial production. In earlier studies by Sebhatu et al. (1994) and Briggner et al. (1994), the amorphous and crystalline components were weighed directly into the sample vessel, thereby eliminating the effects of incomplete mixture homogeneity, environmental stress and the handling of the powders.

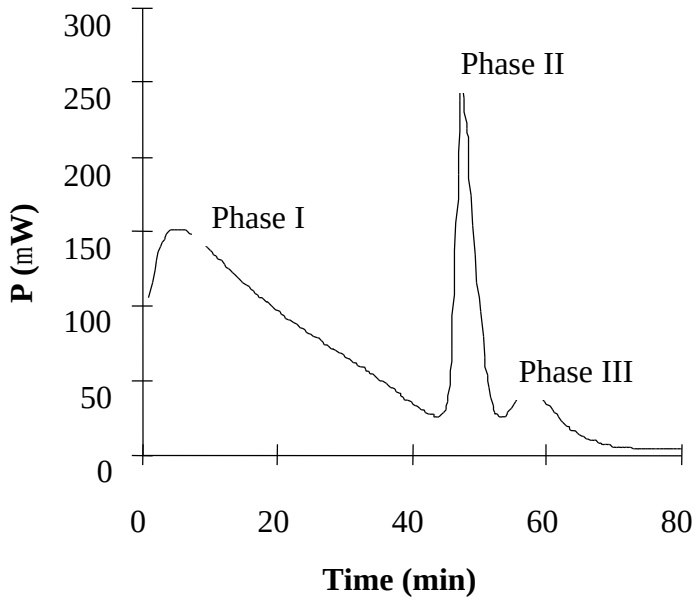


Figure 1. *Example of a microcalorimetric profile of a lactose mixture: Phase I absorption of water vapour; Phase II, crystallisation of the amorphous content; Phase III probably correponds to recrystallisation of anhydrous ß-lactose to the a-monohydrate form.*

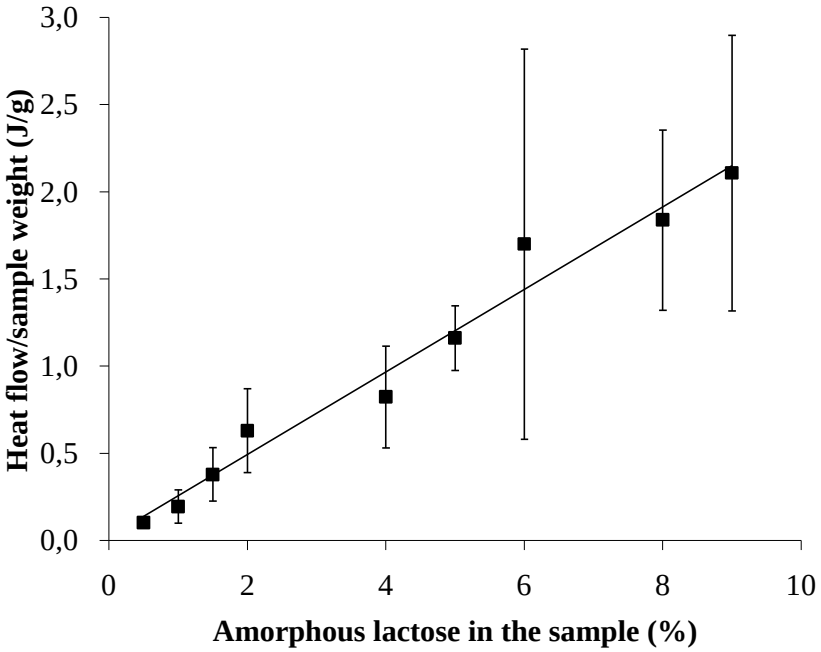


Figure 2. *Heat flow measured by microcalorimetry as a function of amorphous content for lactose mixtures containing 0-9% amorphous lactose (correlation coefficient 0.973, bars represent standard deviations, n = 3)*

CP/MAS ^{13}C-NMR

Examples obtained for the spectra of crystalline and amorphous lactose and a binary mixture are shown in Fig. 3. A typical peak corresponding to amorphous lactose is shown at 93-96 ppm; the intensity of this peak increases as the amorphous content is increased. In addition, a general broadening of all peaks in the spectra is seen when the amorphous content is increased. By integrating the area under the amorphous peak at 93-96 ppm and under a peak corresponding to the crystalline fraction of the same carbon atom (C4), i.e. 86-88 ppm, their ratio can be calculated and used as a rough estimation of the crystallinity of a mixture. However, when dealing with very small portions of amorphous material in a mixture, the integration can not be used since the peak disappears in the baseline noise. Instead, a good correlation between the composition data and the NMR spectra of the lactose mixtures was found by partial least squares (PLS) analysis (Geladi and Kowalski, 1986; Martens and Naes, 1989). As seen in Fig. 4, it is possible to measure low amounts of amorphous content in lactose samples from solid-state NMR. The PLS model was validated by predicting the crystallinity of four freshly prepared lactose mixtures and one mixture also containing acetylsalicylic acid. The estimations from NMR data fitted accurately on the correlation line, demonstrating the high predictive ability of the PLS model.

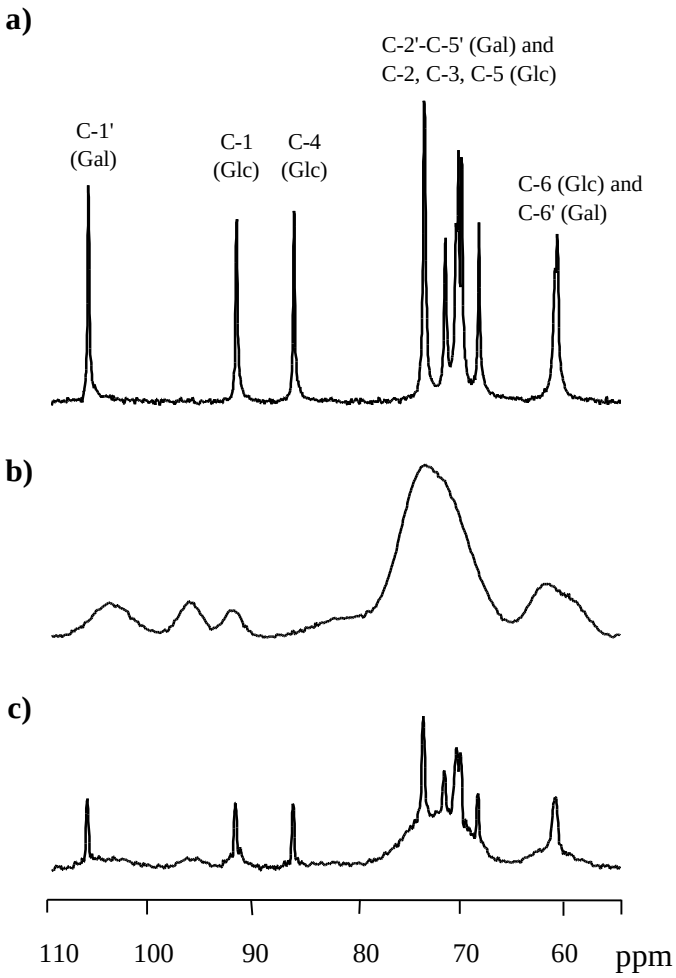


Figure 3. *CP/MAS ^{13}C-NMR spectra of a) 100% crystalline lactose sample; b) 100% amorphous lactose sample; c) 90% crystalline and 10% amorphous lactose sample. Chemical shifts assigned to the corresponding carbon atom in the a-monohydrate lactose molecule i.e. in the a-D-glucose unit and in the ß-D-galactose unit denoted as Glc C-1—C-6 and Gal C-1´--C-6, respectively (Earl and Parrish, 1983).*

Comparison of the techniques

In Table 1, a summary of the results from the two techniques is shown. The detection limit is below 0.5% for both techniques as far as the amorphous content of lactose is concerned and generally the experimental time required is about the same. However, while lower proportions of amorphous lactose in the samples required less time for analysis with microcalorimetry, the reverse was true for solid-state NMR. This can be explained by the differences in the parameters being measured: the response of a reaction or the actual structure of the substance.

The advantages of solid-state NMR are that it is a specific, non-destructive analytical method providing information about the structure of the materials being examined and of contaminants present. Isothermal microcalorimetry, on the other hand, requires smaller samples than NMR, which, however are destroyed, but the technique has the main disadvantage of being non-specific.

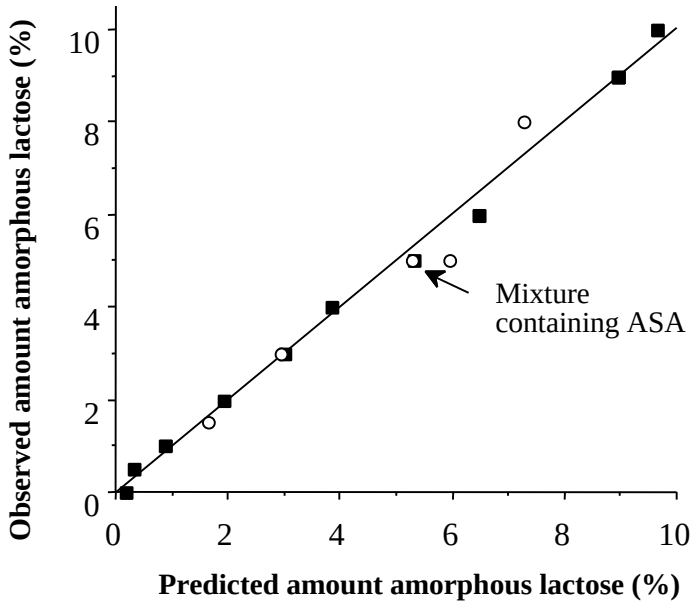


Figure 4. *PLS correlation plot (¦). The Y-axis represents the actual values of the amorphous content (as mixed) and the X-axis represents the predicted values of the amorphous content obtained from NMR spectra (correlation coefficient 0.998). The predicted values from five new lactose mixtures* (?).

Table 1. *Comparison of isothermal microcalorimetry and solid-state NMR for characterisation of the amorphous content of lactose.*

	Isothermal microcalorimetry	CP/MAS ^{13}C-NMR
Detection limit	=0.5% amorphous lactose[a]	=0.5% amorphous lactose
Time for analysis (h)	0.5-4	0.5-10
Destroys sample	Yes	No
Other components detected	No	Yes
Sample weight (mg)	20-300	500-700
Prediction limits	Within 1-2%[a]	Within 1%
Reproducibility[b]	Good	Very good
Provides structural information	No	Yes
Calibration model necessary	Yes	Yes

a) Estimated using the results of this study and those from Buckton et al. (1995).

b) Dependent upon the proportion of amorphous lactose in the sample and the homogeneity of the mixtures.

The importance of specific surface area and mean interparticulate distance in tablets

In an attempt to assess the dominating bonding mechanisms in a series of compacts in Paper II, the tablet tensile strength was normalised for the permeametric tablet surface area and the mean interparticulate distance in the compacts was measured by permeametry.

Effect of tablet surface area and mean pore radius on compact strength and on the interparticulate bond strength

Normalisation of the tablet tensile strength for the specific surface area of the tablets (Fig. 5) showed the surface specific tensile strength to be in agreement with the results by Nyström et al. (1993). In that study it was suggested that a high surface specific tensile strength would correspond to strong interparticulate bonds like solid bridges.

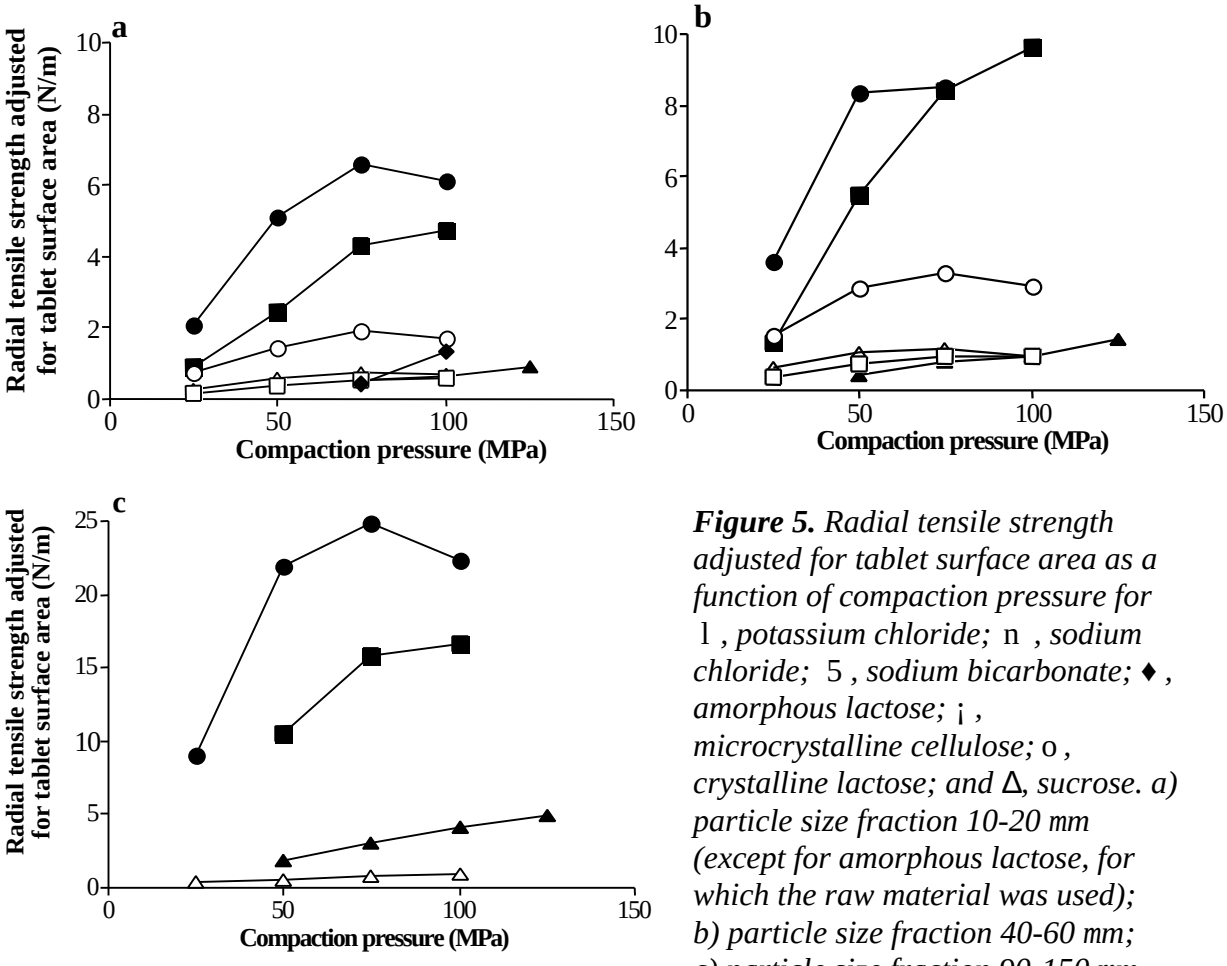


Figure 5. *Radial tensile strength adjusted for tablet surface area as a function of compaction pressure for* l *, potassium chloride;* n *, sodium chloride;* 5 *, sodium bicarbonate;* ♦ *, amorphous lactose;* ¡ *, microcrystalline cellulose;* o *, crystalline lactose; and* Δ*, sucrose. a) particle size fraction 10-20 mm (except for amorphous lactose, for which the raw material was used); b) particle size fraction 40-60 mm; c) particle size fraction 90-150 mm.*

For the materials that mainly bond with weak attraction forces, the adjusted values were lower than for the materials known to also have a contribution from solid bridges. Prerequisites for the development of solid bridges are that the material should have a

simple molecular structure, show a certain level of plasticity when compressed and develop a high stress concentration at contact points between particles (Führer, 1977; Adolfsson et al., 1997). These demands are probably fulfilled by sodium chloride and potassium chloride. Other materials that have been reported to deform plastically are amorphous lactose and sodium bicarbonate (Duberg and Nyström, 1986; Sebhatu et al., 1997). However, in the present study the adjusted values determined for these materials were lower, indicating bonding by weaker interparticulate attraction. In the case of amorphous lactose, the lack of moisture that usually acts as a plastisizer might also have contributed to the lower values. Microcrystalline cellulose showed an intermediate profile in Fig. 5, probably partly beacause of the large increase in surface area when the agglomerate structure (Ek et al., 1994) is broken. The pronounced fragmenting behaviour of crystalline lactose and sucrose must counteract the establishment of a strong interparticulate bond type as these materials had a low surface specific tensile strength.

