The Effect of Ultrasonic Vibration on the Compaction Characteristics of Paracetamol

MARINA LEVINA, MICHAEL H. RUBINSTEIN

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, United Kingdom

Received 2 August 1999; revised 23 November 1999; accepted 23 December 1999

ABSTRACT: An ultrasonic (US) compaction rig has been developed that is 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 US on the compaction properties of paracetamol, a drug that produces tablets that are weak and frequently exhibit capping. It was found that coherent paracetamol tablets could be prepared by US-assisted compaction at pressures as low as 20 to 30 MPa. Application of US before and after compaction was not found to be as effective as US applied during compaction. The breaking forces of the tablets produced with US applied during compaction were found to be consistently significantly higher than when compaction was performed conventionally or with US applied before or after compaction. The application of US during compaction made it possible to increase tablet breaking force, typically by a factor of 2 to 5. It was concluded that pressure should be applied together with US 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.

US application during compaction also resulted in an increase in apparent density, in relation to the apparent density of conventionally prepared paracetamol tablets, of up to 12.8%. US appears to improve particle rearrangement and provide energy for partial melting of particle asperities and subsequent fusion of particle surfaces, thus increasing interparticulate bonding. Development of solid bridges between the particles during US-assisted compaction was observed on scanning electron photomicrographs. Solid bridge formation was thought to result in a reduction of void space, which in turn reduced the rate of water penetration into the compacts and consequently increased tablet disintegration and drug dissolution times.

It was found that the results of US-assisted compaction are influenced by formulation and US time. An increase in binder (polyvinylpyrrolidone) concentration and/or US time resulted in a significant increase in the breaking forces of paracetamol tablets produced with US. When paracetamol was mixed with a second material, such as dicalcium phosphate dihydrate and microcrystalline cellulose, stronger compacts were prepared by US-assisted compaction compared with the tablets containing no filler. Positive interactions were considered to have occurred as a result of US-induced bonding between the two materials.

Overall, the application of US was found to significantly improve the compaction properties of paracetamol. J Pharm Sci 89:705–723, 2000

Keywords: ultrasound-assisted compaction; tableting; paracetamol

INTRODUCTION

High-power ultrasonic (US) vibration has been used for many years to manufacture metallic, ceramic, or plastic compacts. However, US-assisted

Correspondence to: M. H. Rubinstein. (E-mail: M.H. Rubinstein@livjm.ac.uk)

Journal of Pharmaceutical Sciences, Vol. 89, 705–723 (2000)

compaction of pharmaceutical powders is still a rather novel technique and literature reports extend only over the past 6 years.

Gueret[1] applied US simultaneously with pressure to assist the compaction of pharmaceutical and cosmetic preparations 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 nonthermoplastic powders together.

Rodriguez et al.[2–3] described an US-assisted pharmaceutical tableting machine that was used for the compaction of formulations containing theophylline and Eudragit® (Röhm Pharma C.M.B.H., Weiterstadt, Germany). The powder mixtures were subjected to US vibrations at frequencies of between 20 and 40 kHz. Pressures used did not exceed 3 to 6 MPa. It was found that the tablets prepared by US-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 realizing sustained-release matrices by US-assisted compaction of simple mixtures containing theophylline, Eudragit®RL and Eudragit®RS. Tablets were prepared using the experimental US 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 using well-known polymers or copolymers, such as cellulose and its derivatives, polyamides, acrylic polymers, polyesters, polyvinylpyrrolidone, starch, polyethylene glycols, a delayed drug release could be obtained, whereas by selecting excipients, such as solid sugars and cyclodex trins, a much more rapid drug release was achieved.

The principal aims of this study were:

To build an ultrasonic compaction rig
To use the ultrasonic compaction rig to evaluate the compaction and drug release characteristics of paracetamol
To investigate the effects of incorporating excipients in with the drug

DEVELOPMENT OF THE US COMPACTION RIG

An US machining system (Sonorode System 150) manufactured by Kerry Ultrasonics Ltd. (Hitchin, Hertfordshire, UK) was purchased and modified for use in compressing powders. The original equipment was made up of two units: a high-frequency generator and a drill. The system generator had an automatic tuning, direct reading, and calibrated amplitude control. Maximum power output of the generator was equal to 150 W in stepped ratios. The unit used a lead-zirconate-titanate ceramic "sandwich" metal-to-metal construction transducer. It converted 20 kHz input current from the generator into mechanical energy.

Originally the system was used for the machining of hard and brittle materials. The process involved the generation of high-frequency vibrations at the end of a relatively soft metal cutting tool, to which a stream or slurry of abrasive powder, suspended in water, was directed. The cutting tool, vibrating in excess of 20 kHz, imparted a grinding action to the workpiece, although the tip-to-tip movement was very slight and did not normally exceed a total excursion in excess of 0.075 mm.

To be able to use the US system for compaction purposes, a new velocity transformer with amplitude transformation ratio equal to 4 was designed. It was manufactured by Kerry Ultrasonics Ltd. from low-density, high-strength acoustic metal alloy, titanium (6Al 4Va). The material has excellent acoustic properties and transmits US energy virtually without any loss.[7–8] The horn was tuned to give longitudinal rod vibrations at the system frequency (e.g., 19,950 ± 50 Hz).[9]

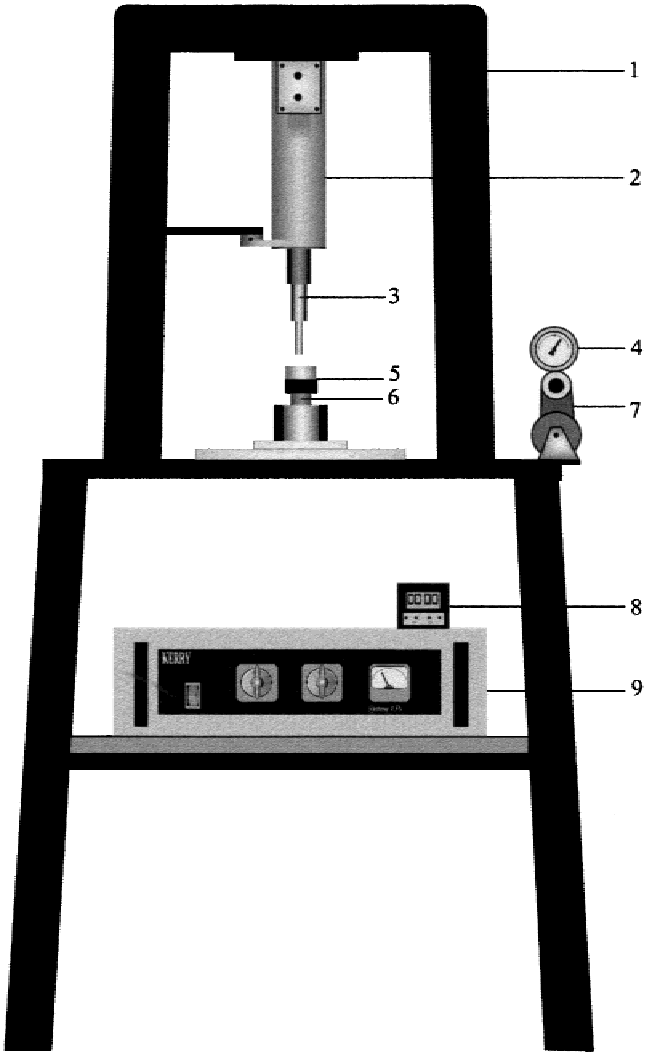
The transducer and horn were located in an assembly stand whose main function was to bring the horn face into contact with the workpiece to drill a hole in it, apply appropriate pressure, and retract the horn afterward. The pressure was not great and was applied with the help of a simple spring.

For compaction purposes higher pressures that could be measured were required. The application of pressure during US compaction serves two major functions. First, it provides good contact between an ultrasonic horn and a tablet for good energy transmission. Second, it causes the surfaces of the powder particles to flow and consolidate with the other particles. Therefore, a hydraulic hand pump (Gildon Ltd., Widnes, UK)

was incorporated into the assembly stand. The assembly stand was modified accordingly to accommodate the pump and to strengthen the whole structure of the system (Fig. 1).

The mechanical vibratory power delivered to a powder in a die is a product of horn velocity and the reaction force to the horn movement produced by the powder and the die. This reaction force is related to the pressure applied to the die. This is why it is important to have precise pressure control during US-assisted compaction. The US compaction rig was provided with a pressure gauge that was calibrated.

