International Journal of Pharmaceutics 360 (2008) 40–46

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Determination of the crushing strength of intact tablets using Raman spectroscopy

Satu Virtanen*, Osmo Antikainen, Jouko Yliruusi

Division of Pharmaceutical Technology, 00014 University of Helsinki, P.O. Box 56, Helsinki, Finland

ARTICLE INFO

Article history:
Received 18 December 2007
Received in revised form 18 March 2008
Accepted 9 April 2008
Available online 22 April 2008

Keywords:
Tablet strength
Raman spectroscopy
Surface roughness

ABSTRACT

In the present study, the Raman spectroscopy technique was used as a non-invasive, rapid analytical method for measuring the crushing strength of tablets. The compressed tablets were individually detected, using Raman spectroscopy, and the respective crushing strength values were measured, using a tablet hardness tester as a reference method. The tablets were compressed from a granule mass containing theophylline anhydrate as an active substance. For measuring the crushing strength of the tablets, Raman spectra were recorded from the tablets. Partial least squares (PLS) regression models were constructed to obtain information from the spectra. The correlation between measured and predicted crushing strength values for the tablets was shown to be very favorable. With Raman spectroscopy, shifting of the baseline was observed as the crushing strengths of tablets (and the smoothness of the tablet surface) were increased. Consequently, correlation between the crushing strength data on the present tablets and Raman spectra was observed. Multiple scanning electron (SEM) and non-contact laser profilometry (LP) micrographs from the surfaces of the tablets were taken to describe the surfaces and applied as supportive information for the proposed spectroscopy approach. In conclusion, Raman spectroscopy is a promising alternative for established off-line/at-line tablet-testing methods for some tablet formulations.

1. Introduction

Testing the mechanical strength of tablets with a conventional indirect diametral hardness-testing apparatus is an invasive and laborious method that breaks up the tablet. The vibrational spectroscopy technique of Raman spectroscopy is a rapid and non-invasive method that can gain real-time quantitative and qualitative information on both the chemical and physical properties of tablets. This technique may provide significant advances as a future process analytical tool, since spectra can be measured directly on the surfaces of non-destructed samples (i.e. tablets) without any pre-treatment (Otsuka and Yamane, 2006). In addition, Raman spectroscopy can be used almost everywhere and is portable. The method is easy to use and the measurements are repeatable. The disadvantages of Raman spectroscopy are the weakness of the signal, warming of the sample caused by the laser and the fluorescence phenomenon. However, the weakness of the signal can also be used to advantage, since it enables measurement straight from the sample with no pre-processing required. The fluorescence can be problematic, even though the measurement conditions are in order. Fortunately, fluorescence is not a problem for most pharmaceutical substances.

Raman spectroscopy is not based on absorption or emission, but on in-elastic scattering. The Kubelka–Munk (KM) theory states that diffusive reflectance increases with decrease in particle size (Kubelka and Munk, 1931; Kubelka, 1948; Schrader et al., 1991), which implies that Raman intensity should increase with increase in particle size. On the other hand, this assumes that when the tablet surface becomes smoother, Raman intensity increases. However, the intensity of the signal, when vibrational spectroscopy methods are used, can be influenced by many factors, e.g. wavelength of the measurement, compression force and compressed material (Wang et al., 2002).

Analysis of the tablet with spectroscopic methods requires considerable experience. Due to spatial variations and inhomogeneities of the tablet spectroscopic assessment is a precise task that can give differing results, depending on how the measurement is done. Raman spectroscopic measurement is critical, because the area measured is very small (scale of scrutiny), which explains the sample must be moved, in this case rotated. When the sample is rotated the measurement covers a larger area and warming of the sample can also be reduced. A rotating sample holder was used to achieve high repeatability (Szostak and Mazurek, 2002). When physical properties are measured the distance between the sample and the probe must be standardized (Lombardi et al., 1994). The change in

* Corresponding author. Tel.: +358 919159146; fax: +358 919159144.
E-mail address: satu.virtanen@helsinki.fi (S. Virtanen).

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.04.022

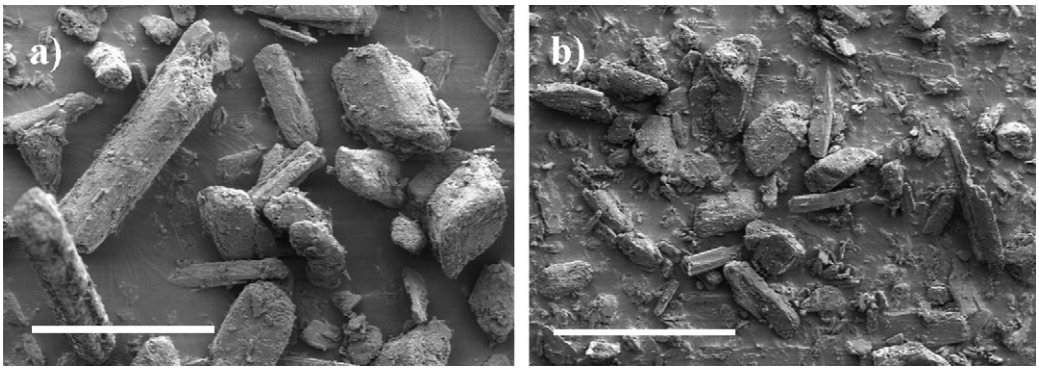

Fig. 1. Scanning electron microscopy (SEM) micrographs of (a) theophylline anhydrate 100-M and (b) theophylline anhydrate 200-M. Scale bar 200 μm.

distance causes the same alterations in the spectra as does increase in the crushing strength of the tablet.