Not for any material in the study was a single unique value obtained for the surface specific tablet tensile strength, suggesting that the influence of particle size and compaction pressure are significant and that further refinements of the model are necessary.

Adjusting the tablet tensile strength for the mean interparticulate distance is one way of refining the model, since the distance between particles has been shown to affect the interaction energy between them (Israelachvili, 1992). Normalisation for the tablet surface area and interparticulate distance was obtained by the following equation:

$$\partial_A = \frac{\partial_R}{S_V} * r$$

where ∂_A is the adjusted radial tensile strength (N), ∂_R the radial tensile strength (N/m^2); S_V the volume-specific surface area (m^2/m^3), and r the mean pore radius (m). For all materials except microcrystalline cellulose, the ranking obtained after this further normalisation was similar to that after normalisation for the tablet surface alone and the results were not greatly affected by this operation (Fig. 6). As expected, the normalisation gave a low and similar value for the materials bonding with distance forces and, especially, the profile of microcrystalline cellulose seemed to improve with the additional adjustment and to fit into the proposed model. However, for the larger particle size fractions, increased compaction loads lead to an over compensation for the materials bonding with some contribution from solid bridges. Consequently, the adjustment for the mean interparticulate distance is not useful for these materials.

Effect of particle size, compaction pressure and surface energy on the interparticulate bond strength

The assessment of dominating bonding types in different materials relies upon obtaining a value for the tensile strength reflecting each distinct bonding type. The compaction load and particle size should not influence this value, provided that changes do not also

result in a change of bonding type. As discussed above, the two-step normalisation was most suitable for materials bonding with long distance forces only. The adjusted tensile strength of these materials was independent of compaction pressure, but not completely independent of particle size (Fig. 6). On the other hand, the materials bonding with a contribution from solid bridges were significantly affected by both particle size and compaction load. A recent study by Olsson and Nyström (2000a) described a theoretical model for tablets including an interaction factor and a structural factor, to assess features of the internal tablet structure affecting the tensile strength of tablets. It was shown that the interaction factors reflecting the dominating bond type in the tablet, were not significantly affected by particle size and compaction pressure for tablets made of lactose or sucrose, i.e., for materials assumed to bond only by long distance forces. However, for the materials bonding by stronger bonds the interaction factor increased with decreasing particle size and increasing compaction pressure.

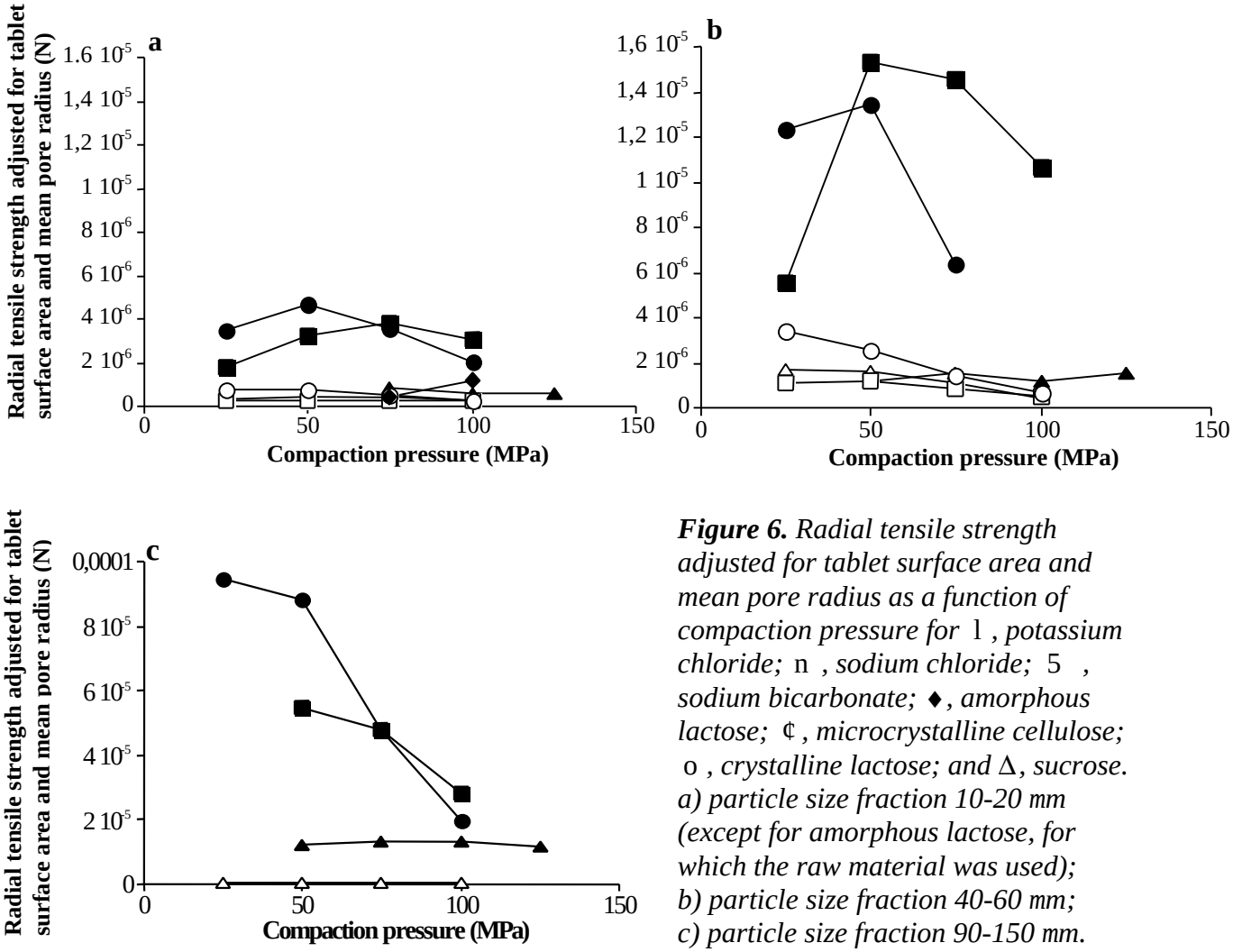


Figure 6. *Radial tensile strength adjusted for tablet surface area and mean pore radius as a function of compaction pressure for* l *, potassium chloride;* n *, sodium chloride;* 5 *, sodium bicarbonate;* ♦*, amorphous lactose;* ¢*, microcrystalline cellulose;* o *, crystalline lactose; and* Δ*, sucrose. a) particle size fraction 10-20 mm (except for amorphous lactose, for which the raw material was used); b) particle size fraction 40-60 mm; c) particle size fraction 90-150 mm.*

Differences in the surface energy of different materials are believed to affect the bond strength and thus the tablet tensile strength (El Gindy and Samaha, 1983; Luangtana-Anan and Fell, 1990), and could thus be of importance. Buckton (1988) showed how the treatment of a material before experimental evaluation affected the surface energy. However in Paper II, all size fractions of the same materials were produced by identical procedures (except for the fractionating step) and it is unlikely that the differences observed in the tensile strength between the particle size fractions are the result of differences in the surface energy.

Important characteristics of hydroxypropyl methylcellulose influencing compactibility and tablet properties

In Papers III and IV the characteristics of three different substitution types of hydroxypropyl methylcellulose were investigated, namely the USP types 2910, 2906 and 2208, the resultant values were related to the compactibility and tablet properties. Three batches of each substitution type were obtained from Colorcon Ltd, Orpington, UK (Methocel) and one of each from Shin Etsu Chemical, Tokyo, Japan (Metolose).

Effect of molecular characteristics on the tablet properties

The hydroxypropyl methylcellulose (HPMC) powders investigated were of the same viscosity grade, but differed in the degree of substitution (Table 2). However, these differences could not be directly related to properties of compacted tablets of the powders, e.g., tensile strength, porosity, or elastic recovery. In addition, an earlier study by Bonferoni et al. (1996) using the same HPMC powders, revealed differences in the drug release performancethat could not be explained by the methoxy/hydroxypropyl ratio. Rather than the ratio of substituents, the absolute amount of each substituent and the total degree of substitution seem to be connected to the behaviour of the compacted polymers. An increased amount of the hydrofobic methoxy group will probably negatively affect the formation of hydrogen bonds within and between particles and will also reduce the rate of hydration. The result may be lower tablet strength (Fig. 7, Table 3) and faster drug release (Table 3) when the drug substance is allowed to escape the matrix due to the slow gelling. Conversely, a high content of the hydroxypropyl substituent would favour the hydration rate, preventing drug release from taking place too rapidly (Alderman, 1984; Mitchell et al., 1993).

The distribution of the substituents along the cellulose chains may possibly also affect the behaviour of the polymer, however when comparing the different polymers using ^{1}H-NMR in Paper III, no differences could be detected. Very low concentrations of HPMC were used to avoid gelling and it cannot be excluded that differences might have been detected at higher concentrations. However, a carbohydrate analysis performed in Paper IV to identify the origin of a carbonyl group, revealed that, some cellulose chains in the same sample were completely unsubstituted while others were fully substituted.

The crystallinity of the HPMC polymers is very low and solid-state NMR analysis of the powders did not reveal any differences in the degree of order, but confirmed the

differences in the degree of substitution. These results were in agreement with X-ray diffraction studies of the powders by Bonferoni et al. (1996).

Table 2. *Primary characteristics of the test materials*

Material	Methoxy[a] (% w/w)	Hydroxy -propyl[a] (% w/w)	Total degree of substitu-tion (%w/w)	Methoxy/ hydroxy-propyl ratio (-)	Heywood's surface to volume shape factor[b] (-)	Volume-specific surface area[c] (cm^2/cm^3)
USP 2910						
Methocel E011 (E4M)	29.1	8.1	37.2	3.6	11.1	786 (16)
Methocel E202 (E4M)	29.0	7.6	36.6	3.8	12.7	1115 (17)
Methocel E511 (E4M)	28.7	8.2	36.9	3.5	10.3	888 (9)
Metolose 60SH4000	29.1	9.3	38.4	3.1	16.9	1864 (9)
USP 2906						
Methocel F211(F4M)	27.4	6.0	33.4	4.6	17.6	2354 (30)
Methocel F803 (F4M)	27.9	8.2	36.1	4.7	19.0	2281 (76)
Methocel F805 (F4M)	28.9	6.1	35.0	4.7	20.4	2237 (27)
Metolose 65SH4000	28.3	5.6	33.9	5.1	18.9	1637 (4)
USP 2208						
Methocel K303 (K4M)	22.3	8.5	30.8	2.6	18.8	2340 (32)
Methocel K803 (K4M)	22.7	8.3	31.0	2.7	16.1	1675 (27)
Methocel K903 (K4M)	22.2	8.4	30.6	2.6	17.6	1779 (28)
Metolose 90SH4000	22.6	9.1	31.7	2.5	17.8	1684 (22)

a) Values obtained from analyses provided by manufacturers
b) Calculated from the volume specific surface area and the volume surface diameter of the particles (Coulter Multisizer, Coulter Electronics Ltd, Luton, England)
c) Measured by Friedrich permeameter (Eriksson et al., 1990): mean values (n=3) with the corresponding standard deviations in parentheses

Effect of particle characteristics on the tablet properties

The USP 2910 qualities deviated clearly from the other two qualities in terms of the apparent, specific surface area and particle shape (Table 2). Furthermore, the particle density was found to be lowest for the 2910 qualities. Generally, the USP 2910 qualities were more isodiametric and had a more regular particle shape and a relatively low content of fibrous particles especially compared to the USP 2906 qualities. This was confirmed by microphotographs of the fracture planes of the tablets (Fig. 8). The particle shape seemed to be one of the most important factors in determining the tablet properties. Comparing the specific surface area of the powders (Table 2) and the tablets compacted at 100 MPa (Table 3), it can be seen that the more fibrous polymers (USP 2906 and 2208) fragmented to a greater extent during compaction than the USP 2910. New surfaces were thereby created that were potentially available for bonding, thus affecting the tablet strength positively. In addition, studying the fracture planes in

Fig. 8, the USP 2910 particles are clearly visible after compaction, while the other polymer particles seemed to have lost their individuality to some extent and to have fused together at some points. The possible occurence of mechanical interlocking would be a contributory factor to the tablet tensile strength may not be excluded for these substitution types because of the surface roughness and the irregular shape of the particles (Karehill et al., 1990).

