AAPS PharmSciTech, Vol. 9, No. 1, March 2008 (© 2007)
DOI: 10.1208/s12249-007-9010-z

Research Article

Themed Issue: Process Analytical Technology
Guest Editor: Ajaz Hussain

Ultrasound Transmission Technique as a Potential Tool for Physical Evaluation of Monolithic Matrix Tablets

M. A. Hakulinen,[1,5] J. Pajander,[2] J. Leskinen,[1] J. Ketolainen,[2] B. van Veen,[2,4] K. Niinimäki,[1] K. Pirskanen,[1] A. Poso,[3] and R. Lappalainen[1]

Received 25 June 2007; accepted 18 October 2007; published online 9 January 2008

Abstract. The aim of this study was to investigate the effects of tablet porosity and particle size fraction of compacted Starch acetate powders, with and without model drug caffeine, on acoustic properties of tablets. The ultrasound velocity was determined from the transmission measurements. Tablets of starch acetate (SA DS 2.7) powder with two particle size fractions of 0–53 and 0–710 μm were compressed with a compaction simulator. Porosities of tablets varied in the range from 12% to 43% for both particle size fractions. Strong associations were found between the ultrasound velocity and physical properties of the tablets such as porosity and particle size fraction. Interestingly, ultrasound velocity was practically insensitive to inclusion of the model drug caffeine with the concentrations used. Based on this study ultrasound transmission method is a potential non-destructive tool for studying structural changes of tablets and other solid dosage forms.

KEY WORDS: caffeine; particle size; porosity; starch acetate; tablet; ultrasound; velocity.

INTRODUCTION

In oral drug delivery technologies, interest has been focused on matrix technologies because these technologies are relatively simple, highly reproducible and have normally the advantage of stable raw materials and dosage form. Development of matrix formulations has enabled easier designs of controlled-release products and improved the feasibility of delivering a wide variety of drugs with different physicochemical and biopharmaceutical properties (1).

Production of pharmaceutical products requires good quality control to ensure both quality and safety of the product. Usually the parameters of quality control are set at certain thresholds depending on the manufacturing characteristics and material properties. Drug dissolution is a result of many parameters influencing drug transport mechanisms from matrix systems. The dynamics of these processes are mainly dependent on polymer properties (e.g. polymer type, hydrophilicity/hydrophobicity, polymer combinations) (1–3), drug-related factors (e.g. drug solubility) (1,2,4,5), and characteristics of other formulation components (formulation geometry, loading dose, processing technique and excipients/additives) (1,2). Especially porosity and pore size are important factors since drug dissolution from porous hydrophobic SA-system in this case is mainly influenced by the penetration of the dissolution medium into the pores of the tablet (6). Moreover, small cracks and other similar defects of the matrix system can affect drug release. Therefore, several parameters, like compaction force, particle size fractions, which affect the properties of the tablet (e.g. porosity), and possible defects in matrix system, should be investigated thoroughly.

Process analytical technology (PAT) encompasses the design and development of analytical methods to validate the quality of manufactured pharmaceutical products. PAT requires fast, reliable and non-invasive techniques for being effective in pharmaceutical industry. At the moment, only limited numbers of techniques are available. A disadvantage of new monitoring techniques is that the resulting models for the correlation between sensor signals and quality parameters generally are case specific and must be developed and validated for each application (7). Ultrasound techniques have been underutilized in the PAT research although these techniques have great potential for being the method of choice for monitoring several pharmaceutical processes. Ultrasound technique introduced in the present study has many advantages: (1) relative low cost of instrumentation, (2) easy implementation, (3) fast computing time and (4) no extensive expertise is required for the use of the technique.

Both destructive and non-destructive testing (NDT) are used to investigate structural, physical and chemical properties and consequently drug release of tablets. Use of near infrared spectroscopy (NIRS) (8), nuclear magnetic resonance (NMR) (9), magnetic resonance imaging (MRI) (10, 11),

[1] Department of Physics, BioMater Centre, University of Kuopio, P.O. Box 1627, 70211, Kuopio, Finland.
[2] Department of Pharmaceutics, University of Kuopio, P.O. Box 1627, 70211, Kuopio, Finland.
[3] Department of Pharmaceutical Chemistry, University of Kuopio, P.O. Box 1627, 70211, Kuopio, Finland.
[4] Orion Pharma R&D, Orion Corporation, P.O. Box 65, 02101, Espoo, Finland.
[5] To whom correspondence should be addressed. (e-mail: mikko.hakulinen@uku.fi)

 1530-9932/08/0100-0267/0 © 2007 American Association of Pharmaceutical Scientists