A 13-mm pellet die made of hardened stainless steel was supplied by Graseby Specac Ltd. (Kent, England). For compaction purposes the die was moved upward toward the coupler by the 16-mm stroke hydraulic cylinder of the Gildon pump, which applied the required static force to the material in the die. Accurate control of US exposure time is another parameter that is as important as pressure during US-assisted compaction. To control the time during which energy is applied to the material in the die, the US compaction rig was modified to include a plug-in digital timer (Model 814, Crouzet Ltd.). By these exten-



1. Assembly stand
2. Forced air cooled transducer assembly
3. Acoustic coupler
4. Pressure gauge
5. Die
6. Hydraulic pump cylinder
7. Hydraulic pump
8. Plug-in digital timer
9. Generator

Figure 1. US compaction rig.

sive modifications, an US machining system was developed into an US compaction rig capable of providing compaction pressure of up to 32 MPa together with high-power ultrasonic vibrations of 20 kHz to the powder or granular material in the die.

MATERIALS

Paracetamol manufactured by Rhone-Poulenc Chimie, France, was used. Crospovidone (Polyplasdone®, ISP Technologies, Wayne, England) was used as a disintegrant. Dibasic calcium phosphate dihydrate (DCP) manufactured as Emcompress® by Forum Chemicals Ltd. and microcrystalline cellulose (MCC) manufactured as Emcocel 90M® by Mendell, Surrey, England, were used as fillers to form 25% w/w, 50% w/w, and 75% w/w mixtures with respect to paracetamol.

Formulations used in this study were produced according to the data in Table 1.

All the mixtures, with the exception of formulations I[a] to VI[a], were prepared as follows:

1. Dry powders (with the exception of magnesium stearate) were weighted using an analytical balance (Model WA 205, Oertling, England) to an accuracy of ±0.5 mg and mixed for 10 min in a glass jar that was fixed to a bent arm attached to an electric motor (Model RZR1, Heidolph, Germany) rotating at 60 rpm.
2. 1% w/w of magnesium stearate (BDH, Poole, England) was added and further mixing was performed for 1 more min.

Formulations I[a] to VI[a] were prepared as follows:

1. Dry powders of paracetamol and polyvinylpyrrolidone (PVP) (Kollidon 90F®, BASF, Germany) were mixed for 10 min.
2. Distilled water was then added to the powder mixture using a fine sprayer (Model 2915, Haws Elliot Ltd., West Midlands, UK) to form a wet mass.
3. The mass obtained was pressed by hand through a 1.4-mm sieve and the fraction less than 0.6 mm was separated with a 0.6-mm sieve.
4. Granules of 0.6 to 1.4 mm were dried on a tray in an electronically controlled oven (Model UE400, Memmert GmbH & Co. KG, Schwabach, Germany) at 50°C for 17 h before use.
5. 1% w/w of magnesium stearate was added and further mixing was performed for 1 more min.

Table 1. Tablet Formulations Used in the Study

	Dry Weight Percentage in Formulation (%w/w)					
Formulation	Paracetamol	DCP	MCC	PVP	Crospovidone	Magnesium Stearate
I	99					1
I[a]	99					1
II[a]	98			1		1
III[a]	94			5		1
IV[a]	89			10		1
V[a]	79			20		1
VI[a]	89			5	5	1
VII		99				1
VIII			99			1
IX	74	25				1
X	49.5	49.5				1
XI	25	74				1
XII	74		25			1
XIII	49.5		49.5			1
XIV	25		74			1

[a] Granular material.

METHODS

US-Assisted Compaction

For most experiments (with the exception of drug dissolution studies, for which tablets of different weight were produced) 500 mg of the material required for each round, flat-faced tablet was separately weighed and manually loaded into the die. Tableting was then carried out on the US compaction rig, providing compaction pressures of up to 32 MPa together with high-power US vibrations of 20 kHz. US parameters (power output and US time) were set up before compression by controls available on the rig.

The dwell time under pressure was at least 1 sec.

US was applied before, during, and after compaction for different periods of time (up to 5 sec). Amplitude was monitored by means of the direct reading amplitude meter and manually recorded.

Before each compression, the face of the horn and die wall was cleaned with acetone.

Determination of Tablet Apparent Volume and Density

Tablet thickness and diameter were measured to ±0.001 mm using a 25-mm digital micrometer (Model 572-460, Mitutoyo). Apparent volume was calculated according to:

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

Where V is tablet apparent volume and 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 compression as the force required to fracture a compact in a diametrical compression test on a Schleuniger tablet hardness tester (Copley Instruments Ltd., Nottingham, England and Model 6D, Pharmatron, Solthurn, Switzerland). Results were presented in kilopounds (1 kp = 1 kg force).

Disintegration Studies

The standard BP[10] disintegration test was performed using a disintegration unit (BWI Manesty, Liverpool, England) 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 for 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[11] basket method at 37°C (±0.5°C).

Dissolution tests were performed with 1,000 mL of 0.1N hydrochloric acid. 0.1N HCl solution was prepared by diluting 8.5 mL of HCl with sufficient water to produce 1,000 mL.

For each test three tablets were weighed individually.

During dissolution, 0.25-mL samples were taken manually with a 1-mL pipette (Gilson, France) and diluted 1:20 with 0.1N hydrochloric acid.

Ultraviolet analyses of paracetamol in the solution were carried out using a diode array spectrophotometer (Model PU8625, Philips, Cambridge, England) at 244 nm. The instrument was calibrated before testing. Absorption was recorded manually. Then "mg drug released" was evaluated using a calibration chart. Percentage of paracetamol released was calculated taking into account dilution and tablet weight. Finally, the data obtained after correction and calculation were presented as dissolution profiles, whereby the amount of drug released was plotted as a function of time.

Temperature Measurement

Temperatures of upper and lower surfaces of 0.5 g paracetamol tablets (formulation I) were measured during compaction at 32 MPa without and with US (US amplitude = 7 μm) applied for up to 5 sec.

Self-adhesive temperature-sensitive labels supplied by RS Components Ltd. (England) were used for temperature measurement in the die during US-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.[12] The labels are normally accurate to ±1°C with an immediate response to temperature (<1 sec).

Scanning Electron Microscopy

Surface characteristics of tablets were assessed using a JSM-T200 scanning electron microscope (SEM) (JEOL, Japan). Specimens of whole tablets or tablet fractions were first mounted onto aluminium studs using silver-deg adhesive. The specimens were positioned so that a punch contact surface or a fractured edge could be seen. The studs were then placed in the coating chamber of a Polaron E5000 diode sputter-coating unit (Polaron Equipment Ltd., Watford, England). The chamber was evacuated, refilled with argon ,and the samples were coated with 24-carat gold emitted at 1.2 kV. During this process, the samples were subjected to elevated temperatures and greatly reduced pressures.

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 of different accelerating voltages were selected: 5, 10, or 15 kV. The choice of voltage depended on the melting point and 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, and the resulting secondary electrons emitted from its surface were collected by an electron detector. The image formed was seen directly on 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

Paracetamol was used to evaluate the effect of US on compaction properties. The material was chosen for detailed examination because it is a common drug that is used in relatively large quantities in pharmaceutical formulations. Paracetamol has poor compaction properties and produces tablets that are soft or that cap. It was found that US significantly improves the compaction properties of the drug (Fig. 2).

The Effect of Different US Regimens, Compaction Pressures, and Time of US Application on Tablet Breaking Force

Figure 2 shows how different US regimens affect the breaking forces of paracetamol tablets. All compacts produced without US were relatively weak, confirming poor compactability of the drug. Application of US *before* and *after* compaction resulted only in a slight, less than 2 kp, increase in tablet breaking force. According to Paul and Crawford[13] and Nayar and Benatar,[14] this can be explained by the absence of sufficient pressure during US application, resulting in poor horn-to-granules and horn-to-tablet contact and therefore poor transmission of energy. However, strong tablets were produced when US was applied *during* compaction. Breaking forces of the tablets made at 32 MPa with US applied *during* compaction significantly increased from 3.1 kp (without US) to 15.6 kp.

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

The results of this study also confirm the Ng and Benatar[15] report that mechanical strengths of the compacts produced with US could be improved with a higher compaction pressure. Figure 2 shows that the higher the pressure the stronger the tablets. With an increase in pressure from 8 to 16, 24, and 32 MPa, breaking force of the tablets produced with US applied during compaction increased from 8.8 to 12.3, 13.5, and 15.5 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 powder particles.