Quantitative measurement with Raman spectroscopy is possible because there is a relationship between signal intensity and the concentration. This enables straightforward concentration measurements and explains why Raman spectroscopy has been used in many pharmaceutical processes. Nevertheless, the number of physical measurements, such as crushing strength of tablets, has been limited in the literature. Some studies determined influence of particle size on Raman intensity (Pellow-Jarman et al., 1996; Fangxin et al., 1997; Wang et al., 2002; Williams et al., 2004; Hu et al., 2006). The results showed that the intensity of the signal changes with change in particle size. The particle shape and crystalline form of the material measured, as well as the wavelength of the signal, also influence the signal intensity.

Few reports are available on the applicability of Raman spectroscopy for tablet hardness determination. Only Wang et al. (2002) and Johansson et al. (2005) groups studied intact tablets and Picker-Freyer and Schmidt (2004) studied broken tablets. Picker-Freyer and Schmidt observed differences in the Raman spectra that were due to structural changes in the tablet. The intensity of the spectra increased with increase in the hardness of the tablets. Johansson et al. (2005) compressed tablets with different compression forces and noted no significant effect of tablet density on the Raman signal. They also stressed that the results were based on measurements of a single type of tablet. Wang et al. (2002) investigated the effects of compression force during tableting on the Raman signal. They studied the effect of the tablet thickness by comparing the Raman signals for tablets of the same particle-size powder. In their measurement the Raman intensity decreased with increasing compression force until a constant density was achieved. The crushing strength of tablets was also investigated with near-infrared spectroscopy (Morisseau, 1996; Morisseau and Rhodes, 1997; Ebube et al., 1999; Kirsch and Drennen, 1999; Chen et al., 2001; Donoso et al., 2003; Otsuka and Yamane, 2006).

The factors that influence the mechanical strength of tablets can be divided into three different groups: (1) material and formulation factors, (2) process factors, and (3) environmental factors. Formulation factors are due to the physical and chemical properties of particles. A process factor may include the equipment used and environmental factors the relative humidity and temperature of the air. In pharmaceutical systems interparticular interactions, triboelectricity, liquid and solid bridges, porosity, particle size and shape, and wetting may also be essential with regard to the mechanical strength of granular systems. The mechanical strength of tablets means the tablets' ability to resist breakdown. Tablets must remain intact until administration. In addition, they must be soft enough so that the active pharmaceutical ingredient can be released in the alimentary tract. The mechanical strength of tablets can be tested in many ways. The method most used in pharmaceutical technology is the diametral compression test. It is important to always use the same test, because this reveals information only on the force needed to breakdown the tablet, not how hard the tablet is. In addition, the size and shape of the tablet influence the mechanical strength. The test most used for mechanical strength is an indirect diametral compression test.

The scanning electron microscope (SEM) and non-contact laser profilometry (LP) were used to investigate tablet surface roughness (Riippi et al., 1998; Podczeck et al., 1999). Riippi et al. examined the effect of compression force on surface structure and tablet parameters, such as crushing strength and friability. They discovered that the surface roughness parameters characterize the tablet surface quite well and noted that the crushing strength of the tablets increased with increasing compression force. Podczeck et al. (1999) investigated tablets of five different compression formulations for their surface roughness, using SEM and LP. They found that the composition of a formulation not only influenced the tableting properties of the powder mixtures, but also the surface properties of the final product. An increase in tableting pressure reduced the tablet surface roughness. The assessment of surface roughness in three dimensions appeared more effective than a simple line profile measurement.

The primary objective of the present study was to determine the applicability of Raman spectroscopy for a rapid mechanical strength determination of intact tablets. LP and SEM methods were used as additional methods to visualise the tablet surface profile and show that Raman method to measure crushing strength of tablets is based on the surface profiles.

2. Materials and methods

2.1. Materials

Theophylline (TP, Ph. Eur.) powders (particle size 100 M and 200 M) (Fig. 1) were granulated in a fluid bed granulator (Glatt WSG 5, Glatt GmbH, Binzen, Germany). The granules were composed of TP anhydrate as an active substance and polyvinylpyrrolidone (PVP, Kollidon K25, BASF, Ludwigshafen, Germany) as a binder. Prior to compression, the granules were mixed with 0.5% (w/w) magnesium stearate (Ph. Eur.) for 3 min in a Turbula mixer with a mixing speed of 46 rpm. The tablets were compressed with an instrumented single-punch eccentric tableting machine (Korsch EK0, Erweka Apparatebau, Hausenstamm, Germany) with a rotating speed of 30 rpm using a feed shoe. Flat-faced 9-mm punches were used in the study. The flat punches were needed to enable the spectroscopic measurement from a straight surface without

disturbance of the convex surface. The tablets were compressed so that their crushing strengths were between 30 N and 200 N and the tablet weight was adjusted to 250 mg. There were five groups of crushing strengths (I–V). Each tablet was treated individually so that the response (crushing strength) could be linked to the corresponding spectra measured from the same tablet. The crushing strengths were measured with an indirect diametral hardness apparatus (Multicheck, Erweka GmbH, Heusenstamm, Germany).

