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RESEARCH PAPER

The Effect of Ultrasonic Vibration on the Compaction Characteristics of Ibuprofen

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ABSTRACT

An ultrasonic (US) compaction rig has been developed, capable of providing compaction pressure together with high-power ultrasonic vibrations of 20 kHz to a powder or granular material in a die. The rig has been used to investigate the effect of ultrasound on the compaction properties of ibuprofen, a drug with poor compaction properties which produces tablets that are weak and frequently exhibit capping. It was found that coherent ibuprofen tablets could be prepared by ultrasound-assisted compaction at pressures as low as 20–30 MPa. Application of ultrasound before and after compaction was found not to be as effective as ultrasound applied during compaction. The breaking forces of the tablets produced with ultrasound applied during compaction were found to be consistently significantly higher than when compaction was performed conventionally, or with ultrasound applied before or after compaction. Application of ultrasound during compaction made it possible to increase tablet mechanical strength, typically by a factor of 2–5. It was concluded that pressure should be applied together with ultrasound in order to achieve a better acoustical contact, which is required to transmit vibrations from the horn to the material, and also to bond the surfaces of the particles.

Ultrasound application during ibuprofen compaction also resulted in an increase in the apparent density, in relation to the apparent density of conventionally prepared tablets, of up to 14.4%. Ultrasound appears to improve particle rearrangement and provides energy for partial melting of particle asperities and subsequent fusion of particle surfaces, so as to increase interparticulate bonding. Solid bridge formation was thought to result in a reduction of void space, which in

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turn reduced the rate of water penetration into the compacts and consequently increased disintegration and dissolution times.

It was found that the results of ultrasound-assisted compaction are influenced by formulation and US time. When ibuprofen was mixed with a second material, such as dibasic calcium phosphate dihydrate (DCP) or microcrystalline cellulose (MCC), stronger tablets were prepared by ultrasound-assisted compaction compared to the compacts containing no filler. Positive interactions were considered to have occurred due to ultrasound-induced bonding between the two materials. With an increase in DCP and MCC concentration in ibuprofen formulations, disintegration and drug dissolution rates of the tablets produced with ultrasound significantly increased.

Using temperature-sensitive labels it was found that thermal changes occurred in powdered solids undergoing ultrasound-assisted compaction. Increases in the temperature of tablets were related to US amplitude and US time. With an increase in US amplitude from 5 to 13 μm, the temperature of the DCP tablet surface increased from 40 to 99°C. With an increase in US time from 1 to 5 sec, the temperature of the surface of ibuprofen tablets increased from 43 to 60°C. Increased tablet temperature was thought to be due to ultrasonic energy dissipation turned into heat.

X-ray powder diffraction (XRD) studies of ibuprofen tablets prepared by ultrasound-assisted compaction at 32 MPa revealed that no changes in chemical or/and crystalline structure of the material occurred when ultrasound was applied for up to 5 sec (US amplitude 7 μm). An XRD study of DCP tablets produced by ultrasound-assisted compaction at 32 MPa with ultrasound of different amplitudes (5, 7, 13 μm) applied for 2 sec indicated that no material deterioration occurred in all the tested samples.

Key Words: *Ibuprofen; Tabletting; Ultrasound-assisted compaction*

INTRODUCTION

High-power ultrasonic vibration has been used for many years to manufacture metallic, ceramic, or plastic compacts. However, ultrasound-assisted compaction of pharmaceutical powders is still a rather novel technique and literature reports extend only over the last eight years.

Gueret (1) applied ultrasound simultaneously with pressure to assist the compaction of pharmaceutical and cosmetic preparations in order to manufacture absorbent or partially friable compacts. Powder mixtures were used containing from 5 to 80% w/w of at least one thermoplastic product, such as polyethylene, polystyrene, polyamide, and polyvinyl chloride. Gueret found that the presence of a thermoplastic product in the formulation allowed the formation of a framework that held the non-thermoplastic powders together.

Rodriguez et al. (2,3) described an ultrasound-assisted pharmaceutical tabletting machine which was used for the compaction of formulations containing theophylline and Eudragit®. The powder mixtures were subjected to ultrasonic vibrations at frequencies of between 20 and 40 kHz. Pressures used did not exceed 3–6 MPa. It was found that the tablets prepared by ultrasound-assisted compaction exhibited a greater degree of hardness (>20 kg) than when conventionally compacted, and they were less friable. In vitro dissolution studies showed that ultrasonically produced compacts had a prolonged release, approximately 50% longer than that of conventionally manufactured tablets.

Saettone et al. (4) reported the possibility of producing sustained-release matrices by ultrasound-assisted compaction of simple mixtures containing theophylline, Eudragit RL, and Eudragit RS. Tablets were prepared using the experimental ultrasound apparatus described by Rodriguez et al. (5). Motta (6) claimed that it was possible to achieve acceptable controlled release of different drugs using mechanical or electromechanical vibrations of

frequency between 1 kHz and 2 MHz. He found that by employing well-known polymers or copolymers, such as cellulose and its derivatives, polyamides, acrylic polymers, polyesters, polyvinylpyrrolidone, starch, polyethylene glycols, etc., a delayed drug release could be obtained. In contrast, by selecting excipients, such as solid sugars and cyclodextrins, a much more rapid drug release was achieved.

The principle aims of this study were to use an ultrasonic (US) compaction rig in order to evaluate the compaction characteristics of ibuprofen and to investigate the effects of incorporating excipients into the drug.

MATERIALS

Ibuprofen manufactured by Knoll Pharmaceuticals (Nottingham, England) was used. Magnesium stearate (BDH, Poole, UK) was used as a lubricant in a quantity of 1% w/w for all mixtures. Crospovidone (Polyplasdone®, ISP Tech-nologies, Wayne, NJ, USA) was used as a disintegrant. Dibasic calcium phosphate dihydrate (DCP) manufactured as Emcompress® by Penwest Pharmaceuticals Ltd. (Reigate, Surrey, UK), and microcrystalline cellulose (MCC) manufactured as Emcocel 90M® by Penwest Pharmaceuticals (Reigate, Surrey, UK), were mixed with ibuprofen to form 25, 50, and 75% w/w mixtures with respect to the drug. Formulations used in this study are detailed in Table 1. Mixing was performed in a glass jar that was fixed to a bent arm attached to an electric motor (Model RZRI, Heidolph Instruments, Schwabach, Germany) rotating at 60 rpm.

METHODS

Ultrasound-Assisted Compaction

For most experiments (with the exception of drug dissolution studies, for which tablets of different weight were produced) 600 mg of the material required for each round, flat-faced tablet was separately weighed and manually loaded into the die. Tabletting was then carried out on the ultrasonic compaction rig (7), providing compaction pressures of up to 32 MPa together with high-power ultrasonic vibrations of 20 kHz. Ultrasonic parameters (power output and US time) were set up prior to compression by controls available on the rig.

Table 1

Tablet Formulations Used in the Study

	Dry Weight Percentage in Formulation (% w/w)				
Formulation	Ibuprofen	DCP	MCC	Crospovidone	Magnesium Stearate
I	99				1
II	94			5	1
III	74	25			1
IV	49.5	49.5			1
V	25	74			1
VI		99			1
VII	74		25		1
VIII	49.5		49.5		1
IX	25		74		1
X			99		1
XI	70.5	23.5		5	1
XII	47	47		5	1
XIII	23.5	70.5		5	1
XIV		94		5	1
XV	70.5		23.5	5	1
XVI	47		47	5	1
XVII	23.5		70.5	5	1
XVIII			94	5	1

The dwell time under pressure was at least 1 sec. Ultrasound was applied before, during, and after compaction for different periods of time (up to 5 sec). Amplitude was monitored via the direct reading amplitude meter and manually recorded. Prior to each compression, the face of the horn and die wall were cleaned with acetone.

Determination of Tablet Apparent Volume and Density

The diameter and thickness of each tablet were measured to ±0.001 mm using a 25-mm digital micrometer (Model 572-460, Mitutoyo Corporation, Kanagawa, Japan). Apparent volume was calculated according to:

$$V = \pi H(D/2)^2 \quad (1)$$

where V is apparent tablet volume, H and D are tablet thickness and diameter, respectively. Apparent tablet density was defined as the quotient of the weight and the apparent volume.

Measurement of Tablet Breaking Force

Breaking force was determined immediately after compaction as the force required to fracture a compact in a diametrical compression test on a Schleuniger tablet hardness tester (Model 6D, Pharmatron, Solthurn, Switzerland). Results were presented in kiloponds (1 kp = 1 kg force).

Tablet Disintegration Studies

The standard BP (8) disintegration test was performed using a disintegration unit (BWI Manesty, Liverpool, UK) in water at 37°C on six tablets from each batch. One tablet was placed in each of the six cylindrical glass tubes in a rigid basket–rack assembly. Disks were then added. The assembly was suspended in a beaker containing water. The total time taken for disintegration of each tablet was recorded, and the means and standard deviations for each batch were calculated.