Figure 3 shows the effect of US time on tablet breaking force. An increase in US time resulted in a significant increase in tablet breaking force values. Forces to break the tablets compressed from

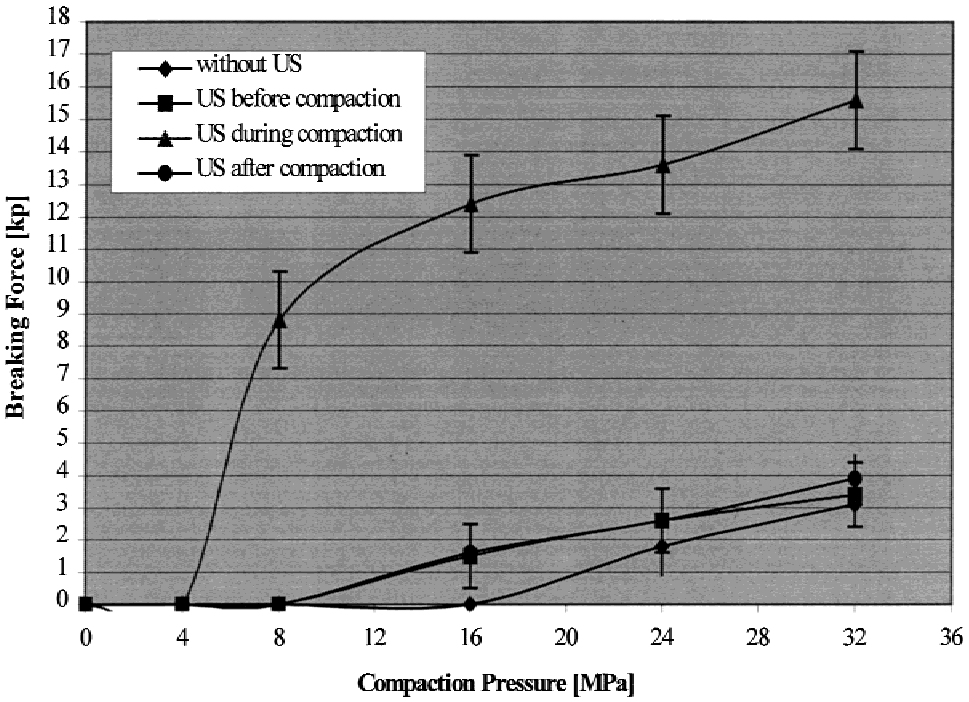


Figure 2. Effect of US (US amplitude = 7 μm; US time = 2 sec) on the crushing strength of paracetamol tablets (formulation IV[a]). Results are the means and standard deviations of 10 determinations.

formulation IV[a] increased from 2.8 kp (without US) to 6.2 kp (US time = 1 sec), 15.4 kp (US time = 2 sec), and 18.4 kp (US time = 3 sec). Breaking forces of the tablets compressed from formulation VI[a] increased from 3.4 kp (without US) to 6.8 kp (US time = 1 sec), 15.3 kp (US time = 1.5 sec), and more than 20 kp (US time = 2 sec).

Bicknell[16], Paul and Crawford[13], Matsuoka and Maeda[17], and Nayar and Benatar[14] suggested that during US-assisted powder compaction, the particles stick together because of melting at their surfaces. Therefore, anything that improves heat input to the material would be expected to increase mechanical strength of the resultant compacts. According to the results of this study, increasing US time had a marked effect on tablet breaking force.

The Effect of US on Tablet Apparent Volume and Density

Table 2 compares thickness, diameter, apparent volume, and apparent density of paracetamol tablets (formulation IV[a]) produced conventionally and by US-assisted compaction. There was a major decrease in the thickness (up to 10.9%) of the tablets produced with US compared with the tablets compressed conventionally, which resulted in a major decrease in the apparent volume (up to 11.4%) and in an increase in the apparent density (up to 12.8%).

It was also found that US application resulted in a slight decrease of 0.3 to 0.4% in tablet diameter compared with the compacts produced conventionally. It can therefore be assumed that after the ejection of the 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 produced compact 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, tablets prepared by US-assisted compaction exhibited better dimensional stability because of stronger bonding between the material particles and because the entrapped air can more easily escape during vibration. Therefore, compacts prepared with US are less likely to cap.

The results of this study (Table 2) confirm the findings of Lehfeldt[18] about the influence of US oscillations on the properties of compacts, their

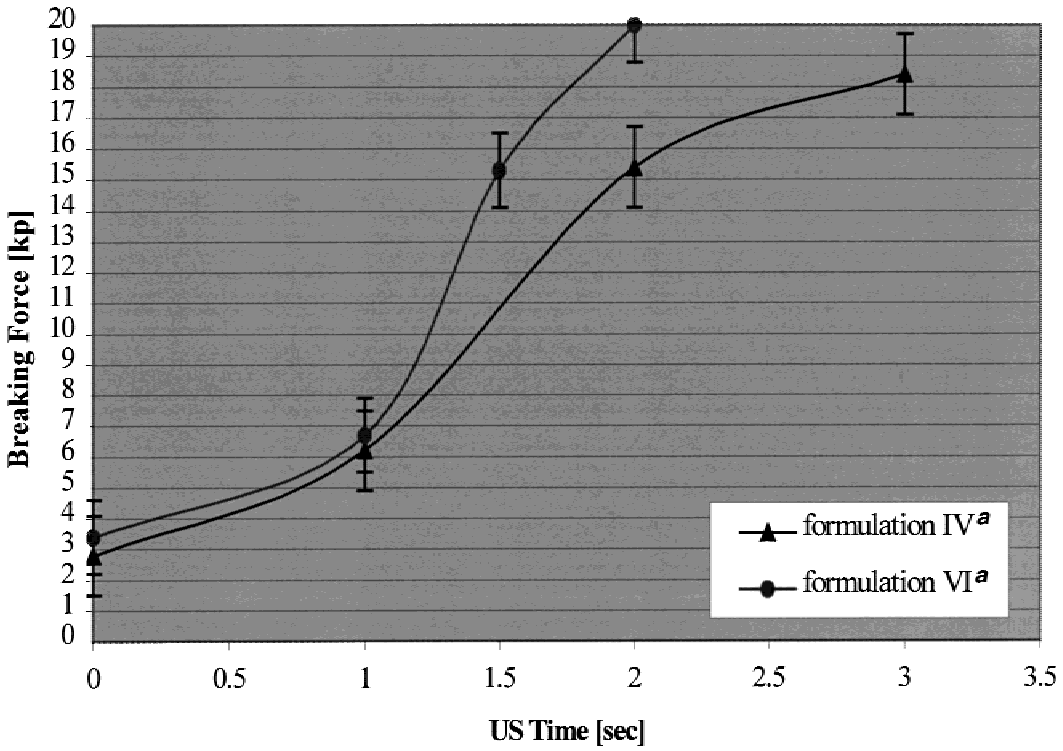


Figure 3. Crushing strength versus US time (US amplitude = 7 μm) of paracetamol tablets compressed at 32 MPa. Scale limit: 0 to 20 kp. Results are the means and standard deviations of 10 determinations.

density increase being greater at low pressures. An apparent density increase of paracetamol tablets prepared by US-assisted compaction in relation to apparent density of conventionally produced tablets was 12.8% and 10.9% for 24 and 32 MPa of compaction pressure, respectively. The increase in apparent density produced by US vibration at low compaction pressures can be explained as the result of "jarring and vibrating" the material particles. This allows particles to flow past each other more easily, reducing friction between the particles and so enhancing consolidation.

The results of this study suggest that US improves particle rearrangement and thereby increases compact density. Therefore, US vibrations can be used to produce more efficient pack-

Table 2. The Effect of Ultrasound (US) Applied for 2 Seconds during Compaction, on Thickness, Diameter, Apparent Volume, and Apparent Density of Paracetamol Tablets (Formulation IV[a])

Compaction Pressure (MPa)	US	Thickness (mm)	Diameter (mm)	Apparent Volume (cm^3)	Apparent Density (g/cm^3)
24	Without US	5.005 ± 0.052	12.613 ± 0.010	0.625 ± 0.007	0.960 ± 0.011
	With US	4.460 ± 0.044	12.574 ± 0.009	0.554 ± 0.006	1.083 ± 0.015
	% Decrease	10.9	0.3	11.4	—
	% Increase	—	—	—	12.8
32	Without US	4.826 ± 0.023	12.627 ± 0.011	0.604 ± 0.003	0.993 ± 0.007
	With US	4.389 ± 0.039	12.579 ± 0.006	0.545 ± 0.004	1.101 ± 0.001
	% Decrease	9.1	0.4	9.8	—
	% Increase	—	—	—	10.9

Results are the means and standard deviations of six determinations.

ing 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 Binder Concentration on Tablet Breaking Force

The effect of polyvinylpyrrolidone (PVP) concentration on the breaking force of paracetamol tablets (formulations I^a to V^a) is shown in Figure 4.