2.2. Raman spectroscopy setup

The Raman spectra were collected using a Raman spectrometer (Control Development Inc., South Bend, IN, USA) equipped with a thermoelectrically cooled CCD detector and a fiber-optic probe (RamanProbe, InPhotonics, Norwood, MA, USA). A 500-mW laser source at 785 nm was used (Starbright 785S, Torsana Laser Technologies, Skodsborg, Denmark). The spectral range recorded was between 100 cm^{-1} and 2200 cm^{-1} with a 2-s integration time and by averaging three scans. At least 20 parallel tablets from each crushing strength group were measured, using Raman spectroscopy from the lower side of the tablets. During Raman measurement the tablet was rotated and the distance between the tablet surface and the probe was standardized (8 mm).

All the measurements concerning the same TP grade were performed within the same day, which prevented day-to-day variance in the results. Replicate measurements were also performed using two different procedures: (1) the tablet measured was removed from the rotating holder, then returned and remeasured, and (2) the tablet measured was rotated and several measurements performed, switching off the laser between measurements. The fluorescence did not interfere in this study because the materials were pure and the measurements performed in the dark under standardized conditions.

2.3. Partial least squares (PLS) regression

The multivariate calibration model was used to define the correlation between the spectra and the crushing strength of the tablets. In this study, partial least squares modeling served as a multivariate calibration model. It can be used to obtain qualitative and quantitative information from spectra that are usually difficult to obtain using traditional univariate methods. It can extract information from regions or entire spectra and is particularly useful for coping with cross-correlated and noisy data (Beebe et al., 1998). The spectral region between 400 cm^{-1} and 1730 cm^{-1} was used in the data analysis. PLS maximizes the covariance between the spectral data and known crushing strength data, so that as much useful information as possible is extracted from the spectra, while unrelated data are discarded (Aaltonen et al., 2007). PLS modeling was performed with SIMCA-P software (Umetrics, Umeå, Sweden). In this study every third spectrum was used to create the PLS model and the rest two thirds served as the test set. Hence, the spectra were collected and the model was tested equally for each crushing strength group. The parameters used to test the model performance were R^2 (correlation coefficient) and Q^2 (test set validation coefficient). The spectra gained were standardized using unit variance (UV) correction before PLS modeling.

2.4. Non-contact laser profilometry and scanning electron microscopy

The surface profile of the tablets, i.e. roughness, was also determined with non-contact LP (UBM Microfocus Optical Measuring System, UBM Messtechnik GmbH, Ettlingen, Germany), using three 100-M TP tablets from each crushing strength group. The image size was 2 mm × 2 mm and the measuring range was ±50 μm. The laser spot was 1 μm and the resolution 200 points/mm. The laser input was 0.2 mW and the wavelength 780 nm. After data collection, the image was leveled to remove slope caused by tilting of the tablet surface, using Ubsoft Software (v 2.8 DOS, UBM Messtechnik GmbH, Ettlingen, Germany). The roughness parameters were calculated from these corrected images. The most important of these were average roughness (R_a) and the root-mean-square roughness (R_q). These parameters were standardized and are presented in full detail in British Standard (1972) and in the UBM System Reference Guide (1995). The parameters described the tablet surface, using comparable numerical values which give better results than many other methods. The surface characteristics of the tablets were examined with contriving micrographs using Mathematica Software (vs 5.1, Wolfram Research Inc., Champaign, IL, USA). SEM images were measured with Zeiss DSM 962 scanning electron microscope (Oberkochen, Germany) and they were used to visually characterize the surface of the tablets.

Table 1
Characteristics of the theophylline tablets (results are expressed as the mean ± S.D., $n = 20$ per group)

	Weight (mg)	Thickness (mm)	Hardness (N)	Diameter (mm)
100-M				
I	250.3 ± 2.2	3.82 ± 0.02	29.1 ± 2.13	8.99 < 0.01
II	253.9 ± 4.5	3.19 ± 0.02	86.6 ± 8.66	9.00 < 0.01
III	258.8 ± 4.5	3.08 ± 0.03	120.3 ± 10.53	8.99 < 0.01
IV	275.7 ± 2.5	3.20 ± 0.03	148.6 ± 7.13	8.99 < 0.01
V	277.2 ± 3.1	3.14 ± 0.04	173.1 ± 7.50	8.99 < 0.01
200-M				
I	252.0 ± 3.7	3.88 ± 0.02	36.3 ± 2.75	8.96 < 0.01
II	261.0 ± 3.2	3.25 ± 0.02	110.3 ± 8.46	8.97 < 0.01
III	272.2 ± 1.7	3.22 ± 0.01	147.6 ± 5.83	8.97 < 0.01
IV	273.7 ± 1.3	3.15 ± 0.02	183.3 ± 5.33	8.97 < 0.01
V	268.0 ± 1.6	3.03 ± 0.03	206.8 ± 7.21	8.96 < 0.01

3. Results

Raman spectroscopy detected changes in the crushing strengths of two different grades of TP tablets, as did the SEM micrographs and LP. The diameters, weights, and crushing strengths of the tablets measured with the Multicheck apparatus are presented in Table 1.