Drug Dissolution Studies

Dissolution studies were conducted on a dissolution testing instrument (Model PTWS, Pharmatest Apparatebau GmbH, Hainburg, Germany) using the USP XXII (9) basket method at 37°C (±0.5°C). Dissolution tests were performed with 900 mL of phosphate buffer (pH 7.2). The phosphate buffer was prepared by dissolving 6.805 g of potassium dihydrogen orthophosphate (KH_2PO_4) and 1.47 g of sodium hydroxide (NaOH) in 1 L of distilled water. The pH of the buffer was adjusted with NaOH to within 7.2 ± 0.05 using a digital automatic temperature controlled pH-meter (Piccolo-2, Hanna Instruments, Inc., Woonsocket, RI, USA).

For each test, three tablets were weighed individually. Samples were taken automatically through filters (Copley Instruments Ltd., Nottingham, UK). The samples were introduced by an IPS (Ismatec, Wertheim, Germany) pump (pump rate 80 mL/min) into the flow cells.

Ultraviolet analysis of ibuprofen in the solution was carried out using a diode array spectrophotometer (Model HP8452A, Hewlett Packard, Waldbronn, Germany) at 266 nm. The instrument was calibrated prior to testing.

Dissolution test data were printed out as a percentage of the drug released in a specified time. The results were then corrected, taking into consideration the weight of an individual tablet. Finally, the data obtained after correction and calculation were presented as dissolution profiles, whereby the amount of ibuprofen released was plotted as a function of time.

Temperature Measurement

Self-adhesive temperature-sensitive labels supplied by RS Components Ltd. (Corby, Northants, UK) were used for temperature measurement in the die during ultrasound-assisted compaction. For each test two labels were used. One was positioned under the powder sample and the other under the horn face. Thermal labels contain fusible materials that change in appearance when heated above a specified temperature. A color change from white to black indicates that the temperature quoted on the indicator has been exceeded. This change is irreversible, whatever the atmospheric conditions (10). The labels are normally accurate to ±1°C with an immediate response to temperature (< 1 sec).

X-ray Diffraction Analyses

X-ray diffraction (XRD) patterns for ibuprofen were obtained using an x-ray diffraction system

(Model APD1700, Philips Electronics Inc., Natick, MA, USA). This system consisted of an x-ray powder diffractometer, a mini-computer with peripherals, and a PC-APD (v3-1) software system. The diffractometer was composed of an x-ray generator (Model PW1729), a goniometer (Model PW1050/81), with stepping motor, detector, radiation shield, PW1710 diffractometer control, and interface. Three types of samples were used for XRD studies: (a) powder, (b) whole tablet, or (c) ground tablet. Ground samples were prepared using a mortar and a pestle. Samples were mounted onto a PW1172/01 aluminum sample holder provided by the manufacturer in such a manner that the face under the x-rays was perfectly flat and uniform, as an uneven surface caused scatter. Whole tablets were used as well in order to examine their upper surfaces. To prepare a tablet for analysis with a PW1172/01 sample holder, a small amount of plasticine was used to hold the sample in place. The sample holder was then inserted into the correct position in the goniometer, where samples were irradiated from a copper target (Cu Kα radiation, $\lambda = 0.15406$ nm). Diffraction patterns were measured from $2\theta = 5^\circ$ to 75°, where θ is the Bragg angle (9).

Scanning Electron Microscopy

The surface characteristics of the tablets were assessed using a JSM-T200 scanning electron microscope (JEOL Ltd., Tokyo, Japan). Tablet specimens were first mounted onto aluminum studs using silver-deg adhesive. The specimens were positioned so that a punch contact surface could be seen. The studs were then placed in the coating chamber of a Polaron E5000 diode sputter-coating unit (Polaron Equipment Ltd., Watford, UK). The chamber was evacuated, refilled with argon, and the samples were coated with 24-karat gold emitted at 1.2 kV. During this process the samples were subjected to elevated temperatures and greatly reduced pressures. Temperature in the coating chamber was approximately 70°C, which was close to the melting point of ibuprofen. Samples containing ibuprofen were therefore coated at a reduced voltage of 0.8 kV for half an hour instead of the usual 5 min.

Coated samples were individually placed on the specimen holder of the scanning electron microscope. The specimen holder with a sample was then inserted into the vacuum chamber. The chamber was evacuated and the voltage required to accelerate electrons from an electron gun was selected. For different samples, different accelerating voltages were selected: 5, 10, or 15 kV. The choice of voltage depended on the thickness of the coating of the samples examined and on the tuning of the microscope. The electron beam was focused by an electromagnetic lens system onto the specimen, the resulting secondary electrons emitted from its surface were collected by an electron detector. The image formed was seen directly via a screen and was recorded photographically. Micrograph data such as the accelerating voltage, magnification, and working distance were recorded on the film.

RESULTS AND DISCUSSION

Ibuprofen was used to evaluate the effect of ultrasound on compaction properties. The material was chosen for detailed examination, as it is a common drug, which is used in relatively large quantities in pharmaceutical formulations. Ibuprofen has poor compaction properties and produces tablets that are soft or that cap. It was found that ultrasound significantly improves the compaction properties of the drug (Fig. 1).

The Effect of Different Ultrasound Regimes, Compaction Pressure, and Time of Ultrasound Application on Tablet Breaking Force

Figure 1 shows how different ultrasound regimes affect the breaking forces of ibuprofen tablets. All compacts produced without ultrasound were relatively weak, confirming the poor compactability of the drug. Application of ultrasound *before* and *after* compaction resulted only in a slight, less than 2 kp, increase in tablet breaking force. According to Paul and Crawford (11) and Nayar and Benatar (12), this can be explained by the absence of sufficient pressure during ultrasound application, resulting in poor horn-to-powder and horn-to-tablet contact and therefore poor transmission of energy. However, strong tablets were produced when ultrasound was applied *during* compaction. The breaking forces of ibuprofen tablets compressed at 32 MPa with ultrasound applied *during* compaction increased from 5.8 kp (without ultrasound) to 11.6 kp.

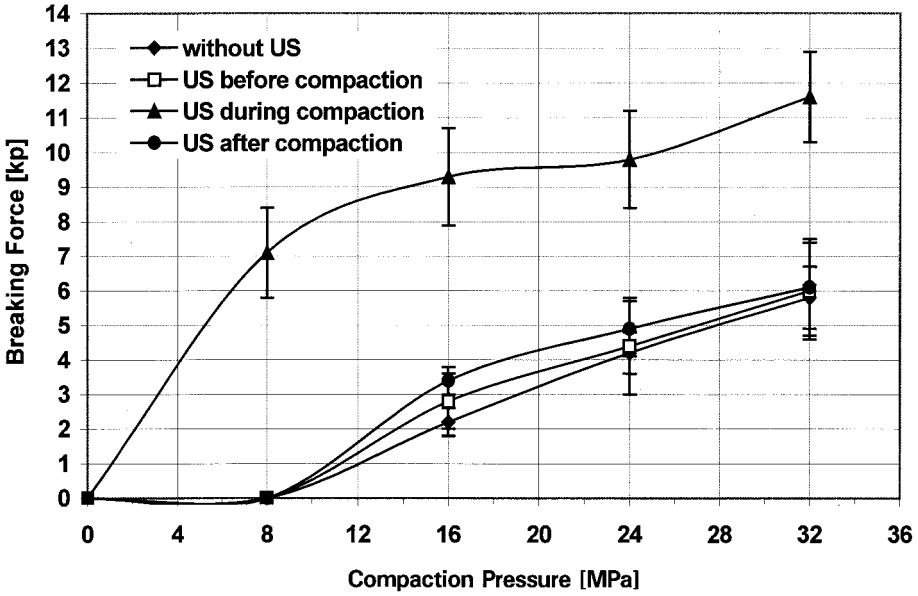

Figure 1. Effect of ultrasound (US amplitude 7 μm, US time 2 sec) on the breaking forces of ibuprofen tablets (formulation I). Results are the means and standard deviations of 10 determinations.

Therefore, it can be concluded that ultrasound should be applied simultaneously with pressure in order to obtain the necessary acoustical contact required to transmit vibrations from the horn to the material. Also, pressure, together with US vibrations, enables the particles to come in close proximity to each other, which causes the particle surfaces to join and their bonding area to increase. Hence, all subsequent experiments were performed using ultrasound applied *during* compaction.

The results of this study also confirm the Ng and Benatar (13) report that mechanical strengths of the compacts produced with ultrasound could be improved with a higher compaction pressure. Figure 1 shows that the higher the pressure, the stronger the tablets. With an increase in pressure from 8 to 16, 24, and 32 MPa, breaking forces of ibuprofen tablets produced with ultrasound applied during compaction increased from 7 to 9.2, 9.8, and 11.6 kp, respectively. An increase in tablet mechanical strength was thought to be due to improved acoustical contact between the horn and the material, improved driving force for flow, and improved contact between the powder particles.