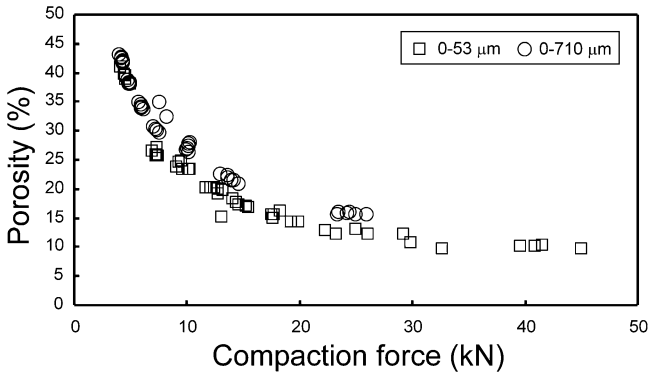

Fig. 1. Compaction force as a function of porosity for particle size fraction of 0–53 μm (*open squares*) and 0–710 μm (*open circles*), respectively

X-ray diffraction (XRD) (12), X-ray microtomography (XMT) (13), scanning electron microscopy (SEM) (14) and Fourier transform infrared (FTIR) spectroscopy (15) have been used to characterize the properties of tablets and powders.

Literature shows an increasing interest in measuring acoustic properties of composite systems having a matrix with inclusions. Those systems are shown to be important in various fields, from medical diagnostics and biotechnology to complicated engineering microstructures (16–21). In those materials, ultrasonic methods have shown to be useful for investigation of the mechanical properties, structural or morphological characteristics. The ultrasound technique in pharmaceutics is usually based on measurement of velocity and attenuation of acoustic waves propagating through materials. Chen et al. (22) demonstrated that both ultrasound attenuation and velocity were sensitive to a model drug and a model excipient concentration in a series of standard solutions and used high resolution ultrasound simultaneously to analyze both concentrations. When ultrasound propagates through solid medium, e.g. tablet, the velocity of transmission and the propagation amplitude are influenced by the medium properties. Thus, the tablet may be characterized by measuring the ultrasound velocity. This study investigates the ultrasound transmission method as a rapid non-destructive technique that requires no sample preparation.

Different theoretical approaches have been introduced to model ultrasound propagation through porous materials. The description of sound propagation through porous materials can be divided roughly to two major cases based on the type of fluid filling the porous space (23). The first case is of a heavy fluid, such as water, and second involves light fluid, e.g. air. The case of light fluids is simpler due to the assumption of motionless matrix (23). Johnson et al. (24) introduced a basic model for the sound propagation in air-filled porous materials as in the case of porous tablets. The model was further improved by Champoux and Allard (25) to express the frequency dependence of the bulk modulus of the saturating fluid at high frequencies. While analytical approaches have to account for a large number of parameters (e.g. complex 3D anisotropic microstructure, fluid/solid interaction and material properties), it becomes quickly intractable. Therefore, numerical simulation offers an alternative and feasible way to estimate sound propagation through porous materials. Numerical propagation models may be coupled with measurement of real porous material structures such as high resolution computed tomography (19,26).

In this study, cylindrical tablet samples with two different origins (Starch acetate powder, DS 2.7, with particle size fraction of 0–53 or 0–710 μm) were prepared to study the different effects of particle size fraction, porosity and drug compound addition on the ultrasound parameter velocity as measured using ultrasound transmission method. As the manufacturing process and used raw materials are responsible for the physical differences between tablets, we investigated the ability of ultrasound technique to visualize these differences.

MATERIALS AND METHODS

Materials and Powder Blend Preparation

Starch acetate (SA DS 2.7; Polymer Corex Ltd., Kuopio, Finland) was sieved through vibration sieves (Type 3D, Retsch, Germany) into two particle size fractions of 0–53 and

Table I. Mean Values and Standard Deviations of Porosity, Height, Diameter and Weight for Batches of Tablets Compressed from SA Powder with Different Particle Size Fractions

Particle Size Distribution	Porosity (%)	Height (mm)	Diameter (mm)	Weight (mg)
0–53 μm	10.4±0.8	3.13±0.06	12.90±0.02	493±7.9
	12.2±0.8	3.19±0.03	12.94±0.02	494±6.2
	15.1±0.8	3.26±0.01	12.97±0.02	490±3.3
	17.0±1.0	3.34±0.01	12.99±0.01	493±3.5
	19.9±0.4	3.45±0.01	13.00±0.01	492±1.7
	23.9±0.7	3.56±0.02	13.04±0.02	486±4.4
	26.1±0.6	3.62±0.02	12.96±0.01	480±2.9
	39.5±1.0	4.32±0.01	13.07±0.01	470±7.8
0–710 μm	15.7±0.2	3.17±0.01	12.92±0.01	500±2.0
	21.7±0.7	3.36±0.01	12.99±0.01	497±3.6
	27.1±0.6	3.60±0.03	13.04±0.03	498±1.3
	31.3±2.0	3.81±0.06	13.03±0.06	496±4.9
	34.1±0.4	4.00±0.01	13.01±0.01	499±2.5
	38.1±0.3	4.26±0.01	13.02±0.01	498±2.2
	42.3±0.5	4.51±0.03	13.04±0.01	496±4.3

0–710 μm. Mixtures containing 85%, 82%, 78% and 75% SA (particle size fraction of 0–53 μm) and 15%, 18%, 22% and 25% caffeine (Sigma-Aldrich, Steinheim, Germany) were prepared on a weight basis. The powders were mixed manually in a mortar in geometric series with a mixing time of 4 min.