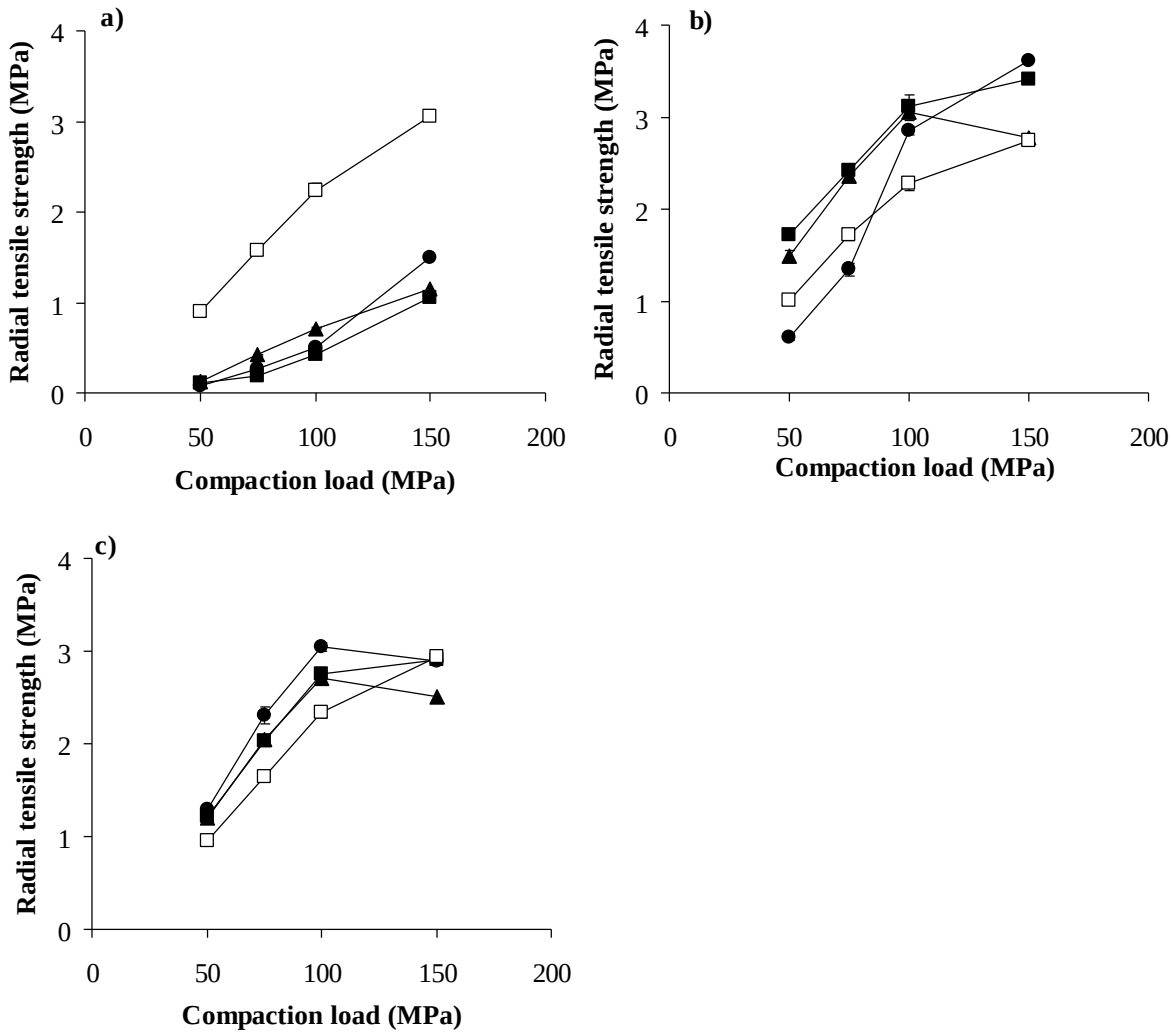


Figure 7. *Radial tensile strength of tablets as a function of compaction load: a) USP 2910, b) USP 2906 and c) USP 2208. Filled symbols represent Methocel batches and open symbols represent Metolose batches, error bars represent confidence intervals for p = 0.05.*

Table 3. *Measured characteristics of tablets compacted at 100 MPa. The results given are mean values with the corresponding standard deviations in parentheses.*

Material	Axial tensile strength[a] (MPa)	Volume specific surface area[b] (cm^2/cm^3)	Elastic recovery after ejection[c] -compaction load 150 MPa (%)	Apparent yield pressure[d] (MPa)	Drug release after 1 hour[e] (%)
USP 2910					
Methocel E011	0.16 (0.036)	1514 (31)	13.73 (0.15)	50.17 (0.58)	80.27
Methocel E202	0.29 (0.032)	2511 (159)	15.21 (1.87)	51.29 (0.69)	63.70
Methocel E511	0.20 (0.052)	1827 (126)	10.01 (0.99)	54.35 (0.59)	76.64
Metolose 60SH4000	0.33 (0.051)	3933 (132)	14.27 (2.53)	54.65 (0.30)	-
USP 2906					
Methocel F211	0.40 (0.062)	5499 (85)	49.80 (0.08)	53.10 (0.70)	53.46
Methocel F803	0.37 (0.107)	5526 (97)	49.00 (1.47)	48.78 (0.24)	53.20
Methocel F805	0.38 (0.085)	5997 (294)	48.35 (0.61)	54.06 (0.29)	54.36
Metolose 65SH4000	0.45 (0.100)	5155 (232)	44.20 (3.97)	54.25 (0.17)	-
USP 2208					
Methocel K303	0.50 (0.040)	7952 (1893)	46.98 (0.87)	49.84 (0.76)	54.36
Methocel K803	0.40 (0.095)	5886 (114)	46.52 (0.17)	50.00 (0.44)	55.74
Methocel K903	0.50 (0.068)	6330 (225)	47.52 (3.98)	51.28 (0.26)	52.68
Metolose 90SH4000	0.46 (0.041)	6006 (654)	47.39 (0.54)	59.06 (0.20)	-

a) Measured as described by Nyström et al. (1978) (M30K, Lloyd Instruments, England)(n=5)
b) Measured using a Blaine permeameter (Alderborn et al., 1985) (n=3)
c) Defined as the relative difference between the minimum and maximum tablet height (Armstrong and Haines-Nutt, 1972)
d) Obtained from the reciprocal of the slope of the linear part of an in-die Heckel plot (n=3)
e) Data obtained from Bonferoni et al. (1996) (USP XXIII basket apparatus and Spectracomp spectrophotometer, Advanced Products, Milan, Italy)

Methocel E011 Methocel F805 Methocel K303

Figure 8. *Scanning electron microscope photomicrographs of the fracture planes of tablets compacted at 100 MPa.*

The particle characteristics also affected the decrease in porosity with increasing compaction pressure (Fig. 9). At a high compaction load (150 MPa), the USP 2910 formed compacts with low porosity, indicating low resistance to volume reduction and permanent deformation. The other qualities seemed to have reached a minimum porosity level and maximum tensile strength at a lower pressure (100 MPa). Thus the limit of densification has been reached and further increases in compaction load probably result in reversible elastic recovery, instead of being useful for the development of bonds (Adolfsson and Nyström, 1996). The higher elastic recovery obtained for the USP 2906 and 2208 at 150 MPa supports this (Table 3).

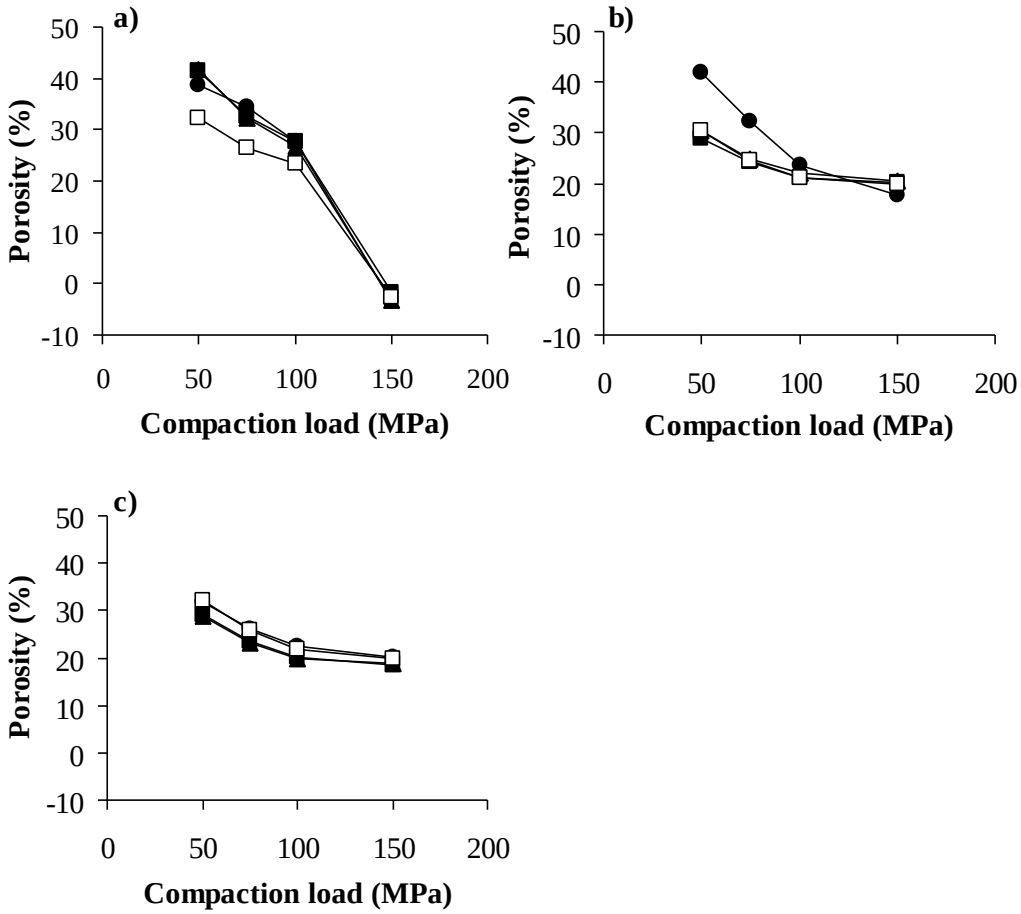


Figure 9. *Porosity of tablets as a function of the compaction load: a) USP 2910, b) USP 2208, c) USP 2906. Filled symbols represent the Methocel batches and open symbols represent the Metolose batches.Confidence intervals for p = 0.05 are given when they exceed the the dimensionsof the symbols.*

Evaluation of essential properties of hydroxypropyl methylcellulose using principal component analysis (PCA)

In Paper IV, PCA was undertaken in an attempt to further evaluate the important characteristics of HPMC for the tablet quality. The score plot of the materials (Fig.10a) shows a clear grouping of the different substitution types, where principal component 1, PC1, separates the USP 2910 from the other powders. The USP 2208 and 2906 qualities are, to a limited degree, separated along PC1, but are more clearly separated along the second principal component, PC2. The loading plot (Fig. 10b) gives an explanation of the grouping of the materials in the PCA plot and here the variations in particle, compact and compaction properties are most apparent in the horizontal direction, i.e., for PC1, while the variations in chemical properties mainly lie along PC2. The particle shape, powder and tablet surface area and fragmentation propensity are found in the same region as the radial and axial tensile strength, indicating that these properties are associated with a high tablet tensile strength in agreement with the findings in Paper III. In addition, these results are supported by Paper II and earlier studies suggesting that a large surface area reflects a large potential effective bonding surface area for some materials (Vromans et al., 1985; te Wieriket et al., 1996). As expected, the porosity and the pore radius are situated to the left in the loading plot at the opposite end of PC1 from the tablet tensile strength, indicating that these values should be low in order to obtain a high tablet tensile strength. This corresponds well with the fact that the importance of weak long distance forces increases with decreasing interparticulate distance between the particles constituting the tablet (Israelachvili, 1992).

The correlation of the hydroxylpropyl content with the particle and tablet properties did not seem to be as strong as suggested in an earlier study (Dahl et al., 1990). The total degree of substitution and the methoxy content seemed to be of greater importance since they are found quite near the elasticity and the porosity variables with large loading values for PC1 and PC2. However, the particle shape and powder surface area seemed to be more important for the tablet tensile strength and the drug release than the total impact of the degree of substitution. The former are also properties most likely to be affected by the manufacturing process for making HPMC polymers. It is possible that the degree of swelling during the initial manufacturing steps, before the substitution takes place, may influence the shape of the final particles and the powder surface area.

Comparison between Methocel and Metolose powders

In both in Papers III and IV, HPMC powders from two different suppliers were investigated. Generally the Metolose qualities varied less between the different substitution types than the Methocel ones (Table 2-3, Fig. 7). The USP 2910 quality of Metolose did not deviate from the other qualities of Metolose as much as for the Methocel powders in terms of, e.g., powder surface area, particle shape and radial tensile strength. However, similar volume reduction behaviour expressed as the decrease in porosity (Fig. 9) and the elastic recovery at 150 MPa was obtained for the USP 2910 quality of Metolose and Methocel. It is important to notice that although the particle shape and powder surface area have been said to be largely responsible for the compaction behaviour and tablet properties of HPMC, the degree of substitution still

plays a role. But rather than the ratio of the methoxy/hydroxypropyl substitution, the absolute amounts of each substituent should be considered, and even then, the connections with the polymer behaviour and properties are not straightforward.