Figure 2 shows that the breaking forces of ibuprofen tablets (formulations I and II) increased with increasing US time up to about 2 sec, and were generally independent of US time when ultrasound was applied for 2 to 5 sec. It can be concluded that tablet breaking force reached a saturation value around a certain energy-input level, which corresponded to US time equal to 2 sec.

When US time was further increased to 10–20 sec, ibuprofen melted in contact with the horn face. The molten material was then forced to the surface of the tablet and subsequently out of the die cavity. The molten material forced through the horn–die space then solidified on contact with the vertical surface of the horn tip, making it difficult to separate the horn from the die.

Bicknell (14), Paul and Crawford (11), Matsuoka and Maeda (15), Nayar and Benatar (12) suggested that during ultrasound-assisted powder compaction the particles stick together due to melting at their surfaces. Therefore, anything that improves the heat input to the particles would be expected to increase the mechanical strength of the resultant compacts. According to the results of this study, increasing the ultrasonic compaction time had a marked effect on the tablet breaking force, although there appears to be little advantage in using US times greater than 2 sec.

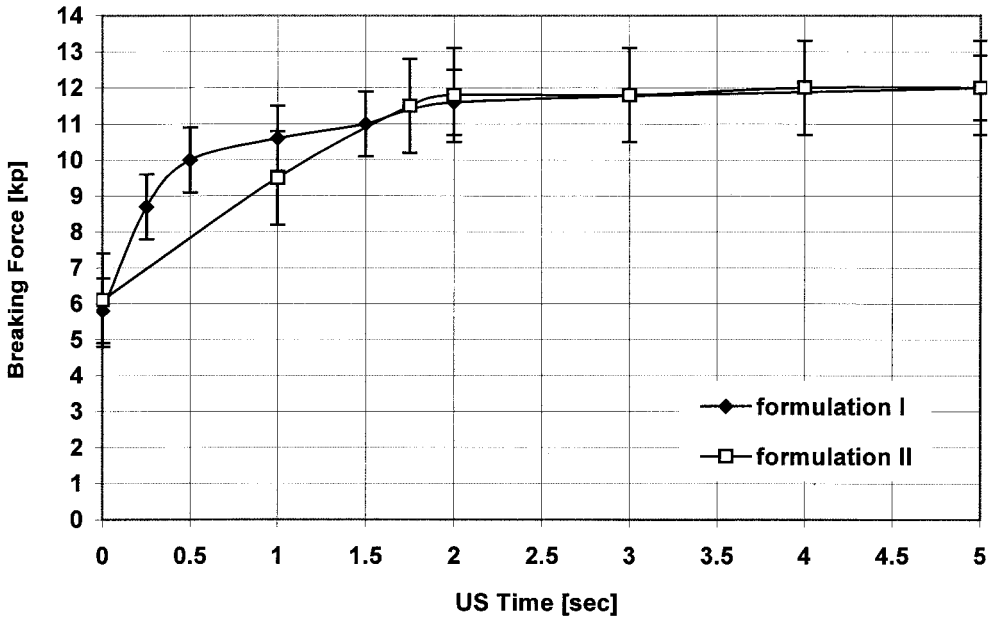

Figure 2. Breaking force vs. US time (US amplitude 7 μm) of tablets produced at 32 MPa. Results are the means and standard deviations of 10 determinations.

Table 2

The Effect of Ultrasound Applied for 2 Sec During Compaction on Thickness, Diameter, Apparent Volume, and Apparent Density of Ibuprofen Tablets (Formulation I). Results Are the Means and Standard Deviations of 10 Determinations

Compaction Pressure (MPa)	US	Thickness (mm)	Diameter (mm)	Apparent Volume (cm^3)	Apparent Density (g/cm^3)
16	Without US	4.956 ± 0.017	12.599 ± 0.010	0.618 ± 0.002	0.981 ± 0.002
	With US	4.360 ± 0.055	12.557 ± 0.012	0.540 ± 0.007	1.122 ± 0.007
	% Change	**−12.0**	**−0.3**	**−12.6**	**+14.4**
24	Without US	4.771 ± 0.014	12.604 ± 0.004	0.595 ± 0.002	1.018 ± 0.002
	With US	4.333 ± 0.036	12.568 ± 0.007	0.537 ± 0.005	1.128 ± 0.005
	% Change	**−9.2**	**−0.3**	**−9.7**	**+10.8**
32	Without US	4.635 ± 0.018	12.597 ± 0.011	0.577 ± 0.002	1.050 ± 0.002
	With US	4.255 ± 0.044	12.569 ± 0.005	0.528 ± 0.005	1.148 ± 0.005
	% Change	**−8.2**	**−0.2**	**−8.5**	**+9.3**

This study also showed that, by changing compaction pressure and US time to an optimum level, the mechanical strength of the tablets could be increased to an adequate value.

The Effect of Ultrasound on Tablet Apparent Volume and Density

Table 2 compares thickness, diameter, apparent volume, and apparent density of ibuprofen tablets (formulation I) produced conventionally and by ultrasound-assisted compaction. There was a major decrease in the thickness (up to 12%) of the compacts produced with ultrasound compared to the tablets compressed conventionally, which resulted in a major decrease in their apparent volume (up to 12.6%) and an increase in their apparent density (up to 14.4%).

It was also found that ultrasound application

resulted in a slight decrease (up to 0.3%) in tablet diameter. It can be assumed that, following the ejection of an ultrasonically produced tablet from the die, the tablet was not able to recover in a radial direction. A change in the dimensions of the conventionally compressed tablet after its removal from the die is attributed to elastic recovery, helped by the pressure of the air trapped in cavities, which is heavily compressed during the compaction process. On the other hand, the tablets prepared by ultrasound-assisted compaction exhibited better dimensional stability, due to stronger bonding between the powder particles compared to the tablets compacted conventionally, and because the entrapped air can more easily escape during ultrasonic vibration. Therefore, tablets compressed with ultrasound are less likely to cap.

The data in Table 2 confirm the findings of Lehfeldt (16) about the influence of ultrasonic oscillations on the properties of compacts, their density increase being greater at low pressures. An apparent density increase of ibuprofen tablets in relation to the apparent density of tablets prepared conventionally was 14.4, 10.8, and 9.3%, for 16, 24, and 32 MPa of compaction pressure, respectively. The increase in apparent density produced by ultrasonic vibration at low compaction pressures can be explained as the result of "jarring and vibrating" of the powder. This allows particles to flow past each other more easily, reducing friction between the particles and so enhancing consolidation.

The results of the present study suggest that ultrasound improves particle rearrangement and thereby increases compact density. Therefore, ultrasonic vibrations can be used to produce more efficient packing of particles under pressure. Various shapes will tend to orient into receptive voids, providing greater density and increased strength through increased particle contact.

The Effect of Filler Concentration on the Compaction Properties of Ibuprofen

Two excipients, DCP and MCC, were chosen as common excipients on the basis of their different mechanisms of compaction. For DCP, compaction takes place primarily by brittle fracture (17). In contrast, MCC has superior binding and compaction characteristics due to its plastic deformation properties (18). The effect of different DCP (formulations I, III–VI) and MCC (formulations I, VII–X) levels in mixtures with ibuprofen on breaking forces at different compaction pressures is illustrated in Figs. 3 and 4 for tablets produced without and with ultrasound. For all formulations, application of ultrasound resulted in a major increase in tablet breaking forces.

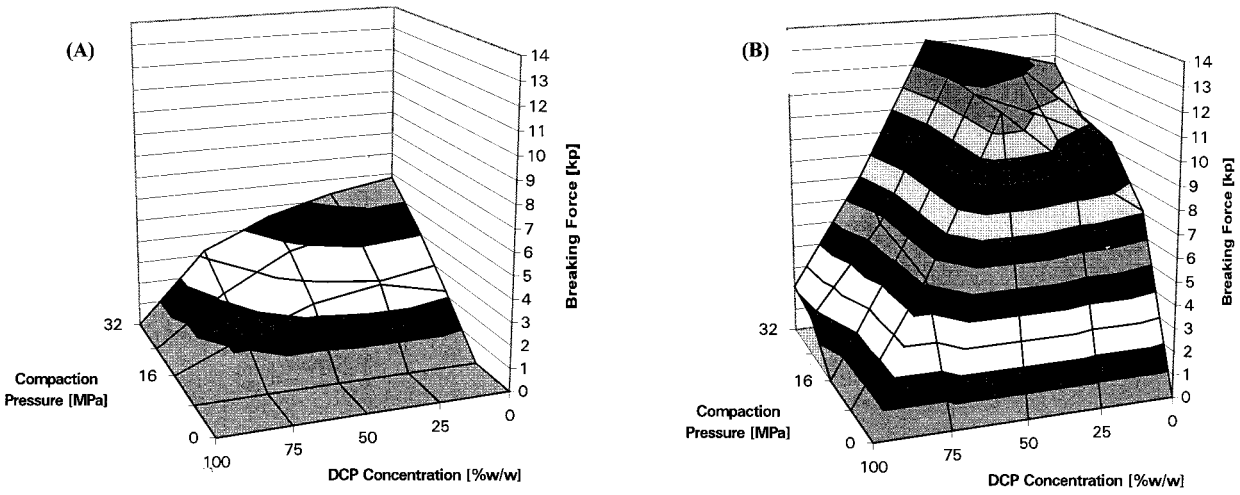

Figure 3. Breaking force vs. compaction pressure and DCP concentration of ibuprofen tablets (formulations I, III–VI) produced (A) conventionally and (B) with ultrasound (US amplitude 7 μm, US time 2 sec). Results are the means of six determinations.