Tablet Compaction

Tablets from both SA particle size fractions and different caffeine–SA powder mixtures were compacted with a compaction simulator (PCS-1, PuuMan Ltd., Kuopio, Finland) to produce cylindrical tablets, weighting 500 mg, with a diameter of 13 mm. A sine wave compaction profile was used for the upper punch, while the lower punch was kept stationary. The die and punches were prelubricated with magnesium stearate powder (Orion Pharma, Espoo, Finland) before each compaction in order to minimize changes in the tablet structures during ejection. The average compaction speed was 4 mm/s and the ejection time was always 1.8 s. The amplitude was adjusted to generate compaction pressures of 4–45 kN in order to produce tablets with different porosities. Figure 1 illustrates the effect of particle size fraction on compaction load–porosity curve. The porosities of the tablets were calculated using the tablet dimensions and the measured densities of SA and caffeine and their respective weight (pure SA) or weight ratio (caffeine–SA) in the prepared mixture. The properties of tablets containing pure SA (particle size fractions of 0–53 and 0–710 μm, respectively) and different mixtures of caffeine and SA are presented in Tables I and II, respectively. Typical output of the vibration sieves (Type 3D, Retsch, Germany) used in this study, was 1.3/6 μm (dv10), 11/152 μm (dv50) and 45/520 μm for particle size fraction of 0–53/0–710 μm, respectively. Axial cross-sections of four representative tablets with different particle size fractions (0–53 and 0–710 μm, respectively) and porosities (15%, 20%, 35% and 40%, respectively) were visually evaluated from electron micrographs taken by the SEM instrument (Philips XL30 ESEM-TPM, FEI company, The Netherlands) using 500 x magnification (acceleration voltage of 20 kV).

Acoustic Measurements

Pulsed ultrasound signal (Optel OPBOX-01/100, a pair of 1 MHz unfocused transducers; Optel, Wroclaw, Poland) was transmitted through dry tablets and recorded (Fig. 2). Parafilm M® Laboratory Film was used to improve the contact between transducers and tablets. A constant load of 0.96 kg was used to further improve the contact between transducers and tablets. A set of tablet samples were manufactured with different porosities (15–45%) and mechanically tested (Instron FastTrackTM 8874, Instron, Canton, MA, USA) to determine the elastic region for each tablet porosity. The contact stress was set to match the elastic region of all porosities and to avoid any plastic deformation during acoustic measurements. Pulse arrival time was determined using the first peak of the ultrasound signal above user defined threshold value (Fig. 3). The threshold was set manually for each measurement in order to remove signal noise and possible measurement artifacts. Finally, velocity of ultrasound was calculated using the pulse arrival time and known thickness of the tablet as measured with micrometer (Mituyoto 500-161U, Mituyoto Absolute Digimatic Ltd., East Kilbride, UK).

Table II. Mean Values and Standard Deviations of Porosity, Height, Diameter, Weight and Ultrasound Velocity for Batches of Tablets Compressed from Mixtures of SA Powder and Caffeine

Caffeine (% *w/w*)	Porosity (%)	Height (mm)	Diameter (mm)	Weight (mg)	Ultrasound Velocity (m/s)
0	17.1±2.4	3.30±0.02	13.00±0.019	487±16	1,510±61
15	15.7±0.4	3.24±0.004	13.03±0.003	489±3	1,571±37
18	14.7±0.6	3.24±0.003	13.04±0.004	495±3	1,606±30
22	13.8±0.2	3.22±0.006	13.04±0.001	497±1	1,627±27
25	13.8±0.7	3.21±0.005	13.04±0.003	496±4	1,657±42

