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Photoacoustic evaluation of elasticity and integrity of pharmaceutical tablets ☆

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Abstract

A nondestructive method based on pulse photoacoustics was applied for evaluation of elasticity and integrity of pharmaceutical tablets. Variations in porosity, density and sodium chloride content of microcrystalline cellulose tablets were found to be related to parameters extracted from the through-transmitted ultrasonic wave forms. By using the amplitudes and ultrasonic velocities of these wave forms, it was possible to obtain values of a transverse to longitudinal amplitude ratio, and also elastic parameters, such as Young's and shear moduli, for the tablets. Poisson's ratio was calculated from the elastic moduli as well as from the amplitudes. An exponential relationship between tablet porosity and the attenuation of longitudinal wave form was noticed. The transverse to longitudinal amplitude ratio and the amplitudinal Poisson's ratio were indicative of structural variations, e.g., changes in the porosity and the sodium chloride content of tablets. Young's and shear moduli of microcrystalline cellulose tablets were found to follow similar porosity trends to those in previously published beam bending and twisting studies, although the absolute values and the values extrapolated to zero porosity were slightly smaller. The Poisson's ratio calculated from the experimental Young's and shear modulus values was also in agreement with earlier studies, but the values extrapolated to zero porosity differed significantly. The method is a promising tool for evaluating the elastic properties of tableting materials and the structural variations in tablets.

Keywords: Tablet; Porosity; Elastic properties; Nondestructive testing; Photoacoustics; Ultrasound

1. Introduction

Changes in mechanical structure can affect the physical and biopharmaceutical properties, and in some cases even the chemical stability, of pharmaceutical tablets (Kitazawa et al., 1975; Hersey and Krycer, 1980). Elastic properties of tableting materials as well as mechanical integrity and internal structure variations affecting the mechanical structure of tablets are usually evaluated with conventional mechanical testers and by microscopic methods. These methods are usually rather slow and laborious to operate and destructive of

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the samples. The three-and four-point bending techniques are commonly used in determining elastic properties, mainly Young's modulus, of pharmaceutical materials. The bending method itself is not very laborious, but the manufacture of the beam specimens is rather time-consuming and the quality of the beams is not always satisfactory (Raatikainen et al., 1994). In recent years, some nondestructive evaluation methods have been introduced to tableting technology. These methods have been based, e.g., on infrared thermography and optics, and are used mainly in the evaluation of the temperature increase and energy expenditure during the tableting process (Bechard and Down, 1992; Ketolainen et al., 1993) or to study the surface and coating properties of pharmaceutical tablets (Wakimoto and Otsuka, 1986; Healy et al., 1994; Twitchell et al., 1994). Radebaugh et al. (1989) used a dynamic mechanical tester (dynamic spectrometer) in studying viscoelastic properties of rectangular beams that could be considered nondestructive, but hitherto, autoradiography has been almost the only nondestructive method used to investigate density or porosity variations in intact, tablet-like compacts (Macleod and Marshall, 1977). Unfortunately, this method can be used only for test materials, and not for real pharmaceutical tablets and it does not give any information on elastic properties of compacts.

In photoacoustics the ultrasound is generated by means of pulsed laser illumination. Normally photoacoustical methods are used in applications where a touching ultrasonic transducer would damage the sample or it itself would be damaged. This can be the case with porous and hygroscopic systems, e.g., pharmaceutical tablets, where the use of a coupling liquid would be detrimental to the structure of the tablets. Despite its low efficiency in producing ultrasound, the so-called thermoelastic regime is attractive in many applications, because the phenomenon is nondestructive to the samples and the theory of such nondestructive testing is well established (Berthelot, 1989; McDonald, 1989). Systems comparable to pharmaceutical tablets, e.g., non-sintered ceramics, have been successfully studied by several authors using photoacoustic sound generation without coupling liquids (e.g., Oksanen and Luukkala, 1990; Lindgren and Rosen, 1993).

The evaluative method for pharmaceutical tablets presented in this paper is based on deriving parameters from the through-transmitted thermoelastically generated sound pulses. Further, these parameters are empirically related to known structural properties of the tablets. The aim of this study was to assess the applicability of the photoacoustic method.