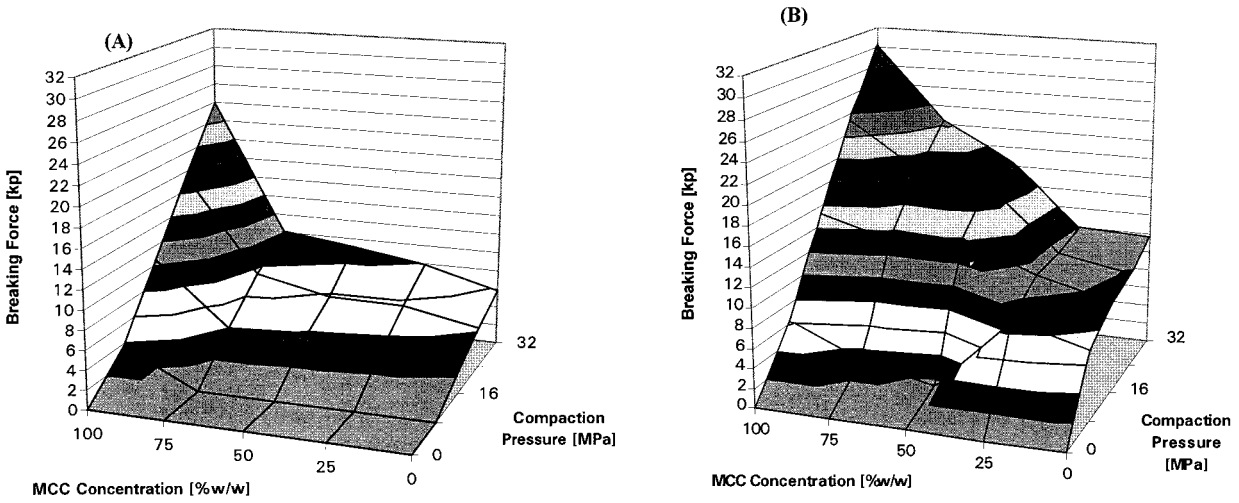

Figure 4. Breaking force vs. compaction pressure and MCC concentration of ibuprofen tablets (formulations I, VII–X) produced (A) conventionally and (B) with ultrasound (US amplitude 7 μm, US time 2 sec). Results are the means of six determinations.

Figure 3 shows that the strongest compacts were produced by ultrasound-assisted compaction for a 50% w/w mixture of ibuprofen and DCP, with breaking forces of up to 13.1 kp, approximately three times higher than the breaking forces of conventionally prepared tablets. It is interesting to note that the tablets produced with ultrasound from 50% w/w and 75% w/w mixtures of ibuprofen with DCP exhibited higher breaking forces compared with tablets made from the individual materials.

Figure 4 shows that at 32 MPa ultrasound application resulted in an increase in the breaking forces, in relation to the breaking forces of the tablets prepared conventionally, from 7.9 to 11.9 kp, from 9.1 to 18.6 kp, and from 10.1 to 22.5 kp, for 75% w/w, 50% w/w, and 25% w/w mixtures of ibuprofen with MCC, respectively.

It was found that for ibuprofen mixtures with DCP and MCC, positive interactions occurred due to the bonding between particles of these materials. The higher breaking force values of the tablets made from the blends of ibuprofen with DCP and MCC compared with the tablets compacted from mixtures containing no filler may be explained by the fact that the drug–drug bonds induced by ultrasound were weaker than the drug–filler bonds.

It was found that the behavior of MCC mixtures appeared to be proportional to the concentration of each component. When MCC concentration was increased, tablets with higher mechanical strengths were obtained. On the other hand, the breaking forces of the tablets prepared from ibuprofen formulations with DCP were not a simple function of the individual components. The effect of ultrasound on breaking forces of the tablets produced from ibuprofen mixtures with DCP could be explained by the fact that the dihydrate starts losing its water of crystallization at temperatures below 100°C. During ultrasound-assisted compaction under the combined influence of temperature and pressure, the material at particle contact points might lose some of its water of crystallization and the area of contact between particles would increase, probably as a result of the formation of crystal bridges. This could be the reason for an increase in the mechanical strength of compacts prepared with ultrasound compared to conventionally produced tablets.

On the basis of these results, it can be concluded that DCP and MCC offer good potential as excipients for ultrasound-assisted compaction of ibuprofen. Blends of these fillers with the drug produced tablets with a wide range of breaking forces, depending on compaction pressure and DCP and MCC concentration.

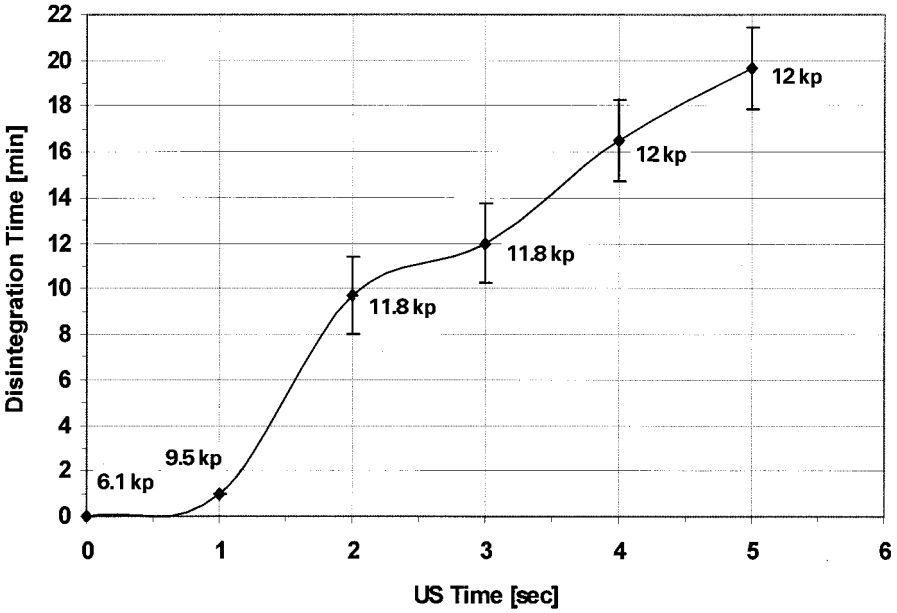

Figure 5. The effect of ultrasound on the breaking forces and disintegration times of ibuprofen tablets (formulation II) produced at 32 MPa. Results are the means and standard deviations of six determinations.

The Effect of Ultrasound on Tablet Disintegration Time

The relationship between US time, breaking force, and disintegration time for ibuprofen compacts (formulation II) is shown in Fig. 5. An increase in US time resulted in an increase in tablet disintegration times.

Taking into account the data presented in Fig. 5 it is possible to determine the optimal US time which would allow a tablet to be produced sufficiently strong to maintain its integrity, but not so strong as to adversely affect its disintegration time. An increase in the breaking force of ibuprofen tablets from 5.5 to 9.5 kp and from 9.5 to 11.7 kp occurred when ultrasound was applied for 1 and 2 sec, respectively. Longer ultrasound applications resulted in an insignificant increase in tablet breaking force, together with a sharp increase in disintegration time from 10 to 20 min. The results suggest that for formulation II, ultrasound should ideally be applied for no more than 2 sec.

The decrease in the disintegration rate of the tablets prepared by ultrasound-assisted compaction is probably due to an increase in compact density together with an increase in the interparticulate bonding due to the fusion of particle surfaces. These changes result in the reduction of void space, which reduces the rate of water penetration into the compact and, consequently, increases the disintegration time. Another possible mechanism for prolonging disintegration times of ibuprofen tablets could be the presence of a hydrophobic (19) outer skin of ibuprofen. This layer forms when melted ibuprofen is forced out of the interparticulate voids within the tablet during ultrasound-assisted compaction. The melted material collects at the surface, restrained by the punches and die, and then solidifies.

Figure 6 shows the effect of ultrasound on disintegration times of ibuprofen tablets containing DCP (formulations XI–XIII) and MCC (formulations XV–XVII). It was found that ibuprofen tablets produced conventionally from DCP and MCC mixtures disintegrated instantly. As far as compacts prepared with ultrasound are concerned, those prepared from blends of ibuprofen with DCP and MCC exhibited faster disintegration than those produced from mixtures containing no fillers. When DCP and MCC concentration was increased, tablet disintegration occurred more readily.