3.1. Dependence of surface texture on mechanical strength of tablets

SEM and LP methods were used as additional methods to visually illustrate the tablet surface profile. The surface morphology and texture are related to the crushing strength of the tablets. This can be seen in the SEM (Fig. 2) and LP micrographs (Fig. 3) from the surfaces of the TP containing tablets. The SEM micrographs representing the tablets containing 200-M TP (Fig. 2), indicate that clear differences exist within the surface textures of the tablets depending on their crushing strength (i.e. the compression force applied in tableting). SEM micrographs were also taken from the tablets containing 100-M TP. Surface profiles of these tablets were very similar than in 200-M tablets (data not shown). As perhaps expected, the higher the crushing strengths of the tablets, the smoother were the surfaces of the tablets. Clear differences in the surface roughness properties of the tablets were observed in tablets compressed using lower compression forces (i.e. tablets with a crushing strength of less than 100 N). However, since the crushing strength of the tablets was 100 N or more, the differences in surface roughness

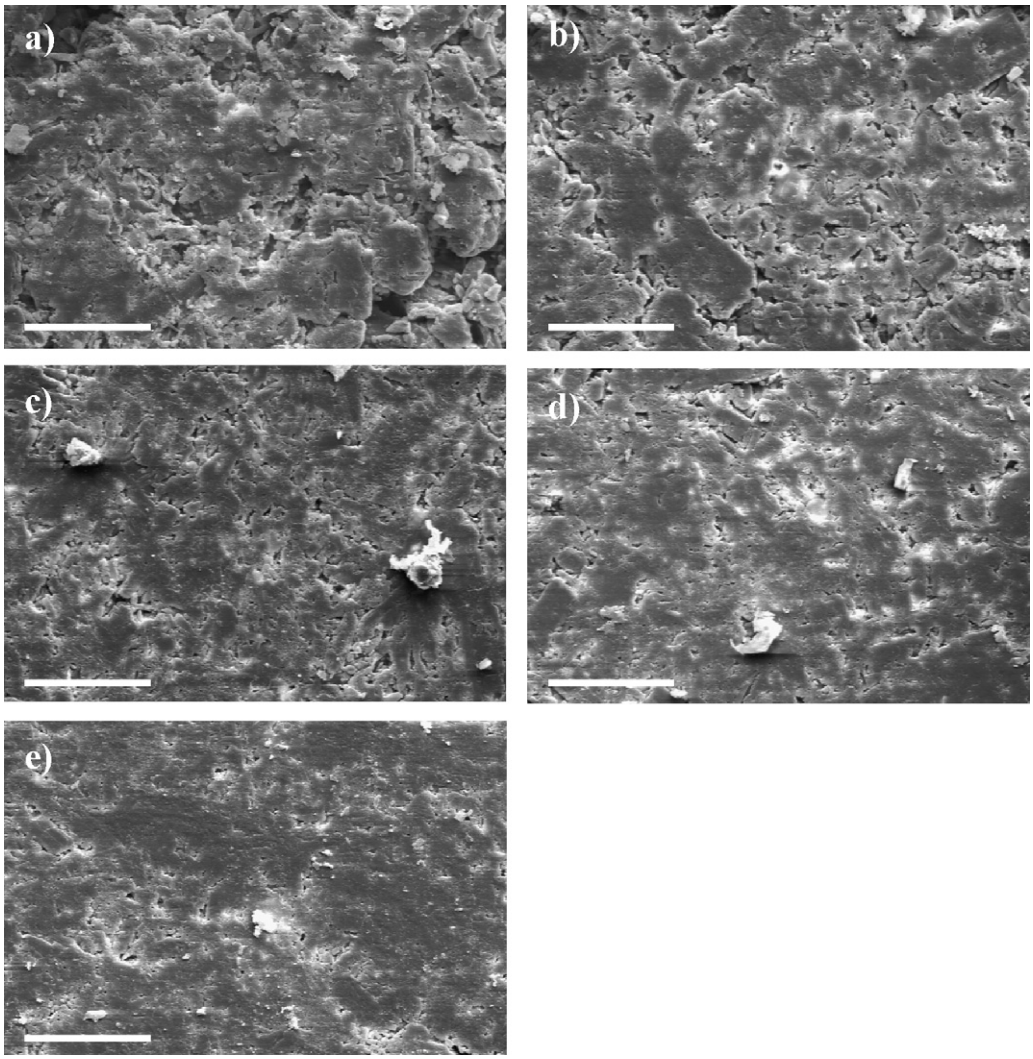

Fig. 2. The surface of theophylline-containing (TP 200-M) tablets became smoother as the compression force was increased. SEM images on tablets with crushing strengths of (a) 35 N, (b) 110 N, (c) 150 N, (d) 185 N, and (e) 205 N. Scale bar 50 μm.

properties within the tablets were no longer as evident. Application of higher compression forces in tableting, results in greater tendency for deformation and/or fragmentation of the individual powder particles and granules, thus making it more challenging to detect differences in the surface texture of the tablets.