Binder additions were less effective in increasing mechanical strengths of conventionally produced tablets compared with the tablets prepared by US-assisted compaction. Breaking forces of the tablets compressed conventionally did not increase with increasing PVP content from 1 to 20% w/w and were generally independent of PVP concentration. On the other hand, the same increase in PVP concentration caused breaking forces of the tablets prepared by US-assisted compaction to rise from 5.3 to 17 kp.

The likely explanation for this phenomenon is that the binder agglomerated particles of paracetamol, producing a thin coat of a polymer around the drug particles. During US-assisted compaction, sinterization occurs as a result of the PVP coating melting. Therefore, an increase in PVP concentration results in an increase in the number of solid bridges developed within the material and consequently in an increase in tablet crushing strength.

The Effect of Filler Concentration on the Compaction Properties of Paracetamol

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.[19] MCC has superior binding and compaction characteristics because of its plastic deformation properties.[20]

Table 3 shows how DCP and MCC concentration affected the breaking forces of paracetamol tablets (formulations I, VII, VIII–XIV), prepared at 32 MPa conventionally and by US-assisted compaction. It can be seen that good overall performance of US-assisted compaction was achieved in relation to tablet breaking force for all formulations under test.

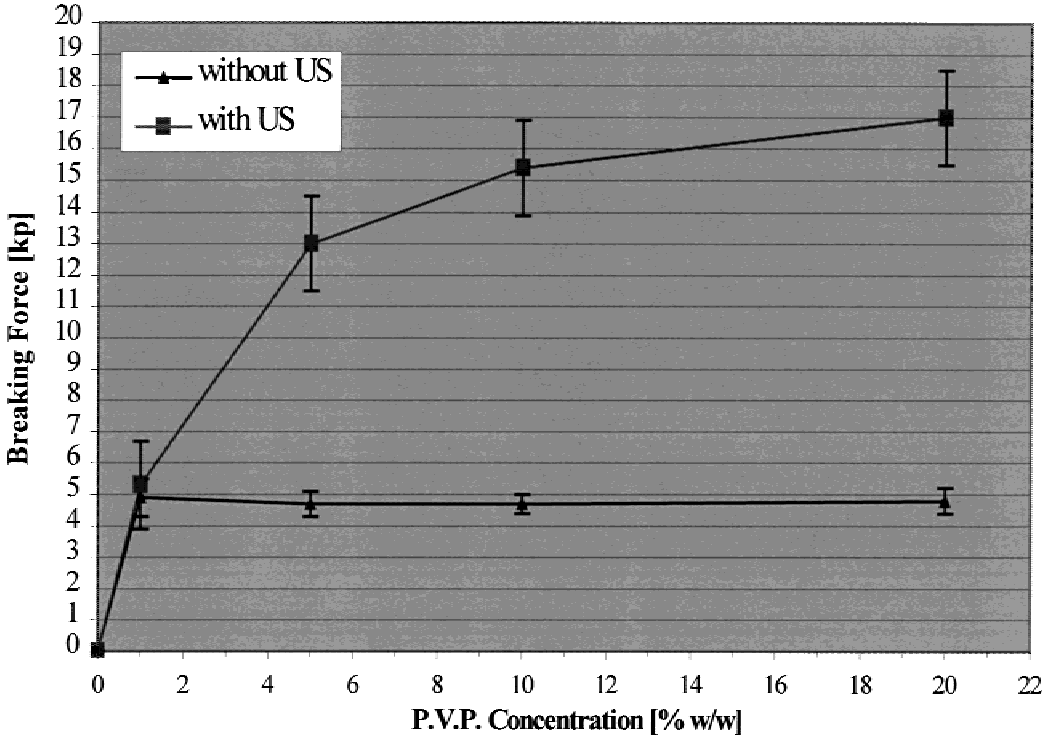


Figure 4. Crushing strength versus PVP concentration of paracetamol tablets (formulations I^a–V^a) compressed at 32 MPa with (US amplitude = 7 μm; US time = 2 sec) and without US. Results are the means and standard deviations of 10 determinations.

Table 3. The Effect of DCP and MCC Concentration on Breaking Force of Paracetamol Tablets (Formulations I, VII, VIII–XIV) Compressed at 32 MPa with and without Ultrasound

		Tablet Breaking Force (kp ± SD)				
Excipient	US	0%w/w of Excipient	25%w/w of Excipient	50%w/w of Excipient	75%w/w of Excipient	100%w/w of Excipient
DCP	Without US	0	0	0	0	0
	US: 2 sec	3.4 ± 0.4	6.4 ± 0.7	7.7 ± 0.9	2.6 ± 0.4	2.1 ± 0.6
MCC	Without US	0	0	3.5 ± 0.1	9.8 ± 0.5	23.9 ± 0.2
	US: 2 sec	3.4 ± 0.4	5.9 ± 0.4	6.1 ± 0.4	14.0 ± 1.0	30.2 ± 0.6

Results are the means and standard deviations of six determinations.

It was found that paracetamol in all formulations with DCP did not produce tablets at 32 MPa and below by compression alone. On the other hand, US-assisted compaction allowed production of relatively strong tablets, with breaking forces of up to 7.7 kp (Table 3 and Fig. 5).

The effect of MCC concentration on the breaking forces at different compaction pressures is illustrated in Figure 6 for conventionally prepared tablets and in Figure 7 for compacts produced with US.

For all formulations, tablets produced with US had higher breaking forces compared with the compacts produced conventionally. The strongest tablets were obtained at 32 MPa by US-assisted compaction with breaking forces of 30.2 kp and 14 kp, from pure excipient and 25% w/w mixture of paracetamol with MCC, respectively.

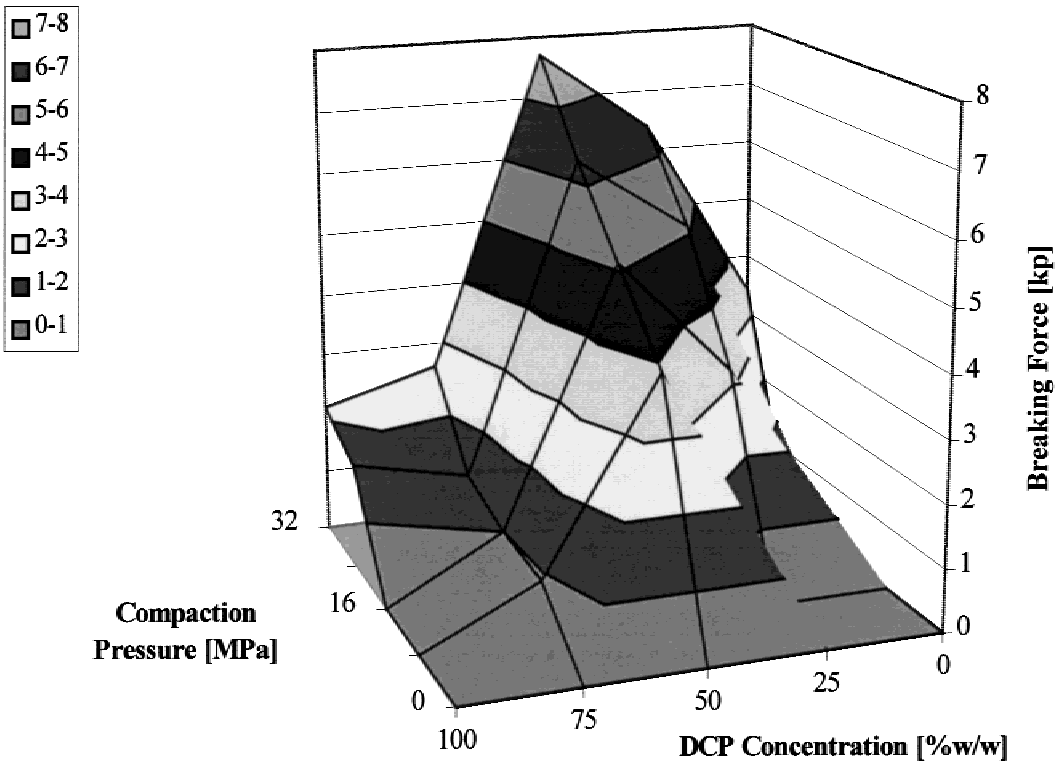


Figure 5. Crushing strength versus compaction pressure and DCP concentration of paracetamol tablets (formulations I, VII, and IX–XI) compressed with US (US amplitude = 7 μm; US time = 2 sec). Results are the means of six determinations.