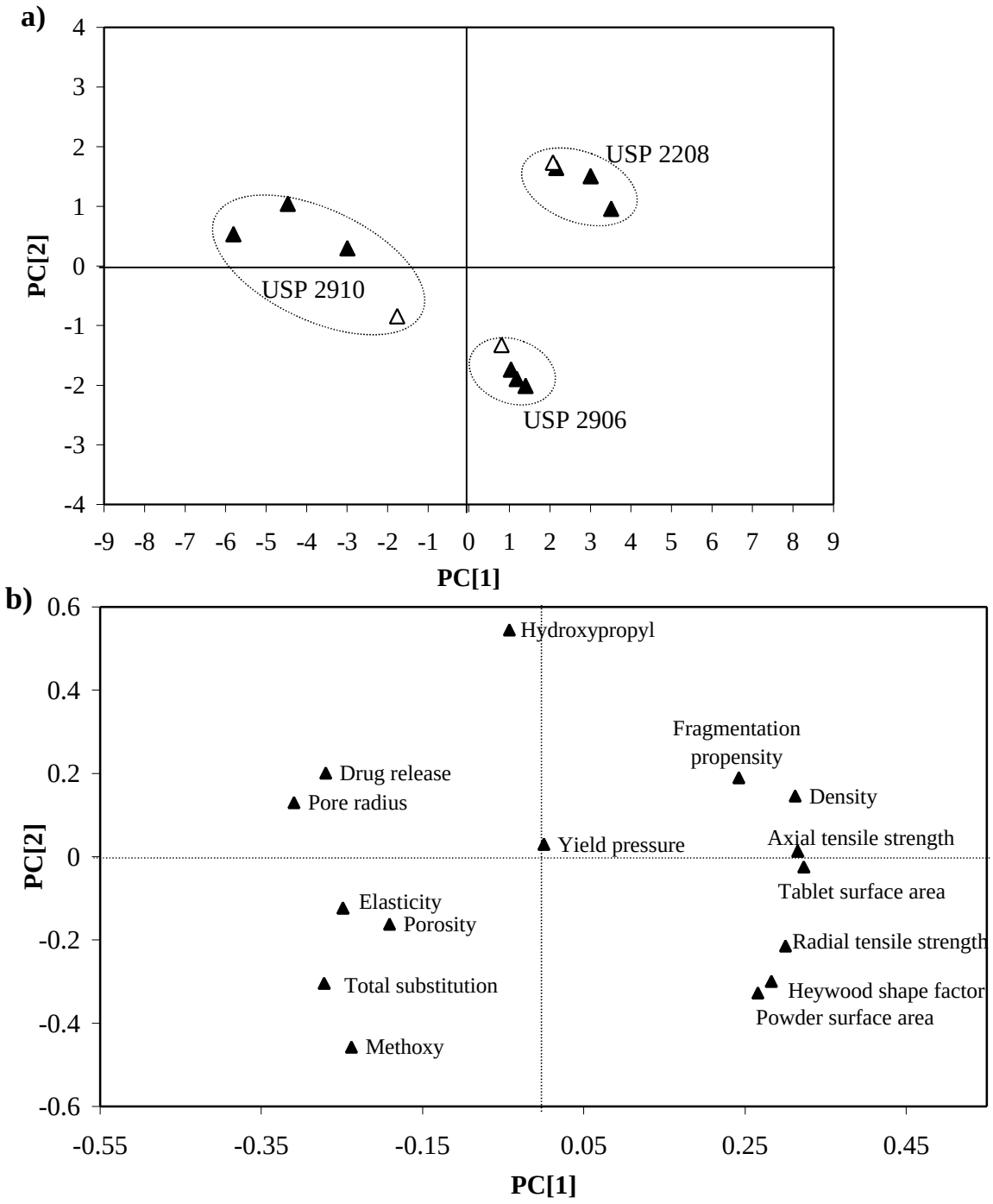


Figure 10. *a) PCA score plot of the materials, the filled symbols represent Methocel powders and the unfilled ones represent the corresponding Metolose powders. b) loading plot of measured properties. The numbers on the axis are in arbitrary units.*

Predictions of hydroxypropyl methylcellulose particle and tablet characteristics

Using infrared spectroscopy and partial least squares (PLS) analysis it was possible to predict the characteristics of HPMC powders and tablets; the results are presented in Paper IV. Although the differences between the powders are difficult to deduce with accuracy when studying the spectra (Fig. 11), the spectral data could be used to obtain good predictions of almost every property of interest (Table 4).

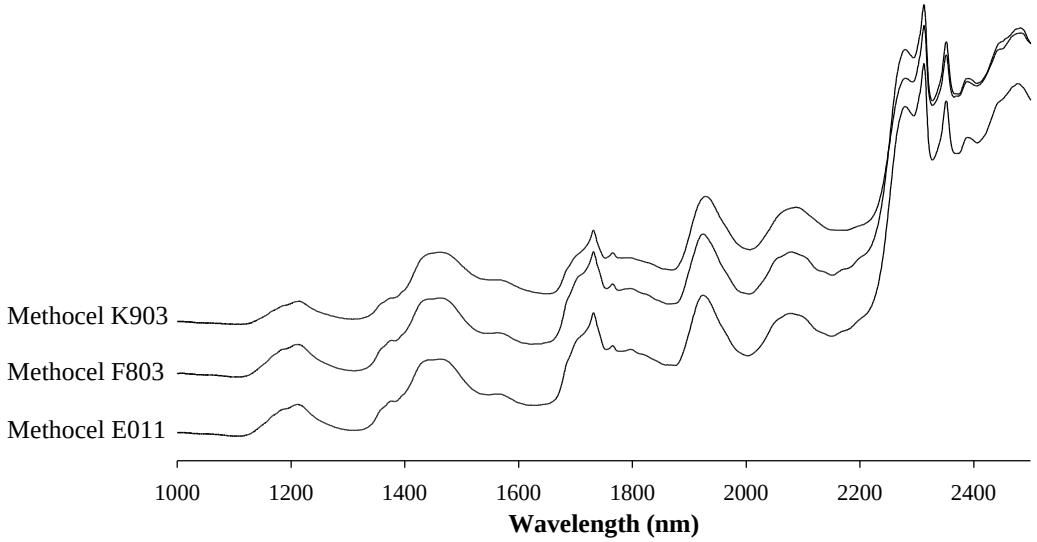


Figure 11. *Examples of NIR spectra for three Methocel batches. In order to show all three spectra clearly, they have been shifted along the y-axis. At 1200 and 1700 nm CH_3, CH_2 and CH vibrations are found in order of increasing wavelength. ROH-vibrations give rise to high intensities around 1450, 1900 and 2100 nm, and in the region 2200-2500 nm, C-H combinations show up as high intensity peaks.*

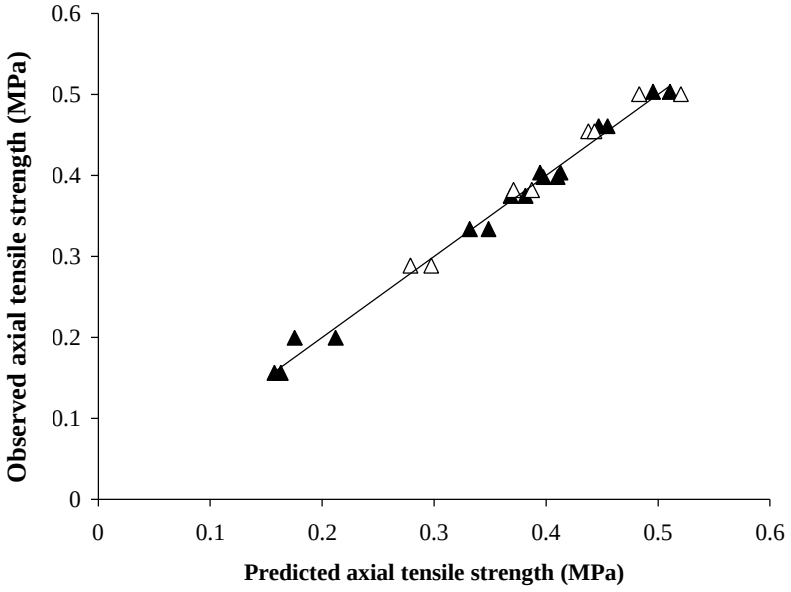


Figure 12. *Model for prediction of the axial tensile strength of tablets from NIR spectral data, R^2=0.99. Filled symbols represent the model and open symbols new samples predicted by the model.*

Table 4. *Predictions obtained using PLS models subjected to OSC (there were two components for all properties)*

	NIR			**FT-IR**		
Property	Explained variance in X	Explained variance in Y	Linear regression coefficient R^2	Explained variance in X	Explained variance in Y	Linear regression coefficient R^2
Methoxy	0.945	0.998	0.998	0.911	0.993	0.993
Hydroxypropyl	0.920	0.993	0.933	0.826	0.881	0.880
Total degree of substitution	0.924	0.968	0.968	0.871	0.959	0.959
Apparent density of powders	0.954	0.993	0.993	0.898	0.987	0.986
Heywood's shape factor	0.972	0.985	0.985	0.911	0.973	0.973
Volume specific surface area of powders	0.966	0.985	0.985	0.935	0.968	0.968
Radial tensile strength	0.972	0.992	0.992	0.913	0.969	0.969
Axial tensile strength	0.942	0.989	0.991	0.860	0.944	0.944
Volume specific surface area of tablets	0.966	0.995	0.995	0.868	0.979	0.979
Porosity	0.808	0.857	0.857	0.804	0.801	0.801
Pore radius	0.957	0.994	0.994	0.917	0.934	0.934
Elastic recovery	0.875	0.899	0.899	0.807	0.829	0.829
Apparent yield pressure	0.673	0.785	0.786	0.658	0.694	0.694
Drug release after 1 hour	0.964	0.990	0.990	0.964	0.857	0.857

For example, the axial tablet tensile strength was predicted from NIR spectral data subjected to orthogonal signal correction (OSC) (Fig. 12). On the other hand, in the PCA loading plot presented earlier (Fig. 10b), the apparent yield pressure was situated in the middle of both principal components, showing that this property does not influence either the grouping of the materials or the other measured properties of the powders. As expected, the predictions of the apparent yield pressure of the powders were not satisfactory because the measured values of apparent yield pressure were very similar (Table 3). This could probably be attributed to experimental variations rather than to real differences between the materials; these values are unsuitable for use in a prediction model.

NIR and FT-IR spectral data both provided good linear prediction models (Table 4), however, slightly higher R^2 values were obtained for the NIR PLS models than for the

PLS models based on FT-IR analysis. FT-IR mainly provides chemical information and is less sensitive than NIR to differences in physical properties of the particles, such as particle size. In addition, FT-IR is strongly dependent on sample preparation like, e.g., the grinding with KBr in this study, that might give rise to physical changes in the powders as well as lead to variations between the samples. Using NIR, there is no need for sample preparation, so this supports the use of NIR or other IR techniques requiring minimal sample preparation to obtain relevant and rapid spectral data of pharmaceutical powders.

The relevance of surface and bulk characteristics of cellulose-I-powders to compaction and tablet properties

In Paper V, the characteristics, the compaction behaviour and the tablet properties of two cellulose powders, the commercially available Avicel PH101 and cellulose powder obtained from the alga *Cladophora* sp. were evaluated.

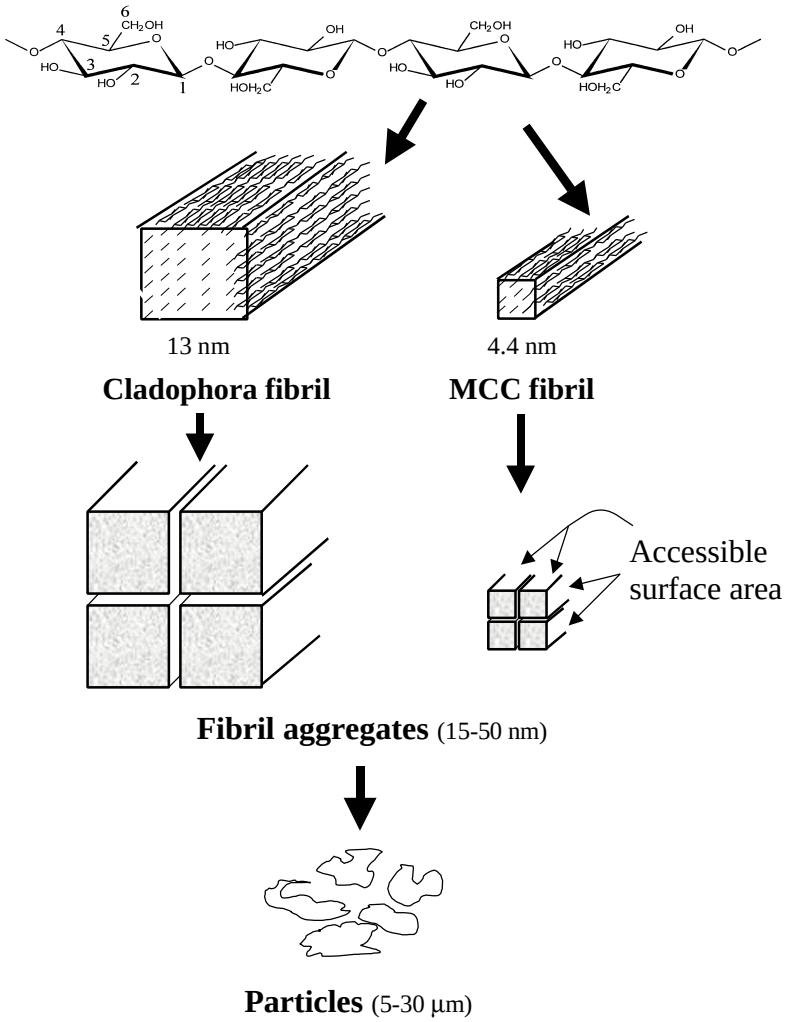


Figure 13. *Schematic picture of cellulose at the molecular-, fibril-, fibril aggregate- and particle level.*

Comparison of the cellulose structure of two cellulose powders

Crystal structure

The most important crystal structural difference between Avicel PH101 and cellulose obtained from the alga *Cladophora* sp., is the size of the fibrils, i.e., the number of cellulose chains arranged parallel to form the fibrils (Fig. 13). The cellulose fibril dimension of wood pulp like Avicel is around 4 nm, while the Cladophora fibril has been reported to have a dimension of 13 nm measured by CP/MAS ^{13}C-NMR (Wickholm et al., 1998). Further, both Avicel PH101 and Cladophora cellulose, consist of cellulose I, which in turn exist in two polymorphic forms, cellulose Iα and cellulose Iß (VanderHart and Atalla, 1984). In algae, cellulose Iα is the dominant form while the more stable cellulose Iß dominates in higher plants (Sugyiama et al., 1991). Based on the width of the fibrils and the assumption that the width of a single cellulose chain is 0.55 nm, the surface area of the wood fibril constitute approximately 47% of the fibril and the remaining 53% will be the core or the bulk of the fibril. For a Cladophora fibril only 16% will be fibril surface area and the bulk will make up 84% of the fibril.

In Fig. 14 CP/MAS ^{13}C- NMR spectra of the celluloses are shown and the shape of the signal cluster reflects the large differences in fibril dimensions, and also the polymorph composition of the celluloses (cellulose Iα and cellulose Iß).