The studies showed that ultrasound application during compaction resulted in a general decrease in tablet disintegration rate. An increase in disintegra-

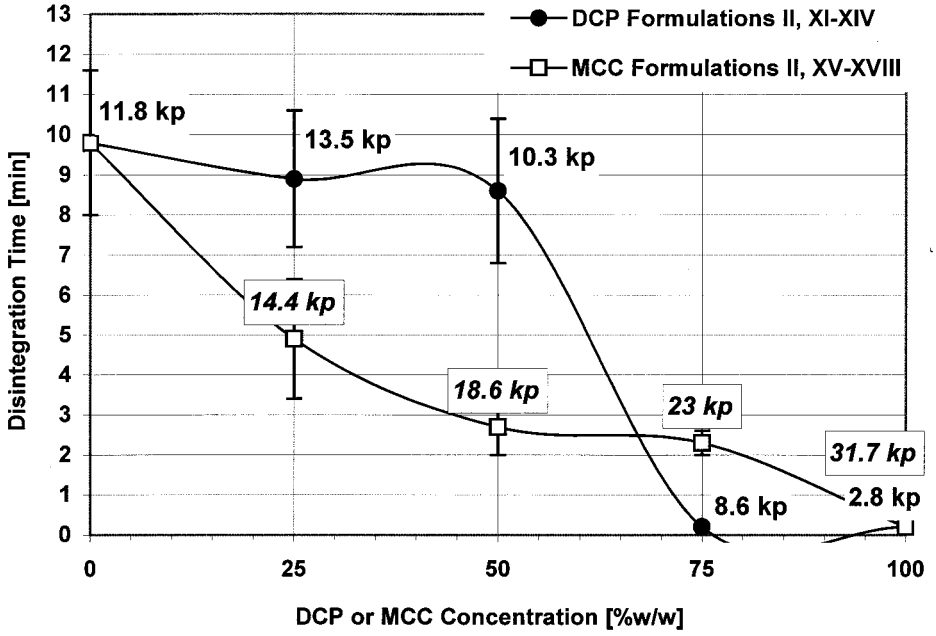

Figure 6. The effect of DCP (formulations II, XI–XIV) or MCC (formulations II, XV–XVIII) concentration on the disintegration times and breaking forces of ibuprofen tablets produced at 32 MPa with ultrasound (US amplitude 7 μm, US time 2 sec). Results are the means and standard deviations of six determinations.

tion time can be attributed to a modification in the rate of water penetration due to the changes in tablet density and interparticulate bonding. It was found that two of the variables in this investigation had a major effect on the disintegration time: formulation and US time. Therefore, it is equally important to choose the right formulation and use the right US time in order to achieve a relatively high disintegration rate corresponding to the desired tablet breaking force.

Effect of Ultrasound on Ibuprofen Dissolution Rate

The dissolution studies were performed and, although it was expected that ibuprofen would dissolve very slowly from formulation I, the tests were carried out in order to evaluate what effect ultrasound had on drug dissolution rate from a simple formulation containing no disintegrant. Figure 7 shows that the dissolution profile of 5.8 kp ibuprofen tablets produced conventionally at 32 MPa is similar to the dissolution profile of the 12 kp tablets made with ultrasound applied for 5 sec.

Figure 8 represents the results of breaking force and dissolution tests for ibuprofen tablets, containing 5% w/w of crospovidone as a disintegrant (formulation II), prepared conventionally at 32 MPa and with ultrasound applied for 1, 2, and 5 sec. With an increase in US time ibuprofen dissolution rate decreased. Ultrasound application for more than 2 sec resulted in almost no increase in tablet breaking force, but there was a significant decrease in drug dissolution rate. At the same time, tablets prepared with ultrasound applied for 1 and 2 sec released 70% of ibuprofen after 11 and 27 min, respectively, which was below the upper limit of 30 min described in USP XXII (9).

In order to prove that a decrease in the dissolution rate of tablets prepared by ultrasound-assisted compaction was caused not only by an increase in density but also by an increase in interparticulate bonding due to the fusion of particle surfaces, two additional studies were performed. The aim of the first study was to compare the dissolution rates of conventionally prepared compacts, which had different apparent density and different breaking forces (Fig. 9). The aim of the second study was to compare the dissolution rates of two different

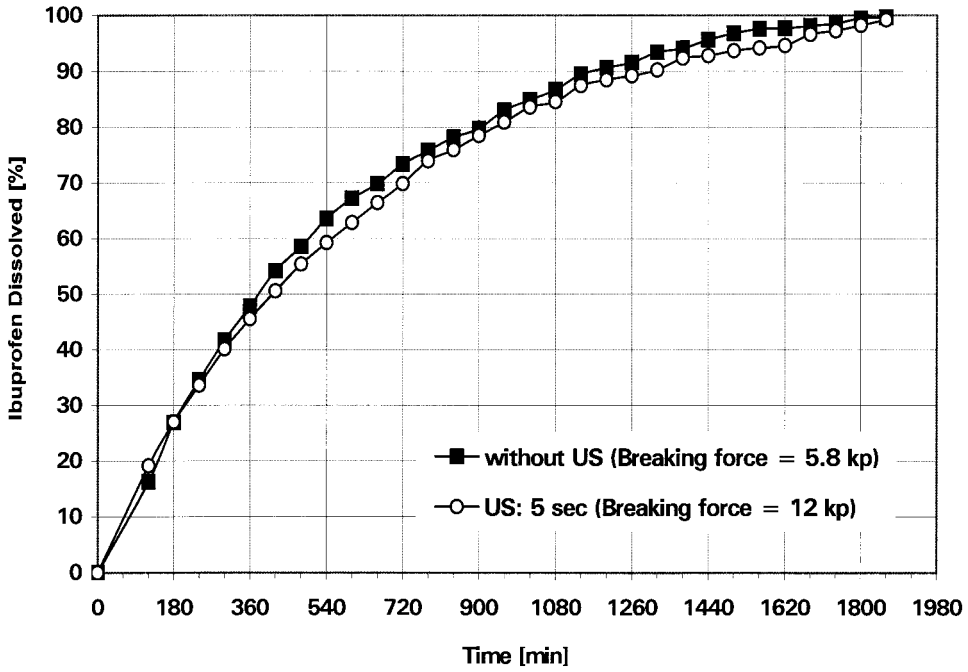

Figure 7. The effect of ultrasound (US amplitude 7 μm; US time 5 sec) on the dissolution rates of tablets containing 600 mg of ibuprofen and no disintegrant (formulation I) produced at 32 MPa. Test conditions: medium = 900 mL phosphate buffer (pH 7.2); basket at 150 rpm, 266 nm.

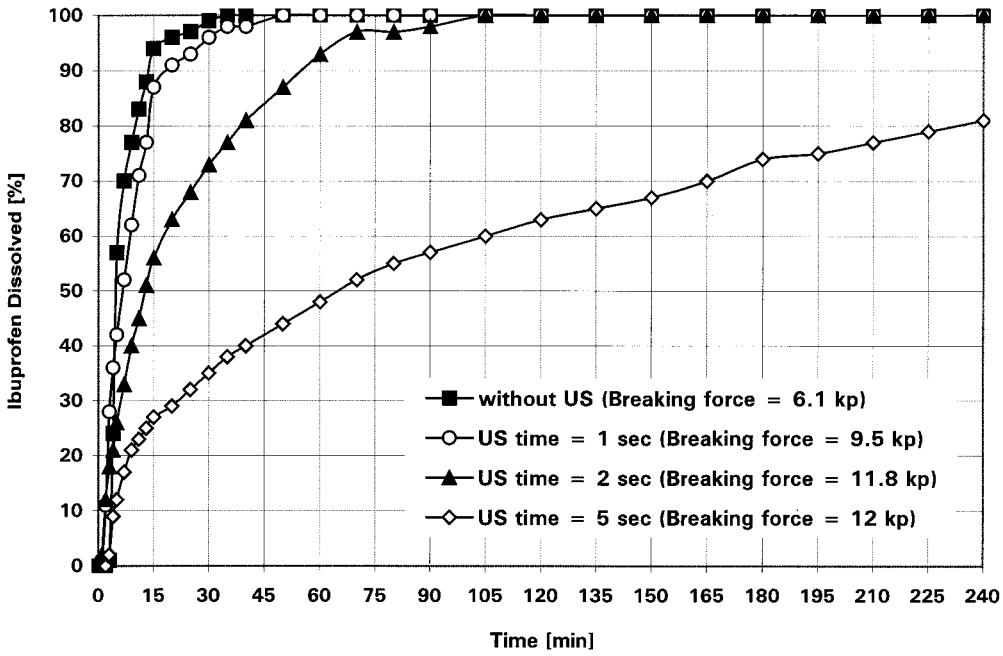

Figure 8. The effect of ultrasound on the dissolution rates of the tablets containing 600 mg of ibuprofen and 5% w/w of Crospovidone (formulation II) produced at 32 MPa. Test conditions: medium = 900 mL phosphate buffer (pH 7.2); basket at 150 rpm, 266 nm.