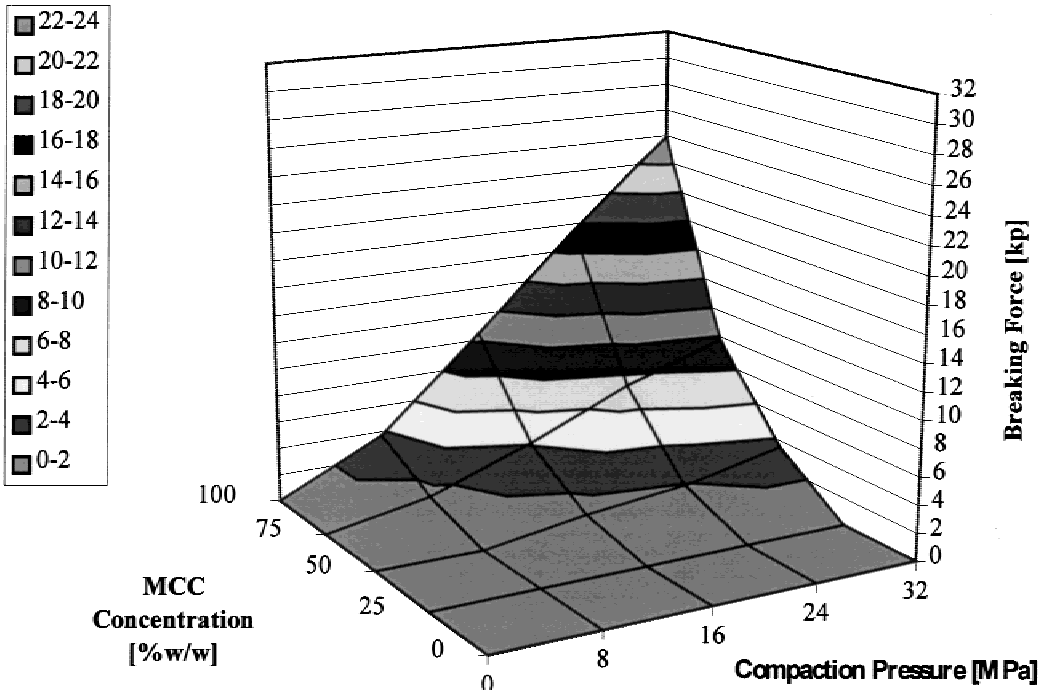


Figure 6. Crushing strength versus compaction pressure and MCC concentration of paracetamol tablets (formulations I, VIII, XII–XIV) compressed conventionally. Results are the means of six determinations.

The studies showed that for paracetamol mixtures with DCP and MCC, positive interactions occurred as a result of the bonding between particles of these materials. The higher breaking force values of the tablets compressed from the blends of the drug with DCP and MCC compared with the tablets compacted from pure paracetamol may be explained by the fact that the drug-drug bonds induced by US 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, stronger tablets were produced. On the other hand, the breaking forces of the tablets prepared from paracetamol formulations with DCP were not a simple function of the individual components.

The effect of US on the strengths of the tablets produced from DCP mixtures could be explained by the fact that the dihydrate starts loosing its water of crystallization at temperatures less than 100°C. During US-assisted compaction under the combined influence of temperature and pressure, the material at particle contact points might loose 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 strength of tablets prepared with US compared with conventionally produced compacts.

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

It was also found that at relatively low pressures (up to 32 MPa) MCC formulations produced stronger tablets compared with DCP mixtures by both conventional and US-assisted compaction. This can be attributed to the plastic nature of MCC and to the fact that solids that undergo plastic deformation to a large extent have a greater area of contact at low pressures and, consequently, a greater degree of bonding.[21] Thus, the plasticity of a crystal lattice may contribute to bonding regardless of the process involved, whether compaction with or without US. Therefore, it can be concluded that for US-assisted compaction at low pressures, materials that deform plastically bind better and can be considered to be

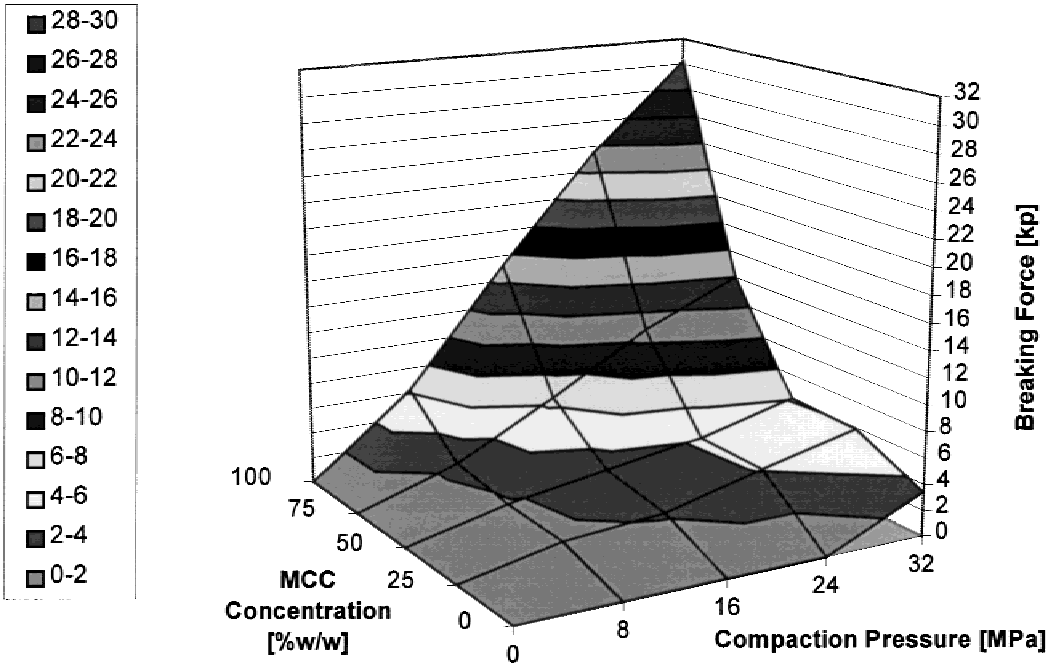


Figure 7. Crushing strength versus compaction pressure and MCC concentration of paracetamol tablets (formulations I, VIII, XII–XIV) compressed with US (US amplitude = 7 μm; US time = 2 sec). Results are the means of six determinations.

more suitable than materials undergoing extensive particle fragmentation.

The Effect of US on Tablet Disintegration Time

Figure 8 shows the relationship between US time, breaking force, and disintegration time for paracetamol tablets (formulation VI[a]) produced at a maximum pressure of 32 MPa.

An increase in US time resulted in an increase in tablet breaking force and disintegration times.

The data presented in Figure 8 also allow determination of 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. The results suggest that for formulation VI[a], the optimal US time would be in a range of 1 to 1.5 sec.

The decrease in the disintegration rate of the tablets prepared by US-assisted compaction is probably due to an increase in compact density together with an increase in the interparticulate bonding caused by 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.

The Effect of US on Paracetamol Dissolution Rate

Figure 9 shows drug dissolution rates in 0.1N HCl for tablets containing 500 mg of paracetamol and no disintegrant (formulation III[a]) prepared with and without US at different compaction pressures and US times. The results of apparent density measurements, breaking force, and dissolution tests are summarized in Table 4.

US application during compaction resulted in an increase in the apparent density, breaking forces, and drug dissolution times of paracetamol tablets compared with compacts prepared conventionally at 32 MPa. With an increase in US time, tablet apparent density, crushing strength, and dissolution time increased. When US was applied for 1, 2, and 5 sec at 32 MPa, the apparent density increased from 0.967 g/cm^3 (without US) to 1.004, 1.093, and 1.185 g/cm^{3,} respectively. The breaking forces of the tablets compacted at 32 MPa increased from 3.4 kp (without US) to 10, 13, and more than 20 kp for 1, 2, and 5 sec of US time, respectively. As a result, the dissolution time for 70% drug release increased from 27.5 min (without US) to 42, 54.5, and 59 min when US was applied for 1, 2, and 5 sec, respectively.