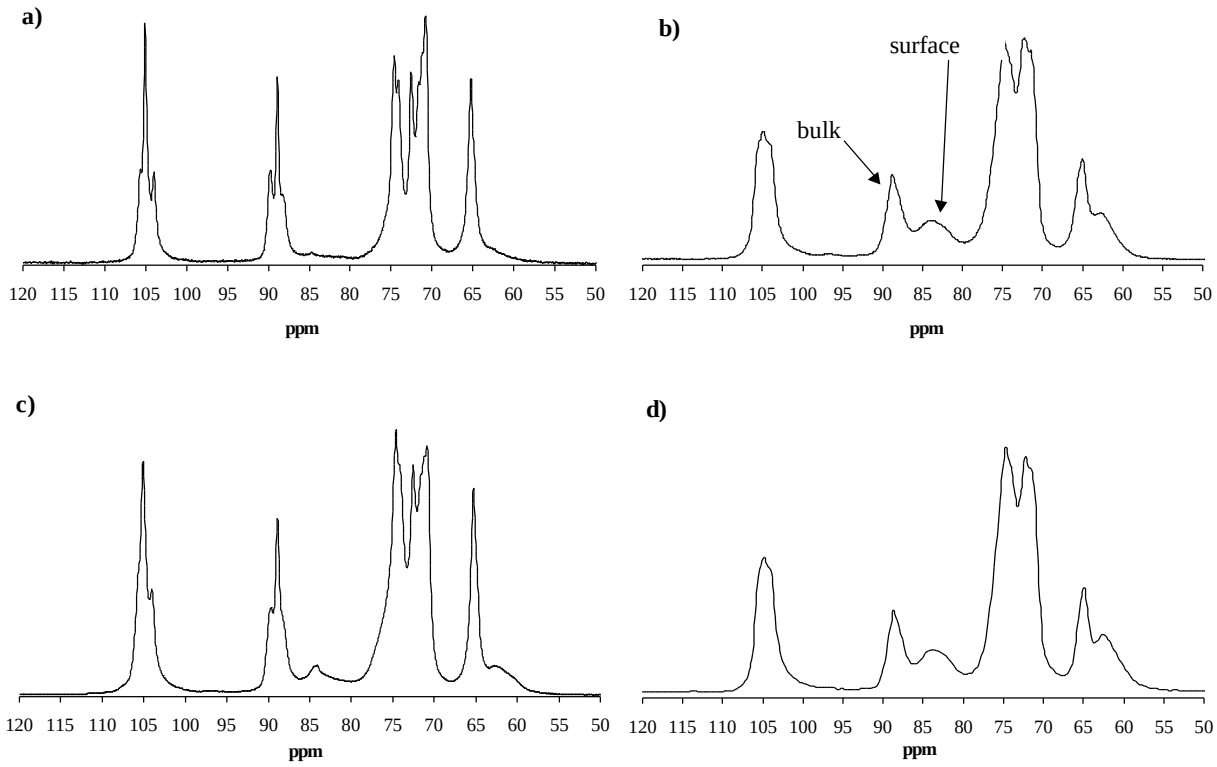


Figure 14. *CP/MAS ^{13}C NMR-spectra of a) A powder sample of Cladophora cellulose; b) A powder sample of Avicel PH101; c) Cladophora tablets compacted at 1200 MPa and d) Avicel PH101 tablets compacted at 1200 MPa.*

Different levels of surface area

Depending on the measurement principle used, the surface area of cellulose could be studied at different levels. The smallest dimension, the *fibrils* (4-20 nm) compose the *fibril aggregates* (15-50 nm) (Fig. 13). A number of fibril aggregates will then form the *particles* (5-30 μm) (Fig. 15) of the *powder* which will finally be compacted into *tablets* (of mm-size).

The surface area of the fibril aggregates (15-50 nm) is reflected by the region of 80-86 ppm in a solid-state NMR-spectra and the bulk by the region of 86-90 ppm (Fig. 14) (Wickholm et al., 1998). For the Cladophora powder, the peak is very small indicating that the surface area on this molecular level is low and, as expected, the peak for Avicel in this region is much larger.

Table 5. *Measured properties of the celluloses*

Properties	**Avicel PH101**	**Cladophora**
Powder		
Apparent particle density (g/cm^3)	1.566 (0,002)	1.612 (0.003)
Bulk density (g/cm^3)	0.335 (0,010)	0.171 (0,002)
Tapped density (g/cm^3)	0.477 (0,008)	0.252 (0,002)
Hausner ratio (-)	1.42	1.47
Moisture content (%)	5.17	2.27
Heywood shape factor (-)	12.5	31
Specific surface area measured by permeametry (m^2/g)	0.42 (0.01)	1.72 (0.001)
Specific surface area measured by Kr-gas adsorption (m^2/g)	1.36 (0.02)	86.64 (0.74)
Micropore area of powder (from pores less than 2 nm) (m^2/g)	0.27	15.50
Crystallinity index of powders obtained by solid-state NMR (%)	55	89
Compaction and tablet properties		
Apparent yield pressure (MPa)	126 (7.0)	159 (11.9)
Elastic recovery (%)	0.53 (0.18)	9.67 (0.88)
Fragmentation propensity measured by permeametry of tablets compacted at 0-100 MPa ($m^2/g*MPa$)	0.0064	0.3672
Apparent particle density of tablets compacted at 1200 MPa (cm^3/g)	1.572 (0.003)	1.517 (0.003)
Crystallinity index of tablets compacted at 1200 MPa obtained by solid-state NMR (%)	52	74

The smaller fibril dimension of Avicel will not only result in more hydrogen bonding within the structure, giving a close fibril aggregate and particle structure, but the surface area available for water sorption (Heiner et al., 1998) will also be higher than that for Cladophora cellulose (Table 5). In addition, the fibril aggregation of the larger fibril surface area will give rise to more dislocations and disturbances, thereby explaining the lower crystallinity index (bulk/surface ratio expression in the NMR spectra) of the

Avicel cellulose compared to the Cladophora cellulose (Table 5). These values are in agreement with the theoretically calculated values of the bulk/surface proportions based on the fibril width. Thus it is surmised the primary factor to determine the other properties of the cellulose is the fibril surface area, and not the crystallinity.

In contrast to the fibril surface area, the particle surface area measured by permeametry was higher for the Cladophora cellulose than for Avicel PH101 (Table 5) and an extreme difference was found in the surface area measured by Kr gas adsorption. The values obtained for the Avicel particle surface area corresponded well to those in the literature (Nakai et al., 1977; Zografi et al., 1984). Cladophora cellulose has previously been reported to have a large surface area (Ek et al., 1998). The folded particle structure and the open pore system (Fig. 15) corresponding to a less close fibril aggregate structure will explain its higher particle surface area.

Comparison of compaction behaviour and tablet properties of two cellulose powders

Changes in surface area during compaction

The Cladophora powder showed a fragmentation propensity 40 times that of the Avicel powder during compaction as measured by permeametry (Table 5). It is most likely that this is caused by the particle structure, which is folded and irregular in comparison to that of the Avicel.

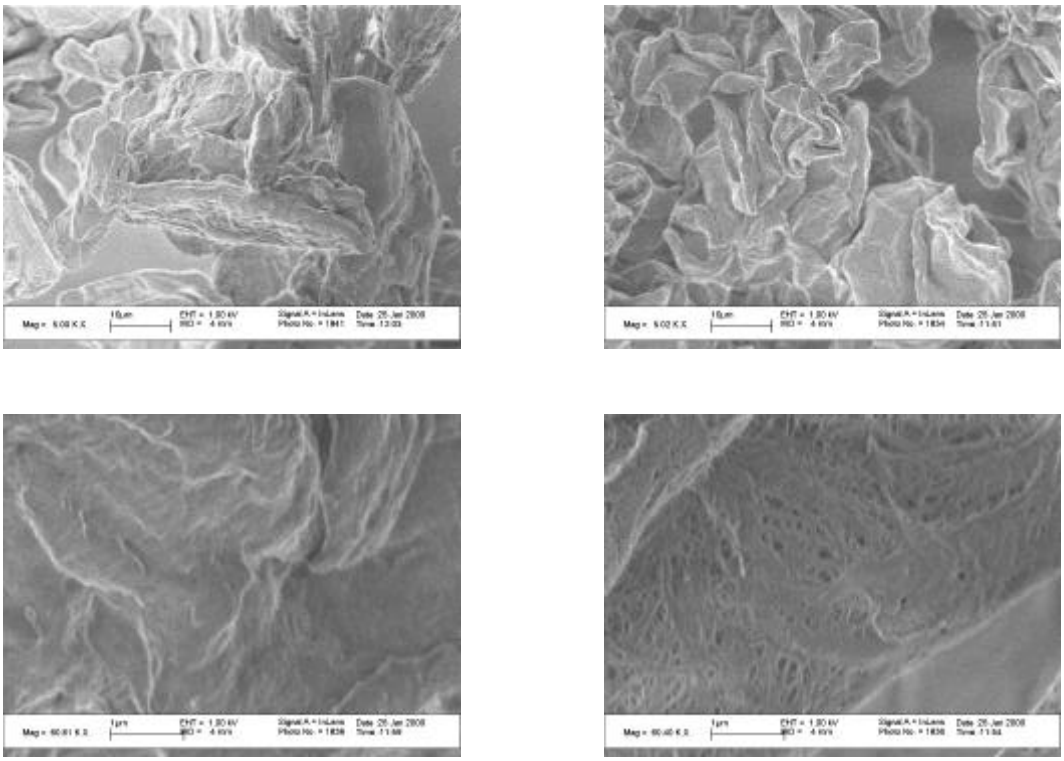
The compaction of the celluloses resulted in a pronounced decrease in the surface area measured by Kr gas adsorption (Fig. 16). The reason for the decreasing surface area may be a reduced ability of the Kr atoms to penetrate the tablets because of the close and compact structure created when the powders are plastically deformed. In the case of the Cladophora cellulose, a sealing of the intraparticulate pores (Fig. 15) will contribute to the significant decrease of surface area in absolute terms (Nyström and Karehill, 1986). The surface area might also decrease through development of bonds between the surfaces of the particles, although the bonding surface area on the particle level is likely to be small compared to the total surface area (Sixsmith, 1976).

In contrast to the gas adsorption measurements on the particle level, the compaction resulted in an increase of the surface area of both the celluloses on the fibril level, as reflected by the increase of the peak at 80-86 ppm in the solid-state NMR spectra (Fig. 14c-d). The compaction will create cracks and dislocations in the fibrils, thereby exposing a larger surface area on the fibril level. In addition, since the surface area has a more disordered structure than the core of the fibrils, a decrease in crystallinity index and apparent particle density of the Cladophora cellulose at high compaction loads were also seen (Table 5).

Volume reduction and mechanical strength

The difference in fibril dimension and thereby in the fibril surface area of the two celluloses was shown to strongly affect their properties and behaviour. The larger fibrils of the Cladophora cellulose resulted in pronounced fragmentation, as mentioned above,

and less plastic deformation than the smaller wood cellulose fibrils. The apparent yield pressure of the Cladophora cellulose was higher, as was the elastic recovery (Table 5). Despite these findings, the radial tablet tensile strength of the Cladophora powder was found to be at least as high as for the corresponding Avicel tablets. (Fig. 17). The extensive fragmentation of the Cladophora and the irregular surface morphology of the particles possibly contributes to the strength of the tablets, offering a large potential bonding surface area (Nyström and Karehill, 1996).



Avicel PH101 Cladophora

Figure 15. *Scanning electron microscopy imaging of Avicel PH101 and the Cladophora cellulose. The top pictures show the particle structure (bar representing 10 mm) and the bottom ones using a higher magnification (bar representing 10 mm) show the pore structure of the powders.*

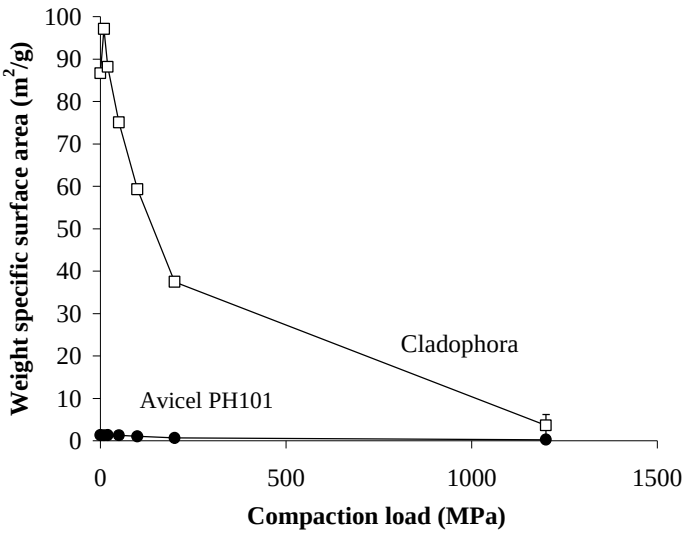


Figure 16. *Specific surface area of the powders and tablets measured by Kr gas adsorption, error bars represent the standard deviations (n = 2).*

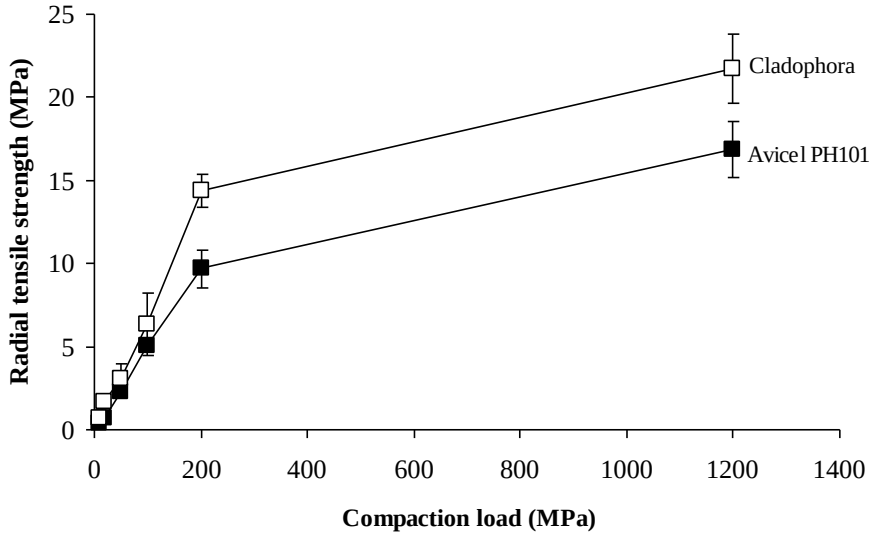


Figure 17. *Radial tablet tensile strength of Avicel PH101 and Cladophora cellulose, error bars represent confidence intervals for p=0.95.*

Disintegration

Despite the high tablet tensile strength of the Cladophora compacts, the tablets disintegrated much faster than tablets of Avicel PH101 (Fig.18). The fact that there are fewer hydrogen bonds between the Cladophora fibril surfaces to be broken in contact with water, will probably favour the faster disintegration of the alga compacts, as also does the higher intra- and interparticulate porosity of these tablets. In addition, calculation of the moisture content per (surface area) square measure on the fibril level will result in a much higher value for the Cladophora cellulose, which may contribute to the fast disintegration.