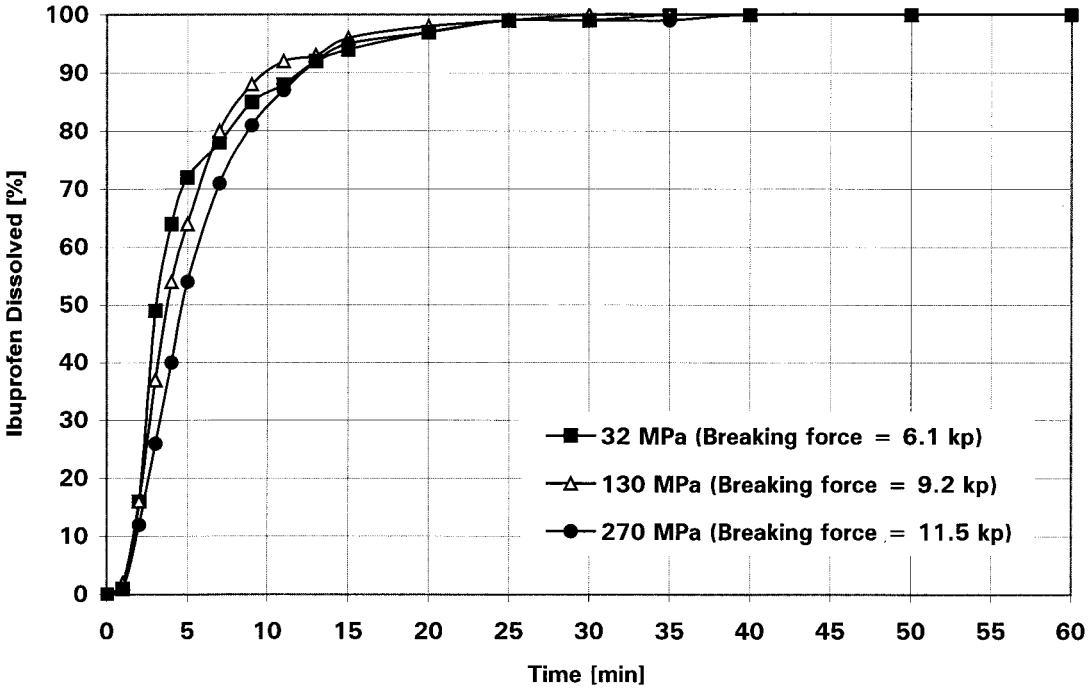

Figure 9. The effect of compaction pressure on the dissolution rates of tablets containing 600 mg of ibuprofen and 5% w/w of Crospovidone (formulation II) produced conventionally at 32 MPa. Test conditions: medium = 900 mL phosphate buffer (pH 7.2); basket at 150 rpm, 266 nm.

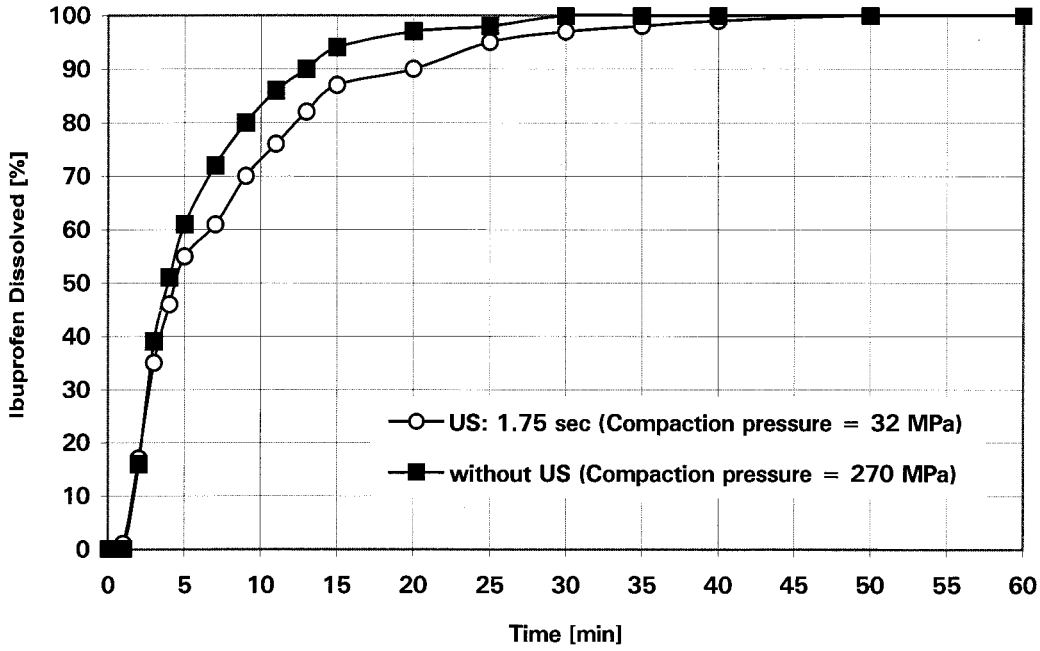

Figure 10. Dissolution profiles of tablets containing 600 mg of ibuprofen and 5% w/w of Crospovidone (formulation II) with the same breaking force (11.5 kp) produced with and without ultrasound at different compaction pressures. Test conditions: medium = 900 mL phosphate buffer (pH 7.2); basket at 150 rpm, 266 nm.

Table 3

The Effect of Compaction Pressure and Ultrasound on Apparent Density, Breaking Force, and Time Values for 50, 70, and 90% Drug Release from Ibuprofen Tablets (Formulation II). Results Are Mean±Standard Deviation, n *Denotes the Number of Determinations ("% Increase" Is the Value Increase in Relation to the Tablets Prepared Conventionally at 32 MPa)*

Compaction Pressure (MPa)	US Time (sec)	Apparent Density ($g/cm^3 \pm SD$) ($n=10$)	Breaking Force ($kp \pm SD$) ($n=10$)	$t_{50\%}$ ($min \pm SD$) ($n=3$)	$t_{70\%}$ ($min \pm SD$) ($n=3$)	$t_{90\%}$ ($min \pm SD$) ($n=3$)
32	—	1.022 ± 0.007	6.1 ± 0.7	3.0 ± 0.0	5.0 ± 0.0	12.0 ± 1.4
130	—	1.076 ± 0.004	9.2 ± 1.0	3.8 ± 0.4	5.5 ± 0.7	10.5 ± 0.7
% Increase		**5.3**	**50.8**	**27**	—	—
270	—	1.091 ± 0.006	11.5 ± 1.0	4.3 ± 0.5	6.8 ± 0.5	13.0 ± 0.7
% Increase		**6.8**	**88.5**	**43**	**36**	—
32	1.75	1.056 ± 0.002	11.5 ± 1.5	4.3 ± 1.1	9.3 ± 1.5	20.0 ± 2.0
% Increase		**3.3**	**88.5**	**43**	**86**	**67**

sets of tablets with the same breaking force of 11.5 kp, produced with and without ultrasound (Fig. 10). The results of both studies are summarized in Table 3. Although the tablets, prepared at higher pressures of 130 and 270 MPa, had higher breaking forces and apparent density, their ibuprofen dissolution rates were similar to those of the tablets produced at 32 MPa. Therefore, for conventionally prepared tablets (formulation II), an increase in apparent density and breaking force did not result in a significant decrease in drug dissolution rate.

Figure 10 and Table 3 show that although tablets compacted at 32 MPa with ultrasound applied for 1.75 sec, had lower apparent density of 1.056 g/cm^3 compared to 1.091 g/cm^3 for the tablets produced conventionally at 270 MPa, their dissolution rate was slightly slower. Therefore, it can be concluded that an increase in tablet density during ultrasound-assisted compaction cannot be the only reason for a decrease in ibuprofen dissolution rate.

Thus, the effect of ultrasound on ibuprofen dissolution rates from the tablets containing 5% w/w of Crospovidone as a disintegrant (formulation II) might be explained as follows. During ultrasound-assisted compaction, the energy delivered to the material in the die is high enough to cause melting and fusion of particle surfaces of ibuprofen and Crospovidone, increasing the bonding of the particles to one another. These changes, together with the changes in tablet density with less void space between particles, modified the rate of water penetration into the tablets and consequently the drug dissolution rate.

The effect of ultrasound on ibuprofen release from tablets containing filler was investigated for DCP and MCC formulations (Table 4). Overall, in both cases of DCP and MCC mixtures, ultrasound application resulted in a decrease in the drug dissolution rate compared to the tablets produced conventionally. An increase in DCP and MCC concentration resulted in an increase in ibuprofen dissolution rate from the tablets produced with ultrasound. It is interesting to note that the difference in the dissolution rates between tablets prepared conventionally and by ultrasound-assisted compaction becomes less profound with an increase in DCP and MCC concentrations.