Figure 9 and Table 4 also allow a comparison to be made between dissolution rates of two tablets

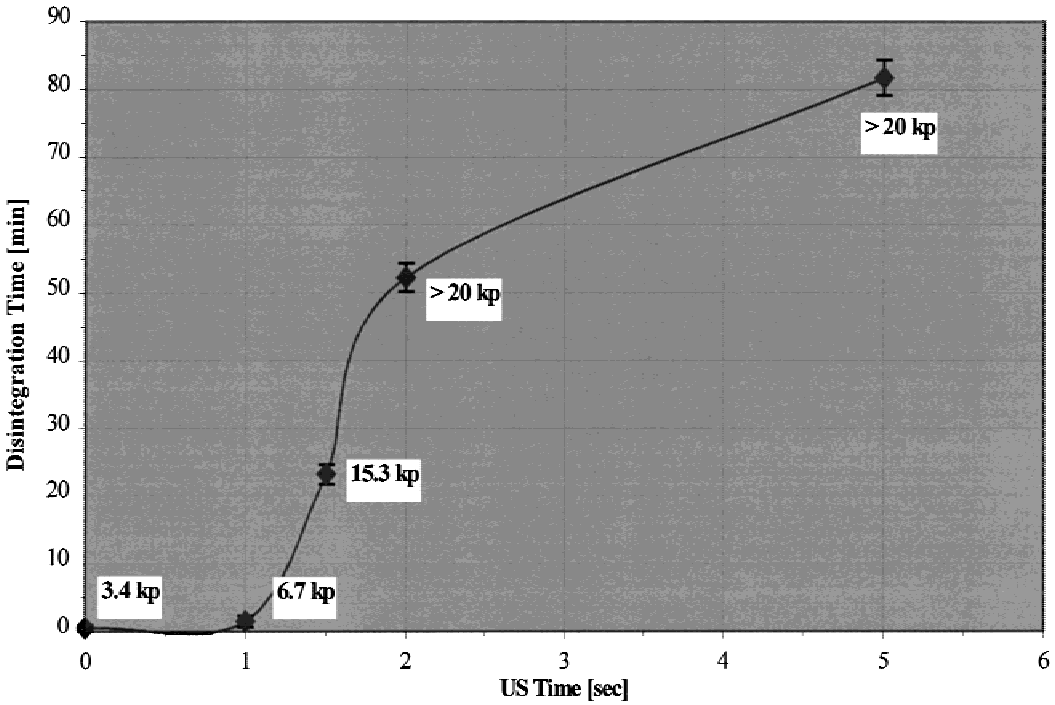


Figure 8. The effect of US on the crushing strengths and disintegration times of paracetamol tablets (formulation VI[a]) compressed at 32 MPa. Results are the means and standard deviations of six determinations.

with the same breaking force of 10 kp. One of the tablets was compacted conventionally at a compaction pressure of 119 MPa, the other by US-assisted compaction at 32 MPa with US applied for 1 sec. Although the compacts had the same breaking force, the tablets prepared at 119 MPa conventionally had a higher apparent density and slower dissolution rate compared with the tablets produced at 32 MPa with US.

Therefore, if a higher dissolution rate is required for tablets with a breaking force of 10 kp, for this particular formulation (formulation III*), it is preferable to use US-assisted compaction at a low pressure of 32 MPa than a conventional-pressure-only method at 119 MPa.

Figure 10 shows the results of breaking force and dissolution tests for tablets containing 500 mg of paracetamol and 5% w/w of crospovidone as a disintegrant (formulation VI[a]), produced conventionally and by US-assisted compaction. Tablets produced with US applied for 2 sec had very high breaking forces of more than 20 kp and relatively short dissolution times for 10, 50, and 70% of paracetamol dissolved.

The main delay in the drug release occurred after $t_{80\%}$. As a result of US application, particularly dense areas in a tablet with low disintegration rate might be created as a result of thermal fusion of the particles. Because US vibrations are directed by the horn to the upper surface of a compact, it can be expected that the density and disintegration time of the resulting tablet are greatest for its upper layers and gradually decrease to a minimum at the bottom of the compact, affecting uniformity of drug dissolution. The dissolution studies revealed that US-assisted compaction compared with 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 US-assisted compaction heating of the material in the die takes place. Temperature rise was thought to be due to US energy dissipation converted into heat.. It was found that tablet surface temperature (TST) increased during conventional compaction from 24 to 34°C. However, US application resulted in a greater TST rise from 24 to 60°C.

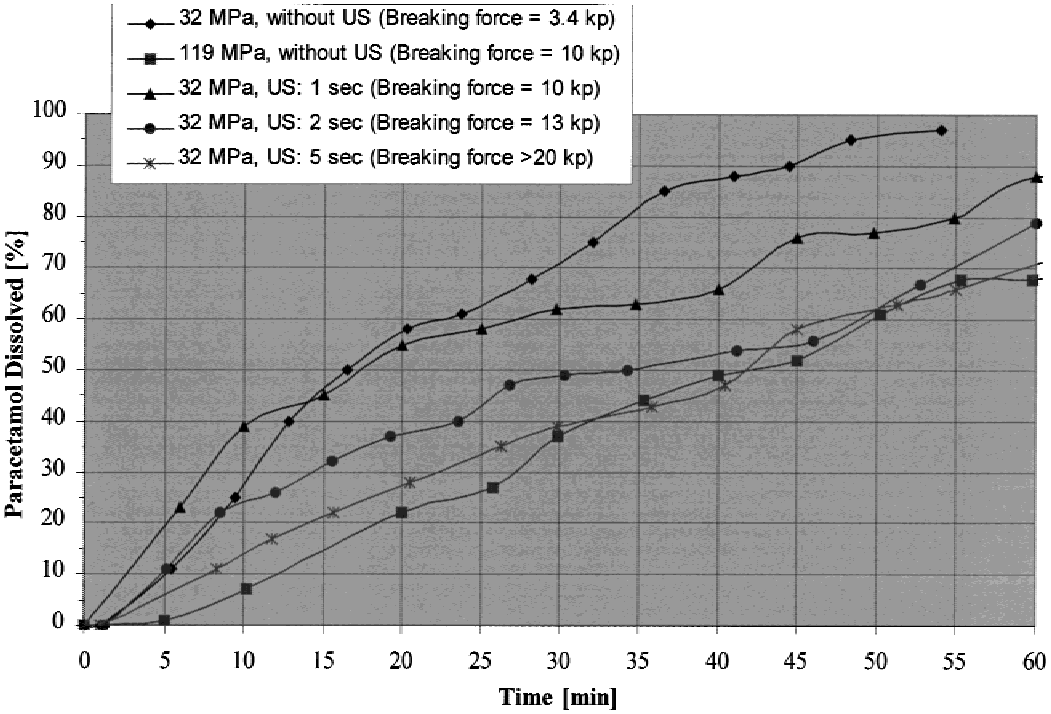


Figure 9. The effect of US on the dissolution rates of tablets containing 500 mg of paracetamol and no disintegrant (formulation III[a]) compressed at 32 MPa. Test conditions: medium = 1,000 mL 0.1N HCl; basket at 150 rpm, 244 nm.

It is important to emphasize that the temperatures reported previously actually represent the mean TST that is not the local temperature achieved at 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 US-assisted powder compaction.

According to Bateman et al.,[23] temperature has an effect on 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 tensile strength. This might also apply to US-assisted compaction. A warmer and more ductile tablet 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 mechanical strength increase of the tablets produced with US. On macro level, tablet surface

Table 4. The Effect of Pressure and US Time on the Apparent Density, Breaking Force, and Time Values for 50 and 70% Drug Release from Paracetamol Tablets (Formulation III[a])

Pressure (MPa)	US Time (sec)	Apparent Density (g/cm^3 ± SD) (n = 6)	Breaking Force (kp ± SD) (n = 6)	$t_{50\%}$ (min) (n = 3)	$t_{70\%}$ (min) (n = 3)
32		0.967 ± 0.009	3.4 ± 0.3	16.5	27.5
119		1.118 ± 0.003	10.0 ± 0.5	42.0	>60.0
32	1	1.004 ± 0.012	10.0 ± 1.0	17.5	42.0
32	2	1.093 ± 0.001	13.0 ± 1.0	34.0	54.5
32	5	1.185 ± 0.003	>20	42.0	59.0

Values are mean ± standard deviation, n denotes the number of determinations.