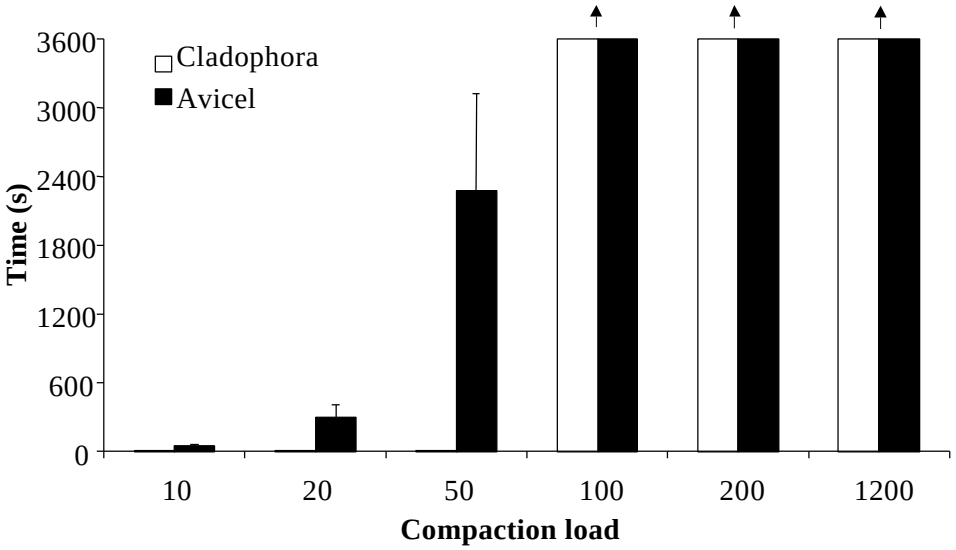


Figure 18. *Disintegration of tablets as a function of the compaction load for Avicel PH101 and Cladophora cellulose. Error bars represent the standard deviations (n = 6) and arrows indicate that the time for disintegration > 60 minutes.*

Summary and conclusions

In this thesis the solid state properties of some pharmaceutical materials have been studied by different spectroscopic techniques as well as bysome of the more conventional methods used for particle characterisation. The spectroscopic techniques used proved to be valuable tools in the estimation of particle and tablet properties, offering both specificity and sensitivity in the measurements. Because of the large amount of information obtained in spectra, it is both convenient and appropriate to take advantage of some kind of multivariate data analysis to process the spectral data and other parameters of interest. Correlations between the solid state structure measured by spectroscopy and particle and tablet properties may then be obtained. In addition, the data processing enables one to identify small changes in the spectra that are not always visible to the eye.

More specifically, CP/MAS ^{13}C-NMR proved to be as sensitive to changes in the amorphous content in lactose mixtures as isothermal microcalorimetry. The specificity of the solid-state NMR technique was shown to be the main advantage making it possible to detect foreign components in the sample. The ability to not only measure the degree of crystallinity, but also the surface area of cellulose fibril aggregates has also been emphasised. Further, FT-IR and especially NIR spectroscopy were shown to provide good models for prediction of particle and tablet properties of HPMC by utilising partial least squares analysis. The sensitivity to changes in physical properties of particles supports the use of NIR and other IR techniques that have minimal requirements for sample preparation to obtain rapid and relevant spectral data of pharmaceutical powders.

The surface area measured by different principles was in this thesis shown to reflect different properties and behaviour of a collection of pharmaceutical powders. Interparticulate bonding mechanisms in compacts were evaluated by adjusting the tablet tensile strength for the tablet surface area measured by permeametry. The results were in accordance with earlier studies of bonding mechanisms where compact strength in air and in liquids were compared (Karehill and Nyström, 1990; Olsson et al., 1996). In conclusion, for the materials that bond mainly with weak attraction forces (e.g. sucrose and crystalline lactose) the adjusted values were lower than for the materials known to also have a contribution from solid bridges (e.g., sodium chloride and potassium chloride). In addition, further normalisation was made for the mean interparticulate distance, which seemed to be an especially important factor for microcrystalline cellulose. However, the adjustment for interparticulate distance seemed less relevant for materials capable of forming solid bridges during compaction.

The permeametric surface area was also shown to be an important factor for the tensile strength of tablets made of hydroxypropyl methylcellulose together with the particle shape. Fibrous particle shape fractions had a higher starting surface area and were more prone to undergo fragmentation than more isodiametrically shaped particles, thereby resulting in stronger compacts. On the other hand, the relationship between the degree of substitution of the HPMC powders and the properties of the particles and tablets was

less clear than anticipated and the correlations found were poorer than expected. Instead of the ratio between methoxy and hydroxypropyl content, a better estimation of the behaviour of the particles during compaction and of the tablets eventually formed was obtained when considering the absolute amount of each substituent. In further studies it would also be of interest to look more closely into the distribution of the substituents along the cellulose chains. This might affect the properties of the HPMC powder and tablets.

In contrast to the findings in Papers III and IV, the permeametric surface area did not directly reflect the compact strength and other properties properly when studying microcrystalline cellulose Avicel PH101 and cellulose powder from the alga *Cladophora* sp. Instead, the fibril surface area estimated by solid-state NMR resulted in better correlations. For the Cladophora cellulose, which had a larger fibril size and a more open pore structure than the MCC, Kr gas adsorption was also able to reflect the surface area on this level. It is proposed that the fibril surface area is the primary factor responsible for properties like the crystallinity and the disintegration. Despite the high tablet tensile strength obtained for Cladophora cellulose, the disintegration of these tablets was fast at moderate compaction loads. It is is thought that this is caused mainly by the higher intra- and interparticulate porosity of these tablets compared to tablets of Avicel PH101and there being less hydrogen bonding between the Cladophora fibril surfaces to be broken in contact with water.

To conclude, this thesis has pointed out spectroscopy in combination with other charaterisation techniques and multivariate data analysis to be very useful in the characterisation of pharmaceutical solids. It has been shown that is is possible to predict the properties of the final product from analysis of the starting materials, which is something that should be of interest for the pharmaceutical industry. Furthermore, the importance of the surface area on different levels of pharmaceutical materials has been emphasised and it is hoped that this thesis has contributed to the understanding of some of the factors imortant for the development of solid dosage forms.

Acknowledgements

The work in this thesis was carried out at the Division of Pharmaceutics, Department of Pharmacy, Faculty of Pharmacy, Uppsala University. Grants to perform the studies has been received from NUTEK (Swedish National Board for Industrial and Technical Development). The experimental work has also benefited from the financial support of the Knut and Alice Wallenberg Foundation, Pharmacia Corporation (Sweden) and AstraZeneca (Sweden) to the division of Pharmaceutics. Funding for the presentation of my research at international meetings has been provided by the IF Foundation for Pharmaceutical Research, the CR Leffman Scholarship Fund, the CD Carlsson Fund and NorFA (the Nordic Academy for Advanced Study).

I would like to express my sincere gratitude to all who in different ways have helped me to make this work possible, and especially:

Professor Christer Nyström, my supervisor, for his encouragement and confidence in me and for sharing his deep knowledge and expertise in powder technology with me.

Dr Helena Lennholm, my co-supervisor, for her positive attitude and support, for inspiring and creative discussions and for her friendship and faith in me.

Professor Göran Alderborn, Head of the Department, for making the department into a great place to work in and for kind interest in my work.

Sofia Mattsson, my room mate for being a wonderful friend, always encouraging and willing to discuss scientific matter as well as non-scientific, and for providing a perfectly ordered literature reference system.

Dr Åsa Adolfsson, co-author, who showed me the charm of powders by being such a great supervisor during my 9th term studies and thereby also inspired me to continue with the post graduate studies.

Professor Tommy Iversen, co-author, for stimulating discussions and for introducing me to the world of cellulose and NMR.

Professor Carla Caramella, Dr Cristina Bonferoni and Dr Ragnar Ek, for being enthusiastic co-authors.

Susanne Bredenberg, for being a terrific travelling companion on Uppsala-pendeln during the years. I will miss our carrot- and fruit sessions and the nice walks.

Eva Nises-Ahlgren, for her positive attitude and help in different ways, especially the final preparation of this thesis.

The powder people, past and present: Dr Åsa Adolfsson, Gunilla Andersson, Jonas Berggren, Susanne Bredenberg, Leif Dahlberg, Torsten Fjellström, Dr Torkel Gren, Dr Barbro Johansson, Dr Mitra Mosharraf, Sofia Mattsson, Dr Fredrik Nicklasson, Dr Helena Olsson, Dr Tesfai Sebhatu, Åsa Tunón, for sharing their enthusiasm for science and for being such good friends.

Roberta Barzé, Donata Bensi, Maria Flodin and Petra Lavéno, for experimentally contributing to this thesis.

Antona Wagstaff and Suzy Lindström, for excellent and rapid linguistic revision of the papers and this thesis.

All past and present members of the Division of Pharmaceutics, for support and for creating a pleasant working atmosphere at galeniken.

My parents in law, Inger Gustafsson and Tage Boqvist, for kind hospitality and good times.

Malin Fjaestad and Anna Runberg, for “girl talk” in cosy coffee shops and for being such great friends always caring for me.

All my other friends outside the department, especially my ”horse friends” at Karbytorp (four- as well as two-legged), for enriching my life in many ways.

Dino, my beauty, for filling my life with so much joy and trouble.

Mia, my sister and best friend in hard times and party times, what would I do without you?

My parents, Eva and Göran, and my grandmother Anna, for always being there for me, supporting me, no matter what. I will do my best to spend more time enjoying the smell of the flowers through the path of life.

Kjelle, my great love, gourmet-chèf and companion through life – you are simply the best!

References

Adolfsson, Å, Nyström, C., 1996. Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads. Int. J. Pharm 143, 95-106.

Adolfsson, Å., Olsson, H., Nyström, C., 1997. Effect of particle size and compaction load in interparticulate bonding structure for some pharmaceutical materials studied by compaction and strength characterisation in butanol. Eur. J. Pharm. Biopharm. 44, 243-251.

van Aerde, P., Remon, J.P., DeRudder, D., Van Severen, R., Braeckman, P., 1984. Polymorphic behavior of chloroquine diphosphate. J. Pharm. Pharmacol., 36, 190-191.

Agafonov, V., Legendre, B., Rodier, N., Wouessidjewe, D., Cense, J.M., 1991. Polymorphism of spironolactone. J. Pharm. Sci., 80, 181-185.

Ahlneck, C., Alderborn, G., 1989. Moisture adsorption and tabletting. I. Effect on volume reduction properties and tablet strength for some crystalline materials. Int. J. Pharm. 54, 131-141.

Ahlneck, C., Zografi, G., 1990. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. Int. J. Pharm. 62, 87-95.

Ahmed, H., Buckton, G., Rowlins, D.A., 1996. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of ahydrophobic powder. Int. J. Pharm. 130, 195-201.

Alderborn, G., Duberg, M., Nyström, C., 1985a. Studies on direct compression of tablets X. Measurement of tablet surface area by permeametry. Powder Technol. 41, 49-56.

Alderborn, G., Pasanen, K., Nyström, C., 1985b. Studies on direct compression of tablets. XI. Characterization of particle fragmentation during compaction by permeamtery measurements of tablets. Int. J. Pharm. 23, 79-86.

Alderborn, G., Glazer, M., 1990. Studies on direct compression of tablets XVIII. Surface areas and particle size distribution of compressed sodium chloride. Acta Pharm. Nord. 1, 11-20.

Alderborn, G., Nyström, C., 1982. Studies on direct compression of tablets IV. The effect of particle size on the mechanical strength of tablets. Acta Pharm. Suec. 19, 381-390.

Alderman, D. A., 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Tech. & Prod. Mfr. 5, 1-9.

Allen, T., 1997. Particle size measurement. 5th Ed., Chapman and Hall, London.

Angberg, M., 1992. Evaluation of isothermal heat-conduction microcalorimetry in pharmaceutical stability studies. Ph. D. Thesis. Department of Pharmacy, Uppsala University, Sweden.

Angberg, M., Nyström, C., Carstensson, S., 1992. Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies. V. A new approach for continuous measurements in abundant water vapour. Int. J. Pharm. 81, 153-167.

Armstrong, N.A., 1996. Tablet surface area. In Pharmaceutical powder compaction technology. Edited by Alderborn, G., Nyström, C., Marcel and Dekker, New York, p. 194.

Armstrong, N. A., Haines-Nutt, R. F., 1970. The compaction of magnesium carbonate. J. Pharm. Pharmacol. 22, 8S-10S.

Armstrong, N. A., Haines-Nutt, R. F., 1972. Elastic recovery and surface area changes in compacted powder systems. J. Pharm. Pharmacol. 24, 135P.

Atkinson, R.M., Bedford, C., Child, K.J., Tomich, E.G., 1962. The effect of griseofulvin particle size on blood levels in man. Antibiot. Chemother. 12, 232-238

Bellows, J.C., Chen, F.P., Prasad, P.N., 1977. Determination of drug polymorphs by laser Raman spectroscopy. 1. Ampicillin and griseofulvin. Drug Dev. Ind. Pharm. 3, 451-458.

Beyrich, T., Junghaenel, J., Mietz, G., 1997. Enantiomeric purity control of chiralic drugs. Pharmazie 52, 512-516.

Black, D.B., Lovering, E.G., 1977. Estimation of the degree of crystallinity in digoxin by X-ray and infrared methods. J. Pharm. Pharmacol. 29, 684-687.

Blair, T.C., Buckton, G., Beezer, A.E., Bloomfield, S.F., 1990. The interactions of various types of microcrystalline cellulose and starch with water. Int. J. Pharm. 63, 251-257.

Blattner, D., Jerzer, W., Leuenberger, H., 1986. Compaction performance of polyethylene glycols. Proc. 4th Int. Conf. Pharm. Technol., APGI, Paris, Vol. I, pp. 308-318.

de Boer, A.H., Bolhuis, G.K., Lerk, C.F., 1978. Bonding characteristics by scanning electron microscopy of powders mixed with magnesium stearate. Powder Technol. 20, 75-82.

de Boer, A. H., Vromans, H., Lerk, C. F., Bolhuis, G. K., Kussendrager, K. D., Bosch, H., 1986. Studies on the tableting properties of lactose Part III. The consolidation behaviour of sieve fractions of crystalline α-lactose monohydrate. Pharm. Weekbl. Sci. 8, 145-150.

Bolton, B.A., Prasad, P.N., 1984. Laser raman investigation of drug-polymer conjugates: sulfathiazole-povidone coprecipitates. J. Pharm. Sci. 73, 1849-1851.

Bonferoni, M. C., Rossi, S., Ferrari, F., Bertoni, M., Caramella, C., 1996. A study of three hydroxypropylmethyl cellulose substitution types: effect of particle size and shape on hydrophilic matrix performances. S.T. P. Pharma Sciences 6(4), 277-284.

Brunauer, S., Emmet, P.H., Teller, E., 1938. Adsorption of gases in multimolecular layers. J.Am. Chem. Soc 60, 309-319.

Briggner, L.-E., Buckton, G., Byström, K., Darcy, P., 1994. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. Int. J. Pharm. 105, 125-135.

Brittain, H.G., 1995. Overview of physical characterization methodology. In Brittain, G. (Ed.), Physical characterization of pharmaceutical solids. Marcel Dekker Inc., New York, p. 16.

Brittain, H.G., Bogdanowich, S.J., Bugay, D.E., DeVincentis, J., Lewen, G, Newman, A.W., 1991. Physical characterization of pharmaceutical solids. Pharm. Res. 8, 963-973.

Brittain, H.G., Morris, K.R., Bugay, D.E., Thakur, A.B., Serajuddin, A.T.M.,1993. Solid-state NMR and IR for the analysis of pharmaceutical solids: polymorphs of fosinopril sodium J. Pharm. Biomed. Anal. 11, 1063-1069.