2. Experimental

2.1. Theoretical background

Photoacoustic sound generation in the case of pulsed surface illumination is the method used in this study (Fig. 1). The energy of the laser pulse is absorbed at the surface of the sample; the spatial shape and temporal propagation of the illumination is explained by the surface center of expansion (SCOE) theory (Rose, 1984). It predicts the form of the on-axis epicentre sound wave detected at the other side of the sample. The most pronounced and easily detectable portions of the expected wave form consist of a longitudinal wave step with an amplitude S_L and a transverse shear wave step with an amplitude S_T. From the arrival times, the respective velocities of sound can be determined. When the surface of the sample is illuminated by the laser pulse, the ultrasound pulses generated at the surface of the sample, are transmitted through it to a thin, adhesive plastic tape layer ($d << \lambda$, where d is layer thickness and λ denotes ultrasonic wavelength), and then further transmitted through the acoustical delay

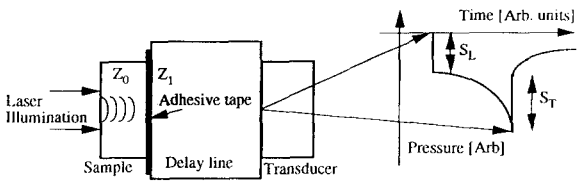

Fig. 1. Photoacoustic energy passing through a tablet and a theoretical wave form as a function of time. Terms are explained in the text.

line to the ultrasound transducer. Rose (1984) showed that the ratio of the pulse amplitudes S_T and S_L at the free opposite surface of the sample is a function of the Poisson's ratio. This applies absolutely only for a free surface but can be used here since the acoustic impedance of the sample Z_0 is much higher than the acoustic impedance of the soft plastic layer Z_1 and therefore the loading of the surface is minimal. Solving for the amplitudinal Poisson's ratio, v, gives (Rose, 1984):

$$v = \frac{2S_L + S_T}{2(S_L + S_T)} \quad (1)$$

The modulated Poisson's ratio obtained from Eq. (1) can be used as a parameter in comparing different samples. Both the Poisson's ratio, v, and the transverse to longitudinal amplitude ratio, S_T/S_L, are relative parameters that do not require absolute measurements of time or amplitude. They can be determined concurrently from the same wave since both types of wave forms are generated. This is an attractive feature for practical purposes. However, it should be noted that this measurement does not give the true Poisson's ratio, but rather a parameter that is the actual Poisson's ratio multiplied by an unknown function of the amplitudes S_T and S_L (Rose, 1984). However, this does not affect the usefulness of the parameter, referred to in this paper as an amplitudinal Poisson's ratio, as a stable, comparative parameter.

The detected signal can be approximated by the convolution of the transducer impulse response with a signal that only contains the two steps, as shown in Fig. 1. The qualitative simulation for the wave forms was performed by taking $S_T/S_L = 2$ and assuming that the transducer response is Gaussian. This gives adequate background information to identify the pulses in the experimental wave form. A convoluted wave form and a typical measured wave form at the delay line-transducer interface are shown in Fig. 2.

The actual longitudinal and transverse transit times can be recorded and Young's modulus, E, and shear modulus, G, can be calculated. If both of the velocities of sound for the longitudinal and transverse components, C_L and C_T, respectively

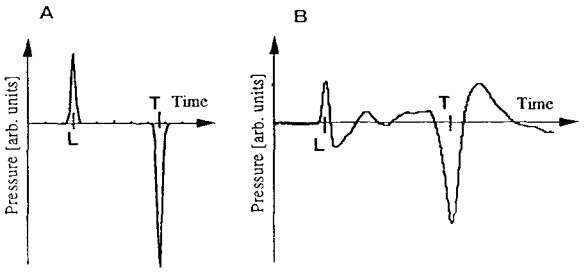

Fig. 2. (A) Theoretical wave form convoluted from the system response and (B) an experimental wave form. L and T are the first arrivals of the transmitted longitudinal and transverse pulses, respectively.