The roughness of the surface of the TP (100-M) tablet can be seen from the images measured with non-contact LP. The 200-M tablets were not measured because LP is mainly a visual reference method in this study. The method is in some cases more efficient because quantitative roughness parameters can also be calculated in contrast to SEM images. The most informative roughness parameters in this setup were R_a, R_z, and R_q. The R_a is an average of the peaks and valleys of a surface, i.e. the arithmetic average roughness of the surface, R_z is an averaged profile depth, and R_q is a root-mean-square deviation of roughness. Both the images and the roughness parameter values were correlated with the crushing strength (Fig. 3 and Table 2). However, since the crushing strength of the tablets was 100 N or more, the differences in surface roughness properties within the tablets were no longer as evident. Crushing strength group I can be differentiated statically from the other groups ($p < 0.05$), but there were no statistical differences among the other groups ($p > 0.05$). The same phenomenon was also seen in the SEM images.

3.2. Correlation between tablet density and crushing strength

The average crushing strengths were plotted against the weight of the tablet divided by its thickness (w/t). The weight per thickness value was used to describe tablet density because the diameter of the tablets was the same. There was an exponential correlation between the crushing strength and w/t. The phenomenon was similar for both TP grades (Fig. 4). However, the 100-M curve was lower than the 200-M curve, suggesting that when the w/t is the same, the 200-M (i.e. the smaller particles) endure higher crushing force than the 100-M particles. This may be the result of increased interactions among the smaller particles during compression. Their surface area versus weight is higher than with the larger particles. TP is known to

Table 2
Roughness parameters measured with non-contact profilometry (results are expressed as the mean, $n = 3$)

100-M	R_z	R_a	R_q
I	56.5	3.3	5.1
II	29.9	1.4	2.1
III	18.7	1.1	1.5
IV	15.4	1.0	1.3
V	12.6	1.1	1.4

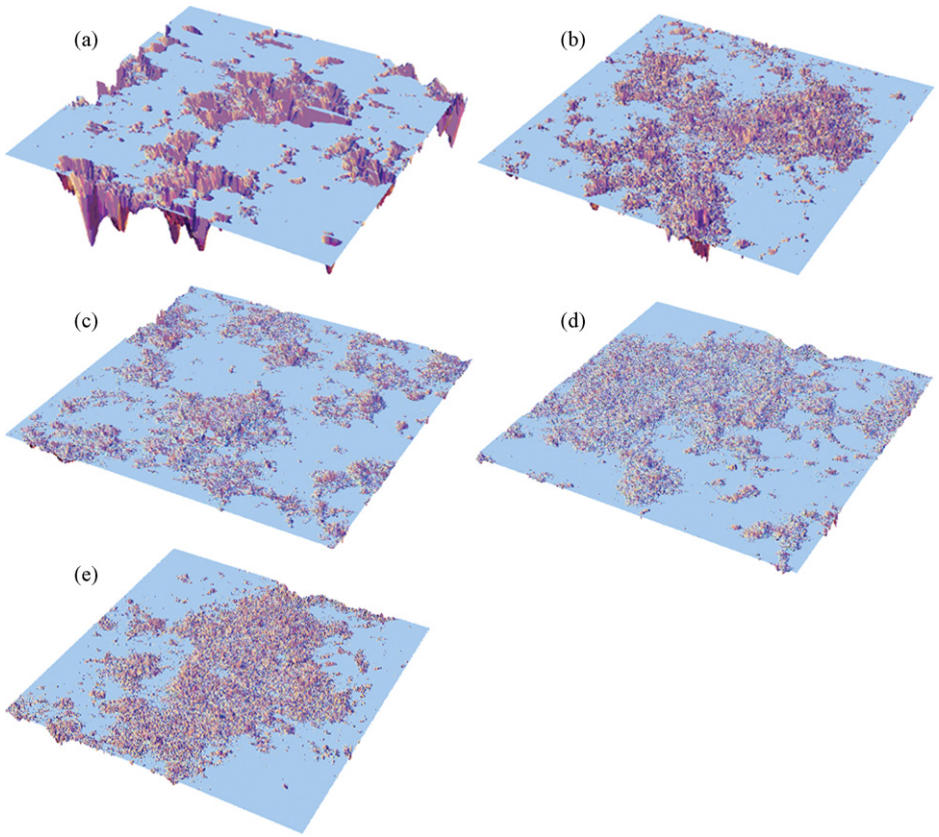

Fig. 3. Surface profiles of the TP tablets (100-M) measured using non-contact laser profilometry. (a) Crushing strength group I, (b) group II, (c) group III, (d) group IV, and (e) group V.

be a plastic material (Suihko et al., 2001), which supports this suggestion. The correlation enables prediction of the crushing strength of the tablets using weight and the thickness of the tablet.