The dissolution studies showed that ultrasound-assisted compaction, in comparison to conventional compaction at the same pressure, produces tablets with higher apparent density, breaking forces, and slower dissolution rates. The decrease in dissolution rate was found to be a function of US time and formulation.

Temperature Measurement

Generally, during ultrasound-assisted compaction heating of the material in the die takes place. Temperature rise is thought to be due to ultrasound energy dissipation converted into heat. Temperatures of upper and lower surfaces of 0.6 g ibuprofen

Table 4

The Effect of Ultrasound Applied for 2 Sec During Compaction at 32 MPa on Ibuprofen Dissolution Rate as a Function of DCP or MCC Concentration. Results Are the Means of Three Determinations

DCP Concentration (% w/w)	Absolute Value/Increase Compared to "Without US"(min)/(min)		
	$t_{50\%}$	$t_{70\%}$	$t_{90\%}$
0 (formulation II)	13/8	27/19	54/39
25 (formulation XI)	10/4	17/7	42/16
50 (formulation XII)	7/1	15/5	36/13
75 (formulation XIII)	4.5/1	10/2	28/4
MCC Concentration (% w/w)	$t_{50\%}$	$t_{70\%}$	$t_{90\%}$
0 (formulation II)	13/8	27/19	54/39
25 (formulation XV)	3/0	6/1	16/4
50 (formulation XVI)	3/0	6/1	12/3
75 (formulation XVII)	2/0	4/0	11/1

Table 5

The Effect of US Time on Temperature Rise During Ultrasound-Assisted Compaction (US Amplitude 7 μm) of 0.6 g Ibuprofen Tablets (Formulation I) at 32 MPa

US Time (sec)	Tablet Surface Temperature (TST) (°C)	Total Temperature Increase (Room Temperature[a] − TST) (°C)
0 (without ultrasound)	34	10
1	43	19
2	54	30
5	60	36

[a]Room temperature = 24± 2°C.

tablets (formulation I) were measured during compaction at 32 MPa with ultrasound applied for 0–5 sec. Table 5 shows that tablet surface temperature (TST) increased during both conventional and ultrasound-assisted compaction. However, ultrasound application resulted in a greater temperature rise compared to that within the tablet produced without ultrasound. An increase in US time from 1 to 2 and 5 sec resulted in a TST rise from 43 to 54 and 60°C, respectively. Therefore, taking into account that ibuprofen melts at 76°C, it can be assumed that on a macro-level no material degradation could occur during ultrasound-assisted compaction.

To investigate the effect of US amplitude on material heating, temperature measurements were taken during ultrasound-assisted compaction of 0.6 g DCP tablets at 32 MPa. Table 6 shows that an increase in US amplitude from 5 to 7 μm and from 7 to 13 μm resulted in an increase in temperature within the compacts from 40 to 54°C and from 54 to 99°C, respectively. Pronounced increases in the temperature of DCP tablets occurring in the course of both conventional and ultrasound-assisted compaction could result in a partial loss of crystalline water of DCP. This loss is most likely to occur during ultrasound-assisted compaction at higher US amplitude of 13 μm. However, the temperatures of 150 and 190°C, which correspond to 0.5 and 2 mol loss of crystallization water (20,21), were not reached.

By comparing the temperatures on the upper and lower surfaces of ibuprofen and DCP tablets it was found that the temperature rise at the interface between the compact and the horn was approximately the same as the temperature rise recorded at the interface between the compact and the lower

Table 6

The Effect of US Amplitude on Temperature Rise During Ultrasound-Assisted Compaction of 0.6 g DCP Tablets at 32 MPa with Ultrasound Applied for 2 sec

US Amplitude (μm)	Tablet Surface Temperature (TST) (°C)	Total Temperature Increase (Room Temperature[a] – TST) (°C)
0 (without ultrasound)	34	10
5	40	16
7	54	30
13	99	75

[a]Room temperature = 24° ± 2°C.

punch. However, it should be taken into account that a possible error of 3–6°C exists in the method used for temperature measurement.

It is important to emphasize that the temperatures reported above actually represent the mean tablet surface temperature, which is not the local temperature achieved on the microscopic level. Even in a case of conventional powder compaction, according to Hanus and King (22), the local temperatures in the powder bed at the points of contact may be momentarily several hundred degrees. That can also be true for ultrasound-assisted powder compaction.

According to Bateman et al. (23), temperature has an effect on the tablet bonding strength. Esezobo and Pilpel (24) found that as the temperature within the tablet was increased during conventional compaction, the extent of plasticity and stress relaxation increased, while elasticity decreased, resulting in an increase in tablet mechanical strength. This might also apply to ultrasound-assisted compaction. A warmer and more ductile compact enables plastic deformation and stress relaxation to occur more readily and produce an increase in particle–particle contact, resulting in stronger tablets. Besides, fusion bonding might contribute to the increase in mechanical strength of the tablets produced with ultrasound. As described above, on the macro-level, the temperatures recorded on the upper and lower tablet surfaces were not high enough to melt or degrade the material. However, on the microscopic level, local temperatures achieved during ultrasound-assisted compaction might be high enough to facilitate interparticular bonding by asperity melting. Therefore, it can be assumed that with an increase in US amplitude and irradiation time, the temperature within the compact increases, more solid bridges develop between particles and, finally, stronger tablets are obtained.

It is most likely that a significant part of the temperature increase generated by ultrasonic vibrations was dissipated to the die due to the relatively high coefficient of thermal conductivity of metal compared to the conductivity coefficients of most materials made into tablets (25). The rest of the mechanical energy delivered by the ultrasonic horn probably manifested itself by increasing compact temperature.

The energy expenditure (Q) in the process of powder compaction may be calculated from the temperature rise (dT, in °C), the weight of the tablet (m), and the specific heat of the compressed material (C) (10,22,25,26):

$$Q = Cm(dT) \tag{2}$$

The specific heat of Emcompess is 2.5 J/(°C g) (27). Consequently, to achieve an increase of 75°C in the temperature of 0.6 g of DCP tablets compressed by ultrasound-assisted compaction (power output at maximum, US amplitude 13 μm, US time 2 sec), the energy needed is approximately 112.5 J. The power output of the ultrasonic compaction rig generator at maximum power output is 150 W. This means that the energy produced by the generator during 2 sec would be 300 J. Therefore, approximately 37.5% of the energy produced by the generator is used in the heating of the sample.

The Effect of Ultrasound on Crystalline Structure of Ibuprofen and DCP

Although the TSTs recorded during ultrasound-assisted compaction of ibuprofen were below the melting point of the drug, this did not eliminate the possibility of partial ibuprofen melting in areas other than the tablet surfaces. X-ray diffraction analyses were performed to study any possible polymorphic changes that could have occurred in the material treated with ultrasound.

The diffraction angles (θ) at which peaks occur (Bragg angles) were converted to crystal interplanar spacings (d) by means of the Bragg equation (9):

$$d = n\lambda/2 \sin\theta \qquad \text{for } n = 1, 2, 3 \ldots \tag{3}$$

where n is the diffraction order and λ is the wavelength of x-rays. The study showed that the XRD pattern of ibuprofen powder (the reference sample), and all ibuprofen samples subjected to ultrasound applied for up to 5 sec, appeared to be identical. Results of the XRD studies confirmed that no changes in crystalline structure of ibuprofen occurred during ultrasound-assisted compaction with ultrasound applied for up to 5 sec (US amplitude 7 μm).

X-ray diffraction studies were also performed for DCP. According to De Haan et al. (21), DCP decomposes below 100°C with a loss of water of crystallization. The study showed that the XRD pattern of DCP powder (the reference sample), and all samples subjected to ultrasound, appeared to be identical. X-ray diffraction observations revealed that no structural rearrangement occurred which otherwise accompanies dehydration of DCP, and the pattern of the hydrate structure persists in all samples ultrasonically treated for 2 sec with US amplitude being in the range of 5–13 μm.

Scanning Electron Microscopy Studies

Qualitative inspection of the tablets by means of electron microscopy was conducted in order to find out what effect ultrasound had on the microstructure of tablets prepared by ultrasound-assisted compaction.

Figure 11 allows a comparison between the upper surface views of two ibuprofen tablets (formulation I) to be made. One of the tablets was produced conventionally, the other by ultrasound-assisted compaction. It can be seen that a tablet produced with ultrasound has a smoother surface in comparison to the surface of the compact prepared conventionally. This suggests that the surface of the tablet treated with ultrasound partially melted and acquired this smooth finish. Rises in temperature of between 19 and 36°C were recorded during ultrasound-assisted compaction of ibuprofen, which represent average temperature rises for the upper and lower surfaces of the tablets. None of the recorded temperatures exceeded the temperature of ibuprofen melting (76°C). However, this does not eliminate the possibility of local temperature rises at the contact points of the powder particles. It can be assumed that when pressure and ultrasonic vibrations are applied to a powder bed, they are transmitted via the surface asperities at their actual points of contact, resulting in high pressures and elevated temperatures existing at these points where melting may occur. Solidification will then take place with the formation of fusion bonds between the particles.