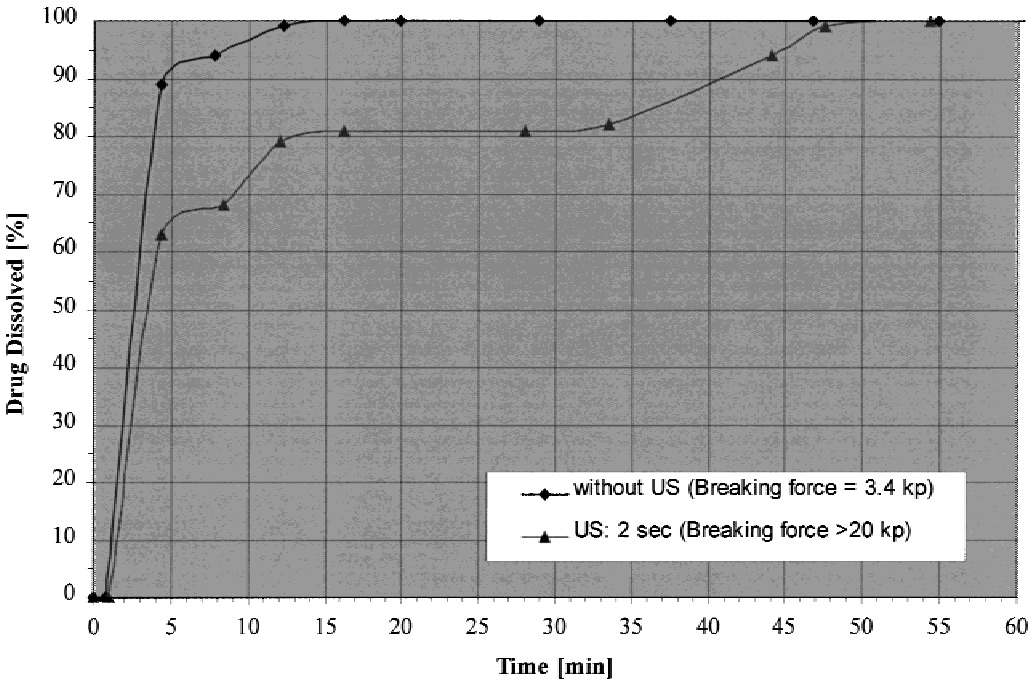


Figure 10. The effect of US on the dissolution rates of tablets containing 500 mg of paracetamol and 5% w/w of crospovidone (formulation VI[a]) compressed at 32 MPa. Test conditions: medium = 1,000 mL 0.1N HCl; basket at 150 rpm, 244 nm.

temperatures, described previously, were not high enough to melt material. However, on the microscopic level, local temperatures achieved during US-assisted compaction might be sufficient to facilitate interparticular bonding by asperity melting.

Scanning Electron Microscopy Studies

Qualitative inspection of the tablets, both upper and fracture surfaces, by means of electron microscopy was conducted to find out what effect US had on the microstructure of tablets prepared by US-assisted compaction.

Figure 11 contains micrographs of the upper tablet surfaces of paracetamol tablets (formulation IV[a]) compressed with and without US. On the micrographs of material treated with US, sinter bridges between particles are clearly seen. These bridges could only occur if the surfaces of the particles partially melted, allowing fusion bonding to take place. Scanning electron microscopy studies showed that local temperature rises during US-assisted compaction were high enough to cause partial material melting at the contact points of the material particles. It can be assumed that when pressure and US vibrations are applied to the material, they are transmitted by way of the surface asperities to 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.[25] assumed that material particles are only in contact at the tips of their asperities. Consequently, when pressure is applied to the material, it will act initially at these points and very high pressures will develop locally. Bowden and Tabor[26] estimated the ratio of the true area of particle contact to the apparent area of contact in the range of 1/1000 to 1/10,000. York and Pilpel[27] suggested that the pressure at points of contact would be on the order of hundreds of atmospheres. According to Jayasinghe et al.[25], such pressure could reduce the melting point of the material by 100 or 200°C. From thermodynamic considerations, Skotnicky[28] derived an equation that predicts that under applied pressure the

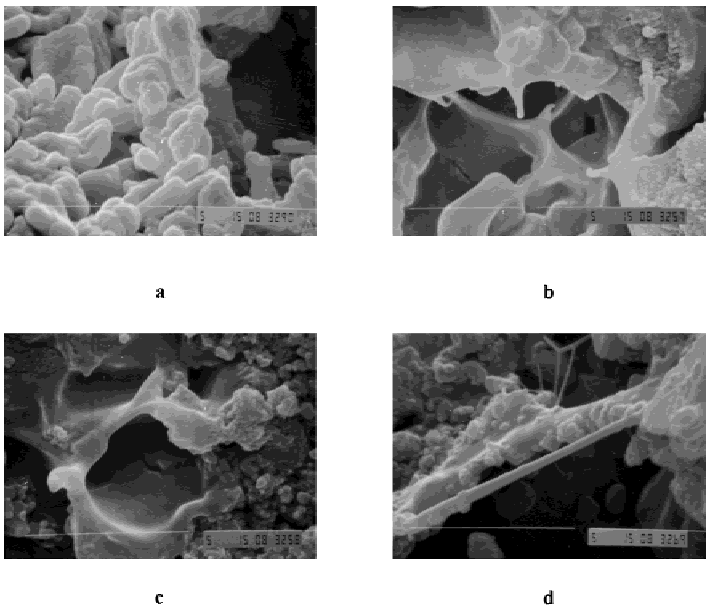


Figure 11. Scanning electron micrographs of the upper surfaces of paracetamol tablets (formulation IV[a]) compressed at 32 MPa without and with US (US amplitude = 7 μm; US time = 2 sec). (Original magnification: [a] ×5,000; [b] ×5,000; [c] ×7,500; [d] ×7,500.)

melting point of a solid (θ_m) is lowered by an amount $d\theta_m$:

$$d\theta_m/dP = -V\theta_m/L \quad (2)$$

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).

Scanning electron microscopy studies showed that as the temperature was raised by US application and as pressure was applied, melting of the particle asperities continued, and in some cases complete melting of the asperities occurred and liquid meniscus formed between the particles, which then solidified on cooling. However, the evidence presented in Figure 11 is not sufficient to prove that local temperature rises reached the point of paracetamol melting (170°C). Formulation IV[a] contained 10% w/w of PVP, which could under the influence of US melt and cause the formation of solid bridges inside the tablets.

This study also showed that the region experiencing the greatest localized temperature rise was the material in contact with the upper punch face, through which US vibrations were delivered. In this region, as a result of asperity melting, the area of contact between the particles increased; the melted material solidified to form solid bridges, causing an increase in the strength of the compact. The presence of many sinter bridges is one of the reasons for the general increase in crushing strength, disintegration, and drug dissolution time of the tablets produced with US. According to Führer,[29] it is to be expected that tablets with sinter bridges between the particles will be very strong, with relatively slow disintegration and dissolution rates.

Figure 12 represents micrographs of paracetamol tablets (formulation III[a]) prepared by US-assisted compaction, confirming the claim of Rodriguez et al.[5] that in some cases US causes material sintering that leads to a progressive transformation of open into close pores.

CONCLUSIONS

An US compaction rig, capable of providing compaction pressure together with high-power US vibrations of 20 kHz to the powder or granular material in the die was used to investigate the effect of US on the compaction properties of paracetamol.

Normally this drug has poor compression properties and produces tablets that are weak and frequently exhibit capping. The results suggest that compaction properties of paracetamol are significantly improved by US. It was found that coher-

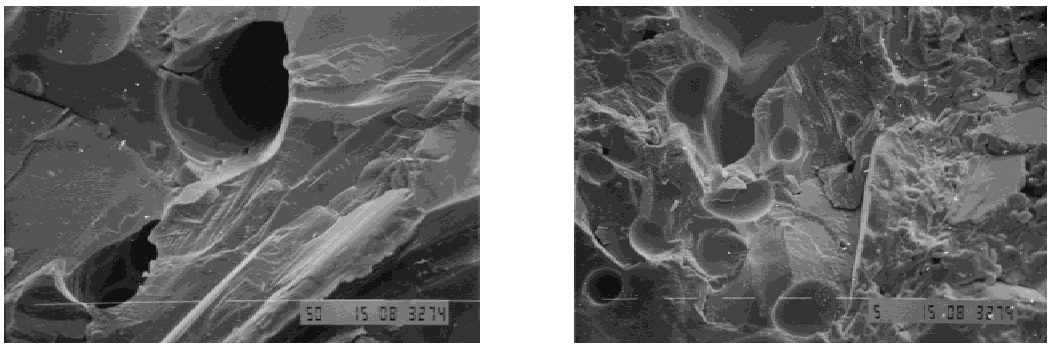


Figure 12. Scanning electron micrographs of the fracture surfaces of paracetamol tablets (formulation III$^{\alpha}$) compressed at 32 MPa with US (US amplitude = 7 μm; US time = 20 sec). (Original magnification: [a] ×500; [b] ×1,000.)

ent tablets could be produced with US application at pressures as low as 20 to 30 MPa, which was impossible by conventional compression.