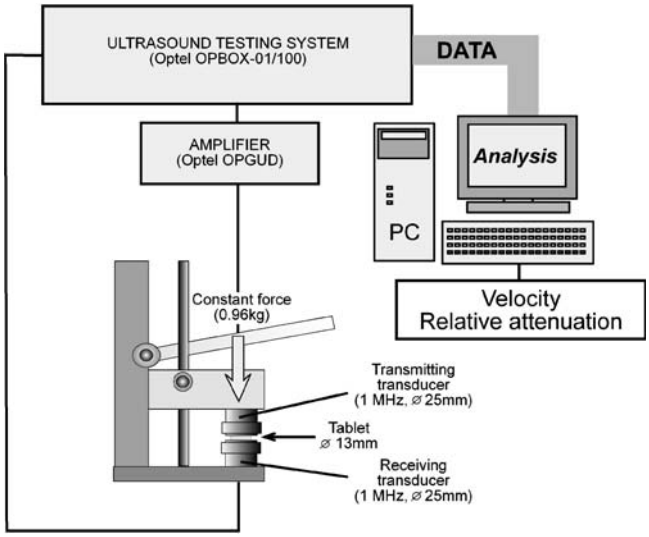

Fig. 2. Ultrasound measurement set-up. Tablets were positioned between a pair of 1 MHz ultrasound transducers with constant force of 0.96 kg. Ultrasound velocity was determined from transmitted ultrasound signal

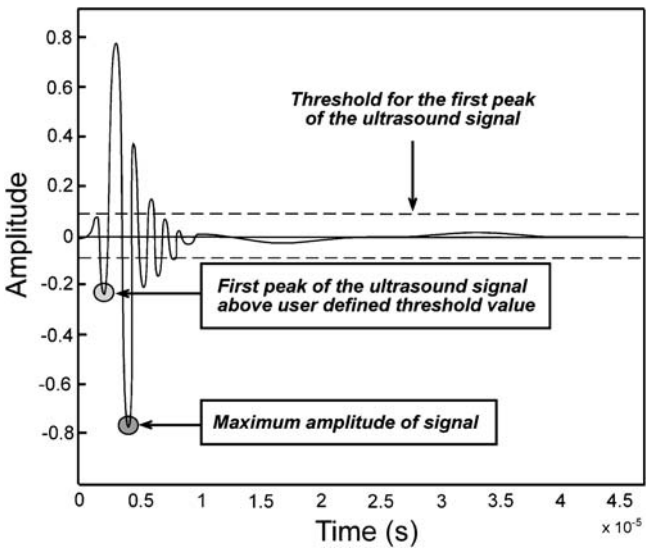

Fig. 3. Determination of transit time for ultrasound velocity measurement

Statistical Analyses

The reproducibility of the ultrasound measurements was investigated by measuring 6 tablets 10 times and calculating the standardized coefficient of variation (sCV, in %) (27) for each sample. Mann–Whitney *U* and independent samples *T* tests were used to reveal particle size fraction variation in the measured ultrasound parameter. Stepwise linear regression analysis was used to investigate the relationship between tablet porosity, model drug content or their combinations and acoustic properties of tablets. Pearson's correlation analysis was used to study the association between tablet porosity and ultrasound parameter. Statistical analyses were performed using SPSS (version 14.0, SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

The axial cross-sections of SA tablets showed significant visual differences in tablet structure between particle size fractions and porosities. Large amount of small pores can be seen in the tablet matrix having particle size fraction of 0–53 μm and porosity of 20% (Fig. 4a). While increasing the porosity of the tablet, larger pore sizes can be observed (Fig. 4b). For tablet with particle size fraction of 0–710 μm, smaller amount of pores can be found with larger size, especially in tablet with porosity of 40% (Fig. 4c,d).

Effect of Porosity

The reproducibility of velocity measurements ranged between 1.0% and 3.2% (sCV%). Ultrasound velocity was found to be sensitive to particle size fraction of starch acetate tablets ($p<0.05$, Mann–Whitney, Fig. 5a). For ultrasound velocity, an average increase of 131 m/s was associated with change of particle size fraction from 0–53 to 0–710 μm at equal tablet porosity (*T* test, $p<0.01$, Fig. 5a). Importantly, association between velocity and porosity was highly significant for both particle size fractions ($r^2>0.98$ for 0–53 and 0–710 μm, respectively, $p<0.01$, Fig. 5a).

The values of ultrasound velocity varied as a function of porosity. Ultrasound velocity showed very strong association with tablet porosity, velocity values ranging from 1,797 to 839 m/s for porosities of 15% and 43% (Fig. 5a), respectively. Evidently, high ultrasound velocity values are associated with low tablet porosities and vice versa. Strong dependency of ultrasound velocity on material porosity has been demonstrated for various materials from engineering to biological materials (19,28). The strong association between ultrasound velocity and tablet porosity is also found in the present study. From theoretical point of view, ultrasound velocity defines the speed in which the ultrasound propagates through the tablet and is dependent on elastic properties and density of the solid material. thus, it can be expressed in terms of