(Fig. 2), and the apparent density of the sample, ρ, are known, E and G can be found from (Rose, 1984):

$$E = 2G\left(1 + \frac{2 - (C_L/C_T)2}{2 - 2(C_L/C_T)^2}\right) \quad (2)$$

and

$$G = C_T^2\rho \quad (3)$$

Using the elastic moduli, E and G, the Poisson's ratio, v, can be found from:

$$v = (E/2G) - 1 \quad (4)$$

2.2. Measurements

The experimental arrangement used for the evaluation of pharmaceutical tablets is shown in Fig. 3. The laser used was an adjustable energy Nd:YAG laser (JK Laser System 2000, JK Laser, UK). The energy used was 100 mJ for the untreated tablet surfaces and 10 mJ for tablets

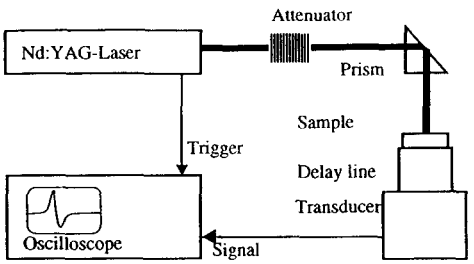

Fig. 3. Experimental arrangement used for photoacoustical measurements.

Table 1
Porosities (%), mean weights (mg) and NaCl contents (%) of microcrystalline cellulose tablets

Sample set no.	Porosity (%)	Weight (mg)	NaCl content (%)
1 [a]	47.1	254	0
2 [a]	41.0	283	0
3 [a]	34.1	316	0
4 [a]	27.3	349	0
5 [a]	21.7	376	0
6 [a]	18.6	390	0
7	12.6	417	0
8	13.6	416	1
9	14.1	414	2
10	14.1	415	3
11	14.1	417	4
12	14.0	418	5
13	14.2	423	7.5
14	12.7	427	10

All values are the means of 10 tablets. In the elastic parameter measurements, plastic tape layer was applied to both sides of tablets marked [a].

covered with an adhesive tape (Fig. 1; Table 1). The unfocused beam diameter was 5 mm and the laser pulse duration 60 ns. Unfocused light was used in order to give a spatial average of the sample properties. The photoacoustic signal was detected at the opposite side of the delay line with a 1–8 MHz wide-band piezoelectric transducer (S 12 HB 1-8, Karl Deutsch, Germany) connected to the oscilloscope (TEK 2430, Tektronix Inc., USA). The length of the delay line in the experiments was 25.0 mm and the material was brass.

2.3. Sample preparation and adjustment for measurements

Three batches of tablets were made from microcrystalline cellulose (Avicel PH 102, FMC Corp., USA), which is a typical white particulate tablet excipient, mixed with sodium chloride (mean particle size 315 μm). The material densities of Avicel and sodium chloride, determined by a pycnometer method (Multipycnometer MVP-1, Quanta Chrome, USA) using helium as an inert gas, were 1.60 and 2.17 g/cm^3, respectively. All the tablets, 13 mm in diameter, were compressed to a constant thickness of 2.4 mm with an instrumented Korsch EK-0 DMS (Korsch Maschinenfabrik, Germany) eccentric tablet press using flat-faced punches.

For sample sets 1–7 (in Table 1), the porosity of the tablets was controlled by varying the weight of the powder and the pressure at which they were compressed (from 27.9 to 203.5 MPa) causing the porosity to vary from 47.1 to 12.6%. Sample sets 1–6 were used for determination of elastic parameters and attenuation of longitudinal sound. In sample sets 8–14 (Table 1), sodium chloride was used as a hygroscopic test material, its content varying from 1 to 10% w/w in tablets compressed at a pressure of 203.5 MPa. The sample sets 15–17 (Table 2) with varying NaCl contents were aged for 24 h at 60% relative humidity at room temperature and were compared with samples of the same batch stored in air-tight containers at the same temperature.

There were 10 replicates in each set: the measured parameter values were averaged. Typical wave forms with both longitudinal and transverse components are given in Fig. 4. Sample sets 1–6 were measured by applying an adhesive tape on both sides of the tablet to enhance the shear wave signal for easier transit-time measurement.