British standard B.S. 2955: 1958. Glossary of terms relating to powders, no. 505, British Standard Institute, Park Street, London, UK.

Buckton, G., Beezer, A.E., 1988. A microcalormetric study of powder surface energetics. Int. J. Pharm. 41, 139-145.

Buckton, G., Choularton, A., Beezer, A.E., Chartham, S.M. 1988. The effect of communition technique on the surface energy of a powder. Int. J. Pharm. 47, 121-128.

Buckton, G., Darcy, P., MacKellar,. A. J., 1995. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders. Int. J. Pharm. 117, 253-256.

Buckton, G., Yonemochi, E., Hammond, J., Moffat, A., Use of infrared spectroscopy to detect changes in the form of amorphous and crystalline lactose. Int. J. Pharm. 168, 231-241.

Burt, H.M., Michell, A.G., 1981. Crystal defects and dissolution. Int J. Pharm. 9, 137-152.

Bugay, D.E., Williams, A.C., 1995. Vibrational spectroscopy. In Brittain, G. (Ed.) Physical characterization of pharmaceutical solids. Marcel Dekker Inc., New York, p 60.

Bugay, D.E., 1995. Magnetic resonance spectrometry. In Brittain, G. (Ed.) Physical characterization of pharmaceutical solids. Marcel Dekker Inc., New York, p. 111.

Byrn, S.R.,1982. Solid state chemistry of drugs. Academic Press, New York, 1982 pp79-86.

Chao, R.S., Vail, K.C., 1987. Polymorphism of 1,2-dihydro-6-neopentyl-2-oxonicotinic acid: characterization, interconversion and quantitation. Pharm. Res. 4, 429-432.

Ciurczak, E.W., 1991. Pharmaceutical mixing studies using near-infrared spectroscopy Pharm. Technol.15, 140-145 .

Coffin-Beach, D.P., Hollenbeck, R.G., 1983. Determination of the energy of tablets formation during compression of selected pharmaceutical powders. Int. J. Pharm. 17, 313-324.

Corti, P., Dreassi, E., Murratzu, C., Corbini, G., Gravina, S., 1989. Application of NIRS to the quantity control of pharmaceuticals: ketoprofen assay in different pharmaceutical formulae. Pharm. Acta Helv. 64, 140-145

Craig, D.Q.M., Newton, J.M., 1991. Characterization of polyethylene glycols using differential scanning calorimetry. Int. J. Pharm. 74, 33-42.

Dahl, T. C., Calderwood, T., Bormeth, A., Trimble, K., 1990. Influence of physico-chemical properties of hydroxypropyl methylcellulose on naproxen release from sustained release matrix tablets. J. Controlled Release 14, 1-10.

Davies P.N., Newton, J.M., 1996. Mechanical strength. In Alderborn, G., and Nyström, C. (Eds), Pharmaceutical powder compaction technology, Marcel Dekker Inc., New York, pp. 165-191.

Deeley, C.M., Spragg, R.A., Threlfall, T.L., 1991. A comparison of Fourier transform infrared and near-infrared Fourier transform Raman spectroscopy for quantitative measurements: An application in polymorphism. Spectrochim. Acta 47A, 1217-1224.

Doelker, E., Gurny, R., Schurz, J., Janosi, A., Matin, N., 1987. Degrees of crystallinity and polymerisation of modified cellulose powders for direct tabletting. Powder Technol. 52, 207-213.

Doherty, C., York, P., 1988. Furosemide crystal forms: Solid state and physicochemical analyses. Int. J. Pharm. 47, 141-156.

Duberg, M., Nyström, C., 1986. Studies on direct compression of tablets. XVII. Porosity-pressure curves for the characterization of volume reduction mechanisms in powder compression. Powder Technol. 46, 67-75.

Duncan-Hewitt, W. C., Grant, D. J. W., 1986. True density and thermal expansivity of pharmaceutical solids: comparison of methods and assessment of crystallinity. Int. J. Pharm. 28, 75-84.

Earl, W.L., Parrish, F.W., 1983. A cross-polarization-magic-angle sample spinning N.M.R. study of several crystal forms of lactose. Carbohydr. Res. 115, 23-32.

Ek, R., Alderborn, G., Nyström, C., 1994. Particle analysis of microcrystalline cellulose: Differentiation between individual particles during compression of tablets. Int. J. Pharm. 111, 43-50.

Ek, R., Gustafsson, C., Nutt, A., Iversen, T. and Nyström, C. Cellulose powder from Cladophora sp. algae. J. Molecular Recognition, 11, (1998), 263-265.

Ek, R., Wormald, P., Östelius, J., Iversen, T., Nyström, C., 1995. Crystallinity index of microcrystalline cellulose particles during compression of tablets. Int. J. Pharm. 125, 257-264.

Elamin, A.A., Ahlneck, C., Alderborn, G., Nyström, C., 1994. Increased metastable solubility of milled griseofulvin, depending on the formation of a disordered surface structure. Int. J. Pharm. 111, 159-170.

Elamin A.A., Sebhatu, T., Ahlneck, C., 1995. The use of amorphous model substances to study mechanically activated materials in the solid state. Int. J. Pharm. 119, 25-36.

El Gindy, N.A., Samaha, M.W., 1983. Tensile strength of some pharmaceutical compacts and their relation to surface free energy. Int. J. Pharm. 13, 35-46.

Eriksson, M., Alderborn, G., 1994. Mechanisms for post-compaction changes in tensile strength of sodium chloride compacts prepared from particles of different dimensions. Int. J. Pharm. 109, 59-72.

Eriksson, M., Nyström, C., Alderborn, G., 1990. Evaluation of a permeametry technique for surface area measurements of coarse particulate materials. Int. J. Pharm. 63, 189-199.

Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wold S., 1999. Introduction to Multi- and Megavariate data analysis using projection methods (PCA &PLS), UMETRICS AB, Umeå, Sweden.

Ertel, K.D., Carstensen, J.T.,1988. Examination of the physical properties of pure magnesium stearate. Int. J. Pharm. 42, 171-180.

Fell, J. T., Newton, J. M., 1970. Determination of tablet strength by the diametral compression test. J. Pharm. Sci. 59, 688-691.

Fletton, R.A., Harris, K., Kenwright, A.M., Lancaster, R.W, Packer, K.J., Sheppard, N., 1987. A comparative spectroscopic investigation of three pseudopolymorphs of testosterone using solid-state IR and high-resolution solid-state NMR. Spectochim. Acta, 43A, 1111-1120.

Florence A.T., Attwood, D., 1998. Physicochemical principles of Pharmacy. 3rd Edition MacMillan Press Ltd, London, Great Britain, pp. 8-14.

Florence, A.T., and Salole, E.G., 1976. Changes in crystallinity and solubility on communiation of digoxin and obsevations on spironolactone and oestradiol. J. Pharm. Pharmacol. 28, 637-642.

Führer, C., 1977. Substance behaviour in direct compression. Labo-Pharma Probl. Techn. 25, 759-762.

Führer, C., 1996. Interparticulate attraction mechanisms. In Alderborn, G., Nyström, C. (Eds.), Pharmaceutical powder compaction technology. Marcel Dekker, New York, p. 14.

Geladi, P., Kowalski, B.R., 1986. Partial least-squares regression: A tutorial. Anal. Chim. Acta 185, 1-17.

Gerber, J.J., vanderWatt, J.G., Lötter, A.P., 1991. Physical characterization of solid forms of cyclopenthiazide. Int. J. Pharm. 73, 137-145.

Giron, D., Remy, P., Thomas, S., Vilette, E., 1997. Quantitation of amorphicity by microcalorimetry. J. Ther. Anal. 48, 465-472.

Goetzel, C.G., 1949. Treatise on powder metallugy. Interscience Publishers (John Wiley & Sons), New York and London, Vol. I, pp. 259-273.

Hailey P.A., Doherty, P., Tapsell, P., Oliver, T., Aldridge, P.K. 1996. Automated system for the on-line monitoring of powder blendning processes using near-infrared spectroscopy Part I. System development and control. J. Pharm. Biomed. Anal. 14, 551-559.

Hameau, S., Jouan, M., Dao, N.Q., 1988. Application of the Raman-laser-fiber optics to the remote in situ quantitative analysis of a solid drug. Analysis 16, 173-178.

Hardman, J.S., Lilley, B.A., 1973. Mechanisms of compaction of powdered materials. Proc. R. Soc. London A. 333, 183-199.

Harris, R., Kenwright, A.M., Say, B.J., Yeung, R.R., Fletton, R.A., Lancaster, R.W., Hardgrove, G.L., 1990. Cross-polarization/magic-angle spinning NMR studies of polymorphism: Cortisone acetate. Spectrochim. Acta 46A, 927-936.

Harris, R., Say, B.J., Yeung, R.R., Fletton, R.A., Lancaster, R.W., 1989. Cross-polarization/magic-angle spinning NMR studies of polymorphism: Androstanolone. Spectrochim. Acta 45A, 465-470.

Hartauer, K.J., Miller, E.S., Guilloty, J.K., 1992. Diffuse reflectance infrared Fourier transform spectroscopy for the quantitative analysis of mixtures of polymorphs Int. J. Pharm. 85, 163-174.

Heckel, R.W., 1961a. Density-pressure relationships in powder compaction. Trans. Metall. Soc. Aime 221, 671-675.

Heckel, R.W., 1961b. An analysis of powder compaction phenomena. Trans. Metall. Soc. Aime 221, 1001-1008.

Heiner, A.P., Kuutti, L., Teleman, O., 1998. Comparison of the interface between water and four surfaces of native crystalline cellulose by molecular dynamics simulations. Carbohydr. Res. 306, 205-220.

Heiner, A.P., Teleman, O., 1997. Interface between monoclinic crystalline cellulose and water: Breakdown of the odd/even duplicity. Langmuir 13, 511-518.

Hersey J.A., Krycer, I., 1980. Biopharmaceutical implications of technological change. Int. J. Pharm. Tech. Prod. Mfr. 1(2), 18-21.

Heywood, H., 1954. Particle shape coefficient. J. Imp. Coll. Chem. Eng. Soc. 8, 25-33.

Hulett, G.A., 1901. Beziehungen zwischen Oberflächenspannung und Löslichkeit. Z. Phys. Chem. 37, 385.

Hüttenrauch, R., 1977. The mechanism of tablet forming – A new conception. Proc. 1st Int. Conf. Pharm. Technol. Vol IV, Paris, 114-120.

Hüttenrauch, R., 1978. Molecular galenics as the basis of modern drug formation. Acta Pharm. Tech. Suppl. 6, 55-127.

Hüttenrauch, R., and Fricke, S., 1981. Influence of lattice defects on the course and rate of drying of particulate solids. Part 45. Molecular pharmaceutics. Int. J. Pharm. Technol. Prod. Manuf. 2, 35-37.

Hüttenrauch, R., Fricke, S., Zielke, P., 1985. Mechanical activation of Pharmaceutical systems. Pharm. Res. 2, 302-306.

Israelachvili, J., 1992. Intermolecular and surface forces, Academic press, 2nd Edn, London, p. 28.

Jacobson, H., Reier, G. J., 1969. Application of differential thermal analysis to compatibility and stability problems in penicillin-stearic acid mixtures J. Pharm. Sci. 58, 631-633.

Jackson, J.E., 1991. A user's guide to principal components, John Wiley, New York.

Jensen R., Peuchant, E., Castagne, I., Boirac, A.M., Roux, G., 1988. One-step quantification of active ingredient in pharmaceutical tablets using near IR spectroscopy. Spectros. Int. J. 6, 63-72.

Juppo, A. M., 1996. Relationship between breaking force and pore structure of lactose, glucose and mannitol tablets. Int. J. Pharm. 127, 95-102.

Karehill, P. G., Glazer, M., Nyström, C., 1990. Studies on the direct compression of tablets XXII. The importance of surface roughness for the compactability of some directly compressible materials with different bonding mechanisms and volume reduction properties. Int. J. Pharm. 64, 35-43.

Karehill, P. G., Nyström, C., 1990. Studies on direct compression of tablets XXI. Investigation of bonding mechanism of some directly compressed materials by strength characterisation in media with different dielectric constants (relative permittivity). Int. J. Pharm. 251-260.

Kaye, B.H., 1967. Permeability techniques for characterizing fine powders. Powder Technol. 1, 11-22.

Kendall, K., 1988. Agglomerate strength. Powder Metallurgy, 31, 28-31.

King, T.H., Mann, C.K., Vickers, T.J., 1985. Determination of phenylpropanolamine hydrochloride and acetaminophen in pharmaceutical preparations by Raman spectroscopy. J. Pharm. Sci., 74, 443-447.

Kitamura, S., Chang, L.-C., Guillory, J.K., 1994. Polymorphism of mefloquine hydrochloride. Int. J. Pharm. 101, 127-144.

Klug H.P., Alexander, L.E., 1974. X-ray diffraction procedures for polycrystalline and amorphous materials. Wiley, New York.

Kontny, M.J., Zografi, G., 1995. Sorption of water by solids. In Physical Characterization of pharmaceutical solids. Ed by Brittain, G., Marcel and Dekker Inc., New York, USA, pp 388-415.

Kuhnert-Brandstätter, M., Ulmer, R., 1973. Thermoanalytical and IR-spectroscopic investigation of tilidine hydrochloride. Arch. Pharm. Weinham 306, 618-621.

Langmuir, I., 1918. The adsorption of gases on plane surfaces of glass, mica and platinum. J.Am. Chem. Soc. 40, 1361-1403.

Larsson, P. T., Hult, E.L., Wickholm, K., Pettersson, E., Iversen, T., 1999. CP/MAS 13C-NMR spectroscopy applied to structure and interaction studies on cellulose I. Solid State Magnetic Resonance 15, 31-40.

Larsson, P. T., Wickholm, K. and Iversen, T.; 1997. A CP/MAS 13C NMR investigation of molecular ordering in celluloses. Carbohydrate Res. 302, 19-25.

Lee, K.C., Hersay, J.A., 1977. Oxytetracycline tablet formulations: preformulation stability screening using differential thermal analysis. J. Pharm. Pharmacol. 29, 515-516.

Lennholm, H., 1994. Investigations of cellulose polymorphs by 13C-CP/MAS-NMR spectroscopy and chemometrics. Ph.D. Thesis Department of pulp and paper chemistry and technology, The Royal Institute of Technology, Stockholm, Sweden.

Leuenberger, H. Bonny, J. D., Lerk, C. F., Vromans, H., 1989. Relation between crushing strength and internal specific surface area of lactose compacts. Int. J. Pharm. 52, 91-100.

Lin, S.-Y., 1992. Isolation and solid-state characteristics of a new crystal form of indomethacin J. Pharm. Sci. 572-576.