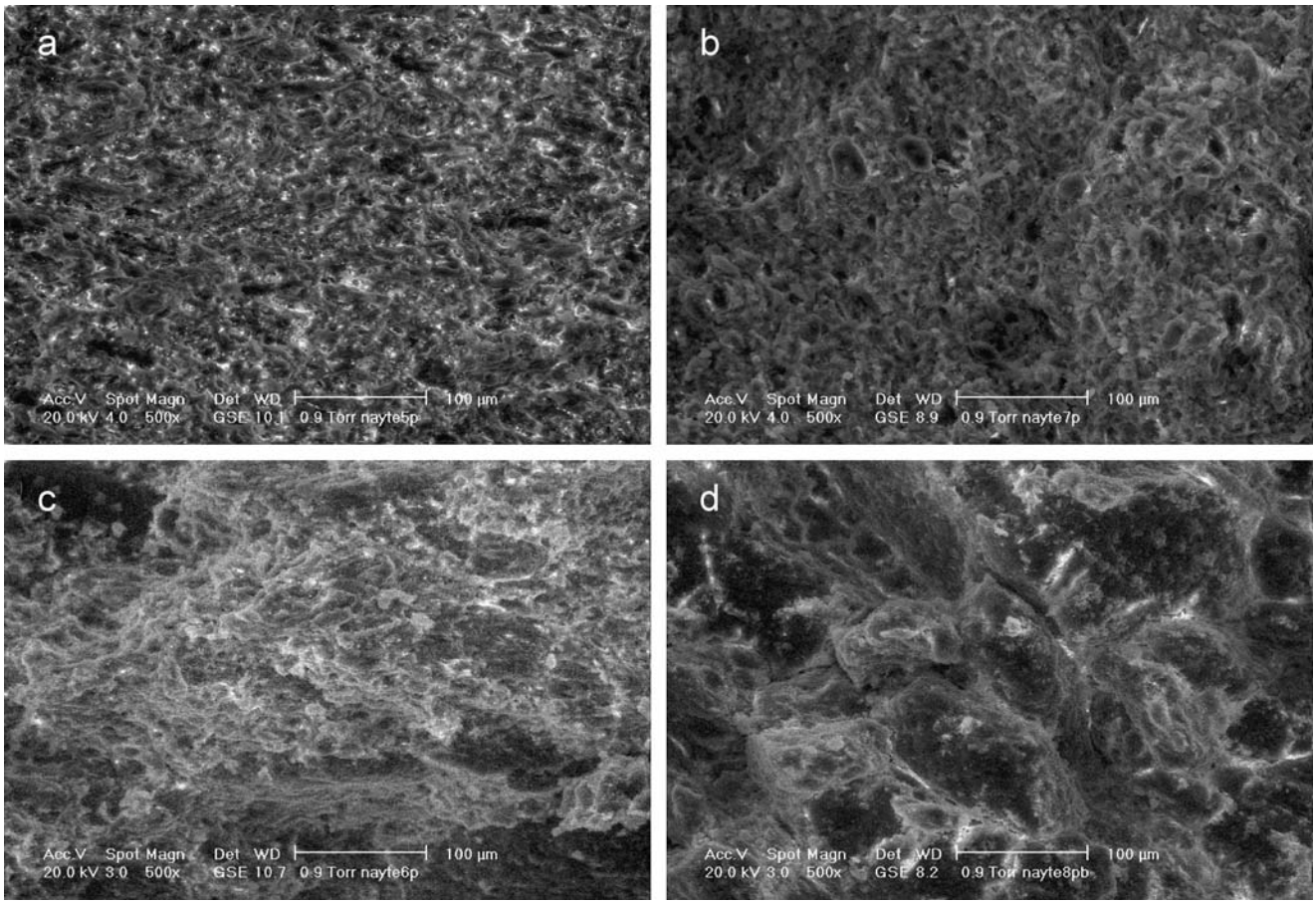

Fig. 4. SEM photographs from different axial cross-sections of the tablets with particle size fractions of **a** 0–53 μm (porosity of 15%), **b** 0–53 μm (porosity of 35%), **c** 0–710 μm (porosity of 20%) and **d** 0–710 μm (porosity of 40%), respectively