3.3. Raman spectroscopy

Raman spectroscopy was examined as an alternative vibrational spectroscopy technique in determining the mechanical strength of the TP tablets; it can detect increases in crushing strength mainly as a smoothing of the tablet surface. When the compression force is high, the surface of the tablet is smoother and there are fewer pores in the tablet. When the compression force increases, the structure of the material condenses as the interfaces between air and the material decrease. In this case, the Raman radiation can penetrate the material more easily because the interfaces are diminished, which decreases scattering from the surface. In the present study we used organic materials, for which compaction is not as severe as for inorganic materials. The measurement was based on the smoothness of the surface; when the surface is smoother the radiation scatters more efficiently because it will not go into the cavities.

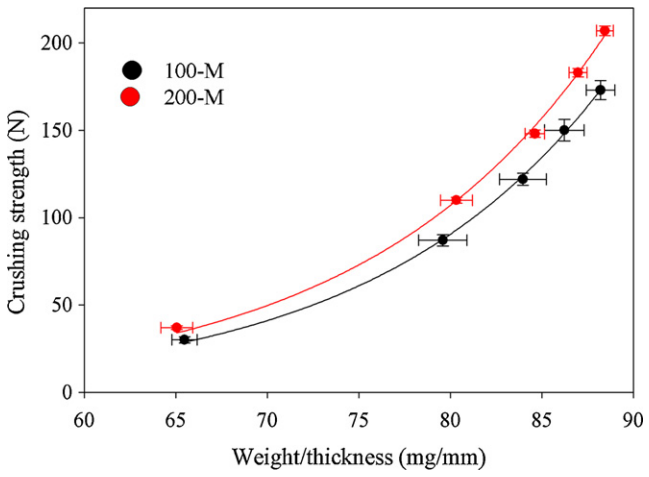

Fig. 4. Correlation between the crushing strength and weight/thickness of the tablets.

No specific peaks in the spectra were sensitive enough to detect changes in the crushing strength values of the tablets, due to baseline shifting which occurs evenly throughout the spectra (Fig. 5). Since the crushing strength is a physical property, one must be careful that preprocessing of the spectra will not destroy the information. Typical preprocessing methods such as mean centering and corrections such as standard normal variation (SNV), multiplicative scatter correction (MSC), and the derivates cannot be used because they lose the baseline-shifting information. The data can be modeled as such or after normalization.

The correlation between the crushing strengths measured with the Multicheck apparatus and with Raman spectrometry was studied, using multivariate modeling. The PLS model was completed, using four principal components (PCs) for both TP grades after UV processing. The modeling gave four PCs for both TP grades. All four components explained 82.7% of the X-variance for the 100-M grade and 98.8% of the X-variance for the 200-M grade. In addition, the X-residuals were small and non-systematic (data not shown), suggesting that the model is able to describe the systematic variation in Raman spectra of the tablet surfaces. The Q^2 value, which describes the goodness of prediction and the predictive ability of the model,

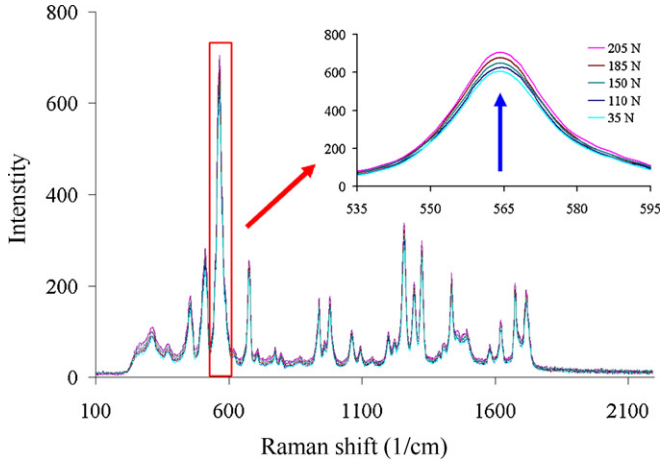

Fig. 5. Raman spectra of the theophylline tablets. The measured spectra (100–2200 cm^{-1}) and magnification from one peak to show the baseline shifting. The intensity increase, which correlates with increase in the crushing strength, is marked with blue arrow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

was 0.839 for 100-M TP and 0.864 for TP 200-M and R^2 values were 0.970 for TP 100-M and 0.951 for TP 200-M. In addition, the loadings for PC 1 substantially resembled the Raman spectra (data not shown). The replicate measurements were also performed using two different procedures: (1) the tablet measured was removed from the rotating holder, then returned and remeasured, and (2) the tablet measured was rotated and several measurements performed, switching off the laser between measurements. Predicted values corresponding these measurements were determined using PLS model and the relative standard deviation (R.S.D.) was calculated. The R.S.D. for the first procedure was 1.02 and for the second procedure 0.95. These results indicate that the measurements were repeatable.