The hypothesis of the melting of particle surface asperities is not a new idea. Jayasinghe et al. (28) assumed that powder particles are only in contact at the tips of their asperities. Consequently, when pressure is applied to a powder bed, it will act initially at these points and very high pressures will develop locally. Bowden and Tabor (29) estimated the ratio of the true area of powder particle contact to the apparent area of contact in the range of 1/1000–1/10,000. York and Pilpel (30) suggested that the pressure at points of contact would be in the order of hundreds of atmospheres. According to Jayasinghe et al. (28), such pressure could reduce the melting point of the material by one or two hundred degrees Celsius. From thermodynamic considerations, Skotnicky (31) derived an equation which predicts that under applied pressure the melting point of a solid (θ_m) is lowered by an amount $d\theta_m$:

$$d\theta_m/dP = -V\theta_m/L \tag{4}$$

where θ_m is a melting point (absolute temperature), $d\theta_m/dP$ is a change in melting point with pressure, V is a volume per gram of solid, and L is the latent heat of fusion (cal/g).

This study also showed that the region experiencing the greatest localized temperature rise was the material in contact with the upper punch

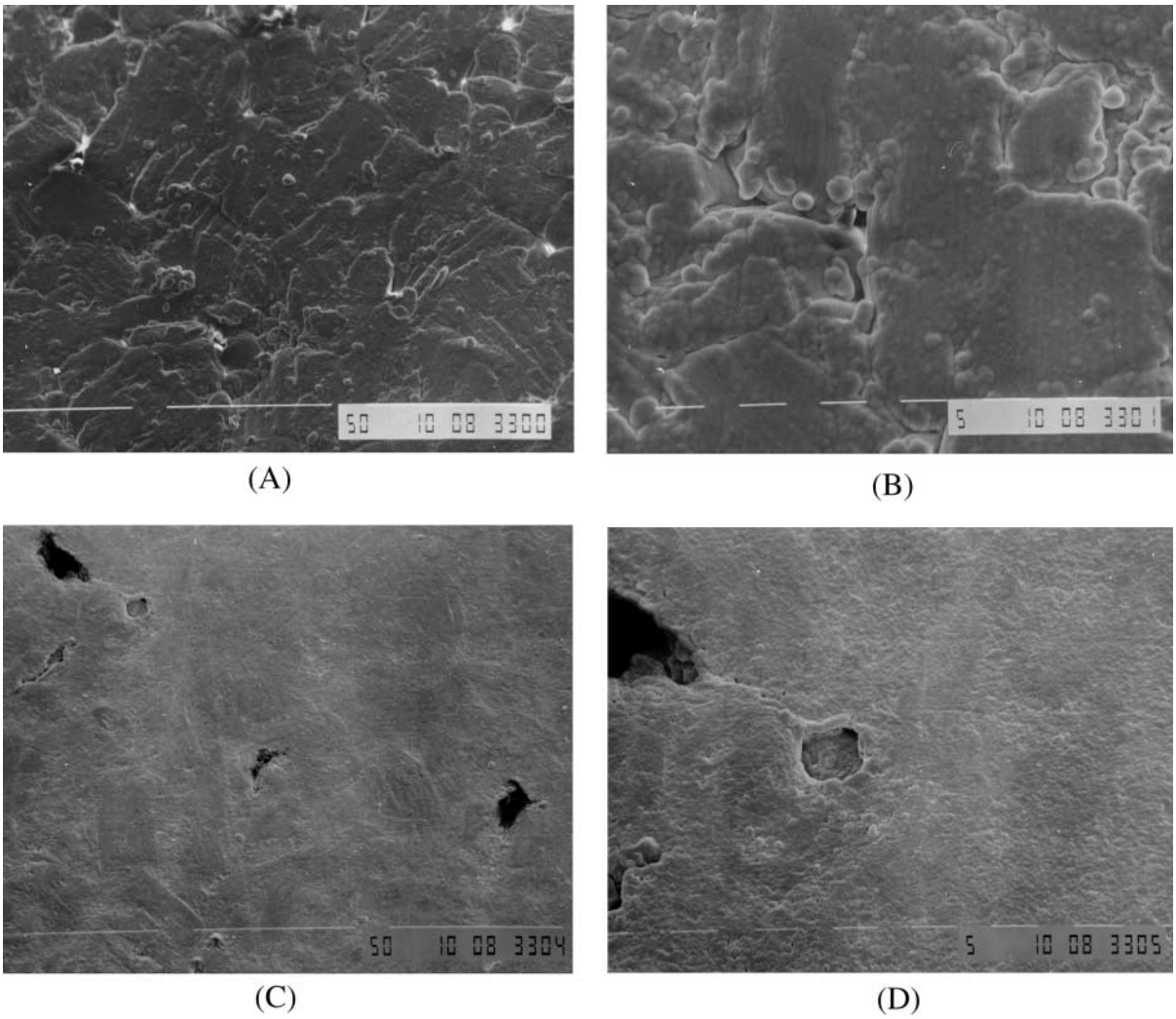

Figure 11. Scanning electron micrographs of upper surfaces of ibuprofen tablets (formulation I) produced at 32 MPa without ultrasound [magnification: (A) ×350, (B) ×1000] and with ultrasound [US amplitude 7 μm, US time 5 sec; magnification: (C) ×350, (D) ×1000].

face, through which the ultrasonic vibrations were delivered. It is believed that in this area, for a material with a low melting point such as ibuprofen, melting may well progress beyond the particle asperities. As a result of asperities melting, the area of contact between the powder particles increases; the melted material solidifies to form solid bridges, causing an increase in the strength of the powder bed. The presence of many sinter bridges is one of the reasons for the general increase in the mechanical strength, disintegration, and dissolution time of the tablets produced with ultrasound. According to Führer (32), it is to be expected that compacts with sinter bridges between the particles will be very strong, with relatively slow disintegration and dissolution rates.

CONCLUSIONS

An ultrasonic compaction rig was used to investigate the effect of ultrasound on the compaction properties of ibuprofen. Normally this drug has poor compaction properties and produces tablets that are weak and frequently exhibit capping. The results suggest that the compaction properties of

ibuprofen are significantly improved by ultrasound. It was found that coherent compacts could be produced with ultrasound application at pressures as low as 32 MPa, which was impossible by conventional compression.

Application of ultrasound before and after compaction was found not to be as effective as ultrasound applied during compaction. It was concluded that pressure should be applied together with ultrasound in order to achieve a better acoustical contact, which is required to transmit vibrations from the horn to the material, and also to cement the surfaces of the particles. It was found that breaking forces of the tablets prepared with ultrasound increased with an increase in compaction pressure, due to improved acoustical contact between the horn and the material, and better interparticulate contact of the powder.

Using temperature-sensitive labels it was found that thermal changes occur in powdered solids undergoing ultrasound-assisted compaction. Increases in temperature of tablets were related to US amplitude and US time. Compact heating was thought to be due to ultrasonic energy dissipation turned into heat.

X-ray powder diffraction studies of ibuprofen tablets prepared by ultrasound-assisted compaction at 32 MPa revealed that no changes in chemical or/and crystalline structure of the material occurred when ultrasound was applied for up to 5 sec (US amplitude 7 μm). An XRD study of DCP tablets produced at 32 MPa with ultrasound of different amplitudes (5, 7, 13 μm) applied for 2 sec showed that no material deterioration occurred in all tested samples.

It was found that formulation had a profound effect on the results of ultrasound-assisted compaction. This study showed that a combination of ibuprofen with DCP and MCC optimized the compaction characteristics of formulations subjected to ultrasound-assisted tabletting. The results show that the application of ultrasound is beneficial for all formulations studied here, since in all cases tablet breaking forces significantly increased. It was also found that formulations of ibuprofen with DCP produced tablets with higher breaking forces than the individual materials. This was attributed to positive interactions taking place due to the bonding between the materials. The higher breaking force values of the tablets compressed from blends of the drug with DCP compared with the compacts compressed from pure ibuprofen may be explained by the fact that the drug–drug bonds induced by ultrasound were weaker than the drug–filler bonds.

This study also showed that the tablets produced by ultrasound-assisted compaction had higher (up to 14.4%) apparent density than those made conventionally. Ultrasound appears to improve the rearrangement of the powder particles, eliminating the badly compacted zones, and provide energy for partial melting of asperities and subsequent fusion of particle surfaces, so increasing interparticulate bonding. These changes were thought to result in a reduction of void space, which reduced the rate of water penetration into the compacts and consequently increased tablet disintegration and drug dissolution times. The studies revealed that disintegration and ibuprofen dissolution times for the tablets produced by ultrasound-assisted compaction were related to US time and tablet formulation. An increase in US time generally resulted in a more or less profound disintegration and dissolution rate decrease, which was a function of the formulation studied.

Tablets prepared by ultrasound-assisted compaction from the blends of ibuprofen with DCP and MCC exhibited faster disintegration and ibuprofen dissolution rate compared to the compacts compressed from the mixture containing no fillers.

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