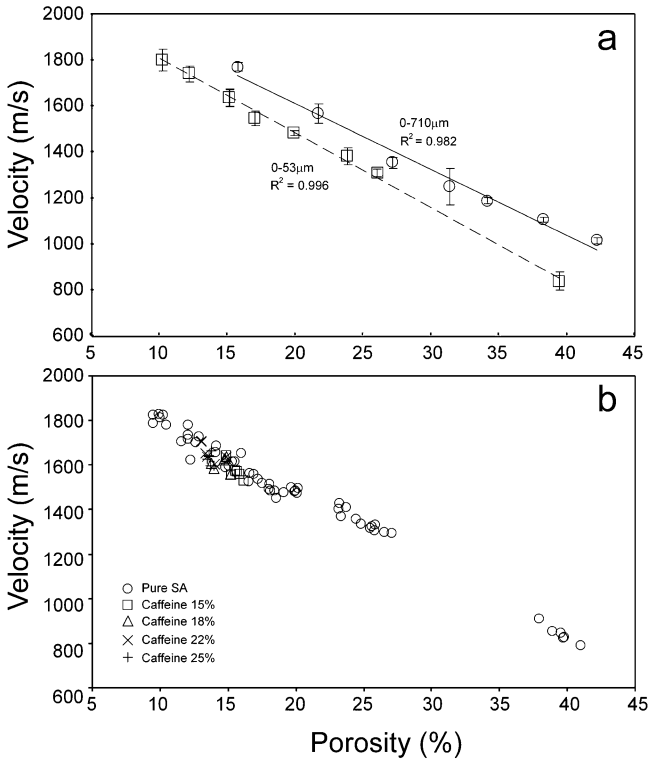

Fig. 5. **a** Mean values of ultrasound velocity as a function of tablet porosity. **b** Ultrasound velocity as a function of porosity for tablets containing pure SA and mixtures of SA and caffeine

compressibility or storage modulus, which is sensitive to the molecular organization, composition and intermolecular interactions. In the present study, the association between ultrasound velocity and porosity of the tablet is related to the strong interrelationship between the elastic properties and porosity of the tablet. An increase in tablet porosity leads to decrease in its elastic modulus (29) and, thus, decrease in ultrasound velocity, as seen in the present study.

In pharmaceutical materials, powders with smaller particle size, more irregular particle shape and larger specific surface area form tablets with lower porosities (30). Moreover, it has been suggested (30) that these powders have numerous contact points and a large bonding surface area that form strong interparticular bonds between the particles, and thus, form firmer tablets at equal porosity. On the other hand, properties of powders with larger particle sizes are unfavorable for interparticular bond formation during compaction (30). An average of 131 m/s increase of ultrasound velocity was associated with increase of particle size fraction from 0–53 to 0–710 μm. Evidently, size of the particles in porous material affects ultrasound velocity. From theoretical point of view, this is interesting phenomenon. One might hypothesize that while tablets compacted from smaller particle size fraction form firmer tablets, the ultrasound velocity would be expected to be higher. However, our results indicate opposite results. One possible explanation for this may be related to the shape and size of the pores and particles in the tablets. Although, tablets with smaller particle size fraction have higher tensile strength (30). Tablets with larger particle size fraction have less pores and consequently shorter continuous path ways for ultrasound propagation. This may possibly lead to higher velocity values. Evidently, more extensive research is required to clearly demonstrate the relative roles of tablet tensile strength and structure (e.g. particle and pore size and shape, connectivity) on ultrasound velocity. Although this study demonstrates the feasibility of ultrasound velocity to discriminate particle size fractions with high difference (i.e. 0–53 and 0–710 μm), further studies are warranted to investigate the ability of ultrasound velocity to discriminate tablets with more closely distributed particle size fractions.

Effect of Model Drug

For tablets containing the model drug (caffeine, 15%, 18%, 22%, 28% *w*/*w*), only a small variation was observed in the values of ultrasound velocity between pure SA and mixtures containing caffeine and SA with similar porosities (Fig. 5b). The variations (max, min) of ultrasound velocity were similar in tablets containing 0% *w*/*w* (velocity=1,685, 1,588 m/s) and 15% *w*/*w* (velocity=1,639, 1,527 m/s) caffeine, respectively. In both sets, tablets had similar porosities ranging from 14.1% and 15.0% to 16.1% and 16.3% for 0% *w*/*w* and 15% *w*/*w* caffeine content, respectively. Based on the linear regression model, porosity remained the primary determinant for ultrasound velocity. Nevertheless, caffeine content contributed only slightly to ultrasound velocity explaining an additional 3.6% of the variance (Stepwise linear regression, $p<0.05$). Ultrasound velocity was insensitive to inclusion of the model drug (caffeine). The particle size fractions and densities of the SA and caffeine are similar (6) and only small non-significant variation was revealed in ultrasound velocity between the plain SA tablets and the binary mixture tablets.