The correlation between the measured and predicted crushing strength values (Raman spectra) for TP tablets is shown in Fig. 6. The results were averaged because actual crushing strength measurement is not possible. For example, alignment of the tablet affects the result when conventional crushing strength equipment is used. If it were possible to measure the same tablet many times with the diametral crushing strength apparatus, the result could be different each time. The standard deviations of the measured and predicted crushing strength values were determined. The Raman spectra were obtained for both TP grades and were very similar (Fig. 6). The values for R^2 were 0.997 and 0.999, thus indicating that the correlation between the crushing strength data for the present TP tablets and the Raman spectra applied was excellent.

To determine whether the Raman technique detects the crushing strength of the TP tablets as smoothness of the surface or whether it detects the structure and bonding in the tablet, we also measured Raman spectra from the plane of fracture of the tablets. The tablets were halved and the spectra measured from the plane of fracture, using a rotating sample. The obtained data were UV-corrected and PLS-modeled. No correlation was found with either of the TP tablet grades. In conclusion Raman spectroscopy detects the crushing strength of the TP tablets as a smoothing of the tablet.

4. Discussion

The results obtained are consistent with the KM theory (Kubelka and Munk, 1931), but contrasted with the results of Wang et al. (2002). In their measurement, the Raman intensity decreased with increasing compression force until a constant density was formed. Wang et al. assumed that when the pressure increases, the space between the particles decreases, which leads to increasing density. In the Raman signal this could be seen as a decrease in intensity. This is in contrast to the expected results and the KM theory because the assumption was that the amount of those molecules from which the Raman radiations scatter is increasing, so that the Raman intensity should increase as well. In their measuring system, the Raman intensity decreased with increase in diffuse reflectance. This occurred because the diffuse reflectance decreases gradually, until the particles form an almost homogenous sample when the pressure increases. The transparency of compacted samples increases with increase in compression, especially in inorganic samples, which Wang et al. used. The greatest differences between our study and that of Wang et al. were (1) the material used, (2) the measuring geometry, and (3) the distance between the probe and the sample. The wavelength and compression force can also affect the intensity of the Raman signal. These results indicate strongly that determination of the crushing strength of tablets, using Raman spectroscopy, demands a very accurate method. The results always depend on the set-up and the material used. Hence, every formulation demands its own model and production parameters have to be constant. For instance, if there is a change in compression process during the tableting, which causes capping or sticking, the Raman method for measuring crushing strength cannot be utilised. Generally, the present Raman method can be used when the surfaces of the tablets will not alter after successful compression process.

Raman spectroscopy is applicable as a rapid and non-invasive method for predicting the crushing strength of tablets. The Raman technique detected the increase in crushing strength mainly as a smoothing of the tablet surface. The intensity of the Raman signal increased with increase in the crushing strength of the TP tablets. The surface roughness of the TP tablets was observed in images measured with non-contact LP and SEM. The surface roughness values were calculated and correlated with the changing mechanical strength of the tablets. The results obtained indicate strongly that determination of the crushing strength of tablet using

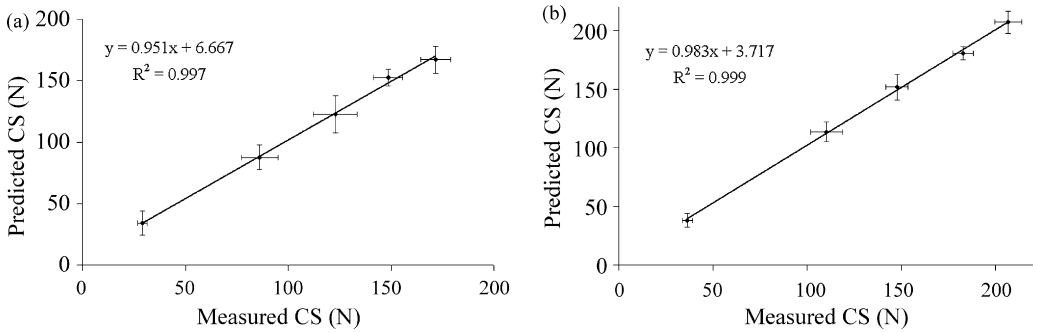

Fig. 6. Correlation between measured and predicted crushing strengths of the theophylline tablets with standard deviations. (a) 100-M and (b) 200-M.

Raman spectroscopy, demands a very accurate method. The present results suggest that Raman spectroscopy, among other vibrational spectroscopy techniques, is a promising analytical tool for non-destructive determination of tablet hardness.

Acknowledgment

Orion is acknowledged for the support of this research. Sari Airaksinen and Heikki Räikkönen are acknowledged for contributing this study.

References

Aaltonen, J., Kogermann, K., Strachan, C.J., Rantanen, J., 2007. In-line monitoring of solid-state transitions during fluidization. Chem. Eng. Sci. 62, 408–415.