Table 2
NaCl content (%), weight (mg), porosity (%) and amplitude ratio of transmitted transverse and longitudinal (S_T/S_L) ultrasound wave forms for microcrystalline cellulose tablets compressed at 203.5 MPa

Sample set no.	NaCl (%)	Weight (mg)	Porosity (%)	S_T/S_L
15 A	0	417	12.6	1.70
16 A	10	421	12.7	0.59
17 A	25	455	12.3	0.26
15 B	0	442	18.2	0.87
16 B	10	579	19.6	0.58
17 B	25	621	17.6	0.24

Measurements were made after storage for 24 h in airtight containers (A) or under a relative humidity of 60% (B). All values are the means of 10 tablets.

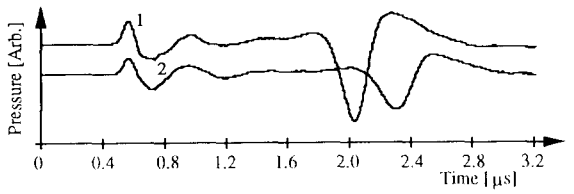

Fig. 4. Typical measured wave forms, on an arbitrary pressure scale, for microcrystalline cellulose tablets with porosities of 12.6% (1) and 27.3% (2) as a function of time (μs).

Amplitudes of the signal peaks varied less than ±5% from one sample to another within the set of 10 similar samples.

3. Results and discussion

The amplitude ratio of the transverse pulse to the longitudinal pulse, S_T/S_L, and the amplitudinal Poisson's ratio (Fig. 5) were determined for pure microcrystalline cellulose tablets at six different porosities (sample sets 1–5 and 7) and with seven different NaCl contents (sample sets 8–14) (Table 1). Below a porosity of 40%, the transverse pulse can be reliably detected, but with porosities higher than 40%, it is too small for practical use. The attenuation of the transverse pulse amplitude became more pronounced (Fig. 5A), thus decreasing the amplitude ratio, S_T/S_L, with increasing porosity, especially in the porosity range of 20 to 40%. With microcrystalline cellulose, this is approximately the porosity range where the internal stress patterns, as well as the structure of the tablet, as reflected by its mechanical strength, are reported to change most dramatically (Pesonen et al., 1989b; Pesonen and Paronen, 1990). The effect of porosity change can also be seen from the amplitudinal Poisson's ratio curve.

For tablets containing NaCl, the S_T/S_L ratio did not track small changes in the NaCl content when it was below 7%, but larger contents were easily detectable (Fig. 5B). This behaviour was most probably due to the relatively large particle size of the NaCl used, which would allow the pulse to circumvent the NaCl grains via intact tablet matrix. At 7% or more, the NaCl grains probably affect more the transmittance of the transverse pulse, the increasing attenuation being seen as a decrease in S_T/S_L values, because the transverse pulse is more prone to disturbance than the usually more linearly attenuating longitudinal component. The increase in tablet weight might also have affected the attenuation of the transverse component, and this could change the amplitudinal Poisson's ratio significantly.

Table 2 shows that humidity exposure clearly affected tablets that had strong transverse components before the aging took place (0% NaCl/203.5 MPa) and that the change was less pronounced in tablets containing sodium chloride. The increase in porosity and the change in S_T/S_L ratio (Table 2) can be explained as being due to expansion and loosening of microcrystalline cellulose tablets because of absorbed

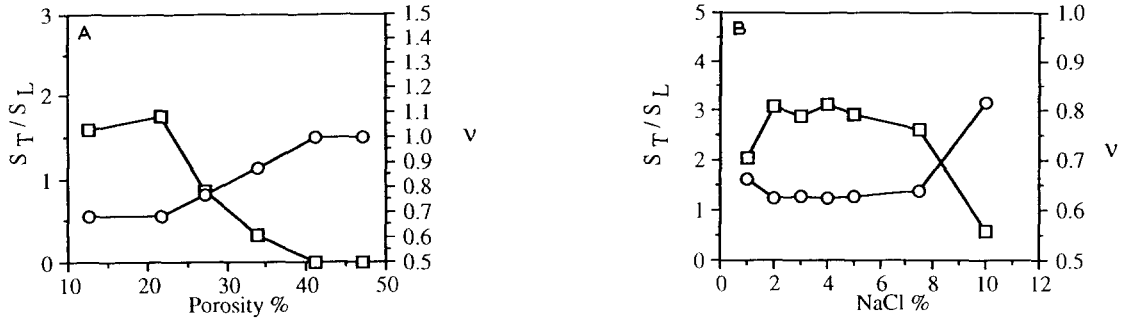

Fig. 5. Ratio of transverse and longitudinal wave form amplitudes, S_T/S_L, (□) and amplitudinal Poisson's ratio, ν, (○) as a function of porosity (%) (A) and NaCl content (%) (B) for microcrystalline cellulose tablets.