Ultrasound Analyses

As a preliminary study, this study introduced relative simple data and signal analysis techniques. In future, the determination of pulse arrival time using signal envelope and phase spectral analysis techniques may provide velocity values that are not so strongly affected by frequency dependent attenuation (31,32). However, it has been demonstrated that frequency dependent attenuation has a significant effect on absolute values of ultrasound velocity while the association between velocity and structural characteristics of composite material has only minor affect (32). On the other hand, it would be useful to investigate the ability of sound dispersion that is the phenomenon related to frequency dependence of ultrasound phase velocity in order to predict the variation in porosity and particle size fraction. In porous media, it has been observed that the attenuation increases as a function of frequency. As a result, higher frequencies of the ultrasound signal are attenuated more than lower frequencies. This frequency dependence is found to be sensitive to both density and structure of composite materials, e.g. in biological tissues (19,33,34). Therefore, parameters reflecting the material specific frequency dependence of ultrasound attenuation may enhance, combined with other acoustic parameters, the sensitivity of ultrasound transmission technique to reveal changes in density and structural characteristics of composite materials like monolithic matrix tablets.

Moreover, in this study the mechanical tests were conducted to ensure that the contact stress of the ultrasound transducers would not induce any plastic deformations (or major elastic deformation) to the samples and to ensure that good contact can be attained with the contact stress. It was noticed that the good signal can be attained with relative low contact stress and, thus only minor deformation is detected. In case of ultrasound attenuation, contact stress may have a major impact to the measured values (as the transmission through interface would be influenced). For the velocity measurement, the most important requirement is that the intensity of the transmitted signal is high enough (i.e. good S/N ratio) to determine transit time (i.e. that good signal is obtained). In future tests, the ultrasound velocity can be measured reliably without the mechanical tests as it was seen that good signal (i.e. good contact) can be obtained with low contact stresses (i.e. much lower that than the possible yield stress).

CONCLUSION

As a conclusion, ultrasound velocity was found to be sensitive on the porosity of tablets. Moreover, it was possible to discriminate tablet with different particle size fractions, though the fractions were overlying, by using ultrasound velocity measurements. Although the literature clearly shows the feasibility of ultrasound technique as a method for providing information on mechanical and structural characteristics of porous materials, it is underutilized and confined only on limited area. Evidently, more experimental and theoretical studies are warranted to investigate the true potential of ultrasound techniques as process analytical tool. Based on this study, transmission ultrasound technique is very potential as a non-destructive method to study tablets and may be feasible in monitoring pharmaceutical processes during manufacturing.

ACKNOWLEDGEMENTS

The financial support from TEKES (Finnish Funding Agency for Technology and Innovation) COMBIO Program and VARMA project is gratefully acknowledged. This study was also financially and technically supported by the Finnish companies Orion Pharma Oyj, Polymer Corex Ltd. and Visipoint Oy. The authors are grateful to M.Sc. Laura Tomppo for her collaboration.