Beebe, K.R., Pell, R.J., Seasholtz, M.B., 1998. Chemometrics: A Practical Guide. John Wiley and Sons, New York.

British Standard 1134, 1972. Method for the Assessment of Surface Texture. British Standard Institution London.

Chen, Y., Thosar, S.S., Forbess, R.A., Kemper, M.S., Rubinovitz, R.L., Shukla, A.J., 2001. Prediction of drug content and hardness of intact tablets using artificial neural network and near-infrared spectroscopy. Drug Dev. Ind. Pharm. 27, 623–631.

Donoso, M., Kildsig, D.O., Ghaly, E.S., 2003. Prediction of tablet hardness and porosity using near-infrared diffuse reflectance spectroscopy as a nondestructive method. Pharm. Dev. Technol. 8, 357–366.

Ebube, N.K., Thosar, S.S., Roberts, R.A., Kemper, M.S., Rubnovitz, R., Martin, D.L., Reier, G.E., Wheatley, T.A., Shukala, A.J., 1999. Application of near-infrared spectroscopy for non-destructive analysis of Avicel powders and tablets. Pharm. Dev. Technol. 4, 19–26.

Fangxin, L., Jinlong, Y., Tianpeng, Z., 1997. Raman and Fourier infrared photoacoustic spectra of granular ZrO_2. Phys. Rev. B 55, 8847–8851.

Hu, Y., Wikström, H., Byrn, S.R., Taylor, L.S., 2006. Analysis of the effect of particle size on polymorphic quantitation by Raman spectroscopy. Appl. Spectrosc. 60, 977–984.

Johansson, J., Pettersson, S., Folestad, S., 2005. Characterization of different laser irradiation methods for quantitative Raman tablet assessment. J. Pharm. Biomed. Anal. 39, 510–516.

Kirsch, J.D., Drennen, J.K., 1999. Nondestructive tablet hardness testing by near-infrared spectroscopy: a new and robust spectral best-fit algorism. J. Pharm. Biomed. Anal. 19, 351–362.

Kubelka, P., Munk, F., 1931. Ein Beitrag zur optic der farbanstriche. Zeits. f. Tech. Physik 12, 593–601.

Kubelka, P., 1948. New contributions to the optics of intensity light-scattering materials. Part I. J. Opt. Soc. Am. 38, 448–457.

Lombardi, D.R., Wang, C., Sun, B., Fountain, A.W., Vickers, T.J., Mann, C.K., Reich, F.R., Douglas, J.G., Crawford, B.A., Kohlasch, F.L., 1994. Quantitative and qualitative analysis of some inorganic compounds by Raman spectroscopy. Appl. Spectrosc. 48, 875–883.

Morisseau, K.M., 1996. The effect of compression force on the near-infrared spectra of tablet dosage forms. Ph.D. Theses. University of Rhode Island, U.S.A.

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

Otsuka, M., Yamane, I., 2006. Prediction of tablet hardness based on near-infrared spectra of raw mixed powders by chemometrics. J. Pharm. Sci. 95, 1425–1433.

Pellow-Jarman, M.V., Hendra, P.J., Lehnert, R.J., 1996. The dependence of Raman signal intensity on particle size for crystal powders. Vibr. Spectrosc. 12, 257–261.

Picker-Freyer, K.M., Schmidt, A.G., 2004. Does temperature increase induced by tableting contribute to tablet quality? J. Therm. Anal. Calorim. 77, 531–539.

Podczeck, F., Brown, S., Newton, M., 1999. The influence of powder properties and tabletting conditions on the surface roughness of tablets. Part. Part. Syst. Char. 16, 185–190.

Riippi, M., Antikainen, O., Niskanen, T., Yliruusi, J., 1998. The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. Eur. J. Pharm. Biopharm. 46, 229–245.

Schrader, B., Hoffmann, A., Keller, S., 1991. Near-infrared Fourier transform Raman spectroscopy: facing absorption and background. Spectrochim. Acta 47A, 1135–1148.

Suihko, E., Lehto, V.P., Ketolainen, J., Laine, E., Paronen, P., 2001. Dynamic solid-state and tableting properties of four theophylline forms. Int. J. Pharm. 217, 225–236.

Szostak, R., Mazurek, S., 2002. Quantitative determination of acetylsalicylic and acetaminophen in tablets by FT-Raman spectroscopy. Analyst 127, 144–148.

UBM Messtechnik GmbH, 1995. Microfocus Non-contacting Measurements (brochure). UBM Messtechnik GmbH, Ettlingen.

Wang, H., Mann, C.K., Vickers, T.J., 2002. Effect of powder properties on the intensity of Raman scattering by crystalline solids. Appl. Spectrosc. 56, 1538–1544.

Williams, A.C., Cooper, V.B., Thoman, L., Griffith, L.J., Petts, C.R., Booth, S.W., 2004. Evaluation of drug physical form during granulation, tableting and storage. Int. J. Pharm. 275, 29–39.