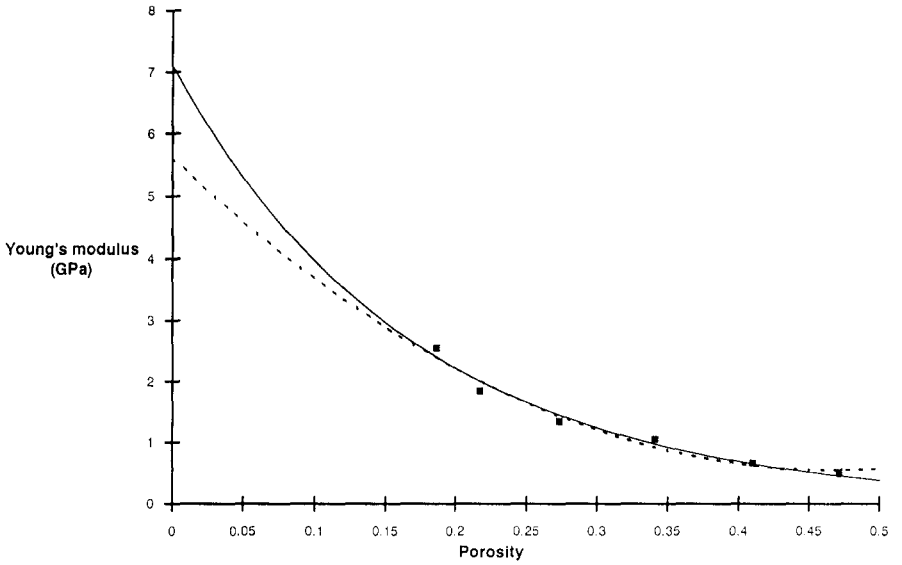

Fig. 6. Experimental (■), Spinner (dashed line) and Spriggs (solid line) fitted Young's modulus values (GPa) as a function of porosity for microcrystalline cellulose tablets.

moisture (Pesonen et al., 1989a). The less significant change in S_T/S_L values for tablets containing large amounts of sodium chloride might be due to the dominating effect of sodium chloride grains in the attenuation of ultrasound. Thus, the expansion of the microcrystalline cellulose tablet matrix had no pronounced effect on the S_T/S_L values.

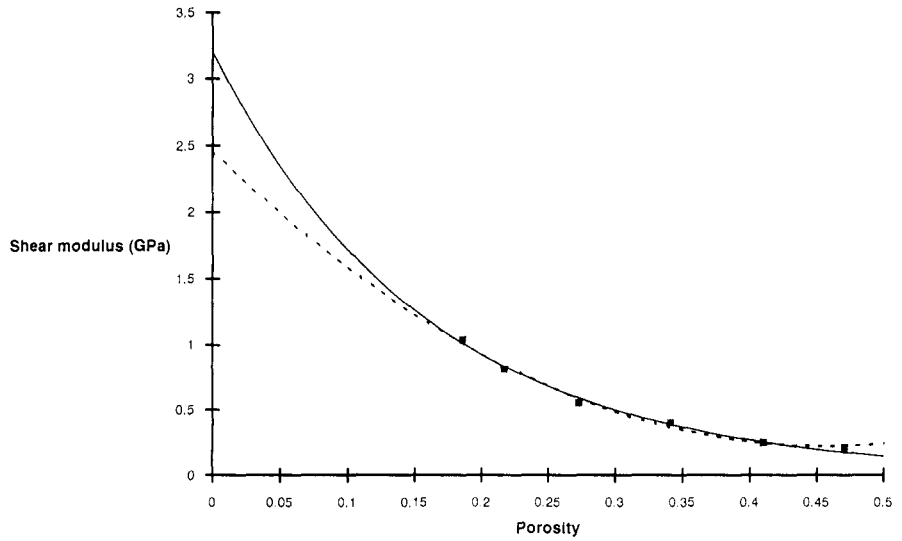

Fig. 7. Experimental (■), Spinner (dashed line) and Spriggs (solid line) fitted shear modulus values (GPa) as a function of porosity for microcrystalline cellulose tablets.