Lonardi, S., Viviani, R., Mosconi, L., Bernuzzi, M., Corti, P., Dreassi, E., Murratzu, C., Corbini, G., 1989. Drug analysis by near-infra-red reflectance spectroscopy-determination of the active ingredient and water content in antibiotic powders. J. Pharm. Biomed. Anal. 7, 303-308.

Luangtana-Anan, M., Fell, J.T., 1990. Bonding mechanisms in tabletting. Int. J. Pharm. 60, 197-202.

MacDonald, B.F., Prebble, K.A., 1993. Some applications of near infrared reflectance analysis in the pharmaceutical industry. J. Pharm. Biomed. Anal. 11, 1077-1085.

Malamataris, S., Karidas, T., Goidas, P., 1994. Effect of particle size and sorbed moisture on the compression behaviour of some hydroxypropyl methylcellulose (HPMC) polymers. Int. J. Pharm. 103, 205-215.

Martens, H., Naes, T., 1989. Multivariate calibration. Wiley, New York.

Martinez-Ohárriz, M.C., Martín, C., Goñi, M.M., Rodríguez-Espinosa, C., Tros de Ilarduya-Apaolaza, M.C., Sánchez, M., 1994. Polymorphism of diflunisal: isolation and solid-state characteristics of a new crystal form. J. Pharm. Sci. 83, 174-177.

Matsuda, Y., Kawaguchi, S., Kobayshi, H., Nishijo, J., 1984. Physicochemical characterization of spray dried phenylbutazone polymorphs. J. Pharm. Sci. 73, 173-179.

McCauley, J.A., Brittain, H.G., 1995. Thermal methods of analysis. In Brittain, G. (Ed.), Physical characterization of pharmaceutical solids. Marcel Dekker Inc., New York, pp 238-243.

McKenna, A., McCafferty, D.F., 1982. Effect of particle size on the compaction mechanism and tensile strength of tablets. J. Pharm. Pharmacol. 34, 347-351.

Mitchell, A.G., Down, G.R.B. 1984. Recrystallization after powder compaction. Int. J. Pharm. 22, 337-344.

Mitchell, K., Ford, J. L. Armstrong, D. J., Elliott, P. N. C., Hogan, J. E., Rostron, C., 1993. The influence of substitution type on the performance of methylcellulose and hydroxypropylmethylcellulose in gels and matrices. Int. J. Pharm. 100, 143-154.

Morisseau, K.M., Rhodes, C.T., 1997. Near infrared spectroscopy as a nondestructive alternative to conventional tablet hardness testing. Pharm. Res. 14, 108-111.

Mosharaff, M., 1999. The effect of solid state properties on solubility and *In Vitro* dissolution behaviour of suspended sparingly soluble drugs. Ph. D. Thesis. Department of Pharmacy, Uppsala University, Sweden.

Mullier, M.A., Seville, J.P.K., Adams, M.J., 1987. A fracture mechanics approach to the breakage of particle agglomerates. Chem. Eng. Sci. 42, 667-677.

Munoz-Ruiz, A., Payan-Villar, T., Justo, A., Velasco, V., Jimenez-Castellanos, R., 1996. X-ray tablet and raw diffraction as a method to study compression parameters in a direct compression excipient, Compril. Int. J. Pharm. 144, 147-152.

Nail, S.L., White, J.L., Hem, S.L., 1975. Comparison of IR spectroscopic analysis and X-ray diffraction of aluminum hydroxide. J. Pharm. Sci., 64, 1166-1169.

Nakai Y., Fukuoka E., Najkajima, S., Hasegawa, J., 1977. Crystallinity and physical characteristics of microcrystalline cellulose. Chem. Pharm. Bull. 25, 96-101.

Nerdal, W., Gundersen, S.A., Thorsen, V., Hoiland, H., Holmsen, H., 2000. Chlorpromazine interaction with glycerophospholipid liposomes studied by magic angle spinning solid state 13C-NMR and differential scanning calorimetry. Biochim. Biophys. Acta 1464, 165-175.

Neville G.A., Beckstead, H.D., Shurvell, H.F., 1992. Utility of Fourier transform-Raman and Fourier transform-infrared diffuse reflectance spectroscopy for differentiation of polymorphic spironolactone samples. J. Pharm. Sci. 81, 1141-1146.

Nyqvist, H., 1983. Saturated salt solutions for maintaining specified relative humidities. Int. J. Pharm. Tech. & Prod. Mfr. 4, 47-48.

Nyström, C., Alderborn, G., Duberg, M., Karehill, P. G., 1993. Bonding surface area and bonding mechanism – two important factors for the understanding of powder compactibility. Drug Dev. Ind. Pharm., 19, 2143-2196.

Nyström, C., Karehill, P.G., 1986. Studies on direct compression of tablets XVI. The use of surface area measurements for the evaluation of bonding surface area in compressed powders. Powder Technol. 47, 201-209.

Nyström, C., Karehill, P. G., 1996. The importance of intermolecular bonding forces and the concept of bonding surface area. In Alderborn, G. and Nyström, C. (Eds.) Pharmaceutical powder compaction technology, Marcel Dekker Inc., New York, pp. 44-51.

Nyström, C., Malmqvist, K., Mazur, J., Alex, W., Hölzer, A., 1978. Measurement of axial and radial tensile strength of tablets and their relation to capping. Acta Pharm. Suec. 15, 226-232.

Olsson, H., Adolfsson, Å, Nyström, C., 1996. Compaction and measurement of tablets in liquids with different dielectric constants for determination of bonding mechanisms – evaluation of the concept. Int. J. Pharm. 143, 233-245.

Olsson, H., Nyström, C., 2000a. Asessing tablet bond types from structural reatures that affect tablet tensile strength. Submitted to Pharm. Res.

Olsson, H., Nyström, C., 2000b. The effect of speed of compression on the compaction of sodium chloride, sodium bicarbonate, lactose, sucrose and pregelatinised starch tablets. In manuscript.

Pedersen S., Kristensen, H. G., 1994. Change in crystal density of acetylsalicylic acid during compaction. S.T.P. Pharm. Sci. 4, 201-206.

Quin, D., Kean, R.T., 1998. Crystallinity determination of polylactide by FT-Raman spectrometry. Appl. Spectroscopy 52, 488-495.

Raghavan, K., Dwivedi, A., Campbell, G.C., Johnston, E., Levorse, D., McCauley, J., Hussain, M., 1993. Spectroscopic investigation of losartan polymorphs. Pharm. Res. 10, 900-904.

Raghavan, K., Dwivedi, A., Campbell, G.C., Nemeth, G., Hussain, M., 1994. A spectroscopic investigation of DuP 747 polymorphs. J. Pharm. Biomed. Anal. 12, 777-785.

Rantanen, J., Lehtola, S., Rämet, P., Mannermaa, J.-P., Yliruusi, J., 1998. On-line monitoring of moisture content in an instrumented fluidized bed granulator with multi-channel NIR moisture sensor. Powder Technol. 99, 163-170.

Roberts, R.J. Rowe, R.C., 1987. Brittle/ductile behaviour in pharmaceutical materials used in tabletting. Int. J. Pharm. 36, 205-209.

Roston, D.A., Walters, M.C., Rhinebarger, R.R., Ferro, L.J., 1993 . Characterization of polymorphs of a new anti-inflammatory drug. J. Pharm. Biomed. Anal. 11, 293-300.

Rowlings, C.E., Wurster, D.E., Ramsey, P.J., 1995. Calorimetric analysis of powder compression:II. The relationship between energy terms measured with a compression calorimeter and tableting behaviour. Int. J. Pharm. 116, 191-200.

Rumpf, H., 1962. The strength of granules and agglomerates. In Knepper, W.A. (Ed.), Agglomeration, Interscience, New York, pp. 379-418.

Rustichelli, C., Gamberini, M.C., Ferioli, V., Gamberini, G., 1999. Properties of the racemic species of verapamil hydrochloride and gallopamil hydrochloride. Int. J. Pharm. 178, 111-120.

Ryan, J.A., Compton, S.V., Brooks, M.A., Compton, D.A.C., 1991. Rapid verification of identity and content of drug formulations using mid-infrared spectroscopy J. Pharm. Biomed. Anal. 9, 303-310.

Sebhatu, T., Angberg, M., Ahlneck, C., 1994. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. Int. J. Pharm. 104, 135-144.

Sebhatu, T., Alderborn, G., 1999. Relationships between the effective interparticulate contact area and the tensile strength of tablets of amorphous and crystalline lactose of varying particle size. Eur. J. Pharm. Sci., 8, 235-242.

Sekulic, S.S., Wakeman, J., Doherty, P., Hailey, P.A., 1998. Automated system for the online monitoring of powder blending processes using near infrared spectroscopy. Part 2. Qualitative approaches to blend evaluation. J. Pharm. Biomed. Anal. 17, 1285-1309.

Segal, B., 1985. Chemistry, experimental and theory. John Wiley and Sons, Inc., New York, USA, pp 800-811.

Sekizaki, H., Danjo, K., Eguchi, H., Yonezawa, Y., Sunada, H., Otsuka, A., 1995. Solid-state interaction of ibuprofen with polyvinylpyrrolidone. Chem. Pharm. Bull., 46, 988-993.

Selkirk, A.B., 1985. Comments on “Studies on direct compression of tablets. X. Measurements of tablet surface area by permeametry”. Powder Technol. 43, p 285.

Shotton, E., Ganderton, D., 1961. The strength of compressed tablets III. The relation of particle size, bonding and capping in tablets of sodium chloride, aspirin and hexamine. J. Pharm. Pharmacol. 13, 144-151.

Sixsmith, D., 1976. The effect of compression on some physical properties of microcrystalline cellulose., J. Pharm. Pharmacol. 29, 33-36.

Sjöblom, J., Svensson, O., Josefsson, M., Kullberg, H., Wold, S., 1998. An evaluation of orthogonal signal correction applied to calibration transfer of near infrared spectra. Chemometrics Intell. Lab. Syst. 44, 229-244.

Stanley-Wood, N.G., Johansson, M.E., 1978. Measurement of interparticle voidage and particle contact area in compacts by nitrogen adsorption. Drug Dev. Ind. Pharm. 4, 69-94.

Sugiama, J., Persson, J. Chanzy, H., 1991. Combined infrared and electron diffraction study of the polymorphism of native celluloses. Macromolecules 24, 2461-2466.

Suryanarayanan, R. 1995. X-ray powder diffractometry. In Physical Characterization of pharmaceutical solids. Ed by Brittain, G., Marcel and Dekker Inc., New York, USA, pp 188-189.

Suryanarayanan, R., Herman, C.S., 1991a. Quantitative analysis of the active tablet ingredient by powder X-ray diffractometry. Pharm. Res. 8, 393-399.

Suryanarayanan, R., Herman, C.S., 1991b. Quantitative analysis of the active ingredient in a multi-component tablet formulation by powder X-ray diffractometry. Int. J. Pharm. 77, 287-295.

Suryanarayanan, R., Mitchell, A.G., 1985. Evaluation of two concepts of crystallinity using calcium gluceptate as a model compound. Int. J. Pharm. 24, 1-17.

Svensson, O., 1999. Vibrational spectroscopy and multivariate methods in chemical analysis. Ph.D. Thesis. Department of Analytical and Marine Chemistry, Gothenburg University, Sweden.

Taylor, L.S., Zografi, G., 1997. Spectroscopic characterisation of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm. Res. 14, 1691-1698.

Taylor, L.S., Zografi, G., 1998. The quantitative analysis of crystallinity using FT-Raman spectroscopy. Pharm. Res. 15, 755-761.

Train, D., 1956. An investigation into the compaction of powders. J. Pharm. Pharmacol. 8, 745-761.

Tudor, A.M., Church, S.J., Hendra, P.J, Davies, M.C., Melia, C.D., Qualitative and quantitative analysis of chlorpropamide polymorphic mixtures by near infrared Fourier transform Raman spectroscopy. Pharm. Res., 1993, 1772-1776.

VanderHart, D.L., Atalla, R.H., 1984. Studies of microstructure in native celluloses using solid-state ^{13}C-NMR. Macromolecules 17, 1465-1472.

Vromans, H., de Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D., 1986. Studies on tablet properties of lactose; The effect of initial particle size on binding properties and dehydration characteristics of a-lactose monohydrate. Drug Dev. Ind. Pharm. 12, 1715-1729.

Vromans, H., de Boer, A. H., Bolhuis, G. K., Lerk, C. F., Kussendrager, K. D., Bosch, H., 1985. Studies on tabletting properties of lactose Part 2. Consolidation and compaction of different types of crystalline lactose. Pharm. Weekbl. Sci. 7, 186-193.

Vromans, H., Bolhuis, G. K., Lerk, C. F., Kussendrager, K. D., 1987. Studies of tableting properties of lactose IX. The relationship between particle structure and compactability of crystalline lactose. Int. J. Pharm. 39, 207-212.

Wade, A., Weller, P.J., 1994. Handbook of Pharmaceutical Sciences, 2nd Ed, The Pharmaceutical Press, London, p. 141.

Wells, J.I., Aulton M. E., 1988. Preformulation. In Aulton, M. E. (Ed.), Pharmaceutics The science of dosage from design. Churchill Livingstone, New York, p. 231.

Westermark, S., Juppo, A.M., Koiranen, K., Yliruusi, J., 1998. Mercury porosimetry of pharmaceutical powders and granules. J. Porous Materials 5, 77-86.

Wickholm, K., Larsson, P. T., Iversen, T., 1998. Assignment of non-crystalline froms in cellulose I by CP/MAS ^{13}C NMR spectroscopy. Carbohydr. Res. 312, 123-129.

te Wieriket, G.H.P., Bergsma, J., Arends-Scholte, A.W., Boersma, T., Eissens, C., Lerk, C.F., 1996. A new generation of starch products as excipient in pharmaceutical tablets. I. Preparation and binding properties of high surface area potato starch products. Int. J. Pharm. 134, 27-36.

Wold, S., Albano, C., Dunn, W.J., Edlund, U., Esbensen, K., Geladi, P., Helleberg, S., Johansson, E., Lindberg, W., Sjöström, M., 1984. Multivariate data analysis in Chemistry. In Kowalski, B.R. (Ed.) Chemometrics: Mathematics and Statistics in chemistry. D. Reidel Publishing Company, Dordrecht, Holland.

Wong, L.W., Pilpel, N., 1990. The effect of particle shape on the mechanical properties of powders. Int. J. Pharm. 59, 145-154.

Yang, S.S., Guillory, J.K., 1972. Polymorphism in sulfonamides. J. Pharm. Sci. 61, 26-40.

York, P., 1983. Solid state properties of powders in the formulation and processing of solid dosage forms. Int. J. Pharm. 14, 1-28.

Zografi, G., Kontny, M.J., Yang, A.Y.S., Brenner, G.S., 1984. Surface area and water vapour sorption of microcrystalline cellulose. Int. J. Pharm. 18, 99-116.