REFERENCES

1. M. Varma, A. Kaushal, A. Garg, and S. Garg. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am. J. Drug Deliv **2**:43–57 (2004)
2. J. Siepmann, A. Streubel, and N. Peppas. Understanding and predicting drug delivery from hydrophilic matrix tablets using the "sequential layer" model. *Pharm. Res* **19**:306–314 (2002).
3. R. Korsmeyer, R. Gurny, E. Doelker, P. Buri, and N. Peppas. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm* **15**:25–35 (1983).
4. K. Rao, K. Devi, and P. Buri. Influence of molecular-size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. *J. Controlled Release* **12**:133–141 (1990).
5. P. Katikaneni, S. Upadrashta, S. Neau, and A. Mitra. Ethylcellulose matrix controlled-release tablets of a water-soluble drug. *Int. J. Pharm* **123**:119–125 (1995).
6. van B. Veen, J. Pajander, K. Zuurman et al. The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets. Eur. J. Pharm. Biopharm **61**:149–157 (2005)
7. J. Boyd and J. Varley. The uses of passive measurement of acoustic emissions from chemical engineering processes. *Chem. Eng. Sci* **56**:1749–1767 (2001).
8. C. Gustafsson, C. Nystrom, H. Lennholm, M. Bonferoni, and C. Caramella. Characteristics of hydroxypropyl methylcellulose influencing compactibility and prediction of particle and tablet properties by infrared spectroscopy. *J. Pharm. Sci* **92**:494–504 (2003).
9. S. Baumgartner, G. Lahajnar, A. Sepe, and J. Kristl. Quantitative evaluation of polymer concentration profile during swelling of hydrophilic matrix tablets using 1H NMR and MRI methods. *Eur. J. Pharm. Biopharm* **59**:299–306 (2005).
10. M. Kojima and H. Nakagami. Investigation of water mobility and diffusivity in hydrating micronized low-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose matrix tablets by magnetic resonance imaging (MRI). *Chem. Pharm. Bull* **50**:1621–1624 (2002).
11. M. Johns and L. Gladden. Magnetic resonance studies of dissolving particulate solids. *Magn. Reson. Imaging* **21**:395–396 (2003).
12. M. Kidokoro, N. Shah, A. Malick, M. Infeld, and J. McGinity. Properties of tablets containing granulations of ibuprofen and an acrylic copolymer prepared by thermal processes. *Pharm. Dev. Technol* **6**:263–275 (2001).
13. X. Fu, M. Dutt, A. Bentham, B. Hancock, R. Cameron, and J. Elliott. Investigation of particle packing in model pharmaceutical powders using X-ray microtomography and discrete element method. *Powder Technol* **167**:134–140 (2006).
14. F. Ravenelle, R. Marchessault, A. Legare, and M. Buschmann. Mechanical properties and structure of swollen crosslinked high amylose starch tablets. *Carbohydr. Polym* **47**:259–266 (2002).
15. T. DiFeo. Drug product development: a technical review of chemistry, manufacturing, and controls information for the support of pharmaceutical compound licensing activities. *Drug Dev. Ind. Pharm* **29**:939–958 (2003).
16. J. Panakkal. Longitudinal ultrasonic velocity as a predictor of Young's modulus in porous materials. *Mater. Eval* **55**:1367–1371 (1997).
17. J. Ketolainen, M. Oksanen, J. Rantala, J. Stor-Pellinen, M. Luukkala, and P. Paronen. Photoacoustic evaluation of elasticity and integrity of pharmaceutical tablets. *Int. J. Pharm* **125**:45–53 (1995).
18. K. Alderson, R. Webber, U. Mohammed, E. Murphy, and K. Evans. An experimental study of ultrasonic attenuation in microporous polyethylene. *Appl. Acoust* **50**:23–33 (1997).
19. M. Hakulinen, J. Day, J. Töyräs, H. Weinans, and J. Jurvelin. Ultrasonic characterization of human trabecular bone microstructure. *Phys. Med. Biol* **51**:1633–1648 (2006).
20. R. Dewhurst, R. He, and Q. Shan. Defect visualization in carbon fiber composite using laser ultrasound. *Mater. Eval* **51**:935–940 (1993).
21. D. Jones and A. Rizkalla. Characterization of experimental composite biomaterials. *J. Biomed. Mater. Res* **33**:89–100 (1996).
22. R. Chen, T. Zelesky, N. Ilasi, and S. Sekulic. Simultaneously measuring concentrations of a model drug and a model excipient in solution using ultrasonic spectrometry. *J. Pharm. Biomed. Anal* **37**:239–247 (2005).
23. A. Moussatov, C. Ayrault, and B. Castagnede. Porous material characterization—ultrasonic method for estimation of tortuosity and characteristic length using a barometric chamber. *Ultrasonics* **39**:195–202 (2001).
24. D. Johnson, J. Koplik, and R. Dashen. Theory of dynamic permeability and tortuosity in fluid-saturated porous-media. *J. Fluid Mech* **176**:379–402 (1987).
25. Y. Champoux and J. Allard. Dynamic tortuosity and bulk modulus in air-saturated porous-media. *J. Appl. Phys* **70**:1975–1979 (1991).
26. E. Bossy, F. Padilla, F. Peyrin, and P. Laugier. Three-dimensional simulation of ultrasound propagation through trabecular bone structures measured by synchrotron microtomography. *Phys. Med. Biol* **50**:5545–5556 (2005).

27. C. Njeh, D. Hans, J. Li et al. Comparison of six calcaneal quantitative ultrasound devices: precision and hip fracture discrimination. Osteoporos. Int **11**:1051–1062 (2000)
28. D. Boccaccini and A. Boccaccini. Dependence of ultrasonic velocity on porosity and pore shape in sintered materials. *J. Nondestr. Eval* **16**:187–192 (1997).
29. S. Pohja, E. Suihko, M. Vidgren, P. Paronen, and J. Ketolainen. Starch acetate as a tablet matrix for sustained drug release. *J. Controlled Release* **94**:293–302 (2004).
30. O. Korhonen, S. Pohja, S. Peltonen, E. Suihko, M. Vidgren, and P. Paronen. Effects of physical properties for starch acetate powders on tableting. *AAPS PharmSciTech* **3**:1–9 (2002).
31. M. Ragozzino. Analysis of the error in measurement of ultrasound speed in tissue due to waveform deformation by frequency-dependent attenuation. *Ultrasonics* **19**:135–138 (1981).
32. P. Nicholson, R. Müller, X. Cheng et al. Quantitative ultrasound and trabecular architecture in the human calcaneus. *J. Bone Miner. Res* **16**:1886–1892 (2001)
33. C. Langton, S. Palmer, and R. Porter. The measurement of broadband ultrasonic attenuation in cancellous bone. *Eng. Med* **13**:89–91 (1984).
34. J. Hull, C. Langton, S. Barker, and A. Jones. Identification and characterisation of materials by broadband ultrasonic attenuation analysis. *J. Mater. Process Technol* **56**:148–157 (1996).