The elastic parameters, Young's modulus and shear modulus, were determined for six different tablet porosities (sample sets 1–6; Table 1). It can be seen from Figs. 6 and 7 that values of both elastic parameters decreased with increasing porosity, which is in agreement with the results obtained by twisting or bending of microcrystalline cellulose beams (Radebaugh et al., 1989; Bassam et al., 1990; Roberts et al., 1994). The previously reported values of Young's and shear moduli obtained for beams were slightly bigger than those obtained in this study. Both elastic moduli were extrapolated to zero porosity with the quadratic Spinner and exponential Spriggs equations to obtain values describing the intact sample elasticity (Spriggs, 1961; Spinner et al., 1963). The Spinner and Spriggs equations are:

$$X = X_0(1 - BP + CP^2) \quad (5)$$

and

$$X = X_0 \exp(-BP) \quad (6)$$

respectively, where X is the elastic modulus in question, P porosity, and B and C are constants. The Young's (E_0) and shear modulus (G_0) values at zero porosity for Avicel PH102 were 5.62 and 2.46 GPa using the Spinner, and 7.09 and 3.20 GPa using the Spriggs equation, respectively (Figs. 6 and 7). With microcrystalline cellulose the E_0 values have been reported to be in the range of 7.13–9.43 GPa (Bassam et al., 1990). The correlation coefficients and the constants of the Spinner and Spriggs fittings are presented in Table 3. The Poisson's ratios calculated using the experimental Young's and shear moduli for each porosity were all in the range of 0.23–0.34, with only one exception, in rather good agreement with the study reported by Roberts et al. (1994)

Table 3
Correlation coefficients (r) and constants, B and C, of the Spinner and Spriggs equations in the fitting of Young's and shear modulus

	Fitting equation	
	Spinner	Spriggs
Young's modulus		
r	0.9867	0.9887
B	3.846	5.809
C	4.110	–
Shear modulus		
r	0.9959	0.9960
B	3.983	6.201
C	4.353	–

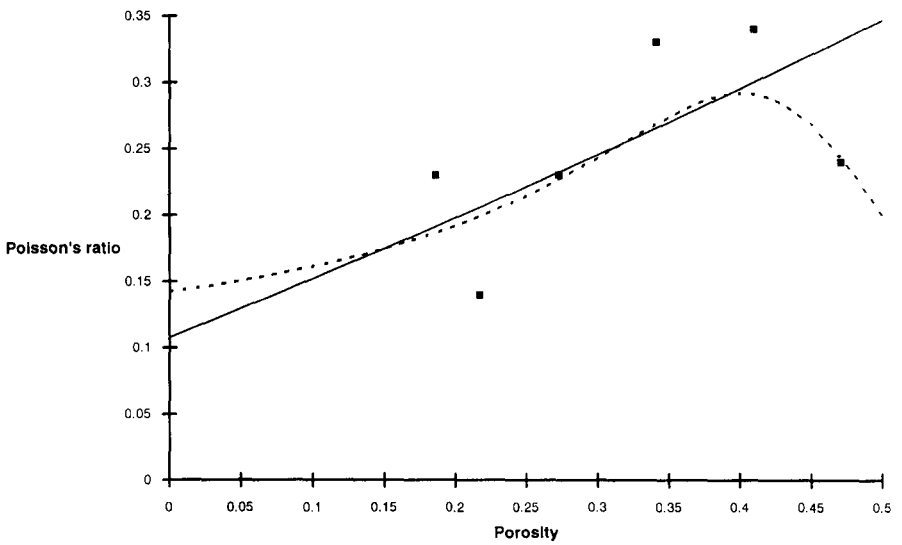

Fig. 8. Poisson's ratio values as a function of porosity for microcrystalline cellulose tablets calculated from the experimental Young's and shear moduli (■), and fitted with Spinner (dashed line) and Spriggs (solid line) equations.