Application of US before and after compaction was found to be not as effective as US applied during compaction. It was found that paracetamol tablets (formulation IV$^{\alpha}$) formed without US at pressures in the range of 8 to 32 MPa had low, less that 4 kp, breaking forces, confirming poor compactability of the material. Application of US *before* and *after* compaction resulted only in a slight, less than 2 kp, increase in tablet breaking forces. However, much stronger tablets were produced when US was applied *during* compaction. For example, breaking forces of the tablets prepared at 32 MPa with US applied *during* compaction increased from 3.1 kp (without US) to 15.6 kp.

It was concluded that pressure should be applied together with US 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 US increased with an increase in compaction pressure because of improved acoustical contact between the horn and the material and better interparticulate contact of the compressed material. When compaction pressure was increased from 8 to 16, 24, and 32 MPa, breaking forces of paracetamol tablets (formulation IV$^{\alpha}$) increased from 8.8 to 12.3, 13.5, and 15.6 kp, respectively.

It was found that formulation had a profound effect on the results of US-assisted compaction. An increase in binder (PVP) concentration in paracetamol granules from 1 to 20% w/w did not affect breaking forces of conventionally produced tablets. On the other hand, the same increase in PVP concentration caused an increase in breaking force of the tablets prepared by US-assisted compaction from 5.3 to 17 kp. The possible explanation for this phenomenon could be that with granulation, the binder agglomerated drug particles, leaving a thin coat of polymer around the paracetamol particles and the agglomerated mass. It can be assumed that during US-assisted compaction, sintering occurs and, therefore, an increase in PVP concentration may have resulted in an increase in the number of solid bridges between particles and, consequently, in an increase in tablet breaking force.

Paracetamol in mixtures with DCP could not produce tablets at 32 MPa by pressure alone. On the other hand, US-assisted compaction allowed the production of relatively strong compacts, with a maximum breaking force of 7.7 kp for a 50% w/w mixture of paracetamol with DCP. An US application at 32 MPa resulted in tablet breaking force increase from 0 kp (without US) to 5.9 kp, from 3.5 kp (without US) to 6.1 kp, and from 9.8 kp (without US) to 14.0 kp, for 75% w/w, 50% w/w, and 25% w/w mixtures of paracetamol with MCC, respectively.

It was also found that formulations of paracetamol with DCP produced tablets with higher breaking forces than the individual materials. This was attributed to positive interactions taking place because of the bonding between the materials. The higher crushing force values of the tablets compressed from blends of the drug with DCP compared with the compacts compressed from the mixture containing no filler could be ex-

plained by the fact that the drug-drug bonds induced by US were weaker than the drug-filler bonds.

This study also showed that US application during compaction resulted in an apparent density increase, in relation to the apparent density of the conventionally prepared tablets, of up to 12.8%. US appears to improve rearrangement of the particles, eliminating the badly compacted zones and provides 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 paracetamol dissolution times.

The studies revealed that disintegration and drug dissolution rates for the tablets produced by US-assisted compaction were related to US time and formulation. An increase in US time generally resulted in a more or less profound tablet disintegration and paracetamol dissolution rate decrease, which was a function of the formulation studied. An increase in US time from 1 to 1.5, 2, and 5 sec resulted in an increase in tablet (formulation VI[a]) disintegration time from 2 to 23, 52, and 82 min, respectively. An increase in US time from 1 to 2 and 5 sec resulted in time increase for 70% drug release for paracetamol tablets (formulation III[a]) from 42 to 54.5 and 59 minutes.

ACKNOWLEDGMENTS

The authors are grateful to Prof. Roger Morgan, School of Electrical Engineering, Electronics and Physics, Liverpool John Moores University, for the help in obtaining and installing the ultrasonic equipment and his expertise in the field of ultrasound and to B. W. I. Manesty for sponsoring this research.

REFERENCES

1. Gueret J-L H. 1993. Process for the compaction of a powder mixture providing an absorbent or partially friable compact product and the product obtained by this process. U. S. Patent 5,211,892.
2. Rodriguez L, Cini M, Cavallari C, Passerini N, Saettone MF, Monti D, Caputo O. 1995. Ultrasound-assisted compaction of pharmaceutical materials. Farm Vestn 46:241–242.
3. Rodriguez L, Cini M, Cavallari C, Passerini N, Saettone MF, Fini A, Caputo O. 1998. Evaluation of theophylline tablets compacted by means of a novel ultrasound-assisted apparatus. Int J Pharm 170:201–208.
4. Saettone MF, Giannaccini B, Monti D, Cabani I, Rodriguez L, Cini M, Cavallari C, Caputo O. 1996. Ultrasound-assisted compaction of pharmaceutical materials. II. Preparation of matrixes for sustained release of theophylline. Boll Chim Farm 135: 142–144.
5. Rodriguez L, Cini M, Cavallari C, Passerini N, Saettone MF, Fini A, Caputo O. 1997. Physicochemical properties of some materials compacted using an ultrasound-assisted tableting machine. 16th Int Conf Pharm Tech 1:267–278.
6. Motta G. 1994. Process for preparing controlled release pharmaceutical forms and the forms thus obtained. Int Patent WO 94/14421.
7. Kolb DJ. 1966. Assembling thermoplastics by ultrasonic vibration. SPE J 22:21–24.
8. Watson MN, editor. 1988. Joining plastics in production. Cambridge: Crampton & Sons Ltd.
9. Rawson FF. 1987. High power ultrasonic resonant horns. I. Basic design concepts: velocity of ultrasound at 20 khz; effects of material and horn dimensions. Conf Proc Ultrasonics Int. 1: 680–685.
10. British Pharmacopoeia. London: Her Majesty's Stationary Office; 1988.
11. United States Pharmacopeia XXII. Rockville, MD: The US Pharmacopeial Convention, Inc.; 1990.
12. Ridgway WP. 1988. Tablet machine instrumentation in pharmaceutics: principles and practice. Chichester: Ellis Horwood Ltd.
13. Paul DW, Crawford RJ. 1981. Ultrasonic moulding of plastic powders. Ultrasonics 19:23–27.
14. Nayar SK, Benatar A. 1989. Ultrasonic moulding of plastic powders. In: Proc. 5th Annual ASM/ESD Conf. Advanced Composites, ASM Int. pp 139–145.
15. Ng W, Benatar A. 1993. Ultrasonic molding of UHMWPE using high-pressure molder. In: Transactions 24th Annual Symposium, Ultrasonics Industrial Association. p 28.
16. Bicknell BR. 1965. Ultrasonic welding of rigid thermoplastics. Industr Electronics 9:410–413.
17. Matsuoka S, Maeda T. 1982. Study on ultrasonic molding of polymeric powders. J Jpn Soc Technol Plast 23:44–50.
18. Lehfeldt E. 1967. The effect of ultrasonic vibrations on the compacting of metal powders. Ultrasonics October:219–223.
19. Carstensen JT, Ertel C. 1990. Physical and chemical properties of calcium phosphate for solid-state pharmaceutical formulations. Drug Dev Ind Pharm 16:1121–1133.
20. Wallace JW, Capozzi JT, Shangraw RF. 1983. Performance of pharmaceutical filler/binders as re-

lated to methods of powder characterization. Pharm Technol 7:94–104.
21. Duberg M, Nystrom C. 1985. Studies of direct compression of tablets. XII. The consolidation and bonding properties of some pharmaceutical compounds and their mixtures with avicel 105. Int J Pharm Tech Prod Mfr 6:17–25.
22. Hanus EJ, King LD. 1968. Temperature measurements in powder compacts. J Pharm Sci 57: 677–684.
23. Bateman SD, Rubinstein MH, Thacker HS. 1990. Pre- and post-compression in tablet production. Pharm Technol Int 2:30–33.
24. Esezobo S, Pilpel NJ. 1986. The effect of temperature on the plasto-elasticity of some pharmaceutical powders and the tensile strength of the tablets. Pharm Pharmacol 38:409–413.
25. Jayasinghe SS, Pilpel N, Harwood CF. 1970. Effect of temperature and compression on the cohesive properties of particulate solids. Mater Sci Eng 5: 287–294.
26. Bowden FP, Tabor D. 1967. Friction and lubrication. New York: Wiley.
27. York P, Pilpel N. 1972. Effect of temperature on the frictional, cohesive and electrical conducting properties of powders. Mater Sci Eng 9:281–291.
28. Skotnicky J. 1953. The dependence of melting point on pressure. Czech J Phys 3:225–230.
29. Führer C. 1977. Substance behavior in direct compression. Labo-Pharma Probl-Tech 25:759–762.