(Fig. 8). The Poisson's ratios extrapolated to zero porosity with the Spinner and Spriggs equations were 0.14 and 0.11, respectively. These values do not compare with the Poisson's ratio (0.30) calculated using the Spinner equation by Roberts et al. (1994). This is most probably due to the extreme sensitivity of Poisson's ratio calculations to small errors or changes in measured values or in extrapolation to zero porosity. Roberts et al. (1994) used in their calculations E_0 and G_0 values of 9.08 and 3.49 GPa, respectively. Interestingly, the Poisson's ratio curve fitted with Spinner equation followed more closely the porosity trend of the Poisson's ratio calculated using the amplitudes of the transverse and the longitudinal pulse components (Figs. 5A and 9). Fig. 8 shows the fact mentioned earlier that at higher porosities than 40%, the method fails, but also that the range where Spinner and Spriggs fits are close to one another is also that where the internal structure and stress pattern changes are reported to be the most dramatic (Pesonen et al., 1989b; Pesonen and Paronen, 1990). The differences in measured and calculated elastic parameters, including Poisson's ratios, compared to those previously reported are most probably due to the differences in methods, but possibly also due to the fact that compressed beams and tablets are not structurally identical, tablets being definitely more homogeneous than compressed beams.

Lindgren and Rosen (1993) found a good correlation between ultrasonic velocity and density for non-sintered ceramics. For tablets, the porosity can be related to the attenuation of longitudinal wave, which was obtained by measuring the peak-to-peak amplitude, i.e., the distance from the highest to the lowest point, of the transmitted signal for the first pulse (Fig. 2B). This attenuation was measured for sample sets 1–6 (Table 1). A clear correlation between porosity and attenuation can be seen in Fig. 9. From the empirical results, it can be seen that the attenuation decreased exponentially with decreasing porosity, and the correlation being:

$$S_{P\_P} = M \exp(-0.115P) \quad (7)$$

where S_{P_P} is the peak to peak amplitude, M denotes a material-dependent constant and P is

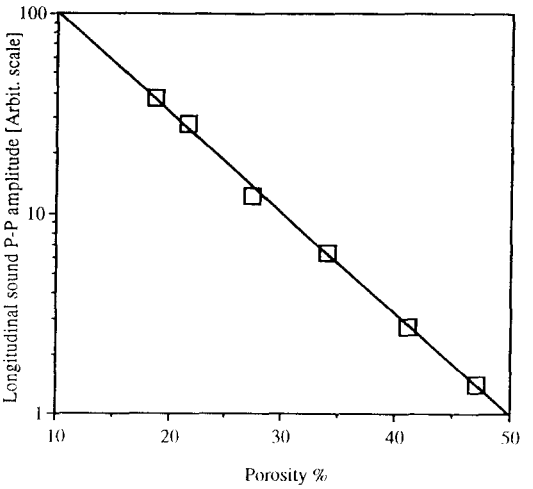

Fig. 9. Peak-to-peak (P – P) amplitude of longitudinal sound on an arbitrary scale as a function of tablet porosity (%).

the porosity of the sample. The correlation coefficient, r, for the least-squares fit was 0.997. The meaning of the constant, M, is unclear. It may depend on the material, the manufacturing procedure or the experimental set up. To resolve this, further studies with several different materials are needed.

It can be concluded that the laser ultrasonic method, measuring the transverse and longitudinal wave amplitudes and their respective ultrasonic velocities, and the attenuation of the longitudinal wave, can detect changes in porosity and integrity of microcrystalline cellulose tablets without destroying their structure. The applicability of the photoacoustic method to the determination of elastic parameters of tableting materials was also demonstrated. They were found to follow the porosity trends of previous studies (Radebaugh et al., 1989; Bassam et al., 1990; Roberts et al., 1994), even though the numerical values differed. This method can thus be used not only for evaluating the elastic properties of tableting materials, but also for evaluating the internal structure of tablets.

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